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Efficacy and safety of valoctocogene roxaparvovec gene transfer for severe hemophilia A: Results from the GENEr8-1 three-year analysis

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Disclosure – conflict of interest

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

- **Receipt of grants/research supports:** BioMarin Pharmaceutical Inc., Novo Nordisk, Novartis, Pfizer, F. Hoffman-La Roche Ltd, Sanofi, Spark Therapeutics, and Takeda
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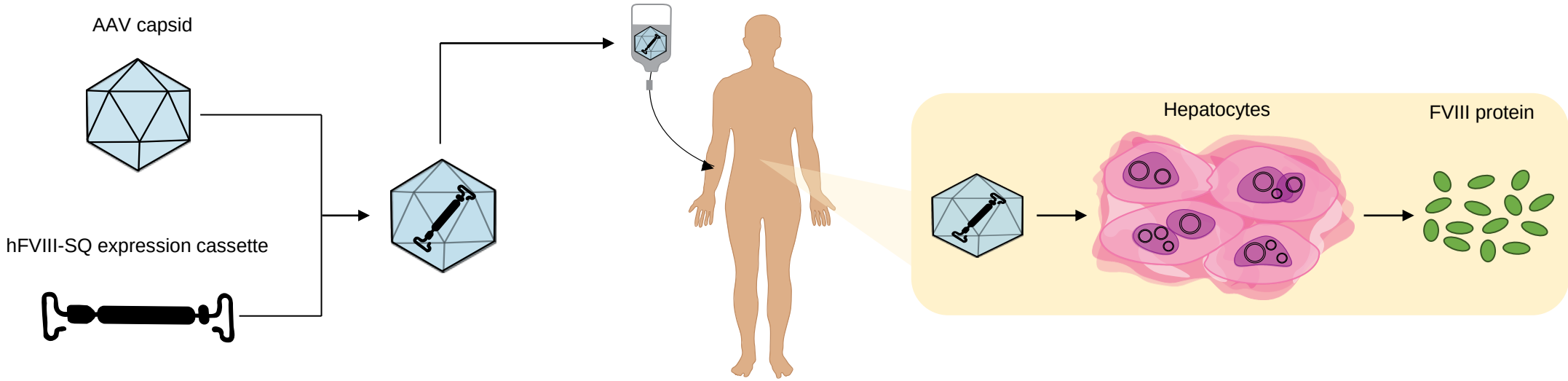
Valoctocogene roxaparvovec for severe hemophilia A

- 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 trial GENEr8-1, 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



1. Ozelo M et al. *N Engl J Med*. 2022;386(11):1013-25. 2. Mahlangu J et al. *Res Pract Thromb Haemost*. 2022;6(Suppl 1):e12787.
AAV, adeno-associated virus; FVIII, factor VIII; hFVIII-SQ, human FVIII, SQ variant.

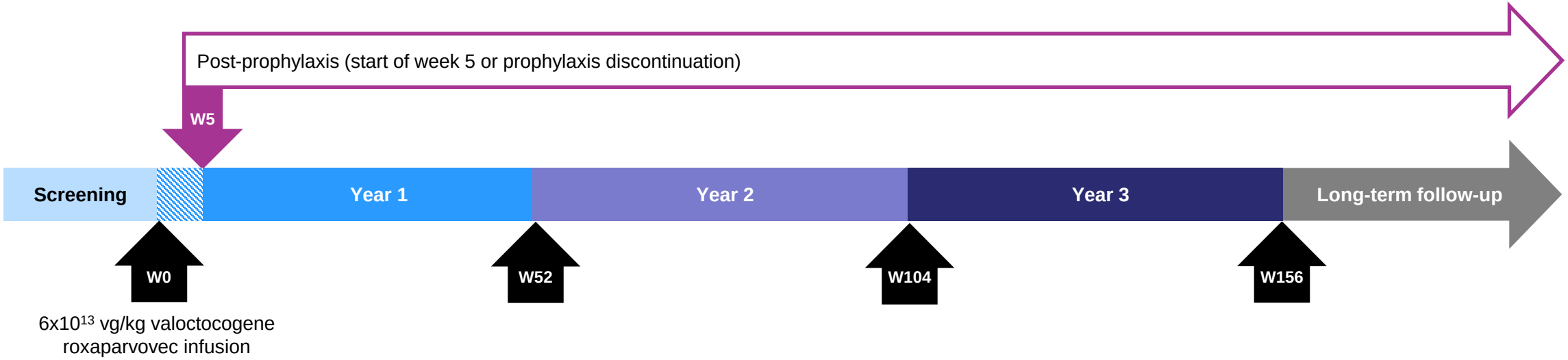
Phase 3 GENEr8-1 study design

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)
- Previously receiving FVIII prophylaxis
- No history of FVIII inhibitors or anti-AAV5 antibodies
- No significant liver dysfunction, significant liver fibrosis, or cirrhosis

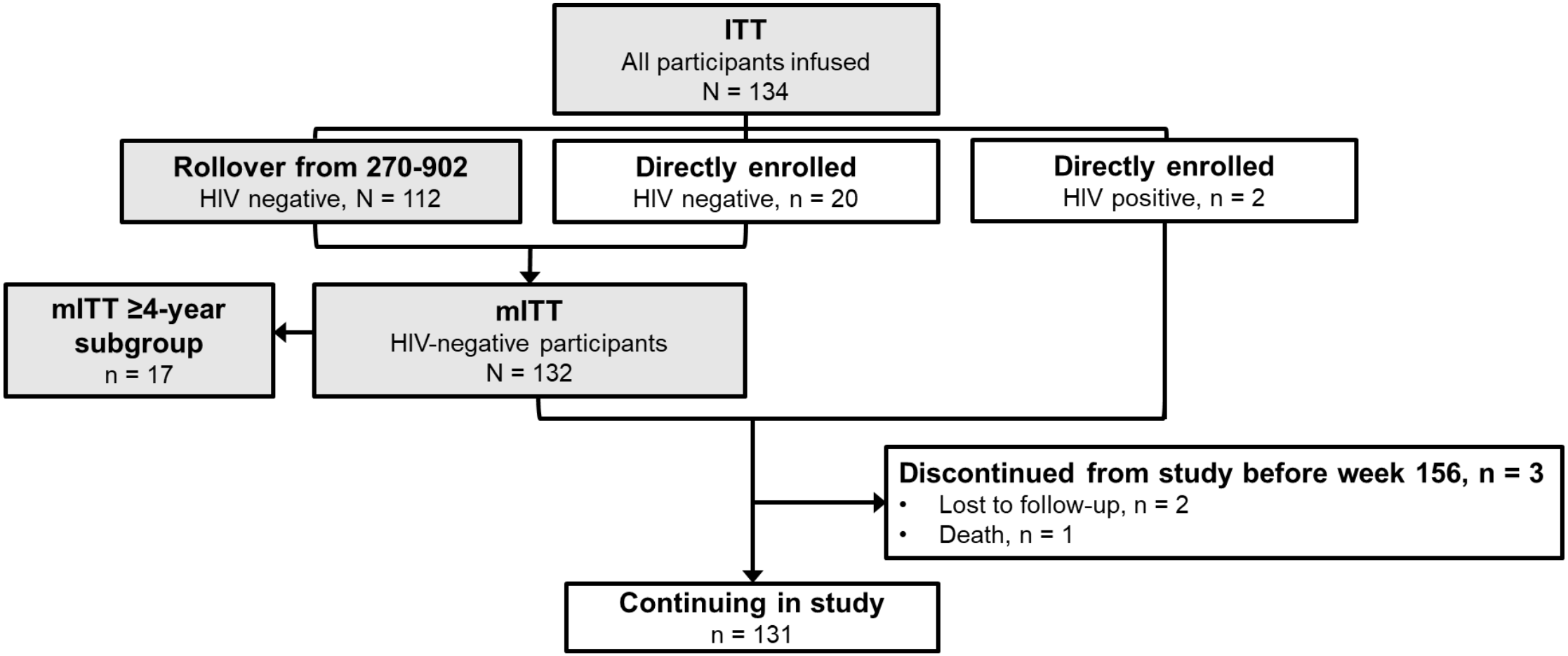
Endpoints

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



AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; W, week.

Participant disposition



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

Baseline demographics

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

[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.

Safety in year 3

- No new safety signals
- Most common AE remains ALT elevation (25%)
  - Others included COVID-19 (22%), arthralgia (13%), headache (7%), pyrexia (6%), and upper respiratory tract infection (6%)
- No new treatment-related Grade 3 AEs occurred
- No treatment-related SAEs
- No participants developed inhibitors or thromboembolic events

Participants, n (%)		ITT N = 134
AEs		103 (76.9)
SAEs		11 (8.2)
Treatment-related AEs		16 (11.9)
Corticosteroid-related AEs		0
AEs of special interest	ALT elevation	34 (25.4)
	ALT elevation ≥ Grade 3	0
	Potential Hy's law case	0
	Infusion-related reactions[a]	0
	Systemic hypersensitivity	0
	Anaphylactic or anaphylactoid reactions	0
	Thromboembolic events	0
	Anti-FVIII neutralizing antibodies	0
	Malignancy (except non-melanoma skin cancer)	1 (0.7)

[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 AE.

One SAE in the past year: 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.

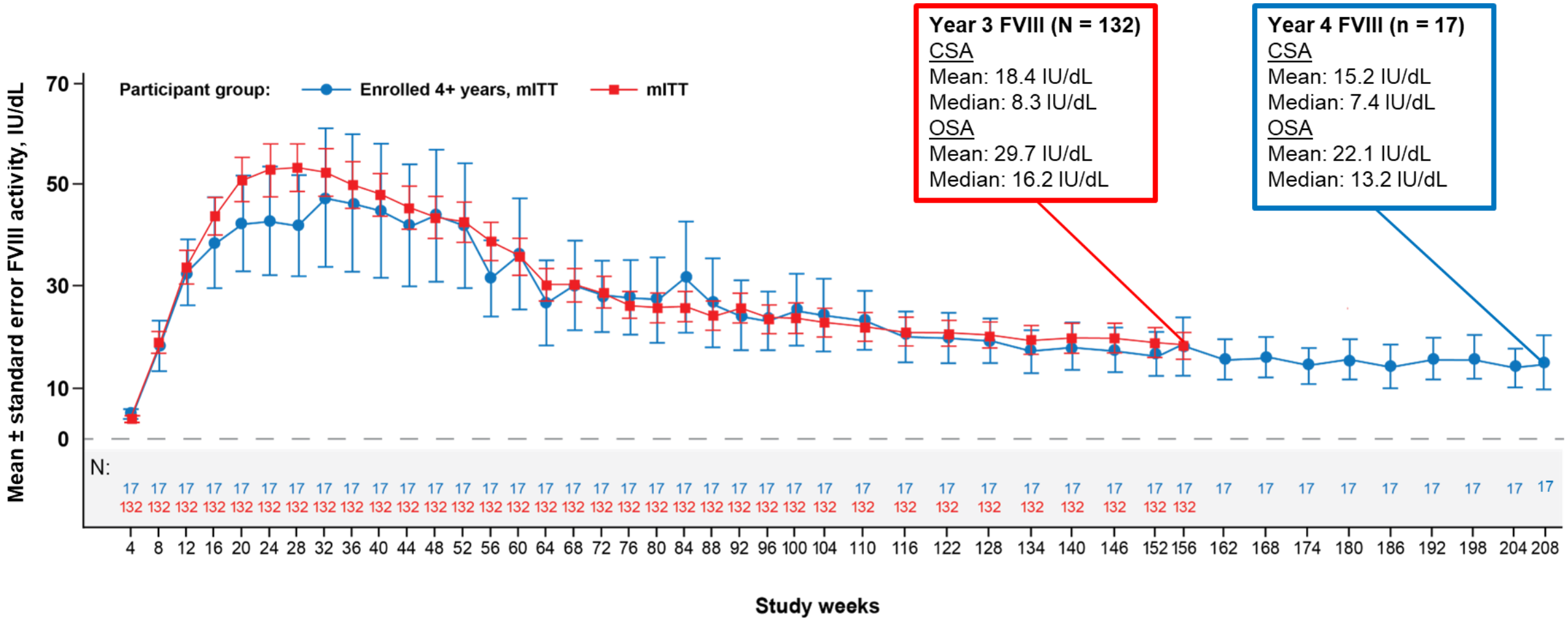
ALT elevation and corticosteroid use

- In the past year of follow-up, 34 (25%) participants had an ALT elevation
  - None initiated corticosteroids after week 104
  - Most events were Grade 1 and less than the ULN
- As of the data cutoff date, 3 participants were using corticosteroids for any indication

Through all follow-up	ITT N = 134
Used corticosteroids for any purpose, n (%)	109 (81.3)
Total duration, weeks, median (min, max)	33 (0.1, 120)
Total dose, mg, median (min, max)	6310 (40, 31760)
Used corticosteroids for ALT elevation, n (%)	106 (79.1)
Total duration, weeks, median (min, max)	33 (3, 120)
Total dose, mg, median (min, max)	6420 (960, 31760)

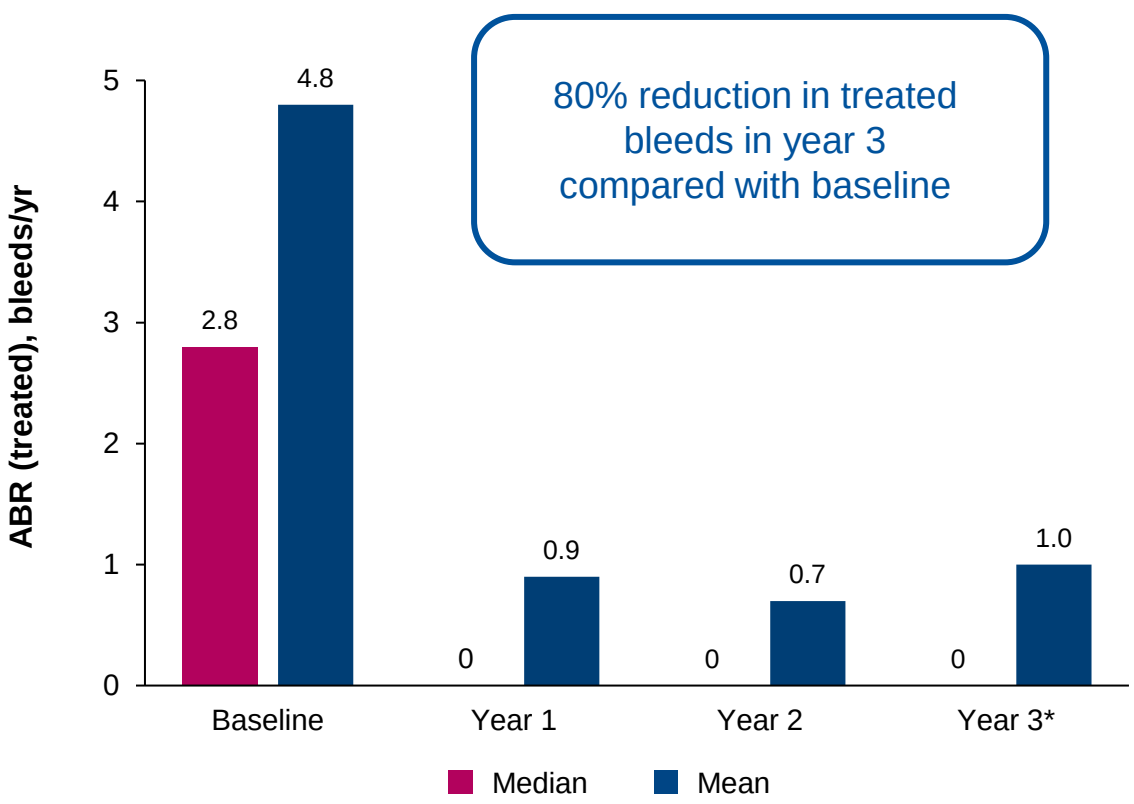
ALT, alanine aminotransferase elevation; ITT, intent-to-treat; min, minimum; max, maximum; ULN, upper limit of normal.

FVIII activity per chromogenic substrate assay up to 4 years

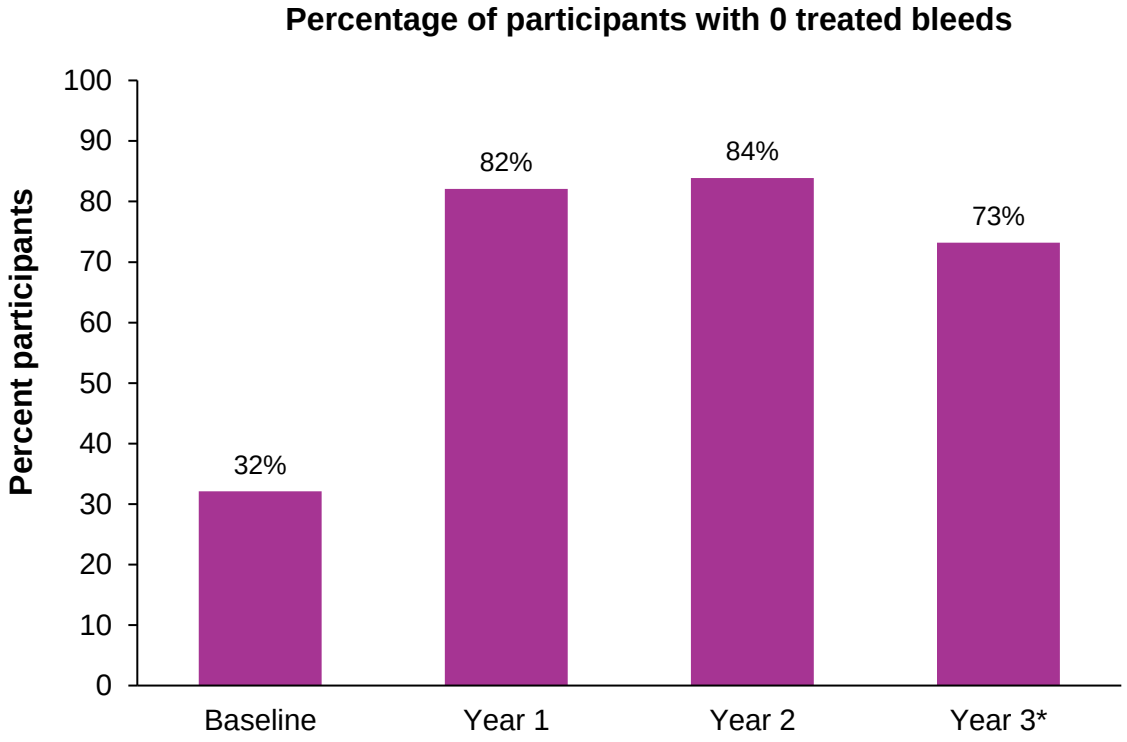


For participants who discontinued the study, missing FVIII values post-discontinuation were imputed to be 0 IU/dL through the data cutoff date for the analysis.
CSA, chromogenic substrate assay; FVIII, factor VIII; mITT, modified intent-to-treat; OSA, one-stage assay.

Reduction in treated bleeds maintained over 3 years



80% reduction in treated bleeds in year 3 compared with baseline

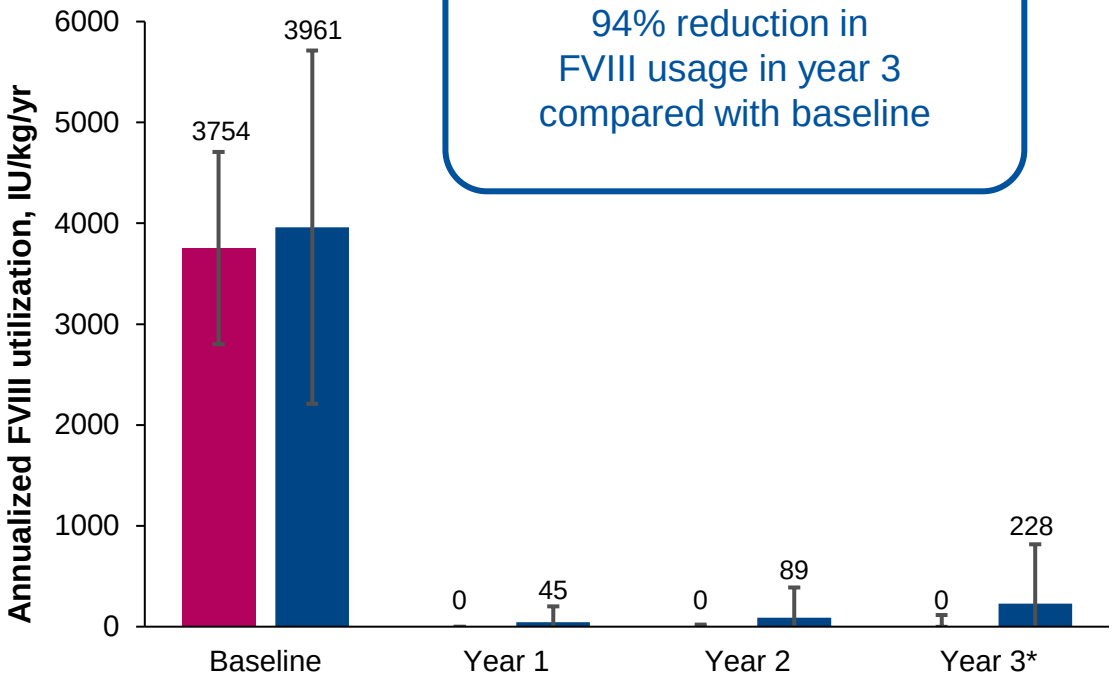


Rollover population (N = 112)

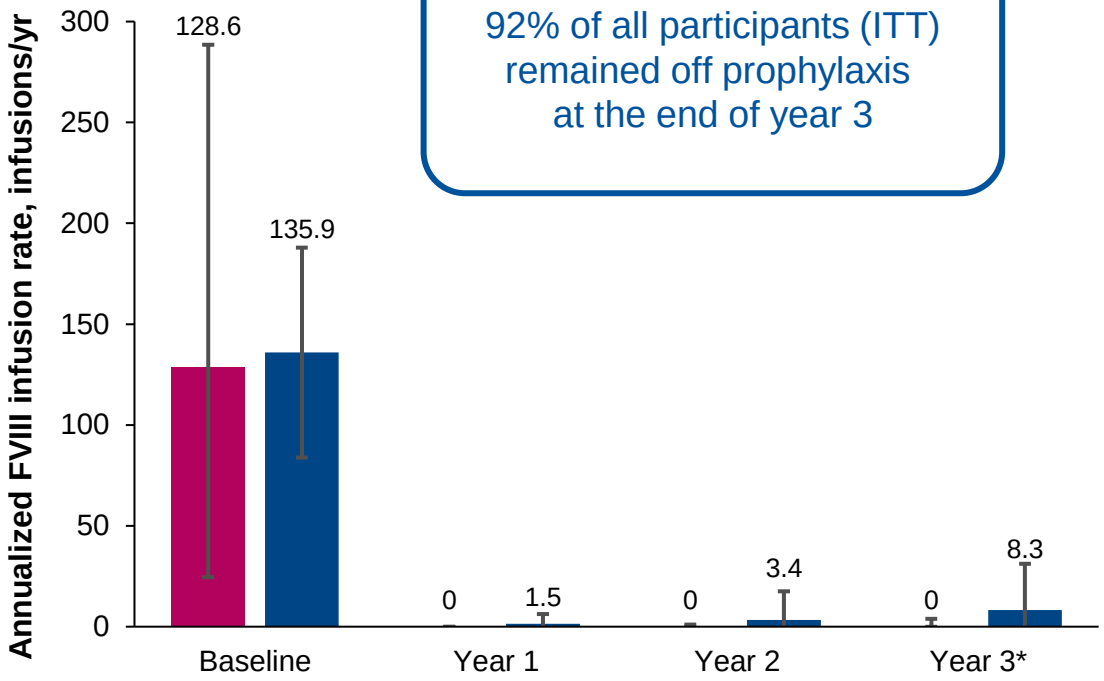
Missing data were not imputed. *Year 3 data were based on N = 110 due to participants who discontinued from the study.
ABR, annualized bleeding rate.

Reduction in FVIII utilization maintained over 3 years

94% reduction in FVIII usage in year 3 compared with baseline



92% of all participants (ITT) remained off prophylaxis at the end of year 3



Median (Q1, Q3) Mean ± SD

Rollover population (N = 112)

Missing data were not imputed. *Year 3 data were based on N = 110 due to participants who discontinued from the study.
FVIII, factor VIII; ITT, intent-to-treat population; Q, quartile; SD, standard deviation.

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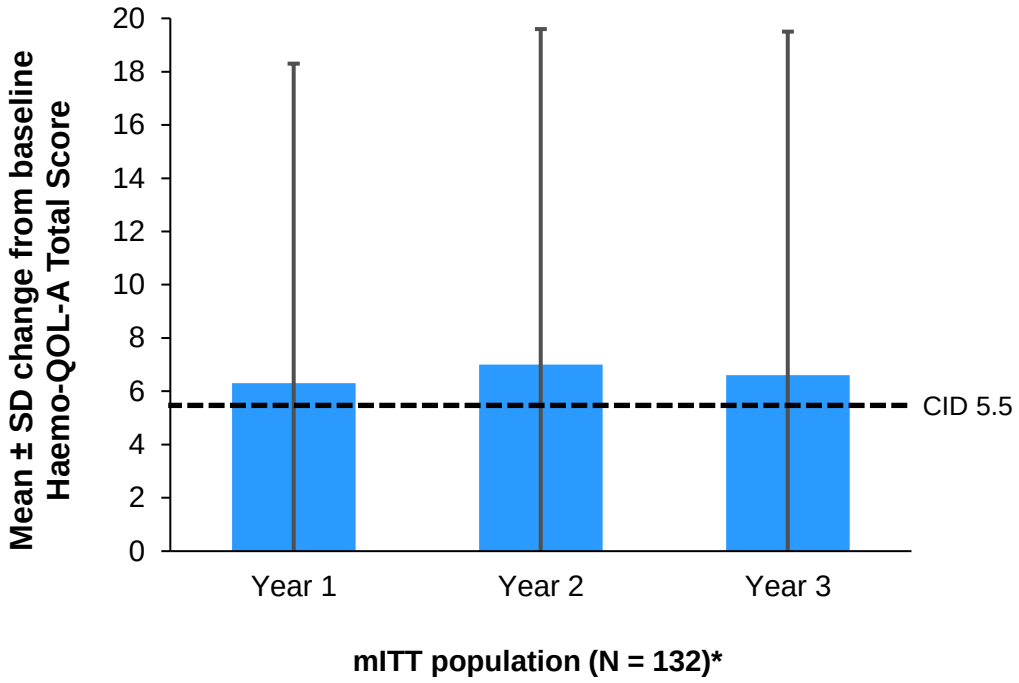
Improvement in Haemo-QOL-A maintained at the end of year 3

- Change in mean Haemo-QOL-A Total Score from baseline to week 156 was 6.6 (*P* <0.0001)
  - This exceeds the anchor-based CID of 5.5[1]

Efficacy evaluation period	N	Haemo-QOL-A Total Score (mean ± SD)	Change from baseline* (mean ± SD)	*P*-value (change from baseline*)
Baseline	130	75.7 ± 16.7	-	-
Year 1	129	82.1 ± 15.4	6.3 ± 12.0	*P* <0.0001
Year 2	128	82.8 ± 15.3	7.0 ± 12.5	*P* <0.0001
Year 3	123	82.3 ± 14.5	6.6 ± 12.9	*P* <0.0001



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

*Haemo-QOL-A Total Score change from baseline results are based on available data at each time point, which may differ from the given N.

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

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Conclusions

- No new safety signals emerged during year 3
  - Safety profile remains unchanged
- Previously observed trends regarding change in FVIII activity were maintained
- A single infusion of valoctocogene roxaparvovec provided robust hemostatic efficacy relative to FVIII prophylaxis over 3 years
  - 80% reduction in treated bleeds in year 3 compared with baseline
  - 94% reduction in FVIII usage in year 3 compared with baseline
  - 92% of participants remained off prophylaxis at the end of year 3
- Improvements in QOL were maintained at the end of year 3

FVIII, factor VIII; QOL, quality of life.

Acknowledgments

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