Hemostatic response is maintained for up to 5 years following treatment with valoctocogene roxaparvovec, an AAV5-hFVIII-SQ gene therapy for severe hemophilia A

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Disclosures for Michael Laffan

In compliance with COI policy, ISTH requires the following disclosures to the session audience:

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Employee	No relevant conflicts of interest to declare
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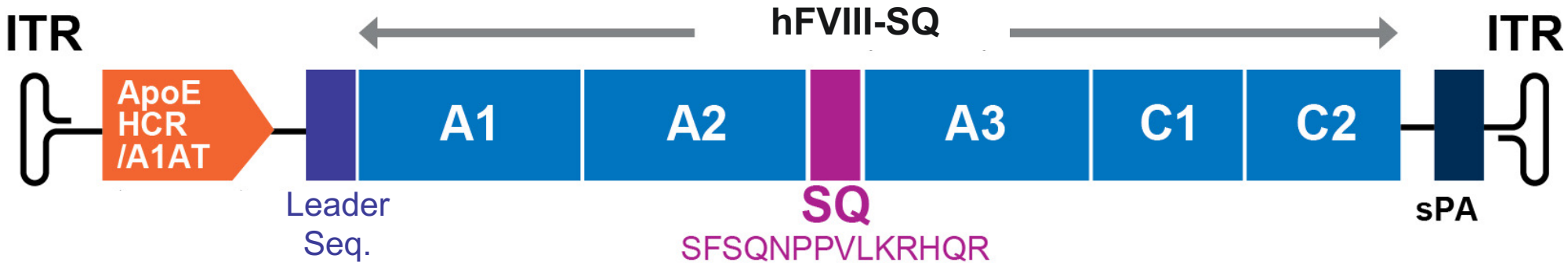
Valoctocogene roxaparvovec gene therapy for severe hemophilia A

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a FVIII coding sequence to hepatocytes using a recombinant AAV5 vector, enabling endogenous FVIII production in people with hemophilia A[1,2]
- Here, we present updated safety and efficacy results for up to 5 years from an ongoing a phase 1/2 trial



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.
A1AT, alpha-1-anti-trypsin promoter; AAV, adeno-associated virus; ApoE, apolipoprotein E; FVIII, factor VIII; HCR, hepatic control region; ITR, inverted terminal repeat.

Participant disposition and baseline characteristics

15 participants enrolled and dosed in 4 cohorts

- **1** participant in the **6×10^{12}** vg/kg dose cohort
- **1** participant in the **2×10^{13}** vg/kg cohort
- **7** participants in the **6×10^{13}** vg/kg dose cohort
- **6** participants in the **4×10^{13}** vg/kg dose cohort

Baseline characteristics	6×10^{13} vg/kg cohort (n = 7)	4×10^{13} vg/kg cohort (n = 6)
Age, years		
Mean (SD)	30.4 (5.8)	31.3 (9.6)
Median	30.0	30.5
Min, max	23.0, 42.0	22.0, 45.0
Race, n (%)		
Asian	1 (14.3)	0
Black	0	1 (16.7)
White	6 (85.7)	5 (83.3)
Baseline annualised FVIII infusion rate, infusions/year		
Mean (SD)	120.1 (45.9)	142.8 (48.8)
Median	121.4	155.8
Min, max	27.4, 158.5	53.8, 184.3
Baseline ABR (treated bleeds), bleeds/year		
Mean (SD)	17.6 (14.7)	12.2 (15.4)
Median	24.0	8.0
Min, max	0, 40.0	0, 41.0

ABR, annualized bleeding rate; FVIII, factor VIII; SD, standard deviation; vg, vector genomes.

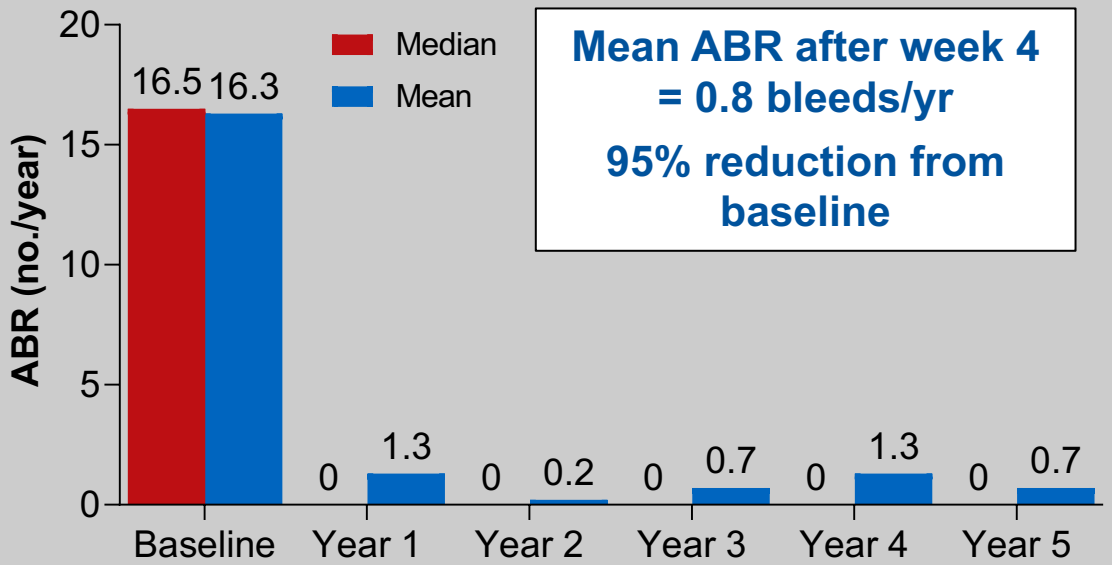
Safety

n	$6x10^{13}$ vg/kg cohort (n = 7)					$4x10^{13}$ vg/kg cohort (n = 6)			
	Y1	Y2	Y3	Y4	Y5	Y1	Y2	Y3	Y4
Any AE	7	6	7	7	**6**	6	5	5	**4**
Any SAE	0	1	1	1	**0**	1	0	1	**1**
Any treatment-related AE	6	1	1	2	**0**	6	0	0	**0**
Any treatment-related SAE	0	0	0	0	**0**	1	0	0	**0**
AEs of special interest									
ALT elevation	6	0	0	1	**1**	4	0	1	**0**
AEs of liver dysfunction	6	1	0	1	**1**	5	0	1	**0**
Infusion-related reactions	3	0	0	0	**0**	4	0	0	**0**

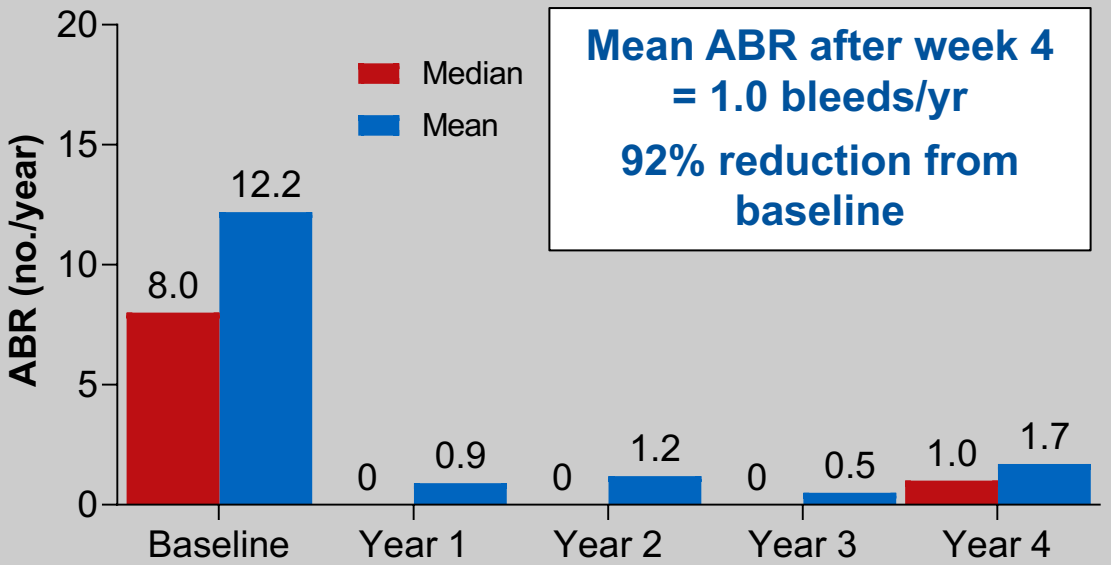
AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event; Y, year.

Sustained reduction in annualized treated bleeding rate

6x10^{13} vg/kg dose cohort (n = 6*)



4x10^{13} vg/kg dose cohort (n = 6)



n (%) participants bleed-free (n = 7)					
Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
1 (14%)	5 (71%)	6 (86%)	6 (86%)	5 (71%)	6 (86%)

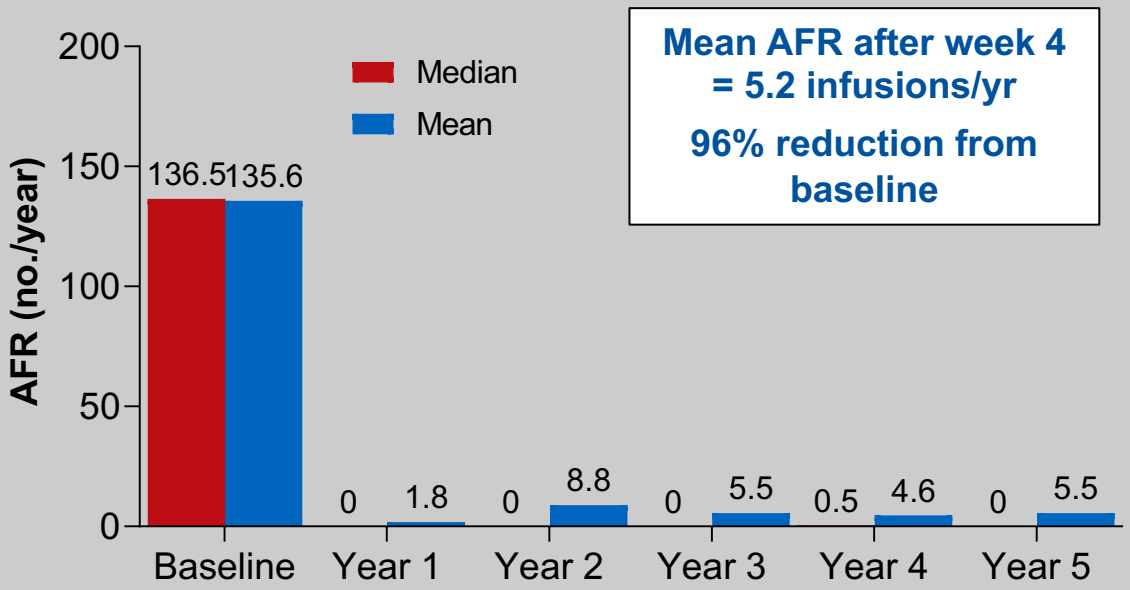
n (%) participants bleed-free (n = 6)				
Baseline	Year 1	Year 2	Year 3	Year 4
1 (17%)	5 (83%)	4 (67%)	4 (67%)	3 (50%)

All participants remain off FVIII prophylaxis

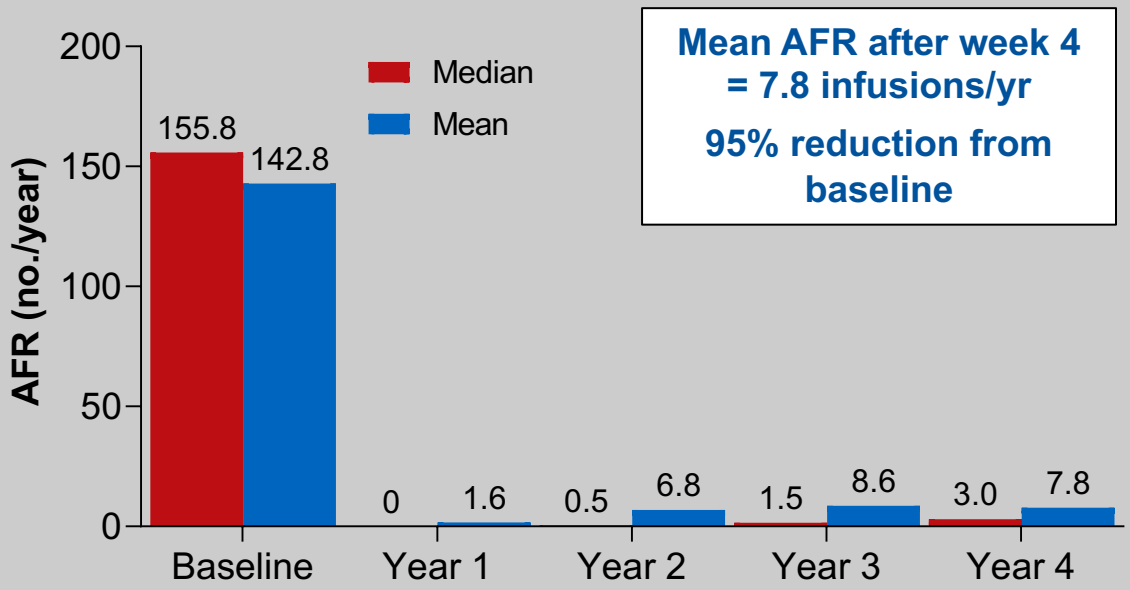
*Excluding the participant receiving on-demand FVIII treatment at baseline.
ABR, annualized bleeding rate; FVIII, factor VIII; no., number.

Sustained reduction in annualized FVIII infusion rate

$6x10^{13}$ vg/kg dose cohort (n = 6*)



$4x10^{13}$ vg/kg dose cohort (n = 6)



Infusion rate by reason after week 4 (n = 6*)

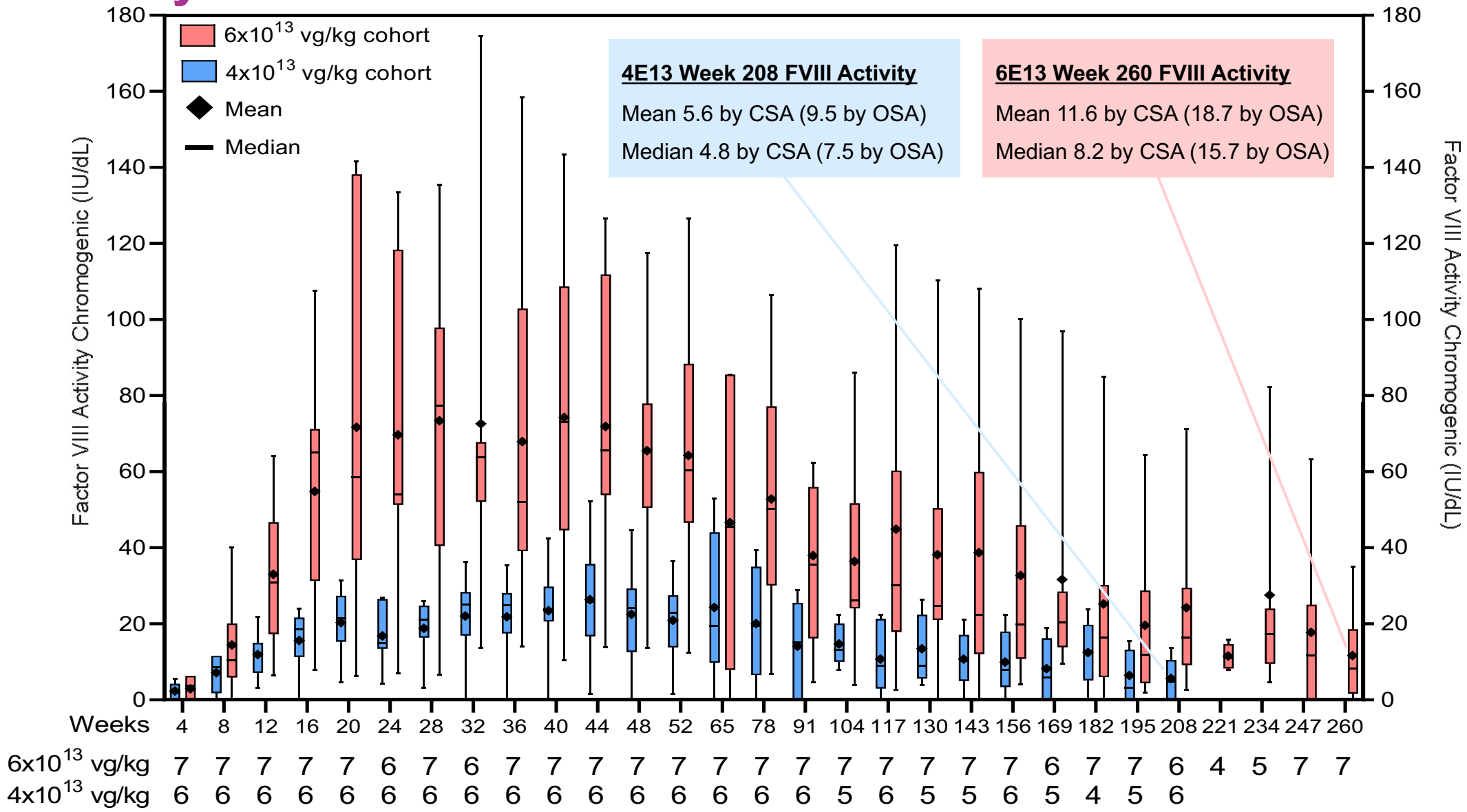
no./year	Treatment for bleed	Usual prophylaxis	Surgery/ procedures	One-time prophylaxis
Mean	1.6	0	2.7	0.9
Median	0	0	0.1	0

Infusion rate by reason after week 4 (n = 6)

no./year	Treatment for bleed	Usual prophylaxis	Surgery/ procedures	One-time prophylaxis
Mean	3.3	0	2.2	2.2
Median	1.1	0	0.6	0

*Excluding the participant receiving on-demand FVIII treatment at baseline.
AFR, annualized FVIII infusion rate; FVIII, factor VIII; no., number.

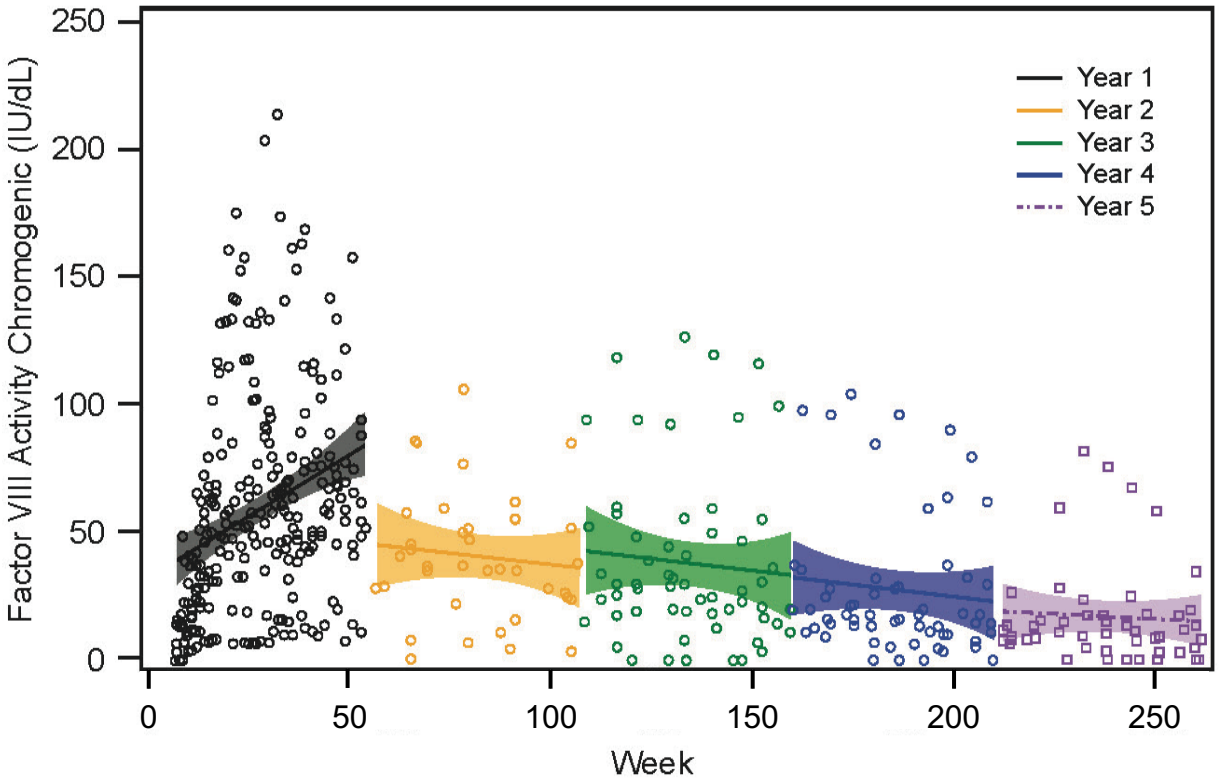
FVIII activity over time



FVIII, factor VIII; CSA, chromogenic substrate assay; OSA, one-stage.

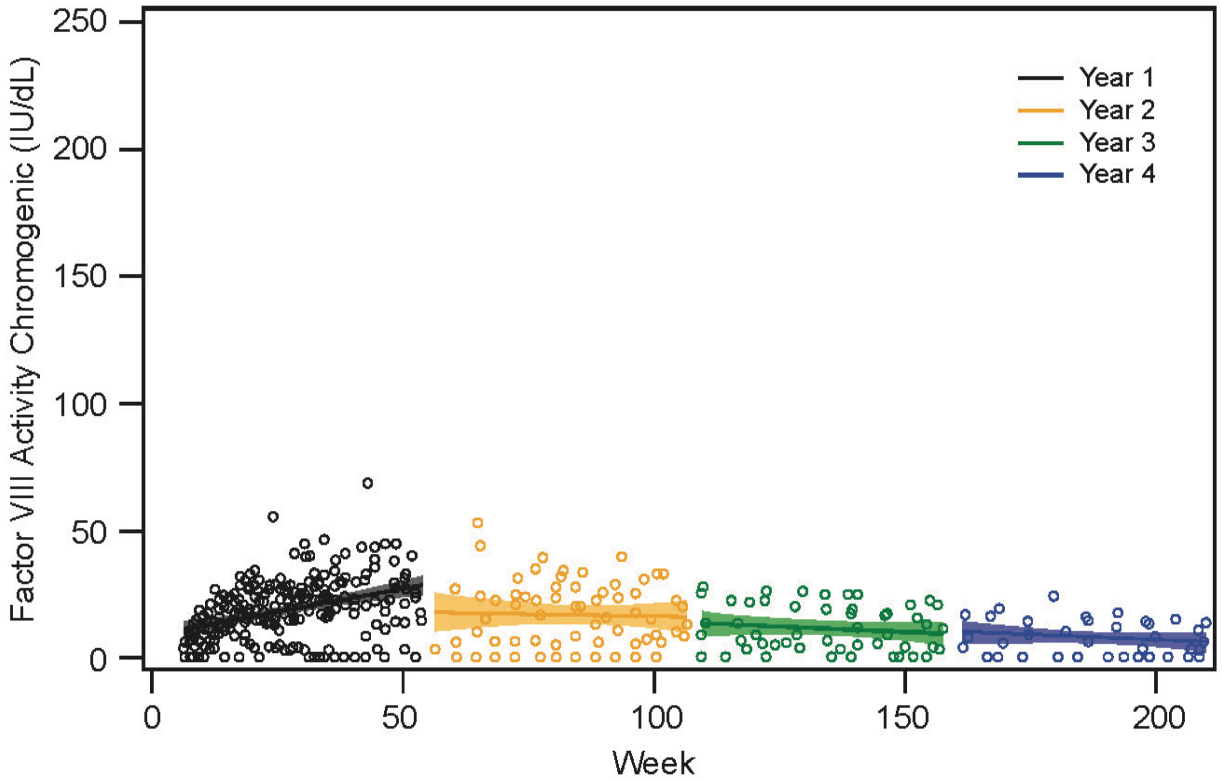
FVIII activity rate of change over time

6x10^{13} vg/kg cohort (n = 7)



Regression of FVIII by follow-up year					
IU/dL/wk	Year 1	Year 2	Year 3	Year 4	Year 5
Slope	1.01	−0.24	−0.15	−0.27	−0.14
95% CI	−0.04, 2.05	−0.68, 0.21	−0.47, 0.16	−0.49, −0.04	−0.32, 0.03

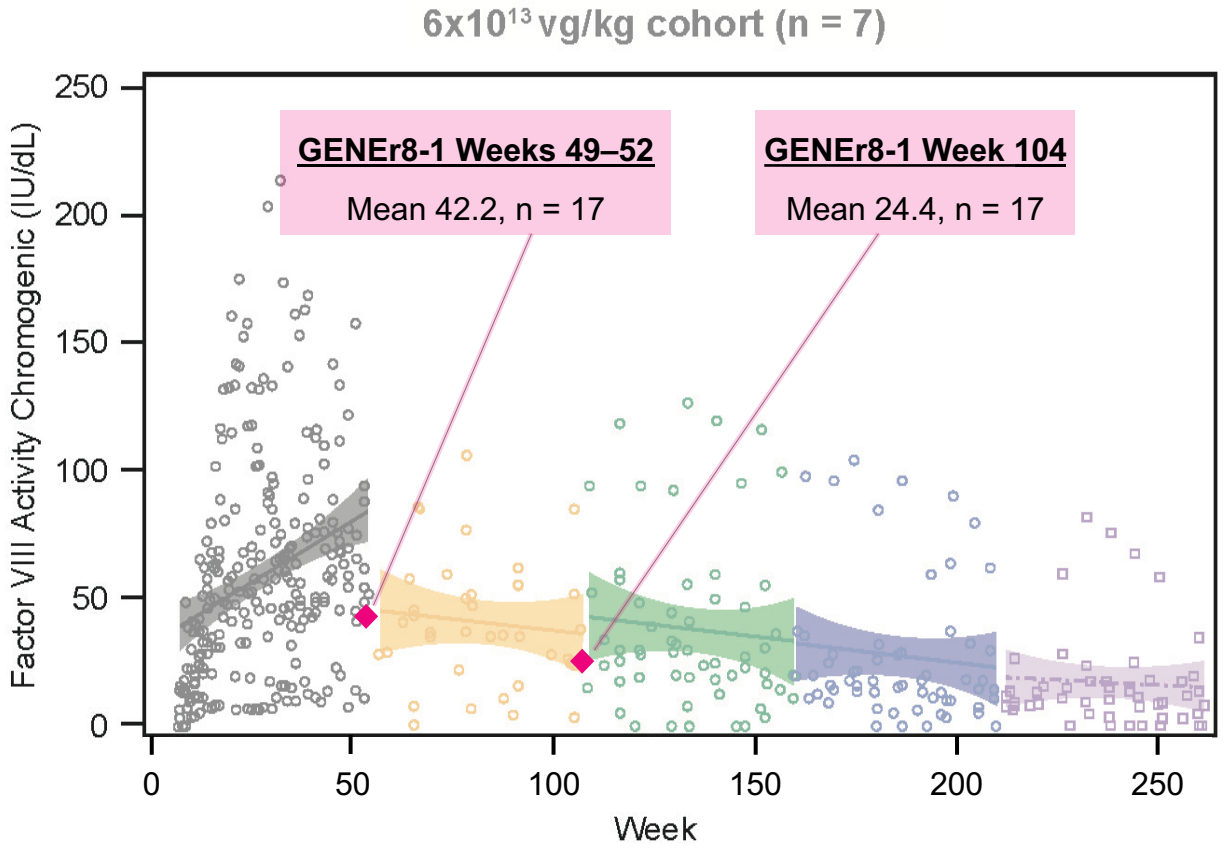
4x10^{13} vg/kg cohort (n = 6)

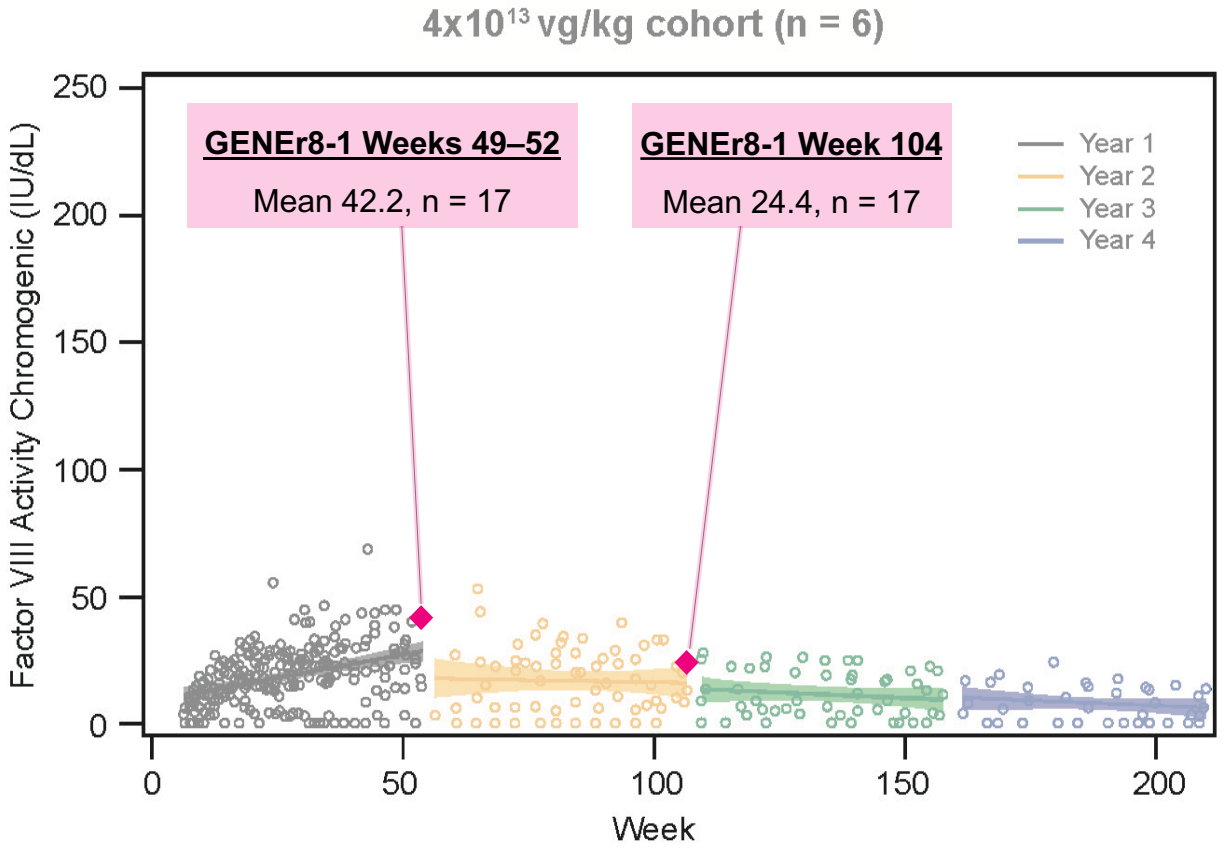


Regression of FVIII by follow-up year				
IU/dL/wk	Year 1	Year 2	Year 3	Year 4
Slope	0.35	−0.15	−0.08	−0.06
95% CI	−0.01, 0.71	−0.37, 0.07	−0.17, 0.02	−0.14, 0.01

CI, confidence interval; FVIII, factor VIII.

Comparison to Phase 3 GENEr8-1 Study

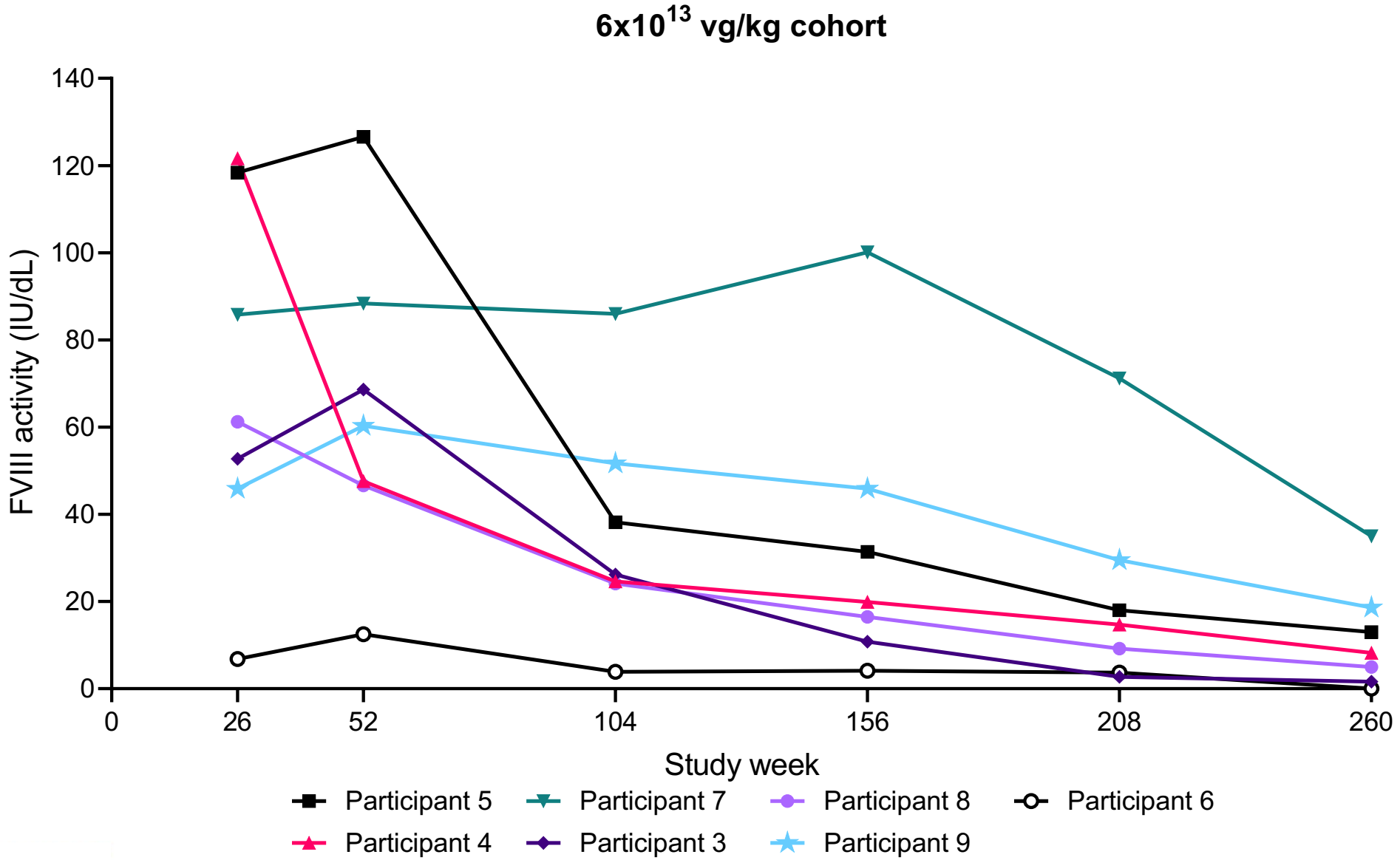




FVIII levels from the phase 3 GENEr8-1 study were below those of the $6x10^{13}$ vg/kg cohort and above those of the $4x10^{13}$ vg/kg cohort from this phase 1/2 study.

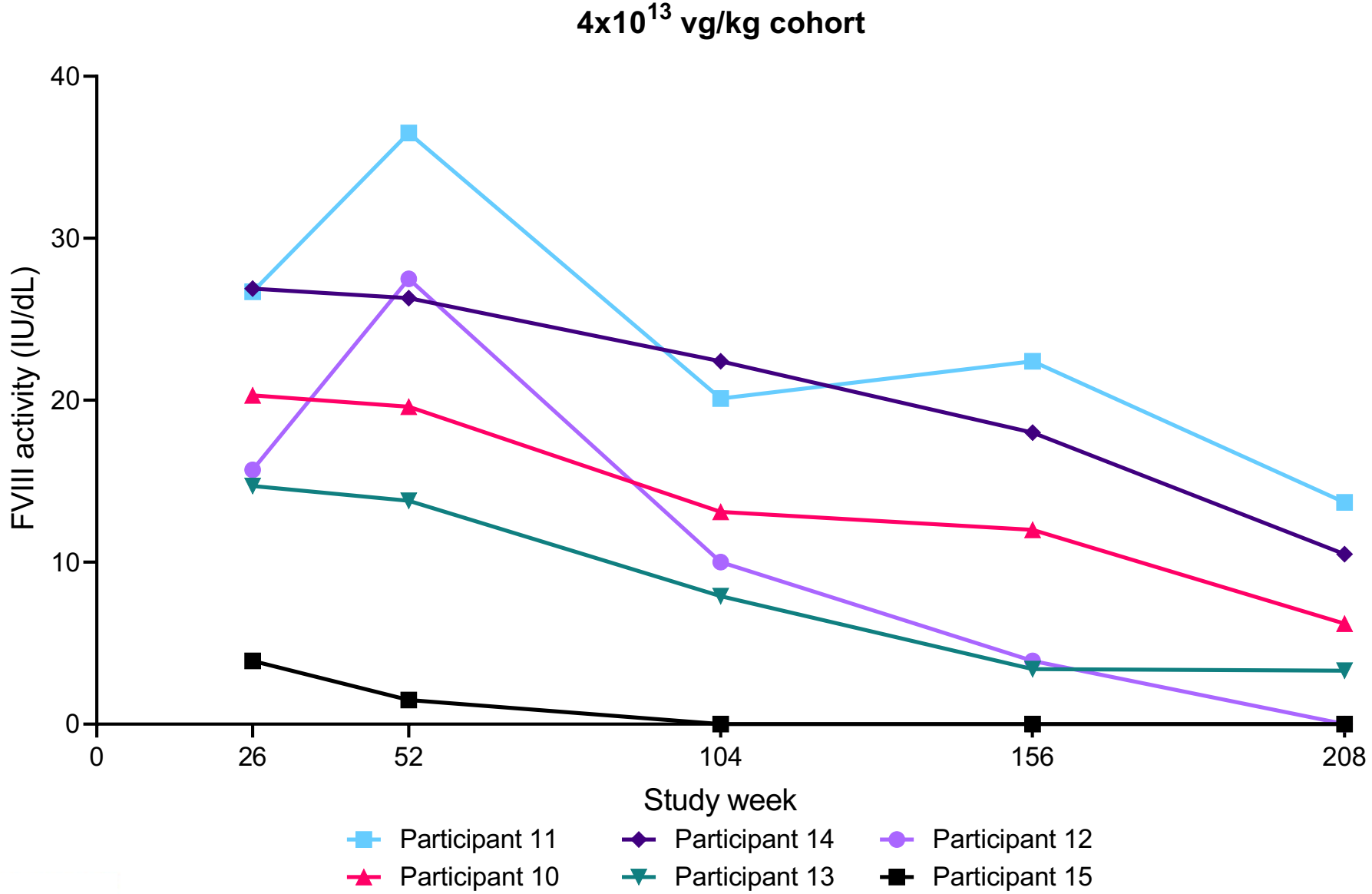
CI, confidence interval; FVIII, factor VIII.

Individual participant FVIII activity per chromogenic assay



FVIII, factor VIII.

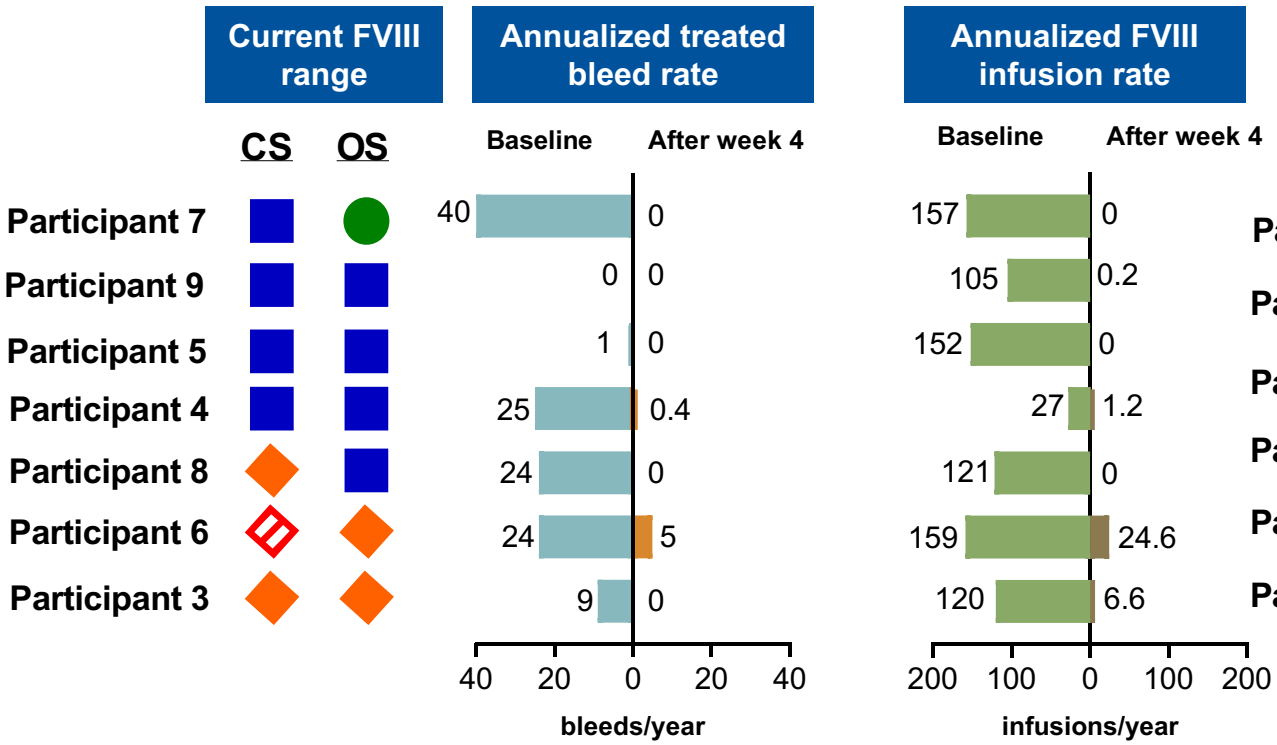
Individual participant FVIII activity per chromogenic assay



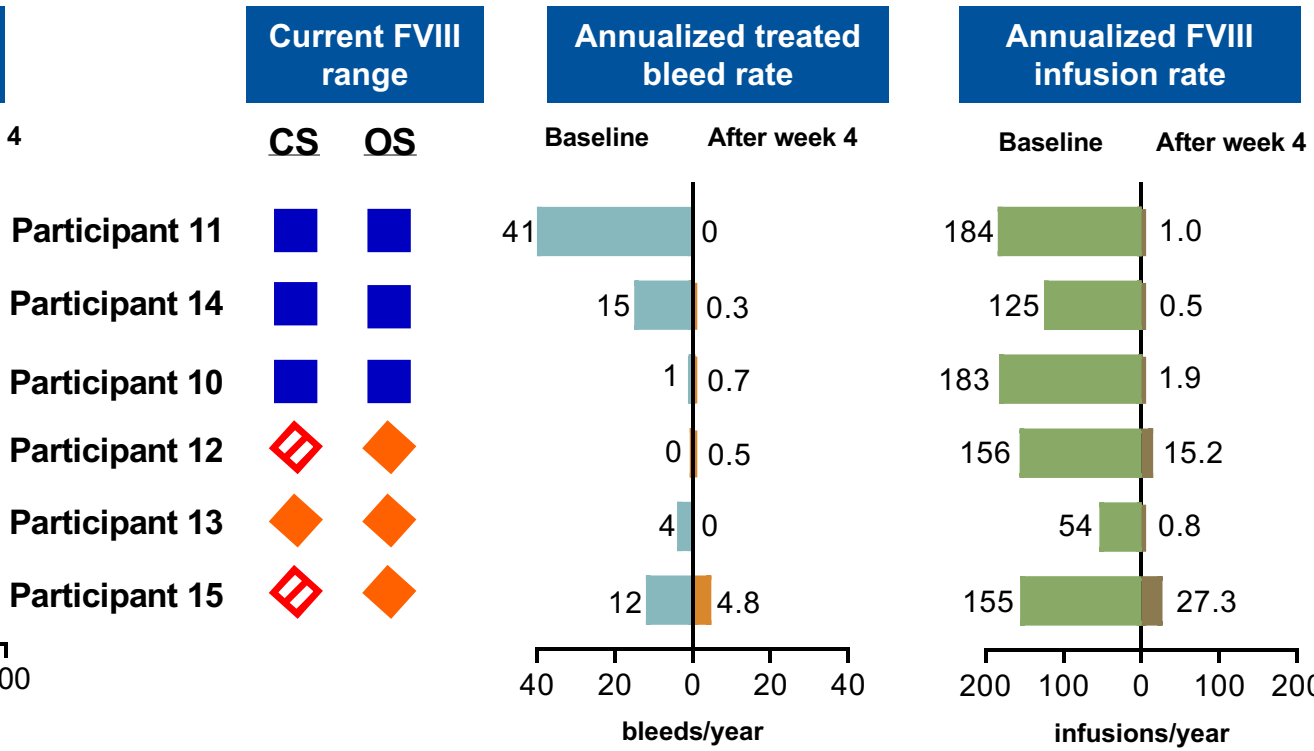
FVIII, factor VIII.

Individual participant FVIII infusion rate, ABR, and FVIII activity

$6x10^{13}$ vg/kg dose cohort (n = 7)



$4x10^{13}$ vg/kg dose cohort (n = 6)



Nonhemophilic (>40 IU/dL)

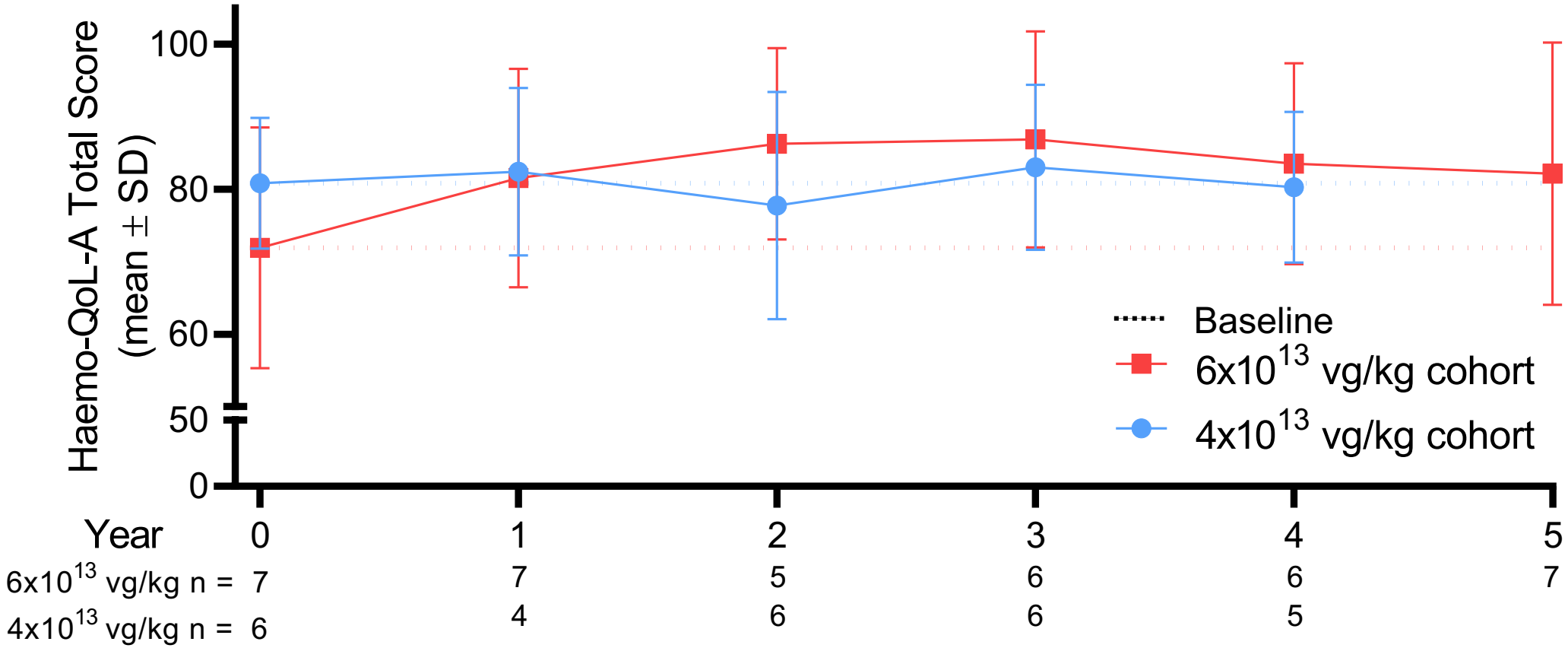
Mild (>5 to 40 IU/dL)

Moderate (3 to 5 IU/dL with CS
1 to 5 IU/dL with OS)

Below LLOQ (<3 IU/dL with CS)

FVIII activity are for week 260 for the $6x10^{13}$ vg/kg cohort and week 208 for the $4x10^{13}$ vg/kg cohort. ABR, annualized bleeding rate; CS, chromogenic substrate; FVIII, factor VIII; LLOQ, lower limit of quantitation; no., number; OS, one-stage.

Haemo-QoL-A Total Score over time



Haemo-QoL-A, hemophilia-specific quality of life questionnaire for adults; SD, standard deviation.

Conclusions

- Safety profile remains unchanged from previous reports
- No systemic hypersensitivity, anaphylaxis, or thromboembolic events
- No participants developed FVIII inhibitors
- Increased clarity on the trajectory of FVIII activity levels over time
- ABR and FVIII utilization reductions from baseline maintained over 4 ($4x10^{13}$ vg/kg cohort) and 5 ($6x10^{13}$ vg/kg cohort) years
- No participants chose to resume FVIII prophylaxis
- QOL maintenance ($4x10^{13}$ vg/kg cohort) or improvement ($6x10^{13}$ vg/kg cohort) for 4 and 5 years

ABR, annualized bleeding rate, FVIII, factor VIII; QOL, quality of life.

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