Seven-year follow-up of valoctocogene roxaparvovec gene therapy for hemophilia A

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Disclosures

- I have received speaker fees from BioMarin Pharmaceutical Inc.

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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 most recent publication of the phase 1/2 trial, participants who received $6x10^{13}$ vg/kg or $4x10^{13}$ vg/kg valoctocogene roxaparvovec had improved protection from bleeds over 6 and 5 years, respectively[3]

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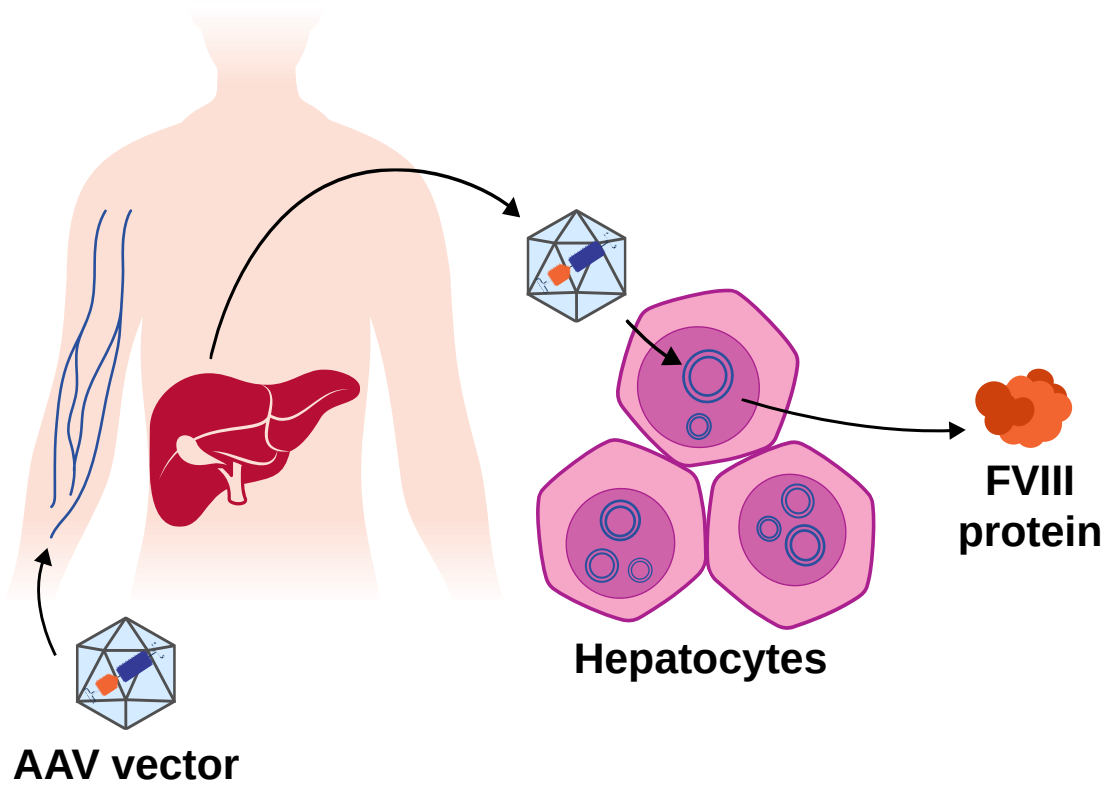
Here, we present outcomes up to 7 years after gene transfer



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. **3.** Symington E, et al. *Haemophilia.* 2024;30:320-330.

AAV, adeno-associated virus; FVIII, factor VIII; hFVIII-SQ, human FVIII, SQ variant; IU, international unit; vg, vector genomes.

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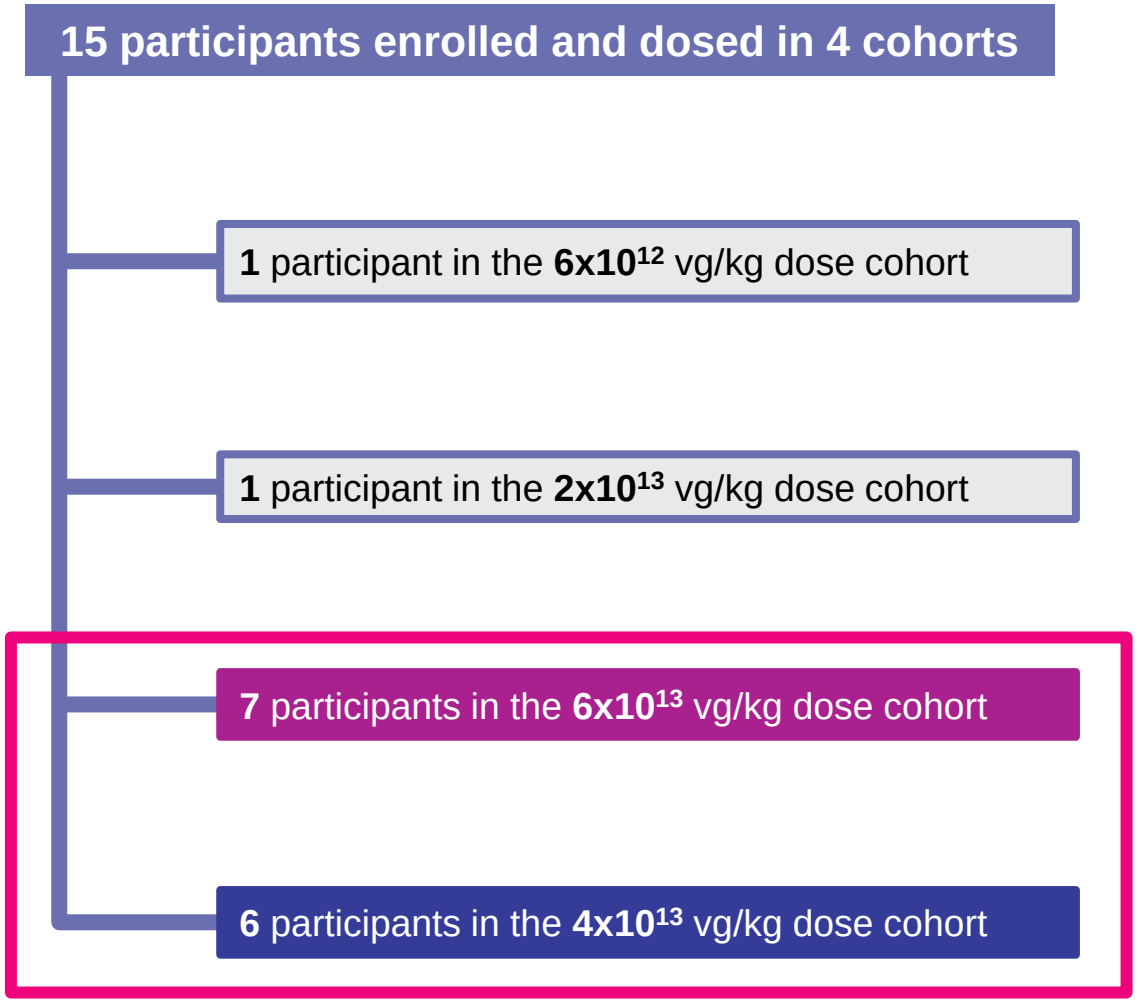
Dosing schema and baseline characteristics



Baseline characteristics	$6x10^{13}$ vg/kg cohort (n = 7)	$4x10^{13}$ 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 annualized 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

All participants were male, not Hispanic or Latino, and from the UK. Eligible participants had no history of FVIII inhibitors or anti-AAV5 antibodies, and exclusion criteria included significant liver dysfunction, significant liver fibrosis, and liver cirrhosis. Enrollment began in 2015.

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

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No new safety signals in years 6–7

In the last year:

No ALT elevations reported

One participant in each cohort reported grade 1 treatment-related AEs:

- Hepatomegaly: one 6x10^{13} cohort participant
- Splenomegaly and hepatic steatosis: one 4x10^{13} cohort participant

No treatment-related SAEs reported

One non-treatment-related SAE reported:

- Grade 4 ICA bleed: one 6x10^{13} cohort participant

n (%)	6x10^{13} vg/kg cohort (n = 7)	4x10^{13} vg/kg cohort (n = 6)
	Y7	Y6
Any AE	**5 (71.4)**	**4 (66.7)**
Any SAE	**1 (14.3)†**	**0**
Any treatment-related AE	**1 (14.3)¥**	**1 (16.7)£**
Any treatment-related SAE	**0**	**0**
AEs of special interest		
ALT elevation§	0	0
AEs of liver dysfunction#	0	0
Infusion-related reactions	0	0

†Grade 4 SAE of spontaneous ICA bleeding during Y7. ¥Grade 1 hepatomegaly during Y7. £Grade 1 splenomegaly, in addition to a worsening of hepatic steatosis during Y6.
§Defined as ALT ≥1.5x ULN or ALT ≥1.5x baseline. #Identified with a MedDRA search strategy using the high-level term "liver function analyses."

AE, adverse event; ALT, alanine aminotransferase; ICA, internal carotid artery; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious AE; ULN, upper limit of normal; vg, vector genomes; Y, year.

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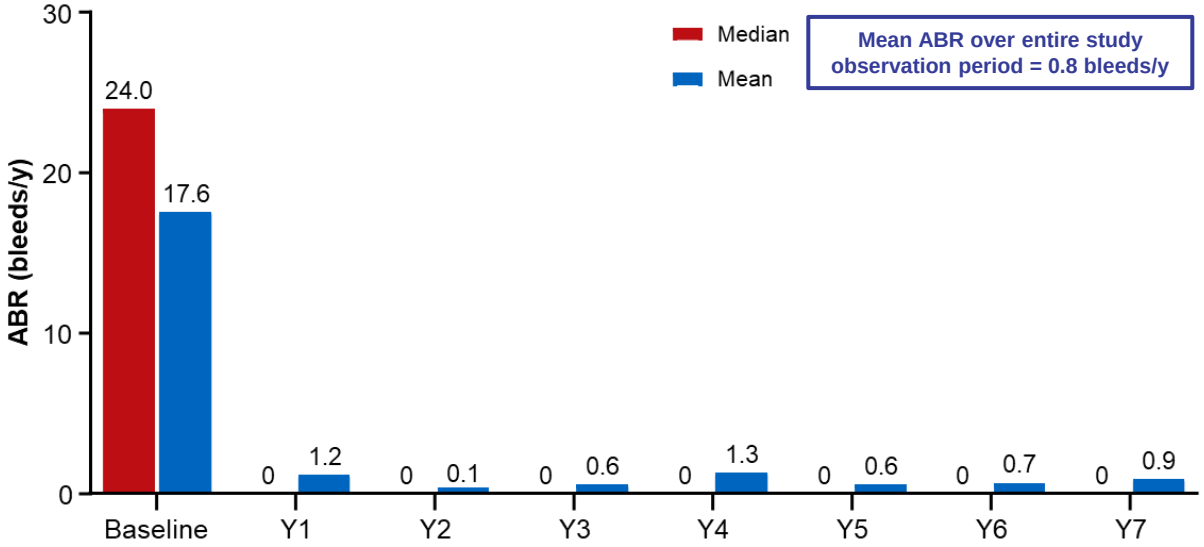
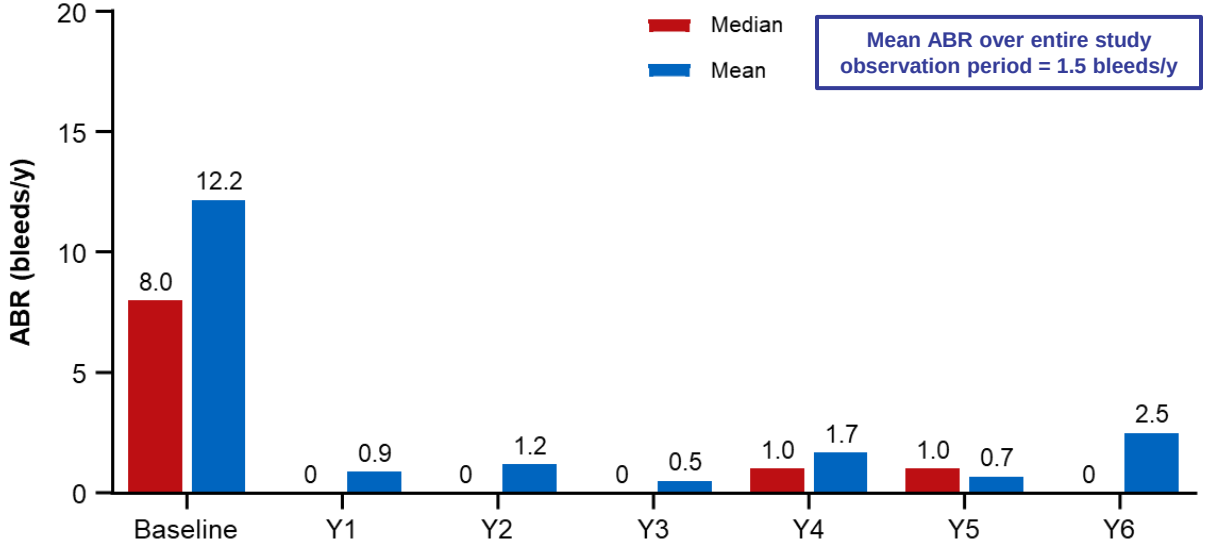
Reduction in treated bleeds maintained over 6–7 years

$6x10^{13}$ vg/kg cohort (n = 7*): ABR for treated bleeds decreased 96% from baseline to year 7



n (%) participants bleed free (n = 7)							
Baseline	Y1	Y2	Y3	Y4	Y5	Y6	Y7
1 (14)	5 (71)	6 (86)	6 (86)	5 (71)	6 (86)	4 (57)	4 (57)

$4x10^{13}$ vg/kg cohort (n = 6): ABR for treated bleeds decreased 88% from baseline to year 6



n (%) participants bleed free (n = 6)						
Baseline	Y1	Y2	Y3	Y4	Y5	Y6
1 (17)	5 (83)	4 (67)	4 (67)	3 (50)	2 (33)	5 (83)

*Six of the 7 participants in the $6x10^{13}$ vg/kg cohort were receiving regular FVIII prophylaxis at baseline (1 participant was receiving on-demand FVIII prophylaxis and was excluded). Baseline (n = 6) mean and median ABR were 16.3 bleeds/y and 16.5 bleeds/y, and the mean ABR over the entire study was 0.8 bleeds/y, representing a 95% decrease from baseline.

ABR, annualized bleeding rate; FVIII, factor VIII; vg, vector genomes; Y, year.

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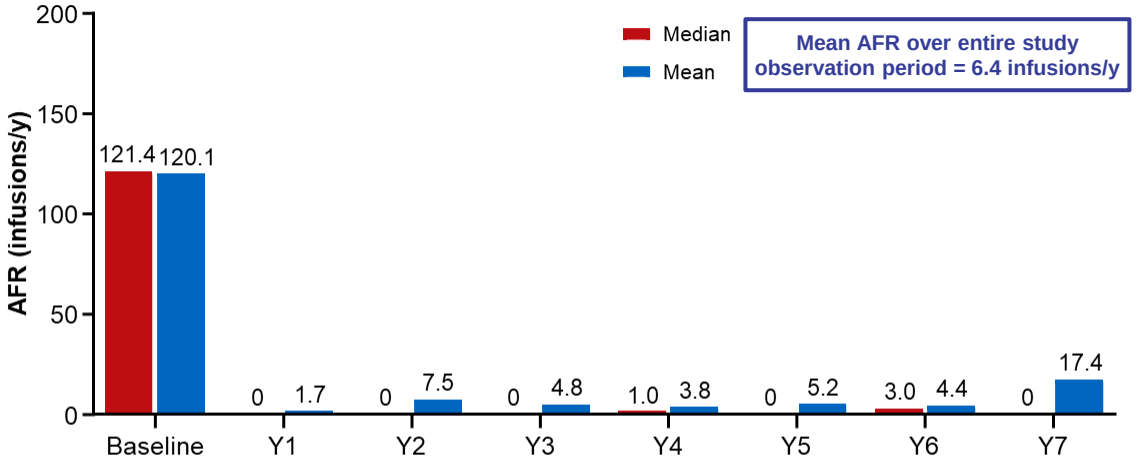
Reduction of FVIII infusion rate maintained through 6–7 years

$6x10^{13}$ vg/kg cohort (n = 7*): AFR decreased 95% from baseline to year 7

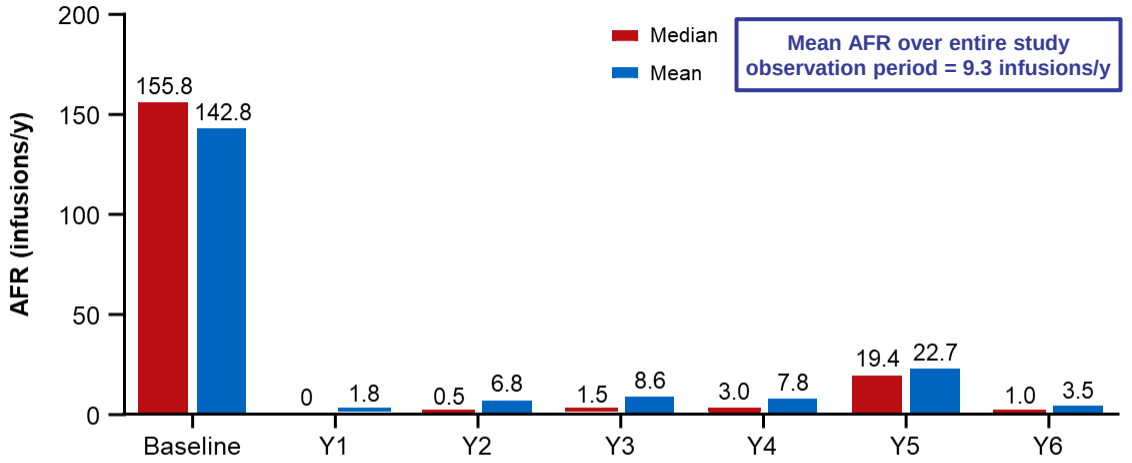


Infusion rate by reason after week 4 (n = 7)				
no./y	Treatment for bleed	Usual prophylaxis	Surgery/ procedures	One-time prophylaxis
Mean	1.5	1.8	2.1	1.0
Median	0.6	0	1.0	0

Two participants returned to prophylaxis (FVIII and emicizumab) during Year 7

Five participants chose to remain off FVIII prophylaxis

$4x10^{13}$ vg/kg cohort (n = 6): AFR decreased 93% from baseline to year 6



Infusion rate by reason after week 4 (n = 6)				
no./y	Treatment for bleed	Usual prophylaxis	Surgery/ procedures	One-time prophylaxis
Mean	3.5	0.7	2.5	2.5
Median	2.1	0	0.7	1.0

All 5 remaining participants chose to remain off prophylaxis

*Six of the 7 participants were receiving regular FVIII prophylaxis at baseline (1 participant was receiving on-demand FVIII prophylaxis and was excluded). Baseline (n = 6) mean and median AFR were 135.6 infusions/y and 136.6 infusions/y, respectively, and the mean AFR over the entire study period was 7.2 infusions/y, representing a 95% reduction from baseline.

AFR, annualized FVIII infusion rate; FVIII, factor VIII; no., number; vg, vector genomes; Y, year.

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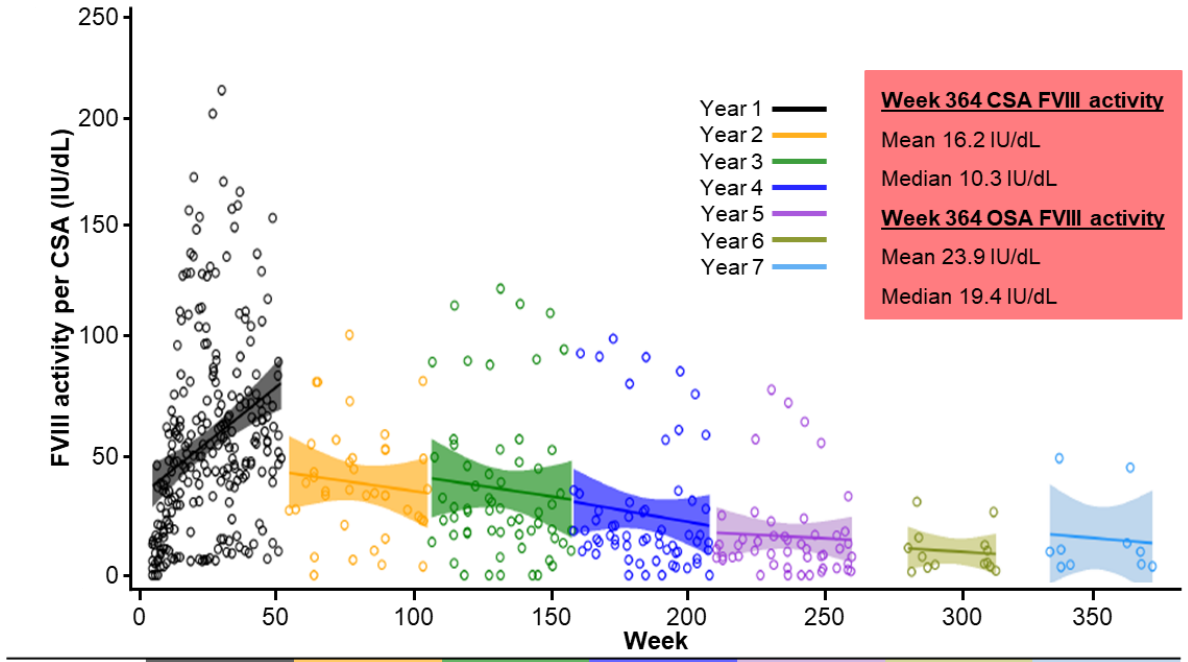
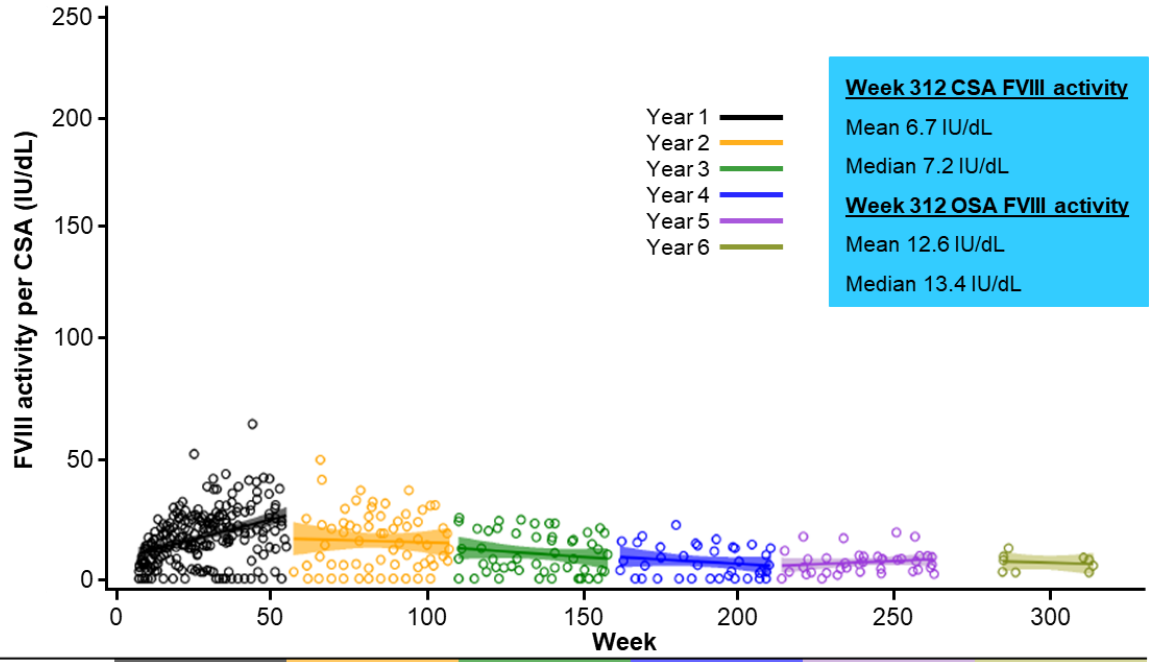
FVIII activity rate of decline slowed in the last year

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



	Y1	Y2	Y3	Y4	Y5	Y6	Y7
Slope, IU/dL/wk (95% CI)	1.01 (−0.04, 2.06)	−0.24 (−0.68, 0.21)	−0.15 (−0.47, 0.16)	−0.26 (−0.49, −0.03)	−0.13 (−0.31, 0.04)	−0.06 (−0.20, 0.08)	−0.001 (−0.18, 0.17)
Annual absolute % change (sample size)	NA	−43% (N = 7)	−10% (N = 7)	−26% (N = 6)	−50% (N = 7)	−19% (N = 7)	65% (N = 5)

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



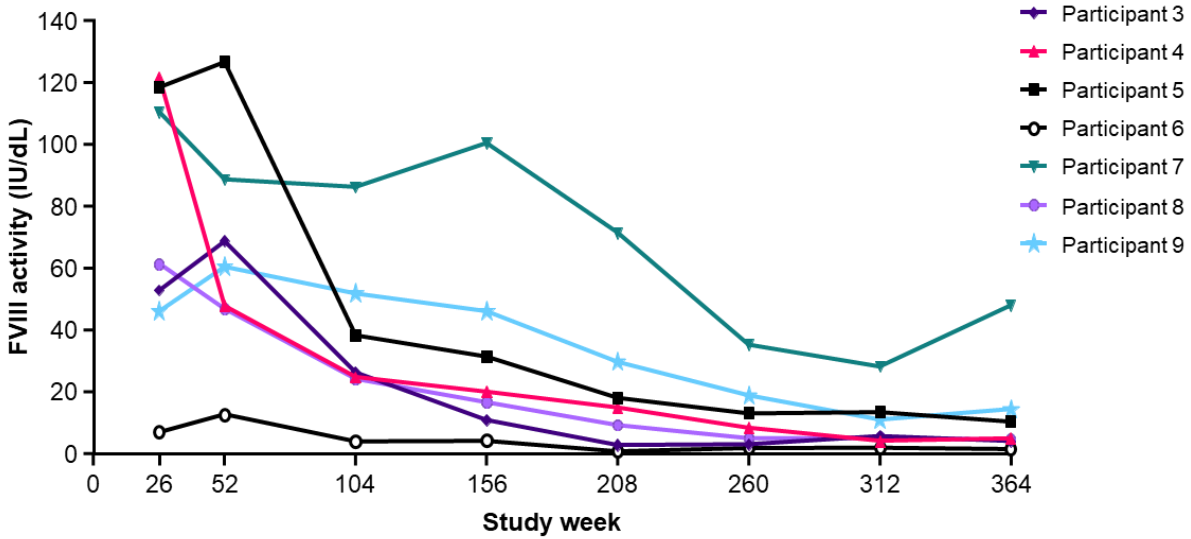
	Y1	Y2	Y3	Y4	Y5	Y6
Slope, IU/dL/wk (95% CI)	0.35 (−0.01, 0.71)	−0.15 (−0.37, 0.07)	−0.08 (−0.17, 0.02)	−0.05 (−0.13, 0.02)	−0.01 (−0.08, 0.07)	−0.07 (−0.20, 0.06)
Annual absolute % change (sample size)	NA	−30% (N = 5)	−33% (N = 6)	−39% (N = 6)	27% (N = 5)	−12% (N = 4)

Values from participants who returned to prophylaxis were excluded after they returned to prophylaxis to reflect the true treatment effect by removing the impact from resuming prophylaxis. Missing data were not imputed. Slope (95% CI) is for FVIII activity per CSA.

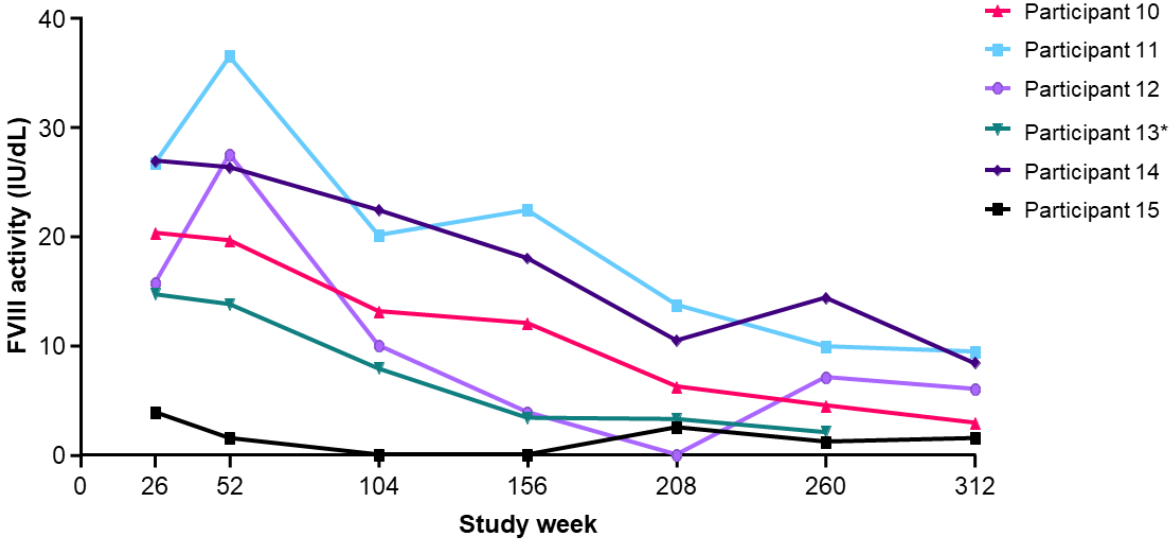
CI, confidence interval; CSA, chromogenic substrate assay; FVIII, factor VIII; IU, international unit; NA, not applicable; OSA, one-stage assay; vg, vector genomes; Y, year.

Individual participant FVIII activity over time per CSA

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



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



*Participant 13 lost to follow-up.

CSA, chromogenic substrate assay; FVIII, factor VIII; IU, international unit; vg, vector genomes.

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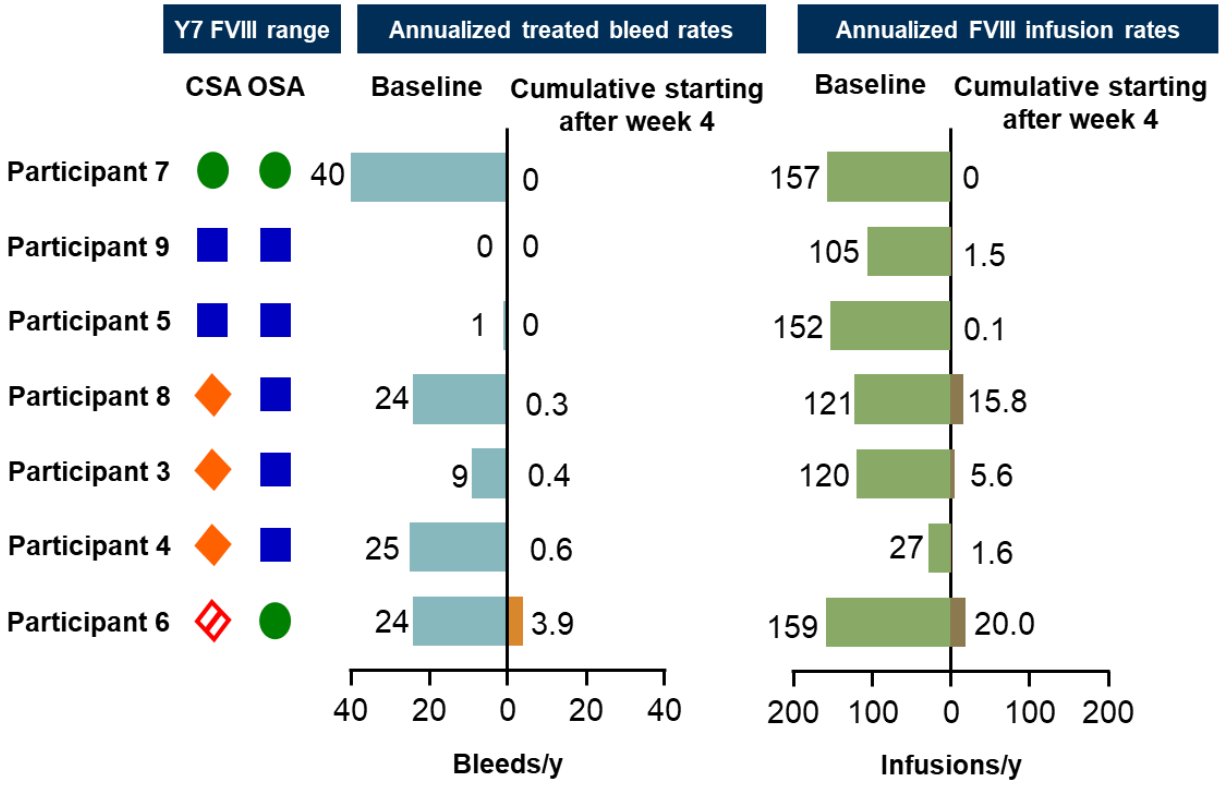
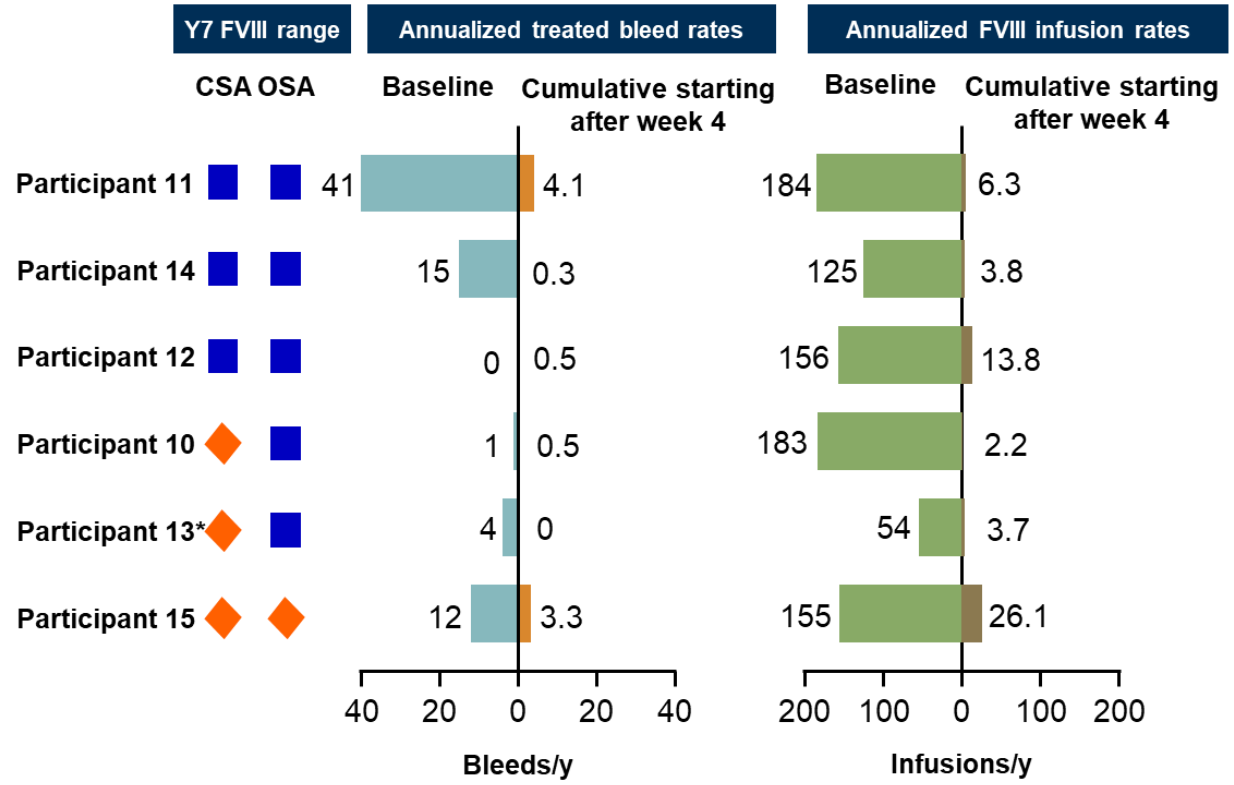
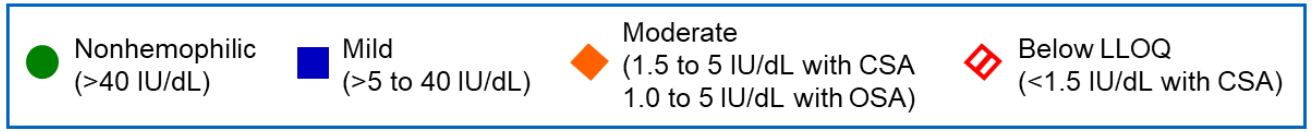
Participants had improvements in ABR and FVIII infusion rates

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



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





Participants 6 and 8 resumed FVIII prophylaxis during Y7. FVIII activity is for week 364 for the $6x10^{13}$ vg/kg cohort and week 312 for the $4x10^{13}$ vg/kg cohort (week 286 for participant 13). *Participant 13 lost to follow-up after week 286.

ABR, annualized bleeding rate; CSA, chromogenic substrate assay; FVIII, factor VIII; LLOQ, lower limit of quantitation; OSA, one-stage assay; vg, vector genomes; Y, year.

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Conclusions

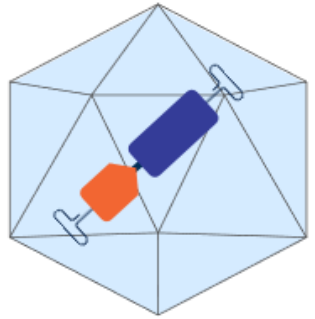
After 6−7 years, a single infusion of valoctocogene roxaparvovec provided durable bleeding protection with an acceptable safety profile

No new safety signals

- No ALT elevations in years 6−7
- No FVIII inhibitors or thromboembolic events

FVIII activity was maintained

- Mean and median FVIII activity remain in the mild hemophilia range in both dose cohorts



Durable hemostatic efficacy

- Rate of treated bleeds during years 6−7 remains decreased ≥88% from baseline

ALT, alanine aminotransferase; FVIII, factor VIII.

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Acknowledgements

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