Hemostatic results for up to 6 years following treatment with valoctocogene roxaparvovec, an AAV5-hFVIII-SQ gene therapy for severe hemophilia A

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Disclosures for MICHAEL A LAFFAN

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

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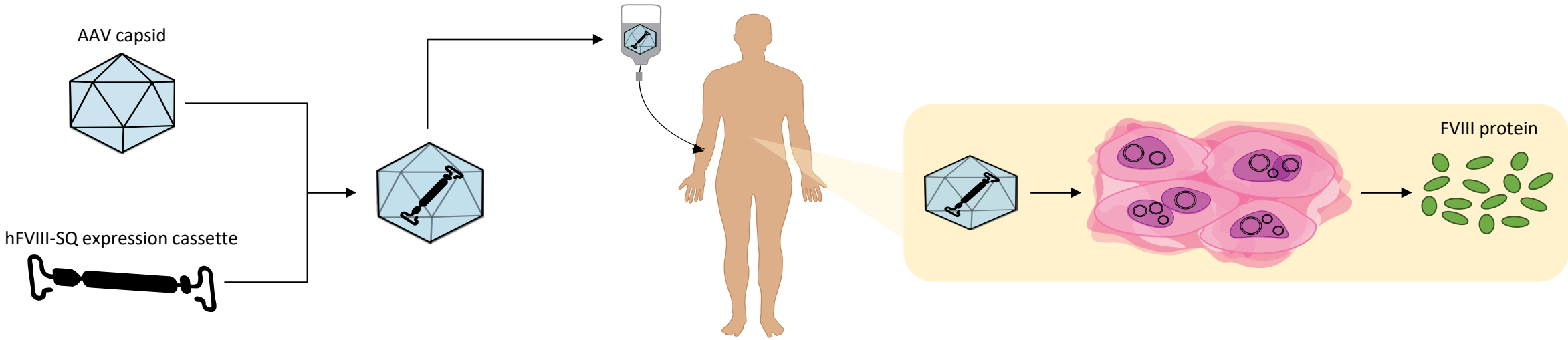
Valoctocogene roxaparvovec gene therapy for severe hemophilia A

- 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[1–3]
- Updated efficacy and safety findings are presented from an ongoing 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; 3. Pasi KJ, et al. *Haemophilia.* 2022;27(6):947–56
AAV, adeno-associated virus; hFVIII-SQ, human FVIII SQ-variant; FVIII, factor VIII

Participant disposition and baseline characteristics

15 participants enrolled and dosed in 4 cohorts

- **1** participant in the **6x10^{12}** vg/kg dose cohort
- **1** participant in the **2x10^{13}** vg/kg cohort
- **7** participants in the **6x10^{13}** vg/kg dose cohort
- **6** participants in the **4x10^{13}** vg/kg dose cohort

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 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

Safety profile of valoctocogene roxaparvovec up to 6 years remains consistent with previous reports

- No new treatment-related safety signals in year 5 ($4x10^{13}$ vg/kg cohort) or year 6 ($6x10^{13}$ vg/kg cohort)
  - Throughout the study, all treatment-related AEs were Grade 1 or 2
  - No treatment-related SAEs occurred after year 1

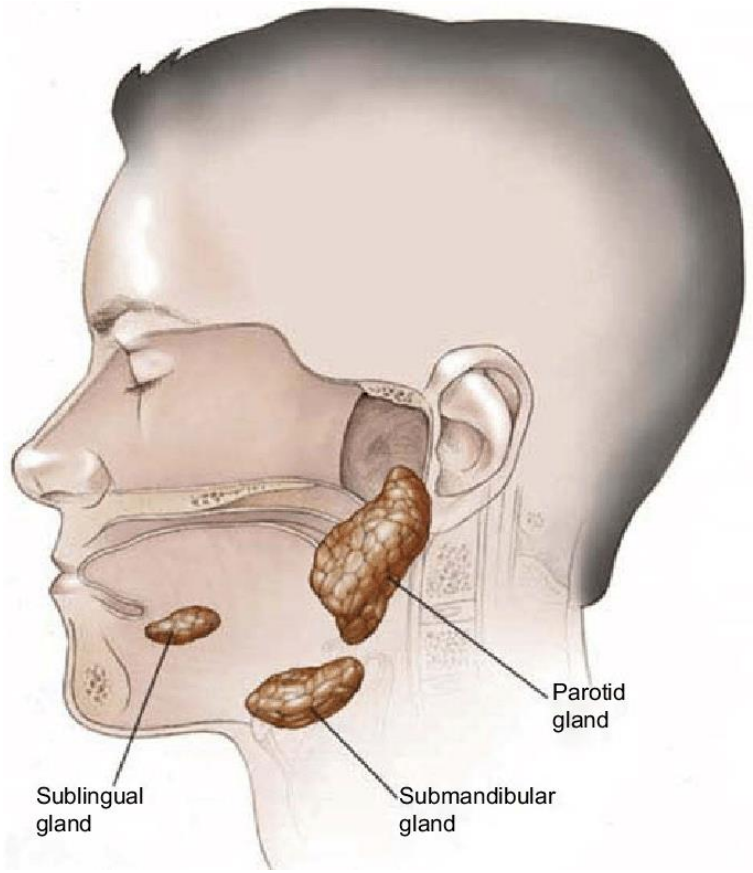
	$6x10^{13}$ vg/kg cohort (n = 7)						$4x10^{13}$ vg/kg cohort (n = 6)				
n	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**	**Y6**	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
Any AE	7	6	7	7	7	**4**	6	5	5	4	**6**
Any SAE	0	1	1	1	0	**1**	1	0	1	1	**1**
Any treatment-related AE	6	1	1	2	0	**0**	6	0	0	0	**0**
Any treatment-related SAE	0	0	0	0	0	**0**	1[a]	0	0	0	**0**
AEs of special interest											
ALT elevation[b]	6	0	0	1	1	**0**	4	0	1	0	**0**
AEs of liver dysfunction[c]	6	1	0	1	1	**0**	5	0	1	0	**0**
Infusion-related reactions	3	0	0	0	0	**0**	4	0	0	0	**0**

[a]Pyrexia on study day 2. [b]Defined as ALT ≥1.5x ULN or ALT ≥1.5x baseline. [c]Identified with a MedDRA search strategy using the high-level term "liver function analyses"
AE, adverse event; ALT, alanine aminotransferase; MedDRA, Medical Dictionary of Regulatory Affairs; SAE, serious adverse event; ULN, upper limit of normal; Y, year

One SAE in the past year: acinar cell carcinoma not linked to valoctocogene roxaparvovec

$6x10^{13}$ vg/kg cohort: Grade 2 acinar cell carcinoma of parotid gland

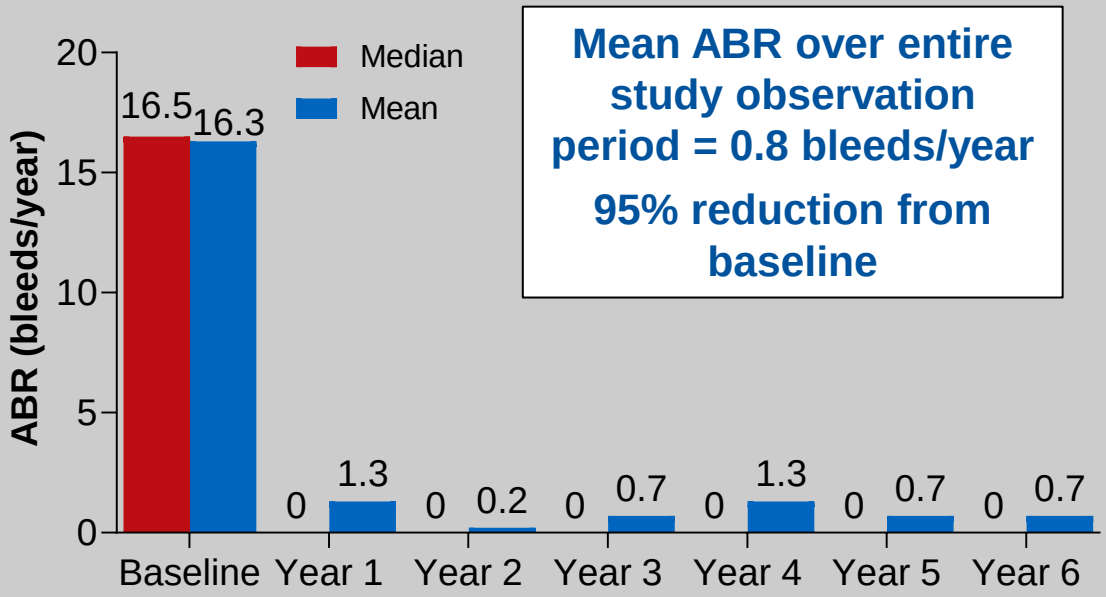
- Vector integration site analyses were performed on tumor-containing and adjacent healthy tissue[a]
  - Integration frequency was low in parotid gland and comparable between healthy and tumor-containing tissue
  - Integration frequency in parotid gland was lower than in liver, which was consistent with decreased vector exposure in non-clinical studies
  - No clonal enrichment of integration sites
  - No shared sites identified across biological replicates of tumor-containing tissue
  - Not linked to valoctocogene roxaparvovec



[a]Analyses were performed by an external laboratory (Protagene)
SAE, serious adverse event

Sustained reduction in treated bleeds at 5 and 6 years of follow-up

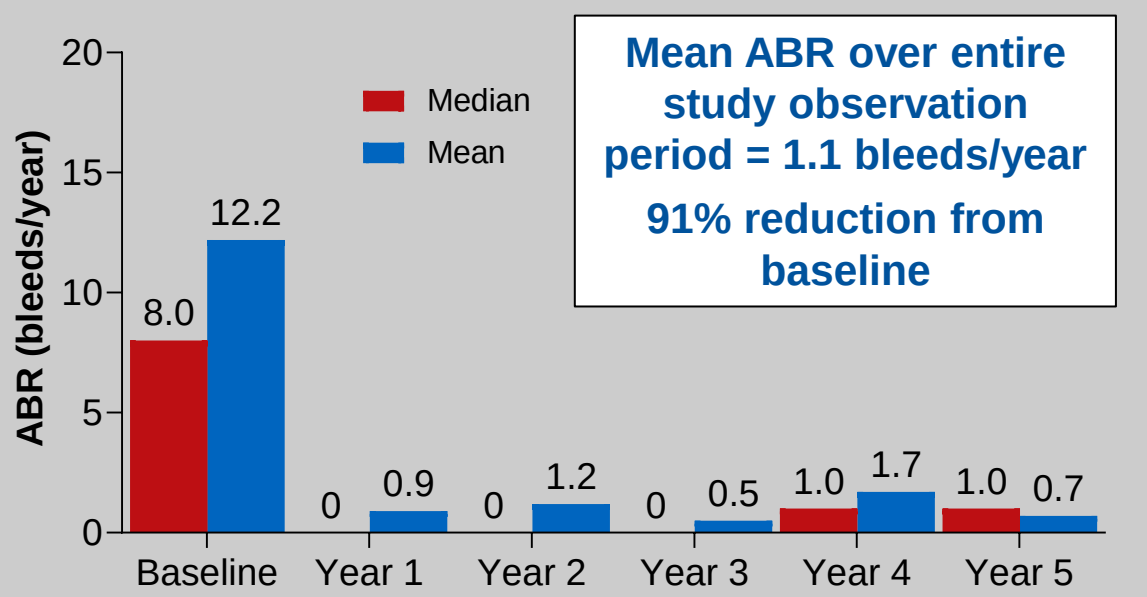
$6x10^{13}$ vg/kg dose cohort (n = 6[a])



n (%) participants bleed-free (n = 7)						
Basline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
1 (14%)	5 (71%)	6 (86%)	6 (86%)	5 (71%)	6 (86%)	4 (57%)

All participants in the $6x10^{13}$ vg/kg cohort remain off FVIII prophylaxis

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



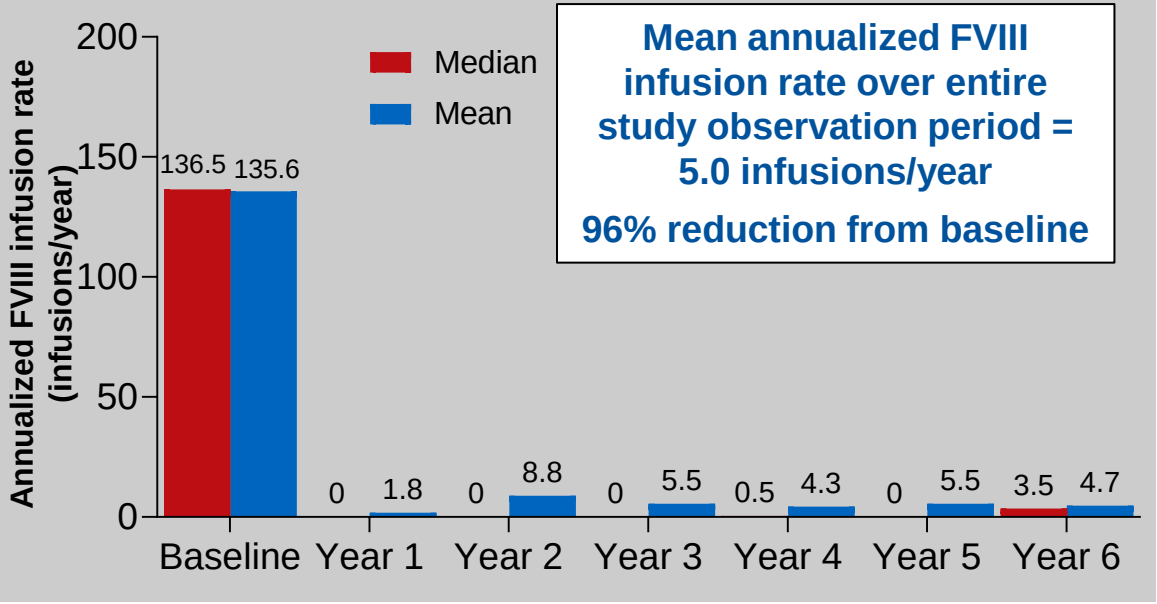
n (%) participants bleed-free (n = 6)					
Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
1 (17%)	5 (83%)	4 (67%)	4 (67%)	3 (50%)	2 (33%)

One participant in the $4x10^{13}$ vg/kg cohort resumed FVIII prophylaxis for 1 month during year 5 and is currently using on-demand FVIII treatment, with no need for FVIII infusions over the past 20 weeks

[a]Excluding the participant receiving on-demand FVIII treatment at baseline
ABR, annualized bleeding rate; FVIII, factor VIII

Sustained reduction in FVIII infusions at 5 and 6 years of follow-up

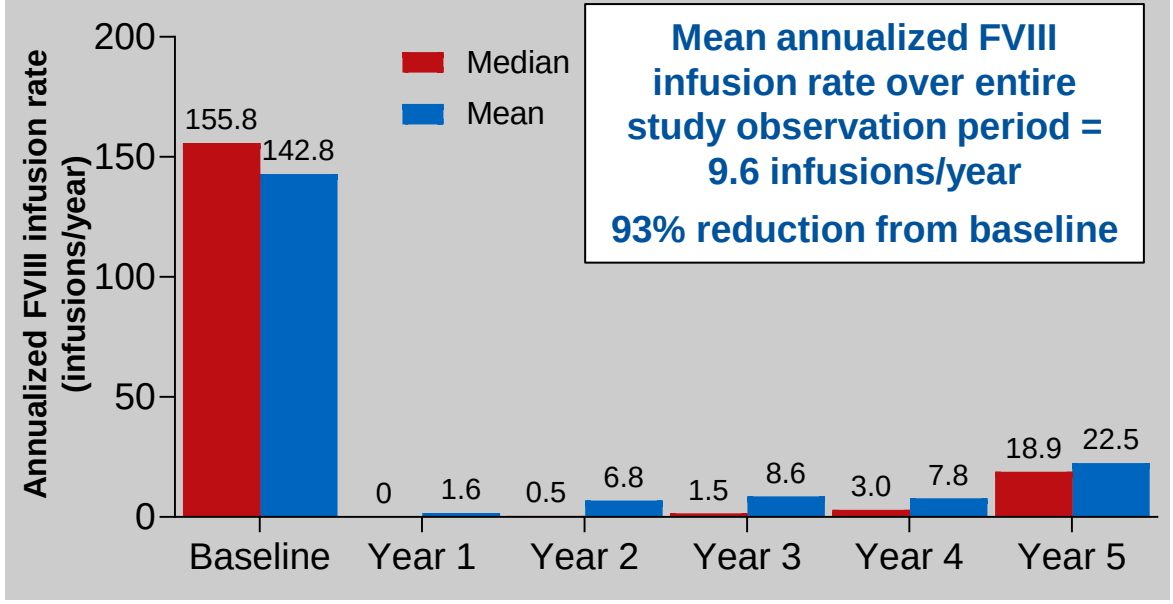
$6x10^{13}$ vg/kg dose cohort (n = 6[a])



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

no./year	Treatment for bleed	Usual prophylaxis	Surgery/ procedures	One-time prophylaxis
Mean	1.5	0	2.6	0.9
Median	0	0	0.9	0

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

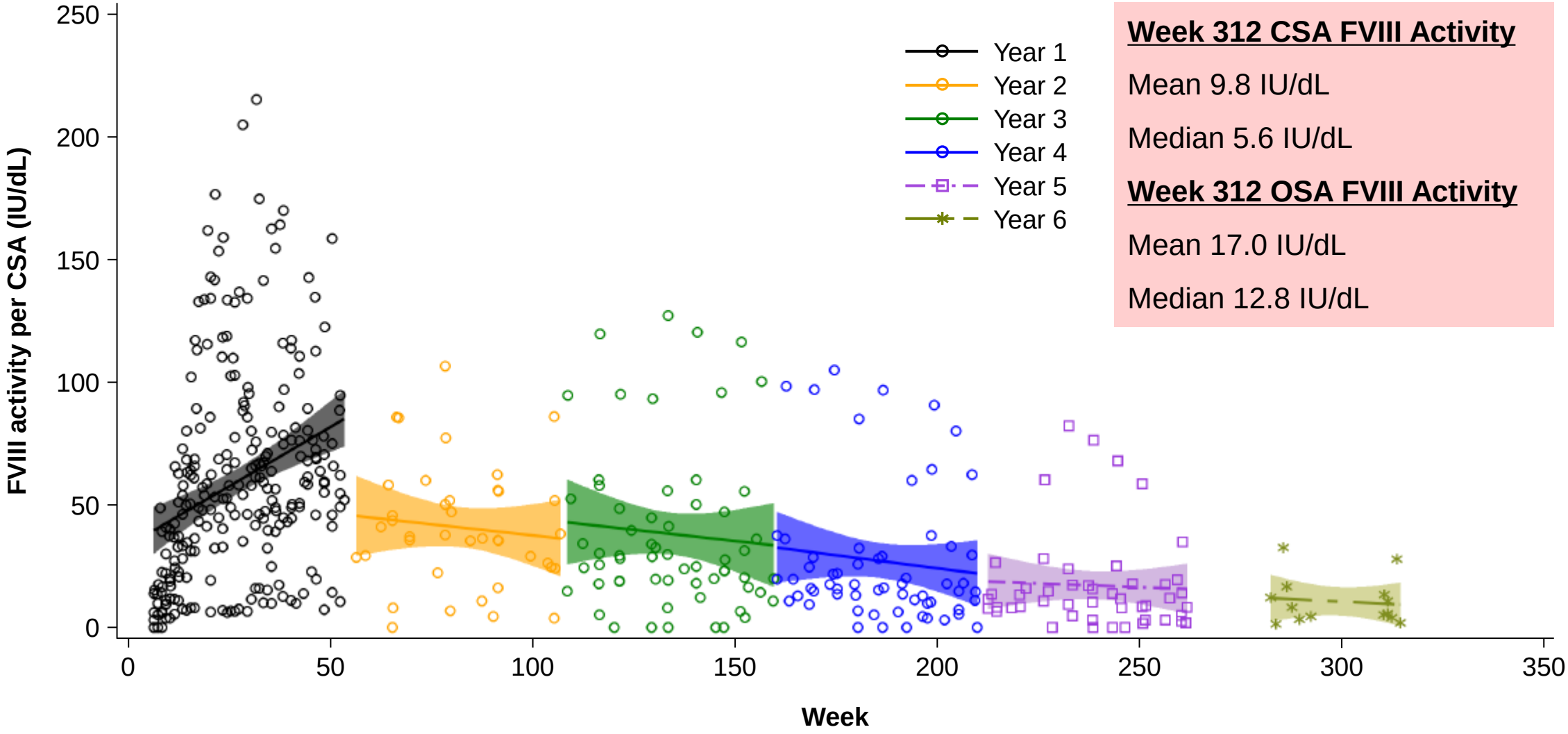


Infusion rate by reason after week 4 (n = 6)

no./year	Treatment for bleed	Usual prophylaxis	Surgery/ procedures	One-time prophylaxis
Mean	3.3	0.7	2.4	3.1
Median	1.3	0	0.8	1.2

[a]Excluding the participant receiving on-demand FVIII treatment at baseline.
FVIII, factor VIII; no., number

FVIII activity sustained over 6 years for participants in $6x10^{13}$ vg/kg cohort



Week 312 CSA FVIII Activity

Mean 9.8 IU/dL

Median 5.6 IU/dL

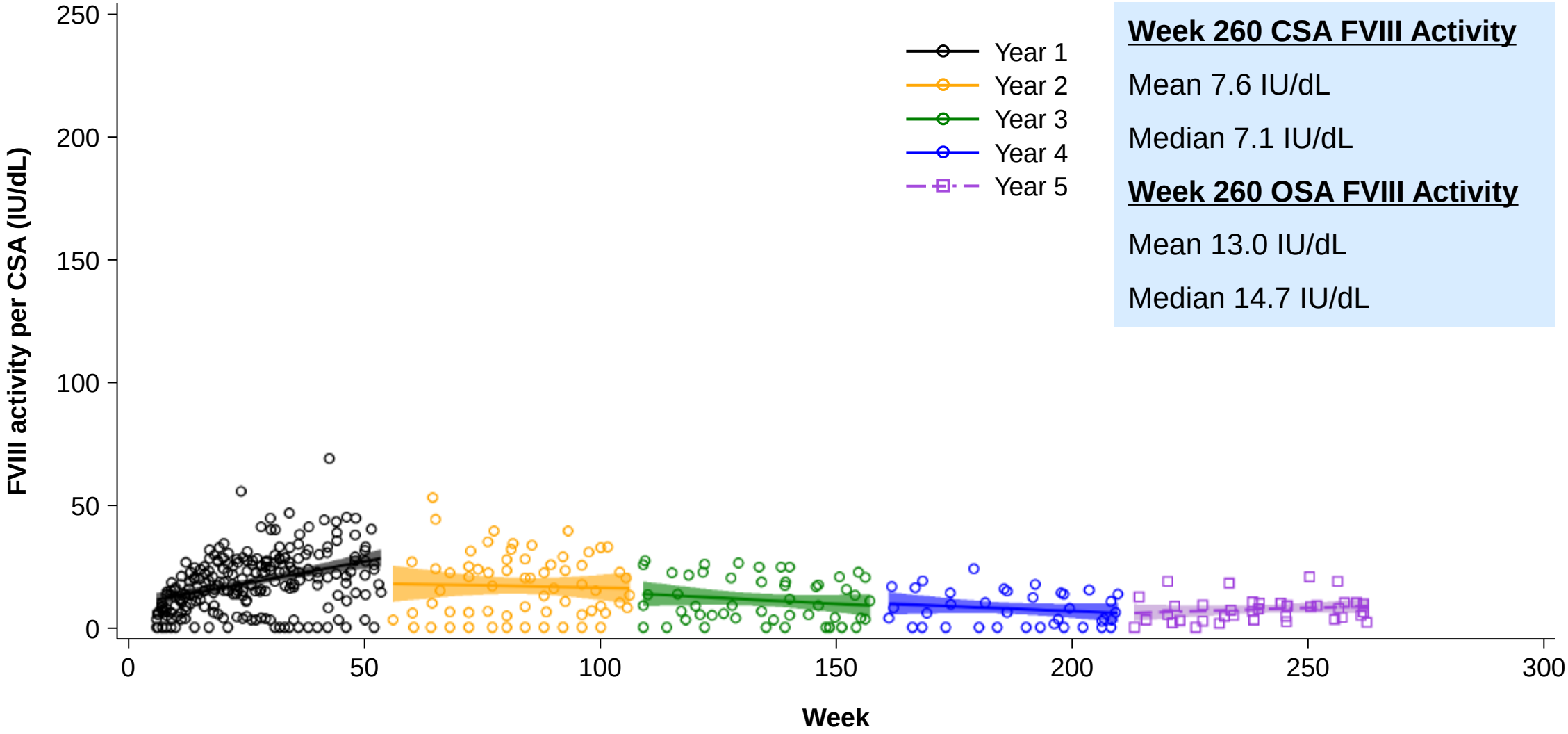
Week 312 OSA FVIII Activity

Mean 17.0 IU/dL

Median 12.8 IU/dL

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

FVIII activity sustained over 5 years for participants in 4x10^{13} vg/kg cohort



Week 260 CSA FVIII Activity

Mean 7.6 IU/dL

Median 7.1 IU/dL

Week 260 OSA FVIII Activity

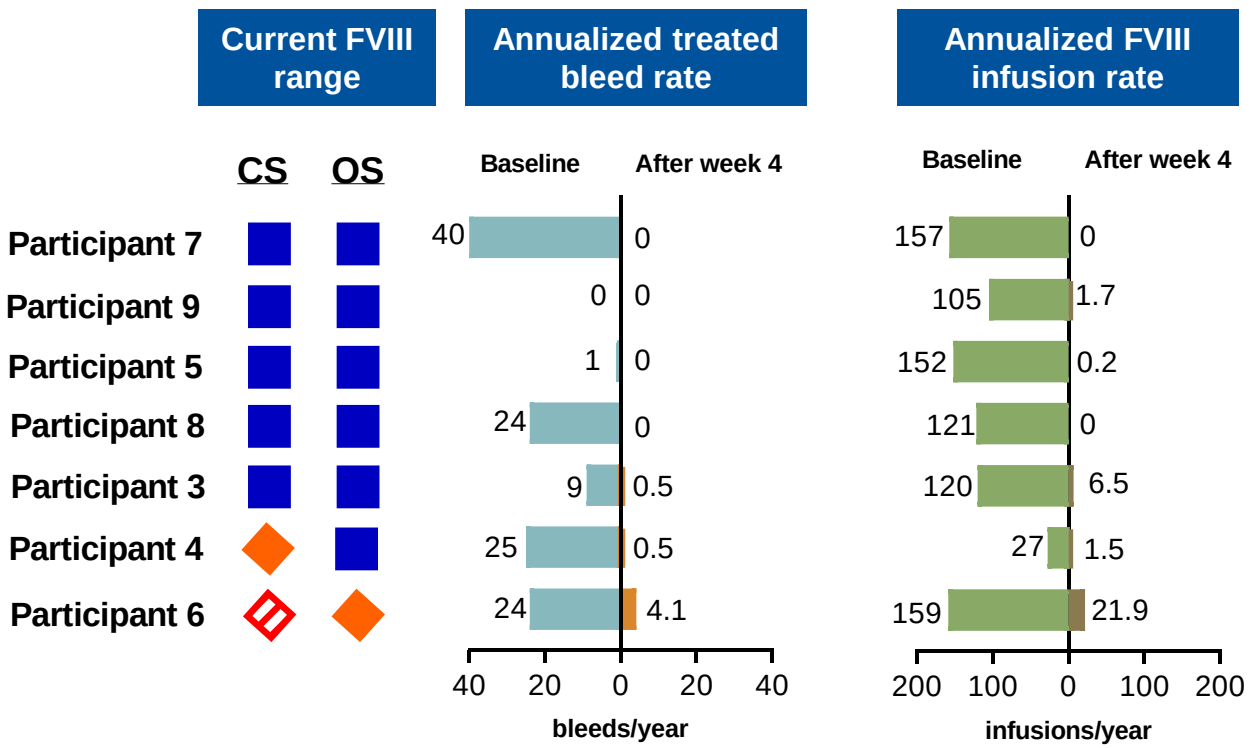
Mean 13.0 IU/dL

Median 14.7 IU/dL

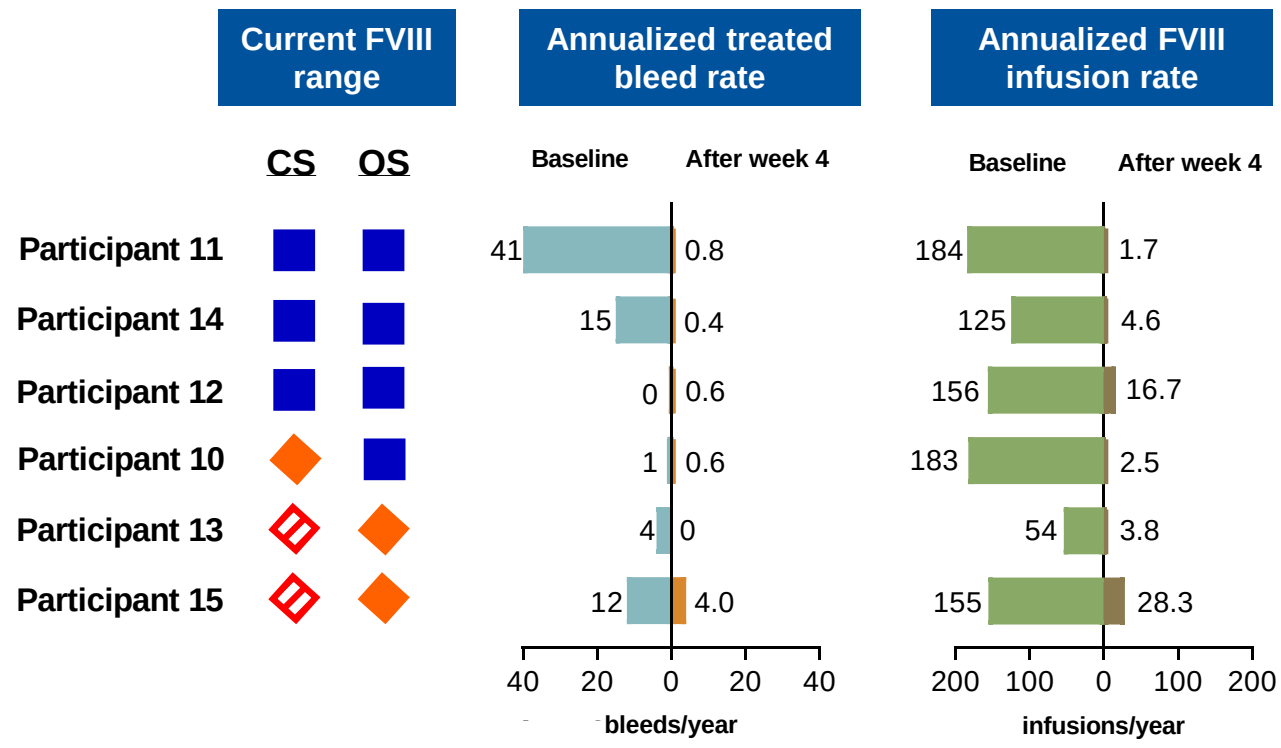
CSA, chromogenic substrate assay; FVIII, factor VIII; OSA, one-stage assay

Individual participants show improvements in ABR and exogenous FVIII infusion rate even at low endogenous FVIII levels

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



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



Mild (>5 to 40 IU/dL)

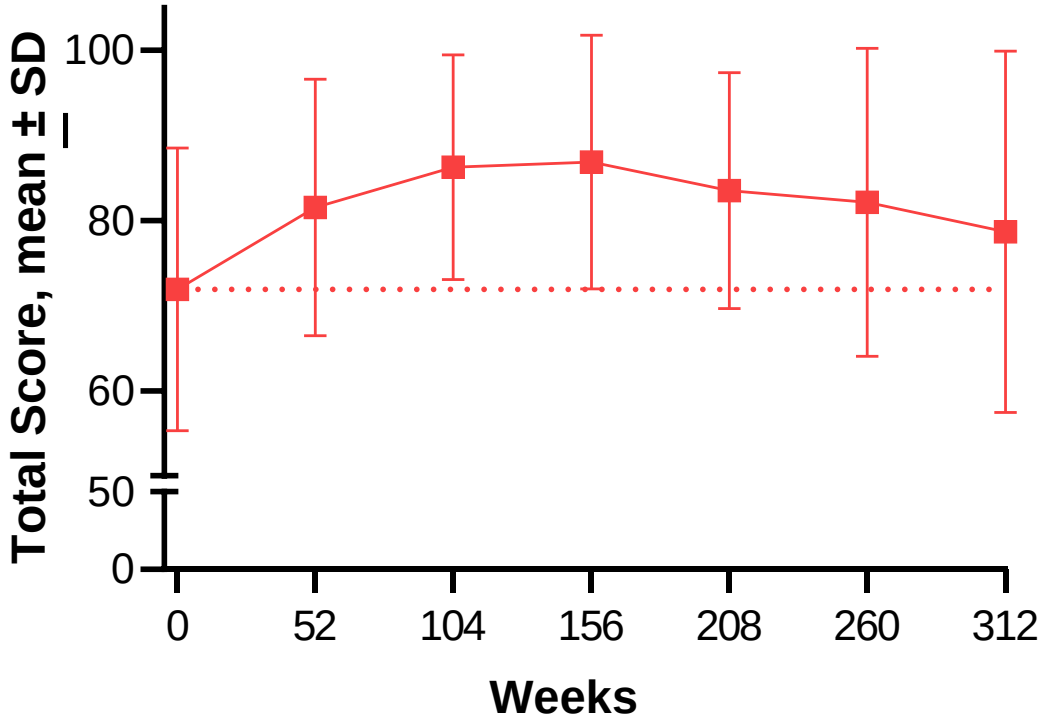
Moderate (3 to 5 IU/dL with CS
1 to 5 IU/dL with OS)

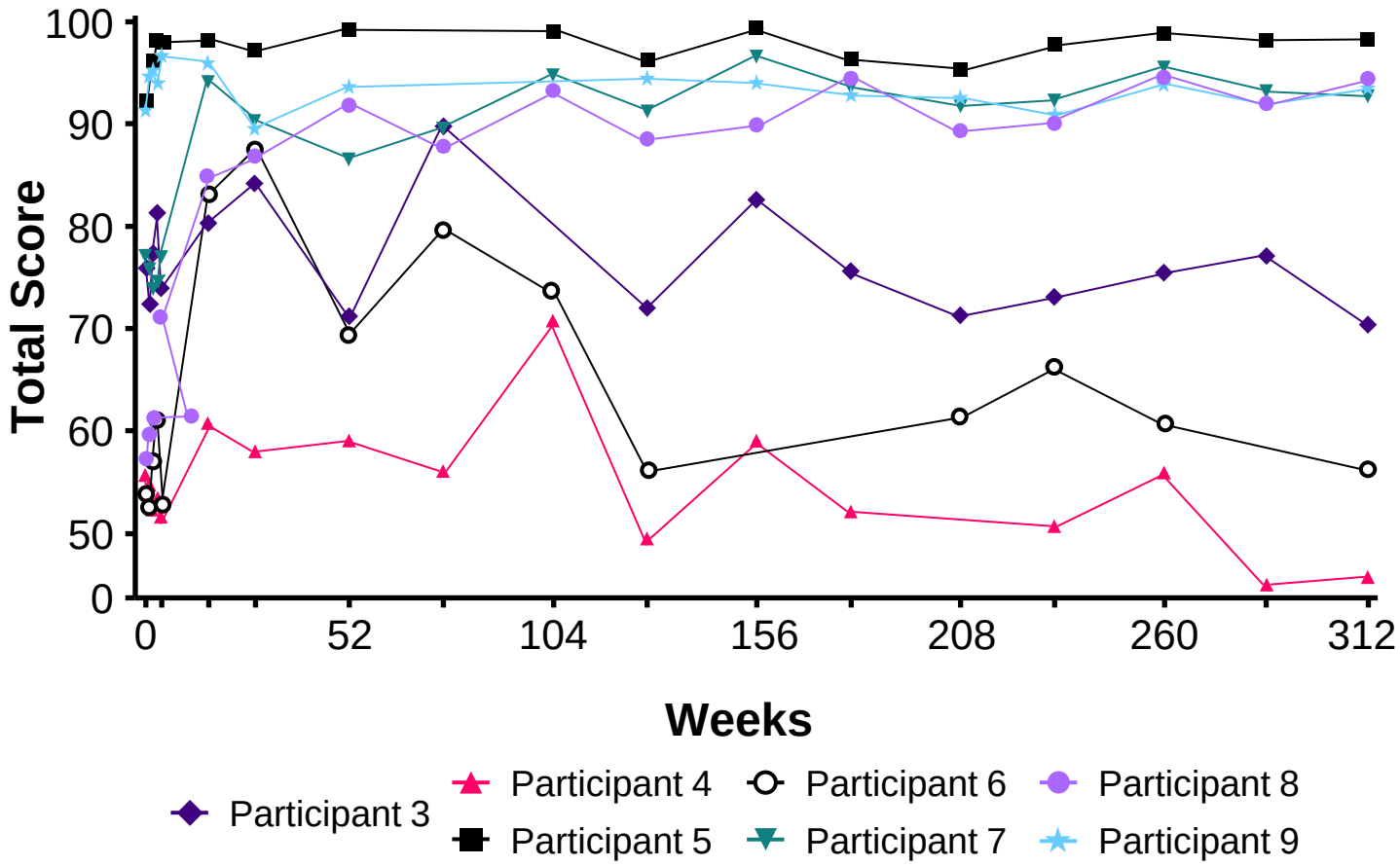
Below LLOQ (<3 IU/dL with CS)

FVIII activity are for week 312 for the 6x10^{13} vg/kg cohort (week 364 for participant 4) and week 260 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

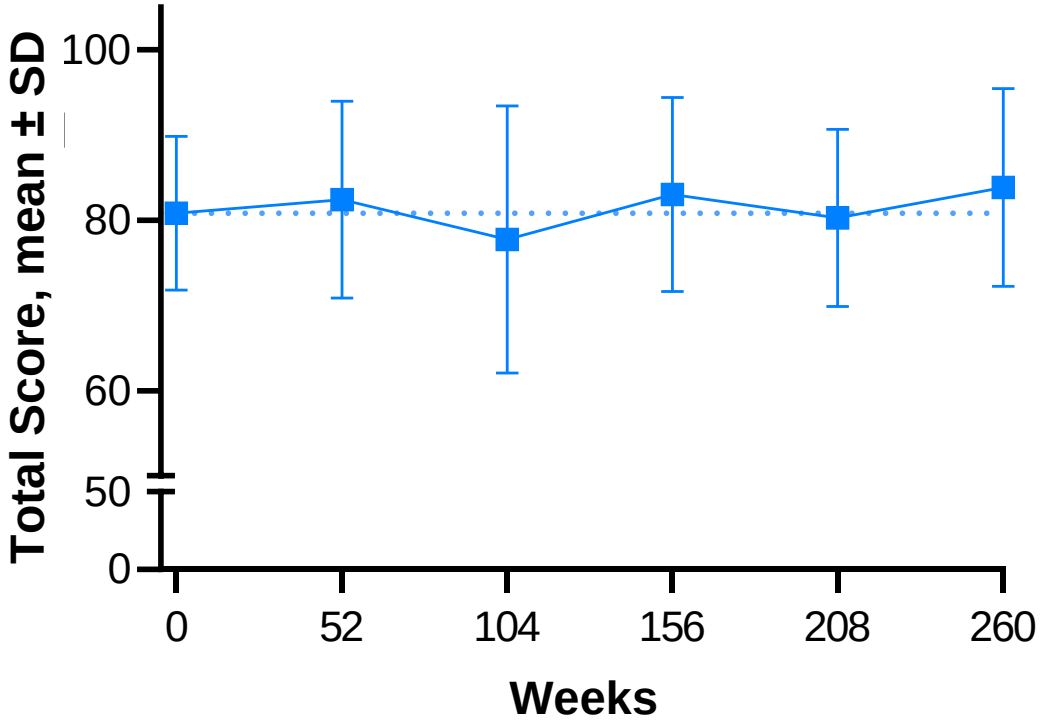
6x10^{13} vg/kg cohort demonstrated sustained improvement in QoL over 6 years, as measured by Haemo-QoL-A

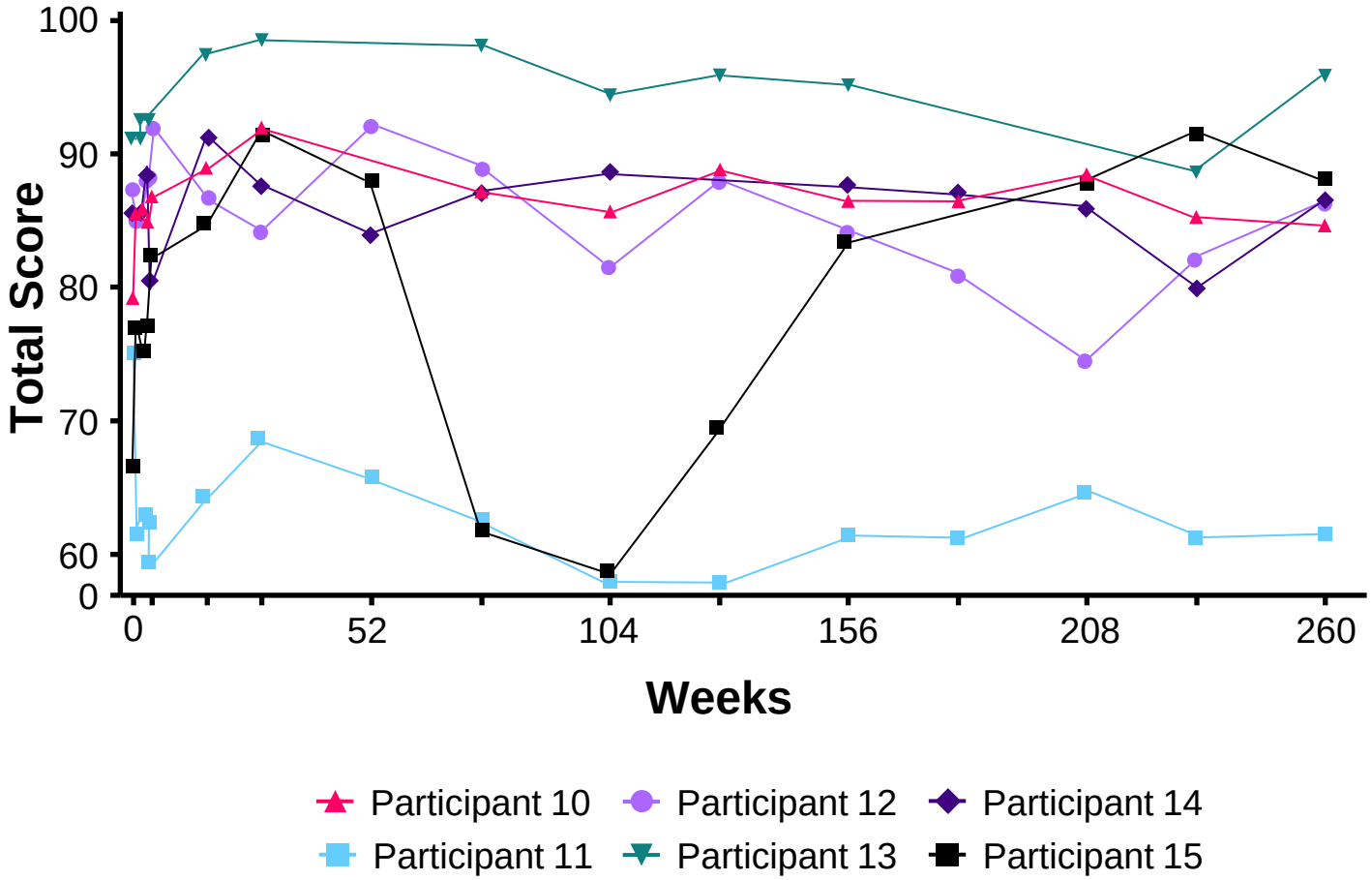




Haemo-QoL-A, hemophilia-specific quality of life questionnaire for adults; SD, standard deviation

Haemo-QoL-A scores were maintained for 4x10^{13} vg/kg cohort over 5 years of follow-up





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

Conclusions

- Safety profile of valoctocogene roxaparvovec remains unchanged from previous reports
  - One event of parotid ACC, reported as unrelated to treatment
    - Genomic analyses supported initial assessment of this event as unrelated to valoctocogene roxaparvovec
- At the time of reporting, all participants are off prophylaxis following a single infusion of valoctocogene roxaparvovec
  - All 7 participants dosed with $6x10^{3}$ vg/kg demonstrate ongoing hemostatic efficacy without routine prophylaxis 6 years post-gene transfer
  - One participant dosed with $4x10^{13}$ vg/kg briefly reinitiated prophylaxis but in now using on demand treatment, with no need for infusions over past 20 weeks
- Previously observed trends regarding change in FVIII activity were maintained
  - Mean and median FVIII activity per CSA was 7.6 and 7.1 IU/dL at year 5 for the $4x10^{13}$ vg/kg cohort and 9.8 and 5.6 IU/dL for the $6x10^{13}$ vg/kg cohort at year 6
- Mean QoL was maintained ($4x10^{13}$ vg/kg cohort) or improved ($6x10^{13}$ vg/kg cohort) over the study period, with individual variation

ACC, acinar cell carcinoma; CSA, chromogenic substrate assay; FVIII, factor VIII; QoL, quality of life

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FVIII, factor VIII; QoL, quality of life