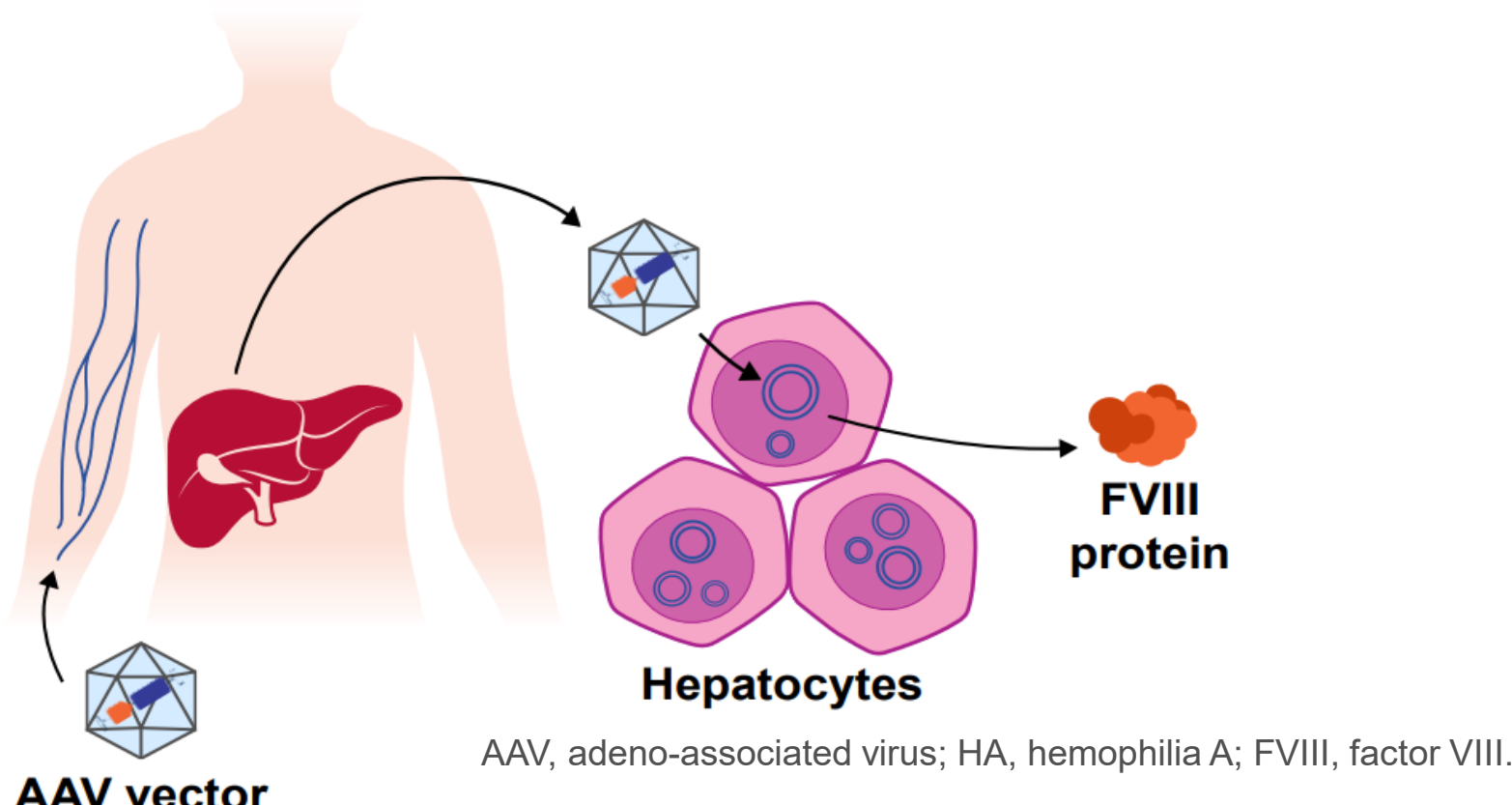


## Introduction

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a factor VIII (FVIII) coding sequence that enables endogenous FVIII production in people with severe hemophilia A (HA; FVIII activity <1 IU/dL; **Figure 1**)<sup>1,2</sup>
- In the global, open-label, phase 3 GENER8-1 trial (NCT03370913), participants who received 6x10<sup>13</sup> vg/kg valoctocogene roxaparvovec achieved FVIII activity that provided improved protection from bleeds compared with FVIII prophylaxis over 104 weeks<sup>1,2</sup>
- Here, we present outcomes after 4 years post-gene transfer in the Brazilian cohort by reporting an exploratory analysis of the bleeding rate, FVIII utilization, safety and quality of life

Figure 1. Valoctocogene roxaparvovec for severe HA



## Study design

### Eligibility

- Adult men with severe HA (FVIII activity ≤1 IU/dL)
- Receiving routine FVIII prophylaxis at the time of enrollment
- No history of FVIII inhibitors or anti-adeno-associated virus serotype 5 antibodies
- No significant liver dysfunction, significant liver fibrosis, or cirrhosis

### Study populations

- The intention-to-treat (ITT) population includes all participants who received an infusion of valoctocogene roxaparvovec
  - The ITT population included 112 participants who rolled over from a noninterventional study (270-902; rollover population) and 22 participants who enrolled directly
- The modified ITT (mITT) population excluded 2 participants who were human immunodeficiency virus-positive
  - A subset of the mITT population originally from Brazil; (n = 19); one patient left the country after receiving gene therapy and is currently followed-up in a study center in Spain. The final mITT population was funneled down to 18 participants (n = 18)

### Endpoints

- Safety was assessed through recording of any grade 3 or above adverse events (AEs)
- Change from baseline in annualized bleeding rate (ABR) for treated bleeds
- Change from baseline in annualized FVIII utilization rate
- Health-related quality of life (HRQOL):
  - Haemophilia-Specific Quality of Life Questionnaire for Adults (Haemo-QOL-A) Total Score and domain scores
  - EQ-5D-5L Utility Index Score

## Results

### Participants

- At week 156, 18 participants from Brazil who received valoctocogene roxaparvovec remained in the study (**Figure 2**, **Table 1**)

Figure 2. Participant disposition

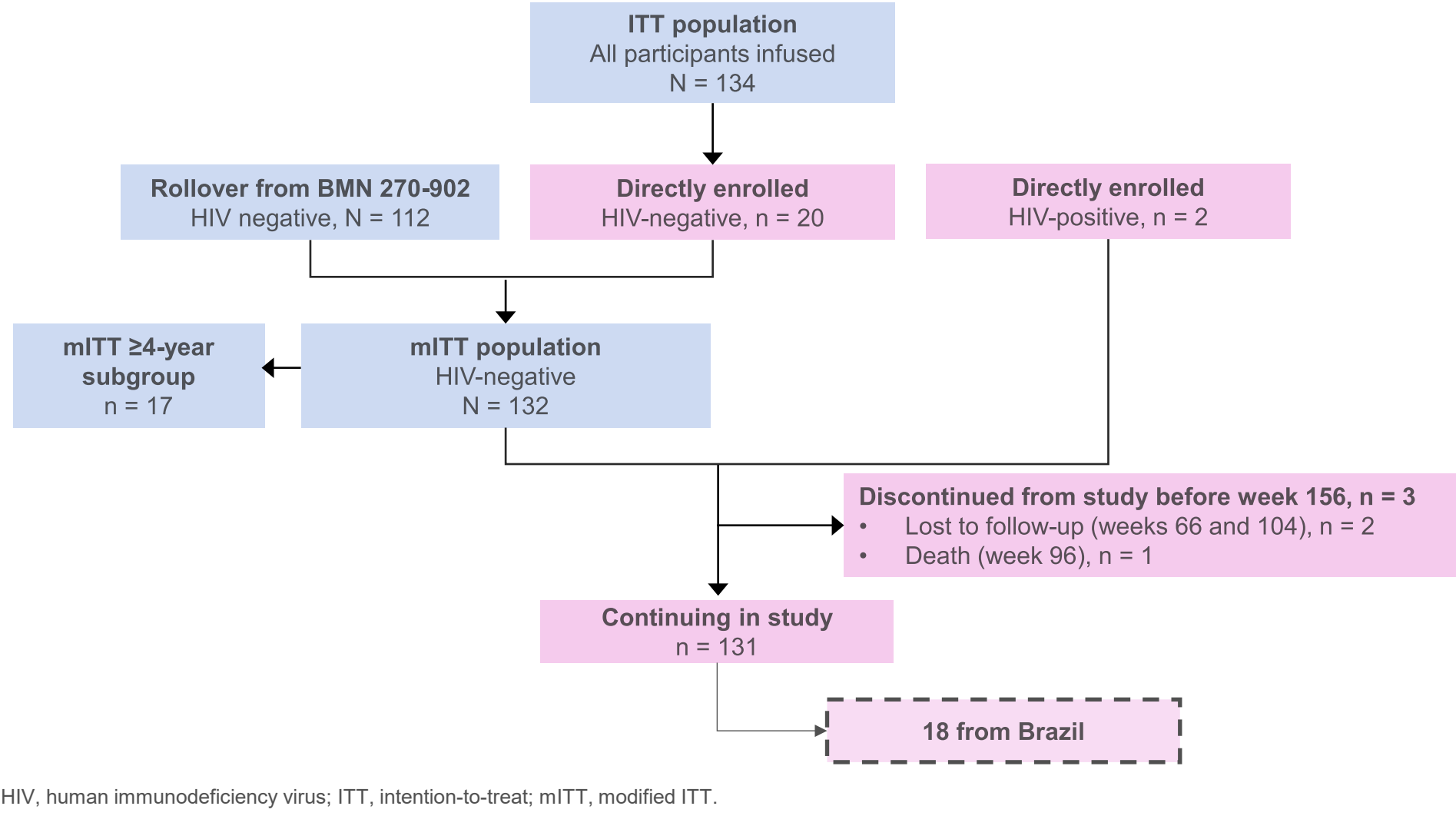


Table 1. Demographics characteristics

Participants	Overall N = 18
Age (years), mean (SD)	28.3 (6.7)
Weight (kg), mean (SD)	81.2 (19.4)
Height (cm), mean (SD)	177.1 (7.1)
Proportion of patients with zero all bleeds, n (%)	10/18 (55.6%)
Proportion of patients with zero treated bleeds, n (%)	10/18 (55.6%)
Proportion of patients with zero joint bleeds, n (%)	11/18 (61.1%)
Proportion of patients with zero spontaneous bleeds, n (%)	13/18 (72.2%)

### Safety and corticosteroid use

- In year 4, AEs grade ≥3 were reported in 6 participants (33.3%) (**Table 2**)
  - No participant initiated corticosteroids after week 13
  - The median duration of corticosteroid use was 290.2 days with a mean total dose of corticosteroid courses per subject of 13,920.6 mg (**Table 3**)
  - By the data cutoff, no participants were using corticosteroids for any indication
- No participants developed FVIII inhibitors

Table 2. AEs grade ≥3 in the Brazilian cohort in 4 years post-gene transfer

Participants, n (%)	Overall N = 18
AE grade ≥3	6 (33.3)
Events	
Alanine aminotransferase increased	3 (16.7)
Aspartate Transferase increased	1 (5.6)
Arthropathy	1 (5.6)
Blood creatine phosphokinase increased	1 (5.6)
Hemarthrosis	1 (5.6)
Hemophilic arthropathy	1 (5.6)
Infection	1 (5.6)
Joint effusion	1 (5.6)
Ligament stretch	1 (5.6)
Osteoarthritis	1 (5.6)
Postoperative Hemorrhage	1 (5.6)

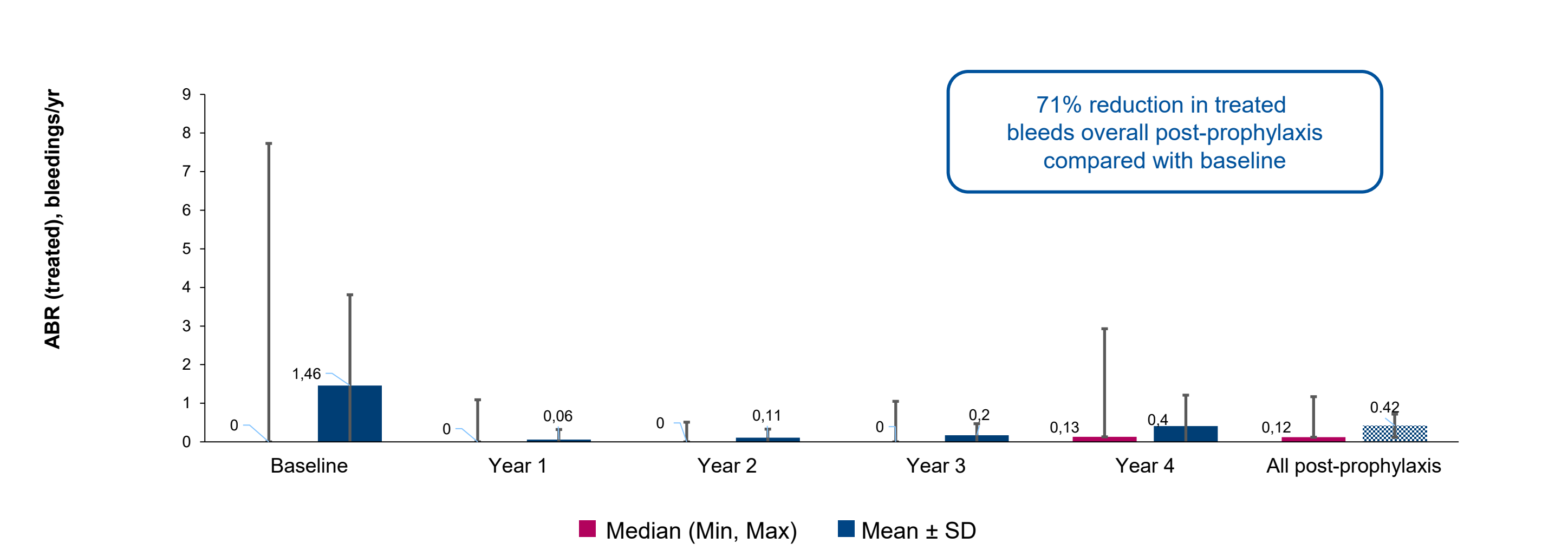
Table 3. Corticosteroid therapy for ALT elevation within 4 years of follow-up in the Brazilian cohort

Participants, n (%)	Overall N = 18
Subjects with any corticosteroid use, n (%)	17.0 (94.4)
Duration (days) of corticosteroid courses per subject, mean ± SD	290.2 ± 88.7
Total dose (mg) of corticosteroid courses per subject, mean ± SD	13,920.6 ± 6169.5

### Bleeds

- During year 4 and during the entire post-prophylaxis period, mean ABR for treated bleeds was lower and the proportion of participants with 0 treated bleeds remained higher compared with baseline (**Figure 3**)

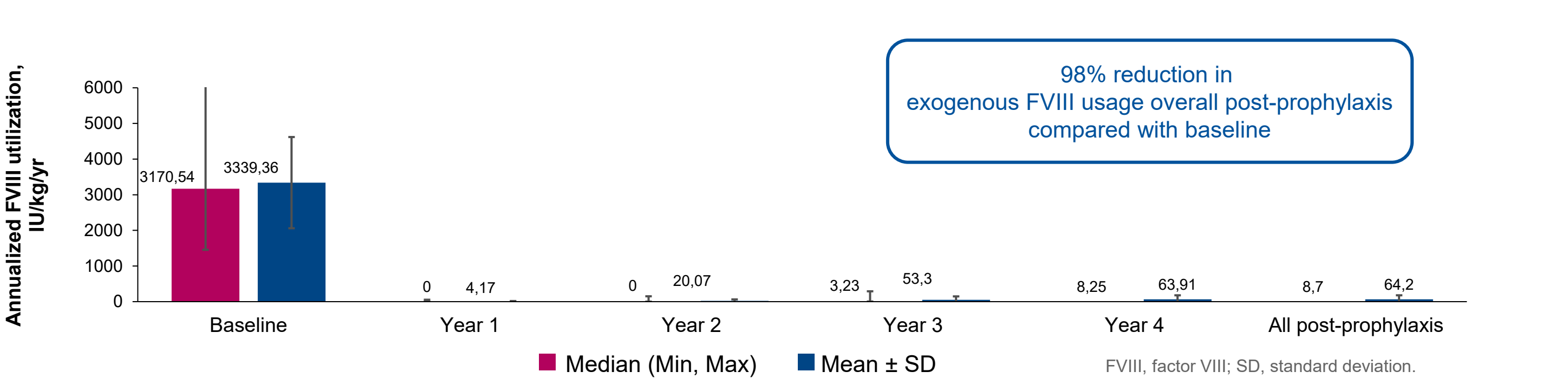
Figure 3. Mean and median ABR for treated bleeds (left) and proportion of participants with 0 treated bleeds (right)



### Exogenous FVIII use

- Annualized FVIII utilization was reduced during year 4 and during the entire post-prophylaxis period compared with week 5 (**Figure 4**)

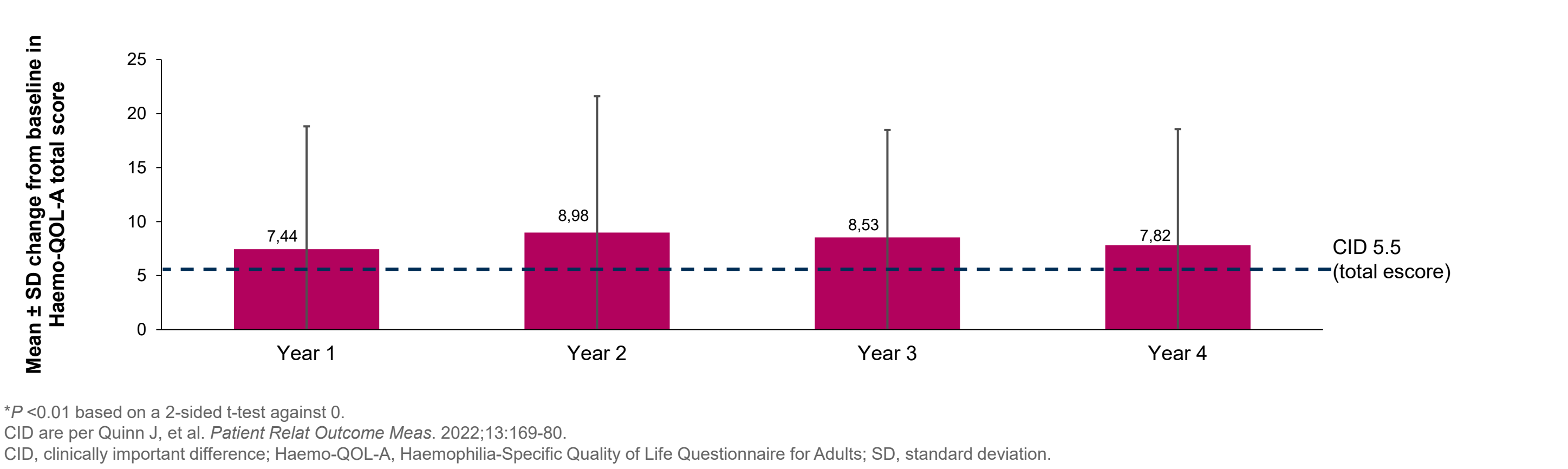
Figure 4. Annualized exogenous FVIII use in the Brazilian population after post-prophylaxis period



### HRQOL

- Change in mean Haemo-QOL-A Total Score from baseline after 4 years was 7.82, which exceeds the anchor-based clinically important difference of 5.5<sup>3</sup> (**Figure 5**)

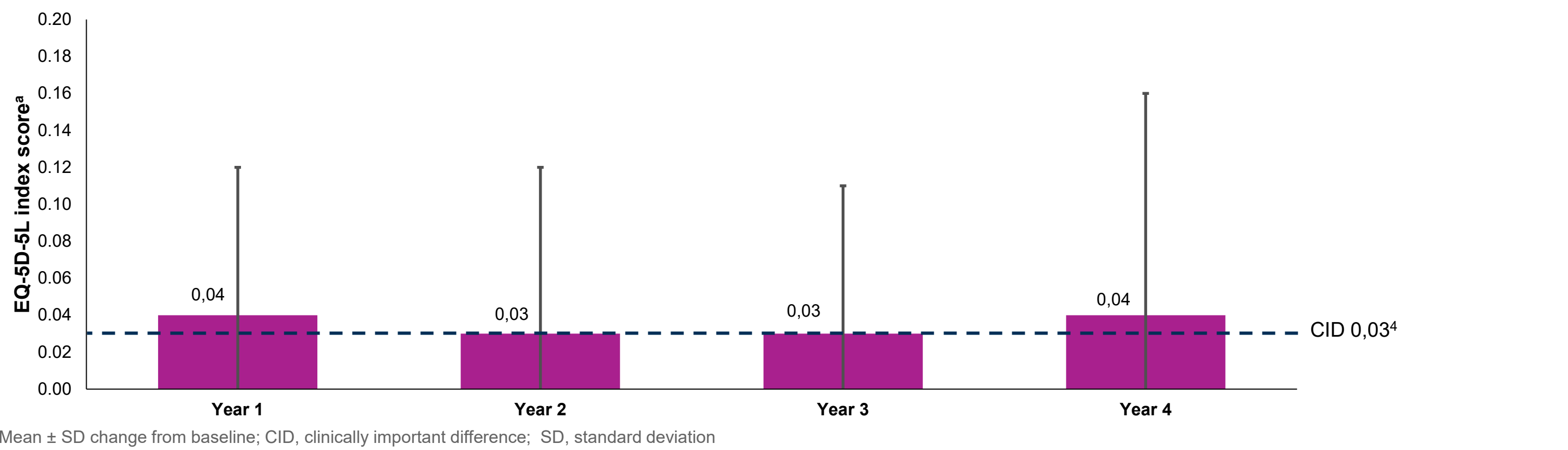
Figure 5. Change from baseline in Haemo-QOL-A Total Score and domain scores



\*P < 0.01 based on a 2-sided t-test against 0.  
CID are per Quinn J, et al. *Patient Relat Outcome Meas.* 2022;13:169-80.  
CID, clinically important difference; Haemo-QOL-A, Haemophilia-Specific Quality of Life Questionnaire for Adults; SD, standard deviation.

- Change in mean EQ-5D-5L Utility Index Score from baseline after 4years was 0.04, which exceeds the anchor-based clinically important difference of 0.03<sup>4</sup> (**Figure 6**)

Figure 6. Change from baseline in EQ-5D-5L Utility Index Score



\*Mean ± SD change from baseline; CID, clinically important difference; SD, standard deviation

## Conclusions

- After 4 years, a single infusion of valoctocogene roxaparvovec provided durable bleeding protection and improved HRQOL with acceptable safety profile
- ALT elevation was the most common AE in Brazilian population as observed in the mITT population
- The treated bleeding rate during year 4 remained reduced by 71% compared to baseline
- Clinically relevant improvements in Haemo-QOL-A Total Score and EQ-5D-5L were observed
- The robust hemostatic efficacy relative to FVIII prophylaxis and the safety profile promoted by valoctocogene roxaparvovec in the Brazilian cohort is not distinct from the one previously observed in the mITT population

### References

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(8):694-705. 3. Quinn J, et al. *Patient Relat Outcome Meas.* 2022;13:169-80. 4. Kaplan RM. *COPD.* 2005;2(1):91-7.

### Acknowledgements

We thank all trial participants, their families, study site personnel, and investigators. Funding for this study was provided by BioMarin Pharmaceutical Inc.

### Disclosures

MO has participated in advisory boards for Bayer, BioMarin, Pfizer, Sanofi and Takeda, and received honoraria from BioMarin, Biotest, Novo Nordisk, Pfizer, Roche, Sanofi and Takeda. GGYH has participated in advisory boards for BioMarin and Pfizer, and received honoraria from BioMarin, Novo Nordisk, Pfizer, Roche, Sanofi, Spark and Takeda, and travel grants from BioMarin. ANLP received honoraria and travel grants from BioMarin. PRV has participated in advisory boards for Bayer, BioMarin, Pfizer and Takeda, and received honoraria from BioMarin, Novo Nordisk, Pfizer and Takeda, and travel grants from BioMarin, Novo Nordisk and Takeda. MHC received honoraria from Novo Nordisk, Bayer, BioMarin, Pfizer and Roche, and travel grants from Novo Nordisk, Takeda and Roche. CL received honoraria from Novo Nordisk, BioMarin and Roche, and travel grants from Novo Nordisk, BioMarin, Roche, Pfizer and Takeda. TMR is a former employee and stockholder of BioMarin.

