

Efficacy, safety and quality of life three years after gene transfer with valoctocogene roxaparvovec in a Brazilian cohort

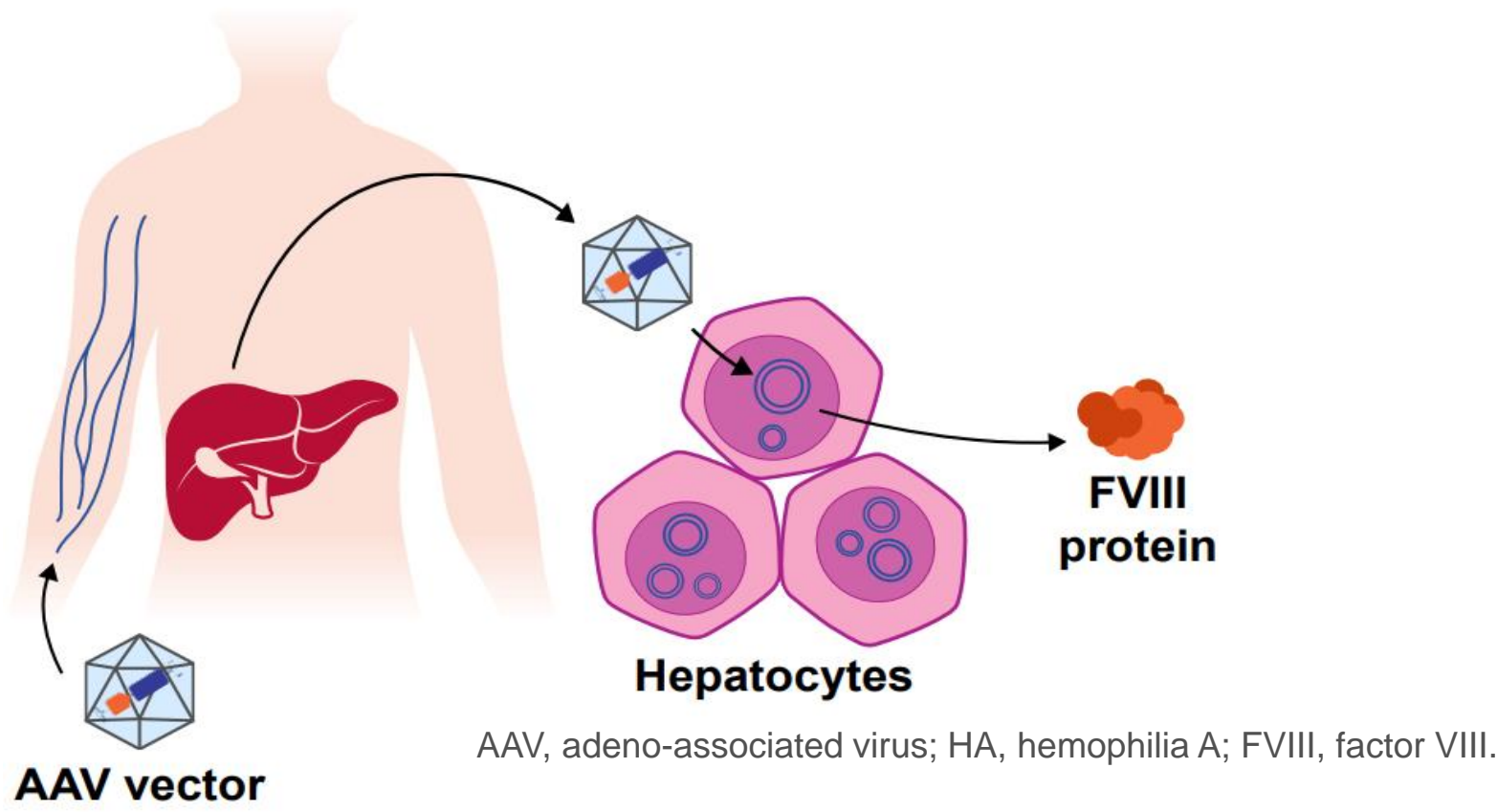
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Introduction

- 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**)^{1,2}
- In the global, open-label, phase 3 GENE8-1 trial (NCT03370913), participants who received 6x10¹³ 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 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
 - A subset of the mITT population originally from Brazil (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

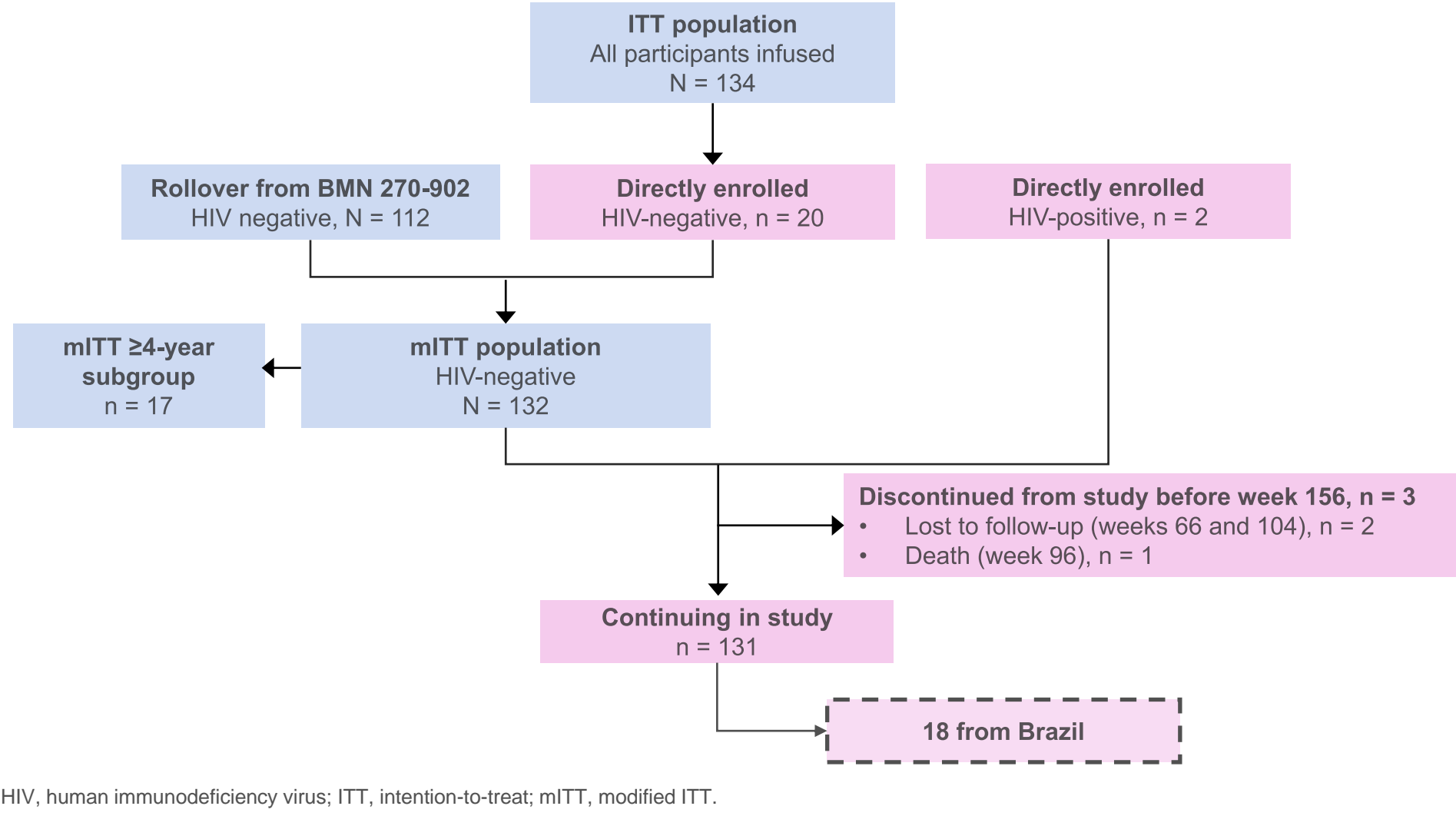


Table 1. Demographics characteristics

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 3, AEs grade ≥3 were reported in 5 participants (27.8%) (**Table 2**)
 - No participant initiated corticosteroids after week 13
 - The median duration of corticosteroid use was 292.4 days with a mean total dose of corticosteroid courses per subject of 13,977.1 mg (**Table 3**)
 - By the data cutoff, no participants were using corticosteroids for any indication
- No treatment-related AEs or serious AEs (SAEs) grade ≥3 occurred in year 3
- No participants developed FVIII inhibitors

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

Participants, n (%)	Overall N = 18
AE grade ≥3	5 (27.8)
Events	
Alanine aminotransferase increased	2 (11.1)
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)

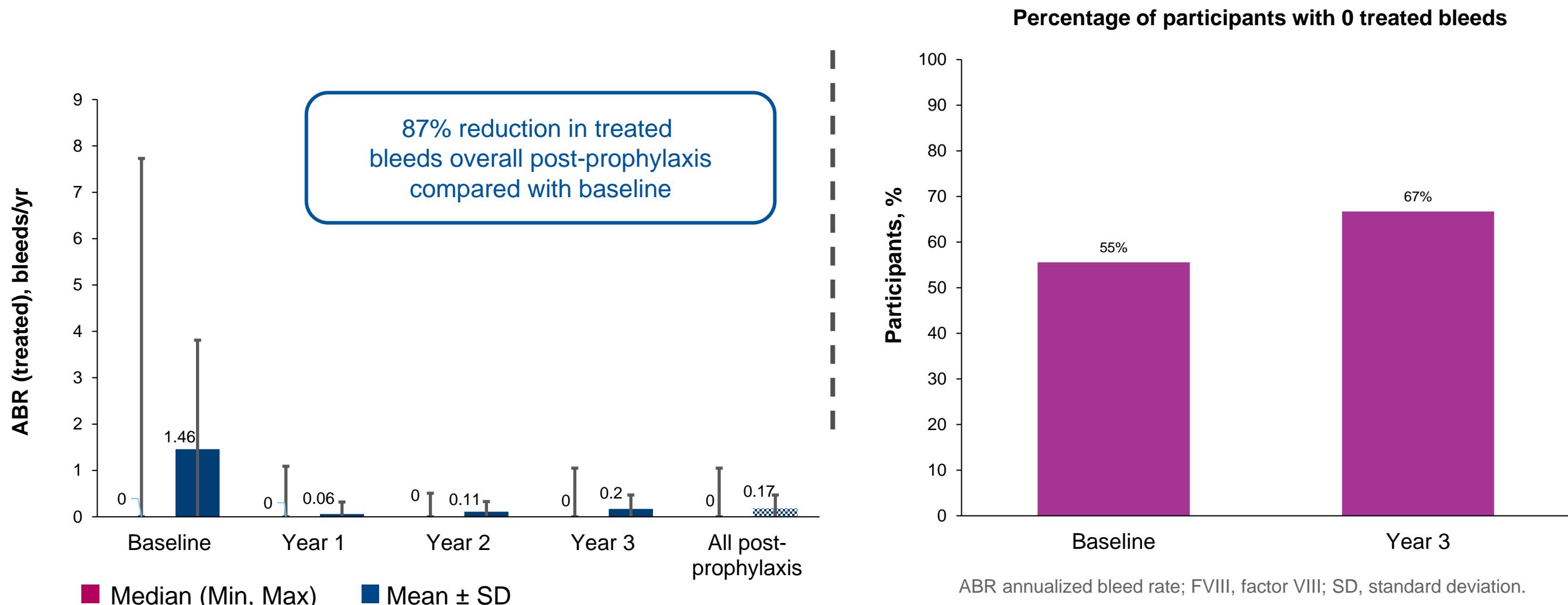
Table 3. Corticosteroid therapy for ALT elevation within 3 years of follow-up in the Brazilian cohort

Participants, n (%)	Overall N = 18
Subjects with any corticosteroid use, n (%)	17.0 (94.4)
Duration (days) of corticosteroid courses per subject, mean ± SD	292.4 ± 90.4
Total dose (mg) of corticosteroid courses per subject, mean ± SD	13,977.1 ± 6,194.2

Bleeds

- During year 3 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**)

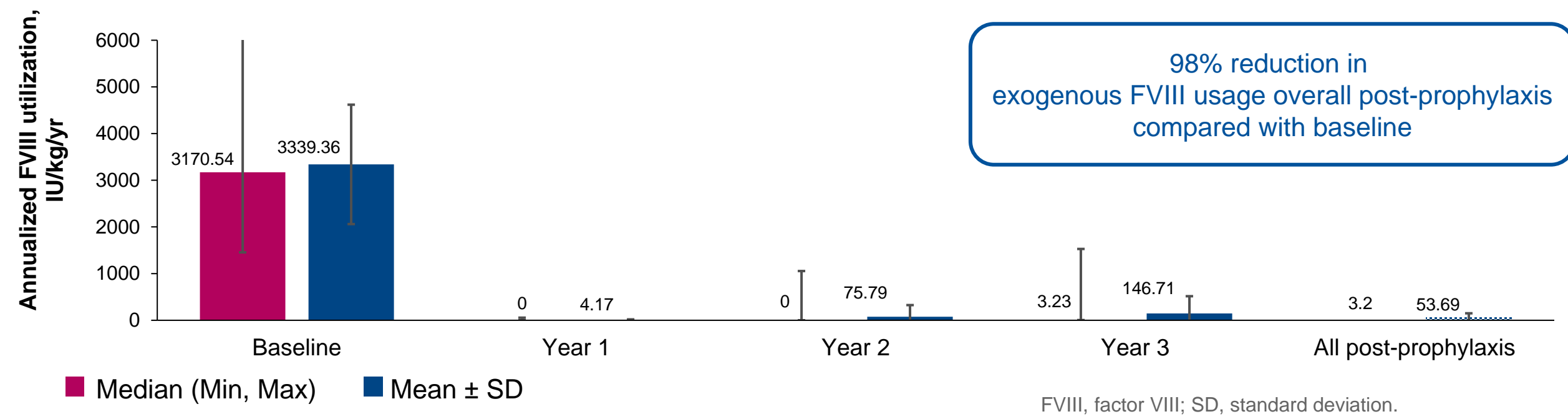
Figure 3. Mean and median ABR for treated bleeds (left) and proportion of participants with 0 treated bleeds (right)



Exogenous FVIII use

- Annualized FVIII utilization was reduced during year 3 and during the entire post-prophylaxis period compared with baseline (**Figure 4**)

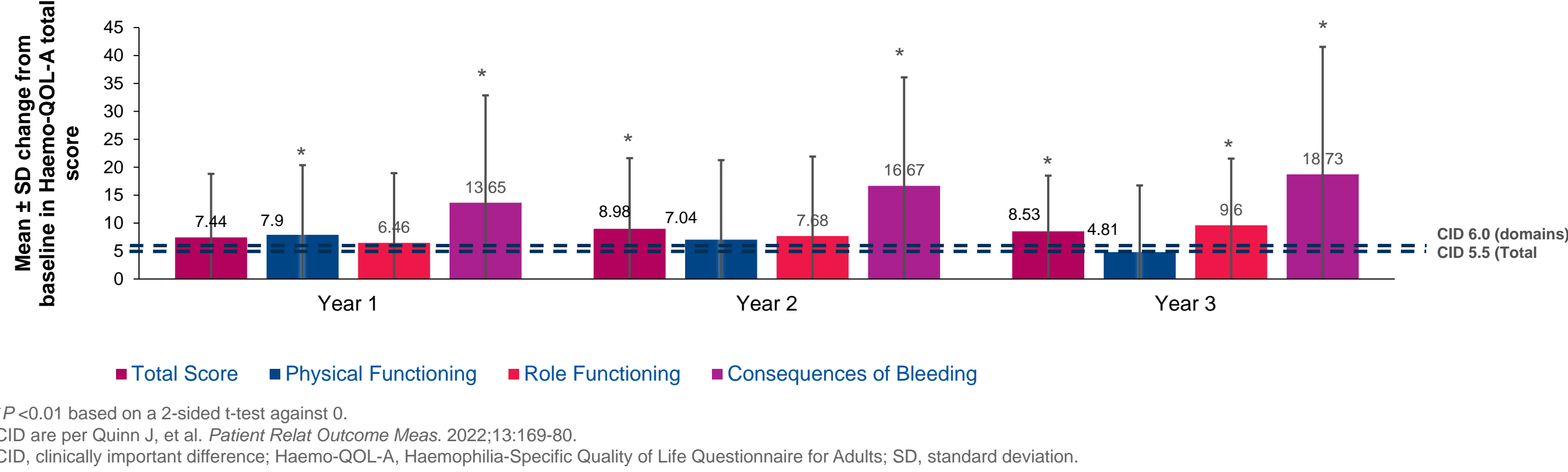
Figure 4. Annualized exogenous FVIII use in the Brazilian population



HRQOL

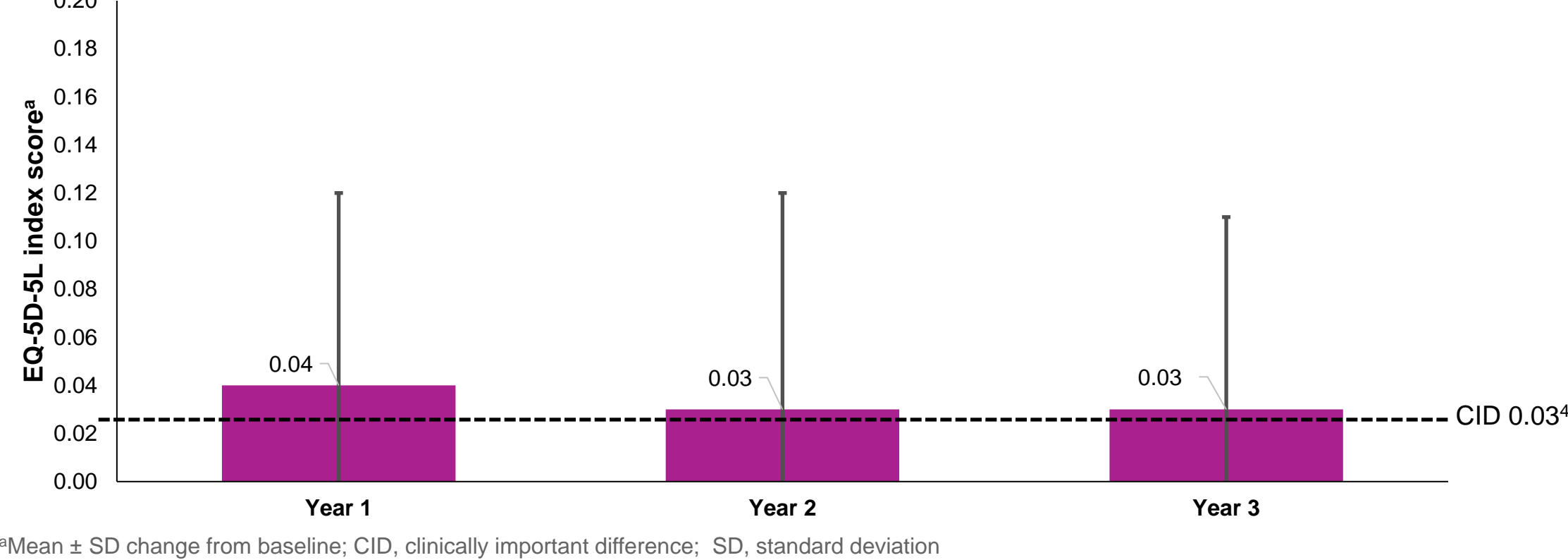
- Change in mean Haemo-QOL-A Total Score from baseline after 3 years was 8.53, which exceeds the anchor-based clinically important difference of 5.5³ (**Figure 5**)

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



- Change in mean EQ-5D-5L Utility Index Score from baseline after 3 years was 0.03, which exceeds the anchor-based clinically important difference of 0.03⁴ (**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 3 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
- FVIII remained in the mild hemophilia range
- Rate of treated bleeds during the year 3 remains decreased nearly 90% from the baseline
- Nearly 70% of patients had no treated bleeds during year 3
- 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.

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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 and PRV received honoraria and travel grants from BioMarin. 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 an employee and stockholder of BioMarin.