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ORIGINAL ARTICLE

Durability of efficacy, safety, and quality of life 5 years after valoctocogene roxaparvovec gene transfer for severe hemophilia A: final phase 3 GENEr8-1 trial results

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Abstract

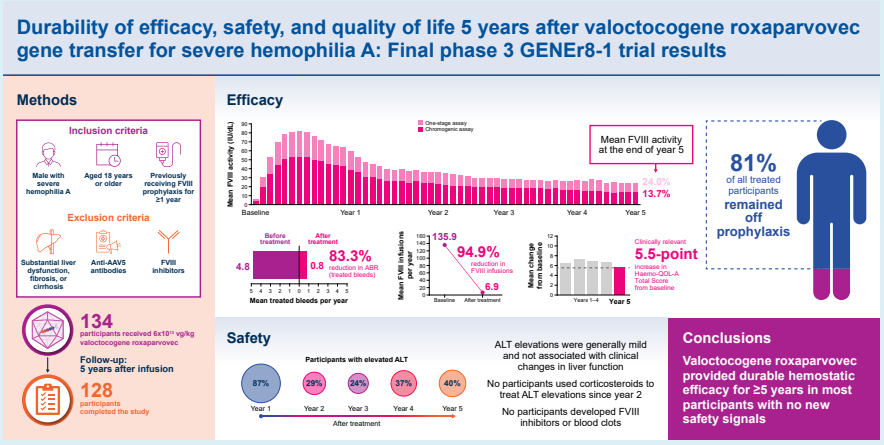
Background: Valoctocogene roxaparvovec, a gene therapy for severe hemophilia A, enables endogenous factor VIII (FVIII) expression and confers bleed control.

Objectives: To present the final 5-year efficacy and safety results from the phase 3 GENEr8-1 trial.

Methods: Adult men (N = 134) with severe hemophilia A without inhibitors who were using FVIII prophylaxis received one 6×10^{13} vg/kg infusion of valoctocogene roxaparvovec. End points included annualized bleeding rate (ABR), FVIII infusion rate, FVIII activity, Haemophilia-Specific Quality of Life Questionnaire for Adults, adverse events, and immunosuppressant use.

Results: Median follow-up was 261.1 weeks; 128 of 134 participants completed the study. For the 112 participants who enrolled from a previous noninterventional study (rollover population), mean ABR for treated bleeds declined by 83.3% ($P < .0001$), mean FVIII infusion rate declined by 94.9% ($P < .0001$), and mean ABR for all bleeds declined by 78.1% in the 5-year efficacy evaluation period vs baseline. In 132 modified intention-to-treat participants, mean and median FVIII activity at week 260 was 13.7 and 6.2 IU/dL, respectively (chromogenic assay). In year 5, 77.8% of rollover participants had 0 treated bleeds. One participant resumed prophylaxis since the 4-year data cutoff (25/134 across all follow-up). Haemophilia-Specific Quality of Life Questionnaire for Adults total score was improved from baseline at year 5. In year 5, alanine aminotransferase elevations occurred in 51 of 129 participants who entered year 5. Immunosuppressants were not used to manage them. No serious treatment-related adverse events occurred after year 1.

Conclusion: Valoctocogene roxaparvovec provides durable hemostatic efficacy, FVIII activity, and improved health-related quality of life for ≥5 years, with no new safety signals.



KEYWORDS
adeno-associated virus, clinical trial, gene therapy, health-related quality of life, hemophilia A

Essentials

- Valoctocogene roxaparvovec enables factor VIII (FVIII) production in people with severe hemophilia A.
- GENEr8-1 enrolled adult men with severe hemophilia A without FVIII inhibitors, previously using FVIII prophylaxis.
- At the end of the 5-year trial, bleeds were reduced, and the safety profile was unchanged.
- Overall, 80.8% of participants remained off regular prophylaxis.

1 | INTRODUCTION

Hemophilia A (HA) is an X-linked bleeding disorder caused by clotting protein factor VIII (FVIII) deficiency [1]. Severe hemophilia A (SHA; FVIII activity <1 IU/dL) is associated with spontaneous bleeding that causes pain, joint stiffness, and arthropathy and adversely impacts health-related quality of life (HRQOL) [1–7]. Currently, the standard of care for SHA is prophylactic treatment with exogenous FVIII or bispecific antibodies that mimic FVIII function (eg, emicizumab) [1,8–10]. However, the need for frequent administration of prophylactic treatments can be burdensome, and breakthrough bleeds can still occur [1,8–13].

Valoctocogene roxaparvovec is an approved gene therapy for SHA that enables endogenous FVIII production and bleed protection without prophylaxis [14–21]. To establish endogenous FVIII production, valoctocogene roxaparvovec uses an adeno-associated virus serotype 5 (AAV5) vector to transfer a B domain-deleted human FVIII coding sequence controlled by a hepatocyte-selective promoter [14]. In the open-label, multicenter, single-arm, phase 3 GENEr8-1 trial (NCT03370913), 134 adult male participants with SHA received a single 6×10^{13} vg/kg dose of valoctocogene roxaparvovec [19,22–24]. In previously published analyses for the year 4 cutoff date, FVIII activity was in the mild hemophilia range (mean, 16.1 IU/dL; median, 6.7 IU/dL), and participants had significantly reduced rates of bleeds and exogenous FVIII use from baseline [24]. The most common adverse events (AEs) were transient alanine aminotransferase (ALT) elevations and subsequent AEs related to glucocorticoid use to treat the ALT elevations [19,22–24]. Further supporting the favorable risk-benefit profile, participants also experienced sustained improvements over baseline in HRQOL 4 years after valoctocogene roxaparvovec infusion [24].

Valoctocogene roxaparvovec is the first approved gene therapy for SHA. Therefore, a detailed characterization of the treatment benefits and durability of valoctocogene roxaparvovec is critical for the hemophilia community. In this study, we present the final results from the phase 3 GENEr8-1 trial that demonstrate durable efficacy and HRQOL improvements 5 years after treatment and a consistent safety profile, and we give a retrospective discussion of all 5 years of the trial.

2 | METHODS

2.1 | Study design

GENEr8-1 (NCT03370913) was a multicenter, single-arm, open-label, phase 3 trial designed to investigate the safety and efficacy of valoctocogene roxaparvovec treatment for SHA. The study protocol and detailed study design were previously published [19]. Briefly, enrolled participants were men aged ≥18 years with SHA (FVIII activity ≤1 IU/dL) and a history of FVIII prophylaxis use for ≥12 months. The participants received a single intravenous infusion of 6×10^{13} vg/kg valoctocogene roxaparvovec, and FVIII prophylaxis was scheduled to end at 4 weeks postinfusion. Exclusion criteria included the presence of FVIII inhibitors, anti-AAV5 antibodies, or significant liver dysfunction.

2.2 | Populations

The intention-to-treat (ITT) population included all 134 participants who received a valoctocogene roxaparvovec infusion and was used for the safety analysis. The modified intention-to-treat (mITT) population included the 132 HIV-negative participants from the ITT population and was used for assessments of FVIII activity and HRQOL. The rollover population included 112 participants from the noninterventional 270-902 study who enrolled from the GENEr8-1 trial, with ≥6 months of prospective FVIII use and bleeding data collected prior to GENEr8-1 enrollment [9]; this population was used for comparisons of bleed rates and FVIII use at baseline and post–valoctocogene roxaparvovec infusion.

2.3 | End points

Bleeds and FVIII use were self-recorded by participants. Neither physician evaluation nor imaging were used to adjudicate participant bleeds. Annualized bleeding rates (ABRs) were evaluated for bleeds that necessitated FVIII treatment within 72 hours (treated bleeds) and for bleeds regardless of whether FVIII treatment was received (all bleeds). Traumatic bleeds were defined as those with an identifiable cause, and all other bleeds were recorded as spontaneous. Bleeding episodes related to an invasive procedure were excluded from this analysis and have been reported separately [25]. However, all FVIII use, including any FVIII use related to an invasive procedure, was included in the analysis. Missing data were not imputed. ABRs and annualized FVIII infusion rates are also reported with data censored after participants resumed prophylaxis.

The chromogenic substrate assay (CSA; ReFacto AF FVIII Chromogenic Assay) and the one-stage assay (OSA; ReFacto AF FVIII OSC Assay) were used to measure FVIII activity. The CSA and OSA have a

lower limit of quantification (LLOQ) of 1.5 and 1.0 IU/dL, respectively; however, the CSA LLOQ was 3.0 IU/dL during year 1 of the GENEr8-1 trial, and therefore, 3.0 IU/dL is considered the LLOQ when aggregate data are presented. FVIII activity derived from the OSA is consistently ~1.5× higher than CSA values, likely due to the accelerated kinetics of FVIII produced by hepatocytes after valoctocogene roxaparvovec treatment [26]. Median FVIII activity was calculated during 4- to 6-week windows. FVIII activity assessments were imputed as 1 IU/dL at baseline and 0 IU/dL if the participant discontinued the study or if the observed value was below the LLOQ. Any measurements of FVIII activity within 72 hours of an exogenous FVIII infusion were not included. For missing values, the FVIII activity was imputed as the smaller of the median value of the previous or next 4- to 6-week window (linear extrapolation was used if the next window was missing). Median FVIII activity for the mITT population is reported beginning 5 weeks after valoctocogene roxaparvovec infusion.

Participants completed the Haemophilia-Specific Quality of Life Questionnaire for Adults (Haemo-QOL-A) at weeks 4, 12, 26, 52, 76, 104, 128, 156, 180, 208, 232, and 260, as previously described [23]. Higher scores indicate higher HRQOL or less impairment. Missing data were not imputed. Once a participant resumed prophylaxis, their Haemo-QOL-A data were reported separately.

Safety was evaluated for all participants who received valoctocogene roxaparvovec. Assessments included AEs, including their severity and relationship to treatment, and any use of corticosteroids to control ALT elevations.

2.4 | Evaluation periods

The primary efficacy evaluation period was from the end of FVIII prophylaxis (scheduled to end 4 weeks postinfusion or when a participant reached FVIII activity of >5 IU/dL) to the last follow-up and is defined as the postprophylaxis period. Data were also analyzed by the year as follows: end of prophylaxis to week 52 (year 1), weeks 53 to 104 (year 2), weeks 105 to 156 (year 3), weeks 157 to 208 (year 4), and weeks 209 to 260 (year 5).

2.5 | Statistical analysis

According to the predefined statistical analysis plan for the GENEr8-1 trial, formal hypothesis testing was completed at the year 2 data cutoff. Therefore, all hypothesis testing presented in this study is for descriptive purposes only ($\alpha = 0.05$). The primary efficacy end point was change from baseline (imputed as 1 IU/dL) in FVIII activity (CSA) at week 260. Secondary efficacy end points were change from baseline during the postprophylaxis period in ABR for treated bleeds and FVIII infusion rate. The tertiary end point was change from baseline to week 260 in Haemo-QOL-A.

2.6 | Ethics

The GENEr8-1 trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The institutional review board or independent ethics committees of each participating site approved the protocol, and all participants provided written informed consent.

3 | RESULTS

3.1 | Participants

Overall, 128 of 134 ITT participants completed the study (Supplementary Figure S1). Since the 4-year data cutoff, 1 participant was lost to follow-up; in total, 6 (4.5%) participants have discontinued. The median follow-up was 261.1 weeks (range, 66.1-275.9 weeks) for all participants. A total of 25 participants resumed prophylaxis across all follow-up. The total postinfusion follow-up time was 660.3 person-years.

3.2 | Annualized bleeding rates

3.2.1 | Treated bleeds

Over the entire postprophylaxis period, the mean ABR for treated bleeds was 0.8 bleeds/y (SD, 1.9 bleeds/y; median, 0.2 bleeds/y) for the rollover population, resulting in an 83.3% reduction from baseline ($P < .0001$; Figure 1A). In year 5, the mean ABR for treated bleeds was 0.6 bleeds/y (SD, 1.6 bleeds/y; median, 0.0 bleeds/y), similar to rates in previous years. When data were censored after a participant resumed prophylaxis, mean ABR for treated bleeds was 1.0 bleeds/y (SD, 2.5 bleeds/y; median, 0.2 bleeds/y) during the postprophylaxis period and 0.3 bleeds/y (SD, 0.9 bleeds/y; median, 0.0 bleeds/y) in year 5 (Supplementary Figure S2A). During year 5, 84 of 108 (77.8%) rollover participants had 0 treated bleeds compared with 36 of 112 (32.1%) participants during baseline (Figure 1B). ABRs for spontaneous treated bleeds and traumatic treated bleeds by year and overall are presented in Supplementary Table 1.

3.2.2 | All bleeds

Over the entire postprophylaxis period, mean ABR for all bleeds was 1.2 bleeds/y (SD, 2.0 bleeds/y; median, 0.4 bleeds/y) for the rollover population (78.1% reduction from baseline; $P < .0001$; Figure 1C). During year 5, the mean ABR for all bleeds was 0.7 bleeds/y (SD, 1.7 bleeds/y; median, 0.0 bleeds/y), consistent with previous years. When data were censored after a participant resumed prophylaxis, mean ABR for all bleeds was 1.4 bleeds/y (SD, 2.6 bleeds/y; median, 0.4 bleeds/y) during the postprophylaxis period and 0.4 bleeds/y (SD, 1.0 bleeds/y; median, 0.0 bleeds/y) in year 5 (Supplementary Figure S2B).

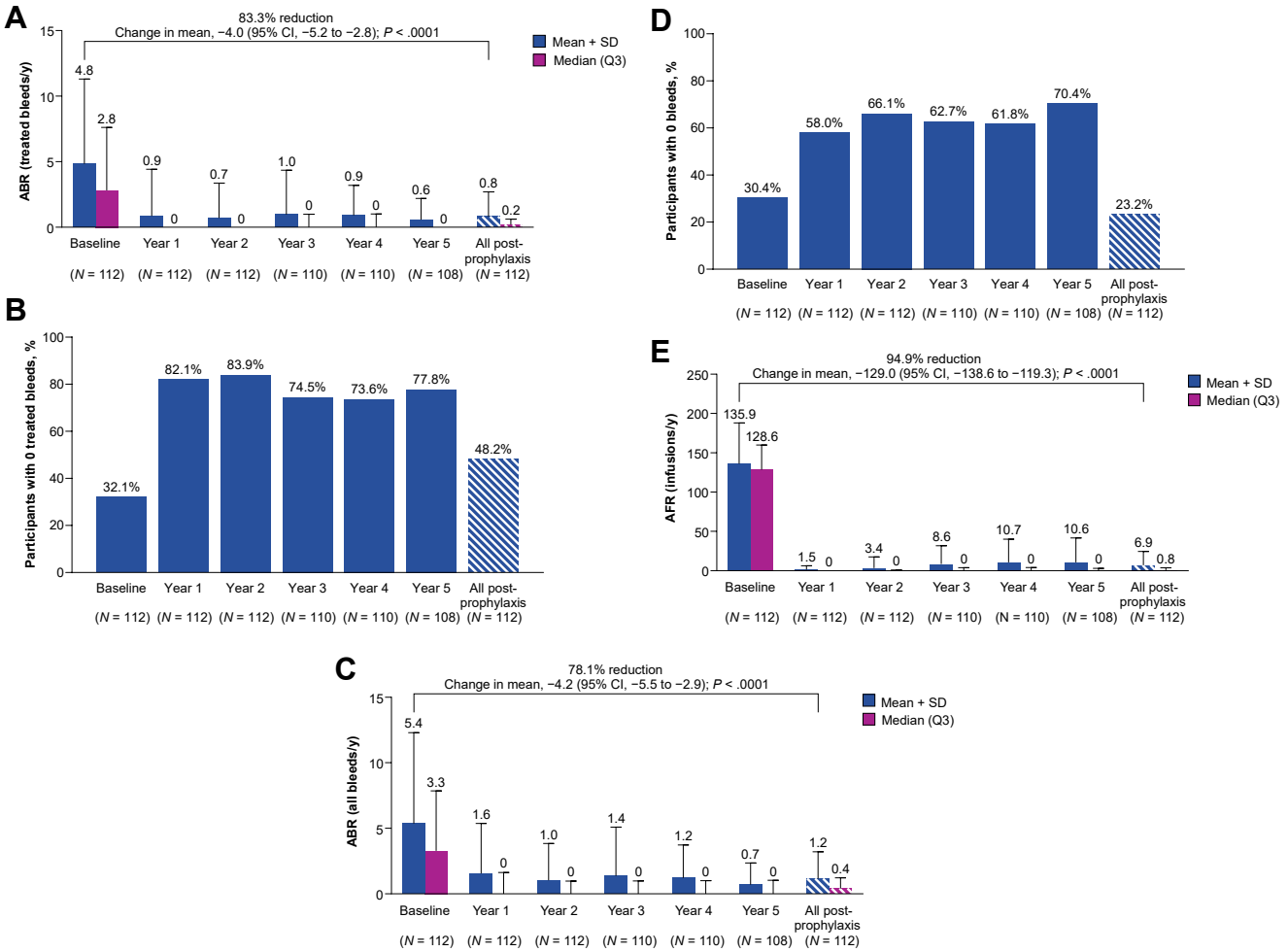


FIGURE 1 Changes from baseline postprophylaxis in the rollover population (*N* = 112) in (A) annualized bleeding rate (ABR) for treated bleeds, (B) proportion of participants with 0 treated bleeds, (C) ABR for all bleeds, (D) proportion of participants with 0 bleeds, and (E) annualized factor VIII (FVIII) infusions. Year 3, 4, and 5 data were not based on *N* = 112 due to participants who discontinued from the study. Data for participants who resumed prophylaxis were not censored. AFR, annualized rate of exogenous FVIII infusions; Q, quartile.

During year 5, 76 of 108 (70.4%) rollover participants had 0 bleeds of any kind compared with 34 of 112 (30.4%) during baseline (Figure 1D).

3.3 | FVIII activity

Consistent with the continued low rates of bleeding, year 5 FVIII activity was in line with year 4 values. The mean week 260 FVIII activity was 13.7 IU/dL per CSA (SD, 23.6 IU/dL per CSA; median, 6.2 IU/dL; IQR, 2.4-14.2 IU/dL) for the mITT population (*N* = 132; Figure 2A). Per OSA, week 260 mean and median FVIII activity were 24.0 IU/dL (SD, 41.8 IU/dL) and 12.6 IU/dL (IQR, 4.2-25.0 IU/dL), respectively (Supplementary Figure S3). At the end of year 5, 11 (8.3%) participants in the mITT population had FVIII activity per CSA in the nonhemophilia range (≥40 IU/dL), 66 (50.0%) had FVIII activity in the mild hemophilia range (<40 and ≥5 IU/dL), 16 (12.1%) had FVIII activity in the moderate hemophilia range (<5 and ≥3 IU/dL), and 39 (29.5%) had FVIII activity below the LLOQ (the moderate to severe hemophilia range, <3 IU/dL; Figure 2B). One participant (0.8%) had FVIII of >150 IU/dL, the upper limit of normal. No thromboembolic events occurred.

3.4 | Exogenous FVIII use

Over the entire postprophylaxis period, the mean annualized FVIII infusion rate was 6.9 infusions/y (SD, 17.5 infusions/y; median, 0.8 infusions/y) for the rollover population, a 94.9% reduction from when participants were receiving FVIII prophylaxis at baseline ($P < .0001$; Figure 1E). During year 5, the mean FVIII infusion rate was 10.6 infusions/y (SD, 31.2 infusions/y; median, 0.0 infusions/y) when including data after participants resumed prophylaxis, similar to the rate during year 4. When data were censored after a participant resumed prophylaxis, the mean rate of FVIII infusions was 3.0 infusions/y (SD, 5.2 infusions/y; median, 0.8 infusions/y) during the

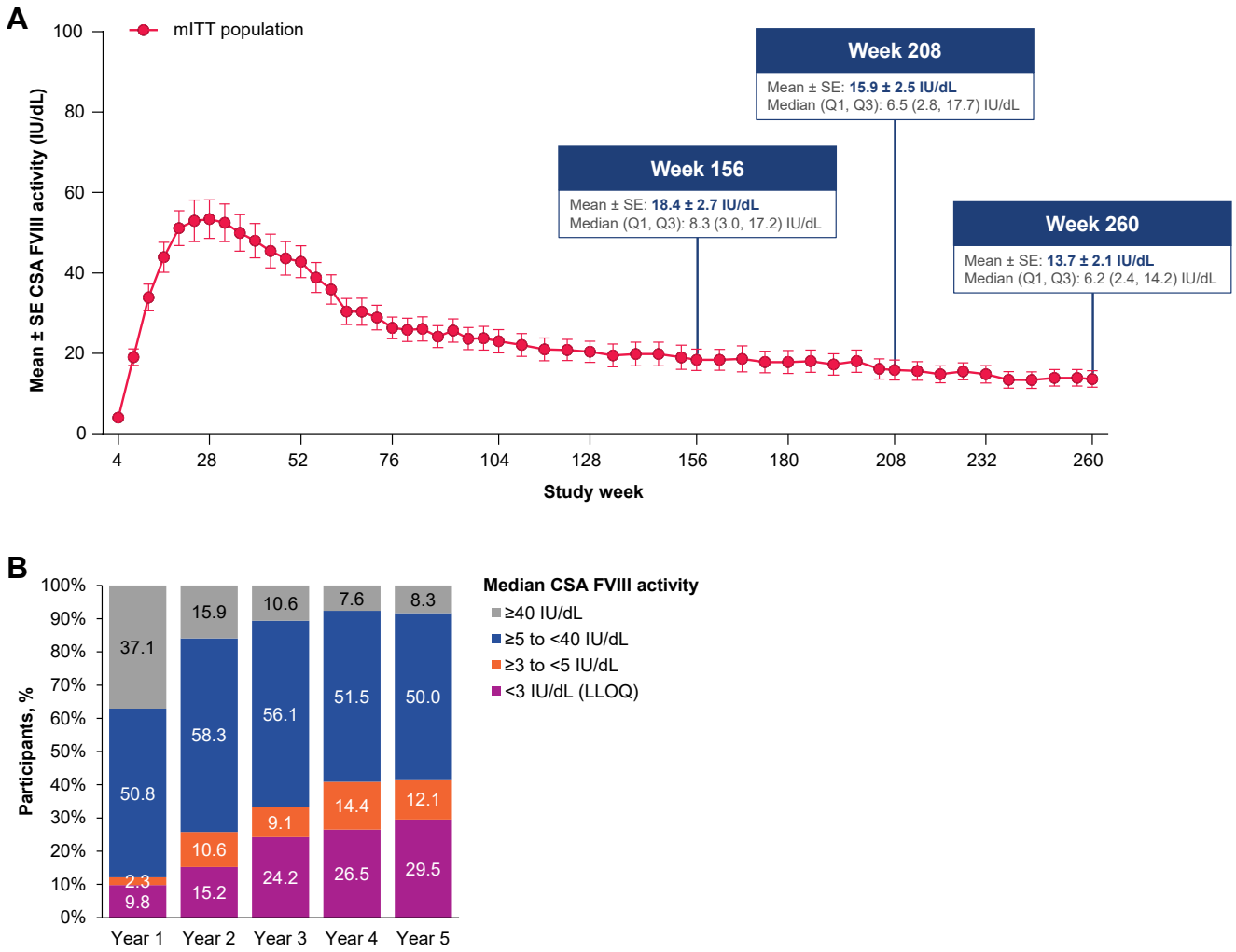


FIGURE 2 (A) Median chromogenic substrate assay (CSA) factor VIII (FVIII) activity >5 years posttreatment with valoctocogene roxaparvovec in the modified intention-to-treat (mITT) population (*N* = 132). (B) Distribution of median CSA FVIII activity at the end of each year after infusion. Median FVIII activity was calculated during 4- to 6-week windows. FVIII activity assessments were imputed as 1 IU/dL at baseline and 0 IU/dL if the participant discontinued the study or if the observed value was below the lower limit of quantification (LLOQ). Participants who resumed prophylaxis are included; however, any measurements of FVIII activity within 72 hours of an exogenous FVIII infusion were not included. For missing values, the FVIII activity was imputed as the smaller of the median value of the previous or next 4- to 6-week window (linear extrapolation was used if the next window was missing). Median FVIII activity for the mITT population is reported beginning 5 weeks after valoctocogene roxaparvovec infusion. Q, quartile.

postprophylaxis period (Supplementary Figure S2C) and 1.9 infusions/y (SD, 5.2 infusions/y; median, 0.0 infusions/y) in year 5. Annualized FVIII utilization (IU/kg/year) across the trial is presented in Supplementary Table 2.

3.5 | Return to prophylaxis

Since the 4-year data cutoff, a single additional participant resumed prophylaxis during week 210 with exogenous FVIII and later transitioned to emicizumab during week 235 [24]. The valid observed FVIII activity reading closest to return to prophylaxis (RTP) for this participant was at week 208 (2.6 IU/dL per CSA; 6.2 IU/dL per OSA). The participant had an ABR for treated bleeds of 0.0 bleeds/y in the postprophylaxis period, which was lower than their baseline value of 2.7 bleeds/y. For all bleeds, the participant had an ABR of 0.3 bleeds/y during the postprophylaxis period, compared with 2.7 bleeds/y during baseline.

At the end of the study, 80.8% (105/130) of the participants who continued on study through year 4 remained off prophylaxis; 25 of 130 ITT participants resumed prophylaxis. The 5-year probability of remaining off prophylaxis was 80.9% (Figure 3A). Median time from week 5 (when prophylaxis with FVIII was scheduled to end) to RTP was 170.0 weeks (IQR, 120.3-188.1 weeks). Most (68%) participants who resumed prophylaxis had a lower ABR for treated bleeds in the period after treatment up to RTP than at baseline (Figure 3B). Individual

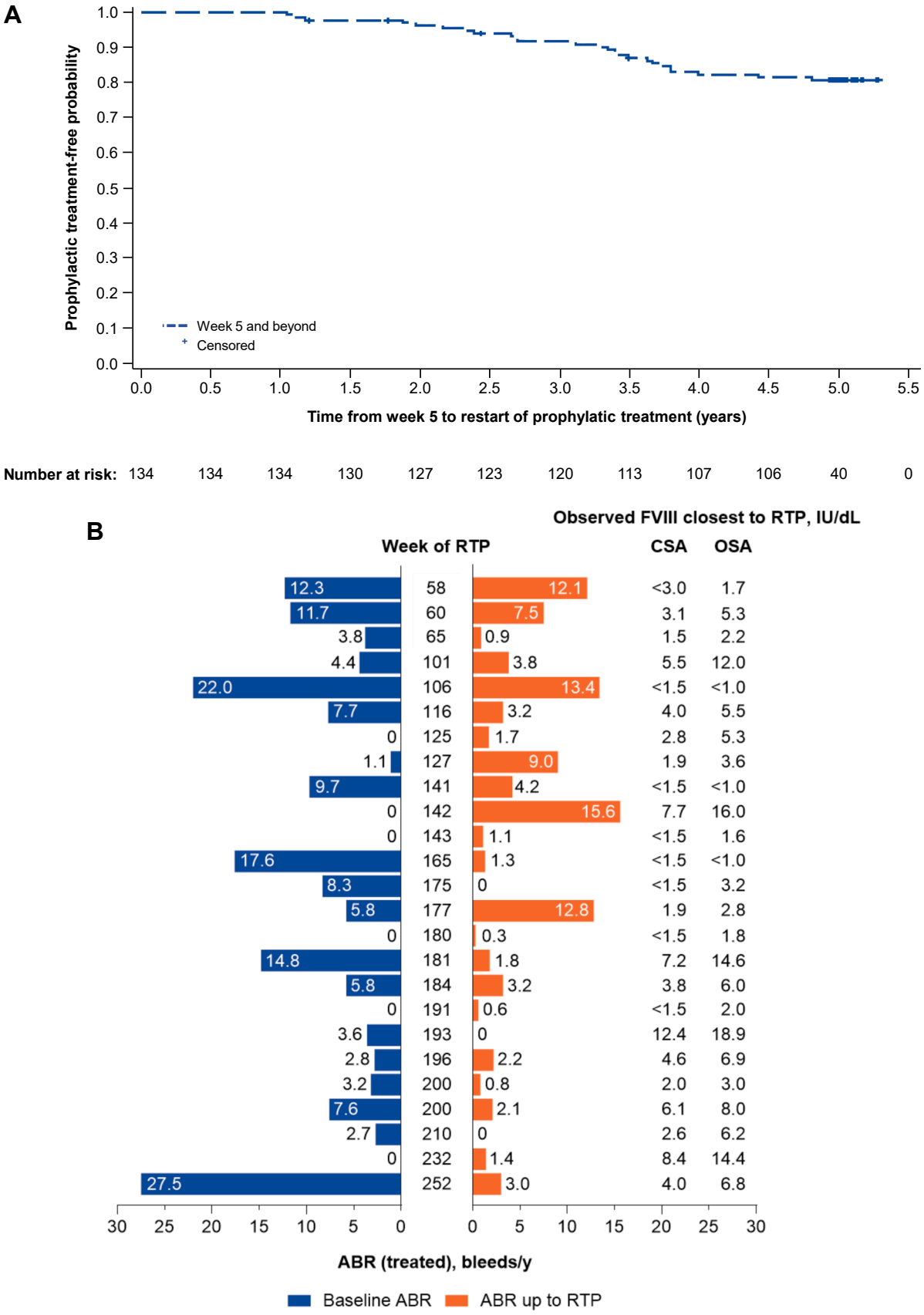


FIGURE 3 (A) Kaplan–Meier curve of prophylactic treatment-free probability in the intention-to-treat population (N = 134). (B) Annualized bleeding rate (ABR) for treated bleeds at baseline, ABR for treated bleeds after treatment up to return to prophylaxis (RTP), and observed factor VIII (FVIII) activity closest to RTP for all participants who resumed prophylaxis across the trial. Analysis began from week 5 postinfusion. Number at risk includes intention-to-treat participants who reached the indicated follow-up plus 5 weeks and did not RTP and excludes censored participants (ie, those who did not reach the time point); thus, by year 5 + 5 weeks, most participants were not being followed up in GENEr8-1. The latest valid FVIII activity value before RTP is presented. The lower limit of quantification for chromogenic substrate assay (CSA) changed from 3.0 to 1.5 IU/dL during the study. OSA, one-stage assay.

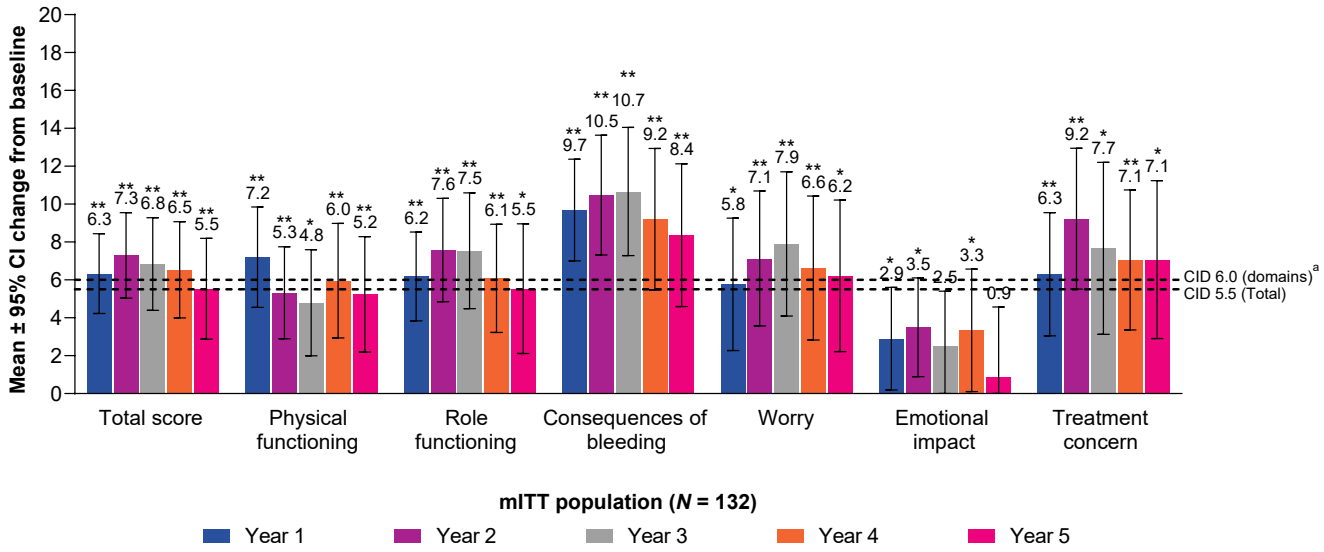


FIGURE 4 Change from baseline in Haemophilia-Specific Quality of Life Questionnaire for Adults total score and domain scores. *$P < .05$; **$P < .001$ based on a 2-tailed t-test against the null hypothesis of no change from baseline. Data were excluded after a participant resumed prophylaxis. [a]A CID for the treatment concern domain has not been estimated. CID, clinically important difference; mITT, modified intention-to-treat.

decisions to resume prophylaxis were made by participants and investigators as part of a shared decision-making process, incorporating personal factors such as bleeds, FVIII activity, and lifestyle choices.

3.6 | Health-related quality of life

Improvements from baseline in HRQOL as measured by the Haemo-QOL-A were observed at year 5, similar to earlier time points after treatment [23,24,27]. Specifically, among a subsample of participants who had not resumed prophylaxis by year 5, mean change from baseline in Haemo-QOL-A total score was 5.5 points (N = 99; P < .0001; Figure 4), which met the clinically important difference (CID) of 5.5 points [28]. Mean change from baseline in the consequences of bleeding and worry domains also exceeded the domain score CID of 6.0 points at year 5. Results for other domains (physical functioning, role functioning, and emotional impact) did not exceed the domain CID threshold. Results were similar for analyses including participants who resumed prophylaxis, with the observed improvements also exceeding the CID estimates for total score and role functioning domain at year 5 (Supplementary Figure S4).

3.7 | Safety

After 5 years, the safety profile of valoctocogene roxaparvovec remains unchanged from previous reports (Table 1). During year 5, 102 of 129 (79.1%) and 4 of 129 (3.1%) participants who entered year 5 experienced an AE or a serious AE (SAE), respectively. Treatment-related AEs occurred in 5 of 129 (3.9%) participants, and there were no treatment-related SAEs. No participants had thromboembolic events or malignancies or developed FVIII inhibitors in year 5.

During year 5, ALT elevations occurred in 51 of 129 (39.5%) participants (Table 1). No ALT elevations were grade ≥3. Most events were below the upper limit of normal (Table 2); 3 participants had an ALT elevation >5× baseline, and none had an ALT elevation >10× baseline. No participants have used corticosteroids for ALT elevations since year 2.

4 | DISCUSSION

Results from the fifth and final year of GENEr8-1, the largest hemophilia gene therapy trial to date, provide insight into the durability of FVIII expression and long-term hemostatic efficacy, which are critical considerations for clinical decision-making. Following a single infusion of valoctocogene roxaparvovec, mean FVIII activity was in the mild hemophilia range by the end of year 5, and ABRs across the trial were significantly reduced from baseline, with an overall reduction of 83.3% for treated bleeds and 78.1% for all bleeds. These reductions in the rate of bleeds corresponded with a significant decrease in the number of annual FVIII infusions and improvements in HRQOL as assessed by the Haemo-QOL-A total score. These data continue to suggest that valoctocogene roxaparvovec provides improved and clinically meaningful hemostatic efficacy compared with FVIII prophylaxis, without the need for ongoing prophylactic treatment for at least 5 years.

Twenty-five participants resumed prophylaxis with FVIII or emicizumab after receiving valoctocogene roxaparvovec. No clear predictors of RTP were identified. While many participants who resumed prophylaxis had FVIII activity in the moderate hemophilia

TABLE 1 Adverse events in the intention-to-treat population.

AEs	Year 1 (*N* = 134)	Year 2 (*N* = 134)	Year 3 (*N* = 132)	Year 4 (*N* = 131)	Year 5 (*N* = 129)	All follow-up (*N* = 134)
Any AE	134 (100)	112 (83.6)	104 (78.8)	98 (74.8)	102 (79.1)	134 (100.0)
AEs occurring in ≥30%						
ALT increased	116 (86.6)	39 (29.1)	31 (23.5)	49 (37.4)	51 (39.5)	125 (93.3)
Arthralgia	37 (27.6)	27 (20.1)	15 (11.4)	12 (9.2)	8 (6.2)	61 (45.5)
Headache	46 (34.3)	19 (14.2)	13 (9.8)	5 (3.8)	6 (4.7)	60 (44.8)
Nausea	50 (37.3)	4 (3.0)	2 (1.5)	4 (3.1)	1 (0.8)	53 (39.6)
AST increased	44 (32.8)	12 (9.0)	5 (3.8)	6 (4.6)	6 (4.7)	53 (39.6)
COVID-19	0	5 (3.7)	23 (17.4)	15 (11.5)	11 (8.5)	47 (35.1)
Upper respiratory tract infection	25 (18.7)	12 (9.0)	5 (3.8)	13 (9.9)	7 (5.4)	44 (32.8)
Fatigue	36 (26.9)	4 (3.0)	4 (3.0)	1 (0.8)	2 (1.6)	42 (31.3)
Any SAE[a]	21 (15.7)	6 (4.5)	9 (6.8)	11 (8.4)	4 (3.1)	37 (27.6)
Any AE grade ≥3	30 (22.4)	13 (9.7)	12 (9.1)	15 (11.5)	6 (4.7)	55 (41.0)
Any fatal AE	0	1 (0.7)	0	1 (0.8)	0	2 (1.5)
Valoctocogene roxaparvovec-related[a]						
AEs	124 (92.5)	27 (20.1)	14 (10.6)	8 (6.1)	5 (3.9)[b]	124 (92.5)
SAEs	5 (3.7)	0	0	0	0	5 (3.7)
Glucocorticoid-related						
AEs	81 (60.4)	10 (7.5)	1 (0.8)	2 (1.5)	0	82 (61.2)
SAEs	3 (2.2)	0	0	0	0	3 (2.2)
Nonsteroidal immunosuppressant-related						
AEs	12 (9.0)	2 (1.5)	2 (1.5)	2 (1.5)	0	18 (13.4)
SAEs	1 (0.7)	0	0	1 (0.8)	0	2 (1.5)
AEs of special interest						
ALT elevation[c]	116 (86.6)	39 (29.1)	31 (23.5)	49 (37.4)	51 (39.5)	125 (93.3)
ALT elevation grade ≥3	10 (7.5)	1 (0.7)	0	0	0	10 (7.5)
AEs related to liver function	118 (88.1)	39 (29.1)	32 (24.2)	50 (38.2)	54 (41.9)	125 (93.3)
Potential Hy's law case[d]	0	0	0	0	0	0
Infusion-related reactions[e]	12 (9.0)	0	0	0	0	12 (9.0)
Infusion-associated reactions[f]	50 (37.3)	0	0	0	0	50 (37.3)
Systemic hypersensitivity	7 (5.2)	0	0	0	0	7 (5.2)
Anaphylactic or anaphylactoid reactions	3 (2.2)	0	0	0	0	3 (2.2)
Thromboembolic events	0	0	0	0	0	0
Anti-FVIII neutralizing antibodies	0	0	0	0	0	0
Malignancy (except NMSC)	0	0	1 (0.8)	0	0	1 (0.7)

Values are *n* (%). AEs were coded using MedDRA v24.0 and graded for severity using Common Terminology Criteria for AEs v4.03. Relationship to study drug was determined by the investigator. Percentages were calculated using the total number of participants (*N*) in each analysis population as the denominator. Participants with >1 AE of the same category were counted only once for that category.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FVIII, factor VIII; MedDRA, Medical Dictionary for Regulatory Activities; NMSC, nonmelanoma skin cancer; SAE, serious AE; ULN, upper limit of normal.

[a]Severity and relationship to study drug was assessed by the investigator.

[b]Valoctocogene roxaparvovec-related AEs in year 5 were as follows: ALT elevation (2 participants), AST elevation (1 participant), FVIII level increased (1 participant), and hepatic steatosis (1 participant).

range and below (≤5 IU/dL), others did not. Conversely, many participants with FVIII activity <5 IU/dL, the recommended threshold for prophylaxis, did not RTP [1,20,23]. ABRs for treated bleeds for participants who resumed prophylaxis were often lower in the period between valoctocogene roxaparvovec treatment and RTP compared with baseline. The decision to RTP is thus considered to be based on shared decision-making that considers many individualized factors apart from bleeding episodes, including personal preference.

HA can have a tremendous impact on a person's life [1,29–32]. Therefore, a treatment that provides effective protection against bleeds without a persistent administration regimen may improve HRQOL. Results from GENEr8-1 suggest that a one-time treatment with valoctocogene roxaparvovec may provide long-term benefits and improvements in meaningful aspects of health, including HRQOL. This benefit is substantiated by statistically significant improvements in Haemo-QOL-A total score each year after treatment, up to 5 years after infusion [24,28]. These results also suggest that improving bleeding rates several years after infusion with a single treatment could improve psychological and behavioral aspects of the experience of hemophilia and its management, as demonstrated by improvements in consequences of bleeding and worry domain scores. It should be noted that although results from the 5-year analysis did not yield values that exceeded the domain CID estimates for the physical functioning, role functioning, and emotional impact domains of Haemo-QOL-A as observed in previous years, these results are not unexpected given the relatively high baseline scores observed (ie, the disability paradox observed in hemophilia and other genetic conditions) and the important context of response shift, where individual values, expectations, and conceptualizations of health change over time [33,34]. Nevertheless, these results represent the longest period of follow-up after HA gene therapy and provide evidence of the long-term benefit of this one-time treatment.

The safety profile of valoctocogene roxaparvovec was consistent with previous years [19,22–24]. Most treatment-related AEs occurred in year 1, and no treatment-related SAEs occurred after year 1. Across the trial, the most common AEs were mild, transient, and asymptomatic ALT elevations, the incidence of which peaked in year 1. No corticosteroids were used to manage ALT elevations after year 2. ALT elevations occurring after year 2 were typically <1.5 times the upper limit of the laboratory normal range and were documented to have resolved or were temporally associated with factors such as substantial weight gain, infections, exposure to hepatotoxic medications or herbal supplements, and/or nonalcoholic steatohepatitis (data not shown). One malignancy, a case of B cell acute lymphoblastic leukemia, occurred during the trial and was determined to be unrelated to valoctocogene roxaparvovec by an independent data monitoring committee based on comprehensive genomic analysis [23].

No participants in GENEr8-1 developed FVIII inhibitors, whereas all participants developed anti-AAV5 antibodies [35]. Previous immunologic analyses found that ALT elevations that occurred within 6 months of infusion slightly overlapped temporally with peak AAV5 capsid-specific immune responses, whereas those that occurred after 6 months generally did not [35]. This suggests that later ALT elevations are caused by other yet-unknown mechanisms and supports the use of corticosteroids to manage early, but not late, ALT elevations. Furthermore, the phase 3b GENEr8-3 trial found that a prophylactic glucocorticoid regimen did not prevent ALT elevations or enhance FVIII activity [36]. At present, the development of anti-AAV antibodies prevents treatment with any other gene therapies based on AAV vectors and should be a consideration during the shared decision-making process, although new techniques may enable redosing in the future [37]. FVIII-specific immune responses were sparse and not associated with either ALT elevations or changes in FVIII activity [35].

The limitations of this study have been extensively discussed [19,22–24]. Participants with FVIII inhibitors, AAV5 antibodies, and HIV were excluded from the study, limiting the applicability of these results. Joint health is an important factor in the health of people with hemophilia but was not longitudinally tracked. Because all participants were using FVIII prophylaxis at baseline, but some participants resumed prophylaxis with emicizumab (administration of which was not counted as a FVIII infusion), annualized FVIII infusion rate may underestimate treatment burden over time. RTP potentially confounded other efficacy results as well; we present results including and excluding post-RTP data to facilitate interpretation.

Combined, data are available for more than 140 participants who received gene therapy in the phase 3 and phase 1/2 trials of valoctocogene roxaparvovec, many with >5 years of posttreatment follow-up [38,39]. The completed phase 1/2 trial demonstrated that reduced mean ABR for treated bleeds (−96%) endured across the 7-year trial period for the 6×10^{13} vg/kg cohort, and mean FVIII activity was 16.2 IU/dL at the end of year 7 [38]. While the sample size was lower in that trial, the data support the durability of the efficacy of valoctocogene roxaparvovec. Previous investigations have found that integration of the valoctocogene roxaparvovec genome is infrequent and that stable episomes underpin the durability of FVIII expression [15,39,40].

[c]The threshold for an AE of special interest of ALT elevation evolved through the trial. First, the threshold was defined as ALT ≥1.5× ULN (ULN: 43 U/L), then amended to include elevations >ULN when ALT was >2× baseline, then amended again to include elevations >ULN or ≥1.5× baseline.
[d]Hy's law cases have 3 components: (1) ALT or AST elevation >3× ULN, often much greater (>5× or >10× ULN); (2) total bilirubin elevations >2× ULN, without findings of obstruction (such as elevated alkaline phosphatase), malignancy, or impaired glucuronidation capacity; and (3) no other explanation can be found for the combination of increased ALT/AST and total bilirubin (eg, viral hepatitis and pre-existing liver disease).
[e]Infusion-related reactions were defined as AEs occurring during infusion or within 6 hours postinfusion, irrespective of causal association with valoctocogene roxaparvovec.
[f]Infusion-associated reactions were defined as AEs occurring within 48 hours postinfusion, irrespective of causal association with valoctocogene roxaparvovec.

TABLE 2 Immunosuppressant use in the intention-to-treat population.

Immunosuppressant use	Year 1 (N = 134)	Year 2 (N = 134)	Year 3 (N = 132)	Year 4 (N = 131)	Year 5 (N = 129)	Overall (N = 134)
With postbaseline ALT >ULN	105 (78.4)	39 (29.1)	20 (15.2)	21 (16.0)	23 (17.8)	111 (82.8)
With postbaseline ALT >1.5× baseline[a]	120 (89.6)	78 (58.2)	46 (34.8)	55 (42.0)	63 (48.8)	127 (94.8)
Used glucocorticoids for any purpose	108 (80.6)	47 (35.1)	4 (3.0)	3 (2.3)	2 (1.6)	109 (81.3)
Total duration (wk)	32.0 (0.1-50.1)	6.7 (0.1-49.9)	1.1 (0.7-33.0)	1.4 (1.0-12.1)	0.8 (0.7-0.9)	32.9 (0.1-120.1)
Total dose (mg)	6272.5 (40-25,110)	735.0 (1-9040)	225.0 (200-1515)	200.0 (200-1475)	70.0 (20-120)	636.0 (40-31,760)
Used glucocorticoids for ALT elevation	105 (78.4)	45 (33.6)	1 (0.8)[b]	0 (0.0)	0 (0.0)	106 (79.1)
Total duration (wk)	32.9 (3.4-50.1)	7.0 (0.1-49.9)	33.0 (33.0-33.0)	NA	NA	32.9 (3.1-120.1)
Total dose (mg)	6360.0 (960-25,110)	735.0 (1-9040)	1515.0 (1515-1515)	NA	NA	6560.0 (960-31,760)

Values are *n* (%) or median (minimum-maximum).

AE, adverse event; ALT, alanine aminotransferase; NA, not applicable; ULN, upper limit of normal.

[a]Not all events qualified as an AE.

[b]Participant initiated use for ALT elevation at the start of year 2 and continued use despite return to normal ALT levels prior to year 3.

The safety results of the phase 1/2 trial were consistent with GENEr8-1. Low-grade, asymptomatic ALT elevations were the most common AEs and were able to be managed with corticosteroids [38]. A case of parotid acinar cell carcinoma occurred 6 years after treatment in 1 participant in the 6×10^{13} vg/kg cohort in the phase 1/2 trial; similar to the malignancy that occurred in GENEr8-1, genomic analyses were performed, and it was determined not related to valoctocogene roxaparvovec [41]. To date, no cancers have been attributed to an AAV vector-based gene therapy [42,43].

The shared decision-making process for undergoing gene therapy encompasses considerations beyond efficacy, safety, and durability and includes the impact of treatment on burden of disease. The efficacy of other currently available treatments is a relevant consideration. A matching-adjusted indirect comparison between GENEr8-1 and the HAVEN 3 study showed that the treated bleeding rate was lower with valoctocogene roxaparvovec treatment than with emicizumab [44]. A pharmacokinetic simulation study demonstrated that people can safely transition to valoctocogene roxaparvovec from emicizumab while managing bleeding risk and individual characteristics; guidelines for transitioning to valoctocogene roxaparvovec from emicizumab are available based on that study [45]. A propensity scoring analysis confirmed that participants who received valoctocogene roxaparvovec experienced fewer bleeds than those who used FVIII prophylaxis [46]. Invasive surgical procedures, which carry increased risk and must be carefully managed for people with hemophilia, have been safely performed in participants of the GENEr8-1 trial after valoctocogene roxaparvovec [25]. In most cases, invasive procedures were performed without concomitant exogenous FVIII therapy [25]. Finally, use of hepatotoxic drugs could impact the decision to undergo gene therapy. A total of 3 participants from the valoctocogene roxaparvovec trials were HIV-positive (2 in GENEr8-1 and 1 in GENEr8-2); while their FVIII responses and safety profiles suggest valoctocogene roxaparvovec treatment is possible with HIV infection, a careful history of the individual's hepatotoxic medications should be taken, and hepatotoxic drugs should be avoided when possible [47].

Long-term follow-up is essential to provide additional insight into long-term outcomes from valoctocogene roxaparvovec treatment, and GENEr8-1 participants are eligible to enroll in the long-term extension study GENEr8-LTE (NCT05768386). More broadly, additional clinical experience from long-term follow-up and commercial treatment with valoctocogene roxaparvovec and other gene therapies for hemophilia may elucidate unknown benefits, concerns, or avenues for investigation. The Gene Therapy Registry by The World Federation of Hemophilia will be important for collecting outcomes and providing a holistic clinical picture [48].

5 | CONCLUSION

Valoctocogene roxaparvovec provided durable hemostatic efficacy and HRQOL benefits for 5 years in the majority of participants

following a single infusion, with a consistent and manageable safety profile.

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AUTHOR CONTRIBUTIONS

A.D.L., J.M., P.R., E.S., D.V.Q., A.G., G.K., G.L., N.S.K., C.M.M., S.W.P., S.-C.C., R.K., J.M., H.C., F.P., E.M., D.P., C.W.T., and M.C.O. were clinical investigators who performed study procedures. H.Y. oversaw statistical analysis. K.-M.C. oversaw study conduct. All authors critically reviewed the article, provided substantive input during its development, and approved the submitted draft.

RELATIONSHIP DISCLOSURE

A.D.L. has received research funding from BioMarin Pharmaceutical Inc and Pfizer and has participated in advisory boards for BioMarin Pharmaceutical Inc, CSL, Pfizer, Sanofi, and Sobi. J.M. has received research funding from BioMarin Pharmaceutical Inc, Novo Nordisk, Pfizer, Roche, Sanofi, Spark Therapeutics, and Vega Therapeutics; participated in speakers bureaus for Novo Nordisk, Pfizer, Roche, and Sanofi; and consulted for BioMarin Pharmaceutical Inc, Novo Nordisk, Roche, Sanofi, Spark Therapeutics, and Takeda. P.R. has received grant/travel support from CSL Behring, Roche, Sobi, and Takeda and advisory honoraria from BioMarin Pharmaceutical Inc, CSL Behring, LFB, Pfizer, and Sobi. E.S. has received travel grants from CSL Behring and Novo Nordisk. D.V.Q. has served on advisory boards and speakers bureaus or as a consultant for Bayer, BioMarin Pharmaceutical Inc, Genentech, Novo Nordisk, Octapharma, Sanofi, Takeda, and uniQure. A.G. has served on advisory boards for BioMarin Pharmaceutical Inc, Genentech, HEMA Biologics, Pfizer, Sanofi Genzyme, and uniQure; served on speaker bureaus for BioMarin Pharmaceutical Inc and Sanofi Genzyme; and received research funding from Freeline, Genentech, Pfizer, Sangamo, Spark Therapeutics, and uniQure. G.K. has received grant funding from Genentech and Pfizer and served on advisory boards or as a consultant for Bayer, BioMarin Pharmaceutical Inc, Genentech, Novo Nordisk, Sanofi, Sobi, Spark, and Takeda. G.L. has received honoraria for participating in educational events from Alexion, LEO Pharma, Novartis, Novo Nordisk, Sanofi, Sobi, and Takeda and consulting fees from UCB. N.S.K. has received consulting fees from Centessa, Novo Nordisk, and Pfizer. C.M.M. has received research funding from CSL Behring, Grifols, and Takeda and has served as a speaker or consultant for CSL Behring, LFB, Novo Nordisk, Octapharma, Takeda, and Sobi. S.W.P. has served as a consultant for Bayer, BioMarin Pharmaceutical Inc, CSL Behring, HEMA Biologics, Inovio, LFB, Metagenomi, Novo Nordisk, Pfizer, Poseida Therapeutics, Roche/Genentech, Sanofi, Spark Therapeutic, and Takeda and serves on a scientific advisory board to Equilibra Bioscience and GeneVentiv. R.K. has received grants from Bayer, CSL Behring, and LEO Pharma; consulting fees from Bayer, BioMarin Pharmaceutical Inc, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, Sobi, and Takeda; and payment of honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Bayer, BioMarin Pharmaceutical Inc, Biotest, CSL Behring, Daiichi Sankyo, Grifols, LEO Pharma, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, Sobi, Shire/Takeda, and uniQure. H.C. has served as a consultant for BioMarin Pharmaceutical Inc, Novo Nordisk, Roche, and Sobi. F.P. has served as a consultant for BioMarin Pharmaceutical Inc, Grifols, Roche, Sanofi, Sobi, and Takeda. E.M. has received consulting fees and travel support from BioMarin Pharmaceutical Inc; served as a clinical trial investigator for BioMarin Pharmaceutical Inc; and participated in advisory boards for Apellis, Roche, and Sanofi. D.P. has received a travel grant from Pfizer, received honoraria for educational events from AstraZeneca and Novo Nordisk, and served as a clinical trial investigator for BioMarin Pharmaceutical Inc. H.Y. and K.-M.C. are employees of BioMarin Pharmaceutical Inc. M.C.O. has received research funding from Bayer, BioMarin Pharmaceutical Inc, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda; has participated in advisory boards for Bayer, BioMarin Pharmaceutical Inc, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda; and received honoraria from Bayer, BioMarin Pharmaceutical Inc, CSL Behring, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda. J.M., S.-C.C., and C.W.T. have no conflicts to declare.

OPEN PRACTICES STATEMENT

The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and supplementary materials) will be made available together with the research protocol and data dictionaries, for noncommercial, academic purposes. Additional supporting documents may be available upon request. Investigators will be able to request access to these data and supporting documents via a data sharing portal beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of relevant product. Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Research proposals will be evaluated relative to publicly available criteria available at https://www.biomarin.com/publication-data-request/ to determine whether access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

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SUPPLEMENTARY MATERIAL

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