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ORIGINAL ARTICLE

Efficacy, safety, and quality of life 4 years after valoctocogene roxaparvovec gene transfer for severe hemophilia A in the phase 3 GENEr8-1 trial

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Abstract

Background: Valoctocogene roxaparvovec, an adeno-associated virus-mediated gene therapy for severe hemophilia A, enables endogenous factor (F)VIII expression and provides bleed protection.

Objectives: Determine valoctocogene roxaparvovec durability, efficacy, and safety 4 years after treatment.

Methods: In the phase 3 GENEr8-1 trial, 134 adult male persons with severe hemophilia A without inhibitors and previously using FVIII prophylaxis received a 6×10^{13} vg/kg infusion of valoctocogene roxaparvovec. Efficacy endpoints included annualized bleed rate, annualized FVIII infusion rate, FVIII activity, and the Haemophilia-Specific Quality of Life Questionnaire for Adults. Adverse events and immunosuppressant use were assessed. Change from baseline was assessed after participants discontinued prophylaxis (scheduled for week 4).

Results: Median follow-up was 214.3 weeks; 2 participants discontinued since the previous data cutoff. Declines from baseline in mean treated annualized bleed rate (−82.6%; $P < .0001$) and annualized FVIII infusion rate (−95.5%; $P < .0001$) were maintained from previous years in the primary analysis population of 112 participants who enrolled from a noninterventional study. During year 4, 81 of 110 rollover participants experienced 0 treated bleeds. Week 208 mean and median chromogenic FVIII activity were 16.1 IU/dL and 6.7 IU/dL, respectively, in 130 modified intention-to-treat participants. Seven participants resumed prophylaxis since the previous data cutoff. Mean change from baseline to week 208 in Haemophilia-Specific Quality of Life Questionnaire for Adults Total Score ($P < .0001$) remained clinically meaningful for modified intention-to-treat participants. Alanine aminotransferase elevation was the most common adverse event during year 4 (56/131 participants); none required immunosuppressants.

Conclusion: Valoctocogene roxaparvovec provides persistent FVIII expression, hemostatic control, and health-related quality of life improvements with no new safety signals.

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

Essentials

- Valoctocogene roxaparvovec is an approved gene therapy for severe hemophilia A.
- The phase 3 GENEr8-1 trial enrolled adult men with severe hemophilia A without factor VIII inhibitors.
- Bleeds were reduced ≥4 years with acceptable safety; 24 of 134 participants resumed prophylaxis.
- Self-reported health-related quality of life remains improved 4 years after treatment.

1 | INTRODUCTION

Hemophilia A (HA) is caused by dysfunctional or deficient factor (F)VIII protein, an essential mediator of blood coagulation [1]. Severe HA (sHA), defined by FVIII activity <1 IU/dL, is associated with spontaneous bleeds in joints and muscles, whereas spontaneous bleeds are rare with mild HA (FVIII 5-40 IU/dL) [1]. Repeated joint bleeding causes chronic arthropathy and long-term disability; thus, prevention of bleeds is critical for hemophilia management [1]. Treatment guidelines recommend prophylaxis with hemostatic agents

to minimize bleeds, but current options require chronic dosing, and breakthrough bleeds may still occur [1–7]. Prophylaxis with exogenous FVIII requires adherence to a demanding treatment schedule involving chronic intravenous infusions, which can disrupt daily activities and cause anxiety [1,8]. Prophylaxis with subcutaneous injections of the FVIIIa-mimicking antibody emicizumab requires a less demanding treatment schedule and uses an easier route of administration but still requires 13 to 52 injections per year [1,5,9]. A treatment that provides durable, efficacious hemostasis without the need for repeated injections may improve health-related quality of life (HRQOL) for people with HA.

Valoctocogene roxaparvovec is a 1-time gene therapy approved in the United States and Europe for treatment of sHA [10,11]. It uses a liver-directed adeno-associated virus (AAV) vector to transfer a B-domain–deleted human FVIII coding sequence controlled by a hepatocyte-selective promoter, resulting in endogenous FVIII production and bleed protection without prophylaxis [12–19]. In the pivotal, multicenter, open-label, single-arm, phase 3 GENEr8-1 trial (NCT03370913), 134 adult male participants with sHA and no history of FVIII inhibitors who were receiving regular exogenous FVIII prophylaxis received a single 6×10^{13} vg/kg dose of valoctocogene roxaparvovec [14,15,19]. After 3 years, mean (18.4 IU/dL) and median (8.3 IU/dL) chromogenic FVIII activity were in the mild hemophilia range, which yielded significantly reduced bleed rates and exogenous FVIII use rates compared with FVIII prophylaxis. Participants also had improved HRQOL over 3 years, including improved physical functioning, reduced concern about treatment, and less impairment at work or school [19,20]. The most common adverse events (AEs) during the study were transient alanine aminotransferase (ALT) elevations and AEs related to the glucocorticoids used to manage them; most glucocorticoid regimens to manage ALT elevations were initiated during year 1 and none after year 2 [14,15,19].

Here, we present data from all follow-ups and the fourth year of GENEr8-1 that show near-stable FVIII activity from the previous year and durable protection from bleeds with no new safety signals. Enduring HRQOL improvements indicate that the hemostatic efficacy of valoctocogene roxaparvovec confers meaningful benefits to people with sHA. These encouraging results from the largest hemophilia gene therapy trial further define the safety and durability of treatment benefits following valoctocogene roxaparvovec gene therapy and provide critical information to guide treatment decisions for patients and physicians [1].

2 | METHODS

2.1 | Study design

GENEr8-1 (NCT03370913) is a multicenter, single-arm, open-label, phase 3 trial investigating the efficacy and safety of valoctocogene roxaparvovec for treatment of sHA. The detailed protocol was published previously [14,15,19]. Briefly, men ≥18 years of age with sHA (FVIII activity, ≤1 IU/dL) who were using FVIII prophylaxis for ≥12 months received a single intravenous infusion of 6×10^{13} vg/kg valoctocogene roxaparvovec. FVIII prophylaxis was scheduled to end 4 weeks after valoctocogene roxaparvovec infusion. Participants were excluded if they had a history of FVIII inhibitors, anti-AAV serotype 5 antibodies, or significant liver dysfunction.

2.2 | Populations

The intention-to-treat (ITT) population included all 134 participants who received a dose of valoctocogene roxaparvovec and was used for safety analyses. The modified ITT (mITT) population included the 132 ITT HIV-negative participants and was used to analyze FVIII activity and HRQOL. Seventeen mITT participants were dosed ≥5 years before the data cutoff. The rollover population included 112 participants who enrolled from the noninterventional 270-902 trial that collected data on FVIII use and bleeds prospectively for at least 6 months [4]. The rollover population was used to compare bleed rates and rates of FVIII use before and after valoctocogene roxaparvovec infusion. Twenty-two ITT participants enrolled in GENEr8-1 directly. A case study of the 2 HIV-positive participants was published previously [21].

2.3 | Predefined efficacy endpoints

Annualized bleed rates (ABRs) were analyzed for bleeds that required treatment with FVIII within 72 hours (treated bleeds) and for bleeds irrespective of treatment (all bleeds). Bleeds with an identifiable cause were categorized as traumatic; otherwise, they were categorized as spontaneous. Bleeds related to invasive procedures have been reported separately and are not included in ABRs reported here [22]. ABRs were based on bleeds from all participants in the rollover population and were not imputed. The reported annualized rate of FVIII infusions includes data from participants who resumed prophylaxis. Bleeds and FVIII use were self-reported by participants and were not adjudicated by imaging or physician evaluation. Baseline ABRs and FVIII utilization and infusion rates were based on the results of a previous noninterventional study of FVIII prophylaxis [4].

FVIII activity was assessed by chromogenic substrate assay (CSA) and 1-stage assay (OSA) with a lower limit of quantification (LLOQ) of 1.5 IU/dL and 1.0 IU/dL, respectively (LLOQ for CSA changed from 3.0 IU/dL to 1.5 IU/dL between year 1 and year 2). OSA values are consistently ∼1.5× higher than CSA values, likely because valoctocogene roxaparvovec-derived FVIII accelerates early FXa generation [23]. Baseline FVIII activity was imputed as 1.0 IU/dL. Median FVIII activity was calculated starting 5 weeks after infusion for 4- or 6-week windows, excluding measurements within 72 hours of FVIII infusion and with values below the LLOQ imputed as 0 IU/dL. Missing values were imputed as the smaller of the median values of the previous or next 4- or 6-week window (or via linear extrapolation if the next window was missing) for participants with intermittently missing FVIII activity values or after a participant resumed prophylaxis (defined as

usual FVIII prophylaxis administered once per week for ≥4 consecutive weeks or ≥2 doses of emicizumab injections in 31 days) and as 0 IU/dL from discontinuation through the data cutoff date for participants who discontinued the study.

HRQOL instruments included the Haemophilia-Specific Quality of Life Questionnaire for Adults (Haemo-QOL-A), the Haemophilia Activities List (HAL), and the Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ:HS); each was completed at week 4, 12, 26, 52, 76, 104, 128, 156, 180, and 208. HRQOL is reported with data censored after a participant resumed prophylaxis, and missing data were not imputed. The Haemo-QOL-A is an HRQOL questionnaire for adults with hemophilia that is validated for people who have undergone gene therapy and consists of a Total Score and 6 domain scores; each score ranges from 0 to 100, with higher values indicating better HRQOL [24–26]. The clinically important difference (CID) for Haemo-QOL-A was 5.5 for Total Score and 6.0 for domain scores [24]. The HAL Summary Score assesses everyday functional ability on a scale of 0 to 100, with higher scores indicating better HRQOL [27]. The WPAI+CIQ:HS assesses work or classroom impairment and activity impairment, with higher percentages indicating greater impairment [28,29].

2.4 | Post hoc efficacy endpoints

Sensitivity analyses that censor data after participants resumed prophylaxis are reported for ABRs and the annualized FVIII infusion rate. Additionally, ABRs for treated bleeds at baseline and at the time of return to prophylaxis (RTP), along with observed FVIII proximal to RTP, are presented for participants who resumed prophylaxis since the previous data cutoff. Sensitivity analyses that include data after participants resumed prophylaxis are presented for Haemo-QOL-A Total Score and domain scores.

2.5 | Time periods

The primary efficacy evaluation period was from end of prophylaxis to last follow-up ("postprophylaxis period"). Year-specific periods are also reported and were defined as cessation of prophylaxis to week 52 (year 1), weeks 53 to 104 (year 2), weeks 105 to 156 (year 3), and weeks 157 to 208 (year 4). Data are also reported for the 17 HIV-negative participants who received an infusion of valoctocogene roxaparvovec ≥5 years before the data cutoff.

2.6 | Statistical analysis

Since formal hypothesis testing was completed after the year 2 data cutoff per the statistical analysis plan, all hypothesis tests reported here are for descriptive purposes ($\alpha = 0.05$). The primary efficacy endpoint was change from baseline in ABR for all bleeds during the postprophylaxis period (superiority null hypothesis, change ≥0). Secondary efficacy endpoints were a change from baseline during the postprophylaxis period for treated ABR (first against noninferiority using CIs [margin, 3.5], then for superiority [null hypothesis, change ≥0]); change from baseline (1 IU/dL) in FVIII activity (CSA) at week 208 (null hypothesis, change ≤0) and FVIII infusion rate (null hypothesis, change ≥0); and change from baseline in Haemo-QOL-A Total Score and domain scores Physical Functioning, Consequences of Bleeding, and Role Functioning at week 208 (null hypothesis, change ≤0). Tertiary efficacy endpoints were change from baseline to week 208 on additional HRQOL measures.

2.7 | Ethics

The Institutional Review Board or Independent Ethics Committees of participating sites approved the protocol, and all participants provided written informed consent. Analysis was performed by authors who are employees of the sponsor. All authors had access to the data.

3 | RESULTS

3.1 | Participants

As of the data cutoff, 15 participants have completed the 5-year study (Supplementary Figure S1). Five participants have discontinued the study overall, 2 of whom discontinued since the publication describing 3 years of follow-up [19]: 1 death unrelated to treatment occurred at week 183 (see the Safety section), and 1 participant withdrew consent at week 262. Median follow-up duration was 214 weeks (range, 66-266 weeks) for all participants, including the 17 mITT participants dosed ≥5 years prior. Of the latter 17 participants, 2 discontinued: 1 during week 66 and 1 during week 262. Since the previous publication [19], an additional 7 participants resumed prophylaxis, bringing the total to 24 of 134 participants over all follow-ups.

3.2 | ABRs

3.2.1 | Treated bleeds

Over the postprophylaxis period, mean (SD) ABR for treated bleeds was 0.8 (2.0) bleeds/y (median, 0.0 bleeds/y) for the rollover population, an 82.6% reduction from baseline ($P < .0001$; Figure 1A). In year 4, mean (SD) ABR for treated bleeds was 0.9 (2.3) bleeds/y (median, 0.0 bleeds/y), an 81.3% reduction from baseline, and 73.6% of participants had no treated bleeds (Figure 1A, B). With data censored after participants resumed prophylaxis, mean (SD) ABR for treated bleeds was 0.9 (2.5) bleeds/y (median, 0.0 bleeds/y) over the entire postprophylaxis period and 0.7 (2.1) bleeds/y (median, 0.0 bleeds/y) during year 4 (Supplementary Figure S2A). Results were similar for the mITT participants dosed ≥5 years ago ($n = 16$), whose mean (SD) ABR

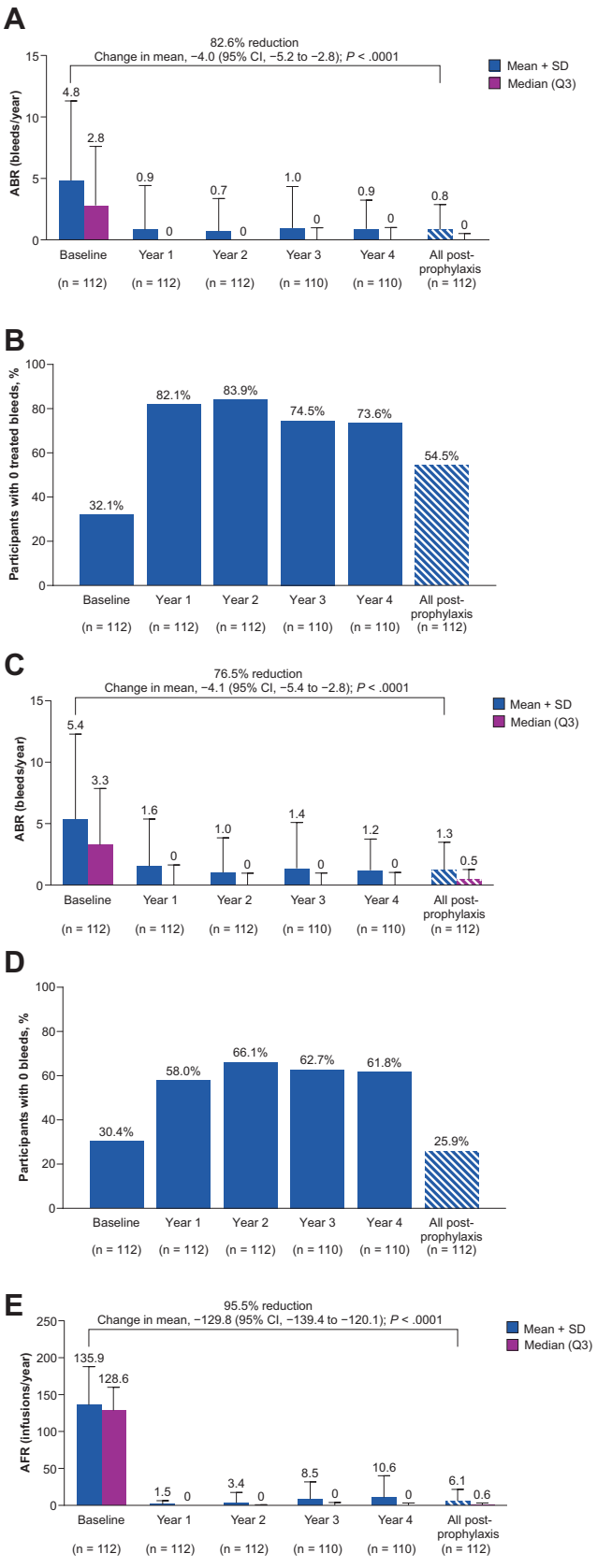

FIGURE 1 Changes from baseline to after prophylaxis in the rollover population (N = 112) in (A) annualized bleed rate (ABR) for treated bleeds, (B) proportion of participants with 0 treated bleeds, (C) ABR for all bleeds, (D) proportion of participants with 0 bleeds, and (E) annualized factor VIII infusions. Years 3 and 4 data were based on n = 110 due to participants who discontinued from the study. AFR, annualized rate of exogenous factor VIII infusions; Q, quartile.

for treated bleeds was 1.0 (3.0) bleeds/y (median, 0.0 bleeds/y) during year 5, an 89.5% reduction from baseline.

When considering only treated spontaneous bleeds, mean (SD) ABR in the rollover population was 0.4 (1.1) bleeds/y (median, 0.0 bleeds/y) across the postprophylaxis period (−79.3% from baseline) and 0.5 (1.7) bleeds/y (median, 0.0 bleeds/y) in year 4 (−74.9% from baseline; Supplementary Table S1). For traumatic bleeds that required treatment in the rollover population, mean (SD) ABRs during the postprophylaxis period and at year 4 were 0.4 (1.3) bleeds/y (median, 0.0 bleeds/y; −84.8% from baseline) and 0.4 (1.2) bleeds/y (median, 0.0 bleeds/y; −85.6% from baseline), respectively.

3.2.2 | All bleeds

During the postprophylaxis period and during year 4, mean (SD) ABR for all bleeds was 1.3 (2.2) bleeds/y (median, 0.5 bleeds/y; −76.5% from baseline) and 1.2 (2.5) bleeds/y (median, 0.0 bleeds/y; −77.5% from baseline), respectively, for the rollover population (P < .0001; Figure 1C). As with treated bleeds, most (61.8%) participants did not experience any bleeds during year 4 (Figure 1D). With data censored after participants resumed prophylaxis, the mean (SD) ABR for all bleeds was 1.4 (2.6) bleeds/y (median, 0.5 bleeds/y) over the entire postprophylaxis period and 1.0 (2.3) bleeds/y (median, 0.0 bleeds/y) during year 4 (Supplementary Figure S2B). For the mITT participants who were dosed ≥5 years ago (n = 16), the mean (SD) ABR for all bleeds was 1.4 (3.3) bleeds/y (median, 0.0 bleeds/y) during year 5, an 86.5% reduction from baseline.

3.3 | FVIII activity

Mean (SE) FVIII activity as measured by CSA increased from the imputed baseline value of 1.0 IU/dL to 16.1 (2.5) IU/dL at week 208 (median, 6.7 IU/dL; Figure 2A) in the mITT population (n = 130), a 3.5% mean decrease from year 3. Using the OSA, week 208 mean (SE) and median FVIII activity was 27.1 (4.0) IU/dL and 13.5 IU/dL, respectively (Supplementary Figure S3A). At the end of year 4, 10 (7.7%) participants in the mITT population had median FVIII activity per CSA in the nonhemophilia range (≥40 IU/dL; 2/10 participants had FVIII activity >150 IU/dL), 68 (52.3%) had FVIII activity in the mild hemophilia range (<40 and ≥5 IU/dL), 18 (13.8%) had FVIII activity in the moderate hemophilia range (<5 and ≥3 IU/dL), and 34 (26.2%) had FVIII activity below the LLOQ (the moderate to severe hemophilia range, <3 IU/dL; Figure 2B); these proportions per OSA are presented in Supplementary Figure S3B. No thromboembolic events occurred, and no anticoagulants were used for the prevention of thromboembolism.

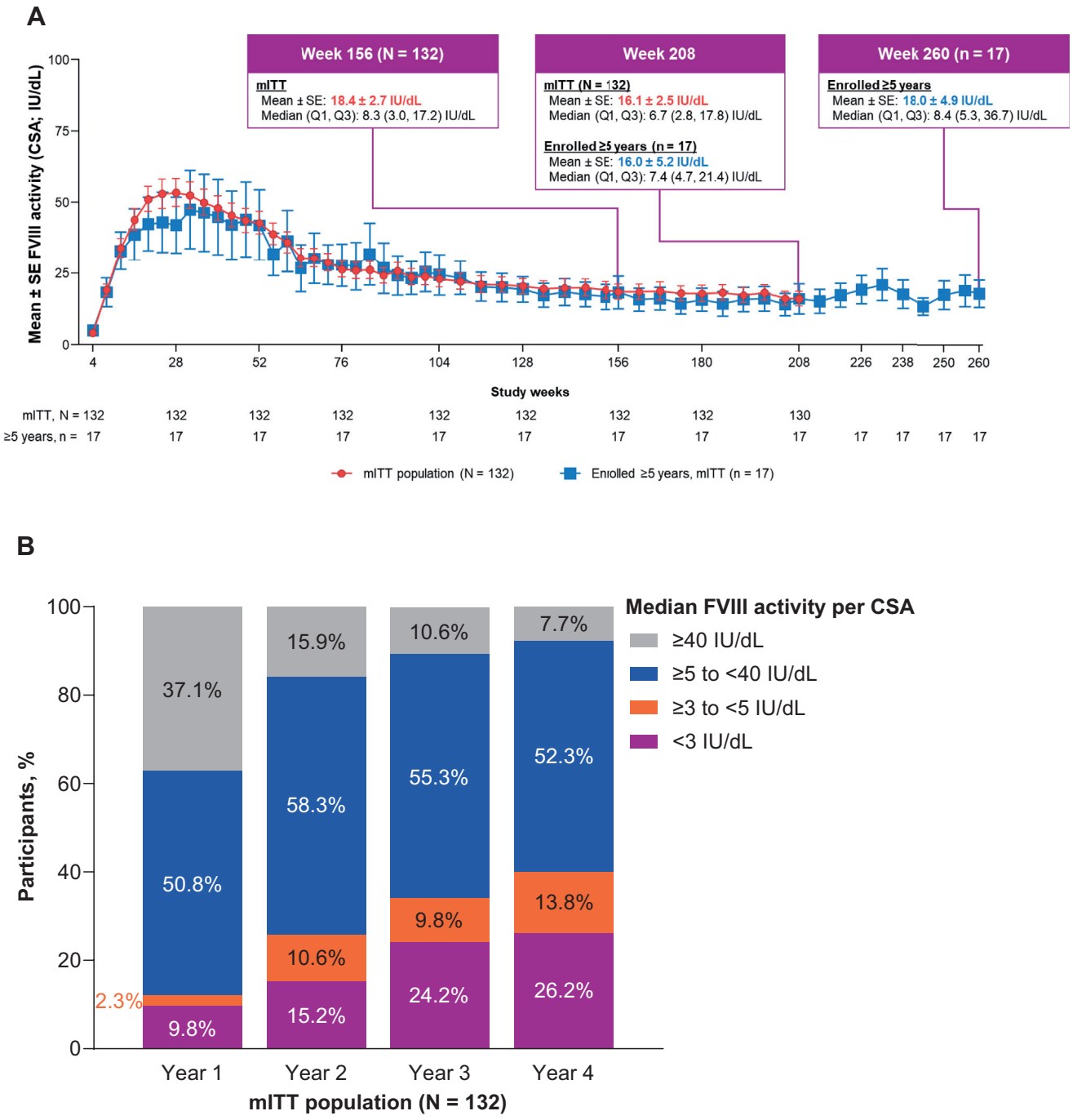

FIGURE 2 Factor (F)VIII activity per chromogenic substrate assay (CSA) over 4 years after treatment with valoctocogene roxaparvovec in the modified intention-to-treat (mITT) population (*N* = 132). (A) Mean FVIII activity over time in the mITT population and a subgroup of the mITT population dosed ≥5 years (*n* = 17). (B) Distribution of median FVIII activity at the end of each year after infusion. Median FVIII activity was calculated for 4- or 6-week windows. FVIII activity was imputed as 1 IU/dL at baseline, 0 IU/dL if the participant discontinued the study, and the smaller of the median values of the previous or next 4- or 6-week window for other missing values (or via linear extrapolation using values of the previous 2 windows if the next window was missing and capped at the value of the previous window). Q, quartile.

Year 5 values were consistent for the 17 mITT participants dosed ≥5 years ago: at week 260, mean (SE) and median FVIII activity per CSA were 18.0 (4.9) IU/dL and 8.4 IU/dL, respectively (Figure 2A). Per OSA, mean (SE) and median FVIII activity at week 260 were 25.5 (7.5) IU/dL and 15.0 IU/dL, respectively (Supplementary Figure S3A).

3.4 | Exogenous FVIII use

During the postprophylaxis period, the mean (SD) annualized FVIII infusion rate was 6.1 (15.6) infusions/y (median, 0.6 infusions/y) in the rollover population, a 95.5% reduction from when participants were using FVIII prophylaxis at baseline ($P < .0001$; Figure 1E); after

censoring data after participants resumed prophylaxis, the rate was 2.9 (5.3) infusions/y (median, 0.6 infusions/y) over the same period (Supplementary Figure S2C). In the mITT subgroup dosed ≥5 years prior (n = 16), mean (SD) annualized FVIII infusion rate was 5.7 (9.7) infusions/y (median, 2.5 infusions/y) over the entire postprophylaxis period, a 96.3% reduction from baseline.

During the postprophylaxis period, the mean (SD) annualized FVIII infusion rate for the mITT population was 0.6 (1.5) infusions/y (median, 0.0 infusions/y) when only considering use for treatment of spontaneous bleeds and 0.6 (1.6) infusions/y (median, 0.0 infusions/y) when only considering use for treatment of traumatic bleeds. During year 4, for the rollover population, the mean (SD) FVIII infusion rate was 10.6 (29.5) infusions/y (median, 0.0 infusions/y) overall, 1.6 (4.3) infusions/y (median, 0.0 infusions/y) for bleeding treatment, and 1.0 (3.9) infusions/y (median, 0.0 infusions/y) for invasive procedures.

Mean (SD) annualized FVIII utilization was 174.2 (406.5) IU/kg/y during the postprophylaxis period and 324.1 (897.4) IU/kg/y during year 4 in the rollover population (Supplementary Table S2). With data excluded after participants resumed prophylaxis, these values were 89.2 (176.4) IU/kg/y (median, 15.8 IU/kg/y) and 118.3 (397.4) IU/kg/y (median, 0.0 IU/kg/y), respectively.

3.5 | RTP

A total of 24 of 134 ITT participants have resumed prophylaxis with either exogenous FVIII or emicizumab, 7 of whom did so after the 3-year data cutoff [19]. Individual decisions to resume prophylaxis were made by participants and investigators as part of a shared decision-making process that considered personal factors such as bleeds, FVIII activity, and lifestyle choices. Overall, the probability of remaining off

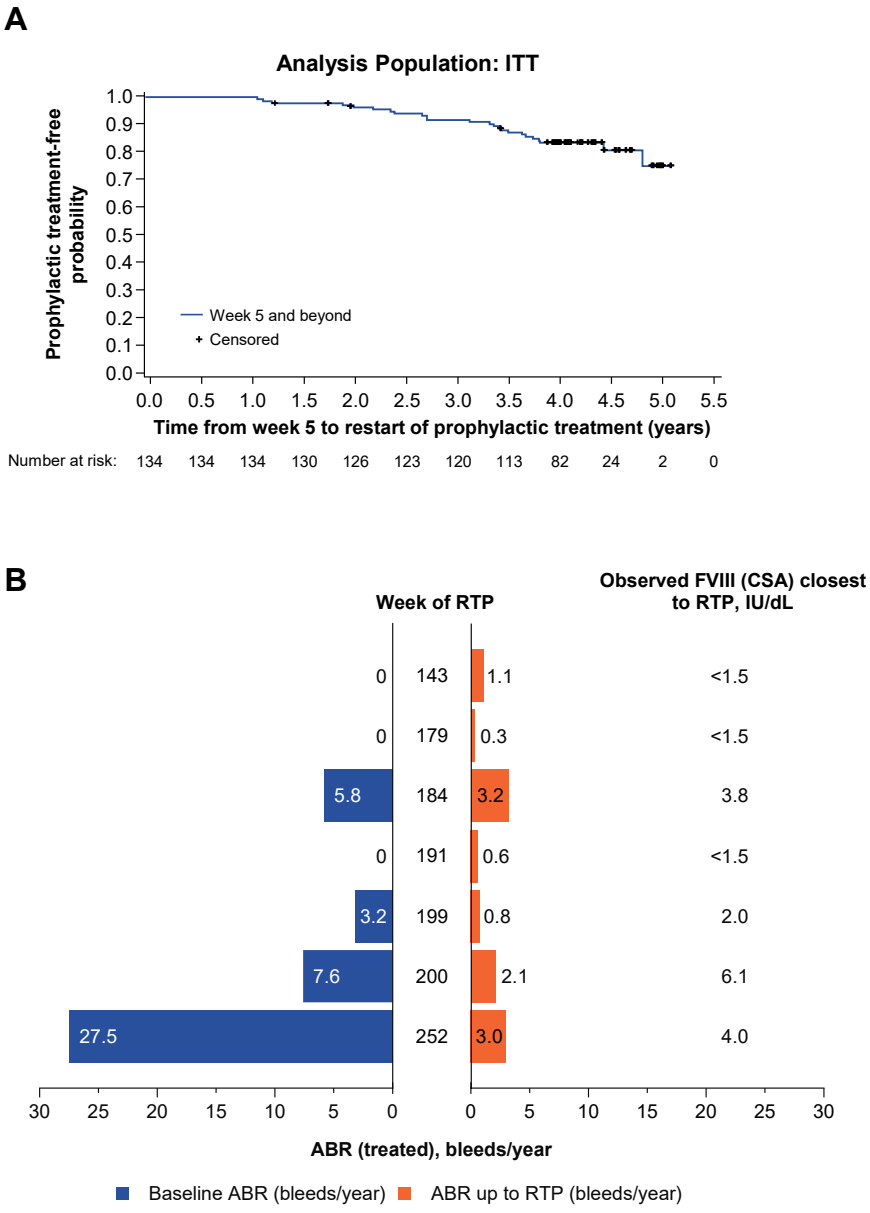

FIGURE 3 (A) Kaplan–Meier curve of prophylactic treatment-free probability. (B) Annualized bleed rate (ABR) for treated bleeds at baseline, ABR for treated bleeds up to return to prophylaxis (RTP), and factor (F) VIII activity for participants who resumed prophylaxis since the previous data cutoff. Prophylaxis was defined as a FVIII infusion categorized as "usual FVIII prophylaxis" administered at least once a week for ≥4 consecutive weeks or ≥2 emicizumab injections in 1 month. The latest valid FVIII activity measurement prior to RTP is presented. The lower limit of quantification for chromogenic substrate assay (CSA) was 1.5 IU/dL (previously 3 IU/dL). ITT, intention-to-treat.

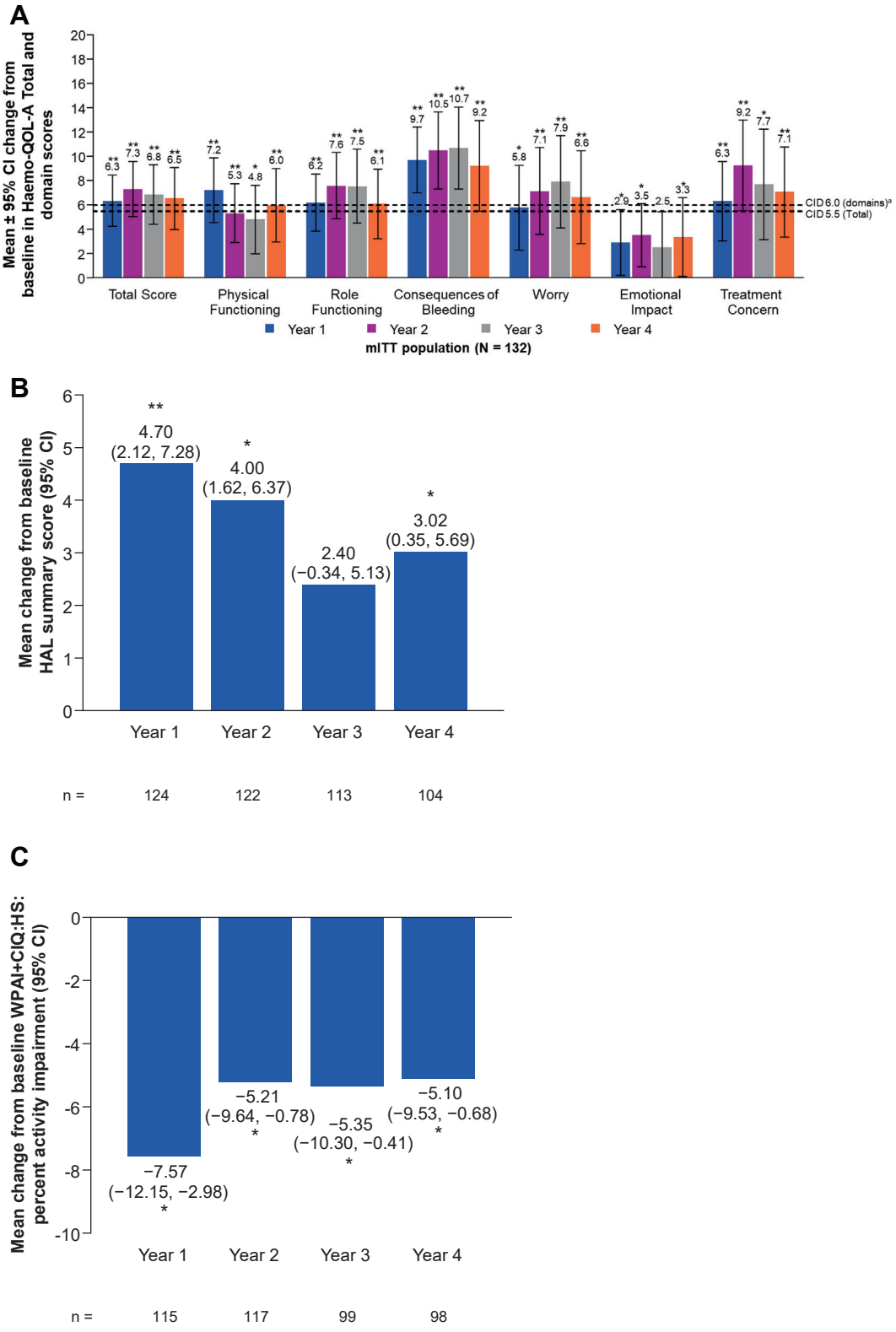

FIGURE 4 Change from baseline in health-related quality of life outcomes in the modified intent-to-treat (mITT) population (*N* = 132) excluding data after participants resumed prophylaxis. (A) Haemophilia-Specific Quality of Life Questionnaire for Adults (Haemo-QOL-A) Total Score and domain scores. (B) Haemophilia Activities List (HAL) Summary Score. (C) Work Productivity and Impairment plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ:HS). [a]A clinically important difference (CID) for the Treatment Concern domain has not yet been estimated. **P* < .05; ***P* < .001 based on a 2-tailed *t*-test against the null hypothesis of no change from baseline. Missing data were not imputed. Mean changes from baseline are based on available data at each time point, which may differ from the given *N*. Data after participants resumed prophylaxis were censored.

prophylaxis was 83.2% from week 5 (when FVIII prophylaxis was scheduled to end) through the data cutoff date (Figure 3A). Of these 7 participants, 6 had observed FVIII activity <5.0 IU/dL proximal to the time of RTP (Figure 3B). ABR for treated bleeds was higher after valoctocogene roxaparvovec infusion compared with baseline for 3 of 7 participants, all of whom had a baseline value of 0 treated bleeds/y, while the remaining 4 of 7 participants had a lower ABR from infusion up to RTP than at baseline. For all 24 participants who resumed prophylaxis up to 5 years following valoctocogene roxaparvovec infusion, the median (IQR) time from week 5 to RTP was 165.0 (115.9-187.2) weeks. Individual results are presented in Supplementary Table S3.

3.6 | HRQOL

Excluding data after participants resumed prophylaxis to eliminate the confounding effects of alternative therapy, Haemo-QOL-A Total Score increased by a mean of 6.5 points from baseline at the end of year 4, indicative of a clinically meaningful improvement compared with FVIII prophylaxis (95% CI, 4.0-9.1; n = 103; P < .0001; Figure 4A) [24]. The mean change from baseline for the domain scores of Physical Functioning (6.0), Role Functioning (6.1), Consequences of Bleeding (9.2), and Worry (6.6) similarly met or exceeded the domain CID of 6.0 at the end of year 4 [24]; while improved from baseline, change in Emotional Impact did not reach the CID (mean, 3.3). Results were generally similar when including data after a participant resumed prophylaxis (Supplementary Figure S4), but the improvement from baseline in the domain scores of Physical Functioning (mean, 4.8; 95% CI, 2.1-7.5; n = 126; P = .0005) and Role Functioning (mean, 5.9; 95% CI, 3.3-8.4; n = 125; P < .0001) did not reach the CID when including RTP data. The mean increase from baseline HAL Summary Score was significantly improved at the end of year 4 (mean, 3.0; 95% CI, 0.4-5.7; n = 104; P = .03; Figure 4B). Similarly, mean percent activity impairment as measured by WPAI+CIQ:HS was significantly reduced by 5.1% at the end of year 4 (95% CI, 9.5-0.7; n = 98; P = 0.02; Figure 4C).

3.7 | Safety

The safety profile of valoctocogene roxaparvovec remains unchanged from previous reports after 4 years (Table 1). During year

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

AE	Year 1 (N = 134)	Year 2 (N = 134)	Year 3 (N = 131)	Year 4 (N = 131)	All follow-up (N = 134)
Any AE	134 (100.0)	113 (84.3)	105 (80.2)	106 (80.9)	134 (100.0)
AEs occurring in ≥30%					
ALT increased	114 (85.1)	40 (29.9)	31 (23.7)	46 (35.1)	121 (90.3)
Arthralgia	37 (27.6)	26 (19.4)	16 (12.2)	13 (9.9)	62 (46.3)
Headache	46 (34.3)	19 (14.2)	13 (9.9)	5 (3.8)	60 (44.8)
Nausea	50 (37.3)	4 (3.0)	2 (1.5)	4 (3.1)	53 (39.6)
AST increased	44 (32.8)	12 (9.0)	5 (3.8)	6 (4.6)	51 (38.1)
COVID-19	0	5 (3.7)	23 (17.6)	14 (10.7)	43 (32.1)
Upper respiratory tract infection	25 (18.7)	12 (9.0)	5 (3.8)	13 (9.9)	43 (32.1)
Fatigue	36 (26.9)	4 (3.0)	4 (3.1)	1 (0.8)	42 (31.3)
Any SAE[a]	21 (15.7)	6 (4.5)	9 (6.9)	13 (9.9)	37 (27.6)
Any AE grade ≥3	31 (23.1)	13 (9.7)	12 (9.2)	17 (13.0)	54 (40.3)
Any fatal AE	0	1 (0.7)	0	1 (0.8)	2 (1.5)
Valoctocogene roxaparvovec–related[a]					
AEs	123 (91.8)	28 (20.9)	15 (11.5)	10 (7.6)[b]	123 (91.8)
SAEs	5 (3.7)	0	0	0	5 (3.7)
Glucocorticoid-related					
AEs	80 (59.7)	10 (7.5)	1 (0.8)	1 (0.8)	81 (60.4)
SAEs	3 (2.2)	0	0	0	3 (2.2)
Nonsteroidal immunosuppressant-related					
AEs	12 (9.0)	2 (1.5)	2 (1.5)	2 (1.5)	18 (13.4)
SAEs	1 (0.7)	0	0	1 (0.8)	2 (1.5)

(Continues)

TABLE 1 (Continued)

AE	Year 1 (*N* = 134)	Year 2 (*N* = 134)	Year 3 (*N* = 131)	Year 4 (*N* = 131)	All follow-up (*N* = 134)
AEs of special interest					
ALT elevation[c]	114 (85.1)	40 (29.9)	31 (23.7)	56 (42.7)	121 (90.3)
ALT elevation grade ≥3	11 (8.2)	1 (0.7)	0	1 (0.8)[d]	12 (9.0)
AEs related to liver function	116 (86.6)	40 (29.9)	32 (24.4)	58 (44.3)	121 (90.3)
Potential Hy's law case[e]	0	0	0	0	0
Infusion-related reactions[f]	12 (9.0)	0	0	0	12 (9.0)
Infusion-associated reactions[g]	50 (37.3)	0	0	0	50 (37.3)
Systemic hypersensitivity	7 (5.2)	0	0	0	7 (5.2)
Anaphylactic or anaphylactoid reactions	3 (2.2)	0	0	0	3 (2.2)
Thromboembolic events	0	0	0	0	0
Anti-FVIII neutralizing antibodies	0	0	0	0	0
Malignancy (except NMSC)	0	0	1 (0.8)	0	1 (0.7)

Data are presented as *n* (%). AEs were coded using Medical Dictionary for Regulatory Activities 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 more than 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; NMSC, nonmelanoma skin cancer; SAE, serious adverse event.

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

[b]Valoctocogene roxaparvovec–related AEs in year 4 were as follows: ALT elevation (4), hepatic steatosis (2), hepatomegaly, splenomegaly (2), AST elevation, decreased ristocetin cofactor, and increased liver echogenicity.

[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× upper limit of normal (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]This event was downgraded after the data cutoff date.

[e]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 preexisting liver disease).

[f]Infusion-related reactions were defined as AEs occurring during infusion or within 6 hours after infusion, irrespective of a causal association with valoctocogene roxaparvovec.

[g]Infusion-associated reactions were defined as AEs occurring within 48 hours after infusion, irrespective of a causal association with valoctocogene roxaparvovec.

4, 106 (80.9%) and 13 (9.9%) participants experienced an AE and serious AE, respectively. Treatment-related AEs occurred in 10 (7.6%) participants, and there were no treatment-related serious AEs. The participant's death during week 183 was deemed unrelated to treatment by the investigators; it was caused by head trauma following a fall with loss of consciousness. There were no thromboembolic events, malignancies, or participants who developed inhibitors.

During year 4, ALT elevations occurred in 56 (42.7%) participants. Most ALT elevations were below the upper limit of normal; 2 of 134 (1.5%) had an ALT elevation >5× baseline, and no ALT elevations were >10× baseline. No participants used glucocorticoids for ALT elevations (Table 2). No unexpected changes in liver structure or liver malignancies were discovered based on qualitative liver ultrasound performed at screening and after infusion.

4 | DISCUSSION

Valoctocogene roxaparvovec enables endogenous FVIII production to prevent bleed episodes in people with sHA. Long-term data from GENEr8-1—the largest gene therapy trial for hemophilia—provide valuable insight into the durability of AAV-vector gene therapies and help inform treatment decisions for patients and physicians [1,30]. Four years after infusion, FVIII activity was near stable compared with 3 years [19], ABRs for treated and all bleeds remained significantly reduced, and HRQOL remained improved compared with baseline when participants were on FVIII prophylaxis. Notably, these results were achieved without the need for immunosuppression for ALT elevations in year 4. The safety profile remains unchanged. These data show that a single valoctocogene roxaparvovec infusion provides durable improvements in hemostatic efficacy compared with FVIII prophylaxis for most participants.

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

Variable	Year 1 (*N* = 134)	Year 2 (*N* = 134)	Year 3 (*N* = 131)	Year 4 (*N* = 131)	Overall (*N* = 134)
With postbaseline ALT >ULN, *n* (%)	105 (78.4)	39 (29.1)	20 (15.3)	21 (16.0)	110 (82.1)
With postbaseline ALT >1.5× baseline,[a] *n* (%)	120 (89.6)	78 (58.2)	46 (35.1)	55 (42.0)	126 (94.0)
Used glucocorticoids for any purpose, *n* (%)	108 (80.6)	47 (35.1)	4 (3.1)	3 (2.3)	109 (81.3)
Total duration (wk), median (min, max)	32.0 (0.1, 50.1)	6.7 (0.1, 49.9)	1.1 (0.7, 33.0)	1.4 (1.0, 12.1)	32.9 (0.1, 120.1)
Total dose (mg), median (min, max)	6272.5 (40, 25,110)	735.0 (1, 9040)	225.0 (200, 1515)	200.0 (200, 1475)	6360.0 (40, 31,760)
Used glucocorticoids for ALT elevation, *n* (%)	105 (78.4)	45 (33.6)	1 (0.8)[b]	0 (0.0)	106 (79.1)
Total duration (wk), median (min, max)	32.9 (3.4, 50.1)	7.0 (0.1, 49.9)	33.0 (33.0, 33.0)	NA	32.9 (3.1, 120.1)
Total dose (mg), median (min, max)	6360.0 (960, 25,110)	735.0 (1, 9040)	1515.0 (1515, 1515)	NA	6560.0 (960, 31,760)

ALT, alanine aminotransferase; max, maximum; min, minimum; NA, not applicable; ULN, upper limit of normal.
[a]Not all events qualified as an adverse event.
[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.

Mean FVIII activity at the end of year 4 (16.1 IU/dL) declined only slightly from year 3 (18.4 IU/dL) [19]. The year-over-year rate of decline in FVIII activity has diminished each year since peaking in year 1, suggesting that FVIII activity may be plateauing. FVIII activity in the mITT population at week 208 was slightly higher than predicted (13.6 IU/dL) by a quantitative pharmacokinetic model that used year 2 data to extrapolate FVIII activity [14]. Considering that the mean week 260 FVIII activity in the ≥5-year mITT subgroup was also higher than predicted (18.0 IU/dL vs 11.8 IU/dL), the model may be a conservative estimate for the trajectory of FVIII activity [14]. After 4 years in GENEr8-1, most participants had FVIII in the mild hemophilia range (5 to <40 IU/dL), consistent with previous reports [1].

Endogenously produced FVIII continued to provide improved hemostasis compared with exogenous FVIII prophylaxis. As in year 3, nearly 75% of participants did not experience a bleed that required treatment in year 4, and more than 60% of participants did not experience any bleeds at all. Furthermore, the mean ABR for treated bleeds has not exceeded 1 bleed/y in any year after infusion. ABRs were similar when post-RTP data were censored, suggesting that inclusion of data after RTP did not artificially deflate ABRs for the rollover population. Overall, hemostatic efficacy was maintained over 4 years. Previously published reports from GENEr8-1 and the phase 1/2 trial of valoctocogene roxaparvovec suggest that consistent expression of endogenously produced FVIII, even at low levels, may confer better bleed protection than can be achieved with FVIII replacement [16–19,31].

Accordingly, <20% (24/134) of participants have resumed prophylaxis. Since the previous publication, 7 participants resumed prophylaxis; similar to the 3-year data cutoff, no clear predictors of RTP were identified. Most of the 7 participants had lower treated bleed rates after infusion to RTP compared with baseline; all but 1 of the 7 participants had FVIII activity <5 IU/dL, the threshold at which consideration of prophylaxis is recommended [10]. Investigators were encouraged to discuss RTP as clinically indicated; as with previous years, the decision to RTP was individual and multifactorial.

Prophylaxis with exogenous FVIII or nonfactor hemostatic agents creates treatment burdens that diminish HRQOL and may impede adherence [32]. After each year, participants consistently reported clinically meaningful HRQOL improvements using the Haemo-QOL-A Total Score. The clinically meaningful increases in Physical Functioning and Role Functioning domain scores at the end of year 4 suggest increased freedom to perform daily activities, and the meaningful improvement in the Worry domain score at the end of year 4 indicates that hemostatic efficacy without the need for repeated injections eases psychological burden. In contrast, the increase in Emotional Impact domain score did not exceed the CID. This domain was previously hypothesized to depend on positive and negative individual emotional responses to the therapy [20,33]. Additionally, the domain considers external factors (eg, societal norms and opportunities) that gene therapy may not address. On average, participants also reported significantly increased HAL Summary Scores and significantly reduced WPAI+CIQ:HS percent impairment, consistent with previous years and indicative of improved functional ability and productivity, respectively. The yearslong improvements in HRQOL measured using Haemo-QOL-A, HAL, and WPAI+CIQ:HS were maintained despite expected declines with aging; additional follow-up is required to provide insight into the durability of HRQOL improvements [34].

No new safety signals emerged in year 4. Across the trial, no thromboembolic events occurred and no participants developed FVIII inhibitors. No malignancies occurred in year 4 or have been attributed to treatment to date, consistent with the lack of evidence for valoctocogene roxaparvovec-associated insertional mutagenesis [14–19,31]. The most common AEs in year 4 continued to be low-grade, asymptomatic ALT elevations. Glucocorticoid use to manage ALT elevation was concentrated in the first year after gene therapy. No glucocorticoid regimens for ALT have been initiated since year 2, and immunosuppressive use for ALT elevation ceased during year 2 except for a single participant who discontinued immunosuppressants during year 3. ALT elevations that occur later than ~6 months after infusion are likely

unrelated to adaptive immune responses [35], and the mildness of the ALT elevations observed here suggests that the elevations are caused by unidentified mechanisms or reflect natural variation. Finally, liver ultrasound data indicate that long-term liver health is likely not impacted.

Limitations of this study have been discussed previously, including lack of adjudication for bleeds by investigators or imaging and lack of longitudinal joint health data [14,15,19]. All participants were using FVIII prophylaxis at baseline, whereas some participants who resumed prophylaxis began using emicizumab. Therefore, the effect of valoctocogene roxaparvovec on change from baseline in FVIII utilization is confounded when data are not censored after participants' RTP. Participants with a history of FVIII inhibitors, anti-AAV serotype 5 antibodies, and HIV were excluded, limiting generalization to the sHA community. Additional research is necessary to understand valoctocogene roxaparvovec efficacy and safety in these populations.

5 | CONCLUSION

After 4 years of follow-up, consistent with earlier time points, valoctocogene roxaparvovec continues to provide long-term FVIII expression with a mean FVIII level of 16.1 IU/dL (median, 6.7 IU/dL) per CSA, persistent bleed control, and improvements in HRQOL for most participants with sHA. No new safety signals emerged.

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AUTHOR CONTRIBUTIONS

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

DATA AVAILABILITY

The deidentified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendices) 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 the 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 www.BioMarin.com/patients/publication-data-request/ to determine if access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

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. Mahlangu has received research funding from BioMarin Pharmaceutical Inc, Catalyst, Roche, Novo Nordisk, Pfizer, Sandoz, Sanofi, and Spark Therapeutics. P.R. has received grant/travel support from CSL Behring, Sobi, and Takeda and advisory honoraria from Idogen, Pfizer, Sigilon, 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 speakers bureaus for BioMarin Pharmaceutical Inc and Sanofi Genzyme; and received research funding from Freeline, Genentech, Pfizer, Sangamo, Spark Therapeutics, and uniQure. M.F.L.F. has participated in advisory boards and received speaking fees from Amgen, Bayer, CSL Behring, LFB, Novo Nordisk, Pfizer, Shire/Takeda, and Sobi. 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 Pharma, Novo Nordisk, Octapharma, Takeda, and Sobi. S.W.P. has served as a consultant for ApcinteX, Bayer, BioMarin Pharmaceutical Inc, CSL Behring, Equilibra Bioscience, GeneVentiv, HEMA Biologics, LFB, Novo Nordisk, Pfizer, Regeneron, Roche, Sanofi, Siemens, Spark, Takeda, and uniQure. 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,

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SUPPLEMENTARY MATERIAL

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