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ORIGINAL ARTICLE

Health-related quality of life following valoctocogene roxaparvovec gene therapy for severe hemophilia A in the phase 3 trial GENEr8-1

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Abstract

Background: Severe hemophilia A (HA) negatively impacts health-related quality of life (HRQOL).

Objectives: We aimed to analyze HRQOL in adult men with severe HA without inhibitors after valoctocogene roxaparvovec gene transfer in the phase 3 trial GENEr8-1.

Methods: Participant-reported outcomes were the hemophilia-specific quality of life questionnaire for adults (Haemo-QOL-A), the EQ-5D-5L instrument, the Hemophilia Activities List (HAL), and the Work Productivity and Activity Impairment Questionnaire: Hemophilia Specific (WPAI+CIQ:HS). Participants completed the questionnaires at baseline and through 104 weeks postinfusion with 6×10^{13} vg/kg of valoctocogene roxaparvovec. Scores were analyzed per participant characteristics and outcomes.

Results: For 132 HIV-negative participants, mean change from baseline in Haemo-QOL-A Total Score met the anchor-based clinically important difference (CID: 5.5) by week 12; the mean (SD) increase was 7.0 (12.6) at week 104. At week 104, improvement in Consequences of Bleeding, Treatment Concern, Worry, and Role Functioning domain scores exceeded the CID (6). EQ-5D-5L Utility Index scores improved above the CID at week 52, but not at week 104. EQ-5D-5L visual analog scale and HAL scores increased from baseline to week 104. Participants reported less activity and work impairment at week 104 than baseline. Participants with problem joints had lower mean baseline Haemo-QOL-A Total and domain scores than those without them, but improved over 104 weeks, except for 11 participants with ≥3 problem joints. Participants with 0 bleeds during the baseline prophylaxis period reported Haemo-QOL-A score improvements above the CID, including in the Consequences of Bleeding domain.

Conclusion: Valoctocogene roxaparvovec provided clinically meaningful HRQOL improvement for men with severe HA.

KEYWORDS
gene therapy, health-related quality of life, hemophilia A, patient-reported outcome, valoctocogene roxaparvovec

1 | INTRODUCTION

Severe hemophilia A (factor VIII [FVIII] ≤ 1 International Units/dL) is associated with recurrent bleeding, predominantly into joints (hemarthroses) [1–3], and negatively impacts health-related quality of life (HRQOL) [2,4–9]. Regular prophylaxis with exogenous FVIII or non-FVIII agents such as emicizumab is the standard of care for severe hemophilia A [1], but individuals may still experience joint bleeding resulting in debilitating arthropathy [10,11]. More than 50% of adults with severe hemophilia A experience chronic pain [12]. Joint damage in people with hemophilia A is associated with pain, anxiety/

Essentials

- Severe hemophilia A (HA) still negatively impacts health-related quality of life (HRQOL).
- We analyzed the impact of valoctocogene roxaparvovec gene therapy on HRQOL in men with severe HA.
- HRQOL improvements were achieved at 12 weeks and maintained through 2 years post gene transfer.
- Even those with a baseline annualized bleeding rate of 0 reported meaningful HRQOL improvement.

depression, and motion limitations [13,14], which further reduce HRQOL. Mental health problems such as depression and anxiety are common among people with hemophilia, and are likely underdiagnosed and inadequately treated [15–17]. The psychological burden of hemophilia is high, and outcomes beyond annualized bleeding rate (ABR) should be considered when assessing the impact of hemophilia A on HRQOL [18–20].

Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) is an adenovirus-associated vector that transfers a B-domain deleted human FVIII coding sequence to hepatocytes using a recombinant AAV5 vector, enabling endogenous FVIII activity in people with severe hemophilia A [21–24]. In the ongoing phase 3 trial GENEr8-1 (NCT03370913), 134 adult men with severe hemophilia A received one 6×10^{13} vg/kg dose of valoctocogene roxaparvovec gene therapy. Previously reported 2-year follow-up results demonstrated a significant increase in endogenous FVIII activity and reduced bleeding and FVIII utilization [24,25].

Here, we analyzed the impact of valoctocogene roxaparvovec gene therapy on the participant-reported outcome (PRO) measures of HRQOL, utility, and ability to perform activities of daily living (ADL) for participants over 104 weeks following valoctocogene roxaparvovec gene therapy. We also assessed whether clinical efficacy outcomes and pre-existing joint damage affected HRQOL outcomes.

2 | METHODS

2.1 | Study design

Details of the ongoing global, open-label, single-arm phase 3 GENEr8-1 trial have been published [24,25]. Briefly, 134 men aged ≥18 years with severe hemophilia A who tested negative for FVIII inhibitors received one 6×10^{13} vg/kg valoctocogene roxaparvovec infusion. For all participants, the investigator identified problem joints at baseline; problem joints were defined as joints associated with any of the following symptoms: chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding [26–28]. Participants discontinued exogenous prophylactic FVIII replacement therapy 4 weeks postinfusion. The primary efficacy endpoint was change from baseline in ABR for treated bleeds from the end of prophylaxis up to the 2-year data cutoff date. Hierarchically tested secondary efficacy endpoints were change from baseline in FVIII activity per chromogenic substrate assay at week 104, in annualized FVIII utilization rates, in ABR for all bleeds, in hemophilia-specific quality-of-life questionnaire for adults (Haemo-QOL-A) Total Score at week 104, and in the domain scores for Physical Functioning, Consequences of Bleeding, and Role Functioning at week 104. Tertiary endpoints were change from baseline at week 104 in other domain scores of Haemo-QOL-A (Worry, Emotional Impact, Treatment Concern), the EQ-5D-5L visual analog scale (VAS), and Utility Index Score in the Hemophilia Activities List (HAL), and the Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ: HS) instrument. Participants completed PRO questionnaires at baseline and weeks 4, 12, 26, 52, 76, and 104. As previously reported, 134 participants received valoctocogene roxaparvovec (the intent-to-treat [ITT] population). In total, 132 participants in the ITT population completed the week 104 study visit. Two participants discontinued from the study before week 104: 1 was lost to follow-up at week 66 and 1 died by suicide at week 96 [25]. Missing data were not imputed. Data collection is ongoing.

2.2 | Statistical methods

Prespecified tertiary PRO endpoints were evaluated up to week 104 in the 132 participants in the modified ITT population (mITT), which included all HIV-negative participants who received valoctocogene roxaparvovec. As previously described, primary and secondary efficacy endpoints at week 104 were tested using a hierarchical testing procedure at the alpha level determined by the fallback procedure to control the type I error rate [25]. For the secondary efficacy endpoints of change from baseline to week 104 in Haemo-QOL-A Total Score and Physical Functioning, Consequences of Bleeding, and Role Functioning domains, significance was assessed using a 2-sided paired *t*-test against the null hypothesis that change = 0. Missing data were not imputed. For Haemo-QOL-A results at other time points, exploratory *P* values not adjusted for multiplicity are presented.

Prespecified tertiary PRO endpoints were change from baseline to week 104 in the Haemo-QOL-A domains Worry, Emotional Impact, and Treatment Concern; EQ-5D-5L VAS and Utility Score; HAL Summary and domain scores; and WPAI+CIQ:HS scores in the mITT. For these PROs, missing data were not imputed and results were summarized descriptively.

Post hoc analyses of change in Haemo-QOL-A Total and domain scores were also performed for participant subgroups in the ITT population (n = 134; all treated participants) categorized by the number of problem joints (investigator-identified joints associated with chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding) and ABR before and after gene therapy. Results were summarized descriptively, and no formal hypothesis testing was performed.

3 | RESULTS

The protocol-specified PRO analyses included the 132 HIV-negative participants in the mITT, of whom 130 completed the week 104 study visit [25]. Baseline demographics and clinical characteristics were as previously reported [24]. Briefly, the mean ± SD age was 31.4 years (10.1) at enrollment. At baseline, 72% (95/132), 12.9% (17/132), 6.8% (9/132), 6.1% (8/132), and 2.3% (3/132) of participants had 0, 1, 2, 3, and >3 problem joints, respectively [24]. While on prophylaxis, ABR was 5.4 ± 10.0, and the annualized FVIII infusion rate was 138.1 ± 57.2 [24].

The post hoc subgroup analyses were performed in the ITT population, which included all 134 participants who received an infusion. Baseline demographics and clinical characteristics were similar to the mITT [24].

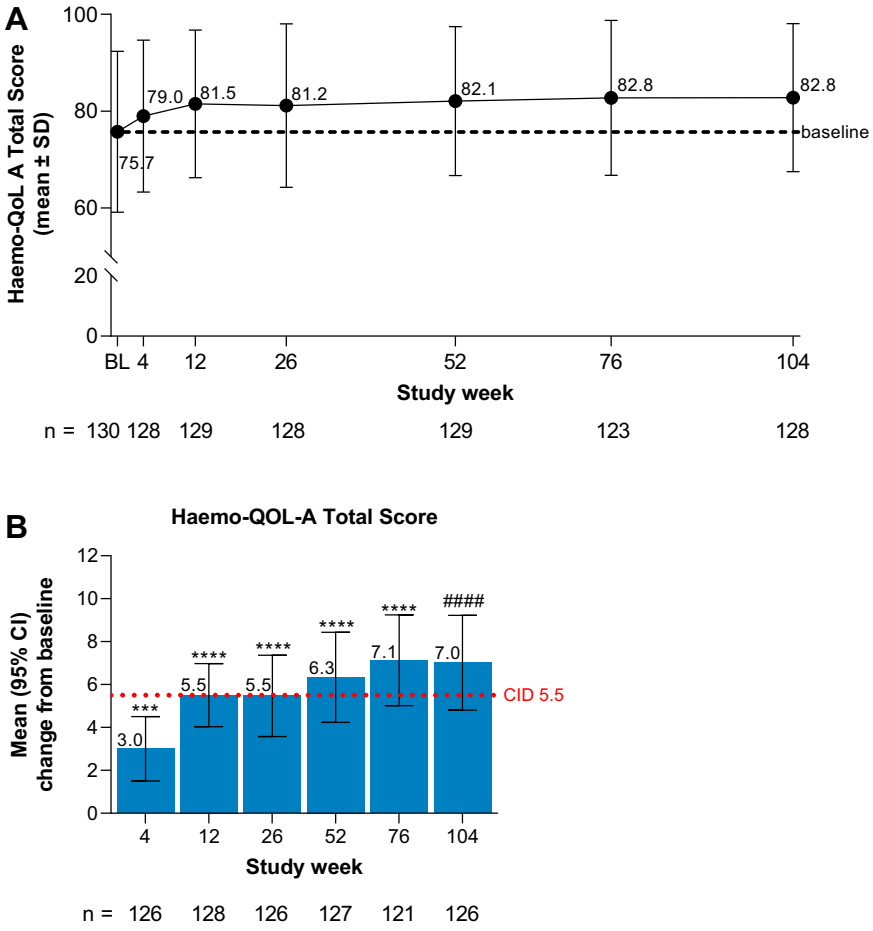

FIGURE 1 Haemo-QOL-A Total Score (A) over 104 weeks and (B) change from baseline over 104 weeks. ***$P < .001$ and ****$P < .0001$ were based on 2-sided *t*-test of change from baseline vs 0 without controlling for multiplicity. ####$P < .0001$ based on 2-sided *t*-test of change from baseline vs 0 performed as part of a hierarchical testing sequence controlling overall type 1 error. CID was 5.5 for Total Score as indicated with red dotted line. BL, baseline; CI, confidence interval; CID, clinically important difference; Haemo-QOL-A, haemophilia-specific quality of life questionnaire for adults.

3.1 | Haemo-QOL-A

The Haemo-QOL-A is a validated hemophilia-specific measure of HRQOL for adults that provides a Total Score with 6 individual domain scores (Physical Functioning, Role Functioning, Worry, Consequences of Bleeding, Emotional Impact, and Treatment Concern) presented as transformed scores from 0 to 100, with higher values indicating greater HRQOL [29]. Forty-one items are rated on a 6-point Likert scale; the estimated completion time is ~30 minutes [30]. The Haemo-QOL-A has been validated in people who have received gene therapy [31]. Distribution- and anchor-based approaches (eg, mean differences between anchor groups, with the key anchor being changes in EQ-5D-5L > ±3) in a population of participants with hemophilia A who received valoctocogene roxaparvovec in the phase 1/2 or phase 3 trial were used to establish the clinically important difference (CID) at 5.5 points in change from baseline for Total Score and 6 points in change from baseline for domain scores [31].

At baseline, the mean (SD) Haemo-QOL-A Total Score for the mITT was 75.7 (16.7); at weeks 52 and 104, the mean (SD) changes in Total Score were 6.34 (12.0) and 7.0 (12.6), respectively, both being above the CID threshold of 5.5 ($P < .0001$; Figure 1A). Improvement in Total Score was noted as early as 4 weeks (mean [SD] change: 3.0 [8.5]), reached the CID by week 12 (5.5 [8.4]), and was maintained up to week 104 (Figure 1B). At week 104, the biggest improvement in individual domain scores from baseline was observed in Consequences of Bleeding (mean [SD] change: 10.3 [17.7]; $P < .0001$), followed by Treatment Concern (mean [SD] change: 8.8 [20.5]), Role Functioning (mean [SD] change: 7.4 [15.2]; $P < .0001$), and Worry (mean [SD] change: 6.9 [19.8]; Table 1). Of note, even though participants reported high scores for Treatment Concern at baseline, improvement above the CID was noted at both weeks 52 and 104.

3.2 | EQ-5D-5L

The EQ-5D-5L tool measures general health status in adults and adolescents, and typically takes a few minutes to complete [32,33]. Participants rated overall HRQOL on the EQ-5D-5L VAS (range: 0–100) from best to worst imaginable health. At baseline, EQ-5D-5L VAS mean (SD) for the mITT was 80.1 (15.3), which increased by 4.5 (13.3) at week 52 and by 3.17 (11.9) at week 104 (Figure 2A, B).

EQ-5D-5L Utility Index Score (range: 0–1) was calculated from population norms using country-based crosswalk value sets and a response mapping approach, with higher scores indicating higher HRQOL [32]. The mean (SD) EQ-5D-5L Utility Index Score at baseline was 0.78 (0.17); mean (SD) change from baseline at week 52 (0.04

TABLE 1 Change from baseline in Haemo-QOL-A domain scores in the mITT.

	Baseline	Week 26	CFB to week 26	Week 52	CFB to week 52	Week 104	CFB to week 104
Total score	75.7 (16.7)	81.2 (16.9)	**5.5 (10.7)******	82.1 (15.4)	**6.3 (12.0)******	82.8 (15.3)	**7.0 (12.6)**####
n	130	128	126	129	127	128	126
Physical functioning	70.3 (20.8)	76.6 (19.9)	**6.6 (13.4)******	77.5 (20.7)	**7.2 (15.3)******	75.1 (20.3)	4.9 (13.8)####
n	132	130	130	130	130	129	129
Role functioning	78.2 (17.8)	84.7 (17.2)	**6.6 (13.4)******	84.4 (15.7)	**6.2 (13.5)******	85.7 (15.6)	**7.4 (15.2)**####
n	131	128	127	130	129	129	128
Consequences of bleeding	73.6 (21.7)	82.0 (19.3)	**8.7 (15.0)******	83.1 (19.1)	**9.7 (15.5)******	83.6 (18.6)	**10.3 (17.7)**####
n	132	130	130	130	130	129	129
Worry	78.4 (22.7)	82.9 (21.6)	4.1 (15.6)**	84.2 (20.2)	**5.8 (20.1)****	85.7 (20.7)	**6.9 (19.8)*****
n	131	128	127	130	129	129	128
Emotional impact	78.1 (16.5)	80.1 (19.6)	1.7 (14.2)	81.1 (16.7)	2.9 (15.5)*	81.5 (18.6)	3.2 (14.7)*
n	131	128	127	130	129	129	128
Treatment concern	76.2 (25.4)	81.0 (25.9)	5.2 (17.0)***	82.7 (24.5)	**6.3 (18.5)*****	84.9 (22.8)	**8.8 (20.5)******
n	130	128	126	129	127	128	126

Data presented as mean (SD). Boldface indicates a mean CFB of ≥5.5 or 6, the CID for Total Score and domain scores, respectively. CFB data are based on participants with data at both time points.

CFB, change from baseline; CID, clinically important difference; Haemo-QOL-A, haemophilia-specific quality of life questionnaire for adults; mITT, modified intent-to-treat.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

**** $P < .0001$ were based on 2-sided *t*-test of CFB vs 0 without controlling for multiplicity.

$P < .0001$ based on 2-sided *t*-test of CFB vs 0 performed as part of a hierarchical testing sequence controlling overall type 1 error.

[0.16]) exceeded the CID of 0.03 [34]; however, change from baseline at week 104 was 0.02 (0.15; Figure 2C, D).

Participants also rated perceived problems in 5 dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) of the EQ-5D-5L on a 5-point scale ranging from "no problems" to "extreme problems/unable to do." For example, in the Self-Care dimension, most participants reported no problems at baseline (83.2%), week 52 (80.8%), or week 104 (81.3%; Figure 2E, Supplementary Table S1). The proportion of participants reporting no problems with Usual Activities and Pain/Discomfort increased from 59.5% and 34.4% at baseline, respectively, to 66.4% and 43.8% at week 104, respectively.

3.3 | HAL

The HAL is a validated measure of self-perceived functional ability that provides a summary score (range: 0–100) and domain scores (Lying/Sitting/Kneeling/Standing, Functions of the Legs, Functions of the Arms, Use of Transportation, Self-Care, Household Tasks, and Sports and Leisure Activities; rated on a 6-point Likert-type scale from 1 to 6), with higher scores indicating greater functional ability [35]. The estimated completion time is <10 minutes [35]. At baseline, mean (SD) HAL Summary Score for the mITT was 78.7 (17.9); Summary Score increased by mean (SD) 4.7 (14.5) at week 52 and 3.9 (13.1) at week 104 (Figure 3). For the individual domains, increase from baseline was observed at weeks 52 and 104 for Lying/Sitting/Kneeling/Standing, Functions of the Legs, Functions of the Arms, Self-Care, Household Tasks, Leisure Activities and Sports, and Use of Transportation (Table 2).

3.4 | WPAI+CIQ:HS

The WPAI+CIQ:HS measured the impact of disease on work and classroom productivity [36,37]. The estimated completion time is 15 minutes, and scores are provided as percent impairment, with higher percentages indicating greater impairment/less productivity (0%, no impairment; 100%, complete impairment) [36,37]. Participants completed either the work or classroom element, as relevant; all participants completed the activities impairment element. At baseline for the entire mITT, mean (SD) Activity Impairment was 18.0% (21.4%), which changed by −7.6% (24.8%) at week 52 and −4.8% (24.0%) at week 104, indicating improvement (Supplementary Table S2). For 101 employed participants, mean (SD) Overall Work Impairment was 11.2% (17.3%) at baseline, which changed by mean (SD) −2.7% (21.8%) at week 52 and −1.2% (20.9%) at week 104. For 28 participants taking classes, mean (SD) Overall Classroom Impairment was 12.6% (23.4%) at baseline; mean (SD) change was −3.5% (18.4%) at week 52 and −7.4% (30.5%) at week 104.

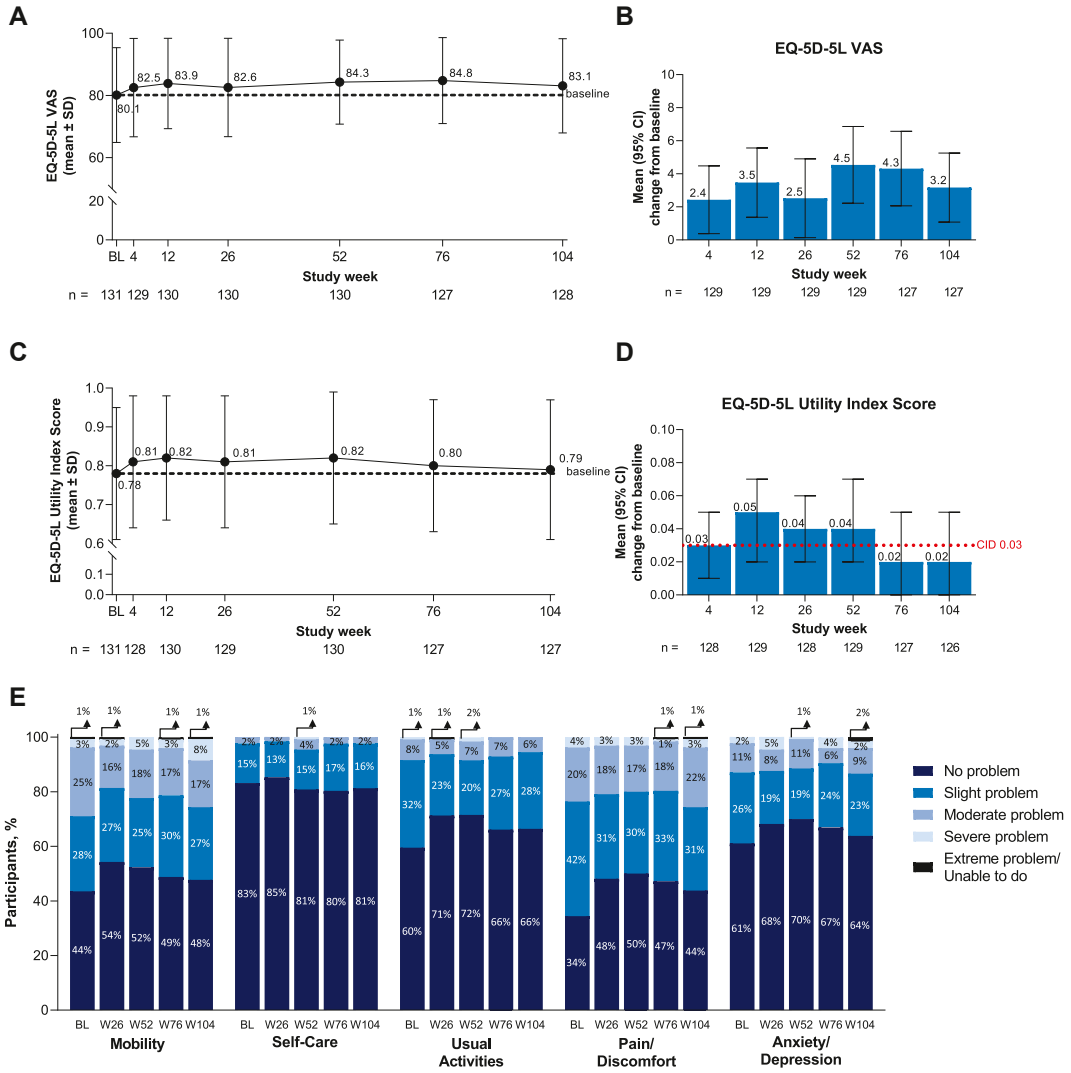

FIGURE 2 EQ-5D-5L over 104 weeks: (A) VAS score, (B) VAS score change from baseline, (C) Utility Index, (D) Utility Index change from baseline, and (E) EQ-5D-5L dimension responses. Change from baseline data are based on participants with data at both time points. For the EQ-5D-5L Utility Index, the CID was 0.03 as indicated by the red dotted line. BL, baseline; CI, confidence interval; CID, clinically important difference; VAS, visual analog scale; W, week.

3.5 | Subgroup analyses

3.5.1 | Problem joints

Haemo-QOL-A results were analyzed based on the presence of pre-existing problem joints, defined as those identified by the investigator at baseline as being associated with chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding (Table 3). At baseline, 97 participants had 0 problem joints, 17 had 1 problem joint, 9 had 2 problem joints, and 11 had ≥3 problem joints; participants with a greater number of problem joints typically had lower baseline domain scores than those who had none (Supplementary Table S3). By week 104, participants with 0 problem joints at baseline reported the highest improvement in the Consequences of Bleeding domain, alongside clinically meaningful improvement in Treatment Concern, Role Functioning, and Worry (Figure 4A). Participants with ≥3 problem joints, as a group, did not appear to derive QOL benefits from gene transfer.

3.5.2 | ABR at baseline

We sought to determine whether participants with well-controlled bleeding on FVIII prophylaxis had improvements in HRQOL by analyzing participants who reported no bleeds during the 6-month baseline period (Table 3). Participants with an ABR of 0 while receiving FVIII prophylaxis during the baseline period had lower mean Consequences of Bleeding, Treatment Concern, and Worry scores at baseline than those who did report bleeds (Figure 4B; Supplementary Table S4). However, participants with no baseline bleeds reported higher HRQOL in all domains except Treatment Concern at week 104 compared with participants who reported bleeding during baseline.

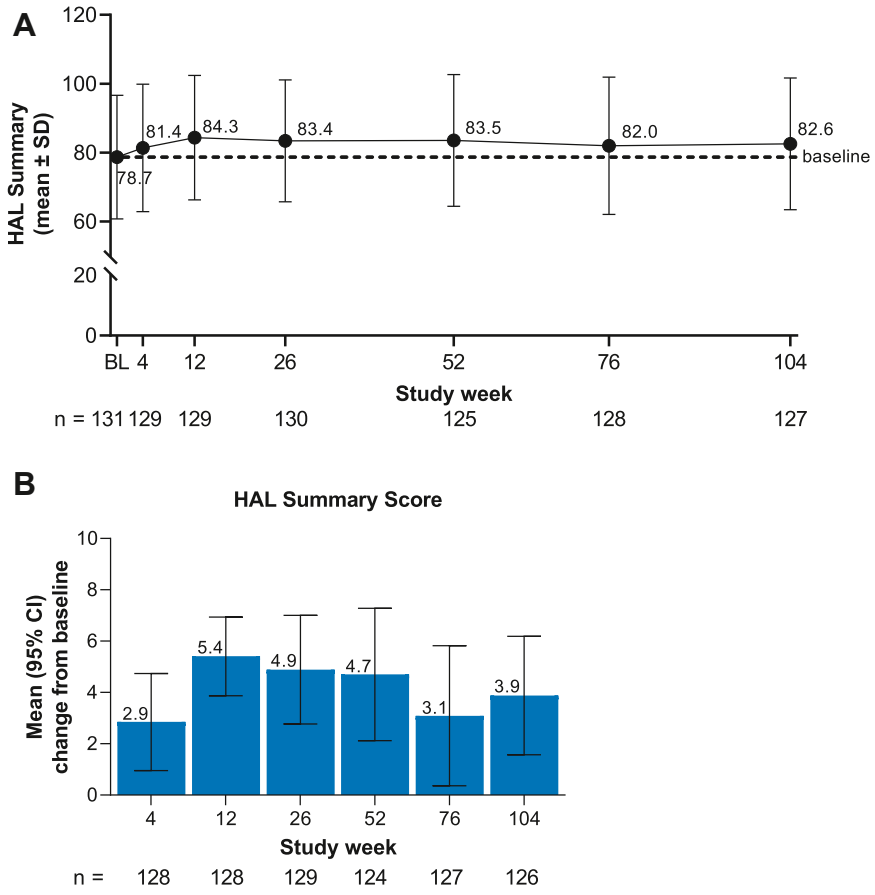

FIGURE 3 HAL Summary score (A) over 104 weeks and (B) change from baseline over 104 weeks. Change from baseline data are based on participants with data at both time points. BL, baseline; CI, confidence interval; HAL, Hemophilia Activities List.

TABLE 2 Change from baseline in HAL domain scores in the mITT.

	Baseline	Week 26	CFB to week 26	Week 52	CFB to week 52	Week 104	CFB to week 104
Summary score	78.7 (17.9)	83.4 (17.7)	4.9 (12.2)	83.5 (19.1)	4.7 (14.5)	82.6 (19.1)	3.9 (13.1)
n	131	130	129	125	124	127	126
Lying/sitting/kneeling/standing	73.5 (22.6)	77.5 (22.1)	4.2 (14.6)	78.1 (23.4)	5.0 (16.3)	77.4 (23.4)	4.2 (14.5)
n	131	130	129	125	124	127	126
Functions of the legs	68.9 (26.5)	75.5 (25.7)	6.9 (16.7)	76.1 (26.9)	6.6 (17.6)	74.0 (26.6)	4.9 (16.7)
n	131	130	129	125	124	127	126
Functions of the arms	80.3 (21.1)	85.9 (19.0)	5.9 (18.0)	85.4 (19.4)	4.9 (20.5)	84.2 (20.9)	4.1 (19.4)
n	131	130	129	125	124	127	126
Use of transportation	83.6 (21.7)	88.5 (21.1)	4.4 (16.5)	87.4 (21.9)	3.7 (18.5)	84.9 (24.1)	2.1 (18.8)
n	120	113	108	109	105	108	105
Self-care	90.2 (15.5)	93.3 (13.6)	3.2 (14.9)	93.5 (13.6)	3.4 (14.7)	92.9 (14.3)	2.9 (13.8)
n	131	130	129	125	124	127	126
Household tasks	87.6 (16.9)	91.0 (14.8)	3.6 (13.8)	91.0 (16.7)	3.3 (16.3)	90.7 (16.8)	3.1 (15.8)
n	130	129	127	123	121	127	125
Leisure activities and sports	80.0 (19.8)	84.7 (19.4)	5.5 (17.1)	86.6 (19.0)	6.8 (18.2)	83.9 (21.8)	5.4 (17.1)
n	119	108	100	103	100	110	103

Data presented as mean (SD).

CFB, change from baseline; HAL, Hemophilia Activities List; mITT, modified intent-to-treat.

TABLE 3 Baseline demographics and clinical characteristics and outcomes of participant subgroups.

	Number of problem joints at baseline				Baseline ABR		Change in ABR from baseline		
	0 (*n* = 97)	1 (*n* = 17)	2 (*n* = 9)	≥3 (*n* = 11)	0 (*n* = 43)	>0 (*n* = 91)	No change (*n* = 36)	Improved (*n* = 87)	Worsened (*n* = 11)
Age at baseline, y	31.3 (10.5)	28.4 (5.8)	36.2 (12.0)	36.5 (11.4)	29.1 (8.5)	32.9 (10.9)	28.7 (9.1)	32.8 (10.9)	32.9 (7.5)
ABR at baseline, treated bleeds/y	4.7 (6.4)	5.8 (8.5)	5.5 (7.7)	11.0 (26.9)	0	8.0 (11.2)	0	8.3 (11.4)	0.7 (1.5)
Participants with problem joints, *n* (%)									
0 joints	97 (100)	0	0	0	33 (76.7)	64 (70.3)	27 (75.0)	60 (69.0)	10 (90.9)
1 joint	0	17 (100)	0	0	5 (11.6)	12 (13.2)	5 (13.9)	12 (13.8)	0
2 joints	0	0	9 (100)	0	2 (4.7)	7 (7.7)	2 (5.6)	7 (8.0)	0
3 joints	0	0	0	8 (72.7)	2 (4.7)	6 (6.6)	2 (5.6)	6 (6.9)	0
>3 joints	0	0	0	3 (27.3)	1 (2.3)	2 (2.2)	0	2 (2.3)	1 (9.1)

Data presented as mean (SD), unless otherwise indicated.

ABR was defined as the number of treated bleeding episodes during the calculation period/total number of calculation period days × 365.25.

ABR, annualized bleeding rate.

3.5.3 | Change in ABR

We also assessed participant HRQOL by whether their ABR improved (*n* = 87; mean baseline ABR: 8.3 bleeds/y), worsened (*n* = 11; mean baseline ABR: 0.7 bleeds/y), or did not change (*n* = 36; mean baseline ABR: 0.0 bleeds/y) from baseline after receiving gene therapy (Table 3). We hypothesized that improvements in ABR may be correlated with improvements in HRQOL. At week 104, participants whose ABRs worsened reported clinically meaningful score increases in all domains except Emotional Impact (Figure 4C; Supplementary Table S5). Participants whose ABRs improved reported a clinically meaningful score increase in Consequences of Bleeding. All participants with no change in bleeding rates had zero bleeds both during baseline and after valoctocogene roxaparvovec treatment; these participants reported the highest clinically meaningful improvements in Role Functioning, Consequences of Bleeding, Emotional Impact, and Treatment Concern, suggesting an improvement in anxiety around bleeds and unmet need with prior therapy. Overall, improvements in mean HRQOL scores were demonstrated in participants regardless of their change in ABR during the study.

4 | DISCUSSION

For adult men with severe hemophilia A, one 6×10^{13} vg/kg valoctocogene roxaparvovec infusion resulted in clinically meaningful improvement in HRQOL at 52 and 104 weeks, as measured by Haemo-QOL-A Total Score. Haemo-QOL-A domain scores for Consequences of Bleeding, Treatment Concern, and Role Functioning exceeded the CID of 6 at both weeks 52 and 104, and Worry and Role Functioning domain scores exceeded the CID at week 104. Increase from baseline in HRQOL was also observed for HAL Summary and domain scores, with the greatest improvements noted in Lying/Sitting/Kneeling/Standing, Functions of the Legs, Functions of the Arms, and Leisure Activities and Sports. EQ-5D-5L VAS increased from baseline to week 104, and EQ-5D-5L Utility Score increased above the CID of 0.03 at week 52, but the increase from baseline was less than the CID at week 104. At week 104, the proportion of participants reporting problems with Usual Activities and Pain/Discomfort decreased from baseline. Percent Activity Impairment per WPAI+CIQ:HS decreased from baseline at 104 weeks, and small decreases in Work Impairment and Overall Classroom Impairment were also observed, though mean baseline values indicated low impairment overall and variability was high. Overall, our results suggest a benefit from treatment with valoctocogene roxaparvovec. As participants were previously receiving FVIII prophylaxis, increases in HRQOL observed here represent continued improvement over what the participant had achieved while on prophylaxis [38].

Improvement in the mental-health-related Haemo-QOL-A Consequences of Bleeding, Treatment Concern, and Worry domains at week 104 show that the benefits of valoctocogene roxaparvovec may extend beyond changes in ABR. Worry about hemophilia A may be engrained and therefore resistant to rapid change following gene therapy as participants adjust to their new treatment paradigm postprophylaxis [19]. The improvements in Worry, Consequences of Bleeding, and Treatment Concern after 2 years might reflect the beginning of mental freedom from constantly managing hemophilia A [20]. Investigators noted some participants appear to have already obtained a "hemophilia-free mind [20]." However, clinically significant changes in Emotional Impact were not observed, and experts suggest that after gene therapy, emotional health might be negatively impacted in the short term, depending on individual psychological and emotional reactions and potential burden of trial participation. Improvements may be observed over the long term as the positive impacts of treatment become more apparent (eg, ability to partake in rigorous activities) [19].

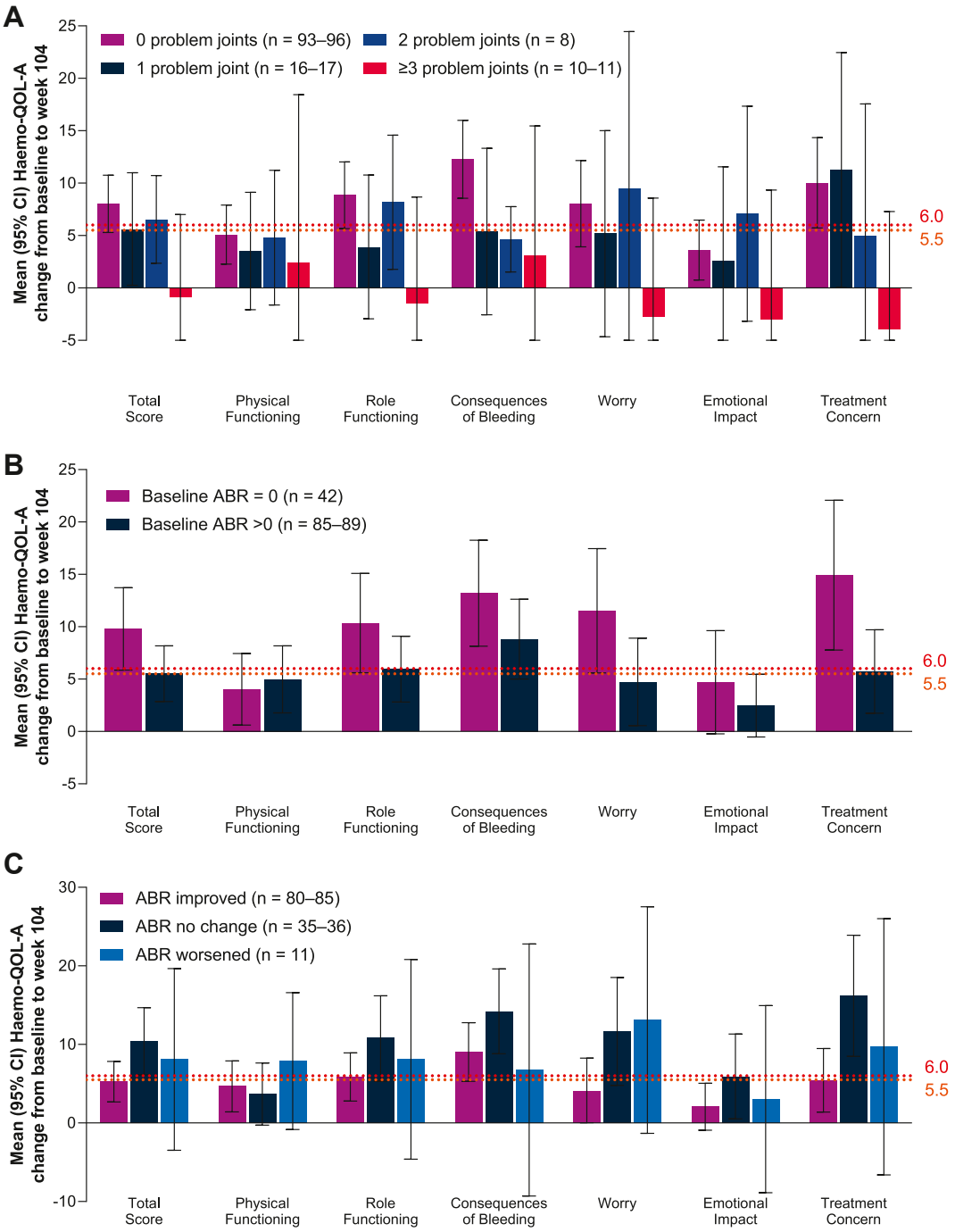

FIGURE 4 Haemo-QOL-A subgroup analyses. (A) Change in Haemo-QOL-A scores from baseline to week 104 by number of baseline problem joints. (B) Change in Haemo-QOL-A scores from baseline to week 104 by ABR at baseline. (C) Change in Haemo-QOL-A scores from baseline to week 104 by change in ABR during the study period. The CID for Total Score was 5.5, marked in orange, and the CID for domain scores was 6, marked in red. ABR, annualized bleeding rate; CI, confidence interval; CID, clinically important difference; Haemo-QOL-A, haemophilia-specific quality of life questionnaire for adults.

Although negative psychological impact associated with valoctocogene roxaparvovec has not been observed, any potential impacts on mental health or loss of identity may be due to a mismatch between expectations and treatment results. Therefore, setting realistic expectations prior to participation is important. Given the innovative nature of gene therapy, patients and clinicians should engage in shared decision making and discuss in a transparent manner unknowns, commitment to follow-up, and data-driven expectations.

At baseline, participants with pre-existing problem joints generally reported lower HRQOL measured by Haemo-QOL-A than those without problem joints, and had clinically meaningful improvement by week 104. The presence of problem joints did not preclude increases

in HRQOL at 104 weeks, except for 11 participants with 3 or more problem joints, who did not appear to derive QOL benefits from gene transfer as a group. Pain and joint damage negatively impact HRQOL [13,15,16], and the small number of participants in this group may have also limited detection of changes. These data demonstrate that HRQOL improvements following gene transfer can occur in spite of prior joint damage, though they may be less likely in individuals with multiple problem joints, emphasizing the need for intervention in early adulthood ideally before significant, irreversible joint damage occurs. For participants with no problem joints, meaningful increases were reported in Consequences of Bleeding, Treatment Concern, Role Functioning, and Worry, demonstrating additional benefit of valoctocogene roxaparvovec for individuals who appear to be in a "good" health state.

Participants with no bleeds at baseline had higher Physical Functioning and Emotional Impact scores at baseline than those who did have bleeds, but they also had lower Consequences of Bleeding scores. Thus, these participants may have high anxiety around bleeding at baseline while on FVIII prophylaxis and were subsequently altering their behavior to prevent bleeds, indicating their prior therapy was not fully meeting their needs. By week 104, both participants who did and did not have bleeds at baseline reported clinically meaningful improvement in the Role Functioning and Consequences of Bleeding domains, suggesting increased confidence in performing daily activities. Notably, participants with a baseline ABR of 0 had higher increases from baseline in almost every domain than those with an ABR of >0, including substantial increases above the CID in Role Functioning, Consequences of Bleeding, Worry, and Treatment Concern.

Additionally, improvements in Haemo-QOL-A domain scores were noted for participants regardless of how their ABRs changed during the study period; both participants who had less bleeding and those who had more bleeding reported improvements in certain domains. Valoctocogene roxaparvovec treatment thus provided improved HRQOL for participants with a variety of bleeding outcomes at week 104. Though the sample size was small, the 11 participants with increased ABRs at week 104 had increases in Total Score, Physical Functioning, Role Functioning, Consequences of Bleeding, Worry, and Treatment Concern at week 104; in particular, the increases in Worry and Treatment Concern suggest that some aspects of the mental burden of hemophilia have been ameliorated. A larger sample of 91 participants with no change in ABR during the study also reported clinically significant improvements in Total Score, Consequences of Bleeding, Worry, and Treatment Concern. Altogether, these results suggest that the benefit of valoctocogene roxaparvovec extends beyond improvements in ABR. It should also be considered that ABR, as self-reported by participants, has a subjective component in that participants must distinguish between bleeding episodes and residual pain; it is possible that participants are more attuned to bleeding events in a clinical trial than they would be otherwise [39]. Additionally, ABR is affected by participant behavior (eg, playing sports), and it may be possible that after receiving valoctocogene roxaparvovec, participants were more willing to engage in increased physical activity that could lead to bleeding events.

The tools used in this trial were chosen because they have been used in the field to measure the impact of hemophilia on HRQOL and were anticipated to measure the most relevant outcomes for participants who have received gene therapy [19], though we note they do have some limitations, including limited experience evaluating treatment effects in single-dose gene therapy trials. It is possible that not all items/domains may fully capture impacts of treatment for all individuals (eg, those who are more involved in contact sports) [19]. Some concepts in the HAL within the Self-Care and Household Tasks domains may be outdated and it does not include common ADLs, such as keyboard and smartphone use [19]. Change in HRQOL is likely underestimated by the EQ-5D-5L in hemophilia, as it may undervalue the negative impact of hemophilia on HRQOL due to both the use of general population norms and the disability paradox, wherein individuals with hemophilia report higher health state valuations than otherwise healthy peers [40]. Therefore, we have chosen to focus on Haemo-QOL-A results, as this measure has been validated in the target population and an anchor-based CID established [31].

Our results are in line with those observed in a phase 1/2 study of valoctocogene roxaparvovec, in which an increase in HRQOL as measured by the Haemo-QOL-A (mean score increased by 10.3, from 71.9 to 82.2) was observed for 7 participants with severe hemophilia A following a single 6×10^{13} vg/kg dose and maintained for 5 years [23]. In a global noninterventional study of 47 people aged ≥12 years with severe hemophilia A receiving FVIII prophylaxis, mean EQ-5D-5L Utility Index Score was 0.9 and VAS was 85.2, slightly higher than baseline values observed here [41]. For 118 clinical trial participants with severe hemophilia A, mean EQ-5D-5L Utility Score and VAS were 0.79 and 81.8, respectively, after 73 weeks on emicizumab prophylaxis [42]. In a sample of 16 participants with severe hemophilia A receiving prophylaxis with extended half-life FVIII in a clinical trial, Haemo-QOL-A Total Score was 73.9 after 36 weeks, and domain scores ranged from 64.6 for Physical Functioning to 81.7 for Emotional Impact [43]. In hemophilia B, factor IX activity is positively associated with HRQOL [44], but these results should be confirmed in hemophilia A. Overall, the results from this large study are an important addition to the literature on HRQOL in severe hemophilia A.

The trial was powered to assess primary and secondary clinical endpoints, which included a small number of Haemo-QOL-A results at week 104; therefore, some *P* values presented here are exploratory and must be interpreted with caution. Post hoc subgroup analyses are also limited by the small sample size of some groups and concerns related to multiple testing. Missing data were not imputed, but few participants discontinued, and the extent of missing data was not such that it would be expected to bias results. The 2-year period of currently available data precludes drawing conclusions on the duration of benefit; forthcoming longer-term follow-up results will be informative and may also allow evaluation of improvement in mental health measures as participants adjust their mindset. During the trial, the burden caused by frequent study visits (including blood and semen sampling), evolving corticosteroid treatment regimens used to manage alanine aminotransferase elevations, and the COVID-19 pandemic may have affected HRQOL. We were unable to assess the effect of

steroids on participant HRQOL in this analysis because PROs were assessed relatively infrequently compared to the timing of steroid use, making it impossible to capture the effect of being on vs off corticosteroids, and only a small proportion of participants received no immunosuppressants during the first 2 years of follow-up [25].

These data demonstrate improvement in the core outcomes of mental health, mobility, and pain and discomfort with hemophilia A following treatment with valoctocogene roxaparvovec when compared with their baseline values while receiving standard-of-care FVIII prophylaxis. While valoctocogene roxaparvovec did not prevent all bleeding, many participants experienced improvement in HRQOL compared to baseline on FVIII concentrate prophylaxis. A benefit from treatment was observed for participants both with and without problem joints and with and without improvement in ABR during the study. These HRQOL results may inform clinical decision making for individuals with severe hemophilia A.

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AUTHOR CONTRIBUTIONS

B.O.M. provided consultation on study design and conduct. A.L.D., A.D.L., F.P., M.C.O., J.M., K.P., J.-D.W., G.L., C.W.T., A.G., H.T., T.-L.K., E.C., D.P., H.C., M.F.L.F., R.Klamroth, E.M., R.Kazmi, and S.W.P. were clinical investigators and performed trial procedures. M.S. provided consultation on QOL analyses. J.Q. designed the QOL subgroup analyses. H.Y. performed the statistical analyses. W.Y.W. and T.M.R. oversaw trial conduct and contributed to study design. All authors contributed to the interpretation of results and provided critical input during drafting of the manuscript.

DECLARATION OF COMPETING INTERESTS

B.O.M. reports consulting fees from BioMarin Pharmaceutical Inc and Freeline. A.L.D. reports research funding from Sanofi, Takeda, Freeline, BioMarin Pharmaceutical Inc, and the American Thrombosis and Hemostasis Network; consulting fees from BioMarin Pharmaceutical Inc, Genentech/Roche, Kedrion, CSL Behring, and uniQure; and service on the board of the World Federation of Hemophilia USA. A.D.L. reports consulting or advisory panel fees from BioMarin Pharmaceutical Inc, Dova, CSL Behring, Merck, Catalyst, and HEME Biologics; and participation as a clinical trial investigator in trials sponsored by BioMarin Pharmaceutical Inc, Sangamo, and Pfizer. F.P. reports honoraria as a speaker for educational symposia by Grifols, Sanofi, and Takeda and as an advisory member for Sanofi and Roche. M.C.O. reports consulting fees from Bayer, BioMarin Pharmaceutical Inc, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda; research grants from Pfizer, Roche, and Takeda; service as a clinical trial investigator for BioMarin Pharmaceutical Inc, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda; speaker honoraria from Bayer, BioMarin Pharmaceutical Inc, Novo Nordisk, Roche, and Takeda; travel support from Novo Nordisk, Roche, and Takeda; and participation in grant reviewing for Grifols. J.M. reports consulting fees from Baxalta, CSL Behring, Catalyst Biosciences, Freeline, LFB, Novo Nordisk, and Spark; research grants from and service as a clinical trial investigator for BioMarin Pharmaceutical Inc, CSL Behring, Novo Nordisk, Pfizer, Sobi, Roche, Novartis, Sanofi, and Unique; and speaker fees from Novo Nordisk, Pfizer, Sanofi, Sobi, Shire, Roche, Takeda, the International Society on Thrombosis and Haemostasis, and the World Federation of Hemophilia. K.P. reports consulting fees and research grants from Sobi, Octapharma, Novo Nordisk, and Pfizer; and served as a clinical trial investigator for uniQure, BioMarin Pharmaceutical Inc, and Roche. J.-D.W. reports consulting fees from Bayer, Novo Nordisk, Pfizer, Chugai, Sanofi, Takeda, and Sobi; speaker fees from Bayer, CSL Behring, Novo Nordisk, Pfizer, Chugai, Sanofi, and Takeda; and service as a clinical trial investigator for Bayer, BioMarin Pharmaceutical Inc, Novo Nordisk, Pfizer, Roche/Chugai, and Sanofi. G.L. has received honoraria for participating in educational events from Novartis, LEO, Sobi, Alexion, Takeda, Novo Nordisk, and Sanofi; and consulting fees from UCB. A.G. reports honoraria for service on advisory boards from BioMarin Pharmaceutical Inc, Genentech, Pfizer, Bayer, ATHN, Novo Nordisk, uniQure, and Sanofi Genzyme; and travel grants from BioMarin Pharmaceutical Inc. E.C. reports consulting fees from Genentech, BioMarin Pharmaceutical Inc, Novo Nordisk, Takeda, Sanofi, HEMA Biologics, and CSL Behring; and speaker fees from Genentech. D.P. reports a travel grant from Pfizer. H.C. reports consulting fees from Bayer, BioMarin Pharmaceutical Inc, Roche, and Sobi; served as a clinical trial investigator for BioMarin Pharmaceutical Inc, Bioverativ, CSL Behring, LFB, Octapharma, Roche, Pfizer, Sobi, and Takeda; reports speaker fees from BioMarin Pharmaceutical Inc, Pfizer, Roche, and Sobi; and reports travel grants from BioMarin Pharmaceutical Inc, CSL Behring, Octapharma, Roche, and Sobi. M.F.L.F. reports participation in advisory boards and receiving speaking fees from Shire/Takeda, Amgen, CSL Behring, Novo Nordisk, Bayer, LFB, Pfizer, and Sobi. E.M. reports consulting fees and travel support from BioMarin Pharmaceutical Inc and served as a clinical trial investigator for BioMarin Pharmaceutical Inc. M.W.S. reports consulting fees from Bayer, BioMarin Pharmaceutical Inc, Pfizer (DMC), Roche/Genentech, Sanofi, Spark (DMC), and Takeda; and research grants from BioMarin Pharmaceutical Inc, Freeline, Roche, Takeda, and uniQure. R.Klamroth reports consulting fees from Bayer, Biotest, BioMarin Pharmaceutical Inc, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, Takeda/Shire, and Sobi; research grants from Bayer and LEO; speaker fees from Bayer, Biotest, BioMarin Pharmaceutical Inc, CSL Behring, Daiichi Sankyo, LEO, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, Takeda/Shire, and Sobi; travel support from Bayer, Biotest, BioMarin Pharmaceutical Inc, CSL Behring, Daiichi Sankyo, LEO, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, Takeda/Shire, and

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DATA SHARING STATEMENT

The de-identified 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 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 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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