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ORIGINAL ARTICLE

Matching-adjusted indirect comparison of bleeding outcomes in severe haemophilia A: Comparing valoctocogene roxaparvovec gene therapy, emicizumab prophylaxis, and FVIII replacement prophylaxis

Jan Astermark[1,2] | Tyler W Buckner[3] | Laurent Frenzel[4] | Anthony J Hatswell[5,6] | Xiaojun You[7] | Hai Liu[7] | Erin Goodman[7] | Sandra Santos[8] | Charles Hawes[8] | David Hinds[7] | Robert Klamroth[9,10]

[1]Department of Translational Medicine, Lund University, Lund, Sweden

[2]Department for Hematology, Oncology and Radiation Physics, Skåne University Hospital, Malmö, Sweden

[3]University of Colorado School of Medicine Hemophilia and Thrombosis Center, Aurora, Colorado, USA

[4]Centre de Traitement de l'Hemophilie, AP-HP, Hôpital Universitaire Necker-Enfants Malades, Paris, France

[5]Delta Hat Limited, Nottingham, UK

[6]Department of Statistics, University College London, London, UK

[7]BioMarin Pharmaceutical Inc., Novato, California, USA

[8]BioMarin UK Ltd, London, UK

[9]Vascular Medicine and Haemostaseology, Vivantes Klinikum im Friedrichshain, Berlin, Germany

[10]Institute of Experimental Hematology and Transfusion Medicine, University Hospital Bonn, Medical Faculty, University of Bonn, Bonn, Germany

Correspondence
Jan Astermark, Department of Translational Medicine, Lund University, Skåne University Hospital, Jan Waldenströms gata 14, Malmö SE-205 02, Sweden.
Email: jan.astermark@med.lu.se

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Abstract

Introduction: Head-to-head evaluation of valoctocogene roxaparvovec, the first gene therapy approved for haemophilia A, with emicizumab is not available. Therefore, phase 3 trial data were indirectly compared.

Aim: To compare bleeding rates in trials evaluating 6×10^{13} vg/kg valoctocogene roxaparvovec (GENEr8-1; NCT03370913), 1.5 mg/kg emicizumab dosed every week (HAVEN 3; NCT02847637), and FVIII prophylaxis (270–902) in participants with severe haemophilia A (FVIII ≤1 IU/dL).

Methods: Valoctocogene roxaparvovec versus emicizumab and FVIII prophylaxis as used in 270–902 versus emicizumab cross-trial comparisons were performed using matching-adjusted indirect comparison (MAIC). Individual participant data from GENEr8-1 and 270–902 were weighted to equalise aggregate participant baseline characteristics from HAVEN 3. After MAIC weighting, annualised bleeding rates (ABR) and proportions of participants without bleeds were compared for treated bleeds, all bleeds, treated joint bleeds, and treated spontaneous bleeds.

Results: After MAIC weighting, ABR for all bleeds was statistically significantly lower with valoctocogene roxaparvovec than emicizumab (rate ratio [95% CI], .55 [.33–.93]). Additionally, significantly higher proportions of participants had no treated joint bleeds (odds ratio [95% CI], 2.75 [1.20–6.31]) and no treated bleeds (3.25 [1.53–6.90]) with valoctocogene roxaparvovec versus emicizumab. When compared with the mainly standard half-life FVIII prophylaxis regimens in 270–902, mean ABRs (except for all bleeds) were significantly lower, and significantly higher proportions reported 0 bleeds for all outcomes with emicizumab.

Conclusion: Valoctocogene roxaparvovec provided generally lower bleeding rates and higher probability of no bleeds, including treated joint bleeds, than emicizumab. Emicizumab was more effective than FVIII prophylaxis regimens used in 270–902.

KEYWORDS
AAV5-hFVIII-SQ, emicizumab, FVIII prophylaxis, haemophilia A, matching-adjusted indirect comparison (MAIC), valoctocogene roxaparvovec

1 | INTRODUCTION

Haemophilia A is an X-linked bleeding disorder caused by deficiency in clotting protein factor VIII (FVIII). Severe haemophilia A (FVIII ≤1 IU/dL) is associated with spontaneous bleeding into joints that can lead to painful, disabling arthropathy.[1–3] Standard of care for severe haemophilia A is regular prophylactic treatment with either standard half-life (SHL) or extended half-life (EHL) FVIII or emicizumab, a bi-specific antibody that mimics the activity of FVIII protein.[1,4,5] The efficacy of emicizumab prophylaxis was demonstrated in the phase 3 trial HAVEN 3 (NCT02847637), including 1 arm (Group D) where participants were receiving FVIII prophylaxis prior to being treated with emicizumab.[5] However, comparative evidence of its effectiveness compared to FVIII products in a real-world haemophilia population is limited.[6,7]

Gene therapy may provide a treatment option for people with severe haemophilia A that prevents bleeding for multiple years with a single infusion rather than the more frequent infusions required by FVIII or emicizumab prophylaxis.[1,8–10] Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) uses an adeno-associated virus vector to transfer a B-domain-deleted human FVIII-coding sequence controlled by a liver-selective promoter, resulting in endogenous production of FVIII protein in hepatocytes.[11–16] Efficacy of a single 6×10^{13} vg/kg dose of valoctocogene roxaparvovec was assessed in the multicentre, open-label, single-arm, phase 3 GENEr8-1 trial (NCT03370913) in 134 adult male participants who had previously been receiving regular prophylaxis with exogenous FVIII, 22 of whom enrolled directly and 112 of whom "rolled over" after participating in the prospective, non-interventional, longitudinal 270—902 study.[16–18] At 104 weeks post-infusion, annualised rates of bleeding events and FVIII utilisation were significantly improved in the rollover participants compared with their baseline values (when receiving FVIII prophylaxis) collected in the non-interventional study.[18] As enrolment in GENEr8-1 excluded individuals using investigational products—which included emicizumab prophylaxis at the time of the study start—an internal comparison of valoctocogene roxaparvovec and emicizumab is not available.[16]

Here, we present indirect comparisons of valoctocogene roxaparvovec treatment outcomes from GENEr8-1 with emicizumab treatment outcomes from HAVEN 3 using matching-adjusted indirect comparison (MAIC) methods to account for differences between study populations at baseline. We use the same procedures to compare treatment outcomes with FVIII prophylaxis (taken from non-interventional study 270—902) to the outcomes observed in the same group of participants treated with emicizumab in HAVEN 3 Group D.

2 | METHODS

2.1 | Data sources and sample selection

2.1.1 | Valoctocogene roxaparvovec versus emicizumab

GENEr8-1 is an open-label, single-group, multicentre, phase 3 trial where 134 participants aged ≥18 years with severe haemophilia A without inhibitors were administered one 6×10^{13} vg/kg dose of valoctocogene roxaparvovec.[16] Data were used from the 132 participants without HIV in the modified intent-to-treat population, including both directly enrolled and rollover participants, from after week 5 post-infusion or 3 days after the end of routine FVIII prophylaxis (whichever was later) through week 52. The median follow-up time was 48.0 (range, 35.6—48.0) weeks.

HAVEN 3 was a phase 3, open-label, multicentre trial where participants aged ≥12 years with severe haemophilia A and no history of inhibitors received emicizumab prophylaxis.[5] Here, we utilised data from 63 participants (Group D) who received emicizumab 3 mg/kg

every week (QW) for 4 weeks followed by a maintenance dose of 1.5 mg/kg emicizumab QW and were previously treated with prophylactic FVIII replacement therapy. In HAVEN 3, FVIII prophylaxis was defined as continuous prophylaxis with a minimal regimen of 15–30 IU/kg/dose 3 times weekly for SHL products or 1–2 times weekly for EHL products; at baseline, 53 (84.1%) of Group D participants were using SHL FVIII prophylaxis, and 10 (15.9%) were using EHL FVIII prophylaxis. This cohort was chosen for comparison because, as in GENEr8-1, participants were previously using FVIII prophylaxis and both enrolled directly or were rolled over for continued observation after participation in a non-interventional study. Publicly available baseline and follow-up data were utilised;[5,19] bleeding outcomes were observed for a median of 33.1 (range, 18.4–48.6) weeks after initiating emicizumab.

2.1.2 | Emicizumab versus FVIII prophylaxis

Study 270–902 was a multicentre, non-interventional, prospective, longitudinal study that enrolled individuals ≥18 years of age with severe haemophilia A who were receiving FVIII prophylaxis; it served as the run-in study for GENEr8-1.[17] Data were used from week 0 to maximum follow-up from the 225 participants who completed at least 6 months of prospective follow-up. The median follow-up time was 32.1 (range, 24.1–67.0) weeks ($n = 222$). The same 63 participants in HAVEN 3 Group D who received a maintenance dose of emicizumab 1.5 mg/kg QW and who were treated previously with prophylactic FVIII replacement therapy were used for this comparison.

2.2 | Variables and outcomes

All published baseline information from HAVEN 3 was carefully reviewed,[5,19,20] and the most medically relevant covariates were identified and assessed for overlap with data collected in GENEr8-1 and 270–902. For matching in the primary analyses, mean age, percent of participants who were White, mean body mass index (BMI), mean annualised bleeding rates (ABR; for all bleeds), percent of participants with ≥9 bleeds in 24 weeks prior to enrolment, and percent of participants who were using SHL FVIII replacement product before study entry were selected. Discrepancies in definitions between trials were considered and only common baseline data were used for analyses.

Outcomes were assessed using ABRs and proportion of participants with 0 bleeds for the following types of bleeds: treated bleeds, all bleeds, treated joint bleeds, and treated spontaneous bleeds. ABRs were calculated using a negative binomial (NB) regression model and compared between groups with rate ratios. Odds ratios were calculated to compare the proportion of participants with 0 bleeds between groups. NB regression models are a class of models that allow for a large number of participants to have an observation of 0; this approach was consistent with that used in HAVEN 3 to account for varying follow-up times.[5] In the NB regression model, the number of bleeds was included as the outcome and the length of the efficacy period included as an offset; the number of bleeds (<9 or ≥9) in the 24 weeks prior to study entry was included as a stratification factor. Bleeds were defined as described previously for each trial.[5,16]

2.3 | Statistical analyses

MAIC is an approach similar to propensity score weighting that allows the comparison of cross-trial outcomes between balanced populations by weighting participant characteristics at baseline from a trial where individual participant data are available to match aggregate baseline data from a second trial of a different treatment.[21] Although propensity score weighting would be preferred, this is only possible with access to individual participant data from both studies. We used MAIC to balance the differences in chosen baseline characteristics between the trial where individual data were available (GENEr8-1 or 270–902) and the trial where only aggregate data were available (HAVEN 3), per methods described previously.[21] Two separate MAIC analyses were performed: first, comparison of participants treated with valoctocogene roxaparvovec in GENEr8-1 (individual data) with those treated with emicizumab prophylaxis in HAVEN 3 (aggregate data), and second, comparison of participants treated with FVIII prophylaxis in 270–902 (individual data) with those treated with emicizumab prophylaxis in HAVEN 3 (aggregate data). In these analyses, all available individual participant data were weighted to match the characteristics of the aggregate participant data.

Differences in mean ABRs as calculated with the NB model were assessed using a rate ratio and 95% confidence interval (CI). Differences in proportion of participants with 0 bleeds were assessed using an odds ratio and its 95% CI. Statistical analyses were performed in the software R version 4.2.0 using the package 'MAIC' version 0.1.4 (The R Foundation, Vienna).

For the valoctocogene roxaparvovec versus emicizumab analyses, additional sensitivity analyses were performed by changing the baseline matching parameters. Because there were differing inclusion criteria related to age in HAVEN 3, where participants could be ≥12 years, and GENEr8-1, where only individuals ≥18 years were eligible,[5,16] investigating the effect of age on weighting was the goal of several of our sensitivity analyses. Individual analyses were conducted omitting the following matching parameters: age, prior bleeding in 6 months preceding enrolment, prior FVIII regimen, and both age and prior FVIII regimen. Additional sensitivity analyses were also conducted using median age to match instead of mean age. Further sensitivity analysis adding the percent of participants with ≥1 target or problem joint at baseline as a matching parameter was also performed, with target/problem joints as defined in each trial.[5,16]

For the FVIII prophylaxis vs emicizumab analysis, sensitivity analyses were performed by removing prior bleeding during the 6 months preceding enrolment and removing prior FVIII regimen from the baseline matching parameters. Additional sensitivity analysis adding percent of participants with ≥1 target or problem joint as defined in each trial was performed.[5,17] Further sensitivity analyses were also performed considering only participants who received SHL FVIII

TABLE 1 Baseline characteristics of participants in HAVEN 3 and GENEr8-1 before and after MAIC.

Characteristic	HAVEN 3 ($n = 63$)	GENEr8-1			
		Unweighted ($n = 132$)		Weighted (ESS = 76.2)	
		Value	*P*-value	Value	*P*-value
Mean age	36.4	31.4	<.001	36.4	1.000
Percent White race	74.6%	71.2%	.427	74.6%	1.000
Mean BMI	25.56	25.31	.524	25.56	.999
Mean ABR	6.4	6.0	.677	6.4	1.000
Percent with <9 bleeds in 24 weeks prior to enrolment	84.1%	90.9%	.043	84.1%	1.000
Percent with SHL FVIII product used before trial entry	84.1%	72.0%	<.001	84.1%	1.000

Abbreviations: ABR, annualised bleeding rate; BMI, body mass index; ESS, effective sample size; FVIII, clotting protein factor VIII; MAIC, matching-adjusted indirect comparison; SHL, standard half-life.

product, with age removed from matching, and considering only participants who received EHL FVIII product, and with age removed from matching, respectively.

3 | RESULTS

3.1 | Comparison of valoctocogene roxaparvovec versus emicizumab

After weighting data from all participants who received valoctocogene roxaparvovec on all 6 parameters in the MAIC, the effective sample size (ESS) fell to 76.2, 57.7% of the original 132 participants. After weighting, all baseline parameters of interest were statistically comparable between GENEr8-1 and HAVEN 3 (Table 1).

The ABR for all bleeds after MAIC was statistically significantly lower with valoctocogene roxaparvovec than with emicizumab treatment (rate ratio [95% CI], .55 [.33–.93]; Figure 1). While ABRs after MAIC for treated bleeds and treated joint bleeds were lower for participants treated with valoctocogene roxaparvovec than for those treated with emicizumab, the difference did not reach statistical significance. For spontaneous bleeds, ABR was slightly lower with emicizumab than with valoctocogene roxaparvovec, but the difference was not significant.

When comparing the proportion of participants with no bleeds, after MAIC, significantly more participants who received valoctocogene roxaparvovec had no treated bleeds (odds ratio [95% CI], 3.25 [1.53–6.90]) and no treated joint bleeds (odds ratio [95% CI], 2.75 [1.20–6.31]) than those treated with emicizumab (Figure 2). After MAIC, a higher proportion of participants with valoctocogene roxaparvovec had no bleeds of any kind and no treated spontaneous bleeds than those with emicizumab, though the difference was not significant.

Sensitivity analyses were performed to investigate the impact of parameters used in MAIC matching on outcomes. In the main analysis, matching on mean age had the largest impact on ESS. When matching only on mean age, the ESS was reduced to 78.9%; in comparison, matching on other individual variables reduced the ESS to only 93.2% or higher. Removing age increased the ESS to 111.5, 84.5% of the original, and produced a less skewed distribution of participant weights (Table S1, Figure 3). In the analysis with age omitted, ABRs for all bleeds (rate ratio [95% CI], .5 [.30–.83]) and treated joint bleeds (.43 [.18–.99]) were significantly lower with valoctocogene roxaparvovec than emicizumab, and a significantly higher proportion of participants had no treated bleeds (odds ratio [95% CI], 2.9 [1.48–5.68]) and no treated joint bleeds (2.57 [1.23–5.39]) with valoctocogene roxaparvovec compared to emicizumab (Figure S1, Table S2). The results of all sensitivity analyses generally supported those of the main analysis.

3.2 | Comparison of FVIII prophylaxis versus emicizumab

After matching by all 6 parameters, the ESS of participants treated with FVIII prophylaxis was reduced to 150.6, 67.8% of the original 222 participants with available data. After weighting, all baseline parameters of interest were statistically comparable between 270–902 and HAVEN 3 (Table S3).

For all types of bleeding, mean ABR was lower for participants who were using emicizumab prophylaxis compared with those using FVIII prophylaxis, and only the rate ratio for all bleeds was not significant (Figure S2). Similarly, the proportion of participants with no bleeds in every category was significantly higher with emicizumab prophylaxis than with FVIII prophylaxis (Figure S3). Overall, the results of sensitivity analyses were generally supportive of the main analysis (Table S4, Table S5, and Figure S4).

4 | DISCUSSION

Participants with severe haemophilia A who received a single 6×10^{13} vg/kg infusion of valoctocogene roxaparvovec gene therapy generally had lower bleeding rates and higher odds of having 0 bleeds than participants who received emicizumab prophylaxis dosed at 1.5 mg/kg QW when compared using MAIC. ABR for all bleeds was significantly lower, and the odds of participants having no treated bleeds and no treated joint bleeds were significantly higher with

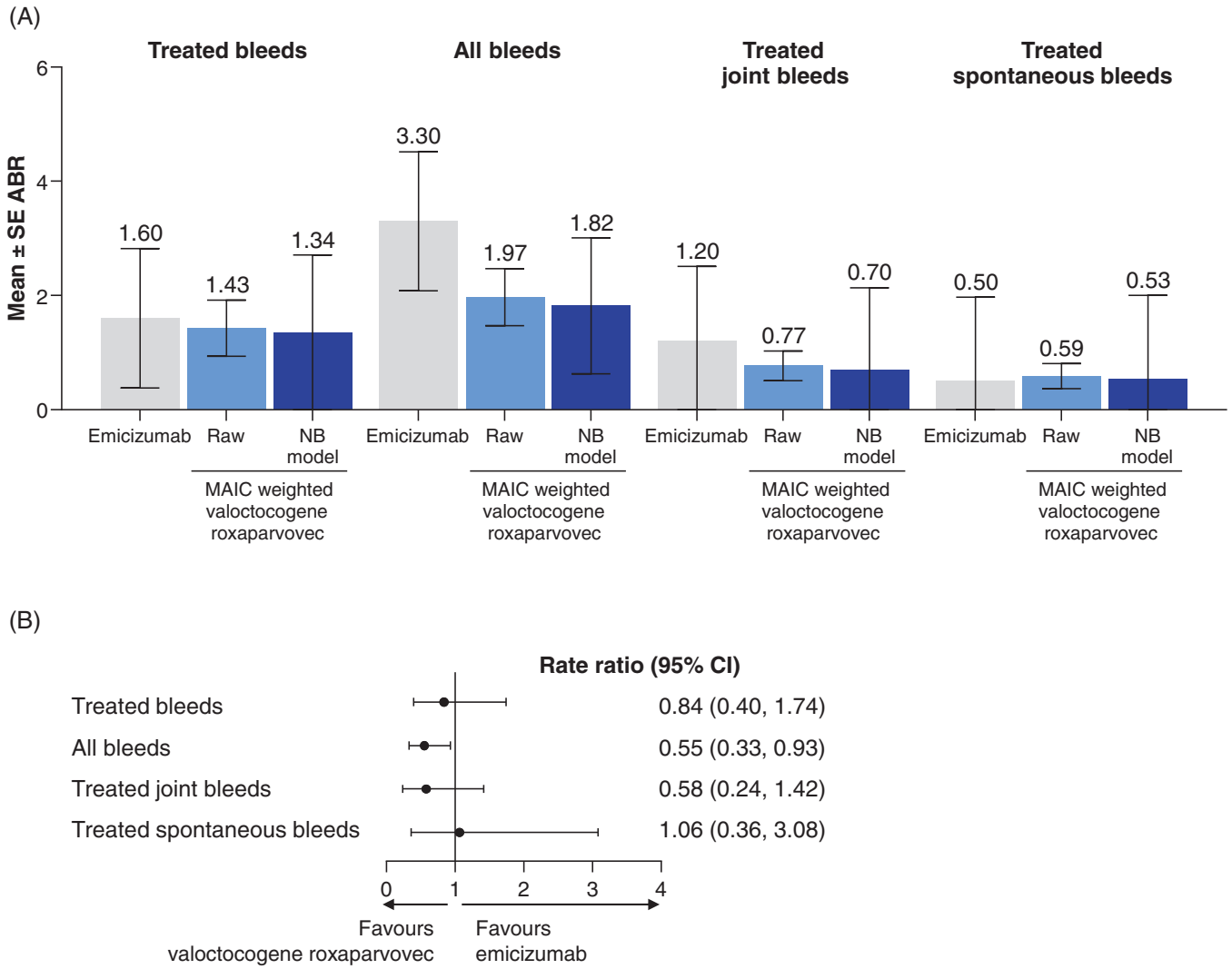

FIGURE 1 Comparison of bleeding rates with emicizumab prophylaxis (HAVEN 3 Group D) and after treatment with valoctocogene roxaparvovec (GENEr8-1). (A) Mean ABR after matching; (B) Relative treatment effect after matching. An NB regression model was used to assess ABRs with emicizumab prophylaxis and, where indicated, with valoctocogene roxaparvovec. ABR, annualised bleeding rate; CI, confidence interval; MAIC, matching-adjusted indirect comparison; NB, negative binomial; SE, standard error.

valoctocogene roxaparvovec compared with emicizumab. Though not statistically significant, other outcomes had lower ABRs or higher proportions of participants with 0 bleeds with valoctocogene roxaparvovec than emicizumab, except ABR for treated spontaneous bleeds, which was slightly lower with emicizumab than valoctocogene roxaparvovec.

A key sensitivity analysis omitted age from baseline matching because of the differences in age inclusion criteria in GENEr8-1 and HAVEN 3. From a methodological perspective, misaligned parameters between trials, such as age (differing low bound) and target joints (differing definition), typically should not be included in MAIC matching. When age was omitted from the baseline matching, ABRs for treated spontaneous bleeds also shifted to favour valoctocogene roxaparvovec. Overall, the inclusion of age in matching had a negative influence on all ABRs for valoctocogene roxaparvovec due to the skew in weights and influence of outlier weights, which increased ABR relative to the observed values. This effect was mitigated when age was removed. Overall, the results across sensitivity analyses examining the impact of factors such as age and presence of target/problem joints on outcomes generally supported those of the main analysis.

While clinical trial results support the superiority of valoctocogene roxaparvovec gene therapy over FVIII prophylaxis in terms of annualised rates of treated bleeds and all bleeds,[18] this analysis is the first to compare outcomes with valoctocogene roxaparvovec and emicizumab prophylaxis. As gene therapy is a new therapeutic option for people with haemophilia A, these comparative data may be useful to inform treatment choices. Overall, the most important indicator of efficacy for any haemostatic therapy is the frequency of bleeding, particularly bleeding in joints;[1] thus, our finding that higher proportions of participants had 0 treated bleeds and 0 treated joint bleeds with valoctocogene roxaparvovec therapy compared with emicizumab is particularly noteworthy. However, additional data on the

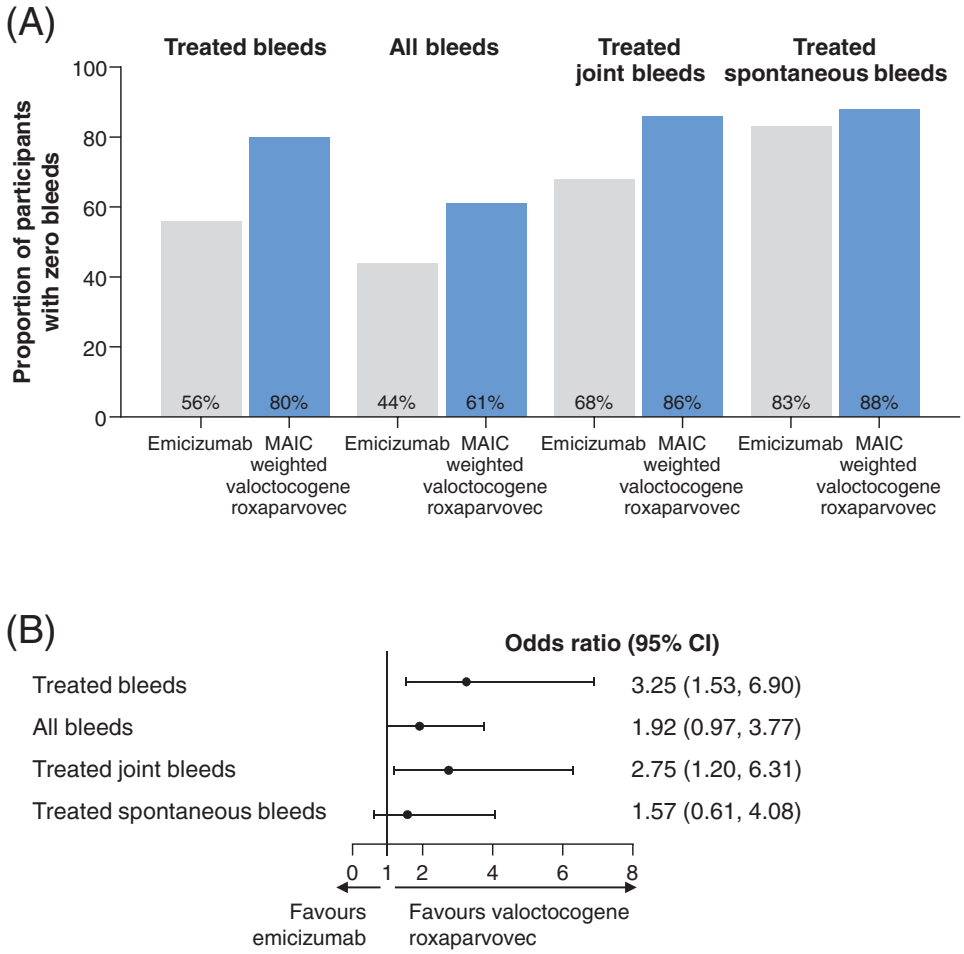

FIGURE 2 Comparison of participants with no bleeding events with emicizumab prophylaxis (HAVEN 3 Group D) and after treatment with valoctocogene roxaparvovec (GENEr8-1). (A) Percentage of participants after matching; (B) Relative treatment effect after matching. CI, confidence interval; MAIC, matching-adjusted indirect comparison.

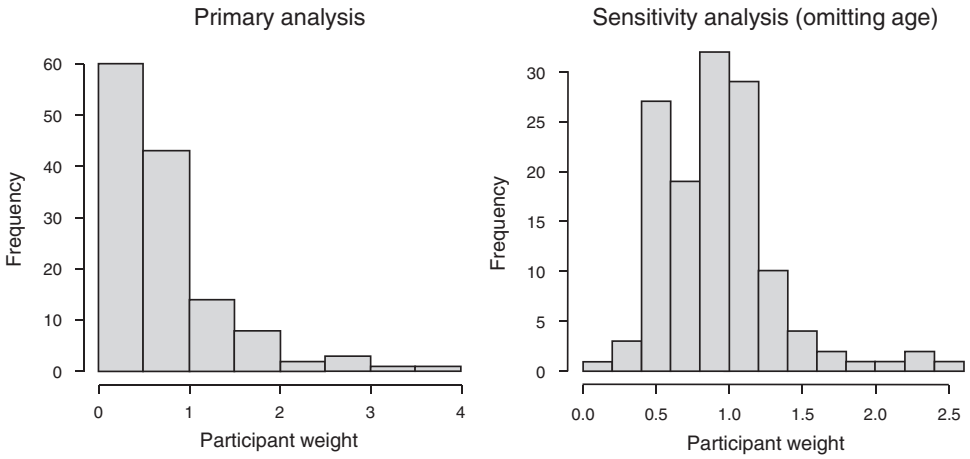

FIGURE 3 Histogram of participant weights after matching in the primary analysis (including mean age) and the sensitivity analysis omitting age.

impact of these treatments on joint health using joint-specific measurements is needed; for example, Haemophilia Joint Health Scores or results from the Haemophilia Early Arthropathy Detection with Ultrasound system.[22,23] Close follow-up of participants treated with these products will be important for evaluating long-term joint health outcomes.

Using the same MAIC methodology, bleeding outcomes for participants who received FVIII prophylaxis in a non-interventional study were compared to emicizumab prophylaxis 1.5 mg/kg QW in HAVEN 3; across all outcomes, emicizumab was associated with lower rates of bleeding and higher proportions of participants reporting 0 bleeds compared with FVIII prophylaxis. In the primary HAVEN 3 analyses, emicizumab treatment for at least 24 weeks resulted in a significant decrease in ABR from the baseline period when participants were using FVIII prophylaxis, as well as an increase in the proportion of participants reporting 0 bleeds.[5] In long-term follow-up, the pooled population of participants with severe haemophilia A without inhibitors in HAVEN 3 maintained similarly low ABR for treated bleeds across 6-month intervals for over 2 years.[4] The results from this MAIC analysis were in agreement with the original results from HAVEN 3[5] and results of network meta-analyses and subgroup analyses with HAVEN 3 data[7] on the efficacy of emicizumab compared with FVIII prophylaxis, which supports the robustness of the MAIC method.

Limitations of these analyses include that only an unanchored MAIC could be performed, as there was no common comparator across the 3 trials evaluated. Randomised controlled trials are not feasible in this area, and at the time the GENEr8-1 trial was designed, head-to-head comparison with emicizumab was not possible. The differing inclusion criteria related to age in HAVEN 3, where participants could be ≥12 years, and GENEr8-1, where only individuals ≥18 years were eligible, also led to poor matching on age;[5,16] however, sensitivity analyses removing age as a matching criteria or using median instead of mean age supported those of the main analysis. The time of follow-up between the 2 trials also differed, as only 24 weeks of data were available from Group D in HAVEN 3. Though additional data beyond 52 weeks was available for participants in GENEr8-1, we chose to use the shorter follow-up period to maintain similarity with HAVEN 3. The MAIC was unable to account for any unobserved differences between studies, or factors not included in reporting that could have affected bleeding outcomes. Potential differences in FVIII prophylaxis utilisation, including injection frequency and IU/kg/year, in 270−902 and the non-interventional study that served as a run-in to HAVEN 3 may also have affected the ABRs as reported at baseline.

Using all available data and the most appropriate methodology, we found participants who received valoctocogene roxaparvovec had generally lower bleeding rates (including treated bleeds, all bleeds, and treated joint bleeds) and a higher probability of having 0 bleeds than those who received emicizumab prophylaxis. These results were strengthened by our finding that emicizumab was more effective than FVIII treatment as implemented in 270−902, validating the study approach and results.

AUTHOR CONTRIBUTIONS

Jan Astermark, Tyler W Buckner, Laurent Frenzel, and Robert Klamroth provided guidance on the clinical relevance of baseline variables and sensitivity analyses. Anthony J Hatswell, Hai Liu, and Xiaojun You provided input on matching-adjusted indirect comparison methods and interpretation of results. Xiaojun You and Erin Goodman performed the statistical analyses and validated the results. Sandra Santos, Charles Hawes, and David Hinds conceived of the research question and oversaw the analyses. All authors contributed to interpretation of the data and provided critical review of the manuscript and approval to submit.

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CONFLICT OF INTEREST STATEMENT

JA has received research grants from Sobi, CSL Behring, Takeda/Shire, and Bayer and speaker's fees and consultancy for Octapharma, Novo Nordisk, Pfizer, Bayer, Sobi, CSL Behring, Takeda/Shire, Idogen, BioMarin Pharmaceutical Inc., uniQure, and Spark Therapeutics. TWB has received honoraria for advisory board participation from Novo Nordisk, Takeda, CSL Behring, Bayer, Tremeau Pharmaceuticals, Spark, and Pfizer; has served as consultant to uniQure, BioMarin Pharmaceutical Inc., and Tremeau Pharmaceuticals; and is on the board of directors for the American Thrombosis and Hemostasis Network. LF has received research grants from Pfizer and CSL Behring and speaker's fees and consultancy for Novo Nordisk, Pfizer, Sobi, CSL Behring, BioMarin Pharmaceutical Inc., and Roche. AJH is an employee of Delta Hat Ltd, which was contracted by BioMarin Pharmaceutical Inc., for input to the study design and execution. XY, HL, and DH are employees and stockholders of BioMarin Pharmaceutical Inc. EG is a contract employee of BioMarin Pharmaceutical Inc. SS and CH are employees and stockholders of BioMarin UK Ltd. RK 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.

DATA AVAILABILITY 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 non-commercial, 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. 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. cd_value_code=text.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov registration numbers are NCT02847637 for HAVEN 3 and NCT03370913 for GENEr8-1.

ETHICS STATEMENT

The 270—902 and GENEr8-1 (NCT03370913) protocols were approved by the Institutional Review Boards or Independent Ethics Committees of all participating sites, and the trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent.

ORCID

Jan Astermark https://orcid.org/0000-0001-8500-2483
Laurent Frenzel https://orcid.org/0000-0002-6085-2163
Robert Klamroth https://orcid.org/0000-0003-4194-8183

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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