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Transitioning from emicizumab prophylaxis to valoctocogene roxaparvovec gene therapy: A simulation study for individuals with severe haemophilia A

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Abstract

Introduction: Valoctocogene roxaparvovec, a gene therapy evaluated in the phase 3 GENEr8-1 trial, supports endogenous factor VIII (FVIII) production to prevent bleeding in people with severe haemophilia A. Individuals receiving emicizumab, an antibody mimicking the function of activated FVIII, were excluded from GENEr8-1 enrolment since emicizumab was an investigational therapy at the time of trial initiation.

Aim: Utilize pharmacokinetic simulations to provide guidance on best practices for maintaining haemostatic control while transitioning from emicizumab prophylaxis to valoctocogene roxaparvovec.

Methods: To estimate bleeding risk at weekly intervals following valoctocogene roxaparvovec infusion, a published emicizumab pharmacokinetic model was used to simulate emicizumab concentrations and merged with FVIII activity time-course data for participants in GENEr8-1. The analysis investigated three approved emicizumab dosing regimens for two transition scenarios that varied whether the last dose of emicizumab was administered on the same day or 4 weeks after valoctocogene roxaparvovec infusion.

Results: Simulations demonstrated administering the last emicizumab dose the day of valoctocogene roxaparvovec infusion and 4 weeks after offered similar levels of haemostatic control, and bleeding risk was similar for all emicizumab dosing regimens.

An algorithm was developed to provide guidance for discontinuation of emicizumab. Theoretical cases based on GENEr8-1 participants are presented to illustrate how decisions may vary among individuals.

Conclusion: Pharmacokinetic simulations demonstrated no clinically meaningful difference in bleeding risk caused by decaying emicizumab levels and rising gene therapy-derived endogenous FVIII for all examined emicizumab doses and dosing regimens. Therefore, multiple approaches can safely transition individuals from emicizumab prophylaxis to valoctocogene roxaparvovec.

KEYWORDS
algorithm, emicizumab, gene therapy, haemophilia A, valoctocogene roxaparvovec

1 | INTRODUCTION

Haemophilia A (HA) is an X-linked recessive bleeding disorder caused by deficiency of factor VIII (FVIII) protein.[1] Severe HA (SHA) is defined by FVIII activity level <1 IU/dL and is associated with recurrent spontaneous bleeds.[2,3] For SHA, FVIII concentrate and recombinant FVIII are used for routine prophylaxis to prevent and treat bleeding episodes. Alternatively, emicizumab can be used for routine prophylaxis.[2,4,5]

Emicizumab is a humanized, recombinant, bispecific monoclonal antibody that effectively mimics the function of activated FVIII[6,7] and is administered subcutaneously with an extended half-life of approximately 4 weeks.[8,9] Clinical trials for emicizumab used three dosing regimens: 3 mg/kg once weekly (QW) for 4 weeks as a loading dose, followed by 1.5 mg/kg QW; 3 mg/kg once every 2 weeks (Q2W); and 6 mg/kg once every 4 weeks (Q4W).[4,10,11] The mean trough concentration for all three dosing regimens is approximately 40 μg/mL[12] and is hypothesized to correspond to a similar level of haemostatic control as FVIII activity levels of 10–15 IU/dL.[2,13] Emicizumab is an approved therapy for SHA in the US and Europe that has been widely adopted for routine prophylaxis regardless of FVIII inhibitor status.[14–16]

Valoctocogene roxaparvovec is a gene therapy approved for SHA in the US and Europe[17,18] that uses an adeno-associated virus serotype 5 vector to transfer a B-domain–deleted human FVIII–coding sequence controlled by a liver-selective promoter.[19,20] In a phase 3, single-arm, open-label study (NCT03370913; GENEr8-1), 134 participants with SHA were treated with a single valoctocogene roxaparvovec infusion that supported endogenous FVIII production and reduced bleeding and FVIII use compared with FVIII prophylaxis.[19] GENEr8-1 and the phase 1/2 trial (NCT02576795)[20,21] demonstrated that for most participants, FVIII production gradually increased during the first 16 to 20 weeks following valoctocogene roxaparvovec infusion.[19–21] At the time of GENEr8-1 initiation, emicizumab was an investigational product, and individuals using emicizumab were excluded from enrollment.[19] This has caused uncertainty around how long individuals should continue emicizumab prophylaxis after receiving valoctocogene roxaparvovec.

This study uses published pharmacokinetic models of emicizumab combined with FVIII kinetics post dosing with valoctocogene roxaparvovec in GENEr8-1 to evaluate bleeding risk during transition from a long-acting haemophilia treatment (emicizumab) to an alternative treatment with slow onset (gene therapy). The objective is to identify ideal timing for emicizumab discontinuation to maintain haemostatic efficacy; aspects of transition such as burden, convenience, cost, joint status, or bleeding phenotypes must be considered on an individual basis by patients and clinicians.

2 | METHODS

2.1 | Emicizumab pharmacokinetic simulations

A population pharmacokinetic model was published previously to evaluate the pharmacokinetics of emicizumab QW, Q2W and Q4W dosing regimens.[22] This study used a database including 389 participants with HA from the phase 3, open-label, randomized HAVEN 1, 2, 3, and 4 clinical trials that evaluated emicizumab prophylaxis.[4,10,11,23] Plasma emicizumab concentrations were measured by a validated enzyme-linked immunosorbent assay.[22] Emicizumab pharmacokinetics were defined by a linear, one-compartment model with first-order absorption and elimination processes with no lag time.[22] Baseline body weight, age, race, and albumin levels were used as model covariates. Accordingly, 500 replicates of simulated emicizumab concentration-time profiles for 134 GENEr8-1 participants were conducted using the same covariates for each of the three emicizumab dosing regimens. Simulation profiles were compared to results of the previously published model to ensure consistency.[22]

2.2 | Bleeding risk estimation

Emicizumab concentrations were merged with the FVIII activity time-course data for GENEr8-1 participants to calculate bleeding risk. The FVIII activity levels from GENEr8-1 participants as assessed by a

TABLE 1 Assumptions used for creating the bleeding risk categories.

FVIII activity levels (IU/dL)	Average emicizumab levels at each week (μg/mL)	Bleeding risk category
<5	<15	Greater than emicizumab
	15 to <100	Same as emicizumab
	≥100	Less than emicizumab
5 to <15	<65	Same as emicizumab
	≥65	Less than emicizumab
≥15	Any	Less than emicizumab

Bleeding risk was defined by emicizumab exposure-response relationships as previously defined; see Section 2 for further details. Briefly, if emicizumab concentrations fell below 15 μg/mL and FVIII activity levels were <5 IU/dL, then individuals were assumed to have a greater bleeding risk compared with emicizumab prophylaxis alone. Alternatively, FVIII activity levels >15 IU/dL were assumed to provide greater haemostatic efficacy compared with emicizumab prophylaxis alone.
Abbreviation: FVIII, factor VIII.

validated chromogenic substrate assay (CSA) in a central laboratory were used for the presented analysis.[19] The proportion of participants in each bleeding risk category was calculated at weekly intervals for 20 weeks for each of the 500 replicates, and the median of those 500 replicates was reported for each emicizumab dosing regimen (QW, Q2W and Q4W) in both transition scenarios described below. Until endogenous FVIII activity levels reached 5 IU/dL, bleeding risk was estimated by emicizumab concentrations alone using published emicizumab exposure-response relationships.[24] Concentrations of emicizumab ranging from 15 to <100 μg/mL are associated with annualized bleeding rates (ABRs) of 0—4 bleeds/year.[13,25–27] When emicizumab concentrations fall to <10 μg/mL, bleeding risk increases substantially.[13,24]

Once endogenous FVIII levels reached >5 IU/dL, bleeding risk was determined by the assumptions in Table 1. FVIII activity levels ≥15 IU/dL were assumed to provide effective haemostatic control.[25,28] Based on these assumptions, bleeding risk was divided into three categories: greater than with emicizumab, same as with emicizumab, or less than with emicizumab prophylaxis. For example, if emicizumab concentrations fell below 15 μg/mL post gene therapy and FVIII activity levels did not rise to at least 5 IU/dL, then the individual was assumed to have a greater bleeding risk compared with emicizumab prophylaxis alone. If FVIII activity levels rose above 15 IU/dL, then the individual was assumed to have a lower bleeding risk than with emicizumab prophylaxis alone.

2.3 | Two scenarios with different timing for discontinuation of emicizumab

The pharmacokinetic simulations and the bleeding risk assumptions were used to evaluate two scenarios for individuals transitioning from emicizumab to valoctocogene roxaparvovec. Scenario 1 estimated outcomes for individuals whose last dose of emicizumab occurred on the day of valoctocogene roxaparvovec infusion. Scenario 2 estimated outcomes for individuals whose last dose of emicizumab occurred 4 weeks after valoctocogene roxaparvovec was administered. Given an emicizumab half-life of approximately 4 weeks,[8,9] emicizumab levels would have declined by greater than 90% by the end of the modelling experiments for either transition scenario.

3 | RESULTS

3.1 | Estimation of bleeding risk

Simulations estimated bleeding risk as individuals transitioned from emicizumab to valoctocogene roxaparvovec in two scenarios that differed based on the last dose of emicizumab administration: either with the valoctocogene roxaparvovec infusion or 4 weeks later. For both transition scenarios, simulations were conducted for three label-approved emicizumab dosing regimens (QW, Q2W and Q4W). Since the majority of individuals reach therapeutic FVIII activity levels ≥5 IU/dL in 4–12 weeks after valoctocogene roxaparvovec infusion, early discontinuation of emicizumab, with the last dose on the day of valoctocogene roxaparvovec infusion (scenario 1), versus additional doses of emicizumab for up to 4 weeks (scenario 2) offered similar levels of haemostatic control (Figure 1). The time course for bleeding risk was also similar across the three emicizumab dosing regimens for both scenarios following valoctocogene roxaparvovec infusion.

3.2 | Timing of discontinuation of emicizumab after gene therapy

An algorithm to guide decisions for emicizumab discontinuation was developed based on these results (Figure 2). FVIII activity levels should be evaluated 4 weeks after valoctocogene roxaparvovec infusion. If FVIII is ≥5 IU/dL at week 4 and remains ≥5 IU/dL at week 5, prescribers may consider discontinuing emicizumab. If FVIII is <5 IU/dL at week 4, prescribers should consider continuing emicizumab prophylaxis and continue weekly FVIII monitoring until two consecutive weekly measurements ≥5 IU/dL are achieved before considering discontinuing emicizumab. Endogenous FVIII activity for individuals receiving emicizumab must be assessed with the CSA using bovine reagents. The CSA with human reagents (i.e., human factor IXa and factor X) yields artificially high results in the presence of emicizumab due to its species-specific nature.[2,29–31]

3.3 | Theoretical case examples

We present theoretical case examples, based on actual study participants, that highlight specific considerations that could arise when transitioning from emicizumab to valoctocogene roxaparvovec. In these examples, details of the response to valoctocogene roxaparvovec

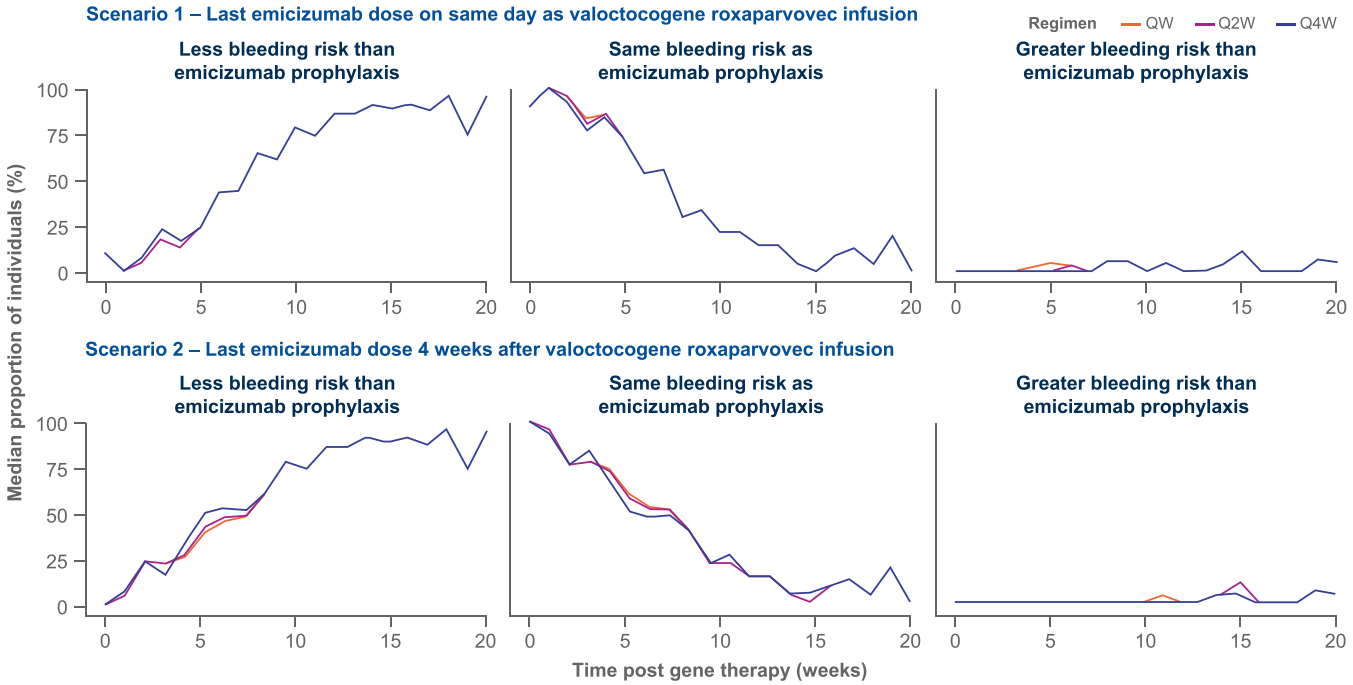

FIGURE 1 Proportion of individuals in each bleeding risk category over time compared with emicizumab prophylaxis. Emicizumab pharmacokinetic simulations were merged with FVIII activity kinetics from participants in GENEr8-1 to estimate the bleeding risk at weekly intervals for individuals as they transitioned from emicizumab to valoctocogene roxaparvovec. In scenario 1, the last emicizumab dose was administered at the same time as valoctocogene roxaparvovec infusion (week 0). In scenario 2, valoctocogene roxaparvovec was administered (week 0) and then 4 weeks later the last dose of emicizumab was given. The *y*-axis represents the median proportion of individuals in each bleeding risk category, with the sum of all three categories equaling 100% at any given time point (i.e., as the proportion of individuals in one category increases over time, the proportion of individuals in another category decreases). The bleeding risk categories of less than emicizumab, same as emicizumab, and greater than emicizumab are based on FVIII activity level and emicizumab blood concentration. Briefly, they rely on the assumption that a FVIII activity level ≥15 IU/dL provides haemostatic efficacy greater than that provided by emicizumab prophylaxis; see Table 1 for further details. FVIII, factor VIII; Q2W, once every 2 weeks; Q4W, once every 4 weeks; QW, once weekly.

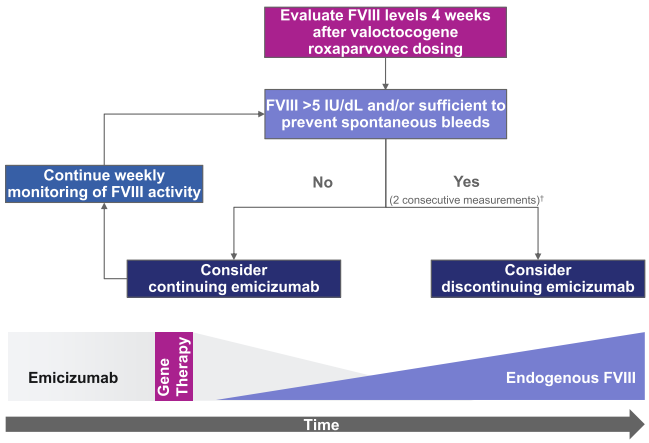

FIGURE 2 Treatment algorithm for discontinuation of emicizumab when transitioning to valoctocogene roxaparvovec. †Prescribers should consider continuing emicizumab prophylaxis and continue weekly monitoring of FVIII activity levels until two consecutive weekly measurements ≥5 IU/dL are achieved before discontinuation of emicizumab. There is an additive effect on hemostatic control from the combination of emicizumab and endogenous FVIII, especially when endogenous FVIII levels derived from the gene therapy are low. FVIII, factor VIII.

are drawn from real GENEr8-1 participants.[19] Figure 3 depicts their respective FVIII activity levels and timing of emicizumab discontinuation. All individuals had baseline FVIII activity levels below the lower limit of quantitation, and endogenous FVIII activity derived from an infusion of 6×10^{13} vg/kg valoctocogene roxaparvovec was monitored starting at week 4 with the CSA using bovine reagents. All individuals previously achieved steady-state plasma levels of emicizumab for routine prophylaxis; a dose of emicizumab was administered within 1 week prior to valoctocogene roxaparvovec infusion.

3.3.1 | Individual with early FVIII expression

A 37-year-old male received valoctocogene roxaparvovec and continued emicizumab 1.5 mg/kg QW for routine prophylaxis. In the past year, he had one traumatic right elbow bleed and three spontaneous left ankle bleeds (target joint) treated with exogenous FVIII. At weeks 4 and 5, his FVIII activity levels were 11.8 IU/dL and 12.4 IU/dL, respectively (Figure 3A). He did not have any further spontaneous bleeds or significant adverse events requiring exogenous FVIII or other medications. Since FVIII activity levels were >5 IU/dL for two consecutive weeks, he discontinued emicizumab at week 5. At week 8, his FVIII

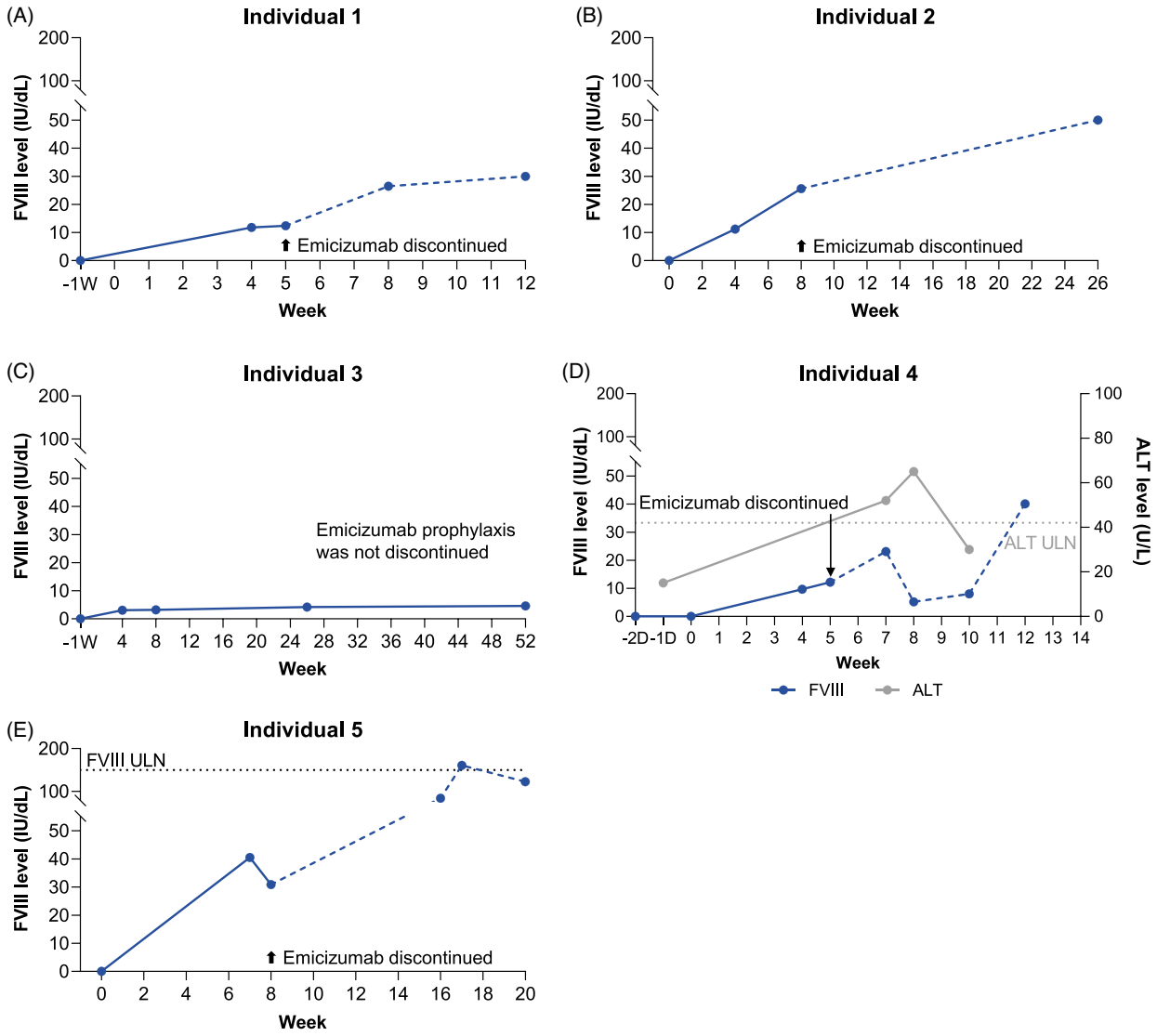

FIGURE 3 FVIII activity levels and emicizumab prophylaxis decisions for individuals identified in the case examples. (A) Individual with early FVIII expression. (B) The 'cautious' approach: continuing emicizumab until 'goal' FVIII expression is reached. (C) Individual who never achieved adequate FVIII activity levels. (D) Individual whose FVIII levels were adequate by week 4 but declined after transaminitis. (E) Individual with high FVIII levels. Valoctocogene roxaparvovec infusion occurred at week 0. The blue line denoting FVIII activity level begins at the last dose of emicizumab administration before valoctocogene roxaparvovec infusion, with the solid portion of the line denoting when individuals were receiving emicizumab prophylaxis. The dashed portion of the blue line denotes the period after discontinuation of emicizumab prophylaxis. FVIII activity level was measured with the CSA using bovine reagents. For individual 4, the ALT ULN was 42 U/L, and for individual 5, the FVIII ULN was 150 IU/dL. ALT, alanine transaminase; CSA, chromogenic substrate assay; D, day; FVIII, factor VIII; ULN, upper limit of normal; W, week.

activity level was 26.5 IU/dL. Twelve weeks after infusion, his FVIII activity levels rose to >30 IU/dL, and he remained bleed-free.

3.3.2 | The 'cautious' approach: continuing emicizumab until 'goal' FVIII expression is reached

A 45-year-old male received valoctocogene roxaparvovec and continued emicizumab 1.5 mg/kg QW for routine prophylaxis. His ABR prior to infusion was 5.0 bleeds/year, and he had four traumatic right-ankle bleeds caused by exercise and treated with exogenous FVIII. He played basketball two to three times per month and maintained a moderate level of physical activity. At week 4, his FVIII activity level was 11.2 IU/dL, and he had one traumatic bleed from exercise and treated with recombinant FVIII. He experienced no other significant bleeds but continued emicizumab prophylaxis due to regular exercise and subsequent risk of bleeding (Figure 3B). His FVIII activity level reached 25.6 IU/dL at week 8 and remained >20 IU/dL at week 9. Per the algorithm, discontinuing emicizumab would have been appropriate, but the individual and his haematologist were cautious given his prior history of bleeding events. However, they were reminded that haemostatic efficacy from emicizumab is roughly equivalent to a FVIII level of

10–15 IU/dL, lower than the individual's current FVIII activity level. They agreed to stop emicizumab with reassurance that FVIII activity would be monitored weekly. At week 26, the individual's FVIII activity remained >50 IU/dL, and there were no additional spontaneous bleeds.

3.3.3 | Individual who never achieved adequate FVIII activity levels

A 53-year-old male received valoctocogene roxaparvovec. In the 2 years prior, his self-reported ABR was 8.6 bleeds/year with prophylactic FVIII. He had knee surgery and unresolved target ankle and elbow joints. His haematologist prescribed emicizumab 3 mg/kg Q2W, and his ABR improved to 2.1 bleeds/year in the year before receiving valoctocogene roxaparvovec. He continued emicizumab prophylaxis after valoctocogene roxaparvovec infusion. At week 4, his FVIII activity level was 3.1 IU/dL measured by the CSA using bovine reagents (Figure 3C). At this point, the individual began additional physical exercise comprising daily walks. He reported experiencing one traumatic forearm bleed and one spontaneous bleed in his target elbow that were treated with exogenous FVIII. At week 8, his FVIII activity level was 3.2 IU/dL. Accordingly, he continued emicizumab prophylaxis with weekly monitoring of FVIII and maintained his regular walks. In weeks 8 through 24, his FVIII activity level remained below 4.8 IU/dL and he experienced two exercise-related traumatic bleeds. At week 26, based on his FVIII activity level of 4.2 IU/dL and his haematologist's assessment, he remained on emicizumab 3 mg/kg Q2W for routine prophylaxis. One year after valoctocogene roxaparvovec infusion, his FVIII activity level was 4.6 IU/dL and, despite the increased daily exercise, his ABR remained approximately half of its value while receiving FVIII prophylaxis. He remained generally well on emicizumab prophylaxis and continued to receive the standard of care recommended for individuals with severe HA receiving emicizumab. Throughout the following year, his ABR did not increase.

3.3.4 | Individual whose FVIII levels were adequate by week 4 but declined after transaminitis

A 26-year-old male received valoctocogene roxaparvovec and continued emicizumab 1.5 mg/kg QW for routine prophylaxis. Before gene therapy, his ABR was 3.5 with no target joints and his alanine transaminase (ALT) was 15 U/L. At week 4, his FVIII activity level was 9.7 IU/dL, and at week 5, his FVIII activity level was 12.2 IU/dL, so he discontinued emicizumab (Figure 3D). At week 7, his FVIII activity level was 23.1 IU/dL, but his ALT had increased to 52 U/L, which was greater than the upper limit of normal (ULN) per lab ranges (ULN, 42 U/L). He denied strenuous exercise, alcohol consumption, and concomitant medications. At week 8, his ALT remained elevated at 65 U/L and his FVIII decreased to 5.2 IU/dL. Prednisone 60 mg was initiated; at week 10, his ALT returned to within normal limits. His FVIII activity gradually increased to 40.1 IU/dL by week 12. His ALT stayed below the ULN after discontinuation of prednisone. He remained off emicizumab prophylaxis due to continued haemostatic control.

3.3.5 | Individual with high FVIII levels

A 33-year-old male received valoctocogene roxaparvovec and continued emicizumab 6 mg/kg Q4W for routine prophylaxis. His prior ABR was 3.5 bleeds/year, with no target joints. At week 7, his FVIII activity level was 40.5 IU/dL. At week 8, his FVIII activity level was 30.9 IU/dL, so he discontinued emicizumab (Figure 3E). His FVIII activity level gradually increased to 84.0 IU/dL at week 16. At week 17, his FVIII activity level was greater than the ULN at 161.0 IU/dL, and his ALT levels remained normal. He was not on any immunosuppression and did not receive exogenous FVIII after valoctocogene roxaparvovec infusion. His haematologist determined he had no risk factors for thromboembolic events, and no events suggestive of thromboembolism were identified. Thus, he was not given any anticoagulation or antiplatelet therapy while his FVIII activity level was above the ULN. After 3 weeks, his FVIII fell below the ULN by week 20 (122.7 IU/dL). No other adverse events associated with elevated FVIII activity level occurred. Due to continued haemostatic control, he remained off emicizumab for prophylaxis.

4 | DISCUSSION

Pharmacokinetic simulations showed no meaningful difference in bleeding risk with valoctocogene roxaparvovec treatment following different emicizumab doses and dosing regimens and that bleeding risk decreases over time as endogenous FVIII levels rise. As highlighted by theoretical case examples based on real study participants, a small number of individuals will not achieve FVIII activity >5 IU/dL following valoctocogene roxaparvovec. However, in the phase 1/2 and 3 valoctocogene roxaparvovec trials, participants who responded positively to gene therapy had FVIII activity levels that gradually increased until weeks 16–20 post infusion.[19,21] Therefore, an algorithm based on FVIII activity levels can help guide prescribers through decisions on when it may be appropriate to discontinue emicizumab earlier than 16–20 weeks after valoctocogene roxaparvovec infusion. In the instance where an individual's endogenous FVIII level either decreases or fails to elevate above 5 IU/dL in the first 16–20 weeks, continued prophylaxis with emicizumab or FVIII replacement therapy should be considered; the individual's risk of bleeding, prior bleeding phenotype, lifestyle, and physical activity are also important factors to consider.

For weekly monitoring of endogenous FVIII activity when transitioning from emicizumab prophylaxis to valoctocogene roxaparvovec, the CSA must be used with bovine reagents. The CSA with human reagents will provide erroneously high results in plasma samples that contain emicizumab.[29,30] If the CSA with human reagents was used for monitoring FVIII activity in individuals receiving emicizumab and valoctocogene roxaparvovec, it would provide a cumulative assessment of FVIII equivalence derived from emicizumab plus gene therapy-derived

endogenous FVIII. Like the CSA, the commonly used one-stage assay will also overestimate gene therapy-derived endogenous FVIII activity in the presence of emicizumab.[30]

Despite potential concerns regarding thrombotic complications due to the combined presence of emicizumab and gene therapy-derived endogenous FVIII, evidence suggests the transition can be made without increased thromboembolic risk to individuals. HAVEN 1, a phase 3 trial evaluating the safety and efficacy of emicizumab, reported five thrombotic events occurring in participants on emicizumab. However, all five events occurred after treatment for an acute bleeding episode with activated bypassing agents >100 U/kg/24 h. Accordingly, concomitant treatment of acute bleeding episodes with activated prothrombin complexes (aPCCs) for individuals receiving emicizumab has been discouraged.[2,12,31] No further thromboembolic events were reported in the HAVEN 2, 3, or 4 trials.[5]

Furthermore, therapeutic levels of emicizumab are associated with an approximate FVIII equivalence of 10–15 IU/dL.[32,33] The median peak FVIII activity in GENEr8-1 at 26 weeks post gene therapy was 66 IU/dL. Given the ULN for FVIII activity is 150 IU/dL,[34] the combined effect of gene therapy-derived FVIII and emicizumab are still well within normal limits for most individuals, even if they are still receiving emicizumab prophylaxis. For the less than 6% of GENEr8-1 participants who reached FVIII activity levels >150 IU/dL by 52 weeks post infusion,[19] none experienced adverse outcomes related to thromboembolic events.[19] While a small percentage of individuals will express very high levels of FVIII from the gene therapy, based on the FVIII activity kinetics from GENEr8-1, it will take weeks or months to achieve these levels, and this window provides more than sufficient time for emicizumab levels to decline or wash out completely. Ultimately, the risk of thrombosis following valoctocogene roxaparvovec infusion will likely be influenced more by the individual's cardiovascular status than any effect from co-treatment with emicizumab and valoctocogene roxaparvovec.

The HAVEN 1 through 4 clinical trials reported surgical outcomes from participants receiving emicizumab, including if surgical procedures were performed with exogenous FVIII supplementation.[35] Regardless of FVIII supplementation status, there was no thrombosis or thrombotic microangiopathy associated with the surgical procedures. Further, no new safety issues were identified by the combination of emicizumab prophylaxis and exogenous FVIII supplementation. While FVIII supplementation was left to the discretion of the investigator, the World Federation of Haemophilia advises that for lower-dose practice patterns, peak FVIII levels of 40–80 IU/dL are recommended during invasive surgical procedures.[2] This range is approximately in line with the median peak FVIII activity of 66 IU/dL observed in participants of GENEr8-1 at 26 weeks post gene therapy. Therefore, the surgical experiences from the HAVEN clinical trials provide further real-world evidence that individuals should be able to safely transition from emicizumab to gene therapy without experiencing increased thrombotic risk due to the combined presence of emicizumab and endogenous FVIII during the transition window. Finally, there was also no postoperative bleeding reported for 85.8% of minor procedures performed without FVIII and 74.3% of minor procedures performed with FVIII. The exogenous FVIII supplementation with emicizumab prophylaxis likely resulted in no additive or synergistic effect on haemostatic control because FVIII has a higher binding affinity for and capacity to generate factor Xa compared with emicizumab.[36] Accordingly, for individuals transitioning from emicizumab to gene therapy, there is no mechanistic rationale for continuing emicizumab administration once therapeutic levels of gene therapy-derived FVIII are established.

Overall, these original data suggest individuals on emicizumab prophylaxis can safely transition to valoctocogene roxaparvovec using several different strategies and appropriate endogenous FVIII monitoring (using the CSA with bovine reagents) while maintaining effective haemostatic control.

AUTHOR CONTRIBUTIONS

Suresh Agarwal, Dane Osmond, Vanessa Newman, and Josh Henshaw conceptualized and performed the modelling experiments. Suresh Agarwal, Cedric Hermans, Wolfgang Miesbach, Flora Peyvandi, Robert Sidonio Jr, Dane Osmond, Vanessa Newman, Josh Henshaw, and Steven Pipe contributed to the interpretation of the study results and provided critical input while drafting the manuscript. Cedric Hermans, Wolfgang Miesbach, Flora Peyvandi, Robert Sidonio Jr, and Steven Pipe provided clinical expertise for the case examples.

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CONFLICT OF INTEREST STATEMENT

Cedric Hermans reports consulting fees and honoraria as a speaker for educational symposia for Bayer, Bioverativ, CAF-DCF, CSL Behring, Kedrion, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Shire, and Sobi. Wolfgang Miesbach reports grant and research support from Bayer, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Sobi, Takeda, and uniQure; reports consulting fees from BioMarin Pharmaceutical Inc., Freeline, LFB, Novartis, Novo Nordisk, Octapharma, Pfizer, Roche, and Sobi; and reports honoraria as a speaker for educational symposia for Alexion Pharmaceuticals, Amgen, Bayer, Grifols, LEO Pharma, Novartis, Novo Nordisk, Pfizer, Roche, Shire, and Sobi. Flora Peyvandi reports honoraria as a speaker for educational symposia for Grifols, Sanofi, and Takeda; and reports honoraria as an advisory member for Roche and Sanofi. Robert Sidonio reports grants and consulting fees from Bayer, BioMarin Pharmaceutical Inc., Genentech, Guardian Therapeutics, HEMA Biologics, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sigilon, Sobi, and Takeda. Steven Pipe reports consulting fees from ApcinteX, ASC Therapeutics, Bayer, BioMarin Pharmaceutical Inc., CSL Behring, Equilibra Bioscience, Freeline, HEMA Biologics, LFB, Novo Nordisk, Pfizer, Roche/Genentech, Sanofi, Spark Therapeutics, Takeda, and uniQure; and service as a clinical trial investigator for BioMarin Pharmaceutical Inc., Freeline, Roche/Genentech, Sanofi, and uniQure. Suresh Agarwal,

Dane Osmond, and Josh Henshaw are employees and stockholders of BioMarin Pharmaceutical Inc. Vanessa Newman is a former employee of BioMarin Pharmaceutical Inc.

DATA AVAILABILITY STATEMENT

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.

ETHICS STATEMENT

Procedures were performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines; participants provided written informed consent.

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REFERENCES

1. Kenet G, Chen YC, Lowe G, et al. Real-world rates of bleeding, factor VIII use, and quality of life in individuals with severe haemophilia A receiving prophylaxis in a prospective, noninterventional study. *J Clin Med*. 2021;10(24):5959.
2. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26(6):1-158.
3. van Vulpen LFD, Holstein K, Martinoli C. Joint disease in haemophilia: pathophysiology, pain and imaging. *Haemophilia*. 2018;24(6):44-49.
4. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med*. 2018;379(9):811-822.
5. Callaghan MU, Negrier C, Paz-Priel I, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1–4 studies. *Blood*. 2021;137(16):2231-2242.
6. Kitazawa T, Igawa T, Sampei Z, et al. A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a hemophilia A model. *Nat Med*. 2012;18(10):1570-1574.
7. Sampei Z, Igawa T, Soeda T, et al. Identification and multidimensional optimization of an asymmetric bispecific IgG antibody mimicking the function of factor VIII cofactor activity. *PLoS One*. 2013;8(2):e57479.
8. Uchida N, Sambe T, Yoneyama K, et al. A first-in-human phase 1 study of ACE910, a novel factor VIII-mimetic bispecific antibody, in healthy subjects. *Blood*. 2016;127(13):1633-1641.
9. Muto A, Yoshihashi K, Takeda M, et al. Anti-factor IXa/X bispecific antibody (ACE910): hemostatic potency against ongoing bleeds in a hemophilia A model and the possibility of routine supplementation. *J Thromb Haemost*. 2014;12(2):206-213.
10. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377(9):809-818.
11. Young G, Liesner R, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. *Blood*. 2019;134(24):2127-2138.
12. European Medicines Agency. Assessment report: Hemlibra (international non-proprietary name: emicizumab). 2018. https://www.ema.europa.eu/en/documents/assessment-report/hemlibra-epar-public-assessment-report_en.pdf
13. Shima M, Hanabusa H, Taki M, et al. Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. *N Engl J Med*. 2016;374(21):2044-2053.
14. Curtis R, Roberts JC, Crook N, et al. Trends in prescribing practices for management of haemophilia: 1999–2021. *Haemophilia*. 2023;29(3):761-769.
15. Krumb E, Fijnvandraat K, Makris M, et al. Adoption of emicizumab (Hemlibra®) for hemophilia A in Europe: data from the 2020 European Association for Haemophilia and Allied Disorders survey. *Haemophilia*. 2021;27(5):736-743.
16. Mahlangu J, Iorio A, Kenet G. Emicizumab state-of-the-art update. *Haemophilia*. 2022;28(4):103-110.
17. VandenDriessche T, Pipe SW, Pierce GF, Kaczmarek R. First conditional marketing authorization approval in the European Union for hemophilia "A" gene therapy. *Mol Ther*. 2022;30(11):3335-3336.
18. Blair HA. Valoctocogene roxaparvovec: first approval. *Drugs*. 2022;82(14):1505-1510.
19. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene roxaparvovec gene therapy for hemophilia A. *N Engl J Med*. 2022;386(11):1013-1025.
20. Pasi KJ, Rangarajan S, Mitchell N, et al. Multiyear follow-up of AAV5-hFVIII-SQ gene therapy for hemophilia A. *N Engl J Med*. 2020;382(1):29-40.
21. Rangarajan S, Walsh L, Lester W, et al. AAV5-factor VIII gene transfer in severe hemophilia A. *N Engl J Med*. 2017;377(26):2519-2530.
22. Retout S, Schmitt C, Petry C, Mercier F, Frey N. Population pharmacokinetic analysis and exploratory exposure-bleeding rate relationship of emicizumab in adult and pediatric persons with hemophilia A. *Clin Pharmacokinet*. 2020;59(12):1611-1625.
23. Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. *Lancet Haematol*. 2019;6(6):e295-e305.
24. Jonsson F, Schmitt C, Petry C, Mercier F, Frey N, Retout S. Exposure-bleeding count modeling of emicizumab for the prophylaxis of bleeding in persons with hemophilia A with/without inhibitors against factor VIII. *Clin Pharmacokinet*. 2021;60(7):931-941.
25. den Uijl IE, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: the association of joint bleeds according to baseline FVIII activity levels. *Haemophilia*. 2011;17(1):41-44.
26. Lehtinen AE, Lassila R. Do we need all that emicizumab? *Haemophilia*. 2022;28(2):e53-e55.
27. Tang ASO, Leong TS, Ko CT, Chew LP. Efficacy of reduced-dose emicizumab in haemophilia A with inhibitors: real world experience in East Malaysia [abstract]. *Res Pract Thromb Haemost*. 2021;5(2). https://abstracts.isth.org/abstract/efficacy-of-reduced-dose-emicizumab-in-haemophilia-a-with-inhibitors-real-world-experience-in-east-malaysia/
28. Soucie JM, Monahan PE, Kulkarni R, Konkle BA, Mazepa MA. The frequency of joint hemorrhages and procedures in nonsevere hemophilia A vs B. *Blood Adv*. 2018;2(16):2136-2144.

29. Adamkewicz JI, Chen DC, Paz-Priel I. Effects and interferences of emicizumab, a humanised bispecific antibody mimicking activated factor VIII cofactor function, on coagulation assays. *Thromb Haemost*. 2019;119(7):1084-1093.
30. Jenkins PV, Bowyer A, Burgess C, et al. Laboratory coagulation tests and emicizumab treatment a United Kingdom Haemophilia Centre Doctors' Organisation guideline. *Haemophilia*. 2020;26(1):151-155.
31. National Bleeding Disorders Foundation. MASAC document 258-recommendation on the use and management of emicizumab-kxwh (Hemlibra®) for hemophilia A with and without inhibitors. Accessed June 2023. https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-258-recommendation-on-the-use-and-management-of-emicizumab-kxwh-hemlibrar-for-hemophilia-a-with-and-without-inhibitors
32. Kizilocak H, Marquez-Casas E, Brown J, Malvar J, Young G. Factor VIII level comparison in patients with severe hemophilia A on emicizumab with inhibitors with one stage, bovine and human chromogenic assays and the factor VIII equivalency of emicizumab using in vivo global hemostasis assays. *Blood*. 2021;138(1):4234-4234.
33. Kizilocak H, Marquez-Casas E, Malvar J, Carmona R, Young G. Determining the approximate factor VIII level of patients with severe haemophilia A on emicizumab using in vivo global haemostasis assays. *Blood*. 2019;27(5):730-735.
34. Lowe AE, Jones R, Kitchen S, et al. Multicenter performance evaluation and reference range determination of a new one-stage factor VIII assay. *J Clin Lab Anal*. 2022;36(4):e24294.
35. Kruse-Jarres R, Peyvandi F, Oldenburg J, et al. Surgical outcomes in people with hemophilia A taking emicizumab prophylaxis: experience from the HAVEN 1–4 studies. *Blood Adv*. 2022;6(24):6140-6150.
36. Lenting PJ, Denis CV, Christophe OD. Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? *Blood*. 2017;130(23):2463-2468.

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