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BRIEF REPORT

Emicizumab use in females with moderate or mild hemophilia A without factor VIII inhibitors who warrant prophylaxis

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Abstract

Background: Hemophilia A (HA) is predominantly associated with males due to X-linked inheritance. Males and females with HA have shared unmet medical needs, highlighting the necessity for comprehensive care irrespective of sex.

Objectives: This analysis investigated the efficacy and safety of emicizumab prophylaxis in 3 females with HA.

Methods: HAVEN 6 (NCT04158648) is a phase III study of emicizumab in people with non-severe HA without factor (F)VIII inhibitors warranting prophylaxis per investigator assessment, and the study methodology has been reported previously. Female-specific endpoints included menstruation-related quality of life and menstruation heaviness.

Results: HAVEN 6 enrolled 3 females aged ≥18 years and within reproductive age (n = 2 mild HA; n = 1 moderate HA; n = 2 receiving prior FVIII prophylaxis; n = 1 receiving prior episodic FVIII). Participants presented with diverse bleeding phenotypes at baseline: 2 had no bleeds in the 24 weeks prior to enrollment, while 1 had an annualized bleed rate for all bleeds of 208.6. On-study annualized bleed rates for all bleeds were 0, 2.8, and 11.6, respectively. The 2 evaluable participants indicated improved menstruation-related quality of life vs baseline. Two participants experienced 3 grade 1/2 treatment-related adverse events; no new safety signals were identified. All 3 participants preferred emicizumab over their previous treatment and reported a better score for treatment burden and preoccupation domains of the Comprehensive Assessment Tool of Challenges in Hemophilia questionnaire.

Conclusion: Overall, results were consistent with those reported in the male population enrolled in the HAVEN 6 study, suggesting efficacy and a favorable safety profile for emicizumab in females with non-severe HA warranting prophylaxis.

KEYWORDS
emicizumab, female, hemophilia A, prophylaxis

Essentials

- Currently, data are limited on the efficacy and safety of emicizumab prophylaxis in females.
- This analysis reports on emicizumab use in 3 females enrolled in HAVEN 6, a phase III study.
- Emicizumab led to improved bleed control and menstruation-related quality of life vs prior treatment.
- There were no new safety signals and efficacy was consistent with male participants in HAVEN 6.

1 | INTRODUCTION

Congenital hemophilia A (HA) is a rare, X-linked bleeding disorder caused by deficiency of coagulation factor (F)VIII. HA severity is categorized according to plasma FVIII activity: severe (<1% of normal levels), moderate (≥1% to ≤5%), and mild (>5% to <40%) [1]. However, people with non-severe HA have variable bleeding phenotypes not explained by FVIII activity levels alone [1]. Some people with non-severe HA present with a bleeding phenotype resembling severe disease, with spontaneous bleeds and bleeding into joints that may lead to long-term musculoskeletal complications [2]. The latest HA management guidelines recommend prophylaxis for bleed prevention in those with severe HA or a severe bleeding phenotype [3,4].

Females are an important population with non-severe HA. The Centers for Disease Control and Prevention have estimated that approximately 0.5% of severe, 1.4% of moderate, and 18% of mild HA cases in the United States surveillance database in 2021 were female [5]. In 2022, 448 females with HA (6 with severe, 10 with moderate, and 432 with mild disease) were registered in the FranceCoag database, representing 6.2% of all people with HA in this database [6]. According to the United Kingdom Haemophilia Centre Doctors' Organisation report released in 2021, 759 females with HA (9 with moderate and 750 with mild disease) were registered in their database, accounting for 11% of all people with severe, moderate, or mild HA in the United Kingdom [7]. Females with HA typically present with bleeding symptoms similar to males but also face their own specific symptoms and challenges, such as frequent hematomas and heavy and prolonged menstrual bleeding [8]. The medical community has traditionally recognized females as "carriers" of the gene responsible for hemophilia, perpetuating the erroneous idea that female carriers are asymptomatic [9,10]. The Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis recently proposed new nomenclature describing 5 categories: females with severe (<1% of normal FVIII levels), moderate (≥1% to ≤5%), or mild hemophilia (>5% to <40%), as defined in males with HA, but also symptomatic and asymptomatic hemophilia carriers (FVIII ≥40% of normal levels with and without a bleeding phenotype, respectively) [8,11]. This nomenclature, and increasing recognition of the shared unmet medical needs of males and females with HA, highlight the need for comprehensive care plans that do not exclude patients based on their sex [12].

Emicizumab is a recombinant, humanized, bispecific monoclonal antibody that bridges activated FIX and FX to substitute the function of deficient activated FVIII and improve hemostasis in people with HA. The HAVEN 1 to 5 clinical trials, which demonstrated the efficacy and safety of emicizumab in people with severe HA with or without FVIII inhibitors or HA with FVIII inhibitors, did not enroll female participants, despite eligibility being open to all sexes [13–17]. Following emicizumab approval, real-world data from 3 reports show a total of 7 females (aged 5, 6, 6, 6, 10, 11, and 47 years) with emicizumab exposures of 34 to 94.9 weeks [18–20]. Two of the reports described 4 females with severe HA without FVIII inhibitors (n = 1 [18] and n = 3 [19]) who received emicizumab. An analysis of the third report (ATHN 7 Natural History study) described 2 females with severe HA and 1 female with moderate HA receiving emicizumab [20]. All 3 reports corroborate the efficacy and safety profile previously established in the male population with severe HA.

The HAVEN 6 study (NCT04158648), the first phase III trial conducted in people with moderate or mild HA who warrant prophylaxis, enrolled 3 female participants with non-severe HA [21]. Here, we report the efficacy and safety of emicizumab prophylaxis in these females. Of note, female-specific assessments to evaluate menstruation-related quality of life (QoL) and menstruation heaviness during emicizumab prophylaxis are also reported. To our knowledge, this is one of the first reports describing the use of emicizumab in females with non-severe HA without FVIII inhibitors who warrant prophylaxis.

2 | METHODS

2.1 | Study design and participants

This analysis was undertaken in female participants of the HAVEN 6 study, a phase III, multicenter, open-label, single-arm study that evaluated the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab (1.5 mg/kg weekly, 3.0 mg/kg every 2 weeks, 6.0 mg/kg every 4 weeks) in people with moderate or mild HA without FVIII inhibitors. Eligible participants were males and females of all ages with a diagnosis of moderate (FVIII activity ≥1% to ≤5%) or mild (FVIII >5% to <40%) HA without FVIII inhibitors, who warranted prophylaxis based on investigator assessment. Mean FVIII activity was derived by bovine chromogenic assay and excluded samples collected after FVIII administration. Study locations, inclusion/exclusion criteria, methods, and types of data collected have been reported previously [21].

This study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice

TABLE Baseline characteristics.

Characteristic	Participant 1	Participant 2	Participant 3
Age	≥18 y and within reproductive age	≥18 y and within reproductive age	≥18 y and within reproductive age
Hemophilia severity at baseline	Moderate	Mild	Mild
Inhibitor status	No history of FVIII inhibitors	No history of FVIII inhibitors	Past history of FVIII inhibitors
Prior treatment	FVIII prophylaxis	FVIII prophylaxis	Episodic FVIII treatment
Reason for warranting prophylaxis	History of severe bleeding	History of frequent bleeding and joint bleeding	History of frequent bleeding
Number of bleeds in the past 24 wks	0	96	0
Presence of target joint at study entry	No	No	No

FVIII, factor VIII.

and the Declaration of Helsinki; written informed consent or assent for study participation was obtained before any study-related procedures. The protocol was approved by the institutional review board or ethics committee at each participating site and conducted in accordance with applicable regulations.

2.2 | Menstrual bleeding, quality of life, and treatment preference

The effect of emicizumab prophylaxis on menstruation-related QoL and menstruation heaviness was assessed using the Menstrual Bleeding Questionnaire (MBQ) on day 1 and every 4 weeks thereafter, with a possible score of 0 to 75; a reduction in score indicated improved menstruation-related QoL [22]. A Menstruation Diary with the Pictorial Blood Assessment Chart (PBAC) was completed monthly and menstrual blood loss was quantified using the PBAC score; lower scores indicated improved menstrual health [23,24]. Participant treatment preferences were gathered using the EmiPref questionnaire [25]. Health-related QoL was assessed via the Comprehensive Assessment Tool of Challenges in Hemophilia.

3 | RESULTS AND DISCUSSION

3.1 | Demographics

At the data cut-off (May 17, 2022), 72 participants were enrolled and had received treatment in the HAVEN 6 study. Of these, 3 were female, all were aged ≥18 years and within reproductive age. Two had a diagnosis of mild HA (FVIII levels >5% to <40%) and one had a diagnosis of moderate HA (FVIII levels ≥1% to ≤5%).). All warranted prophylaxis was determined by the investigator (Table). One participant was on each emicizumab administration schedule.

3.2 | Bleeding profiles and efficacy

The female participants with moderate HA had received FVIII prophylaxis prior to study entry. The investigator reported a history of severe bleeding as the reason for warranting prophylaxis. The participant reported no bleeding events in the 24 weeks prior to study entry and a total absence of bleeding episodes while receiving emicizumab prophylaxis for an on-study efficacy period of approximately 86 weeks.

One female participant with mild HA had mean endogenous FVIII activity of 7% in the study. The participant had a history of frequent bleeds and joint bleeding, with 4 joint bleeds per year reported prior to prophylaxis use; these factors warranted prophylaxis per investigator assessment and the participant had received FVIII prophylaxis prior to study entry. The participant also presented with hyperlaxity and a history of easy bruising, with a high number of untreated bleeds (mainly hematomas); consequently, this participant's estimated annualized bleed rate (ABR) for all bleeds was 208.6 in the 24 weeks prior to study entry. She reported frequent, untreated, spontaneous hematomas on her legs during the first 9 weeks of receiving emicizumab during the study. The hematomas were superficial and of minor clinical significance per investigator's assessment. After week 9, the occurrence of spontaneous hematomas resolved. The on-study ABR for all bleeds was 11.6, with no treated bleeds or joint bleeds reported during an efficacy period of approximately 63 weeks. Improved hemostatic efficacy was achieved during emicizumab prophylaxis compared with 24 weeks prior to study entry.

The other female participant with mild HA had a mean endogenous FVIII activity of 15% in the study. The participant was on episodic FVIII treatment due to treatment accessibility issues but warranted prophylaxis due to a history of frequent bleeding from birth, based on historical data. The participant had a resolved history of FVIII inhibitors and reported no bleeding events in the 24 weeks prior to study entry. The participant also presented with joint hypermobility syndrome. On day 42, the participant reported one

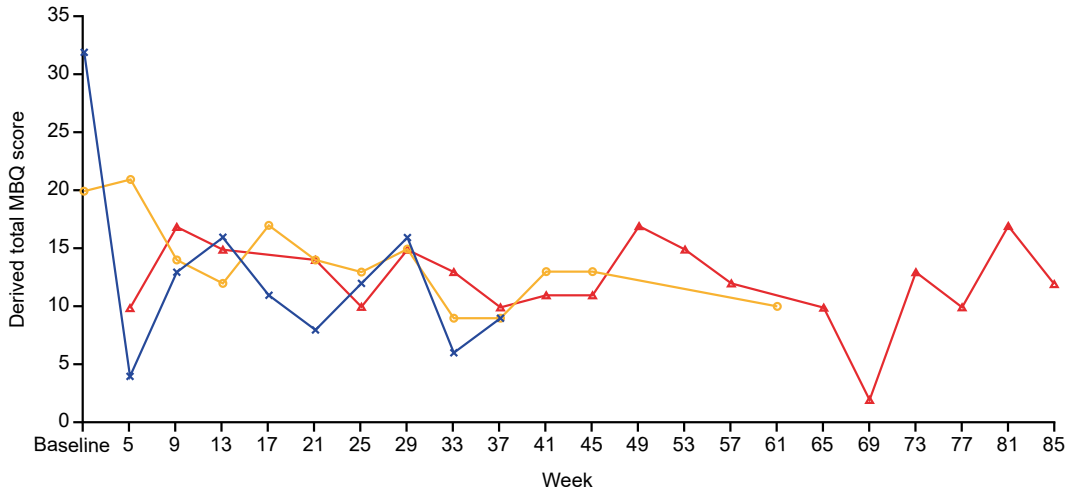

FIGURE 1 Menstrual Bleeding Questionnaire (MBQ) derived total score over time. Each colored line represents one participant.

spontaneous joint bleed in the left ankle, an area with longstanding problems likely due to the participant's hypermobility. The bleed was treated for 2 consecutive days with FVIII. Of note, the participant underwent a preplanned left ankle arthroscopy plus stabilization with an internal brace on day 51, confirming that the previous bleeding event occurred in an already compromised anatomical region. This major surgery was managed with additional prophylactic hemophilia medication, including FVIII and tranexamic acid, with no postoperative bleeds reported, no associated adverse events (AEs), and no recurrence of FVIII inhibitors. On day 247, the participant experienced a new spontaneous joint bleed in the left ankle, which was treated with FVIII for 2 consecutive days. Overall, the participant had an on-study ABR for all bleeds of 2.8.

The MBQ, which assessed menstruation-related QoL, indicated improvements in menstrual health for 2 participants who completed the questionnaire before receiving emicizumab (Figure 1). One participant did not complete the questionnaire prior to initiation of emicizumab prophylaxis. For one participant with a history of menorrhagia, the MBQ score was 32 at baseline but decreased and remained consistently <18 during emicizumab prophylaxis, indicating improved menstrual health-related QoL (Figure 1). Similarly, the PBAC monthly score at baseline was 300, decreasing to <100 by month 4, indicating a general improvement in menstrual health (Figure 2). For another participant, previously receiving prophylactic treatment, the MBQ score decreased from 20 at baseline to 12 at week 9, remaining consistently below the baseline value thereafter. The PBAC monthly score remained generally stable with an on-study median value of 93 (Figure 2). Of note, one participant previously receiving FVIII prophylaxis stopped tranexamic acid use to control heavy menstrual flow on day 1 of the study. Two of 3 participants received hormonal contraception (progestin-only) before starting the study and continued this while receiving emicizumab. The participant without baseline assessment who was previously on prophylactic treatment had an MBQ score of 10 at week 5, which remained consistent

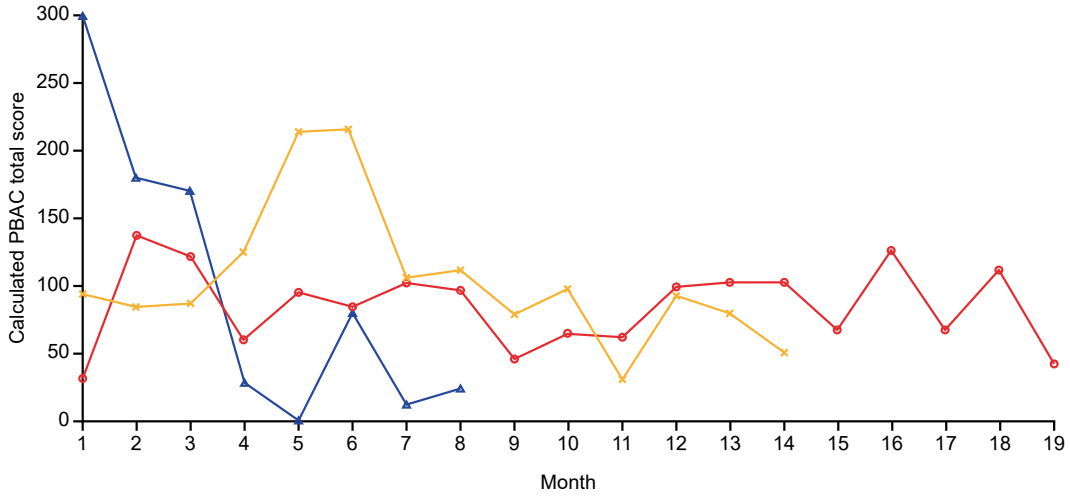

FIGURE 2 Calculated Pictorial Blood Loss Assessment Chart (PBAC) score per month. Each colored line represents one participant.

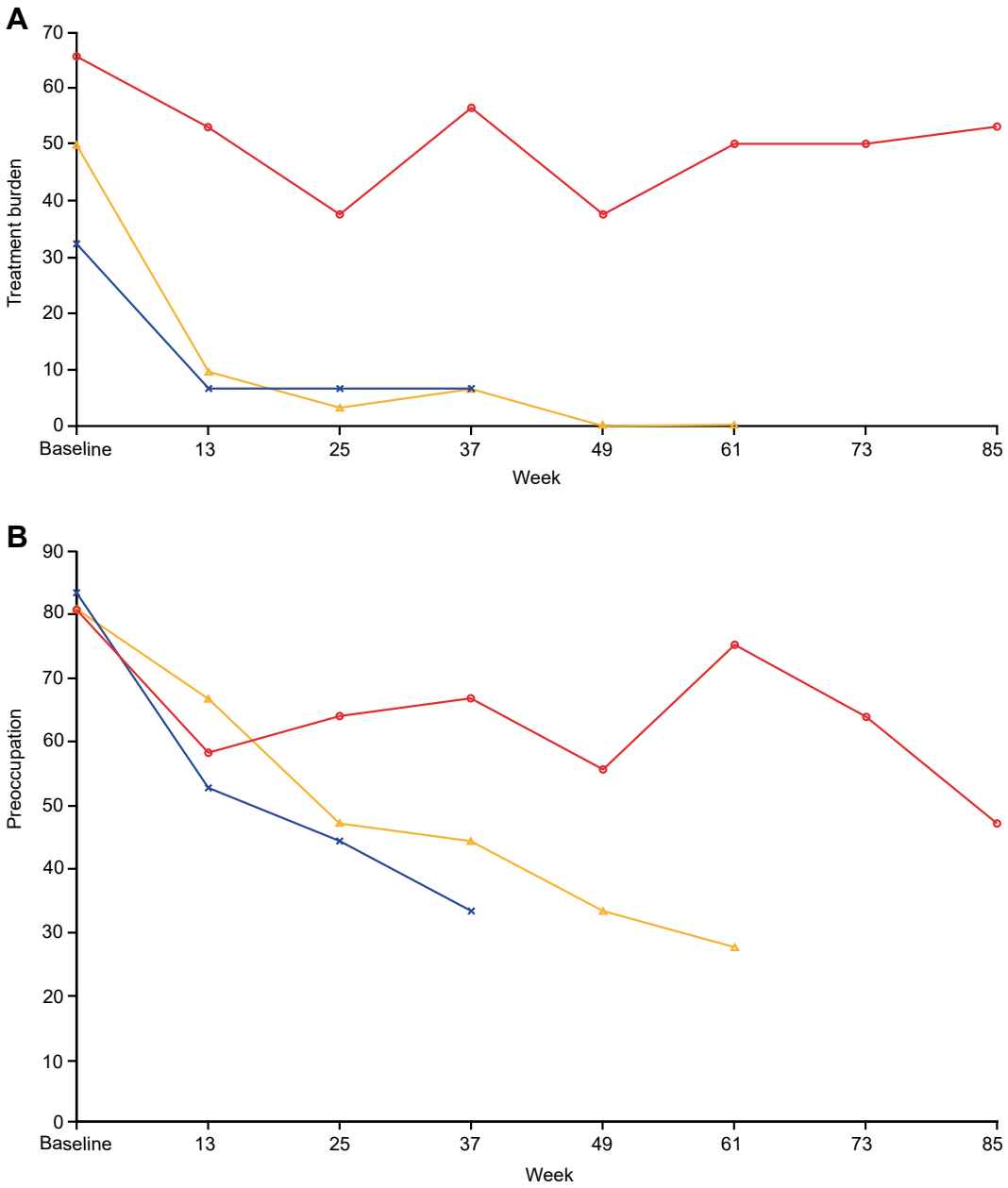

FIGURE 3 Treatment burden (A) and preoccupation domains (B) of Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH). Each colored line represents one participant.

throughout the study. The PBAC monthly score remained generally stable, with an on-study median of 95 (Figure 2).

Treatment burden and preoccupation domains of the Comprehensive Assessment Tool of Challenges in Hemophilia showed improved scores from baseline, indicating better QoL (Figures 3A and 3B). All 3 female participants preferred emicizumab over their previous i.v. HA medication when completing the EmiPref questionnaire, with all citing the convenience of administration as the most important factor in their treatment preference. Chosen items related to the administration convenience included "frequency of treatment was lower" and "the route of administration was easier."

3.3 | Safety

Emicizumab prophylaxis showed no new safety signals in these female participants with non-severe HA. Two participants experienced a total of 3 treatment-related AEs; all resolved spontaneously during the study. One participant experienced 2 grade 1 injection-site reactions, while one experienced a grade 2 headache. No thromboembolic events, thrombotic microangiopathies, or serious AEs had been reported by the female participants at the data cut-off. Concomitant use of progestin-only oral contraception and emicizumab in 2 participants did not result in any safety signals. Females of childbearing age should

consider using contraception while receiving emicizumab, due to the lack of data available for emicizumab during pregnancy and lactation.

4 | CONCLUSION

People with non-severe HA present with heterogeneous bleeding phenotypes, which may warrant prophylaxis. The bleeding phenotypes of the 3 female participants in HAVEN 6 were similar to the overall HAVEN 6 population, including a history of severe bleeds, frequent bleeding, frequent hematomas, and joint bleeding. Emicizumab prophylaxis generally led to improved bleed control, although one participant experienced 2 spontaneous bleeds in a compromised anatomical region. In the 2 participants who completed the MBQ, reductions in score indicated improved menstruation-related QoL. All 3 participants preferred emicizumab over their previous i.v. hemophilia treatment. No new safety signals were reported. Overall, results were consistent with those reported in the male population in HAVEN 6, suggesting efficacy and a favorable safety profile for emicizumab irrespective of hemophilia severity or sex. However, the study was limited by a small sample size; additional real-world data are needed to further understand emicizumab prophylaxis in females with non-severe HA.

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ETHICS STATEMENT

This study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki; written informed consent or assent for study participation was obtained before any study-related procedures. The protocol was approved by the institutional review board or ethics committee at each participating site and conducted in accordance with applicable regulations.

AUTHOR CONTRIBUTIONS

M.L. contributed to the study design. G.V., S.O., B.M.B., M.L., R.d'O. contributed to the study conduct. C.H., G.V., S.O., B.M.B., M.L., R.d'O., L.F. contributed to data collection. C.H., G.V., B.M.B., M.L., O.C., R.d'O. contributed to data analysis and interpretation. All authors revised the manuscript critically and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

RELATIONSHIP DISCLOSURE

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DATA AVAILABILITY

For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

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