







## ORIGINAL ARTICLE

# Safety and efficacy of long-term emicizumab prophylaxis in hemophilia A with factor VIII inhibitors: A phase 3b, multicenter, single-arm study (STASEY)

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## Abstract

**Background:** The bispecific monoclonal antibody emicizumab bridges activated factor IX and factor X, mimicking the cofactor function of activated factor VIII (FVIII), restoring hemostasis.

**Objectives:** The Phase 3b STASEY study was designed to assess the safety of emicizumab prophylaxis in people with hemophilia A (HA) with FVIII inhibitors.

**Methods:** People with HA received 3 mg/kg emicizumab once weekly (QW) for 4 weeks followed by 1.5 mg/kg QW for 2 years. The primary objective was the safety of emicizumab prophylaxis, including incidence and severity of adverse events (AEs)

Trial registration: This trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03191799).

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and AEs of special interest (thrombotic events [TEs] and thrombotic microangiopathies). Secondary objectives included efficacy (annualized bleed rates [ABRs]).

**Results:** Overall, 195 participants were enrolled; 193 received emicizumab. The median (range) duration of exposure was 103.1 (1.1–108.3) weeks. Seven (3.6%) participants discontinued emicizumab. The most common AEs were arthralgia ( $n = 33$ , 17.1%) and nasopharyngitis ( $n = 30$ , 15.5%). The most common treatment-related AE was injection-site reaction ( $n = 19$ , 9.8%). Two fatalities were reported (polytrauma with fatal head injuries and abdominal compartment syndrome); both were deemed unrelated to emicizumab by study investigators. Two TEs occurred (myocardial infarction and localized clot following tooth extraction), also deemed unrelated to emicizumab. The negative binomial regression model-based ABR (95% confidence interval) for treated bleeds was 0.5 (0.27–0.89). Overall, 161 participants (82.6%) had zero treated bleeds.

**Conclusions:** The safety profile of emicizumab prophylaxis was confirmed in a large population of people with HA with FVIII inhibitors and no new safety signals occurred. The majority of participants had zero treated bleeds.

#### KEYWORDS

antibody, blood coagulation factors, clinical trial, hemophilia A, hemostasis

#### Essentials

- Emicizumab is indicated for routine bleeding prophylaxis in people with hemophilia A.
- STASEY assessed the safety and efficacy of emicizumab prophylaxis over 2 years.
- The emicizumab safety profile was confirmed in a large population with factor VIII inhibitors.
- Results were consistent with other Phase 3 studies; most participants had zero treated bleeds.

## 1 | INTRODUCTION

Hemophilia A (HA) is a rare bleeding disorder caused by deficiency or dysfunction of coagulation factor VIII (FVIII).<sup>1</sup> Emicizumab is a recombinant, humanized, bispecific, monoclonal antibody that bridges activated factor IX (FIX) and factor X (FX), thereby mimicking the cofactor function of activated FVIII and restoring hemostasis.<sup>2</sup> Emicizumab is indicated for routine prophylaxis in people with HA, reducing annualized bleeding rates (ABRs) regardless of FVIII inhibitors.<sup>3–6</sup> Due to the pharmacokinetic (PK) properties of emicizumab, the subcutaneous dosing schedule is once weekly (QW), once every 2 weeks, or once every 4 weeks, as demonstrated in the HAVEN clinical trials.<sup>3–6</sup>

The HAVEN clinical program was pivotal in establishing the efficacy and safety of emicizumab for people with HA with and without FVIII inhibitors. In HAVEN 1, three thrombotic microangiopathies (TMAs) and two thrombotic events (TEs) occurred in participants who received a cumulative dose of  $>100$  U/kg/24 h of activated prothrombin complex concentrate (aPCC) for  $\geq 24$  h.<sup>7</sup> A small number of additional TEs (not associated with aPCC) have since been reported in people treated with emicizumab; however, these occurred

in people with known comorbidities or preexisting risk factors.<sup>8</sup> In a pooled analysis of HAVEN 1–4, the most common adverse event (AE) was injection-site reaction (ISR) (26.8%), and the model-based ABR for treated bleeds across the study period was 1.4 (95% confidence interval [CI], 1.1–1.7). During Weeks 121–144, 82.4% of participants had zero treated bleeds.<sup>7</sup>

Emicizumab does not share sequence homology with FVIII and does not have the potential to induce or enhance the development of direct inhibitors to FVIII.<sup>9</sup> However, the presence of anti-drug antibodies (ADAs) was observed during the HAVEN clinical program.<sup>10</sup> The presence of ADAs may alter the pharmacokinetics (PK) and pharmacodynamics (PD) of emicizumab, affecting its efficacy and safety.<sup>10,11</sup>

With any new treatment, it is important to assess safety and efficacy in a broader population, for an extended time, and in a postmarketing setting. The STASEY study (Study to Assess Safety of Emicizumab Prophylaxis) was conducted to evaluate the safety and tolerability of emicizumab prophylaxis in people with HA with FVIII inhibitors. The incidence and severity of AEs including TEs and TMAs were recorded in people with HA receiving emicizumab treatment for up to 2 years.

## 2 | METHODS

### 2.1 | Study conduct

The STASEY study (NCT03191799) was a Phase 3b, multicenter, single-arm study performed in people aged 12 years or older, with congenital HA and FVIII inhibitors. The study was designed by the sponsor (F. Hoffmann–La Roche Ltd). Data were collected by participants and site investigators. Data analysis was conducted by the trial statistician and pharmacologist employed by the sponsor, who vouch for accuracy and data completeness.

This study was conducted in accordance with the International Conference on Harmonization (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. The study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). The study protocol was approved by the relevant independent ethics committee or institutional review board at each participating institution, and an independent Data Monitoring Committee was established to monitor safety and study conduct.

All participants provided written informed consent prior to any study-related procedures being performed; participants aged less than 18 years had informed consent provided by their legal guardian. The first patient's first visit was September 5, 2017, and the last patient's last visit was November 19, 2020.

### 2.2 | Participants

People aged 12 years or older with congenital HA and FVIII inhibitors were eligible to participate if they had documented treatment with bypassing agents or FVIII concentrates in the past 6 months (on-demand or prophylaxis), adequate hematologic function, and a history of persistent FVIII inhibitors (inhibitor titer at study entry did not influence eligibility). People were excluded from study entry if they had ongoing (or planned to receive during the study period) immune tolerance induction therapy. A full list of inclusion and exclusion criteria is provided in Appendix S1.

All participants who received more than one dose of emicizumab formed the safety-evaluable population. The intent-to-treat population included all enrolled participants who signed the consent form.

### 2.3 | Study design

Enrolled participants received emicizumab administered subcutaneously at 3 mg/kg QW for 4 weeks (loading dose) followed by 1.5 mg/kg QW (maintenance dose) for the remainder of the 2-year treatment period. The dose could be increased to 3 mg/kg/week in cases of suboptimal bleed control on the 1.5 mg/kg/week emicizumab dose.

### 2.4 | End points

The primary end point was to evaluate the overall safety and tolerability of emicizumab. This included recording the incidence and severity of AEs, grouped according to their Medical Dictionary for Regulatory Activities System Organ Class, including AEs of special interest such as TEs, TMAs, hypersensitive reactions, anaphylaxis and anaphylactoid events, AEs of Grade 3 or above, AEs and serious AEs (SAEs) related to study treatment, AEs that led to modification/interruption of study treatment, and AEs that led to discontinuation of study. The incidence of AEs was presented as the number and percentage of participants with these events.

The secondary end point was to evaluate the efficacy of emicizumab. Participants were provided with an electronic patient-reported outcome (ePRO) device to record information on bleeds, including the site and type of bleed, time of each individual bleed (day, start and stop time), and treatment for the bleed, via the Bleed and Medication Questionnaire. The number of all bleeds, treated bleeds, treated joint bleeds, treated target joint bleeds, and treated spontaneous bleeds were recorded. Bleeds due to surgery/procedure were excluded. Definitions of bleeding events were adapted from the ISTH Scientific and Standardization Committee<sup>12</sup> (Appendix S1).

Additional secondary end points included health-related quality-of-life (HRQoL) measures to investigate the impact of prophylactic administration of emicizumab and to evaluate the longitudinal changes in HRQoL with emicizumab compared with the previous treatment regimen received by the participants. HRQoL was assessed using the Hemophilia Quality-of-Life Questionnaire (Haem-A-QoL)<sup>13,14</sup> for participants aged 18 years or older or Haemo-QoL-Short Form (Haemo-QoL-SF)<sup>14,15</sup> for participants aged 12–17 years. The impact of emicizumab prophylaxis on health status was assessed using the EuroQoL Five-Dimension Five-Level Questionnaire (EQ-5D-5L version 2),<sup>16,17</sup> All questionnaires were completed at Week 1; Months 3, 6, 12, 18; and at study completion (Month 24) or early termination. Participant preference for emicizumab compared with previous regimens was assessed through a paper version of the Emicizumab Preference (EmiPref) survey.<sup>18</sup>

Other secondary end points included the measurement of emicizumab PK at Weeks 1–5 and Months 3, 6, 12, 18, and 24; quantification of exploratory safety biomarkers including prothrombin time (PT), reported as international normalized ratio (INR), and D-dimer monitoring; PD biomarker analysis, including activated partial thromboplastin time (aPTT) and FVIII-like activity using chromogenic assays with human factors. A safety follow-up visit was conducted 24 weeks after the last dose of emicizumab in participants who discontinued emicizumab.

Finally, immunogenicity was analyzed by measuring the presence of ADAs using a validated sandwich ELISA method and plasma samples taken at baseline; Week 5; Months 3, 6, 12, 18, and 24; and at the safety follow-up visits when they occurred. For further information on the ADA assay, please see the publication by Schmitt et al.<sup>10</sup> ADA-positive samples from ADA-positive participants were further analyzed for neutralizing capacity using a modified FVIII chromogenic assay that measured emicizumab activity after ADA

enrichment. ADAs were considered transient if they were detected at only one postdose sample (with the exclusion of the last sampling time point). Immunogenicity was assessed by examining the incidence and clinical significance of antibodies to emicizumab, and immunogenicity analysis included participants with one or more postdose ADA assessments.

Further information on the assays used to measure PK, biomarkers, and ADAs can be found in Appendix S1.

## 2.5 | Statistical analysis

A sample size of approximately 200 people with HA with FVIII inhibitors was planned to allow estimation of the AE incidence rate with a sufficient degree of precision (between 2.5% and 15%) in this safety study. A planned interim analysis was performed when 100 participants had received treatment with emicizumab for 24 weeks or more, and a second interim analysis was performed when 100 participants had received treatment with emicizumab for 52 weeks or more.<sup>19</sup> The final analysis was planned when all participants had completed 2 years of treatment or had withdrawn, whichever occurred first.

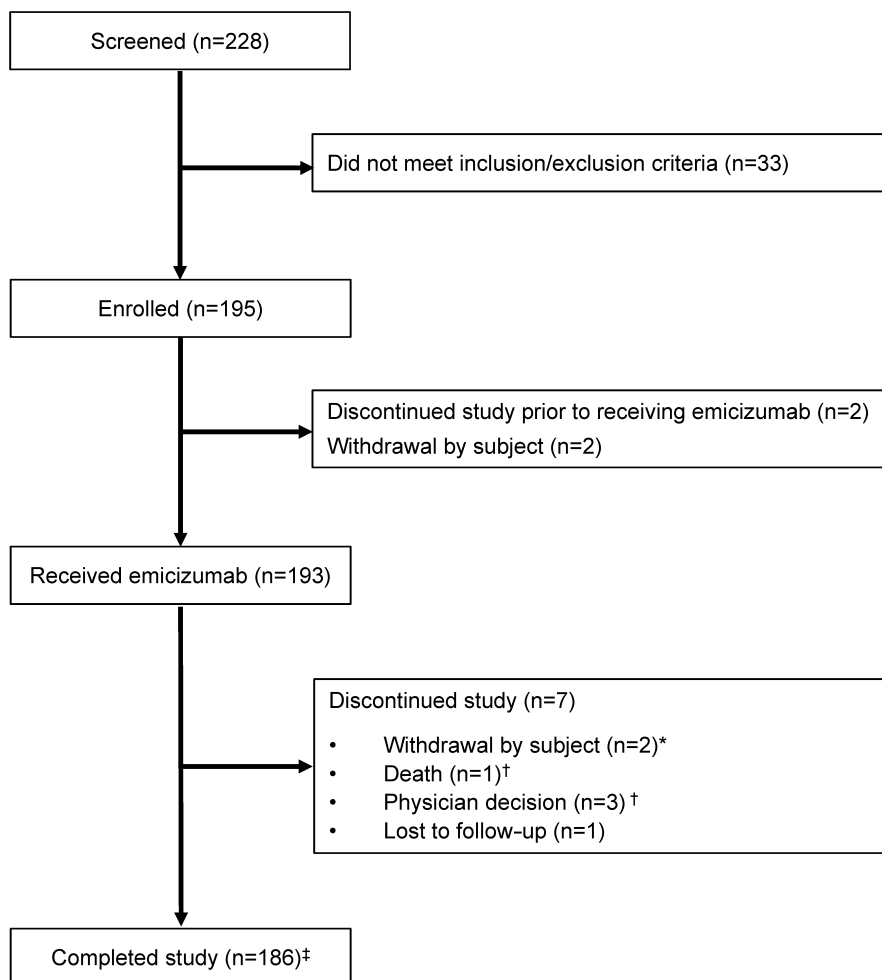
No formal statistical hypothesis tests were performed, and all analyses were considered descriptive. Categorical data were

summarized using frequencies and percentages. Continuous data were summarized using descriptive statistics. The World Health Organization scale was used to assess AE severity. For bleed-related end points, a negative binomial regression model, which accounts for different follow-up times, was used to determine ABRs. Mean ABRs were also calculated with standard descriptive summary statistics. Quality-of-life (Haem-A-QoL and Haemo-QoL-SF) and EQ-5D-5L data were summarized descriptively over time.<sup>20,21</sup> For the EmiPref survey, 95% CIs were calculated using the Pearson-Clopper one-sample binomial method.

## 3 | RESULTS

### 3.1 | Participant disposition

A total of 195 people with HA were enrolled across 72 sites. Participants were enrolled across the globe, including from countries not involved in the HAVEN program: India, Mexico, Russia, Saudi Arabia, Colombia, Panama, Portugal, Sweden, Hungary, Finland, Guatemala, and Romania (Table S1). All participants were male. Of the 195 participants enrolled, 193 (99.0%) received emicizumab prophylaxis QW (Figure 1). The study was completed by



**FIGURE 1** Participant disposition. \*Includes one participant who discontinued emicizumab by participant choice, following an AE of nephrotic syndrome owing to underlying Type 1 diabetes mellitus. †One participant discontinued emicizumab due to physician decision on Day 31 and died on Day 128 due to polytrauma head injury (counted under physician decision as the reason for study discontinuation), and one participant died due to adenocarcinoma of the colon and abdominal compartment syndrome, with the cause of death being aspiration pneumonitis. ‡Includes two participants treated for 694/695 days who were considered to have completed the study; final study visits were not completed due to the COVID-19 pandemic. AE, adverse event

186 participants (95.4%), including two participants who received emicizumab for less than 104 weeks (99 weeks) but were unable to attend their final study visits or finish the 2-year treatment period due to the COVID-19 pandemic. Owing to the circumstances, these two participants were considered to have completed the study. Nine participants (4.6%) discontinued from the study, including the two participants who discontinued before receiving emicizumab; the most common reason for discontinuation was withdrawal by participant (4 [2.1%]) (Figure 1). Reasons given for withdrawal by participant included two withdrawals of consent prior to receiving emicizumab; and two withdrawals due to AEs (unrelated to emicizumab; reported below under Safety). Three of the nine participants who discontinued from the study withdrew due to physician decision; one due to noncompliance with the ePRO completion, despite repeated attempts to contact the participant; one due to noncompliance with the protocol (this participant later died due to an AE that was unrelated to emicizumab; reported below under Safety); and another due to the participant being unable to manage a breakthrough bleed with recombinant factor VIIa (rFVIIa). One participant chose to discontinue emicizumab treatment and was lost to follow-up, and the remaining participant discontinued the study due to death (unrelated to emicizumab; reported below under Safety).

### 3.2 | Demographics and baseline characteristics

The median (interquartile range [IQR]) age of participants was 28.0 (19.0–44.0) years; the majority were aged 18 or older to less than 65 years ( $n = 145$  [75.1%]) (Table 1). Almost all participants had severe HA ( $n = 181/193$  [93.8%]), and all participants had FVIII inhibitors. Over half of the participants had previously been treated episodically ( $n = 114$  [59.1%]) and around a third (34.7%) prophylactically. Twelve (6.2%) participants had a history of both episodic and prophylactic treatment regimens. At baseline, the majority of participants had more than one target joint ( $n = 86$  [67.7%]), and 23.4% ( $n = 45$ ) had nine or more bleeds during the 24 weeks prior to enrollment. The median (IQR) number of bleeds during the 24 weeks prior to enrollment was 4.0 (2.0–8.0). The most common associated disorder was hemophilic arthropathy ( $n = 42$  [21.8%]) (Table S2).

### 3.3 | Safety

The median (range) duration of exposure for the safety-evaluable population ( $n = 193$ ) was 103.1 (1.1–108.3) weeks. Overall, 163 participants (84.5%) experienced a total of 800 AEs during the study (Table 2). For participants whose dose was up-titrated ( $n = 2$ ), safety outcomes presented include data before up-titration only. One of the two people whose dose was up-titrated experienced one AE (headache) after up-titration. The other person experienced nine AEs after up-titration: seven counts of posttraumatic pain, one of dengue fever, and one of arthralgia. All of these AEs were nonserious, Grade 1–2, and unrelated to emicizumab.

**TABLE 1** Baseline characteristics and demographics

	1.5 mg/kg emicizumab QW ( $n = 193$ ) <sup>a</sup>
Age (years)	
Median (IQR)	28.0 (19.0–44.0)
Age group (years), $n$ (%)	
$\geq 12$ to $< 18$	39 (20.2)
$\geq 18$ to $< 65$	145 (75.1)
$\geq 65$	9 (4.7)
Sex, $n$ (%)	
Male	193 (100)
Race, $n$ (%)	
White	119 (61.7)
Asian	38 (19.7)
American Indian or Alaska Native	19 (9.8)
Unknown	9 (4.7)
Black or African American	7 (3.6)
Native Hawaiian or other Pacific Islander	1 (0.5)
Ethnicity, $n$ (%)	
Hispanic or Latino	41 (21.2)
Not Hispanic or Latino	141 (73.1)
Not reported	8 (4.1)
Unknown	3 (1.6)
Hemophilia severity at baseline, $n$ (%)	
Mild	3 (1.6)
Moderate	9 (4.7)
Severe	181 (93.8)
Hemophilia treatment history, $n$ (%)	
Episodic treatment only	114 (59.1)
Prophylactic treatment only	67 (34.7)
Both episodic and prophylactic treatments	12 (6.2)
Prior hemophilia treatment in the past 24 weeks, $n$ (%)	192 (99.5)
Prothrombin complex concentrate	98 (51.0)
Recombinant factor VIIa	94 (49.0)
Factor VIII	46 (24.0)
Other	8 (4.2)
Historical peak inhibitor titer	$n = 192$
Median (range)	85.0 (0–32,700.0)
$< 5$ BU/ml, $n$ (%)	19 (9.8)
$\geq 5$ BU/ml, $n$ (%)	173 (89.6)
Unknown, $n$ (%)	1 (0.5)
Previously treated with ITI, $n$ (%)	
Yes	100 (51.8)
No	93 (48.2)
Number of bleeds in the past 24 weeks	$n = 192$

(Continues)

TABLE 1 (Continued)

	1.5 mg/kg emicizumab QW (n = 193) <sup>a</sup>
Median (IQR)	4.0 (2.0–8.0)
<9, n (%)	147 (76.6)
≥9, n (%)	45 (23.4)
Number of target joints prior to study entry, n (%)	
No target joint	66 (34.2)
Any target joint	127 (65.8)
1 joint	41 (32.3)
>1 joint	86 (67.7)

Note: n represents the number of participants contributing to summary statistics. Participants started with loading dose of 3 mg/kg/week emicizumab for 4 weeks.

Abbreviations: BU, Bethesda unit; ITI, immune tolerance induction; IQR, interquartile range; QW, once weekly.

<sup>a</sup>Demographic data are presented for the safety-evaluable population.

This excludes two participants who were enrolled but withdrew consent prior to receiving emicizumab prophylaxis.

In the safety-evaluable population, the most frequently reported AEs were arthralgia, nasopharyngitis, and headache (Table S3). A total of 20 participants (10.4%) had ISRs of Grade 1 severity, and two participants (1.0%) had ISRs of Grade 2 severity. In most cases (19/22 participants [86.4%]), ISRs were assessed by the investigators as related to emicizumab treatment.

During the study, 31 participants (16.1%) reported 50 SAEs (Table S4). The SAEs with the highest incidence were femur fracture, wound dehiscence, catheter-site abscess, and hematoma of the muscle, which occurred in two participants each. One SAE (2.0%) was considered related to emicizumab: a catheter-site abscess, which was treated with antibiotics and tranexamic acid; bleeds related to Hickman line removal were treated with rFVIIa. The abscess resolved, and the dosing of emicizumab was not changed.

Thirty-five participants (18.1%) reported AEs that were considered by the investigator to be related to emicizumab; all but two (the catheter-site abscess and a postprocedural hematoma) were Grade 1 (Table S5). The most frequent treatment-related AEs reported were ISRs (19 participants [9.8%]) and pruritus and somnolence in two participants each (2.0%).

Two participants had fatal AEs during the study that were assessed by the investigators as unrelated to emicizumab. One participant (27-year-old man) received the last dose of emicizumab on Study Day 31, and discontinued emicizumab by physician decision due to the participant's noncompliance with the protocol. The participant later died due to polytrauma with fatal head injuries on Study Day 128. The second participant (59-year-old man) underwent multiple surgeries with rFVIIa as pre- and postoperative treatment between Study Days 662 and 679. On Study Day 680, the participant was diagnosed with Grade 4 abdominal compartment syndrome (organ dysfunction caused by intra-abdominal hypertension). On Study Day 693, the participant developed Grade 4 aspiration pneumonitis and died due to sepsis, aspiration pneumonitis, and respiratory

TABLE 2 Safety summary

	1.5 mg/kg emicizumab QW (n = 193)
Total number of participants with ≥1 AE, n (%)	163 (84.5)
Total number of AEs	800
Total number of participants with ≥1, n (%)	
Fatal AE	2 (1.0)
Serious AE	31 (16.1)
AE leading to withdrawal from treatment	1 (0.5)
AE leading to dose modification/interruption	4 (2.1)
AE leading to study discontinuation	1 (0.5)
Grade ≥3 AE	39 (20.2)
Related AE	35 (18.1)
Local injection-site reaction	22 (11.4)
AEs of special interest, n (%)	
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	0
Thrombotic event	2 (1.0)
Thrombotic event related to aPCC and emicizumab	0
Thrombotic microangiopathy	0

Note: n represents the number of participants. The numbers for systemic hypersensitivity/anaphylactic/anaphylactoid reaction using the Sampson Criteria<sup>34</sup> included all participants who experienced indicative symptoms. Multiple occurrences of the same AE in one individual were counted only once except for the "total number of AEs" row, in which multiple occurrences of the same AE were counted separately. Included data before up-titration only, for participants whose dose was up-titrated. Included treatment-emergent AEs starting on or before the end of the AE reporting period. Participants started with loading dose of 3 mg/kg/week emicizumab for 4 weeks. Abbreviations: AE, adverse event; aPCC, activated prothrombin complex concentrate; QW, once weekly.

failure. The investigator believed the abdominal compartment syndrome and sepsis led to multiorgan failure, while aspiration led to severe pneumonitis. The investigator considered the hemorrhage, abdominal compartment syndrome, and pneumonia aspiration, to be unrelated to emicizumab and related to the participant's HA, concurrent illness, procedures, and other unknown causes. The last dose of emicizumab was received on Study Day 687. Further details are available in Appendix S1.

One participant (0.5%) chose to discontinue emicizumab following an AE of nephrotic syndrome. Following an extensive nephrology evaluation, the investigator considered nephrotic syndrome to be unrelated to emicizumab and related to Type 1 diabetes mellitus. The participant was offered the option to continue emicizumab following this event but chose not to, and consequently emicizumab was permanently discontinued, with the last dose administered on Day 43. Notably, this participant was

reported by the investigator to have diabetic nephropathy with microalbuminuria and poor nutrition prior to study enrollment, and therefore was in violation of the exclusion criteria at study entry. Further details are available in Appendix S1.

Four participants (2.1%) had AEs that led to dose interruption. These included exacerbation of hepatitis C, which led to a 2-week interruption; syncope during first emicizumab administration, which led to a delay of less than 1 h (recorded as an interruption); nasopharyngitis and ear congestion, which led to an interruption of 1 week; and exacerbation of chronic pancreatitis (Grade 2) and a retroperitoneal hematoma, which was recorded as an interruption, but the participant received his last dose of emicizumab on Study Day 162 and chose to withdraw from the study on Study Day 183. None of these AEs were considered to be related to emicizumab.

No participants in the study had a TMA. Two participants (1.0%) had TEs, both of which were considered by the investigator to be unrelated to emicizumab. One participant had ST-segment-elevation myocardial infarction due to thrombus in a coronary artery. The participant was not receiving any bypassing agents at the time of the event. The participant had preexisting risk factors, including smoking, hypertension, and family history of coronary heart disease, and the investigator considered the event to be related to an ischemic heart attack. The participant received treatment with clopidogrel, lysine acetylsalicylate, and heparin. Coronary angiography revealed critical stenosis of the right coronary artery due to thrombotic sub-occlusion by an atheromatous lesion and diffuse atherosclerotic disease of the coronary artery. The participant received further treatment with protamine sulfate (to antagonize heparin), atorvastatin, ramipril, acetylsalicylic acid, and potassium chloride. The event was considered resolved 5 days later. The second participant had postoperative thrombosis at the site of a tooth extraction (a localized hypertrophic clot); this participant was receiving a combination of antifibrinolytics and rFVIIa. Treatment with etoricoxib, amoxicillin, and clavulanic acid was maintained, and the event was considered resolved 6 days later.

No TEs or TMAs were observed in any of the five participants who received aPCC alongside emicizumab prophylaxis during the course of the study. Guidance regarding aPCC (maximum dose, 100U/kg/24h of aPCC for 24h or more) was followed (for further details on aPCC doses given to treat bleeds, please refer to Table 3).

### 3.4 | Efficacy

Overall, compliance with the Bleed and Medication Questionnaire was high, with 96.8% of days completed. The model-based ABR (95% CI) for treated bleeds was 0.5 (0.27–0.89) and the mean ABR (95% CI) calculated for treated bleeds was 0.6 (0.00–4.85). Overall, 161 participants (82.6%) had zero treated bleeds. A summary of bleed-related end points is presented in Table 4.

Of 136 treated bleeds recorded during the STASEY trial, 13 were treated with aPCC, and 112 were treated with rFVIIa (Table 3). Of those treated with aPCC, most (61.5%) were treated with one infusion;

**TABLE 3** Non-emicizumab hemophilia medication given to treat bleeds (ITT population,  $N = 195$ )

	Treated bleeds ( $N = 136$ ) <sup>a</sup>	
	aPCC ( $n = 13$ )	rFVIIa ( $n = 112$ )
Number of infusions per bleed, $n$ (%)		
1	8 (61.5)	79 (70.5)
2	5 (38.5)	13 (11.6)
≥3	0 (0)	20 (17.9)
Number of infusions per bleed		
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Range	1.0–2.0	1.0–92.0
Cumulative dose per bleed		
Median (IQR)	10.9 (8.6–14.5) units/kg	62.6 (51.6–96.3) µg/kg
Range	4.2–34.0 units/kg	3.9–7663.2 µg/kg

Note:  $N$  indicates number of bleeds. Treated bleeds: bleeds followed by a hemophilia medication reported to be a “treatment for bleed,” with the 72-hour rule. Bleeds due to surgery/procedure are excluded. Includes data before up-titration only, for people with HA whose dose was up-titrated.

Abbreviations: aPCC, activated prothrombin complex concentrate; HA, hemophilia A; ITT, intent-to-treat; rFVIIa, activated recombinant factor VII.

<sup>a</sup>The remainder of the treated bleeds were treated with short-acting FVIII ( $n = 8$ ) and cryoprecipitate ( $n = 3$ ). Two bleeds treated with rFVIIa were also treated with long-acting FVIII.

the remainder were treated with two infusions. The mean cumulative dose given per bleed was 13.7 units/kg. Of the bleeds treated with rFVIIa, most (70.5%) were treated with one infusion, while 17.9% required 3 or more infusions. The mean cumulative dose given per bleed was 202.2 µg/kg.

Two participants had dose up-titration of their maintenance dose to 3 mg/kg emicizumab prophylaxis QW, due to suboptimal bleed control with no indication of ADAs throughout the study. Up-titration was implemented based solely on bleeding phenotype. The first participant had an emicizumab trough concentration of 45.8 µg/ml at Week 5 (Study Day 28). He had a large hematoma in the iliopsoas muscle on Study Day 49 and received treatment with piperacillin/tazobactam, tramadol, and rFVIIa. Due to this, another spontaneous bleed, and clinical conditions, his dose was up-titrated at Week 12 (Study Day 77). His subsequent average emicizumab trough concentration was 105.6 µg/ml, and he reported no further bleeds. The second participant had an emicizumab trough concentration of 29.4 µg/ml at Week 5 (Study Day 28). He experienced several episodes of spontaneous bleeds: spontaneous bleeds on the right shoulder on Study Days 15–19 and 36–38, and spontaneous bleeding in the right knee on Study Days 20–21 and Study Day 49. As a result, the participant underwent emicizumab up-titration at Week 8 (Study Day 55), and his subsequent average emicizumab trough concentration was 88.4 µg/ml. Following dose up-titration, he reported 12 joint bleeds, including 10 spontaneous and two traumatic, all of which were treated.

**TABLE 4** Bleeding events in the ITT population

	1.5 mg/kg emicizumab QW (N = 195)
<b>Treated bleeds</b>	
Participants with zero bleeds, n (%)	161 (82.6)
ABR, model based (95% CI)	0.5 (0.27–0.89)
Mean ABR, calculated (95% CI)	0.6 (0.00–4.85)
Median ABR, calculated (IQR)	0.0 (0.00–0.00)
Min–max, calculated ABR	0.00–40.58
<b>All bleeds</b>	
Participants with zero bleeds, n (%)	107 (54.9)
ABR, model based (95% CI)	1.1 (0.80–1.47)
Mean ABR, calculated (95% CI)	1.3 (0.06–6.02)
Median ABR, calculated (IQR)	0.0 (0.00–1.01)
Min–max, calculated ABR	0.00–40.58
<b>Treated joint bleeds</b>	
Participants with zero bleeds, n (%)	176 (90.3)
ABR, model based (95% CI)	0.4 (0.15–0.86)
Mean ABR, calculated (95% CI)	0.4 (0.00–4.55)
Median ABR, calculated (IQR)	0.0 (0.00–0.00)
Min–max, calculated ABR	0.00–40.58
<b>Treated target joint bleeds</b>	
Participants with zero bleeds, n (%)	183 (93.8)
ABR, model based (95% CI)	0.2 (0.07–0.68)
Mean ABR, calculated (95% CI)	0.3 (0.00–4.28)
Median ABR, calculated (IQR)	0.0 (0.00–0.00)
Min–max, calculated ABR	0.00–40.58
<b>Treated spontaneous bleeds</b>	
Participants with zero bleeds, n (%)	174 (89.2)
ABR, model based (95% CI)	0.3 (0.15–0.73)
Mean ABR, calculated (95% CI)	0.4 (0.00–4.49)
Median ABR, calculated (IQR)	0.0 (0.00–0.00)
Min–max, calculated ABR	0.00–33.82

Note: n represents the number of participants. Bleeds due to surgery/procedure were excluded. The 72-hour rule was implemented. Treated bleeds: bleeds followed by a hemophilia medication reported to be a “treatment for bleed.” All bleeds: included both treated and nontreated bleeds. Treated joint bleeds: treated bleeds where bleed type was “joint bleed” accompanied by at least one of the following symptoms: “increased swelling or warmth of the skin over the joint,” “increasing pain,” or “decreased range of motion or difficulty using the joint compared with baseline.” Treated target joint bleeds: treated joint bleeds that occurred in a target joint, defined as a joint in which  $\geq 3$  treated joint bleeds occurred during the 24 weeks prior to study entry. Treated spontaneous bleeds: treated bleeds with no other known contributing factor such as trauma or procedure/surgery. Included data before up-titration only, for participants whose dose was up-titrated. Participants started with loading dose of 3 mg/kg/week emicizumab for 4 weeks.

Abbreviations: ABR, annualized bleed rate; CI, confidence interval; IQR, interquartile range; ITT, intent-to-treat; max, maximum; min, minimum; QW, once weekly.

### 3.5 | Quality of life

The Haem-A-QoL (participants aged 18 years or older) and Haemo-QoL-SF (participants aged 12 to less than 18 years) completion rates were high (89% or greater) across visits. Improvements from baseline were seen for Physical Health and Total Scores in the Haem-A-QoL and Haemo-QoL-SF questionnaires (Figure 2). Haem-A-QoL Physical Health score and Total Score saw a mean (standard deviation [SD]) change from baseline of  $-23.29$  (25.16) and  $-14.13$  (13.70 [ $n = 70$ ]) at Month 24/early termination, respectively. Haemo-QoL-SF Physical Health score and Total Score saw a mean (SD) change from baseline of  $-34.03$  (25.66) and  $-18.37$  (17.53; [ $n = 18$ ]) at Month 24/early termination, respectively. The proportion of participants with an improvement from baseline larger than the responder threshold<sup>21,22</sup> was 75% or greater for the Physical Health score and 64% or greater for the Total Score.

The EQ-5D-5L completion rate was high (95% or greater) across visits, with the exception of Month 24/early termination, when considerably fewer participants completed the questionnaire. The mean (SD) change from baseline score on the EQ-5D-5L visual analogue score was 9.49 (21.08 [ $n = 170$ ]) at Month 18, with 50% or more of participants recording an improvement from baseline larger than the responder threshold. Similarly, more than 45% of participants achieved improvements from baseline larger than the responder threshold in the EQ-5D-5L index utility scores by Month 18, with a mean (SD) change from baseline of 0.07 (0.21 [ $n = 170$ ]).

The completion rate of the EmiPref survey was high (95.2%); 173 participants (96.6%) preferred subcutaneous emicizumab treatment to their old treatment. One participant preferred their old treatment (0.6%) and five participants had no preference (2.8%).

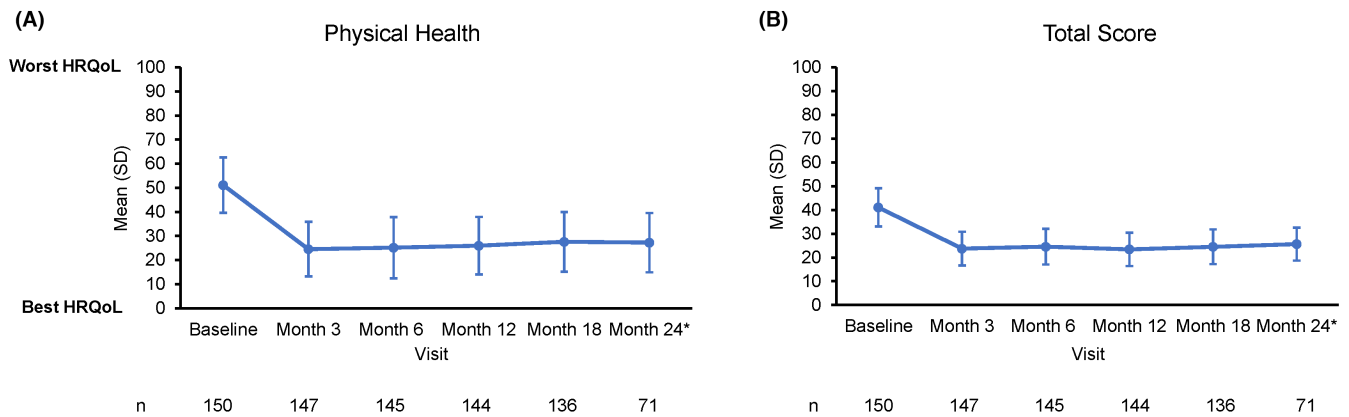
### 3.6 | Emicizumab pharmacokinetics

Pharmacokinetic data were available for 191 participants. Mean (SD) emicizumab plasma trough concentrations increased with weekly loading doses of 3 mg/kg, from 16.7  $\mu\text{g/ml}$  (5.5) at Week 2 and 30.7  $\mu\text{g/ml}$  (9.2) at Week 3, to achieve 52.4  $\mu\text{g/ml}$  (15.5) at Week 5. Mean trough concentrations above 50  $\mu\text{g/ml}$  were maintained thereafter with weekly doses of 1.5 mg/kg (Figure 3). As detailed under efficacy, two participants had their doses up-titrated due to sub-optimal bleed control, and following this, their average emicizumab trough concentrations were well above 50  $\mu\text{g/ml}$ .

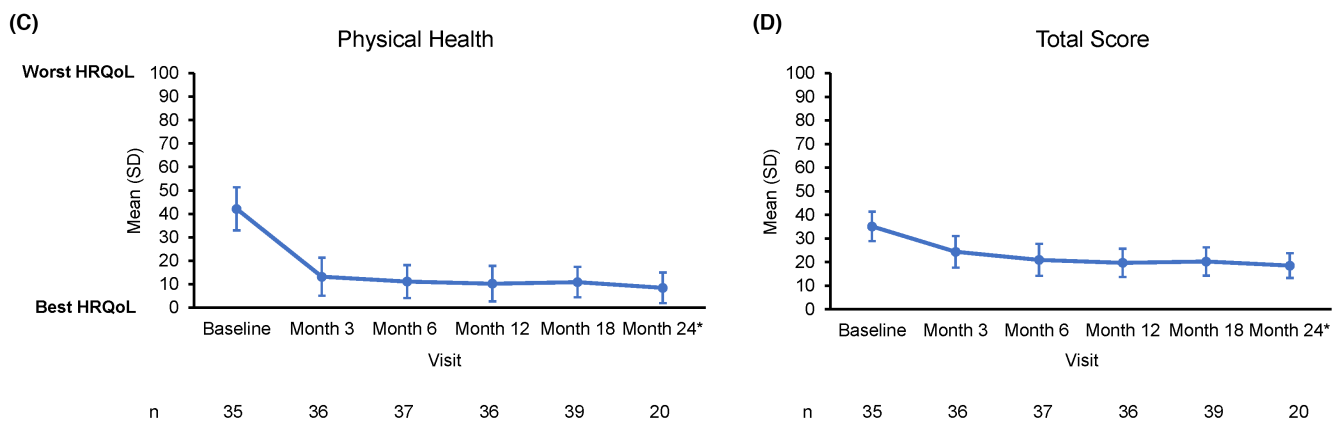
### 3.7 | Pharmacodynamics and biomarkers

Emicizumab did not affect PT (INR) or D-dimer concentrations (Figure S1). Mean aPTT was elevated at baseline and then normalized by Week 5, including in those participants whose dose was

## Haem-A-QoL Domain Scores, ITT Population



## Haemo-QoL-SF Domain Scores, ITT Population



**FIGURE 2** Haem-A-QoL (adult ITT population) Physical Health (A) and Total Score (B) domain scores and Haemo-QoL-SF (adolescent ITT population) Physical Health (C) and Total Score (D) domain scores over time. \*Study completion visits. Also includes early terminations. The Haem-A-QoL is completed by participants aged 18 years and above. The Haemo-QoL-SF is completed by participants aged under 18 years. Includes data before up-titration only, for participants whose dose was up-titrated. Lower scores indicate better quality of life. ITT, intent-to-treat; HRQoL, health-related QoL; SD, standard deviation; SF, short form

later up-titrated (Figure S1). At baseline, mean FVIII-like activity was below the limit of quantification (less than 1 U/dl). Mean FVIII-like activity increased to approximately 20 U/dl at Week 5 and was maintained above this value throughout the study duration (Figure S2). Participants' FVIII inhibitor titers remained stable or declined over time. The median (IQR) FVIII inhibitor titer decreased from 6.5 (2.3–18.0) Chromogenic Bethesda Unit (CBU)/ml at baseline to 1.8 (0.8–5.2) CBU/ml at the end of the 2-year treatment period (Figure S3).

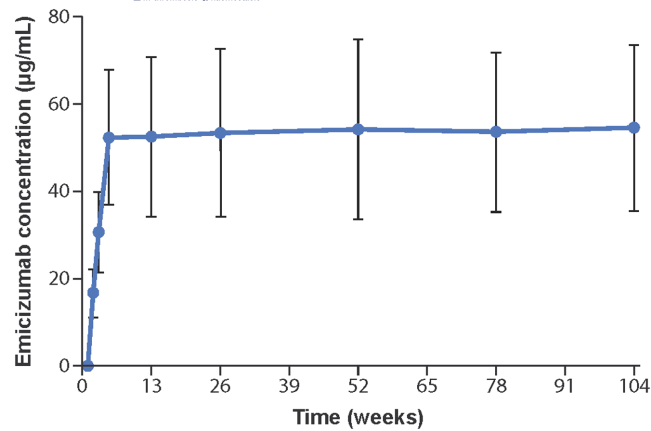
### 3.8 | Immunogenicity of emicizumab

Ten of 193 (5.2%) evaluable participants tested positive for ADAs, of whom five participants (2.6%) had neutralizing ADAs (nADAs) in vitro (Table S6). The majority of ADAs were of low titer and/or transient (single occurrence) or of short duration, and all participants tested negative for ADAs at the last visit. The presence of ADAs,

including nADAs, did not have an impact on PK, PD, or bleeding and did not alter the safety profile of emicizumab.

## 4 | DISCUSSION

The safety profile observed in people with HA with FVIII inhibitors during the STASEY study was consistent with that observed in the HAVEN clinical program.<sup>3–6,23</sup> The most frequently reported AE in the STASEY study was arthralgia (17.1% of participants); this was unsurprising, as the most common associated disorder in this population was hemophilic arthropathy, present in 21.8% of participants enrolled, and the high incidence of reported arthralgia is likely to be related to the difficulty in differentiating between these two conditions. Four participants had interruptions of emicizumab due to AEs, which resulted in two participants missing doses. As these doses (one missed dose in one participant and two consecutive missed doses in another) occurred during the maintenance phase



**FIGURE 3** Mean (SD) emicizumab plasma concentrations over time. SD, standard deviation

and the maximum interval between 1.5 mg/kg doses was 3 weeks, this would not be expected to cause emicizumab plasma concentrations to fall below the therapeutic range.<sup>24</sup> One participant chose to discontinue emicizumab following an AE of nephrotic syndrome. The investigator believed this event was unrelated to emicizumab; however, due to the lack of a renal biopsy, the study sponsor cannot exclude the possibility of a relationship between emicizumab and the event of nephrotic syndrome.

During the study, no TMAs were reported. In the two participants who experienced TEs, these were deemed unrelated to emicizumab prophylaxis by the investigator; however, an association with emicizumab cannot be definitively excluded. The investigator considered the localized clot following a tooth extraction, a known complication of tooth extractions in people with HA,<sup>25</sup> to be related to concomitant tranexamic acid and rFVIIa. This was not considered to be a typical intravascular TE such as a pulmonary embolism or deep vein thrombosis, as the nature of the event, the pathophysiology, and the clinical outcome are different. The participant continued receiving emicizumab and completed the study. Although no AEs were associated with the concomitant use of emicizumab and bypassing agents within the STASEY study, the authors acknowledge that only a prospective surveillance study based on national or international registries will be able to fully capture the safety of prolonged concomitant use of emicizumab and bypassing agents in a real-world setting.

In the STASEY study, 82.6% of participants had zero treated bleeds across 2 years, and ABRs were consistently low and similar between the model-based and calculated ABRs. The model-based ABR for treated bleeds was lower in participants who were aged less than 18 years at the time of entry into the study (0.1) compared with participants who were aged 18 years or older (0.6), in line with outcomes from the HAVEN 1 and HAVEN 2 studies.<sup>6,26</sup> This may reflect the lower rate of existing joint damage in younger people with HA.

Interestingly, the proportion of participants with nine or more bleeds during the 24 weeks before enrollment was lower in STASEY (23.4%) compared with HAVEN 1 (53% in Group C, who were previously receiving bypassing agent prophylaxis).<sup>6</sup> The authors speculate

that there may be multiple reasons for this difference. First, this may be an example of channeling of people with the greatest unmet medical need (i.e., those experiencing more bleeds even though they were receiving prophylaxis) to an alternative treatment (emicizumab) as soon as it became available, an effect previously noted in the field of HA.<sup>27</sup> This may have led to preferential enrollment of people with more severe bleeding phenotypes in HAVEN 1 compared with STASEY, which was initiated later. The STASEY study identified a correspondingly lower model-based treated bleed ABR while receiving emicizumab (0.5) compared with HAVEN 1 (5.3 in Group C, who previously received bypassing agent prophylaxis);<sup>6</sup> this may be reflective of participants in the HAVEN 1 trial having a higher baseline bleeding rate, and therefore a greater tendency towards breakthrough bleeding on emicizumab. Furthermore, an additional factor could be greater heterogeneity in access to bypassing agents across countries with different health care resources in countries participating in STASEY compared with HAVEN 1. The STASEY study recruited participants from several countries that were not involved in HAVEN 1, and differences seen in the number of treated bleeding events could reflect contrasting approaches to treating bleeds in this broader range of countries, perhaps due to variability or lack of resources.

The majority of participants (96.6%) preferred emicizumab treatment compared with their previous treatment due to subcutaneous administration, low bleed rates, and improved quality of life. Notably, this is the first assessment of participant preference in a trial with a large population of people with HA with FVIII inhibitors and is in line with previous assessments in HAVEN 3 (without FVIII inhibitors) and HAVEN 4 (with or without FVIII inhibitors).<sup>18</sup>

Mean emicizumab trough concentrations were in line with findings from the HAVEN program.<sup>3,5,6</sup> aPTT normalization was consistent with previous studies;<sup>28,29</sup> however, aPTT does not reflect the true hemostatic effect of emicizumab and is a poor marker for bleed protection in people with HA receiving emicizumab.<sup>30</sup>

FVIII-like activity was consistent with previous PD analyses of emicizumab.<sup>28,29</sup> Measured FVIII-like activity increased between Month 12 and Month 18; however, this was due to assay drift, as there was a change of kit lot for the assay during this time. Emicizumab and FVIII have different biochemical properties,<sup>31</sup> and emicizumab activity depends on the amount of FIXa that is available in the assay. It has previously been reported that FIXa amounts are variable between assays from different manufacturers and may differ in a lot-to-lot manner in chromogenic assay kits that use the same reagents, as some assays are intended for research use only.<sup>32</sup> Consequently, different FVIII-like activity values are generated. Data from the STASEY study confirm that lot-to-lot variability is an important consideration if chromogenic assays with human factors are used to measure samples containing emicizumab. The increase was not associated with an increase in emicizumab plasma trough concentrations, which remained stable. Given the biochemical differences between emicizumab and FVIII, these results should not be viewed as equivalent to data obtained in participants treated with FVIII concentrates.<sup>33</sup>

Throughout the study, FVIII inhibitor titers remained the same or declined. Of note, this reduction likely reflects the absence of new exposure to FVIII via reduced use of aPCC (which contains a few units of FVIII) or FVIII products, rather than true eradication of FVIII inhibitors.

The presence of ADAs in 5.2% of participants was in line with the established immunogenicity profile of emicizumab, as demonstrated in a pooled analysis of seven Phase 3/3b studies including the STASEY study, along with HAVEN 1-5 and HOHOEMI.<sup>10</sup> Across the pooled analysis, 5.1% of study participants developed ADAs; in 2.7% of participants, these ADAs were neutralizing *in vitro*.<sup>10</sup> Excluding the 0.6% of participants who experienced decreased emicizumab concentrations, ABRs for treated bleeds remained low in ADA-positive and ADA-negative participants,<sup>10</sup> similar to ABRs reported here for the STASEY study.

The principal strengths of the STASEY study are the representation of the largest population of people with HA with FVIII inhibitors receiving emicizumab evaluated to date; the use of clinical end points aligned with the HAVEN 1 study, which allows for comparison; and the inclusion of participants from a wider range of countries than the HAVEN studies, including countries with varied health care resources and treatment approaches, to confirm safety and efficacy outcomes with emicizumab in a postmarketing setting. Limitations of the STASEY study include the single-arm study design, which precludes comparison of emicizumab in this population with another form of prophylaxis, and the use of only one approved dosing regimen. As 1.5 mg/kg QW was the only dosing regimen used, caution should be exercised when extrapolating these results to the other two approved dosing regimens.

## 5 | CONCLUSIONS

The STASEY study confirmed the safety profile and efficacy of emicizumab 1.5 mg/kg QW in adolescent and adult people with HA with FVIII inhibitors over a 2-year treatment period. No new or unexpected safety signals were observed. The dosing guidance for aPCC was followed, and no TMAs occurred with the use of either aPCC or rFVIIa concomitantly with emicizumab. The majority of participants had zero treated bleeds.

### AUTHOR CONTRIBUTIONS

Study design: S. Robson, C. Schmitt, AK, OM. Study conduct: VJ-Y, FP, RK, GC, C. Shanmukhaiah, S. Rangarajan, JGC, RM, GK, HA, MO. Recruitment and follow-up of patients: VJ-Y, FP, RK, GC, C. Shanmukhaiah, S. Rangarajan, JGC, RM, GK, HA, MO. Data collection: VJ-Y, FP, RK, GC, C. Shanmukhaiah, S. Rangarajan, JGC, RM, GK, HA, MO. Data analysis and interpretation: VJ-Y, FP, RK, GC, C. Shanmukhaiah, S. Rangarajan, JGC, RM, GK, HA, S. Robson, C. Schmitt, AK, OM, MO. 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.

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### RELATIONSHIP DISCLOSURE

VJ-Y has received reimbursement for attending symposia/congresses, honoraria for speaking, and consultation and/or research funding from Takeda, Bayer, CSL Behring, Grifols, Novo Nordisk, Sobi, F. Hoffmann–La Roche Ltd, Octapharma, BioMarin, Sanofi, and Pfizer. FP has received speaker fees for participating in educational symposia and advisory boards for F. Hoffmann–La Roche Ltd, Sanofi, Sobi, and Takeda. RK has received honoraria from Bayer, Biotest, BioMarin, CSL Behring, Daiichi Sankyo, LEO Pharma A/S, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann–La Roche Ltd, Chugai Pharmaceutical Co. Ltd, Sanofi, Takeda/Shire, and Sobi; consultation fees from Bayer, Biotest, BioMarin, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann–La Roche Ltd, Chugai Pharmaceutical Co. Ltd, Sanofi, Takeda/Shire, and Sobi; speaker's bureau from Bayer, Biotest, BioMarin, CSL Behring, Daiichi Sankyo, LEO Pharma A/S, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann–La Roche Ltd, Chugai Pharmaceutical Co. Ltd, Sanofi, Takeda/Shire, and Sobi; research funding from Bayer and LEO Pharma A/S; and travel expenses from Bayer, Biotest, BioMarin, CSL Behring, Daiichi Sankyo, LEO Pharma A/S, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann–La Roche Ltd, Chugai Pharmaceutical Co. Ltd, Takeda/Shire, and Sobi. GC has received honoraria from UniQure, Bayer, Sobi, CSL Behring, Novo Nordisk, Kedrion, LFB, Grifols, Werfen, BioMarin, Sanofi, and F. Hoffmann–La Roche Ltd. C. Shanmukhaiah has received honoraria from Takeda and Novo Nordisk, consultation fees from Novo Nordisk, and speaker's bureau from Novo Nordisk, Intas Pharmaceuticals Ltd, and Zydus. S. Rangarajan has acted in a consultancy or advisory role for Reliance Life Sciences, Pfizer, Sanofi, and Sigilon; and has received speaker's bureau from Takeda/Shire and Pfizer, and travel expenses from Takeda/Shire and Reliance Life Sciences. JGC has received honoraria from Novo Nordisk, F. Hoffmann–La Roche Ltd, and Bayer; consultation fees from LFB and Novo Nordisk; and has provided expert testimony for Novo Nordisk, F. Hoffmann–La Roche Ltd, and Bayer. RM has received honoraria from F. Hoffmann–La Roche Ltd. GK has received consultation fees from OPKO Biologics, Bayer, Pfizer, Alnylam Pharmaceuticals, CSL Behring, Sanofi, Takeda, F. Hoffmann–La Roche Ltd, Novo Nordisk, BioMarin, and UniQure; speaker's bureau from Bayer, Pfizer, CSL Behring, Shire, Novo Nordisk, and F. Hoffmann–La Roche Ltd; and research funding from OPKO Biologics, Bio Products Laboratory Ltd, Shire, Bayer, Pfizer, Alnylam Pharmaceuticals, and F. Hoffmann–La Roche Ltd. HA has

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### DATA AVAILABILITY STATEMENT

Qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli. <https://vivli.org/ourmember/roche/>. 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 [https://go.roche.com/data\\_sharing](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 reidentification.

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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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