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ORIGINAL ARTICLE

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Emicizumab dose up-titration in case of suboptimal bleeding control in people with haemophilia A

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[Correction added on 29 November 2022, after first online publication: Affiliation 2 was removed from the 2nd author.]

Abstract

Introduction: Emicizumab promotes effective haemostasis in people with haemophilia A (PwHA). It is indicated for routine prophylaxis of bleeding episodes in PwHA with or without factor (F)VIII inhibitors.

Aim: To investigate the effect of emicizumab dose up-titration in PwHA with suboptimal bleeding control.

Methods: Data from seven completed or ongoing phase III studies were pooled. Pharmacokinetics, pharmacodynamics and bleeding events were evaluated before and after dose up-titration. Adverse events (AEs) were compared between PwHA with and without dose up-titration.

Results: Of 675 PwHA evaluable for the analysis, 24 (3.6%) had their maintenance dose up-titrated to 3 mg/kg once weekly (QW). Two participants had neutralising antibodies (nAbs) associated with decreased emicizumab exposure, and dose increase did not compensate for the effect of nAbs. In the other 22 participants, mean emicizumab steady-state trough concentrations increased from 44.0 to 86.2 μg/mL after up-titration. The median (interquartile range [IQR]) efficacy period prior to up-titration was 24.6 (24.0–32.0) weeks. The model-based annualised bleed rate for 'treated bleeds' and 'all bleeds' decreased by 70.2% and 72.9%, respectively, after a median (IQR) follow-up of 97.1 (48.4–123.3) weeks in the up-titration period. Incidences of injection-site reactions and serious AEs were higher in PwHA with up-titration; however, this was already observed in these participants before the dose up-titration. Overall, the safety profile appeared similar between PwHA with and without up-titration.

Conclusion: The dose up-titration to 3 mg/kg QW was well tolerated. Bleed control improved in most participants whose bleeding tendency was inadequately controlled during clinical trials.

KEYWORDS
bleeding control, clinical study, dosage up-titration, emicizumab, haemophilia A, monoclonal antibodies

1 | INTRODUCTION

People with haemophilia A (PwHA) have a deficiency of coagulation factor (F)VIII.[1,2] Symptoms are characterised by recurrent bleeding, especially into joints, leading to long-term complications if inadequately treated (e.g., haemophilic arthropathy).[3] Replacement therapy with FVIII has been the standard treatment for PwHA without FVIII inhibitors, while bypassing agents (BPAs) have been the primary therapeutic option for PwHA with FVIII inhibitors.

Non-factor substitution therapy was recently introduced into haemophilia care. Emicizumab is the first approved drug in this category. This humanised bispecific antibody bridges activated FIX and FX, substituting for the function of deficient activated FVIII by enhancing generation of activated FX, thereby improving haemostasis in PwHA.[4,5] In phase III studies, prophylactic treatment with emicizumab resulted in significant reductions in annualised bleed rates (ABRs), with high proportions of participants reporting no treated bleeds, and was shown to be well tolerated.[6–12] Thrombotic microangiopathy (TMA) and thromboembolic events (TE) were reported in the HAVEN 1 study in participants treated with high doses of activated prothrombin complex concentrate (aPCC) for breakthrough bleeds.[6] However, no further occurrences of aPCC-related events were reported in clinical studies following the risk mitigation measures that were put in place, which provide dosing guidance for treatment with BPAs during emicizumab prophylaxis.[6,13–15]

Emicizumab is approved for routine prophylaxis to prevent or reduce the frequency of bleeding in PwHA with or without FVIII inhibitors. It is injected subcutaneously at 1.5 mg/kg once-weekly (QW), 3 mg/kg every two weeks (Q2W) or 6 mg/kg every four weeks (Q4W), after a 4-week loading dose phase of 3 mg/kg QW.[14,15]

The severity of haemophilia A is traditionally classified according to the residual plasma levels of FVIII, with severe defined as an FVIII activity <1 U/dL (<1% of normal levels).[16] Nevertheless, phenotypic heterogeneity exists beyond measured FVIII activity: some PwHA with FVIII < 1 U/dL have little-to-no spontaneous bleeding, while others with FVIII > 1 U/dL can exhibit frequent spontaneous bleeds. This is because the clinical severity of haemophilia depends on several determinants, including joint health status, comorbidities and levels of physical activity/lifestyle. As such, the traditional categorisation of haemophilia severity according to FVIII activity may not be sufficient to determine the optimum treatment approach for a given individual.[17] In this light, treatment individualisation is becoming the epitome of patient management in haemophilia.[17] Similarly, despite the demonstrated consistent pharmacokinetic (PK) and pharmacodynamic (PD) behaviour across age and body weight strata,[6–12] emicizumab dose adaptation might be beneficial for some individuals. The present analysis investigated the effect of emicizumab dose up-titration on PK, PD, efficacy and safety in PwHA whose bleeding control was suboptimal in phase III/IIIb clinical studies.

2 | MATERIALS AND METHODS

2.1 | Clinical study design

Seven clinical studies (HAVEN 1–5, HOHOEMI and STASEY) were included in this analysis (Table 1). The study designs have been published previously.[6–12] Study protocols were approved by the relevant institutional review board/independent ethics committee prior to initiation at each site. All enrolled PwHA, or their legal representative, provided informed consent to participate. The studies included paediatric and adult PwHA, with or without FVIII inhibitors. PwHA received emicizumab prophylaxis with maintenance doses of 1.5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W.

Per protocol, the dose of emicizumab could be up-titrated to 3 mg/kg QW in cases of suboptimal bleeding control, generally defined as ≥2 spontaneous and clinically significant bleeds (verified by a physician) in the last 12 or 24 weeks on emicizumab, or at the initiative of the investigator who believed that a specific patient warranted dose up-titration. The protocol-specified requirements in each study for participants to have their dose up-titrated are detailed in Supporting Information Table S1.

2.2 | Study assessments

Bleeding event data were recorded by participants/caregivers using an electronic handheld device.[6] Safety endpoints included adverse events (AEs), drug-related AEs, serious AEs (SAEs), drug-related SAEs and injection-site reactions (ISRs).

Blood samples for the determination of emicizumab concentration, detection of anti-drug antibodies (ADAs) and for PD analyses were collected at baseline prior to dosing and at regular intervals during treatment. Emicizumab plasma concentrations were determined by a validated enzyme-linked immunosorbent assay (ELISA).[18] ADAs were detected using a validated bridging ELISA, and ADA-positive

TABLE 1 Phase III clinical studies of emicizumab in PwHA included in the analysis

Study name	Registration number	Data cut-off date	Population	No. of PwHA enrolled/evaluable
HAVEN 1[6]	NCT02622321	1 December 2020[a]	With FVIII inhibitors; ≥12 years	113/112
HAVEN 2[7]	NCT02795767	11 November 2020[a]	With FVIII inhibitors; <12 years[b]	88/88
HAVEN 3[8]	NCT02847637	15 May 2020	Without FVIII inhibitors; ≥12 years	152/151
HAVEN 4[9]	NCT03020160	15 May 2020	With/without FVIII inhibitors; ≥12 years	48/48
HAVEN 5[10]	NCT03315455	21 June 2019	With/without FVIII inhibitors; ≥12 years	70/70
HOHOEMI[12]	JapicCTI-173710	3 July 2019[a]	Without FVIII inhibitors; < 12 years	13/13
STASEY[11]	NCT03191799	19 November 2020[a]	With FVIII inhibitors; ≥12 years	195/193

FVIII, factor VIII; PwHA, people with haemophilia A.
[a]Last patient last visit (final analysis).
[b]PwHA ≥12 to <18 years with body weight <40 kg were also eligible for enrolment.

samples were further analysed for their neutralising capacity (neutralising antibody [nAb]) using a modified FVIII chromogenic assay measuring emicizumab activity.[19] PD endpoints included FVIII-like activity, peak height of thrombin generation (TG) and activated partial thromboplastin time (aPTT), which were measured as previously reported.[19,20]

2.3 | Statistical analysis

Intra-individual mean emicizumab concentrations at steady state were calculated for two treatment periods, as the mean trough concentrations in a given participant from Week 5 (end of the loading-dose period) to the time of up-titration (i.e., period before up-titration), and from the time of up-titration until the last available time point (i.e., period after up-titration). Corresponding intra-individual mean values for FVIII-like activity, TG and aPTT were derived in the same way. It should be noted that, for PwHA treated with emicizumab, FVIII activity determined using this assay cannot be compared with, or interpreted as equivalent to, FVIII activity reported for PwHA treated with FVIII; as such, this parameter will be referred to as FVIII-like activity throughout the present article. Intra-individual mean actual steady-state trough emicizumab concentrations were also calculated for the period after up-titration, excluding the first 24 weeks immediately after the dose was up-titrated.

Treated bleeds, all bleeds and efficacy period were calculated as previously described.[6] Individual ABRs for treated bleeds and all bleeds were calculated for two treatment periods: (1) from treatment initiation until up-titration (i.e., before up-titration) and (2) from time of up-titration until the last available time point (i.e., after up-titration), using the following formula:

$$\text{ABR} = \frac{\text{Number of bleeds}}{\text{Number of days during the efficacy period}} \times 365.25$$

Mean ABRs were calculated before up-titration and in discrete consecutive 24-week time intervals after up-titration. Model-based ABRs were also calculated for both treatment periods (before and after up-titration) with the use of a negative binomial regression model, as previously described.[6] When applicable and meaningful, proportions were compared used Fisher's exact test.

Descriptive statistics were used to assess the effect of dose up-titration on PK and PD. The effect of dose up-titration on emicizumab efficacy was evaluated by comparing the model-based ABR before and after dose up-titration. The effect of dose up-titration on safety was assessed by comparing the incidences of AEs in participants with and without up-titration, and before and after dose up-titration in participants whose dose was up-titrated. Safety coagulation markers (D-dimer, prothrombin fragment 1 and 2 [PF1.2], and fibrinogen) were examined in participants before and after dose up-titration.

3 | RESULTS

3.1 | Participants

A total of 675 PwHA (98 [14.5%] children aged <12 years; 577 [85.5%] adolescents and adults aged ≥12 years) from the seven phase III/IIIb studies were evaluable for the analysis. All participants were male. Twenty-four participants (3.6%) had their maintenance dose up-titrated to 3 mg/kg QW due to suboptimal bleeding control. The median (interquartile range [IQR]) age of participants with and without up-titration was 46.5 (25–58) and 28.0 (15–42) years, respectively. Three (12.5%) of the 24 participants with and 95 (14.6%) of the 651 without up-titration were aged <12 years (Table 2). At baseline, 13 (54.2%) and 404 (62.1%) of those with and without up-titration, respectively, had FVIII inhibitors. Overall, participants were exposed to emicizumab for a median (IQR) of 125.1 (77.8–153.1) weeks for those with up-titration and 103.6 (88.3–148.1) weeks for those without.

Up-titration was performed for 15 (3.0%) of the 501 participants initially treated with emicizumab 1.5 mg/kg QW, 1 (1.5%) of the 68 participants initially treated with 3 mg/kg Q2W, and 8 (7.5%) of the 106 participants initially treated with 6 mg/kg Q4W (QW and Q2W combined vs Q4W: $p = .0387$). Of the 220 participants who were known to have received prior prophylaxis, 13 (5.9%) underwent up-titration, while 9 (3.4%) of the 262 who were known to have been treated on

TABLE 2 Baseline demographic and clinical characteristics

Participant characteristic	Analysis population ($N = 675$)	
	Without up-titration ($n = 651$)	With up-titration ($n = 24$)
Male, *n* (%)	651 (100)	24 (100)
Age (years), median (IQR)	28.0 (15–42)	46.5 (25–58)
<12 years, *n* (%)	95 (14.6)	3 (12.5)
≥65 years, *n* (%)	21 (3.2)	2 (8.3)
Body weight (kg), mean (SD)	65.4 (23.6)	69.0 (20.4)
Race, *n* (%)		
Asian	192 (29.5)	4 (16.7)
Black/African American	38 (5.8)	1 (4.2)
White	366 (56.2)	19 (79.2)
Other[a]	55 (8.4)	0 (.0)
Initial maintenance dosing regimen, *n* (%)		
1.5 mg/kg QW	486 (74.7)	15 (62.5)
3 mg/kg Q2W	67 (10.3)	1 (4.2)
6 mg/kg Q4W	98 (15.0)	8 (33.3)
FVIII inhibitor status, *n* (%)		
With inhibitors	404 (62.1)	13 (54.2)
Without inhibitors	247 (37.9)	11 (45.8)
Prior prophylaxis, *n* (%)	207 (45.0)[b]	13 (59.1)[b]
≥9 bleeding events in the 24 weeks prior to study entry, *n* (%)	278 (42.7)	12 (50.0)
Presence of target joints[c] at baseline, *n* (%)	283 (61.5)[d]	13 (61.9)[d]

FVIII, factor VIII; IQR, interquartile range; ISTH, International Society on Thrombosis and Haemostasis; Q2W, once every 2 weeks; Q4W, once every 4 weeks; QW, once weekly; SD, standard deviation.

[a]Other includes 'American Indian/Alaska Native', 'Native Hawaiian/Pacific Islander', 'Multiple' and 'Unknown'.

[b]Details of prophylaxis use (either FVIII or bypassing agent) at baseline was available for 460 and 22 participants without and with up-titration, respectively.

[c]In line with ISTH definitions, target joints were defined as major joints in which ≥3 spontaneous bleeding events occurred over a 24-week treatment period[29].

[d]Target joint assessment was available for 460 and 21 participants without and with up-titration, respectively.

demand underwent up-titration. No participants from the PK run-in phase of HAVEN 4 had their dose up-titrated.

Two participants with dose up-titration had previously developed nAbs; in both participants, these were associated with decreased emicizumab exposure.

3.2 | Pharmacokinetics and pharmacodynamics

With the exception of the two participants with nAbs, emicizumab steady-state trough concentrations increased following up-titration (Figure 1 and Supporting Information Figure S1). In participants without nAbs, mean (standard deviation [SD]) emicizumab steady-state trough concentrations increased from 44.0 (13.8) to 86.2 (29.5) μg/mL (Table 3). When excluding the 24 weeks immediately following the dose up-titration, the actual steady-state trough mean (SD) emicizumab concentration after up-titration was similar, at 88.2 (13.0) μg/mL. In the two participants with nAbs, and despite dose up-titration, plasma concentrations decreased below 10 μg/mL in one participant and were not detectable in the other (Table 4). The mean (SD) steady-state trough emicizumab concentration prior to up-titration was 48.6 (13.3) μg/mL for the 15 participants who were treated with the 1.5 mg/kg QW regimen, 24.0 μg/mL for the one participant treated with the 3 mg/kg Q2W regimen and 31.2 (11.4) μg/mL for the eight participants treated with the 6 mg/kg Q4W regimen.

Similarly, FVIII-like activity generally increased following up-titration (Figure 2). In the participants without nAbs, mean (SD) steady-state FVIII-like activity increased from 20.7 (9.8) to 31.9 (13.0) U/dL with dose up-titration (Table 3). In contrast, FVIII-like activity decreased following dose up-titration in both participants with nAbs, from 8.7 to 3.3 and 23.0 to 1.0 U/dL, respectively (Table 4).

Only 14 participants had evaluable TG data for both periods, before and after up-titration. TG data were not evaluable for the two patients with nAbs. TG generally increased after up-titration (Supporting Information Figure S2). Mean (SD) steady-state TG increased from 135.1 (69.3) to 157.4 (60.2) nM with dose up-titration (Table 3).

Dose up-titration had no effect on aPTT (Figure 3). In the participants without nAbs, mean (SD) steady-state aPTT was 24.9 (3.4) s

TABLE 3 Summary of ABRs, PK and PD before and after up-titration to 3 mg/kg QW in PwHA without nAbs

Parameters	Before up-titration ($n = 22$)	After up-titration ($n = 22$)
Duration of efficacy period (weeks), median (IQR)	24.6 (24.0–32.0)	97.1 (48.4–123.3)
ABR for treated bleeds (95% CI)[a]	11.2 (5.5–22.9)	3.3 (1.7–6.5)
Steady-state trough concentration (μg/mL), mean (SD)	44.0 (13.8)	86.2 (29.5)
Steady-state TG (nM), mean (SD)[b]	135.1 (69.3)	157.4 (60.2)
Steady-state FVIII-like activity (U/dL), mean (SD)	20.7 (9.8)	31.9 (13.0)
Steady-state aPTT (s), mean (SD)	24.9 (3.4)	24.2 (5.2)

ABR, annualised bleed rate; aPTT, activated partial thromboplastin time; CI, confidence interval; FVIII, factor VIIII; IQR, interquartile range; PwHA, people with haemophilia A; QW, once weekly; SD, standard deviation; TG, thrombin generation.
[a]Derived using a negative binomial regression model.
[b]$n = 14$.

TABLE 4 ABRs, PK and PD before and after up-titration to 3 mg/kg QW for the two participants with nAbs

	Participant A[a]		Participant B[b]	
	Labelled dose	Up-titrated dose	Labelled dose	Up-titrated dose
Duration of efficacy period (weeks)	24.1	41.0	8.9	7.0
ABR for treated bleeds[c]	25.93	29.27	11.78	37.27
Steady-state trough concentration (μg/mL)	16.8	9.6	18.3	BLQ
Steady-state FVIII-like activity (U/dL)	8.7	3.3	23.0	1.0
Steady-state aPTT (s)	25.9	29.3	23.5	85.2

ABR, annualised bleed rate; ADA, anti-drug antibodies; aPTT, activated partial thromboplastin time; BLQ, below the limit of quantification; FVIII, factor VIIII; QW, once weekly.
[a]ADA titre at the time of the most recent test prior to up-titration was 40 (Week 23 of study).
[b]ADA titre at the time of the most recent test prior to up-titration was 10,200 (Week 9 of study).
[c]Calculated as (number of bleeds/number of days in efficacy period) × 365.25.

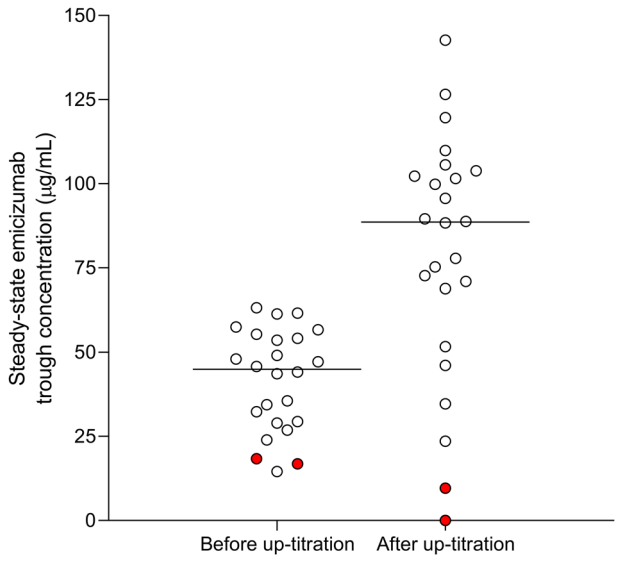

FIGURE 1 Steady-state emicizumab trough concentration before and after dose up-titration to 3 mg/kg QW. Horizontal bars represent the mean values; red dots correspond to participants with nAbs; values BLQ were set to zero for graphical display. BLQ, below the limit of quantification; nAbs, neutralising antibodies; QW, once weekly

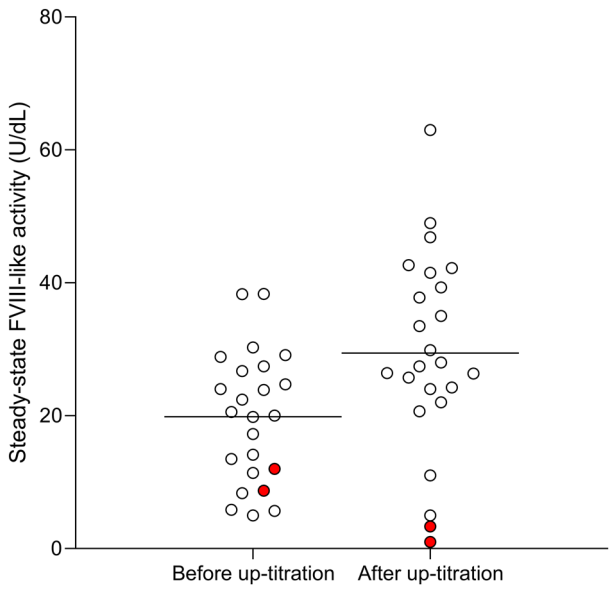

FIGURE 2 Steady-state FVIII-like activity before and after dose up-titration to 3 mg/kg QW. Horizontal bars represent the mean values; red dots correspond to participants with nAbs. FVIII, factor VIII; nAbs, neutralising antibodies; QW, once weekly

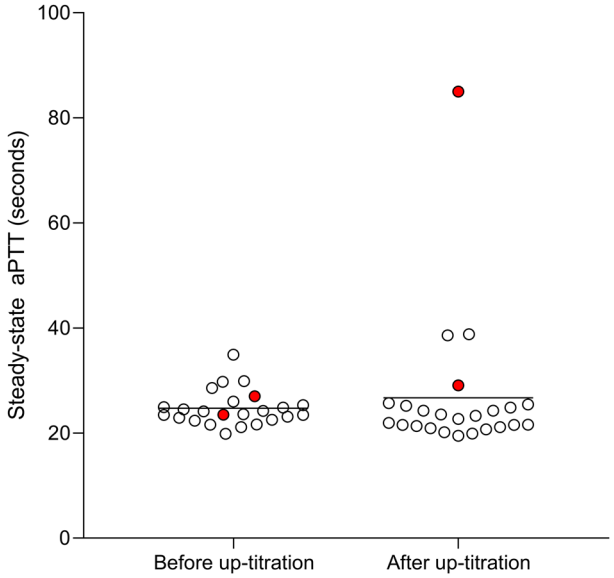

FIGURE 3 Steady-state aPTT before and after dose up-titration to 3 mg/kg QW. Horizontal bars represent the mean values; red dots correspond to participants with nAbs. aPTT, activated partial thromboplastin time; nAbs, neutralising antibodies; QW, once weekly

before and 24.2 (5.2) s after up-titration (Table 3). In the two participants with nAbs, aPTT increased from 25.9 to 29.3 s and 23.5 to 85.2 s, respectively (Table 4).

3.3 | Efficacy

Individual ABRs for treated bleeds before and after dose up-titration are displayed in Figure 4. With the exception of the two participants who developed nAbs, ABRs for treated bleeds decreased or remained at zero after up-titration. Similar decreases were observed for ABRs for all bleeds. Three PwHA had increased ABR for all bleeds after up-titration, including the two participants with nAbs (Supporting Information Figure S3).

Since participants with nAbs did not respond to up-titration, analysis of model-based ABRs was restricted to the participants who did not develop nAbs (n = 22; Figure 5, Table 3). These participants were treated with emicizumab at the labelled dosing regimens for a median (IQR) duration of 24.6 (24.0–32.0) weeks before having their dose up-titrated and were then monitored after the up-titration for a median (IQR) duration of 97.1 (48.4–123.3) weeks. The model-based ABR for treated bleeds decreased by 70.2% following up-titration, from 11.2 to 3.3. A similar decrease of 72.9% was seen for the ABR for all bleeds, from 15.4 at the original maintenance dose to 4.2 after up-titration. The calculated mean ABR for treated bleeds markedly decreased in the 24-week interval immediately after up-titration, from 11.5 to 5.2, with a less notable decrease over the subsequent 24-week treatment intervals (Supporting Information Figure S4A). A consistent trend was seen for the proportion of participants with zero treated bleeds, which increased from 9.1% prior to up-titration to 59.1% in the 24-week period immediately following up-titration (Supporting Information Figure S4B). Again, the proportion remained quite stable throughout the subsequent 24-week intervals.

Of note, three participants had their dose up-titrated for a limited period before returning to one of the standard maintenance dosing regimens (Supporting Information). As a sensitivity analysis, the evaluation of the model-based ABRs was repeated for the 19 participants who remained at the up-titrated dose and who did not develop nAbs (Supporting Information Table S2). This same evaluation was also performed for all 24 participants, including the two individuals with nAbs and the three who had their dose up-titrated for a limited period (Supporting Information Table S3). Results did not differ greatly, with reductions in ABRs for treated bleeds following up-titration of 70.3% (n = 19) and 55.0% (n = 24), respectively.

3.4 | Safety

The proportions of PwHA with AEs and drug-related AEs were similar for the two populations (Table 5). The proportions of participants who reported SAEs (29.2% [n = 7] vs 18.9% [n = 123]) and drug-related SAEs (4.2% [n = 1] vs .9% [n = 6]) were higher in PwHA with up-titration compared with those without. However, this imbalance in SAEs was already present before the dose up-titration, with SAEs being reported for 25% (n = 6) and drug-related SAEs for 4.2% (n = 1) in the pre-up-titration period. Of note, all SAEs, except one, occurring in PwHA with up-titration, were considered not related to emicizumab. The only drug-related SAE (neutralising ADA, clinically manifesting as an increase in bleed frequency), which was reported in an individual with up-titration, occurred during treatment at the original maintenance dose, before up-titration.

ISRs were reported for 29.2% (n = 7) of participants with up-titration and 20.9% (n = 136) of those without. This difference in the incidence of ISRs was already evident before dose up-titration took place, with six of the seven participants experiencing an ISR prior to their dose being changed. No TEs or TMAs were reported for any participant who underwent up-titration.

No changes were observed in the safety coagulation markers of D-dimer, PF 1.2 and fibrinogen with dose up-titration (Supporting Information Figure S5).

4 | DISCUSSION

We investigated the effect of emicizumab dose up-titration in PwHA whose bleeding control was suboptimal in clinical trials.

The dose allowed per protocol for up-titration was 3 mg/kg QW, which corresponded to the maximum well-tolerated dose tested in the phase I/II multiple ascending dose study in PwHA, and was justified by PK modelling studies.[5,21–23] Only a small number of participants (n = 24, 3.6%) had their maintenance dose up-titrated due to suboptimal bleeding control. The model-based ABR for treated bleeds at the labelled doses was relatively high for these individuals, at 11.5

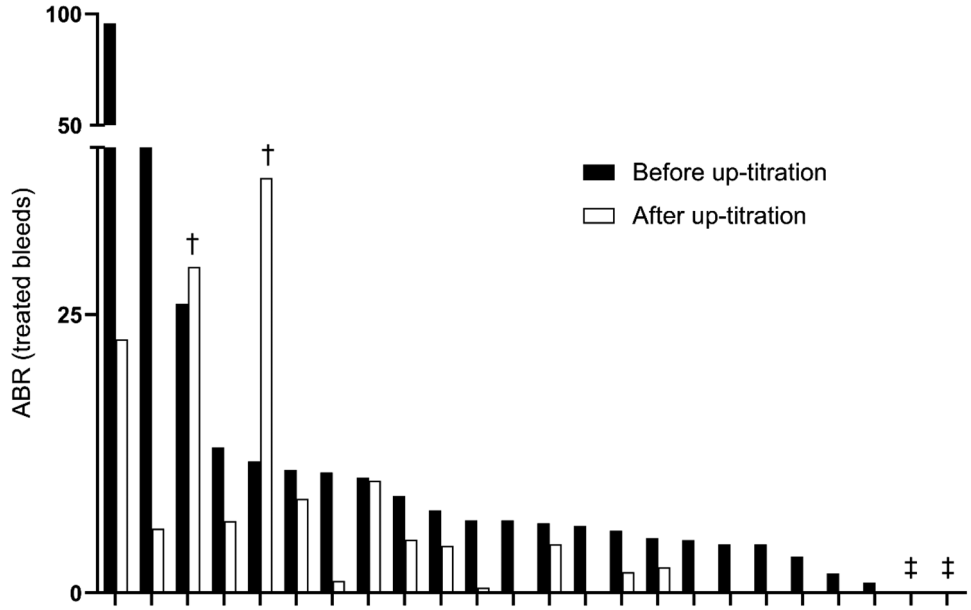

FIGURE 4 Calculated ABRs for treated bleeds before and after dose up-titration to 3 mg/kg QW. †Participants with nAbs. ‡Two participants had an ABR for treated bleeds of zero before and after up-titration; their ABRs for all bleeds were reduced after up-titration from 4.41 to .76 and from 3.01 to 0, respectively (with the exception of the HOHOEMI study, criteria for dose up-titration were based on bleeding events, regardless of whether a bleed was treated or not; see Supporting Information Table S1). ABR, annualised bleed rate; nAbs, neutralising antibodies; QW, once weekly

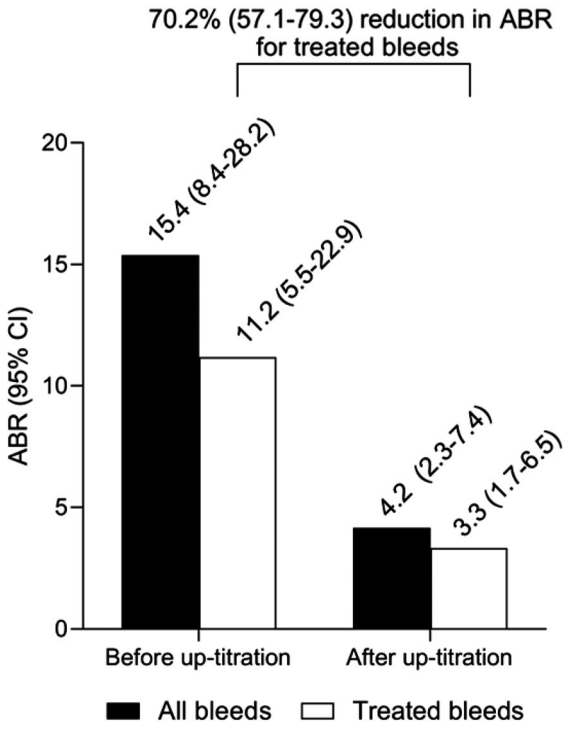

FIGURE 5 Model-based ABRs before and after dose up-titration to 3 mg/kg QW for participants without nAbs ($n = 22$). ABRs were derived using a negative binomial regression model. For 'All bleeds', there was a 72.9% (95% CI: 61.1–81.2) reduction in ABR. ABR, annualised bleed rate; CI, confidence interval; QW, once weekly

(Supporting Information Table S3). For the majority of the participants, up-titration to 3 mg/kg QW was associated with improved bleed control.

For the two participants who developed nAbs against emicizumab, dose up-titration did not compensate for the presence of these antibodies; emicizumab concentration declined, despite dose up-titration, becoming undetectable in one participant, and the ABR for these two participants increased accordingly. Details of the immunogenicity of these individuals have been reported previously.[19]

In the PwHA who did not develop nAbs ($n = 22$), dose up-titration resulted in an approximately two-fold increase in mean steady-state trough concentrations of emicizumab, reflecting the two-fold increase in dose. Of note, up-titration was more frequently adopted in adults versus children/adolescents, in those who had previously been treated with prophylaxis and in those who received emicizumab 6 mg/kg Q4W. Indeed, recent real-world evidence has indicated that, in some adult individuals, standard emicizumab regimens are not able to control all bleeds.[24] Such heterogeneity in response to prophylaxis is also known for PwHA being treated with FVIII, with ongoing debate surrounding the benefit of FVIII peaks for some individuals.[25] Furthermore, the proportion of participants treated with the emicizumab Q4W dosing regimen who underwent up-titration was higher compared with the other dosing regimens, possibly reflecting that the 6 mg/kg Q4W regimen might be perceived as less effective. The small number of participants who underwent up-titration, however, and the fact that investigator judgement was involved in the decision to up-titrate, should be noted when considering this apparent difference.

TABLE 5 Safety summary in emicizumab-treated PwHA with and without dose up-titration

	PwHA without up-titration ($n = 651$)	PwHA with up-titration to 3 mg/kg QW ($n = 24$)		
		Before up-titration	After up-titration	Whole study period
Duration of exposure period, weeks median (IQR)	103.6 (88.3–148.1)	23.3 (21.5–26.6)	91.6 (40.1–119.1)	125.1 (77.8–153.1)
PwHA with at least one AE, *n* (%)	590 (90.6)	20 (83.7)	21 (87.5)	23 (95.8)
PwHA with at least one drug-related AE, *n* (%)	195 (30.0)	7 (29.2)	4 (16.7)	8 (33.3)
PwHA with at least one SAE, *n* (%)	123 (18.9)	6 (25.0)	3 (12.5)	7 (29.2)
PwHA with at least one drug-related SAE, *n* (%)	6 (.9)	1 (4.2)	0 (.0)	1 (4.2)
PwHA with at least one ISR, *n* (%)	136 (20.9)	6 (25.0)	1 (4.2)	7 (29.2)

AE, adverse event; IQR, interquartile range; ISR, injection-site reaction; PwHA, people with haemophilia A; QW, once weekly; SAE, serious AE.

The enhanced haemostatic activity following dose up-titration was associated with improved control of bleeding. Overall, ABRs for treated bleeds and all bleeds were reduced by 70.2% and 72.9%, respectively. In an analysis of 24-week treatment intervals, mean ABR sharply declined immediately after up-titration, and later stabilised at around 3.

While being treated with the original maintenance doses of emicizumab, the mean steady-state trough concentration in participants with suboptimal bleeding control was 44.0 μg/mL, an exposure level well above the suggested efficacy threshold.[26] Moreover, emicizumab concentration was not notably different for the participants whose dose was up-titrated compared with the values previously reported for the overall populations of participants in the phase III/IIIb studies.[6–12,18] This underlines again that bleeding risk in PwHA is not exclusively related to measurable levels of FVIII/FVIII surrogate activity in plasma. Similar to PwHA treated with FVIII, phenotypic heterogeneity exists and some PwHA with emicizumab concentrations at or above the suggested efficacy threshold may exhibit recurrent spontaneous bleeds. In such individuals, dose up-titration appears to be beneficial.

The dose of 3 mg/kg QW was deemed to be well tolerated in a small number of PwHA treated for more than 4 years in the phase I/II study.[21] Results of the present analysis are aligned with previous studies demonstrating the tolerability of this dose level in PwHA. The higher incidence of selected AEs (e.g., SAEs or ISRs) reported in the participants with up-titration did not appear to be related to the increase in emicizumab dose, as the difference was already observed before the dose up-titration took place. Furthermore, the steady levels of coagulation markers indicated no increased prothrombotic risk at the up-titrated dose. Overall, the safety profile at 3 mg/kg QW was similar to that seen at the maintenance dose regimens employed prior to up-titration.

The limitations of this analysis include its lack of appropriate control, the fact that the studies were not designed to specifically assess the effect of up-titration, and the small number of participants whose dose was up-titrated. Moreover, while the criteria for performing dose up-titration were defined in the study protocols, investigator judgement was required; therefore, some participants with qualifying bleeds may not have had their dose up-titrated or conversely, some participants may have been unduly up-titrated. The improvement in bleeding control following up-titration may have been biased by the improvement observed over longer durations of emicizumab treatment, as previously reported,[27] and by a possible regression to the mean effect.[28] However, the more pronounced decrease in ABR in the time interval immediately after up-titration compared with later time intervals likely reflects a true effect.

In summary, dose up-titration was used in a minority of PwHA treated with emicizumab across seven clinical trials and was associated with improved bleed control in most cases. Emicizumab at 3 mg/kg QW was tolerated, with no indication of increased prothrombotic risk. Overall, emicizumab dose up-titration appears to be a potential option for PwHA whose bleeding control is suboptimal on standard dosing regimens, but would warrant further investigation in an appropriately designed trial.

AUTHOR CONTRIBUTIONS

Christophe Schmitt wrote the manuscript; Christophe Schmitt, Tiffany Chang, Koichiro Yoneyama and Michaela Lehle contributed to/designed the research; Christophe Schmitt, Maria Elisa Mancuso, Tiffany Chang, Maria Podolak-Dawidziak, Claire Petry, Robert Sidonio Jr, Koichiro Yoneyama, Nigel S. Key, Markus Niggli, Michaela Lehle, Flora Peyvandi and Johannes Oldenburg performed the research; Christophe Schmitt, Claire Petry and Markus Niggli analysed the data. All authors reviewed and approved the final version submitted.

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CONFLICT OF INTERESTS

CS is an employee and stockholder in F. Hoffmann-La Roche Ltd., and is co-inventor of a patent related to an anti-FIXa/FX bispecific antibody. MEM has provided consultancy for Bayer, CSL Behring, Novo

Nordisk, F. Hoffmann-La Roche Ltd., Octapharma, Pfizer, Sanofi, Sobi, Kedrion, Grifols, BioMarin, Catalyst, UniQure and LFB; and has been on a speakers bureau for Bayer, CSL Behring, Novo Nordisk, F. Hoffmann-La Roche Ltd., Octapharma, Pfizer, Sobi, Kedrion, Grifols, BioMarin and Spark Therapeutics. TC is an employee of Spark Therapeutics, which is part of the Roche group and holds stock in F. Hoffmann-La Roche Ltd. MPD has received a research grant from Takeda; has participated as a speaker and/or on advisory boards for Amgen, Novartis, Novo Nordisk, F. Hoffmann-La Roche Ltd., Sanofi and Takeda; and has received reimbursement for attending congresses from CSL Behring, F. Hoffmann-La Roche Ltd., Sobi and Takeda. CP is an employee of F. Hoffmann-La Roche Ltd. and holds stock in F. Hoffmann-La Roche Ltd. RSJ has received research funding from Genentech, Inc.; consultancy fees from Genentech, Inc./F. Hoffmann-La Roche Ltd.; honoraria from Genentech, Inc./F. Hoffmann-La Roche Ltd.; and expenses from Genentech, Inc./F. Hoffmann-La Roche Ltd. KY is an employee of Chugai Pharmaceutical Co., Ltd. and an inventor/co-inventor of patents related to anti-FIXa/FX bispecific antibodies. NSK has acted as a paid consultant for Takeda, Novo Nordisk and UniQure/CSL Behring. MN is an employee of F. Hoffmann-La Roche Ltd. and holds stock in F. Hoffmann-La Roche Ltd. ML is an employee of F. Hoffmann-La Roche Ltd. and holds stock in F. Hoffmann-La Roche Ltd. FP has received speaker fees for participating in advisory boards from Sanofi, Sobi, Takeda, F. Hoffmann-La Roche Ltd., BioMarin and educational meetings from Grifols and F. Hoffmann-La Roche Ltd. JO has received research funding from Bayer, Biotest, Chugai Pharmaceutical Co., Ltd., CSL Behring, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd., Swedish Orphan Biovitrum and Takeda; consultancy, speakers bureau, honoraria, scientific advisory board and travel expenses from Bayer, Biogen Idec, BioMarin, Biotest, Chugai Pharmaceutical Co., Ltd., CSL Behring, Freeline, Grifols, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd., Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum and Takeda.

DATA AVAILABILITY STATEMENT

Research data are not shared. Given the small study population the data cannot be adequately anonymised to give an acceptably low risk of patient identification. 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.

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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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