

# Bridging the Missing Link with Emicizumab: A Bispecific Antibody for Treatment of Hemophilia A

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## Abstract

Hemophilia A, characterized by absent or ineffective coagulation factor VIII (FVIII), is a serious bleeding disorder that entails severe and potentially life-threatening bleeding events. Current standard therapy still involves replacement of FVIII, but is often complicated by the occurrence of neutralizing alloantibodies (inhibitors). Management of patients with inhibitors is challenging and necessitates immune tolerance induction for inhibitor eradication and the use of bypassing agents (activated prothrombin complex concentrates or recombinant activated factor VII), which are expensive and not always effective. Emicizumab is the first humanized bispecific monoclonal therapeutic antibody designed to replace the hemostatic function of activated FVIII by bridging activated factor IX and factor X (FX) to activate FX and allow the coagulation cascade to continue. In the majority of hemophilic patients with and without inhibitors, emicizumab reduced the annualized bleeding rate to almost zero in several clinical trials and demonstrated a good safety profile. However, the concurrent use of emicizumab and activated prothrombin complex concentrate imposes a high risk of thrombotic microangiopathy and thromboembolic events on patients and should be avoided. Yet, the management of breakthrough bleeds and surgery remains challenging with only limited evidence-based recommendations being available. This review summarizes published clinical trials and preliminary reports of emicizumab and discusses the clinical implications of emicizumab in treatment of hemophilia A.

## Keywords

- ▶ hemophilia
- ▶ emicizumab
- ▶ bleeding
- ▶ bispecific antibody
- ▶ coagulation

## Introduction

Deficiency of coagulation factor VIII (FVIII), commonly known as hemophilia A, is a severe bleeding disorder,<sup>1</sup> representing 80 to 85% of the total hemophilia population.<sup>2</sup> Hemophilia A is an X-linked recessive bleeding disorder, thereby primarily affecting males.<sup>3</sup> Hemophilia A is classified based on the residual FVIII activity level and is defined as severe (coagulation factor activity level <1%), moderate (1–5%), or mild (6–40%).<sup>4</sup> The residual FVIII level depends on the type of mutation in the FVIII gene. Classification of hemophilia also correlates well with clinical

profiles and bleeding symptoms.<sup>4,5</sup> Approximately two-thirds of patients with hemophilia A suffer from severe FVIII deficiency.<sup>6</sup> Predominantly in patients with severe hemophilia A, total deficiency of FVIII can lead to serious joint bleedings, muscle bleedings, soft tissue bleedings, and life-threatening bleeding manifestations such as intracranial hemorrhages,<sup>7,8</sup> which can occur spontaneously.<sup>6</sup> Hemophilic arthropathy is a serious complication of hemophilia-induced joint bleedings,<sup>9</sup> caused by synovial inflammation with subsequent release of inflammatory cytokines and matrix-metalloproteases leading to progressive degradation of the cartilage.<sup>10</sup>

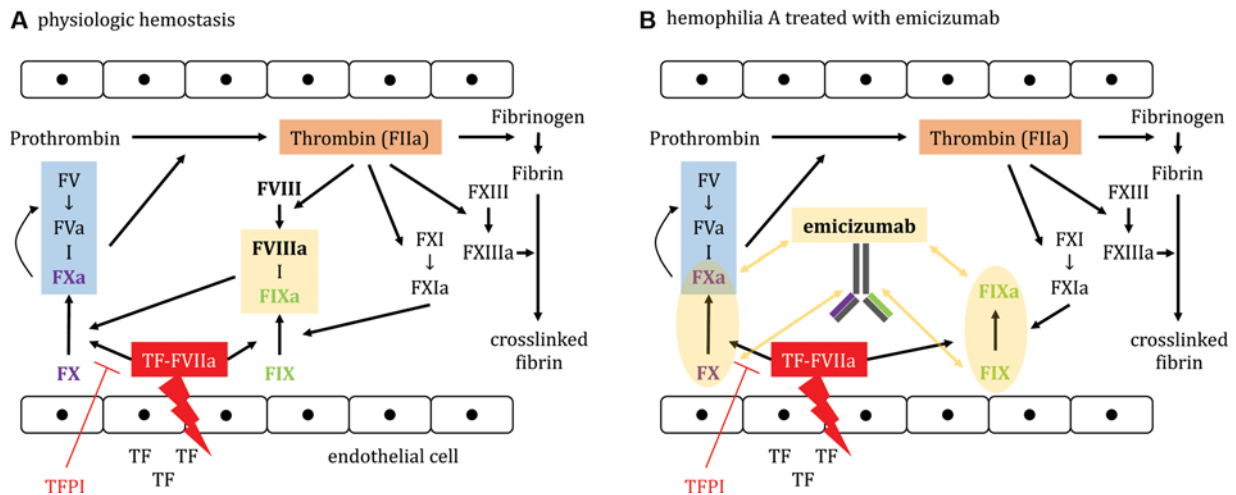
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**Fig. 1** Schematic comparison of (A) physiologic hemostasis and (B) hemostasis in hemophilia A under treatment with emicizumab.

## Role of Factor VIII in the Coagulation Cascade

It is well recognized that the intrinsic pathway is not an accurate model of hemostasis *in vivo*.<sup>11</sup> Activation of the coagulation cascade is mostly triggered by the tissue factor (TF) pathway, which involves complex formation of TF and activated factor VII (FVIIa) at the site of injury (► **Fig. 1A**). The TF/FVIIa complex not only activates factor X (FX) directly, but also activates factor XI (FXI) which further sustains activated FX (FXa), leading to generation of thrombin. Thrombin itself may also activate FXI and FVIII, thereby creating a positive feedback loop.<sup>12</sup> FXa when associated with phospholipids or the TF/FVIIa complex is also a potent activator of FVIII.<sup>13,14</sup> Although not causally involved in the activation process of coagulation, FVIII helps to further maintain and strengthen the production of FXa, ultimately resulting in the generation of thrombin and formation of a stable fibrin clot. In patients with hemophilia A, lack or dysfunction of FVIII impedes physiologic coagulation function and increases the risk of bleeding.<sup>15</sup>

## Factor Replacement Therapy

FVIII replacement with FVIII concentrates is still the treatment of choice in patients suffering from moderate and, in particular, severe hemophilia.<sup>2,16</sup> FVIII concentrates can either be plasma-derived (originating from human donor blood) or recombinant (biotechnologically produced from genetically modified cells). Several modified recombinant FVIII products with extended half-lives have been released to increase dosing intervals and obtain higher trough levels.<sup>17</sup> Treatment can either be prophylactic or episodic. Prophylactic FVIII replacement has been shown to significantly reduce bleeding events<sup>18–22</sup> and slow down joint deterioration.<sup>23</sup> While prophylactic treatment is the more effective way to prevent bleeding and long-term complications,<sup>18</sup> it is expensive, burdensome, and may rarely necessitate central venous access which is associated with infection and thrombosis. Alternatively, episodic FVIII replacement therapy may be

suitable for patients with mild or moderate factor deficiency and a milder bleeding phenotype. The decision which patient population is eligible for and should receive episodic or prophylactic replacement therapy depends on individual patient-related factors (rate and severity of bleeding, venous access, personal preference, etc.).<sup>2</sup>

Yet, there are considerable downsides to FVIII replacement. First, it is expensive and not available everywhere. So far, FVIII can only be given intravenously, implicating that repeated venipunctures are required for a regular, long-term treatment. This often coincides with a reduced patient compliance followed by a worse outcome.<sup>24</sup> The use of FVIII replacement therapy is further complicated by a high interindividual variability in FVIII pharmacokinetics (PK), which necessitates tailored treatment regimens for individuals leading to frequent dose corrections to maintain sufficient FVIII trough levels.<sup>25</sup> In the past, FVIII replacement using plasma-derived concentrates has led to the transmission of blood-borne diseases including hepatitis B and C, and human immunodeficiency virus,<sup>26–30</sup> which has caused significant morbidity and mortality. Since then, improvement in processing of FVIII concentrates has led to a significant decrease of viral infections; however, pathogen transmission through plasma-derived FVIII concentrate infusion yet remains a potential risk.

## Inhibitors

Probably the most challenging aspect of factor replacement therapy in patients with hemophilia A is the occurrence of inhibitory alloantibodies against FVIII. Such inhibitors can rise to very high titers (high responders) and neutralize circulating FVIII rendering replacement therapy ineffective. In patients with severe hemophilia A, anti-FVIII antibodies form in 25 to 40% within the first 50 exposure days.<sup>24</sup> FVIII inhibitors are associated with increased mortality,<sup>31</sup> limitations of physical function,<sup>32</sup> orthopedic complications,<sup>33</sup> and decreased quality of life<sup>34</sup> and increased health care costs when compared with patients without inhibitors.<sup>35,36</sup> Inhibitors necessitate alternative treatment approaches such as

immune tolerance induction (ITI) or the use of bypassing agents (BPAs), recombinant FVIIa (rFVIIa, NovoSeven), and activated prothrombin complex concentrate (APCC, FEIBA).<sup>37,38</sup> However, the use of BPAs is not as effective as replacement of FVIII,<sup>38–40</sup> and has several other disadvantages (very high costs, short half-life, and risk of thromboembolic events). Despite its mechanism of inhibitor elimination still being unclear, ITI shows a response rate of 50 to 75%,<sup>41,42</sup> yet, it requires long-term infusion of high doses of FVIII concentrates and can take years to show effect.<sup>43</sup> Treatment of hemophilia A complicated by FVIII inhibitors requires a high amount of human and economic resources.<sup>44</sup>

In recent years, multiple novel FVIII products have been made available, mostly improving PK aspects, but showing varying results with respect to immunogenicity.<sup>7,45</sup> However, development of FVIII inhibitors substantially limits the use of factor replacement therapy. Therefore, the unmet medical need for a treatment approach for hemophilia that is easy to use, with a long-lasting effect regardless of the presence of FVIII inhibitors, has led to the development of emicizumab, a new bispecific therapeutic antibody mimicking the effect of FVIII.

This review focuses on the safety and efficacy of emicizumab and discusses its clinical implications and potential extended use.

## Emicizumab

Emicizumab (Hemlibra, Roche, Switzerland) is the first commercially available nonfactor replacement product for treatment of congenital hemophilia A. In the United States, it was first approved by the Food and Drug Administration (FDA) in 2017 for the use in patients with congenital hemophilia A with inhibitors, with its indication subsequently being extended for prophylactic use in hemophilic patients with and without inhibitors in 2018. In the European Union, emicizumab is approved for the routine prophylaxis of bleeding episodes in patients with congenital hemophilia A with FVIII inhibitors or severe hemophilia A without inhibitors.<sup>46</sup>

Emicizumab is injected subcutaneously with FDA-approved maintenance dose regimens of 1.5 mg/kg once every week (QW), 3 mg/kg once every 2 weeks (Q2W), or 6 mg/kg once every 4 weeks (Q4W). The recommended loading dose for all treatment regimens is 3 mg/kg QW for the first 4 weeks.

So far, results from four large HAVEN trials have been published (► **Tables 1** and **2**).

## Mechanism of Action and Pharmacodynamic Profile

Emicizumab is a humanized bispecific monoclonal antibody (IgG4) that binds to both the activated FIX (FIXa) and FX. It is therefore designed to mimic the function of missing or deficient FVIII, which is an essential part of effective hemostasis. Emicizumab aligns FIXa and FX in a suitable spatial position, thereby promoting the interaction between the two coagulation factors and accelerating FX activation by FIXa<sup>47,48</sup> (► **Fig. 1B**). However, there are considerable differences be-

tween the natural FVIII and emicizumab. As expected for an antibody, emicizumab binds only to a single site within the FIX and FX molecules, whereas FVIII has multiple interaction sites. Therefore, emicizumab shows substantially less affinity for its substrates, it cannot differentiate between zymogen and enzyme (FIX and FX vs. FIXa and FXa), and it lacks natural regulation of its activity, i.e., the activation by thrombin and the inactivation by protein C.<sup>49</sup> Due to its structural difference to FVIII, emicizumab does not induce the development of FVIII inhibitors.<sup>50</sup>

The pharmacodynamic (PD) response to emicizumab correlates with plasma concentrations of emicizumab. In ex vivo FVIII-neutralized plasma from healthy subjects who received emicizumab in different doses, emicizumab dose-dependently shortened the activated partial thromboplastin time (aPTT). Similarly, peak thrombin generation increased in a dose-dependent manner. In healthy volunteers without FVIII neutralization, emicizumab only slightly shortened the aPTT but did not increase peak thrombin generation.<sup>51</sup> This minimal effect of emicizumab in healthy volunteers can be explained by the higher affinity of FVIIIa than that of emicizumab for FXa.<sup>49</sup> In patients with hemophilia A, emicizumab dose-dependently shortened the aPTT and increased peak thrombin generation.<sup>52</sup> Initiation of emicizumab (6 mg/kg) in hemophilic patients normalized the aPTT within 8 hours and increased peak thrombin generation over the following weeks.<sup>53</sup>

## Pharmacokinetic Profile and Immunogenicity

Following subcutaneous injection of 1 mg/kg, emicizumab showed an absolute bioavailability of 80 to 93% and a mean absorption half-life of 1.7 days.<sup>54</sup> The mean elimination half-life of emicizumab is 1 month ranging from 28.8 to 34.4 days (► **Table 3**).<sup>51</sup> The long half-life of emicizumab is assumed to be due to its IgG4 structure including an altered amino acid sequence that lowers its isoelectric point and reduces its elimination.<sup>54</sup> The mean apparent volume of distribution of emicizumab is 11.4 L. Plasma concentrations of emicizumab increased in a dose-dependent manner.<sup>51,52</sup> Emicizumab showed a first-order elimination phase.<sup>51</sup> Mean trough plasma concentrations depend on the applied dose regimen (after a loading dose of 3 mg/kg QW for 4 weeks): when emicizumab was given QW at a dose of 1.5 mg/kg, mean trough plasma levels were above 50 µl/mL.<sup>55–57</sup> Dosing regimens injecting emicizumab Q2W (3 mg/kg) and Q4W (6 mg/kg) resulted in mean trough plasma levels of 45 to 50<sup>55,57</sup> and 38 to 40 µg/mL,<sup>53,57</sup> respectively (► **Table 3**). The PK of emicizumab are unaffected by age (1–77 years), race, inhibitor status, mild or moderate hepatic impairment, and mild or moderate renal impairment.<sup>46,58</sup>

Further, the immunogenic potential of emicizumab remains to be better defined. Six studies provide data on the occurrence of antidrug antibodies in healthy subjects or patients undergoing treatment with emicizumab (► **Table 3**).<sup>51–53,55–57</sup> In the first-in-man trial, one subject tested positive for anti-emicizumab antibodies even at baseline (before drug administration) and another developed de novo antibodies causing a shortening

**Table 1** Key demographics of included trials

Key demographics	HAVEN 1	HAVEN 2	HAVEN 3	HAVEN 4	First-in-man trial	First-in-patient trial	HOHOEMI	STASEY
Authors (publication year)	Oldenburg et al (2017)	Young et al (2019)	Mahlangu et al (2018)	Pipe et al (2019)	Uchida et al (2016)	Shima et al (2016)	Shima et al (2019)	Data cut-off: October 15, 2018
Population	Adult/adolescent ( $\geq 12$ y) PwHA with inhibitors	Pediatric ( $< 12$ y) PwHA with inhibitors	Adult/adolescent ( $\geq 12$ y) PwHA without inhibitors	Adult/adolescent ( $\geq 12$ y) PwHA with or without inhibitors	Healthy Japanese and white male subjects (20–44 y)	Adult/adolescent (12–59 y) PwHA with or without inhibitors	Pediatric ( $< 12$ y, $> 3$ kg) PwHA without inhibitors	Adult/adolescent ( $\geq 12$ y) PwHA with inhibitors
Treatment duration	24 wk	52 wk	24 wk	24 wk	Single-dose, follow-up ranging from 4 to 24 wk	12 wk	24 wk	24 wk
Dosing	1.5 mg/kg QW	1.5 mg/kg QW, 3 mg/kg Q2W, 6 mg/kg Q4W	1.5 mg/kg QW, 3 mg/kg Q2W	6 mg/kg Q4W	0.001 mg/kg, 0.01 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg	0.3 mg/kg QW, 1 mg/kg QW, 3 mg/kg QW	3 mg/kg Q2W, 6 mg/kg Q4W	1.5 mg/kg QW
Median duration of exposure [wk] (IQR)	107.4 (84.2–127.1)	75.1 (46.2–80.4)	84.4 (79.1–92.6)	68.1 (66.2–68.1)	n/a	n/a	Q2W 39.1 (36.4–40.3), Q4W 32.1 (24.1–36.4)	39.2 (4.4–57.1)

Abbreviations: IQR, interquartile range; kg, kilogram; mg, milligram; PwHA, persons with hemophilia A; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks.

**Table 2** Overview of study design, sample size, and inclusion and exclusion criteria of included trials

Methods	HAVEN 1	HAVEN 2	HAVEN 3	HAVEN 4	First-in-man trial	First-in-patient trial	HOHOEMI	STASEY
Design	Phase III, open-label, multicenter, randomized	Phase III, multicenter, open-label	Phase III, open-label, multicenter, randomized	Phase III, single-arm, multicenter, open-label	Phase I, first-in-human, single-center, double-blind, randomized, placebo-controlled, interindividual dose-escalation	Open-label, nonrandomized, interindividual dose-escalation	Multicenter, open-label, nonrandomized	Phase IIIb, single-arm, open-label, multicenter
N	113	88	152	48	64	18	13	88
Inclusion criteria	12 years of age or older, congenital hemophilia A, high titer of FVIII inhibitors, receiving episodic or prophylactic treatment with bypassing agents	Children with congenital hemophilia A with FVIII inhibitors, receiving episodic or prophylactic treatment with bypassing agents	12 years of age and older, severe congenital hemophilia A without FVIII inhibitors, receiving episodic or prophylactic FVIII infusions	12 years of age or older, severe congenital hemophilia A (<1% of normal FVIII activity in blood) or hemophilia A with FVIII inhibitors, undergoing treatments with either FVIII concentrates or bypassing agents	Healthy subject, age between 20 and 44 years, BMI 18.5 to <25.0 (Japanese subjects), BMI 18.5 to <30.0 (white subjects)	Severe congenital hemophilia A, with/without FVIII inhibitors, age 12–59 years, chronic prophylaxis with FVIII in patients without inhibitors, episodic or prophylactic treatment with bypassing agents in patients with inhibitors, six or more bleeding episodes in the last 6 months	<12 years old, weighing over 3 kg, severe congenital hemophilia A without FVIII inhibitors, testing negative for inhibitors (<0.6 BU/ml) within the 8 weeks prior to enrolment	12 years of age or older, diagnosis of hemophilia A with persistent inhibitors against FVIII, treatment with bypassing agents or FVIII concentrates over the last 6 months (episodic or prophylactic), adequate hematologic, hepatic, or renal function
Exclusion criteria	Inherited or acquired bleeding disorder other than hemophilia A, ongoing ITI or prophylaxis treatment with FVIII, other disease that may increase the risk of bleeding or thrombosis	Inherited or acquired bleeding disorder other than hemophilia A, ongoing ITI or prophylaxis treatment with FVIII, other disease that may increase the risk of bleeding or thrombosis	Inherited or acquired bleeding disorder other than hemophilia A, treatment within the past 12 months for, or current signs of, thromboembolic disease	Inherited or acquired bleeding disorder other than hemophilia A, ongoing or planned ITI therapy, participants at high risk for TMA, previous (within the last 12 months) or current treatment for thromboembolic disease or signs of thromboembolic disease	Current history of clinically significant allergy, hypersensitivity associated with globulin preparations, thromboembolic diseases, FVIII:C $\geq$ 120%, abnormal protein C, protein S, or antithrombin activity, lupus anticoagulant, anticardiolipin- $\beta$ -2 glycoprotein I complex antibody	History of a bleeding disorder other than congenital hemophilia A, clinically significant infection (hepatitis B or C virus), value for protein C activity, free protein S antigen level, reduced antithrombin activity	Complication of a bleeding disorder other than congenital hemophilia A, thromboembolic diseases within the past 12 months and high risk of TMA based on previous or familial history of TMA (e.g., thrombotic thrombocytopenic purpura, atypical hemolytic uremic syndrome)	Inherited or acquired bleeding disorder other than hemophilia A, ongoing (or plan to receive during the study) ITI therapy, High risk for TMA, previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of catheter-associated thrombosis) or current signs of thromboembolic disease

Abbreviations: FVIII, factor VIII; ITI, immune tolerance induction; TMA, thrombotic microangiopathy.

**Table 3** Pharmacokinetic data and immunogenicity of included trials

Pharmacokinetics and immunogenicity	HAVEN 1	HAVEN 2	HAVEN 3	HAVEN 4	First-in-man trial	First-in-patient trial	HOHOEMI	STASEY
Half-life	n/a	n/a	Approx. 30 d	29.5 d	4–5 wk	n/a	n/a	n/a
Mean trough plasma concentration	>50 µg/mL	50 µg/mL (QW), 45–50 µg/mL (Q2W), 38 µg/mL (Q4W)	>50 µg/mL (QW), 45–50 µg/mL (Q2W)	>40 mg/mL	n/a	10.3 ± 4.54 µg/mL, 29.9 ± 6.99 µg/mL, 87.9 ± 20.0 µg/mL	48.7 µg/mL (Q2W), 48.4 µg/mL (Q4W)	n/a
% Antidrug antibodies	1.8	4.5	3.3	4.2	4.2	None	None	n/a

Abbreviations: QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks.

of emicizumab half-life.<sup>51</sup> The first study of emicizumab in hemophilic patients found antidrug antibodies in one patient at baseline, but without neutralizing ability.<sup>52</sup> In the HAVEN 1 trial, no subject tested positive for antidrug antibodies; however, two patients showed PK profiles indicative of such.<sup>56</sup> The HAVEN 2 trial identified four patients with antidrug antibodies, two of which had neutralizing ability.<sup>57</sup> In HAVEN 3, no de novo antidrug antibodies were identified; however, measurement discrepancies occurred in two patients and one patient intermittently tested positive after ITI.<sup>55</sup> No antidrug antibodies were found in patients in HAVEN 4.<sup>53</sup> Due to the limited sample size of studies available, it is difficult to accurately derive the incidence of antidrug antibodies and the proportion of antibodies with neutralizing potential. Further studies with long-term follow-up periods are needed to better characterize immunogenicity.

## Efficacy

### Overall Analysis

Pooled data from HAVEN 1–4 revealed the annualized bleeding rate (ABR) under treatment with emicizumab to be 1.5 (95% confidence interval [CI]: 1.20–1.84) over a median duration of exposure of 83 weeks.<sup>59</sup> Three different treatment regimens have been tested in the HAVEN trials (►Table 4): subcutaneous injection of emicizumab of 1.5-mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg Q4W. All treatment regimens were preceded by four loading doses of 3 mg/kg QW. Emicizumab QW, Q2W, and Q4W regimens were associated with a mean ABR across HAVEN 1–4 of 1.6, 0.8, and 2.3, respectively. ABRs of the four individual HAVEN trials are shown in ►Table 4. In every treatment cohort of the HAVEN trials, at least 50% of patients (range 56–90%) had zero treated bleeding events. The proportion of patients with no bleeding events increased over time in all four trials. Across HAVEN 1–4, emicizumab was associated with an ABR for spontaneous bleeds of 0.6 (95% CI: 0.5–0.8) and for joint bleeds of 1.0 (95% CI: 0.8–1.3). Again, the proportion of patients with zero bleeding events (spontaneous and joint) increased over time. Further, emicizumab was associated with a resolution of 99% of target joints (target joints were defined as major joints [e.g., hip, elbow, wrist, shoulder, knee, and ankle] in which ≥3 bleeding events occurred over a 24-week period; target joint resolution was defined as ≤2 bleeding events in a 52-week period in a joint previously defined as a target joint) in patients across HAVEN 1–4.<sup>59</sup>

In the Japanese pediatric HOHOEMI trial, although small in sample size, Q2W and Q4W treatment regimens showed ABRs for treated bleeding events of 1.3 and 0.7, respectively.<sup>60</sup> Similar to previous studies, interim results from the STASEY trial report an ABR of 0.5 for treated bleeding events.<sup>61</sup>

### Comparison of Efficacy in Patients with versus without FVIII Inhibitors

Three studies, HAVEN 1, 2, and STASEY, evaluated the efficacy of emicizumab in hemophilic patients with FVIII inhibitors only.<sup>56,57</sup> Emicizumab resulted in ABRs of treated bleeds of 2.9, 0.3, and 0.5 (all QW), respectively.

**Table 4** Efficacy outcomes of included trials

Efficacy	HAVEN 1	HAVEN 2	HAVEN 3	HAVEN 4	First-in-man trial	First-in-patient trial	HOHOEMI	STASEY
Dosing regimen(s)	QW	QW, Q2W, Q4W	QW, Q2W	Q4W	n/a	0.3 mg, 1 mg, 3 mg QW	Q2W, Q4W	QW
ABR of treated bleeding events (95% CI) (% reduction vs. reference arm)	2.9 (1.7–5.0) (87% reduction)	0.3 (0.17–0.50), 0.2 (0.03–1.72), 2.2 (0.69–6.81)	1.5 (0.9–2.5) (96% reduction), 1.3 (0.8–2.3) (97% reduction)	2.4 (1.4–4.3)	n/a	n/a	1.3 (0.6–2.9), 0.7 (0.0–3.1)	0.5 (0.29–1.00)
% Zero bleeding events	63	76.9, 90.0, 60.0	55.6, 60.0	56.1	n/a	73 (with inhibitors), 71 (without inhibitors)	33.3, 71.4	80.7
All bleeding events	5.5 (3.6–8.6)	3.2 (1.94–5.22), 1.5 (0.62–3.40), 3.8 (1.42–10.11)	2.5 (1.6–3.9), 2.6 (1.6–4.3)	4.5 (3.1–6.6)	n/a	4.4 (0.0–59.5), 0.0 (0.0–4.3), 0.0 (0.0–4.2)	14.1 (7.6–26.2), 21.8 (9.2–51.8)	1.4 (0.91–2.24)
Treated spontaneous bleeding (ABR)	1.3 (0.7–2.2) vs. 16.8 (9.9–28.3)	0.0 (0.01–0.10) not estimable 0.8 (0.05–12.00)	1.0 (0.5–1.9), 0.3 (0.1–0.8)	0.6 (0.3–1.5)	n/a	n/a	0.2 (0.0–1.6), n/a	0.2 (0.08–0.34)
Treated joint bleeding (ABR)	0.8 (0.3–2.2) vs. 6.7 (2.0–22.4)	0.2 (0.08–0.29), 0.2 (0.03–1.72), 1.7 (0.60–4.89)	1.1 (0.6–1.9), 0.9 (0.4–1.7)	1.7 (0.8–3.7)	n/a	n/a	0.9 (0.3–2.3), n/a	0.3 (0.10–0.84)
Treated target-joint bleeding (ABR)	0.1 (0.0–0.6) vs. 3.0 (1.0–9.1)	Not estimable 0.2 (0.03–1.72), 0.5 (0.05–5.88)	0.6 (0.3–1.4), 0.7 (0.3–1.6)	1.0 (0.3–3.3)	n/a	n/a	n/a, n/a	0.1 (0.03–0.18)
Proportion of resolved target joints (%)	98.7	100	99.2	100	n/a	n/a	n/a, n/a	n/a

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks.

Two studies, HAVEN 3 and HOHOEMI, only included patients without FVIII inhibitors.<sup>55,60</sup> Emicizumab was associated with ABRs of treated bleeds of 1.5 (QW) and 1.3 (Q2W), respectively. HAVEN 4 included both patients with and without inhibitors; however, 88% of patients in the expansion cohort had no FVIII inhibitors. The ABR for treated bleeds in HAVEN 4 was 2.4 (Q4W).

### Comparison of Efficacy According to Different Treatment Regimens (QW versus Q2W versus Q4W)

Six studies evaluated three treatment regimens. The median ABR of treated bleeds of the QW, Q2W, and Q4W treatment regimens, pooled from all studies, was 1, 1.3, and 2.2, respectively.

### Safety and Drug Interactions

Injection-site reactions were the most common treatment-related adverse events and frequently reported across all HAVEN trials ( $n = 104$ ; 26.1%).<sup>59</sup> All injection-site reactions were of mild or moderate severity, most of which (93%) resolved without treatment. Other adverse events included headache (15%), arthralgia (15%), pyrexia (6%), and diarrhea (6%).<sup>58</sup> A total of 103 serious adverse events were reported in 71 participants with hemorrhage and hemarthrosis being reported by  $\geq 5$  participants.

Adverse events of special interest occurred in five patients of the HAVEN 1 trial. Of these, three patients developed thrombotic microangiopathy (TMA), one patient suffered from cavernous sinus thrombosis, and another patient suffered from skin necrosis/superficial thrombophlebitis. One patient with TMA developed rectal bleeding, refused treatment with blood transfusions, and subsequently died. His death was considered unrelated to emicizumab due to the resolving TMA at the time.

Notably, the occurrence of all five coagulation-associated adverse events was associated with the concomitant use of APCC at doses of  $>100$  U/kg/d for a time period of more than 1 day. None of the patients receiving concomitant treatment with emicizumab and APCC of any dose for only 1 day had any thromboembolic events. Otherwise, in a retrospective analysis of real-world patients, one patient developed postoperative thrombosis/TMA in association with APCC despite emicizumab discontinuation 1 month prior to the surgery.<sup>62</sup> The pathomechanism of TMA caused by concomitant use of emicizumab and APCC is probably the crosslinking of the activated factors contained in the APCC.<sup>54</sup> Interestingly, the incidence of TMA was limited to APCC only; no cases of TMA or thromboembolic events have been linked to the concomitant use of rFVIIa. Moreover, management of bleeding episodes with FVIII in emicizumab-treated patients without inhibitors was also not associated with the occurrence of TMA or thromboembolic events.

One patient in the HAVEN 2 trial was believed to suffer from a systemic hypersensitivity reaction due to symptoms of abdominal pain and cough but upon later medical review his symptoms were confirmed not to be linked to anaphylaxis.

In the HOHOEMI trial, two patients experienced serious adverse events unrelated to the study drug. No thromboembolic events, TMA, or systemic hypersensitivity reactions were observed.<sup>60</sup>

In the STASEY trial, of 17 patients who experienced a treated bleeding event, 16 were concomitantly treated with rFVIIa and one was treated with standard FVIII. There was no occurrence of any thromboembolic event or TMA.<sup>61</sup>

### Surgery

In total, 31.6% (126/399) of patients in HAVEN 1–4 underwent at least one surgical procedure.<sup>63</sup> Of 233 surgeries performed, 18 were deemed major surgeries and 215 were deemed minor surgeries. One hundred forty-one of the minor surgeries were managed without prophylactic infusion of coagulation factor and over 90% of patients had no treated postoperative bleeding events. Of the 18 major surgeries, all three that were managed without prophylactic administration of coagulation factor had no treated postoperative bleeds. Of the remaining 15 patients treated with prophylactic coagulation factor, only one had a treated bleeding event. Major surgeries included five cases of arthroplasty with only one occurrence of bleeding due to surgery.

Further, the successful use of emicizumab with perioperative administrations of rFVIIa in a major surgery has been described in patients receiving total hip arthroplasty.<sup>64,65</sup> Another patient with acquired hemophilia A under treatment with emicizumab underwent percutaneous coronary intervention and received periprocedural loading with 325 mg aspirin and 600 mg clopidogrel. He was successfully treated and continued dual-antiplatelet therapy without breakthrough bleeding events or need for BPA administration.<sup>66</sup>

### Health-Related Quality of Life

Health-related quality of life (HR-QoL) was assessed using the *Haem-A-QoL physical health subscale score at week 25*. Generally, improvement of HR-QoL was seen across all published HAVEN trials. Further, emicizumab was associated with fewer missed days at school or work<sup>53,67</sup> and a reduced number of days hospitalized.<sup>67</sup> Almost all patients preferred emicizumab treatment over prophylaxis with FVIII or BPAs.<sup>53,55</sup>

### Laboratory Testing

Assessment of the hemostatic function and FVIII activity in patients under treatment with emicizumab needs special attention.<sup>68,69</sup> Since emicizumab causes a significant shortening of the aPTT even at very low concentrations,<sup>52,69</sup> use of conventional aPTT tests is futile. Diluted aPTT, however, correlates well with the plasma emicizumab concentration.<sup>70</sup>

Conventional FVIII activity assays were found to be either oversensitive or insensitive to emicizumab, which precludes their use. However, a modified FVIII one-stage assay calibrated against emicizumab accurately quantifies FVIII activity and measures emicizumab concentrations.<sup>71</sup>



To differentiate between the PD effect of emicizumab and the endogenous residual FVIII activity, chromogenic FVIII assays using two different reagents need to be used.<sup>72</sup> While the chromogenic assay using bovine reagents can detect the endogenous FVIII activity, the one using human reagents assesses emicizumab's effect.<sup>69</sup>

For measurement of inhibitors under concurrent treatment with emicizumab, a chromogenic Bethesda assay using bovine reagents can be used.<sup>73</sup>

Although not routinely done, rotational thromboelastometry (ROTEM; Pentapharm GmbH, Munich, Germany) may be used for assessment of coagulation function in emicizumab-treated patients. In particular, clotting time and clot formation time of the nonactivated thromboelastometry test (native coagulation, NATEM) showed a dose-dependent response to emicizumab.<sup>74</sup> Thromboelastometry has also been used to assess coagulation function in an *in vitro* experiment involving emicizumab, APCC, and rFVIIa.<sup>75</sup> Clot waveform analysis may also be a promising tool for coagulation assessment.<sup>76</sup> The thrombin generation assay has been shown to be a useful marker of hemostatic function in patients under treatment with emicizumab<sup>77</sup> and is also helpful in the assessment of coagulation in emicizumab-treated patients receiving concomitant treatment with BPAs.<sup>78</sup>

## Discussion

So far, three large trials (HAVEN 1, 3, and 4), evaluating the safety, efficacy, and PK of emicizumab in adults and adolescents with hemophilia A, have been published.<sup>53,55,56</sup> All three of them showed emicizumab to significantly reduce ABRs. Additionally, results from the HAVEN 2 trial, including only children <12 years (2–11 years), have been published, further substantiating the findings of previous studies.<sup>57</sup> The recently published HOHOEMI trial and interim results from the STASEY trial also confirmed emicizumab's efficacy.<sup>60,61</sup>

While showing a significant decrease in bleeding events, the HAVEN trials lack prospective data comparing emicizumab versus standard prophylaxis with either FVIII or BPAs. Instead, direct comparison of emicizumab with standard care is performed through a noninterventive study, comparing intra-individual patient data. Of note, HAVEN 4 features only a single experimental arm (Q4W).

Intraindividual comparison of HAVEN 3, including hemophilic patients without inhibitors, who previously received prophylaxis with FVIII, showed emicizumab prophylaxis to be associated with a 68% lower ABR.

Noninterventive study results from HAVEN 1 and 2, including hemophilic patients with inhibitors under previous prophylactic treatment with BPAs, showed a 79 and 99% decreased ABR, respectively, with emicizumab prophylaxis, indicating a larger effect size of emicizumab prophylaxis in inhibitor patients.

### Bleeding under Treatment with Emicizumab

Regardless of the impressive clinical performance of emicizumab, breakthrough bleeding events may still occur and call for additional episodic treatment with either FVIII or BPAs,

depending on the presence of inhibitors. Management of breakthrough bleeding proves especially challenging in patients with inhibitors as outlined by the HAVEN 1 trial.

While the concurrent use of APCC and emicizumab imposes a high prothrombotic risk, the concomitant use of rFVIIa in the context of breakthrough bleeding events under emicizumab prophylaxis has so far not been associated with TMA or thromboembolic events<sup>79</sup> and is recommended as first-line treatment in a recent guidance paper by the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO).<sup>80</sup> If, after administration of rFVIIa, the bleeding event does not resolve, treatment with FVIII should be initiated. Usage of APCC should only be considered unless no other option is available.<sup>80</sup>

Another review from the French network on inherited bleeding disorders (MHEMO), the French Reference Centre on Haemophilia, in collaboration with the French Working Group on Perioperative Haemostasis (GIHP) also favors rFVIIa as first-line treatment in a bleeding patient with inhibitors treated with emicizumab, with a similar downstream treatment algorithm. Optionally, tranexamic acid can be given as a supportive measure to rFVIIa.<sup>81</sup>

Further, the Italian Association of Haemophilia Centres (AICE) have provided a practical guidance paper on how to manage patients with hemophilia A and inhibitors under treatment with emicizumab in the emergency department.<sup>82</sup>

However, the uncritical, permissive use of rFVIIa in emicizumab-treated patients is unwarranted, since the results of the bleeding analysis from HAVEN 1, 2, and 4 show some major limitations.<sup>79</sup> First, universal application of the study is precluded by the exclusion of patients with a high thrombotic risk from the included trials. Second, around half of the patients were exposed to only a single-dose treatment of rFVIIa, leaving information on repeated use unknown. Lastly, the study lacks information on patients in the clinical setting of infection (sepsis), trauma, and major surgery.<sup>83</sup>

In hemophiliacs without inhibitors, however, breakthrough bleeding can easily be treated with FVIII concentrates, which should be administered as soon as possible. For joint bleeds and soft tissue bleeds, a dose of approximately 25 units/kg is recommended.<sup>84</sup>

### Emicizumab versus Standard-of-Care Treatment

Emicizumab's exact place in future guidelines remains to be further discussed, yet, convincing arguments can be made for its primary use.

First, patients with poor venous access are spared repeated venipuncture attempts or even the installation of an intravenous catheter, which involves the risk of thrombosis and infection.

Second, in previously untreated patients (PUPs), the initiation of emicizumab could enable (almost) complete discontinuation of FVIII replacement, which includes the prevention of inhibitor development in the first place. In that case, FVIII concentrates would exceptionally be used to treat breakthrough bleeding events, which might potentially slow down or even preclude the development of inhibitors. Inhibitor development is not only dependent on the timing of FVIII

infusion but also on the frequency and intensity of treatment (e.g., during bleeding episodes).<sup>85,86</sup> During HAVEN 3, emicizumab reduced the ABR to zero in more than 50% of patients, thereby completely eliminating the need for FVIII coadministration in these patients. If, in the remaining patients, episodic administration of FVIII was required (in total 215 coexposure events with emicizumab and FVIII were reported in 64 patients), most doses of FVIII administered were very low (<50 IU/kg bodyweight) and given over a time frame of less than 24 hours. Assuming an even distribution of coexposure events lasting less than 24 hours among patients, this would result in 3.4 exposure days per patient over the course of 6 months. Consistently, no patients from the HAVEN 3 trial (or the HOHOEMI trial) developed new FVIII inhibitors. Compared with data from the INSIGHT study, inhibitors developed with a cumulative incidence of 5.3% after a median of 28 exposure days.<sup>87</sup> It is therefore conceivable that, even in case FVIII concentrates are needed to cope with breakthrough bleeding under treatment with emicizumab, exposure to FVIII is most often limited to less than 24 hours (= 1 exposure day), involves mostly low doses of FVIII, and thereby allows keeping inhibitor development to a minimum.

Further, emicizumab treatment in infants or small children would preclude constant intravenous injections, which presents a great burden of illness and leads to traumatization of young patients. Importantly, early treatment initiation in PUPs may be able to decrease the incidence of intracranial hemorrhage, a potentially fatal complication encountered in infants with impaired hemostasis.<sup>88</sup>

The efficacy of emicizumab prophylaxis has been successfully proven in infants and small children.<sup>89</sup> However, uncertainties about the PK and clinical pharmacology of monoclonal antibodies in pediatric patients remain, with evidence suggesting age-associated PK/PD differences in addition to size-based differences.<sup>90</sup>

Third, an emicizumab-only treatment regimen may just as well be used in patients with inhibitors as prophylaxis with emicizumab has been shown to be superior to prophylaxis with BPAs. ABRs under emicizumab have become so low that treatment of breakthrough bleedings with BPAs (primarily rFVIIa) seems to be a more reasonable treatment option compared with undergoing inhibitor eradication with ITI.

### **Emicizumab versus Immune Tolerance Induction**

Despite the unprecedented efficacy of emicizumab in patients with hemophilia A with or without inhibitors in reducing the rate of bleeding events, doubts about its unrestricted routine use have been expressed.<sup>91</sup>

First, hemophilic patients with inhibitors show both an increased risk of bleeding-associated death and a 70% increase in overall mortality,<sup>31</sup> concluding that inhibitor eradication by ITI should remain the primary goal in this particular patient population. *On the other hand, the efficacy of emicizumab is independent of presence of FVIII inhibitors, possibly rendering inhibitor eradication irrelevant. Further, even in the presence of inhibitors, emicizumab significantly reduced the ABR, which may also result in a reduction of mortality.*

Second, as mentioned above, treatment of bleeding episodes in hemophilic patients with inhibitors receiving emicizumab is problematic and the procoagulatory potential of concomitant emicizumab and APCC or even rFVIIa yet remains insufficiently studied.<sup>92</sup> However, due to the inferiority of BPAs to FVIII<sup>38–40</sup> with regard to treatment of bleeding episodes and possibly serious adverse events when using APCC in a patient receiving emicizumab, the use of APCC should be avoided as much as possible, which is only feasible when patients undergo inhibitor eradication with ITI.<sup>91,93</sup>

Another argument in favor of ITI rather than treatment with emicizumab involves a possible future treatment method of hemophilia A—gene therapy. This is discussed below.

Last, the lack of sufficient long-term data regarding efficacy, safety, and immunogenicity precludes the universal application of emicizumab but, on the other hand, warrants generation of more data which will help inform health care treatment decisions.

There are multiple treatment regimens for ITI consisting of high and low FVIII dosing regimens. Patients undergoing high-dose ITI have fewer bleeding events during treatment and achieve tolerance faster<sup>41,94</sup>; however, high-dose ITI implies an intense treatment schedule and is very expensive. Patients undergoing low-dose ITI bleed more but treatment is less burdensome and more cost-effective.<sup>41</sup>

Prophylactic use of emicizumab may be used in patients undergoing ITI as supportive treatment to minimize bleeding events. This has already been successfully tested<sup>95</sup> and is considered a potential new approach for the management of inhibitor patients.<sup>96</sup>

Subsequently, instead of continued FVIII replacement, patients could be switched to emicizumab-only treatment; however, the question of whether completed ITI necessitates the continued administration of FVIII to maintain tolerance remains unanswered.<sup>91</sup>

Given the quite recent introduction of emicizumab, its use is not included in the 2012 guidelines for the management of hemophilia.<sup>2</sup> Emicizumab's place in succeeding guidelines will be of interest, given the presence of widely different treatment approaches.

### **Q4W Emicizumab Dosing Regimen**

Of the three currently approved dosing intervals, Q4W was associated with higher ABRs of treated bleeding rates (HAVEN 2: 2.2 and HAVEN 4: 2.4). Consistently, increased ABRs were combined with lower PK results (Q4W mean trough level: 38–40 µg/mL), which were, however, expected based on PK simulations<sup>97</sup> and associated with efficacy, similar to those of the other tested dosing intervals. The larger peak–trough fluctuation combined with moderate to high interindividual variability in emicizumab exposure leading to suboptimal emicizumab plasma concentrations may account for increased ABRs of treated bleeds as found in HAVEN 2 and 4. The decision to choose the Q4W dosing regimen, which appeals to both patients and physicians, must be carefully weighed against its potential ABR increase compared with the QW and Q2W regimens and is therefore ultimately chosen based on individual patient preferences.

### Emicizumab in Acquired Hemophilia A

While emicizumab has not been approved by health authorities for the treatment of acquired hemophilia A, there are published reports of benefit from treatment with emicizumab.<sup>98–100</sup> So far, over 15 male and female patients with acquired hemophilia A have been reported to be treated with emicizumab, all of which had excellent response to treatment.<sup>101,102</sup> The use of emicizumab in this patient population may also offer the option to scale down on the immunosuppressive treatment with corticosteroids to avoid side effects in a typically frail elderly population, and to save the enormous costs of bypassing therapy. A clinical trial with emicizumab and reduced immunosuppression is currently under development (NCT04188639) and is scheduled to start in mid-2020.

### Emicizumab in von Willebrand Disease

The bleeding phenotype for the expected persistent complete absence of von Willebrand Disease, as in type 3 von Willebrand disease, together with moderate FVIII-like activity provided by emicizumab remains to be demonstrated.<sup>103</sup>

### Economic Considerations

Given the lifelong persistence of hemophilia A, the use of emicizumab greatly depends on its costs. In a cost-effectiveness analysis, emicizumab prophylaxis was associated with fewer bleeding events and increased quality of life at a lower total cost compared with prophylaxis using BPAs and no prophylaxis.<sup>104</sup> A study involving a model-based prediction of clinical and economic outcomes confirmed emicizumab's lower financial impact while at the same time improving patient outcomes.<sup>105</sup> A recent cost-effectiveness analysis, comprising a Markov model and a budget impact model, further substantiates the findings of previous studies.<sup>106</sup>

### Novel Therapeutic Options to Treat Hemophilia

Several other novel treatment strategies to combat hemophilia are currently under investigation.<sup>107</sup>

One approach to restoring hemostatic balance is by targeting the natural anticoagulant TF pathway inhibitor (TFPI). TFPI is part of the endogenous anticoagulation system and suppresses early stages of coagulation by inhibiting TF-VIIa (► Fig. 1A) and early forms of prothrombinase.<sup>108</sup> Inhibition of TFPI could lead to increasing procoagulant activity thereby counteracting the anticoagulative nature of hemophilia and achieving hemostatic balance. A phase 1 trial of concizumab, a monoclonal antibody directed against TFPI, showed a favorable safety profile and increased d-dimer levels and prothrombin 1 + 2 fragments in a dose-dependent manner.<sup>109</sup> Phase 2 and 3 trials are currently ongoing.

Another way to induce a more procoagulant state is interference with antithrombin, a central component of the coagulation system. Fitusiran, a novel RNA interference therapy, was able to lower antithrombin levels and increase thrombin generation in patients with hemophilia A or B in a phase 1 dose-escalation study.<sup>110</sup>

A third promising treatment approach for hemophilia A is gene therapy. In a phase 1/2, dose-escalation, safety, tolerability, and efficacy study, nine men with hemophilia A

without inhibitors received a single intravenous infusion of a codon-optimized adeno-associated virus serotype 5 (AAV5) vector encoding a B-domain-deleted human FVIII (AAV5-hFVIII-SQ).<sup>111</sup> The study yielded promising results as patients receiving the high dose ( $6 \times 10^{13}$  vector genomes,  $n = 7$ ) showed FVIII activity of more than 5 IU/dL between weeks 2 and 9, with six of seven patients even reaching normal FVIII activity of  $>50$  IU/dL that were maintained at 1 year after infusion. This potential treatment option is only viable provided no FVIII inhibitors are present, further alluding to a benefit of continued indication for ITI treatment.

### Conclusion

Emicizumab is a novel, bispecific antibody that restores the hemostatic balance in patients with hemophilia A irrespective of the presence of inhibitors. Across all three dosage regimens, it impressively reduced the ABR of the majority of patients to zero in several clinical trials. Emicizumab showed a good safety and tolerability profile, but concurrent use of emicizumab and APCC should be avoided due to increased risk of TMA and thromboembolic events. Use of emicizumab may be extended to patients with acquired hemophilia A in the future. While additional long-term follow-up data are accumulated, emicizumab is set to revolutionize the treatment of hemophilia A as it unifies both efficacy and practicality compared with other currently available treatment options.

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