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ADISINSIGHT REPORT

Emicizumab-kxwh: First Global Approval

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Abstract Emicizumab-kxwh (Hemlibra®) is a bispecific humanized monoclonal antibody that restores the function of missing activated FVIII by bridging activated FIX and FX to facilitate effective haemostasis in patients with haemophilia A. Subcutaneous emicizumab-kxwh is approved in the USA for use as routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and paediatric patients with haemophilia A (congenital FVIII deficiency) with FVIII inhibitors. Subcutaneous emicizumab-kxwh is awaiting approval in several countries worldwide, including in the EU and Japan, and is undergoing phase 3 development in haemophilia A without FVIII inhibitors. This article summarizes the milestones in the development of emicizumab-kxwh leading to its first global approval for use as prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with haemophilia A.

1 Introduction

F. Hoffman-La Roche and Chugai Pharmaceutical are co-developing emicizumab-kxwh (Hemlibra®) for the treatment of haemophilia A, which is characterized by the congenital absence or deficiency of plasma clotting factor VIII (FVIII) [1, 2]. When bound to activated FIX (FIXa) and FX, activated FVIII (FVIIIa) acts as a pro-coagulation cofactor and potent generator of thrombin [2]. Although intravenous recombinant and plasma-derived FVIII products are available for prophylaxis to prevent bleeding and for the treatment of bleeding episodes, these infusions need to be repeated several times a week, and approximately 30% of patients with severe FVIII deficiency develop FVIII antibodies (inhibitors) that neutralize the function of infused FVIII [2, 3]. Subcutaneous emicizumab-kxwh, a bispecific FIX- and FX-directed antibody that mimics the function of FVIIIa [4], received approval in the USA on 16th of November 2017 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and paediatric patients with haemophilia A (congenital FVIII deficiency) who have FVIII inhibitors [5, 6]. The recommended dosage of emicizumab-kxwh is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, then 1.5 mg/kg once weekly thereafter [5].

This profile has been extracted and modified from the AdisInsight database. AdisInsight tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

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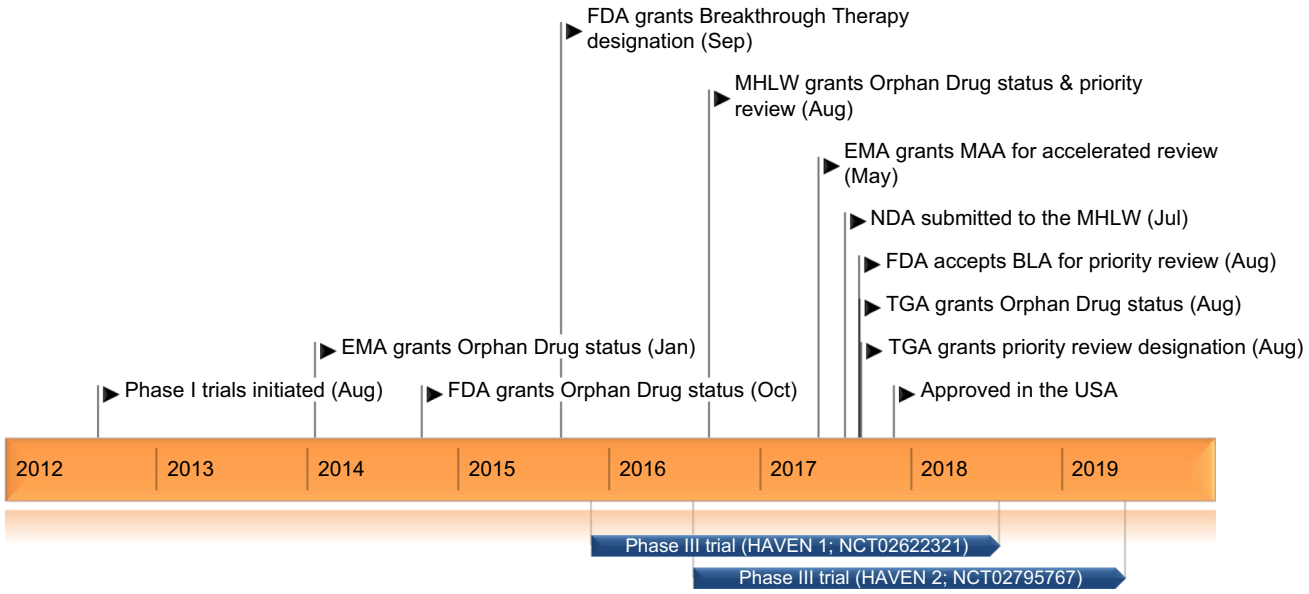

Key milestones in the development of emicizumab-kxwh for the prophylactic treatment of patients with haemophilia A and factor VIII inhibitors, with the focus on phase 3 trials on which the US approval was based. *BLA* biologics license application, *EMA* European Medicines Agency, *MAA* marketing authorisation application, *MHLW* Ministry of Health, Labour and Welfare (Japan), *NDA* new drug application, *TGA* Therapeutic Goods Administration (Australia)

There are no contraindications to the use of emicizumab-kxwh therapy [5]. There is a boxed warning regarding the risk of thrombotic microangiopathy (TMA) and thromboembolism in patients receiving emicizumab-kxwh and activated prothrombin complex concentrate (aPCC); cases of TMA and thrombotic events were reported when on average, a cumulative amount of >100 U/kg/24 h of aPCC was administered for 24 h or more to patients receiving emicizumab-kxwh prophylaxis. If aPCC is coadministered, patients should be monitored for the development of TMA and thrombotic events; if symptoms occur, emicizumab-kxwh should be suspended and aPCC discontinued [5].

Subcutaneous emicizumab-kxwh is awaiting approval in several countries worldwide, including in the EU and Japan, and is undergoing phase 3 development in haemophilia A without inhibitors [1].

2 Scientific Summary

2.1 Pharmacodynamics

Emicizumab-kxwh, a humanized monoclonal modified immunoglobulin G4 antibody, is a bispecific antibody, without any homology to FVIII, which binds to FIX and FX [4, 5, 7]. By bridging activated FIXa and FX, emicizumab restores the function of missing FVIIIa to facilitate effective haemostasis in patients with haemophilia A, irrespective of the presence or absence of FVIII inhibitors [5].

In preclinical studies in primate models of haemophilia, emicizumab-kxwh demonstrated haemostatic effects [8–11]. For example, emicizumab-kxwh prophylaxis prevented the occurrence of the bleeding symptoms associated with the control group in a primate model of acquired haemophilia, with no bleeding symptoms observed in the emicizumab-kxwh group [9].

In the pivotal HAVEN 1 trial ($n = 103$ evaluable patients), emicizumab-kxwh exhibited concentration-dependent pharmacodynamic effects on FXIa-triggered thrombin generation and FVIII activity, with the activated partial thromboplastin time (i.e. <40 s) normalized after the first dose (i.e. at subtherapeutic levels) and remaining stable thereafter (abstract) [12]. There was an approximately 30% increase from baseline ($<1\%$ activity) in mean chromogenic FVIII activity during the maintenance phase (week 5 onwards). During emicizumab-kxwh treatment, there were no significant changes over time for other evaluated coagulation assays, including antigen levels of FIX, FX, von Willebrand factor, D-dimer and prothrombin fragment 1.2, which is consistent with the overall safety profile of emicizumab-kxwh [12].

2.2 Pharmacokinetics

The pharmacokinetics of subcutaneous emicizumab-kxwh were similar after administration into the abdomen, upper arm or thigh [5]. Subcutaneous emicizumab-kxwh exhibits dose-proportional pharmacokinetics over a dose range of 0.3 mg/kg (0.1 × approved initial loading dosage) to 3 mg/kg once weekly. In haemophilia A patients receiving once weekly emicizumab-kxwh 3 mg/kg, the trough plasma concentration at week 5 was 54.6 μg/mL, with trough plasma concentrations maintained at > 50 μg/mL thereafter with the recommended weekly dosage of 1.5 mg/kg. The absorption half-life of emicizumab-kxwh was 1.7 days and its absolute bioavailability following a 1 mg/kg dose was 80.4–93.1%. The mean apparent volume of distribution (Vd) of emicizumab-kxwh was 11.4 L. The mean apparent clearance of emicizumab-kxwh was 0.24 L/day and the mean elimination half-life was 27.8 days [5].

The pharmacokinetics of emicizumab-kxwh are not influenced by age (3–75 years), race (Caucasian, Black or Asian [13]), inhibitor status, mild hepatic impairment [i.e. total bilirubin 1 to ≤ 1.5 × the upper limit of normal (ULN) and any AST level)] or moderate hepatic impairment (i.e. total bilirubin 1.5 × to ≤ 3 × ULN and any AST level) [5]. The apparent clearance and Vd of emicizumab-kxwh increased with increasing bodyweight (bodyweight of 14.2–131 kg), with dosing by bodyweight (mg/kg) providing similar exposure to emicizumab-kxwh across bodyweights [5].

No drug–drug interaction studies of emicizumab-kxwh have been conducted in humans [5].

2.3 Therapeutic Trials

Subcutaneous emicizumab-kxwh prophylaxis significantly reduced the rate of bleeding events compared with no prophylaxis in adolescents and adults with congenital haemophilia A and FVIII inhibitors in the randomized, open-label, multinational, phase 3, HAVEN 1 trial ($n = 109$ enrolled) [NCT02622321] [14]. All patients were male and had a history of having a high titre of FVIII inhibitors (≥ 5 Bethesda units/mL), the median age of patients was 28 years (range 12–75 years), the majority of patients (94%) had severe haemophilia, 61% had ≥ 9 bleeding events in the 24 weeks leading up to trial entry and 70% of patients had target joints. Patient groups consisted of those who previously received episodic (on-demand) treatment with bypassing agents (aPCC or recombinant activated FVII) before trial entry (groups A and B), those who received prophylactic treatment with bypassing agents before trial entry (group C; patients were rolled over from the noninterventional NCT02476942 study) and those who were unable to enroll in the other groups before they were closed to enrolment (group D). Patients received emicizumab-kxwh prophylaxis (3 mg/kg once weekly for 4 weeks, then 1.5 mg/kg once weekly thereafter) [groups A, C and D] or no prophylaxis at all (group B). Data from group D were not included in the analysis at the time of data cut-off because of the short follow-up period in this group [14].

Over a period of ≥ 24 weeks, the annualized bleed rate (ABR) for treated bleeding events was reduced by 87%

Features and properties of emicizumab-kxwh

Alternative names	ACE 910; Anti-factor IXa x anti-factor X humanized bispecific antibody; CH5534262; Emicizumab-kxwh; HEMLIBRA; RG 6013; RO 5534262
Class	Antihaemorrhagics; Bispecific antibodies; Monoclonal antibodies; Recombinant proteins
Mechanism of Action	Factor VIII replacements
Route of Administration	Injection
Pharmacodynamics	Humanized monoclonal antibody modified immunoglobulin G4 antibody; bispecific antibody structure that bind to FIX and FX; by bridging activated FIX and FX, it restores the function of missing activated FVIII to provide effective haemostasis
Pharmacokinetics	Similar irrespective of whether it is injected subcutaneously into the abdomen, upper arm or thigh
	Exhibits linear pharmacokinetics, with the volume of distribution and apparent clearance increasing with increases in bodyweight
	Trough plasma concentration of 54.6 μg/mL attained at week 5 following once weekly 3 mg/kg doses, with trough levels maintained at > 50 μg/mL thereafter with the recommended weekly dosage of 1.5 mg/kg
Adverse events	
Most frequent	Injection site reactions, headache, arthralgia
ATC codes	
WHO ATC code	B02B-D (Blood Coagulation Factors)
EphMRA ATC code	B2D (Blood Coagulation)
Chemical Name	Immunoglobulin G4-kappa, bispecific, anti-(homo sapiens F9a (activated coagulation factor F9, activated coagulation factor IX) and anti-[homo sapiens F10 (coagulation factor 10, coagulation factor X)], humanized monoclonal antibody

(95% CI 72.3–94.3; $p < 0.0001$) with emicizumab-kxwh prophylaxis (Group A) compared with no prophylaxis (Group B) (2.9 vs. 23.3 events) [primary endpoint] [5, 14]. The beneficial effects of emicizumab-kxwh prophylaxis in reducing the ABR for treated bleeds (vs. no prophylaxis) was generally consistent across all subgroups regardless of baseline characteristics, including age, ethnicity, the bleeding rate in the 24 weeks prior to trial entry, or the presence of target joints [14]. Compared with no prophylaxis, emicizumab-kxwh prophylaxis significantly ($p \leq 0.005$) reduced the ABRs of all bleeds (i.e. those treated and not treated with coagulation factors) by 80%, treated spontaneous bleeds by 92%, treated joint bleeds by 89% and treated target joint bleeds by 95% [5]. In the emicizumab-kxwh prophylaxis group, 63% of patients experienced no treated bleeding events (vs. 6% in the group receiving no prophylaxis). At week 25, adjusted mean changes in Haem-A-Qol total score and physical health subscale score were significantly ($p \leq 0.003$) better with emicizumab-kxwh prophylaxis than with no prophylaxis; this scale assesses patient-reported haemophilia-related symptoms and physical functioning [5, 14].

For patients who had received prior prophylactic treatment with bypassing agents (group C), the ABR for treated bleeding events was reduced by 79% (95% CI 11.1–22.3; $p < 0.001$) with emicizumab-kxwh prophylaxis compared with the rate during previous bypassing-agent prophylaxis (3.3 vs. 15.7 events), based on a prospective intra-individual comparison [5, 14].

In the single-arm, multinational, phase 3 HAVEN 2 trial ($n = 60$) [NCT02795767], an interim analysis showed that emicizumab-kxwh prophylaxis led to clinically meaningful reductions in the rates of bleeding events in paediatric patients with haemophilia A and FVIII inhibitors [5, 15]. The trial enrolled children aged < 12 years or aged 12–17 years with a bodyweight < 40 kg who had previously been treated with bypassing age [16]. Patients received subcutaneous emicizumab-kxwh 3 mg/kg once weekly for the first 4 weeks, then 1.5 mg/kg once weekly thereafter for ≥ 5 week [16]. At the interim analysis cut-off date of 8th May 2017, all enrolled patients were male (median age 7 years; range 1–15 years) [15]. For 23 evaluable patients aged < 12 years who were followed for ≥ 12 weeks (median observation time 38.1 weeks; range 12.7–41.6 weeks), the ABRs for treated bleeds, all bleeds, treated spontaneous bleeds and treated joint bleeds were 0.2, 2.9, 0.1 and 0.1, respectively, with 87% of patients reporting no treated bleeds. Eighteen patients aged < 12 years had previously participated in the noninterventional NCT02476942 study, 13 of whom had ≥ 12 weeks' follow-up and were evaluable for intra-individual comparison. In these patients, the ABR was reduced by 99% with emicizumab-kxwh prophylaxis versus prior bypassing agent treatment [15].

In a 12-week, phase 1 study (JapicCTI 121934) in 18 Japanese patients with severe haemophilia, prophylaxis with once-weekly emicizumab-kxwh 0.3, 1 or 3 mg/kg (cohort 1, 2 and 3, respectively; $n = 6$/cohort) reduced the median ABR for all bleed events compared with that in the 6 months prior to enrollment [17]. Median ABRs for all bleeds were reduced from 32.5 to 4.4 in cohort 1, from 18.3 to 0 in cohort 2 and from 15.2 to 0 in cohort 3. In patients with ($n = 11$) and without ($n = 7$) FVIII inhibitors, 73 and 71% experienced no bleeding events [17]. Low ABRs were maintained in the subsequent long-term extension phase (JapicCTI 121935) of this study, in which 16 patients continued to receive emicizumab-kxwh prophylaxis for up to 33.3 months [18]. The median ABRs in the extension phase in cohort 1, 2 and 3 were 1.4, 0.2 and 0, respectively, with 50% of patients in the overall population experiencing no bleeds. A similar improvement in median ABRs for joint bleeding events was observed during emicizumab-kxwh prophylaxis in the initial and extension study. In the extension phase, patients continued on their assigned emicizumab-kxwh dosage, with potential up-titration to 1 (cohort 1) or 3 mg/kg (cohort 1 and 2) [18].

2.4 Adverse Events

Subcutaneous emicizumab-kxwh was generally well tolerated as prophylaxis to prevent bleeding events in patients with haemophilia A participating in clinical trials. Discussion focuses on a pooled safety analysis of HAVEN 1, HAVEN 2 and a dose-finding trial, in which 189 male patients with haemophilia A received ≥ 1 dose of emicizumab-kxwh as routine prophylaxis. Of these patients, 94 (50%) were adults, 38 (20%) were adolescents (aged 12 to < 18 years), 55 (29%) were children (aged 2 to < 12 years) and two (1%) were infants (aged 1 month to < 2 years [5]. The median duration of exposure to emicizumab-kxwh across the studies was 38 weeks (range 0.8–177.2 weeks) [5].

Adverse reactions occurring in ≥ 10% of emicizumab-kxwh recipients were injection site reactions (ISRs), headache and athralgia [5]. ISRs, including injection site bruising, discomfort, erythema, haematoma, induration, pain, pruritus, rash, reaction, swelling, urticaria and warmth, were all of mild to moderate intensity and generally resolved without treatment (88%). Adverse reactions reported in ≥ 5% of patients receiving emicizumab-kxwh were ISRs (19% of patients), headache (15%), arthralgia (10%), pyrexia (7%) diarrhoea (6%) and myalgia (5%). Four patients (2.1%) discontinued emicizumab-kxwh because of adverse reactions (one due to TMA, one due to skin necrosis and superficial thrombophlebitis, and two due to ISR) [5].

Key clinical trials of subcutaneous emicizumab-kxwh

Drug(s)	Indication	Phase	Status	Location(s)	Identifier(s)	Sponsor(s)
EMI vs. no prophylaxis	Prophylaxis in adolescents and adults with congenital haemophilia A (any severity) with FVIII inhibitors	3	Ongoing	Multinational	HAVEN 1; NCT02622321	Hoffmann-La Roche; Chugai Pharmaceutical
EMI	Prophylaxis in paediatric patients with congenital haemophilia A (any severity) with FVIII inhibitors	3	Ongoing/ recruiting	Multinational	HAVEN 2; NCT02795767	Hoffmann-La Roche; Chugai Pharmaceutical
EMI vs. no prophylaxis	Prophylaxis in adolescents and adults with severe congenital haemophilia A without FVIII inhibitors	3	Ongoing	Multinational	HAVEN 3; NCT02847637	Hoffmann-La Roche; Chugai Pharmaceutical
EMI	Prophylaxis in adolescents and adults with severe congenital haemophilia A (regardless of FVIII inhibitor status)	3	Ongoing	Multinational	HAVEN 4; NCT03020160	Hoffmann-La Roche; Chugai Pharmaceutical
EMI vs. no prophylaxis	Prophylaxis in adolescents and adults with severe congenital haemophilia A (regardless of FVIII inhibitor status)	3	Not yet recruiting	China, Hong Kong, Malaysia	HAVEN 5; NCT03315455	Hoffmann-La Roche
EMI	Prophylaxis in adolescents and adults with congenital haemophilia A with FVIII inhibitors	3b	Recruiting	Multinational (excluding USA)	STASEY; NCT03191799	Hoffmann-La Roche
EMI	Paediatric patients with severe congenital haemophilia A without FVIII inhibitors	3	Ongoing	Japan	JapicCTI-173710	Chugai Pharmaceutical
EMI	Prophylaxis in paediatric ($\geq$ 2 years) and adult patients with congenital haemophilia A with FVIII inhibitors undergoing minor surgical procedures	4	Not yet recruiting	USA	NCT03361137; ML39791	Genentech
EMI	Patients who completed ACE001JP (extension study)	1/2	Ongoing	Japan	ACE002JP; JapicCTI-132195	Chugai Pharmaceutical
EMI	Healthy adult volunteers (Japanese and Caucasian) and adolescent and adult patients (Japanese) with severe congenital haemophilia A (regardless of inhibitors)	1	Completed	Japan	ACE001JP; JapicCTI-121934	Chugai Pharmaceutical

EMI emicizumab-kxwh, *FVIII* factor VIII

In clinical trials, cases of TMA and thrombotic events were reported when on average a cumulative amount of $>$ 100 U/kg/24 h of aPCC was administered for 24 h or more to emicizumab-kxwh recipients [5]. Thirty-six patients received aPCC on 125 occasions, with 10.4% of these instances involving administration of $>$100 U/kg/24 h of aPCC for $\geq$ 24 h. Of these 13 instances, two were associated with a thrombotic event and three with TMA, with no such events associated with remaining instances. TMA occurred in 3 of 189 patients (1.6%) receiving emicizumab-kxwh and in 3 of 36 patients (8.3%) who received $\geq$ 1 dose of aPCC during emicizumab-kxwh prophylaxis. Thrombotic events occurred in two patients (1.1%) receiving emicizumab-kxwh and two patients (5.6%) who received $\geq$ 1 dose of aPCC during emicizumab-kxwh prophylaxis, with none of these events requiring anticoagulation therapy. Evidence of improvement or resolution of TMA or thrombotic events was observed within 1 week and 1 month, respectively, after discontinuation of aPCC, with one patient resuming emicizumab-kxwh prophylaxis after resolution of TMA and one patient after resolution of a thrombotic event [5].

As with all therapeutic proteins, there is a potential for immunogenicity with emicizumab-kxwh [5]. No patients tested positive for anti-emicizumab-kxwh antibodies in HAVEN 1 and HAVEN 2, with 4 of 18 patients testing positive for anti emicizumab-kxwh antibodies in the dose-finding trial; however, these were not believed to be neutralizing antibodies as the pharmacokinetics and efficacy of emicizumab-kxwh were not affected. The emicizumab-kxwh antibody rate may be under-reported due to the limitation of the assay [5].

2.5 Ongoing Clinical Trials

Phase 3 trials are ongoing to evaluate the efficacy and safety of subcutaneous emicizumab-kxwh prophylaxis in paediatric patients with haemophilia A with (HAVEN 2) or without (JapicCTI-173710) FVIII inhibitors, and in adolescent and adult patients with haemophilia A with

(HAVEN 1), without (HAVEN 3) or regardless of the presence or absence (HAVEN 4) of FVIII inhibitors. These trials are also investigating alternative dosing regimens, including once every 2 weeks and once every 4 weeks. A phase 3b trial is currently recruiting patients to evaluate the safety and tolerability of emicizumab-kxwh in adolescent and adult patients with haemophilia A with FVIII inhibitors (STASEY; multinational study, excluding USA), with an additional phase 3 trial planned to evaluate the efficacy and safety of emicizumab-kxwh prophylaxis in adolescent and adult patients with haemophilia A regardless of FVIII inhibitor status (HAVEN 5; conducted in China, Hong Kong and Malaysia).

3 Current Status

Subcutaneous emicizumab-kxwh received its first global approval on 16th of November 2017 in the USA for use as routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and paediatric patients with haemophilia A (congenital FVIII deficiency) with FVIII inhibitors [5, 6].

Compliance with Ethical Standards

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Additional information about this Adis Drug Review can be found at http://www.medengine.com/Redeem/4FFCF0605E76CF9D.

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