Supplementary information

Methods: Bleed and target joint definitions

A treated bleed were those directly followed by administration of a coagulation product, reported to be a “treatment for bleed,” without an intervening bleed and irrespective of the time between the treatment and the preceding bleed. A bleed and the first treatment thereafter were connected as a pair (i.e., one treatment belonged to one bleed only), with the following exception: if multiple bleeds occurred on the same calendar day, the subsequent treatment was considered to apply for each of these multiple bleeds (which were, however, counted as separate bleeds). Bleeds due to surgeries/procedures were not included in the primary analysis. Only treatments that were recorded as “treatment for bleed” were included in analyses of treated bleeds.

All bleeds included all that were recorded, regardless of management with coagulation product.

Target joints were defined as major joints (e.g. hip, elbow, wrist, shoulder, knee, ankle) with three or more bleeds during a 24-week period.[16] Presence or absence of target joints was recorded for each patient according to bleeding events occurring during the 24 weeks that preceded study enrolment. Target joint resolution was defined as ≤2 spontaneous or traumatic bleeding events during any continuous 52-week period of emicizumab treatment. To be included in the target joint analysis, participants had to have ≥1 target joint at baseline and ≥52 weeks of emicizumab treatment (including up-titration, if applicable).

Supplementary table 1. Reported emicizumab efficacy at primary analysis of the HAVEN 1–4 studies[8-11]

	HAVEN 1 NCT02622321			HAVEN 2 NCT02795767			HAVEN 3 NCT02847637				HAVEN 4 NCT03020160	
	Arm A n = 35	**Arm B n = 18**	**Arm C n = 49**	**Arm A n = 68**	**Arm B n = 10**	**Arm C n = 10**	**Arm A n = 36**	**Arm B n = 35**	**Arm C n = 18**	**Arm D n = 63**	**PK run-in n = 7**	**Expansion n = 41**
Participant demographics												
Prior treatment regimen	Ex	Ex	Px	Ex or Px	Ex or Px	Ex or Px	Ex	Ex	Ex	Px	Ex	Ex or Px
FVIII inhibitor status	+	+	+	+	+	+	–	–	–	–	+ or –	+ or –
Age, median (range)	38.0 (12–68)	35.5 (13–65)	17.0 (12–75)	6.0 (1–15)	8.0 (2–10)	9.0 (2–11)	36.5 (19–77)	41.0 (20–65)	40.0 (16–57)	36.0 (13–68)	37.0 (14–50)	39.0 14–68)
Median (range) efficacy period, weeks	29.29 (0.1–48.9)	24.14 (23.0–26.0)	19.14 (6.9–45.3)	57.6 17.9–92.6)	21.3 (18.6–24.1)	19.9 (8.9–24.1)	29.6 (17.3–49.6)	31.3 (7.3–50.6)	24.0 (14.4–25.0)	33.1 (18.4–48.6)	43.7 (41.7–45.7)	25.6 (24.1–29.4)
Emicizumab dosing regimen	1.5 mg/kg QW	NA	1.5 mg/kg QW	1.5 mg/kg QW	3.0 mg/kg Q2W	6.0 mg/kg Q4W	1.5 mg/kg QW	3.0 mg/kg Q2W	NA	1.5 mg/kg QW	6.0 mg/kg Q4W	6.0 mg/kg Q4W
Select efficacy endpoints												

Model-based ABR (95% CI)	2.9 (1.69–5.02)	23.3 (12.33–43.89)	5.1 (2.28–11.22)	0.3 (0.17–0.50)	0.2 (0.03–1.72)	2.2 (0.69–6.81)	1.5 (0.9–2.5)	1.3 (0.8–2.3)	38.2 (22.9–63.8)	1.6 (1.1–2.4)	0.6 (0.5–2.5)	2.4 (1.4–4.3)
% reduction versus control arm	87	–	NA	NA	NA	NA	96	97	NA	68*	NA	NA
% of participants with zero treated bleeds	62.9	5.6	69.4	76.9	90.0	60.0	56.0	60.0	0	55.6	71.4	56.1
Safety endpoints												
TEs	2			0			0				0	
TMAs	3			0			0				0	
Fatalities	1			0			0				0	

*In this case, the control arm was the equivalent cohort in the previous non-interventional study (NCT02476942), rather than the no prophylaxis arm.

ABR, annualized bleeding rate; BPA, bypassing agent, CI, confidence interval; Ex, episodic; NE, not evaluated; NR, not reported; Px, prophylactic; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; TE, thrombotic event; TMA, thrombotic microangiopathy.

Supplementary table 2. Participants exposed to emicizumab during the entirety of each time interval and thereby included in the efficacy analyses across time

Period (weeks)	Pooled analysis, n	HAVEN 1, n	HAVEN 2, n	HAVEN 3, n	HAVEN 4, n
1–24	391	109	86	148	48
25–48	374	101	84	144	45
49–72	343	98	62	140	43
73–96	283	79	42	131	31
97–120	207	50	26	104	27
121–144	170	37	17	89	27
145–168	79	28	0	48	3
169–192	19	19	0	0	0

Supplementary table 3. Most common adverse events (reported in ≥5% of participants) over a median (range) exposure of 130.3 (3.4–221.1) weeks

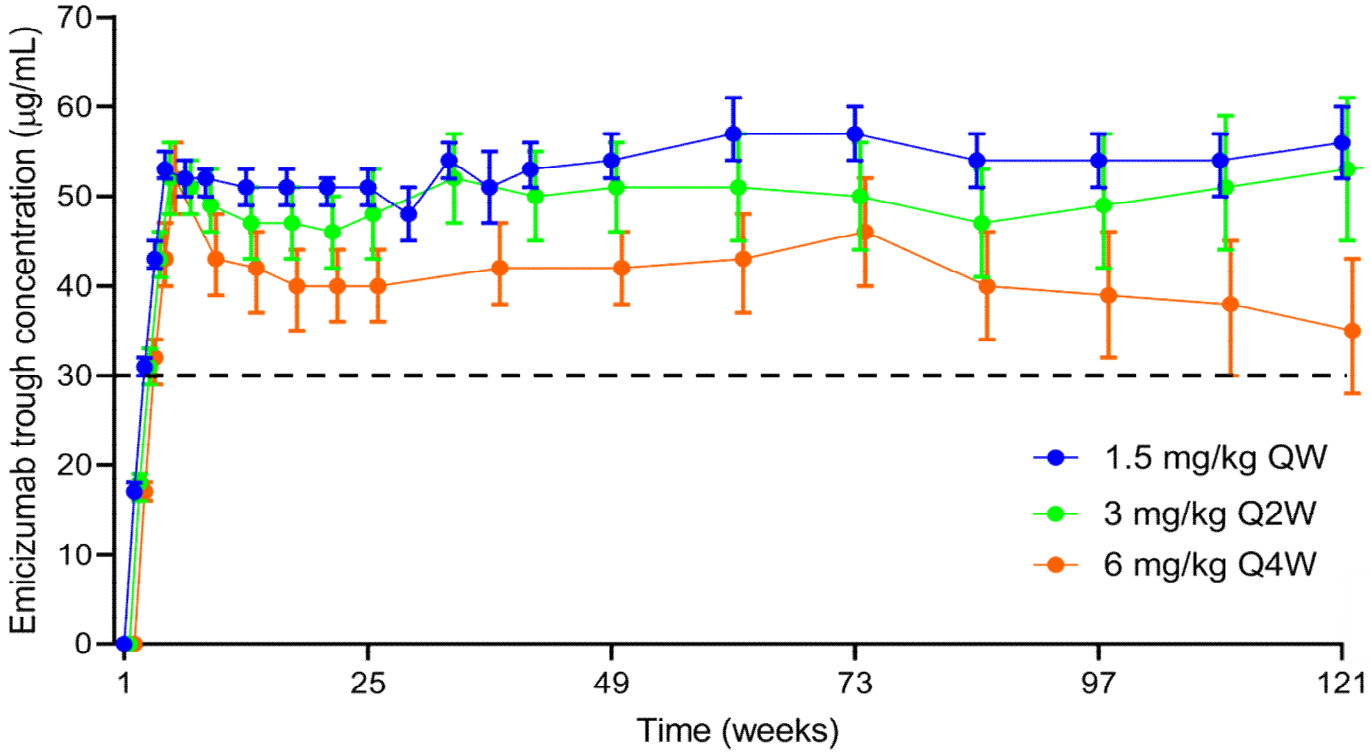
Adverse event, n (%)	**TOTAL (N = 399)**
Nasopharyngitis	126 (31.6)
Injection site reaction	111 (27.8)
Arthralgia	103 (25.8)
Headache	83 (20.8)
Upper respiratory tract infection	79 (19.8)
Pyrexia	61 (15.3)
Influenza	47 (11.8)
Cough	46 (11.5)
Diarrhea	45 (11.3)
Fall	31 (7.8)
Back pain	30 (7.5)
Contusion	30 (7.5)
Pain in extremity	30 (7.5)
Ligament sprain	27 (6.8)
Vomiting	27 (6.8)
Rash	24 (6.0)
Nausea	23 (5.8)
Toothache	23 (5.8)
Bronchitis	22 (5.5)

Limb injury	22 (5.5)
Abdominal pain	20 (5.0)
Dental caries	20 (5.0)
Myalgia	20 (5.0)

Multiple occurrences of the same adverse event in a participant were counted only once.

Adverse events are MedDRA (version 23.0); injection site reactions were reported using an electronic case report form-specific tick-box; all other adverse events are preferred terms.

Supplementary figure 1. Mean (95% CI) emicizumab trough concentration over time



*Data shown for timepoints when sample size n was ≥30% of total sample size N in a given dosing regimen group.

The dashed line indicates the target efficacious exposure of >30 µg/mL.

CI, confidence interval; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.