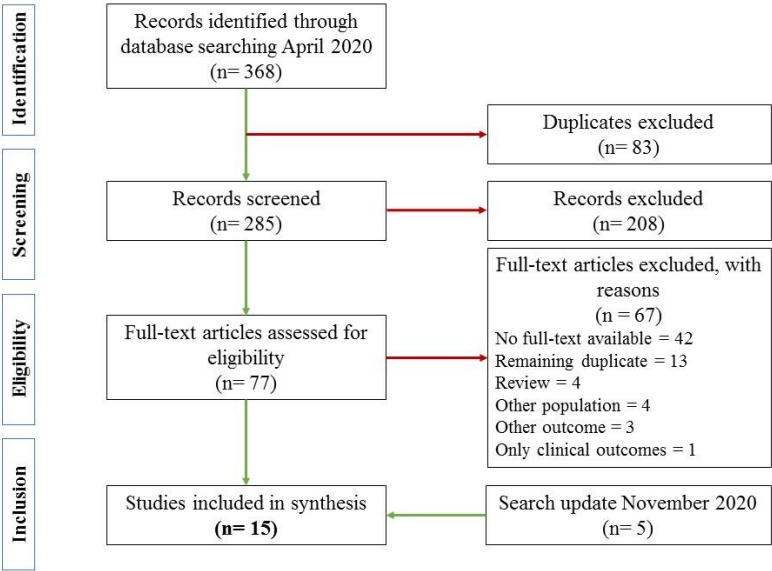


Supplemental Data SD1

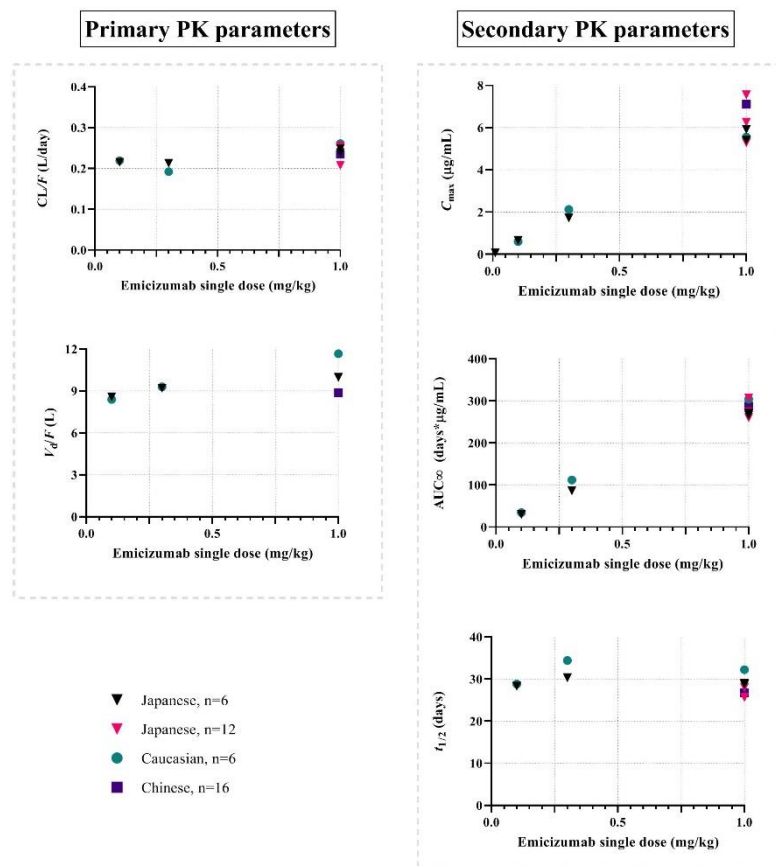
Embase Search Algorithm

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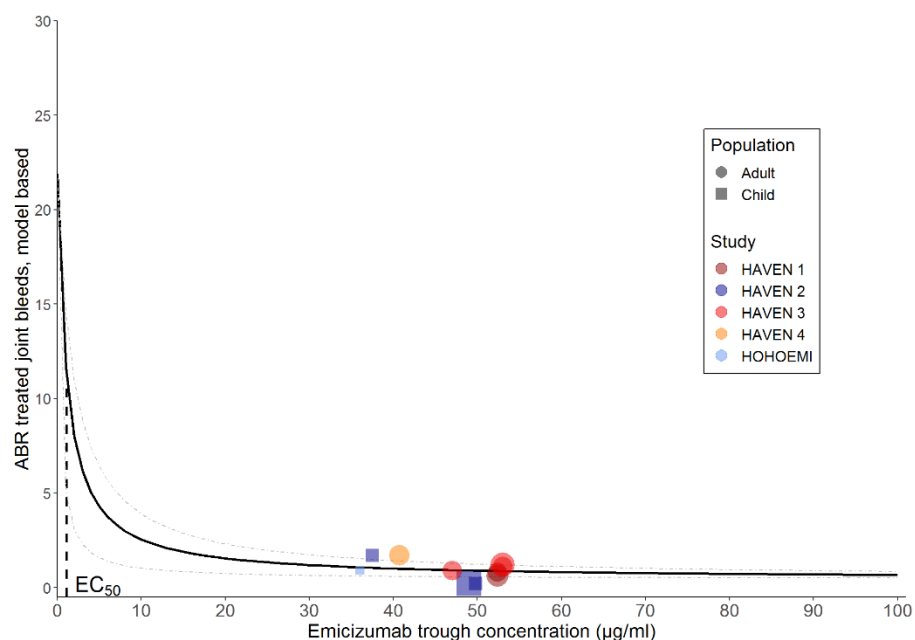
Supplemental Figure SF1. Flowchart study selection



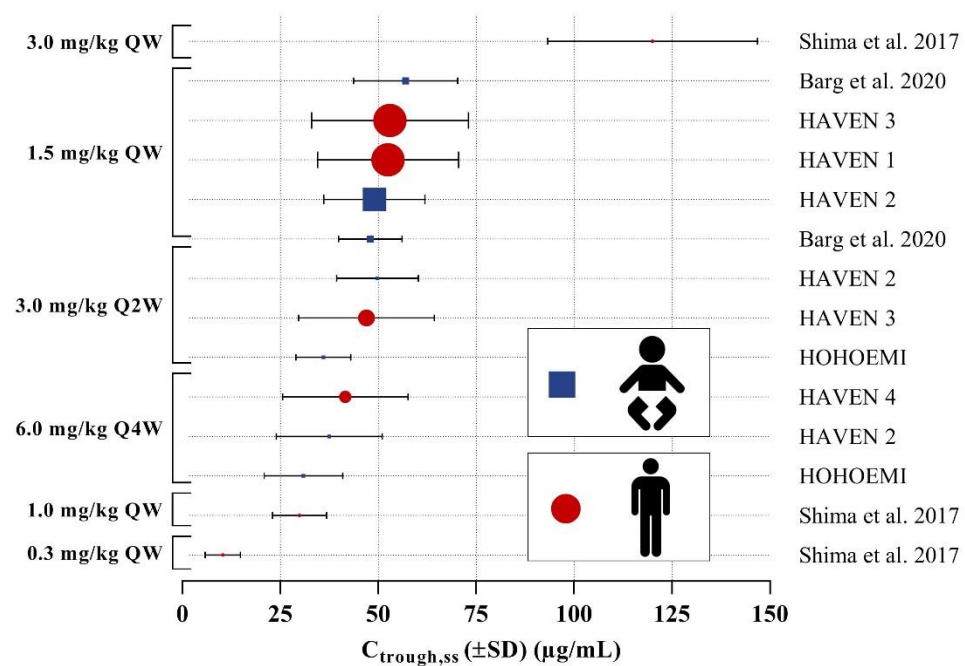
Supplemental Figure SF2. PK parameters in volunteers (n=112) with single doses of emicizumab.[27, 29, 30] With increasing single dose injections of emicizumab (0.1, 0.3 and 1 mg/kg), the primary PK parameters (CL/F and V_d/F) remained constant and the secondary PK parameters (C_{max} , AUC_{∞} and $t_{1/2}$) increased dose-linearly.



Supplemental Figure SF3: Emax model with concentration-response relation of emicizumab in PwHA. Fit of an Emax model of ABRs of treated joint bleeds according to $C_{\text{trough,ss}}$ of emicizumab in PwHA (n=342), described by $\text{ABR} = \text{ABR}_{\text{baseline}} * (1 - (\frac{C_{\text{trough,ss}} * E_{\text{max}}}{C_{\text{trough,ss}} + EC_{50}}))$. Included ABRs were model-based, estimated using negative binomial regression. The EC_{50} was estimated at 1.09 $\mu\text{g/ml}$ and effectiveness plateau was established. Dashed line is 95%-confidence interval and symbol size equals sample size. Data from PwHA receiving maintenance were included, see 'III' for 10 study subgroups in Supplemental Table ST2.



Supplemental Figure SF4: Overview of emicizumab trough concentrations per study subgroup in PwHA (n=460). Bars implicate SD. Dose regimens from high (above) to low (below). Squares (blue) represent study subgroups of children <12 years, circles (red) adults/adolescents (≥ 12 years), symbol size corresponds with sample size.



Electronic Supplemental Material: Systematic review on PK of emicizumab in humans

Supplemental Table ST1: PK data from male volunteers in three single dose studies (data used in Supplemental Figure SF2 (n=122)). Abbreviations: IP initial product; FP final market product; SII single intravenous injection; SSI single subcutaneous injection. *if necessary, multiplied with corresponding mean body weight of study subgroup.

Study	n=	Dose (mg/kg)	Body weight (kg) mean (SD) or median (range)	Ethnicity	Regimen	C _{max} (µg/mL) mean (SD)	T _{max} (days) median (range)	AUC _{-last} (days*µg/mL) mean (SD)	AUC _{-inf} (days*µg/mL) mean (SD)	t _{1/2,eli} (days) mean (SD)	Cl/F (L/day) mean*	Vd/F (L) mean [†]
Uchida et al. 2016	6	0.001	62.9 (4.21)	Japanese	SSI, IP	0.01	NA	NA	NA	NA	NA	NA
	6	0.01	62.9 (4.24)	Japanese	SSI, IP	0.0675 (0.0120)	14.1 (5.00-28.0)	NA	NA	NA	NA	NA
	6	0.1	61.3 (6.04)	Japanese	SSI, IP	0.655 (0.0837)	12.0 (7.00-14.1)	NA	30.2 (9.28)	28.3 (4.77)	0.215	8.58
	6	0.3	59.0 (3.28)	Japanese	SSI, IP	1.72 (0.377)	10.1 (7.00-11.1)	NA	86.5 (17.9)	30.3 (4.12)	0.213	9.20
	6	1	61.2 (5.04)	Japanese	SSI, IP	5.92 (1.24)	10.1 (4.00-14.2)	NA	266 (50.0)	29.0 (3.26)	0.239	9.98
	6	0.1	69.4 (6.65)	Caucasian	SSI, IP	0.603 (0.0825)	12.6 (7.00-21.2)	NA	34.6 (12.6)	28.8 (10.4)	0.219	8.40
	6	0.3	69.9 (7.06)	Caucasian	SSI, IP	2.12 (0.244)	7.00 (3.00-14.2)	NA	112 (18.2)	34.4 (6.55)	0.192	9.30
Kotani et al. 2018	6	1	74.8 (9.21)	Caucasian	SSI, IP	5.56 (0.812)	8.53 (7.00-15.2)	NA	304 (79.3)	32.2 (6.68)	0.261	11.7
	12	1	62.4 (6.02)	Japanese	SSI, IP abdomen	5.40 (0.907)	6.97 (3.99-10.9)	247 (56.8)	271 (76.2)	28.7 (7.43)	0.248	NA
	12	1	66.2 (9.78)	Japanese	SSI, FP abdomen	6.26 (1.26)	6.97 (3.98-14.0)	253 (47.7)	274 (53.3)	28.0 (5.53)	0.254	NA
	12	1	63.8 (7.61)	Japanese	SSI, FP upper arm	5.29 (0.960)	11.4 (6.97-21.0)	241 (40.4)	260 (47.5)	25.6 (6.97)	0.255	NA
	12	1	62.3 (5.46)	Japanese	SSI, FP thigh	7.56 (1.38)	8.47 (3.99-10.9)	284 (38.2)	307 (45.6)	28.7 (4.21)	0.207	NA
Li et al. 2020	16	0.25	58.7 (5.95)	Japanese	SII, FP	5.10 (0.509)	0.104 (0.104-0.396)	74.7 (10.9)	79.2 (12.8)	26.7 (6.62)	0.191	NA
Li et al. 2020	16	1	60.1 (51.8-75.1)	Chinese	SSI	7.11 (1.77)	7.01 (3.00-15.0)	268 (63.7)	287 (74.2)	26.7 (4.25)	0.235	8.87 (2.950)

Supplemental Table ST2: PK and outcome data from PwHA in the multiple dose emicizumab studies. ^a Data used in Figure 1 and Figure 2 (n=469), ^b data used in Figure 3 (n=349).										
Study	n= (cohort ID)	Dosing regimen	Mean C _{trough,ss} (µg/ml)	±SD C _{trough,ss} (µg/ml)	%CV C _{trough,ss} (µg/ml)	Ranges of indiv. C _{trough,ss} (µg/ml)*	ABR of treated bleeds, mean (95%-CI) or median (range/IQR)	ABR treated joint bleeds, mean (95%-CI) or median (range/IQR)	Zero treated bleeds, % (95%-CI)	Efficacy period, median weeks (range)
Shima et al. 2016	6 (1)	0.3 mg/kg QW	10.3	4.5	44.1	NA	4.4 (r 0.0-59.5)	4.3 (r 0.0-59.5)	NA	12
	6 (2)	1.0 mg/kg QW	29.9	6.9	23.0	NA	0.0 (r 0.0-4.3)	0.0 (r 0.0-0.0)	NA	12
	6 (3)	3.0 mg/kg QW	87.9	20.0	22.8	NA	0.0 (r 0.0-4.2)	0.0 (r 0.0-0.0)	NA	12
Shima et al. 2017 ^a	6 (1)	0.3 mg/kg QW	10.3	4.5	44.1	NA	1.4 (r 0.0-59.5)	1.1 (r 0.0-59.5)	NA	140 (138-143)
	5 (2)	1.0 mg/kg QW	29.9	6.9	23.0	NA	0.2 (r 0.0-2.7)	0.2 (r 0.0-1.9)	NA	116 (35-123)
	5 (3)	3.0 mg/kg QW	120.0	26.8	22.3	NA	0.0 (r 0.0-0.6)	0.0 (r 0.0-0.0)	NA	92.5 (47.7-97.2)
Yoneyama et al. 2018	NA	1.5 mg/kg QW	51.5	NA	NA	NA	NA	NA	NA	NA
	NA	3.0 mg/kg Q2W	48.0	NA	NA	NA	NA	NA	NA	NA
	NA	6.0 mg/kg Q4W	40.7	NA	NA	NA	NA	NA	NA	NA
Oldenburg et al. 2017 ^b HAVEN 1	35 (A)	1.5 mg/kg QW	52.4	15	28.6	2.8 - 148	2.9 (1.7-5.0)	0.80 (0.3-2.2)	62.9 (44.9-78.5)	29.3 (0.1-48.9)
	18 (B)						NA	NA	NA	NA
	49 (C)						5.1 (2.3-11.2)	0.60 (0.2-1.5)	69.4 (54.6-81.7)	19.1 (6.9-45.3)
	7 (D)						NA	NA	NA	NA
Schmitt et al. 2020 ^a HAVEN 1	112	1.5 mg/kg QW	52.5	18	34.3	NA	NA	NA	NA	NA
Young et al. 2019 ^{a b} HAVEN 2	68 (A)	1.5 mg/kg QW	49	13.8	28.2	19.2 - 88.7	0.3 (0.2-0.5)	0.20 (0.08-0.29)	76.9 (64.8-86.5)	57.6 (17.9-92.6)
	10 (B)	3.0 mg/kg Q2W	49.8	10.4	20.9	NA	0.2 (0.0-1.7)	0.20 (0.03-1.72)	90.0 (55.5-99.7)	21.3 (18.6-24.1)
	10 (C)	6.0 mg/kg Q4W	37.5	13.5	35.9	NA	2.2 (0.7-6.8)	1.70 (0.6-4.89)	60.0 (26.2-87.8)	19.9 (8.9-24.1)
Mahlangu et al. 2018 ^{a b} HAVEN 3	36 (A)	1.5 mg/kg QW	53	19	38	16.8 - 128	1.5 (0.9-2.5)	1.10 (0.6-1.9)	56 (38-72)	29.6 (17.3-49.6)
	63 (D)						1.5 (1.0-2.3)	1.20 (0.7-2)	55.6 (42.5-68.1)	33.1 (18.4-48.6)
	35 (B)						1.3 (0.8-2.3)	0.90 (0.4-1.7)	60 (42-76)	31.3 (7.3 - 50.6)
	18 (C)	3.0 mg/kg Q2W	47	18	37	12.0 - 103	NA	NA	NA	24.0 (14.4-25.0)
Pipe et al. 2019 ^{a b} HAVEN 4	7 (run in)	6.0 mg/kg Q4W	38.4	8.1	21.0	23-53	NA	NA	NA	NA
	41 (expansion)	6.0 mg/kg Q4W	40.7	14.8	36.4	9.4-83.9	2.4 (1.4-4.3)	1.70 (0.8-3.7)	56 (39.7-71.5)	25.6 (24.1-29.4)
Shima et al. 2019 ^{a b} HOHOEMI	6 (Q2W)	3.0 mg/kg Q2W	36.0	6.9	19.0	20.9-50.5	1.3 (0.6-2.9)	0.90 (0.3-2.3)	33.3	39.9 (37.9-41.4)
	7 (Q4W)	6.0 mg/kg Q4W	31	10	32.0	13.4-55.2	0.7 (0.2-2.6)	NA	71.4	34.1 (24.1-37.1)
Retout et al. 2020	NA	1.5 mg/kg QW	51.1	15.3	29.9	NA	NA	NA	NA	NA
	NA	3.0 mg/kg Q2W	46.7	14.9	31.9	NA	NA	NA	NA	NA
	NA	6.0 mg/kg Q4W	38.3	14.3	37.3	NA	NA	NA	NA	NA
Hooimeijer et al. 2020	1	2 mg/kg QW	NA	NA	NA	18-90	NA	NA	NA	NA
Barg et al. 2020 ^{a b}	22 (non-inhibitor)	1.5 mg/kg QW	48 (median)	8.1	17.0	NA	1 (IQR 0-3)	NA	NA	27 (18-40)
	18 (inhibitor)	1.5 mg/kg QW	57 (median)	13.3	23.4	NA	1 (IQR 0-3)	NA	NA	57 (45-73)

Supplemental Table ST3: Sensitivity analyses results with different settings for Emax model of treated bleeds.					
	Settings assumed		Estimated EC₅₀ (SE) µg/ml	Estimated ABR for C_{trough,ss} of 30 µg/ml	Estimated ABR for C_{trough,ss} of 50 µg/ml
	Emax	Baseline ABR			
	0.96 (ABR 1)	28	1.47 (0.9)	2.4	1.9
Without HAVEN 1 ABR outliers	0.96 (ABR 1)	28	0.32 (0.44)	1.4	1.3
	1 (ABR 0)	28	3.52 (0.96)	2.9	1.8
	1 (ABR 0)	21.9	4.61 (1.28)	2.9	1.9
	0.96 (ABR 1)	21.9	2.5 (1.20)	2.5	1.9
	0.96 (ABR 1)	38.2	0.52 (0.63)	2.2	1.9
	0.90 (ABR 4)	38.2	-2.46 (0.58)	1.9	1.9