WFH GLOBAL FORUM

Emicizumab: Low dose or non-standard interval doses

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Friday, November 17, 2023

Inequities in health care delivery

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Disclosures for: Alfonso Iorio

Conflict	Disclosure - if conflict of interest exists
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Director, Officer, Employee	McMaster
Shareholder	
Honoraria	
Advisory Committee	
Consultant	

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Emicizumab

Emicizumab has revolutionized our management of haemophilia A

Lehtinen, A. *Haemophilia* 2022, Vol. 28, Issue 2, pp. e53–e55

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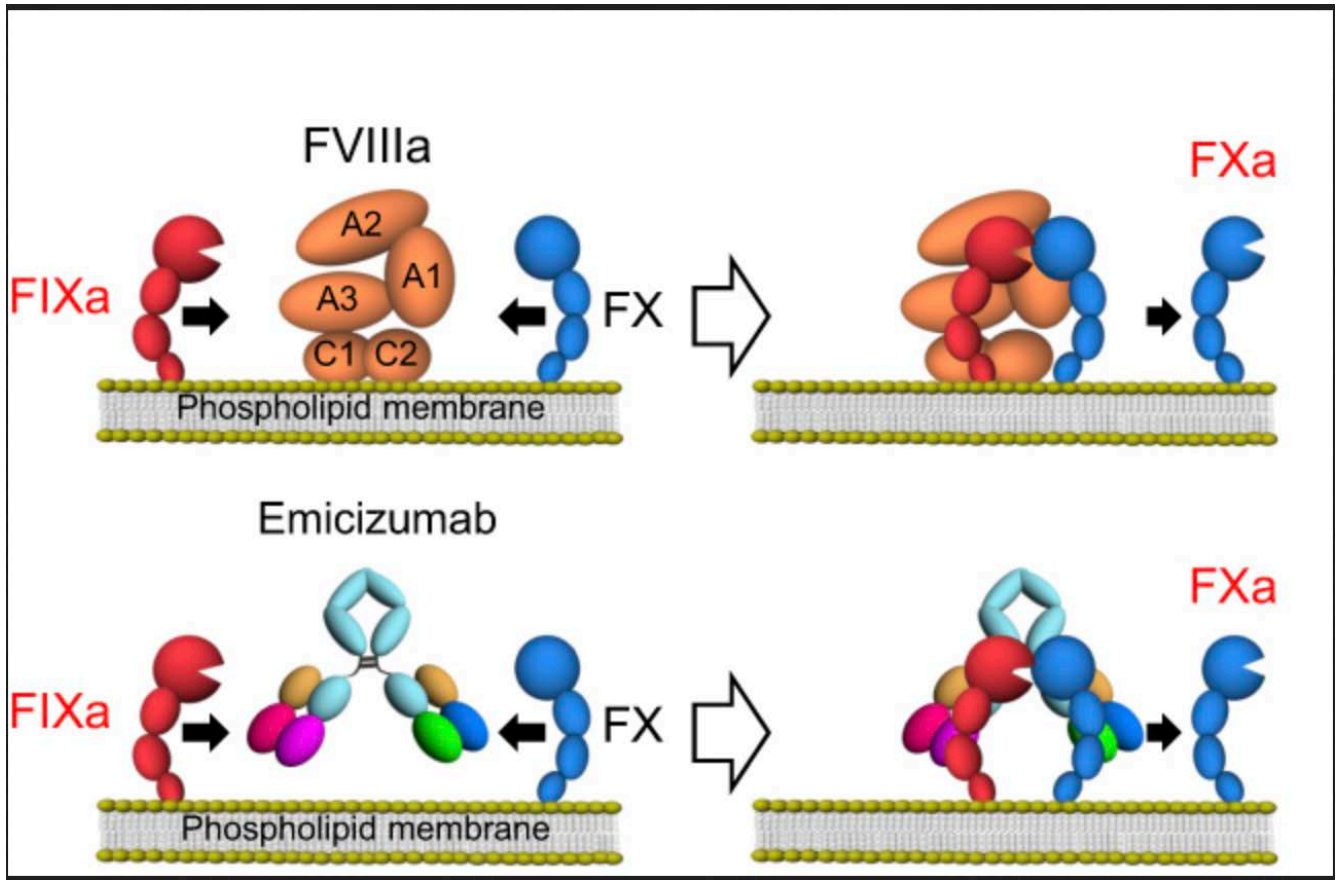
Pure breakthrough innovation



Yada K, Nogami K. Spotlight on emicizumab in the management of hemophilia A: patient selection and special considerations. J Blood Med. 2019 Jul 2;10:171-181.

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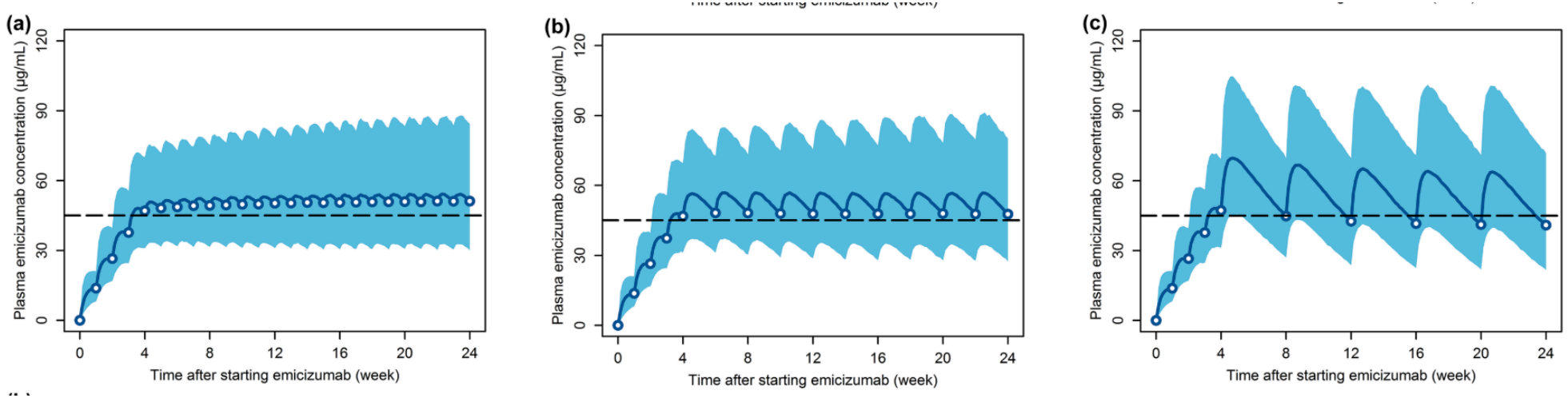
Strong and convincing clinical evidence

First author (year of publication)	Number of centers	Study design	Size	Follow-up	Funding
Shima *et al.* (2016) [24]	Multicentric	Open non- randomized study	18 *	12 weeks	Chugai Pharmaceutical
Oldenburg *et al.* (2017) [7]	Multicentric	Open randomized study	109	≥ 24 weeks	F. Hoffmann-La Roche
Mahlangu *et al.* (2018) [9]	Multicentric	Open randomized study	152	≥ 24 weeks	F. Hoffmann-La Roche e Chugai Pharmaceutical
Oldenburg *et al. (*2019) [26]	Multicentric	Open randomized study	109	≥ 24 weeks	F. Hoffmann-La Roche Ltd
Shima *et al.* (2019) [25]	Multicentric	Open non- randomized study	13	≥ 24 weeks	Chugai Pharmaceutical
Young *et al.* (2019) [8]	Multicentric	Open non- randomized study	88	≥ 52 weeks	F. Hoffmann-La Roche e Chugai Pharmaceutical
Misgav *et al.* (2021) [13]	Single center	Prospective cohort	17	400 days (range 89 to 809, IQR 211 to 479)	F. Hoffmann-La Roche
Skinner *et al.* (2021) [27]	Multicentric	HAVEN 3, HAVEN 4:	176	73 weeks	F. Hoffmann-La Roche e Chugai Pharmaceutical
Zharkov *et al.* (2022) [14]	Multicentric	Retrospective cohort	29	NR	No funding
Batt *et al.* (2022) [16]	Multicentric	Retrospective cohort	121	Mean 1.1 years (SD 0.4)	Takeda
Glonneger *et al.* (2022) [15]	Single center	Retrospective cohort	13	Median 23.8 months (range 0.7 to 40.0)	No funding
Liu *et al.* (2022) [17]	Single center	Retrospective cohort	13	≥ 24 weeks	No funding

A non-conventional dose finding step



Yoneyama, K et al. A Pharmacometric Approach to Substitute for a Conventional Dose-Finding Study in Rare Diseases: Example of Phase III Dose Selection for Emicizumab in Hemophilia A.

Clinical Pharmacokinetics, 2018, *57*(9), 1123–1134.

Uchida N at al. Blood. 2016;127:1633–41.
Shima M et al. N Engl J Med. 2016;374:2044–53.
Shima M et al. Blood Adv. 2017;1:1891–9.

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Additional observations

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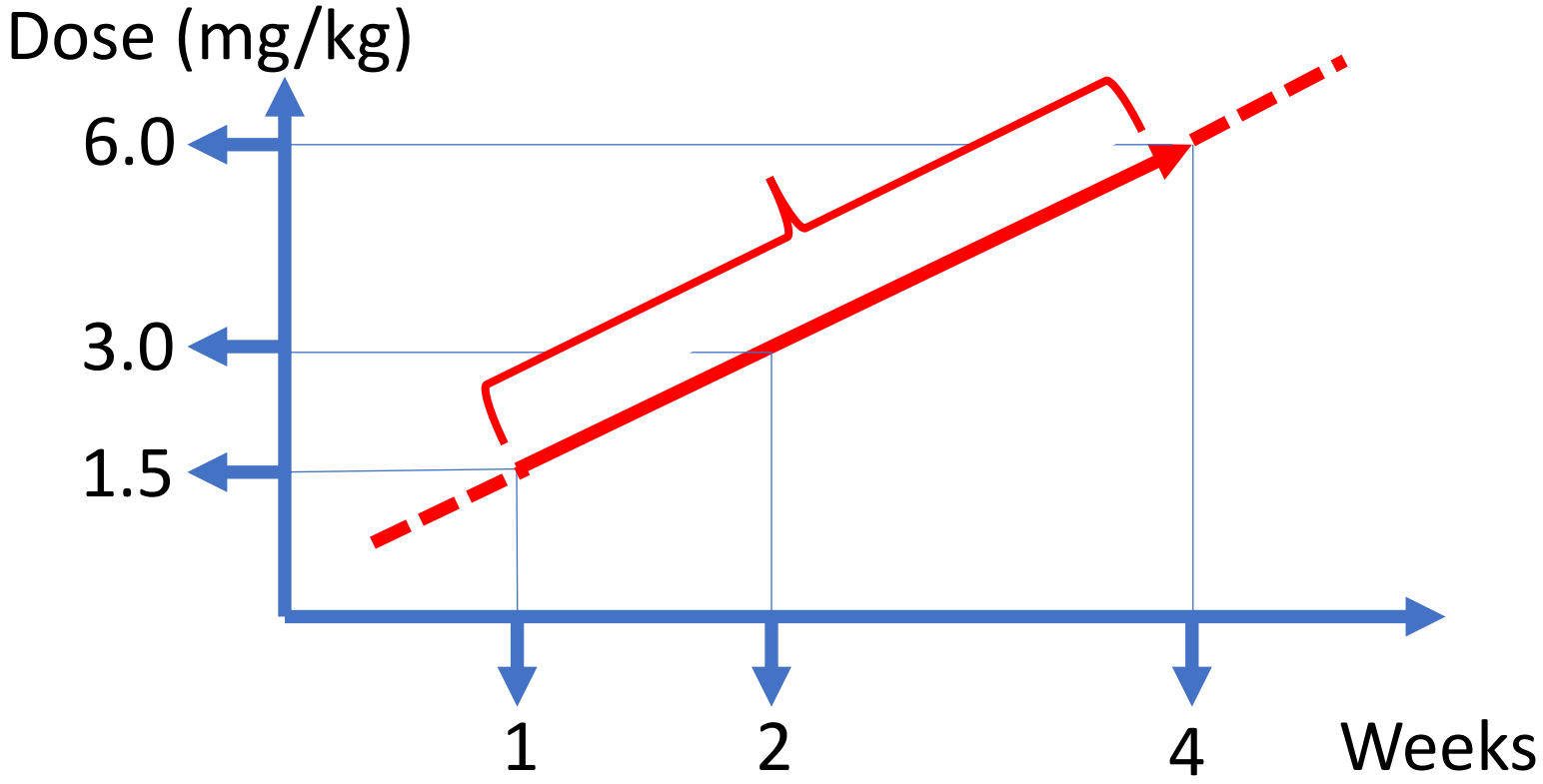
#1 – Linearity dose to frequency



Dirks NL, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet. 2010;49(10):633-659.

Yu, J. K., Iorio, A., Chelle, P., & Edginton, A. N. (2021). Pharmacokinetic implications of dosing emicizumab based on vial size: A simulation study. *Haemophilia*, *27*(3), 358–365.

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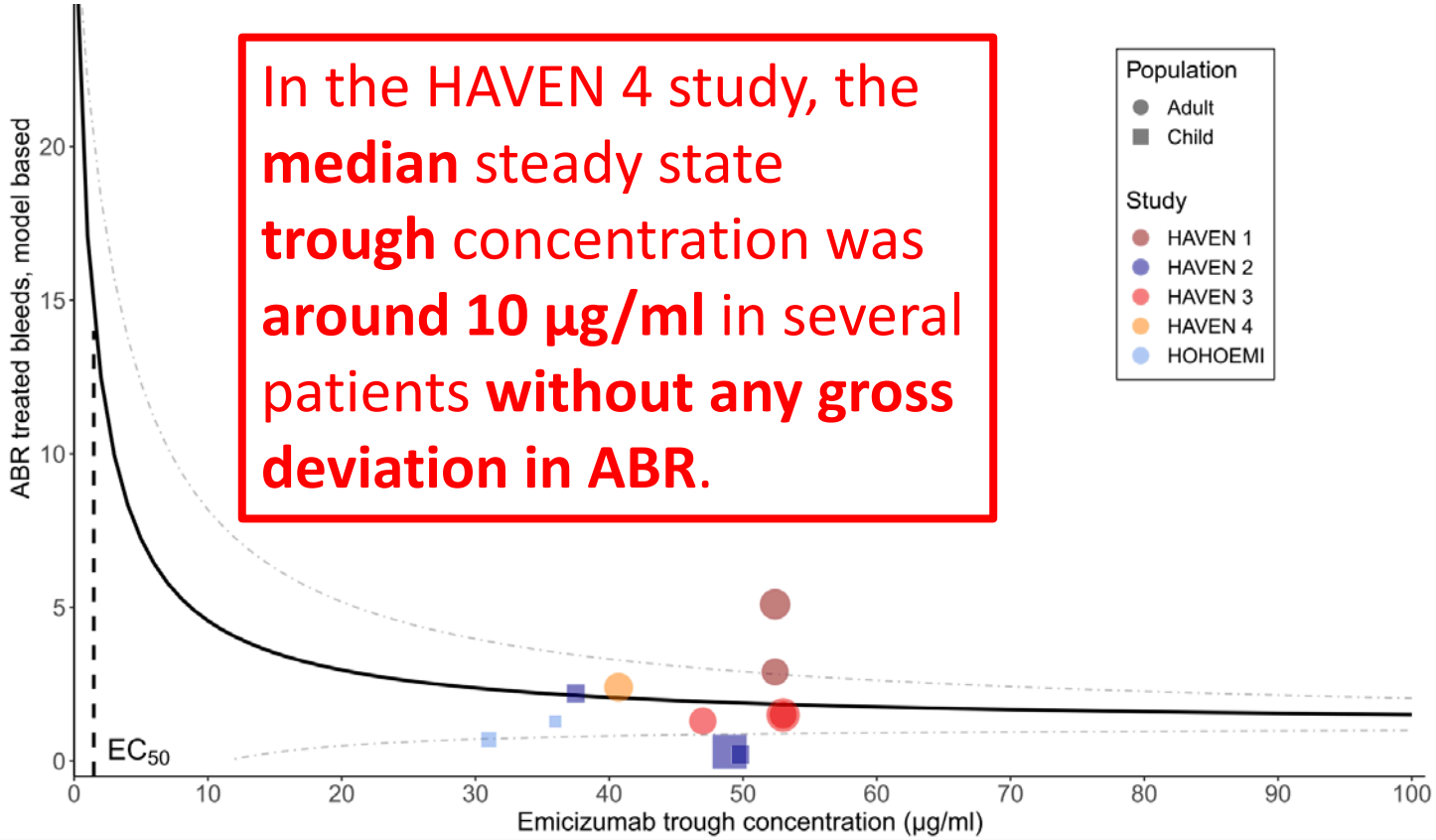
#2 – A lower dose may be protective

In the HAVEN 4 study, the **median** steady state **trough** concentration was **around 10 µg/ml** in several patients **without any gross deviation in ABR**.



Donners, A. A. M. T. et al. Pharmacokinetics and Associated Efficacy of Emicizumab in Humans: A Systematic Review. *Clinical Pharmacokinetics*, 2021; *60*(11), 1395–1406.

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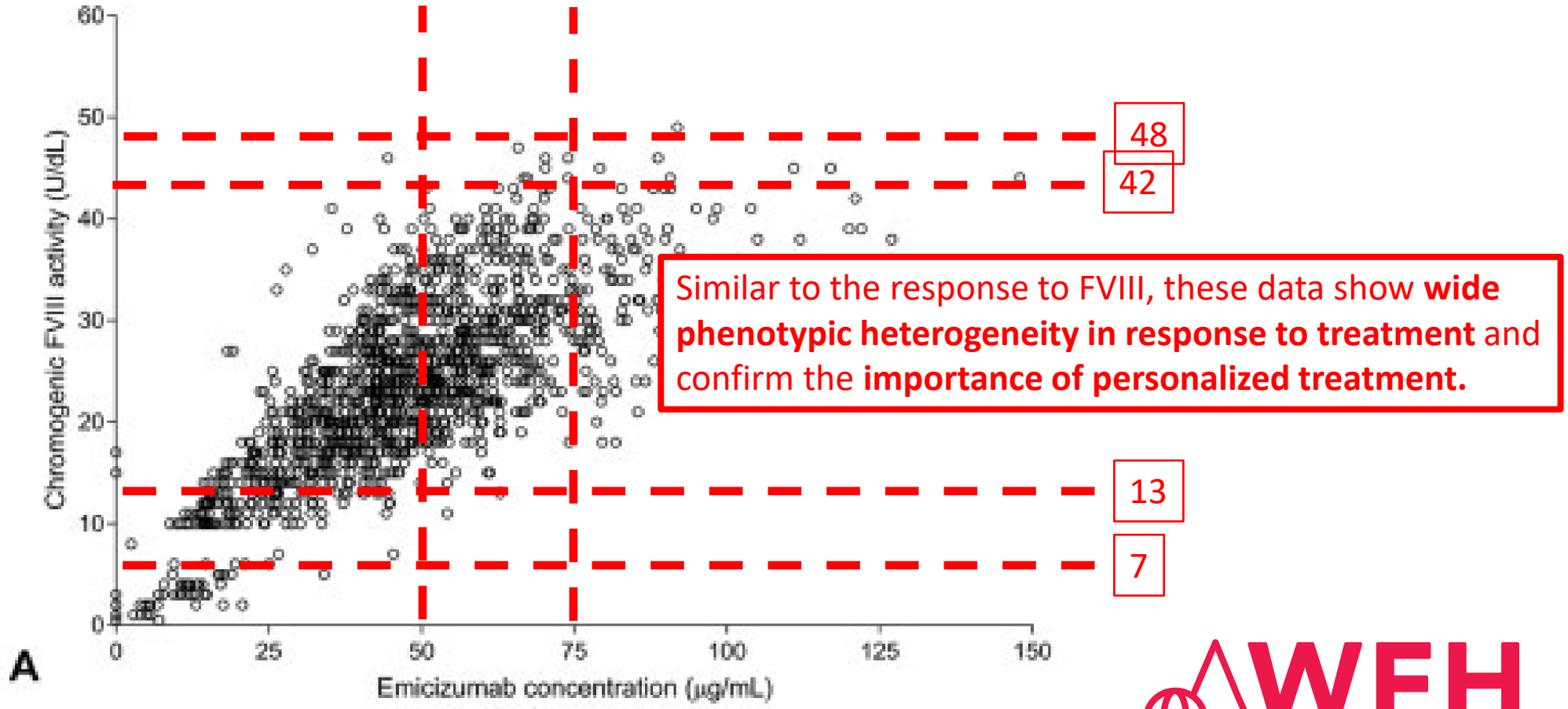
#3 – Plasma level versus activity



Similar to the response to FVIII, these data show **wide phenotypic heterogeneity in response to treatment** and confirm the **importance of personalized treatment.**

Schmitt, C., *Thrombosis and Haemostasis*, 2021, *121*(03), 351–360.

Mahlangu, J et al. *Haemophilia*, 2022; *28*(S4), 103–110.

Retout, S et al. *Clinical Pharmacokinetics*, 2020; *59*(12), 1611–1625.

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Implications

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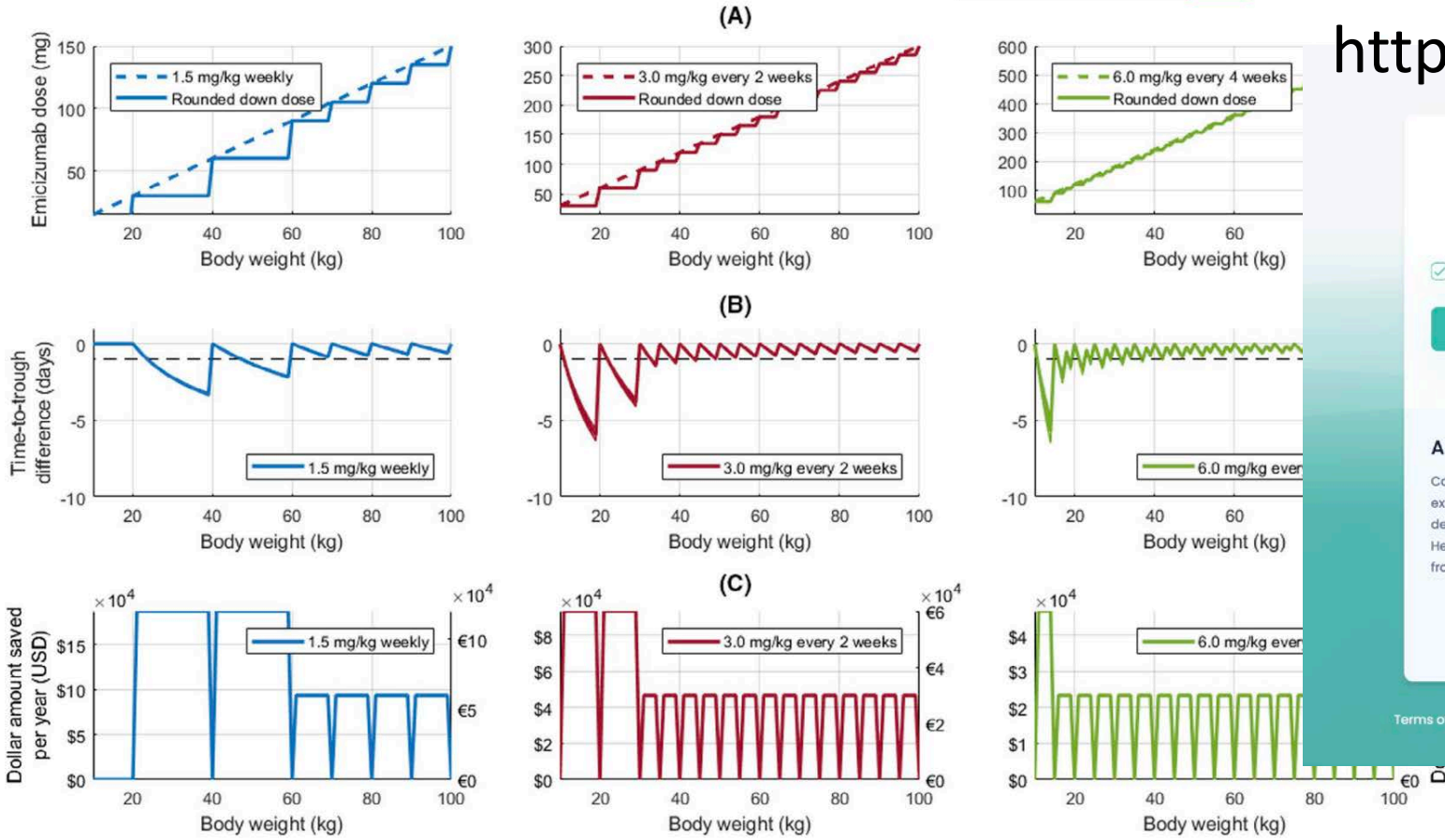
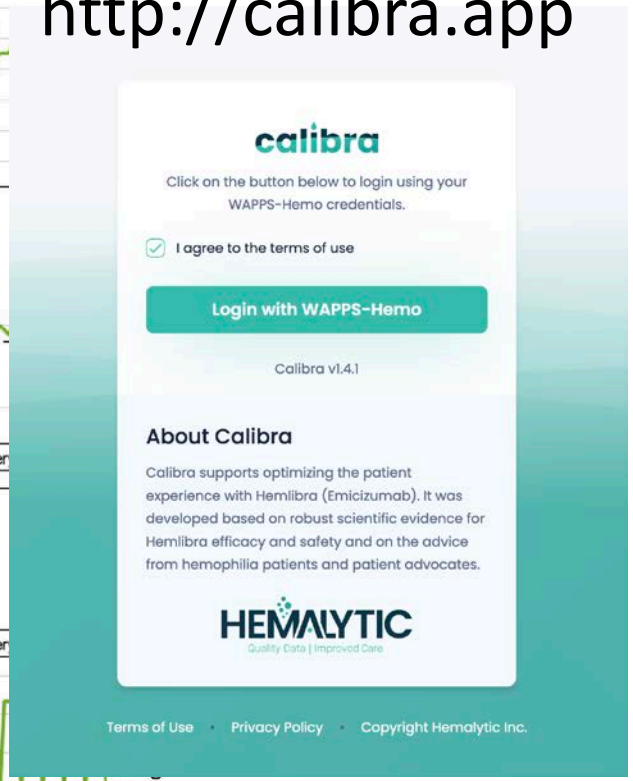
#1 – Linearity of the dose-response



http://calibra.app



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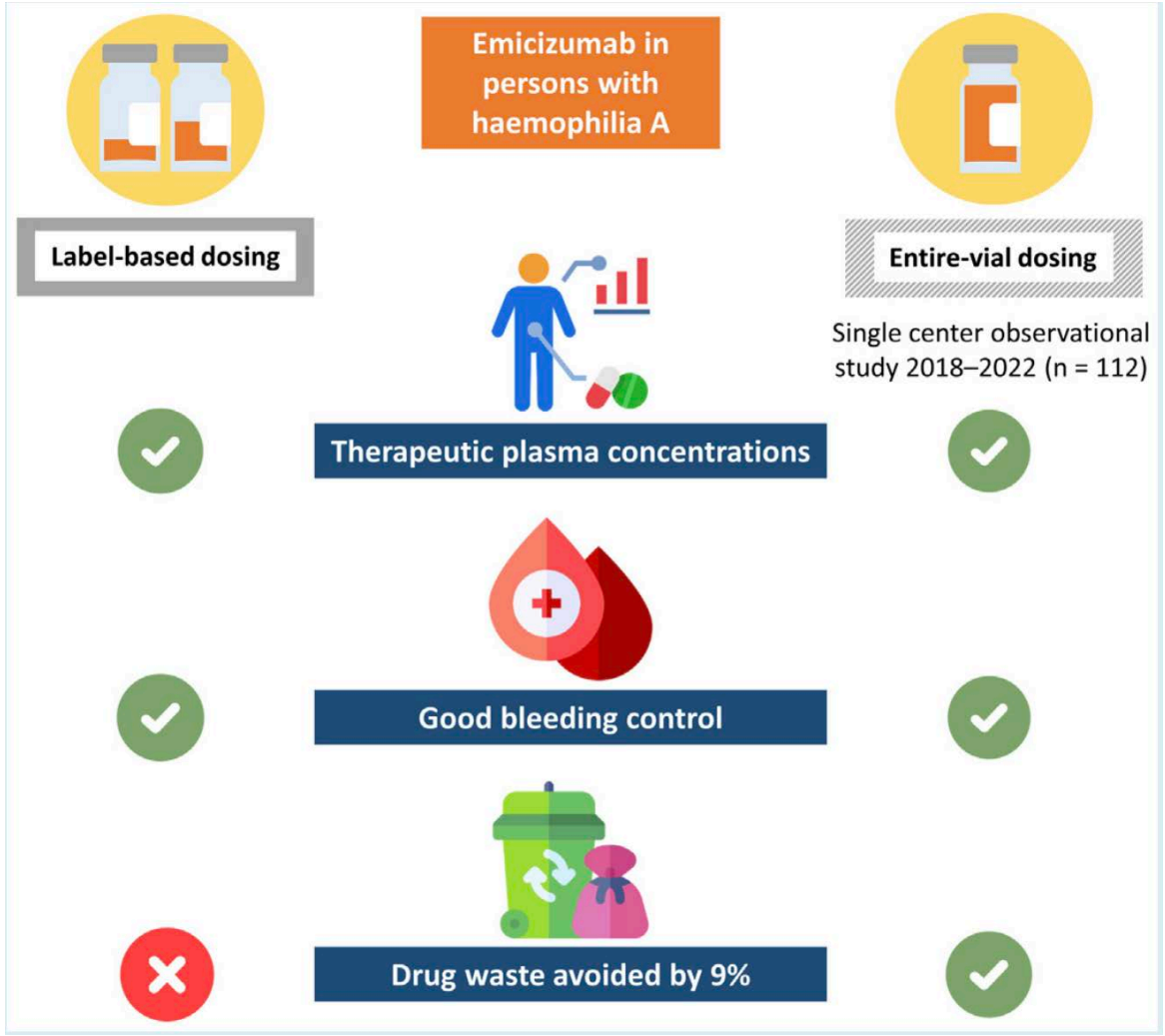
Entire-vial dosing: plasma concentrations, bleeds, and drug waste

Donners AAMT et al RPTH 2023, 7(2) 100074



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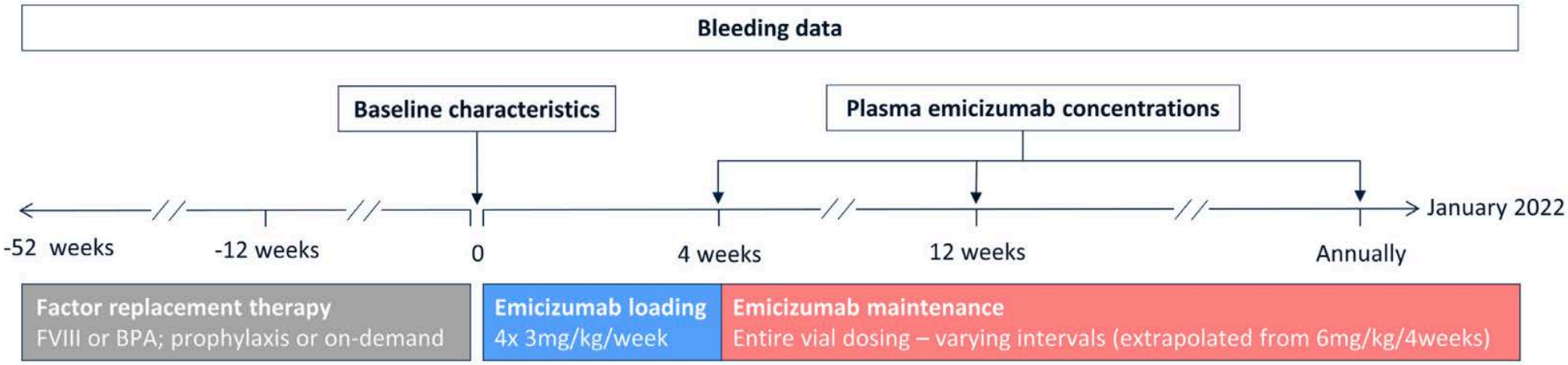

A total of 115 individuals treated with emicizumab were studied from July 2018 to January 2022

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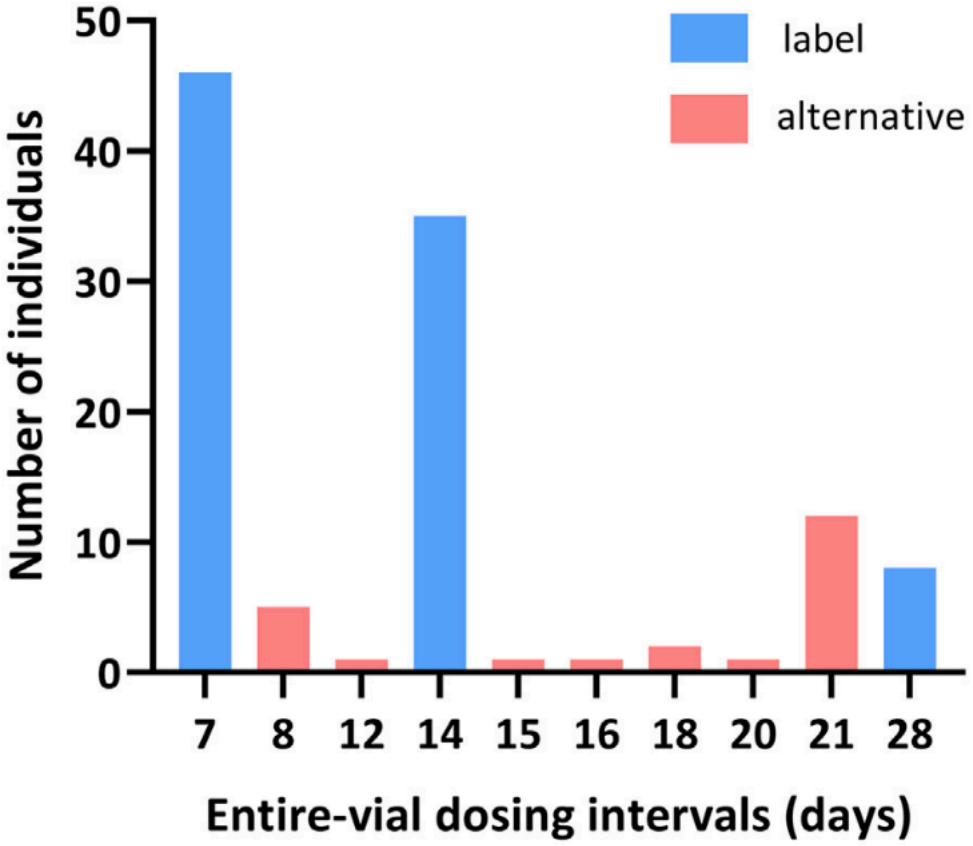

- Most adult/adolescent PwHA (n= 74) were treated with the registered dosing intervals of 7 or 14 days with entire-vial dosing
- Most children (n= 17) had alternative dosing intervals, usually 21 days (n= 12, 38%).

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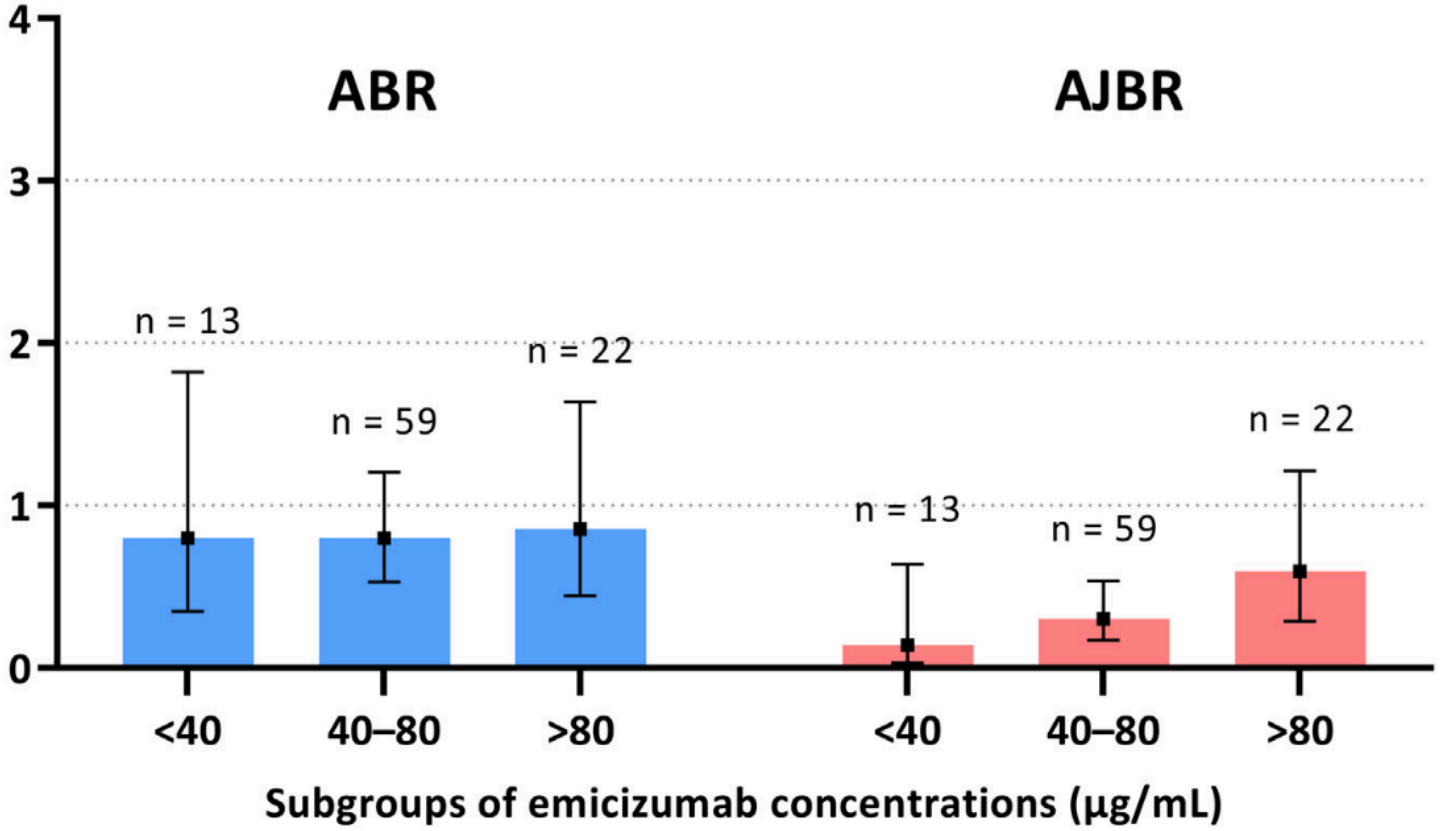

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Entire-vial dosing: plasma concentrations, bleeds, and drug waste

Donners AAMT et al RPTH 2023, 7(2) 100074

- Drug waste (mean, relative):
  - 9% per individual (0% to 40%).
  - 260 mg per adult per year.

- Contribution of drug waste to the overall cost of emicizumab
  - 6% for adolescents/adults
  - 26% for children

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Dosing to product labeling while minimizing drug waste: RATIONALE

D'Albini, L *J Manag Care Spec Pharm. 2023;29(1):47-57*

(1) Precision to the 0.1 mg is unachievable…

(2) Body weigh can fluctuate 1-2 kg per day…

(3) Decreased potential for dosing errors when patients are instructed to draw up full vial(s) for self-injection

(4) PK is linear

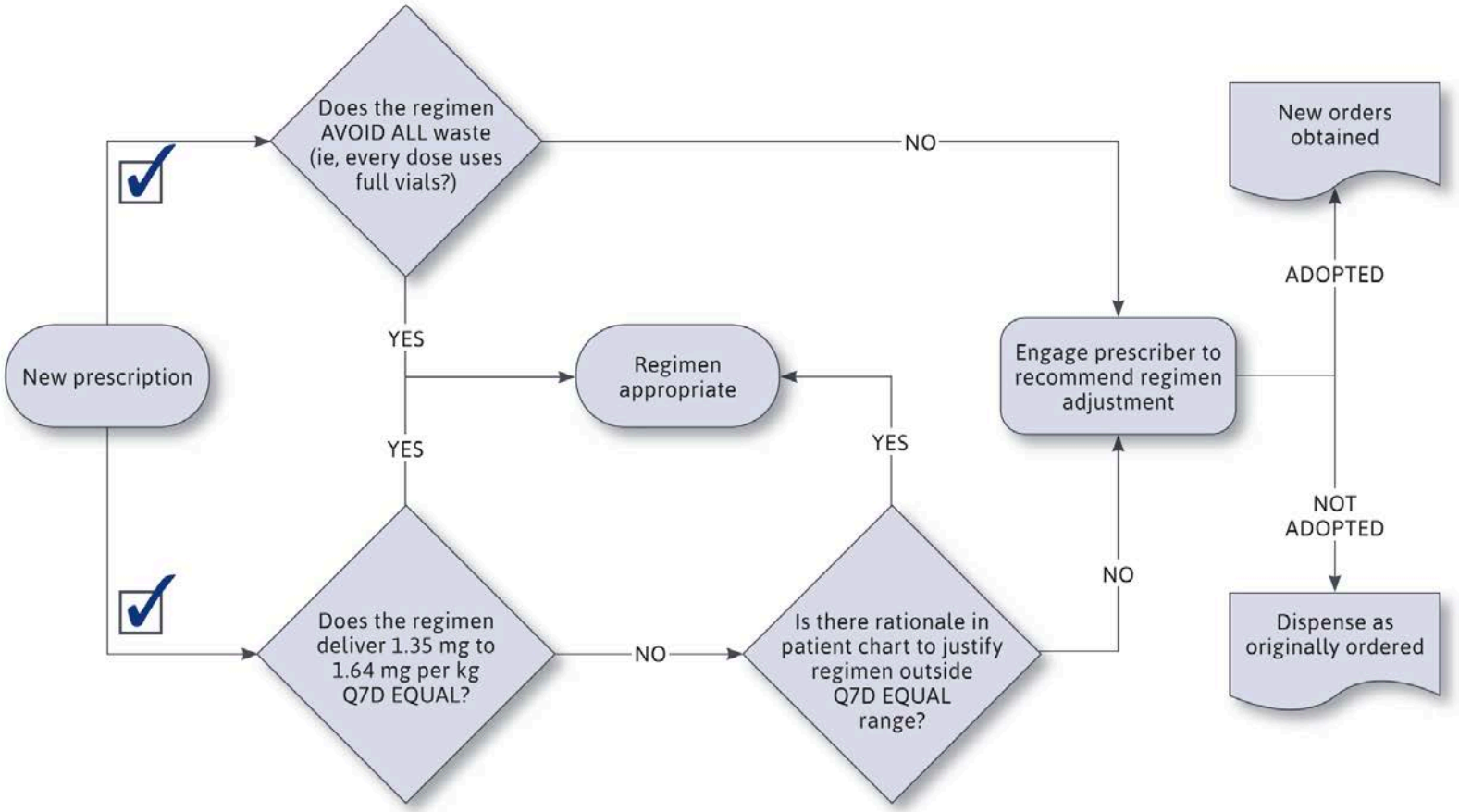
(5) Literature validation in support of rounding most emicizumab-kxwh doses to the nearest vial(s) to avoid or eliminate waste and decrease cost without negatively impacting outcomes is published (*)

(6) Reduction of injection burden

(*) Yu, J. K., Iorio, A., Chelle, P., & Edginton, A. N. *Haemophilia*, 2021 *27*(3), 358–365.

Dosing to product labeling while minimizing drug waste. METHODS

D'Albini, L *J Manag Care Spec Pharm. 2023;29(1):47-57*



Q7D = every 7 days.

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Dosing to product labeling while minimizing drug waste: RESULTS

D'Albini, L *J Manag Care Spec Pharm. 2023;29(1):47-57*

- 48% (176/370) regimens failed specialty pharmacist review (sub-, supra-therapeutic and/or partial vials)
  - 112 (64%) met criteria for prescriber engagement
  - 48 (of 112, 43%) recommendations were adopted with resulting savings of 600 mg per dose
    - (also avoiding significant subtherapeutic or supratherapeutic dosing).
- Cumulative annual savings to payers across these 48 accepted recommendations was $1,793,549.76 per year
  - while increasing doses for 42% (20/48) patients

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Dosing to product labeling while minimizing drug waste. RESULTS

D'Albini, L *J Manag Care Spec Pharm. 2023;29(1):47-57*

- Common reasons for keeping wasting:
  - Willingness to strictly adhere to the FDA labeling
  - Willingness to limit the patient to a single injection per dose
    - ordering a 105-mg vial (vs a 30-mg plus a 60-mg vial) to accommodate doses between 61 mg and 89 mg

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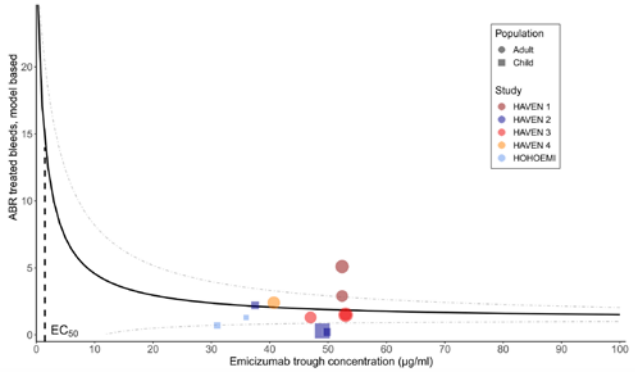
#2 – A lower dose may be sufficient



- Rationale for low-dose prophylaxis approach

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Efficacy of Reduced-dose Emicizumab in Haemophilia A with Inhibitors: Real World Experience in East Malaysia

A.S.O. Tang[1], T.S. Leong[1], C.T. Ko[1], L.P. Chew[1] [1]Sarawak General Hospital, Kuching, Malaysia

Patient #	1	2	3			
Folluw up (days)	133	80	117			
3 mg/kg, EOW	5-96	5-44	5-72			

Tang, A., Leong, T., Ko, C., & Chew LP. (2021). Efficacy of Reduced-dose Emicizumab in Haemophilia A with Inhibitors: Real World Experience in East Malaysia. *Res Pract Thromb Haemost*, *5*(Suppl 2).

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3 mg/kg, EOW	5-96	5-44	5-72			
1.8 mg/kg, EOW	97-113	45-71	73-87			
1.8 mg/kg, E4W	114-132	72-90	88-117			

Following dose reduction, one patient had an episode of haematuria, whereas no bleeding event was observed in two others. None had any adverse events. No thromboembolic events were reported.

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Patient #	1	2	3	Haemao-QoL-A		
Folluw up (days)	133	80	117	Overall	Physical	Role
				31.7 (12.9)	11.9 (8.4)	29.0 (13.7)
3 mg/kg, EOW	5-96	5-44	5-72	76.1 (2.3)	65.9)11.2)	81.7 (11.1)
1.8 mg/kg, EOW	97-113	45-71	73-87	76.7 (3.8)	79.5 (7.5)	80.6 (8.6)
1.8 mg/kg, E4W	114-132	72-90	88-117			

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Effectiveness of monthly low dose emicizumab prophylaxis without 4-week loading doses among patients with haemophilia A with and without inhibitors: A case series report

- Patients
  - Six male patients with haemophilia A
    - 4 severe, 2 moderate
    - 5 without inhibitor, 1 with inhibitor
    - aged 4–40 years.
- Treatment
  - Whole vial of emicizumab
    - to achieve a minimal dose of => 1mg/kg/month
    - Administered sc monthly for 1 year
    - without the standard loading dose.

A Chuansumrit, N Sirachainan, S Jaovisidha, T Jiravichitchai, P Kadegasem, K Kempka, M Panuwannakorn, W Rotchanapanya, T Nuntiyakul.
Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand.

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Effectiveness of monthly low dose emicizumab prophylaxis without 4-week loading doses among patients with haemophilia A with and without inhibitors: A case series report

- Outcomes
  - Dosing of emicizumab
    - 1.05 to 1.66 mg/kg/month
  - Emicizumab levels (median, IQR, µg/m)
    - Peak plasma concentration (7 days) 20.8 (13.6, 22.6)
    - Trough plasma concentration (28 days) 9.7 (8.8, 10.4)
  - Bleeds
    - 23 bleeding episodes;
    - 16 (target) joints bleeds
      - 1 from trauma
      - 15 spontaneous

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A Chuansumrit et al. *Haemophilia*, 2023, *29*(1), 382–385.

Effectiveness of monthly low dose emicizumab prophylaxis without 4-week loading doses among patients with haemophilia A with and without inhibitors: A case series report

Outcome	Baseline	Study end	Reduction (%)	P value
ABR (median, IQR)	27.0 (5.8, 36.2)	4.0 (1.7, 5.5)	81.9	0.027
AsJBR (median, IQR)	15.0 (2.2, 21.0)	2.5 (0, 4.5)	76.4	0.042
HJHS (median, IQR)	27.0 (13.7, 44.0)	20.5 (9.7, 31.2)	25	0.028

All bleeding episodes were responsive to one administration of factor VIII concentrate 10–30 units/kg or recombinant factor VIIa 50 µg/kg accordingly.

Interestingly, annual zero joint bleed status was found among 2 of 6 enrolled patients (33.3%).

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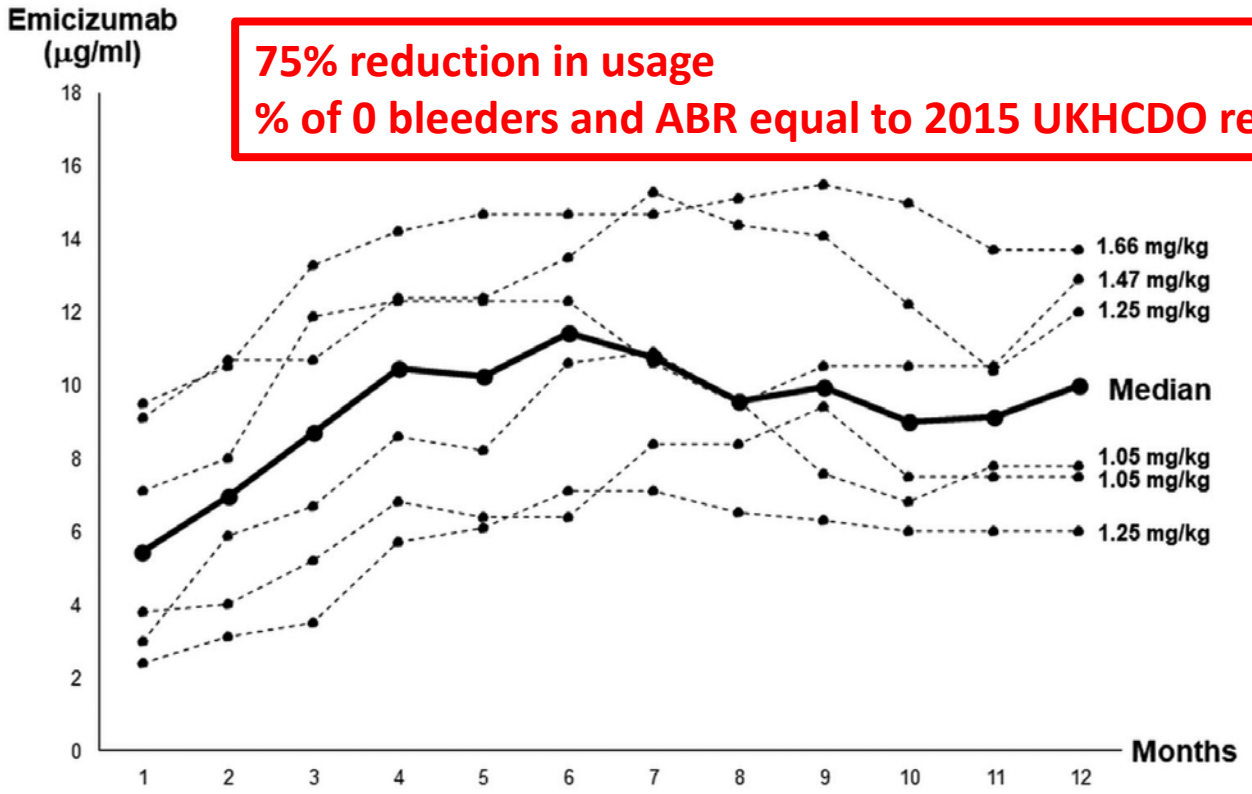

Annual bleeding rate	
Before	After
5	1
37	4
36	7
6	2
30	5
24	4

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A Chuansumrit et al. *Haemophilia*, 2023, *29*(1), 382–385.

Low dose emicizumab prophylaxis in haemophilia A patients: A pilot study from India

- Patients:
  - 8 patients with severe hemophilia A (6 inhibitor positive)
  - 5 patients from the STASEY trial (NCT03191799)
  - 3 patients were on episodic treatment with factor VIII or bypassing agents
- Treatment:
  - Once to 4-weekly, sc, low dose emicizumab (0.84–2.6 mg/Kg/4 weeks)
  - Only entire vials of emicizumab were used and all patients received home treatment
- Follow up:
  - Prospective, 1 year.
- Outcomes
  - The patients were contacted every month for bleeding assessment and adverse events
  - Annualized bleed rates (ABR),and annualized joint bleed rates (AJBR) were calculated.
  - Emicizumab concentrations were measured before, 7 and 14 days after infusion.

S Bansal, A Donners, K Fischer, S Kshirsagar, S Rangarajan, V Phadke, S Mhatre, B Sontate, M D' Silva, S Ansari, S Shetty. - *Haemophilia*, 2023, *29*(3), 931–934. **K.J.Somaiya Hospital**

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Low dose emicizumab prophylaxis in haemophilia A patients: A pilot study from India

- Median follow-up
  - 52 weeks (range 12−136 weeks)
- Median emicizumab concentrations
  - Trough: 8.3 µg/mL (range 3.7−11.9 µg/mL)
  - Peak: 12.9 µg/mL (range 3.3−20.7 µg/mL)[day 7th].
- Bleeding before emicizumab
  - Median ABR was 15 (range 10−30)
  - Median AJBR was 12 (range 5−24)
- Bleeding on emicizumab
  - Standard dose: no treated bleed events
  - Low dose: no treated bleed events

S Bansal, A Donners, K Fischer, S Kshirsagar, S Rangarajan, V Phadke, S Mhatre, B Sontate, M D' Silva, S Ansari, S Shetty. - *Haemophilia*, 2023, *29*(3), 931–934. **K.J.Somaiya Hospital**

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Low dose emicizumab prophylaxis in haemophilia A patients: A pilot study from India

Prior treatment	Emicizumab dosage (mg/Kg /4 weeks)	Dosing frequency	Trough concentration (µg /mL)	Total duration (weeks)
Episodic BPA	1.6	Q2W	11.1	32
Episodic FVIII	0.84	Q2W	3.7	136
SDE	2	Q3W	7.3	52
SDE	1.2	Q4W	8.9	52
SDE	2	Q4W	7.6	52
Episodic FVIII	2.6	Q2W	11.9	12
SDE	2.4	Q3W	10.2	52
SDE	1.2	Q4W	5.9	52

S Bansal, A Donners, K Fischer, S Kshirsagar, S Rangarajan, V Phadke, S Mhatre, B Sontate, M D' Silva, S Ansari, S Shetty. - *Haemophilia*, 2023, *29*(3), 931–934. **K.J.Somaiya Hospital**

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Do we need all that emicizumab?

Patient #	Age	Inhib	Dose/ frequency, follow up (months)	% of approved dose	Number of treated bleeds
1	26	+	1.5 / 1 × 43	100	0; 0
2	21	+	1.5 / 1 × 42; **1.5** / 2 × 15	100; 43	0; 0
3	50	(+)	1.5 / 1 × 1; 1.0 / 1 × 5 1.0 / 2 × 10; 1.0 / 3 × 17	100; 67 33; 16	0; 1 0: 0
4	46	+	1.4 / 1 × 1; 1.4 / 2 × 19	90; 45	0; 0
5	21	(+)	1.5 / 1 × .5; 1.0 / 1 × 2 1.5 / 1 × 10; 1.5 / 2 × 2 3.0 / 4 × 4	100; 70 100; 50 50	0; 1; 0; 0 0
6	31	(+)	1.3 / 1 × 2; 1.3 / 2 × 14	86; 43	0; 0
7	60	–	1.2 / 1 × 2; 1.2 / 2 × 2	40; 20	0; 0
8	69	–	3.0 / 2 × 3	100	0
9	42	(+)	1.38 / 1 × 2	92	0
10	69	–	1.45 / 1 × 2	96	0
11	82	–	2.4 / 2 × 1.5	80	0

Lehtinen, A. E., & Lassila, R. (2022). Do we need all that emicizumab? In *Haemophilia* (Vol. 28, Issue 2, pp. e53–e55)

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It was low before it was high…

- In the early emicizumab program one patient group (n = 6) with a low dose (0.3 mg/kg/week) significantly improved annual bleeding rate (ABR) (from 32 to 4); higher doses (1 and 3 mg/kg) lead to 0 bleeds.
- In the Japanese study the lowest dose of emicizumab produced a plasma concentration equal to 25% (i.e., 10 µg/ml) of the currently recommended dose.

Shima M, Hanabusa H, Taki M, et al. Nogami K factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. NEnglJMed.2016;374(21):2044-2053.

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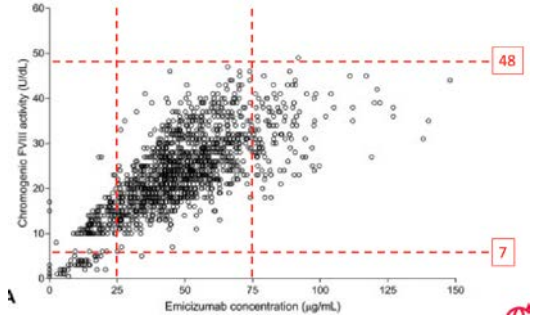
#2 – Plasma level versus activity



Emicizumab PK/PD

- There are several ways emicizumab can be measured in the plasma
  - ELISA (company-measured)
  - Human chromogenic FVIII assay
  - r2 assay (OSCA-modified)
  - Mass spectometry (LCMS; Fischer)

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Thrombotic complications

- Aledort LM. Deaths Associated with Emicizumab in Patients with Hemophilia A. N Engl J Med. 2019; 381: 1878-9.
- Wall C, et al. Emicizumab prophylaxis in haemophilia A with inhibitors: Three years follow-up from the UK Haemophilia Centre Doctors' Organisation (UKHCDO). Haemophilia. 2023; 29: 743-52.
- Makris M, et al. Emicizumab and thrombosis: the story so far. J Thromb Haemost. 2019; 17:1269-72.
- Tiede A. Thromboembolic risks of non-factor replacement therapies in hemophilia. Hamostaseologie. 2017; 37:370-10.
- Howard M, et al. Evaluation of the Safety of Emicizumab Prophylaxis in Persons with Hemophilia A: An Updated Summary of Thrombotic Events and Thrombotic Microangiopathies. Blood. 2021; 138: 3186.
- Abbatista M et al. Hemorrhagic and thrombotic adverse events associated with emicizumab and extended half-life factor VIII replacement drugs: EudraVigilance data of 2021. J Thromb Haemost. 2023; 21: 546-52.

Thrombotic AEs in the FDA/AERS data were 3x for emicizumab than for FVIII products

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Leading into the Q&A session…

- During 1-year prophylaxis, patients received the whole vials …. except patients #. 4 and 5 … **[who] shared the second vial of 30 mg among siblings** to achieve …, respectively

A Chuansumrit et al. *Haemophilia*, 2023, *29*(1), 382–385. https://doi.org/10.1111/hae.14707

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