Il trattamento del paziente con emofilia: trattamento sostitutivo e non a confronto

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Prophylaxis is the standard of care in hemophilia

- ✓ **Principle 8**: the *standard of care* for all patients with severe hemophilia is *regular* replacement *therapy* with CFCs or other hemostatic products *to prevent bleeding started early in life* (before age of 3) *to prevent musculoskeletal complications* from recurrent joint and muscle bleeds.

- ✓ **Recommendation 6.1.1**: For patients with haemophilia A or B with a severe phenotype, *the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times*, but that prophylaxis should be individualized taking into account patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference.

Srivastava A et al. Haemophilia 2020; 26 (Suppl 6): 1-158

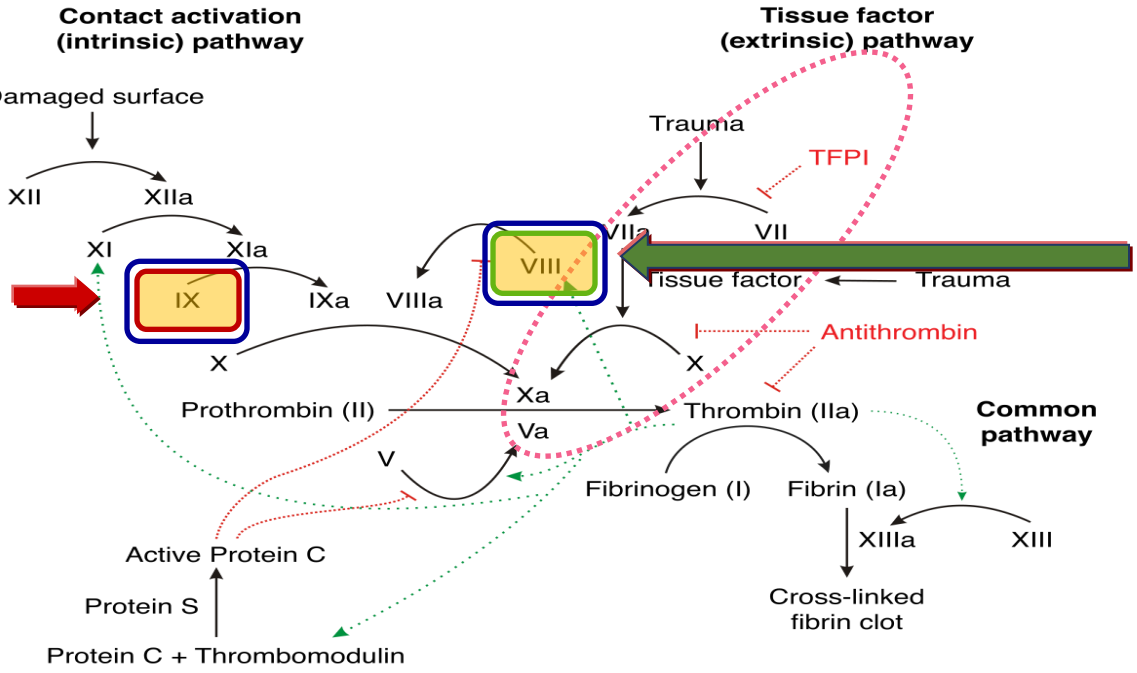
Replacement therapies

EHL-FIX products:

- rFIXFc
- rIXFP
- N9-GP

SHL-FIX products

- rFIX
- pdFIX



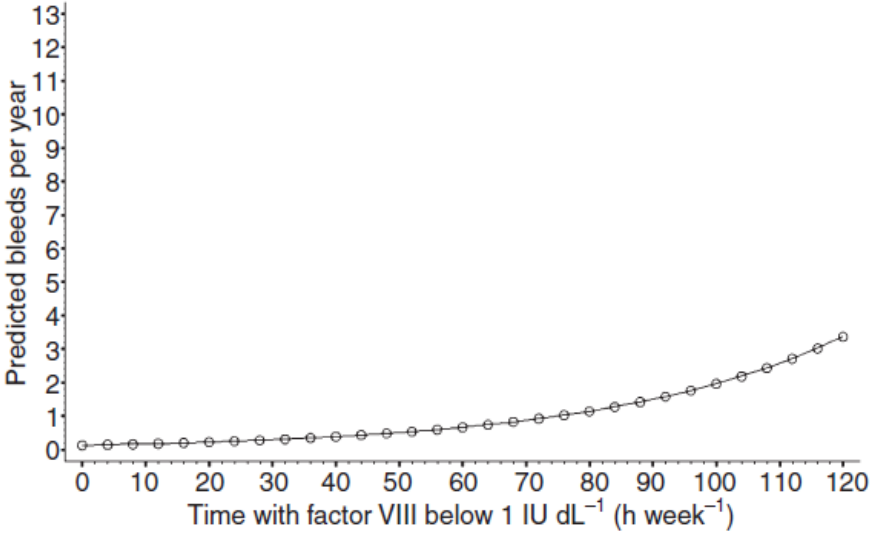
EHL-FVIII products:

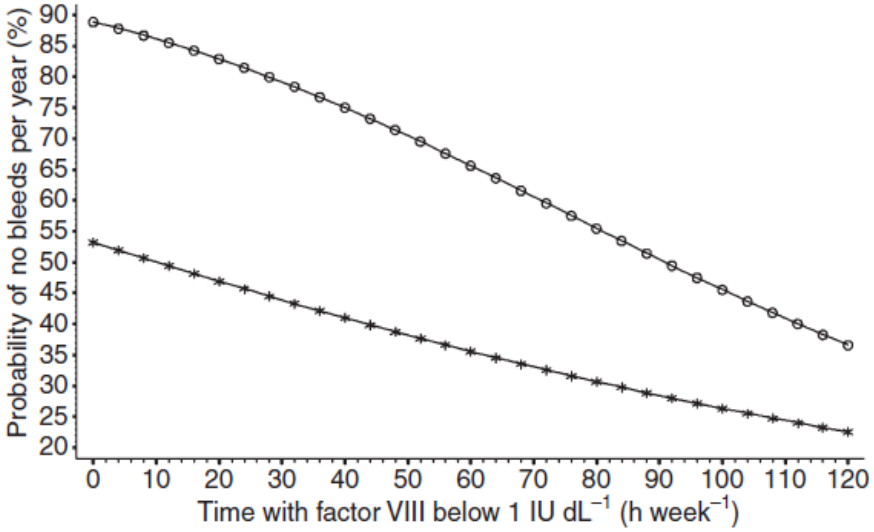
- rFVIIIFc
- N8-GP
- Rurioctocog alfa pegol
- Damoctocog alfa pegol

SHL-FVIII products

- rFVIII
- pdFVIII

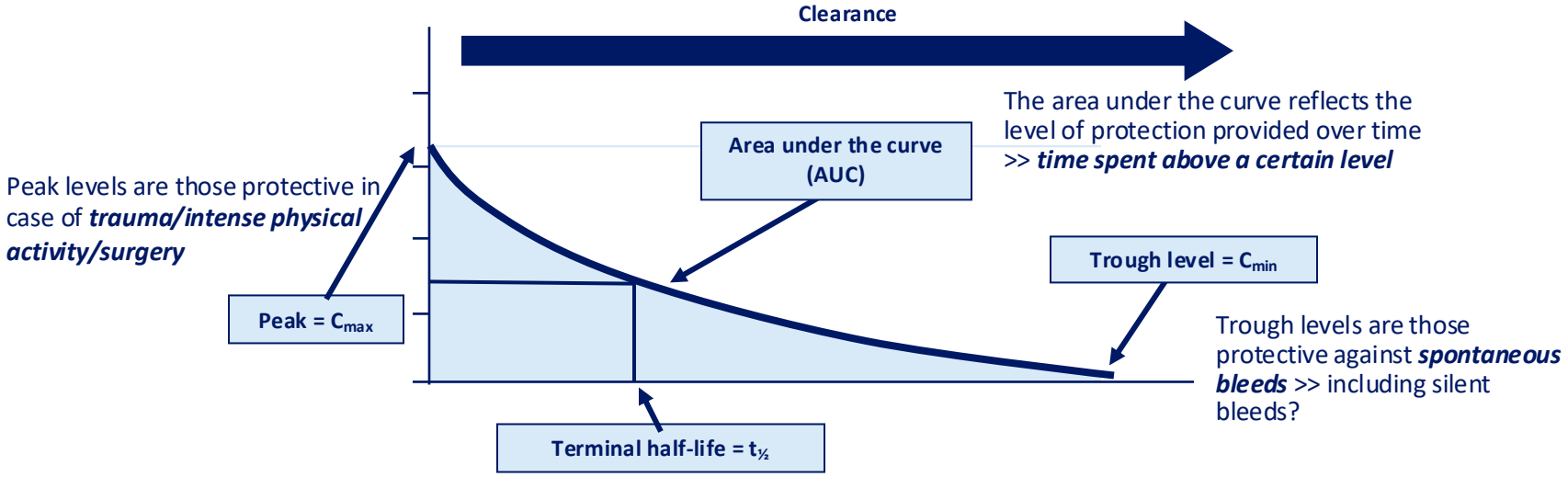
Bleeding risk – the value of factor levels





Collins PW et al. JTH 2009; 7: 413-20

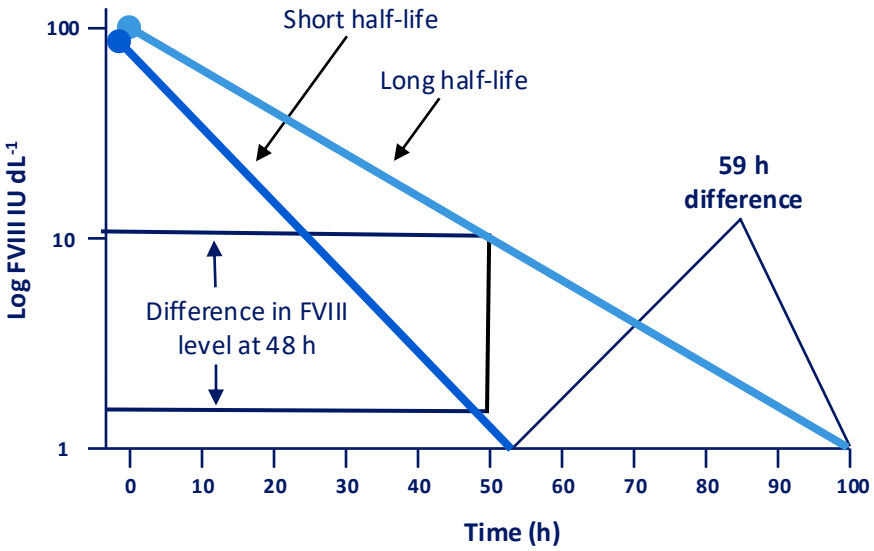
Treatment individualisation for better outcomes: the example of PK-guided replacement therapy



Prophylaxis with clotting factor concentrates is done according to repeated IV injections, whose frequency is related to the PK properties of FVIII/FIX

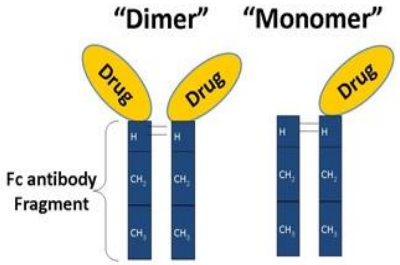
Interindividual variability: replacement therapy

Effect of half-life on FVIII level following a bolus infusion

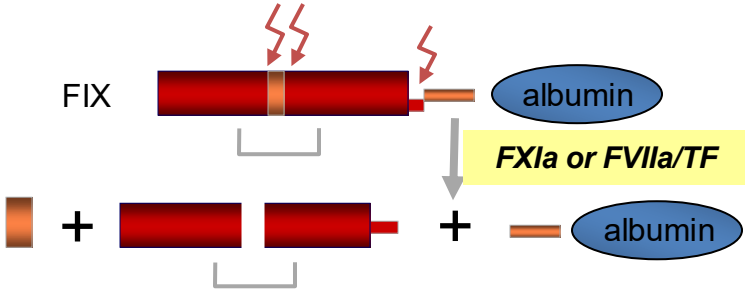


Collins PW, et al. Haemophilia 2011;17:2–10
Hermans C et al. Ther Adv Hematol 2020 Oct 20;11:2040620720966888

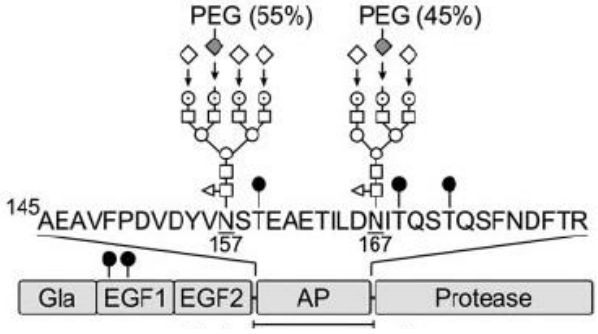
Fusion with Fc fragment of Ig



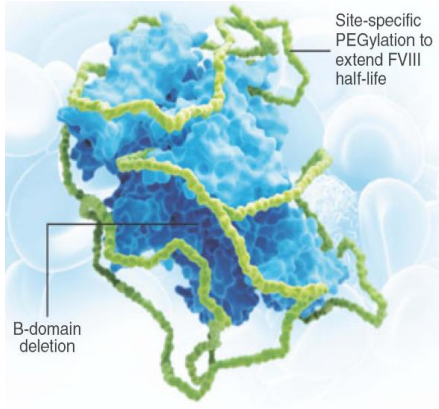
Fusion with albumin



GlycoPEGylation

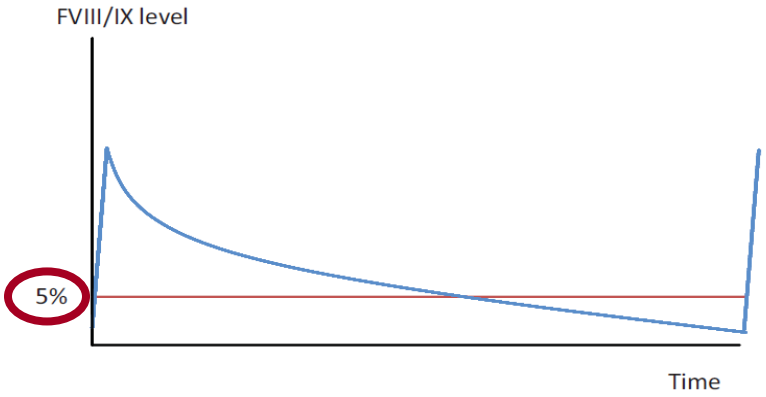


Random or site-specific PEGylation



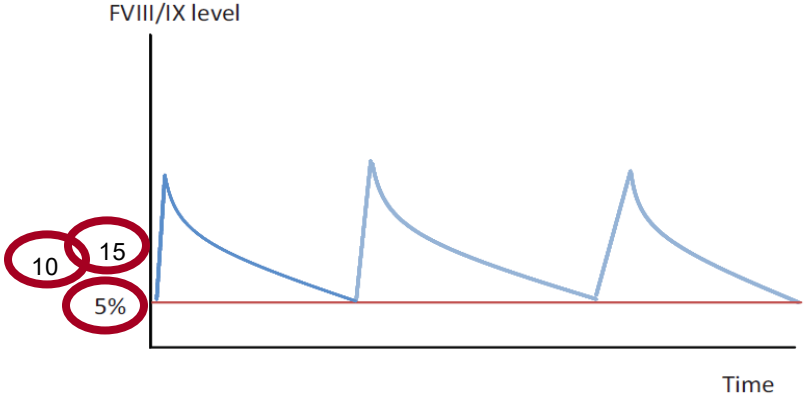
Replacement therapy - individualization

Reduced number of injections



- **Sedentary individuals**
- **Prophylaxis onset in young children**
- **Poor venous access**
- **End stage joint damage**

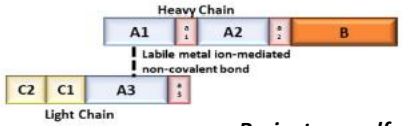
Increased trough levels



- **Active individuals**
- **Levels optimization**
- **Healthy joints**
- **Synovitis**

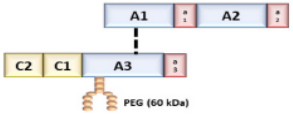
Replacement therapies for HA

Octocog alfa



Rurioctocog alfa pegol

Damoctocog alfa pegol



Turoctocog alfa pegol

Efmoroctocog alfa

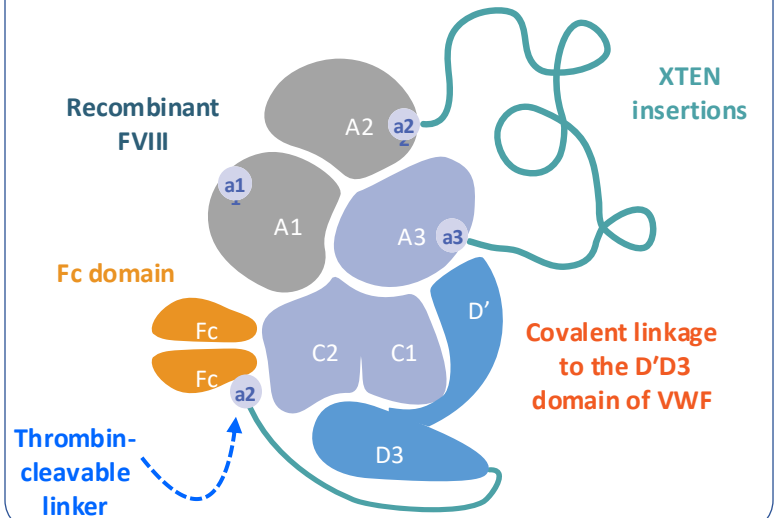
Efanesoctocog alfa

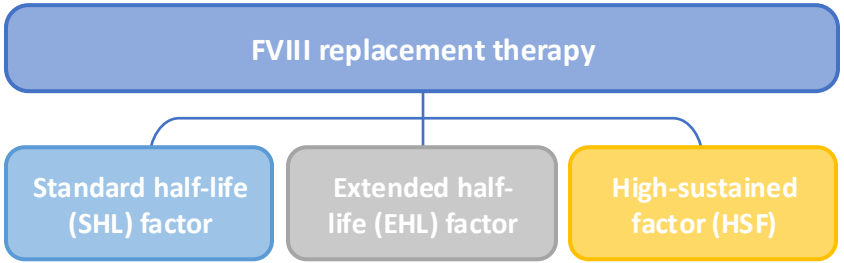
Molecule	Structure	Prophylaxis regimen
Octocog alfa	Full length rFVIII (CHO or BHK cells)	2-4 times weekly
Moroctocog alfa	BDD-rFVIII	2-4 times weekly
Turoctocog alfa	BDT-rFVIII	2-4 times weekly
Simoctocog alfa	Full length rFVIII (HEK cells)	2-4 times weekly
Lonoctocog alfa	Single-chain BDD-rFVIII	2-4 times weekly
Efmoroctocog alfa	BDD-rFVIII, Fc-fused	Every 3-4 days
Rurioctocog alfa pegol	Full lenght rFVIII, non-site-specific PEGylation (20 kDa)	Twice weekly
Damoctocog alfa pegol	BDD-rFVIII, site-specific PEGylation (60 kDa)	Every 3-7 days
Turoctocog alfa pegol	BDT-rFVIII, GlycoPEGylation (40 kDa)	Every 4-5 days
Efanesoctocog alfa	BDD-rFVIII, Fc-VWF D'D3-XTEN fused	Once weekly

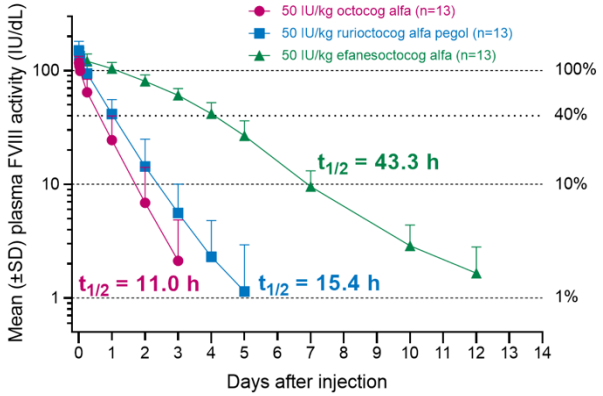
Adapted from Abdelgawad HAH et al Blood Rev 2024; 64: 101164

Efanesoctocog alfa: first-in-class high-sustained FVIII replacement

Efanesoctocog alfa is a novel fusion protein that **overcomes the VWF-imposed half-life ceiling**



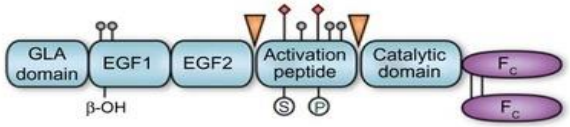




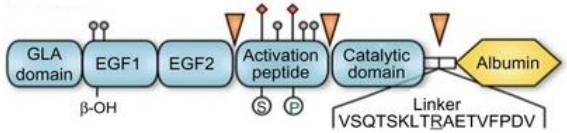
A single dose of efanesoctocog alfa resulted in a 3- to 4-fold longer half-life than other FVIII products

Replacement therapies for HB

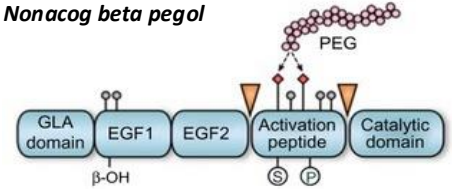
Eftrenonacog alfa



Albutrepenonacog alfa



Nonacog beta pegol



Molecule	Structure	Prophylaxis regimen
Nonacog alfa	rFIX	Twice weekly
Eftrenonacog alfa	rFIX fused with Fc	Every 7-10 days
Albutrepenonacog alfa	rFIX fused with albumin	Every 7-21 days
Nonacog beta pegol	GlycoPEGylated rFIX	Every 7-14 days

Powell JS et al. N Engl J Med 2013;369:2313–2323
Santagostino E et al. Blood 2016;127:1761–1769
Collins PW et al. Blood 2014;124:3880–3886

Prophylaxis with replacement therapy

Pros

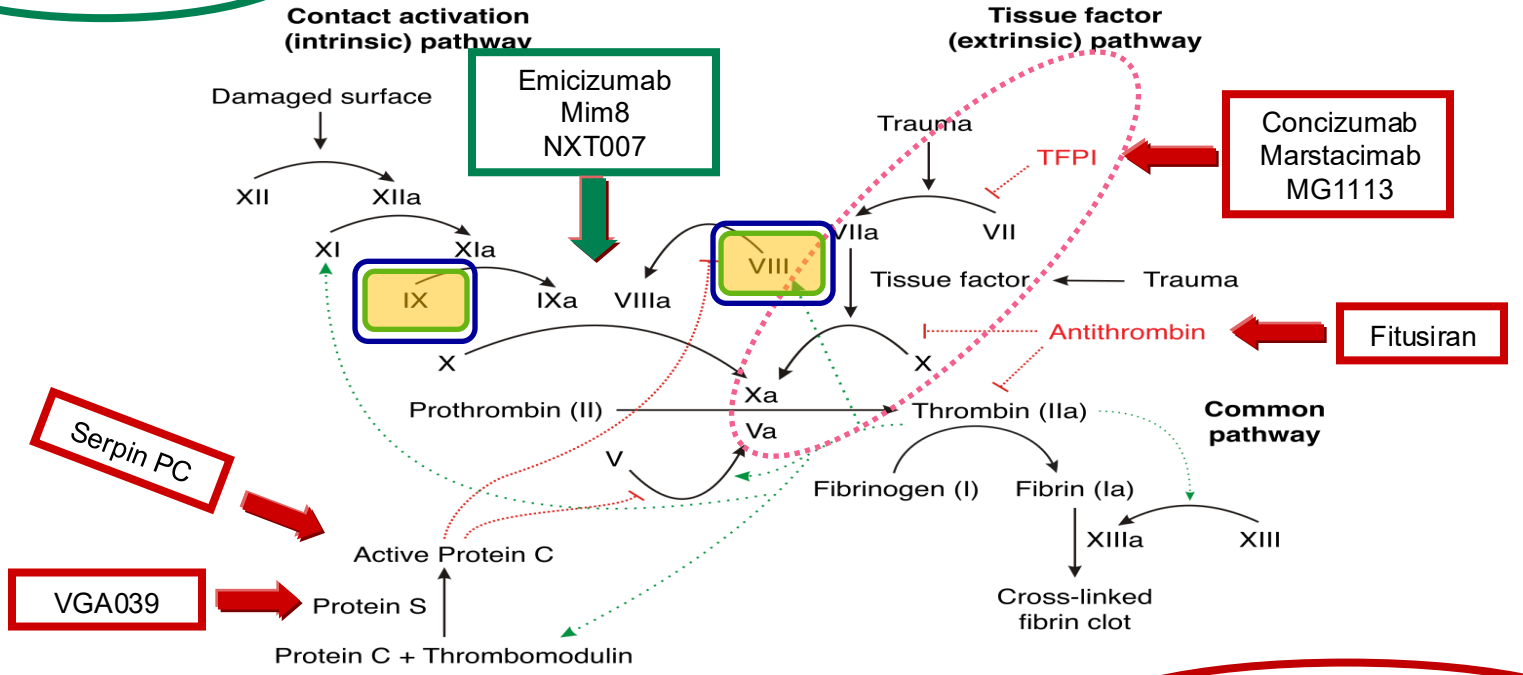
- Replacing the missing protein
- Protection against joint bleeds and ICH
- Normal FVIII/FIX levels (peaks)
- Possibility to individualize and tailor levels to clinical needs and lifestyle
- Measurable levels >> haemostatic efficacy

Cons

- Intravenous injections
- Adherence
- Interindividual PK variability
- Not a single protocol that fits all
- Not effective in patients with inhibitors

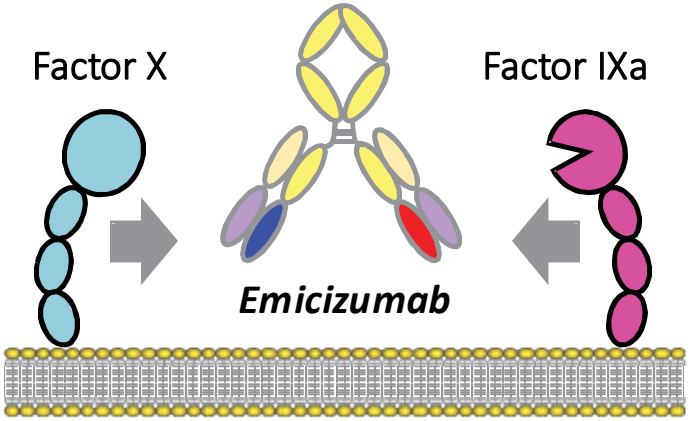
Non replacement therapies

FVIII mimetics



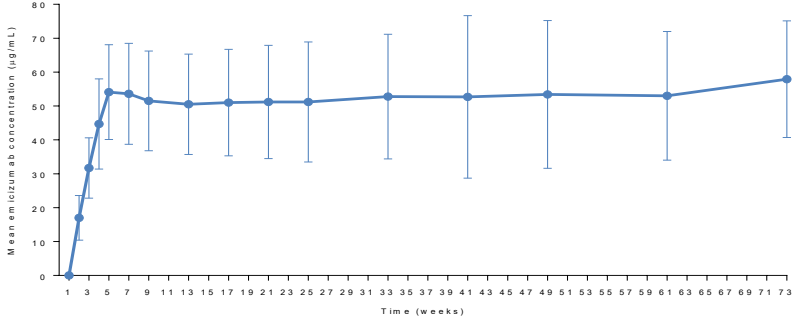
Rebalancing agents

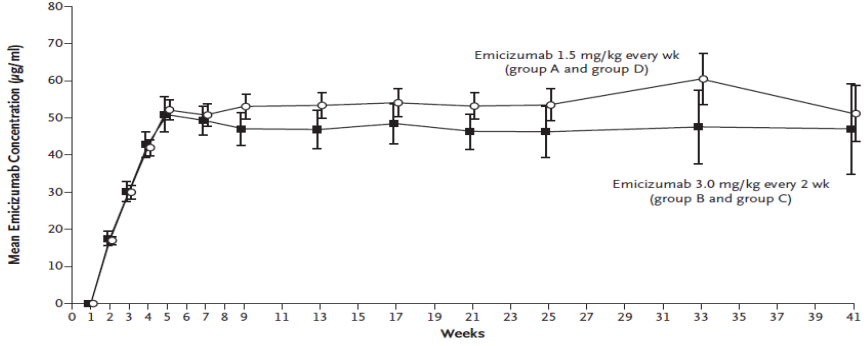
Emicizumab



- Humanized bispecific monoclonal antibody
- No structural homology to FVIII (not recognized by anti-FVIII antibodies)
- Only for HA patients
- Long half-life of ~30 days
- Administered subcutaneously every 7, 14 or 28 days

- Approved worldwide for QW, Q2W and Q4W prophylaxis in PwHA with and without inhibitors





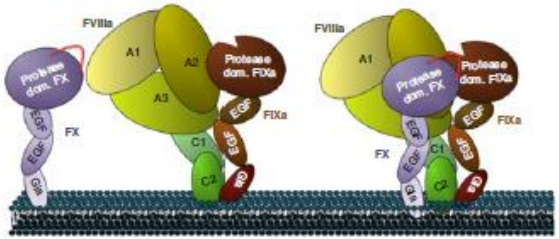
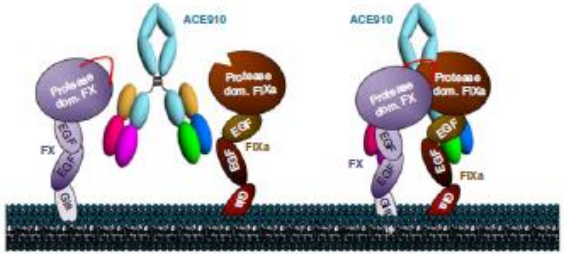
Shima S, et al. N Engl J Med 2016;374:2044–53

Oldenburg J et al. NEJM 2017;377:809-18

Mancuso ME et al. Blood 2017;130:1071

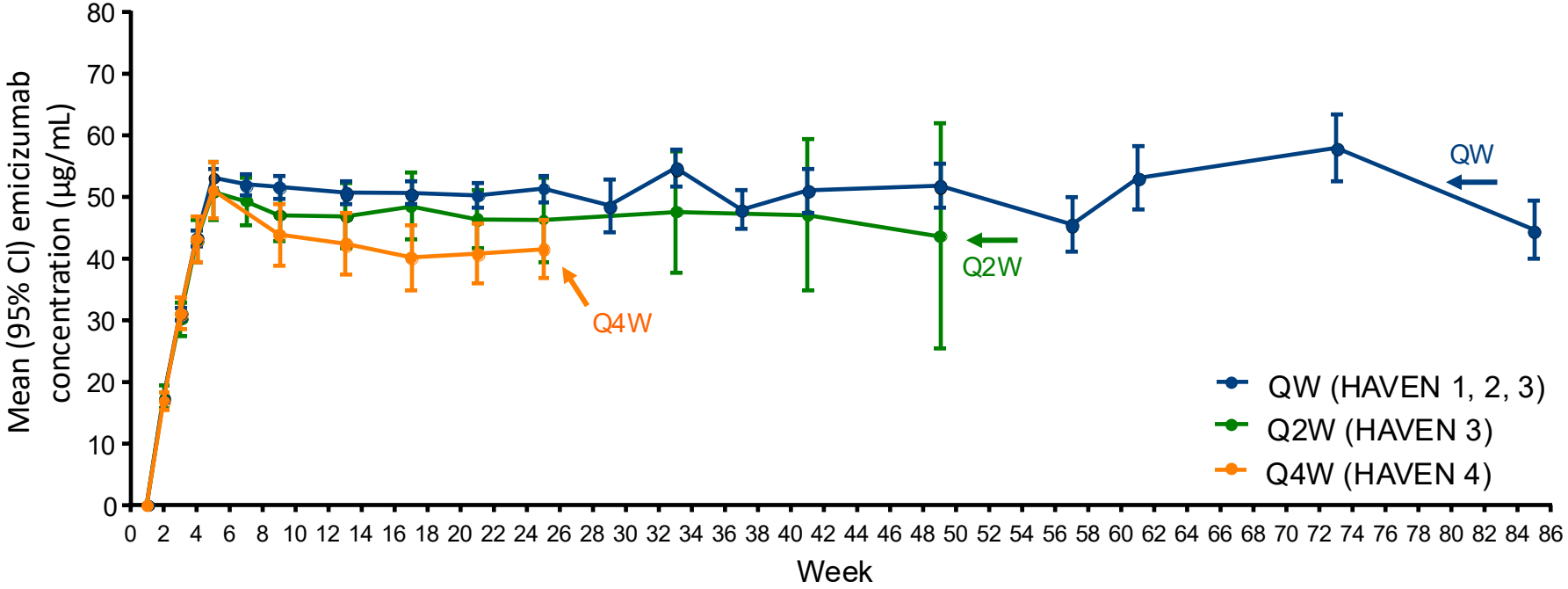
Mahlangu J et al. NEJM 2018;379:811-22

Emicizumab: a monoclonal bispecific antibody

FVIIIa	ACE910/Emicizumab
	
Multiple sites of interaction	Single sites of interaction
High affinity for enzyme & substrate *(low to high nanomolar range)*	Low affinity for enzyme & substrate *(micromolar range)*
Specific for FIXa and FX *(no binding to FIX and FXa)*	No distinction between zymogen and enzyme *(FIX vs FIXa and FX vs FXa)*
Full cofactor activity - *promotes phospholipid binding* - *stabilizes FIXa active site* - *bridges FIXa to FX*	Partial cofactor activity - *bridges FIXa to FX*
Enzyme and substrate are in excess over cofactor	Antibody is in excess over enzyme and substrate
FVIIIa has on/off mechanism	Emicizumab has no on/off mechanism
High level of self-regulation	Low level of self-regulation

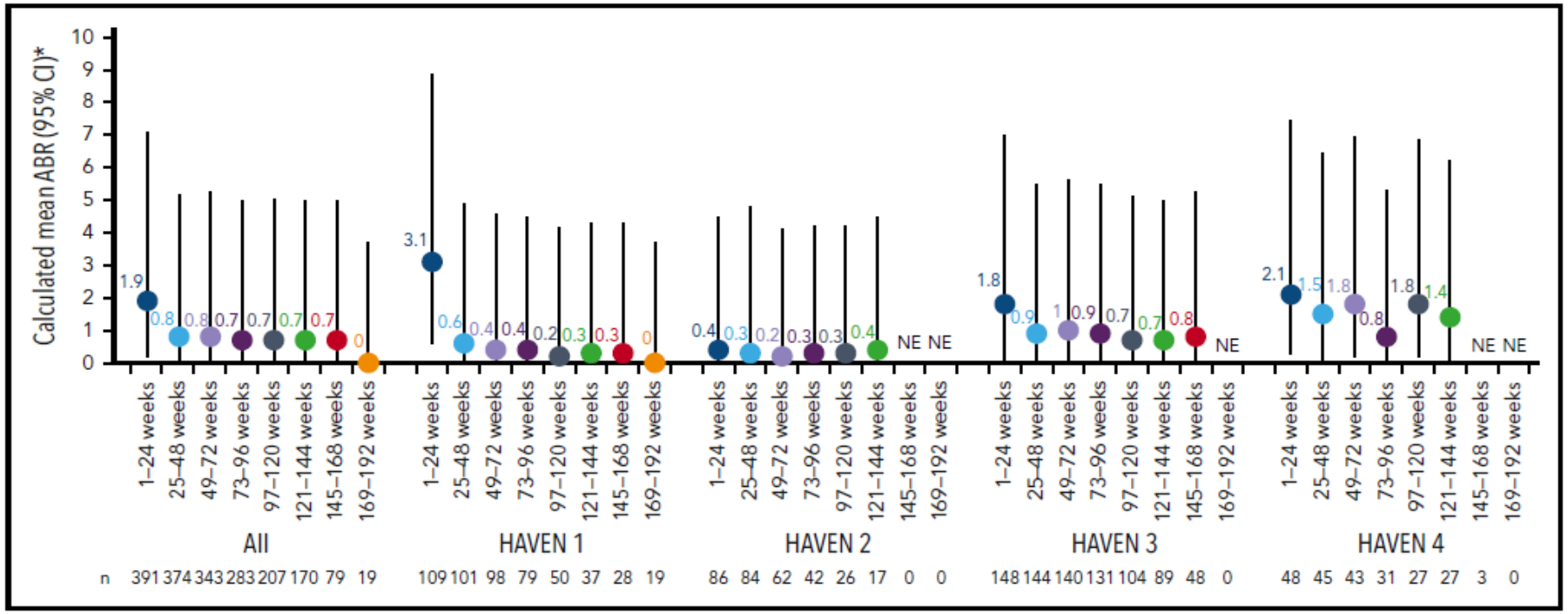
Lenting P et al Blood 2017;130:2463-8

HAVEN 1 – 4: Emicizumab pharmacokinetics
Trough concentrations by dosing regimen (QW, Q2W and Q4W)



- Clinically efficacious concentrations obtained with all 3 dosing regimens (consistent with PK model predictions)
- **Independent from age and body weight**

Emicizumab – ABRs reduction maintained over time



Callaghan M et al. Blood 2021; 137: 2231-42

Emicizumab: efficacy data from a scoping review

	Clinical trials	Real-world data	All studies
Calculated mean ABR for treated bleeds			
Range	0.7-1.3	0.2-1.4	0.2-1.4
Sample size	85	570	655
Calculated median ABR for treated bleeds			
Range	0.0-1.4	0.0-1.0	0.0-1.4
Sample size	604	503	1107
Zero treated bleeds			
Range %	33.3-82.6	50.8-85.7	33.3-85.7
Median %	62.9	70.5	66.7
Sample size	680	213	893

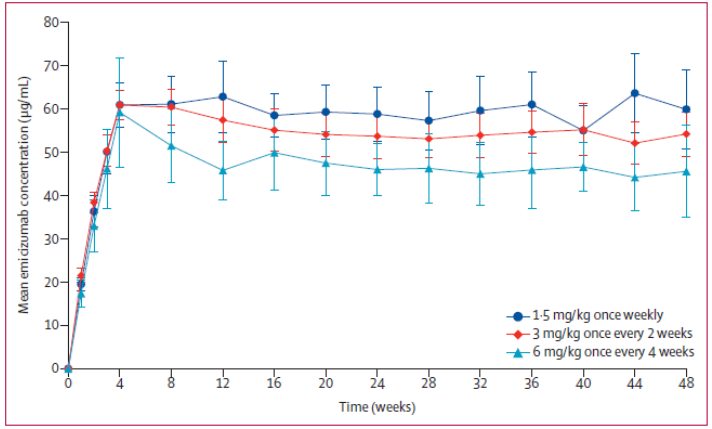
Young G et al Res Pract Thromb Haemost 2024; 8: e102415

Emicizumab in non-severe HA – HAVEN 6 study

	Treated bleeds	Treated joint bleeds	Treated spontaneous bleeds	Treated target joint bleeds	All bleeds
Model-based ABR (95% CI)	0·9 (0·55–1·52)	0·2 (0·09–0·57)	0·2 (0·11–0·33)	0·1 (0·03–0·40)	2·3 (1·67–3·12)
Calculated mean ABR (95% CI)†	0·9 (0·02–5·48)	0·2 (0·00–4·15)	0·3 (0·00–4·23)	0·1 (0·00–3·92)	2·3 (0·35–7·75)
Calculated median ABR (IQR)†	0·0 (0·00–0·98)	0·0 (0·00–0·00)	0·0 (0·00–0·00)	0·0 (0·00–0·00)	1·0 (0·00–3·11)
Calculated ABR range†	0·00–7·05	0·00–3·63	0·00–6·09	0·00–3·21	0·00–21·04
Participants with zero bleeds, n (%)‡	48 (67%)	64 (89%)	59 (82%)	68 (94%)	24 (33%)§

Median (range) follow-up time: 55·6 weeks (8·7–89·9). Compliance with bleed reporting on-study via the BMQ was >90%. ABR=annualised bleed rate. BMQ=bleed and medication questionnaire. *One participant (1%) had <24 weeks of follow-up, and 57 (79%) of 72 participants had ≥52 weeks of follow-up. †Calculated as: (number of bleeds/total number of days during the efficacy period) × 365·25. ‡At interim analysis (median follow-up time of 27·5 weeks), participants with zero bleeds were: 57 (80%) treated bleeds; 33 (47%) all bleeds; 64 (90%) treated joint bleeds; 68 (96%) treated spontaneous bleeds; 67 (94%) treated target joint bleeds.[28] §The pre-study bleed model-based ABR for all bleeds in the 33% of patients (n=24) who had no bleeds on study was 5·4 (95% CI 3·25–9·08).

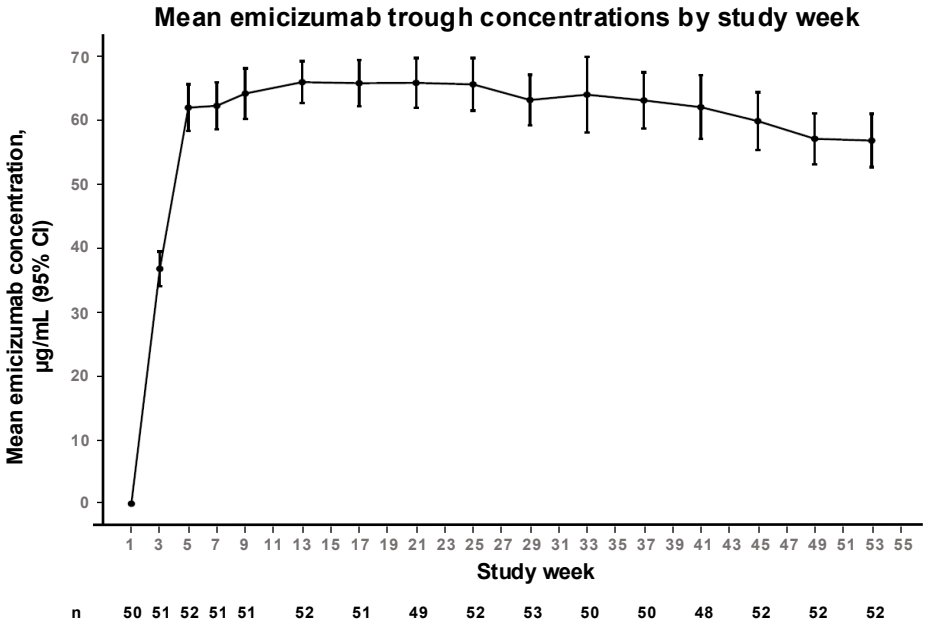
Table 3*: Efficacy summary



- 72 patients enrolled: ***51 moderate*** and 21 mild
- ISR in 17%
- Median FVIII activity in mild pts: 6.4% (IQR 3.6-11.1)
- 37 (51%) were already on FVIII prophylaxis
- 24 (33%) had TJ

Negrier C et al Lancet Haematol 2023;10:e168-e177

HAVEN 7: effective emicizumab concentrations in infants



- Following loading doses, the mean (95% CI) trough concentration of emicizumab was **62.0 (58.3–65.6) µg/mL** at Week 5
- Steady-state trough concentrations of emicizumab were **~57–66µg/mL**

Pipe SW et al Blood 2024; 143: 1355-64

No new safety signals were identified

	Emicizumab (N=55)
Total number of adverse events (AEs), n	631
Participants with ≥1 AE, n (%)	55 (100)
AE with fatal outcome	0 (0)
AE leading to withdrawal from treatment	0 (0)
AE leading to dose modification / interruption	0 (0)
AE of Grade ≥3	17 (30.9)
AE related to treatment	9 (16.4)
SAEs	16 (29.1)*
AEs of special interest, n (%)	
Systemic hypersensitivity reactions and anaphylactic / anaphylactoid reactions	1 (1.8)†
Thromboembolic event	0 (0)
Thrombotic microangiopathy	0 (0)

No intracranial hemorrhages were reported

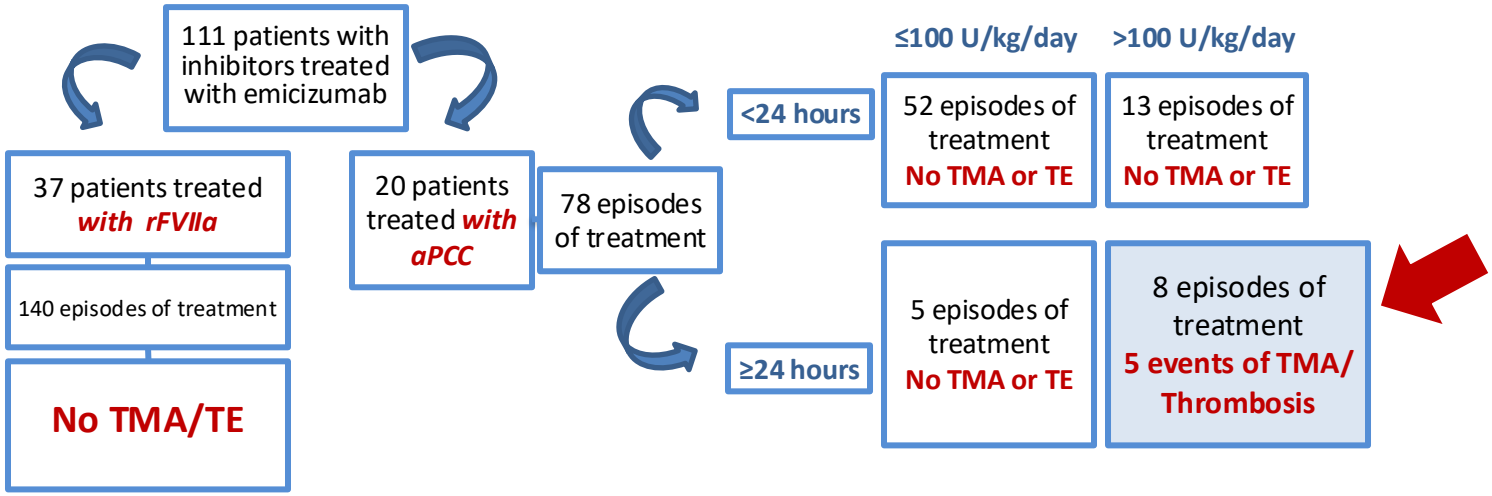
No adverse events led to withdrawal or dose modification or interruption

All treatment-related adverse events were **Grade 1 local injection-site reactions**

No serious adverse events were considered related to treatment; most were common infant-specific events

Pipe SW et al Blood 2024; 143: 1355-64

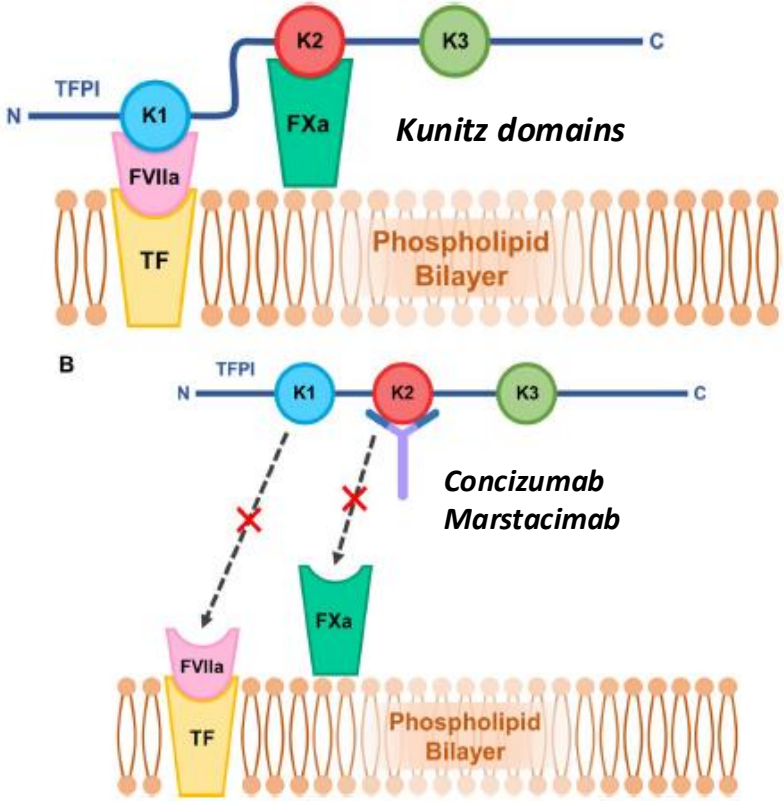
Drawbacks of emicizumab prophylaxis



- ***No TE/TMA in patients treated with Emicizumab alone or in combination with rFVIIa or FVIII***
- ***Injection Site Reactions*** (ISR) represent the most common AE (around 20%; mild in severity)
- ***Development of anti-drug antibodies*** (ADA) with neutralizing potential is very rare ***(18/668, 2.7% >> 11 persistent, 1.6%)***

Oldenburg J et al N Engl J Med 2017;377:809-18
Schmitt C et al Haemophilia 2021;27:984-92

Anti TFPI-antibodies – Mode of action and approval status



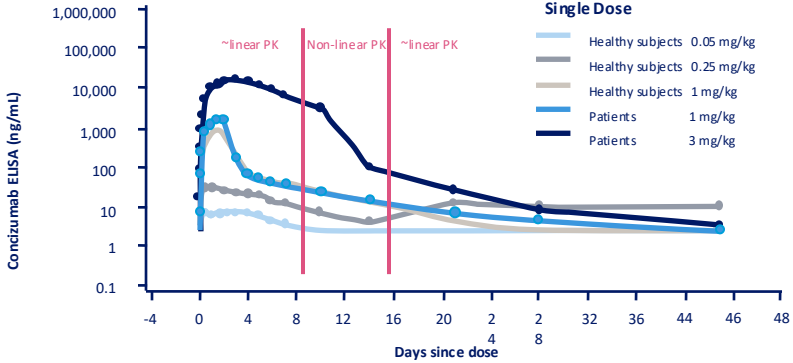
Concizumab (humanised monoclonal IgG4)
Approved in Canada, Switzerland, Japan, New Zealand for HB with inhibitors
EMA positive opinion on 17 Oct 2024 for HA and HB ***with inhibitors***
Route of administration: s.c. daily
Thrombosis events reported that led to dosing schedule adaptations

Marstacimab (human monoclonal IgG1)
FDA approval on 11 Oct 2024 for HA and HB without inhibitors
EMA approval on 18 Nov 2024 for HA and HB ***without inhibitors***
Route of administration: s.c. weekly
One case of DVT

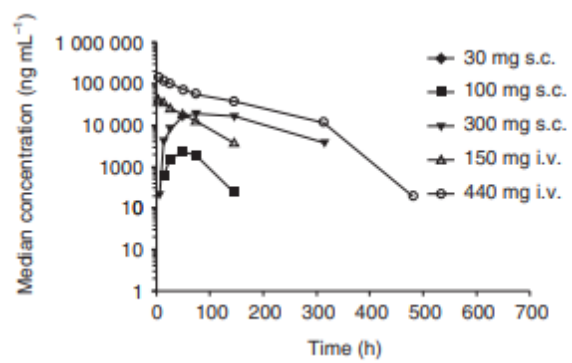
Okaygoun D et al. J Biomed Sci 2021; 28: 64

PK of anti TFPI: Concizumab & Marstacimab

Result from phase 1



Result from phase 1



Due to high-affinity binding with endothelial TFPI, concizumab exhibits Target Mediated Drug Disposition (TMDD)

Once daily dosing would minimize within-patient concizumab PK variability and allow a normalization of thrombin generation

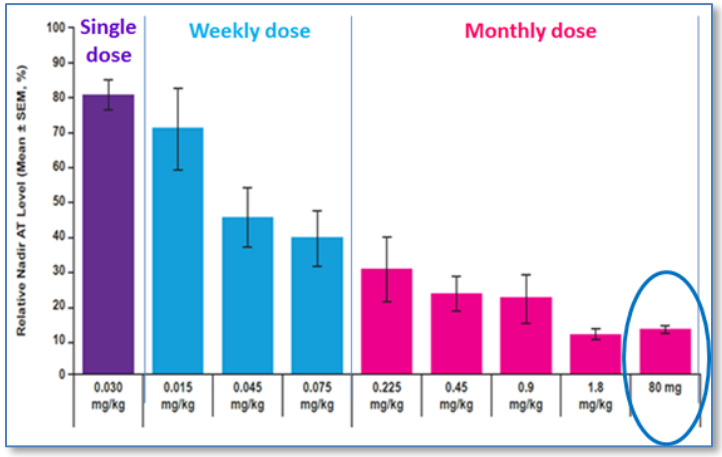
Marstacimab exhibited dose dependent PK and target mediate drug disposition causes non-linear PK

The PK profile of the 300 mg subcutaneuous dose level indicates that this single dose is sufficient to maintain a concentration of > 5000 ng mL for > 168 h (i.e. 7 days)

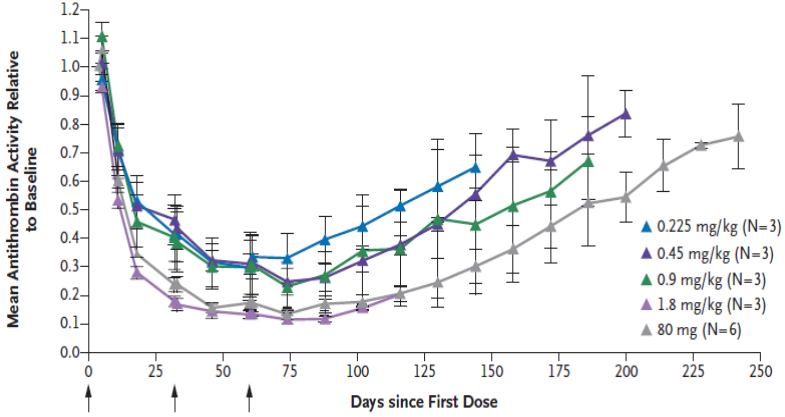
Chowdary P et al. J Thromb Haemost. 2015;13:743–54 2.Eichler H et al. Haemophilia 2019; 25: 60–66 3.Parng C., J Pharm Sci, 107 (2018), pp. 1995-2004 4Cardinal M,. J Thromb Haemost. 2018 Sep;16(9):1722-1731.

Fitusiran

- ✓ Subcutaneous administration (50 mg every other month)
- ✓ Target is Antithrombin: small interference RNA (siRNA)
- ✓ Phase 3 resumed after “on hold” due to thrombotic events
- ✓ Half-life is one month
- ✓ Asymptomatic ALT increase > 3 folds

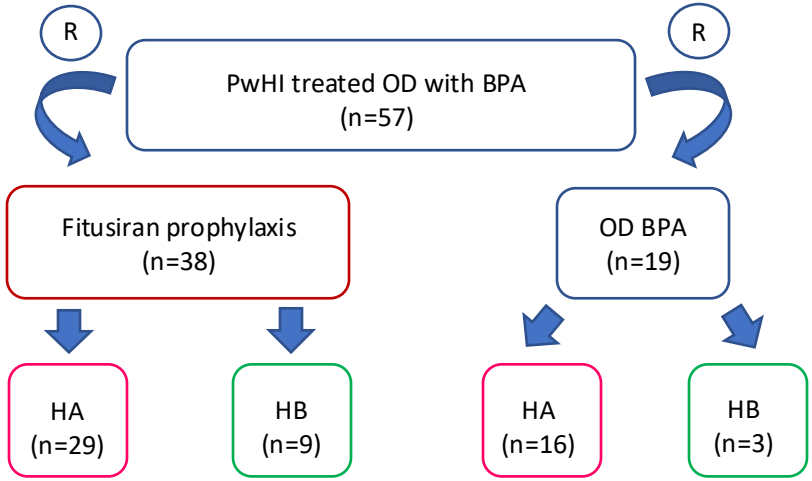


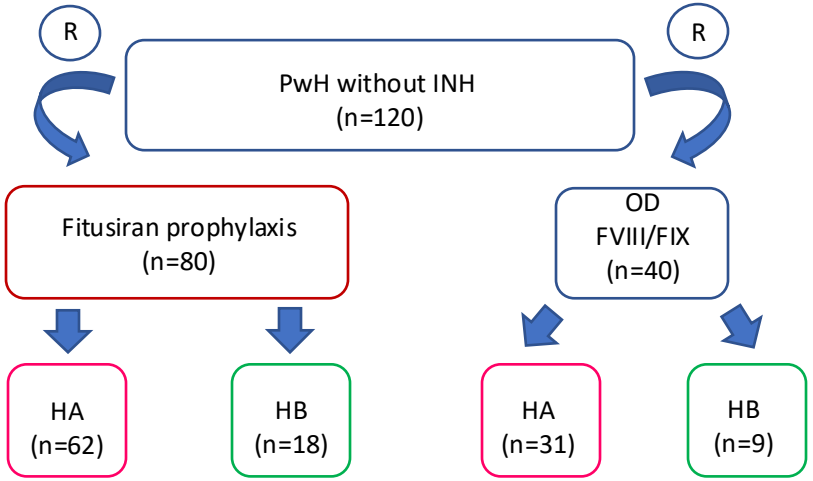
Pasi J et al. NEJM 2017;377:819-28



- ✓ Clear guidance on concomitant hemostatic treatment (low dose)
- ✓ To minimize thrombotic risk AT levels should be maintained between 15 and 35%
- ✓ ***March 2025: FDA approval for HA and HB ≥ 12 yrs***

Fitusiran Phase 3 Study in PwH with and without inhibitors





- Median exposure to fitusiran: 252 days (203-271)
- AESI: ALT/AST increase >> 24% (within 60 days from Rx onset)
- ***Cholecystitis or cholelithiasis: 6 patients***
- **4 thrombotic events in 2 pts >> AT levels: 7.8-11.6%**

- Median follow-up: 7.8 months
- AESI: ALT/AST increase >> 19% (within 60 days from Rx onset)
- ***Cholecystitis or cholelithiasis: 3 patients***
- No thrombotic events

Young G et al. Lancet 2023; 401: 1427-37

Srivastava A et al. Lancet Haematol 2023; 10: e322-32

Benefits of NRT

- *Prophylaxis for inhibitor patients*
- *Favor prophylaxis implementation in non-inhibitor patients with limited compliance and adherence*
- *Subcutaneous route of administration*
- *Consistent PK/PD profile*
- *Standard treatment protocols*

Drawbacks of NRT

- *Increased thrombotic risk*
- *Need for additional hemostatic agents in case of bleed/trauma/surgery*
- *Little room for treatment individualization*
- *No routine lab tests to measure specific activity*
- *Unknown long-term impact on joint health*

Terapia sostitutiva

- Via endovenosa
- Ogni 2-7 gg/7-21 gg (FVIII/FIX), laboratorio utile nei senza inibitori
- Picchi e valli
- By-passing in presenza di inibitori
- Emostasi «fisiologica»
- Profilassi e trattamento
- Prevenzione del danno articolare

Terapie non sostitutive

- Iniezioni sottocutanee
- Una volta al giorno; ogni 7, 14 o 28 gg, test cromogenico per valutazione Fattore e inibitore in emicizumab
- Plateau
- Efficaci in presenza di inibitori
- Generazione di trombina
- Solo per profilassi
- Impatto sulla salute articolare lungo termine non noto