Nuove opportunità terapeutiche per l’emofilia

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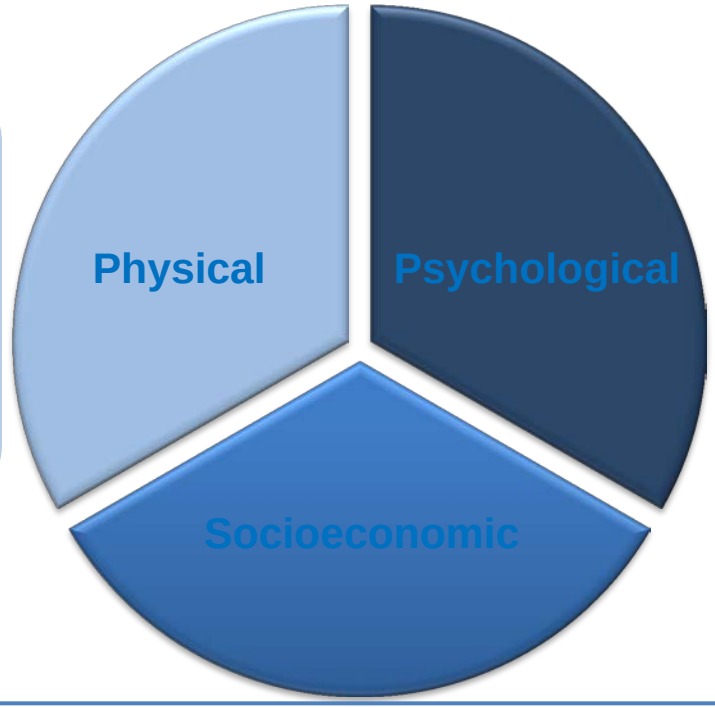
SISET SOCIETA' ITALIANA PER LO STUDIO DELL'EMOSTASI E DELLA TROMBOSI

The long-term impacts of haemophilia A

- Development of haemophilic arthropathy can lead to disability [1,2]
- Venous access complications (due to life-long treatment with IV medication)[3]
- Adult life expectancy 5 years less than non-haemophiliac [4]

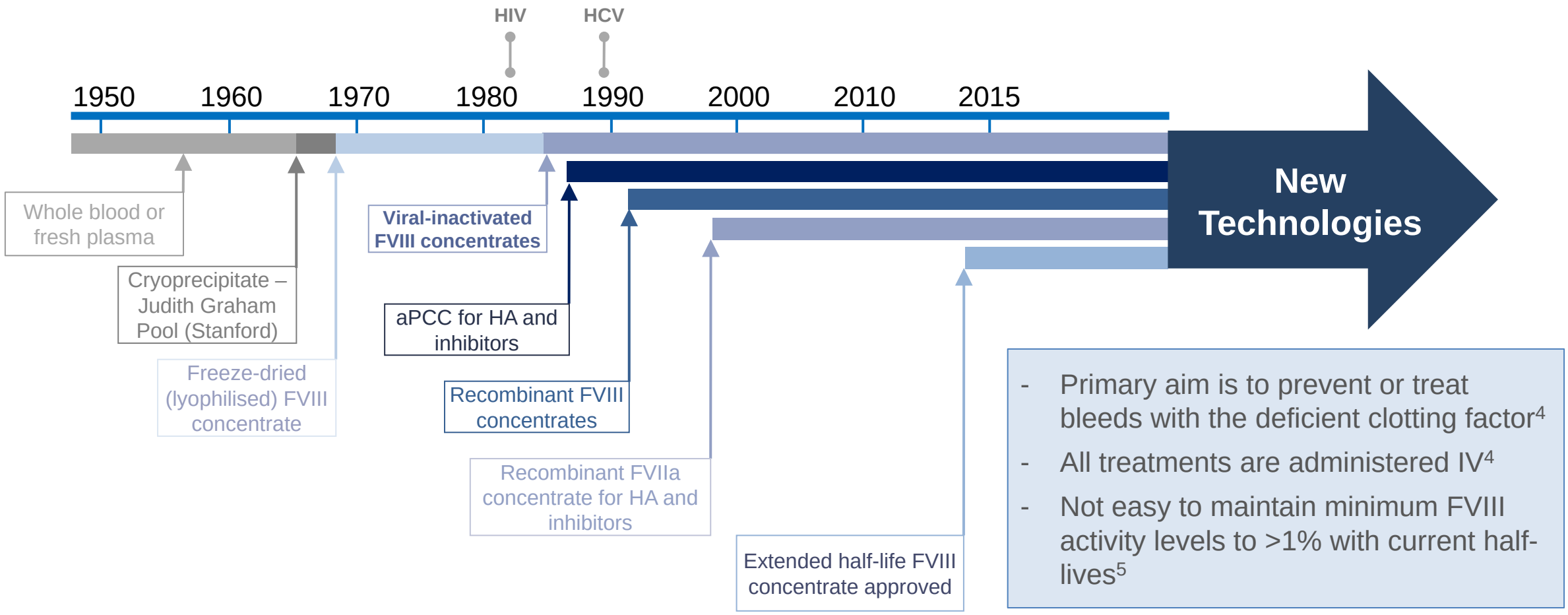


- Psychological impacts vary with life stage [5,6]
- Coping strategies and emotional reactions to a life-restricting illness vary by person [7]

- Life-long treatment funding required[8,9]
- Drug costs make up 95% of overall cost[10]
- 60% of non-drug costs are indirect (work lost and caregiver burden)[8]
- **Inhibitor development and comorbidities such as HIV/HCV can hugely increase costs[11]**

[1] Rosendaal et al, Haemophilia 2006;12(Suppl3):117-21; [2] Morfini M. Haemophilia 2008; 14(S6): 20–2; [3] Srivastava A, Haemophilia 2013; 19(1): e1-e47; 9: Suppl 1:1-4; [4] Mauser-Bunschoten EP et al. Haemophilia 2009;15:853–63; [5]Coppola et al Haemophilia 2011;17:21-7; [6] Iannone et al Haemophilia 2012;18:868-74; [7] Wiedebusch et al Haemophilia 2008;14:1014-22; [8] Abbonizio et al Haemphilia 2014;20:e243-e250; [9]Coppola et al Haemophilia 2017;1-8; [10] O'Hara et al Orphanet J Rare Dis. 2017;31:12:106; [11] Rocha P, et al. BMC Health Serv Res 2015;15:484

Haemophilia A: evolution of modern treatments[1,2,3]



- Primary aim is to prevent or treat bleeds with the deficient clotting factor[4]
- All treatments are administered IV[4]
- Not easy to maintain minimum FVIII activity levels to >1% with current half-lives[5]

FVIII, factor VIII; aPCC, activated prothrombin complex concentrated; HA, Haemophilia A; FVIIa, activated factor VII; HCV, hepatitis C virus; HIV, human immunodeficiency virus

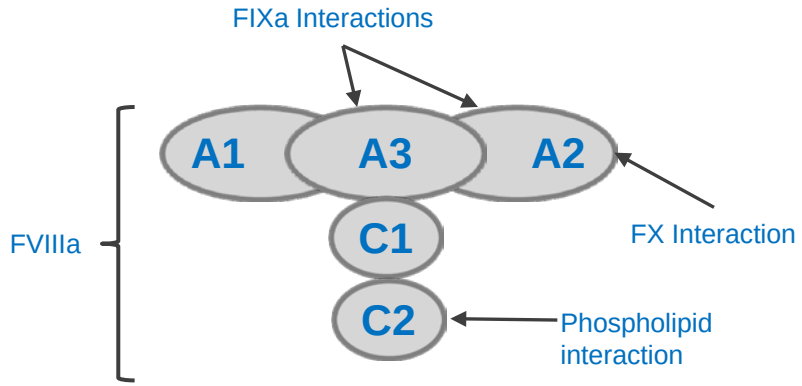
[1] Franchini M et al Blood Rev 2013;27:179–84; [2] Berntorp E et al. Lancet 2012;379:1447–56; [3] Peyvandi F et al. Lancet 2016;388:187-97; [4] Srivastava A Haemophilia 2013,19:e1-e47; [5]Jiménez-Yuste et al - *Blood Transfus 2014*

Inhibitor development:

the most serious complication of current FVII replacement therapies

- Therapy with purified FVIII may lead to the development of **neutralising anti-FVIII antibodies (inhibitors)** [1,2]
- Inhibitors bind to FVIII and significantly reduce the effectiveness of FVIII treatment[3]
- Cumulative incidence (i.e. lifetime risk) of inhibitor development is 20-30% in severe disease and 5-10% in moderate or mild disease[4]
  - Median age of inhibitor development: 3 years or less (severe disease) [4]
  - The majority of inhibitors develop within the first 50 days of treatment [5]

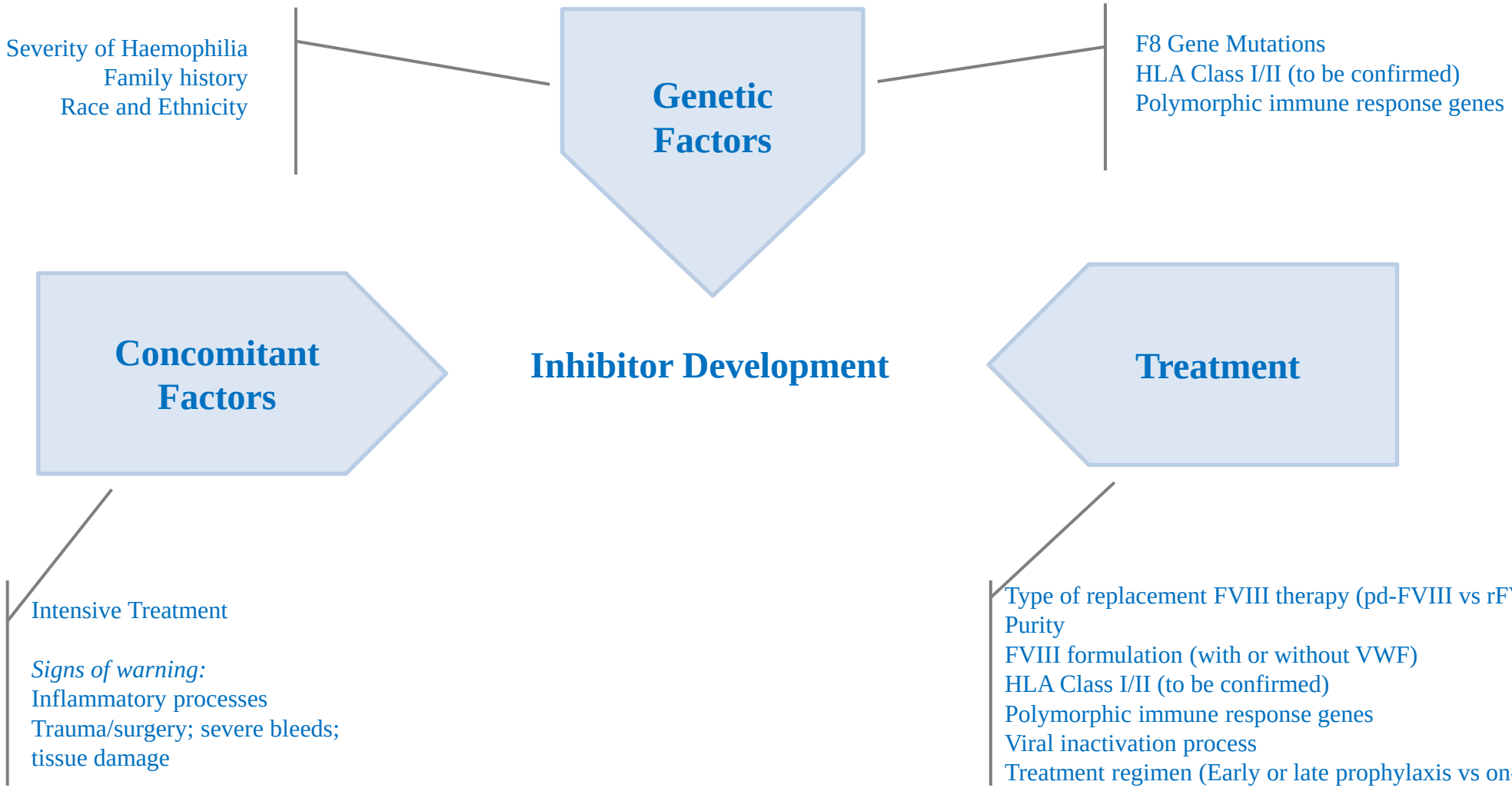
Mechanism of FVIII Inhibitor Action [6]



F, factor.

[1]Astermark J. Blood 2015; 125(13): 2045-2051; [2] Berntorp E, Shapiro AD. Lancet 2012; 379(9824): 1447-5146; [3]Whelan SF, et al. Blood 2013; 121(6): 1039-1048; [4] Srivastava A, Haemophilia 2013;19:e1-e47; [5] Wight et al, Haemophilia 2003;8:418-35; [6] Graphical elaboration from Scandella D. Vox Sang. 1999;77(suppl1):17-20

Risk Factors for development of FVIII inhibitors[1,2]



F, factor; HLA, human leukocyte antigen; vWF, von Willebrand factor; pd, plasma derived; r, recombinant

[1] Castaman G et al. Semin Thromb Hemost. 2016 Jul;42(5):507-12;
[2]Astermark J Blood 2015;125:2045-51.

Treatment approaches in patients with inhibitors[1]

	BLEEDING CONTROL	INHIBITORS ERADICATION *(Immune Tolerance Induction)*
Product	• High dose of factor FVIII replacement therapy • Porcine factor FVIII • Bypassing agents - Prothrombin complex concentrates (aPCC) - Recombinant factor VIIa (rFVIIa)	• High dose of purified FVIII or VWF-containing FVIII concentrates
Aim	• To manage bleeding episodes → **on demand** • To decrease frequency of bleeding episodes and improve QoL → **prophylaxis**	• To render the immune system tolerant to exogenous FVIII • Successful in 70–80% of hemophilia A patients [2]

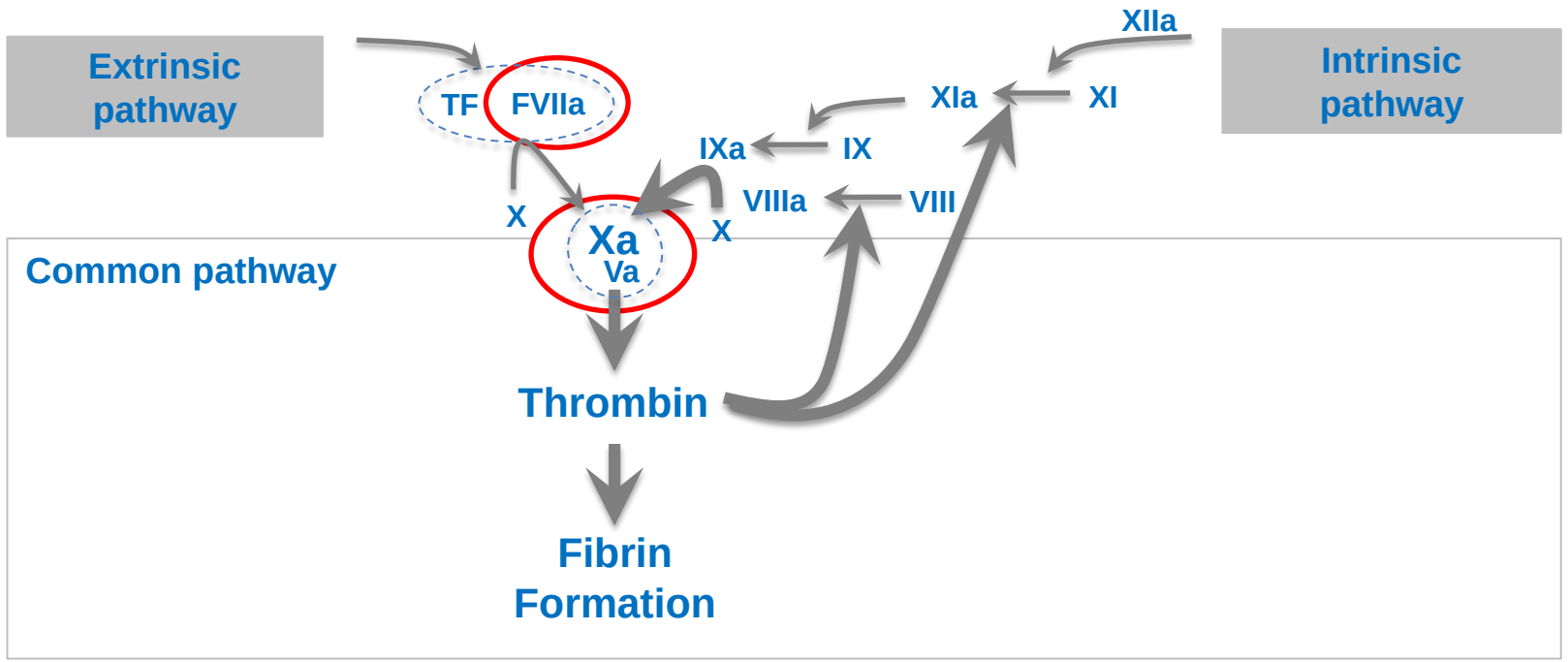
aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII; ITI, Immune Tolerance Induction

[1] Franchini M, Mannucci PM Blood Rev 2013;27:179-84;
[2] Valentino LA, et al. Haemophilia 2015; 21(5):

Bypassing agents in patients with inhibitors [1,2]

aPCC	Source: **pooled human plasma** → containing activated FII, FVII, FIX, FX and small amounts of FVIII → Varying half-life for the single components
rFVIIa	Source: **recombinant FVIIa** → activates factors IX and X, which leads to the formation of small initial amount of thrombin → Half-life 2.3 h (range 1.7–2.7)

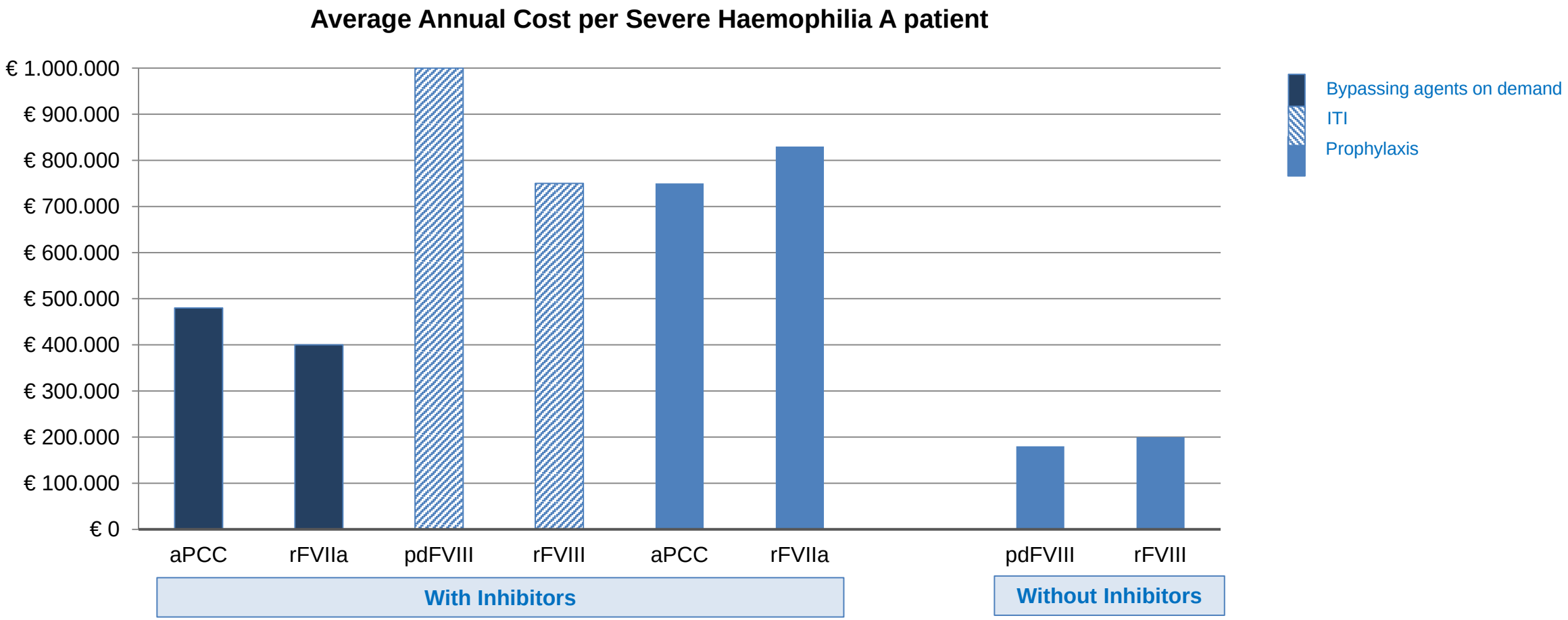
→ **Thrombin**



aPCC, activated prothrombin complex concentrate; FVIII, factor VIII; rFVIIa, activated recombinant factor VII; FII, factor II; FIX, factor IX; FX, factor X.

[1] Butenas S, et al. Blood. 2002; 99(3): 923–930;
[2] Rocino et al J Clin Med. 2017 Apr 17;6(4).
Figure adapted from Achneck et al. Circulation 2010;122:2068–2077

Inhibitors development can hugely increase costs[1]



aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII; ITI, Immune Tolerance Induction

[1] Graphical elaboration from Abbonizio et al., Haemophilia. 2014 Jul;20(4):e243-50.

Unmet needs with current Haemophilia A therapies

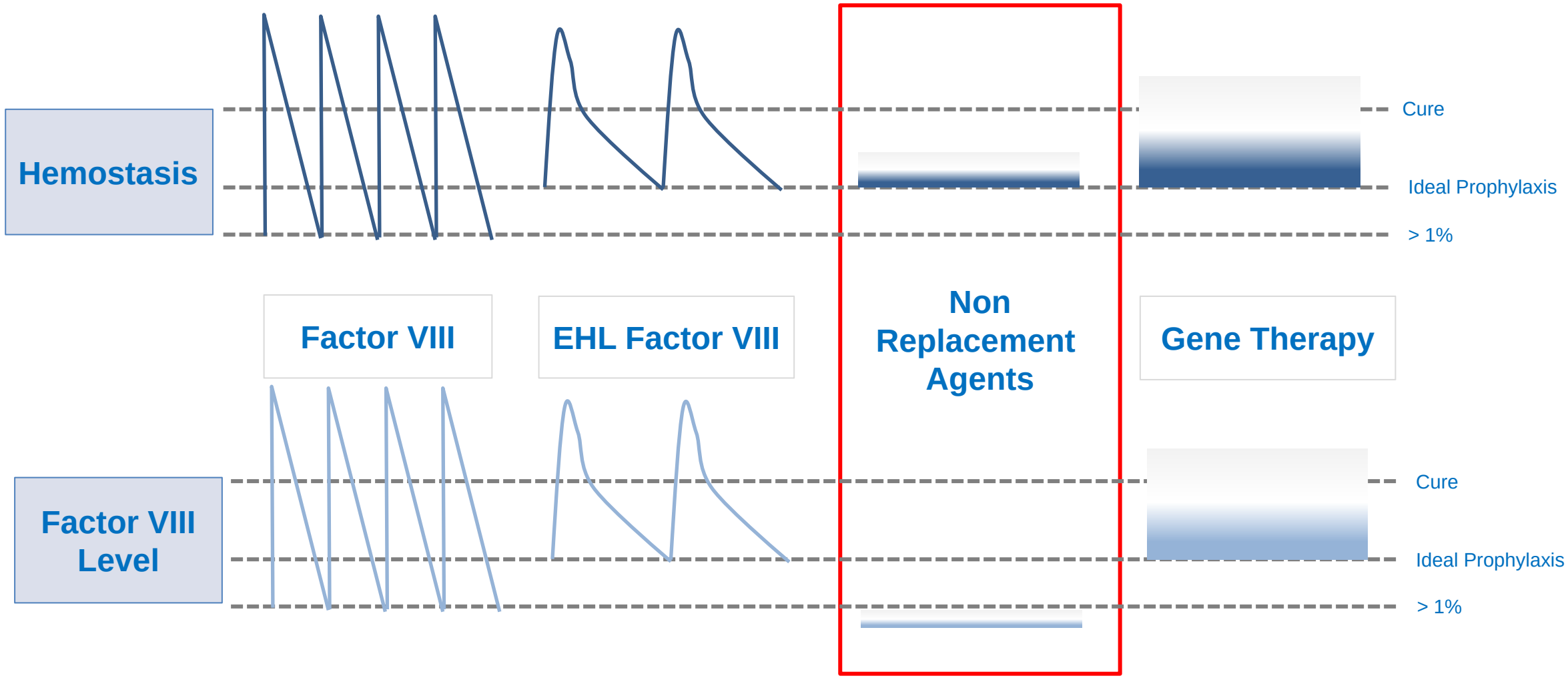
PwHA with inhibitors	PwHA without inhibitors
Burden of treatment *(IV administration; frequent dosing)*[1,2]	
High ABR, even in prophylaxis [3,4,5]	
Bleeding episodes more difficult to treat[6,7]	**Reduced protection during 'troughs'**[8]
Limited options for prophylaxis[6,7]	Risk of developing FVIII inhibitors[9]
Long-term disability due to repeated joint bleeds[10]	**Not easy to maintain trough FVIII activity levels to >1% with current treatments**[8]
ITI complications *(i.e. CVAD infections)* [11]	Adherence issues with prophylactic FVIII[12]
ITI not successful in all cases[13]	

How is clinical research trying to solve these unmet needs?

PwHA, persons with haemophilia A; IV, intravenous; ABR, annualized bleeding rate FVIII, factor VIII; ITI, immune tolerance induction

[1] Srivastava A, Haemophilia 2013; 19(1): e1-e47; [2] Berntorp E, Haemophilia 2003; 9: Suppl 1:1-4; [3]Mahlangu J, Blood 2016 128:3800 Abstract, [4]Mahlangu J, ISTH 2017, [5]Oldenburg J, Haemophilia 2017,23 11-27; [6] Berntorp E, Haemophilia 2006;12 (S6):1–7, [7] Kempton et al, Blood 2014;124:3365-3372; [8]Jiménez-Yuste et al - *Blood Transfus 2014; **12**: 314-9;* [9]Astermark J Blood 2015;125:2045-51; [10]Morfini M. Haemophilia 2008; 14(S6): 20–2; [11] Rodriguez V Haemophilia (2015), 21, e369–e374; [12]Schrijvers LH Haemophilia (2013), 19, 355–361; [13]Valentino A et al Haemophilia 2015;21:559-567

New strategies for Haemophilia A[1]



These compounds and their uses are investigational and have not been approved or licensed for any medical condition. The efficacy and safety of these molecules have not been established yet and are currently being evaluated

EHL, Extended Half Life

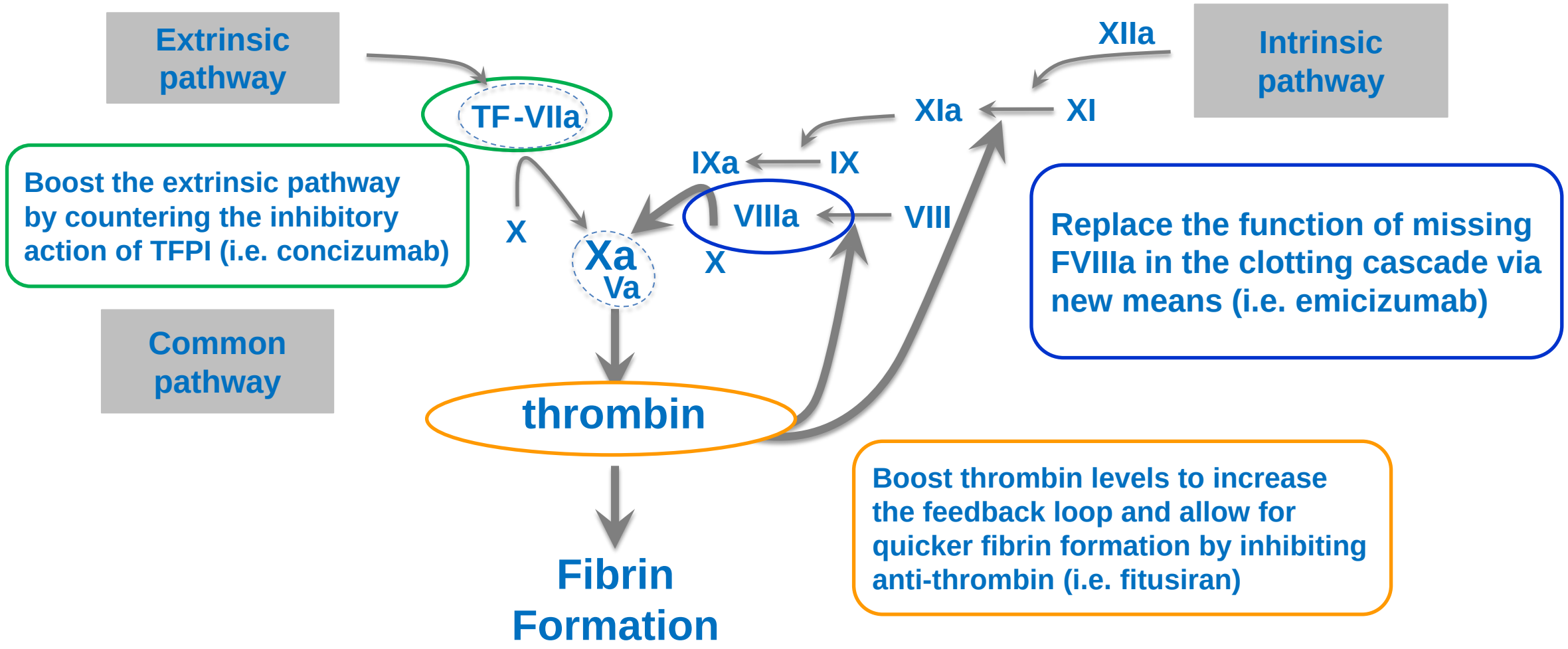
Graphical elaboration from Arruda V et al, Blood 2017 Oct 10 [Epub ahead of print]

New non-factor replacement therapy for haemophilia

	Product		
	Emicizumab	**Fitusiran**	**Concizumab**
Manufacturer	Chugai Pharmaceutical/ Hoffman-La Roche	Alnylam Pharmaceuticals	Novo Nordisk
Technology	Chimeric bispecific humanised antibody	siRNA	Humanised monoclonal antibody
Mechanism of action	FVIIIa-mimetic	Antithrombin inhibition	TFPI inhibition
Dosing frequency	Weekly	Weekly to monthly	To be determined
Route of administration	SC	SC	SC
Stage of development	FDA approved	Phase II-III	Phase II

siRNA: short interfering RNA; TFPI: tissue factor pathway inhibitor; SC: subcutaneous; IV: intravenous; FDA: Food and Drug Administration.

Non-replacement approaches for Haemophilia A [1]



These compounds and their uses are investigational and have not been approved or licensed for any medical condition. The efficacy and safety of these molecules have not been established yet and are currently being evaluated

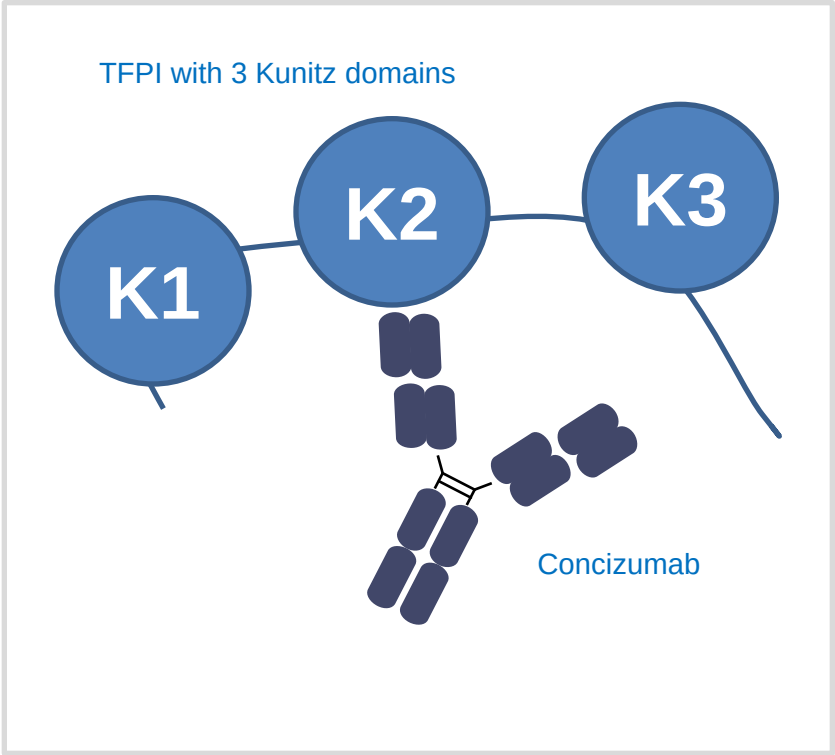
FVIIIa, activated factor VIII; TFPI, tissue factor pathway inhibitor; mAb, monoclonal antibody

Figure adapted from Achneck et al. Circulation 2010;122:2068–2077

[1] Hartmann J, Croteau S Am J Hematol 91:1252-1260, 2016

Concizumab: a mAb against TFPI

- Humanized monoclonal antibody
  - High-affinity for the KPI-2 domain of TFPI [1]
- Blockage of the KPI-2 domain prevents TFPI binding to FXa and FVIIa/TF
  - downregulation of TFPI inhibition of the coagulation cascade that allows thrombin generation via FXa/TF/FVIIa [2]
- Phase I data (Explorer™ 3):
  - no safety concerns preventing further development, confirmation of PK/PD relationship for Concizumab dose, unbound plasma TFPI and TG [3]
- Currently under investigation, daily SC administration [4,5]

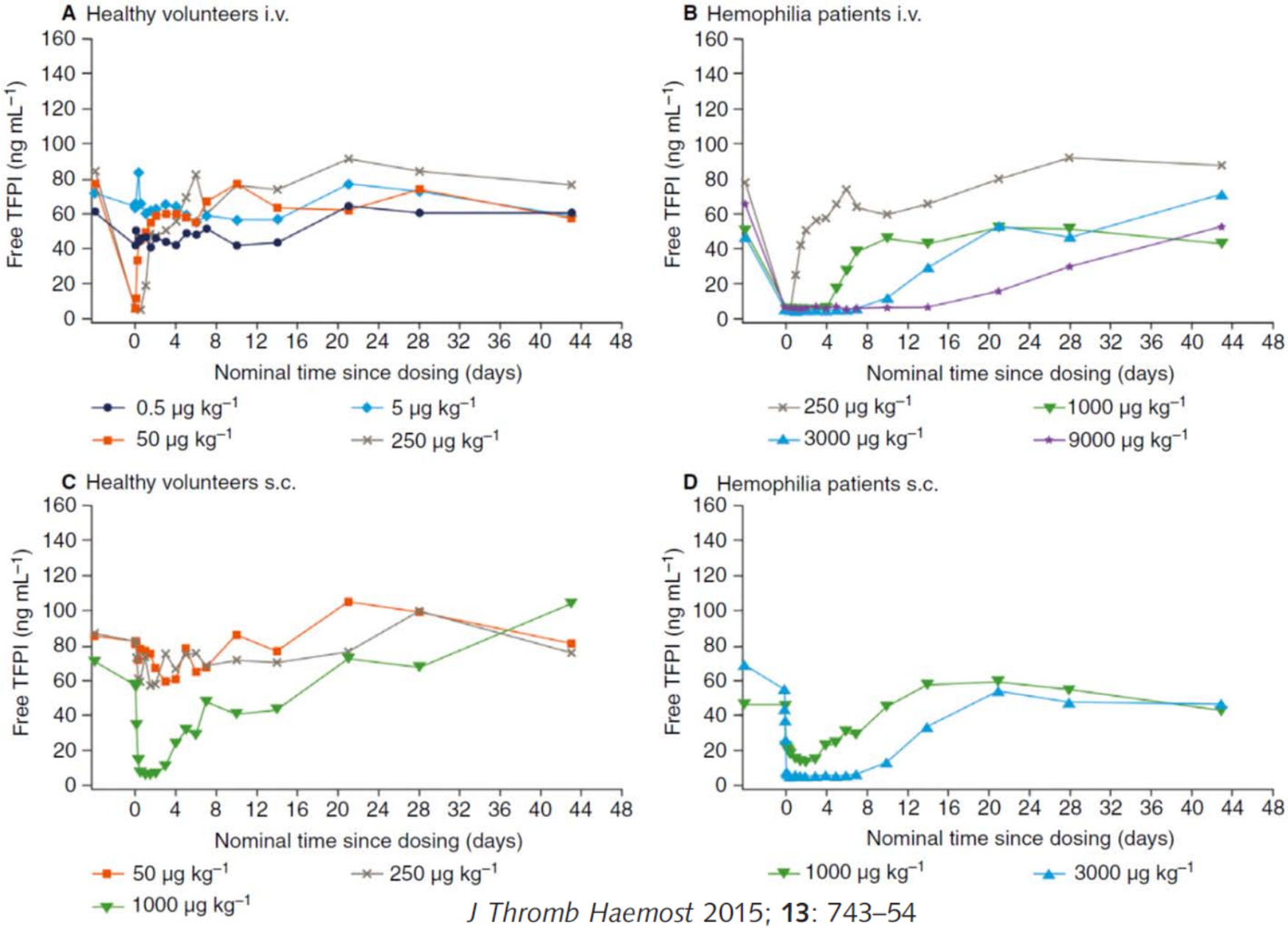


mAb, monoclonal antibody; TFPI, Tissue factor pathway inhibitor; KPI-2, Kunitz-type Protease Inhibitor domain 2; Fxa, activated Factor X; FVIIa, activated Factor VII; TF, Tissue Factor; phI Phase I.

[1] Hilden I et al Blood 2012;119:5871-8; [2]Chowdary P et al JTH 2015, [3] Eichler H et al ISTH 2017, [4]NCT03196284, [5]NCT03196297

Figure adapted from Chowdary P et al JTH 2015

Concizumab: a mAb against TFPI



J Thromb Haemost 2015; **13**: 743–54

Concizumab: a mAb against TFPI

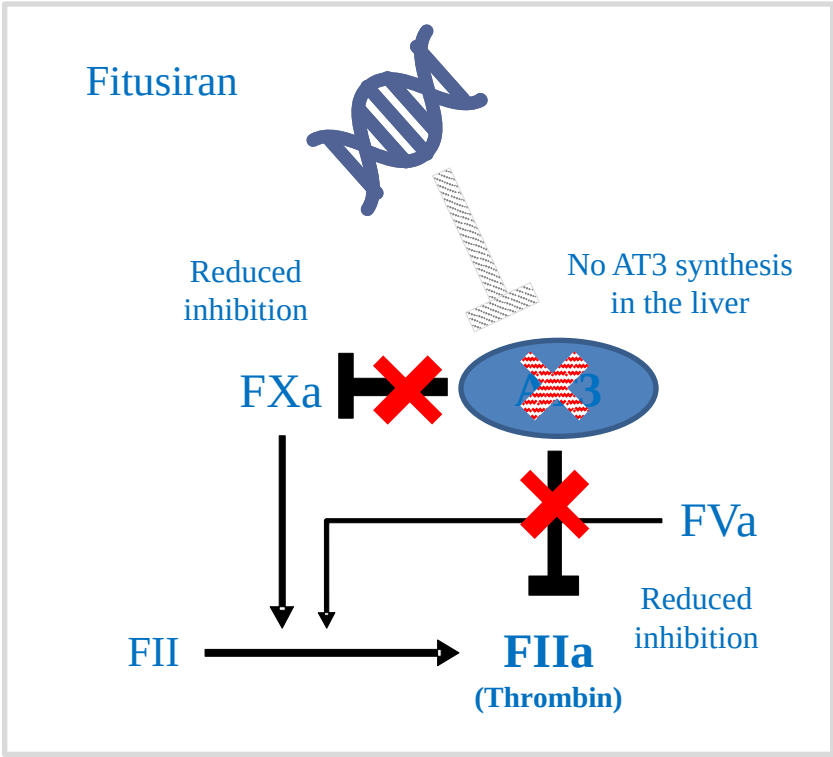
Two phase II trials evaluating the safety and efficacy of prophylactic administration of concizumab in haemophilia A and B with (Explorer™4, NCT03196284) and without (Explorer™5,NCT03196297) inhibitors are currently ongoing.

Fitusiran: an RNAi agent targeting antithrombin

- Investigational RNA interference (RNAi) agent
  - Designed to suppress liver production of antithrombin;
  - Targets antithrombin messenger RNA (encoded by SERPINC1)[1,2]

- Phase I/II study (OLE) exploratory post-hoc analysis of bleed events[3]
  - Median ABR: 1 (pts. without inhibitors)
  - Median ABR: 0 (pts. with inhibitors)
  - Majority of AEs mild or moderate, asymptomatic ALT increases in HCV Ab+ patients; chronic HCV patients not included in Phase III program unless cured

- Company has recently communicated the suspension of Fitusiran dosing due to a thrombotic event [4]



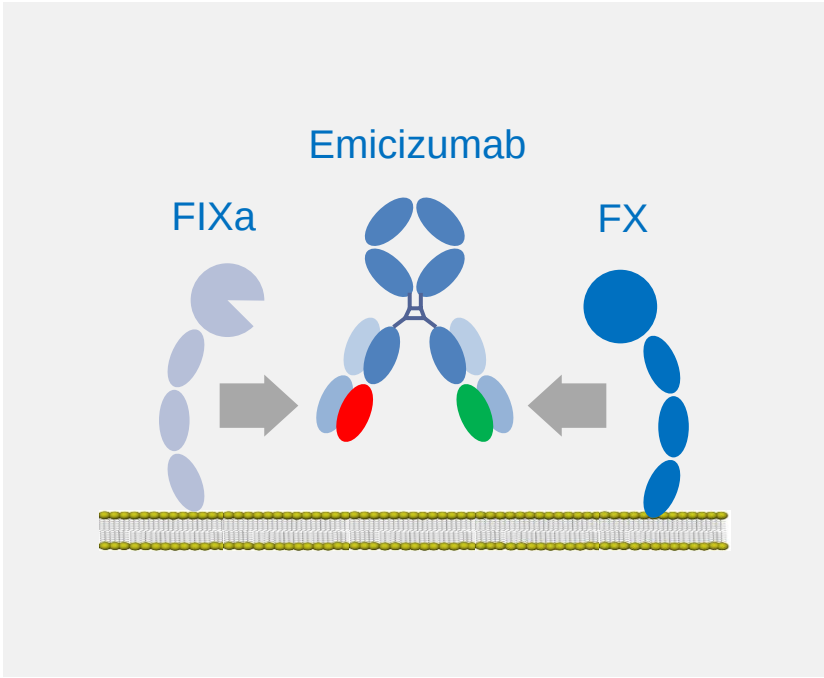
RNAi, RNA interference; SERPINC1, Serpin Family C Member 1; OLE, open label extension; ABR, annualized bleeding rate; AE, adverse event; ALT, alanine aminotransferase; HCV, hepatitis C virus; SC, sub-cute; AT, antithrombin; FXa, activated Factor X; FVa, activated Factor V; FII, Factor II; FIIa, activated Factor II

[1] Sehgal A et al Nat Med 2015;21:492-7; [2] Pasi KJ et al NEJM 2017; [3] Pasi KJ et al, abstract ISTH 2017; [4] http://investors.alnylam.com/releases.cfm [Accessed 18 Oct 2017]

Figure adapted from Sehgal A et al Nat Med 2015;21:492-7

Emicizumab: a humanised bispecific antibody

- Designed to bridge FIXa and FX [1]
- Promotes the coagulation by replacing the haemostatic function of missing FVIIIa [1]
- Half-life of 4–5 weeks [2]
- Administered by weekly subcutaneous injection or less frequently [2, 3]
- Not neutralised by anti-FVIII antibodies (inhibitors)[4]

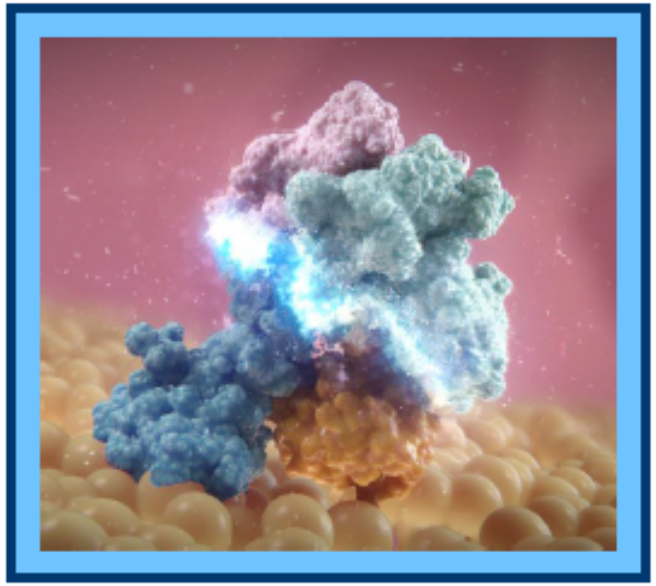


F, factor; a, activated.

[1] Kitazawa T, et al. Nat Med 2012; 18(10): 1570-1574; [2]Uchida N, et al. Blood 2016; 127(13): 1633-1641;
[3] https://clinicaltrials.gov/ct2/results?cond=&term=emicizumab&cntry1=&state1=&recrs= [Accessed 18 Oct 2017];
[4]Shima M, et al. N Engl J Med 2016; 374(21): 2044-2053

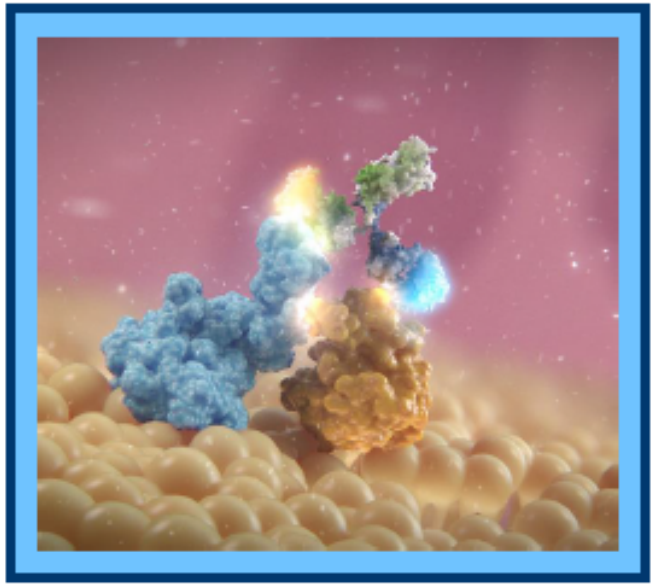
Emicizumab MoA compared with FVIII

Factor VIII



- Where sufficient FVIII is present, it will bind with thrombin to become activated (FVIIIa)
- This FVIIIa then binds with FIXa to form the tenase complex on the surface of platelets
- The complex then binds with FX to allow its activation by FIXa
  - this part of the coagulation cascade can not occur in the absence of FVIII

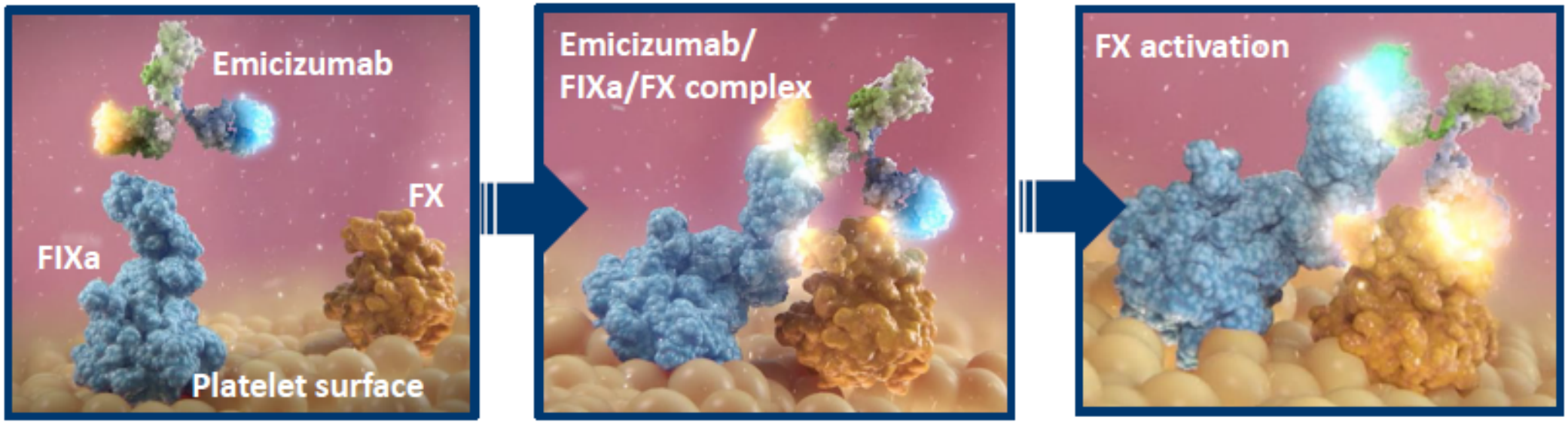
Emicizumab



- As a bispecific, monoclonal antibody, emicizumab replaces the haemostatic function of FVIII by binding to FIXa and FX, which allows the coagulation cascade to continue normally
- FVIII inhibitors do not bind to or neutralise emicizumab, therefore have no impact on its haemostatic activity

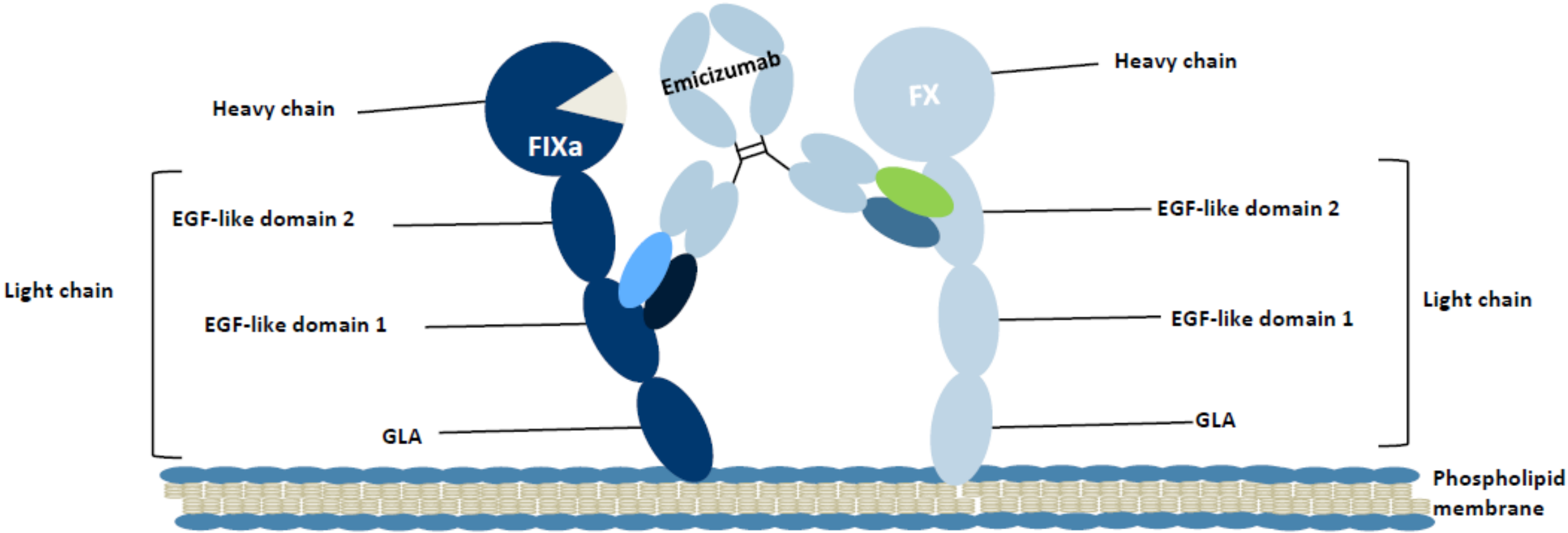
a, activated; F, factor; MoA, mechanism of action

Emicizumab MoA



- As a bispecific monoclonal antibody, emicizumab replaces the action of FVIIIa by binding with both FIXa and FX to bring them close enough to allow the activation of FX by FIXa
- This triggers the activation of the rest of the coagulation cascade, restoring normal clotting function

Emicizumab MoA: binding sites



Emicizumab binds the EGF-like domain 1 on FIXa and the EGF-like domain 2 on FX

- EGF, endothelial growth factor; GLA, gamma-carboxyglutamic acid

- Kitazawa T, et al. Thromb Haemost 2017;117:1348–57

Emicizumab: Clinical Development Plan in Haemophilia A[1,2]

Phase I/II studies

- **ACE001JP** – *Phase I, cohort A+B healthy Volunteers (N=40) single dose*
- **ACE001JP + ACE002JP** – *Phase Ib/II, cohort C and extension PwHAwI + PwHA (**N=18**)*

Phase III program

- **NON INTERVENTIONAL STUDY** – *Patients ≥ 2 years (N=221) prospective, Standard of Care* [3]
- **HAVEN 1** – *Patients ≥ 12 years (**N=113**) weekly dosing* [4]
- **HAVEN 2** – *Children <12 years (**N=60**) weekly dosing* [5]
- **HAVEN 3** – *Patients ≥ 12 years (**N=145**) weekly + every 2 weeks dosing*
- **HAVEN 4** – *Patients ≥ 12 years (**N=48**) monthly dosing*

Phase IIIb study

- **STASEY** – *Patients ≥ 12 years (**planned N=200**) weekly dosing*

HA, haemophilia A
SC, subcute

✓ Healthy volunteers ✓ Inhibitors Patients ✓ Non - Inhibitors Patients

[1]https://clinicaltrials.gov/ct2/results?cond=&term=emicizumab&cntry1=&state1=&recrs= [Accessed 17 Oct 2017];
[2]http://www.clinicaltrials.jp/user/cteDetail_e.jsp [Accessed 17 Oct 2017];
[3] Mahlangu J, et al. ISTH 2017 (abstract PB 1784); [4]Oldenburg J NEJM 2017, [5]Young et al ISTH 2017

The NEW ENGLAND JOURNAL of MEDICINE

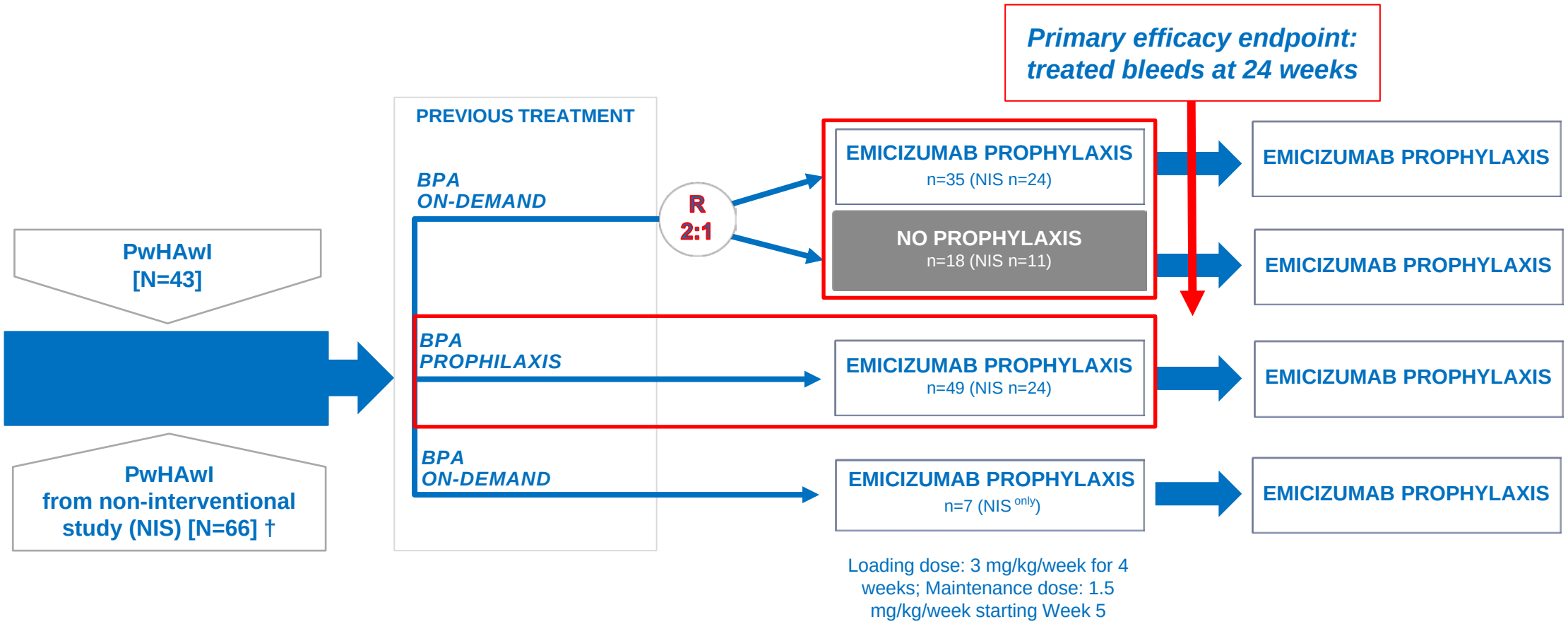
ESTABLISHED IN 1812 AUGUST 31, 2017 VOL. 377 NO. 9

Emicizumab Prophylaxis in Hemophilia A with Inhibitors

Johannes Oldenburg, M.D., Ph.D., Johnny N. Mahlangu, M.D., Benjamin Kim, M.D., Christophe Schmitt, Pharm.D., Michael U. Callaghan, M.D., Guy Young, M.D., Elena Santagostino, M.D., Ph.D., Rebecca Kruse-Jarres, M.D., M.P.H., Claude Negrier, M.D., Ph.D., Craig Kessler, M.D., Nancy Valente, M.D., Elina Asikanius, M.Sc., Gallia G. Levy, M.D., Ph.D., Jerzy Windyga, M.D., and Midori Shima, M.D., Ph.D.

HAVEN 1[1,2]

A randomized phase III study in people with Haemophilia A with Inhibitors (≥ 12 years)

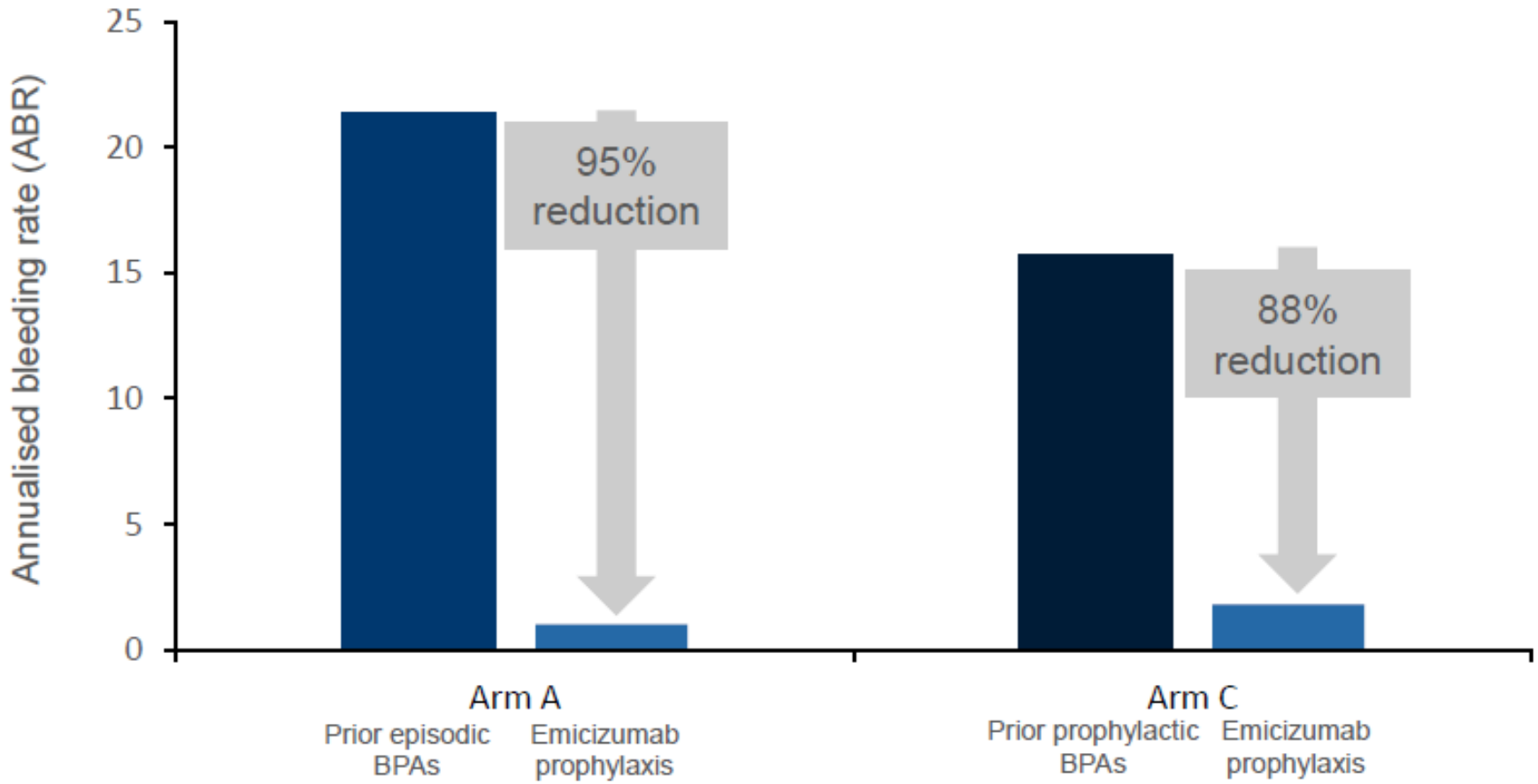


†patients previously in the NIS (NCT02476942) and entering Arms A or C of HAVEN 1 permitted an intra-individual comparison of outcomes on emicizumab prophylaxis vs their prior BPA treatment (episodic for Arm A, prophylactic for Arm C);

PwHAwI, persons with haemophilia A with Inihibitors; BR, bleeding rate; NIS, non-interventional study; R, randomization; QW, every week; SC, subcutaneous; BPA, bypassing agent, ; Haem-A-QoL=Haemophilia A-Specific Quality of Life; EQ-5D-5L=European quality of life-5 Dimensions-5 levels

[1] https://clinicaltrials.gov/ct2/show/NCT02622321?term=emicizumab&rank=5 [Accessed 18 October 2017]; [2] Oldenburg J, et al. N Engl J Med 2017; 377(9):809-818.

Comparison of ABR vs prior BPA treatment* (September 8 2017 cut-off)



*Comparison with data obtained from the NIS
BPAs, bypassing agents; NIS, non-interventional study

- Mancuso ME et al. ASH 2017; poster 1071

Health-related quality of life and health status: randomised comparison[1]

Measure	Number of patients (Arm B/Arm A)	Clinically meaningful difference[2,3,4]	Difference in adjusted means (95% CI) (Arm B vs Arm A)	P-value
Haem-A-QoL *(in patients aged ≥18 years)*				
Total score	14/25	+10 points	14.01 (5.56; 22.45)	**0.0019**
Physical health score	14/25	+7 points	21.55 (7.89; 35.22)	**0.0029**
EQ-5D-5L				
Visual analogue scale	16/30	–7 points	–9.72 (–17.62; –1.82)	**0.0171**
Index utility score	16/30	–0.07 points	–0.16 (–0.25; 0.07)	**0.0014**

Statistically significant, clinically meaningful improvements in HRQoL and health status with emicizumab prophylaxis vs no prophylaxis.

1. Oldenburg J, et al. ISTH 2017; 2.Wyrwich KW, et al. Haemophilia 2015; 21(5): 578-584; 3. Walters SJ, et al. Qual Life Res 2005; 14(6): 1523-1532; 4. Pickard AS, et al. Health Qual Life Outcomes 2007; 5: 70.

HAVEN 1: overall safety with emicizumab (all arms)

	Total (N=103)
Total number of adverse events (AEs), n	198
Total patients with ≥1 AE, n (%)	73 (70.9)
Serious AE*	9 (8.7)
Thrombotic microangiopathy (TMA)**	3 (2.9)
Thrombotic event	2 (1.9)
Death**	1 (<1)
AEs leading to withdrawal	2 (1.9)
Grade ≥3 AE	8 (7.8)
Related AE	23 (22.3)
Local injection site reaction	15 (14.6)

*Additional serious AEs included one event each of: iron deficiency anaemia, sepsis, haemarthrosis, muscle hemorrhage, gastric ulcer hemorrhage, headache and hematuria.
**TMA/thrombotic events only occurred with aPCC treatment averaging >100 U/kg daily for ≥24 hours
- aPCC contains activated and non-activated coagulation factors, including FII, FVII, FIX and FX, which can accumulate with repeat dosing
- Risk may be mitigated with clear dosing guidance
- No further SAEs of TE/TMA in >350 patients treated in emicizumab development program to date
- Third TMA event occurred after primary data cut-off; patient also experienced fatal rectal hemorrhage, considered unrelated to emicizumab, patient refused blood products and TMA was resolving at the time of aPCC cessation.

Two additional withdrawals not related to AEs; one withdrawal by patient, one withdrawal due to physician decision

AE, adverse events

Oldenburg J, et al. N Engl J Med 2017; 377(9):809-818

HAVEN 1: Study Conclusions[1]

Primary and secondary endpoints were met

- Reduction in bleed rates of **87%** vs no prophylaxis (Arm A vs Arm B)
- Majority of patients **(67.3%)** on emicizumab prophylaxis had zero treated bleeds
- Intra-patient comparison showed a **79%** reduction in bleed rates vs prior prophylactic BPAs (Arm C)
- Significant reductions in bleed rates for all bleeds as well as treated spontaneous, joint, and target joint bleeds
- Clinically meaningful benefits on patients' HRQoL and health status

Emicizumab had an acceptable safety profile

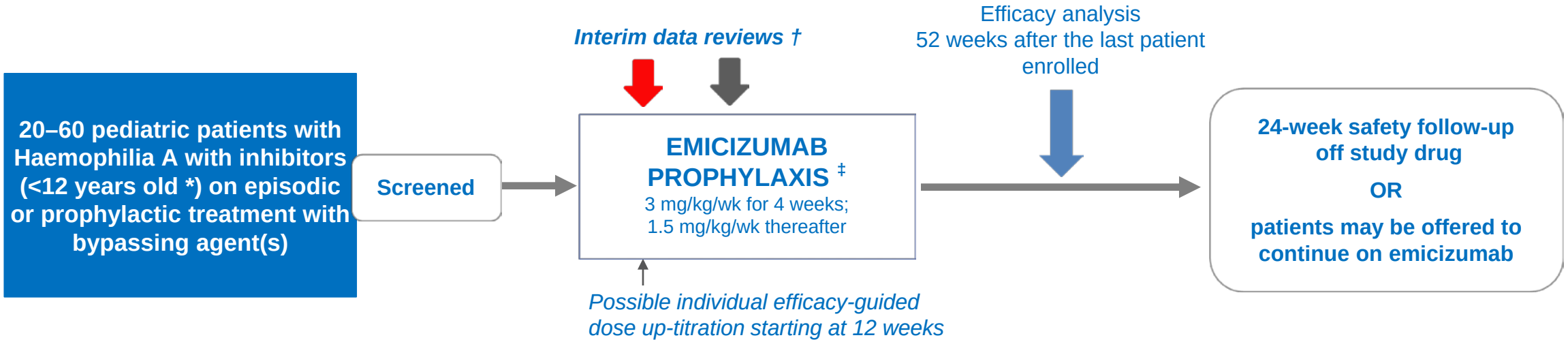
- Most AEs were mild to moderate, with injection site reactions being the most common AE
- Commonality between all cases of thromboembolic events and TMA is that they occurred in people who were on emicizumab prophylaxis and received more than 100 U/kg/day of the BPA aPCC on average for 24 hours or more before the onset of the event
- Neither thromboembolic event required anti-coagulation therapy and one individual restarted emicizumab. The cases of TMA observed were transient, and one patient restarted emicizumab
- No neutralizing ADAs were detected

BPA=bypassing agent; HRQoL=health-related quality of life; AE, adverse event; TE, thromboembolic; TMA, thrombotic microangiopathy; BPA, bypassing agent; aPCC, activated prothrombin complex concentrate; ADA=anti-drug antibody.

[1] Oldenburg J, et al. N Engl J Med 2017; 377(9):809-818

HAVEN 2, preliminary results [1]

A single-arm phase III study in people with Haemophilia A with Inhibitors (<12 years)



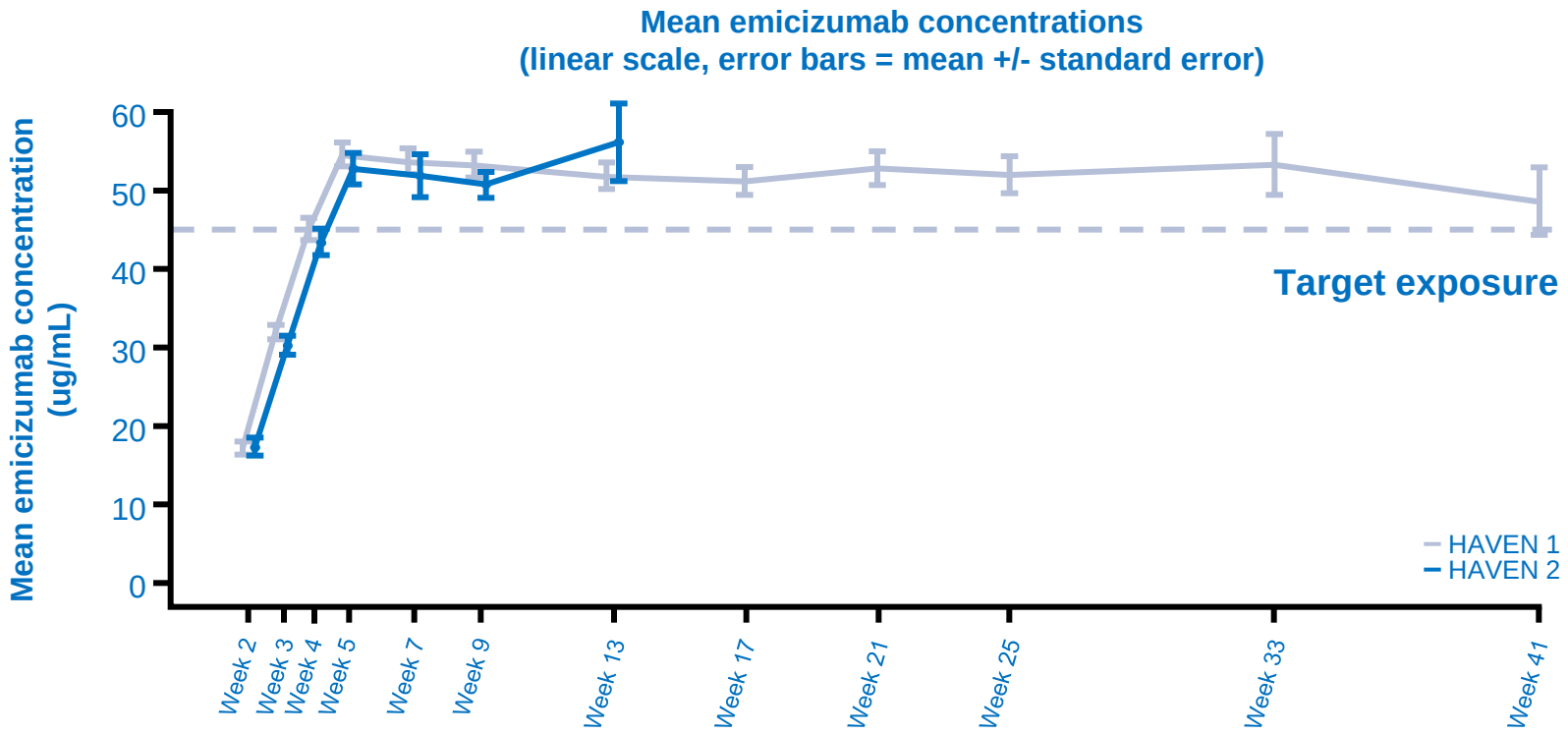
Study objectives	No formal hypothesis testing
Efficacy	Bleeding Rate (treated, all, treated spontaneous, treated joint and treated target joint); intra-patient bleed rate comparison (vs NIS); HRQoL; aspects of caregiver burden
PK	Emicizumab exposure characterisation

* With allowance of patients 12–17 years old who weigh <40 kg;
† For evaluation of starting dose (first 20 patients) and determination of whether dose modification is needed;
‡ Paediatric dosing regimen selected to target a similar C_{trough} to adult population with uncertainty of maintenance dose due to potential effects of body weight and clearance maturation. Loading dose: 3 mg/kg/week for 4 weeks; Maintenance dose: 1.5 mg/kg/week starting Week 5

BR, bleeding rate; HRQoL, health-related quality of life; NIS, non-interventional study; PK, pharmacokinetics

[1] Available at https://clinicaltrials.gov/ct2/show/NCT02795767?term=emicizumab&rank=4 [Accessed 18 October 2017]

PK analysis: HAVEN 1 and HAVEN 2



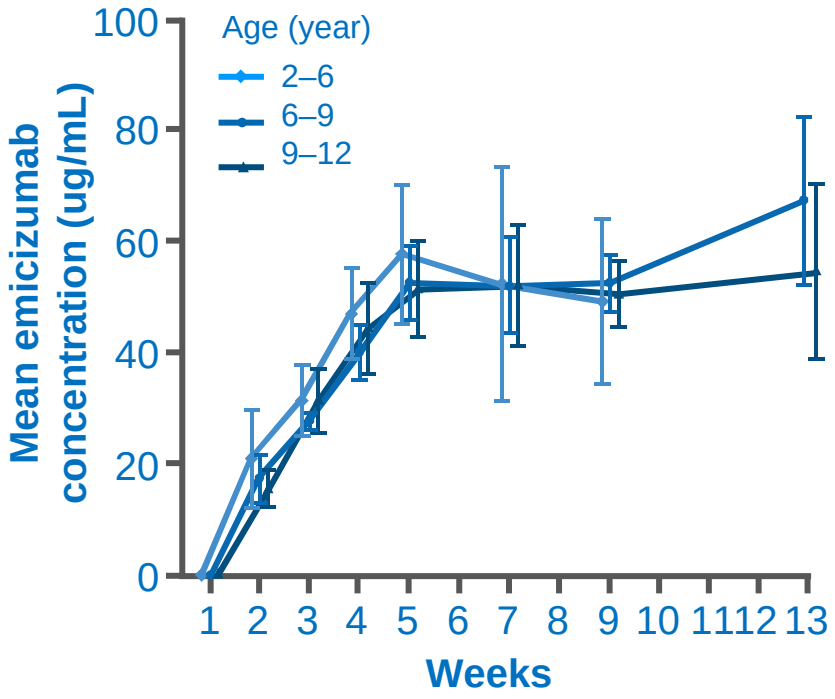
- No effect of body weight or age on PK was seen in paediatric study
- Only two patients up-titrated in HAVEN 1; none in HAVEN 2
- Target exposure achieved at 50 µg/mL in adult and paediatric population (>2 years old)

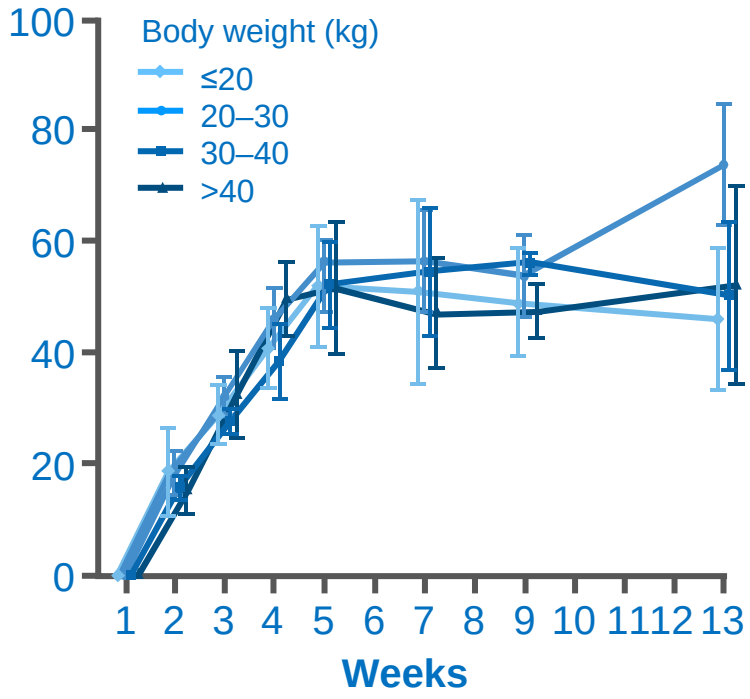
PK, pharmacokinetics.

Young G, et al. ISTH 2017.

HAVEN 2 PK profiles by age and body weight

Mean emicizumab concentrations
(linear scale, error bars = mean +/- standard error)





- Mean trough emicizumab concentrations in plasma were consistent across age groups and body weight*

*Four loading doses of 3 mg/kg/week, followed by maintenance doses of 1.5 mg/kg/week.
PK, pharmacokinetics.

Young G, et al. ISTH 2017.

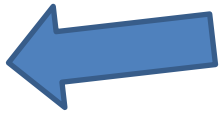
HAVEN 2 – summary of preliminary results

- At 12-week follow-up, efficacy results are promising and clinically meaningful in pediatric PwHA with inhibitors
- Safety profile of emicizumab was favorable, with no thromboembolic or thrombotic microangiopathy events reported
- PK profile consistent with the adolescent/adult population, thus confirming the pediatric dose for emicizumab is the same as the adult dose

PwHA, people with haemophilia A

Young G, et al. ISTH 2017

How could clinical practice potentially evolve?

- New technologies with different mechanisms of action
- Better treatment outcome with achievable prophylaxis even in PwHAwI
- Improved Patients' Quality of Life
- Less organizational burden at Haemophilia Sites
- Impact on laboratory practice 
- Education will be needed (→ clinicians, patients & caregivers)
- Long term Real World Data (effectiveness & safety) will be crucial

PwHAwI, persons with haemophilia A with inhibitors

Grazie per l'attenzione