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webinar

HEALTH PROFESSIONALS

Topic on Focus on Rare Coagulation Disorders

The treatment landscape for Haemophilia A and B

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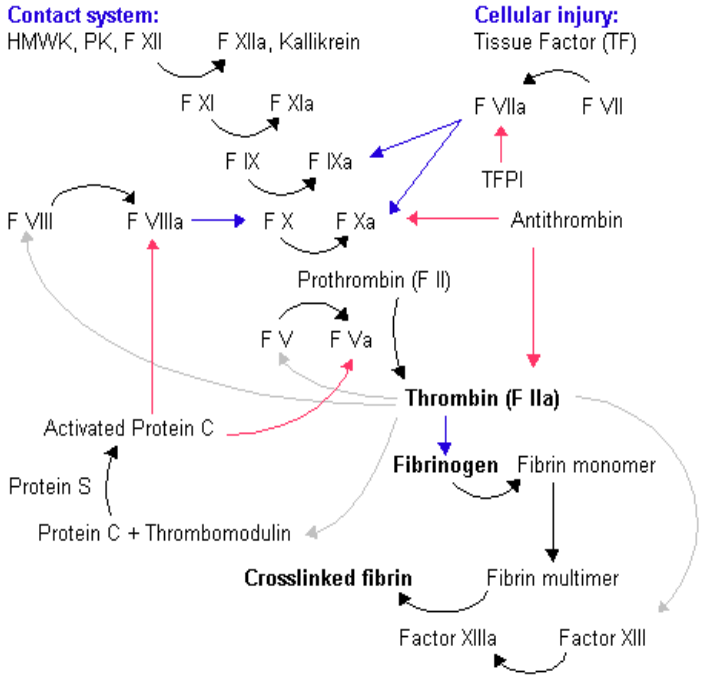
Introduction

- **Coagulation bleeding disorders** are a heterogeneous group of rare hereditary diseases, characterized by **deficiency or dysfunction of a single or a combined coagulation protein** or factor deficiency which has an essential role in the coagulation cascade

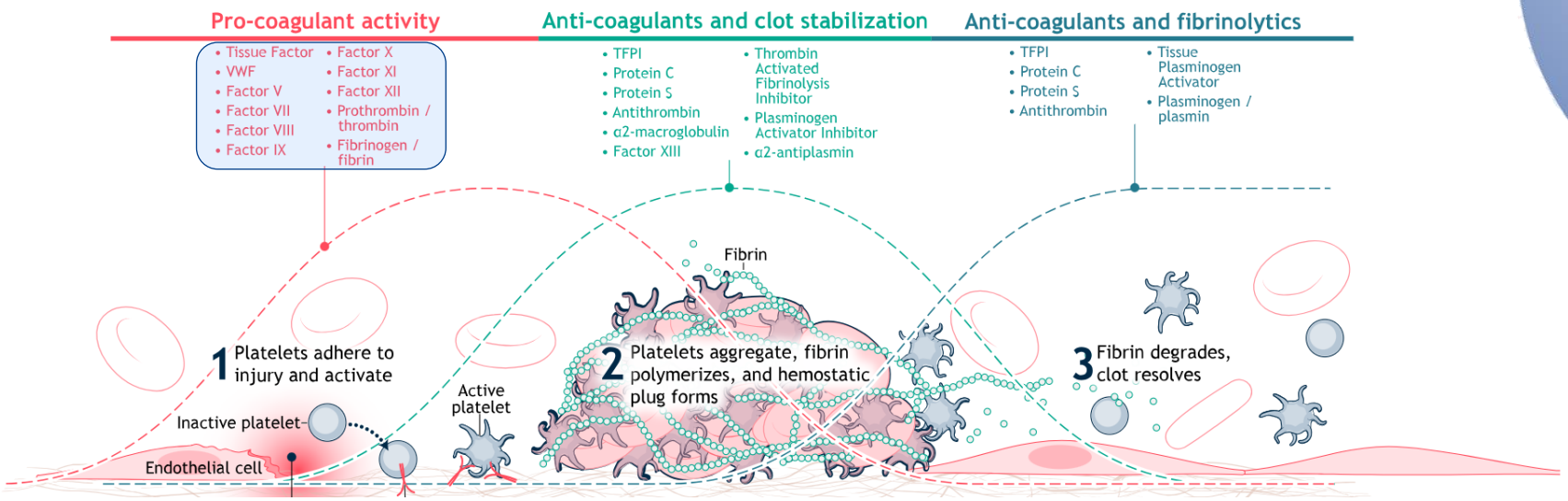
- These dysfunctions cause a **defect in clot formation** and consequent **bleeding diathesis**
  - Spontaneous bleeding or after trauma/surgical procedures
  - The severity of the condition, in most cases, depends on the extent of the deficiency



Peyvandi F et al. Lancet 2016; 388: 187–197; Figure from Versteeg HH et al. Physiol Rev. 2013;93:327-58.

Coagulation bleeding disorders

- Haemophilia A and B
- Von Willebrand Disease (VWD)
- Rare Coagulation Disorders (RBDs)
- Platelet Defects



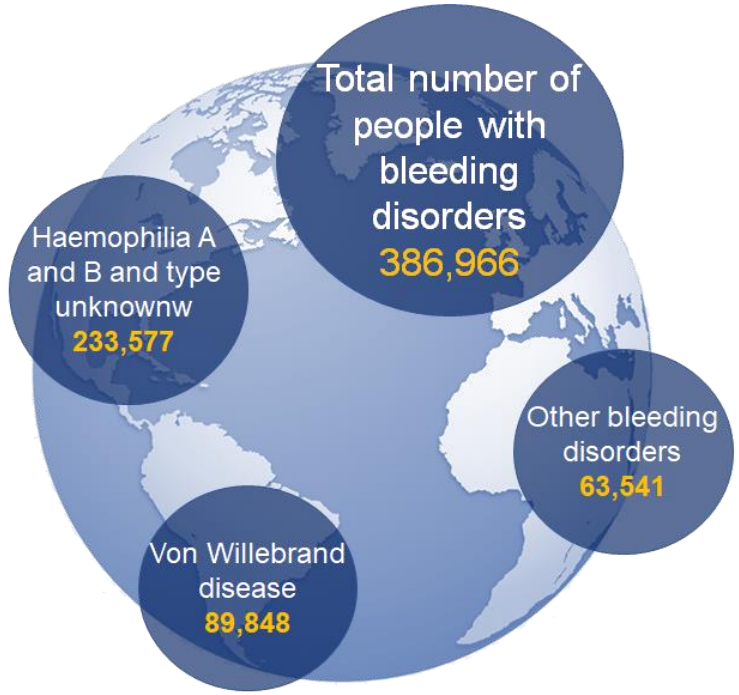


Figure from https://hemab.com/; https://wfh.org/research-and-data-collection/annual-global-survey/

Diagnosis

- Personal and family bleeding history
- First-level tests
  - Complete blood count
  - Prothrombin time (PT)
  - Activated partial thromboplastin time (aPTT)
  - Mixing study in case of a prolonged PT and aPTT
  - Fibrinogen
- Second- and third-level tests
  - Factor assays and von Willebrand factor assay
  - Platelet function
  - Factor XIII assay
  - Fibrinolysis study

Haemophilia

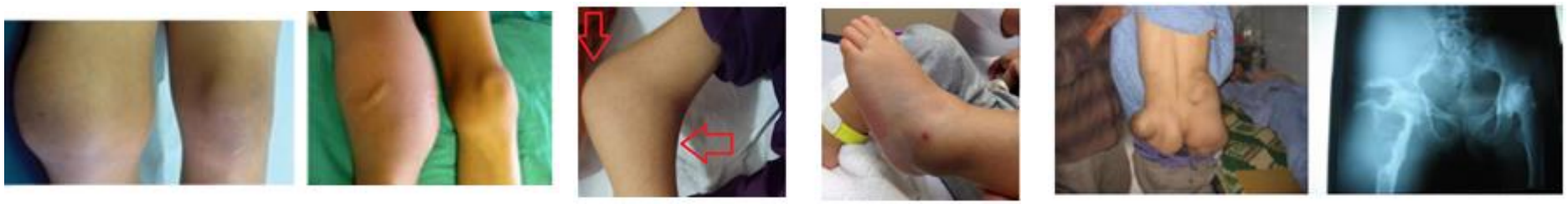
- Is inherited by an **X-linked recessive trait**
- Is caused by **deficiency or dysfunction of the coagulation proteins FVIII (haemophilia A) and FIX (haemophilia B)**
- Severity is defined by factor activity level:
  - Mild 5-40 IU/dL
  - Moderate 1-5 IU/dL
  - Severe < 1 IU/dL

- Prevalence for severe haemophilia
  - 6.0/100,000 males for severe Haemophilia A
  - 1.1/100,000 males for severe Haemophilia B

Peyvandi F et al Lancet 2016; 388: 187–197; Berntorp E et al. Nat Rev Dis Primers. 2021;7:45; Annual Global Survey 2022 WFH

Bleeding symptoms

- Haemophilia is characterized by spontaneous or post-traumatic bleeding, primarily into **joints and soft tissues**
- **Recurrent joint bleeding** results in haemophilic **arthropathy**, which is the most serious long-term complication



Mannucci PM, Tuddenham EG. N Engl J Med. 2001;344:1773-9; Peyvandi F et al Lancet 2016; 388: 187–197

The Impact of haemorrhagic events on Quality of Life

Joint damage

- Chronic arthropathy
- Disability
- Orthopaedic surgery

Limitations in daily life

- School
- Work productivity

Acute and chronic pain

Limitations in physical activities

Psychosocial impacts

- Quality of life
- Family

Standard care

- The **standard of care** for **all patients with severe haemophilia** is **regular prophylaxis** with replacement products

- In **2007**, the first randomized study demonstrated the **superiority of prophylaxis** over on-demand treatment when started early in childhood

Manco-Johnson MJ et al. N Engl J Med. 2007;357:535-44

The evolving goals of haemophilia therapy

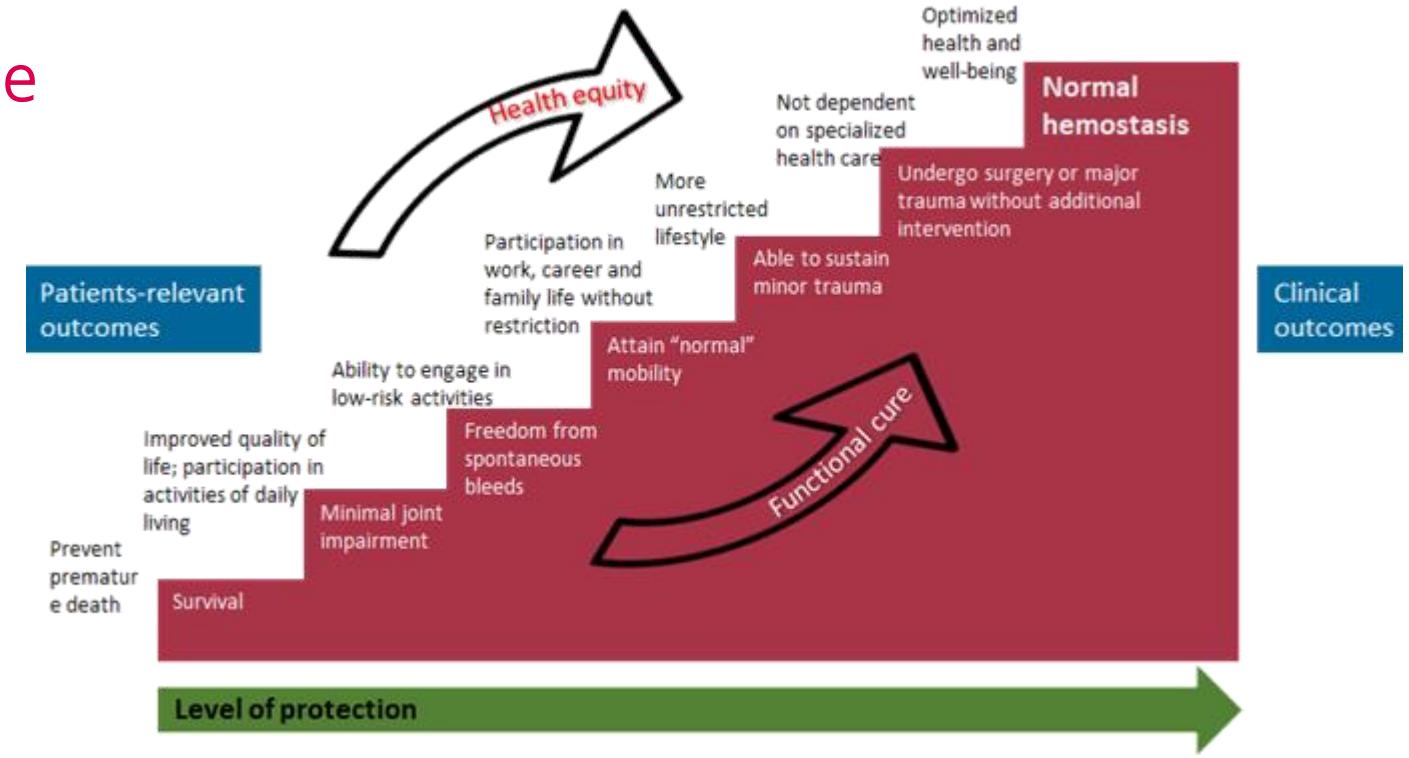
- Past haemophilia treatment
  - to **convert severe disease** to a **moderate form** (FVIII/FIX levels ~1–2%) to prevent life-threatening bleeds

- New therapies
  - to **maintain** minimum levels in the **moderate range** (3-5%) and providing similar protection to mild haemophilia, offering better prevention of bleeding

Holme PA et al. Haemophilia. 2024;30:1109–1114

New standard of care

Could a higher factor levels open the possibility of achieving a lifestyle unimpaired by disease complications?



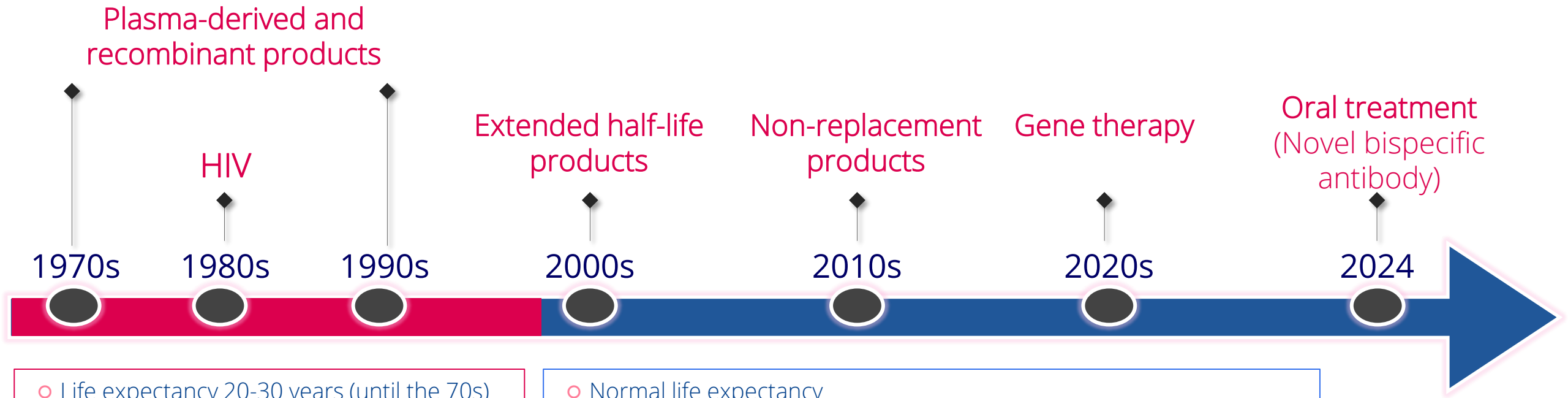
Skinner MW et al. Haemophilia. 2020;26:17–24

Normalization of haemostasis: A new target?

- Normalization of hemostasis to allow patients to live a normal life, free from the limitations imposed or associated with haemophilia:
  - No bleeding
  - No joint deterioration
  - Reduced pain
  - Improved quality of life

Holme PA et al. Haemophilia. 2024;30:1109–1114

Evolution of Haemophilia therapy

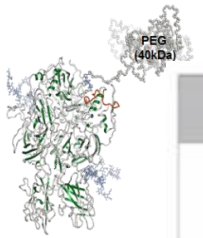


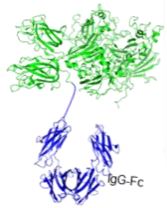
- Life expectancy 20-30 years (until the 70s)
- Joint diseases and physical disabilities in early adolescence
- A life defined by pain and limitation
- High risk of life-threatening bleeding

- Normal life expectancy
- Widespread use of prophylactic therapies to prevent joint bleeding
- Greatly reduced joint disease (nearly non-existent in young patients with no inhibitor)
- Low risk of life-threatening bleeding

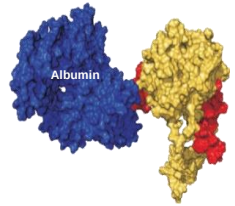
Innovation begins with extended half-life products

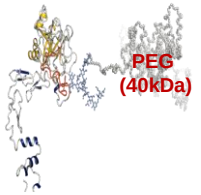
- Strategy to increase half-life
- PEGylation
  - Chemical coupling of Polyethylene glycol (**PEG**)
- Fusion proteins
  - Fusion of the Fragment crystallizable (**Fc**) region of an Immunoglobulin (IgG) or **albumin** to recombinant proteins





FVIII products	FIX products
Reduction of infusion number: **30%**	Reduction of infusion number: **60%**
Trough levels: **2-3 IU/dL** *Patients with severe hemophilia A are converted to a moderate phenotype*	Trough levels: **5-10 IU/dL** *Patients with severe hemophilia B are converted to a mild phenotype*
Half-life: **1.3-1.7 fold increase**	Half-life: **4-6 fold increase**





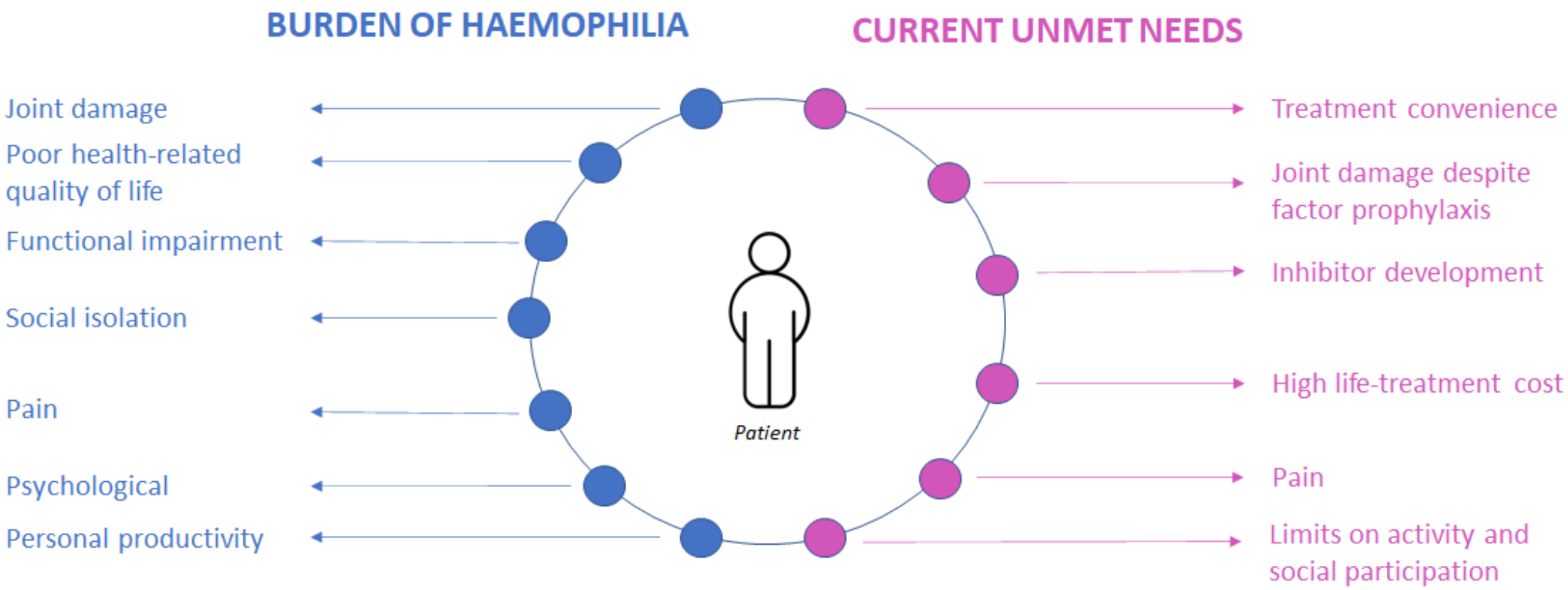
Mannucci PM. Haematologica 2020;105:545-553

Breakthrough bleeds may occur despite prophylaxis with extended half-life products

- Patients with haemophilia A
  - A total of **74%** of patients on extended half-life therapies experienced **bleeding episodes** (US/European Adelphi programme)
- Patients with haemophilia B
  - **70%** of patients had **≥ 2 bleeding events** per year (CHESS II study)

Chhabra A et al. Blood Coagul Fibrinolysis. 2020;31:186-192; Burke T et al. Orphanet J Rare Dis. 2021:16:143

Burden of treatment and unmet needs in haemophilia



Miesbach W et al Haemophilia 2019; 25:545-457

Subclinical bleeding at joint level and pain

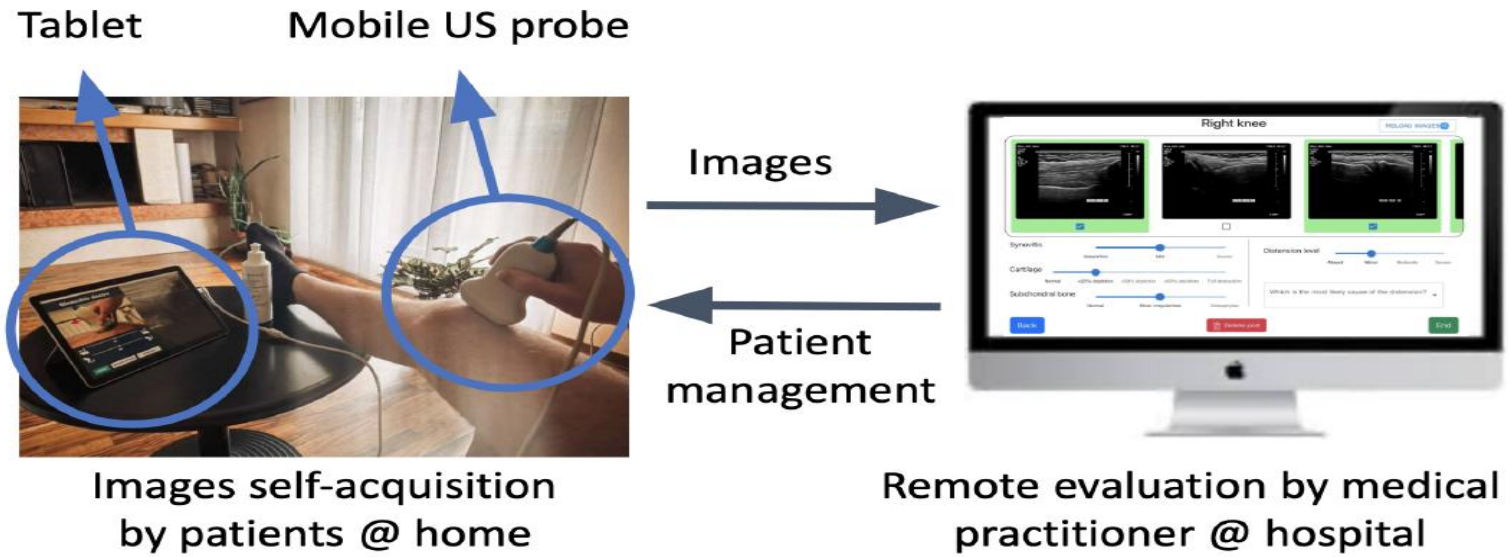
- People with haemophilia still experienced **sub-clinical bleeds**, **arthropathy and pain** which impacts health-related quality of life
- **Joint pain remains a major problem** for both young and adult patients, significantly affecting their quality of life
- What needs to be done:
  - **Early diagnosis** to prevent bleeding damage
  - **Treatment optimization** (greater protection/easier treatment)

Auerswald G et al Blood Coagul Fibrinolysis. 2016 Dec;27(8):845-854; Escobar M et al. J Thromb Haemost. 2013;11:1449-1453; Blanchette VS et al. J Thromb Haemost 2014;12:1935-1939; Witkop M et al. Haemophilia. 2012;18:e115-e119; Humphries TJ et al. Haemophilia. 2015;21:41-51; Lobet S et al. J Blood Med. 2014;5:207-218

Early diagnosis of bleeding disorders

Remote Ultrasound Assessment

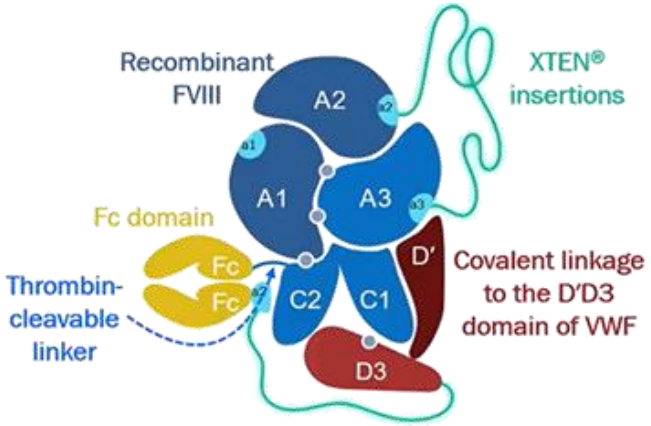
- Advancements in early detection of blood effusion in haemophilic patients
- A novel remote evaluation system for at-home monitoring



Mascetti S. 18th Annual EAHAD Congress 2025

Latest generation extended half-life products

- Efanesoctocog alfa is a **single rFVIII protein** fused to **dimeric Fc**, a **D'D3 domain of VWF**, and **two XTEN polypeptides**
- **FDA (2023) and EMA (2024) have approved Efanesoctocog alfa**
  - Once-weekly prophylaxis (intravenous injection)
  - On-demand treatment
  - Perioperative management of bleeding

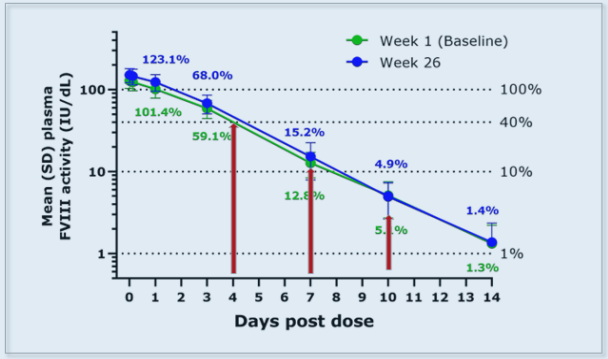


Dhillon S. Fidanacogene Elaparvovec: First Approval. Drugs. 2024;84:479-486; 2https://www.ema.europa.eu/en/medicines/human/EPAR/altuvoct

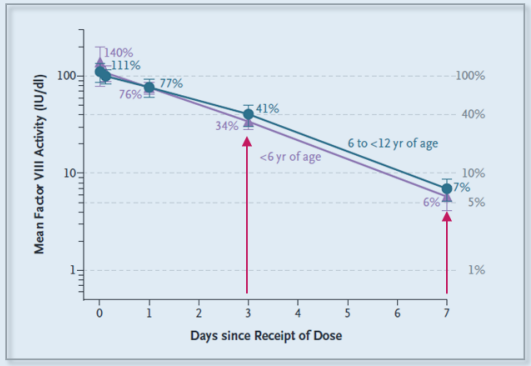
Effectiveness of efanesoctocog in prophylaxis

- **Weekly prophylaxis** with 50 IU/kg of efanesoctocog in severe haemophilia A patients:

  - Adults (≥12 years)
    - mean FVIII activity **>40 IU/dL for 4 days** and **>15 IU/dL for 7 days**
    - mean **ABRs** were **0.69** compared to **2.96 with** prior prophylaxis
    - **65%** had **no treated bleeding** episodes



  - Children (6-12 years)
    - mean FVIII activity **>40 IU/dL for 3 days** and **~10 IU/dL for 6 - 7 days**
    - mean **ABRs** were **0.00** compared to **0.61** with prior prophylaxis
    - **64%** had **no treated bleeding** episodes



Extending the time within the **normal range** significantly **improves bleeding control** and markedly **reduces** the annualized **bleeding rate**

Konkle B et al. N Engl J Med 2020; 383; 1018-1027; von Drigalski A et al N Engl J Med 2023;388:310-8; Malec L et al N Engl J Med 2024;391:235-46

Treatment-emergent adverse events (TEAEs) with efanesoctocog alfa

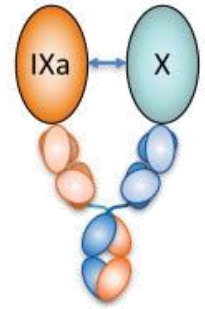
- Most common TEAEs were:
  - Headache 21%
  - Arthralgia 16%
  - Back pain 6%
- Treatment emergent **serious adverse events** were reported in **9%** (15/159) of patients
- **Thromboembolic events** occurred in **1%** (3/206) of subjects in the long-term safety extension study (XTEND-ed;NCT04644575), all of whom had pre-existing risk factors
- Transient anti-drug antibodies in 2.2%
- The prevalence of inhibitors in both PUPs and PTPs is needed

PUPs: previously untreated patients; PTPs: previously treated patients
von Drigalski A et al N Engl J Med 2023;388:310-8; Keam S Drugs 2023;83:633-8

Non-replacement therapy

- Indirect and creative approach to enhance the haemostatic potential independently of replacement factor administration

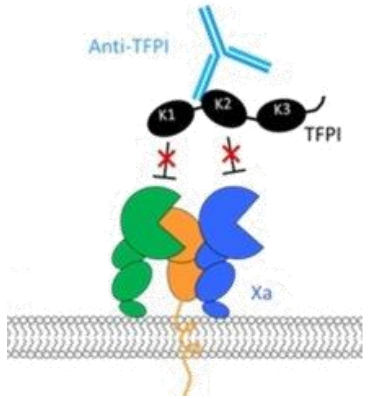
Bispecific antibodies
FVIIIa Mimetics



Bispecific antibody

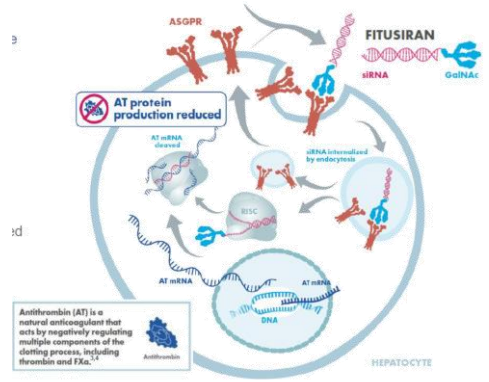
Emicizumab, MIM8, NXT007, Inno8

Monoclonal antibodies
Anti-TFPI



Concizumab, Marstacimab

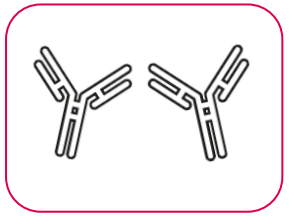
siRNA
Anti-thrombin



Fitusiran

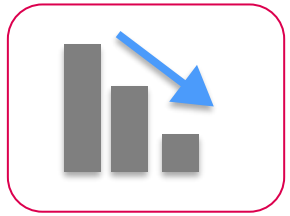
Non-replacement therapies share key similarities

- May be used in people **with and without inhibitors**

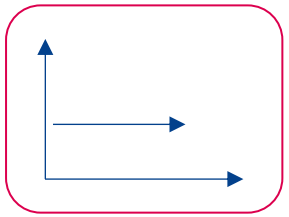


- **Subcutaneous dosing**

- **Reduced** frequency of administrations



- **No peaks and troughs** between doses



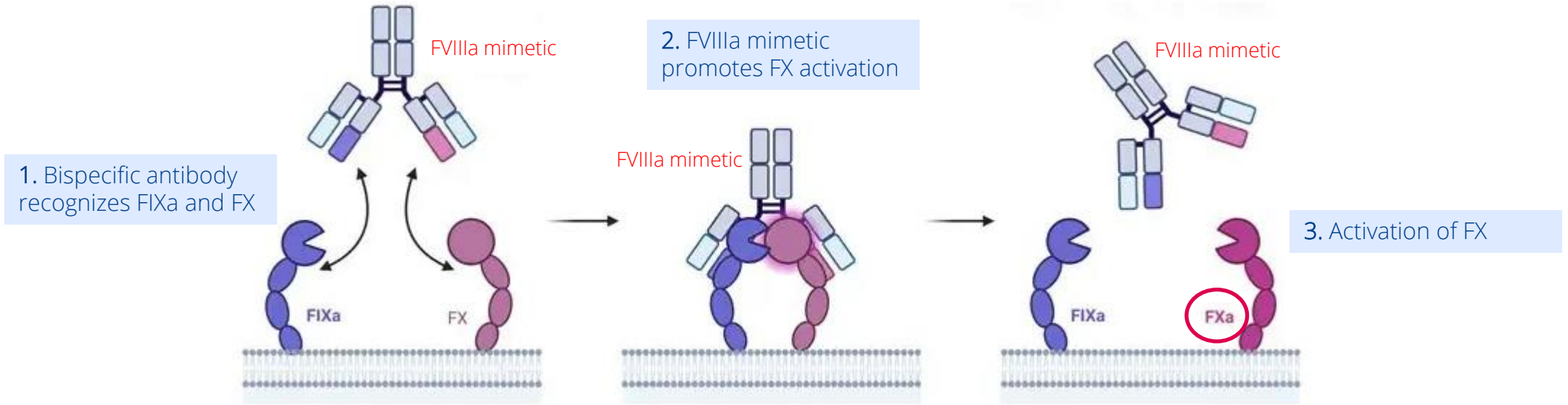
- **Effective** in haemophilia **A and B**

- **Prophylaxis**

  Concomitant use of other hemostatic agents for breakthrough bleeds and/or surgeries

Mimetic drugs

- Mimic FVIII acts by enhancing coagulation
- The first **mimetic bispecific monoclonal antibody of FVIII** was **emicizumab**
  - Is a humanised bispecific monoclonal antibody that simultaneously binds two antigens: FIXa and FX, mimicking the cofactor function of FVIIIa



Kitazawa et al. Nat Med 2012;18:1570-1574; Sampei et al. Plos One 2013;8:e57479; Mahlangu J. Expert Opin Biol Ther 2019;19:753-761

Emicizumab: first non-replacement therapy approved

- Approved in 2017/2018 for **prophylaxis** in individuals with haemophilia A, for all age groups, **with or without inhibitors**, by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA)
- Several thousand people treated worldwide, including children <1 year of age
- **Not indicated** for the **acute phase** of bleeding

Caution is required when using **emicizumab concurrently with activated prothrombin complex concentrate (aPCC)** due to the risk of serious side effects when high doses of aPCC **(>100 IU/kg)** are used

- Thrombotic events
- Thrombotic microangiopathy (TMA)

Efficacy and safety in clinical trials

Efficacy

- Pooled data from **401 paediatric and adult** patients with haemophilia A with/without FVIII inhibitors enrolled in **HAVEN 1, HAVEN 2, HAVEN 3, and HAVEN 4 studies**

	HAVEN 1	HAVEN 2	HAVEN 3	HAVEN 4	Total
Patients enrolled, n*	113	88	152	48	401
FVIII inhibitors at baseline, n (%)					
Yes	113 (100)	88 (100)	0 (0)	8 (16.7)	209 (52.1)
No	0 (0)	0 (0)	152 (100)	40 (83.3)	192 (47.9)

- Across all studies, the **mean ABR** for treated bleeds consistently **declined** over each 24-week treatment interval
- **82.4 %** reported **zero treated bleeds** at weeks 121-144

Safety

- **Injection site reaction** is the **most common** treatment-related **adverse event**
- **3 thrombotic microangiopathies (TMAs) and 2 thrombotic events (TEs)** were associated with **concomitant aPCC use** (HAVEN 1)

	Total (N = 399)*
Participants with ≥1 AE	381 (95.5)
AE with fatal outcome	1 (0.3)
SAE	93 (23.3)
AE leading to withdrawal from treatment	5 (1.3)
AE leading to dose modification/interruption	9 (2.3)
Grade ≥3 AE	87 (21.8)
ISR†	111 (27.8)
AEs of special interest	
Systemic hypersensitivity/anaphylactic/ anaphylactoid reaction‡	1 (0.3)
TMA associated with concomitant aPCC and emicizumab	3 (0.8)
Other TMA	0
TE associated with concomitant aPCC and emicizumab	2 (0.5)
Other TE	2 (0.5)

Callaghan MU et al. Blood 2021;137:2231-2242

Emicizumab: efficacy in real-world data

ORIGINAL ARTICLE
Clinical haemophilia

Haemophilia WFH WILEY

Emicizumab prophylaxis in haemophilia A with inhibitors: Three years follow-up from the UK Haemophilia Centre Doctors' Organisation (UKHCDO)

- 117 haemophilia A patients with inhibitors
  - 40 patients <12 years
  - 77 patients ≥12 years
- The overall mean ABR was 0.32 (95% CI, 0.18 to 0.58)
- 89% (104 /117) of emicizumab-treated individuals report no bleeding events
- Three arterial thrombotic events were reported, two possibly drug related

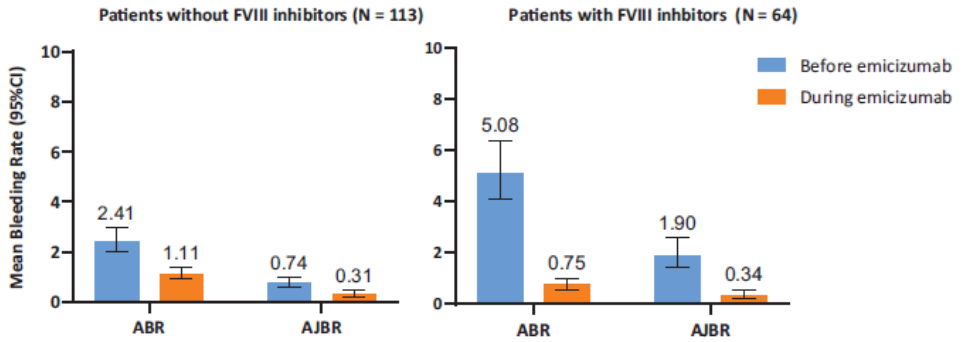
Wall C et al. Haemophilia. 2023;29:743–752

ORIGINAL ARTICLE
Clinical haemophilia

Haemophilia WFH WILEY

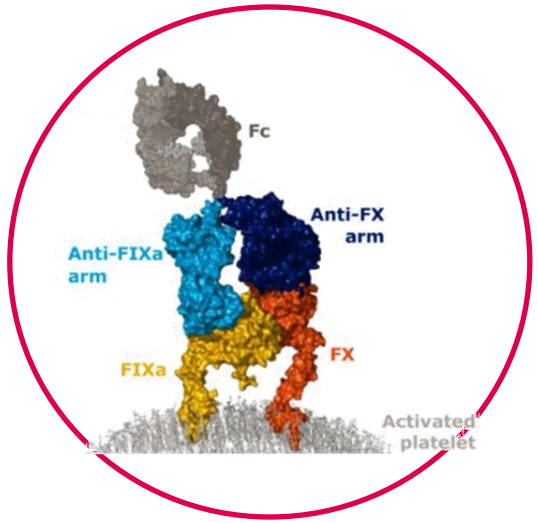
Bleeding control improves after switching to emicizumab: Real-world experience of 177 children in the PedNet registry

- 177 children (113 with inhibitors and 64 without inhibitors), age start emicizumab therapy (years) 8.6 (4.8–13.1)
- Bleeding rates were significantly reduced during emicizumab prophylaxis
- 4 patients reported injection site reactions and one patient with antidrug antibodies



ABR: annualised bleeding rate; AJBR: annualized joint bleed rate; van der Zwet K et al. Haemophilia 2024;30:685-692

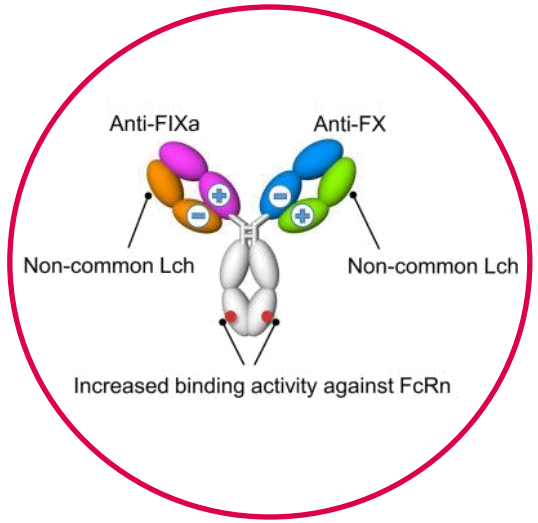
FVIIIa mimetics: Mim8



- Is a fully **human IgG4 bispecific antibody**
- In *in vitro* and *ex vivo* analysis, Mim8 showed a **higher thrombin generation at ~15-fold lower concentration compared with emicizumab**
- Mim8 was well tolerated, and there were **no severe treatment-emergent adverse events**
- Currently in **Phase 3** clinical trials

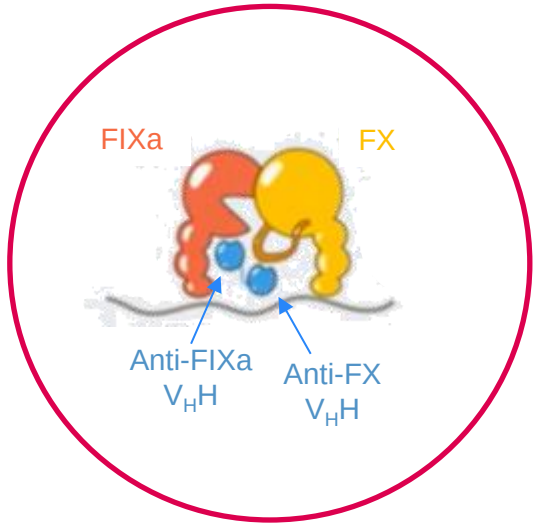
Østergaard H et al. Blood 2021;138:1258-1268; Lund J et al. J Thromb Haemost. 2023;21:1493-1502

FVIIIa mimetics: NXT007



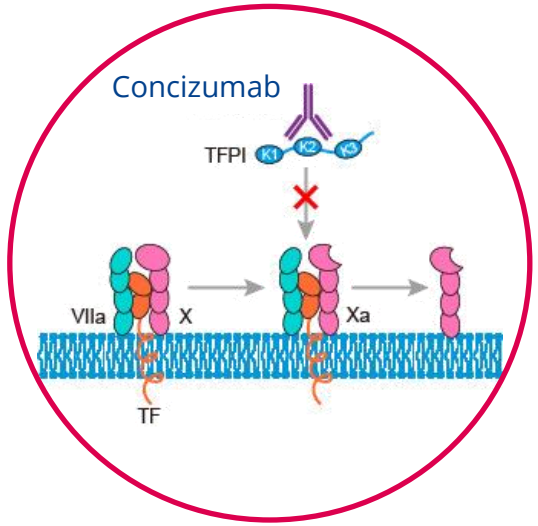
- Is an **IgG bispecific antibody** developed based on emicizumab
- Enhanced anti-FX and anti-FIXa arms for **greater potency and thrombin generation**
- **Fc region** modified to extend half-life
- Demonstrated significantly improved FVIIIa-mimetic activity *in vitro* and *in vivo*, leading to:
  - Increased thrombin generation
  - Improved clot formation and fibrinolysis
  - Reduced bleeding in preclinical models
- Currently in **Phase 1/2** clinical trials

FVIIIa mimetics: Inno8



- Inno8 is made by connecting **two VHH fragments of camelid heavy-chain** to make a small FVIIIa mimetic antibody
- Inno8 is formulated with sodium N-[8-(2-hydroxybenzoyl)amino]caprylate **(SNAC) for oral delivery**
- Inno8 achieved **similar *in vitro* effect as emicizumab** sequence-identical analogue at **approximately 90-fold lower concentrations**
- Inno8 was shown to be **orally available** and exhibited a **long systemic half-life of approximately 113 hours** in beagle dogs
- Currently in **Phase 1** clinical trials to prove safety in healthy men

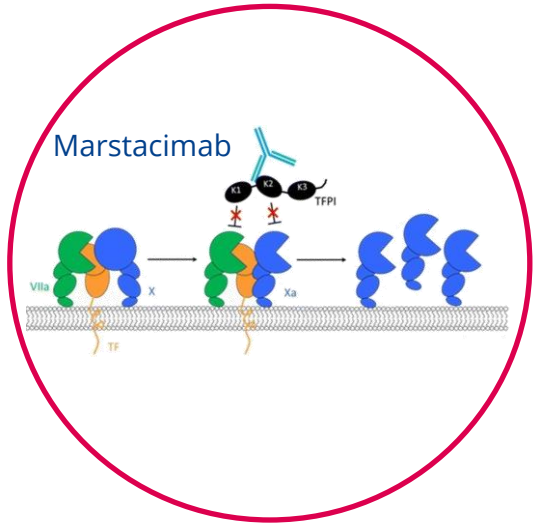
Monoclonal antibodies - Anti-TFPI: Concizumab



- Concizumab is a high-affinity, **humanized, monoclonal IgG4 antibody**
- Concizumab selectively targets and **inhibits the Kunitz-2 domain** of tissue factor pathway inhibitor (**TFPI**), blocking FXa activity
- **FDA and EMA:** Approved for **prophylaxis in haemophilia A and B** patients **with inhibitors**, aged ≥12 years
- **Canada and Japan:** Approved for **prophylaxis in haemophilia A or B** patients **with inhibitors**, ≥12 years
- Concizumab is administered **once daily** via **subcutaneous** injection
- **Non-fatal thrombotic events** were observed during phase 3 clinical trials (explorer7 and explorer8)

FDA: U.S. Food and Drug Administration; EMA: European Medicines Agency
Peyvandi F et al Res Pract Thromb Haemost. 2024;8:e102434

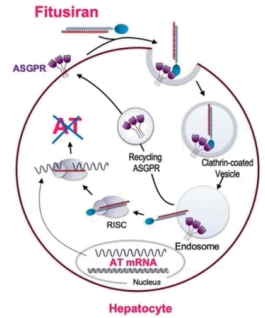
Monoclonal antibodies - Anti-TFPI: Marstacimab



- Marstacimab is a human IgG1 mAb that **binds the Kunitz-2 domain** of **TFPI**, preventing its interaction with FXa
- **FDA and EMA:** Approved for **prophylaxis in haemophilia A and B** patients **without inhibitors**, aged ≥12 years
- Marstacimab is administered **weekly** via **subcutaneous** injection
- **One thromboembolic event** was reported during phase 3 clinical trials (OLE) non-drug related
- ADAs reported in 20.5% (23/112) of patients, titres were low

FDA: U.S. Food and Drug Administration; EMA: European Medicines Agency; ADA: anti-drug antibody
Peyvandi F et al Res Pract Thromb Haemost. 2024;8:e102434

Fitusiran – A siRNA based new drug to treat people with haemophilia A and B



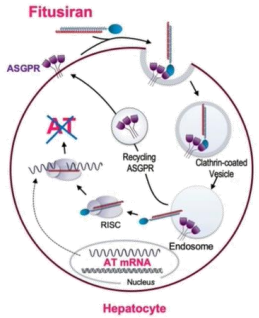
- Is an **RNA interference therapeutic** in development, specifically **inhibits antithrombin** to restore sufficient thrombin and rebalance haemostasis
- Fitusiran **prophylaxis significantly reduces ABR** in patients with haemophilia A or B, with or without inhibitors, as demonstrated in clinical trials

ATLAS-INH (n=57)	**ATLAS-A/B (n=120)**	**ATLAS-PPX (n=80)**	**ATLAS-OLE (n=136)** Antithrombin-based dosing regimen
90.8% reduction in **bleeding rate** vs on-demand BPAs	**89.9% reduction** in **bleeding rate** vs on-demand factor concentrates	**61.1% reduction** in **bleeding rate** vs prior factor/BPAs prophylaxis with and without inhibitors	**73% reduction** in **bleeding rate** for people with inhibitors vs 71% for without vs on-demand factor concentrates
65.8% zero bleeds vs 5.3% with on-demand BPAs	**50.6% zero bleeds** vs 5.0% with on-demand factor concentrates	**63.1% zero bleeds** vs 16.9% with on-demand factor/BPAs prophylaxis	**31.5% zero bleeds** with fitusiran prophylaxis; 28.1% people without inhibitors and 37.7% with inhibitors

ABR: annualised bleeding disorders

Young G et al. Lancet. 2023;401:1427-1437; Srivastava A et al. Lancet Haematol. 2023;10(e322-e332; Kennet G et al. Blood 2024;143:2256-69; Young G et la. Hematol Transfus Cell Ther 2024;46:5564-5; Pipe S et al. Blood 2024;144(Suppl):128-9; 18th Annual EAHAD Congress 2025

Fitusiran – A siRNA based new drug to treat people with haemophilia A and B



- **Thrombotic risk** with fitusiran is **associated with antithrombin (AT) levels**, which led to the implementation of an **adjusted dosing regimen** to maintain a safe AT threshold (target AT levels between **15% and 35%**)

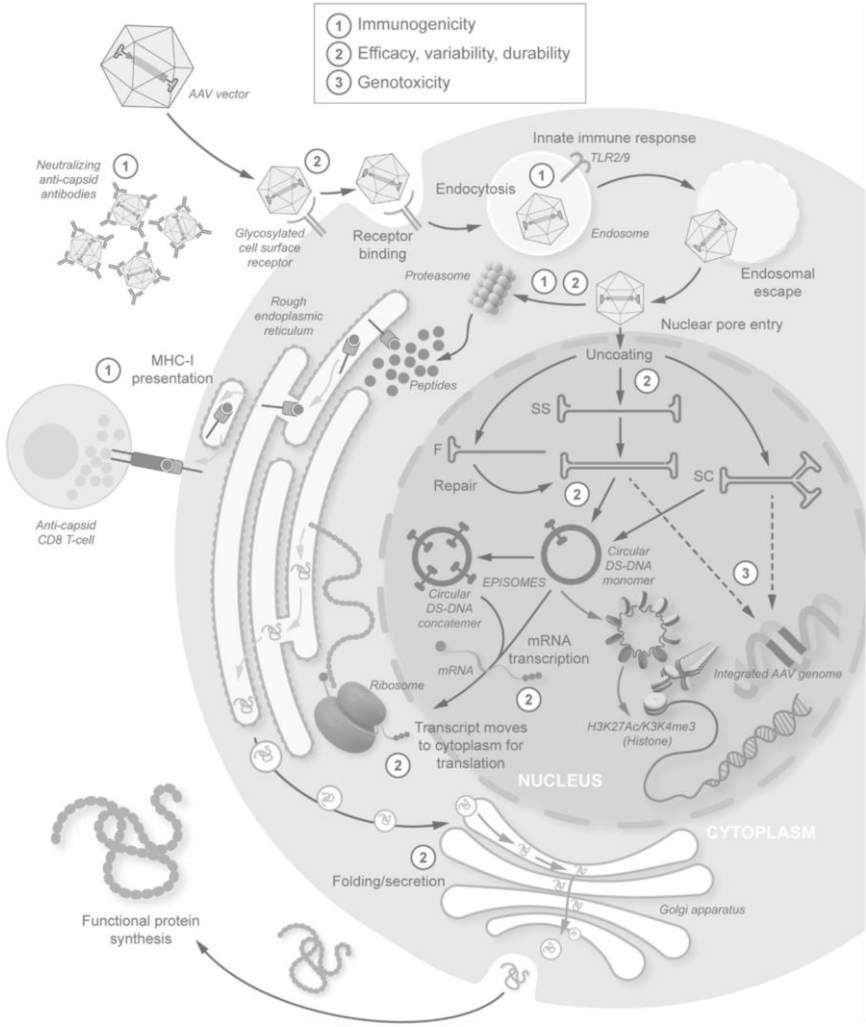
- Patients with **AT levels <10%** might have a **greater risk of vascular thrombosis**

Vascular thrombotic event	AT level
- Deep vein thrombosis (cerebrovascular accident)	<10%
- Cerebral infarct	<10%
- Suspected thrombosis involving a spinal injury	<10%
- Atrial thrombosis, concomitant use of BPA (rFVIIa)	10-20%
- Cerebral venous sinus thrombosis, concomitant use of factor concentrate	10-20%

FDA: Approved for **prophylaxis in haemophilia A and B** patients with and without inhibitors, aged ≥12 years

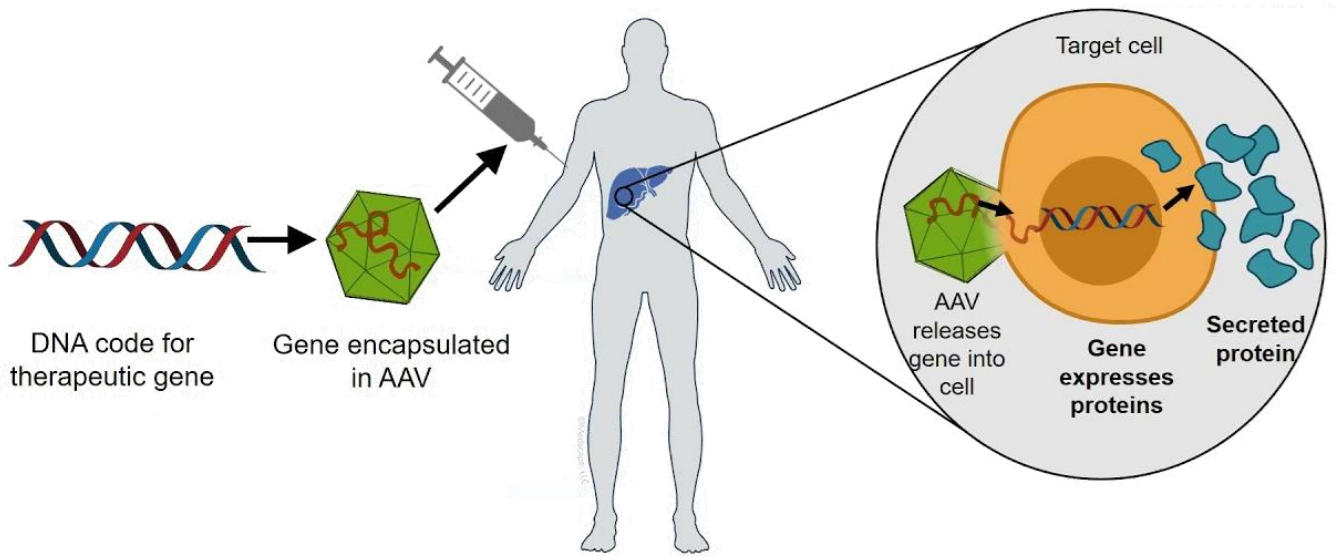
Young G, et al. Res Pract Thromb Haemost. 2023;7:100179

Gene therapy



Gene therapy definition

- Gene therapy is a method of treatment currently undergoing clinical trials for a variety of genetic conditions
- The goal is to introduce an exogenous functional gene (transgene) into target cells using a vector (vehicle) to cure the disease with a single treatment



Wang D et al. Nat Rev Drug Discov 2019;18:358-378

Status of gene therapy trial – Haemophilia A

Product name	Trial Name/NCT	Study phase	Sponsor	Vector	Patients enrolled (n)	EMA approval	FDA approval	Note
Valoctocogene roxaparvovec (BMN-270)	GENEr8-1	1/2	BioMarin	AAV5	13	//	//	//
Valoctocogene roxaparvovec (BMN-270)	GENEr8-1	3	BioMarin	AAV5	134	Yes	Yes	//
Giroctocogene fitelparvovec (PF-07055480/SB-525)	Alta	1/2	Pfizer	AAV2/6	11	//	//	//
Giroctocogene fitelparvovec (PF-07055480/SB-525)	AFFINE	3	Pfizer	AAV2/6	NA	No	No	Pfizer: Termination of Sangamo collaboration
Dirloctocogene samoparvovec (SPK-8011)	NCT03003533	1/2	Spark Therapeutics	AAV3 (subtype LK03)	24	//	//	//
Dirloctocogene samoparvovec (SPK-8011)	KEYSTONE 1	3	Spark Therapeutics	AAV3 (subtype LK03)	0	//	//	Withdrawn
GO-8	GO-8	1/2	UCL	AAV2/8-HLP-FVIII-V3	12	//	//	Active, not recruiting
BAX888 (TAK-754)	NCT03370172	1/2	Baxalta-Shire (Takeda)	AAV8	4	//	//	Active, not recruiting
BAY2599023	NCT03588299	1/2	Bayer	AAVhu37	9	//	//	Active, not recruiting

https://clinicaltrials.gov/

Status of gene therapy trial – Haemophilia B

Product name	Trial Name/NCT	Study phase	Sponsor	Vector	Patients enrolled (n)	EMA approval	FDA approval	Note
Fidanacogene elaparvovec (PF-06838435/SPK-9001)	BENEGENE-2	1/2	Pfizer	AAV- SPK-100	15	//	//	//
Fidanacogene elaparvovec (PF-06838435/SPK-9001)	BENEGENE-2	3	Pfizer	AAV- SPK-100	45	Yes	Yes	February 2025 Pfizer discontinues development and commercialization of hemophilia B treatment
AMT-060	NCT05360706	1/2	CSL Behring	AAV5	10	//	//	//
Etranacogene dezaparvovec (AMT-061)	HOPE-B	2b	CSL Behring	AAV5-hFIXco-Padua	3	//	//	//
Etranacogene dezaparvovec (AMT-061)	HOPE-B	3	CSL Behring	AAV5-hFIXco-Padua	54	Yes	Yes	//
Verbrinacogene setparvovec (FLT180a)	B-AMAZE	1/2	Spur Therapeutics (Freeline)	AAV-LK03d-Padua	10	//	//	Terminated
Dalnacogene Ponparvovec (BBM-H901)	NCT05203679	3	Shanghai Belief-Delivery BioMed Co	AAV843-Padua	26	//	//	April 2025 China grants first official approval for hemophilia B gene therapy
BAX335	AskBio009-101	1/2	Baxalta-Shire (Takeda)	AAV8-Padua	8	//	//	Active, not recruiting
scAAV2/8-LP1-hFIXco	NCT00979238	1/2	St. Jude Children's	AAV8	10	//	//	Active, not recruiting

https://clinicaltrials.gov/

Approved Haemophilia gene therapy products

Haemophilia A

- Valoctocogene roxaparvovec (**Roctavian**) approved by EMA (2022) and FDA (2023)

Haemophilia B

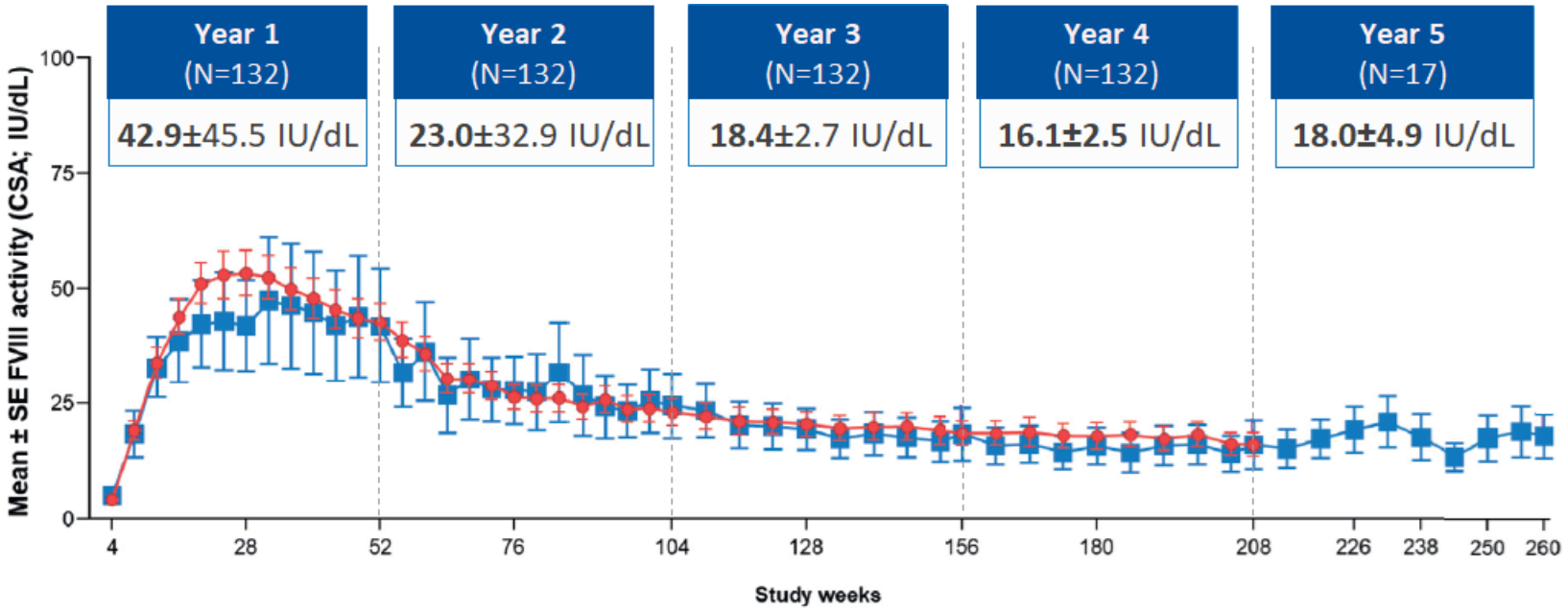
- Etranacogene dezaparvovec (**Hemgenix**) approved by FDA (2022) and EMA (2023)
- Fidanacogene elaparvovec approved by FDA (2024) and EMA (2024) (**Beqvez and Durveqtix**, respectively)

February 2025
Pfizer **discontinues** development and commercialization of haemophilia B treatment **Fidanacogene elaparvovec**

- **Dalnacogene Ponparvovec** (BBM-H901) approved by National Medical Products Administration in China (April 2025)

FVIII Expression 5 Years after gene transfer - Phase 3 Trial Valoctocogene roxaparvovec

- 134 participants received an infusion of $6x10^{13}$ vg/kg of AAV5 vectors
- FVIII activity declines most in year 1, then slows in the following years reaching a plateau

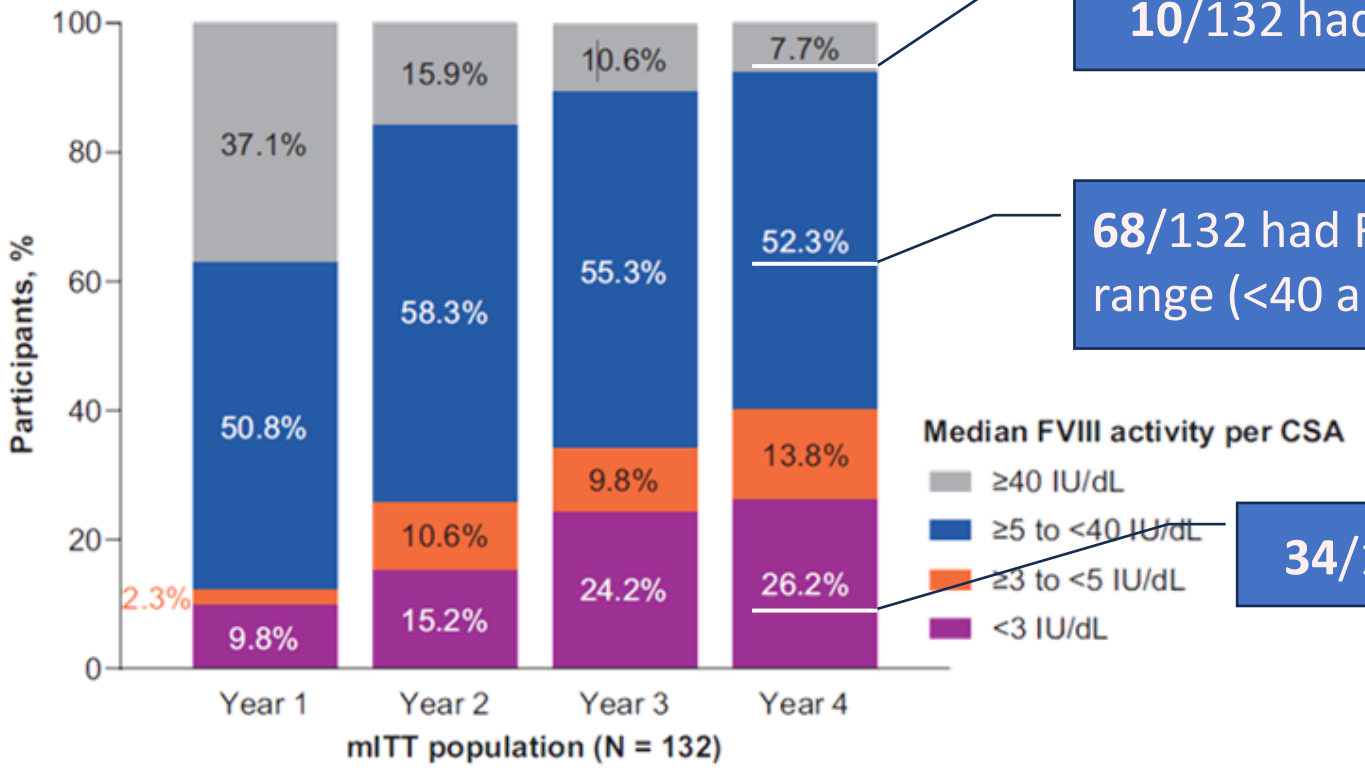


Leavitt AD et al Res Pract Thromb Haemost. 2024;8:e102615

Distribution of median FVIII activity at the end of each year
Valoctocogene roxaparvovec

The majority of participants maintain mild haemophilia

4 year after gene transfer



10/132 had FVIII activity ≥40 IU/dL

68/132 had FVIII activity in the mild haemophilia range (<40 and ≥5 IU/dL)

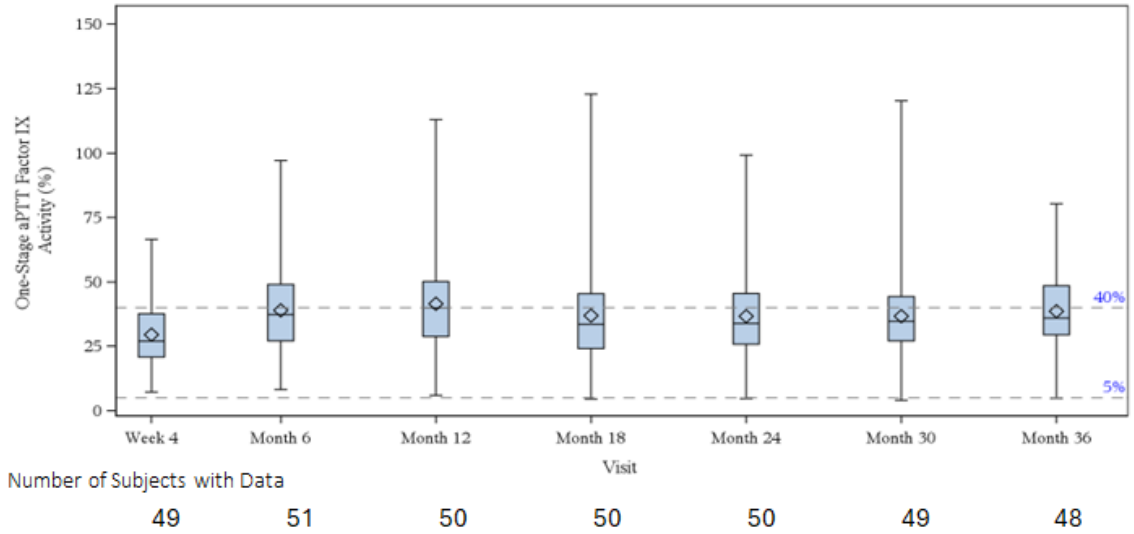
34/132 had FVIII activity <3 IU/dL

Leavitt AD et al Res Pract Thromb Haemost. 2024;8:e102615

FIX Expression 4 Years after gene transfer - Phase 3 Trial Etranacogene dezaparvovec

- 54 participants received an infusion of $2x10^{13}$ vg/kg of AAV5 vectors

Year 1 (N=50)	Year 2 (N=50)	Year 3 (N=48)
41.5 IU/dL	**36.7** IU/dL	**38.6** IU/dL



Overall stable FIX activity (37.4 IU/dL) levels over 4 years post-treatment

At year 4 post-treatment:

98% (46/47) with FIX activity level ≥5%

34% (16/47) with FIX activity level ≥40%%

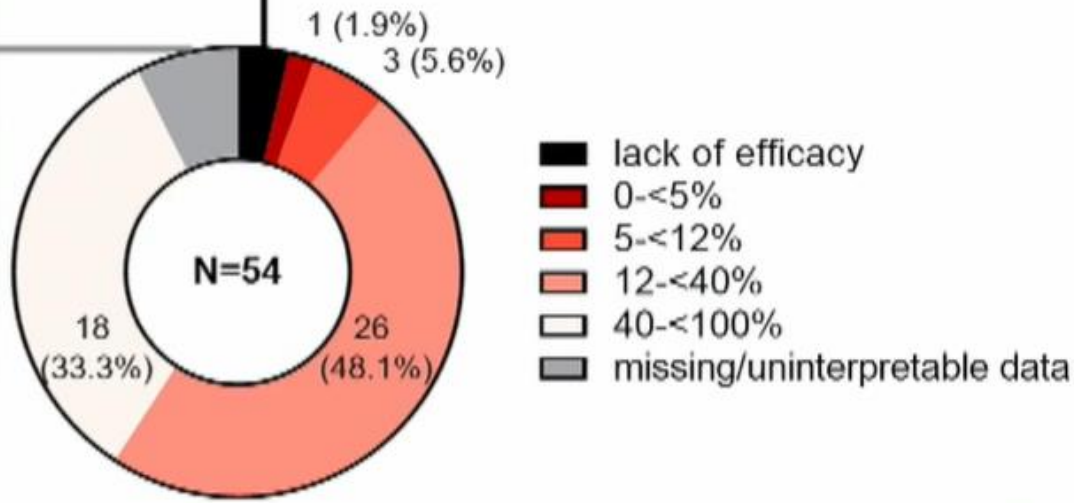
Leebeek FWG et al. 18th Annual Congress of EAHAD congress 2025

FIX activity level ranges at 3 years post-treatment Etranacogene dezaparvovec

2 (3.7%) lack of efficacy
- Participant with highest NAb titer
- Participant who received ~10% of the planned dose

4 (7.4%) missing/uninterpretable data

Reason for missing/uninterpretable data	Last FIX activity level*
Death at Month 15 (unrelated to treatment)	43.7%
Liver transplant (HCC unrelated to treatment)	36.7%
Return to FIX prophylaxis at month 30	3.6%
Non-analysable sample (hemolysis)	33.5%

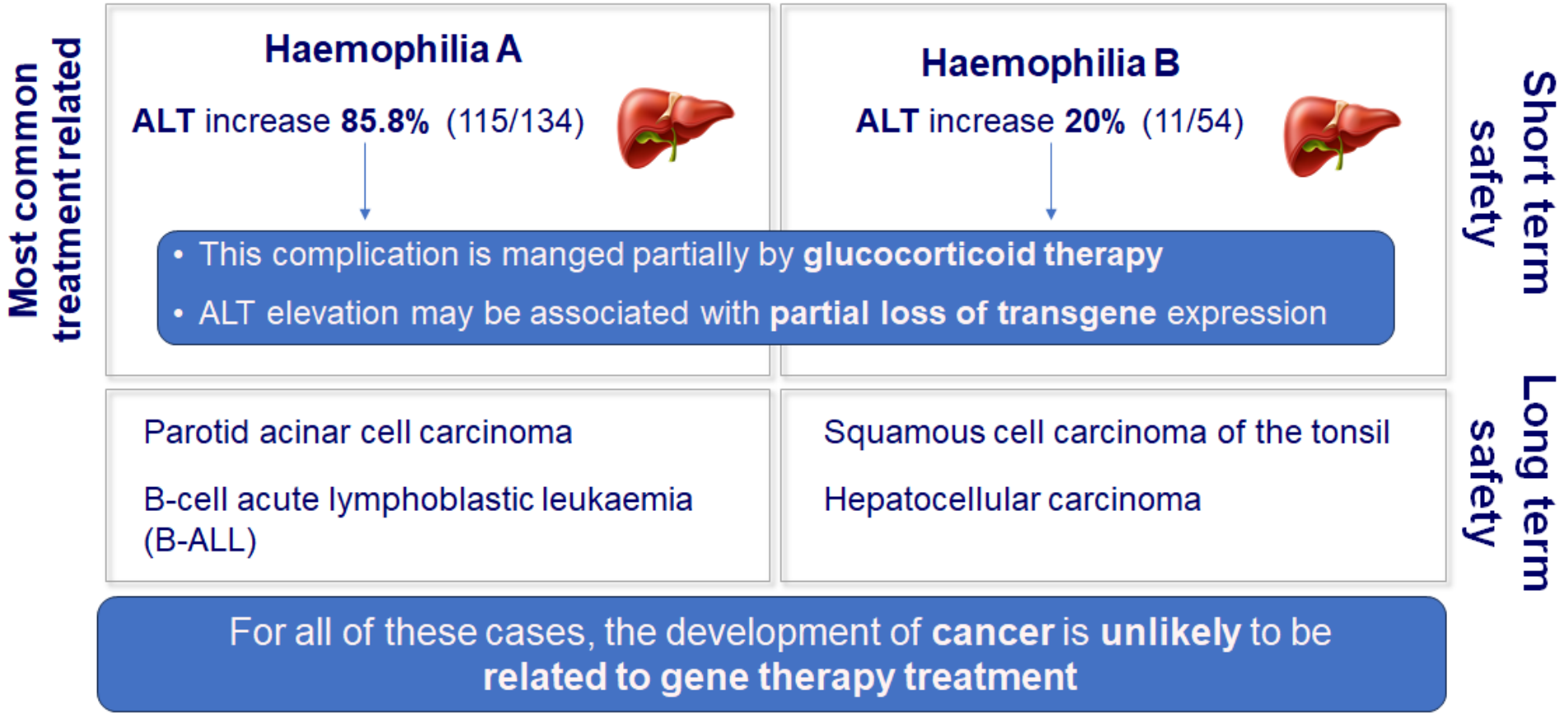


> 87% of total participants were in the mild and normal range at 3 years post-treatment

*Based on one-stage FIX activity levels from central laboratory results. Only "uncontaminated" samples were included in analysis, i.e., blood sampling did not occur within 5 half-lives of exogenous FIX use

Pipe SW et al. EAHAD Congress 2024

Safety of the first approved gene therapies for Haemophilia



Mahlangu J et al. N Engl J Med 2023;388:694-705; Pipe SW et al. N Engl J Med 2023;388:706-18; Jiaan-Der Wang et al. ISTH Congress 2024; Mucke MM et al J Hepatol. 2024;80:352-361; Schmidt M et al Res Pract Thromb Haemost. 2021;5(Suppl 2):93; Eggan K et al. Presentation at WFH 2022 Congress, Montreal, Canada, 8-11 May 2022; Update for the Haemophilia Communit. Last accessedSeptember 2023. Accessible from: https://www.Haemophilia.org/sites/default/files/document/files/BioMarin%20Haemophilia%20NORAM%20Program%20Update%20for%20Patient%20Associations%2012SEP22.pdf .

Conclusion

- Extraordinary progress has occurred in the treatment of Haemophilia, especially in the last 10 years
- Improved quality of life for patients with less invasive and more effective treatments
- Physicians need to balance efficacy, safety, patient preferences, and practical considerations to optimize treatment outcomes
- Personalized medicine: adjusting treatment based on individual needs and lifestyle