Extended half-life (EHL) clotting factor concentrates

With the help of members of the
Medical Advisory Board of the DHG

Content

March 2017, 2nd Edition

History of Haemophilia Treatment

Up until the 1960's, bleeding episodes in haemophilia were treated with whole blood or plasma. The proportion of clotting factor present in whole blood or plasma was so low that there was very little effect for bleeding episodes. Prior to the development of viral inactivation procedures in the mid-1980s, people with haemophilia who had previously received large pool plasma-derived factor concentrates were infected with the hepatitis C virus (HCV). A considerable number of these patients were also infected with human immunodeficiency virus (HIV).

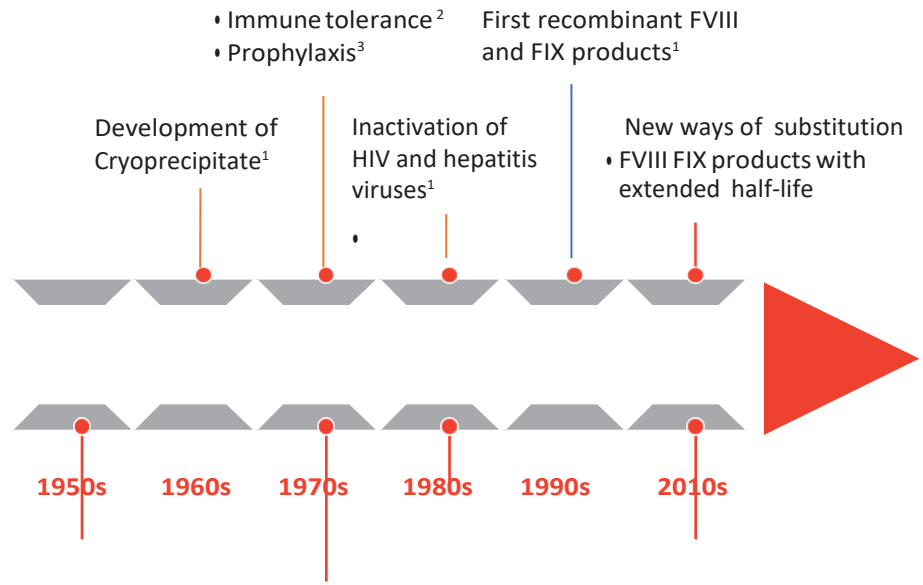
Today's optimum therapy is prophylaxis with clotting factor concentrates, in which it is attempted to

prevent bleeding by regular intravenous infusion of the plasmatic or recombinant clotting factor which is deficient (with haemophilia A factor VIII and with haemophilia B factor IX). This greatly reduces bleeding and allows the patient to live a relatively normal life.

Factor VIII (haemophilia A) and factor IX (haemophilia B) can be manufactured as recombinant proteins using a cell line. Since the beginning of the 1990's recombinant factor concentrates have been available in order to avoid contamination with viruses. Currently, some recombinant products with an extended half-life are available, which can increase the protection and / or reduce the number of infusions. There are also new and exciting therapies being developed that will allow subcutaneous administration, much extended dosing intervals and in the long run, the cure for both haemophilia A and B, as the ongoing gene therapy trials progress.

This brochure is aimed to provide an overview of these developments with a focus on products with extended half-life, currently available or soon to be available.

• WFH Timeline. http://www1.wa.org/2/1/1_1_3_Link1_Timeline.htm attached on 1st November 2015.



1. Brackmann HH & Gomsen J. Lancet 1977; 2: 933. 3. Manco-Johnson M et al. NEJM 2007; 357: 535–44.
2. Manco-Johnson M et al. NEJM 2007; 357: 535–44.

Factor levels, bleeding and arthropathy

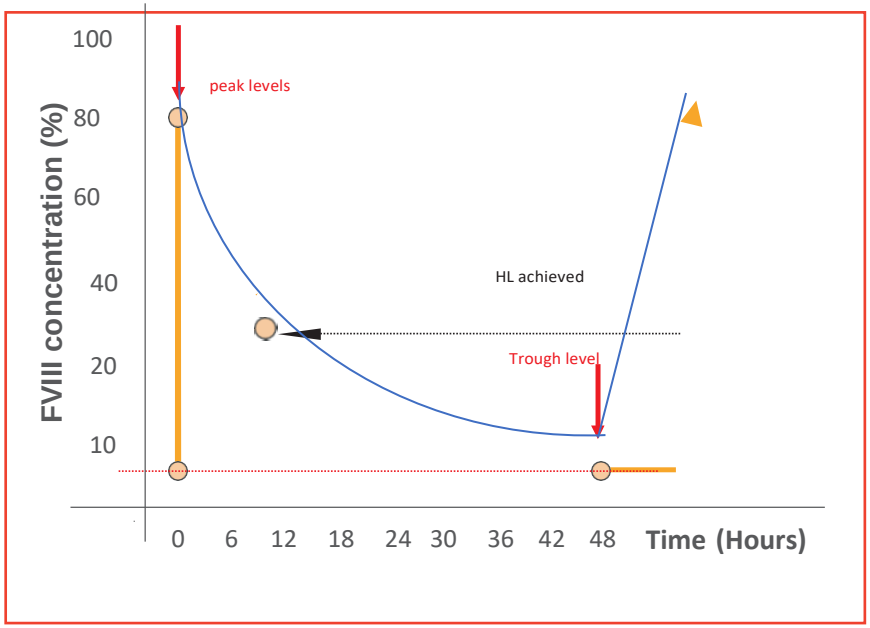
Haemophilia is a chronic lifelong disease, which can lead to pain, joint damage or life-threatening bleeding if the treatment is insufficient. Joint damage can lead to a considerable reduction in the quality of life. The prevention of joint damage is an important treatment goal. The main goal of treatment is to enable patients to live a normal life. While treatment has been significantly improved in the last 30 years, people with haemophilia are still faced with difficulties due to their condition as demonstrated in longitudinal studies with follow-ups as long as 30 years[1]. Despite seemingly optimal prophylactic therapy, patients reported marked joint damage in early to middle age. After 10 years patients reported changes in ankle joints, after 15 years patients reported changes in knee joints and after 20 years patients reported changes in elbow joints, all of which were clinically confirmed. Despite low bleeding rates, a trough level (ie a factor level directly before the next injection) of 1% appears to be insufficient. Trough levels of 3%, 5% or even 10% are being discussed; however, some patients with a trough level of 3% may continue to experience bleeding episodes whereas a patient with a trough level maintained at 1% may not bleed at all. This emphasizes the importance of tailored individual treatment for patients.

Extended half-life products allow not only less frequent infusions, but also higher troughs than standard half-life products when used at the same frequency and dosing. Thus, these products may help manage patients who do well with a trough level of 1% as well as those who need higher troughs to prevent all bleeds. A long-term effect on the joints will, of course, only occur after a similar long observation period as in the study described above.

1. Oldenburg J. Blood. 2015;125(13):2038-44.

- Pharmacokinetics (half-life, course of degradation of FVIII / FIX) varies with each patient.
- Dosage must be adapted to the patient.
- Factor level must be adapted to the patient.

Post-infusion changes in factor VIII level



Half-life extension and alternative technologies

There are several new treatment pathways and technologies that will become available to patients with haemophilia A and B in the coming years. These technologies may seem complex, but we can divide them easily as follows:

- PEGylation: **chemical modification of** FVIII and FIX molecules by attachment of PEG. PEGs (polyethylene glycols) are chemical substances that the body cannot degrade, but may shed via different routes. The rate of excretion via the kidney depends on the size of the PEG molecule and is not yet fully understood.
- Protein fusion: genetic engineering to produce factor VIII or factor IX in the form of a large protein that consists of a coagulation factor linked with another protein. The fusion partner protein may be full-length or part of an endogenous protein (albumin or immunoglobulin fragment, respectively). These **fusion proteins** can be completely degraded and recycled by the body. Some of these products are produced in a human cell line so that they are extremely similar to the body's proteins.
- **Modification of** clotting factor **amino acid sequence:** genetic engineering to change the primary structure of a clotting factor. This approach was used to obtain the single-chain FVIII. In the body, factor VIII is cleaved before release into the bloodstream. The products of this cleavage, called FVIII light and heavy chain, circulate together as a protein complex. Introduction of changes at specific sites of the FVIII protein through genetic engineering prevents the cleavage and extends the FVIII half-life.

In most cases in haemophilia A the injection interval can be prolonged from three times per week to twice per week or from every two to every three days. In Haemophilia B the dosing frequency can be reduced from twice per week to once per week. Some patients may be able to extend their infusions to every 10-14 days. In many cases a much better protection of the patient is also achieved. In the medium term further advances in treatment for haemophilia A (including patients with inhibitors) will be available such as an antibody that wiil be administered subcuaneously (under the skin). In the long term, gene therapy will also be available.

Approaches to extended half-life

In short-term or already available

➜ **Chemical modification**[1,2]

- PEGylation

➜ **Protein fusion**

- FVIII or IX + Fc region of immunoglobulin G[3]
- FVIII or IX + albumin[4]

➜ **Protein sequence modification**

- Single-chain FVIII molecule[5]

PEG = polyethylene glycol

1. Jevsevar S et al. Biotechnol J. 2010;5:113-128.
2. DeFrees S et al. Glycobiology. 2006;16:833-843.
3. Fogarty PF. Hematol Am Soc Hematol Educ Program. 2011:2011:397-404.
4. Schulte S. Thromb Res. 2013; 131 Suppl 2:S2-6.
5. Schmidbauer S et al. Thrombosis Research 2015;136(2):388-395.

Medium to long term possible therapies

There are several therapies currently being investigated that aim to extend the half-life of clotting factors or otherwise achieve a prolonged therapeutic effect.

➜ **Antibodies**

- Emicizumab (ACE910, factor VIII-mimetic antibody)[1]
- Concizumab (TFPI inhibitor)

➜ **Chemical modifications**

- Polysialylation (conjugation with polysialic acid)[2]

➜ **Protein fusion**

- XTENylation[3]

➜ **RNAi (gene silencing)**

- Antithrombin III downregulation[3]

➜ **Gene therapy**

- Viral vectors with a correct copy of FVIII or FIX gene

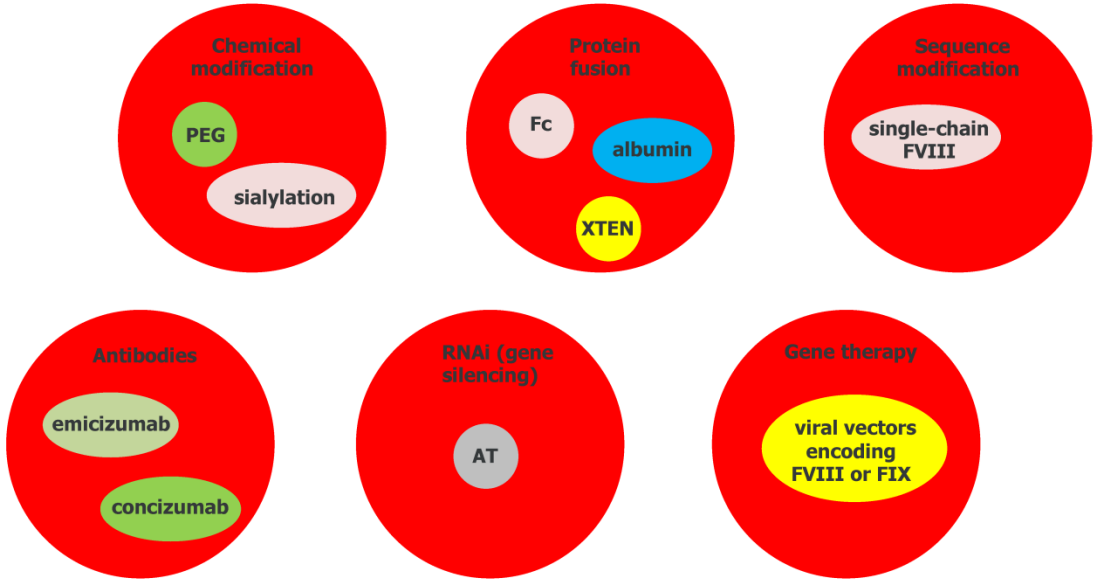
FVIII-mimetic antibody: a monoclonal bispecific antibody that binds FIXa and FX. Normally, FIXa activates FX, but requires FVIII to do so. Emicizumab mimics that function of FVIII.

Polysialic acid: a biocompatible and biodegradable natural sugar polymer.

XTENylation: XTEN is a large, unstructured recombinant protein consisting of 864 natural amino acids, which when merged to a peptide or protein, prolongs its half-life in the plasma.

1. Sampei Z et al., MAbs. 2015;7(1):120-8.
2. Peyvandi F. J Thromb Haemost 2013; 11 (suppl. 1): 84-98.
3. Schellenberger V et al. Nat Biotechnol. 2009;27:1186-1190.

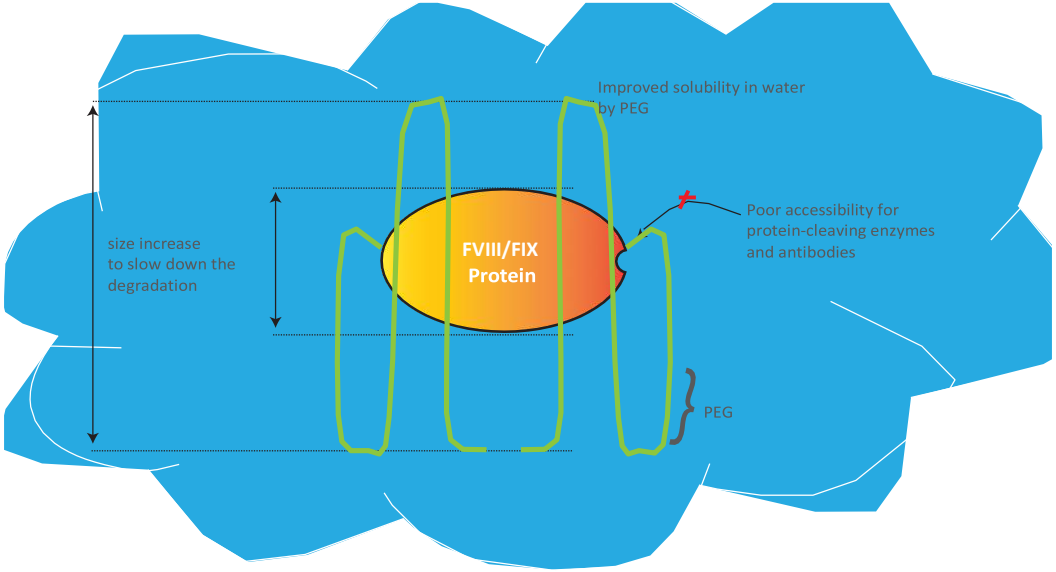
The following are major methods for the half-life extension as well as non-replacement therapies under development:



XTEN = polypeptide composed of natural amino acids

PEG = polyethylene glycol
TFPI = tissue plasminogen factor pathway inhibitor
AT = antithrombin

The mechanism of half-life extension by PEGylation



The illustration shows how PEGylation extends the clotting factors' half-life. The polymer (PEG), represented as a green chain molecule, shields the protein from degrading substances and slows down its clearance.

Veronese F & Pasut G. Drug Discovery Today 2005;10:21: 1451-1458.

PEGylation of proteins (clotting factors)

➜ Chemical attachment of PEG molecules of different sizes to specific sites on the protein via covalent bonds

➜ **Site-specific and controlled**

▶ **Site-specific**

- rFVIII (BAY94-9027) – 60 kDa PEG
- rFVIII (N8-GP) – 40 kDa PEG
- rFIX (N9-GP) – 40 kDa PEG
- rFVII (N7-GP9) – 40 kDa PEG

▶ controlled

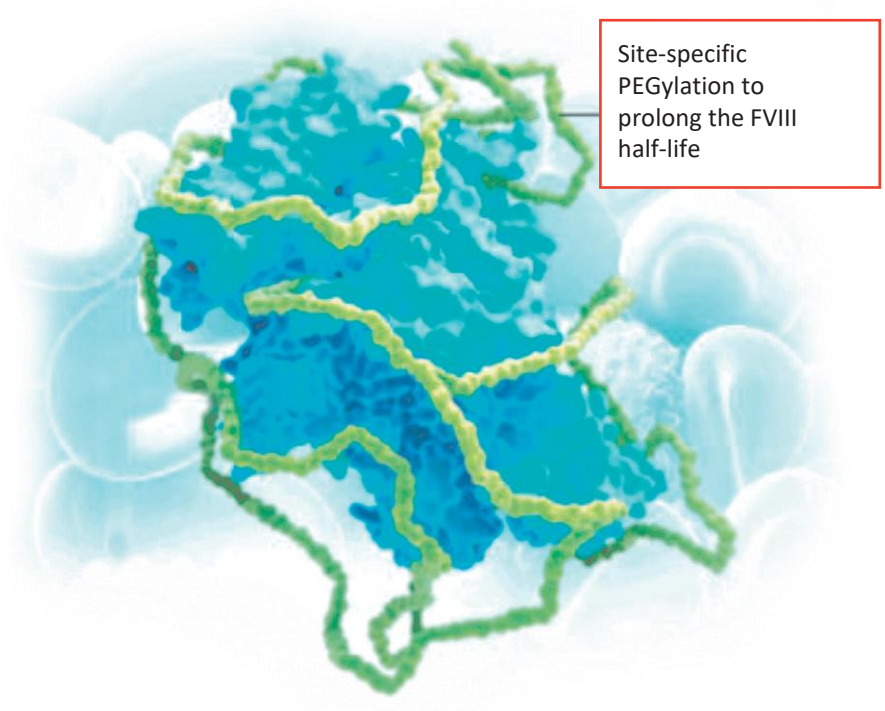
- rFVIII (BAX855) – 20 kDa PEG

The individual manufacturers use differently sized PEG molecules and bind these at different sites of the clotting factor.

kDa = kilodalton = size of the PEG molecule
BAY = Bayer
N = Novo Nordisk
BAX = Baxalta / Shire
GP = glycopegylation
Site-specific = binding site is predetermined (all procedures), very specific structures are created, to which PEG binds
In Bax 855, PEG binds to 1-2 lysines (therefore controlled)
Covalent bond = strong chemical bond

PEGylation
BAY94-9027

➜ site-specific, covalent attachment of a branched PEG molecule of 60 kDa total size (about 2 x 30 kDa)

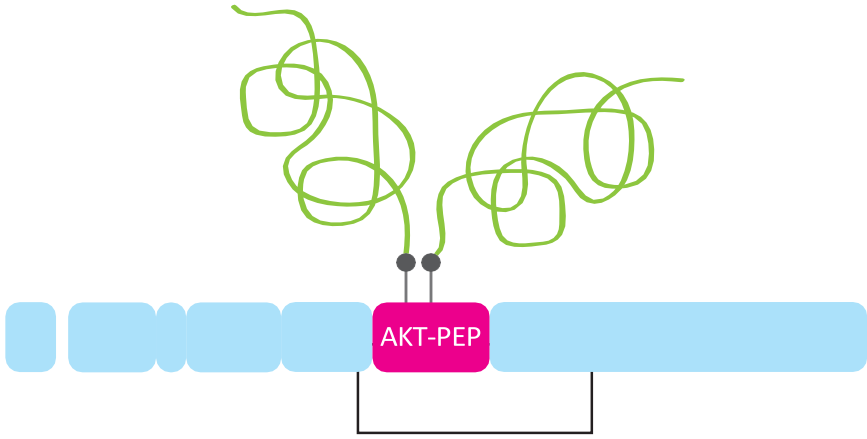


The illustration shows the clotting factor VIII or IX (light blue) and a PEG polymer (green). The green PEG polymer slows down clearance.

1. Mei B et al. Blood 2010; 116 (2): 270-9.
2. Coyle TE et al. J Thromb Haemost. 2014; 12 (4): 488-96.
3. Bayer HealthCare Pharmaceujcals, Inc. Press release, February 18, 2014

GlycoPEGylated
rFVIII (N8-GP) and rFIX (N9-GP)

➜ Site-specific PEGylation
➜ Covalent binding of **40 kDa PEG** molecules
➜ PEGylation of N-glycans (FIX) or O-glycans (FVIII)



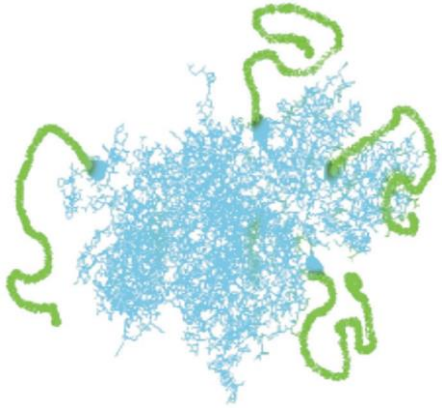
The illustration shows the key features of glycoPEGylation in the case of factor IX. PEG molecules are attached to N-glycans (complex carbohydrates linked to proteins) on the activation peptide (pink) within the clotting factor (light blue). This modification protects the factor from premature degradation. When bleeding ensues and the factor is needed to stop it, the activation peptide is cleaved off together with the PEG, which activates the clotting factor and allows it to promote clotting. FVIII differs in structure from FIX and so in the case of N8-GP PEG is attached to a different carbohydrate chain (called O-glycan), but FVIII activation proceeds in a similar way, with the protein fragment containing the PEGylated O-glycan being cleaved off.

ACT-PEP = activation peptide

1. 1. Østergaard H et al. Blood 2011, 118: 2333-2341.
2. 2. Negrier C et al. Blood 2011, 118: 2695-701.

Full-length PEGylated rFVIII (BAX855)

- **B**AX 855 is a PEGylated full-length (with the whole B domain retained, as opposed to B domain-deleted) recombinant FVIII . [1]
- Covalent binding of **20 kDa PEG** molecules
- Controlled PEGylation of exposed amino acid side-chains



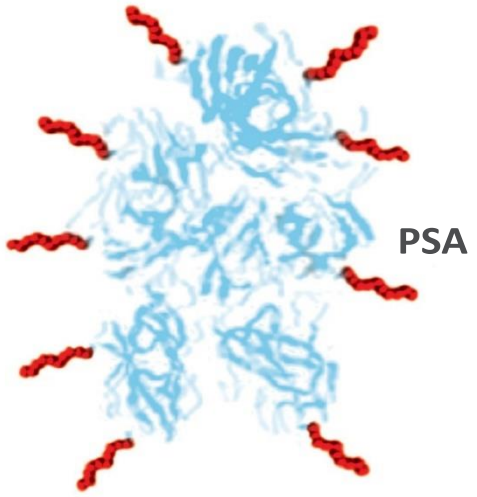
Light blue: FVIII
Green: PEG

The illustration shows the clotting factor (blue) and 4 polymers (green), which represent PEG. The PEG polymers slow down clearance of the clotting factor.

1 Horling FM et al. Blood 2011;118(21):3323.

Polysialylation (conjugation with polysialic acid)

- **Biocompatible and Biodegradable Natural Polymer** [1]
- Polysialic acid (PSA) could significantly improve half-life [2], although a clinical trial of factor VIII-PSA was discontinued due to disappointing results. Opportunities to use this technology with other clotting factors are being explored.



The illustration shows the clotting factor (blue) and 9 worm-shaped polymers (polysialic acid) (red). The red polymers protect the clotting factor from rapid degradation and slow down its renal clearance .

Polysialic acid is a complex carbohydrate produced and degraded by the body itself as part of glycoproteins and glycolipids.[3]

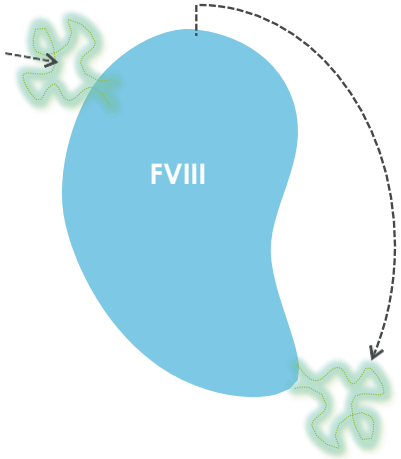
The mechanism of action is similar to the PEGylation.

1. Peyvandi et al. J Thromb Haemost. 2013;11 Suppl 1:84-98.
2. Rottensteiner H et al. Blood 2007, 110(11): 3150.
3. Zhang T. et al Asian Journal of Pharmaceutical Sciences 2014;9:75-81.

XTENylation

➜ XTENylation:

- ➜ a clotting factor is modified by fusion with XTEN, a biocompatible and biodegradable, physiologically inert polypeptide[1]
- ➜ XTEN could significantly improve half-life[2]



rFVIII-XTEN/D'D3 fusion protein

The illustration shows the clotting factor (blue) and 2 coil-shaped polymers (XTEN, amino acid sequence) (green). The green polymers delay clearance of the clotting factor.

1. Liu T et al. Haemophilia 2014; 20 (Suppl. 3), 1-186. [Abstract].
2. Podust VN. et al. J Control Release 2015; S0168-3659(15)30205-4.

Protein fusion

➜ **Fusion of the clotting factor with another blood protein or a protein fragment (e.g. albumin and IgG-Fc, respectively), whose half-life is longer.**

In protein fusion technology, a recombinant clotting factor is fused with another protein (immunoglobulin fragment or albumin) by genetic engineering, resulting in a single fusion protein. Immunoglobulins and albumins show longer half-lives (weeks) than clotting factors (hours). The fusion prolongs the half-life of the clotting factor. These fusion proteins are completely degraded and recycled naturally by the body.

rFIX-FP
Factor IX-albumin fusion protein

- **Albumin is a protein with a long half-life[1], produced in large quantities in the body**
- **Genetic fusion of recombinant albumin and rFIX with a cleavable linker[4]**
- **Recycling by FcRn (neonatal Fc receptor)[3]**
- **When activated, FIXa is released and albumin is split off[2]**

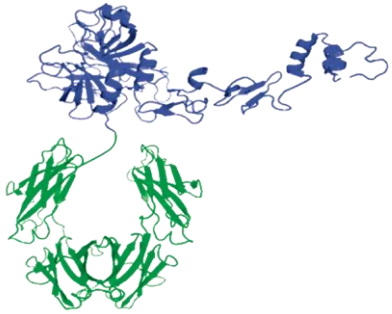
rIX-Albumin fusion[2]
CSL-654, rIX-FP

The illustration shows the clotting factor IX (dark blue) fused with albumin (yellow). The activation peptide (connecting the two functional parts of the protein is shown in green). The arrows indicate cleavage sites (the cleavage activates FIX). The albumin protects the factor from rapid degradation. When bleeding starts and the clotting factor is needed at the site of blood vessel injury, the activation peptide is excised, the albumin molecule split off and the activated clotting factor promotes blood clotting.

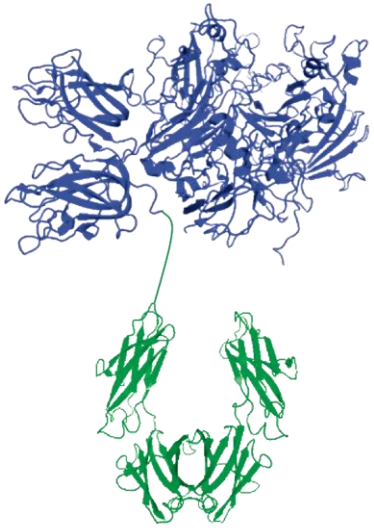
1. Schulte S. Thromb Res. 2011;128 Suppl 1:S9-S12.
2. Metzner HJ et al. Thromb Haemost. 2009;102(4):634-644.
3. Lillicrap D. Curr Opin Hematol. 2010;17(5):393-397.
4. Schulte S. Thromb Res. 2013; 131 Suppl 2:S2-6.

rFIX-Fc and rFVIII-Fc fusion proteins

- **r FIX-Fc and rFVIII-Fc each consist of a single FIX or FVIII molecule fused to two Fc domains of the human IgG1.[1,2,3]**
- **Recycling by FcRn**



A cartoon model of rFIX-Fc



A cartoon model of rFVIII-Fc

A single FIX molecule (blue) or FVIII molecule (blue) is fused to a dimeric (double) Fc region of human IgG1 (green). FcRn (neonatal Fc receptor) reverses the uptake of FVIII-Fc or FIX-Fc and recycles it back to the bloodstream. Recycling by FcRn protects the clotting factor from degradation.

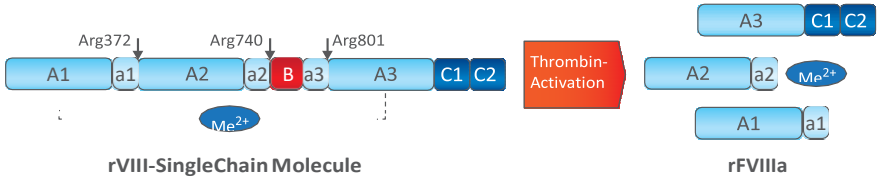
rFIX-Fc = recombinant factor IX-Fc fragment fusion protein
IgG = immunoglobulin G

1. Peters RT et al. Blood 2010;115(10):2057-64.
2. Shapiro A et al. Blood 2012;119(3):666-72.
3. Dumont J et al. TherapeuPc Monoclonal AnPbodies: John Wiley & Sons, Inc.; 2009. S. 779-95.

Sequence modification

Single-chain FVIII molecule [1-5]

- ➜ **rFVIII with a truncated B-domain**
- ➜ **Covalently bound FVIII-HCh (heavy chain) and FVIII-LCh (light chain)**
- ➜ **Increased binding affinity to VWF**
- ➜ **Activation by thrombin generates native FVIIIa**



rVIII-SingleChain Molecule rFVIIIa

Site-specific changes in the FVIII gene nucleotide sequence, and thus in its protein amino acid sequence, lead to formation of a stronger, covalent bond between the heavy (light blue) and light chain (dark blue) of the clotting factor, generating a single molecule, as opposed to two parts (heavy and light chain) of FVIII held together by weaker interactions in the unmodified FVIII. This also results in stronger binding to VWF, which protects FVIII from rapid degradation. Activation by thrombin produces a normal active clotting factor VIII.

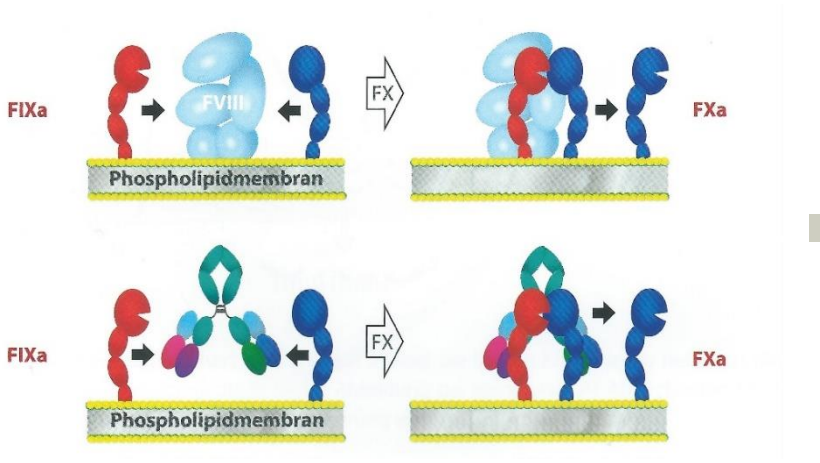
1. Schulte S. Thromb Res. 2013; 131 Suppl 2:S2-6.
2. Thompson AR. Semin Thromb Hemost 2003; 29(1):011022.
3. Lacroix-Desmazes S et al. Blood 2008;112:240-9.
4. Pipe SW. Haemophilia 2009:15(6):1187-96.
5. Schmidbauer S et al. Thrombosis Research 2015;136(2):388-395.

Antibodies: emicizumab

Concept of a FVIIIa-mimetic bispecific antibody

The antibody imitates (mimics) the function of the activated factor VIII molecule, binding both factor IXa and factor X (bispecific).

- ➜ **The bispecific antibody allows interaction between FIXa and FX, thereby activating FX and promoting blood clotting.**



a = is for activated clotting factor

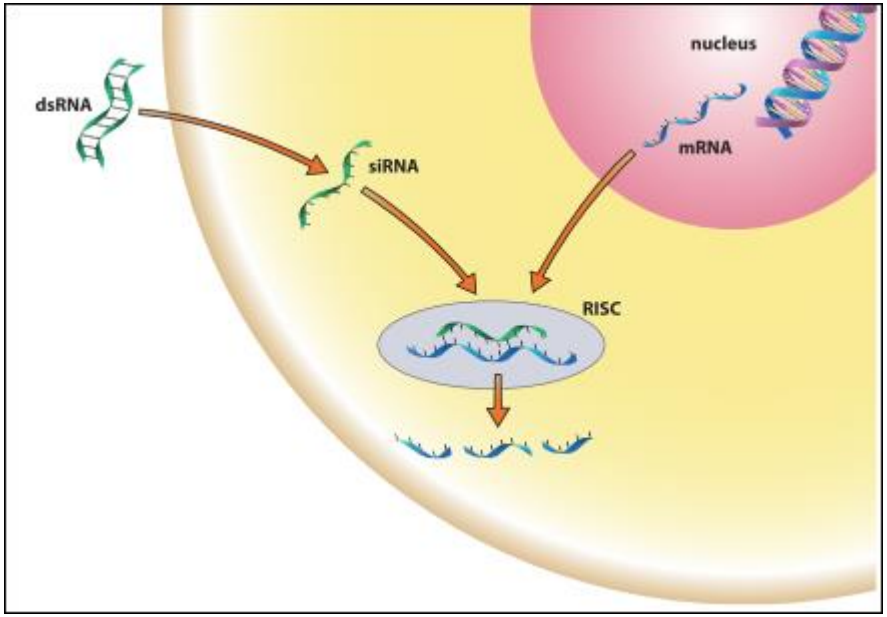
Monoclonal bispecific antibody binds FIXa and FX (lower panel), so that FIXa can activate FX. This is exactly what FVIII does (upper panel).

1. Kitazawa T et al. Nature Medicine 2012;18(10):1570.
2. Sampei Z et al. PLoS One 2013;8(2):e57479.
3. Muto A et al. J Thromb Haemost 2014;12(2):206-213.

Downregulation of antithrombin by RNAi

➜ **Antithrombin is a clotting inhibitor that is normally present in the body of healthy individuals, which prevents blood from clotting excessively.**

➜ **RNA interference (RNAi) is a natural mechanism of gene silencing (to decrease synthesis of respective proteins) in many organisms.**



The siRNA molecule (ALN-AT3) that downregulates antithrombin is conjugated with *N*-acetylgalactosamine (a type of sugar), which allows its uptake by the liver cells. Once in the liver cell, the siRNA molecule targets the mRNA encoding antithrombin, leading to its breakdown, so that no antithrombin can be synthesized.

dsRNA = double stranded; siRNA = small interfering RNA (ribonucleic acid); RISC = RNA-induced silencing complex; mRNA = messenger RNA; RNA = ribonucleic acid

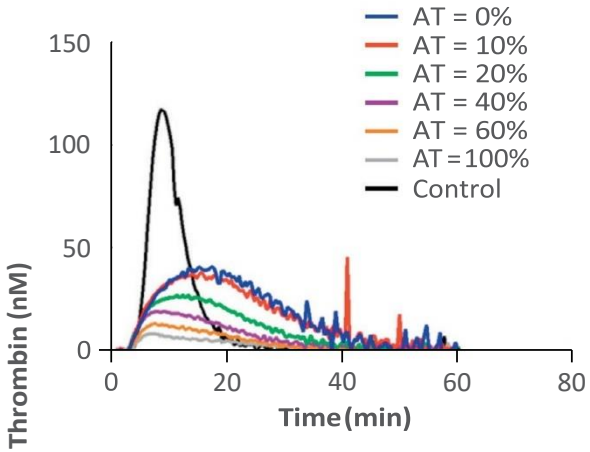
R. Robinson PLoS Biology 2004; Vol. 2(1):E28.

Gene silencing:
Downregulation of antithrombin (AT)

ALN-AT3

Antithrombin (AT) inhibits thrombin, which hinders blood clotting.

➜ **AT depletion by ALN-AT3 boosts thrombin generation in severe haemophilia A individuals (FVIII <1%)**



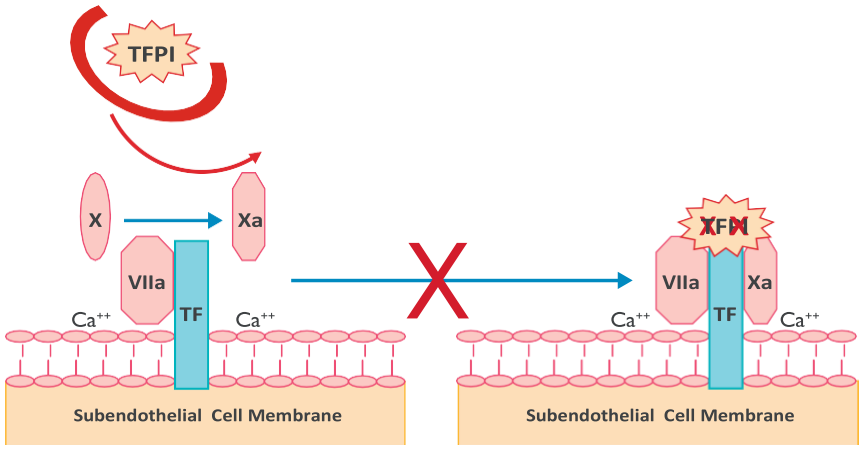
Increase in thrombin generation correlates well with AT depletion. Total AT depletion (blue curve) boosts thrombin generation to about 50% of normal (black curve).

Sehgal A et al. Nat Med. 2015;21(5):492-7.

Antibodies:
Blocking a clotting inhibitor (TFPI)

Blocking a clotting inhibitor (TFPI)

To prevent the blood clotting from turning into thrombosis, there are natural pathways of clotting inhibition, for example tissue factor pathway inhibitor (TFPI). In patients with haemophilia, the clotting process is already hindered, so blocking a clotting inhibitor rebalances the procoagulant and anticoagulant factors, which promotes normal blood clotting in people with haemophilia.

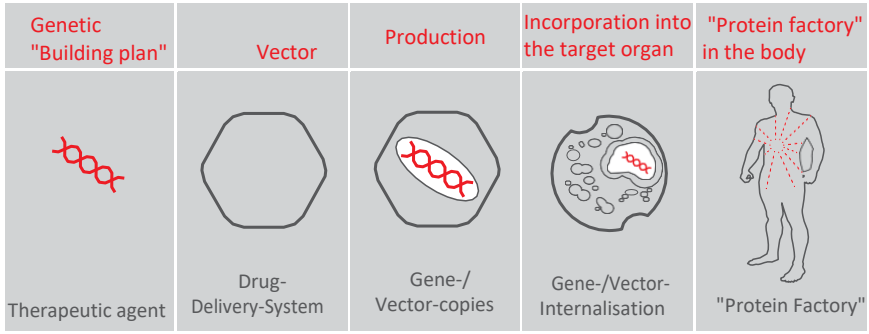


Blocking Tissue Factor Pathway Inhibitor (TFPI)

The FVIIa /TF complex activates FX to FXa. This process is inhibited by TFPI (tissue factor pathway inhibitor), so that less FXa is produced. Thus, inhibition of TFPI produces more FXa. FXa is also generated in another pathway, which involves FVIII and FIX.

Gene therapy

- **The essential components of gene therapy**
- **Forcing the body's cells to produce the missing protein**



The desired gene sequence is first inserted into a vector (transport vehicle, often a nonpathogenic virus). The viral vector brings the DNA sequence into the target cell. There, it is deposited (episomally) separately from the patient's DNA outside the chromosomes or integrated into the patient's DNA (chromosomes). In both cases, the gene sequence can be read off by the cell's machinery, leading to synthesis of the missing protein (protein factory).

- Illustration modified according to UnicQure lecture "GeneTherapy for Haemophilia, Is the Technology Ready for Prime Time? ", presented at the Hamburg Haemophilia Symposium, 7-8 November 2014.
- Naldini L. Nature 2015;526(7573):351-60.

Half-life extension

The following pages provide an overview of the extended half-life products already approved and products under development.

Notably, factor VIII products show half-lives extended 1.7 fold at best (1.5 fold on average). None of the different technologies presented in the previous chapter provide any major difference in the half-life extension.

This is in contrast to the extended half-life FIX products, each of which shows on average a 5-fold half-life extension.

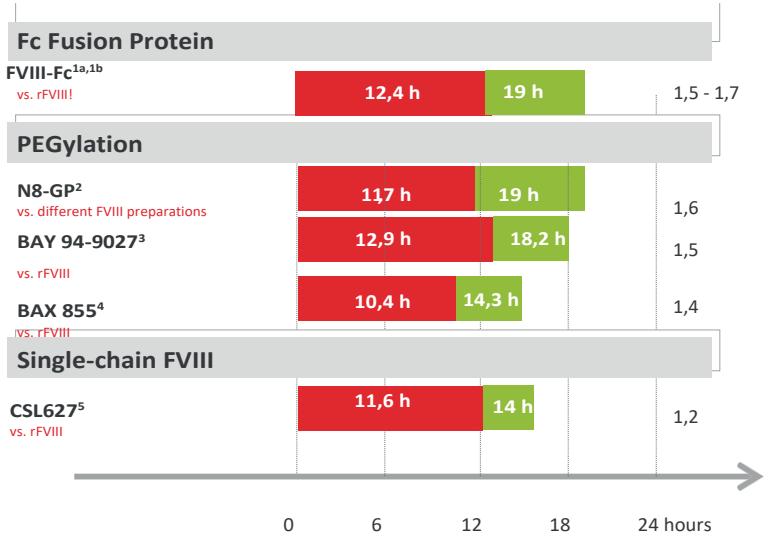
Since individual rFVIII and the rFIX products differ in terms of patient populations they were tested on and the study design, it would be inaccurate to make side-by-side comparisons of the products described here. The production cell line (animal or human) or the technology of modification (e.g. chemical or by genetic engineering) of individual products may all prove to have unique and specific advantages in different patients.

On the other hand, despite encouraging initial results of non-replacement therapies and

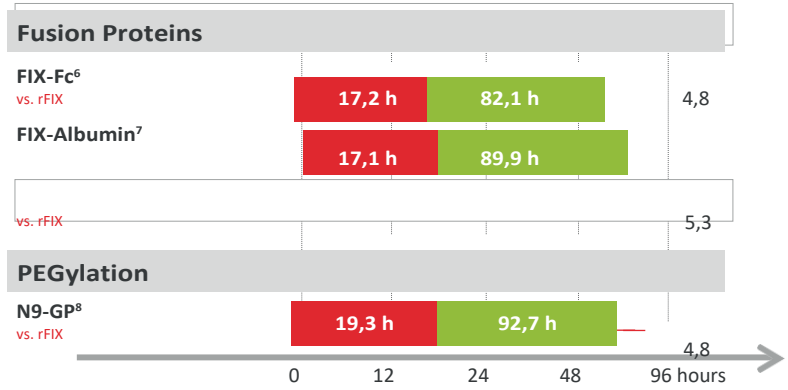
gene therapy, large phase III studies are yet to be completed.

Therefore, at the end of this chapter, the advantages and disadvantages of the initially presented extended half-life FVIII and FIX products are primarily summed up.
What exactly will be the impact of the half-life extension on the clinical practice is described from page 32 onwards, including different scenarios.

FVIII Products



FIX Products



1. a) Powell JS et al. Blood 2012; 119: 3031–7.; b) Mahlangu J et al. Blood 2014;123(3):317-25.;
2. Tiede A et al. J Thromb Haemost 2013; 11: 670–8.;
3. Coyle TE et al. J Thromb Haemost 2014;12: 488–96.;
4. a) Konkle BA et al. Blood 2015;126(9):1078-85.; b) Bevan DH et al. Haemophilia 2013; 19 (Suppl. 2), 10-82. PO53.
5. Mahlangu J et al. Haemophilia 2016; 22 Suppl.2, P063.
6. Powell JS et al. N Engl J Med. 2013;369(24):2313-23.
7. Santagosjno E et al. Blood 2012; 120(12): 2405-11.
8. Negrier C et al. Blood 2011;118(10):2695-701.

Emicizumab (ACE910)

- Once weekly prophylaxis with emicizumab (administered subcutaneously) showed good efficacy in individuals with severe haemophilia A and inhibitors[1]. The drug will be licensed in Europe for treatment of these patients in the coming months.

Gene Therapy

- Clinically significant factor levels have been achieved, even in patients who mounted an immune response to viral vectors. This response remains a serious obstacle in some studies.[2] Yet, phase III studies of gene therapies for both haemophilia A and B will soon commence.
- Some patients achieved sustained high factor levels, which made replacement therapy with factor substitution unnecessary. To maintain factor production in the liver, some patients who show immune response to vectors may require treatment with cortisone.
- In the case of haemophilia A, the first promising results with this technology were presented in 2016.[3]

1. Shima M et al. Journal of Thrombosis and Haemostasis 2015; 13 (Suppl. 2):1–997. AS017.
2. Monahan P et al. Journal of Thrombosis and Haemostasis 2015; 13 (Suppl. 2):1–997. LB010.
3. Pasi J et al. Haemophilia 2016; 22 (Suppl. 4): 151–152. Late-breaking Abstract.

Pros:

- Reduced frequency of infusions
- Better protection against bleeding and joint damage
- Better adherence to prophylaxis

Cons:

- Immune response
- Allergic reactions
- Difficult laboratory monitoring
- Potential accumulation of PEG in the body
- Adverse events may occur that might be difficult to prepare for and respond to
- Gene therapy cannot be repeated with the same vector

Different scenarios for using products with extended half-life

In the following section, three possible scenarios of prophylaxis with extended half-life rFVIII and an example for rFIX are shown. The choice of treatment regimen should be made jointly by the patient and the physician based on the individual clinical picture.
A patient with FVIII deficiency with a lot of breakthrough bleeds, for example, may not benefit from less frequent infusions, since it would waste an opportunity to achive better protection of the patient from bleeding.
On the other hand, a patient with FVIII deficiency who experiences few spontaneous bleeds on prophylaxis with standard half-life products may do well on fewer infusions and consume less factor while enjoying the same level of protection.

The example of using EHL FIX for haemophilia B presented at the end involves reducing the number of injections from two to one per week. However, the intervals between infusions may be extended to 10 or even 14 days, with appropriate dosage adjustment.

In terms of weighing all the different needs and aspects of care (venous access, adherance, bleeding tendency etc.), it seems reasonable to choose the longest possible prophylaxis interval with the new products, as long as it does not compromise the protection from bleeding.

Fewer infusions per week with the *same* dose (haemophilia A)

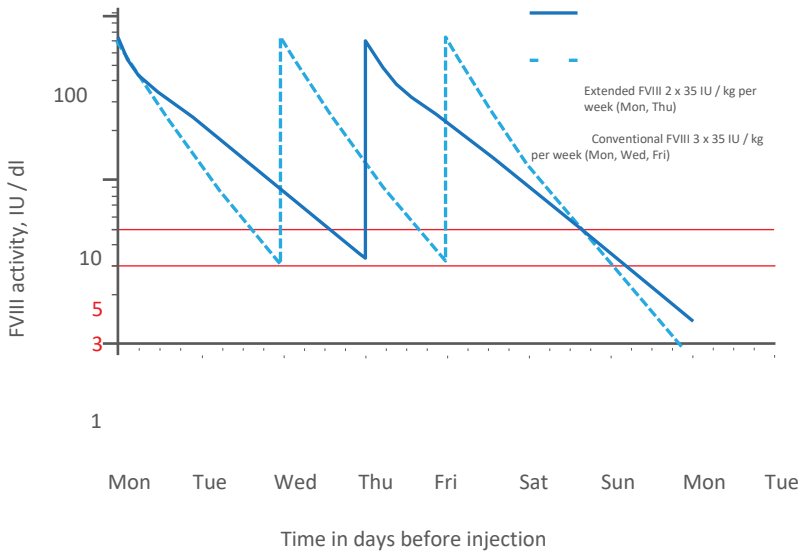
➜ Frequency of injections

- reduced from 3x weekly to 2x weekly

➜ **Dosage**

- extended rFVIII: **2 x 35 IU / kg** per week (e.g., Monday, Thursday)
- conventional FVIII: **3 x 35 IU / kg** per week (e.g., Monday, Wednesday, Friday)
- reduced weekly consumption

➜ **The same trough level and fewer injections (presumably the same protection against spontaneous bleeding)**



1. Berntorp E. et al. Haemophilia 2016;22(3):389-96.
2. Nestorov I et al. Clinical Pharmacology in Drug Development 2015; Volume 4, Issue 3: 163–174.
3. Shapiro AD et al. J Thromb Haemost. 2014;12(11):1788-800.

Fewer infusions per week with *higher* dose (haemophilia A)

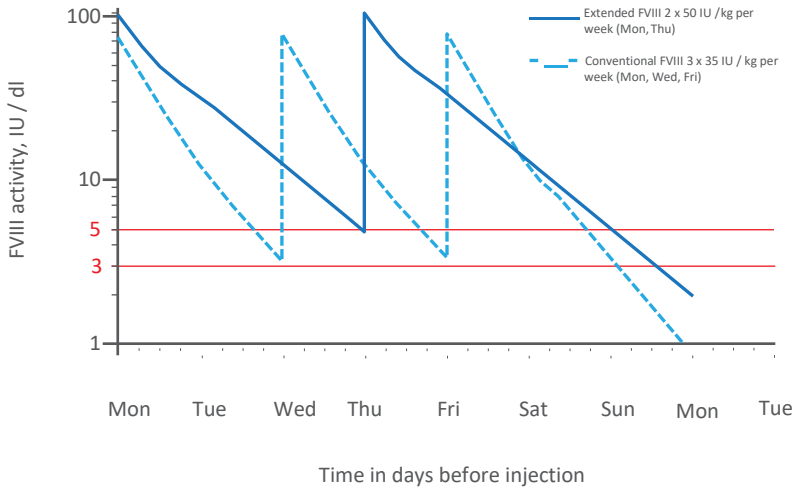
➜ Frequency of injections

- reduced from 3x weekly to 2x weekly

➜ Dosage

- extended rFVIII: **2 x 50 IU / kg** per week (e.g., Monday, Thursday)
- Conventional FVIII: **3 x 35 IU / kg** per week (e.g., Monday, Wednesday, Friday)
- Approximately the same weekly consumption

➜ **Higher trough levels and fewer injections (presumably higher protection against spontaneous bleeding)**



1. Berntorp E. et al. Haemophilia 2016;22(3):389-96.
2. Nestorov I et al. Clinical Pharmacology in Drug Development 2015; Volume 4, Issue 3: 163–174.
3. Shapiro AD et al. J Thromb Haemost. 2014;12(11):1788-800.

The *same* treatment regimen with the *same* dose (haemophilia A)

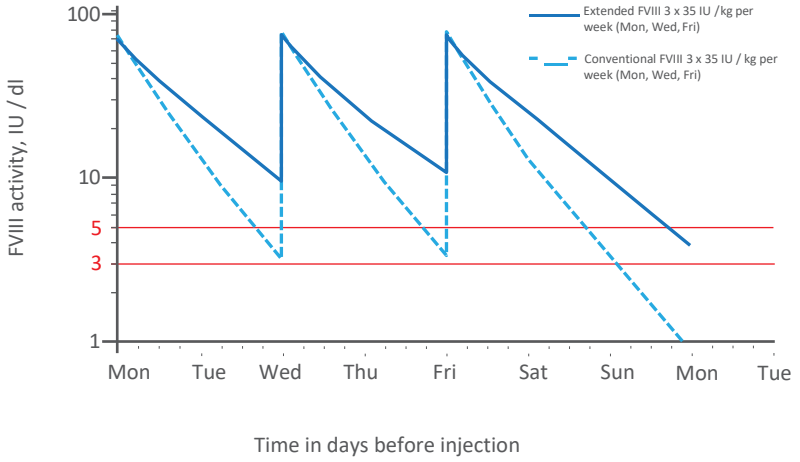
➜ Frequency of injections

- 3x weekly

➜ Dosage

- extended rFVIII: **3 x 35 IU / kg** per week (e.g., Monday, Wednesday, Friday)
- Conventional FVIII: **3 x 35 IU / kg** per week (e.g., Monday, Wednesday, Friday)
- the same weekly consumption

➜ **Much higher trough levels with the same number of injections (presumably significantly higher protection against spontaneous bleeding)**



1. Berntorp E. et al. Haemophilia 2016;22(3):389-96.
2. Nestorov I et al. Clinical Pharmacology in Drug Development 2015; Volume 4, Issue 3: 163–174.
3. Shapiro AD et al. J Thromb Haemost. 2014;12(11):1788-800.

Fewer infusions per week with the *same* dose (haemophilia B)

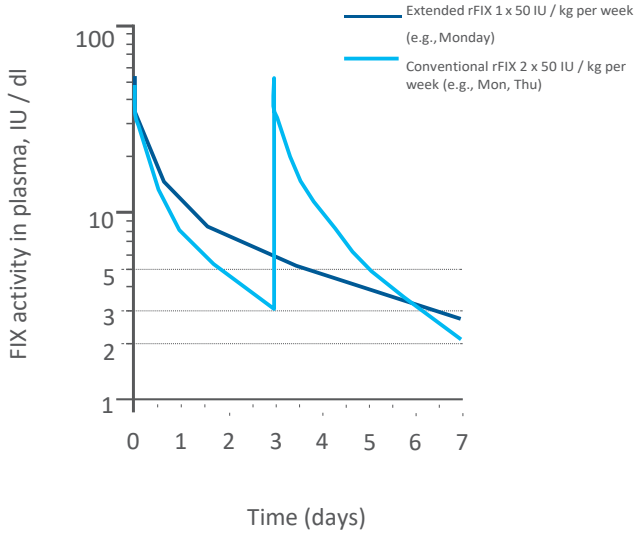
➜ Frequency of infusions

- reduced from 2x weekly to 1x weekly

➜ Dosage

- extended rFIX: **1x 50 IU / kg** per week (e.g., Monday)
- conventional rFIX: **2x 50 IU / kg** per week (e.g., Monday, Thursday)
- reduced weekly consumption

➜ **The same trough level and fewer infusions (presumably the same protection against spontaneous bleeding)**



Summary

Summary

- **Various technologies have been developed to extend half-life.**
- **Since 2016, two rFIX and three rFVIII have already been licensed and available in Europe.**
- **Further products will be licensed from 2018 onwards.**
- **The half-life can be extended**
  - Factor IX: approximately 5-fold / 1 infusion every 1-2 weeks
  - Factor VIII: approximately 1.5 fold/ 2 infusions per week
- **Improvement in treatment outcomes is the main goal**
  - higher factor levels / better protection
  - less spontaneous bleeding
  - better treatment adherence / less dependence on therapy
- **Non-replacement therapies will be available in the medium term.**

Note of thanks

For scientific support:

- Dr. Robert Klamroth
- PD Dr. Karin Kurnik
- Prof. Wolfgang Miesbach
- Prof. Johannes Oldenburg
- Prof. Andreas Tiede

For the provision and friendly approval of the use of illustrations as well as the factual verification:

- Alnylam
- Bayer
- Baxalta/Shire
- Chugai/Roche
- CSL Behring
- Novo Nordisk
- Sobi

For the coordination of this initiative and the compilation of this brochure:

- Werner Kalnins
- Dr. Sylvia von Mackensen

For the EHC translation and adaption:

- Anush Smbatya
- Team of EHC: Radoslaw Kaczmarek, Fiona Brennan, Raia Mihaylova, Jo Eerens

Bibliography

1. Bayer HealthCare Pharmaceuticals, Inc. Press release, Feb. 18, 2014; http://www.prnewswire.com/news-releases/bayers-long-acting-recombinant-factor-viii-demonstrated-prophylaxis-with-less-frequent-infusions-in-haemophilia -a-in-phase-iii-trial-245924561.html; most recently accessed on 23 February 2017.

2. Berntorp E, Negrier C, Gozzi P, Blaas PM, Lethagen S. Dosing regimens, FVIII levels and estimated haemostatic protection with special focus on rFVIIIFc. Haemophilia 2016, 22 (3): 389-96. Bevan D, Conlan M, Mant T, Lissitchkov T, Kazmi R, Chowdary P, Langer F, Shima M, Fukutake K, Singer J, Grigorian A, Ewenstein B, Wong WY. A phase 1 study of safety and pharmacokinetics (pk) of bax 855, a longer acting pegylated full-length recombinant factor VIII (PEG-RFVIII), in patients (pts) with severe haemophilia A. Haemophilia 2013;19 (Supp.2):10-82. PO53.

3. Bevan D, Conlan M, Mant T, Lissitchkov T, Kazmi R, Chowdary P,Langer F, Shima M, Fukutake K, Singer J, Grigorian A, Ewenstein B, Wong WY. A phase 1 study of safety and pharmacokinetics (pk) of bax 855, a longer acting pegylated full-length recombinant factor VIII (PEG-RFVIII), in patients (pts) with severe haemophilia A. Haemophilia 2013;19 (Supp.2):10-82. PO53.

4. Brackmann HH, Gormsen J. Massive factor-VIII infusion in haemophiliac with factor-VIII inhibitor, high responder. Lancet 1977;2(8044):933.

5. Coyle TE, Reding MT, Un JC, Michaels LA, Shah A, PoweU J. Phase 1 study of BAY 94-9027, a PEGylated 8-domain-deleted recombinant factor VIII with an extended half-life, in subjects with haemophilia A. J Thromb Haemost. 2014; 12:488-496.

6. DeFrees S, Wang ZG, Xing R, Scott AE, Wang J, Zopf D, Gouty DL, Sjoberg ER, Panneerselvam K, Brinkman-Van der Linden EC, Bayer RJ, Tarp MA, Clausen H. GlycoPEGylation of recombinant therapeutic proteins produced in Escherichia coli. Glycobiology 2006;16(9):833-43.

7. Diao L, Li S, Ludden T, Gobburu J, Nestorov I, Jiang H. Population pharmacokinetic modelling of recombinant factor IX Fc fusion protein (rFIXFc) in patients with haemophilia B. Clin Pharmacokinet. 2014;53(5):467-77.

8. Dumont JA, Low SC, Peters RT, Bitoni AJ. Monomeric Fc Fusion Molecules. In: Zhiqiang An (ed.). Therapeutic Monoclonal Antibodies. From Bench To Clinic: John Wiley & Sons, Inc., Hoboken, New Jersey; 2009: 779-95.

9. Fogarty PF. Biological rationale for new drugs in the bleeding disorders pipeline. Hematology Am Soc Hematol Educ Program. 2011;2011:397-404.

10. Horling FM, Schwele S, Lubich C, Ahmad RU, Weiller M, Spatzenegger M, Schwarz HP, Reipert BM. Preclinical Immunogenicity Assessment of Baxter's Longer-Acting FVIII Candidate BAX 855 Using Novel Preclinical Models. Blood 2011;118(21):3323.

11. Jevsevar S, Kunstelj M, Porekar VG. PEGylation of therapeutic proteins. Biotechnol J. 2010;5(1):113-28.

12. Kitazawa T, Igawa T, Sampei Z, Muto A, Kojima T, Soeda T, Yoshihashi K, Okuyama-Nishida Y, Saito H, Tsunoda H, Suzuki T, Adachi H, Miyazaki T, Ishii S, Kamata-Sakurai M, Iida T, Harada A, Esaki K, Funaki M, Moriyama C, Tanaka E, Kikuchi Y, Wakabayashi T, Wada M, Goto M, Toyoda T, Ueyama A, Suzuki S, Haraya K, Tachibana T, Kawabe Y, Shima M, Yoshioka A, Hattori K. A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a haemophilia A model. Nat Med. 2012;18(10):1570-4.

13. Konkle BA, Stasyshyn O, Chowdary P, Bevan DH, Mant T, Shima M, Engl W, Dyck-Jones J, Fuerlinger M, Patrone L, Ewenstein B, Abbuehl B. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe haemophilia A. Blood 2015;126(9):1078-85.

14. Lacroix-Desmazes S, Navarrete AM, André S, Bayry J, Kaveri SV, Dasgupta S. Dynamics of factor VIII interactions determine its immunologic fate in haemophilia A. Blood 2008;112(2):240-9.

15. Lillicrap D. Improvements in factor concentrates. Curr Opin Hematol. 2010;17(5):393-397.

16. Liu T, Chhabra ES, Kulman J, Patarroyo-White S, Drager D, Johnson B, Pierce G, Schellenberger V, Peters R and Iang HJ. Prolongedefficacy in haemophilia AmousebleedingmodelsofarecombinantFVIII-XTEN/D'D3heterodimerwithfour-fold extended half-life in circulation. Haemophilia 2014; 20 (Suppl. 3), 1-186. [Abstract].

17. Mahlangu J, Lepatan LMP, Boggio L, Klamroth R, Djambas Khayat C, Fischer K, Iosava G, Bensen-Kennedy D, Limsakun T, Veldman A, Ledger KST, Pabinger I on behalf of the AFFINITY investigators. Haemophilia 2016; 22 Suppl. 2, 13-111, P063.

18. Mahlangu J, Powell JS, Ragni MV, Chowdary P,Josephson NC, Pabinger I, Hanabusa H, Gupta N, Kulkarni R, Fogarty P,Perry D, Shapiro A, Pasi KJ, Apte S, Nestorov I, Jiang H, Li S, Neelakantan S, Cristiano LM, Goyal J, Sommer JM, Dumont JA, Dodd N, Nugent K, Vigliani G, Luk A, Brennan A, Pierce GF; A-LONG Investigators. Phase 3 study of recombinant factor VIII Fc fusion protein in severe haemophilia A. Blood 2014;123(3):317-25.

19. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, Ingram JD, Manco-Johnson ML, Funk S, Jacobson L, Valentino LA, Hoots WK, Buchanan GR, DiMichele D, Recht M, Brown D, Leissinger C, Bleak S, Cohen A, Mathew P,Matsunaga A, Medeiros D, Nugent D, Thomas GA, Thompson AA, McRedmond K, Soucie JM, Austin H, Evatt BL. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe haemophilia . N Engl J Med. 2007;357(6):535-544.

20. Mathew P,Matsunaga A, Medeiros D, Nugent D, Thomas GA, Thompson AA, McRedmond K, Soucie JM, Austin H, Evatt BL. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe haemophilia . N Engl J Med. 2007;357(6):
535-544. 19.

21. Mei B, Pan C, Jiang H, Tjandra H, Strauss J, Chen Y, Liu T, Zhang X, Severs J, Newgren J, Chen J, Gu JM, Subramanyam B, Fournel MA, Pierce GF, Murphy JE. Rational design of a fully active, long-acting PEGylated factor VIII for haemophilia A treatment. Blood. 2010;116(2):270-9.

22. Metzner HJ, Weimer T, Kronthaler U, Lang W, Schulte S. Genetic fusion to albumin improves the pharmacokinetic properties of factor IX. Thromb Haemost. 2009;102(4):634-644.

23. Monahan P,Walsh CE, Powell JS, Konkle BA, Josephson NC, Escobar M, McPhee SJ, Litchev B, Cecerle M, Ewenstein BM, Rottensteiner H, Rosa MDl, Reipert BM,Samulski RJ, Orloff J and Scheiflinger F. Update on a phase 1/2 open-label trial of BAX335, an adeno-associated virus 8 (AAV8) vector-based gene therapy program for haemophilia B Journal of Thrombosis and Haemostasis 2015; 13 (Suppl. 2):1–997. LB010.

24. Muto A, Yoshihashi K, Takeda M, Kitazawa T, Soeda T, Igawa T, Sakamoto Y, Haraya K, Kawabe Y, Shima M, Yoshioka A, Hattori K. Anti-factor IXa/X bispecific antibody (ACE910): hemostatic potency against ongoing bleeds in a haemophilia A model and the possibility of routine supplementation. J Thromb Haemost. 2014;12(2):206-213.

25. Naldini L. Gene therapy returns to centre stage. Nature 2015;526(7573):351-60.

26. Negrier C, Knabe K, Tiede A, Giangrande P,Møss J. Enhanced pharmacokinetic properties of a g1lycoPEGylated recombinant factor IX: a first human dose trial in patients with haemophilia B. Blood 2011;118(10):2695-2701.

27. Nestorov I, Neelakantan S, Ludden TM, Li S, Jiang H, Rogge M. Population pharmacokinetics of recombinant factor VIII Fc fusion protein. Clinical Pharmacology in Drug Development 2015; Volume 4, Issue 3: 163–174.

28. Ostergaard H, Bjelke JR, Hansen L, Petersen LC, Pedersen AA, Elm T, Møller F, Hermit MB, Holm PK, Krogh TN, Petersen JM, Ezban M, Sørensen BB, Andersen MD, Agersø H, Ahmadian H, Balling KW, Christiansen ML, Knobe K, Nichols TC, Bjørn SE, Tranholm M. Prolonged half-life and preserved enzymatic properties of factor IX selectively PEGylated on native N-glycans in the activation peptide. Blood 2011;118(8):2333-2341.

29. Oldenburg J. Optimal treatment strategies for haemophilia : achievements and limitations of current prophylactic regimens. Blood 2015;125(13):2038-44.

30. Pasi J, Wong W, Rangarajan S, Wilde J, Perry D, Madan B, Pierce G, Rouy D. Interim results of an open-label, phase 1/2 study of BMN 270, an AAV5-FVIII gene transfer in severe haemophilia A. Haemophilia 2016; 22 (Suppl. 4): 151–152. Late-breaking Abstract.

31. Peters RT, Low SC, Kamphaus GD, Dumont JA, Amari JV, Lu Q, Zarbis-Papastoitsis G, Reidy TJ, Merricks EP, Nichols TC, Bitonti AJ. Prolonged activity of factor IX as a monomeric Fc fusion protein. Blood. 2010;115(10):2057-64.

32. Peyvandi F, Garagiola I, Seregni S. Future of clotting factor replacement therapy. J Thromb Haemost. 2013;11 Suppl 1:84-98.

33. Pipe SW. Functional roles of the factor VIII B domain. Haemophilia 2009;15(6):1187-96.

34. Podust VN, Balan S, Sim BC, Coyle MP, Ernst U, Peters RT, Schellenberger V. Extension of in vivo half-life of biologically active molecules by XTEN protein polymers. J Control Release 2015; S0168-3659(15)30205-4.

35. Powell JS, Josephson NC, Quon D, Ragni MV, Cheng G, Li E, Jiang H, Li L, Dumont JA, Goyal J, Zhang X, Sommer J, McCue J, Barbetti M, Luk A, Pierce GF. Safety and protonged activity of recombinant factor VIII Fe fusion protein in haemophilia A patients. Blood 2012; 119(13):3031-3037.

36. Powell JS, Pasi KJ, Ragni MV, Ozelo MC, Valentino LA, Mahlangu JN, Josephson NC, Perry D, Manco-Johnson MJ, Apte S, Baker RI, Chan GC, Novitzky N, Wong RS, Krassova S, Allen G, Jiang H, Innes A, Li S, Cristiano LM, Goyal J, Sommer JM, Dumont JA, Nugent K, Vigliani G, Brennan A, Luk A, Pierce GF; B-LONG Investigators. Phase 3 study of recombinant factor IX Fe fusion protein in haemophilia B. N Engl J Med. 2013;369(24):2313-2323; Supplementary material, table S2, p.12.

37. Robinson R. RNAi Therapeutics: How Likely, How Soon? PLoS Biology 2004; Vol. 2(1):E28.

38. Rottensteiner H, Turecek PL, Pendu R, Meijer AB, Lenting P,Mertens K, Muchitsch EM, Ehrlich H, Schwarz HP. PEGylation or Polysialylation Reduces FVIII Binding to LRP Resulting in Prolonged Half-Life in Murine Models. Blood 2007, 110(11): 3150.

39. Sampei Z, Igawa T, Soeda T, Okuyama-Nishida Y, Moriyama C, Wakabayashi T, Tanaka E, Muto A, Kojima T, Kitazawa T, Yoshihashi K, Harada A, Funaki M, Haraya K, Tachibana T, Suzuki S, Esaki K, Nabuchi Y, Hattori K. Identification and multidimensional optimization of an asymmetric bispecific IgG antibody mimicking the function of factor VIII cofactor activity. PLoS One. 2013;8(2):e57479.

40. Sampei Z, Igawa T, Soeda T, Funaki M, Yoshihashi K, Kitazawa T, Muto A, Kojima T, Nakamura S, Hattori K. Non-antigen-contacting region of an asymmetric bispecific antibody to factors IXa/X significantly affects factor VIII-mimetic activity. MAbs. 2015;7(1):
120-8.

41. Santagostino E, Negrier C, Klamroth R, Tiede A, Pabinger-Fasching I, Voigt C, Jacobs I, Morfini M. Safety and pharmacokinetics of a novel recombinant fusion protein linking clotting factor IX with albumin (rIX-FP) in haemophilia B patients. Blood 2012; 120(12):2405-2411.

42. Schellenberger V, Wang CW, Geething NC, Spink BJ, Campbell A, To W, Scholle MD, Yin Y, Yao Y, Bogin O, Cleland JL, Silverman J, Stemmer WP. A recombinant polypeptide extends the in vivo half-life of peptides and proteins in a tunable manner. Nat Biotechnol. 2009;27(12):1186-90.

43. Schmidbauer S, Witzel R, Robbel L, Sebastian P,Grammel N, Metzner HJ, Schulte S. Physicochemical characterisation of rVIII-SingleChain, a novel recombinant single-chain factor VIII. Thrombosis Research 2015;136(2):388–395.

44. Schulte S. Pioneering designs for recombinant clotting factors. Thromb Res. 2011;128 Suppl 1:S9-S12.

45. Schulte S. Innovative clotting factors: albumin fusion technology and recombinant single-chain factor VIII. Thromb Res. 2013;131 Suppl 2:S2-6.

46. Sehgal A, Barros S, Ivanciu L, Cooley B, Qin J, Racie T, Hettinger J, Carioto M, Jiang Y, Brodsky J, Prabhala H, Zhang X, Attarwala H, Hutabarat R, Foster D, Milstein S, Charisse K, Kuchimanchi S, Maier MA, Nechev L, Kandasamy P,Kel'in AV, Nair JK, Rajeev KG, Manoharan M, Meyers R, Sorensen B, Simon AR, Dargaud Y, Negrier C, Camire RM, Akinc A. An RNAi therapeutic targeting antithrombin to rebalance the clotting system and promote hemostasis in haemophilia . Nat Med. 2015;21(5):492-7.

47. Shapiro AD, Ragni MV, Kulkarni R, Oldenburg J, Srivastava A, Quon DV, Pasi KJ, Hanabusa H, Pabinger I, Mahlangu J, Fogarty P, Lillicrap D, Kulke S, Potts J, Neelakantan S, Nestorov I, Li S, Dumont JA, Jiang H, Brennan A, Pierce GF. Recombinant factor VIII Fc fusion protein: extended-interval dosing maintains low bleeding rates and correlates with von Willebrand factor levels. J Thromb Haemost. 2014;12(11):1788-800.

48. Shapiro A, Ragni MV, Valentino LA, Key NS, Josephson NC, Powell JS, Cheng G, Thompson AR, Goyal J, Tubridy KL, Peters RT, Dumont JA, Euwart D, Li L, Hallén B, Gozzi P, Bitonti AJ, Jiang H, Luk A, Pierce GF. Recombinant factor IX-Fc fusion protein (rFIXFc) demonstrates safety and prolonged activity in a phase 1/2a study in haemophilia B patients. Blood. 2012;119(3):666-72.

49. Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, Fukazawa N, Yoneyama K, Yoshida H, Takahashi H and Nogami K. Long-term safety and prophylactic efficacy of once weekly subcutaneous administration of ACE910, in Japanese haemophilia A patients with and without FVIII inhibitors: interim results of the extension study of a phase 1 study. Journal of Thrombosis and Haemostasis 2015; 13 (Suppl. 2):1–997. AS017.

50. Thompson AR. Structure and function of the factor VIII gene and protein. Semin Thromb Hemost. 2003 Feb;29(1):11-22.

51. Tiede A, Brand B, Fischer R,. et al. Enhancing the pharmacokinetic properties of recombinant factor VIII: first-in-human trial of glycoPEGylated recombinant factor VI 11 in patients with haemophilia A. J Thromb Haemost. 2013; 11:670-678.

52. Veronese FM, Pasut G. PEGylation, successful approach to drug delivery. Drug Discov Today. 2005;10(21):1451-8.

53. WFH Timeline. http://www1.wfh.org/2/1/1_1_3_Link1_Timeline.htm last accessed on February 23, 2017.

54. Zhang T, She Z, Huang Z, Li J, Luo X, Deng Y. Application of sialic acid/polysialic acid in the drug delivery systems. Asian Journal of Pharmaceutical Sciences 2014;9: 75-81.

Glossary

Albumins	soluble proteins synthesized in the liver, which are about 52-62% of the total protein of the blood plasma
Antibody ACE910	ACE910, or emicizumab, is a bispecific antibody mimicking the function of factor VIII
Antithrombin (AT)	antithrombin, short AT, also called antithrombin III, is a protein that inhibits blood clotting to prevent it from clotting excessively
Bispecific	as in bispecific antibodies, which refers to their ability to specifically bind two different antigens (as opposed to normal antibody, which is monospecific)
Hepatitis C	one of various forms (A, B, D, E) of liver inflammation caused by viruses
Chromosomes	highly organised genomic DNA
Dimer	a dimer is a molecule, or a molecular compound, consisting of two often identical subunits (which individually would be called monomers)
DNA/DNS	deoxyribonucleic acid, a key carrier of gene information (genes) in the cell
dsRNA	double-stranded RNA
Episomes	Episomes are extragenomic DNA elements, which may be introduced into a cell (as is the case with gene therapies), persist there and encode proteins
Fusion proteins	a fusion protein (or hybrid protein) is formed by joint expression of two genes or gene segments that lie one next the other in a stretch of DNA. By removing the stop codon behind the first gene both genes are read as if they were a single gene, which allows synthesis of two unrelated proteins as one protein

Fc region	in contrast to the antigen-binding Fab fragment, the Fc fragment is a conserved part of the antibody
FcRn	neonatal Fc receptor, a cell surface protein, which recognizes the Fc fragment of immunoglobulin G and albumin, and recycles them back to the circulation. This mechanism is used to extend half-lives of clotting factors by fusing them with the Fc fragment or albumin
Clotting factors	are enzymes or cofactors (mostly proteins) which form complexes in the presence of Ca-ions to promote blood clotting
Glycans	Also referred to as polysaccharides, are carbohydrates in which a large number (at least ten) monosaccharides (single sugars) are linked via glycosidic bonds
Haemophilia	is a congenital lifelong bleeding disorder caused by a deficient activity of the clotting factor VIII (haemophilia A) or IX (haemophilia B)
IgG1	a subclass of IgG
Immunoglobulins	are endogenous proteins which defend from infections
Immunoglobulin G	antibodies are divided into different classes, one of them being immunoglobulin G
Covalent Bond	a strong chemical bond between two molecules
Cryoprecipitate	By freezing and thawing blood plasma, a precipitate (cryoprecipitate) is formed, which can be separated from the rest of the plasma by centrifugation. The proteins which are important for blood clotting, factor VIII, von Willebrand factor and fibrinogen accumulate in the cryoprecipitate
Mimetic	is based on the principle of imitation

mRNA	messenger RNA
N-acetylgalactosamine	is a type of sugar and a building block of carbohydrate parts of glycolipids and glycoproteins
N-glycans	complex carbohydrate chains linked to a specific amino acid side-chain (asparagine) in the protein
O-glycans	complex carbohydrate chains linked to a specific amino acid side-chain (serine or threonine) in the protein
Pasteurisation	considerate heating of plasma products (e.g. 10 hours at 60 ° C) to inactivate viruses vulnerable to heat treatment
PEG	polyethyleneglyco
PEGylation	in the so-called PEGylation, bio-pharmaceutical active substances or diagnostics are chemically combined (conjugated) with polyethylene glycol (PEG). Chain-shaped structures are attached to the active substance or the diagnostic agent, almost completely enveloping them and thus reliably protecting them against the premature degradation by endogenous enzymes, for example proteases
Plasma derivatives	Biological medicines manufactured from the human blood plasma
Polyethylene glycol	liquid or solid, chemically inert, water-soluble and non-toxic polymer
Polysialic acid	is an "acidic sugar" that, as a component of the glycocalyx, is responsible for the negative charge of all animal cells

Recycling	Here used to describe the redirection of Fc or albumin fusion proteins to the bloodstream following uptake by tissues
Recombinant	produced by recombinant DNA technology. For example, recombinant factor VIII concentrates, are manufactured using hamster or human cell lines in a growth medium and purified by elaborate methods.
Renal clearance	excretion via the kidney
Ribosome	a part of the machinery employed by the cells to synthesize proteins. Proteins are produced in the cells according to the nucleotide sequence of the deoxyribonucleic acid (DNA), which contains the information on the amino acid sequence of the proteins
RISC	RNA-induced silencing complex; Complex of RNA and proteins. The production of specific proteins is switched off (gene knockout) or decreased (gene knockdown), while the complex is degrading the mRNA coding for these proteins or inhibiting their translation to the protein
RNA/RNS	ribonucleic acid, a complex molecule, whose main function is conversion of genetic information into proteins
RNAi	RNA interference (RNAi or RNA silencing) is an important natural mechanism of gene silencing in the cells of living organisms with a cell nucleus (eukaryotes).
siRNA	Small interfering RNA, abbreviated siRNA, are short, single-stranded or double-stranded ribonucleic acid molecules of 20 to 25 base pairs length. They do not encode proteins, but bind with complementary single-stranded ribonucleic acid molecules, thus preventing their normal function
Substitution	Replacement/administration of factor concentrates
Subcutaneous	Injected under the skin
TFPI	Tissue Factor Pathway Inhibitor is a single chain polypeptide that can reversibly inhibit factor Xa. While Xa is inhibited, the Xa-TFPI complex can also inhibit the FVIIa-tissue factor complex
Thrombin	Thrombin (factor IIa) is the most important enzyme of blood clotting and breaks fibrinogen down to fibrin
Viruses	Viruses are infectious particles which can spread as virions outside cells (extracellularly) by transmission but can only multiply as viruses within a suitable host cell (intracellularly)
XTEN	is a polypeptide that can be metabolized by the body. By introducing XTEN into proteins, e.g. clotting factors, their half-life can be prolonged

Imprint

If you have any questions, please contact the office of your patient association.

Publisher

German Haemophilia Society (GHS)

Neumann-Reichardt-Str. 34
D-22041 Hamburg
Tel.: +49 - (0)40 - 672 29 70
Fax: +49 - (0)40 - 672 49 44
E-Mail: dhg@dhg.de

Austrian Haemophilia Society (AHS)

Mariahilfer Gürtel 4
A-1060 Wien
Tel.: +43(1)59 537-33
Fax: +43(1)59 537-33 67
E-Mail: vorstand@bluter.at

Swiss Haemophilia Society (SHS)

Mühlibachstrasse 5
CH-9450 Altstätten
Tel.: +44 - 977 28 68
Fax: +44 - 977 28 69
E-Mail: administration@shg.ch

European Haemophilia Consortium
Rue de l'Industrie 10
1000 Brussels
Belgium
office@ehc.eu

Editing by:
Werner Kalnins
Dr. Sylvia von Mackensen

Cover illustration by:
Fotolia/©jpgon

Graphics and layout

Integrated design

Advertising agency

Münchner Str. 2
83626 Valley
Te.: +49 - (0)8024 - 470 28 80
info@angererdesign.de

Duplication

Further copies in German (original language edition) of this brochure can be obtained from the respective office the GHS, AHS and SHS.
The English translation was produced by the EHC, with the support of an unrestricted grant from Sobi.

Courtesy of the company
Swedish Orphan Biovitrum (Sobi) GmbH Germany

EHC
european haemophilia consortium

Blut verbindet alle
DEUTSCHE HÄMOPHILIEGESELLSCHAFT

ÖSTERREICHISCHE
HÄMOPHILIE GESELLSCHAFT

Schweizerische Hämophilie-Gesellschaft
Association Suisse des Hémophiles
Società Svizzera Emofilia