



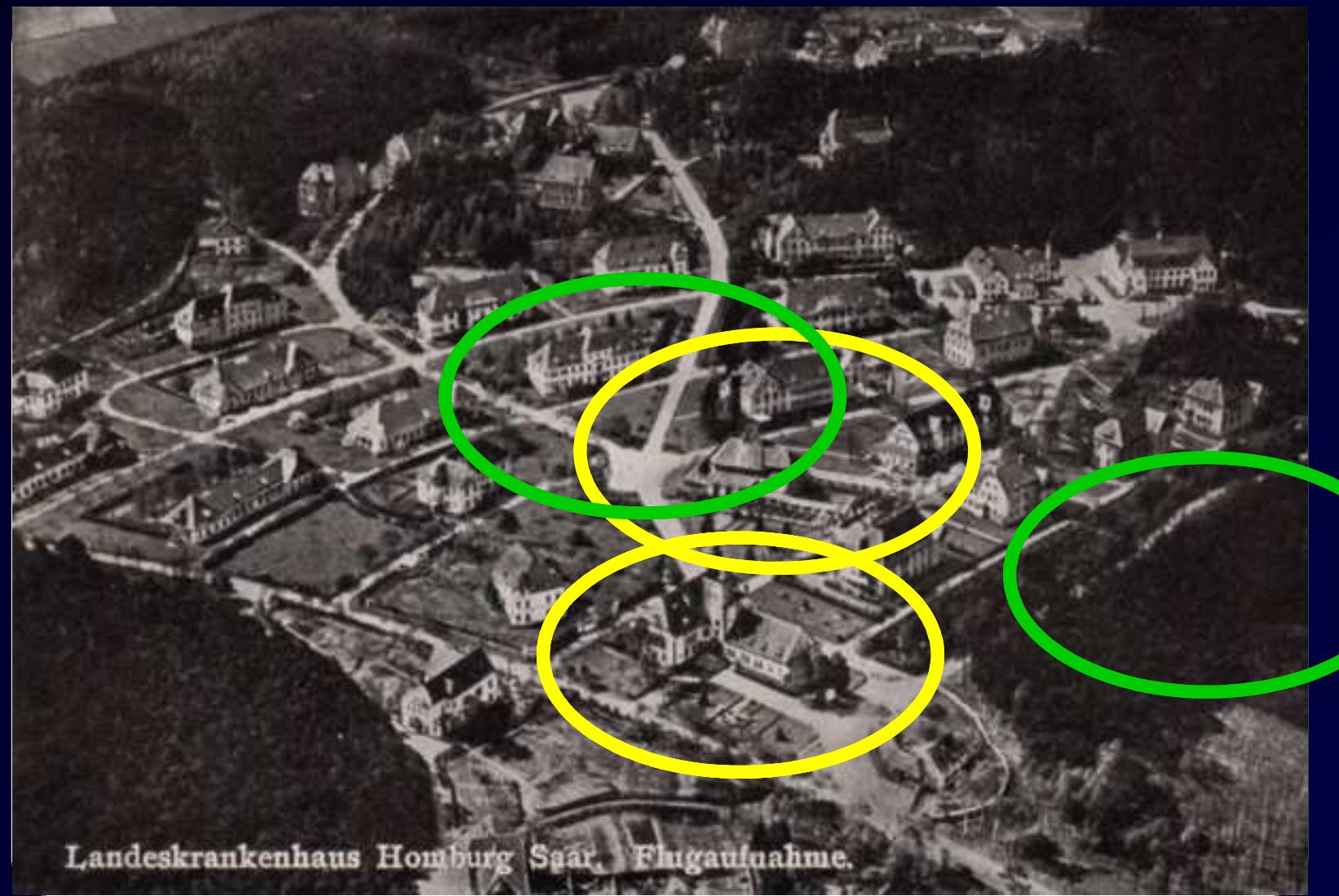
Entwicklung und Zukunft der Hämophilie- Therapie in Homburg – aus Perspektive der Kinder

Sabine Heine

**10. Hämophilie-Symposium
Homburg
19. November 16**



Universitätsklinikum des Saarlandes





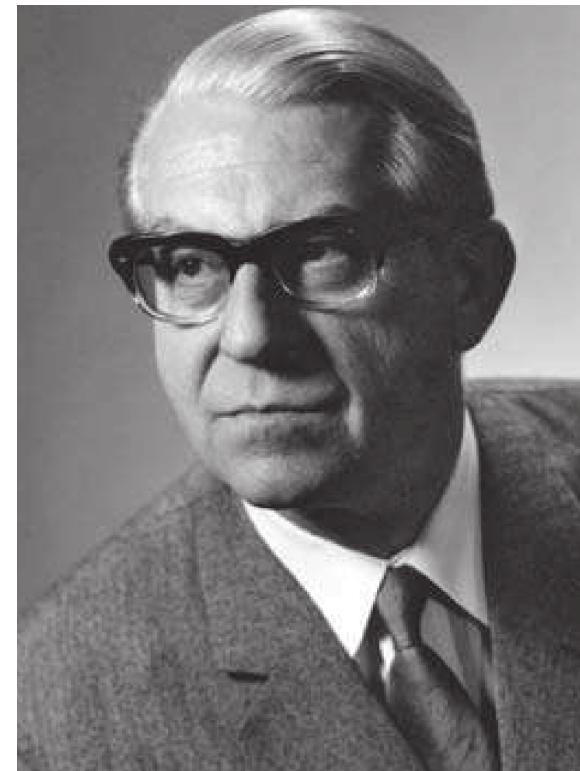
Universitätsklinikum des Saarlandes

Professor Ernst Wenzel



Lehrstuhlinhaber des Instituts für
klinische Hämostaseologie und
Transfusionsmedizin 1974 - 2003

Professor Johann Baptist Mayer



Lehrstuhlinhaber für
Kinderheilkunde
1952 - 1976



Universitätsklinikum des Saarlandes

Professor Ernst Meindl



Lehrstuhlinhaber des Instituts für
klinische Hämostaseologie und
Transfusionsmedizin seit 2003

Professor Dr. Michael Sitzmann



Lehrstuhlinhaber für Pädiatrische
Onkologie und Kinderhautkämatologie
seit 2004



CCC

Comprehensive Care Center, Hämophiliezentrum mit umfassenden Behandlungsmöglichkeiten



Blut verbindet alle
DEUTSCHE HÄMOPHILIEGESELLSCHAFT



40 Patienten mit schwerer Hämophilie A und B

24 Std.-Erreichbarkeit

Notfalldepot über 24 Std. verfügbar

Arzt für Hämostaseologie

Qualifizierter Stellvertreter

Stationäre interdisziplinäre Versorgung vor Ort

Vereinbarung eines ZE (Zusatzentgelt) für die stationäre Abrechnung von für die Behandlung notwendigen Gerinnungsfaktoren-Konzentraten

Eigenkontrollierte Labordiagnostik vor Ort

DHR (Teilnahme am Deutschen Hämophilie-Register)

Zusatzentgeltvereinbarung ambulant



CCC

Comprehensive Care Center, Hämophiliezentrum mit umfassenden Behandlungsmöglichkeiten

EUHANET

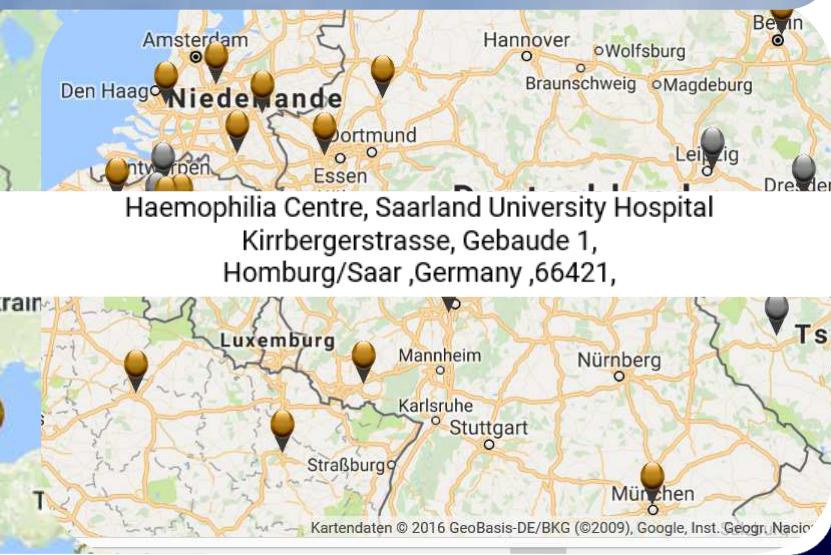
European Haemophilia Network
www.EUHANET.org

HOME ABOUT CONTACT US



EUHANET

*Improving the care of European citizens
with inherited bleeding disorders.*



Haemophilia Centre, Saarland University Hospital
Kirrbergerstrasse, Gebaude 1,
Homburg/Saar ,Germany ,66421,

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uks report



Kinder brauchen Spezialisten

Eine blutende Verletzung wird von Bestandteilen des Blutes schnell wieder verschlossen, sonst würde der Verletzte langsam verbluten. Dieser Mechanismus funktioniert aber nicht bei allen Menschen.

TEXT Christiane Roos FOTO privat





Universitätsklinikum des Saarlandes und Medizinische Fakultät der Universität des Saarlandes

Klinik für Pädiatrische Onkologie und Hämatologie

Leitung: Prof. Dr. Norbert Graf



Inzidente Patienten

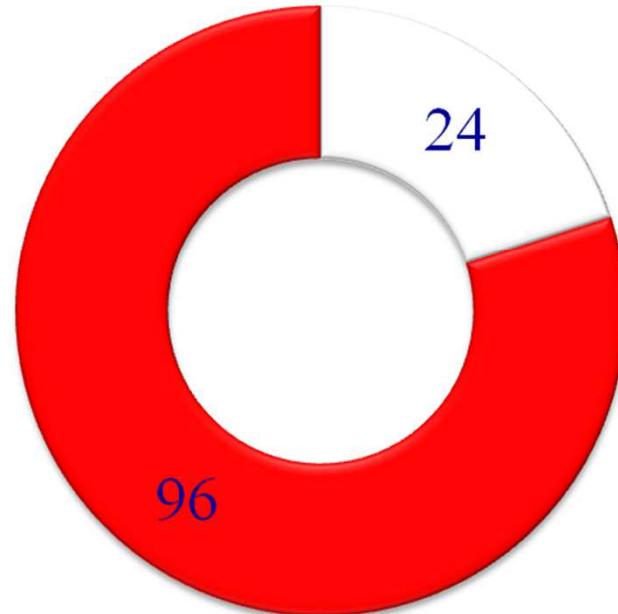
pro sechs Monate



Inzidente Patienten

Klinik für Pädiatrische Onkologie & Hämatologie

120 inzidente
Patienten



- Abklärung Thrombophilie
- Abklärung Blutungsneigung



2

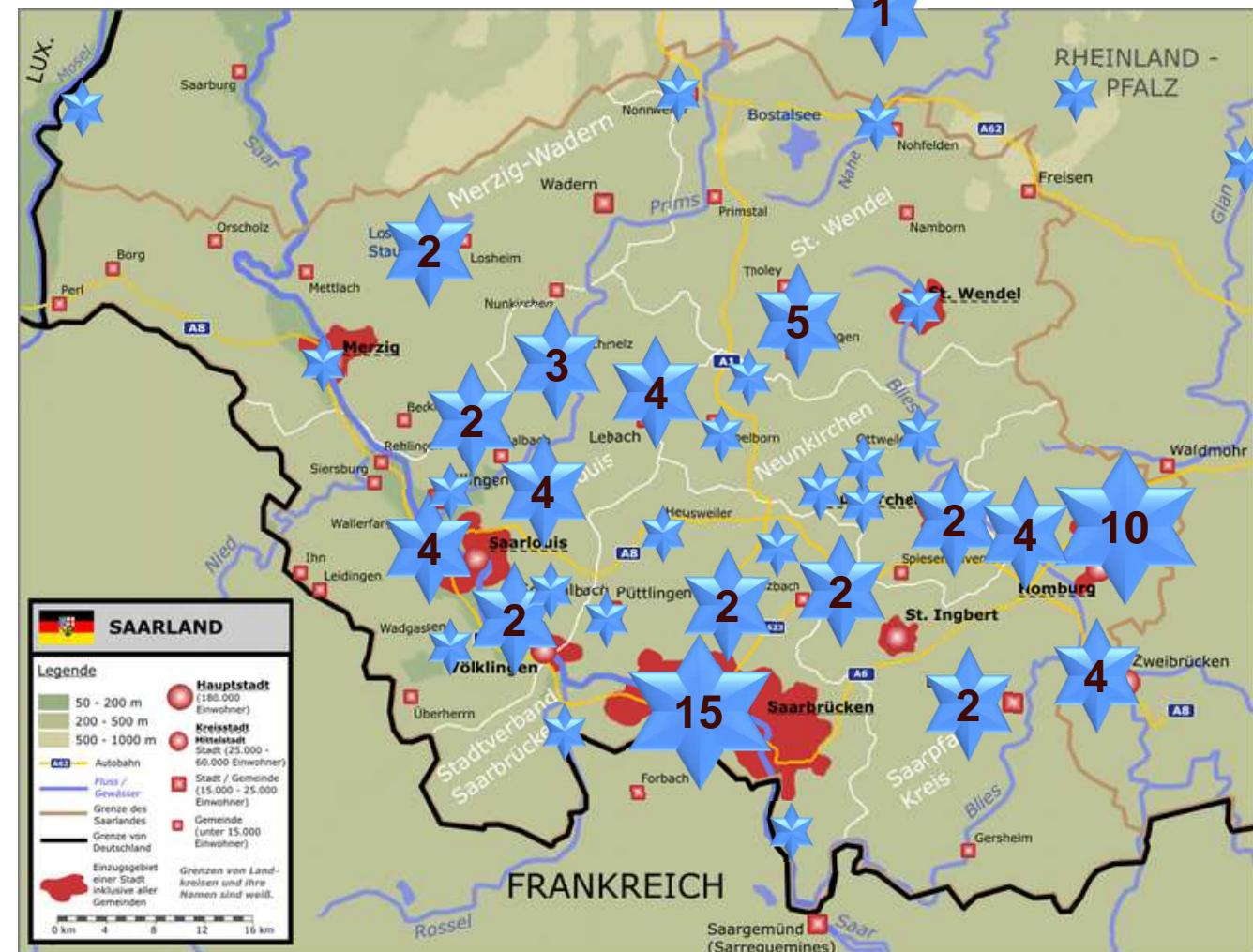
Inzidente Patienten*

Klinik für Pädiatrische Onkologie & Hämatologie

7

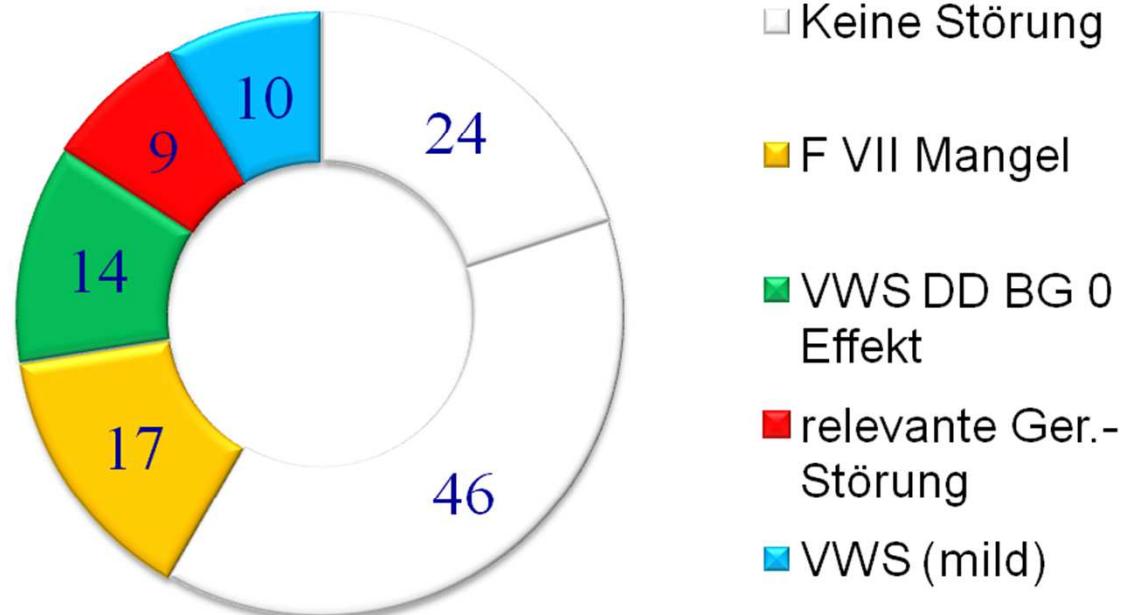
2

1



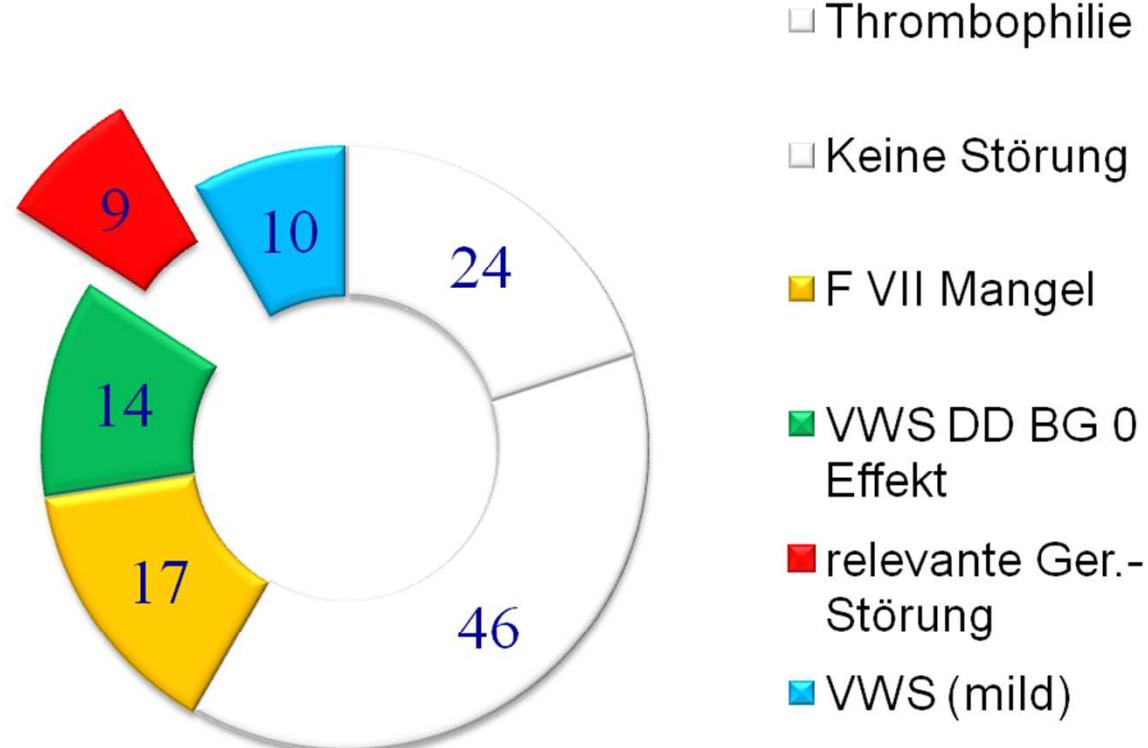
Inzidente Patienten

Klinik für Pädiatrische Onkologie & Hämatologie



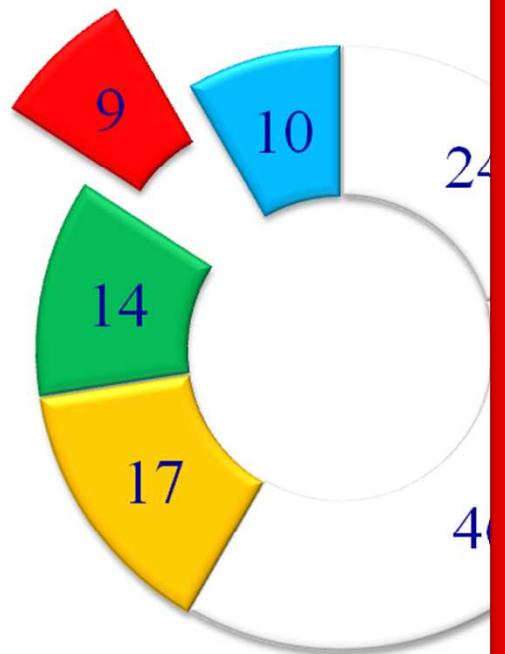
Inzidente Patienten

Klinik für Pädiatrische Onkologie & Hämatologie



Inzidente Patienten

Klinik für Pädiatrische Onkologie & Hämatologie



Faktor V-Mangel mild	2
Faktor X-Mangel mild	2
Subhämophilie A	2
Milde Hämophilie A	1
Dysfibrinogenämie	1
VWS-Typ 2 N	1



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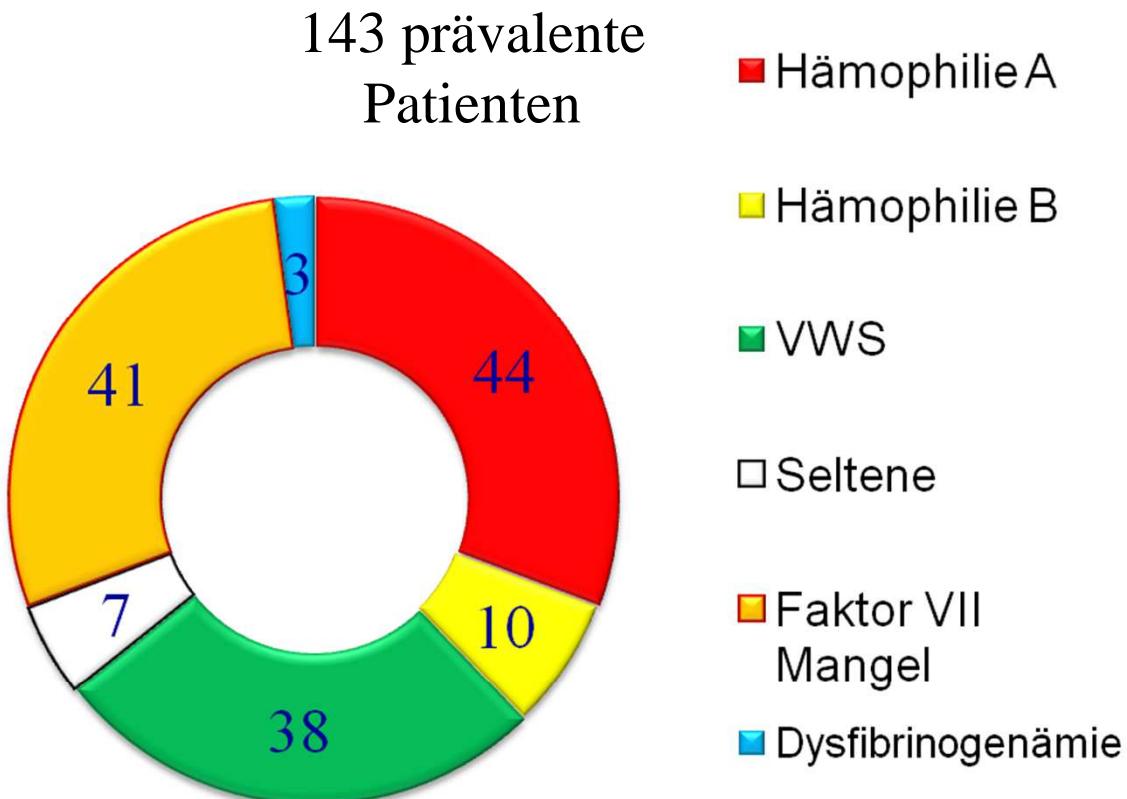
Leitung: Prof. Dr. Norbert Graf



Prävalente Patienten

Prävalente Patienten

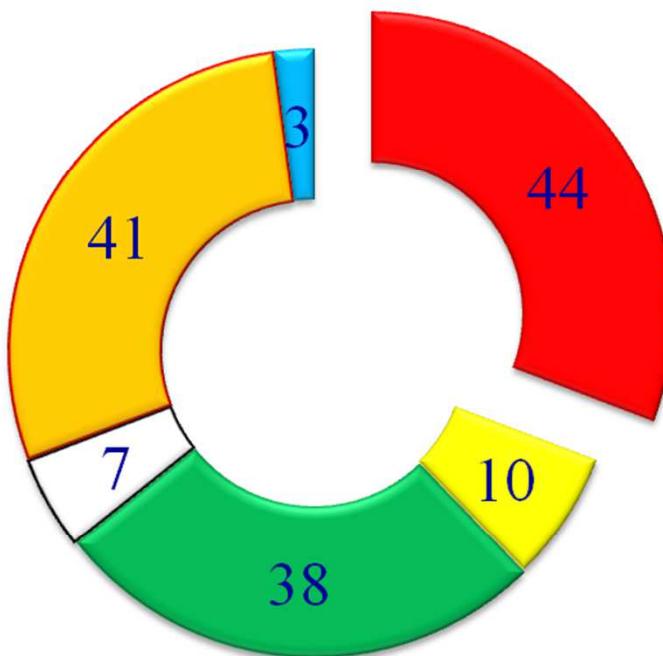
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Prävalente Patienten

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143 prävalente
Patienten



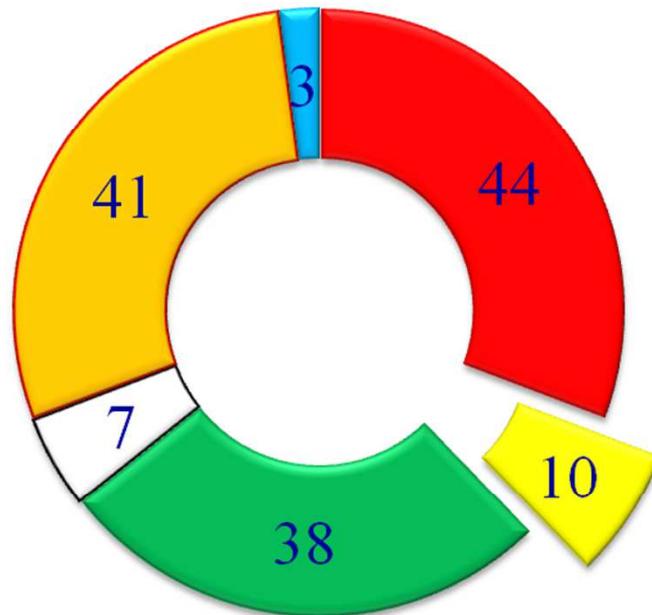
Hämophilie A

Schwer	17
Mittelschwer	2
Mild	6
Subhämophilie	19

Prävalente Patienten

Klinik für Pädiatrische Onkologie & Hämatologie

143 prävalente
Patienten



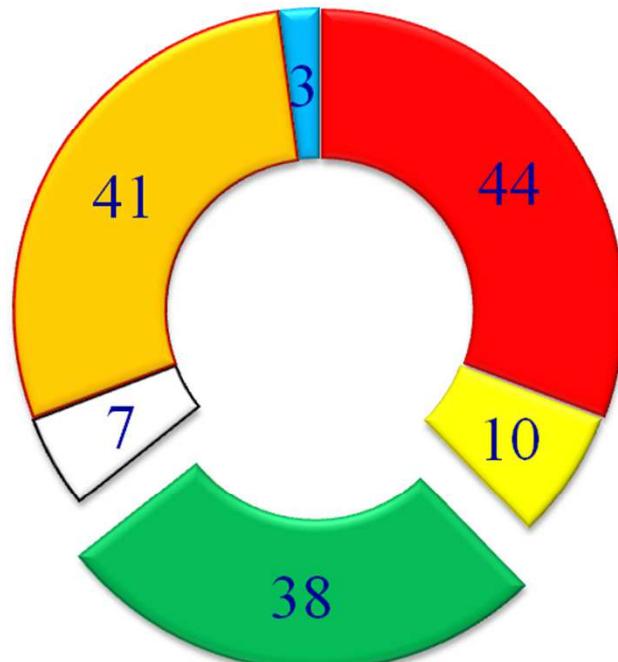
Hämophilie B

Schwer	2
Mittelschwer	0
Mild	2
Subhämophilie	6

Prävalente Patienten

Klinik für Pädiatrische Onkologie & Hämatologie

143 prävalente
Patienten



VWS

Typ I	22
V mit niedr. Thr.VWF	3
V mit verwischener Stru.	2
Typ II A	9
Typ 2 N	1
Typ 3	1



Long-acting coagulation factors

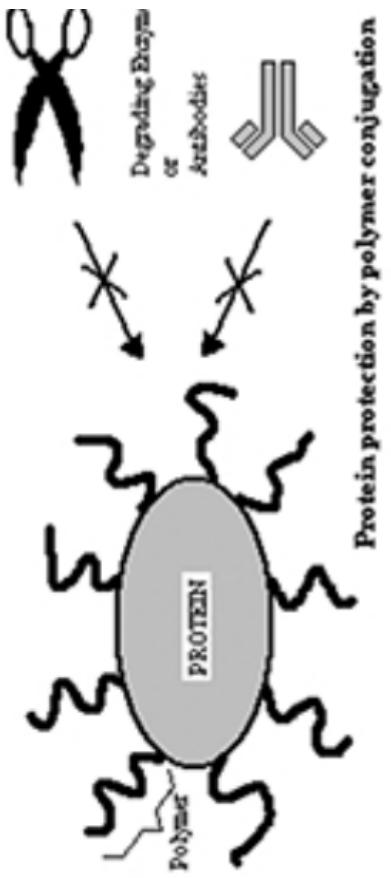
Peyvandi F / Garagiola Semin Thromb Haemost 2015

Strategies to develop long-acting coagulation factors

Technology	Description	Mechanism of prolonged half-life
PEGylation	Covalent attachment of long-chained PEG molecules.	Improves stability and reduces clearance of conjugated proteins.
Fc- and albumin fusion	Fusion of the Fc domain of human IgG or albumin to protein.	Binding of Fc or albumin to FcRn delays lysosomal degradation of the fusion protein and recycles it back into the circulation.
Polysialylation	Conjugation of linear polymers of N-acetylneurameric acid.	Improves enzymatic stability and decreases renal excretion by increasing molecular mass.
Half-life extension technology	A non-structured polypeptide chain composed of six residues alanine, glutamic acid, glycine, proline, serine, and threonine.	Fully biodegradable, avoiding organ accumulation not toxic or immunogenic in animals, improves the half-life of proteins.
Carboxyl terminal peptide	Fusion of the C-terminus peptide of human chorionic gonadotropin to target protein.	Improves the half-life of therapeutic proteins and maintains their biological activity.
Modification of amino acid sequence	Introduction of variants in the amino acid sequence.	Improves stability and specific activity of the therapeutic proteins.
Aptamer	Single-stranded oligonucleotides.	Binds with high affinity and specificity to their targets, inhibiting disease processes.
Antibody	Monoclonal antibody and humanized bispecific antibody	Binds with high affinity and specificity to the target molecule, abolishing the activity.
RNA interference	Small interference RNA, fundamental cellular pathway of gene silencing.	RNAi therapeutics offer the potential to potently and specifically reduce the expression of disease-causing genes.

Main technologies used to extend half-life of factor

Hydrophilic cloud around a protein



Protein protection by polymer conjugation
e.g. Cimzia, Neupogen & Peg-asparaginase (Oncaspar)

Pegylation

Pegylation of proteins (20 yrs)
1. ↓ renal clearance
2. Protects against enzyme digestion
3. Blocks interaction with receptors (**LRP**)

Main technologies used to extend half-life of factor

Fusion	Fc (of IgG)
Albumin	$T_{1/2} \approx 3$ wks Neonatal Fc receptors on endothelial cells

Fc fusion drugs
Etanercept & romiplostim

Albumin fusion drugs
albiglutide & neogranin

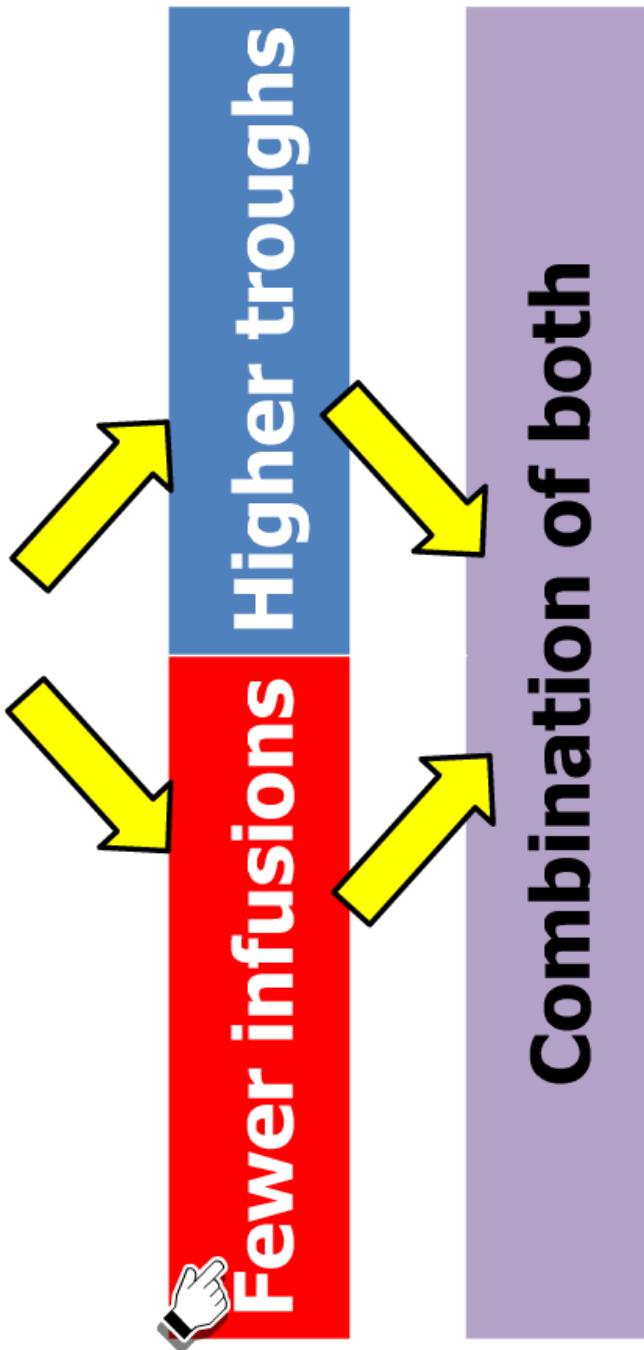
Internalize IgG & albumin
protect them from lysosomal degradation

recycle them back into blood

Product / Manufacturer	Technology	Cell line	$T_{1/2}$ vs. FIX	\approx time to 1% after 50 U/kg
FIXFc (Biogen Idec)	Fc-Fusion protein	HEK	57-83	3X 10 days
NFCN	FIX-FP (CSL-Behring)	CHO	96-110	>5X 2-3 weeks
	Albumin Fusion protein	CHO	89-96	>5X 2-3 weeks

Very Significant prolongation of $T_{1/2}$

**How will these longer acting
concentrates impact on
prophylaxis?**





Long-acting coagulation factors

Peyvandi F / Garagiola Semin Thromb Haemost 2015

Peculiarities of rFVIII long-acting molecules

Coagulation factors	Product	Recombinant protein	Modification	Manufacturer	Cell line
FVIII	BAY94-9027	BDD - rFVIII (Ser743-Gln1638)	Site specific PEGylation ^a (PEG 60 kDa in A3 domain)	Bayer	BHK21
	N8-GP	BDD - rFVIII (Ser750-Gln1638)	Site specific PEGylation ^b (PEG 40 kDa in B-domain linker region)	Novo Nordisk	CHO
	BAX 855	FL - rFVIII	PEGylation (PEG molecule of 20 kDa)	Baxter	CHO
	rFVIII-Fc	BDD - rFVIII (Ser743-Gln1638) Fusion		Biogen Idec	HEK293

Efficacy end point

A-LONG, KIDS A-LONG,
ASPIRE, INHIBIT, ITI

epidic treatment

Coagulation Factors	Efficacy end point	A-LONG, KIDS A-LONG, ASPIRE, INHIBIT, ITI				Patients with no bleeding episodes, %
		Prophylaxis every 3–5 d	Prophylaxis every 7 d	Other	Pathogen	
FVIII	PATHFINDER 3, B-YOND, PARADIGM	33.6	45.3	17.4	30.9	33.6
	N8-GP (nonacog alfa)	1.3	–	–	–	23
	Alprolix (eftrenonacog alfa)	–	3 ^a	1.4	17.7	44
FIX	N9-GP (nonacog β pegol)	–	1 - 2.9 ^b	–	15.6	37

^aPatients treated with weekly doses of 50 IU/kg.

^bPatients treated with weekly doses of 40 and 10 IU/kg, respectively.

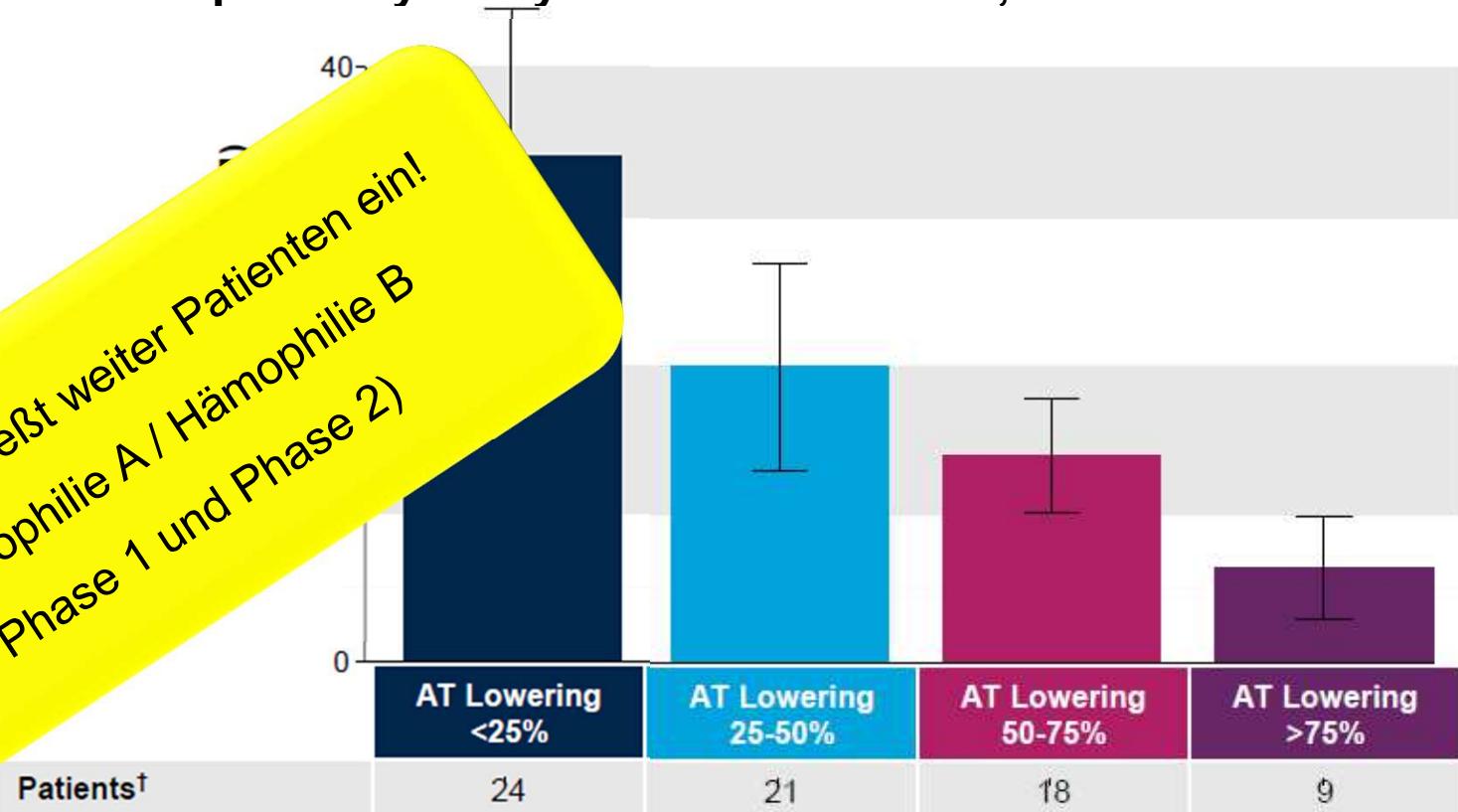
Long-acting coagulation factors

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Interim Fitusiran Phase 1 Study Results

Exploratory Analysis of Bleed Events, Parts B & C

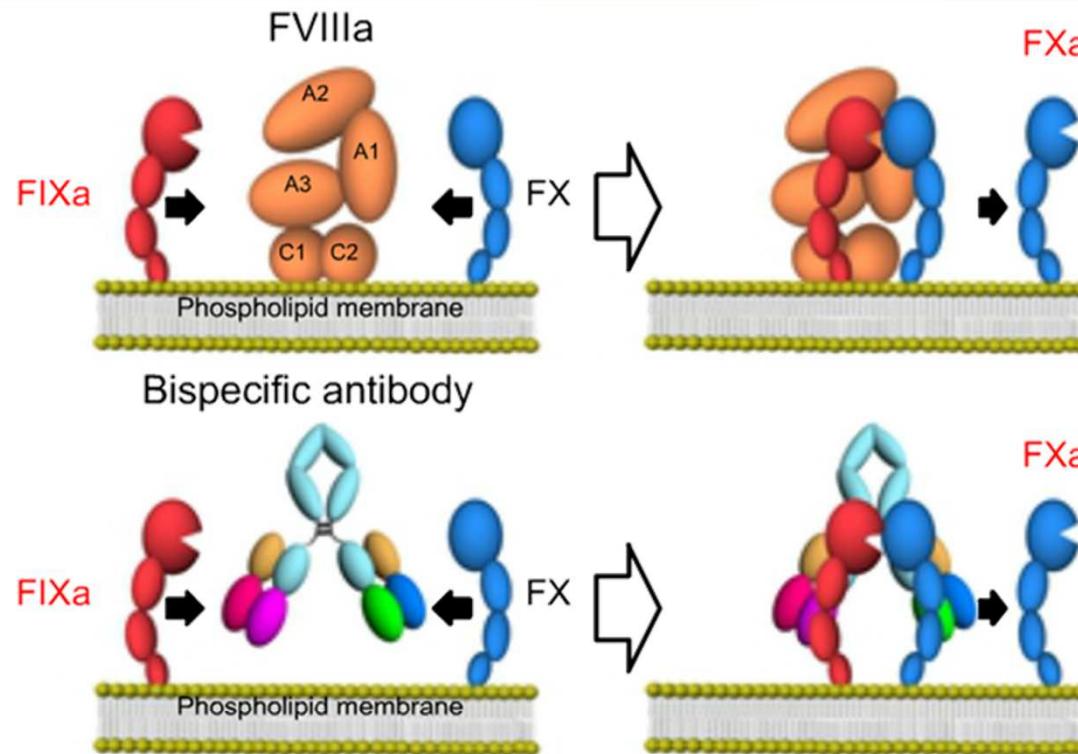
Studie schließt weiter Patienten ein!
(Hämophilie A / Hämophilie B
Phase 1 und Phase 2)



Source: Alnylam Pharmaceuticals

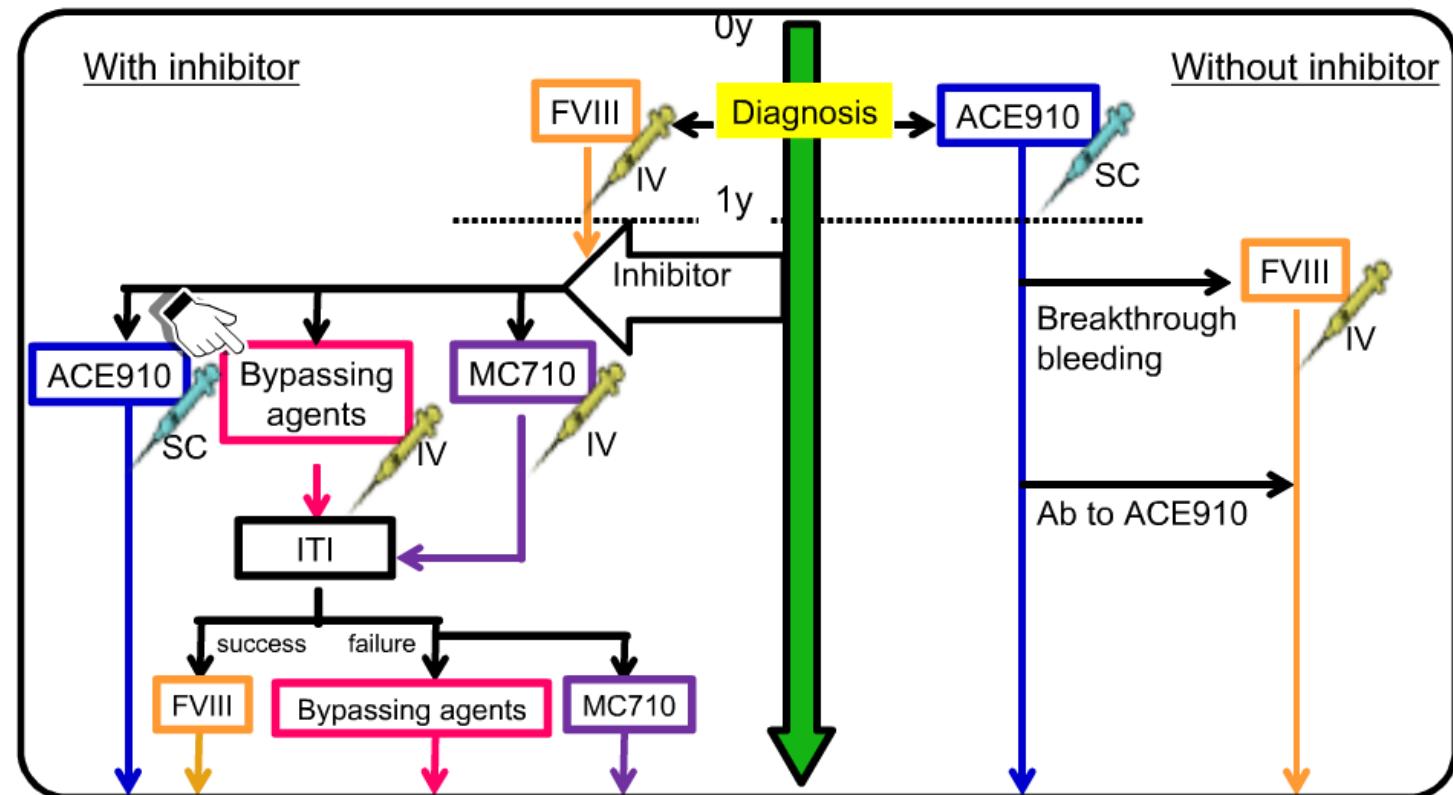


Concept of FVIIIa-mimetic bispecific Ab



- Subcutaneous available, longer half-life, low dosing frequency
- Effective in patients irrespective of the presence of FVIII inhibitors
- Not expected to induce FVIII inhibitors

Future therapy for HA patient



ACE910 can be used as the 1st line treatment from early childhood.

WFH 2014



ISTH 2015 / ASH 2015

Midori Shima *et al.*

Interim results of a Phase 1 extension study: Long-term safety and prophylactic efficacy of once-weekly subcutaneous administration of ACE910, in Japanese hemophilia A patients with and without FVIII inhibitors.

Clinical Course and Management of Surgical Emergency in a Severe Hemophilia a Patient Under Weekly Subcutaneous Administration of a

Bis Phase 3 Studie schließt und X (ACE910).
momentan Patienten auch in
D ein!



Neue Therapien in Hämophilie A / B

Hemophlilia With Inhibitors

New Recombinants

BAX817 – rFVIIa
Transgenic rhFVIIa

Longer Acting

OBI 1 - rpFVIII
CB813d – rVIIa analogue
CSL689 – rVIIa albumin fusion
rVIIa: CTP

Hemophlilia A

Longer Acting

rFVIII Fc*
BAY94-9027 PEGylated rFVIII
BAY855 – PEGylated rFVIII*
CSL627- SingleChain rFVIII

Hemophlilia B

New Recombinants

IB1001 – rFIX
BAX326 – rFIX *

Longer Acting

rFIX:Fc*
CSL654 – rFIX albumin fusion*

Cross-Segment

Longer Acting

MC710 – pdFVIIa + pdFX
ACE910 – SC bispecific Ab siRNA vs Antithrombin

*: approved



Gentherapiestudien in Hämophilie A / B

- AAV Vektor Hämophilie B St. Jude Children's Research Hospital
 - Phase 1 Recruiting Patients
- AAV V Hämophilie B (UniQure Biopharma B. V.)
 - Phase 1 / 2
- Zinc Finger Protein (ZFP) Trial Hämophilie B Phase 1



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