



Early prophylaxis as a way to reduce the formation of inhibitors

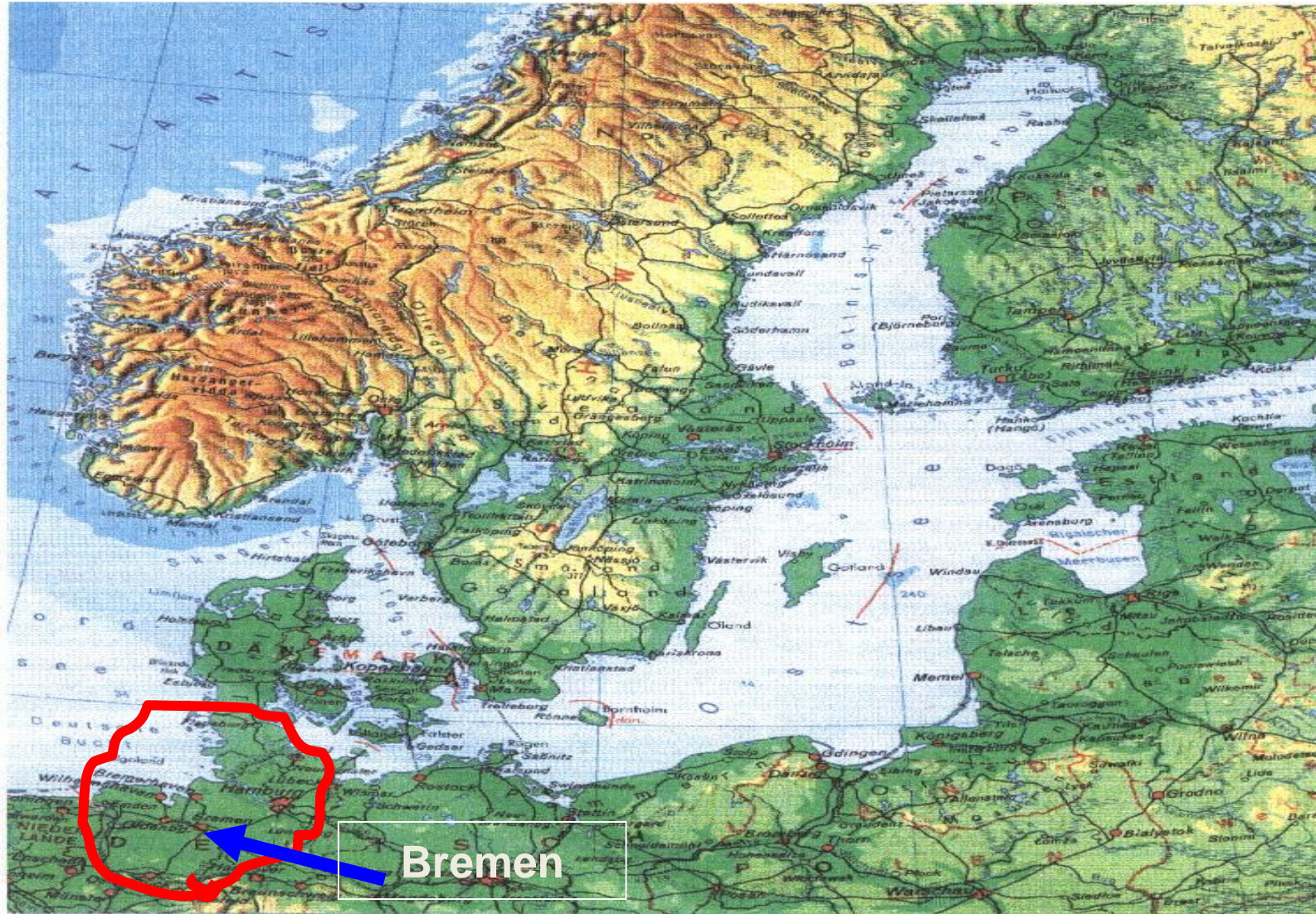
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Disclosure Statement

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- Novo Nordisk A/S,
- CSL Behring,
- Bayer,
- Pfitzer and
- Baxter.

North-Germany and Scandinavia / Baltic Sea



Treatment of Haemophilia

Five major risk factors:

- to become crippled
- to become poor
- to bleed to death
- to get a virus infection, (vCJD?)
- to develop an inhibitor**
 - hemophilia A 25-35%,
 - hemophilia B 2-3%



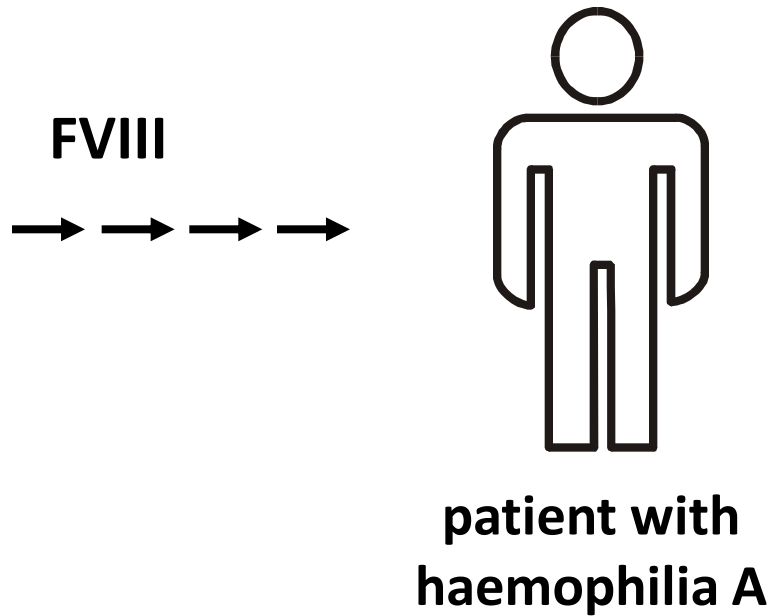
Haemophilia treatment

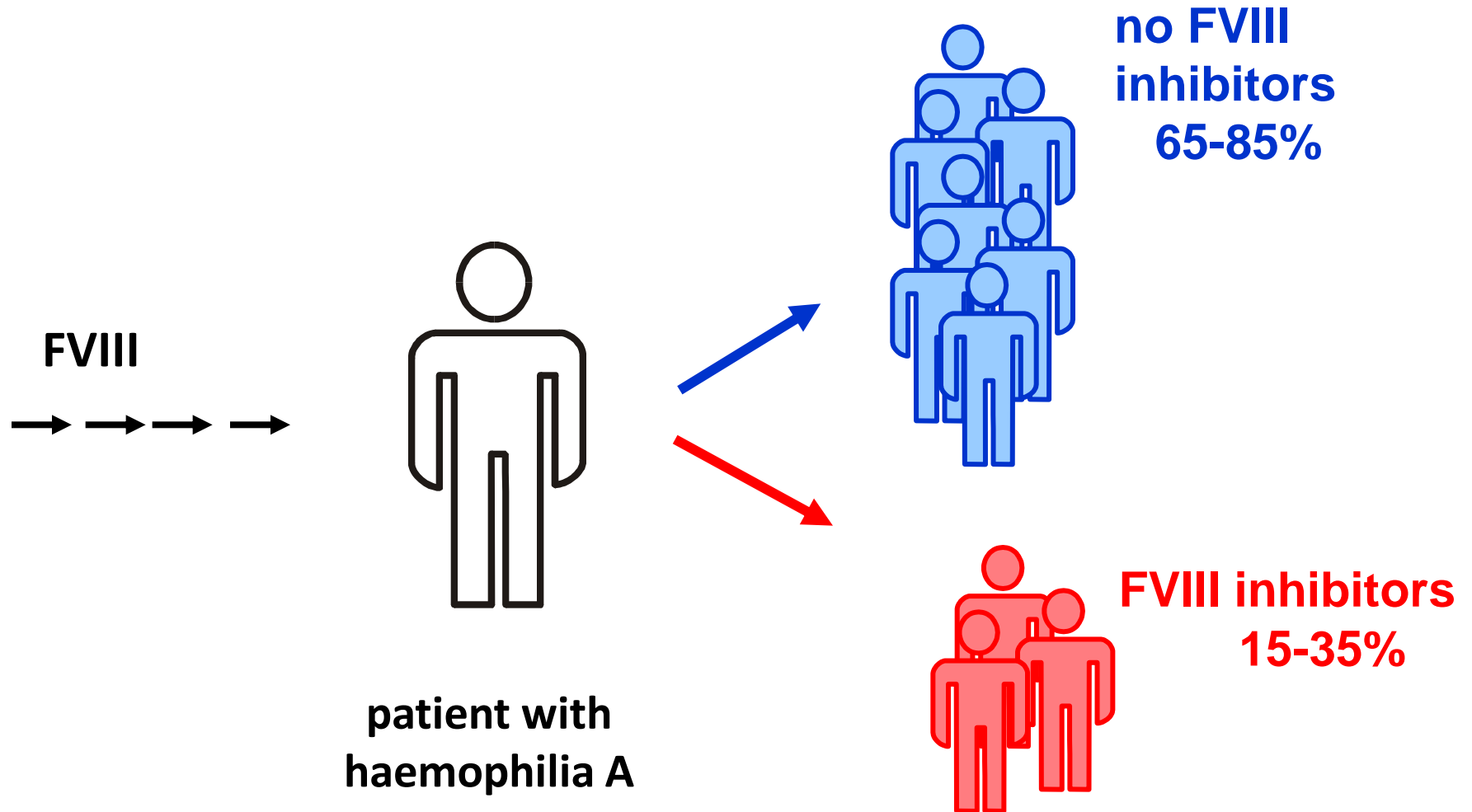
- Complex due to
 - rarity of disease
 - life-long nature
 - variable severity
- Delivery for treatment for haemophilia
 - WHO / WFH / ISTH Meeting London 2002

Case Report

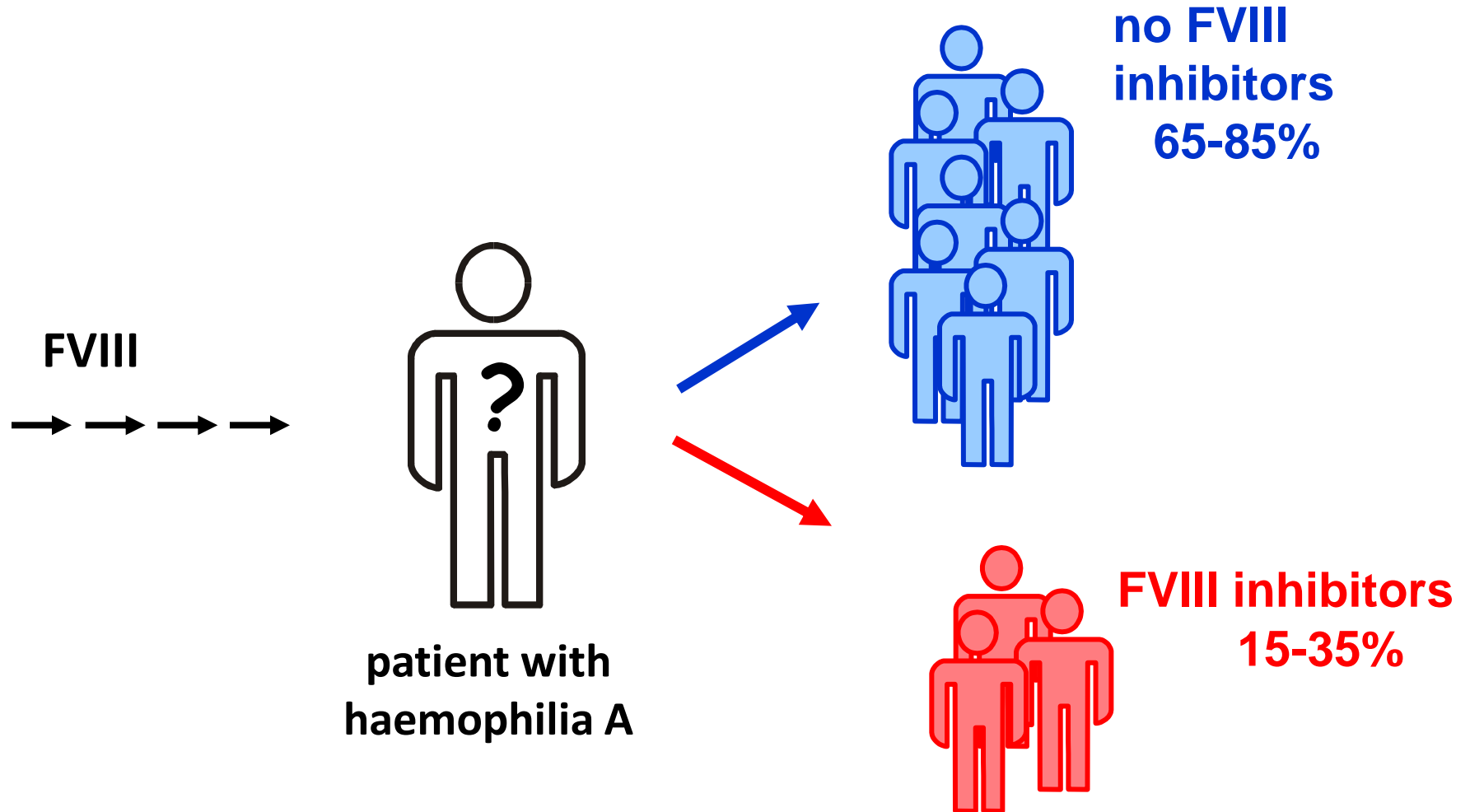
- S.A. (born 2008)
postpartum:
 - Haemophilia A, FVIII <1%
 - 3 uncles in the family with haemophilia A, FVIII <1%
 - Intron 22 Inversion
 - All have clinically relevant high titer inhibitor (>10 BU)
 - After maximal 14 ED
 - All were treated first on demand, mostly because of joint and muscle bleeds
 - The question of the parents: is there any way to avoid the development of an inhibitor?

What do we know and what is not exactly known





What do we know and what is not exactly known



What do we know and what is not exactly known



Prophylaxis has two aspects

Bleed prevention

- Avoidance of live threatening bleeds
- Prevention of joint bleeds
- Prevention of arthropathy and disability
- Improval of quality of life

Inhibitor prevention ?

- Avoidance of danger signals
- Tolerization against FVIII



Inhibitor risk factors – confirmed or under discussion

Predisposing genetic factors

FVIII mutation type

Family history of inhibitors

Severity of haemophilia

Race/ethnicity

Polymorphism in immune response genes

(IL10 134 positive;
TNF-alpha A2 positive
CTLA4-318 T negative)

Predisposing environmental factors

Age at 1st exposure

Immunological challenges (infections, vaccination)

Treatment regimen (prophylaxis/on demand)

Intensity of treatment (FVIII doses and intervals)

Invasive clinical procedures (surgery, CI)

Socioeconomic aspects (family income)

Abnormal FVIII molecules (immunogenicity)

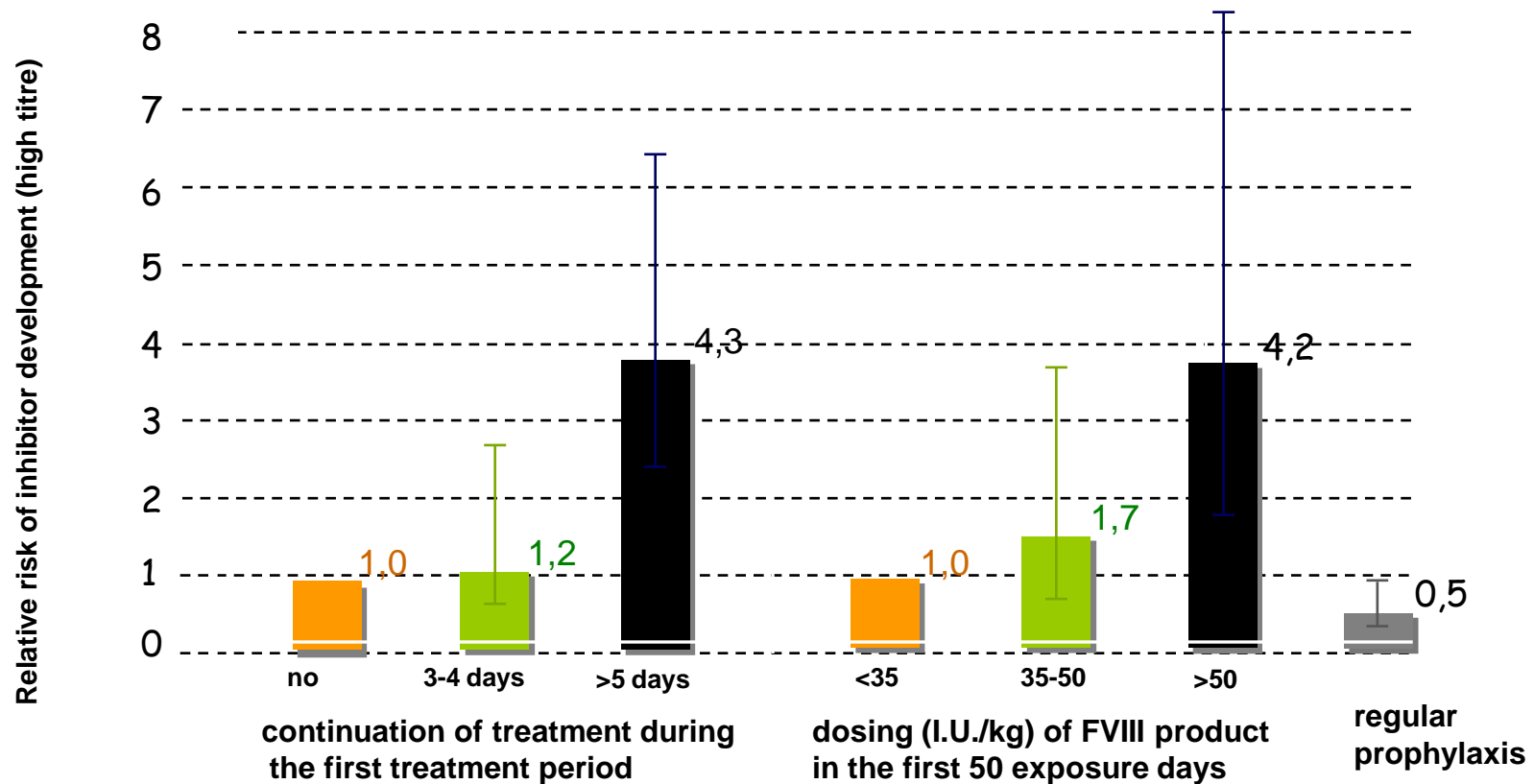
Infant diet (breast feeding)

Difficult to influence



CANAL-study: treatment on demand

longer treatment / higher dose increase the risk of inhibitor development





Genetics or treatment – what has a bigger influence on inhibitor risk?

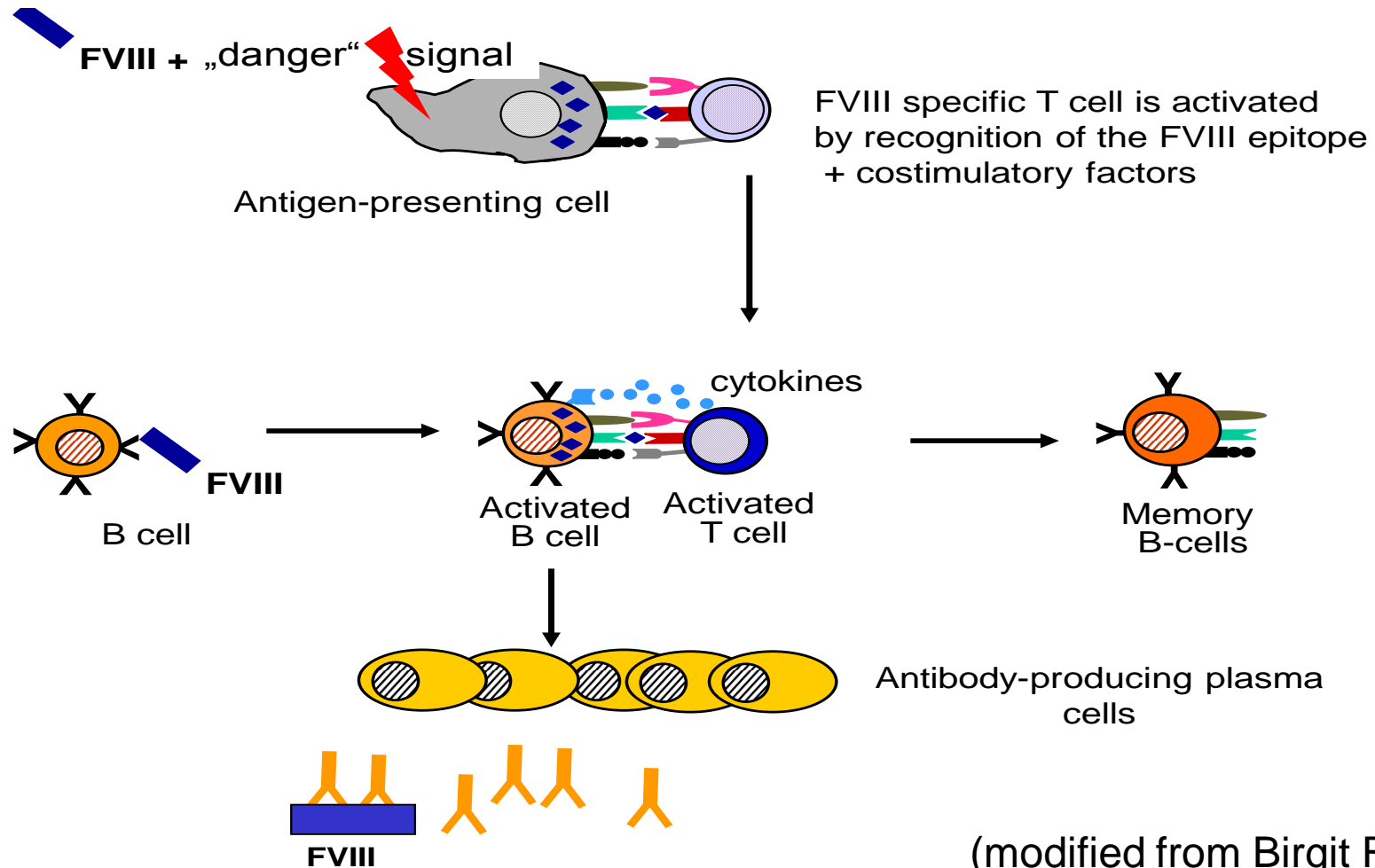
Opinion 1:

Inhibitor risk is exclusively determined by the patient's genetic background. Patients with a high risk genetic background will develop an inhibitor very likely independent of environmental risk factors.

Opinion 2:

Inhibitors can be avoided even in patients with a high genetic inhibitor risk by treatment related measures.

Model of the immunological process that leads to the development of an antibody response against a protein such as FVIII. Presence of additional danger signal required:



„danger“ signal

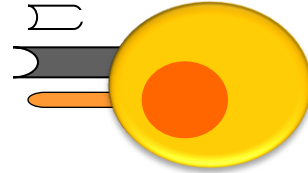
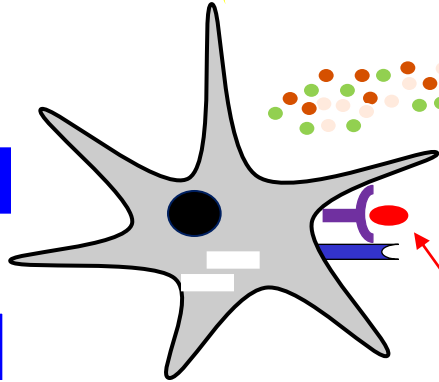
MHCII

co-stimulation/co-stimulation

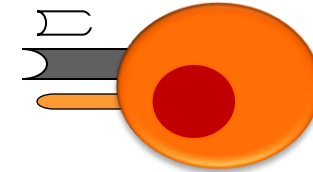
cytokines

FVIII

peptides



Activation



activated CD4+ T cell that drives antibody responses in B cells

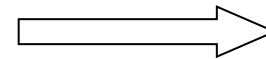
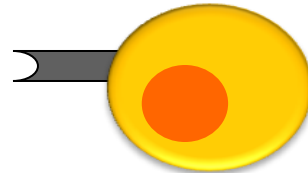
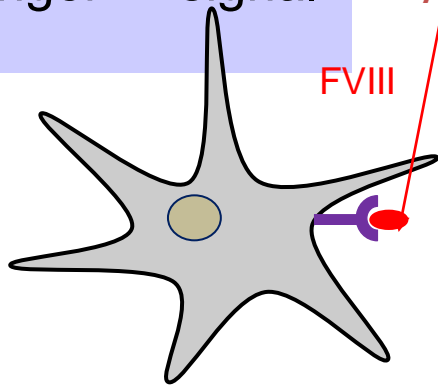
peptides

Naïve CD4+ T cell

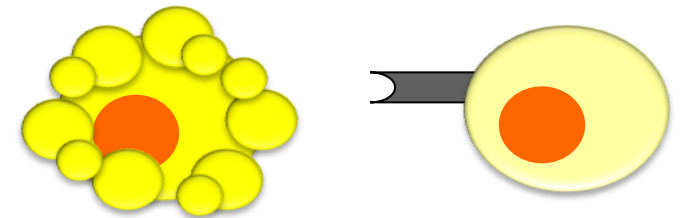
no „danger“ signal

Absence of co-stimulation

FVIII



No activation



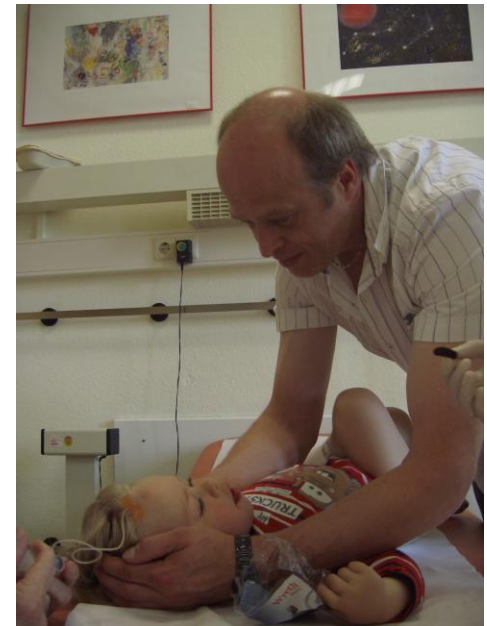
Apoptotic or tolerogenic CD4+ T cell that suppresses antibody responses in B cells

Dendritic cell

Naïve CD4+ T cell

How to avoid immunological danger signals

- Avoid first FVIII treatments into a bleed or during an infection,
- Avoid surgery within the first 20 (30 – 40) Eds,
- Do not vaccinate at a FVIII treatment day,
- Vaccinate s.c. (instead of i.m.),
- **Start early with prophylaxis**



But which prophylaxis regimen would be the most effective in preventing from inhibitors?



Current regimens for primary prophylaxis have been optimized for avoiding joint disease but might not be optimal for the avoidance of inhibitors

Recommended prophylaxis regimen to protect joints

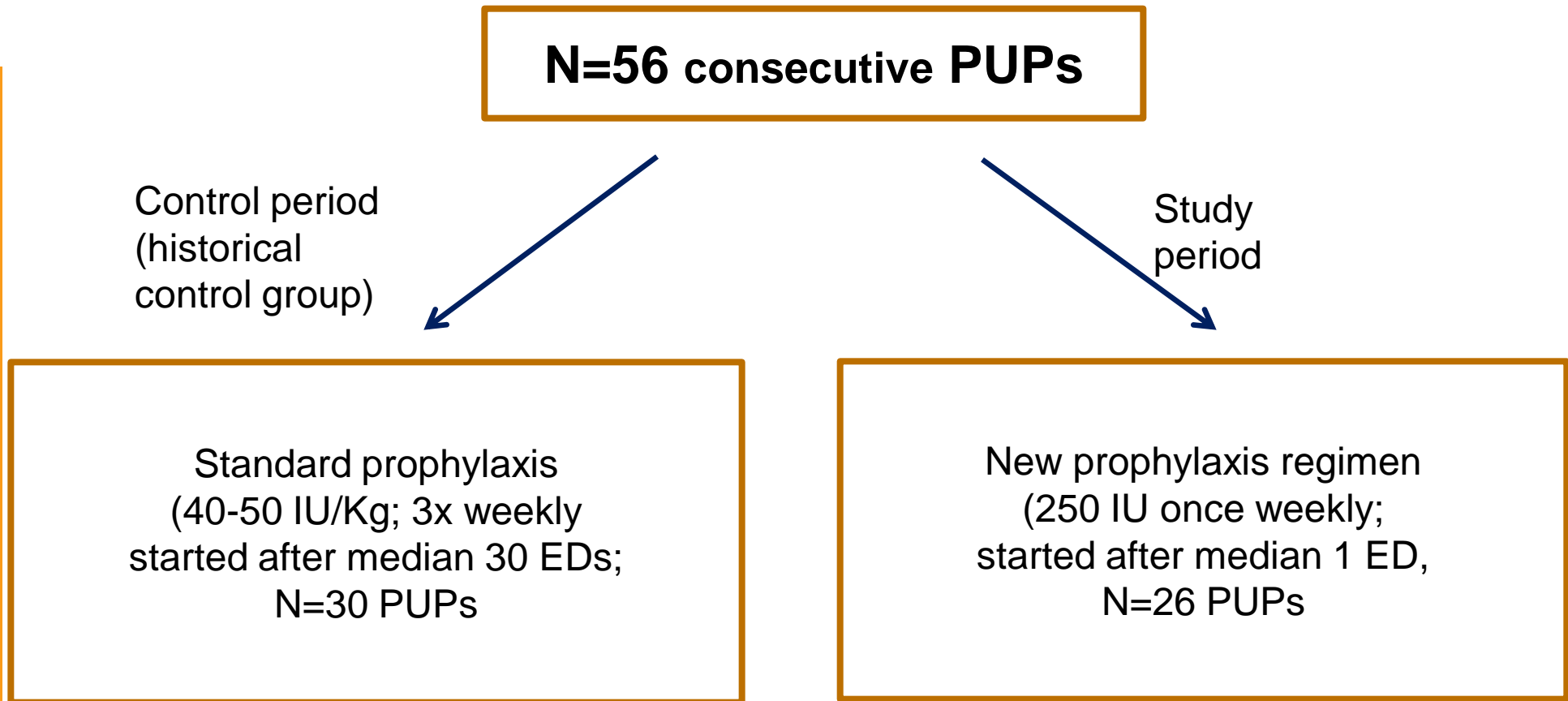
Potential danger factor

At least 3 times per week up to 50 IU/kg FVIII
Start with or after the first joint bleed
Often Port-A-Cat implementation via surgery necessary

High dose FVIII
Bleed
Surgery, bleed, infection



Comparison of standard prophylaxis with a new regimen



K. Kurnik, C. Bidlingmaier, W. Engl, H. Chehadeh, B. Reipert, G. Auerswald: New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development . *Haemophilia* 2010; 16: 256-62



Comparison Control Group: Genetic Factors

Kurnik K,... Auerswald G et al *Haemophilia* 2010; 16: 256-62

	Control group (standard prophylaxis regimen) N=30	Study group (new prophylaxis regimen) N=26	Statistical significance
GENETIC FACTORS			
Severity of haemophilia A	All <1% FVIII activity	All <1% FVIII activity	Not significant
Ethnicity	All Caucasian	All Caucasian	Not significant
<u>FVIII mutation type*</u> :			
High risk (%)	24 (80)	18 (69)	Not significant
Low risk (%)	5 (17)	8 (31)	Not significant
Unknown (%)	1 (3)		

*Categorization of genetic risk according to Oldenburg J & Pavlova A. Genetic risk factors to inhibitors against FVIII and IX. *Haemophilia* 2006



Genetic inhibitor risk factors were not different in the study group and the control group

Comparison Control Group: Product Type

	Control group (standard prophylaxis regimen) N=30	Study group (new prophylaxis regimen) N=26	Statistical significance
Product type:			
rFVIII (%)	16 (53)	15 (58)	Not significant
pdFVIII (%)	14 (47)	11 (42)	



Product type used was not different in the study and the control group

Study Group: Results

	Control group (standard prophylaxis regimen) n=30	Study group (new prophylaxis regimen) n=26	Statistical significance
Inhibitors (%)	14 (47%)	1 (3.8%)	Highly significant p=0.0003 Odds ratio = 0.048 (95% CI: 0.001 to 0.372)
High responders (%) Low responders (%)	8 (27%) 6 (20%)	0 1 (3.8%)	Highly significant p=0.005 Odds ratio of high response = 0.00 (95% CI: 0.00 to 0.57)

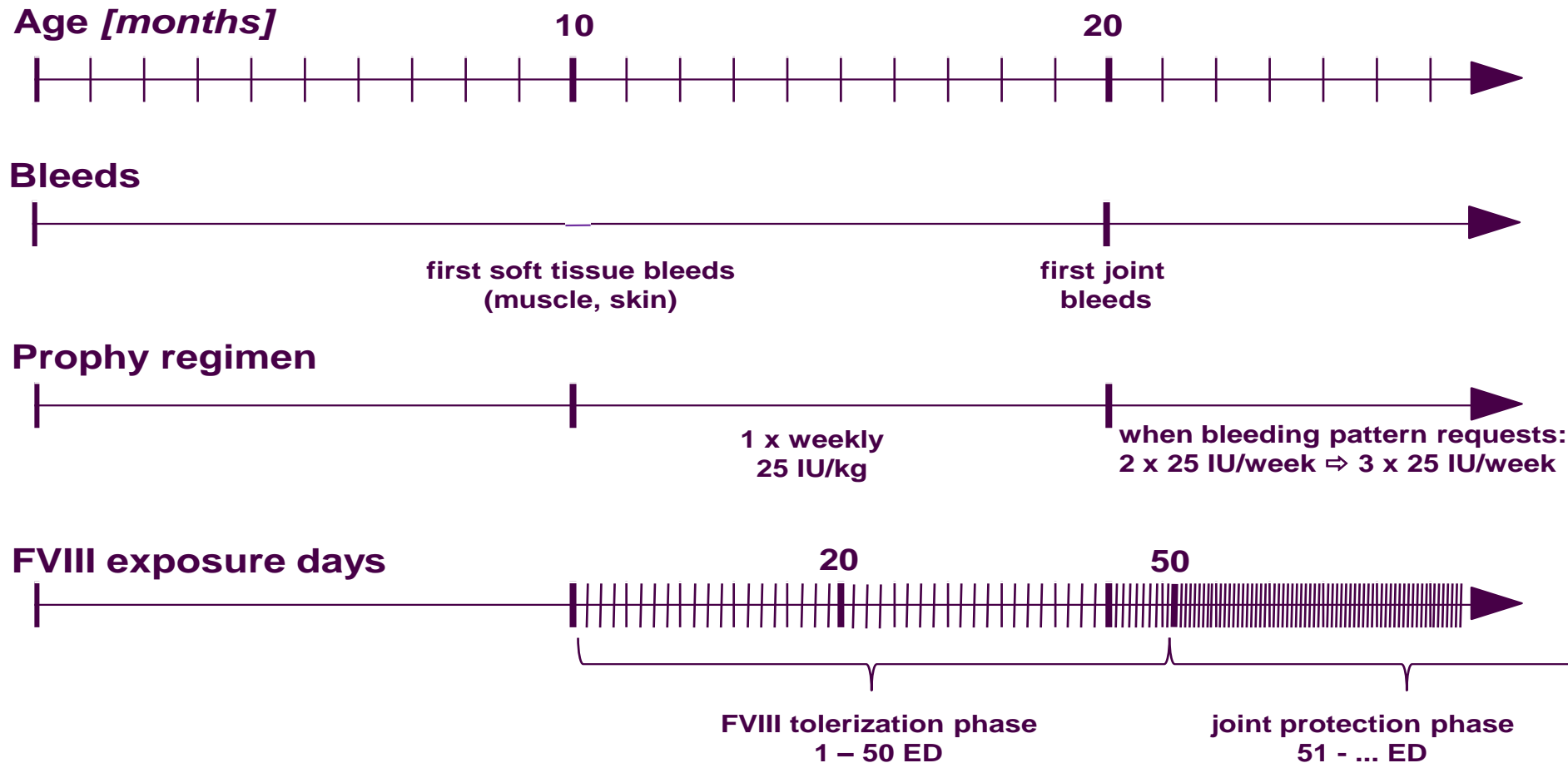


95% reduced inhibitor risk with the new prophylaxis regimen

Venous access !!!



Treatment scheme for PUPs receiving the new prophylaxis regimen





After finishing the study in Bremen and Munich

- in total **14 new patients** with severe haemophilia A diagnosed and treated with early tolerisation / prophylaxis (**all of these with > 40 ED**).
- in 8 patients genetics: high risk mutations,
- in 4 patients genetics: low risk mutations,
- in 2 patients results pending.
- **So until now no inhibitor - development!**

Study Group: New results after publication

	Control group (standard prophylaxis regimen) n = 30	Study group (new prophylaxis regimen) n = 40
Inhibitors (%)	14 (47%)	1 (2.5%)
High responders (%)	8 (27%)	0
Low responders (%)	6 (20%)	1 (2.5%)



97,5% reduced inhibitor risk with the new prophylaxis regimen



Comparison Control Group: Genetic Factors, new results after publication

	Control group (standard prophylaxis regimen) n = 30	Study group (new prophylaxis regimen) n = 40	
Severity of hemophilia A	All <1% FVIII activity	All <1% FVIII activity	
Ethnicity	All Caucasian	All Caucasian	
<u>FVIII mutation type*</u> :			
High risk (%)	24 (80)	26 (65)	
Low risk (%)	5 (17)	12 (30)	
Unknown (%)	1 (3)	3 (7,5)	

*Categorization of genetic risk according to Oldenburg J & Pavlova A. Genetic risk factors to inhibitors against FVIII and IX. *Haemophilia* 2006



Case Report cont.

- (born 2008) postpartum:
 - Haemophilia A, FVIII <1%
 - 3 uncles in the family with haemophilia A, FVIII <1%
 - Intron 22 Inversion and all with high titre inhibitor (>10 BU)
- We started early prophylaxis after the first soft tissue bleeds at the age of 8 months after first minor hematoma with 250 IU of recombinant FVIII (= 27 IU / kg bw);
- After 8 months, more haematomas and a traumatic elbow bleed that needed an additional 2 days treatment.
- No inhibitor development after > 150 EDs
- No further joint bleeds; still on a treatment two times per week.
- Now 4 more cases with >2 inhibitor patients in the family history without inhibitors



Aims of New “Early Prophylaxis / Tolerization” Regimen



Summary and conclusions

- FVIII may be not immunogenic on its own and should generally not induce inhibitor formation. Additional danger signals may be required for the development of inhibitors (only about 30% of PWH develop inhibitors).
- As bleeding is a known danger signal, treatment with FVIII in a non bleeding status of the patient (as practiced in early prophylaxis) might reduce the risk of inhibitor development.
- The currently practiced regimens for primary prophylaxis are tailored for joint protection rather than for inhibitor protection.



Early Prophylaxis Immunologic Challenge (EPIC) Study

Phase III B study ...

... to test the hypothesis that regular administration of low dose FVIII at an early age, before the onset of a severe bleeding phenotype, and in the absence of danger signals, can reduce the incidence of inhibitors by preferentially inducing tolerance to FVIII.



Study Design & Primary Endpoint

- Phase III B Study
 - Prospective, open-label, controlled, single arm
 - PUPs
 - Study drug: Advate®
- Inhibitor incidence rate of study regimen compared with:
 - Historical cohorts *
(including PUP studies where subjects were treated on-demand or with a standard prophylactic regimen, typically starting after the first major bleed)
- Estimated number of subjects: 100
- 75 centers globally



Early Prophylaxis Immunologic Challenge (EPIC) Study

Endpoints

- **Primary Endpoint**

- Incidence of inhibitor formation in severe haemophilia A (FVIII <2%) within the first 50 exposure days to rFVIII



Endpoints

Secondary Endpoints

- Time to inhibitor formation
- Incidence rate for low-titer, high-titer, transient, and all inhibitors
- Incidence of SAEs and ns AEs at least possibly related to the study drug
- Number, type and severity of all bleeds experienced
- Number, type and severity of all bleeds experienced when different prophylactic dosing frequencies are used (once/week vs. 2-3 times/week)
- Number and type of surgeries which can not be postponed until after 50 ED
- Correlation of FVIII gene structure, FVIII haplotype, and HLA haplotypes to inhibitor formation
- Total FVIII consumption (IU) for each patient
- FVIII-specific Ab isotype for all patients at entry and every 10 ED
- Immunologic markers potentially associated with inhibitor development



Inclusion Criteria

- Severe haemophilia A (FVIII <2%)
- ≤ 3 ED to any FVIII concentrate
 - having been used for treating minor bleeds with ≤ 2 infusions/event
 - or for preventative or precautionary infusions following possible injury
- Circumcision only allowed if cause for original diagnosis
- Adequate venous access as determined by the physician
- Written informed consent from legal guardian



Exclusion Criteria

- Subjects with FVIII $\geq 1\%2$
- Lack of adequate venous access as determined by physician
- Life threatening conditions (ICH, trauma, or serious surgery)
- Evidence of inhibitor ≥ 0.6 BU (Njimegen-modified Bethesda Assay)
- Any other Inherited or acquired haemostatic defect
- Any clinically significant, chronic disease or infection
- Enrolment in another interventional study
- Known hypersensitivity to the study drug
- Planned elective surgery that can not be postponed for 50 EDs
- Application of packed red cells or platelets



Executive Committee Members

- Günter Auerswald (Bremen, Germany)
- Karin Kurnik (Munich, Germany)
- Johannes Oldenburg (Bonn, Germany)
- Steven Pipe (Michigan, USA)
- Jan Astermark (Malmo, Sweden)
- Manuel Carcao (Toronto, Canada)
- Elena Santagostino (Milan, Italy)
- Chantal Rothschild (Paris, France)
- Elizabeth Chalmers (Yorkhill, UK)
- Bruce Ewenstein (Baxter)
- Armin Reininger (Baxter)

→ Start: August, 2011



The „town musicians“



Thank You very much for Your attention

Thanks to:

Team of the Prof.-Hess-Kinderklinik in Bremen

Team of the von Hauner Kinderspital in München

- Dr. Carolin Moorthi,
- Dr. David Overberg,
- Gabi Wilken,
- PD. Dr. Karin Kurnik,
- Dr. Christoph Bidlingmeier

