FACTANE®
A specific approach in hemophilia A treatment

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LFB – Les Ulis - France

Adana May 25th 2011

Plan

- The LFB : company profile and portfolio

- Factane®
  - Preclinical data
  - Clinical development
    - → Safety and efficacy study
    - → Inhibitor retrospective study
    - → ITI extension

- Summary

Plan

- **The LFB : company profile and portfolio**

- Factane®
  - Viral Safety studies
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- Summary

LFB : a biopharmaceutical group specialised in the treatment of hemorrhagic diseases

- Leading manufacturer of plasma-derived medicinal products in France.
- Exclusive right to the supply of plasma collected by the EFS, the French National Blood Organization *(Article 77 of law no. 2009-879, the French HPST law)*
- Growth strategy focused on :
  - Activities at international level
  - Development of innovative therapies.

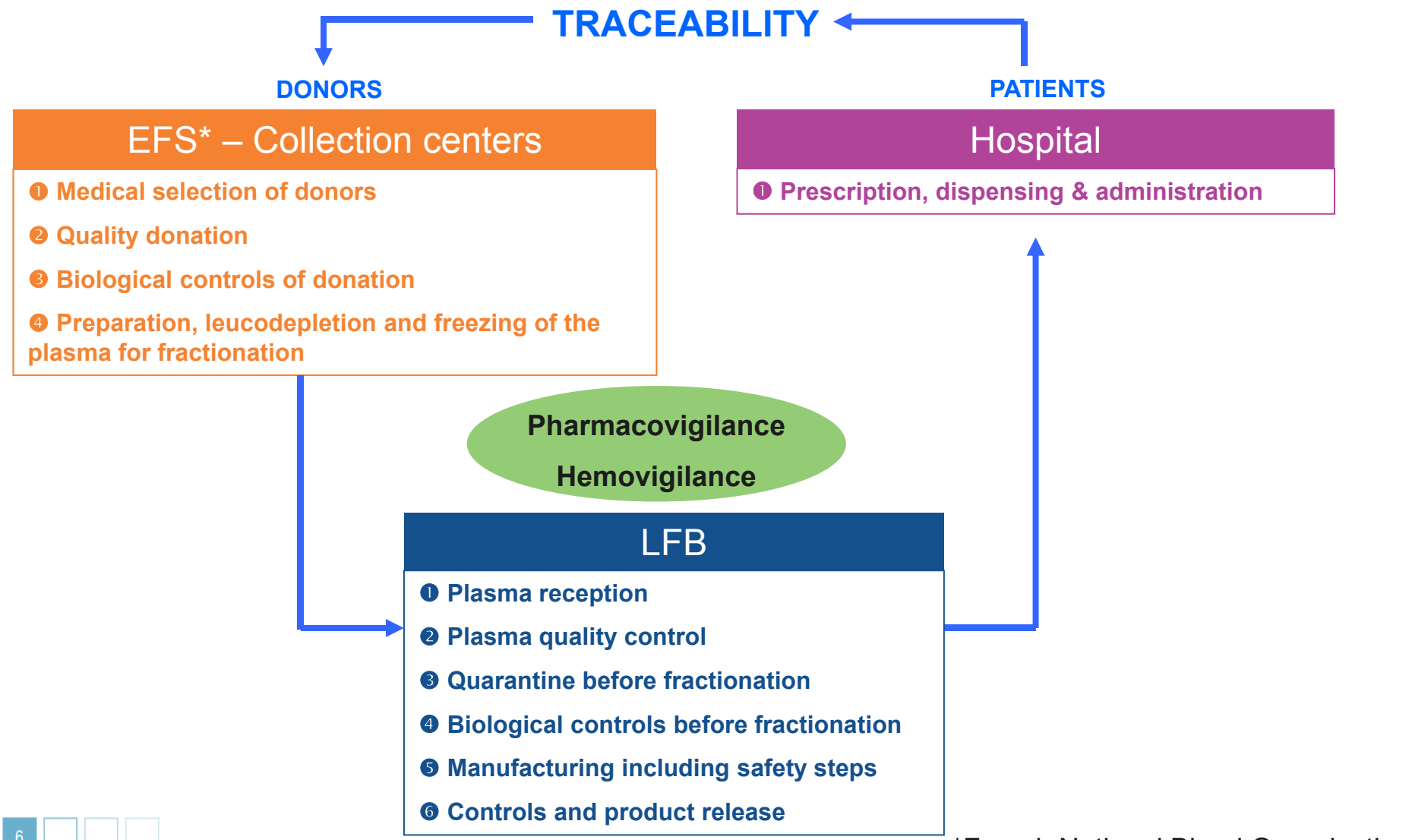
Key figures

- 2nd pharmaceutical company serving hospitals in France
- 6th pharmaceutical company worldwide specialised in plasma-derived medicinal products
- 1.700 employees
- 20% of turnover invested in R&D budget
- 1 plant in 2 manufacturing facilities

Lille…

And Les Ulis …

Multiple actors in security chain



*French National Blood Organisation

Plasma Quality: Biological tests on donations undertaken in the blood transfusion institution

Tests	European Union Recommendations (1)	Standards for Plasma collected on French territory (2)	LFB requ.
Deleukocytation	0	≤ 10^6/l	≤ 10^6/l
Blood donation tests			
Ac anti-HIV-I and 2	+	+	+
Ac anti-HCV	+	+	+
Ag HBs	+	+	+
Ac anti-HBc	0	+	+
Ac anti-HTLV I et II	0	+ (not obligatory for plasma for fractioning)	+
Syphilis	+	+	+
Malaria (at-risk patients)	+	+ (not obligatory for plasma for fractioning)	+
VGD*HIV-I	0	+	+
VGD*HCV	0	+	+

(1) COUNCIL RECOMMENDATION 98/463/CE, Directive 2002/98/CE, Explanatory note CPMP/BWP/269/95rev3
(2) Articles D.1221-6, D.1221-11, D. 1221-13 and D. 1221-14 of the Public Health Code and ruling of 29 April 2003
* Viral Genome Detection

Plasma Quality: Biological qualification of plasma for fractioning

Viral tests performed

after receipt of the plasma

Upon receipt

By Nucleic Acids Amplification (NAA)

PV B19 **HAV**

QUARANTINE

First step fractionation

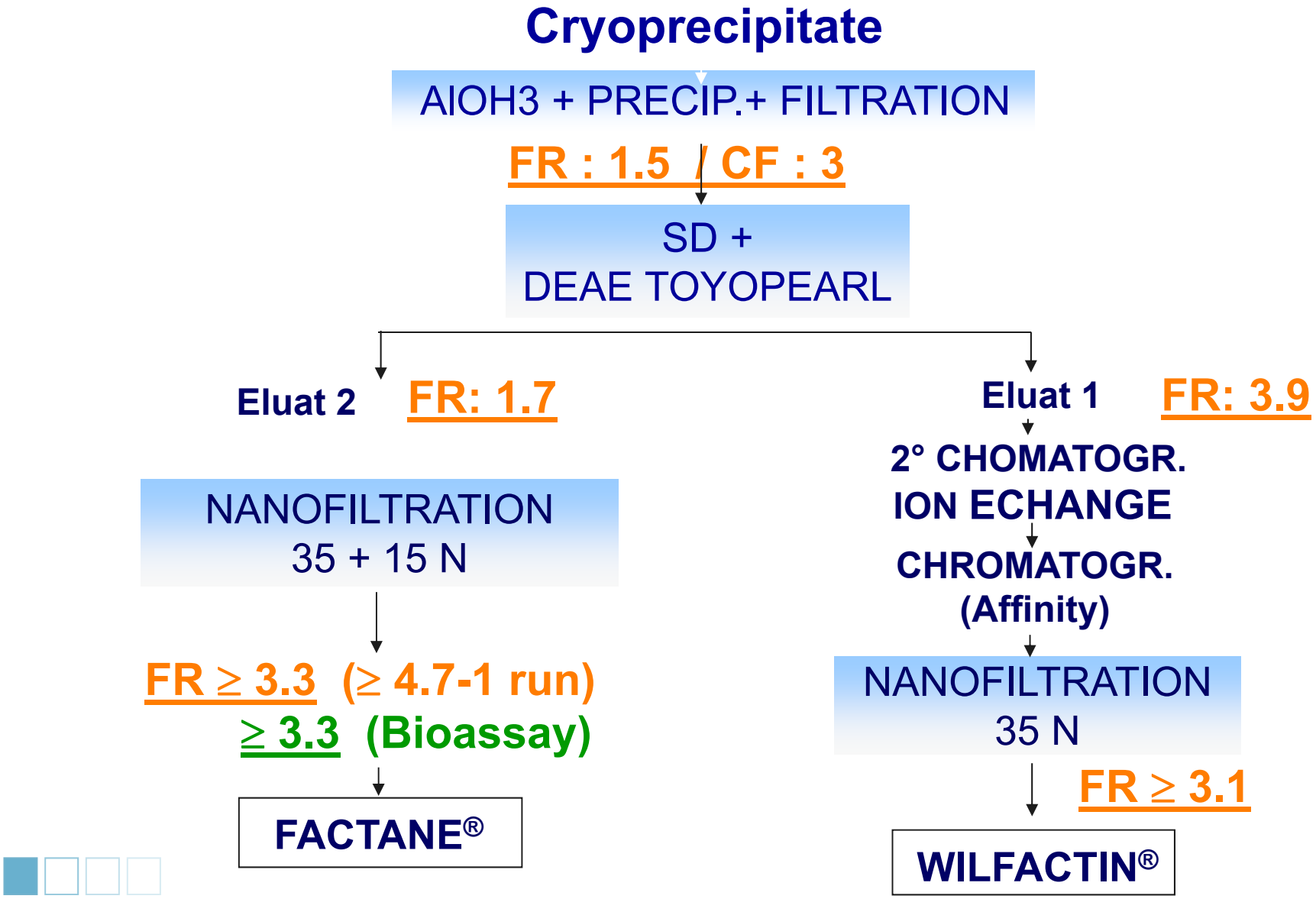
By immuno-enzymology	By NAA
Ac anti-HIV 1 and 2 (sub-type 0)	**PV B19**
Ac anti-HCV	**HIV**
Ag HBs	**HAV / HBV / HCV**

Factane®: Viral safety

Type of virus	Virus tested	Model virus of:	Solvent/detergent treatment	15 nm nanofiltration	Overall reduction factor
Enveloped	HIV-1	HIV	≥ 4.4	≥ 3.8	≥ 8.2
	BVDV	HCV	nd	≥ 4.1	≥ 4.1
	PRV	DNA virus	≥ 4.1	≥ 4.9	≥ 9.0
	VSV	-	> 6.5	nd	> 6.5
Non-enveloped	VHA	-	nd	≥ 3.6	≥ 3.6
	PPV	Parvovirus B19	nd	≥ 5.5 (1)	≥ 5.5
	SV40	Highly resistant virus	nd	5.3	5.3

HIV: human immunodeficiency virus
BVDV: bovine viral diarrhoea virus
PRV: pseudorabies virus (high total protein content)
VSV: vesicular stomatitis virus
HAV: hepatitis A virus
PPV: porcine parvovirus, model of parvovirus B19
SV40: particularly resistant simian virus
nd: not done
(1): results under worst-case conditions

Elimination of EST



The LFB commitment in the treatment of hemorrhagic diseases

1 deficiency = 1 medicinal product

- 2 approaches

Conventional approach

Cryoprecipitate

→ **1 batch : FVIII/VWF**
→ **Hemophilia A**
→ **VWD**

LFB's approach

Cryoprecipitate

→ **FVIII: Factane® (SD-35-15 nm) → Hemophilia A**

→ **VWF: Wilfactin® → VWD**

↓

→ **Better therapeutic valuation of human plasma**
→ **More flexibility to increase the viral safety**
→ **Avoid exposure to unnecessary proteins that may be harmful**

Concentrates for the treatment of bleeding disorders including rare diseases

Product	Factor VIII	Factor IX	Von Willebrand Factor	Factor XI	PCC	Fibrinogen
Trade mark	Factane®	Betafact®	Wilfactin®	Hemoleven®	Kanokad ®	Clottafact®
Biological Safety	SD-35-15nm	SD-15nm	SD-35nm-DH	SD-15nm	15nm – 15nm	SD-35nm-DH
Applications submitted	France & Belgium, Luxembourg, Portugal, Brazil, Iran, Lebanon, Morocco, Syria, Tunisia, Turkey	France & Greece, Netherlands, Portugal, United Kingdom, Austria, Germany Belgium, Luxembourg, Brazil, Lebanon, Morocco, Syria, Tunisia, Turkey	France & Finland, Greece, Italy, Belgium, Luxembourg, Netherlands, Brazil, Lebanon, Portugal, Estonia, Sweden, Norway, Austria, UK, Denmark, Turkey	France	France	France, Turkey

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Factane® : Objectives of the development

- Very high purity plasma-derived FVIII
  - → specific activity > 100 IU/mg total protein

- SD treatment and 35nm-15nm filtration

- VWF content : 20 to 40 IU/100 IU FVIII with full structural and functional characterisation in order to minimize the inhibitor risk

Very High Purity FVIII concentrate → state of the art viral safety profile

Role of the VWF – FVIII immunogenicity

FVIII stabilisation [1,2,3,4]

- Protection → against proteolytic actions of enzymes
- → against FVIII PL/activated platelets fixation
- Regulation of FVIIIa inactivation
- Regulation of FVIII catabolism

Possible reduction of FVIII immunogenicity [5,6]

- Haemophilia mice model: → less inhibitors with pdFVIII-VWF than with rFVIII
  → rFVIII+VWF incubation : ↓ inhibitor titers
- *in vitro* VWF inhibits: → dendritic cells capture of FVIII
  → dose-dependant specific FVIII L_T activation
  → FVIII endocytosis (FVIII catabolism)

VWF may reduce FVIII immunogenicity

[1] Weiss HJ. J Clin Invest 1977; 60:390-404. [2] Koedam JA. Eur J Biochem 1990;189:229-34. [3] Fay PJ. J Biol Chem 1991;266:2172-7.
[4] Saenko EL. J Biol Chem 1995;270:13826-33. [5] Delignat S. Haematologica 2007;92(10):1423-26. [6] Dasgupta S. Blood 2007;109:610-2

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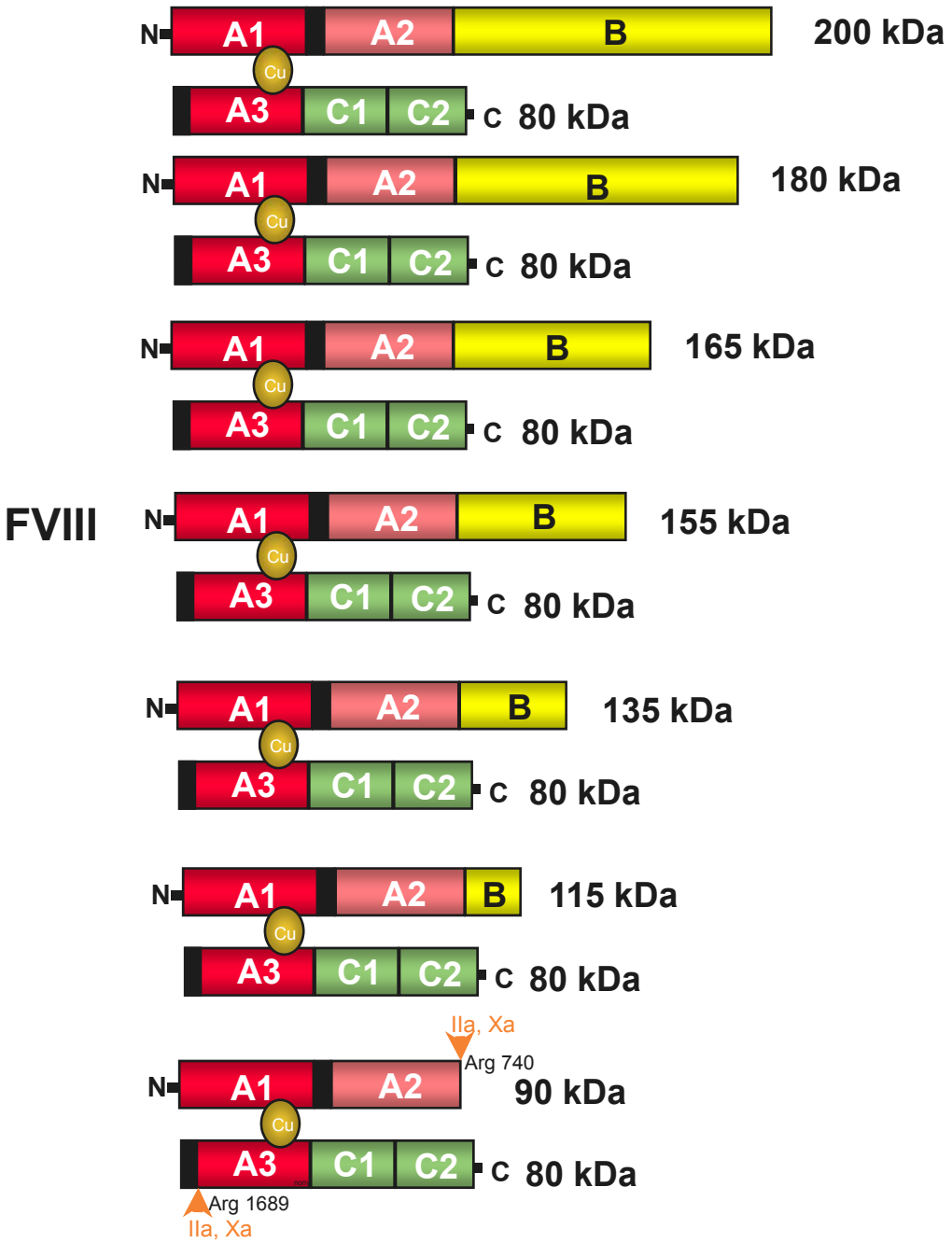
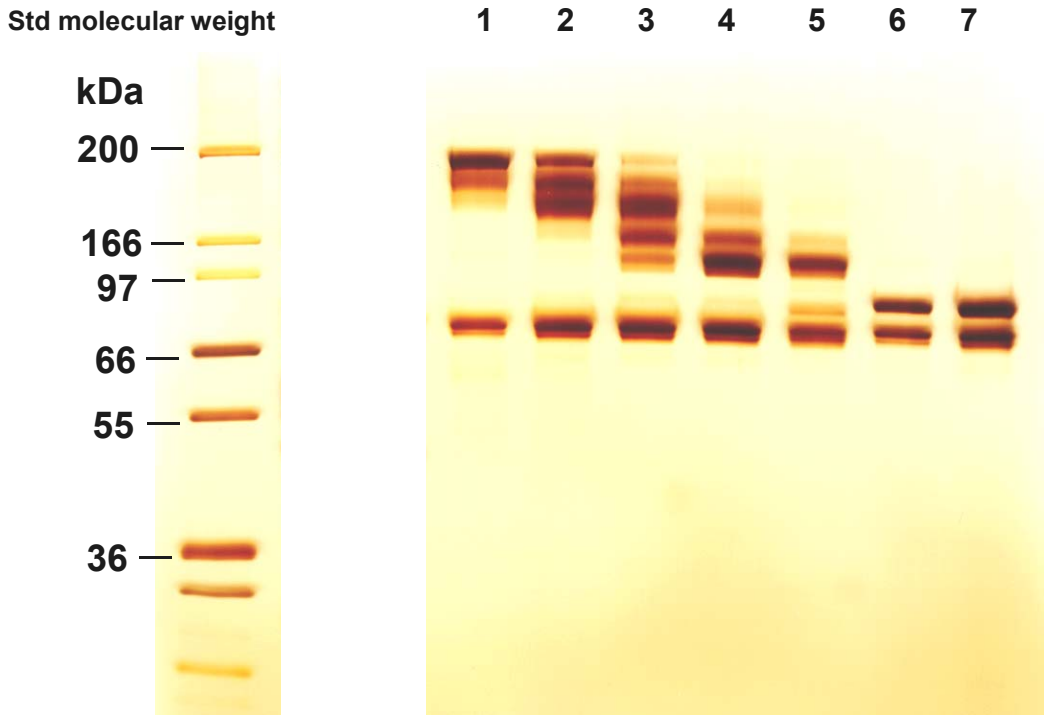
Schematic representation of the FVIII different forms



Factane® : different molecular forms of FVIII (SDS –PAGE)



- Physiological representation of FVIII heterodimers in Factane®
- No fragments or activated forms of FVIII or thrombin generated degradation products

Factane® manufacturing process respects physiological FVIII molecule

EMA requirements

Requirements of the emea

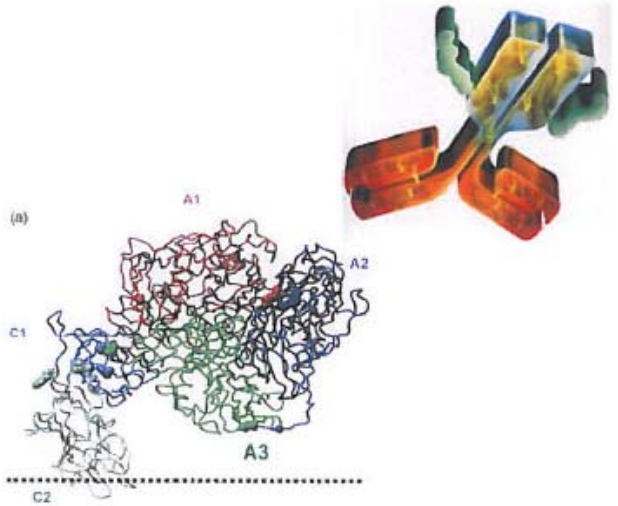
- European Medicines Evaluation Agency -

Rainer Seitz, M.D.

Division of Haematology/
Transfusion Medicine

Paul-Ehrlich-
Institute

63225 Langen, Germany



EMA requirements

Preclinical Testing ?

- Assessment by laboratory tests ?
  - Extensive characterization of novel products
  - Proposal for specific tests based on experience with a double-inactivated (SD + past.) FVIII causing a cluster of inhibitors:
    - slower FVIII cleavage by thrombin, more rapid Xa generation, enhanced PL binding (NIBSC data)
    - 40 kD impurity (company)
  - So far no established predictive test available

Functional characterisation Factane®

- 5 batches

	FVIII:C Chromogenic assay (IU/ml)	FVIII:C One-stage assay (IU/ml)	FVIII:Ag (IU/ml)	FVIII:C One-stage assay / FVIII:C Chromogenic assay	FVIII:C Chromogenic assay / FVIII:Ag	FVIII:C One-stage assay / FVIII:Ag
Factane®	89 ± 7	121 ± 10	101 ± 14	1.36 ± 0.18	0.90 ± 0.11	1.2 ± 0.18
FVIII-LFB®	103 ± 3	128 ± 4	121 ± 10	1.24 ± 0.07	0.85 ± 0.07	1 ± 0.12
				No FVIII activation	No FVIII degradation	No FVIII degradation

FVIII was not denatured during the process

Chtourou et al. Vox Sanguinis 2007;92:327-37

FVIII binding to phospholipids

FVIII sample	Binding to phospholipid PC:PS Dissociant constant K_D(M)
Factane® Geometric mean (GCV)	1.43 X 10^{-8} (2.37) (1)
FVIII-LFB® Geometric mean (GCV)	1.34 X 10^{-8} (3.78) (1)
Physiological data	0.6 X 10^{-8} (2)

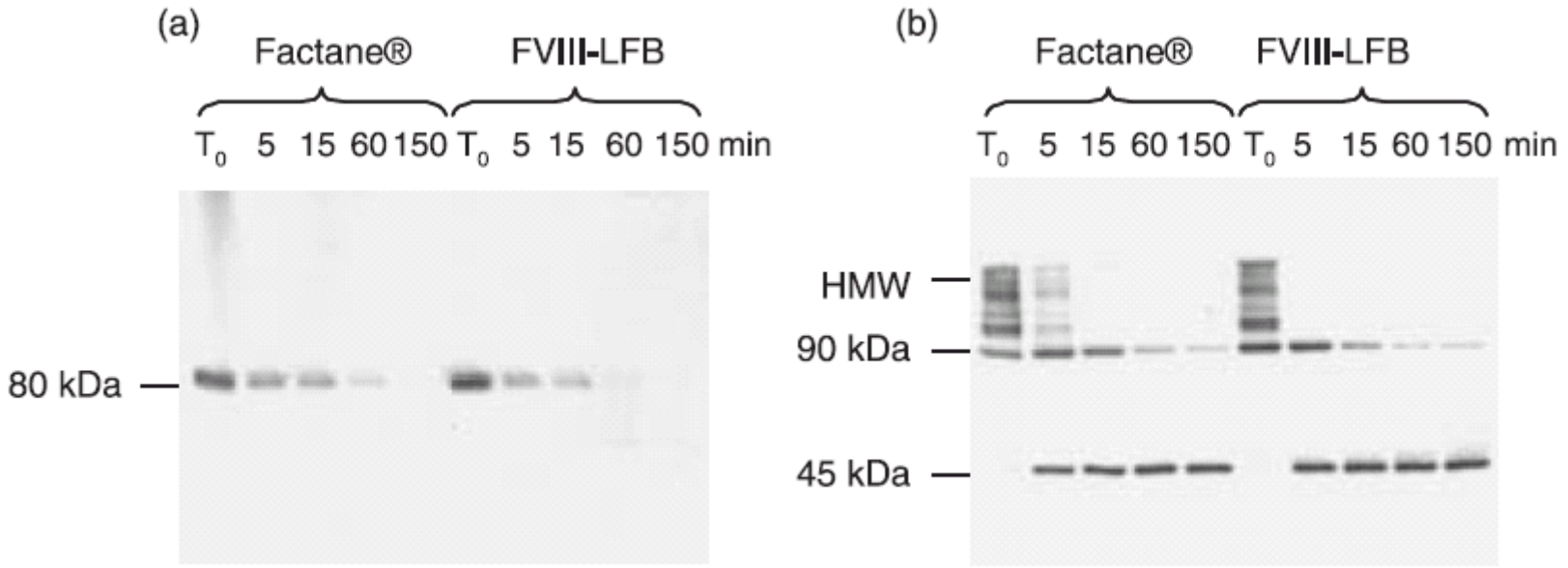
- The student's t-test sowed no significant difference between Factane® and FVIII-LFB® ($p<0.05$)

Factane® binds to phospholipids with a physiological affinity

(1) Chtourou S et al. Vox Sanguinis 2007;92:327-37

(2) Saenko E et al. J Chromatogr A; 1999;852:59-71

Cleavage by thrombin: physiological timing



- Fig. (a) : progressive disappearance of the 80 kDa light chain that occurred within 60 min.
- Fig. (b) : degradation of the high molecular weight forms of FVIII's heavy chain complete within 60 min. for both products.

Chtourou et al. Vox Sanguinis 2007;92:327-37

VWF:Ag quantity in Factane®

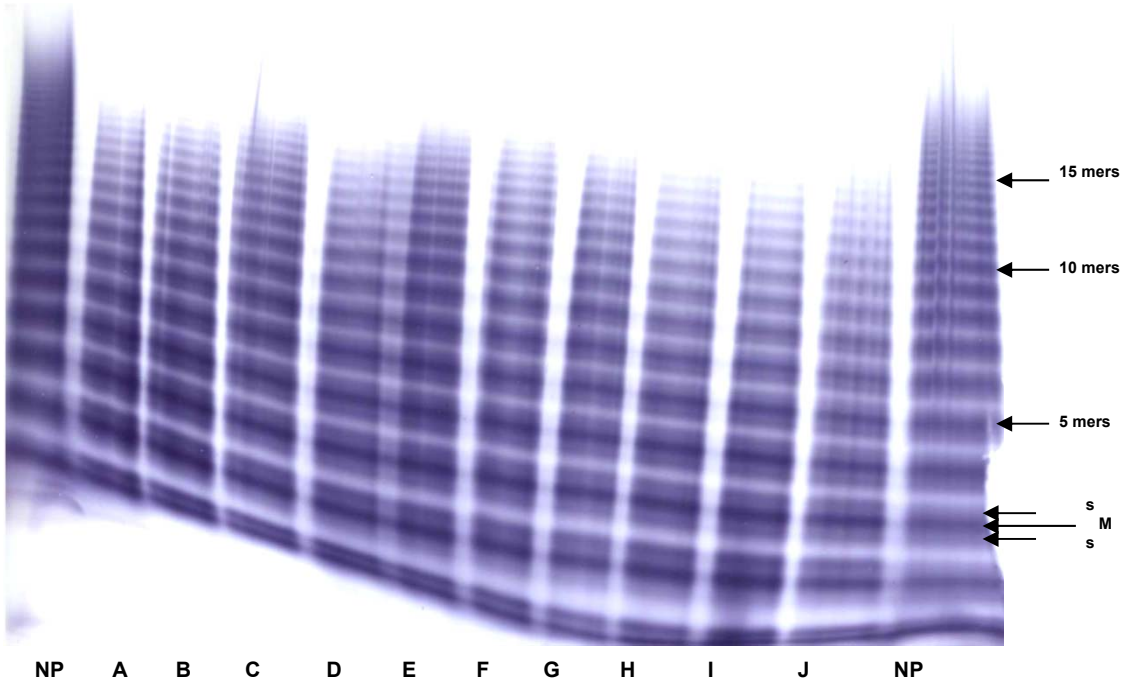
- Dosage not requested by health authorities
- ELISA test – calibration against the international standard 00/154
- **79** batches : determined at random between 2006 and 2009

	VWF:Ag (IU/ml)	Total Proteins (g/l)	VWF:Ag/ total proteins (%)
FACTANE® 100 IU/ml	**37 ± 11**	**0.8 ± 0.12**	**46 ± 13**

VWF is the major co-purified protein in Factane®

Factane® : preservation of VWF structure

- Results

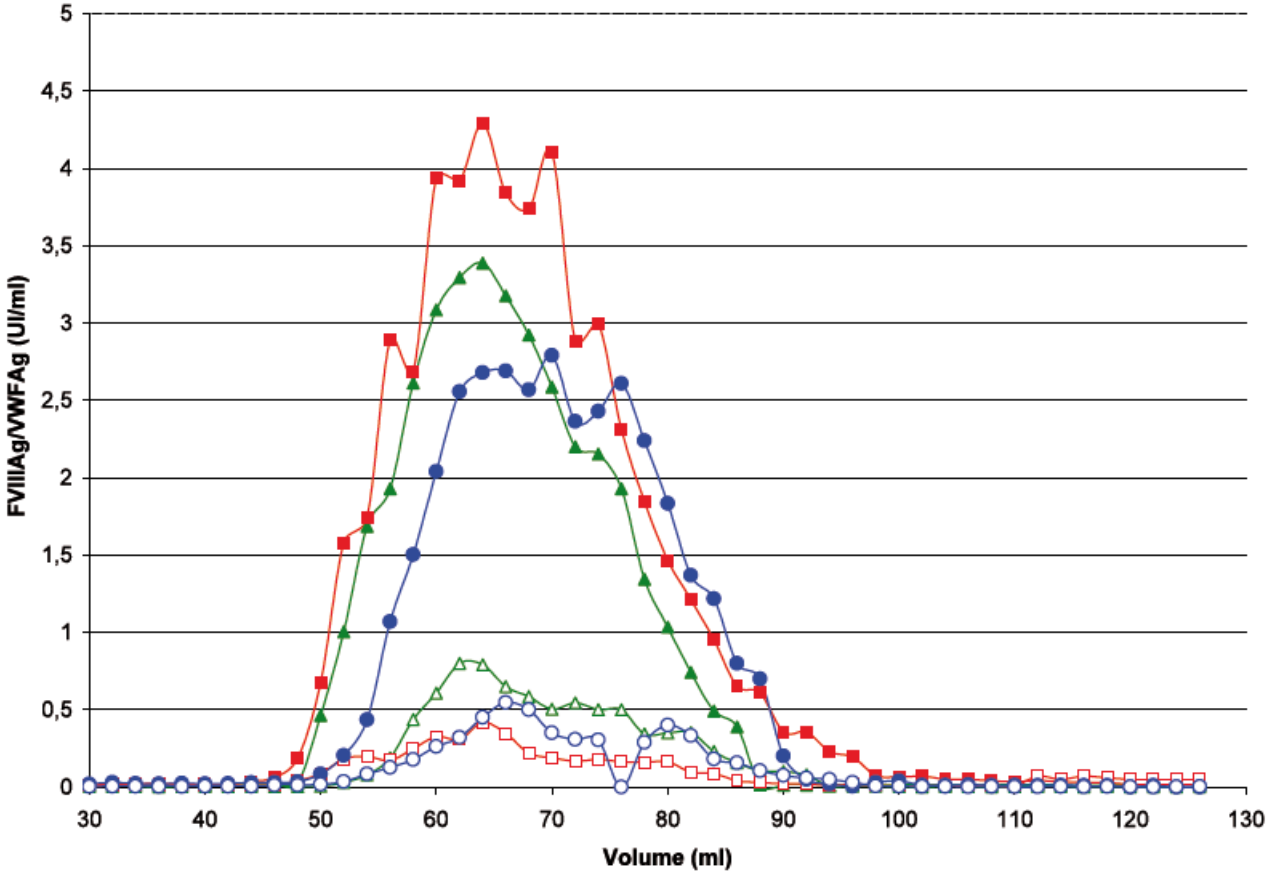


s: satellite; m: major ; A to J : batches of VHP pdFVIII (Factane®)

- Triplet structure similar to that of normal plasma
- No degradation product
- Multimeric profile is fully represented up to decamers

Samor et al. submitted

FVIII/VWF binding in Factane®

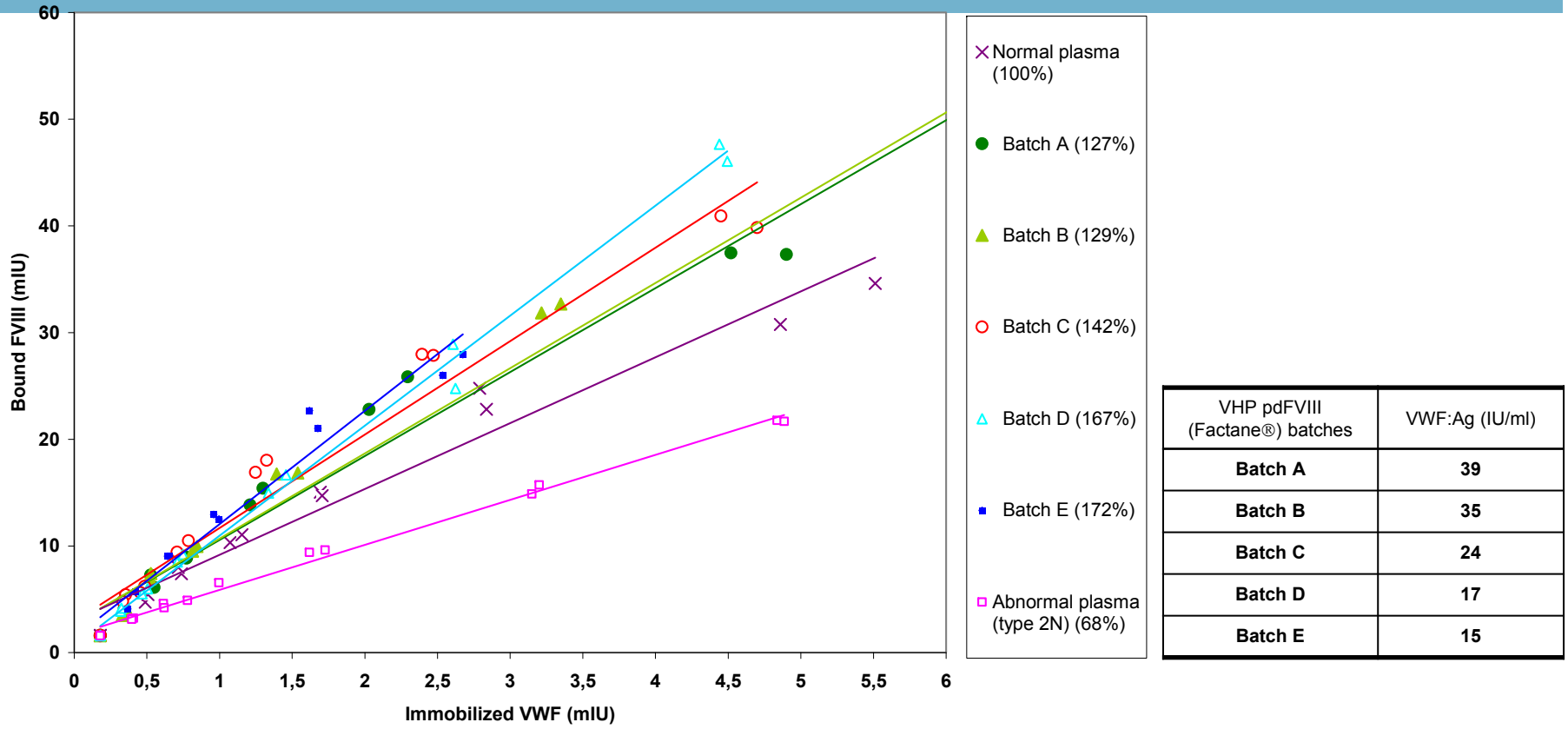


VHP pdFVIII (Factane®) batches	VWF:Ag (IU/ml)
Batch A	**39**
Batch C	**24**
Batch E	**15**

- **FVIII-VWF complex linked**
- **Absence of free FVIII**
- **Same profile for the 10 studied batches of Factane®**

Samor et al. submitted

VWF capacity to bind FVIII

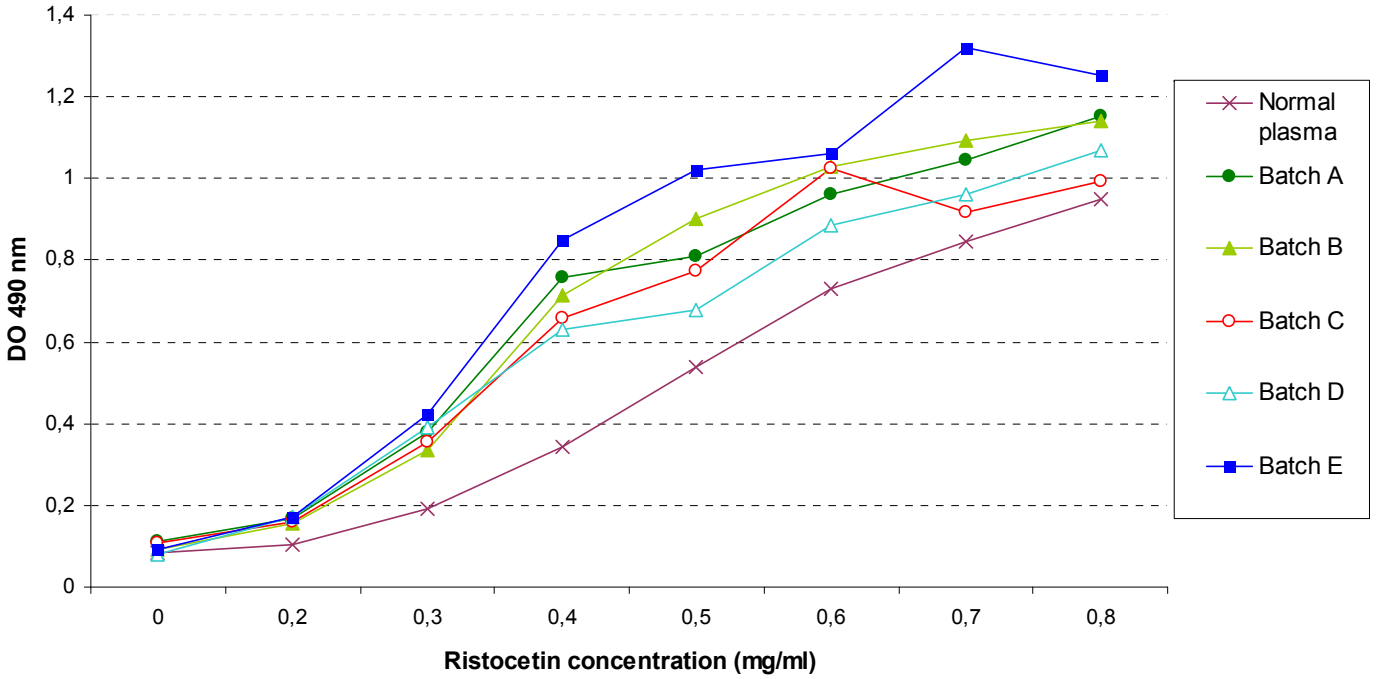


VHP pdFVIII (Factane®) batches	VWF:Ag (IU/ml)
Batch A	**39**
Batch B	**35**
Batch C	**24**
Batch D	**17**
Batch E	**15**

- **All batches have a similar capacity for FVIII binding, even those with a low VWF: Ag content**
- **VWF capacity to bind exogenous recombinant FVIII comparable to that of normal plasma**

Samor et al. submitted

VWF capacity to bind GPIb



VHP pdFVIII (Factane®) batches	VWF:Ag (IU/ml)
Batch A	**39**
Batch B	**35**
Batch C	**24**
Batch D	**17**
Batch E	**15**

- **VWF binding to GPIb were similar to the binding profile of normal plasma**

Samor et al. submitted

Factane® : preclinical characterisation

- FVIII structural studies
- FVIII functional studies
  - FVIII dosage : different assays
  - FVIII binding to phospholipids
  - FVIII cleavage by thrombin
- VWF content : structure and function
  - VWF:Ag

A comprehensive preclinical file

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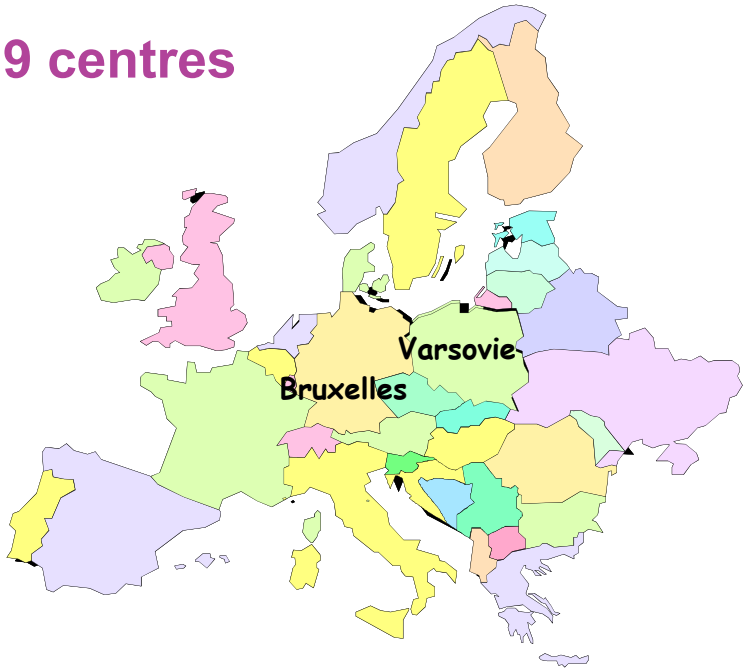
Pivotal studies

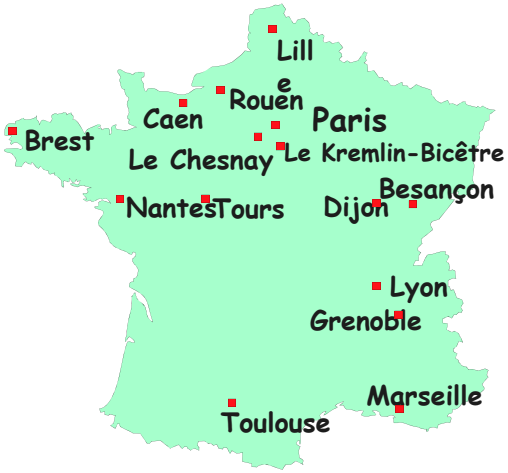
Study of the efficacy and safety of FACTANE® in previously-treated patients (PTPs)

Factane® : pivotal studies

73 treated PTPs (42 France + 31 Europe) in 19 centres

- 71 pts evaluated in efficacy study
- 73 pts evaluated in safety study
- Severe haemophilia A FVIII:C ≤ 1%: 67 patients
- PTPs : majority of patients > 150 CED
- Follow-up
  - ≥ 6months 70/73 pts (96%)
  - ≥ 12 months 35/73 (48%)





Factane® : pivotal studies results

		Number of episodes/procedures	Outcomes
Bleeding episodes	*Minor*	1672 (64 pts)	92.2% excellent/good
	Major	5 (5 pts)	100% excellent/good
Surgical procedures		29 (24 pts)	100% excellent/good

No appearance of inhibitors

Factane® : pivotal studies results

Prophylaxis

	N	Outcomes
Short- term *(school activities, sports, medical condition)*	**458 infusions** **(38 pts)**	**9 bleeds in 6pts** **- 8 minor** **- 1 severe** (concomitant pseudo-tumour)
***Long-term*, median & [range]** **19.1 months [5.9 – 27.5]**	**1759 infusions** **(11 pts)**	**Bleedings *per year*, median & [range]):** **from 40, [3-150] ➔ 2.3, [0-17]**

Factane® : safety

	Number of related adverse events	Event type	Outcomes
Not serious AE	10 related (6pts)	-Injection site reaction (1) -Allergic reaction (1) - Hot flushes (4) -Nausea (1) -Decrease of CD4 (1) and CD8 (1) - Increase of pain (1)	Spontaneously resolved
Serious AE	2 related (2pts)	-Increase of pre-existing FVIII inhibitor (1) - Migraine syndrome (1)	Included by error Spontaneously resolved

Excellent safety profile

Retrospective study

anti-FVIII inhibitor incidence in PUPs treated with FVIII VHP/LFB from 1988 to 2001

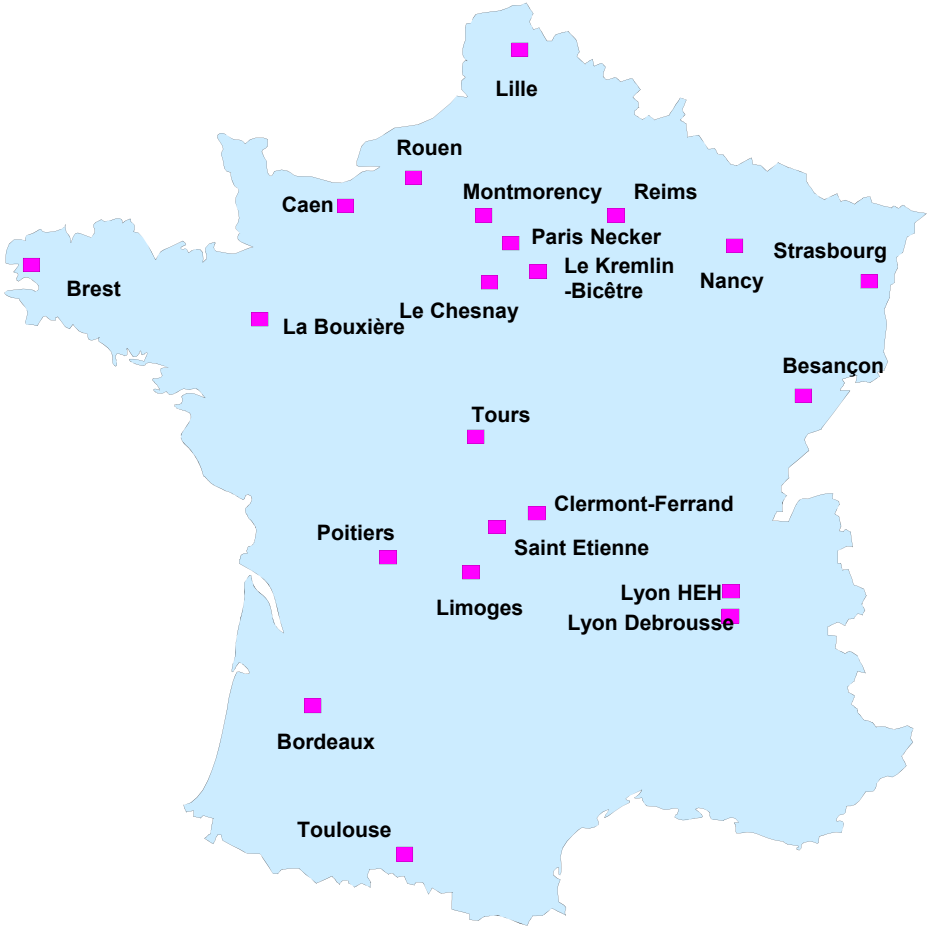
Inhibitor Incidence: methods

22 centres participated

Data collection and verification

Validation of all files by the Scientific Committee

104 PUP files evaluated



Inhibitor Incidence: patients characteristics

FVIII:C<1%	Intron 22 inversion	Non caucasian	Family history of inhibitors
104/104	43/80	9/73	16/47
100%	54%	12%	34%

Homogenous population with severe hemophilia A

Inhibitor Incidence

RESULTS n = 104

Frequency

14.4% (15/104)

95 CI%: 7.7-21.2

- **High responders 5.8%** (6/104)
- **Low responders: 6.7%** (7/104)
- **'1 test +': 1.9%** (2/104)

Cumulative incidence at 50 CED

16.7%

95 CI%: 8.9-24.5

High responders > 5 BU:

7.2%

95CI%: 1.6-12.7

Confirmation of low inhibitor incidence (1),(2)

(1) Guérois C, *et al* Thromb Haemost 1995;73(2):215-8
(2) Goudemand J, Sang Thromb et Vaisseaux, 2001;13:31-71

Factane® in Immune tolerance induction (ITI)

- Retrospective LFB study : **6 patients**
  - 4 high responders
  - 2 low responders
  - →Immune tolerance achieved in 5/6 patients within 2 to 26 months (total success rate 83.3%)
  - →Partial response for the 6th (high responder) patient after 19 months of treatment

- Retrospective study by *Orsini et al.*: **8 patients**
  - Total immune tolerance achieved in 7/8 patients
  - 1 partial success

Efficacy in ITI → Factane® sole FVIII concentrate with an ITI marketing authorization in France

Orsini et al. Haematologica 2005;90-1288-1290

Summary

- **Extensive preclinical characterisation**
  - Molecular analysis
  - Functional studies
  - Structural functions and VWF contained in Factane®
- **Multicenter clinical development** according to EMA regulatory requirement (CPMP/BPWG/198/95.rev.1)
- **Specific investigation**
  - Inhibitor issue
  - Efficacy in ITI