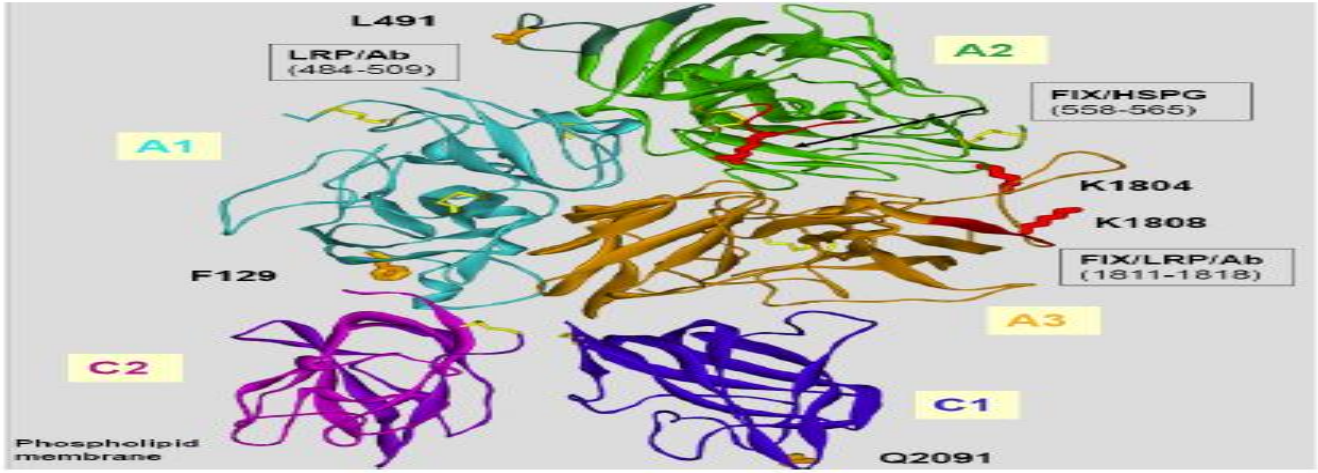


Traitements innovants dans l'hémophilie

M.Bensadok

Service d'hématologie,CTS,Centre de traitement de l'hémophilie Benimessous

Post WFH

16 Décembre 2016,Hotel Mercure

Nombreuses technologies
Prolonger la demi-vie des protéines (FVIII / FIX)

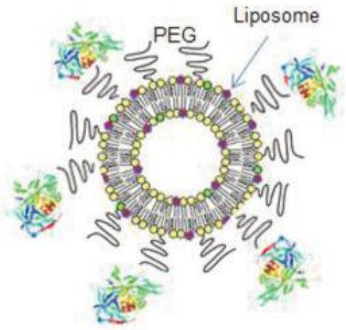
Modification chimique
Modification génétique
Fusion avec des protéines porteuses
(Fc fusion, Albumin)

- Réduit le nombre d'injections intraveineuses requises
- Amélioration de la commodité
- Amélioration de la qualité de vie et les patients pourraient maintenir un mode de vie plus actif sans craindre d'avoir un saignement
- Offrir une meilleure protection contre les saignements lors d'une chirurgie majeure
- Réduire le besoin d'infusions multiples lors du TRT à la demande
- Réduction du nombre d'enfants nécessitant l'utilisation d'un P.Cath

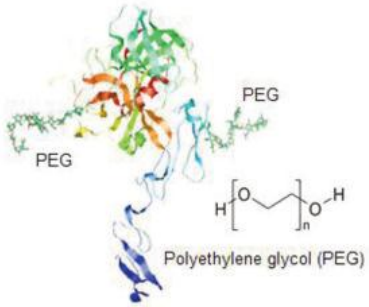
Facteurs anti-hémophiliques à durée de vie prolongée

Protéine recombinante

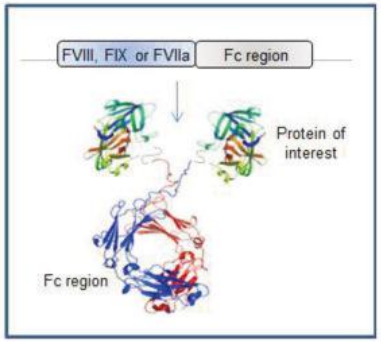
Liposomes pégylés*

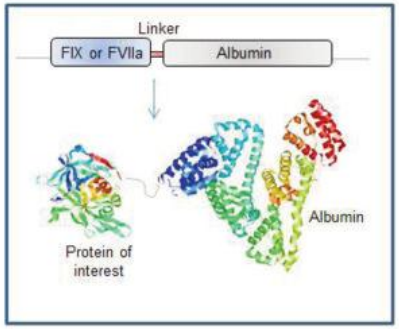


Pégylation*
- Au hasard
- Sur un site spécifique



Protéine de fusion
- Fragment Fc des immunoglobulines
- Albumine





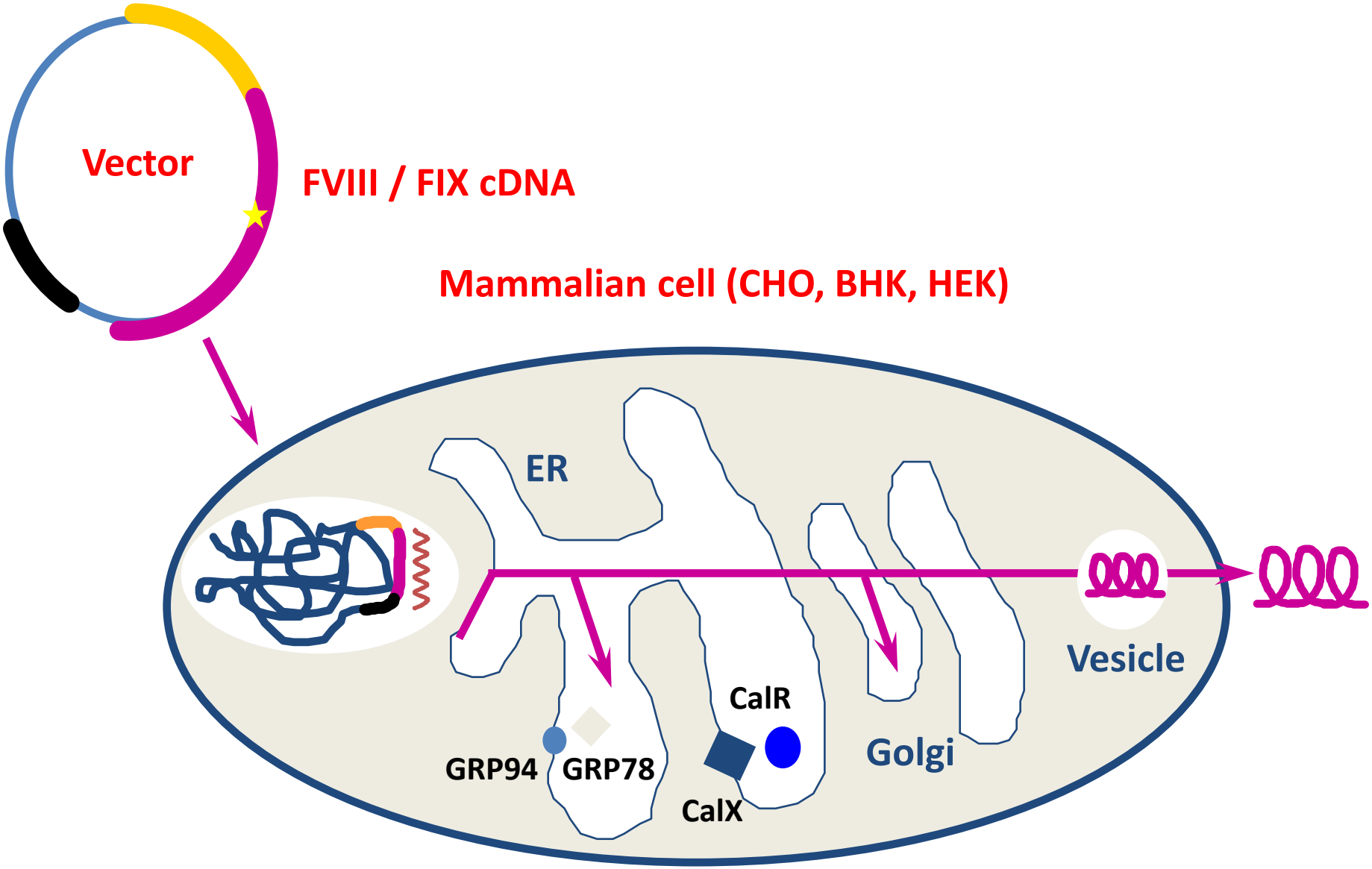
Modification de la séquence en acides aminés

Pégylation : Elle a pour but d'augmenter la durée d'efficacité d'une protéine en diminuant sa vitesse d'élimination par augmentation de son poids moléculaire en la liant au polyéthylène glycol (PEG)

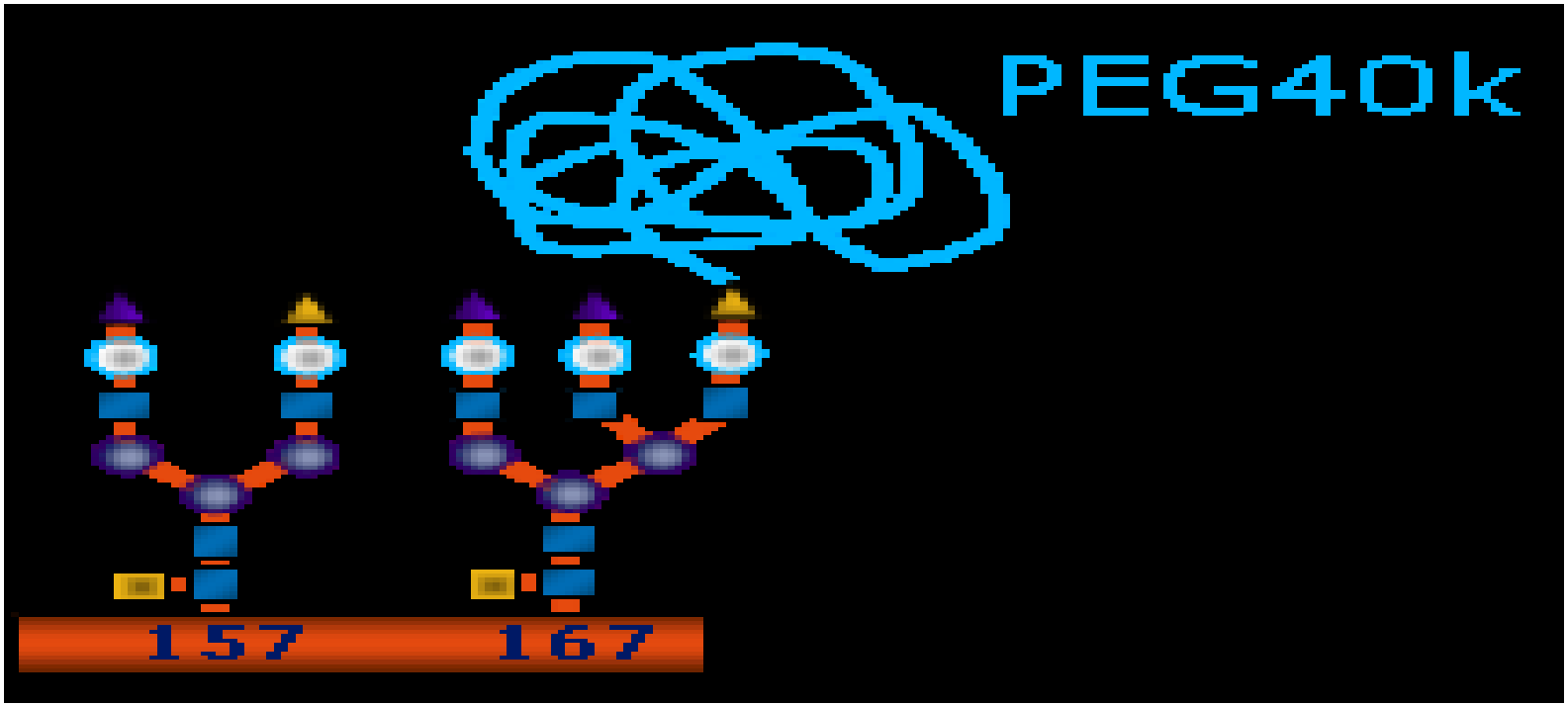
Principe pegylation

- Augmentation de la durée de vie d'une protéine
- En diminuant sa vitesse d' élimination
- Par augmentation de son poids moléculaire
- En la liant au Polyéthylène Glycol(PEG)

Recombinant FVIII / FIX production

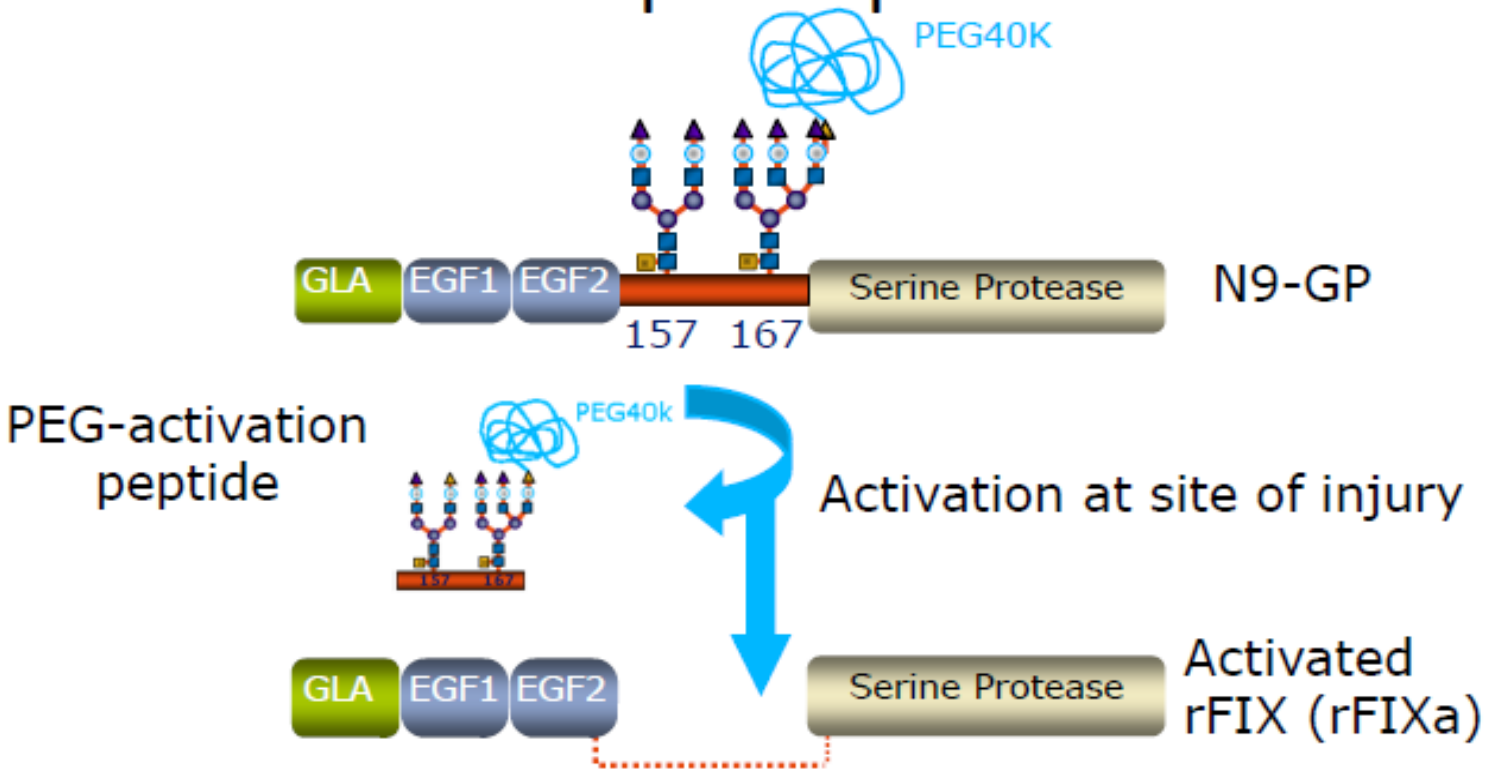


GlycoPEGylated rFIX (N9-GP): The principle



Ajout d'un groupement chimique le polyéthylène glycol (PEG)

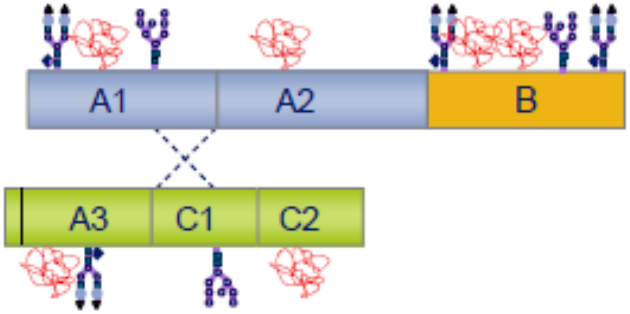
GlycoPEGylated rFIX (N9-GP): The principle



Upon activation, the PEGylated activation peptide is cleaved off, leaving native activated rFIX

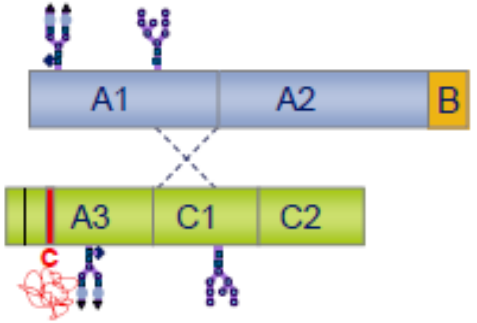
Long-acting FVIII compounds presented at meetings and described in the patent literature

Random Pegylation



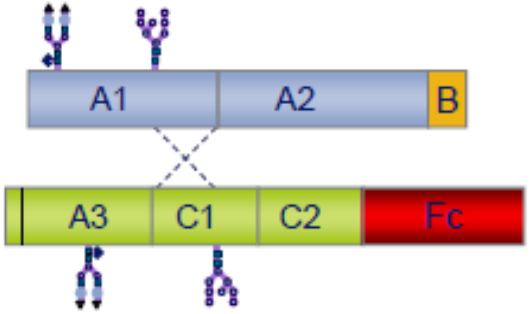
PEGylated FVIII

Directed Pegylation



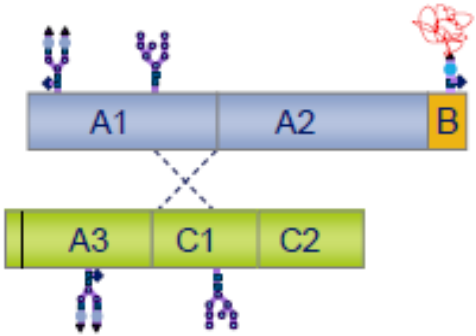
PEGylated mutant FVIII

Fusion Proteins



FVIII:Fc hybrid protein

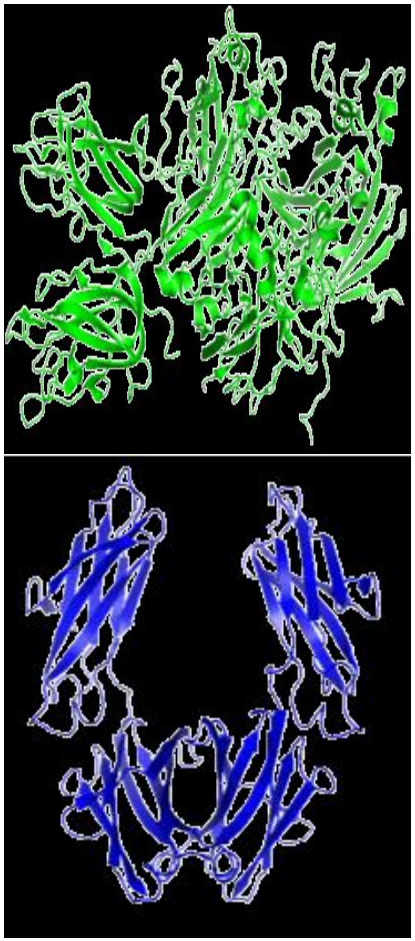
Glyco-Pegylation



FVIII GlycoPegylated

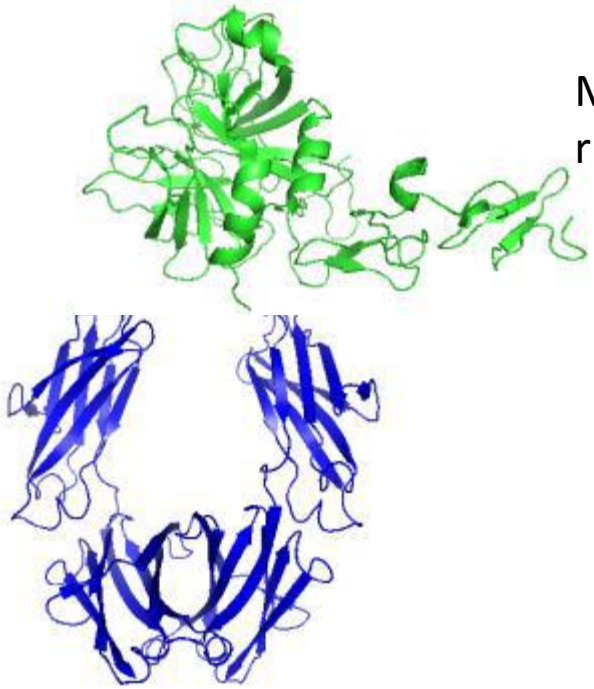
Turecek PL et al. *Blood* 2007;110:3147; Murphy JE et al. *J Thromb Haemost* 2007;5(2):P-T-022; Dumont JA et al. *Blood* 2009;114:545; Stennicke HR et al. *Haemophilia* 2010;16(4):08P37

Proprietary Monomer Technology Applied to rFVIIIFc & rFIXFc



Model of rFVIIIFc

Model of rFVIIIFc



Model of rFIXFc

rFVIIIFc: Single B-domain-deleted rFVIII fused to dimeric Fc region of human IgG1

- **rFIXFc: Single FIX fused to dimeric Fc region of human IgG1**

rIX-FP: Advanced concept

- **rIX-FP with proteolytically cleavable linker**
  - Albumin fused to the C-terminus of FIX
  - Cleavable linker between FIX and albumin derived from FIX activation region

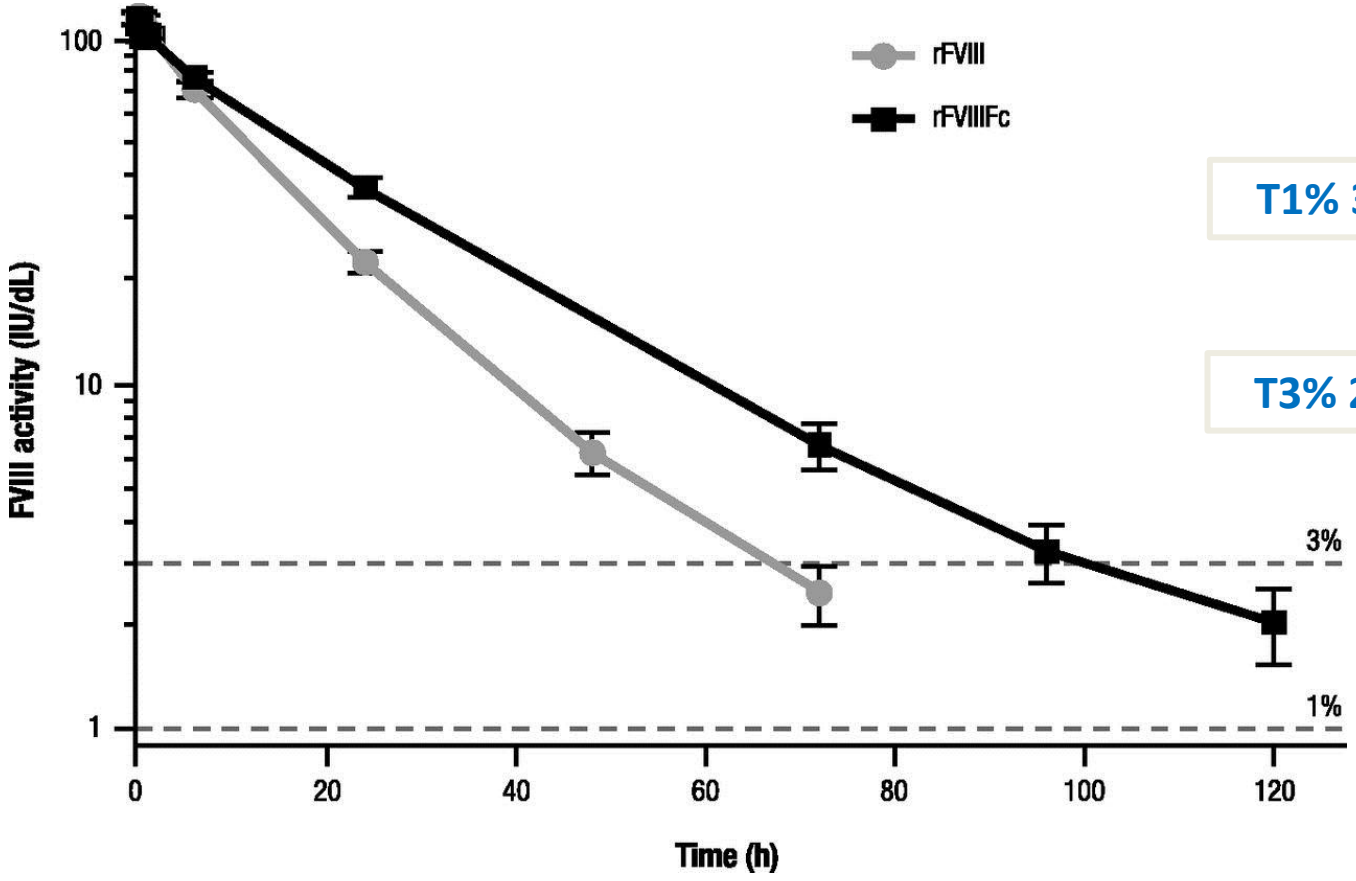
(Courtesy of S. Schulte)

Characteristics of the EHL FVIII

Product	Company	Cell line	Biochemical strategy	Age (years)	Subjects	Incremental recovery (IU dL^{-1})/(IU kg^{-1})	Half-life (h)
rFVIII-Fc	Sobi	HEK293H	B-domain-deleted rFVIII fused with human IgG_1 Fc domain	≥12	15	Mean (95% CI) 1.83 (1.6–2.1)	Mean (95% CI) 18.8 (14.3–24.5)
				≥12	28	Mean 2.2	Mean 19
				6–<12	31	Mean (95% CI) 2.44 (2.07–2.80)	Mean (95% CI) 14.9 (12–17.8)
				<6	23	Mean (95% CI) 1.92 (1.8–2.0)	Mean (95% CI) 12.7 (11.2–14.1)
Bax 855	Baxalta	CHO	Full-length rFVIII with lysine PEGylation (20 kDa PEG ×2)	12–65	26	Mean (SD) 2.49 (0.69)	Mean (SD) 14.3 (3.8)
Bay 94-9027	Bayer Healthcare	BHK	B-domain-deleted rFVIII with site-specific PEGylation (single 60 kDa PEG)	≥18	14	Mean (range) 2.9 (2.1–4.1)	Mean (range) 18.2 (13.7–28.1)
N8-GP	Novo-Nordisk	CHO	B-domain-truncated rFVIII with site-specific PEGylation (single 40 kDa PEG)	≥18	26	Mean (SD) 2.4 (0.6)	Mean (SD) 19 (5.53)

Collins P et al, Haemophilia 2016

A-LONG : FVIII activity vs. time profile for rFVIIIFc and rFVIII, 50 IU/kg intravenous injection

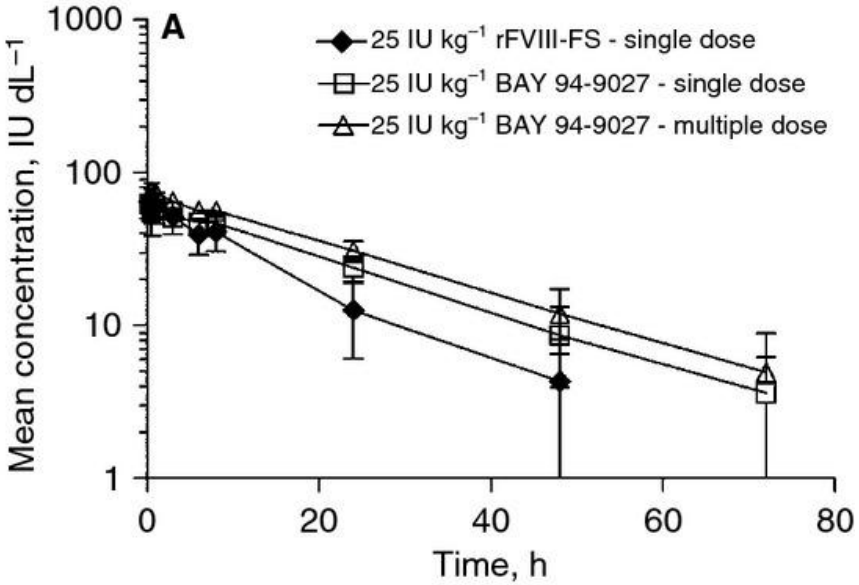


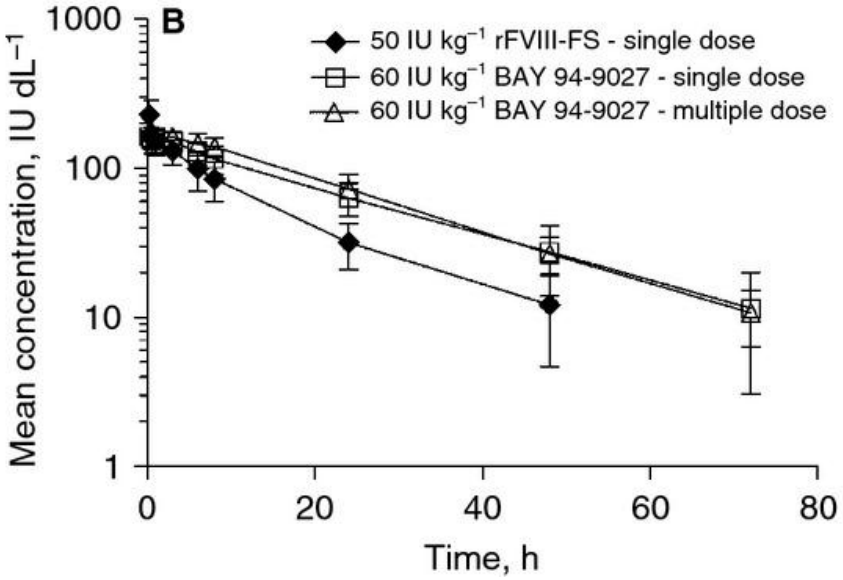
T1% 3.3 vs 4.9 days

T3% 2.5 vs 3.7 days

Mahlangu J et al. Blood 2014; 123:317-325

BAY 94-9027 (Phase I study)





Coyle TE et al. J Thromb Haemost 2014;12:488-96

Prophylactic treatment with EHL-FVIII

Product	Age	Regimen	Number of subjects	ABR
Bax 855	12–65	45 IU kg^{-1} twice weekly	120	Median (IQR) 1.9 (0–2)
N8GP	≥12	50 IU kg^{-1} every 4 days	175	Median 1.3
FVIII-Fc	≥12	25 IU kg^{-1} day 1 and 50 IU kg^{-1} day 4	118	Mean (95% CI) 2.9 (2.3–3.7)
		65 IU kg^{-1} weekly	24	Mean (95% CI) 8.9 (5.5–14.5)
	<6	25 IU kg^{-1} day 1 and 50 IU kg^{-1} day 4	36	Median (IQR) 0 (0–4)
	6–12		35	Median (IQR) 2 (0–4)
Bay 94-9027	12–65	25 IU kg^{-1} twice weekly for 10 weeks: >1 bleed changed to 30–40 IU kg^{-1} twice weekly	13	4.1
		25 IU kg^{-1} twice weekly for 10 weeks: ≤1 changed to 45 IU kg^{-1} every 5 days	43	1.9
		25 IU kg^{-1} twice weekly for 10 weeks: changed to 60 IU kg^{-1} once weekly	43	Median (IQR) 3.9 (0–6.5) (all patients) 11 dropped out with median ABR 16.9 32 completed ABR 0.96 (0–4.3)

Collins P et al, Haemophilia 2016

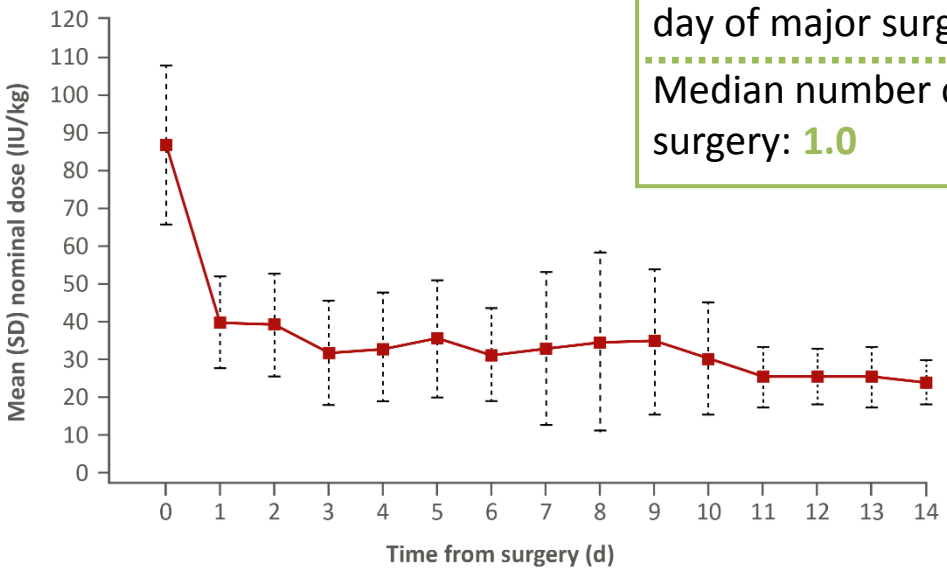
ASPIRE Major surgery (n=13): rFVIIIFc dosing[1]

- Daily dose of rFVIIIFc administered tended to **decline after the day of surgery**.
- All but one surgery required a single injection of rFVIIIFc to maintain haemostasis during surgery.

Median loading dose of rFVIIIFc: **59.2 IU/kg**

Median total rFVIIIFc consumption on day of major surgery: **80.5 IU/kg**

Median number of injections during surgery: **1.0**



Number of subjects[a]	12	12	11	12	11	12	9	12	10	9	7	5	6	5	4
Number of injections[b]	25	20	18	18	16	16	13	14	13	10	8	6	7	6	5

[a]The total number of subjects included in the analysis on the specified day. In 8 of 14 surgeries subjects were observed to receive dosing that was consistent with routine rFVIIIFc prophylactic regimens towards the end of the 2 weeks following surgery: once subjects returned to their regular treatment regimens they were no longer included in the analysis for the subsequent time points; [b]The total number of rFVIIIFc injections administered to all subjects in the analysis on the specified day. For 7 major surgeries subjects were on an every-other-day regimen towards the end of the 14-day period

rFVIIIFc: Recombinant factor VIII Fc fusion protein

1. Mahlangu et al. EAHAD 2015 Poster PP116

Résumé :FVIII à action prolongée

- Une prophylaxie de 3 à 7 jours peut être obtenue
- Taux plus élevés de 1 à 5% en considérant la 1 / 2 amélioré de 1,5 fois
- Médiane AsBR de 1-2 dans les schémas prophylactiques chez les adultes et les adolescents
- Excellent profil de tolérance et de sécurité
- Interventions chirurgicales

  Moins d'unités de FVIII utilisées

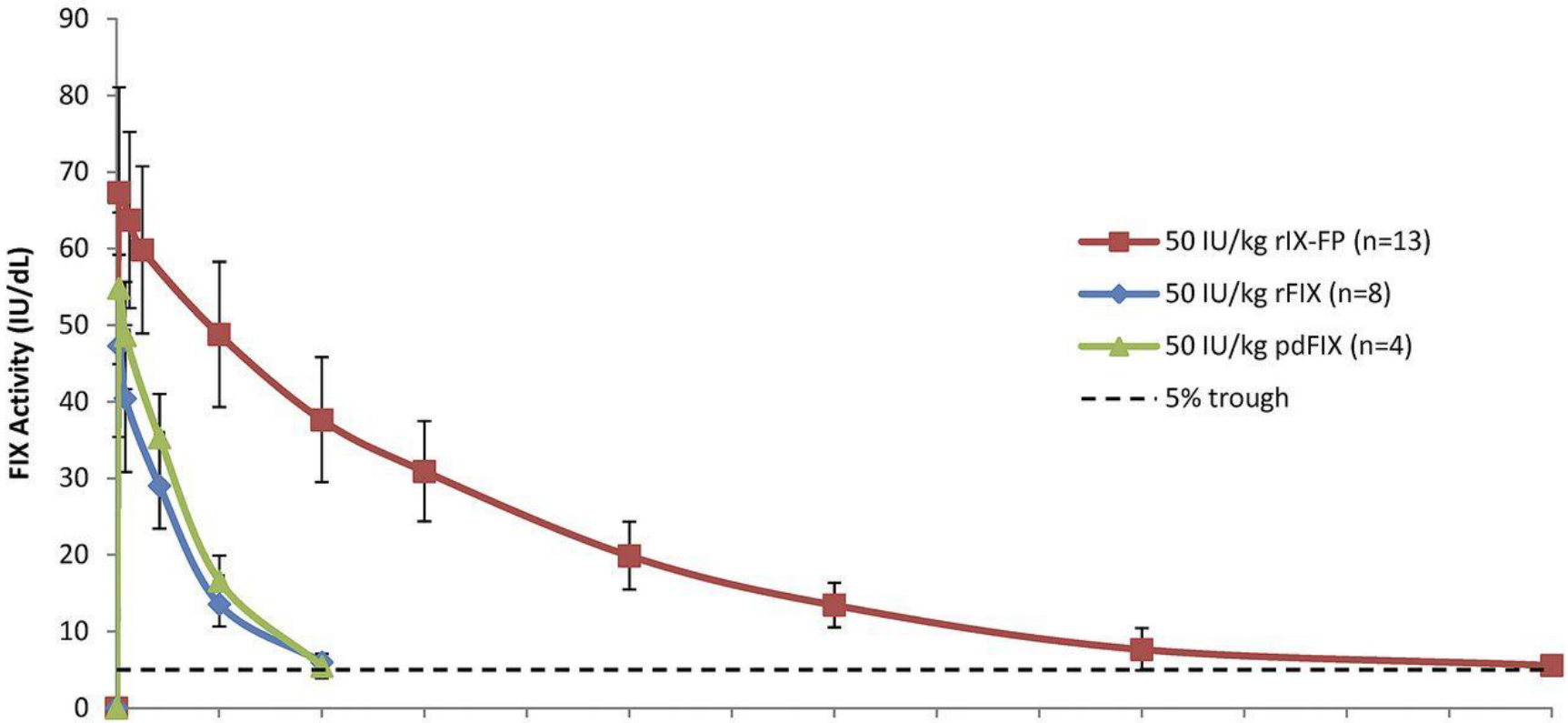
  plus faciles à manipuler pour l'équipe de soins infirmiers administrations moins fréquentes
- Permet aux patients souffrant d'hémophilie A sévère et modérée de bénéficier d'un phénotype hémorragique plus léger

Characteristics of the EHL FIX

Product	Company	Cell line	Biochemical strategy	Age	Subjects	Incremental recovery (IU dL^{-1})/(IU kg^{-1})	Half-life (h)
N9-GP	Novo-Nordisk	CHO	rFIX with site-specific PEGylation (single 40 kDa PEG)	12–65	15	Mean (SD) 1.4 (0.4)	Mean (SD) 96 (42)
				12–65	30	Mean (CV) 2.0 (14.5)	Mean (CV) 93 (19.5)
				≥6–<12	13	Mean 1.6	Mean 76.3
				<6	12	Mean 1.5	Mean 69.6
rFIX-Fc Alprolix	Sobi	HEK293H	rFIX fused with IgG_1 Fc	≥18	11	Mean (range) 0.87 (0.63–1.2)	Mean (range) 57.6 (47.9–67.2)
				≥12	22	Mean (95% CI) 0.92 (0.77–1.1)	Mean (95% CI) 82.1 (71.4–94.5)
				≥6–<12	13	Mean (95% CI) 0.72 (0.61–0.84)	Mean (95% CI) 70.3 (61.0–81.2)
				Median (range) 8 (6–11)			
				<6	11	Mean (95% CI) 0.59 (0.52–0.68)	Mean (95% CI) 66.5 (55.9–79.1)
				Median (range) 2 (1–4)			
rFIX-FP	CSL Behring	CHO	rFIX fused with recombinant human albumin	12–65	28	Mean (SD) 1.4 (0.28)	Mean (SD) 91.6 (20.7)
				12–65	15	Mean 1.5	Mean 94.8
				≥6–<12	15	Mean (SD) 1.06 (0.239)	Mean (SD) 92.8 (19)
				<6	12	Mean (SD) 0.95 (0.20)	Mean (SD) 89.6 (11.2)

Collins P et al, Haemophilia 2016

Summary profiles comparing rIX-FP ,rFIX, pdFIX



Prophylactic treatment with EHL-FIX

Product	Age (years)	Regimen	Number	ABR
rFIX-FC	12–65	50 IU kg^{-1} once weekly: dose adjusted to trough 1–3 and to prevent bleeds	61	Mean (95% CI) 3.12 (2.46–3.95)
		100 IU kg^{-1} every 10 days: interval adjusted to trough 1–3 and to prevent bleeds	26	Mean (95% CI) 2.40 (1.67–3.47)
	<6 Median (range) 2 (1–4)	50–60 IU kg^{-1} once weekly: adjusted up to 100 IU kg^{-1} and between once and twice weekly	15	Median (IQR) 1.1 (0.0–2.9)
	6–<12 Median (range) 8 (6–11)		15	Median (IQR) 2.1 (0.0–4.2)
N9-GP	12–65	10 U kg^{-1} once weekly	30	Median IQR 2.9 (1.0–6.0)
	12–65	40 U kg^{-1} once weekly	29	Median (IQR) 1.0 (0.0–4.0)
	<6	40 IU kg^{-1} once weekly	12	Med (range) 0 (0–3)
	6–<12	40 IU kg^{-1} once weekly	13	Med (range) 2 (0–6.5)
FIX-FP	12–65	30 IU kg^{-1} adjusted to bleeding pattern	13	Mean 4.35
	12–65	40 IU kg^{-1} weekly	40	Median (IQR) 0 (0–1.87)
		75 IU kg^{-1} every 14 days	21	1.08 (0–2.7)
	<12	46 IU kg^{-1} weekly	27	Med (IQR) 0 (0–0.91)

Collins P et al, Haemophilia 2016

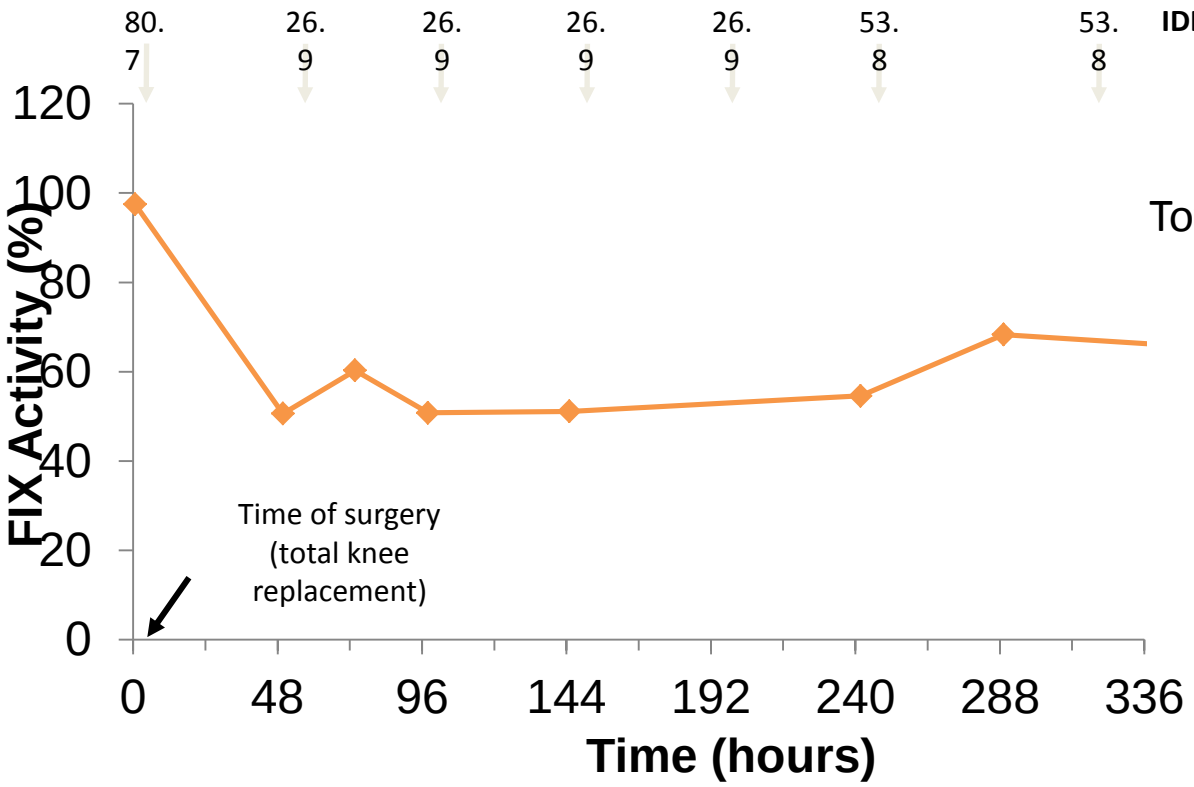
Treatment of breakthrough bleeds with EHL CFC

Product	Age (years)	Average units kg^{-1} for treatment of bleeds	% treated with one infusion	% treated with one or two infusions
Factor VIII				
rFVIII-Fc	≥12	27.35	87.3	97.8
	<12	49.7	81.4	93
N8-GP	≥12	ND	ND	95.3
Bax 855	12–65	29.0	85.5	95.9
Bay 94-9027	ND	ND	ND	ND
Factor IX				
Fc Fusion	≥12	46	90.4	97.3
FIX	<12	63.5	75	91.7
N9-GP	12–65	40	84.1	98.6
	0–<12	43	85.7	97.6
rIX-FP	12–65	62	95.3	100
	12–65	35–50	93.6	98.6
	<12	ND	ND	97

Collins P et al, Haemophilia 2016

rFIX-FP maintains FIX activity with prolonged dosing intervals

In major orthopedic surgeries, IDELVION dosing approximately every two days postoperatively maintains FIX activity at or above the desired levels



Total knee replacement

FIX activity was maintained above 50%

Reproduced with permission from Négrier *et al.* Efficacy and safety of long-acting recombinant fusion protein linking factor IX with albumin in haemophilia B patients undergoing surgery. *Haemophilia* 2016; 22:e259–66.

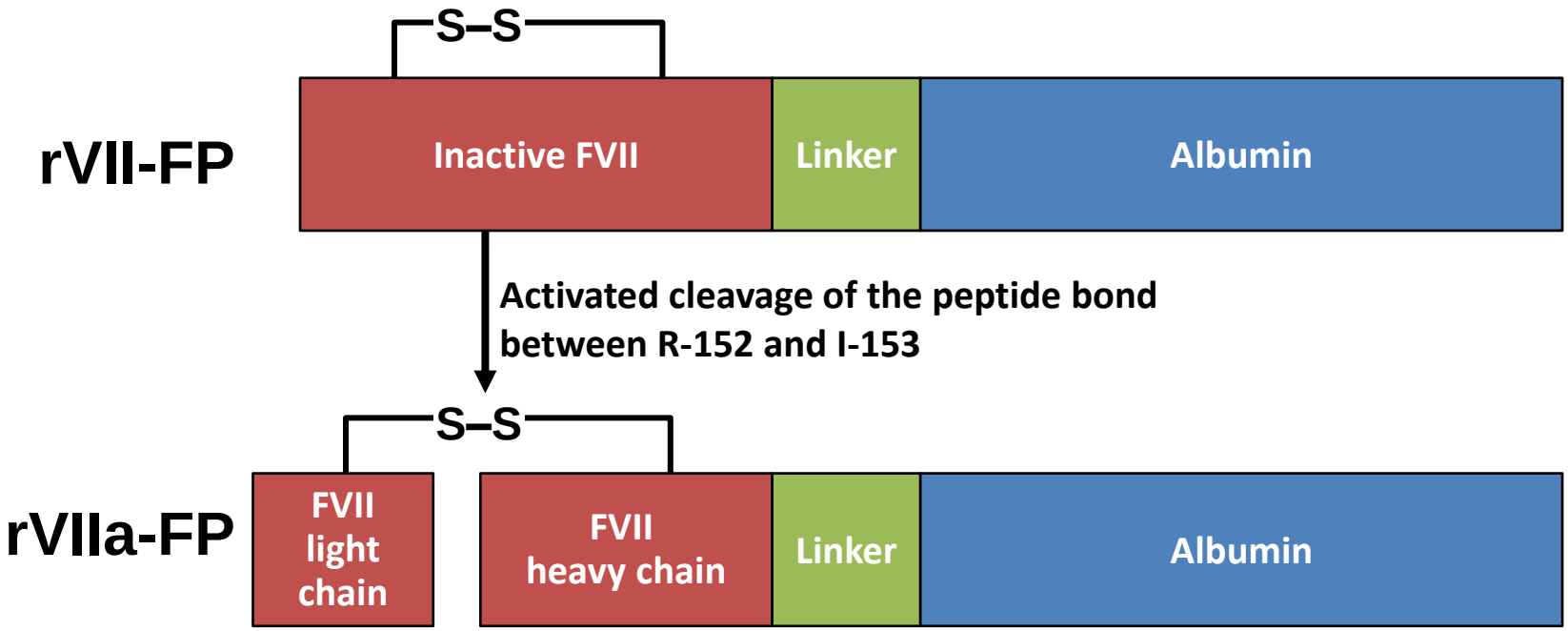
BL/IDN/16-0011

Négrier et al. Haemophilia 2016; 22: e259–e266.

Résumé : FIX à action prolongée

- Une prophylaxie à 7, 10 et 14 jours peut être obtenue avec une dose unique
- de 5 à 20% en considérant le t1 / 2 amélioré de ~ 4 à 5 fois,
- Médiane AsBR de 0-2 dans tous les schémas prophylactiques chez les adultes et les adolescents
- Excellent profil de tolérance et de sécurité
- Réduction de 30 à 50% de la consommation par rapport au FIX précédent
- Les différences majeures dans les schémas thérapeutiques pour les chirurgies (moins d'unités FIX utilisées, plus faciles à manipuler pour l'équipe infirmière avec des administrations moins fréquentes, pourraient diminuer les niveaux minimaux sous-thérapeutiques associés à un risque plus élevé de saignements postopératoires, diminuer la durée d'hospitalisation, Avec une réadaptation plus facile et diminuer les coûts associés
- Les études du PUP sont en cours

rVIIa-FP: molecule



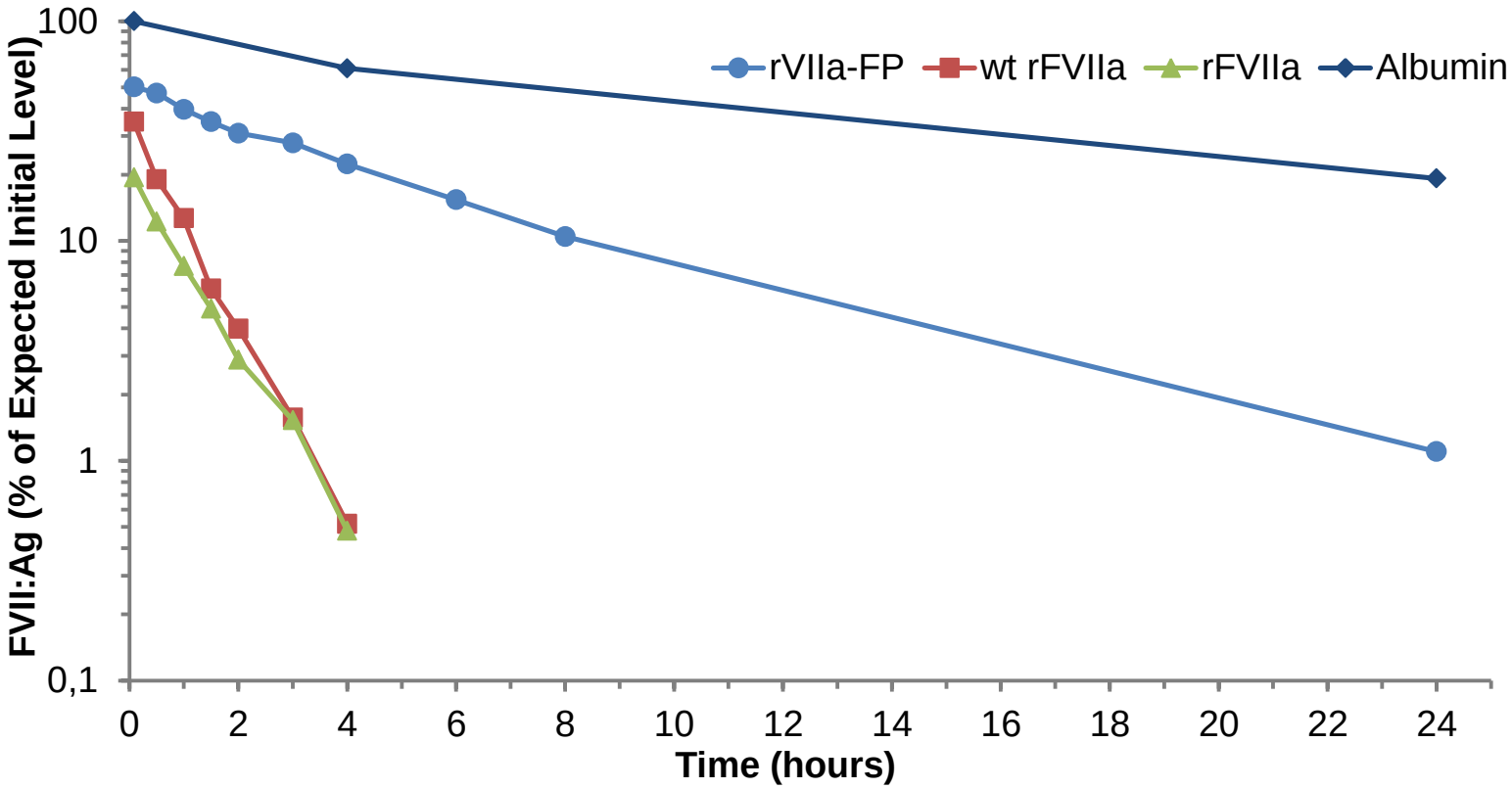
For reasons of clarity, the only disulphide bridge depicted in this diagram is the one linking the FVII light and heavy chains. No other post-translational modifications are shown. The FVII light chain contains the gamma (γ) carboxylated glutamic acid (Gla), epidermal growth factor (EGF)-1 and EGF-2 domains, whilst the FVII heavy chain contains the serine protease domain.

- **"Wild-type" rFVIIa fused to recombinant albumin by a 31 AS flexible linker**
- No modification of the FVIIa AS sequence.
- Expressed as a single moiety by CHO cells

CHO, Chinese Hamster Ovary; rVIIa-FP, recombinant fusion protein linking recombinant factor VIIa with recombinant albumin

Schulte. *Thromb Res* 2008;122(Suppl. 2):S14–19.

rVIIa-FP: Pharmacokinetics in Rats



p<0.005 for rVIIa-FP vs wt rFVIIa and rFVIIa

rFVIIa, recombinant factor VIIa (NovoSeven®); Wt, wild type

Weimer *et al. Thromb Haemost* 2008;99:659–67

rVIIa-FP: Phase I (2)

- 5 dose-escalation cohorts in healthy volunteers (140, 300, 500, 750 and 1000 µg/kg)

- No SAEs, one related AE: pain and hardening of vein at injection site

Cohort	Median Half-life (Hours)
140 µg/kg	6.01
300 µg/kg	9.66
500 µg/kg	8.73
750 µg/kg	7.77
1000 µg/kg	8.5

AE, adverse event; SAE, serious adverse event

Golor *et al*. *J Thromb Haemost* 2013;11:1977–85

Stratégies thérapeutiques alternatives

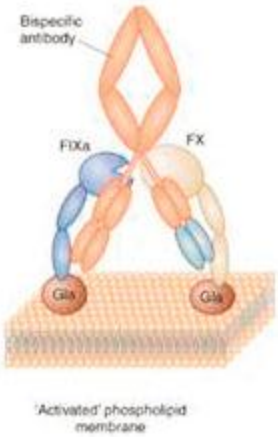
Inhibition du TFPI*

- Anticorps (anti-TFPI)
- Inhibiteurs synthétiques (aptamers*)

Inhibition de l'antithrombine (AT)

- Aptamers*
- RNAi*

Anticorps bispécifique dirigé contre le FIX activé et le FX

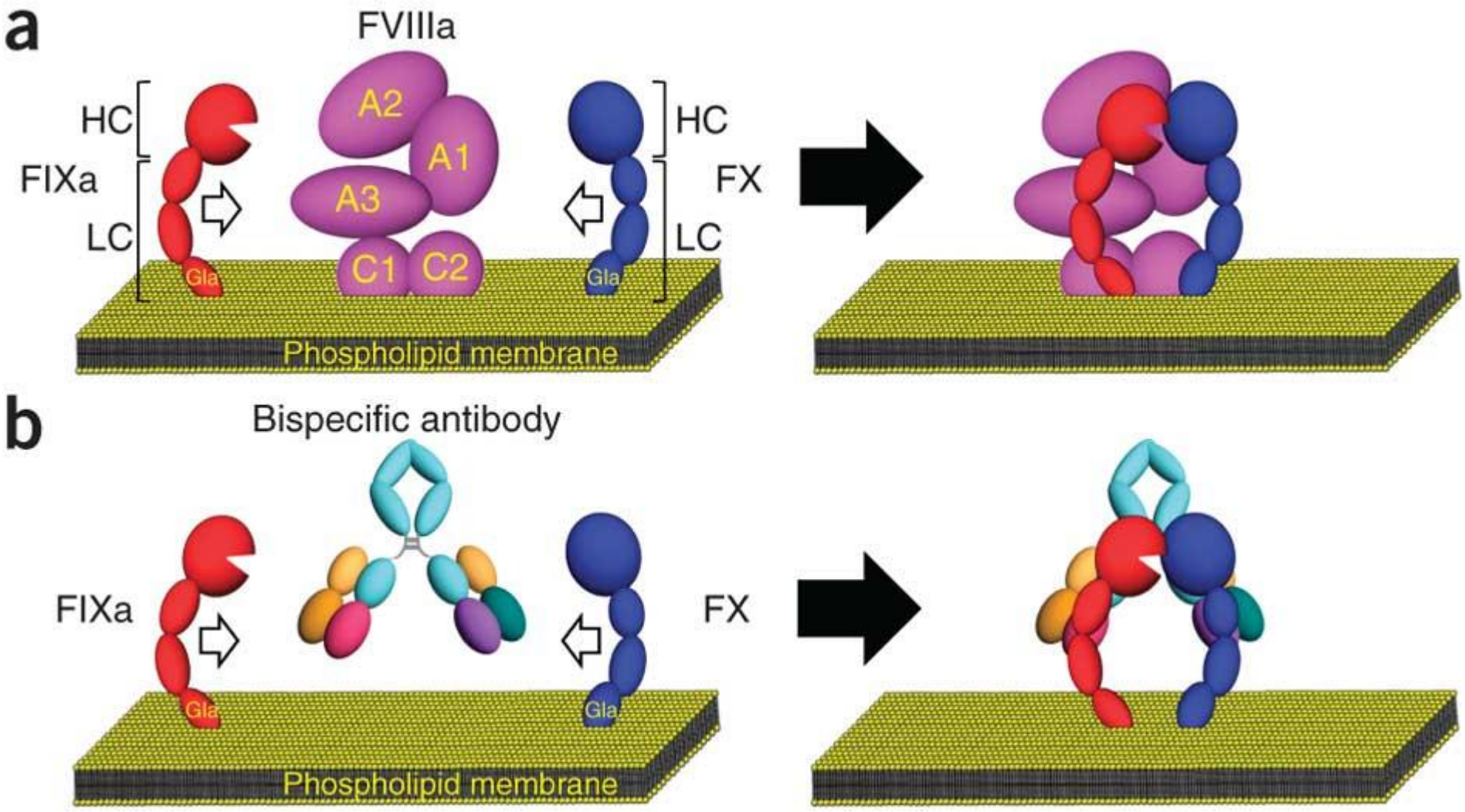


TFPI : Tissue Factor Pathway Inhibitor.
Aptamers : courtes séquences de nucléotides spécifiques d'une cible notamment une protéine
RNAi : ARN interférence, courte séquence de nucléotides permettant d'inhiber l'expression d'un gène

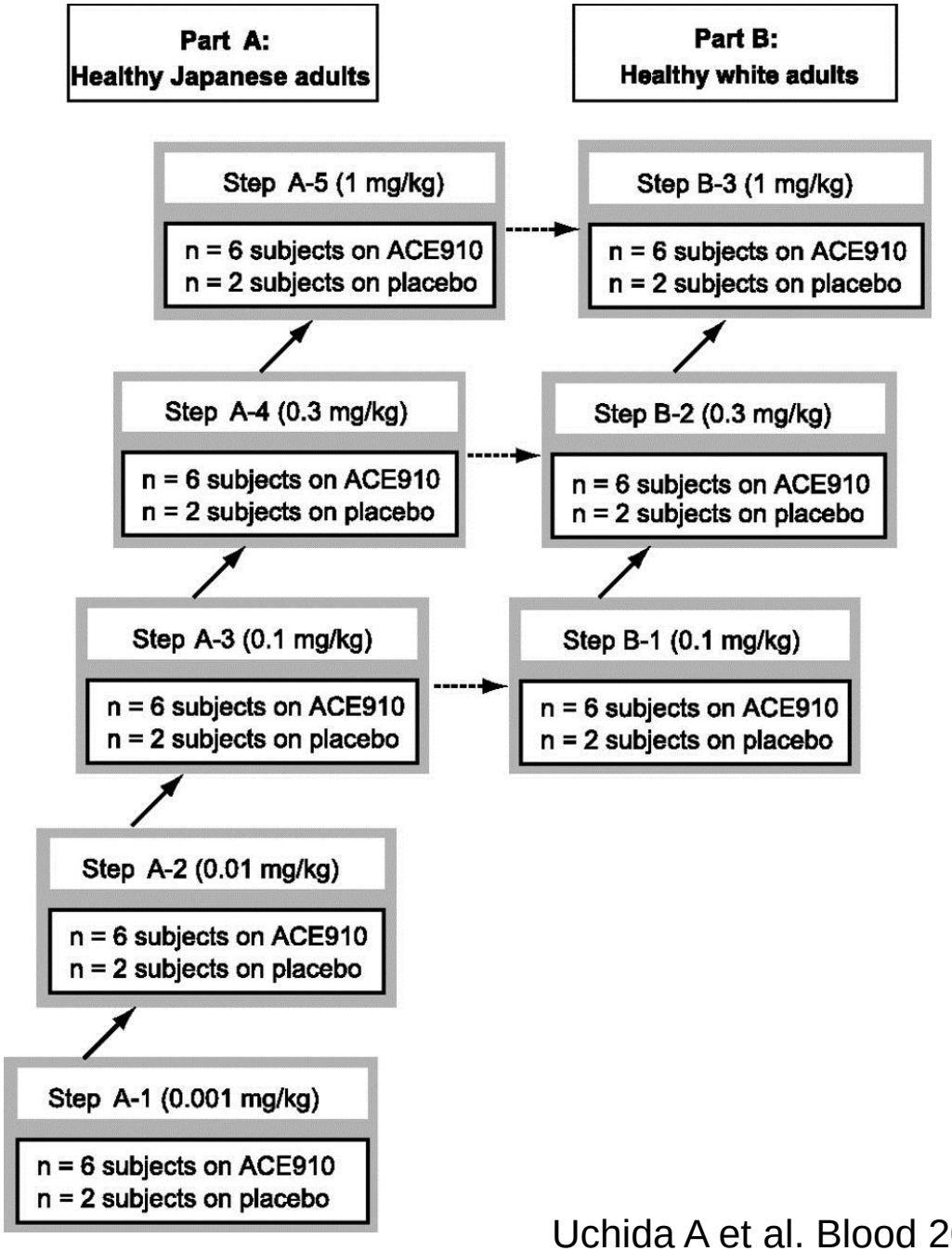
Roche obtient de la FDA le statut de percée thérapeutique pour son médicament expérimental ACE910 lors d'hémophilie A avec inhibiteurs du facteur VIII

- L'ACE910 est un anticorps monoclonal bispécifique humanisé expérimental conçu
- Pour lier simultanément les facteurs IXa et X.
- L'ACE910 imite ainsi la fonction de cofacteur du facteur VIII et vise à promouvoir la coagulation sanguine chez les patients atteints d'hémophilie A, qu'ils aient ou non développé des inhibiteurs du facteur VIII.
- L'ACE910 est administré une fois par semaine par voie sous-cutanée et,
- Sa structure étant distincte de celle du facteur VIII, ne devrait pas conduire à l'apparition d'inhibiteurs anti-facteur VIII.

Schematic illustrations of the action of FVIIIa or of a bispecific antibody as a cofactor promoting the interaction between FIXa and FX

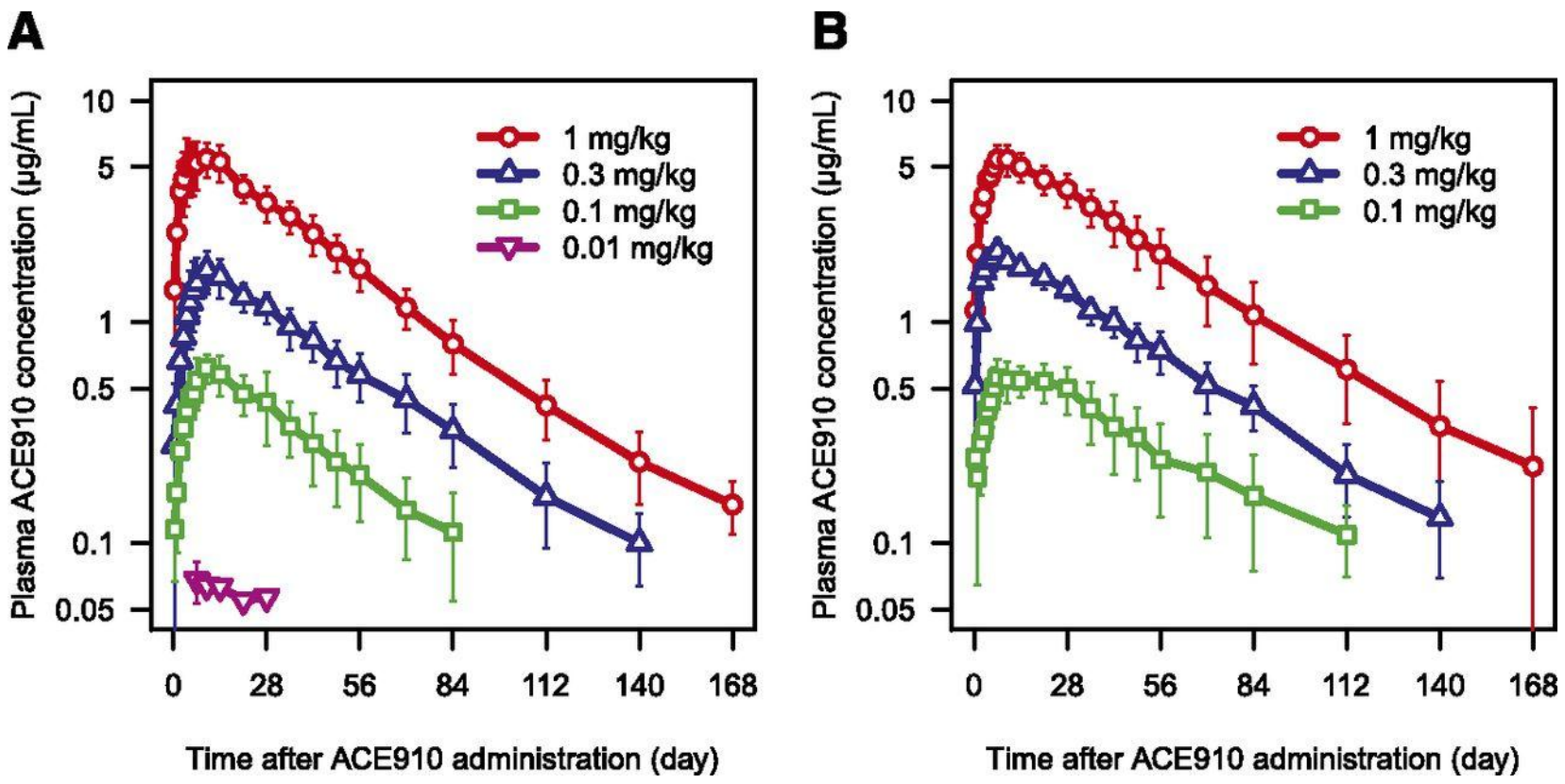


Kitazawa T et al, Nature Med 2012; 18: 1570–1574 (2012)



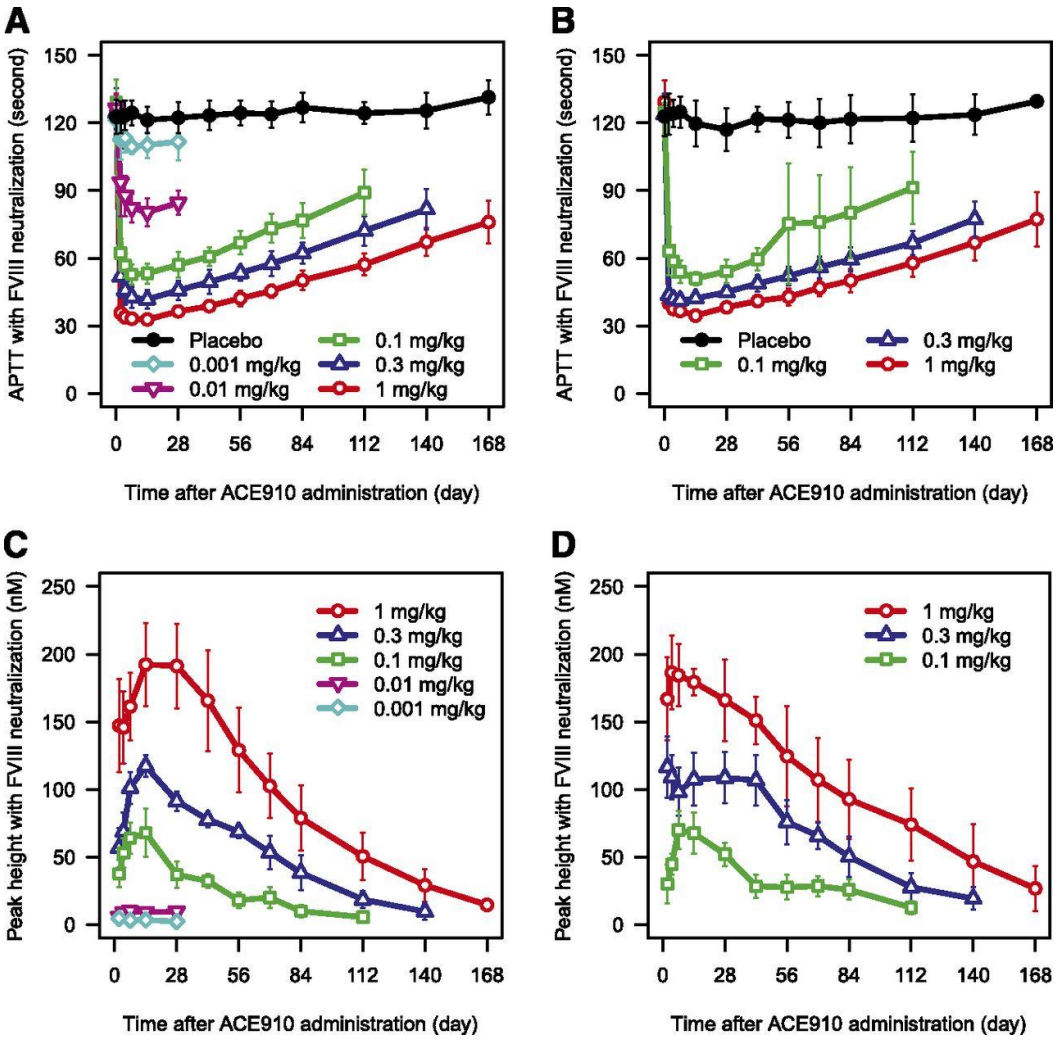
Uchida A et al. Blood 2016;127:1633-1641

Plasma ACE910 concentration after single subcutaneous injection of ACE910



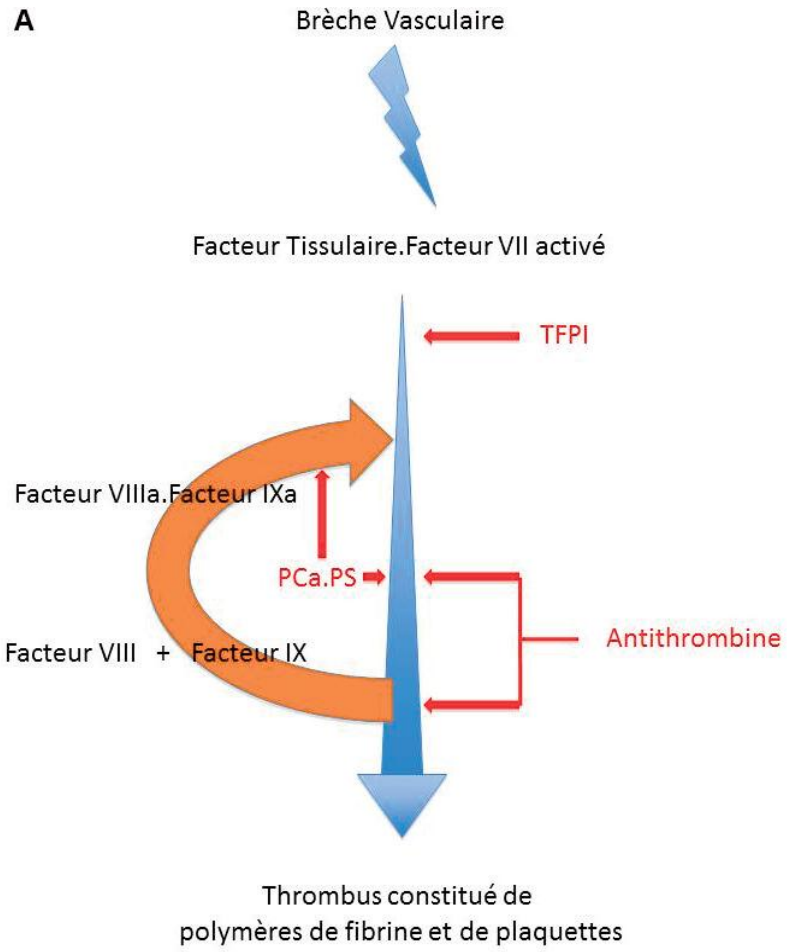
Uchida A et al. Blood 2016;127:1633-1641

PD responses after single subcutaneous injection of ACE910 with neutralization of the endogenous FVIII. The time courses of APTT (A-B) and peak height of TG (C-D)



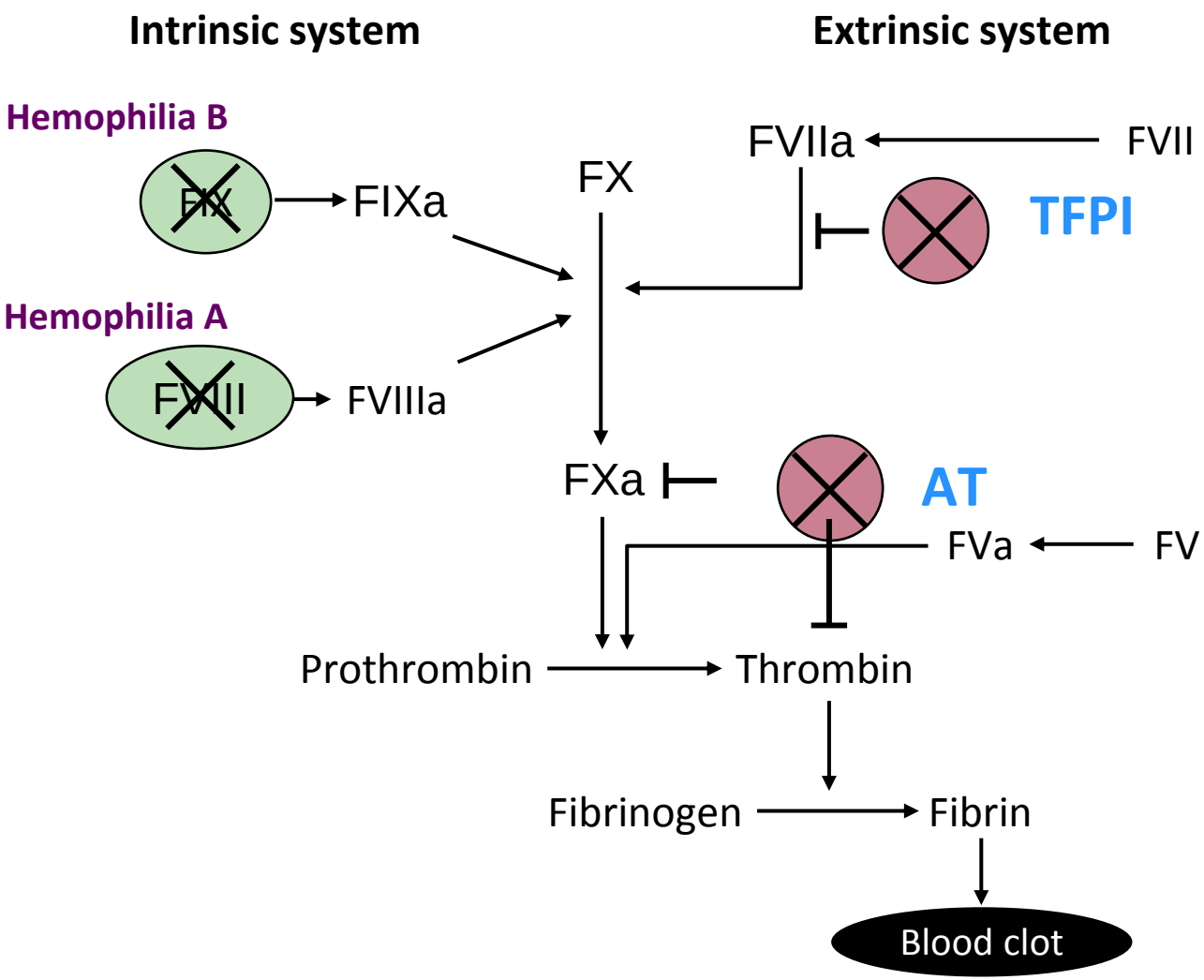
Uchida A et al. Blood 2016;127:1633-1641

Une voie a particulièrement été ciblée avec succès, celle du TFPI ou Tissue Factor Pathway



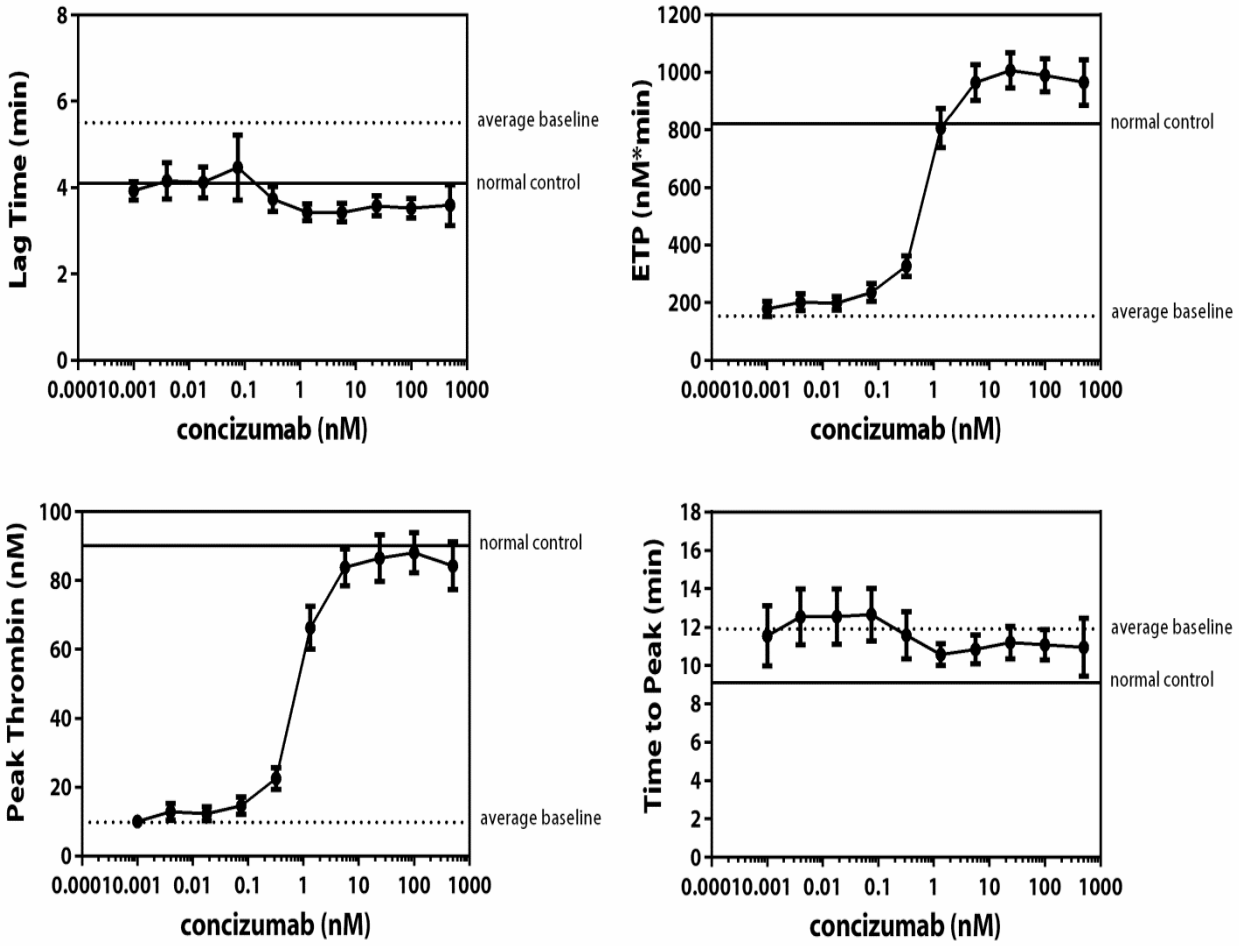
- Une voie a particulièrement été ciblée avec succès,
- celle du TFPI ou Tissue Factor Pathway
- Le TFPI lié au facteur Xa agit sur la phase d'initiation de la coagulation en inhibant l'action duFVIIa associé à son cofacteur le facteur tissulaire (FT).
- Un anticorps bloquant l'interaction entre le FXa et le TFPI a été développé.
- Les résultats obtenus renforcent l'hypothèse que l'activité pro-coagulante du GDXa serait liée à la formation d'un complexe GDXa-TFPI limitant la formation du complexe Xa-TFPI nécessaire à l'inhibition physiologique du complexe ténase extrinsèque

Therapeutic Hypothesis: Targeting TFPI and Antithrombin to Rebalance the Coagulation System



Concizumab (TFPI antibody) improves thrombin generation

Platelet-poor plasma from patients with severe haemophilia A or B, or haemophilia with inhibitors was spiked with 0.001 to 1000 nM concizumab

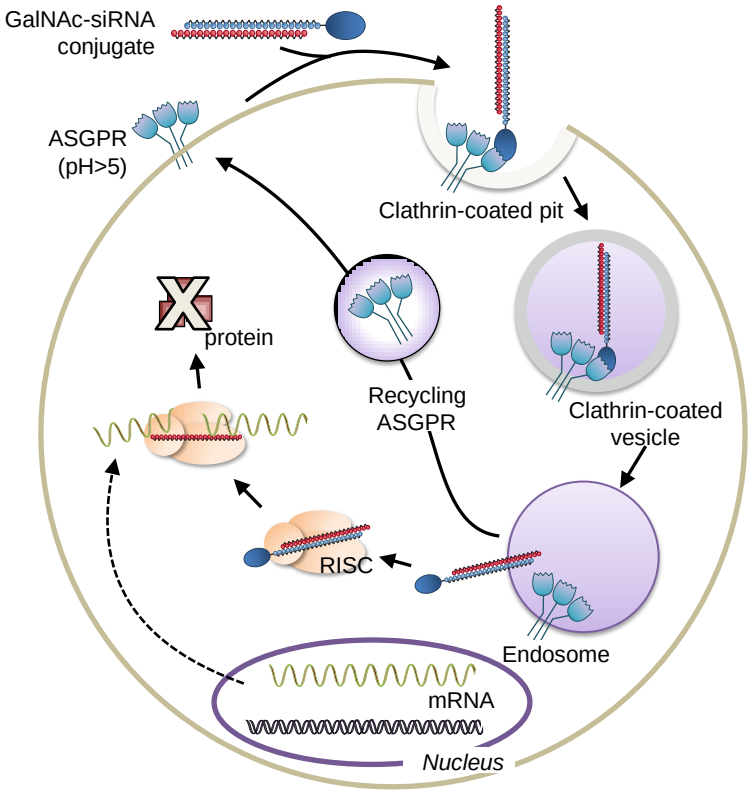


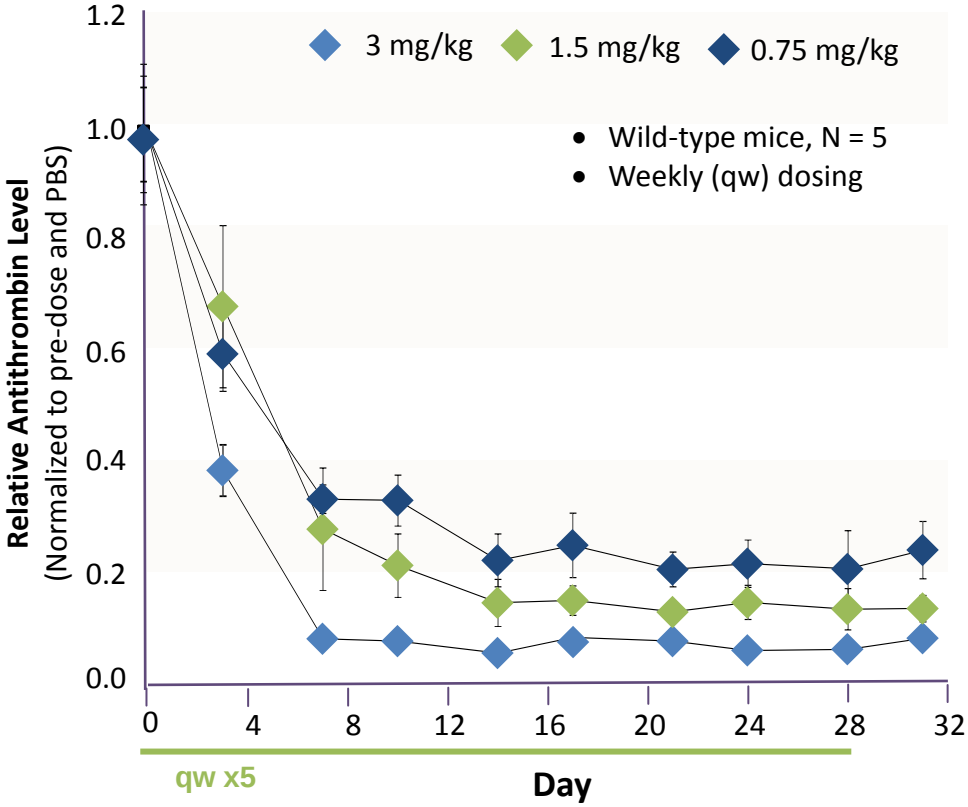
Platelet poor plasma with 1 pM TF and 4 µM phospholipids; mean ± sem (n=7-18)

Waters EK, et al. XXV congress of the ISTH 2015, Toronto Poster: PO454-TUE

Fitusiran

- SC-Administered GalNAc-Conjugated siRNA Targeting Antithrombin





- "Enhanced stabilization chemistry" (ESC) utilized for potency and durability of effect
- Weekly SC dosing results in potent and sustained suppression of AT levels

Fitusiran Phase 1 Study

- Dose-Escalation Study in Three Parts

Primary objectives

- Safety, tolerability

Secondary objectives

- AT lowering, thrombin generation

Part A: Single-Ascending Dose (SAD) | Randomized 3:1, Single-blind, Placebo-controlled, Healthy volunteers

30 mcg/kg x 1 SC, N=4 ✓

Presented January 2015[1]

Part B: Multiple-Ascending Dose (MAD) – Weekly dosing | Open-label, Patients with Hemophilia A or B

15 mcg/kg qW x 3 SC, N=3 ✓

45 mcg/kg qW x 3 SC, N=6 ✓

75 mcg/kg qW x 3 SC, N=3 ✓

Presented June 2015[2]

Part C: Multiple-Ascending Dose (MAD) – Monthly dosing | Open-label, Patients with Hemophilia A or B

225 mcg/kg qM x 3 SC, N=3 ✓

450 mcg/kg qM x 3 SC, N=3 ✓

900 mcg/kg qM x 3 SC, N=3 ✓

1800 mcg/kg qM x 3 SC, N=3

Presented December 2015[3]

Ongoing

Up to 2 additional cohorts

[1]Akinc A et al. Goring Coagulation Conference (2015)
[2]Sorensen B, et al. ISTH (2015)
[3]Pasi KJ, et al. ASH (2015)

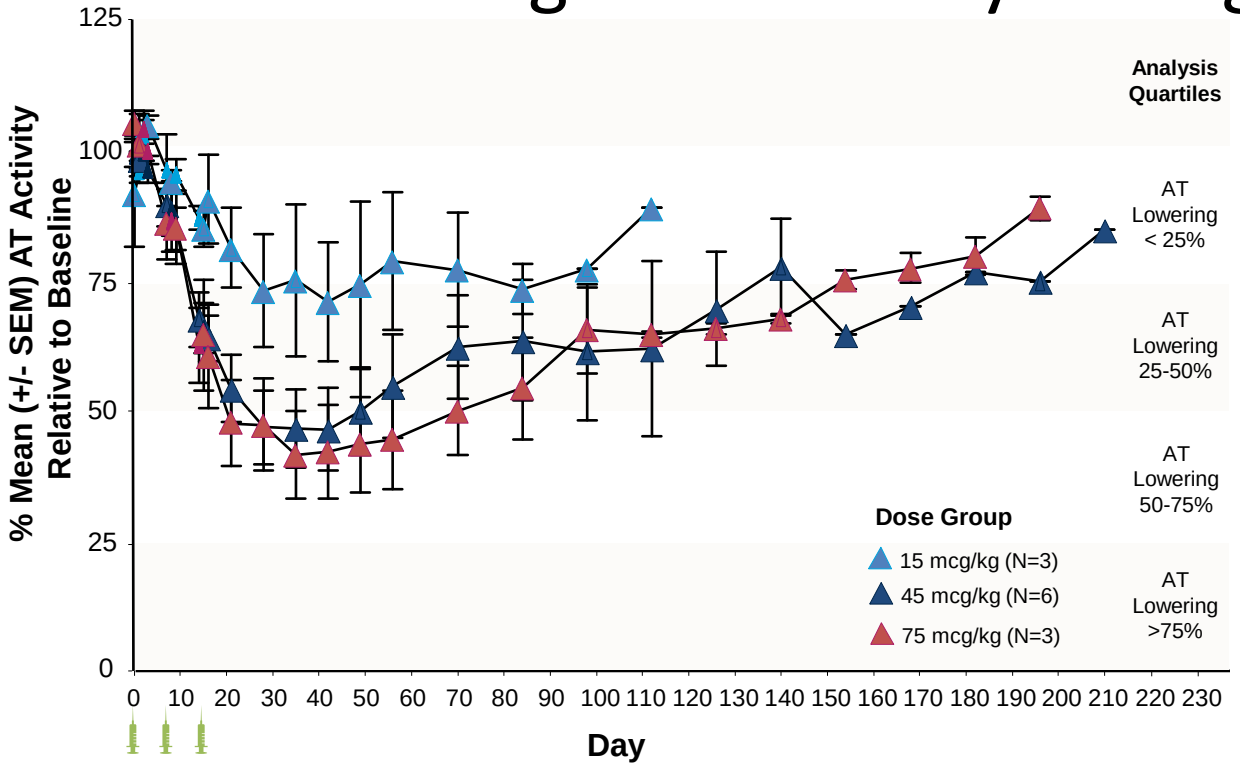
Interim Fitusiran Phase 1 Study Results*

- Safety/Tolerability, Parts B & C[†]
  - No SAEs related to study drug and no discontinuations
    - One subject was hospitalized due to re-activation of hepatitis C, not drug related
  - AEs reported
    - Total of 35 AEs occurred in 14 patients
  - 33 single AEs + 2 AE episodes of arthritis
  - 34 Mild/Moderate, 1 Severe[‡]
    - 3 drug related AEs were observed – all mild:
  - Injection site reactions:
    - » One patient (45 mcg/kg) experienced mild transient pain
    - » One patient (1800 mcg/kg) experienced mild transient erythema & pain
  - Other:
    - » Headache, transient
    - No thromboembolic events or clinically significant D-dimer increases
    - No drug related clinically significant changes in physical exams, vital signs, ECG or laboratory parameter (LFTs, CBC, coagulation)
    - Bleed events successfully managed with standard replacement factor administration
  - No instances of anti-drug antibody (ADA) formation

*Data as of 12 November 2015: Pasi KJ, et al. ASH (2015)
[†]Adverse event grouping based on MedDRA-coded terms, excluding bleed events
[‡]Hypertriglyceridemia

Interim Fitusiran Phase 1 Study Results*

- AT lowering, Part B
- AT lowering after weekly dosing in patients

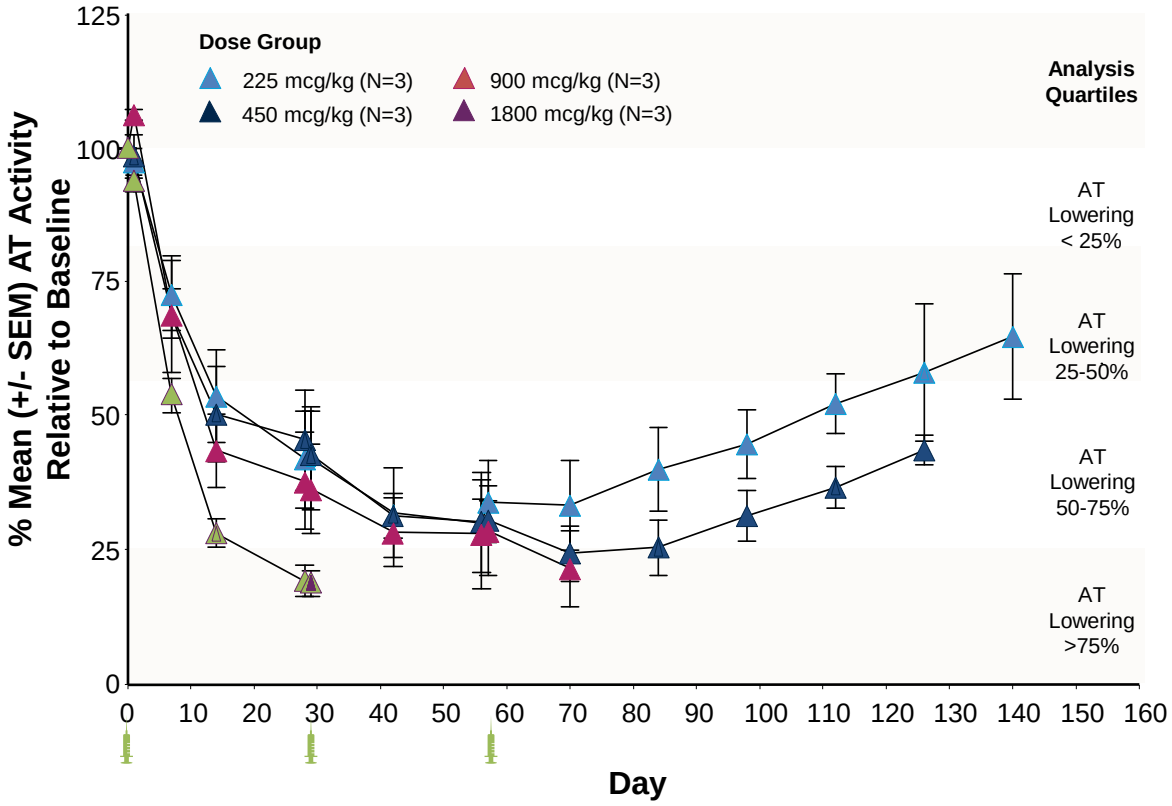


	Mean Max AT Lowering ± SEM	Max AT Lowering
15 mcg/kg (N=3)	29 ± 12%	53%
45 mcg/kg (N=6)	55 ± 9%	86%
75 mcg/kg (N=3)	61 ± 8%	74%

*Data as of 12 November 2015
Pasi KJ, et al. ASH (2015)

Interim Fitusiran Phase 1 Study Results*

- AT Lowering, Part C
- AT lowering after monthly dosing in patients with hemophilia A and B

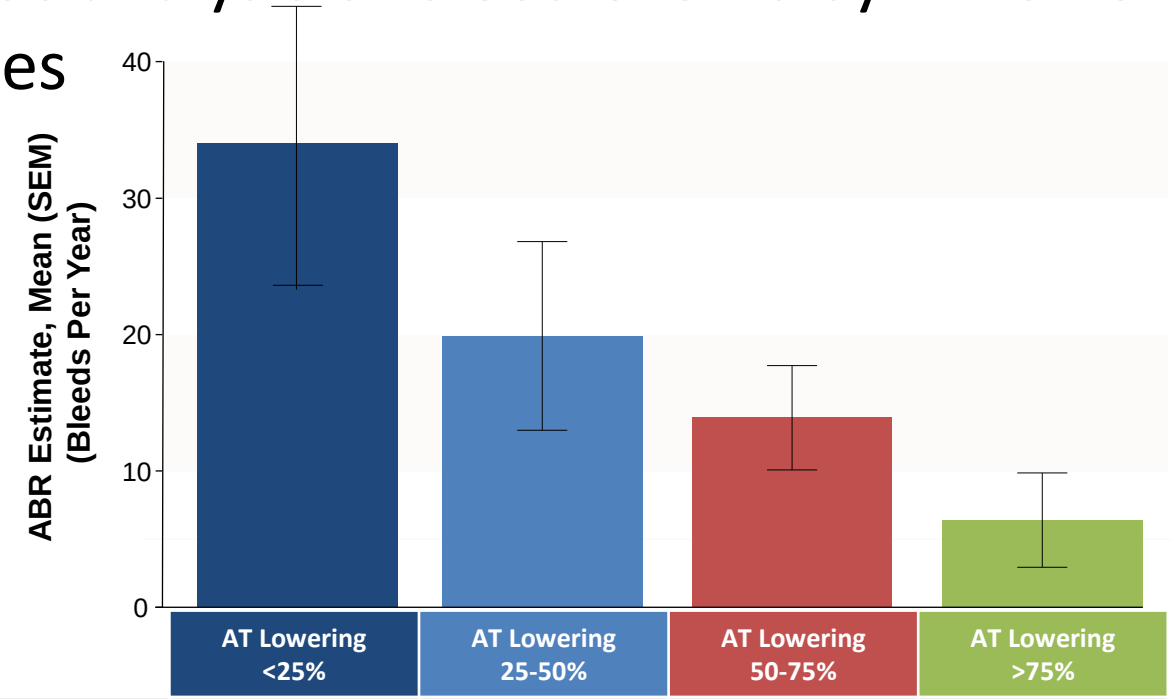


	Mean Max AT Lowering ± SEM	Max AT Lowering
225 mcg/kg (N=3)	70 ± 9%	80%
450 mcg/kg (N=3)	77 ± 5%	85%
900 mcg/kg (N=3)	78 ± 7%	88%
1800 mcg/kg (N=3)	79 ± 3%	84%

*Data as of 12 November 2015
Pasi KJ, et al. ASH (2015)

Interim Fitusiran Phase 1 Study Results*

- Exploratory Analysis of Bleed Events, Parts B & C
- Post hoc analysis of bleed events by AT lowering quartiles



	AT Lowering <25%	AT Lowering 25-50%	AT Lowering 50-75%	AT Lowering >75%
Patients†	24	21	18	9
Cumulative Days	602	838	862	304
Cumulative Bleeds	43	34	35	3
ABR‡, Mean (SEM)	34 ± 10	20 ± 7	14 ± 4	6 ± 3
ABR, Median	13	11	10	0

**p<0.05

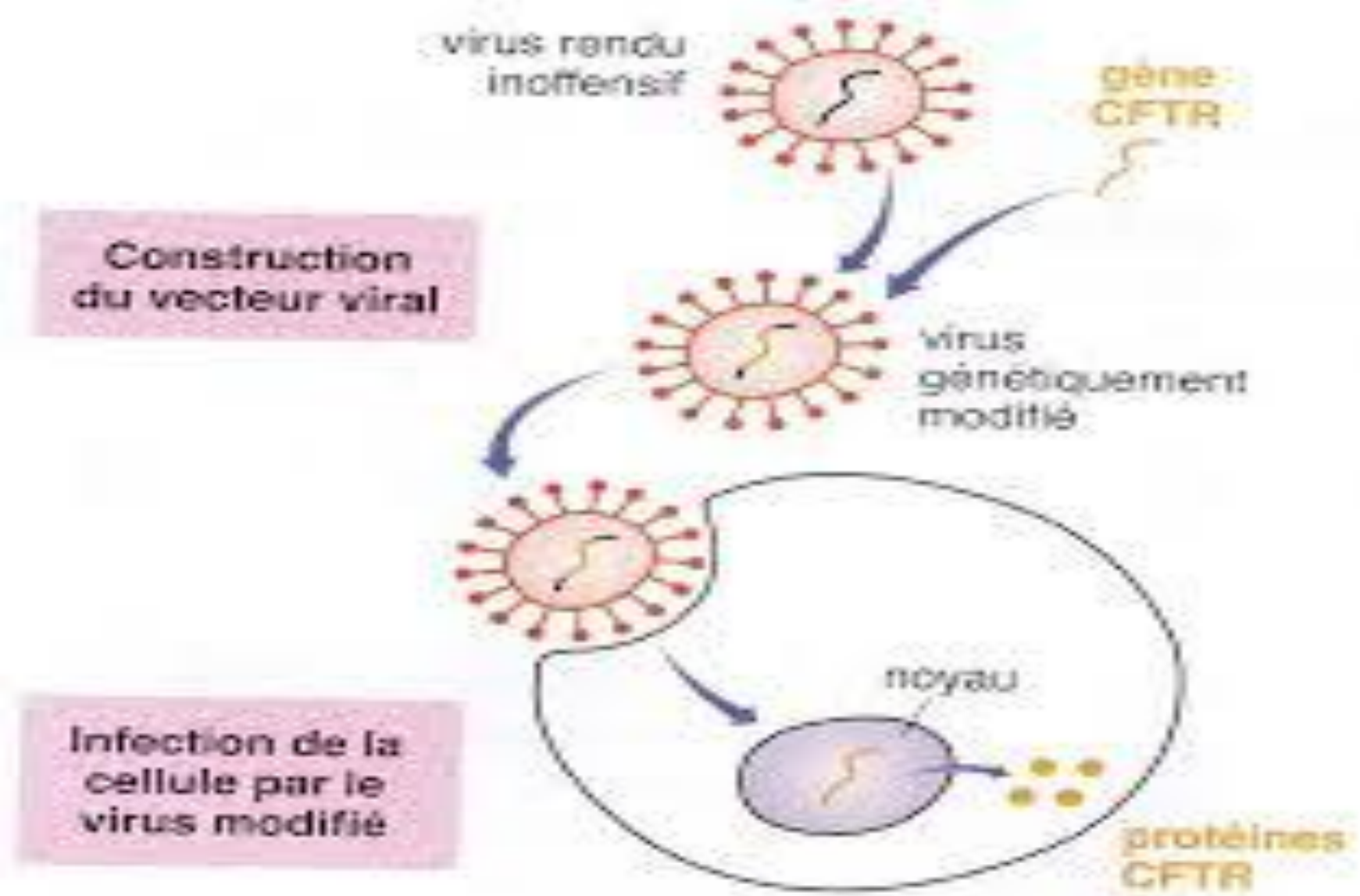
Data as of 12 November 2015; Pasi KJ, et al. ASH (2015)

†*Number of patients with time spent in quartile*

‡*For each subject, the ABR in each quartile is calculated by 365.24*(number of bleed events/number of days in quartile).*

***Based on negative binomial regression model*

Les avancées de la thérapie génique ?



Conclusion

- Place facteurs demi vie prolongée dans l'arsenal thérapeutique mais le coût pourrait représenter une limitation
- Des schémas thérapeutiques plus individualisés et plus rentables seront visibles dans un proche avenir
- Des concepts thérapeutiques novateurs et prometteurs sont apparus au cours des dernières années et sont en voie d'être évalués dans le cadre d'essais cliniques en cours:
- Remplacement partiel de l'activité biologique du FVIII: ACE910
- Rééquilibrer le système de coagulation en inhibant les inhibiteurs de coagulation naturels: anti-TFPI MoAb, inhibition de l'antithrombine avec siRNA
- La thérapie génique est toujours à l'horizon

Nouvelles perspectives de prise en charge des hémophiles