# TRATAMIENTO NO SUSTITUTIVO EN HEMOFILIA

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# HEMOFILIA

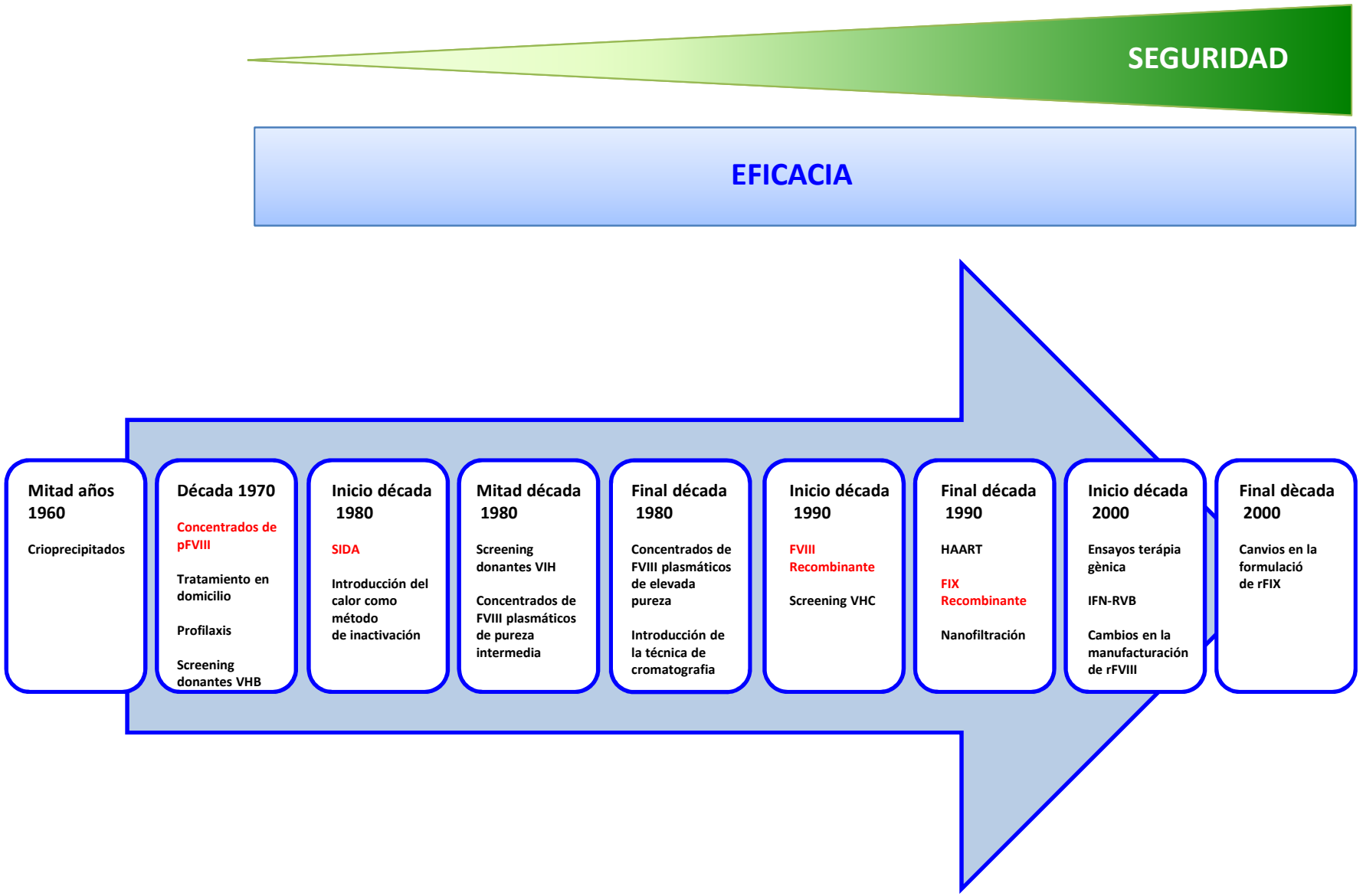
Alteración genética que resulta
en una incapacidad de generar
trombina para detener la hemorragia

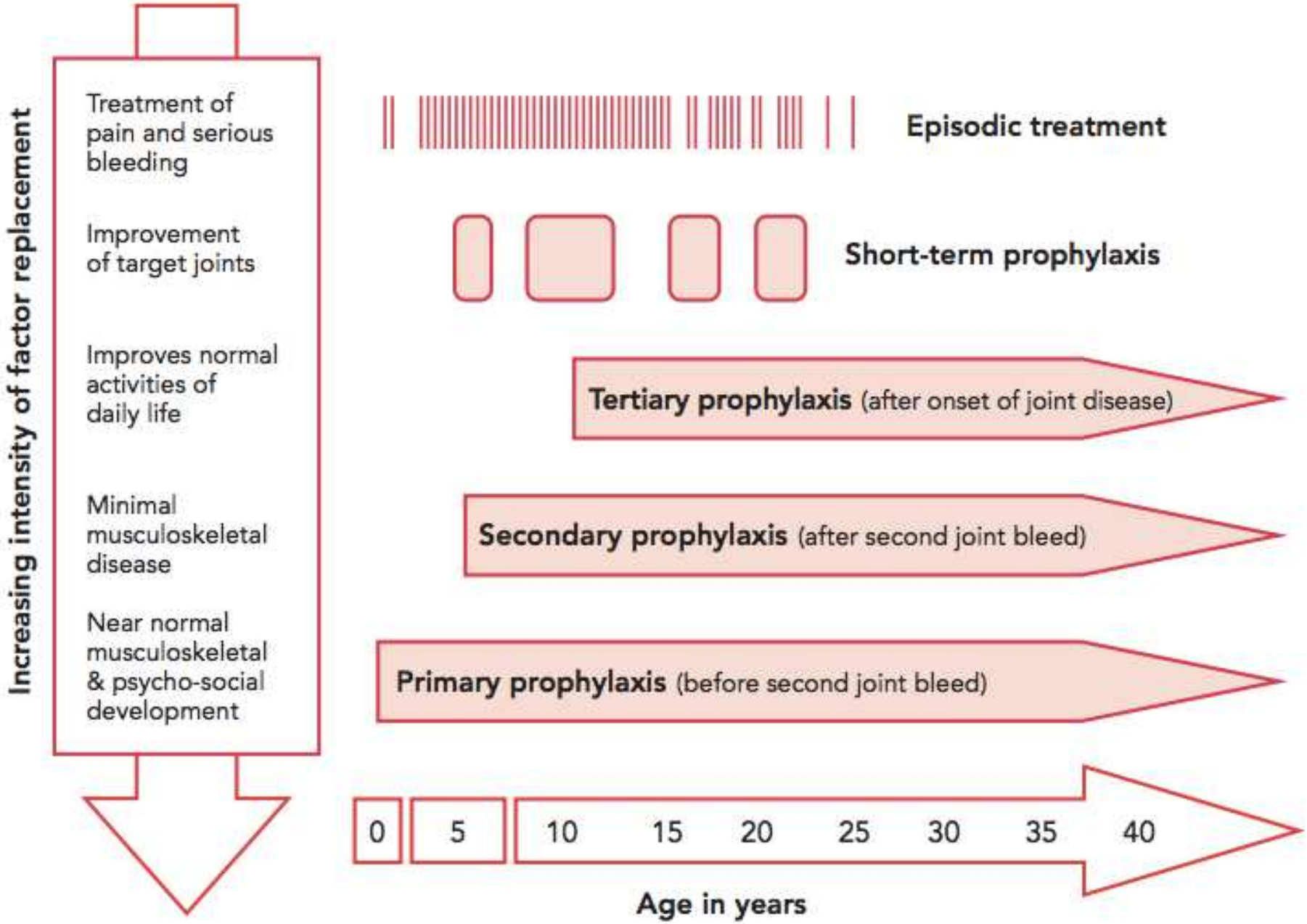

## PROFILAXIS

## INHIBIDOR

>5-25 hemorragias / año;
>5 dias hospitalización / año
300.000 $/año (media);
hasta 1 M $/año

MERCADO > 11.000 M$


SEGURIDAD
EFICACIA
Mitad años 1960
Crioprecipitados
Década 1970
Concentrados de pFVIII
Tratamiento en domicilio
Profilaxis
Screening donantes VHB
Inicio década 1980
SIDA
Introducción del calor como método de inactivación
Mitad década 1980
Screening donantes VIH
Concentrados de FVIII plasmáticos de pureza intermedia
Final década 1980
Concentrados de FVIII plasmáticos de elevada pureza
Introducción de la técnica de cromatografia
Inicio década 1990
FVIII Recombinante
Screening VHC
Final década 1990
HAART
FIX Recombinante
Nanofiltración
Inicio década 2000
Ensayos terápia gènica
IFN-RVB
Cambios en la manufacturación de rFVIII
Final dècada 2000
Canvios en la formulació de rFIX




Adapted from Blood Transfus 2008 Sep;6 Suppl 2:s4-11

# INDIVIDUALIZACION DEL TRATAMIENTO

| | | | | |
|---|---|---|---|---|
| 1 inyección cada 2 sem | 1 inyección cada sem | 2 inyecciones cada sem | 1 inyección cada sem | 1 inyección cada 2 sem |

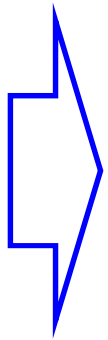
# LIMITACIONES ACTUALES DEL TRATAMIENTO

VIDA MEDIA CORTA
(INFUSIONES FRECUENTES)

ACCESO VENOSO

INHIBIDOR

COSTE

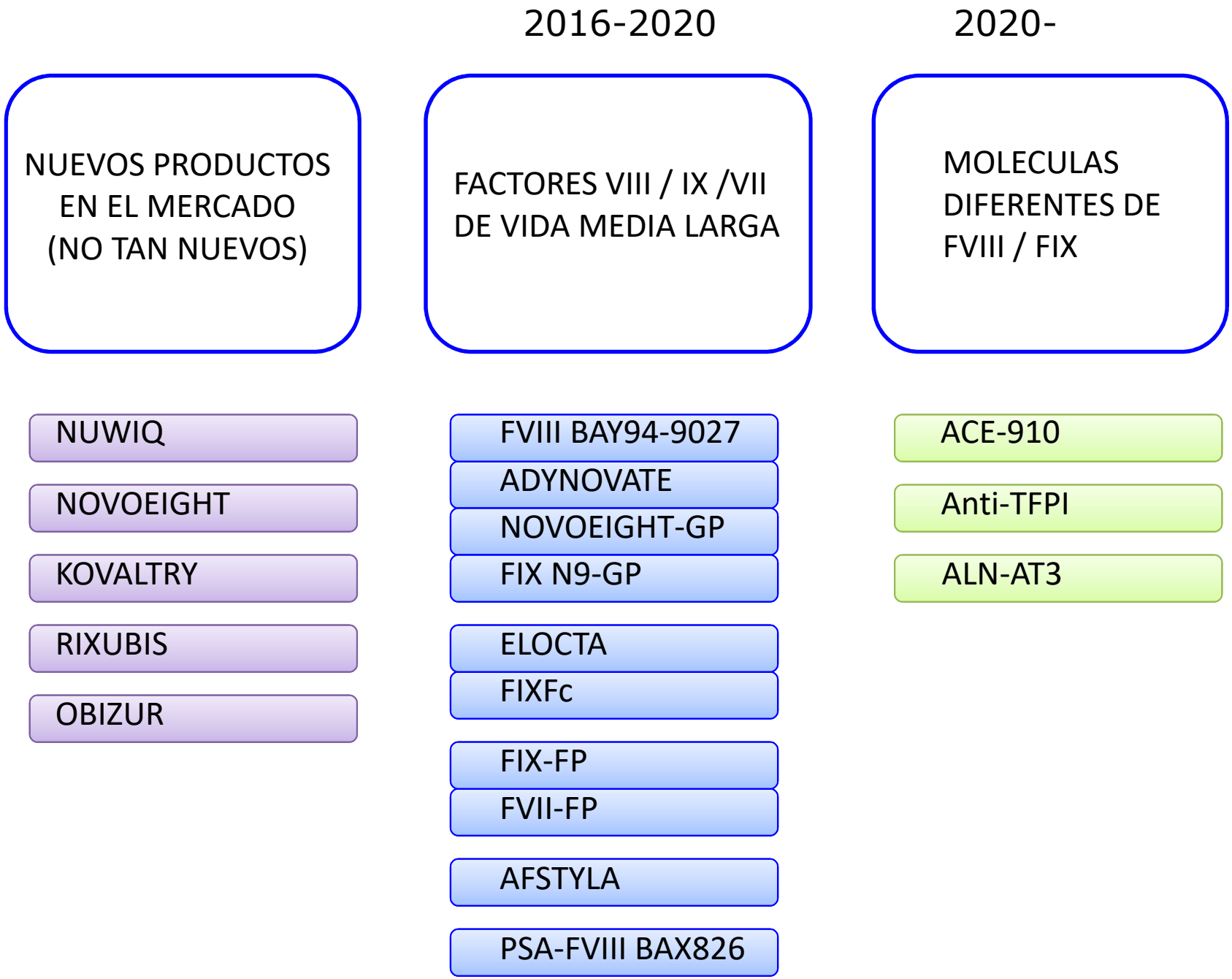


FACTORES DE VIDA
MEDIA LARGA

DIANAS
TERAPEUTICAS
ALTERNATIVAS

DIFERENTE VIA
DE ADMINISTRACION
(SUBCUTANEA)

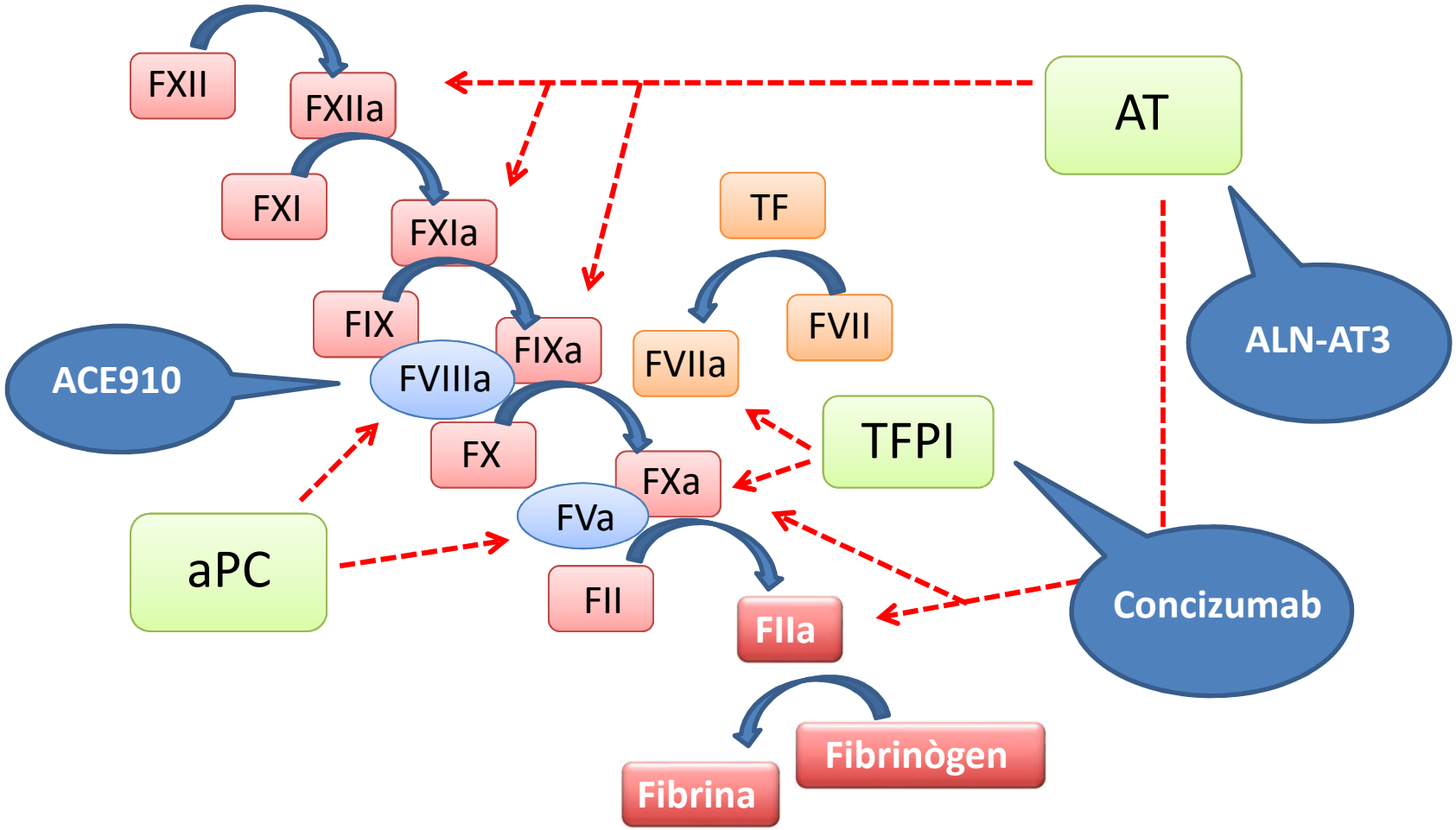
NO O MÍNIMA
RESPOSTA INMUNE

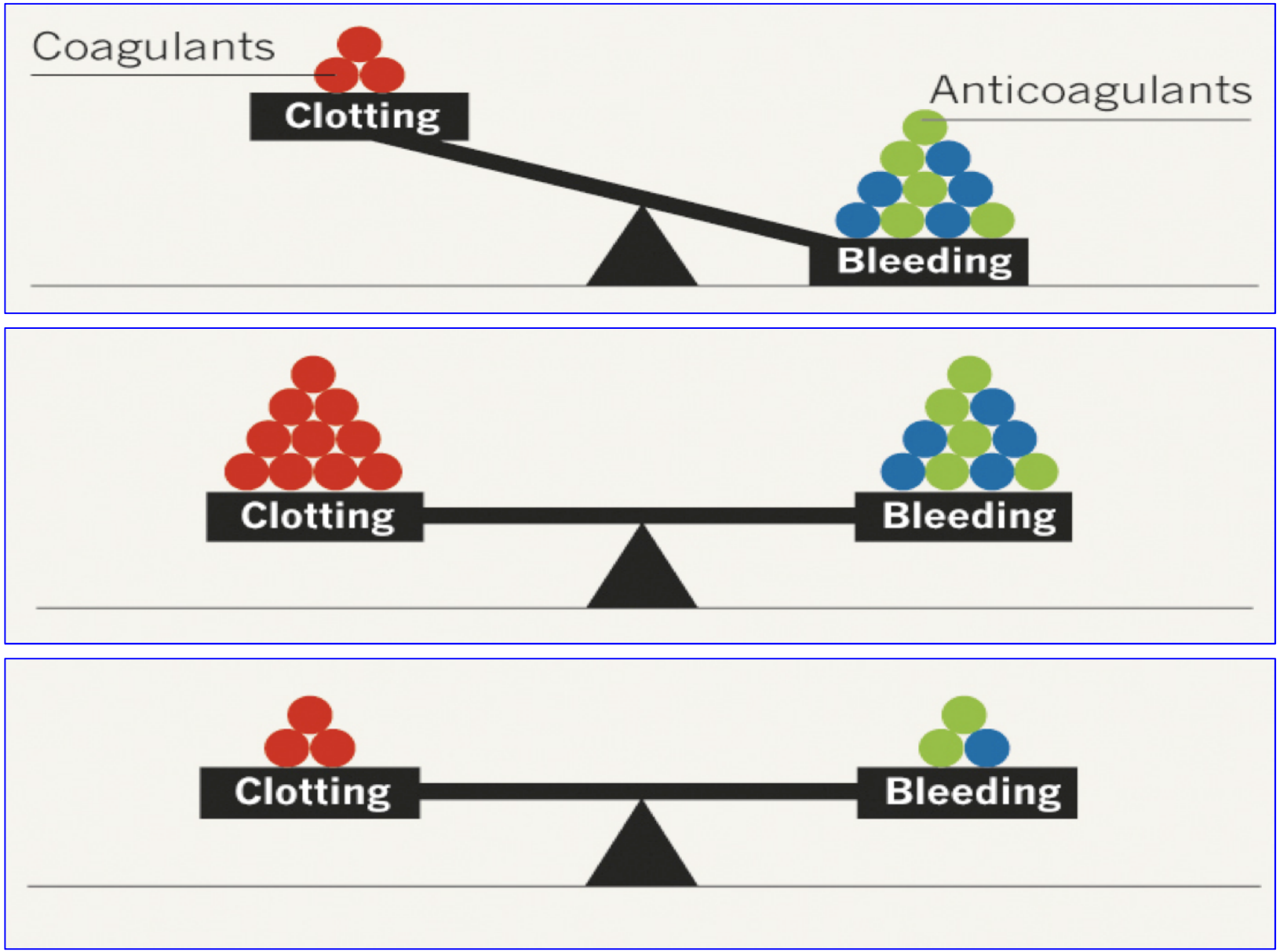

2016-2020
2020-
NUEVOS PRODUCTOS EN EL MERCADO (NO TAN NUEVOS)
FACTORES VIII / IX /VII DE VIDA MEDIA LARGA
MOLECULAS DIFERENTES DE FVIII / FIX
NUWIQ
NOVOEIGHT
KOVALTRY
RIXUBIS
OBIZUR
FVIII BAY94-9027
ADYNOVATE
NOVOEIGHT-GP
FIX N9-GP
ELOCTA
FIXFc
FIX-FP
FVII-FP
AFSTYLA
PSA-FVIII BAX826
ACE-910
Anti-TFPI
ALN-AT3

# TRATAMIENTO NO SUSTITUTIVO

| Empresa farmacéutica | Clase | Nombre | Mecanismo de acción |
|---|---|---|---|
| Novo Nordisk | Anti-TFPI | NN-7415 | Anticuerpo anti-TFPI para disminuir el TFPI |
| Alnylam | Anti-AT3 Reduce la producción de la antitrombina | ALN-AT3 | RNAi terapéutico con diana en la antitrombina |
| Chugai Roche | Factor no coagulante que sustituye el FVIII | ACE910 | Anticuerpo bivalente unido a FIXa y FX para "sustituir" la actividad del cofactor de FVIII |

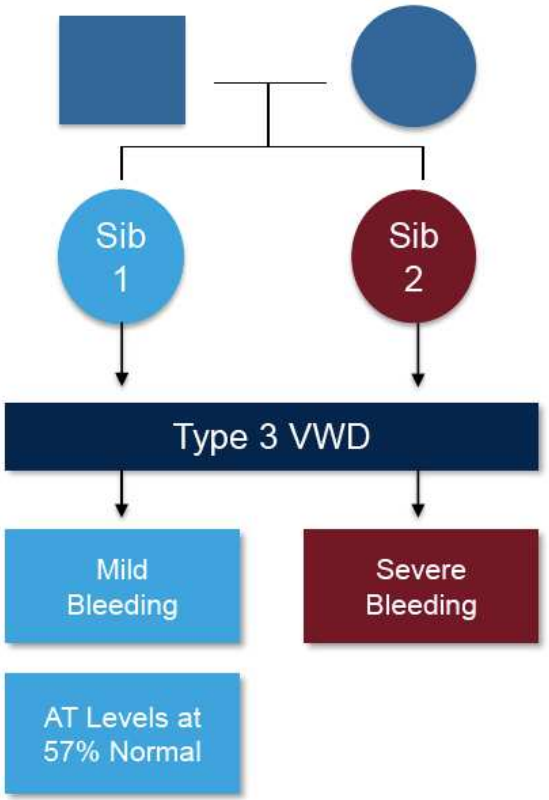
# MOLECULAS DIFERENTES DE FVIII / FIX




Coagulants
Clotting
Anticoagulants
Bleeding
Clotting
Bleeding
Clotting
Bleeding

## HERENCIA DE RASGOS TROMBOFILICOS EN HEMOFILIA

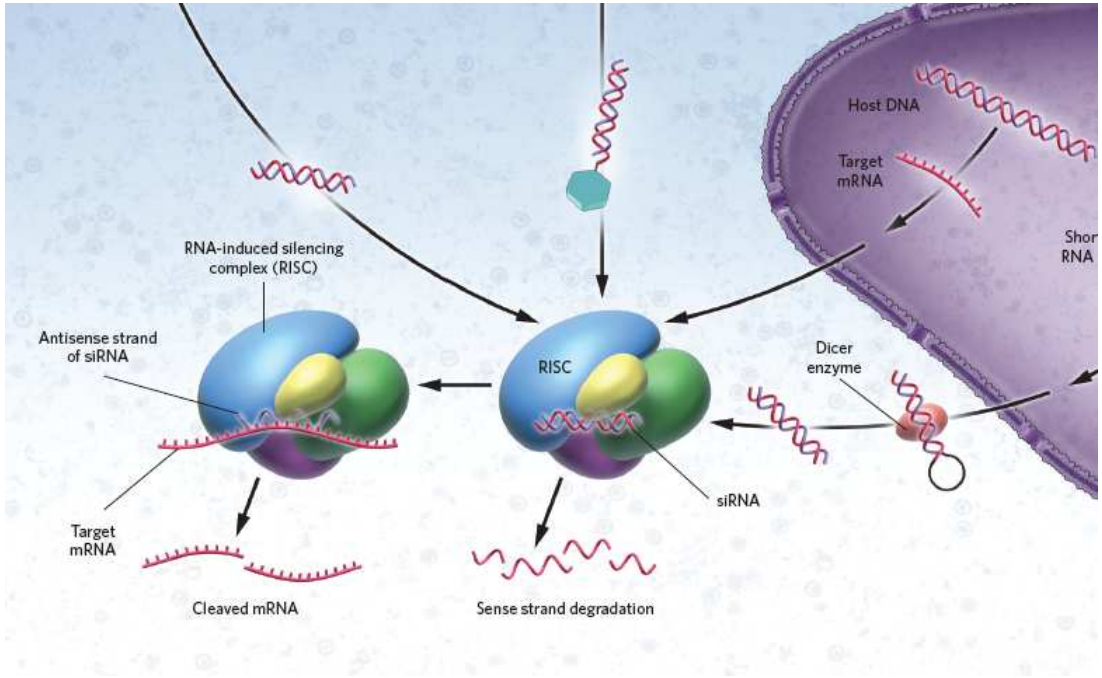
- Fenotipo hemorrágico menos grave
- Defecto heterocigoto
- Déficit AT
- FV Leiden
- Déficit Proteïna C
- Déficit Proteïna S

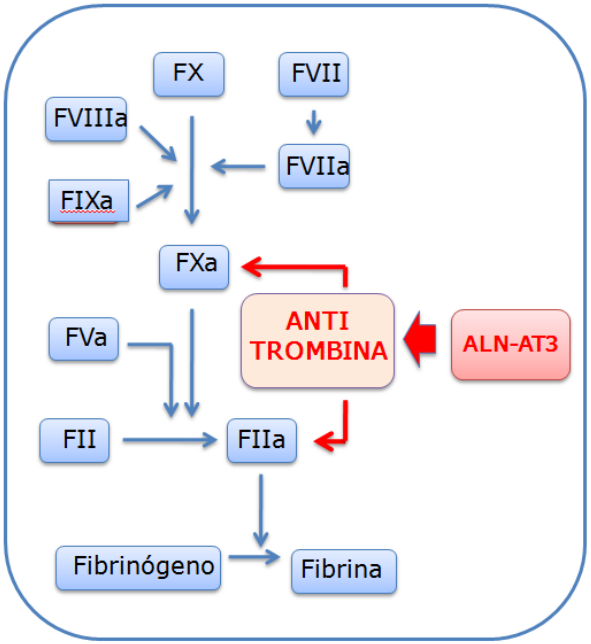


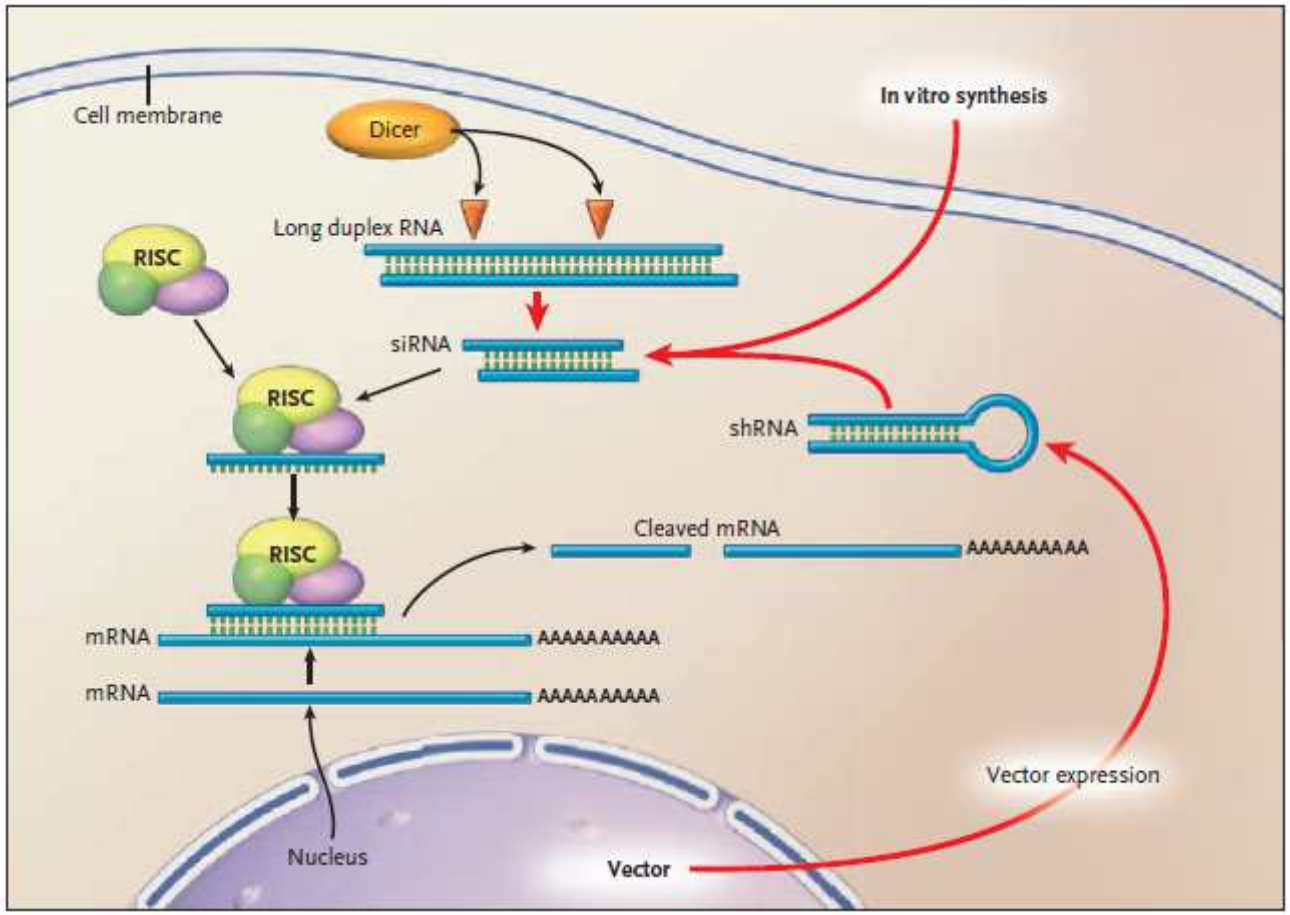

Fischer, WFH May 2014

# ALN-AT3

ALN-AT3 es una molécula RNA de interferencia que silencia el gen asociado a la producción de AT por los hepatocitos





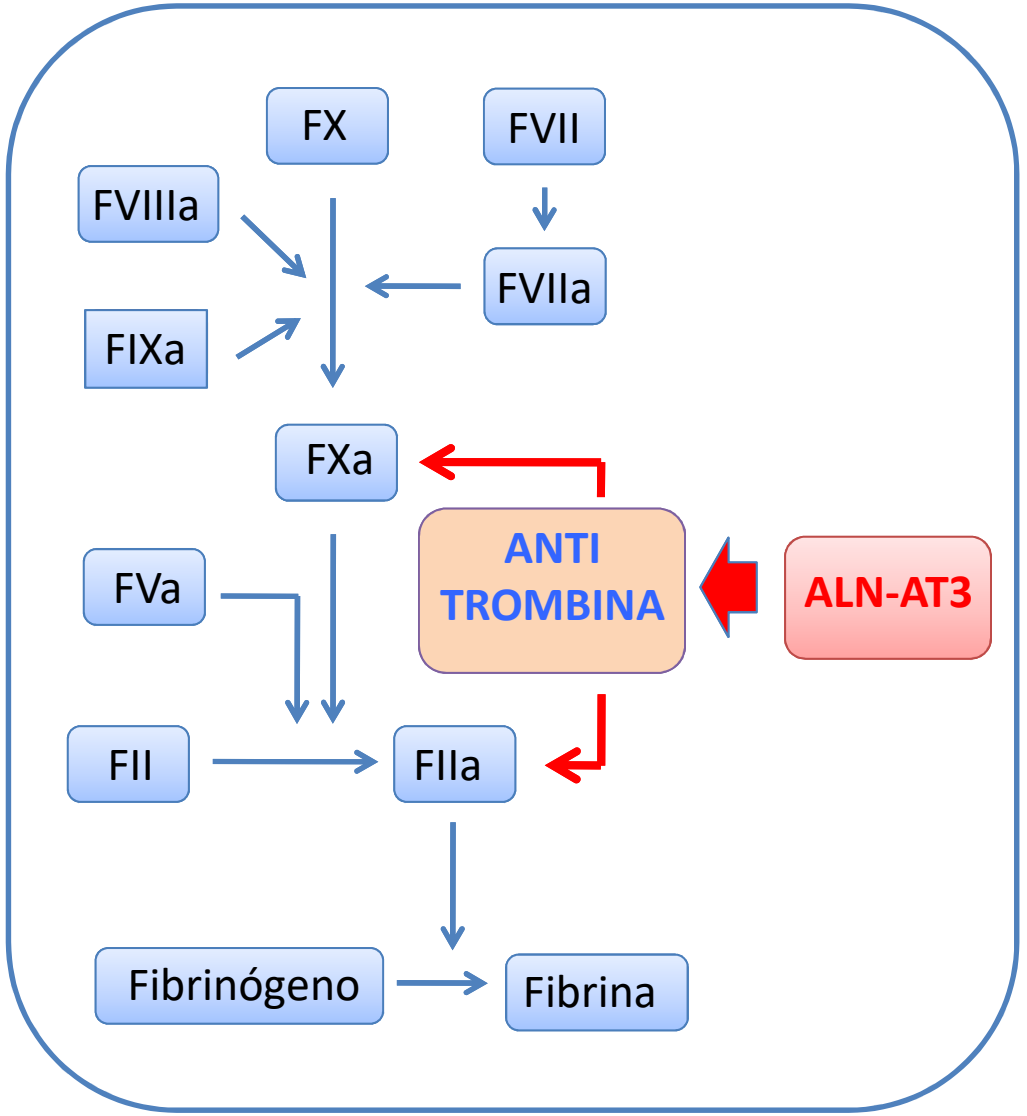

Tomado de N Engl J Med 2006; 355:2391-2393

# ANTITROMBINA

- Uno de los principales anticoagulantes naturales
- Inactiva FXa y Trombina
- El déficit se asocia con un aumento en la generación de trombina.
- Síntesis hepática, circula en plasma

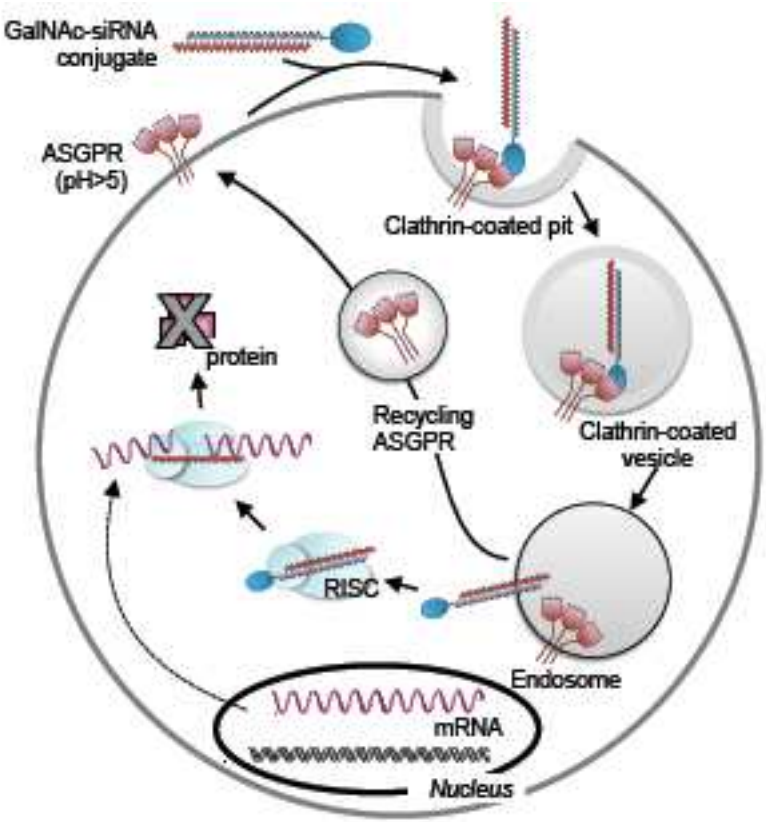
# ALN-AT3

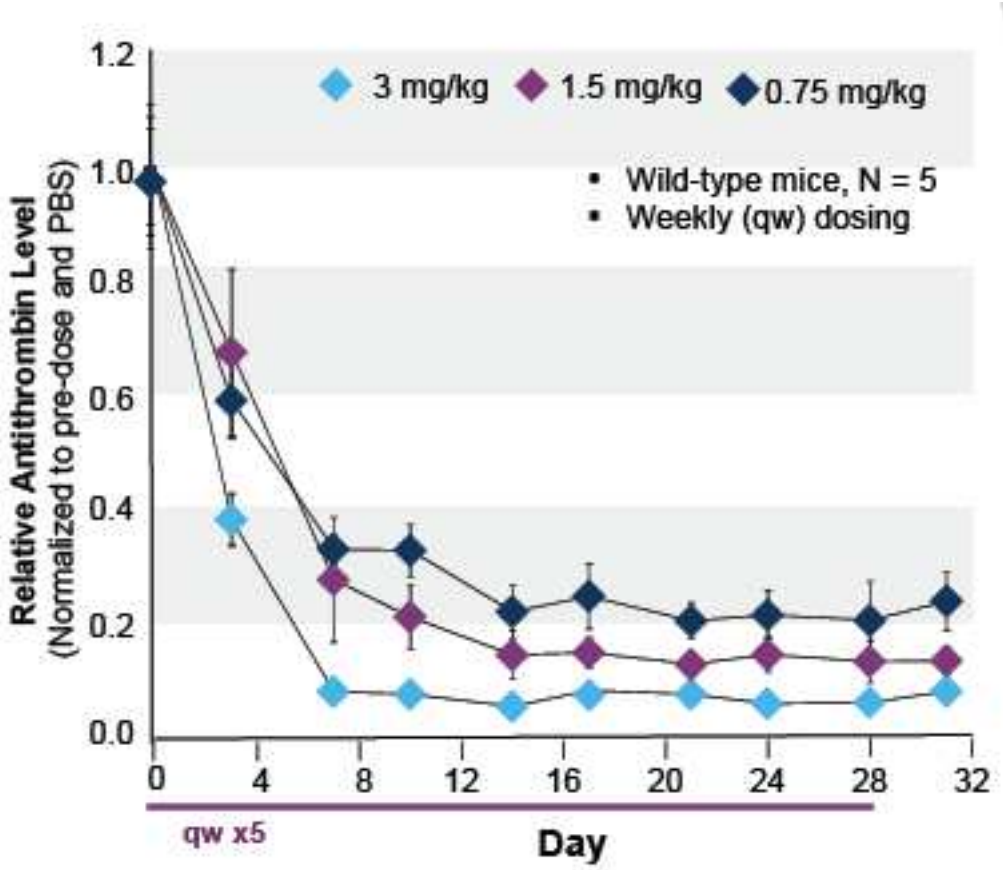
RNAi que silencia la síntesis endógena de AT en hígado



Alnylam PHARMACEUTICALS

# ALN-AT3



nature medicine

# An RNAi therapeutic targeting antithrombin to rebalance the coagulation system and promote hemostasis in hemophilia

Alfica Sehgal[1], Scott Barros[1], Lacramioara Ivanciu[2], Brian Cooley[3], June Qin[1], Tim Racie[1], Julia Hettinger[1], Mary Carioto[1], Yongfeng Jiang[1], Josh Brodsky[1], Harsha Prabhala[1], Xuemei Zhang[1], Husain Attarwala[1], Renta Hutabarat[1], Don Foster[1], Stuart Milstein[1], Klaus Charisse[1], Satya Kuchimanchi[1], Martin A Maier[1], Lubo Nechev[1], Pachamuthu Kandasamy[1], Alexander V Kel'in[1], Jayaprakash K Nair[1], Kallanthottathil G Rajeev[1], Muthiah Manoharan[1], Rachel Meyers[1], Benny Sorensen[1], Amy R Simon[1], Yesim Dargaud[4], Claude Negrier[4], Rodney M Camire[2] & Akin Akinc[1]

published online 13 April 2015;

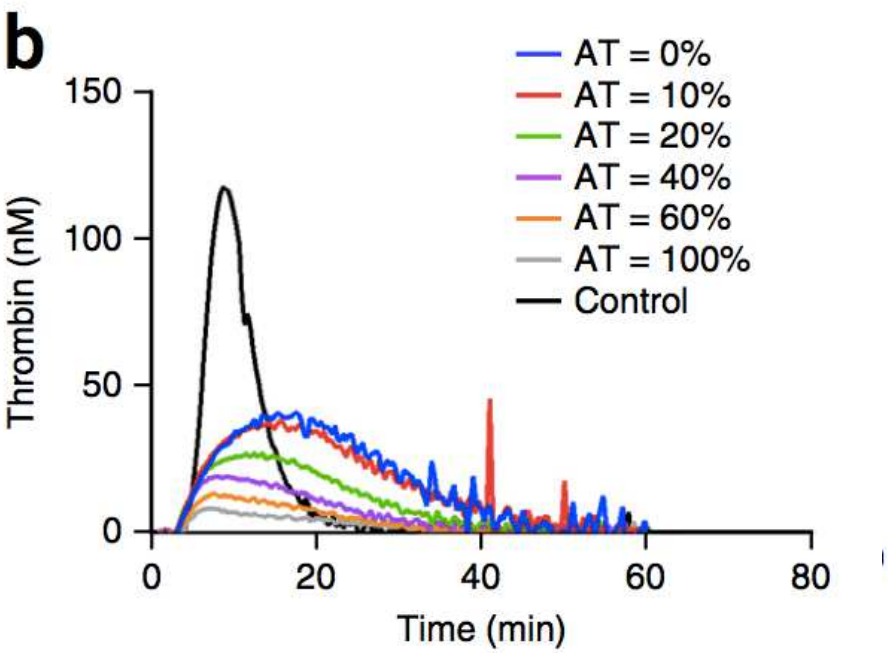
The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

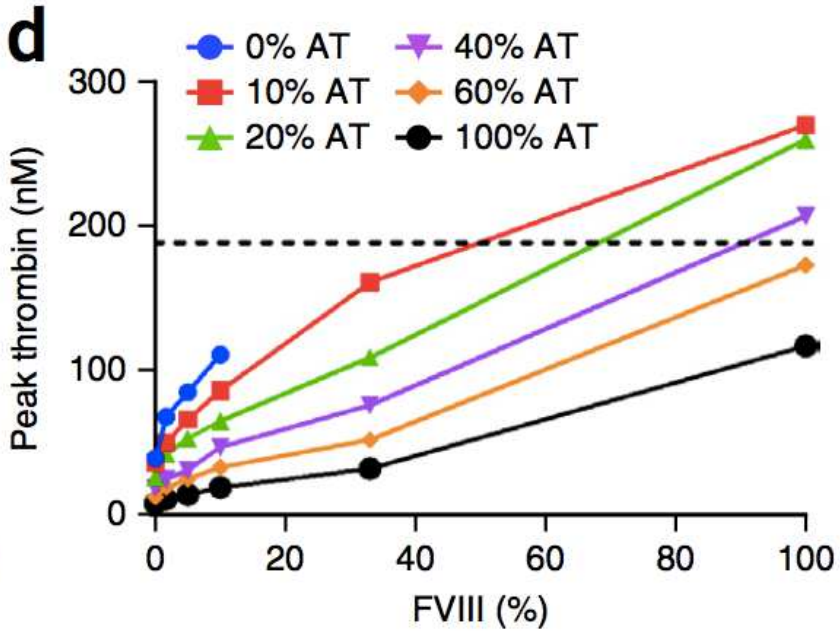
Elizabeth G. Phimister, Ph.D., *Editor*

## Targeting Antithrombin to Treat Hemophilia

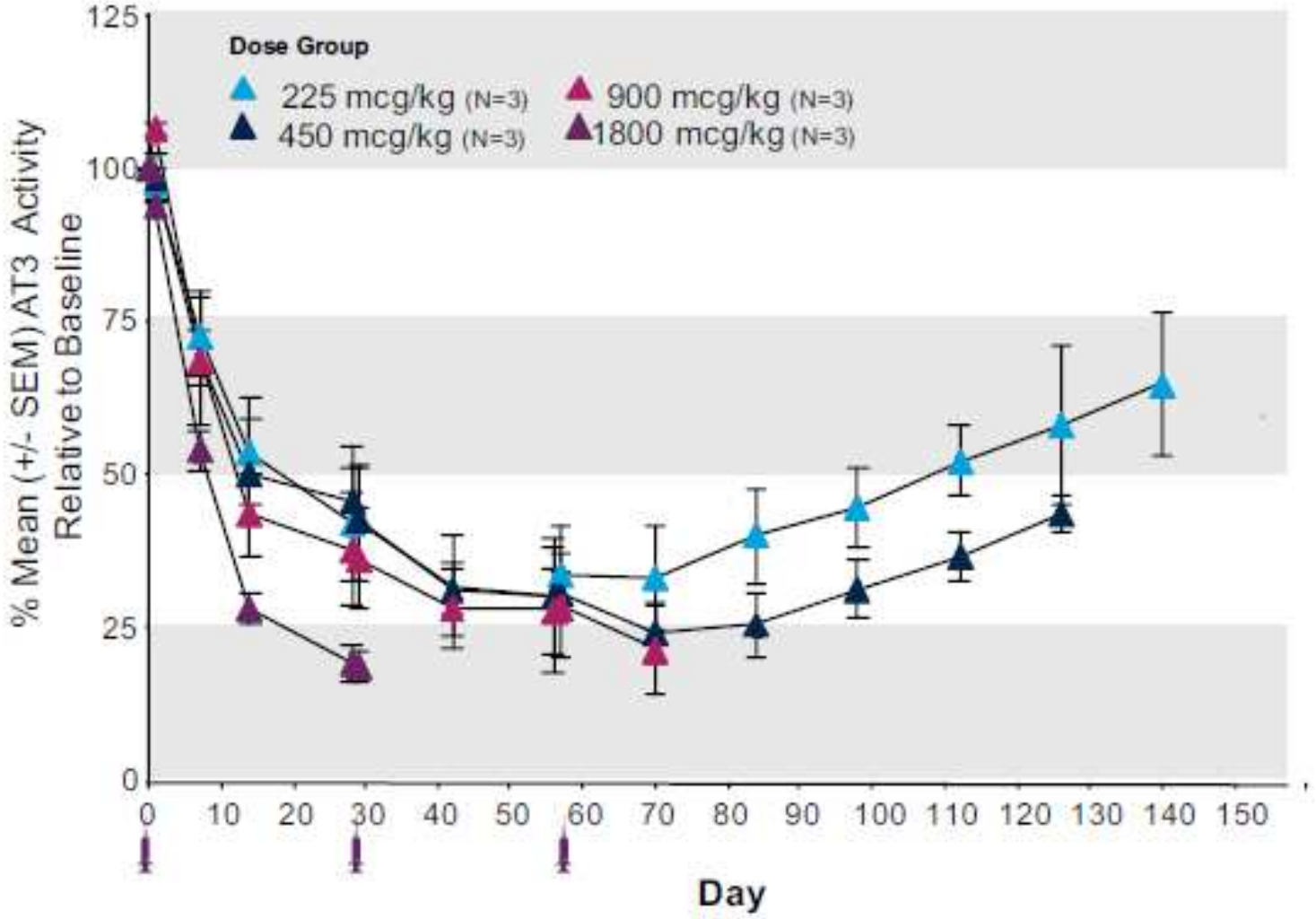
Margaret V. Ragni, M.D.



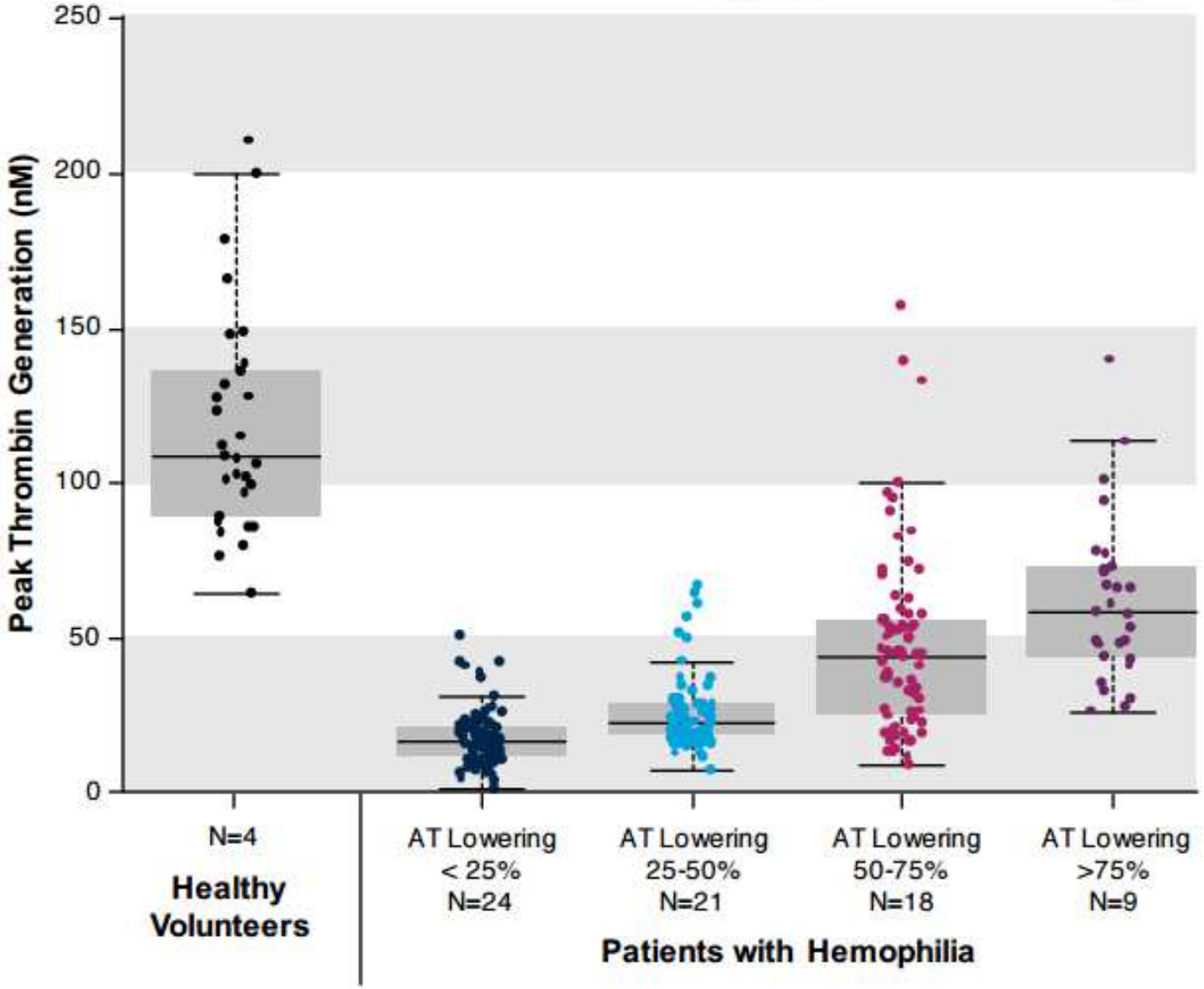

Trombograma en hemofilia A grave; plasma donante con niveles de AT depleccionados hasta los niveles indicados




Niveles pico de trombina generados según diferentes niveles de depleccion de AT y adición de FVIII en plasma hemofila A grave

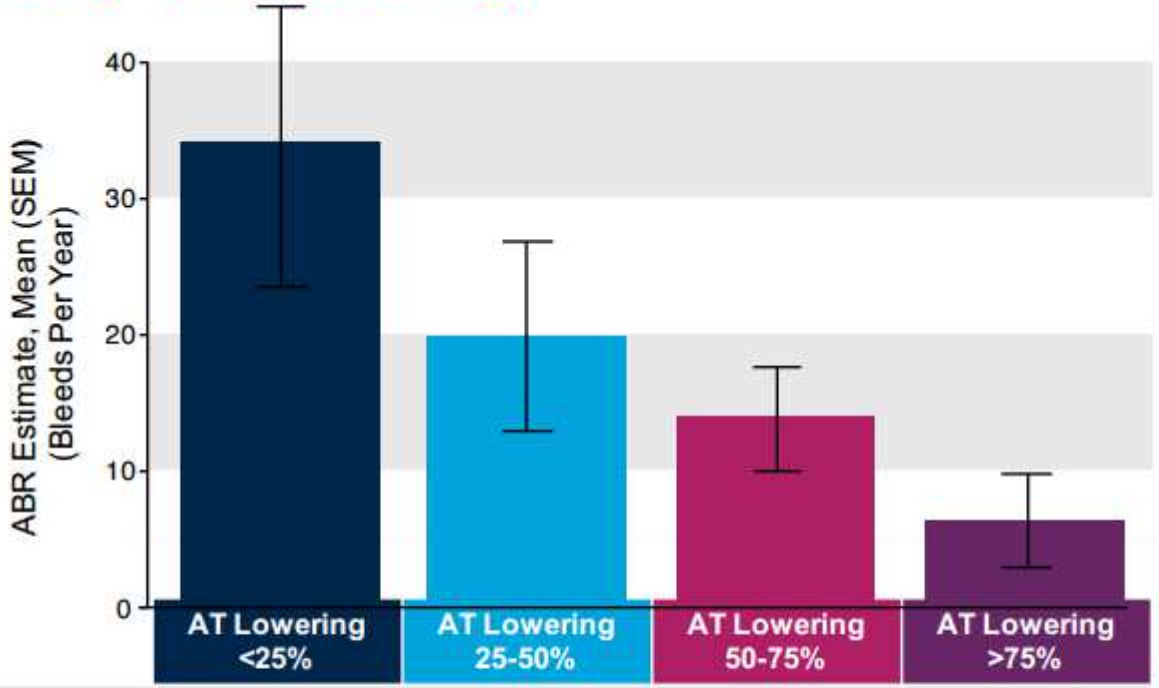

Dose Group
225 mcg/kg (N=3)
450 mcg/kg (N=3)
900 mcg/kg (N=3)
1800 mcg/kg (N=3)
% Mean (+/- SEM) AT3 Activity Relative to Baseline
125
100
75
50
25
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
Day

# Thrombin Generation by % AT Lowering




*Pasi KJ et al, ASH 2015*

# Bleed Events by % AT Lowering




| | AT Lowering <25% | AT Lowering 25-50% | AT Lowering 50-75% | AT Lowering >75% | |
|---|---|---|---|---|---|
| **Patients** | N=24 | N=21 | N=18 | N=9 | |
| **ABR, Mean (SEM)** | 34 ± 10 | 20 ± 7 | 14 ± 4 | 6 ± 3 | |
| **ABR, Median** | 13 | 11 | 10 | 0 | p<0.05 |

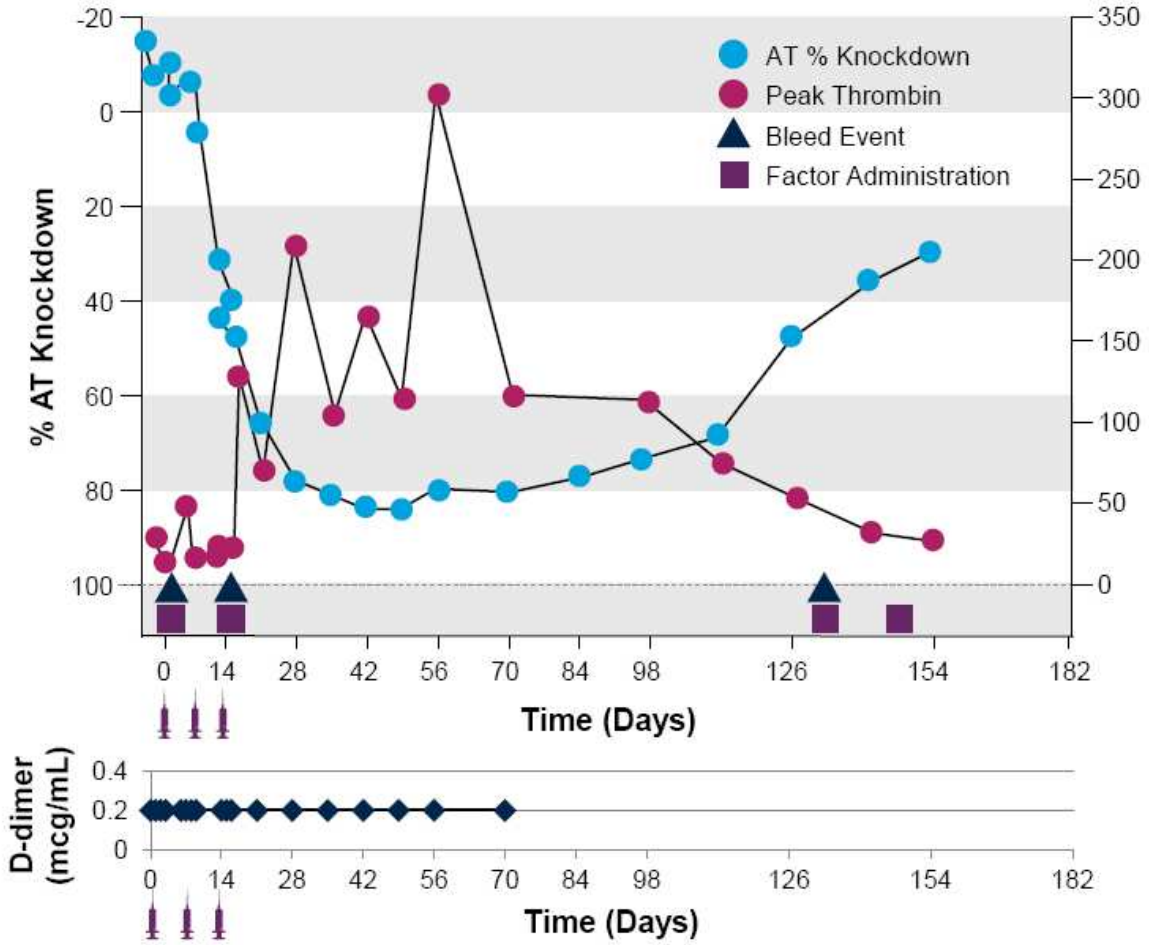
**Conclusions: With AT lowering by quartile, <25% to >75%, there is reduction in ABR.**

***Pasi KJ, et al. Blood 2015***

**ABR = Annualized bleed rate**

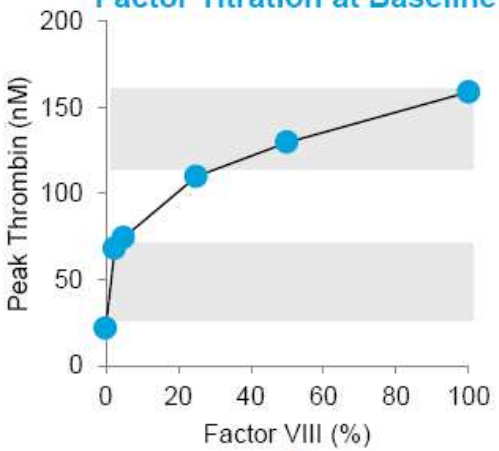
# Hemophilia Patient 400-002*

## Bleed-free period of 114 days correlates with AT KD and increase in thrombin generation, with no increase in D-dimer




100-150 nM peak thrombin represents >25% factor VIII in this subject

**Factor Titration at Baseline**




**Patient 400-002 has severe hemophilia A and has a self-reported ABR of 22; enrolled in 45 mcg/kg dose cohort*

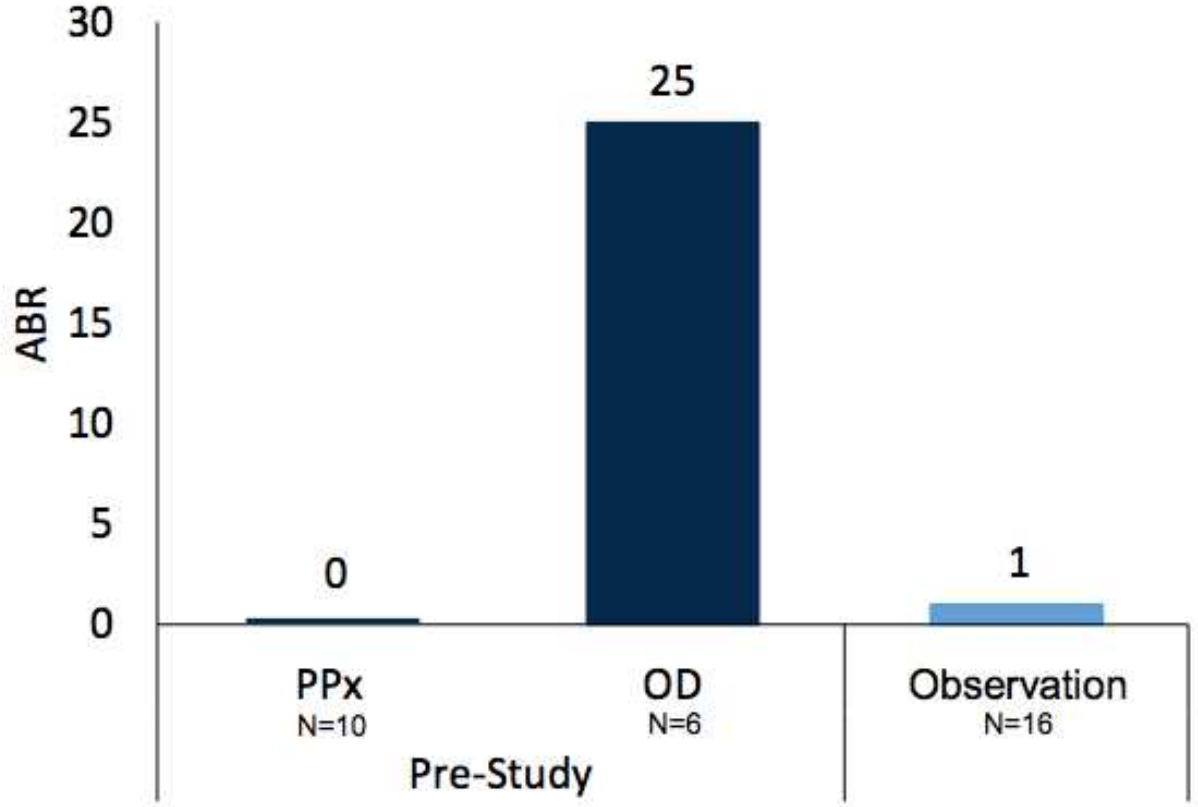
Sorensen, *ISTH*, June 2015



Alnylam PHARMACEUTICALS

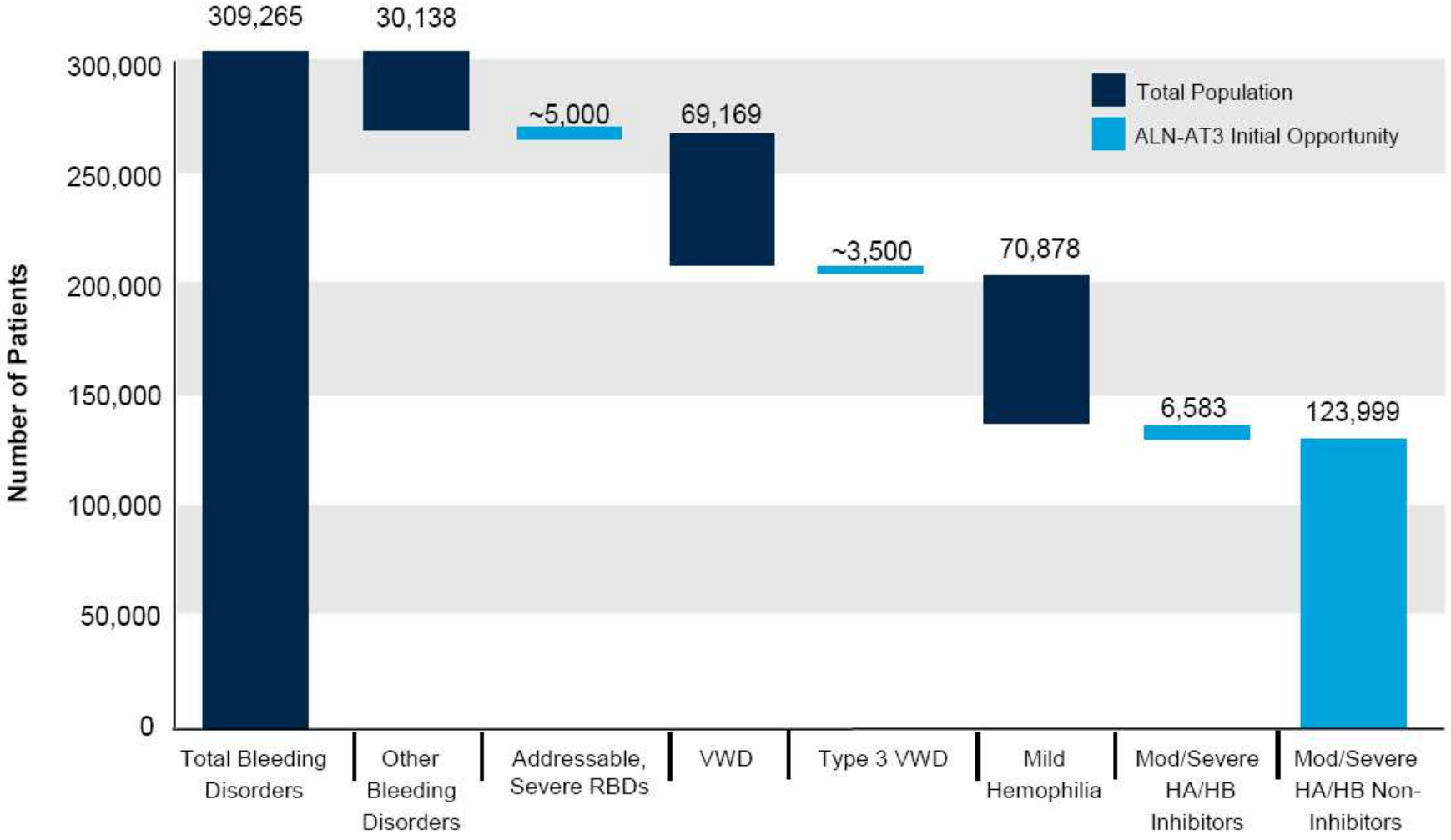
# Interim Fitusiran Phase 2 OLE Study Results*

## Summary of Median ABRs in Patients without Inhibitors




- Median ABR, Observation period = 1
  - Patients reporting no bleeds: 8/16 (50%)
  - Patients reporting no spontaneous bleeds (AsBR = 0): 11/16 (69%)
- Median duration in observation period = 170 days (5.7 months)

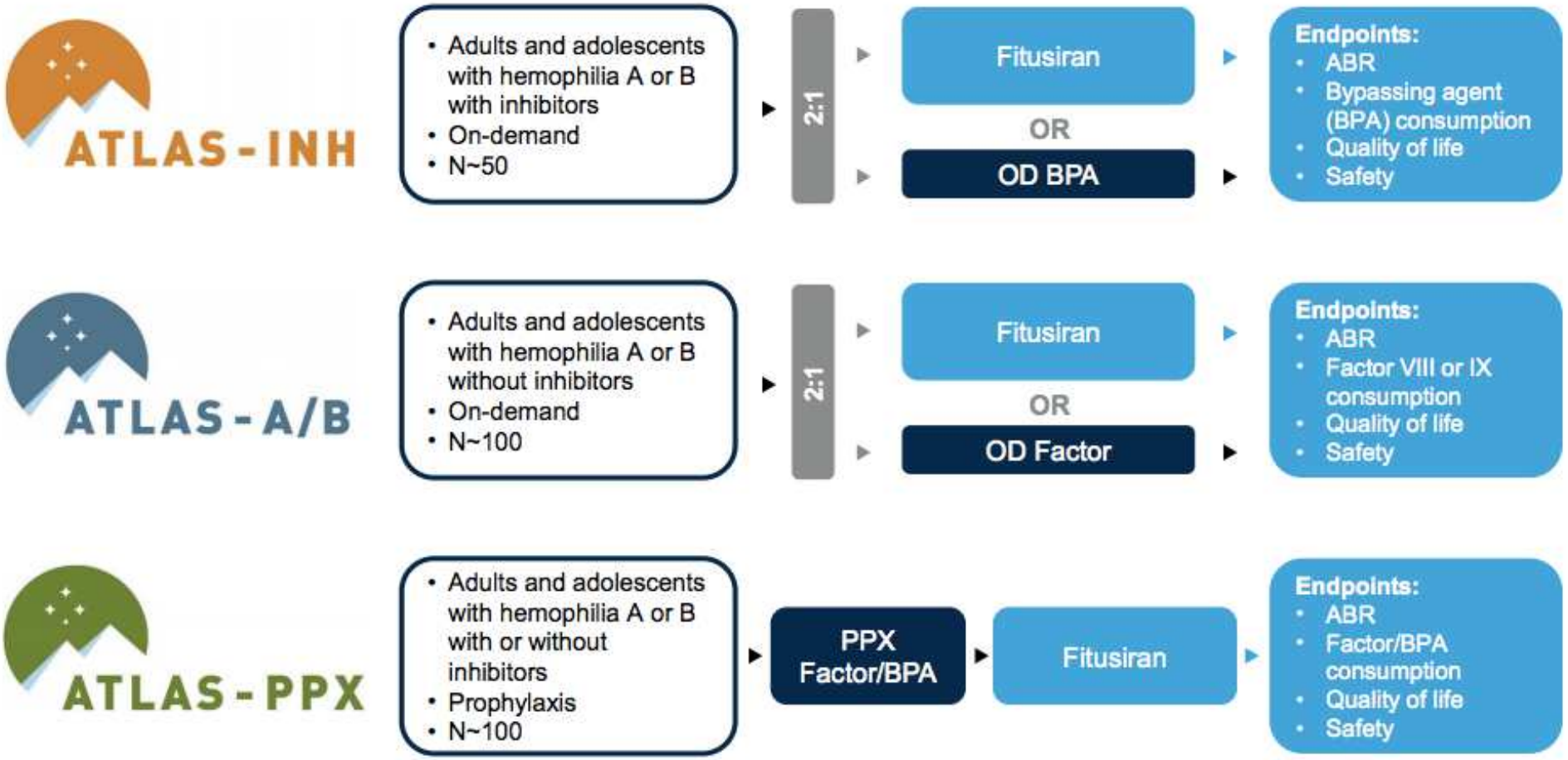
# Potential Target Bleeding Disorder Segments






Adapted from WFH Annual Global Survey 2013, extrapolated to 2015

# Preliminary Fitusiran ATLAS Phase 3 Program*
## Plan to Initiate in Early 2017

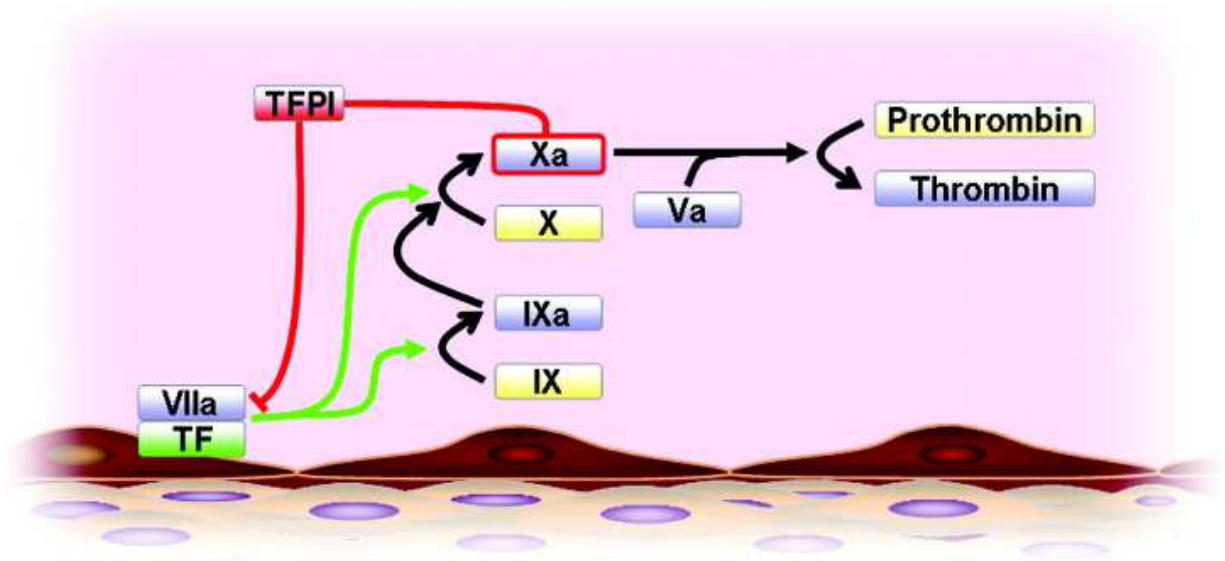



*All completers will be eligible for fitusiran treatment in Phase 3 OLE study (ATLAS-OLE)*

# TFPI (Tissue Factor Pathway Inhibitor)

Proteina anticoagulante producida por células endoteliales y plaquetas.

Regula estrechamente la generación de FXa.

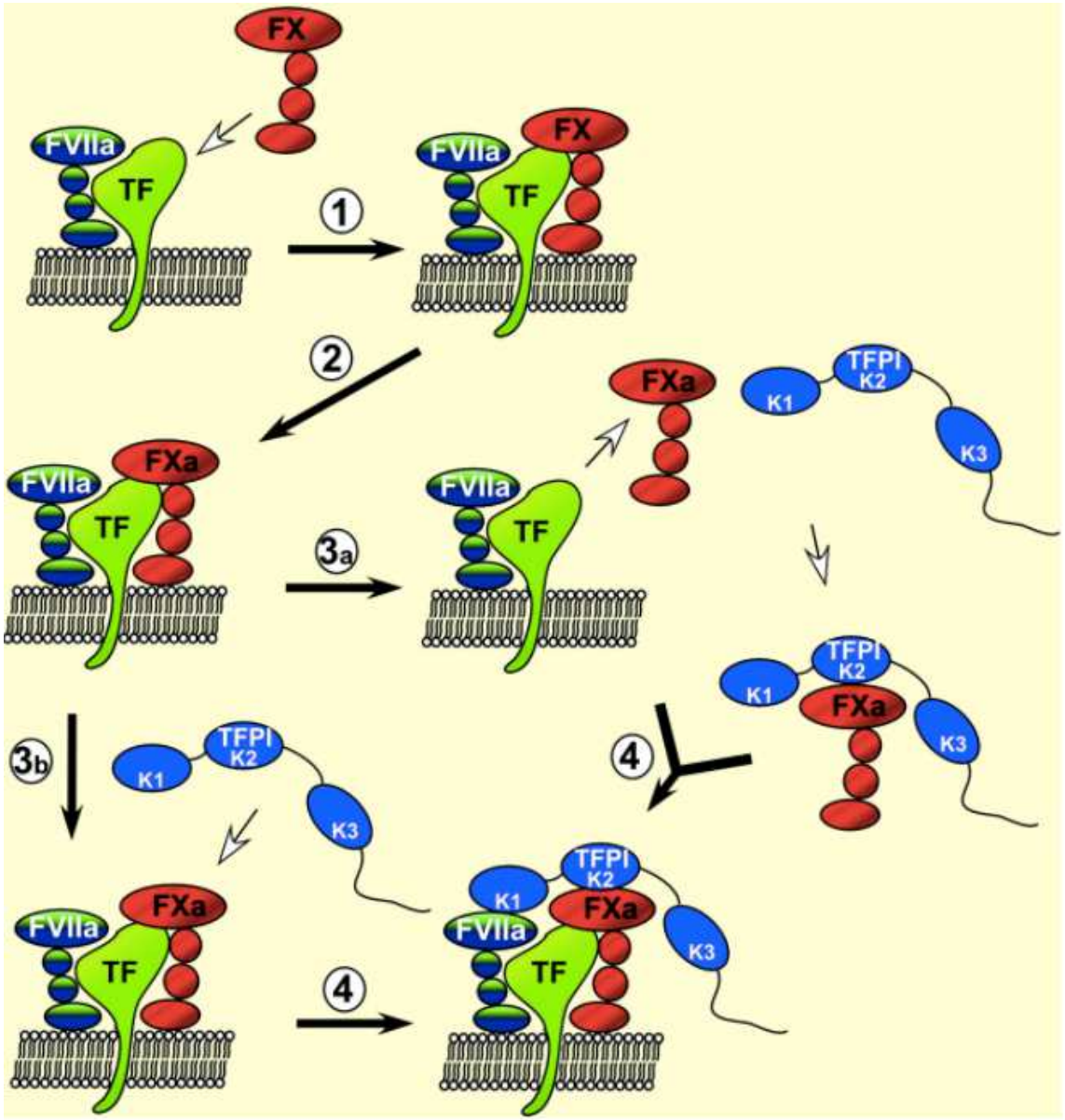



# CONCIZUMAB

Anticuerpo monoclonal humanizado anti-TFPI

Evita la unión de FXa a TFPI y la inhibición del complejo TF-FVIIa

Aumento de FXa y de generación de trombina.




Tomado de Arteriosclerosis, Thrombosis, and Vascular Biology. 2008;28:233-242

journal of thrombosis and haemostasis™

Original Article - Clinical Haemostasis and Thrombosis

# Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial

Pratima Chowdary[1,*], Stefan Lethagen[2,3], Ute Friedrich[2], Brigitte Brand[4], Charles Hay[5], Faraizah Abdul Karim[6], Robert Klamroth[7], Paul Knoebl[8], Mike Laffan[9], Johnny Mahlangu[10], Wolfgang Miesbach[11], Jørn Dalsgaard Nielsen[12], Mónica Martin-Salces[13], Pantep Angchaisuksiri[14] and The Explorer™1 Investigators[†]

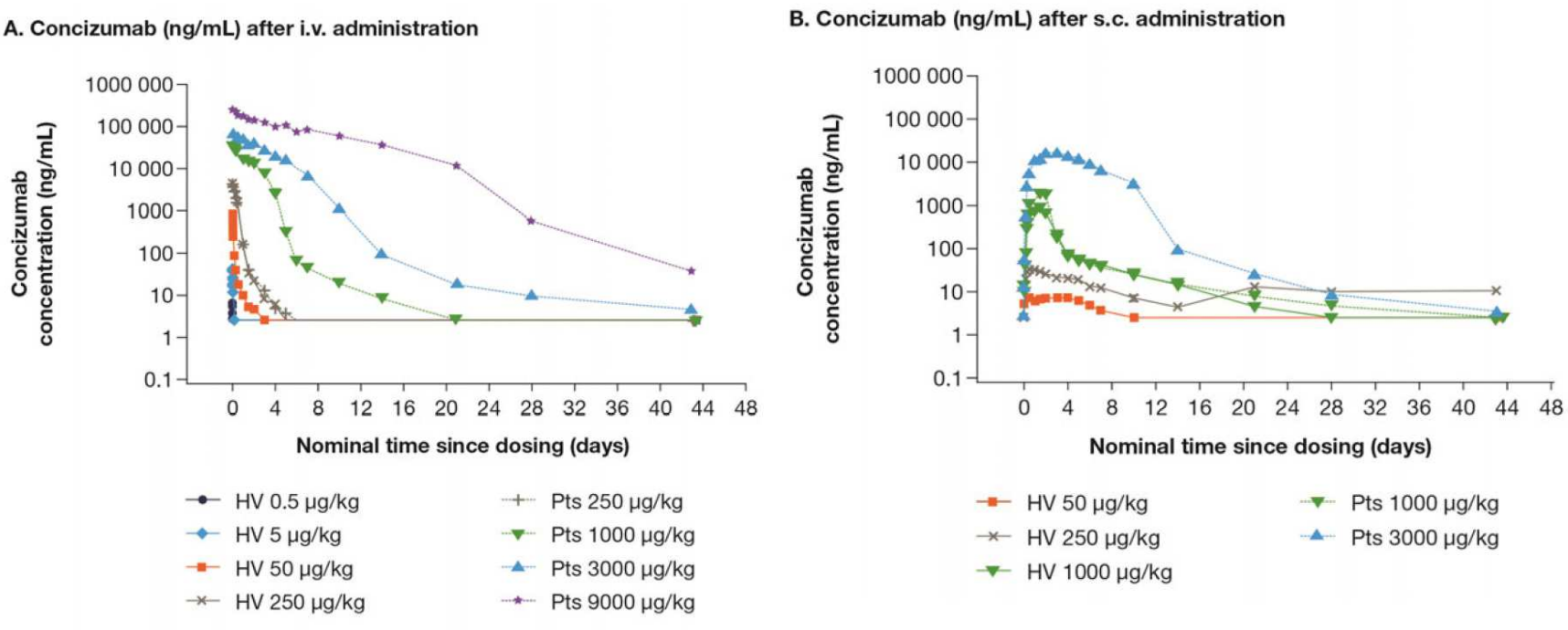
DOI: 10.1111/jth.12864

Issue

Journal of Thrombosis and Haemostasis

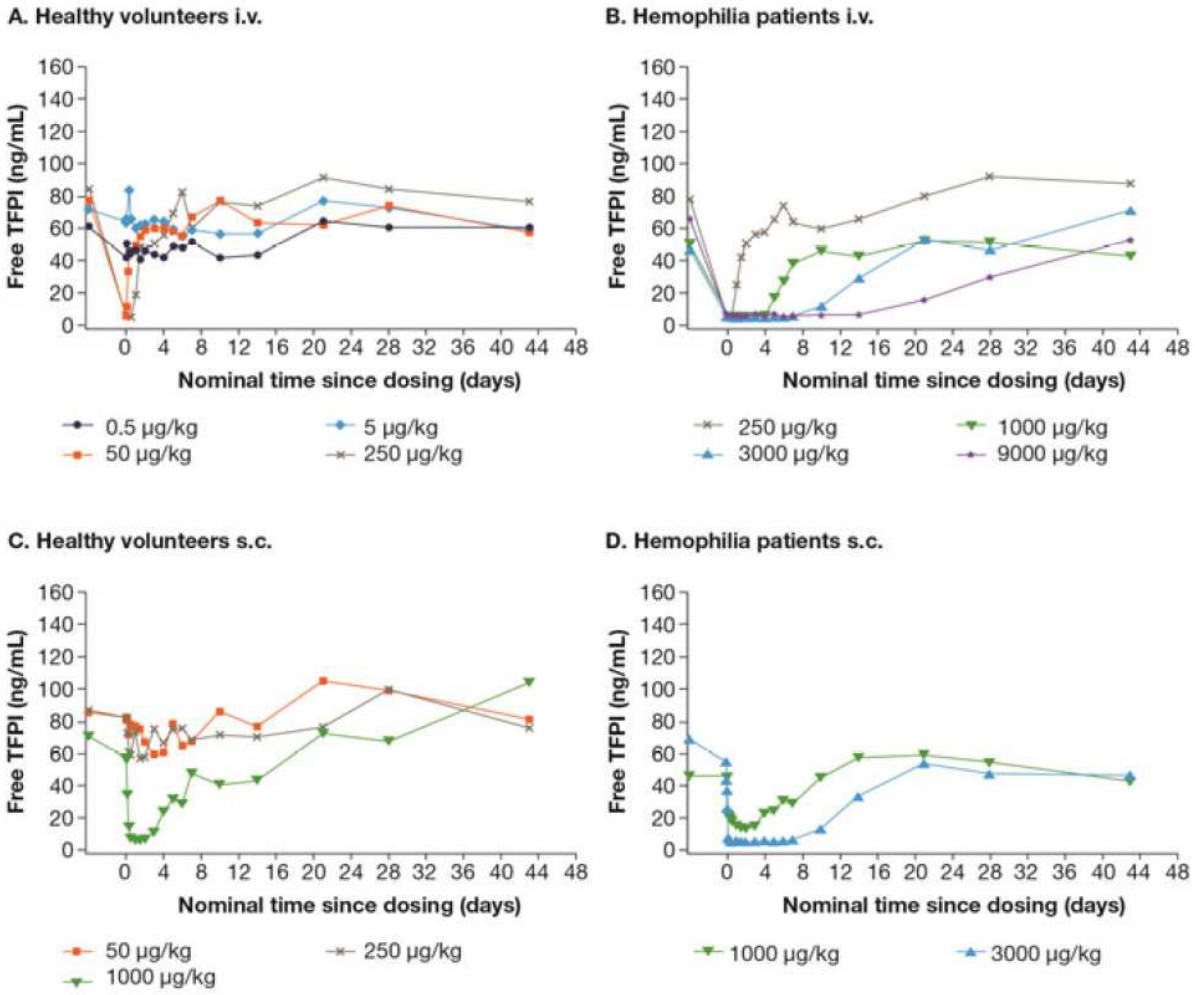
Accepted Article (Accepted, unedited articles published online and citable. The final edited and typeset version of record will appear in future.)

# CONCIZUMAB. PK



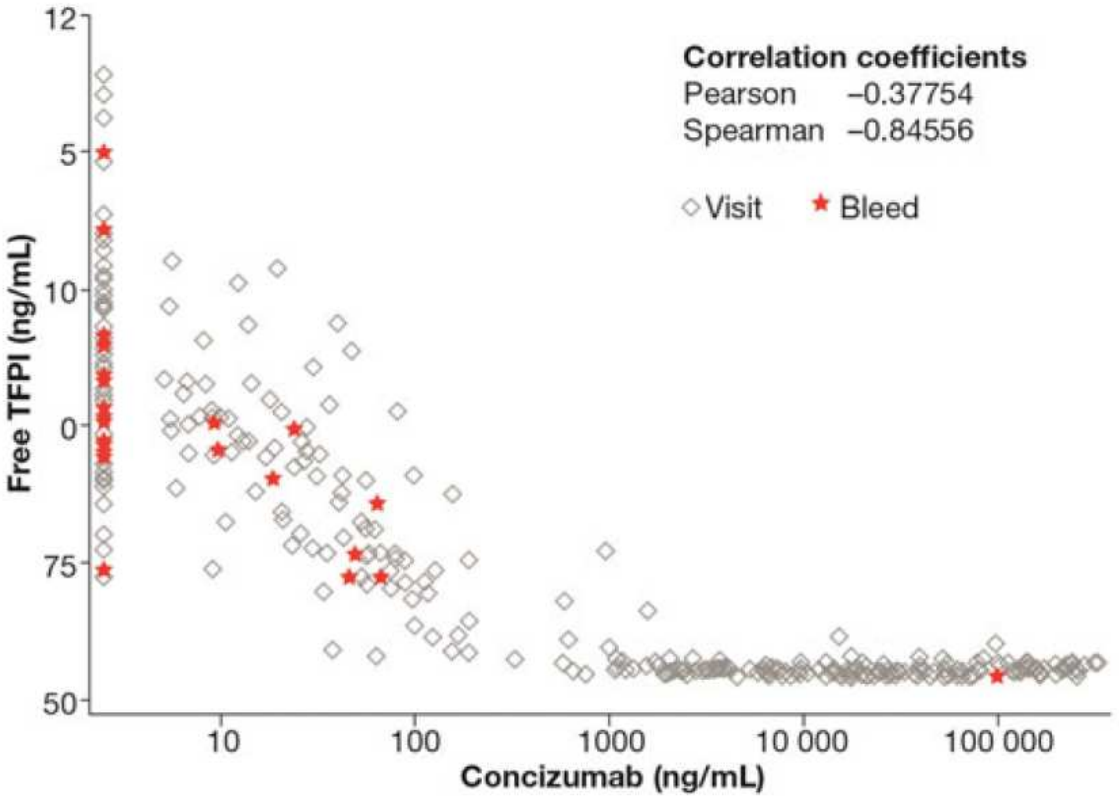

- Detección de Concuzimab en plasma hasta 43 dias tras la administración.
- Curva farmacocinética no lineal (rapida eliminación a bajas concentraciones y lenta eliminación a altas concentraciones (Target mediated clearance)
- PK similar en voluntarios sanos y en hemofilicos.

# TPFI EN PLASMA TRAS CONCIZUMAB (iv, sc)




[TFPI] disminuida >14 dias post dosis (dosis más alta)

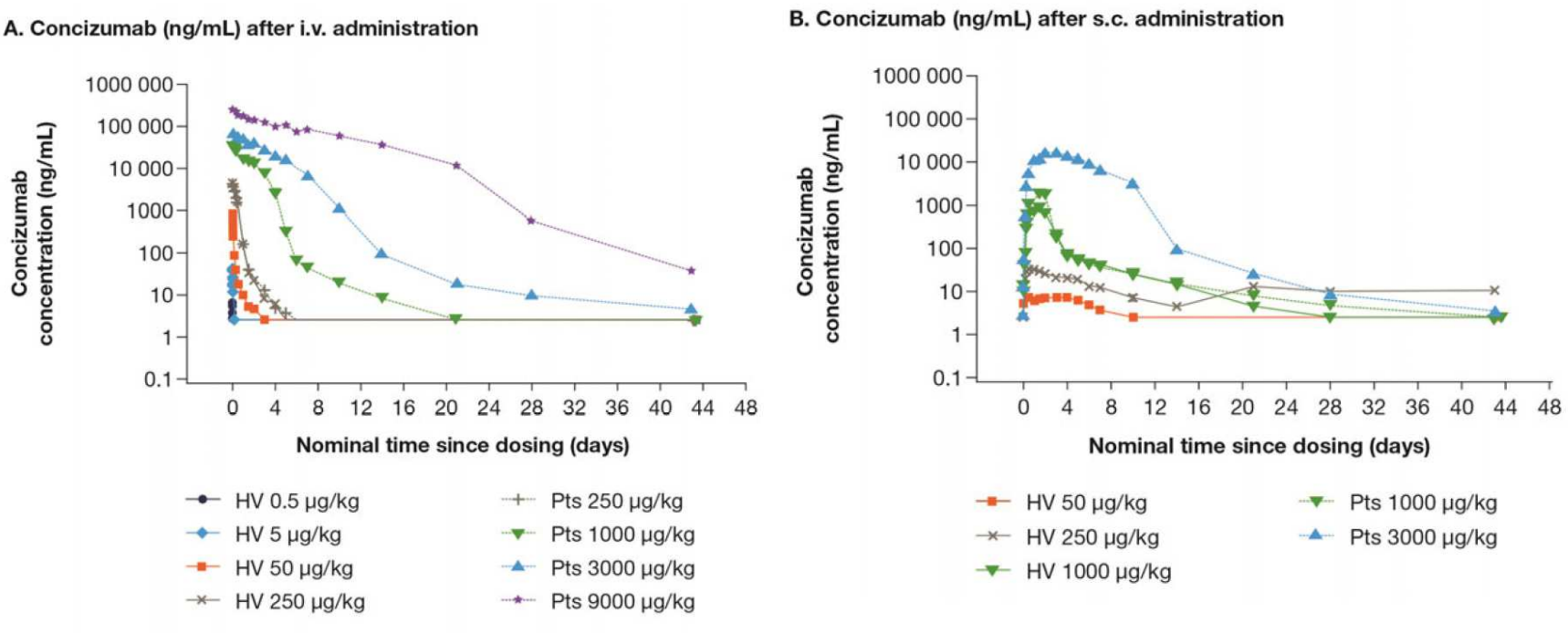
# TFPI vs CONCIZUMAB




- La concentración de TFPI en plasma disminuye de manera dosis dependiente: [TFPI] disminuye al aumentar [Concizumab]

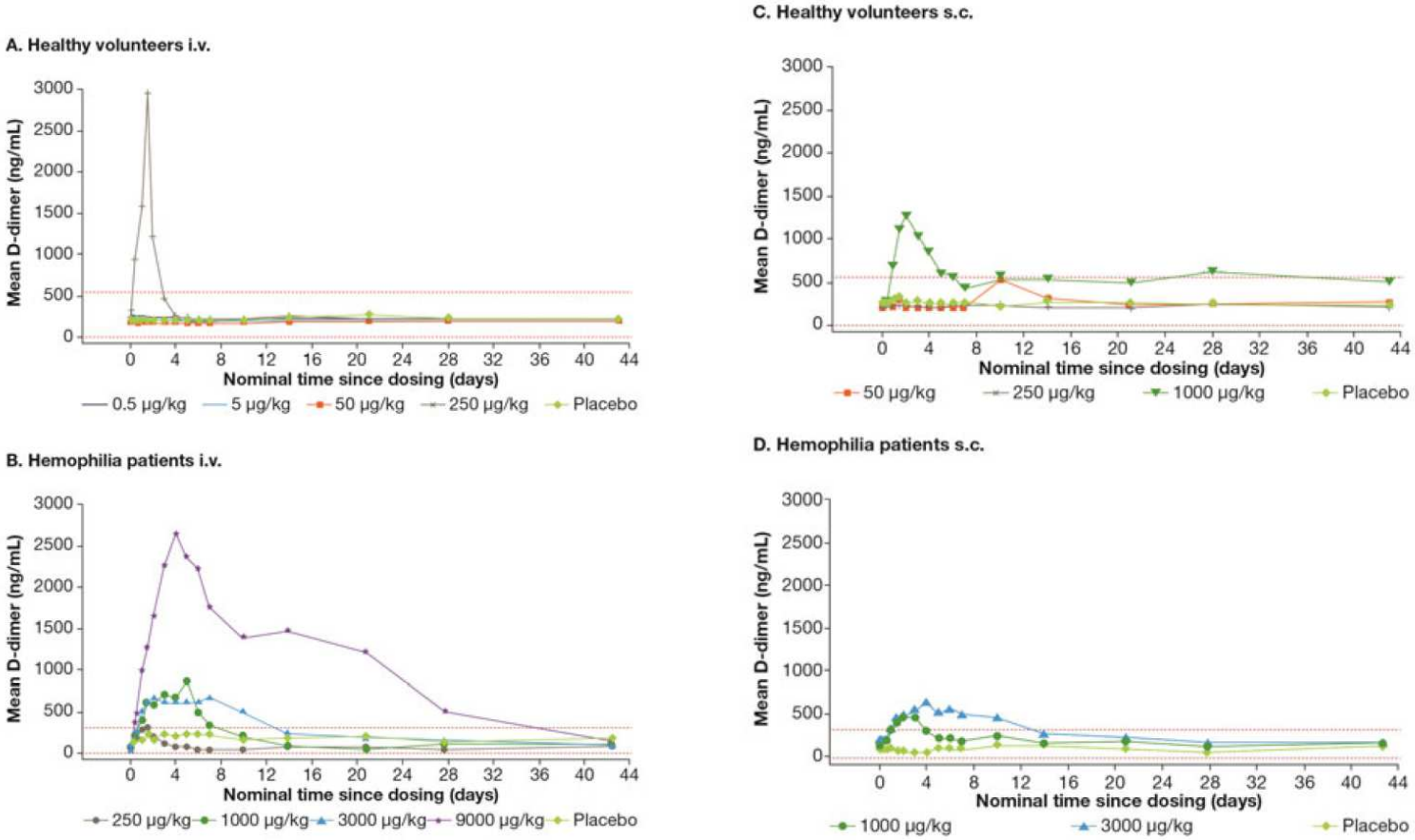
- Episodios hemorràgicos: 24 en 14 paciente hemofilics (9 Concizumab, 5 placebo) Ningún episodio con concentraciones altas de Concizumab o bajas de TFPI.

# CONCIZUMAB. PK




- Detección de Concuzimab en plasma hasta 43 dias tras la administración.
- Curva farmacocinética no lineal (rapida eliminación a bajas concentraciones y lenta eliminación a altas concentraciones (Target mediated clearance)
- PK similar en voluntarios sanos y en hemofilicos.

# CONCIZUMAB. DIMERO-D




- Aumento de dimero-D dosis dependiente: Efecto procoagulante de Concizumab
- Respuesta menor en pacientes hemofílicos en comparación con voluntarios sanos para el mismo nivel de Concizumab

# CONCIZUMAB. CONCLUSION

**SEGURIDAD**

- 52 individuos tratados. Una única dosis.
- No AE grave. Reacción leve en punto de punción (Tromboflebitis superficial). No anticuerpos anti-Concizumab.

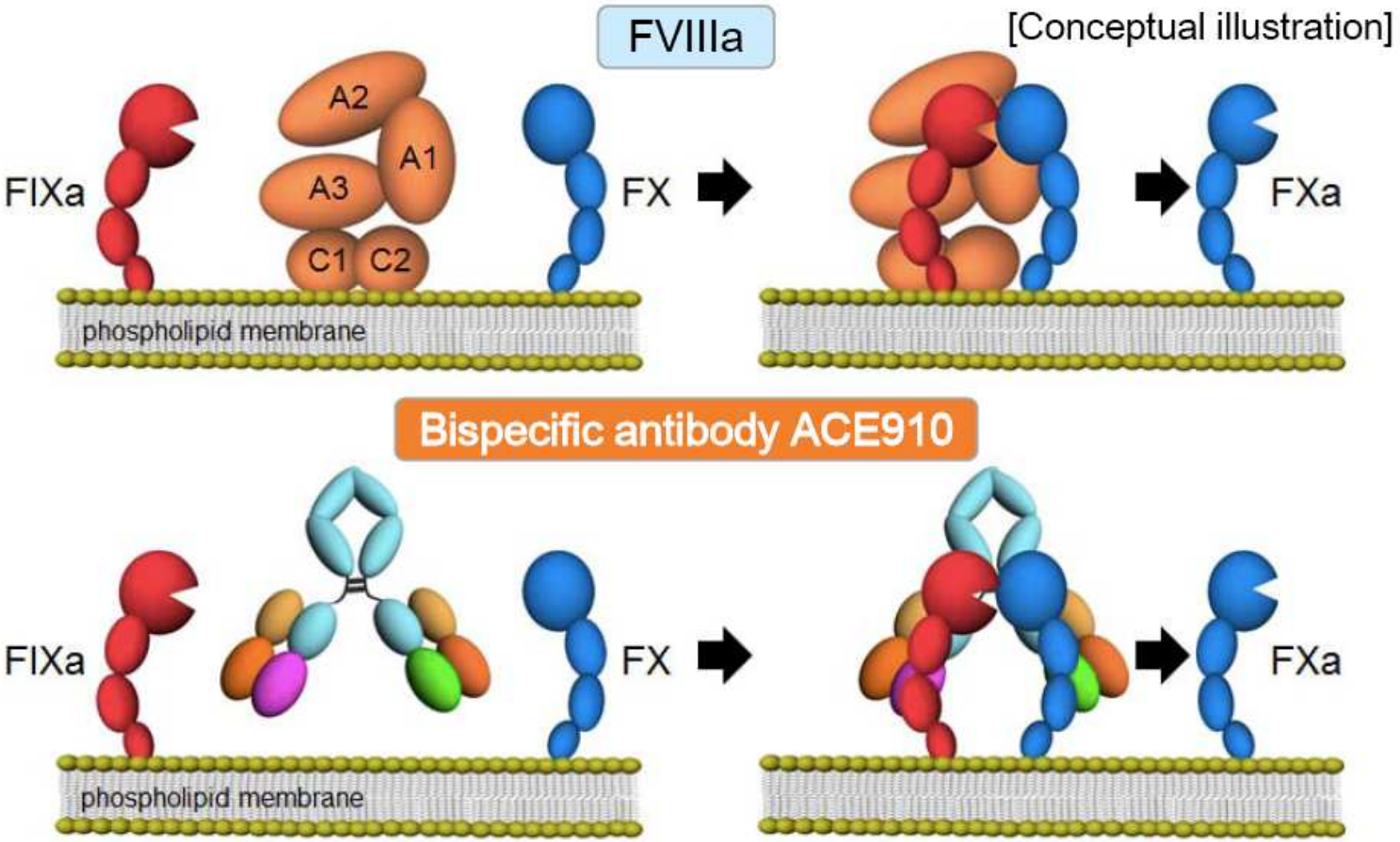
**PK & PD**

- PK no lineal. Target-mediated clearance. Típico de MoAb.
- Actividad TFPI en plasma disminuye de manera directamente relacionada a la concentración de Concizumab.
- Sin cambios clínicos en plaquetas, PT, aPTT o AT.
- Efecto procoagulante dosis dependiente: aumento niveles de dimero-D y Protrombina F1 + 2 (evidencia indirecta).
- Efecto procoagulante mayor en voluntarios sanos.

**EFICACIA**

- No datos interpretables sobre eficacia hemostática.
- Potencial para prevenir hemorragias en hemofilia A o B con o sin inhibidor, en tratamiento subcutáneo.
- Pendiente definir la ventana terapéutica de la inhibición de TFPI

# ACE910 (EMICIZUMAB)



# Potency of FVIII-mimetic activity of ACE910 in coagulable reaction

## Kinetics analysis

Method: The rate of FXa generation in the presence of ACE910 or FVIIIa was determined by FXa generation assay. The data were fitted to Michaelis-Menten equation to calculate kinetics parameters.

$K_m$: Michaelis-menten constant
$V_{max}$: Maximum velocity
$k_{cat}$: Catalytic rate constant
$k_{cat}/K_m$: Catalytic efficacy

**Table2** Kinetics parameters

| Condition | $K_m$ (μM) | $V_{max}$ (nM/min) | $k_{cat}$ (/min) | $k_{cat}/K_m$ | (x-fold) |
|---|---|---|---|---|---|
| FIXa+FX+PL | 0.0986 | 0.0257 | 0.000643 | 0.00652 | (1) |
| + ACE910 | 0.00505 | 2.88 | 2.88 | 570 | 87400 |
| + FVIIIa | 0.0195 | 126 | 126 | 6460 | 991000 |

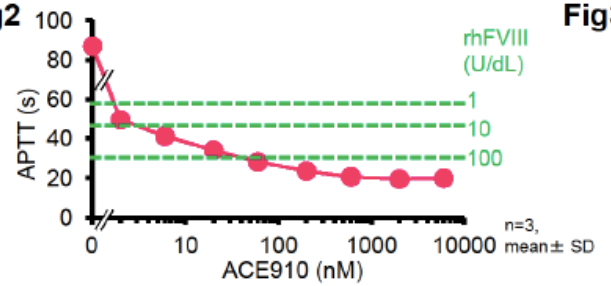
1/11

n=3, mean

## APTT assay

Method: ACE910 or rhFVIII (Kogenate FS, Bayer) was added to FVIII-deficient human plasma (George King). APTT assay was performed using Thrombocheck APTT-SLA (Sysmex).

**Fig2**

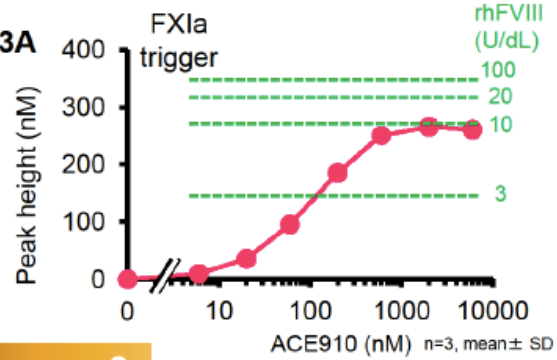



Much shorter APTT with ACE910 beyond the level achieved with 100 U/dL FVIII (=normal level) can be explained by the additional time FVIII requires to be activated by thrombin.

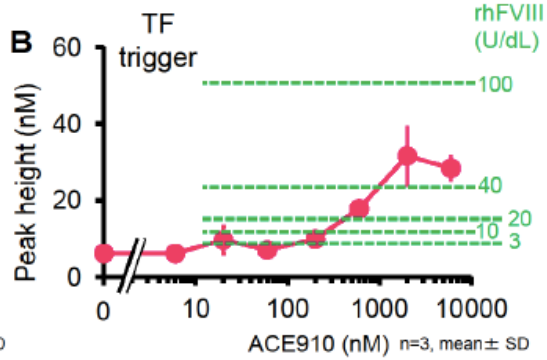
## TG assay

Method: Thrombin generation (TG) used two kinds of triggering solutions: 0.16 nM human FXIa and 20 μM PL as the FXIa trigger, and PPP-Reagent LOW (Thrombinoscope) as the TF trigger

**Fig3A**



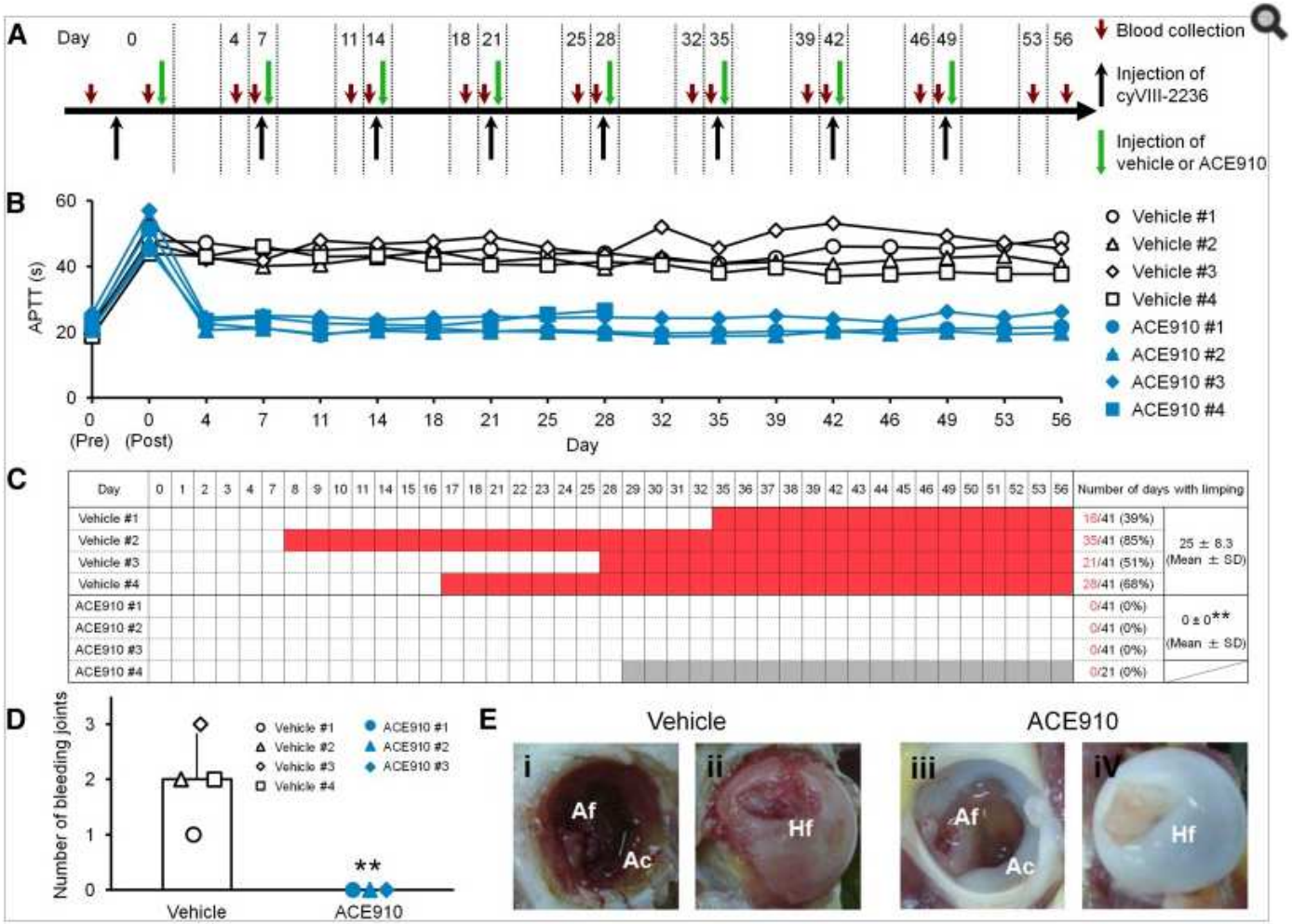

**B**




**Summary2**

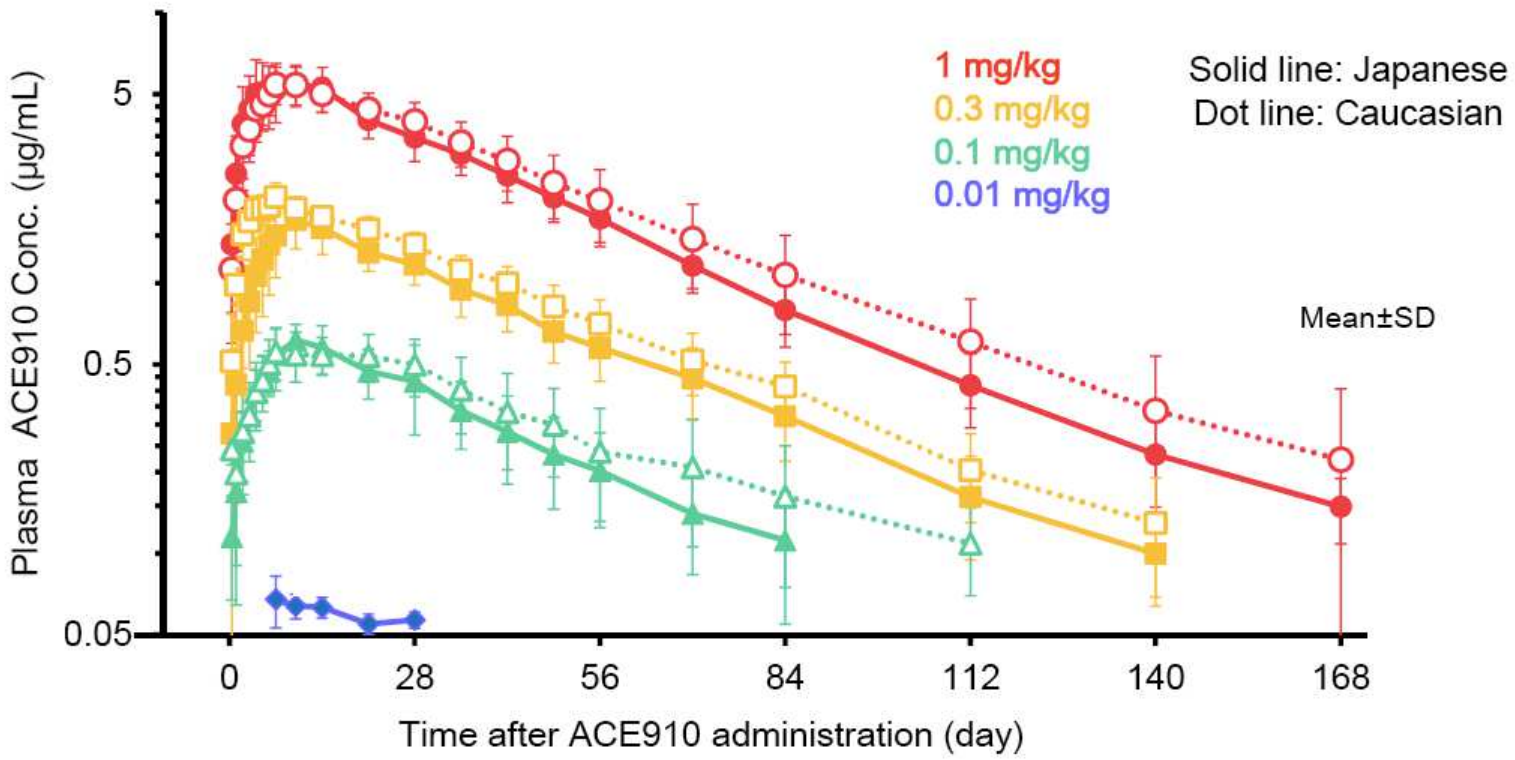
ACE910 exerted an equivalent activity to 10 U/dL or above of FVIII (Fig 3).

# EFECTO DE ACE910 EN HEMARTROS ESPONTANEO MODELO DE HEMOFILIA ADQUIRIDA EN PRIMATES




Muto A. Blood 2014; 124 (20) 3165-3171

# Concentración ACE910 en el tiempo




- Aumento en Cmax y AUC proporcional a la dosis administrada
- Vida media: 28.3 – 34.4 dias

September 2015

US FDA grants breakthrough therapy designation for Roche's investigational medicine ACE910 for people with haemophilia A with factor VIII inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Factor VIII–Mimetic Function of Humanized Bispecific Antibody in Hemophilia A

Midori Shima, M.D., Ph.D., Hideji Hanabusa, M.D., Ph.D., Masashi Taki, M.D., Ph.D., Tadashi Matsushita, M.D., Ph.D., Tetsuji Sato, M.D., Katsuyuki Fukutake, M.D., Ph.D., Naoki Fukazawa, B.Sc., Koichiro Yoneyama, M.Sc., Hiroki Yoshida, M.Sc., and Keiji Nogami, M.D., Ph.D.

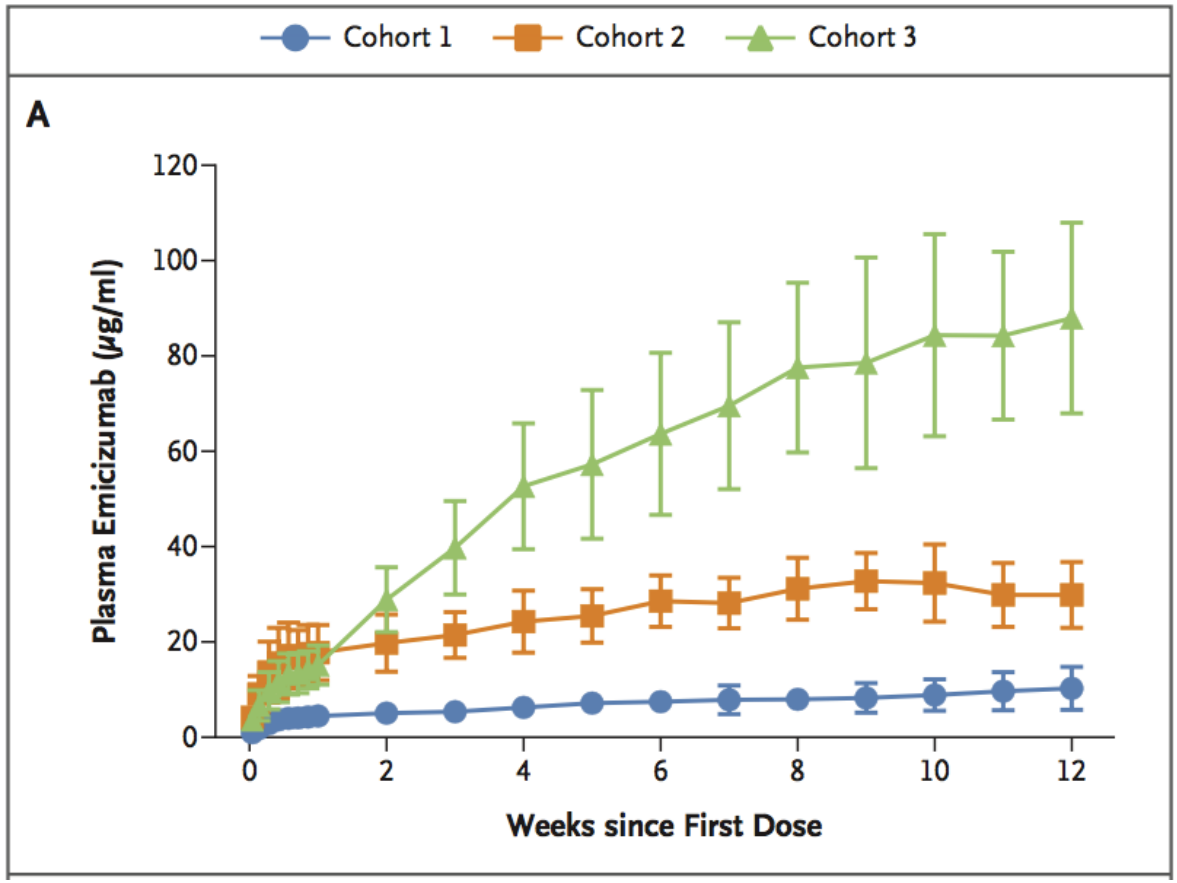
# EMICIZUMAB: PACIENTES TRATADOS

| | | C-1 cohort n=6 | C-2 cohort n=6 | C-3 cohort n=6 |
|---|---|---|---|---|
| Median age, years (min - max) | | 32 (17 - 51) | 30 (12 - 58) | 33 (12 - 58) |
| Pts age <18 years, n (%) | | 1 (16.7) | 1 (16.7) | 1 (16.7) |
| Median weight, kg (min - max) | | 60.4 (40.8 - 81.2) | 56.1 (48.1 - 81.7) | 66.0 (48.8 - 78.2) |
| Non-inhibitor pts, n (%)<br>Inhibitor pts, n (%) | | 2 (33.3)<br>4 (66.7) | 2 (33.3)<br>4 (66.7) | 3 (50.0)<br>3 (50.0) |
| ABR 6M prior to study entry, | Mean (SD)<br>Median<br>(min - max) | 37.9 (25.2)<br>32.5<br>(8.1 - 77.1) | 19.6 (9.8)<br>18.3<br>(10.1 - 38.6) | 15.9 (11.9)<br>15.2<br>(0 - 32.5) |
| Target Joint*, n (%) | | 6 (100) | 6 (100) | 3 (50.0) |

* Joint in which 3 or more spontaneous bleeds have occurred within a 6-month period.

Cohorte 1: Dosis de carga: 1 mg. Despues 0.3 mg/Kg/semana
Cohorte 2: Dosis de carga: 3 mg. Después 1 mg/Kg/semana
Cohorte 3: Dosis de carga: 3 mg. Después 3 mg/Kg/semana

# EMICIZUMAB: PK



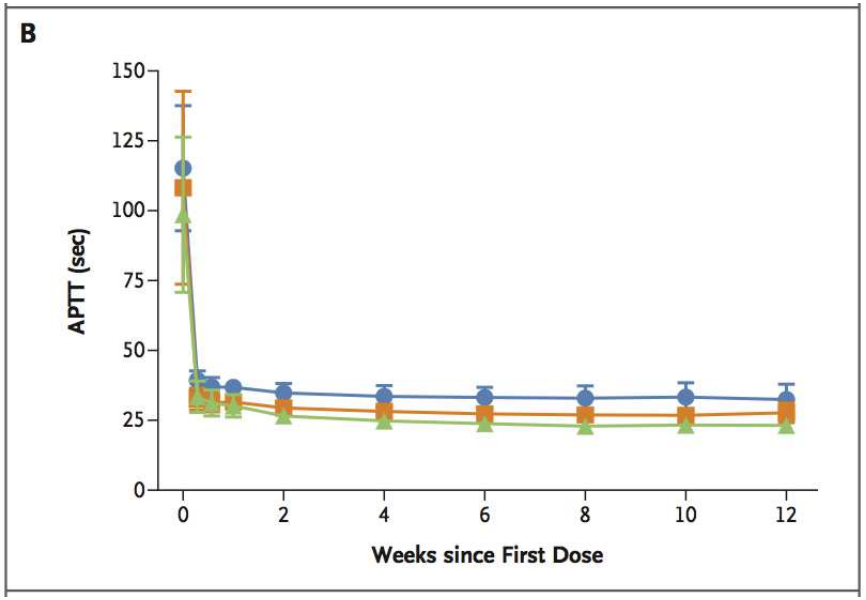

≈27 UI/dL

≈9 UI/dL

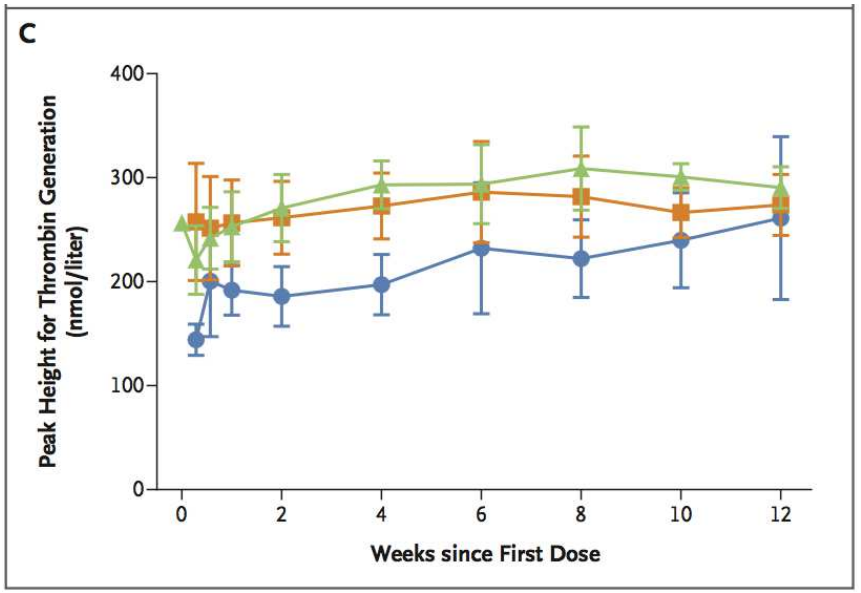
≈3 UI/dL

Factor de conversión de 0.3 para equiparar a la actividad hemostática equivalente de FVIII

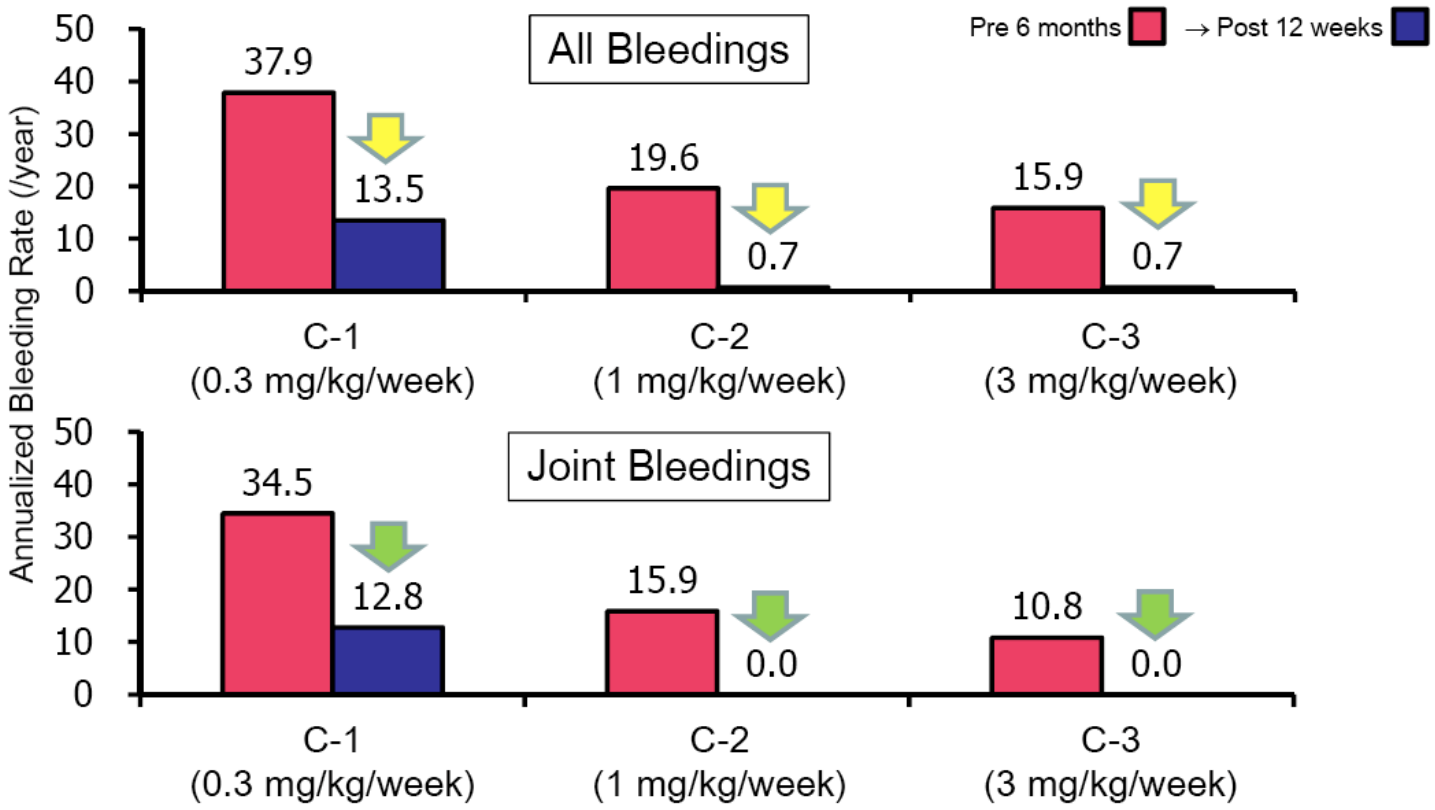
# EMICIZUMAB: TESTS DE LABORATORIO




Acortamiento APTT




Aumento en la generación de trombina




- Reducción de la tasa anual de hemorragia en los 3 grupos
- No hemorragia articular en C2 y C3

# EMICIZUMAB. CONCLUSION

**SEGURIDAD**

- ACE910 administrado sc una vez a la semana en dosis hasta 3 mg/Kg es bien tolerado
- No anti-ACE910 durante las 12 semanas del estudio.

> In conclusion, this study showed that once-weekly subcutaneous administration of emicizumab as prophylaxis is safe and has the potential to reduce or prevent bleeding episodes in patients who have severe hemophilia A with or without factor VIII inhibitors.

3mg/Kg).

HEALTH NEWS | Wed Nov 2, 2016 | 4:41pm EDT

# Adverse events in trial dent hopes for Roche hemophilia drug

Four patients have suffered serious adverse events in a clinical trial of an experimental hemophilia medicine from Roche, the Swiss group said on Wednesday, clouding prospects for its potential blockbuster product.

The problems relate to thrombosis, or blood clots, with two thromboembolic events and two cases of thrombotic microangiopathy in patients who were being treated for breakthrough bleeding in the trial of Roche's ACE910.

The drugmaker is hoping to win a slice of the $11 billion-a-year hemophilia drug market with ACE910, which represents a threat to more traditional treatments from Novo Nordisk and Shire.

"We view the news as the first blemish on ACE910's profile," |

- Based on the available details of the case and our initial assessment, we believe our current protocol guidance in the trial regarding the use of bypassing agents remains appropriate.
    - This guidance includes the recommendation to avoid the use of aPCC, if possible, as well as to use the lowest doses of approved bypassing agents in patients receiving emicizumab.

February 21, 2017 at 10:57 pm

We are saddened to share that in the past week, the EHC has been informed of the death of a person with haemophilia with inhibitors, who was on the clinical trial (HAVEN 1) with the bi-specific antibody Emicizumab.

- It is our understanding that a patient experienced a serious rectal haemorrhage (first reported SAE) and received bypassing agents, including repeated doses of activated prothrombin complex (aPCC), after which the patient developed signs of Thrombotic Microangiopathy (TMA) (second SAE).
- The preliminary assessment is that the clinical and laboratory characteristics of this case of TMA are consistent with what was observed in the two previously reported cases; however, our evaluation of the available information is ongoing.
- According to the report, treatment of the haemorrhage was complicated because the patient declined blood transfusions.

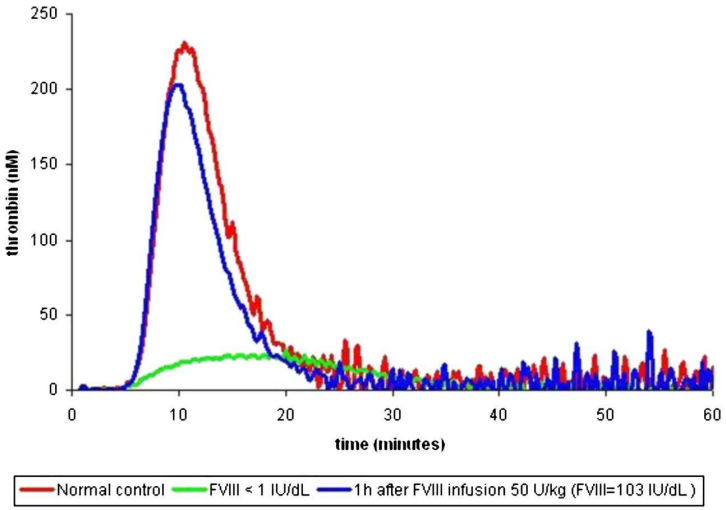
The investigator's assessment is that the cause of death was the rectal haemorrhage, and that this is not related to emicizumab.

# ESTUDIOS CLINICOS EMICIZUMAB

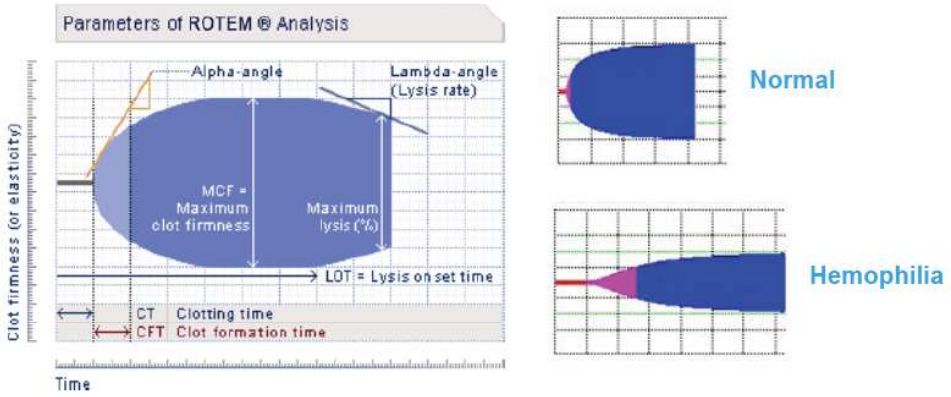
| Ensayos clínicos (Fase III) | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|
| Adolescentes/adultos con inhibidor HAVEN1 | | | | |
| Adolescentes/adultos sin inhibidor HAVEN3 | | | | |
| Niños con inhibidor HAVEN2 | | | | |
| Adolescentes/adultos con o sin Inhibidor, cada 4 semana HAVEN4 | | | | |

# MONTORIZACION

Tests globales de coagulación




TEST DE GENERACION DE TROMBINA




TROMBOELASTOGRAMA

# DOSIFICACION / INTERVALO

## TECNOLOGIA ANTI-TFPI (CONCIZUMAB)

1.000 – 3.000 ugr/Kg/ semana

## RNAsi ANTITROMBINA

50-80 mg / mes

## ANTICUERPO BIESPECI

1.5 g/Kg/ semana – 6

Comment on Uchida et al, page 1633

# Hemophilia A treatment: disruptive technology ahead

Michael Makris UNIVERSITY OF SHEFFIELD

**EN COMUN**: ADMINISTRACION SUBCUTANEA
VIDA MEDIA LARGA (HASTA 1-4 SEMANAS)
RESULTADOS PROMETEDORES EN LA REDUCCION DE LOS EPISODIOS HEMORRAGICOS.

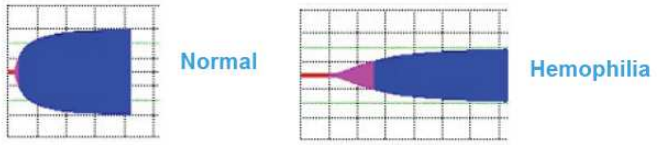
**DIFERENCIAS**: MODO DE ACCION, EFICACIA, EFECTOS SECUNDARIOS
TRATAMIENTO DE LAS HEMORRAGIAS, CIRUGIA
MONITORIZACION

**PENDIENTE CONOCER**: RESULTADOS ESAYOS FASE III
EXPERIENCIA DEL MUNDO REAL

# NUEVAS MOLECULAS CON EL POTENCIAL DE CAMBIAR EL PARADIGMA ACTUAL DEL TRATAMIENTO DE LA HEMOFILIA.


Niveles FVIII

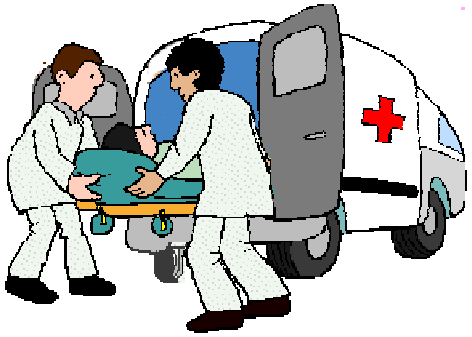
ANTES


DESPUES

COEXISTENCIA CON EL TRATAMIENTO CONVENCIONAL FVIII / FIX (?)

MAYOR COMPLEJIDAD TERAPEUTICA.



COMO INFLUIRA EL PRECIO
EN SU UTILITZACION CLÍNICA?

# CONCLUSIONES

TRACTAMIENTO ACTUAL SEGURO Y EFICAZ

NUEVAS MOLECULAS EN LOS PROXIMOS AÑOS CON EL POTENCIAL DE CAMBIAR DE MANERA SIGNIFICATIVA EL TRATAMIENTO.

SON NECESARIOS ESTUDIOS PARA EVALUAR EXTENSAMENTE:

- EFICACIA
- SEGURIDAD
- CALIDAD DE VIDA
- RELACION COSTE-BENEFICIO

OBJECTIVO DEL TRACTAMIENTO:

TRATAMIENTO MAS EFICAZ Y SEGURO Y QUE OFREZCA UNA MAYOR CALIDAD DE VIDA A LAS PERSONAS CON HEMOFILIA.

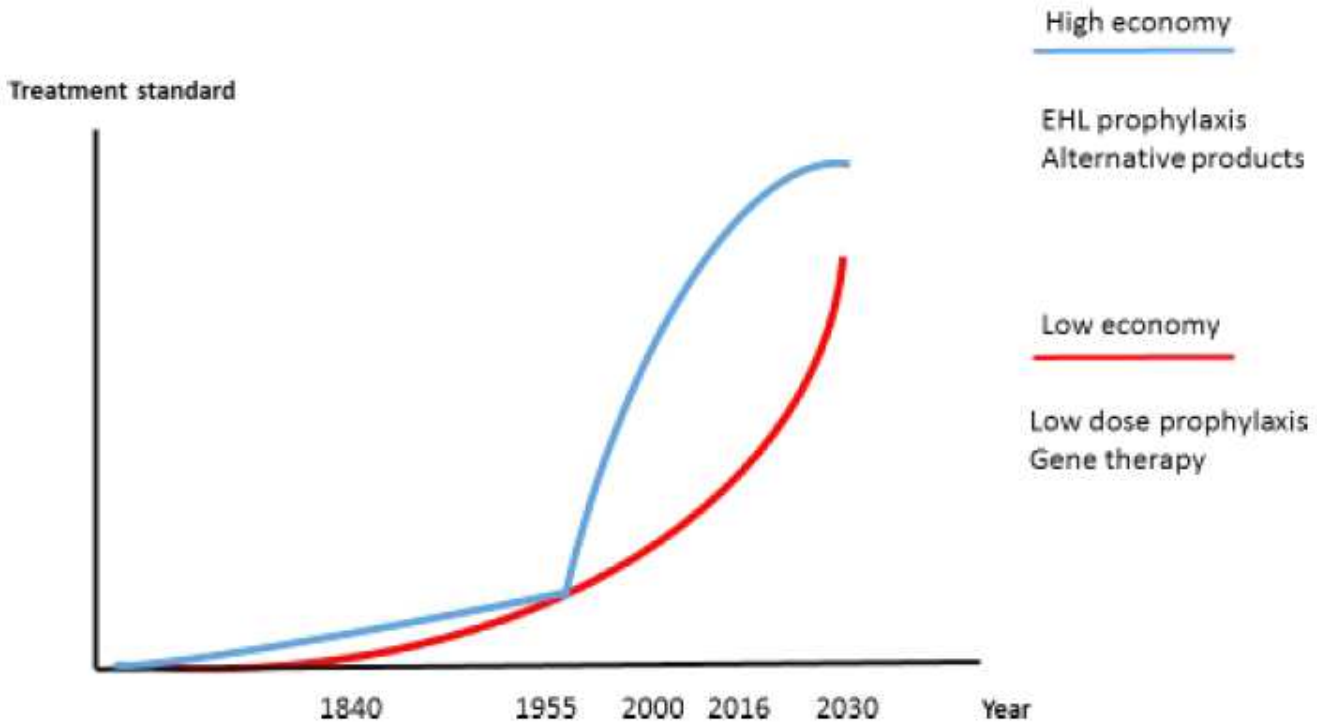
MUCHAS GRACIAS POR SU ATENCION!!!

# PROGRAMAS DE TERÀPIA GÈNICA PER HEMOFILIA

| Empresa | Indicació | Vector | Construcció | Fase projecte |
|---|---|---|---|---|
| Baxter/Asklepio/Bios | Hem B | AAV8 | FIX Padua | Fase I (2014) |
| Pfizer/Spark | Hem B | AAV8-hFIX19 | FIX Padua | Fase I (2015) |
| UniQure BV/Chiesi | Hem B | AAV5-hFIX | Wt FIX | Fase I |
| St Jude | Hem B | scAAV 2/8-LPI-hFIXco | Wt FIX | Fase II |
| Bayer/Dimension | Hem A | | FVIII | Discovery |
| BioMarin/St Jude/UCL | Hem A | BMN270 (hFVIII) | BDD FVIII | Preclinical |
| Baxter/Chatham/ReGenX | Hem A | BAX 888 (BNP-FVIII) | BDD FVIII | Discovery |
| St Jude/Royal Free Hosp | Hem A | AAV-HLP-codop-hFVIIIV3 | BDD FVIII | Preclinical |
| Emory Univ/Lentigen Ther | Hem A | Lentiviral HSC | FVIII-expressin stem cells | Preclinical |
| Biogen Idec/Fonda Tele/ Ospe San Raffaele | Hem A/B | Lentiviral | | Discovery |

# Haemophilia treatment in 2030

E. BERNTORP




*Haemophilia* (2016), 22 (Suppl. 5), 15–19

# ALN-AT3. CONCLUSION

**SEGURIDAD**

- La administración de ALN-AT3 sc (dosis única o varias dosis) es bien tolerada en voluntarios sanos (3) y en pacientes con hemofilia (6). No AE graves.

**PK & PD**

- Dosis única 30 mcg/Kg resulta en una supresión de AT de hasta 28% con una duración > 60 dias en voluntarios sanos.
- En pacientes hemofílicos el tratamiento con ALN-AT3 resulta en una supresión de AT de hasta el 70%.
- El pacientes hemofílico con mayor seguimiento tratado con 45 mcg/Kg /sem x 3 muestra un efecto durable con una supresión de AT del 54% el dia +42.

**EFICACIA**

- Con supresión de AT > 50% el pico medio de generación de trombina aumenta 112 ± 38%.
- Mejoría marcada y durable en la formación del coágulo medido por ROTEM. Paciente con mayor seguimiento: sin hemoragia durante 47 días.

Sorensen B. ASH 2014