VENTAJAS DE LOS NUEVOS TRATAMIENTOS

Mª TERESA ÁLVAREZ ROMÁN
Jefe de Sección de Hemostasia
Hospital Universitario La Paz

RECUERDO HISTÓRICO

1965 — 1970 — 1990-2000

CRIOPRECIPITADO

CONCENTRADOS PLASMÁTICOS

CONCENTRADOS RECOMBINANTES

TRATAMIENTOS DISPONIBLES

CONCENTRADOS PLASMÁTICOS

CONCENTRADOS RECOMBINANTES

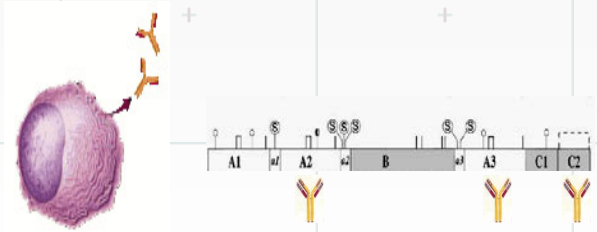
✓ ***EFICACES***

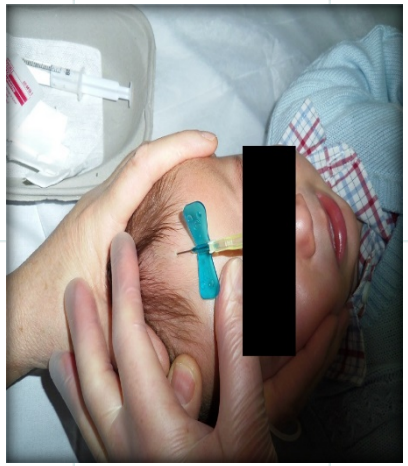
- *Antes de 1960, la edad media de fallecimiento por una hemorragia grave era de 14 años.*
- *La esperanza de vida no superaba los 27 años.*

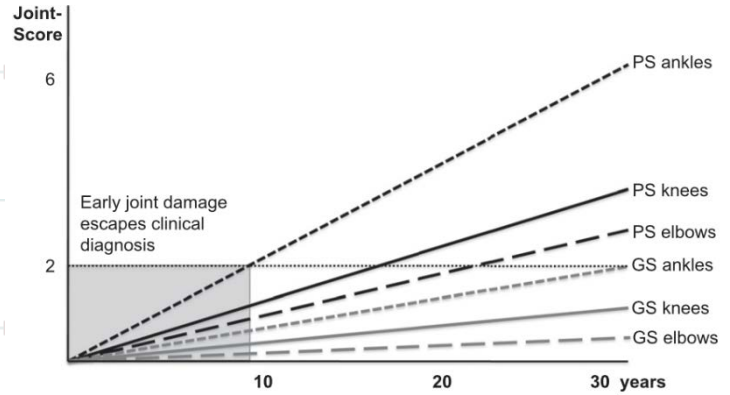
✓ ***SEGUROS***

- *En los últimos años ni el CDC, ni la OMS, ni el Instituto Carlos III, ni la EUHASS han reportado casos de patógenos emergentes en pacientes con hemofilia.*

PROBLEMAS CON LOS TRATAMIENTOS ACTUALES







Oldenburg J. Blood. 2015 Mar 26;125(13):2038-44

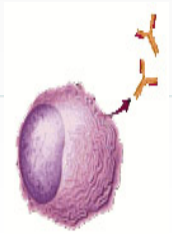
SOLUCIONES A ESTOS PROBLEMAS (I)

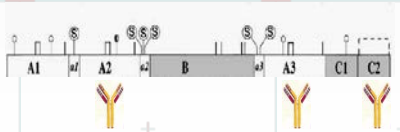
WFH 50 Years of Advancing Treatment for All
World Federation of Hemophilia

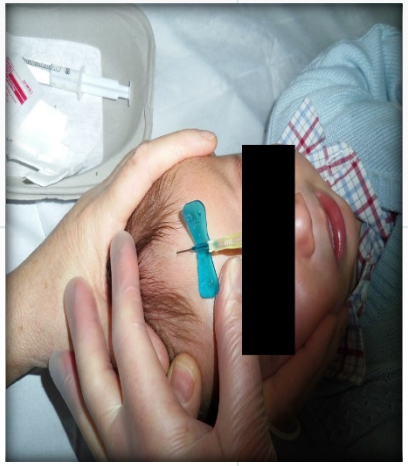
GLOBAL ALLIANCE FOR PROGRESS

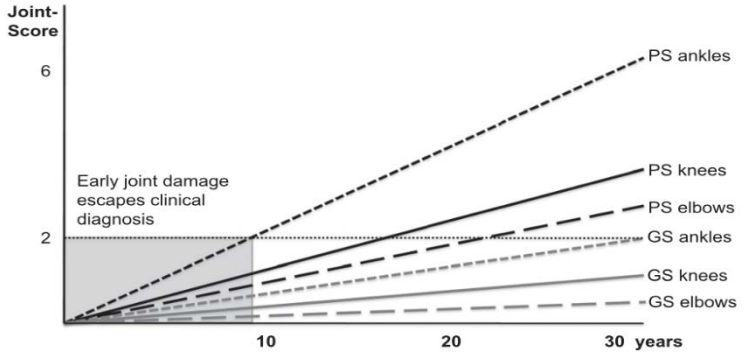
www.wfh.org

SOLUCIONES A ESTOS PROBLEMAS (II)







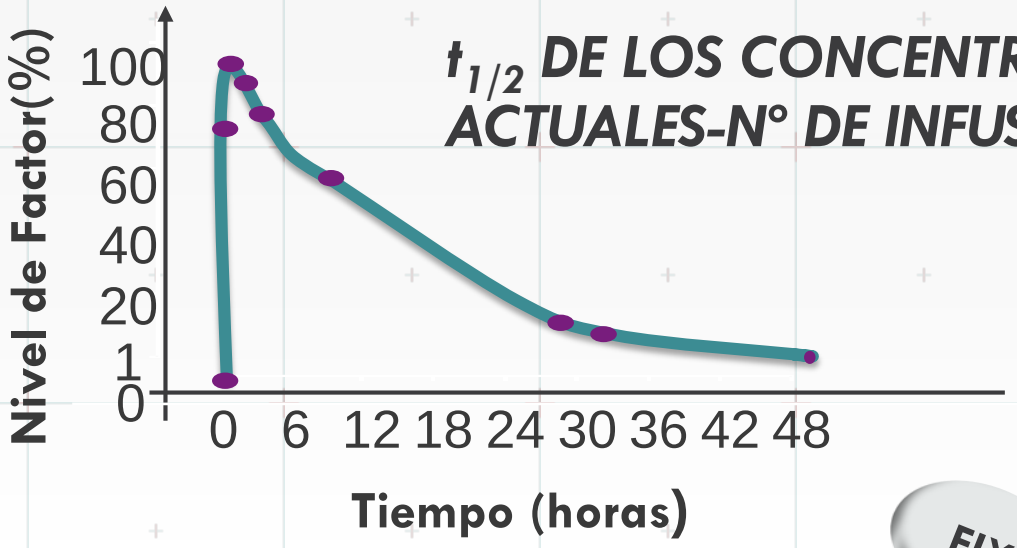


Oldenburg J. Blood. 2015 Mar 26;125(13):2038-44

- EHL

- OTRAS ALTERNATIVAS (emicizumab, Fitusiran, Anti-TFPI)

$t_{1/2}$ DE LOS CONCENTRADOS ACTUALES-N° DE INFUSIONES



FVIII

$t_{1/2}$ 8-12 horas

156-209 infusiones/año

FIX

$t_{1/2}$ 18-24 horas

104 infusiones /año

CONCENTRADOS ACTUALES VS EHL

CONCENTRADOS ACTUALES

- pdFVIII/pdFIX
- rFVIII/rFIX

→ **IGUAL PK**

NUEVOS CONCENTRADOS

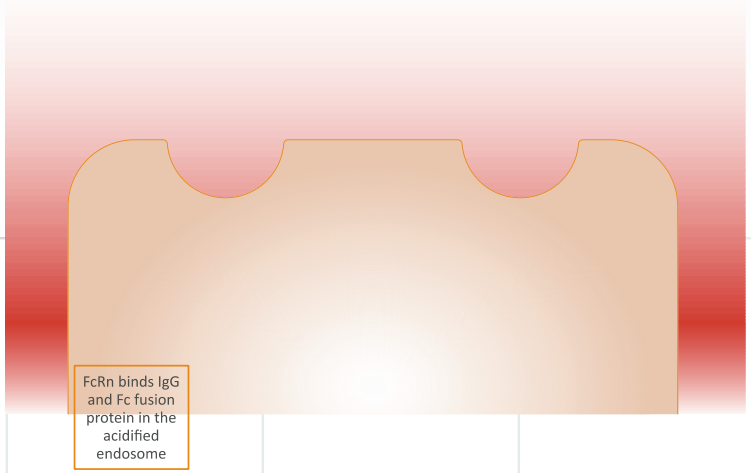
- PEG
- FP
  - Albúmina
  - Fc

→ **≠ PK**
MAYOR VIDA MEDIA

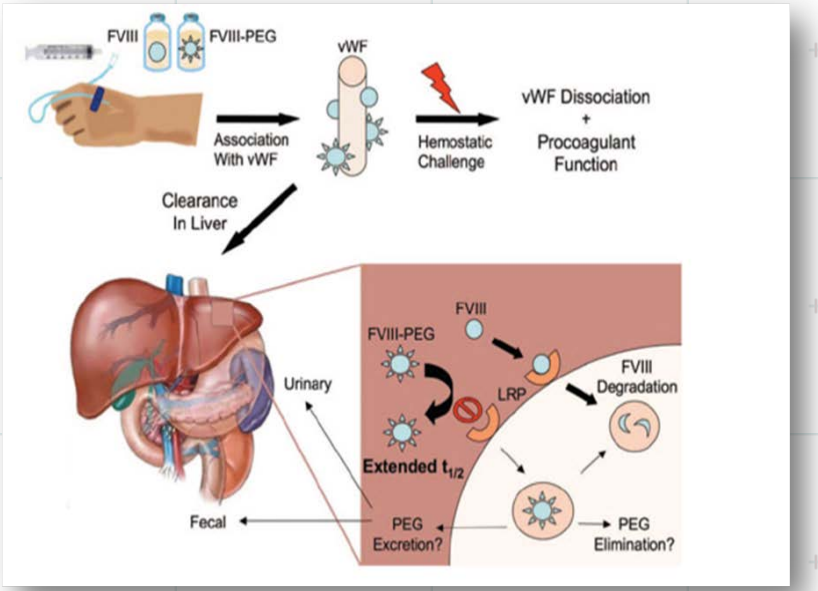
Peyvandi F Semin Thromb Haemost Feb 2015
Rath T et al. Critical Reviews in Biotechnology 2013

ESTRATEGIAS PARA PROLONGAR LA $t_{1/2}$

FP-PROTEÍNAS DE FUSIÓN



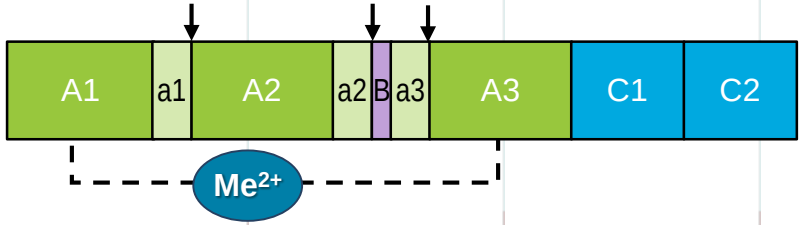
UNIÓN A MOLÉCULAS DE PEG



Roopenian DC et al. FcRn: The neonatal Fc receptor comes of age. *Nat Rev Immunol* 2007;7(9):715–725.

ESTRATEGIAS PARA PROLONGAR LA $t_{1/2}$

MODIFICACIONES EN LA MOLÉCULA



Mayor afinidad por el FVW (3 veces más que el Novoeight o el Nuwiq):

- *Disminuye la degradación, probablemente* ***menos inhibidor,*** *al disminuir la captación por las células presentadoras de antígenos.*
- ***Aumenta la $t_{1/2}$ sin añadir moléculas de PEG ni ninguna proteína de fusión.***

EHL FVIII

Product	Company	Technology	Cell line	Subjects	Mean $t^{1}/_{2}$ (h)	References
ELOCTATE	Biogen Idec	Fusion with Fc fragment of IgG1	HEK293H	Mice, dogs	13·7	Dumont *et al* (2012)
				Human, *n* = 19	18·8	Powell *et al* (2012b)
				Human, *n* = 28	19	Mahlangu *et al* (2014)
Bay 94-9027	Bayer Healthcare	Site-specific pegylation 60 kDa PEG	BHK	Mice, rabbits	18·2	Mei *et al* (2010)
				Human, *n* = 14	19	Coyle *et al* (2014)
Bax 855	Baxter	Chemical pegylation at specific lysines 20 kDa PEG	CHO	Mice, dogs, monkeys	~18	Turecek *et al* (2011)
				Human	1·4× Advate	*
N8-GP	Novo-Nordisk	Site-specific glycopegylation 40 kDa PEG-modified sialic acid	CHO	Mice, rabbits, monkeys	18 (monkeys)	Stennicke *et al* (2013)
				Dogs	16	Agersø *et al* (2012)
				Human, *n* = 26	19	Tiede *et al* (2013)
Bay 79-4980	Bayer Healthcare	PEG liposome with standard rFVIII	BHK	Mice	8·8	Pan *et al* (2009)
				Human, *n* = 26	10·8	Powell *et al* (2008)

BHK, baby hamster kidney; CHO, Chinese hamster ovary; HEK293H, human embryonic kidney 293 cells.

Collins P et al. Br J Haematol. 2015 Jun;169(6):768-76

XXI CURSO INTRODUCCIÓN A LA FARMACOTERAPIA DE LOS HEMODERIVADOS

RESULTADOS DE LOS ESTUDIOS PIVOTALES EHL FVIII

CLINICAL TRIALS AND OBSERVATIONS

Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A

Johnny Mahlangu,[1] Jerry S. Powell,[2] Margaret V. Ragni,[3] Pratima Chowdary,[4] Neil C. Josephson,[5] Ingrid Pabinger,[6] Hideji Hanabusa,[7] Naresh Gupta,[8] Roshni Kulkarni,[9] Patrick Fogarty,[10] David Perry,[11] Amy Shapiro,[12] K. John Pasi,[13] Shashikant Apte,[14] Ivan Nestorov,[15] Haiyan Jiang,[15] Shuanglian Li,[15] Srividya Neelakantan,[15] Lynda M. Cristiano,[15] Jaya Goyal,[15] Jurg M. Sommer,[15] Jennifer A. Dumont,[15] Nigel Dodd,[15] Karen Nugent,[15] Gloria Vigliani,[15] Alvin Luk,[15] Aoife Brennan,[15] and Glenn F. Pierce,[15] for the A-LONG Investigators

blood 2015 126: 1078-1085
doi:10.1182/blood-2015-03-630897 originally published online July 8, 2015

Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A

Barbara A. Konkle, Oleksandra Stasyshyn, Pratima Chowdary, David H. Bevan, Tim Mant, Midori Shima, Werner Engl, Jacqueline Dyck-Jones, Monika Fuerlinger, Lisa Patrone, Bruce Ewenstein and Brigitt Abbuehl

blood® Prepublished online June 21, 2016;
doi:10.1182/blood-2016-01-687434

Efficacy and safety of rVIII-SingleChain: results of a phase I/II multicenter clinical trial in severe hemophilia A

Johnny Mahlangu, Kazimierz Kuliczkowski, Faraizah Abdul Karim, Oleksandra Stasyshyn, Marina V. Kosinova, Lynda Mae Lepatan, Aleksander Skotnicki, Lisa N. Boggio, Robert Klamroth, Johannes Oldenburg, Andrzej Hellman, Elena Santagostino, Ross I. Baker, Kathelijn Fischer, Joan C. Gill, Stephanie P'Ng, Pratima Chowdary, Miguel A. Escobar, Claudia Djambas Khayat, Luminita Rusen, Debra Bensen-Kennedy, Nicole Blackman, Tharin Limsakun, Alex Veldman, Katie St. Ledger and Ingrid Pabinger

N8GP

ClinicalTrials.gov
A service of the U.S. National Institutes of Health
Now Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

5 studies found for: N8GP
Modify this search | How to Use Search Results

List | By Topic | On Map | Search Details

Show Display Options — Download — Subscribe to RSS

Include only open studies | Exclude studies with Unknown status

Rank	Status	Study
1	Enrolling by invitation	Safety and Efficacy of Turoctocog Alfa Pegol (N8-GP) in Previously Untreated Patients With Haemophilia A Conditions: Congenital Bleeding Disorder; Haemophilia A Intervention: Drug: turoctocog alfa pegol
2	Active, not recruiting	A Multinational, Open-Label, Non-Controlled Trial on Safety, Efficacy and Pharmacokinetics of NNC 0129-0000-1003 in Previously Treated Paediatric Patients With Severe Haemophilia A Conditions: Congenital Bleeding Disorder; Haemophilia A Intervention: Drug: turoctocog alfa pegol
3	Active, not recruiting	Evaluation of Safety and Efficacy, Including Pharmacokinetics, of NNC 0129-0000-1003 When Administered for Treatment and Prophylaxis of Bleeding in Subjects With Haemophilia A Conditions: Congenital Bleeding Disorder; Haemophilia A Intervention: Drug: turoctocog alfa pegol

BAY94-9027

ClinicalTrials.gov
A service of the U.S. National Institutes of Health
Now Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

3 studies found for: BAY 94-9027
Modify this search | How to Use Search Results

List | By Topic | On Map | Search Details

Show Display Options — Download — Subscribe to RSS

Include only open studies | Exclude studies with Unknown status

Rank	Status	Study
1	Active, not recruiting	A Trial Investigating Safety and Efficacy of Treatment With BAY94-9027 in Severe Hemophilia A Condition: Hemophilia A Intervention: Biological: BAY94-9027
2	Completed	Trial to Evaluate the Pharmacokinetics and Safety Profile of BAY94-9027 Following Single and Multiple Dose Administration Condition: Hemophilia A Intervention: Biological: BAY94-9027 + Kogenate FS (Recombinant Factor VIII, BAY14-2222)
3	Active, not recruiting	Safety and Efficacy of BAY94-9027 in Previously Treated Male Children With Haemophilia A Condition: Hemophilia A Intervention: Biological: BAY94-9027

XXI CURSO INTRODUCCIÓN A LA FARMACOTERAPIA DE LOS HEMODERIVADOS

EHL FVIII APROBADOS POR LA EMA

'Elocta' (Sobi) ha obtenido la aprobación de reembolso en España y ya está disponible en varios mercados de UE

03.10.16 | 13:56h. **EUROPA PRESS | MADRID** Compartir 0 Twittear correo

Efmoroctocog alfa, registrado por Sobi con el nombre de 'Elocta', ha recibido la aprobación de reembolso en España, estando ya disponible en los mercados del Reino Unido, Francia, Italia, Alemania, Suecia, Dinamarca, Noruega, Suiza, Holanda, Eslovenia y en la República de Irlanda.

Se trata del primer factor VIII de coagulación recombinante humano, proteína de fusión Fc (rFVIIIFc) con una vida media extendida, para el tratamiento de la hemofilia A. "Esta aprobación supone un importante hito para nuestro producto, pues es el último de los cinco mercados principales de la Unión Europea donde ya está disponible. Nuestros esfuerzos deben focalizarse en asegurar el acceso a las personas con hemofilia A que viven en estos países y también en el resto del territorio de Sobi", ha declarado el CEO y presidente de Sobi, Geoffrey McDonough.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2016
EMA/699392/2016
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

Afstyla
Ionoctocog alfa

CSL Behring
Biotherapies for Life™

Home > News Room > News Releases> All Releases

AFSTYLA®, for Haemophilia A, Receives European Commission Approval

MARBURG, Germany — 09 January 2017

- *CSL Behring's* **AFSTYLA** *is the first and only single-chain therapy for haemophilia A*
- *The therapy has been specifically designed for greater molecular stability and duration of action through strong affinity to von Willebrand factor (VWF)*
- **AFSTYLA** *has been shown to offer excellent haemostatic efficacy in both prophylaxis and on-demand treatment, and the option of twice weekly dosing with low unit consumption*
- *European Commission approval of* **AFSTYLA** *delivers on CSL Behring's promise to develop and provide patients in the European Union with specialty biotherapies that help them lead full lives*

Global biotherapeutics leader CSL Behring announced today that the European Commission has granted marketing authorisation for **AFSTYLA®** [Recombinant Human Coagulation Factor VIII, Single Chain] for children and adults with haemophilia A. **AFSTYLA**, CSL Behring's novel, recombinant factor VIII therapy, is the first and only single-chain product for haemophilia A. It is specifically designed for protection from bleeds with two or three times weekly dosing and low unit consumption at both dosing regimens. In clinical trials, **AFSTYLA** demonstrated a strong safety profile with no inhibitors observed in previously treated patients undergoing prophylaxis.

AFSTYLA is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). **AFSTYLA** can be used for all age groups.

"European Commission approval of **AFSTYLA**, an innovative and effective haemophilia A therapy, delivers on CSL Behring's promise to develop and provide novel products that have the potential to improve patients' lives," said Dr. Andrew Cuthbertson, Chief Scientific Officer and R&D Director, CSL Limited. "We are very excited to add this treatment to our industry-leading portfolio of coagulation therapies and look forward to the positive impact **AFSTYLA** can have on haemophilia A patients in the European Union."

XXI CURSO INTRODUCCIÓN A LA FARMACOTERAPIA DE LOS HEMODERIVADOS

¿CUÁNTO HEMOS CONSEGUIDO PROLONGAR LA $t_{1/2}$ EN EL CASO DEL FVIII?

blood®
2016 128: 2007-2016
doi:10.1182/blood-2016-04-713289 originally published online September 1, 2016

Life in the shadow of a dominant partner: the FVIII-VWF association and its clinical implications for hemophilia A

Steven W. Pipe, Robert R. Montgomery, Kathleen P. Pratt, Peter J. Lenting and David Lillicrap

$t_{1/2}$ DE LOS DIFERENTES EHL

Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2016), **22** (Suppl. 5), 25–30 DOI: 10.1111/hae.13028

ORIGINAL ARTICLE

Extended half-life clotting factor concentrates: results from published clinical trials

G. YOUNG* and J. N. MAHLANGU†
*Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA; and †Haemophilia Comprehensive Care Centre, Charlotte Maxeke Johannesburg Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand and National Health Laboratory Service, Johannesburg, South Africa

$t_{1/2}$ 1.4-1.6

	BAY94-9027	BAX855	rFVIIIFc	N8-GP
Minimum-Maximum half-life, h	13.7–28.1	14.3–16.0	17.1–21.1	11.6–27.3
Mean half-life, h	18.7	14.3	19.0	19.0
Fold increase in half-life	1.4	1.4	1.5	1.6

14.1-14.2
14.1
1.4

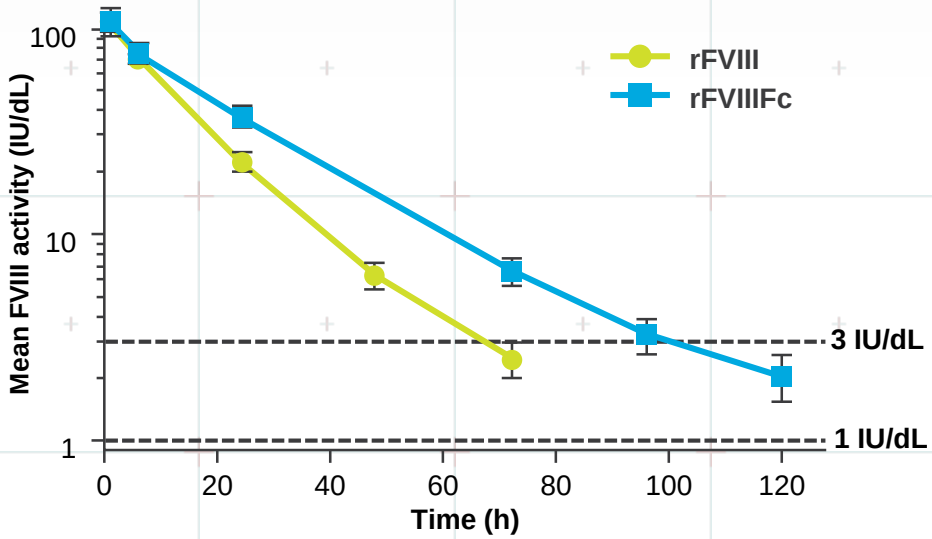
Single Chain

XXI CURSO INTRODUCCIÓN A LA FARMACOTERAPIA DE LOS HEMODERIVADOS

¿QUÉ NOS APORTARÁN LOS EHL EN LA PRÁCTICA CLÍNICA HABITUAL?

- ¿SERÁN MÁS EFICACES?
- ¿REDUCIRÁN EL NÚMERO DE INFUSIONES?
- ¿REDUCIRÁN EL CONSUMO?
- ¿REDUCIRÁN LA TASA DE INHIBIDORES?

¿SERÁN MÁS EFICACES?



Comparado con rFVIII, rFVIIIFc muestra un promedio:

- **Un aclaramiento 33% menor** (2.0 versus 3.0 mL/h/kg*†)
- **Un 56% más de AUC** (51.2 versus 32.9 IU x h/dL per IU/kg*†)
- **Un aumento de $t_{1/2}$ 1.5 veces más** (19.0 versus 12.4 hrs†)
- **1.5 veces más tiempo con niveles entre 1 y 3 IU/dL (%)**

- *Mahlangu et al. Blood 2014*
- *Mahlangu et al. Blood 2014. Supplementary Information 3*
- *Shapiro et al. J Thromb Haemost 2014*

EFICACIA EN PROFILAXIS

	ELOCTA	AFSTYLA	ADYNOVI
ABR	1.6	1.14	1.9

	ELOCTA (P. personalizada)	AFSTYLA (2 ó 3 v/s)	ADYNOVI (2 v/semana)
CERO SANGRADOS	45%	43%	39.9%

EFICACIA A DEMANDA

	ELOCTA	AFSTYLA	ADYNOVI
1-2 infusiones para parar sangrado	97.7%	93.5%	95.9%

EFICACIA EN CIRUGÍA

	ELOCTA (N: 8 cirugías)	AFSTYLA (16 cirugías)	ADYNOVI (15 cirugías)
Excelente	88% (12% buena)	94%	95% (6% buena)

¿REDUCIRÁN EL NÚMERO DE INFUSIONES?

CLINICAL TRIALS AND OBSERVATIONS

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blood
2015 126: 1078-1085
doi:10.1182/blood-2015-03-630897 originally published online July 8, 2015

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blood
Prepublished online June 21, 2016;
doi:10.1182/blood-2016-01-687434

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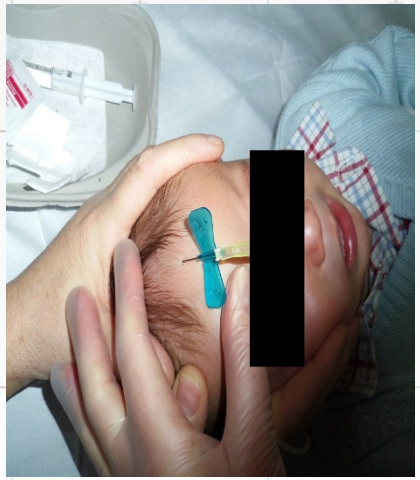
Los ensayos clínicos muestran una reducción de al menos una infusión a la semana sin comprometer su eficacia.

XXI CURSO INTRODUCCIÓN A LA FARMACOTERAPIA DE LOS HEMODERIVADOS



Nº DE INFUSIONES CON LOS SHL VS EHL FVIII

XXI CURSO INTRODUCCIÓN A LA FARMACOTERAPIA DE LOS HEMODERIVADOS

¿REDUCIRÁN EL CONSUMO?

Journal of Thrombosis and Haemostasis, **14**: 2141–2147 DOI: 10.1111/jth.13440

ORIGINAL ARTICLE

Predicting the outcomes of using longer-acting prophylactic factor VIII to treat people with severe hemophilia A: a hypothetical decision analysis

A. H. MINERS,* S. KRISHNAN† and K. J. PASI‡§

**Department of Health Services Research, London School of Hygiene and Tropical Medicine; †Biogen, Cambridge, MA, USA; ‡Barts and The London School of Medicine and Dentistry; and §The Royal London Hospital, London, UK*

To cite this article: Miners AH, Krishnan S, Pasi KJ. Predicting the outcomes of using longer-acting prophylactic factor VIII to treat people with severe hemophilia A: a hypothetical decision analysis. *J Thromb Haemost* 2016; **14**: 2141–7.

XXI CURSO INTRODUCCIÓN A LA FARMACOTERAPIA DE LOS HEMODERIVADOS

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*Department of Health Services Research, London School of Hygiene and Tropical Medicine; †Biogen, Cambridge, MA, USA; ‡Barts and The London School of Medicine and Dentistry; and §The Royal London Hospital, London, UK

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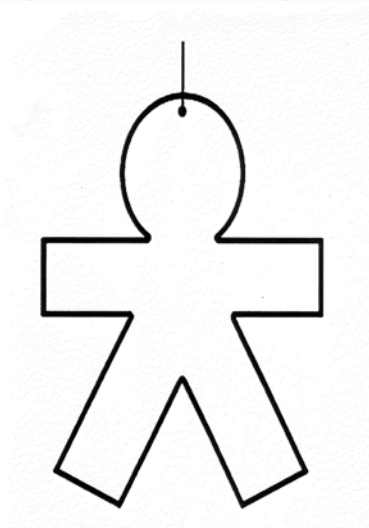


Hemofilia A grave con 30 años de edad

rFVIII
33.7 UI/kg cada 2.5 días

rFVIIIFc
42.7 UI/kg cada 3.5 días

Comparación para mantener niveles valle de FVIII >1%, espaciando las infusiones de rFVIIIFc

Scenario	Inputs					Outcomes		
	FVIII product	Half-life (h)	Time between infusions (h)	Dose per infusion (IU kg^{-1})	Adherence rate (%)	Total bleeds per year	Total FVIII/ year (× 10^3 IU)	Price factor†
Base case	rFVIII	12.4	56	33.75	83	1.64	420	1.18
	rFVIIIFc	19.0	84	42.7		1.56	350	
Increased adherence with rFVIIIFc	rFVIII	12.4	56	33.75	83	1.64	420	1.19
	rFVIIIFc	19.0	84	42.7	**90**	1.41	350	
Shorter rFVIII half-life	rFVIII	**10.4**	56	33.75	83	1.86	420	1.19
	rFVIIIFc	19.0	84	42.7		1.56	350	
Shorter rFVIIIFc half-life	rFVIII	12.4	56	33.75	83	1.64	420	1.18
	rFVIIIFc	**17.1**	84	42.7		1.70	350	
Once-weekly rFVIIIFc dose	rFVIII	12.4	56	33.75	83	1.64	420	1.33
	rFVIIIFc	19.0	**168**	**75**		3.29	320	
rFVIII every other day with smaller doses	rFVIII	12.4	**48**	**25**	83	1.53	360	1.02
	rFVIIIFc	19.0	84	42.7		1.56	350	
Smaller FVIII doses	rFVIII	12.4	56	30	83	1.67	370	1.05
	rFVIIIFc	19.0	84	42.7		1.56	350	
Higher rFVIII doses	rFVIII	12.4	56	**35**	83	1.63	430	1.23
	rFVIIIFc	19.0	84	42.7		1.56	350	
Both FVIIIs more frequently with smaller doses	rFVIII	12.4	**48**	**20**	83	1.642	290	0.94
	rFVIIIFc	19.0	**56**	**25**		1.25	310	

rFVIII, recombinant factor VIII; rFVIIIFc, recombinant factor VIII Fc fusion protein. *Values in bold represent changes from the base case scenario. †Values represent the multiplication factor of the price of rFVIIIFc compared with the price of FVIII, which may exactly match the consumption values due to rounding.

Journal of Thrombosis and Haemostasis, **14**: 2141–2147 DOI: 10.1111/jth.13440

ORIGINAL ARTICLE

Predicting the outcomes of using longer-acting prophylactic factor VIII to treat people with severe hemophilia A: a hypothetical decision analysis

A. H. MINERS,* S. KRISHNAN† and K. J. PASI‡§
*Department of Health Services Research, London School of Hygiene and Tropical Medicine; †Biogen, Cambridge, MA, USA; ‡Barts and The London School of Medicine and Dentistry; and §The Royal London Hospital, London, UK

To cite this article: Miners AH, Krishnan S, Pasi KJ. Predicting the outcomes of using longer-acting prophylactic factor VIII to treat people with severe hemophilia A: a hypothetical decision analysis. *J Thromb Haemost* 2016; **14**: 2141–7.

Essentials

- No randomized trials have compared long-acting factor VIII (FVIII) with currently used products.
- A comparison was undertaken using a decision model to predict FVIII use and number of bleeds.
- In the base case, longer acting FVIII reduced factor use by 17% while resulting in similar bleeds.
- The value of longer acting FVIII will be largely determined by existing regimens and unit price.

¿REDUCIRÁN LA TASA DE INHIBIDORES?

Perfil de inmunogenicidad se encontraron:

- Menos epítopes derivados de AFSTYLA™ que de FL-rFVIII (43 vs 68 para DR; 14 vs 27 para DP y 20 vs 20 para DQ).

- AFSTYLA™ presentaba menos epítopes capaces de generar una respuesta inmune que FL-rFVIII y que otros BDD-rFVIII.

- Además se observó que la captación del BDD-rFVIII (incluyendo el AFSTYLA™) por las células dendríticas era menor que el FL-rFVIII, debido a la fuerte unión del AFSTYLA ™ al FVW.

En este aspecto concluyen que AFSTYLA™ es menos inmunogénica que los concentrados con los que se comparó.

XXI CURSO INTRODUCCIÓN A LA FARMACOTERAPIA DE LOS HEMODERIVADOS

¿REDUCIRÁN LA TASA DE INHIBIDORES?

Published in final edited form as:
Cell Immunol. 2016 March ; 301: 30–39. doi:10.1016/j.cellimm.2015.12.008.

Recombinant factor VIII Fc (rFVIIIFc) fusion protein reduces immunogenicity and induces tolerance in hemophilia A mice

Sriram Krishnamoorthy[a,*], **Tongyao Liu**[a], **Douglas Drager**[a], **Susannah Patarroyo-White**[a], **Ekta Seth Chhabra**[a], **Robert Peters**[a], **Neil Josephson**[b], **David Lillicrap**[c], **Richard S. Blumberg**[d], **Glenn F. Pierce**[a], and **Haiyan Jiang**[a,*]

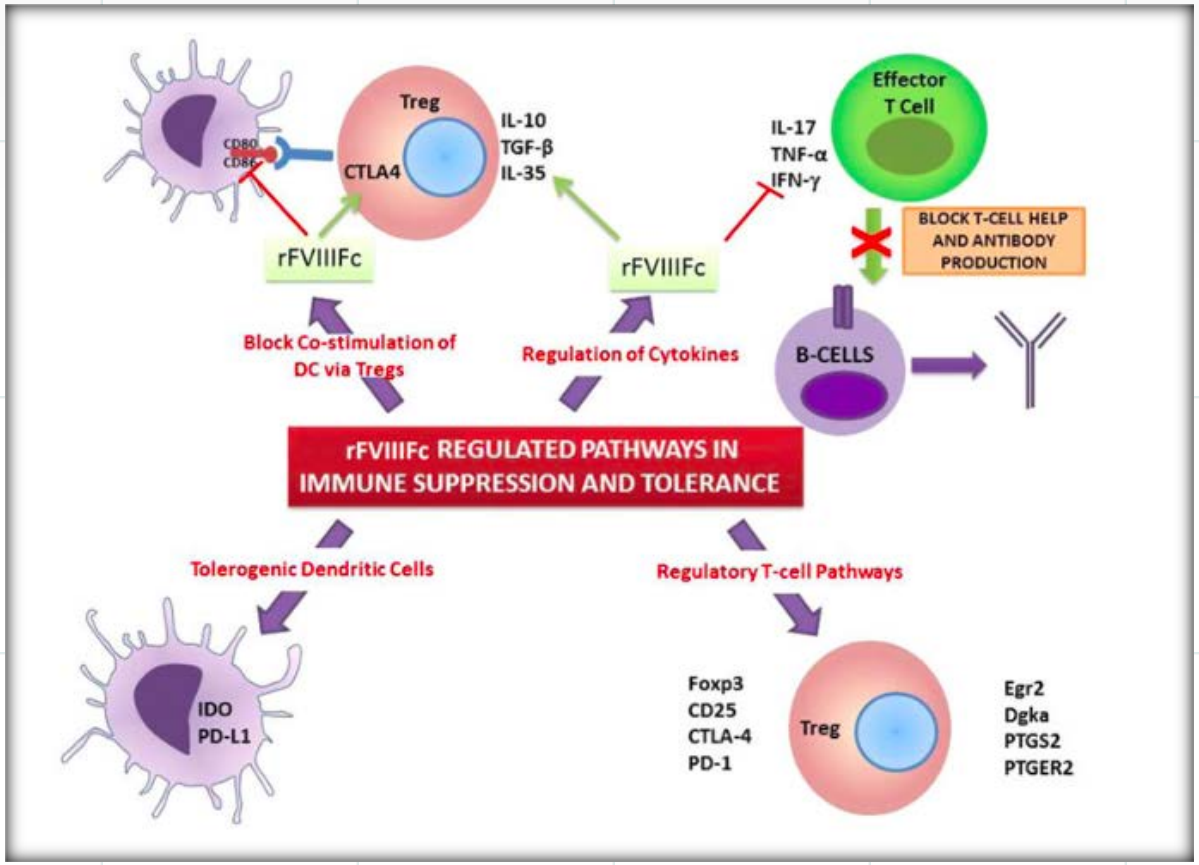
[a]Hematology Research, Biogen, 115 Broadway, Cambridge, MA 02142, United States

[b]Division of Hematology, University of Washington School of Medicine, Puget Sound Blood Center, Seattle, WA 98104, United States

[c]Department of Pathology and Molecular Medicine, Queen's University, Kingston, Canada

[d]Division of Gastroenterology, Hepatology and Endoscopy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

¿REDUCIRÁN LA TASA DE INHIBIDORES?



EHL DE FIX

Product	Company	Technology	Cell line	Subjects	Mean t½ (h)	References
rIX-FP	CSL Behring	Fusion to recombinant albumin	CHO	Dogs, monkeys	42·2 (monkeys)	Nolte *et al* (2012)
				Human, *n* = 25	~92	Shapiro *et al* (2012)
				Human, *n* = 17	95	Lissitchkov *et al* (2013)
Alprolix	Biogen Idec	Fusion with Fc fragment of IgG1	HEK293H	Mice, dogs, monkey	47 (monkeys)	Peters *et al* (2010)
				Human, *n* = 14	56·7	Shapiro *et al* (2012)
				Human, *n* = 22	82·1	Powell *et al* (2013)
N9-GP	Novo-Nordisk	Site-specific pegylation 40 kDa-PEG	CHO	Mice, dogs, mini-pig	76 (mini-pig)	Østergaard *et al* (2011)
				Human, *n* = 15	93	Negrier *et al* (2011)

CHO, Chinese hamster ovary; HEK293H, human embryonic kidney 293 cells.

Collins P et al. Br J Haematol. 2015 Jun;169(6):768-76

XXI CURSO INTRODUCCIÓN A LA FARMACOTERAPIA DE LOS HEMODERIVADOS

RESULTADOS DE LOS ESTUDIOS PIVOTALES EHL FIX

blood®
2016 127: 1761-1769
doi:10.1182/blood-2015-09-669234 originally published online January 11, 2016

Long-acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial

Elena Santagostino, Uri Martinowitz, Toshko Lissitchkov, Brigitte Pan-Petesch, Hideji Hanabusa, Johannes Oldenburg, Lisa Boggio, Claude Negrier, Ingrid Pabinger, Mario von Depka Prondzinski, Carmen Altisent, Giancarlo Castaman, Koji Yamamoto, Maria-Teresa Álvarez-Roman, Christine Voigt, Nicole Blackman and Iris Jacobs

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Study of Recombinant Factor IX Fc Fusion Protein in Hemophilia B

Jerry S. Powell, M.D., K. John Pasi, M.B., Ch.B., Ph.D., Margaret V. Ragni, M.D., M.P.H., Margareth C. Ozelo, M.D., Ph.D., Leonard A. Valentino, M.D., Johnny N. Mahlangu, M.D., M.Med., Neil C. Josephson, M.D., David Perry, M.D., Ph.D., Marilyn J. Manco-Johnson, M.D., Shashikant Apte, M.D., Ross I. Baker, M.D., Godfrey C. Chan, M.D., Nicolas Novitzky, M.D., Ph.D., Raymond S. Wong, M.D., Snejana Krassova, M.D., Geoffrey Allen, M.D., Haiyan Jiang, Ph.D., Alison Innes, B.Sc., Shuanglian Li, M.D., Ph.D., Lynda M. Cristiano, M.D., Jaya Goyal, Ph.D., Jurg M. Sommer, Ph.D., Jennifer A. Dumont, Ph.D., Karen Nugent, M.Sc., Gloria Vigliani, M.D., Aoife Brennan, M.B., B.Ch., Alvin Luk, Ph.D., and Glenn F. Pierce, M.D., Ph.D., for the B-LONG Investigators

ABSTRACT

BACKGROUND
Prophylactic factor replacement in patients with hemophilia B improves outcomes but requires frequent injections. A recombinant factor IX Fc fusion protein (rFIXFc) with a prolonged half-life was developed to reduce the frequency of injections required.

METHODS
We conducted a phase 3, nonrandomized, open-label study of the safety, efficacy, and pharmacokinetics of rFIXFc for prophylaxis, treatment of bleeding, and perioperative hemostasis in 123 previously treated male patients. All participants were 12 years of age or older and had severe hemophilia B (endogenous factor IX level of ≤2 IU per deciliter,

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Pierce at Biogen Idec, 225 Binney St., Cambridge, MA 02142, or at glenn.pierce@biogenidec.com.

This article was published on December 4, 2013, at NEJM.org.

N Engl J Med 2013;369:2313-23.
DOI: 10.1056/NEJMoa1305074

blood®
2014 124: 3880-3886
doi:10.1182/blood-2014-05-573055 originally published online September 26, 2014

Recombinant long-acting glycoPEGylated factor IX in hemophilia B: a multinational randomized phase 3 trial

Peter W. Collins, Guy Young, Karin Knobe, Faraizah Abdul Karim, Pantep Angchaisuksiri, Claus Banner, Türkiz Gürsel, Johnny Mahlangu, Tadashi Matsushita, Eveline P. Mauser-Bunschoten, Johannes Oldenburg, Christopher E. Walsh and Claude Negrier

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SCIENCE MEDICINES HEALTH

EHL FIX

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[Coagulation Factor IX (Recombinant), Fc Fusion Protein]

COMPRATIVA DE PK DE LOS DIFERENTES EHL FIX

$t_{1/2}$ 3.8 veces más (2.4-4.8)

	rFIXFc	rFIX-FP	N9-GP
Mean half-life for EHL product (number of patients)	82.1 (n = 22)	102 (n = 46)	96.25 (n = 7)
Mean half-life for standard rFIX (number of patients)	33.8 (n = 22)	24.2 (n = 8)	19.3 (n = 7)
EHL-rFIX to SHL-rFIX ratio	2.4-fold	4.2 fold	4.8-fold

	rFIXFc	rFIX-FP	N9-GP	SHL-FIX
Dose used, IU kg^{-1}	50	50	40	50
Area under the curve (AUC), h-IU dL^{-1}	3664	7176	14 130	548
Clearance. mL kg^{-1}	0.74	0.77	0.42	8.62
Incremental recovery, IU dL^{-1} IU^{-1} kg^{-1}	0.92	1.27	2	0.084

Young G et al. Haemophilia 2016, 22 (Suppl. 5), 25-30

¿QUÉ NOS APORTARÁN LOS EHL DE FIX EN LA PRÁCTICA CLÍNICA HABITUAL?

- ¿SERÁN MÁS EFICACES?
- ¿REDUCIRÁN EL NÚMERO DE INFUSIONES?
- ¿REDUCIRÁN EL CONSUMO?
- ¿REDUCIRÁN LA TASA DE INHIBIDORES?

¿SERÁN MÁS EFICACES?

	rIXFc 50 UI/kg	rIX-FP 50 UI/kg	N9GP 40 UI/Kg	SHL-FIX
AUC (UI.h/dl)	3664	7176	14130	548
Aclaramiento (mL/kg)	0.74	0.77	0.42	8.62
IVR	0.92	1.27	2	0.084

Mayor AUC menos sangrados subclínicos y mayores niveles valle menos sangrados espontáneos.

¿SERÁN MÁS EFICACES?

	rFIXFc		rFIX-FP		N9-GP	
Dose, IU kg^{-1}	50 IU kg^{-1}	100 IU kg^{-1}	40 IU kg	75 IU kg^{-1}	10 IU kg^{-1}	40 IU kg^{-1}
Dosing frequency, days	Every 7 days	Every 10 days	Every 7 days	Every 14 days	Every 7 days	Every 7 days
Number of participants	61	26	40	21	30	29
Annualized bleeding rate, median (IQR)	3.0 (1.0, 4.4)	1.4 (0.0, 3.4)	0.0 (0.0, 1.87)	1.08 (0.0, 2.7)	2.93 (0.9, 6.0)	1.0 (0.0, 4.0)
Number of injections required for bleed resolution	1–2		1–2		1–2	
Overall Haemostatic efficacy of products, %	97.2		96.7		97.1	

Young G et al. Haemophilia 2016, 22 (Suppl. 5), 25-30

Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2016), **22**, e259–e266 DOI: 10.1111/hae.12972

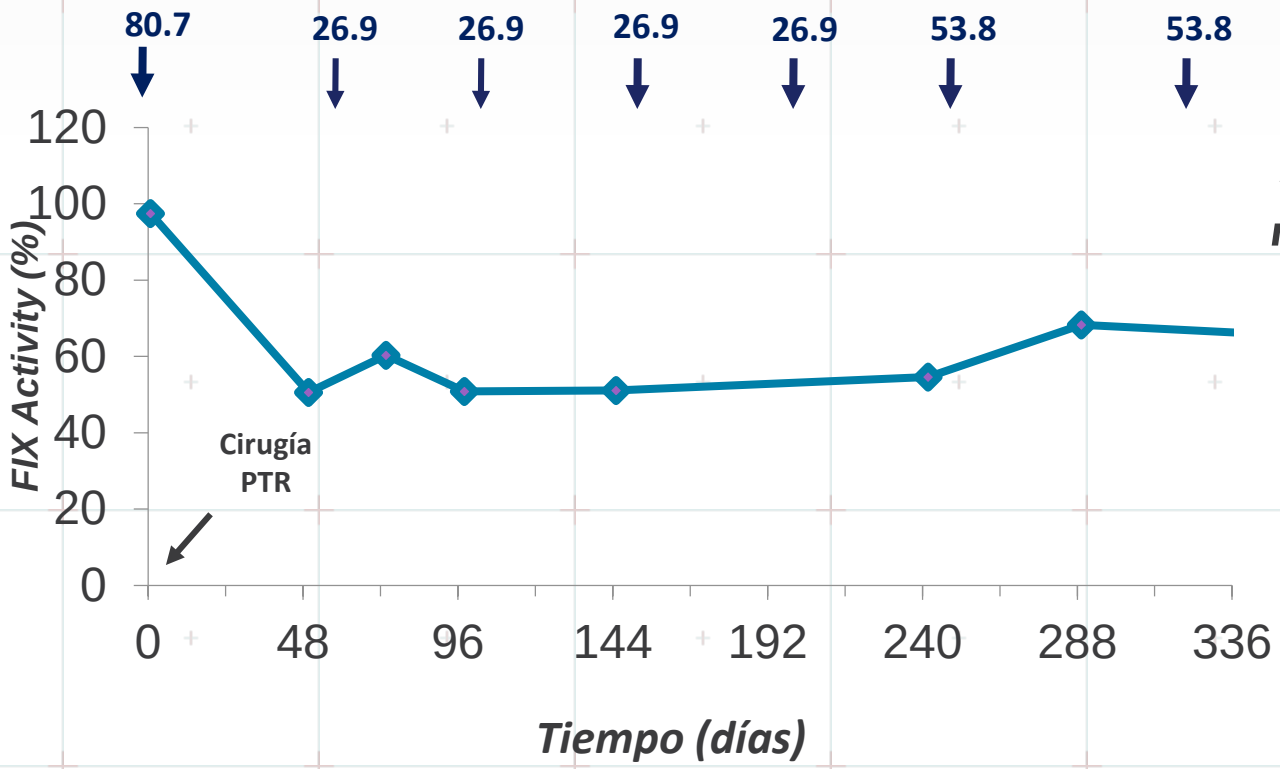
ORIGINAL ARTICLE *Clinical haemophilia*

Efficacy and safety of long-acting recombinant fusion protein linking factor IX with albumin in haemophilia B patients undergoing surgery

C. NÉGRIER,* F. ABDUL KARIM,† L. M. LEPATAN,‡ A. LIENHART,* M. F. LÓPEZ-FERNÁNDEZ,§ J. MAHLANGU,¶** I. PABINGER,†† Y. LI,‡‡ D. WOLKO,‡‡ C. VOIGT,‡‡ I. JACOBS‡‡ and E. SANTAGOSTINO§§

**Centre Régional de Traitement de l'Hémophilie (CRTH)/Unite d'Hemostase Clinique, Hôpital Cardiologique Louis Pradel University Lyon I, Lyon, France; †National Blood Centre, Kuala Lumpur, Malaysia; ‡Perpetual Succour Hospital, Cebu City, Philippines; §Complexo Hospitalario Universitario A Coruña, A Coruña, Spain; ¶Haemophilia Clinic, Comprehensive Care Centre Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand; **NHLS South Africa, Johannesburg, South Africa; ††Clinical Division of Haematology and Haemostaseology, Medical Clinic I Medical University Vienna, Vienna, Austria; ‡‡Clinical Research and Development, CSL Behring, King of Prussia, PA, USA; and §§A. Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Ca' Granda Foundation, Maggiore Hospital Policlinico, Milan, Italy*

En cirugía ortopédica mayor, la administración en el postoperatorio de Idelvion aproximadamente cada 2 días mantuvo la actividad de FIX a los niveles o por encima de los deseados.



Actividad de FIX se mantuvo por encima del 50%.

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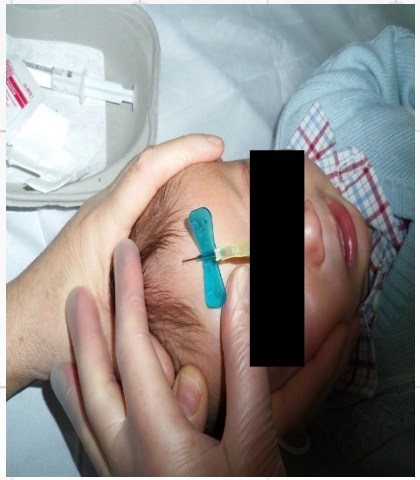


¿REDUCIRÁN EL NÚMERO DE INFUSIONES?

¿REDUCIRÁN LOS EHL FIX EL NÚMERO DE INFUSIONES?

En cuanto a los EHL del FIX podemos decir que han superado los beneficios esperados, pues mantienen su eficacia administrándolos con intervalos de 10-14 días

- *Santagostino, E. et al. Blood 2016; 127(14): p. 1761-9.*
- *Powell J.S. et al. N Engl J Med 2013; 369(24): p. 2313-23.*
- *Collins P.W. et al. Blood 2014; 124: 3880-3886*

ESTUDIO DE EXTENSIÓN, FASE 3b, on-going

SEGURIDAD Y EFICACIA A LARGO PLAZO CON IDELVION®, 83 pacientes incluídos

PTPs:

Profilaxis cada 7, 10, 14 ó 21 días (100 UI/kg)

- *45/52 (87%) de los pacientes (≥12 años) cambiaron desde profilaxis semanal a infusiones cada 10 ó 14 días.*

  ✓***10 pacientes (≥18 años) cambiaron desde intervalos cada 14 días a cada 21 días.***

  ✓***11 (46%) niños (<12 años) cambiaron a infusiones cada 10 ó 14 días.***

Santagostino et al. 2016. Poster presented at WFH 2016 World Congress. 24-28 July, Orlando.

P045

Safety and Efficacy of RIX-FP in Patients With Hemophilia B: Interim Results From A Phase IIIB Extension Study

E. SANTAGOSTINO[1,*], K. ST. LEDGER[2], A. VELDMAN[3], Y. LI[2], M. STRELECKI[2], G. COLE[2], N. BLACKMAN[2]

[1]*Angelo Bianchi Bonomi Hemophilia and Thrombosis Center IRCCS Ca' Granda Foundation, Maggiore Hospital Policlinico, Milan, Italy;* [2]*CSL Behring, King of Prussia, United States;* [3]*CSL Behring, Marburg, Germany*

- *La media de AsBR:*
  - *en adultos con administraciones cada 7, 10, 14 ó 21 fue de 0.85, 0, 0 y 0.*
  - *en población pediátrica con profilaxis cada 7, 10 y 14 días fue 0, 0, 1.16.*
- *Mediana de EDs 67 y más del 84.3% habían alcanzado los 100 EDs sin desarrollo de inhibidor.*

Se validan los resultados de eficacia y seguridad del estudio pivotal. ES POSIBLE ESPACIAR LAS INFUSIONES a cada 21 DÍAS EN ADULTOS Y CADA 10 ó 15 DÍAS EN NIÑOS.

¿REDUCIRÁN LA TASA DE INHIBIDORES?

	rFIXFc	rFIX-FP	N9-GP
Number of patients with inhibitors	0	0	0
Number of patients with non-inhibitor antibodies	3	0	3
Number of deaths, thromboembolism	0	0	0
Number of drug-related serious adverse events	0	0	0
Number of drug-unrelated serious adverse events	11	3	4

Journal of Thrombosis and Haemostasis, 15: 1–14 DOI: 10.1111/jth.13649

ORIGINAL ARTICLE

Modulating immunogenicity of factor IX by fusion to an immunoglobulin Fc domain: a study using a hemophilia B mouse model

D. LEVIN,* H. A. D. LAGASSÉ,* E. BURCH,‡ S. STROME,‡ S. TAN,§ H. JIANG,¶ Z. E. SAUNA* and B. GOLDING†

**Hemostasis Branch; †Plasma Derivatives Branch, Division of Plasma Protein Therapeutics, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring; ‡Department of Otorhinolaryngology–Head and Neck Surgery, University of Maryland School of Medicine, Baltimore, MD; §CRISPR Therapeutics; and ¶Editas Medicine, Cambridge, MA, USA*

To cite this article: Levin D, Lagassé HAD, Burch E, Strome S, Tan S, Jiang H, Sauna ZE, Golding B. Modulating immunogenicity of factor IX by fusion to an immunoglobulin Fc domain: a study using a hemophilia B mouse model. *J Thromb Haemost* 2017; DOI: 10.1111/jth.13649.

Essentials

- Fc-fusion increases a therapeutic's half-life, but FcγR interactions may impact immunogenicity.
- Species-specific Fc-FcγR interactions allow for mechanistic *in vivo* studies using mouse models.
- Fc fusion modulates the immune response to factor IX in hemophilia B mice by eliciting Th1 bias.
- This model could inform future studies of IgE-associated anaphylaxis in hemophilia B patients.

¿REDUCIRÁN EL CONSUMO?

blood®
2016 127: 1761-1769
doi:10.1182/blood-2015-09-669234 originally published online January 11, 2016

Long-acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial

Elena Santagostino, Uri Martinowitz, Toshko Lissitchkov, Brigitte Pan-Petesch, Hideji Hanabusa, Johannes Oldenburg, Lisa Boggio, Claude Negrier, Ingrid Pabinger, Mario von Depka Prondzinski, Carmen Altisent, Giancarlo Castaman, Koji Yamamoto, Maria-Teresa Álvarez-Roman, Christine Voigt, Nicole Blackman and Iris Jacobs

El número de unidades anuales administrado se redujo ostensiblemente (un 40% menos de consumo con respecto al FIX convencional)

CONSUMO DE rFIXFP

El consumo de rFIXFP en los diferentes regímenes de profilaxis:

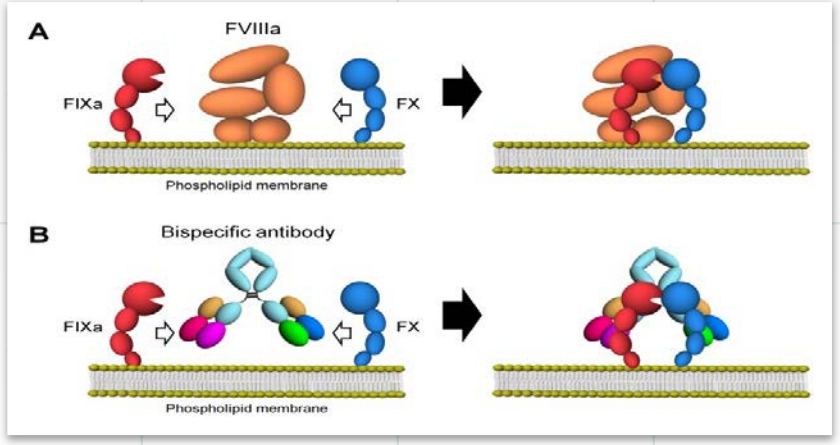
- *rFIXFP a 40 UI/kg cada 7 días, 194.7 UI/kg/mes*
- *rFIXFP a 75 UI/kg cada 2 semanas, 162.3 UI/kg/mes (IQ:158.6-164.2)*

ANTES DE ENTRAR EN EL ESTUDIO, EL CONSUMO MEDIO DE FIX ERA DE 256.6 UI/Kg/MES

¿QUÉ DATOS NOS QUEDAN POR CONOCER?

OTRAS ALTERNATIVAS

PRODUCTO		DOSIS	VÍA DE ADMINISTRACIÓN	ENSAYOS CLÍNICOS
INHIBICIÓN DE ANTICOAGULANTES NATURALES				
Anticuerpo anti TPFI	Anticuerpo monoclonal 2021	Semanal	Subcutánea	Ensayo fase I en desarrollo (NCT02490787)
EnsaRNAi-AT-III	ALN-AT3	Semanal	Subcutánea	• Ensayo fase I en desarrollo (NCT02035605) • Ensayo fase I/II en desarrollo (NCT02554773)
PROMOCIÓN DE LA GENERACIÓN DE TROMBINA IMITANDO LA ACTIVIDAD DEL COFACTOR DEL FVIII				
Anticuerpo específico frente a FIXa y FX	ACE910	Semanal	Subcutánea	Ensayo fase I/II completado (JapicCTI-121934)



ACE 910

- *Es un anticuerpo monoclonal humanizado bioespecífico (hBS23), dirigido contra el FIXa y el FX, que mimetiza la acción del FVIII como cofactor.*
- *Puede conseguir hemostasia en pacientes con hemofilia congénita con o sin inhibidor, así como en hemofilia adquirida.*
- *Es de administración subcutánea y tiene una vida media de hasta 3 semanas.*
- *Fase 3. Laboratorio Roche*

Muto A et al Blood, 2014. 124(20): p. 3165-71
Sampei Z. PloS One. 2013: 8(2): e57479

RESULTADOS DEL FASE I

CLINICAL TRIALS AND OBSERVATIONS

A first-in-human phase 1 study of ACE910, a novel factor VIII–mimetic bispecific antibody, in healthy subjects

Naoki Uchida,[1,2] Takehiko Sambe,[1,2] Koichiro Yoneyama,[3] Naoki Fukazawa,[3] Takehiko Kawanishi,[3] Shinichi Kobayashi,[1] and Midori Shima[4]

[1]Showa University Clinical Research Institute for Clinical Pharmacology and Therapeutics, Tokyo, Japan; [2]Department of Pharmacology, School of Medicine, Showa University, Tokyo, Japan; [3]Translational Clinical Research Division, Chugai Pharmaceutical Co. Ltd., Tokyo, Japan; and [4]Department of Pediatrics, Nara Medical University, Nara, Japan

(*Blood.* 2016;127(13):1633-1641)

✓***PD*** *se hace ex-vivo, con y sin depleción de FVIII con Ac monoclonales, se mide TTPa y TGT. Acortamiento de TTPa y aumento de pico de generación de trombina, dosis dependiente. Con una dosis de 1 mg/kg de peso se normalizaba el TTPa.*

✓***Seguridad,*** *6 meses de duración del estudio. Dosis de hasta 1mg/kg son bien toleradas y no tienen efectos adversos graves. Se detectaron 2 inhibidores (uno previo al ACE 910 y otro durante el estudio, éste último neutralizante). Trombosis, ninguna, ni elevación de Dímero-D ni complejos trombina-antitrombina.*

XXI CURSO INTRODUCCIÓN
A LA FARMACOTERAPIA
DE LOS HEMODERIVADOS

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58th Annual Meeting & Exposition

San Diego, California • December 3-6, 2016

A Novel Clot Waveform Analysis to Measure the Plasma Coagulation Potency in the Presence of Anti-Fixa/Fx Bispecific Antibody, Emicizumab
Result Type: Paper
Number: 1388
Presenter: Keiji Nogami
Program: Oral and Poster Abstracts
Session: 321. Blood Coagulation and Fibrinolytic Factors: Poster I
Time and Location:
Saturday, December 3, 2016: 5:30 PM–7:30 PM
Hall GH (San Diego Convention Center)
Search Result:
. . . Nara, Japan3Hemostasis Product Engineering, Sysmex Corporation, Kobe, Japan4Research Division, Chugai Pharmaceutical Co., Gotemba, Japan5Research Division, Chugai Pharmaceutical Co., Kamakura, Japan **Emicizumab** (also termed ACE910) is a humanized anti-factor (F)IXa/FX bispecific antibody with FVIIIa cofactor function. A clinical phase 3 study was . . .

321. Blood Coagulation and Fibrinolytic Factors: Poster I
Result Type: Session
Program: Oral and Poster Abstracts
Time and Location:
Saturday, December 3, 2016: 5:30 PM–7:30 PM
Hall GH (San Diego Convention Center)
Search Result:
. . . Israel 1388 A Novel Clot Waveform Analysis to Measure the Plasma Coagulation Potency in the Presence of Anti-Fixa/Fx Bispecific Antibody, **Emicizumab** Keiji Nogami, MD, PhD1*, Tomoko Matsumoto, PhD1,2*, Yuka Tabuchi3*, Tetsuhiro Soeda, PhD4*, Nobuo Arai3*, Takehisa Kitazawa5*, Hidenari Takaoka3*, Kunihiro Hattori, . . .

Activated FVIII Released from FVIII/VWF Complex Facilitates Thrombus Development Under High Shear Flow Condition
Result Type: Paper

Bleeding Events and Safety Outcomes in Patients with Hemophilia a with Inhibitors: A Prospective, Multicenter, Non-Interventional Study

Result Type: Paper
Number: 3800
Presenter: Johnny Mahlangu
Program: Oral and Poster Abstracts
Session: 322. Disorders of Coagulation or Fibrinolysis: Poster III
Time and Location:
Monday, December 5, 2016: 6:00 PM-8:00 PM
Hall GH (San Diego Convention Center)

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- ✓ ***Real world data (RWD)**, providing the possibility of intra-patient comparison for those who may be subsequently eligible to participate in a pivotal emicizumab Phase 3 study (NCT02622321).*

- ✓ *pt demographics/characteristics; global distribution of pts by country; summary of hemophilia medical history, concomitant medications and surgeries; pts' self-reported information on bleeding events and treatment (all, and by episodic and prophylactic treatment), including bleeding rates, types and locations, reason for coagulation product use, product type used, dose; and, safety.*

XXI CURSO INTRODUCCIÓN A LA FARMACOTERAPIA DE LOS HEMODERIVADOS

ACE910: Emicizumab

HEALTH NEWS | Wed Nov 2, 2016 |
Adverse events in trial dent hopes for Roche hemophilia drug

- What we have so far are 4 spontaneously reported SAE (serious adverse events). And **these events were seen with the concomitant use of multiple doses of a bypassing agent with emicizumab while treating a breakthrough bleed; in some cases the bypassing agent at doses exceeding the recommended labeled doses.**

ACE910: Emicizumab

- ***The current recommendation is to avoid the use of one specific bypassing agent and if necessary, to use it starting with the lower range of the recommended labeled dose and perform dosing under monitoring.***

- *Importantly, all of these adverse events have resolved and two of the patients have since restarted emicizumab and have not experienced a recurrence of the adverse event to date.*

ACE910: 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. The investigator's assessment is that the cause of death was the rectal haemorrhage, and that this is not related to emicizumab*

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

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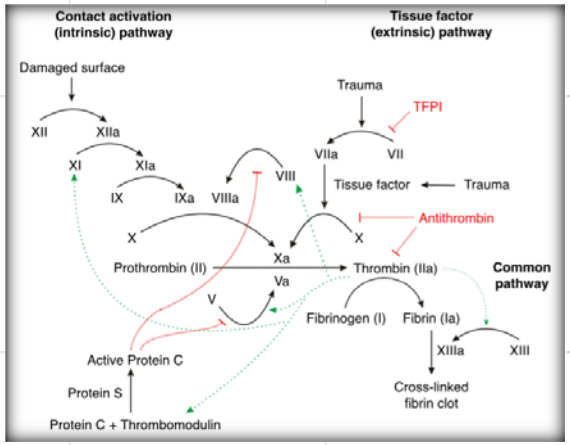
FVIII
FIX

FÁRMACOS CON OTRAS DIANAS TERAPÉUTICAS



ATIII
Prot S
Prot C

FVIII
FIX

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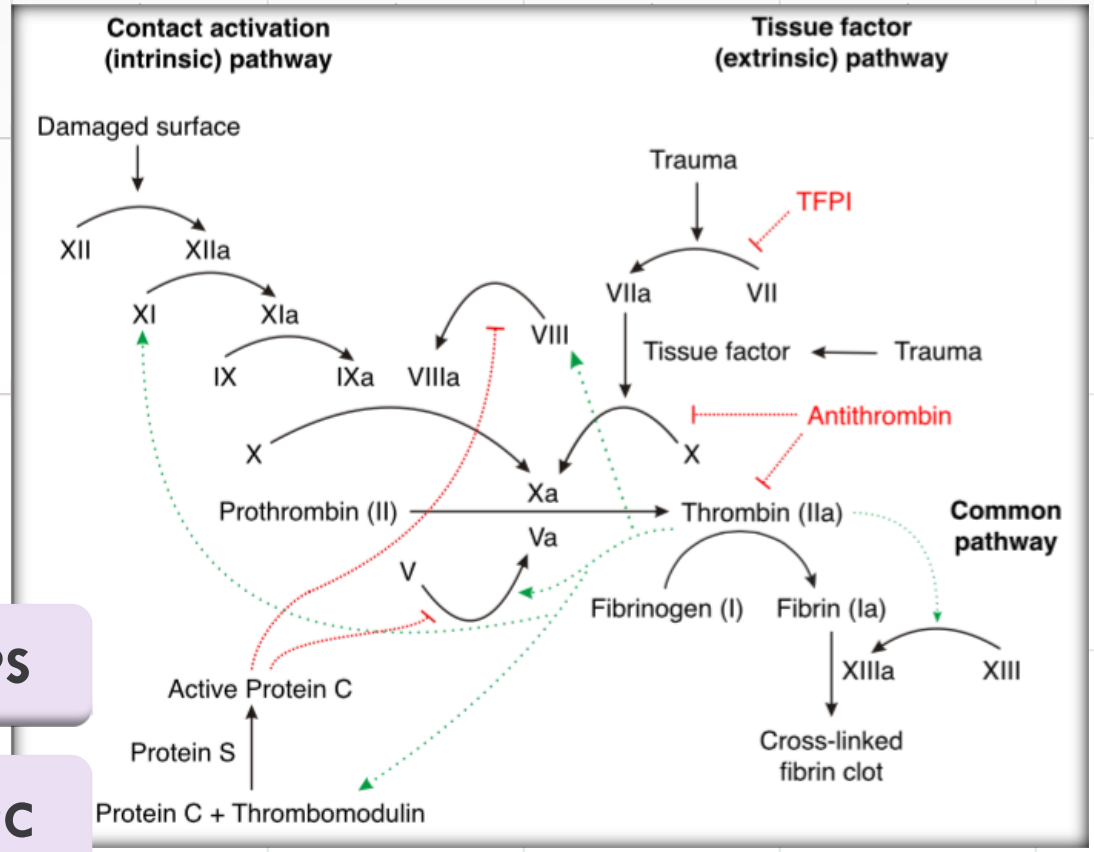
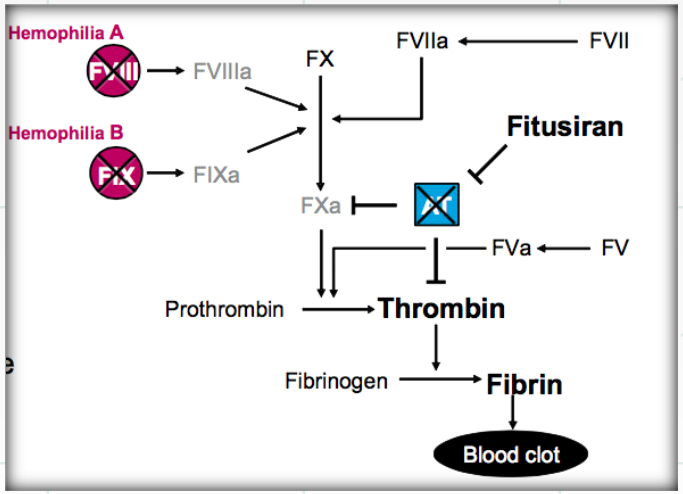
OTRAS DIANAS TERAPÉUTICAS



Anti-PS

Anti-PC



ALN-AT3-FITUSIRAN

- *Es un RNAi que reduce la síntesis de AT-III, aumentando la generación de trombina.*
- *Fase I con una administración semanal o mensual, vía subcutánea.*
- *Anylam, Pharmaceuticals*
- *Se han comunicado los datos del fase I con buen perfil de eficacia y de seguridad.*

Pasi K.J., Abstract 551 Hematology Am Soc Hematol 57th, Orlando, Florida. December 5-8, 2015.
Pasi K.J. Abstract 1397 Hematology Am Soc Hematol, San Diego, California. December 3-6, 2016

XXI CURSO INTRODU
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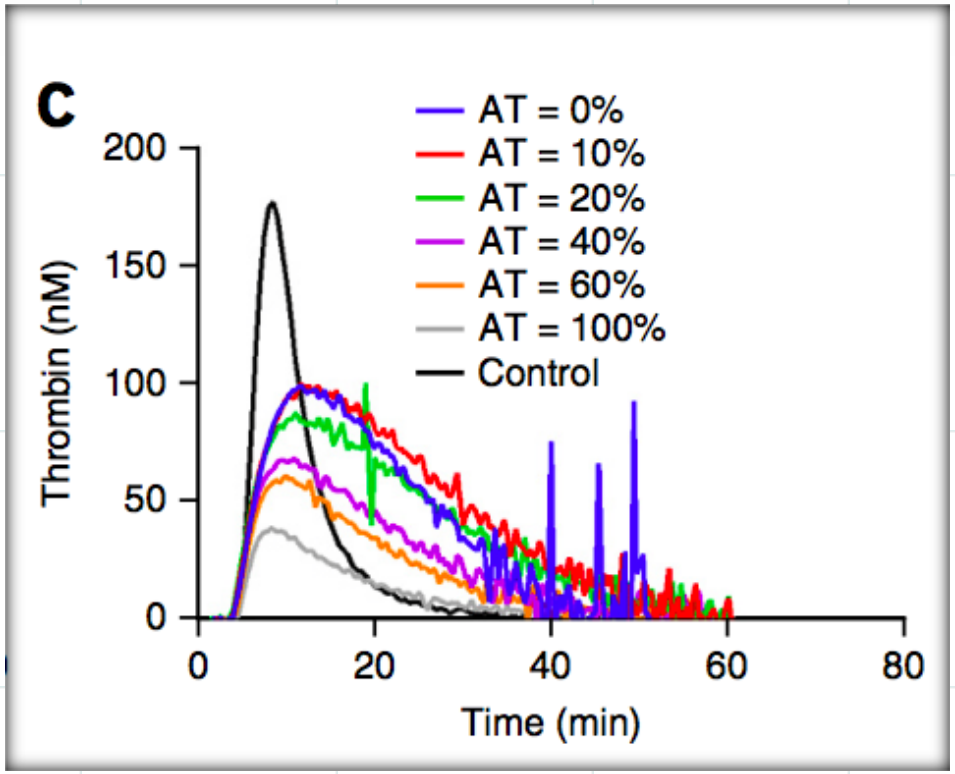
DE LOS HEMODERIV

LETTERS

nature medicine

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

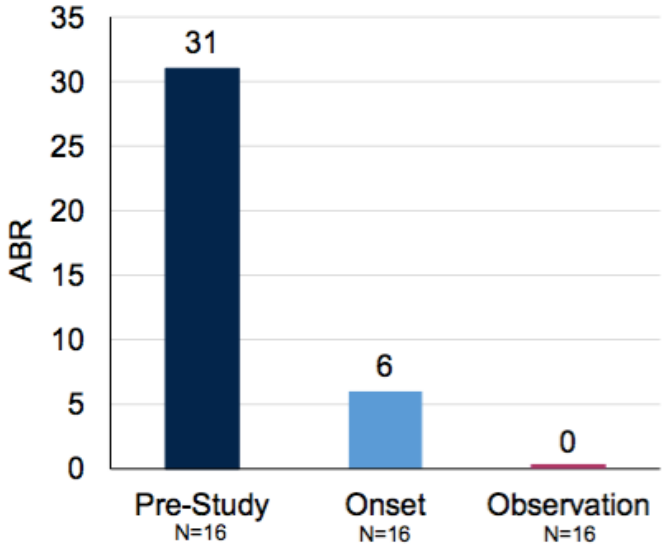
Alfica Sehgal[1], Scott Barros[1], Lacramioara Ivanciu[2], Brian Cooley[3], June Qin[1], Tim Racie[1], Julia Hettinger[1], Mary Carioto[1], Yongfeng Jiang[1], Josh Brodsky[1], Harsha Prabhala[1], Xuemei Zhang[1], Husain Attarwala[1], Renta Hutabarat[1], Don Foster[1], Stuart Milstein[1], Klaus Charisse[1], 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]



Interim Fitusiran Phase 1 (Part D) and OLE Study Results*

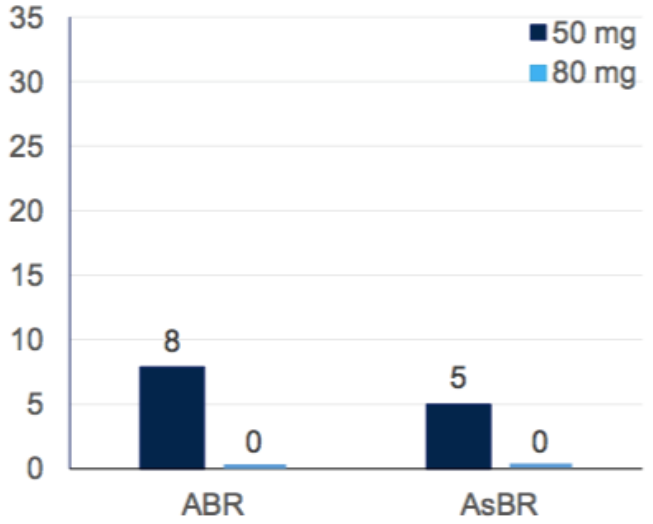
Summary of Median ABRs

All Inhibitor Patients



- Median ABR, Pre-study period: 31
- Median ABR, Observation period: 0
  - Patients reporting no bleeds: 9/16 (56%)
  - Patients report no spontaneous bleeds (AsBR = 0): 11/16 (69%)

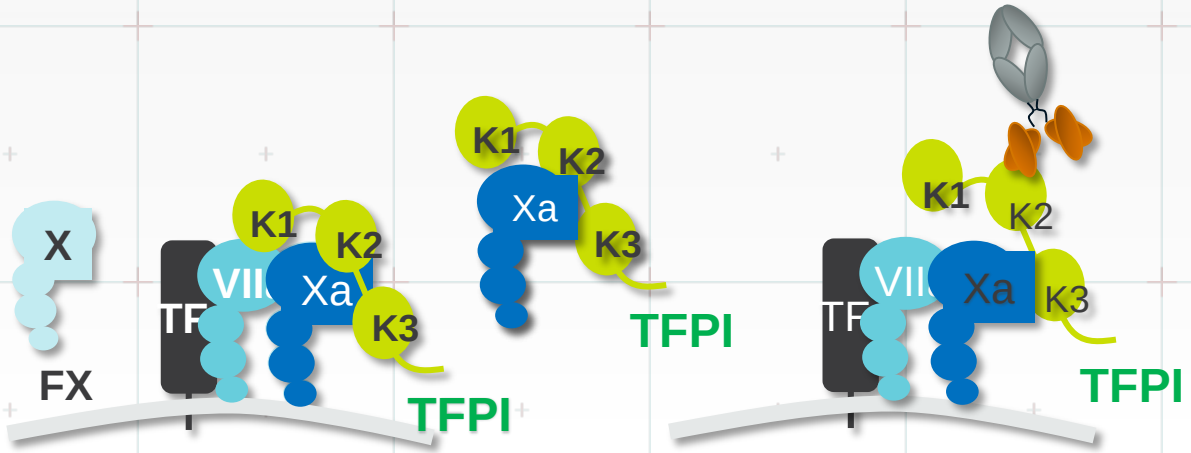
Observation Period, 50 mg vs 80 mg



- 50 mg: Median ABR = 8, median AsBR = 5
- 80 mg: Median ABR = 0, median AsBR = 0
  - Patients reporting no bleeds: 7/10 (70%)
  - Patients report no spontaneous bleeds (AsBR = 0): 9/10 (90%)

Alnylam PHARMACEUTICALS

Anti-TFPI, CONCIZUMAB

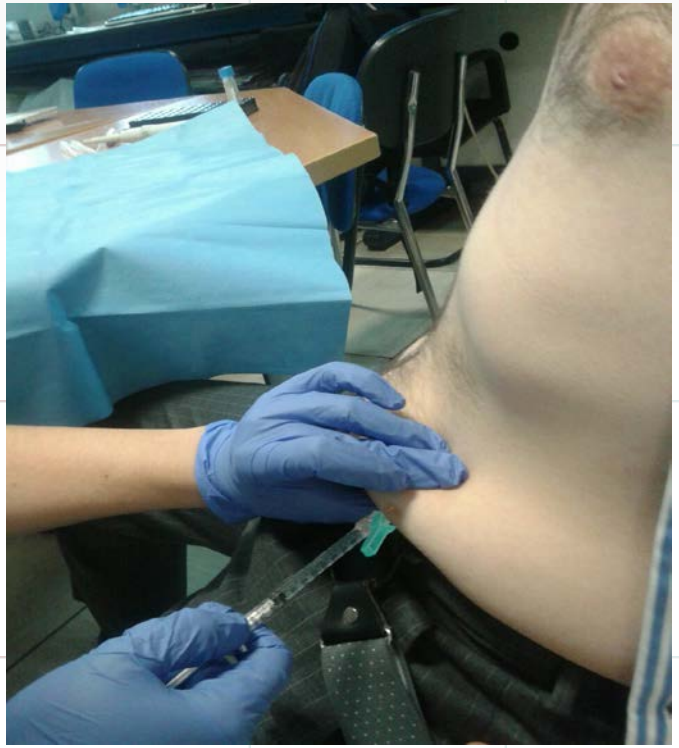


- *Ac monoclonal humanizado (mAb 2021) que bloquea la interacción entre el FXa y el TFPI, facilitando la generación de trombina.*
- *Administración IV como en la SC, $t_{1/2}$: 12-20 días*
- *Explorer™3, fase I, Novonordisk*

Chowdary, P. et al. J Thromb Haemost, 2015. 13(5): p. 743-54.

VENTAJAS

ADMINISTRACIÓN SUBCUTÁNEA



INDICACIÓN

VENTAJAS

ACE 910	Pacientes con Hemofilia A con o sin inhibidor
Anti-TFPI	Pacientes con Hemofilia A y B con o sin inhibidor
RNAi ATIII	Pacientes con Hemofilia A y B con o sin inhibidor

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INTERVALO DE ADMINISTRACIÓN

VENTAJAS

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5 studies found for: emicizumab

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Only show open studies

Rank	Status	Study
1	Recruiting	A Clinical Trial to Eva… Prophylaxis in Hemo… Condi… Interven…
2	Recruiting	A Study to Evaluate t… Weeks in Participant… Condi… Interven…
3	Recruiting	A Study of Once-Weekly Emicizumab in Children and Adolescents With Hemophilia A and Factor VIII (FVIII) Inhibitors (HAVEN 2) **Condition:** Hemophilia A **Intervention:** Drug: Emicizumab
4	Active, not recruiting	A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Participants With Inhibitors **Condition:** Hemophilia A **Interventions:** Drug: Emicizumab; Drug: rFVIIa
5	Available	An Expanded Access Program of Emicizumab in Participants With Hemophilia A With Inhibitors **Condition:** Hemophilia A **Intervention:** Biological: Emicizumab

Intervention: Drug: Emicizumab

2 Recruiting A Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Emicizumab Given Every 4 Weeks in Participants With Hemophilia A

Condition: Hemophilia A

Intervention: Drug: Emicizumab

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Abstract 1397 Fitusiran, an Investigational RNAi Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: Updated Results from a Phase 1 and Phase 1/2 Extension Study in Patients with Inhibitors.

K John Pasi et al

- ✓ Here we report the updated safety, pharmacodynamic (PD) effect, and clinical activity of fitusiran in patients with **hemophilia with inhibitors** as well as long term data from the Phase 1/2 extension study.

- ✓ In Part D, patients with inhibitors received once-monthly SC fixed doses of 50 or 80 mg fitusiran. After receiving 3 **monthly doses** in the Phase 1 study, all patients were eligible to continue monthly dosing in the Phase 1/2 extension study. Utilization of BPA for breakthrough bleed management was permissible in these patients.

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TERAPIA GÉNICA EN HEMOFILIA

Changing Paradigm of Hemophilia Management: Extended Half-Life Factor Concentrates and Gene Therapy

Riten Kumar, MD, MSc[1] Amy Dunn, MD[1] Manuel Carcao, MD, MSc[2]

[1] Division of Hematology/Oncology, Department of Pediatrics, The Ohio State University, Nationwide Children's Hospital, Columbus, Ohio
[2] Division of Haematology/Oncology, Department of Paediatrics, University of Toronto, The Hospital for Sick Children, Toronto, ON, Canada

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Semin Thromb Hemost 2016;42:18–29.

Study identifier*	NCT00979238	NCT01687608	NCT02396342	NCT02484092/ NCT01620801
Phase	Phase 1	Phase 1/2	Phase 1/2	Phase 1/2
Sponsor	St. Jude Children's Research Hospital/ UCL	Baxalta Healthcare Corporation	UniQure Biopharma B.V.	Spark Therapeutics/CHOP
Inclusion criteria	Adults/severe HB	Adults/HB	Adults/severe HB	Adults/HB
Type of AAV	scAAV8	scAAV8	AAV5	ssAAV8
Transgene	hFIXco	hFIX Padua	hFIXco	hFIXco
Method	Peripheral vein	Peripheral vein	Peripheral vein	Peripheral vein
Results	Recruiting/persistent dose-dependent expression of FIX at 1–6%	Recruiting/no results available	Recruiting/no results available	Not recruiting/ recruitment is complete for NCT01620801—results are not available

XXI CURSO INTRODUCCIÓN A LA FARMACOTERAPIA DE LOS HEMODERIVADOS

CONCLUSIONES (I)

- Nuevos concentrados los EHL, con **resultados muy alentadores:**
  - ✓ Mayor eficacia (menor ABR, menor nº de infusiones para parar el sangrado, mayor porcentaje de pacientes sin sangrado, muy buena cobertura en cirugía)
  - ✓ Menos infusiones, probablemente más adherencia
  - ✓ Menor consumo
  - ✓ Parecen tener menor tasa de inhibidores
  - ✓ Nuevos grupos de pacientes se podrán beneficiar de la profilaxis

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CONCLUSIONES (II)

- **Otras moléculas** anti-TFPI, ACE 910, ALN-AT3:
  - ✓ Posiblemente mayor eficacia
  - ✓ Administración subcutánea
  - ✓ Más indicaciones (RBDs?)
  - ✓ Período de administración más conveniente para el paciente

XXI CURSO INTRODUCCIÓN A LA FARMACOTERAPIA DE LOS HEMODERIVADOS

CONCLUSIONES (III)

- **Terapia génica**
  - ✓ En el caso de la hemofilia B conocemos el gen adecuado (IX Padúa), el vector adecuado (AAV8) y ya hay pacientes con niveles de FIX mantenidos a largo plazo (ensayo Pfizer/Spark).
  - ✓ Expectativas también para las diferentes técnicas de reparación celular como las CRISPR-Cas9.