Malattie emorragiche su base costituzionale

Mariasanta Napolitano

Disclosures of Mariasanta Napolitano

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Bayer			X		X	X	
Novonordisk					X	X	
Kedrion					X	X	
Sobi					X		
Takeda					X	X	
Amgen						X	
Novartis						X	
CSL Behring			X		X	X	
Sanofi					X		

Topics

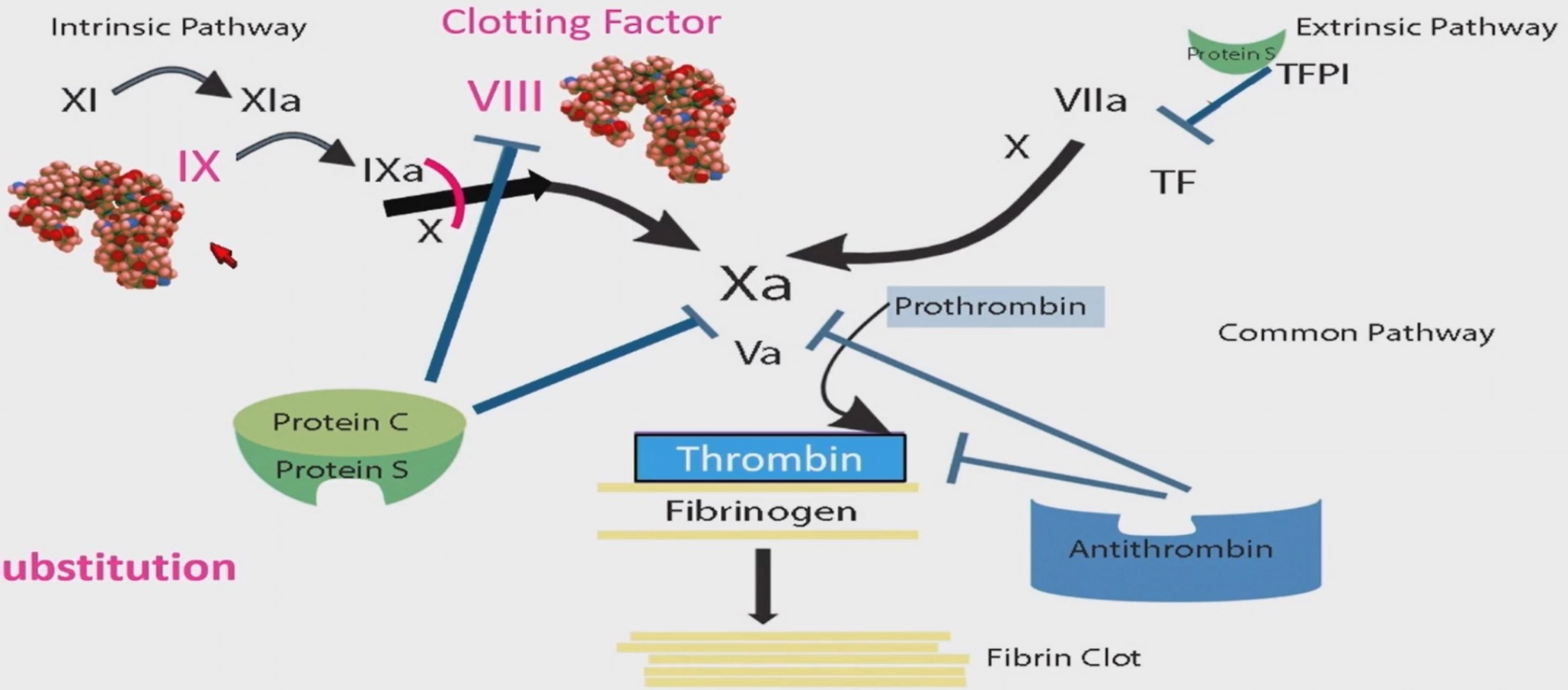
Emofilia A e B: terapie innovative (non sostitutive)

Emofilia A : terapie innovative (sostitutive)

Emofilia A : terapia genica

Haemophilia carriers

PARADIGM SHIFTS
FACTOR REPLACEMENT, MIMETICS AND RE-BALANCING AGENTS



1. Substitution

Adapted from Weyand AC and Pipe SW, Blood 2019

Quali outcomes vengono valutati negli studi clinici in emofilia?

Efficacia

Riduzione/abolizione dei sanguinamenti
ABR (Annual Bleeding rates)
AjBR (Annual joint rates)

Risoluzione di target joints
(articolazione sede di tre o più sanguinamenti in 6 mesi)

Salute articolare (HjHS, HEAD-US)

Trough levels (FVIII/FIX post-infusione)
Farmacocinetica (PK)

Qualità di vita (PRO)

Dolore

Sicurezza

Tollerabilità

Trombosi

Side effects

Emicizumab

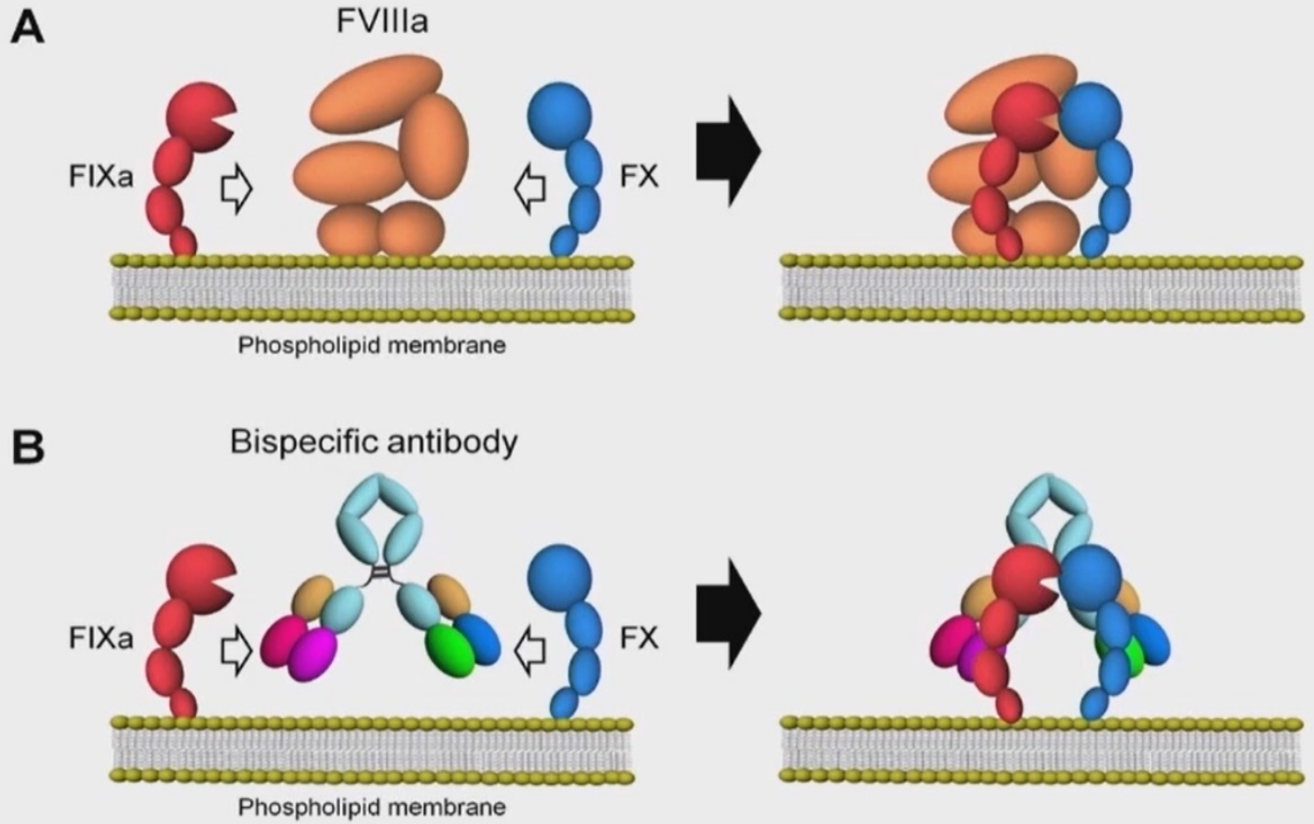
FVIII-mimicking antibody[1]

- Effective in reducing bleeding rates
- Subcutaneous use
- Long half life (t ½ ~ 27 days)

Fixed body weight dose

- 1.5mg/kg/wk
- 3.0mg/kg/2wks
- 6.0mg/kg/4wks

Costs limit widespread access [2]



[1] Oldenburg (2017), NEJM
[2] Mannucci (2024), Haemophilia
Figure: Kitazawa, Nature Med 2012

Preventing Long-Term Neurologic Disability in Hemophilia A:Cost-Effectiveness of Emicizumab Prophylaxis for the Prevention of Intracranial Hemorrhage in Infants with Severe Hemophilia A

Samira Glaeser-Khan, BS, Rhys Richmond, BS, Satoko Ito, MD, PhD, Robert D Bona, MD, Harlan M.Krumholz, MD, SM, Adam Cuker, MD, MS and George Goshua, MD, MSc, FACP

Results: base-case and scenario (low-dose)

Strategy	Cost (USD)	Incremental cost (USD)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)
Base case				
On-demand FVIII	$9,664,000	--	25.8	--
Emicizumab	$9,790,000	$126,000	26.9	1.1
Incremental cost-effectiveness ratio (ICER) = **$110,000** [95% CI: $89,000- 166,000]				
Scenario analysis (50% emicizumab dose reduction)				
On-demand FVIII	$9,664,000	--	25.8	--
Emicizumab	$9,722,000	$58,000	26.9	1.1
Incremental cost-effectiveness ratio (ICER) = **$51,000** [95% CI: $39,000-$79,000]				

Profilassi con Emicizumab in pazienti di età <2aa risulta cost-effective
Emicizumab a basse dosi risulta anche cost-effective

Blood (2024) 144 (Supplement 1): 157.

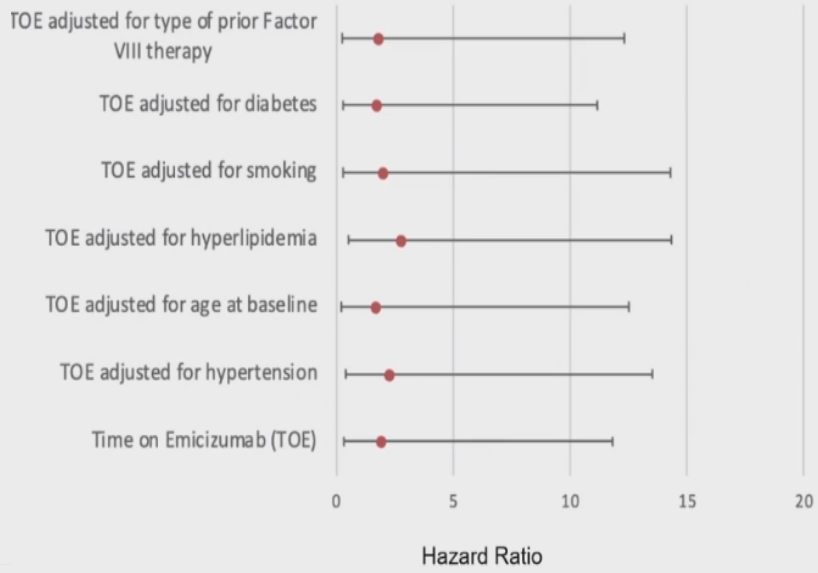
Comparing the Risk of Thrombotic Events in Older Persons with Hemophilia A on Emicizumab Prophylaxis to Non-Emicizumab Products: A Single-Center Observational Cohort Study

Shalini Vemuru, MD, Stacey Fedewa, PhD, MPH, Christine L. Kempton, MD, MSc

Results: Demographics

Categories	Total	Not Emicizumab	Emicizumab	p-value
	N=32	N=5	N=27	
	N (%)	N (%)	N (%)	
Sex				
Male	32 (100)	5 (100)	27 (100)	
Race				.623
Asian/PI	1 (3.13)	0 (0)	1 (3.7)	
Black	5 (15.63)	0 (0)	5 (18.52)	
White	26 (81.25)	5 (100)	21 (77.78)	
Inhibitor History				.047
Current	1 (3.13)	0 (0)	1 (3.7)	
Never	26 (81.25)	3 (60)	23 (85.19)	
Past	3 (9.38)	0 (0)	3 (11.11)	
Unknown	2 (6.25)	2 (40)	0 (0)	
HIV Viral Load Suppression				
Suppressed	16 (50)	1 (20)	15 (55.56)	.173
Unsuppressed	4 (12.5)	0 (0)	4 (14.81)	
Past Hepatitis C Infection	31 (96.9)	4 (80)	27 (100)	.156

The Risk of Thrombotic Events on Emicizumab



No significant increase in thrombotic events while on emicizumab

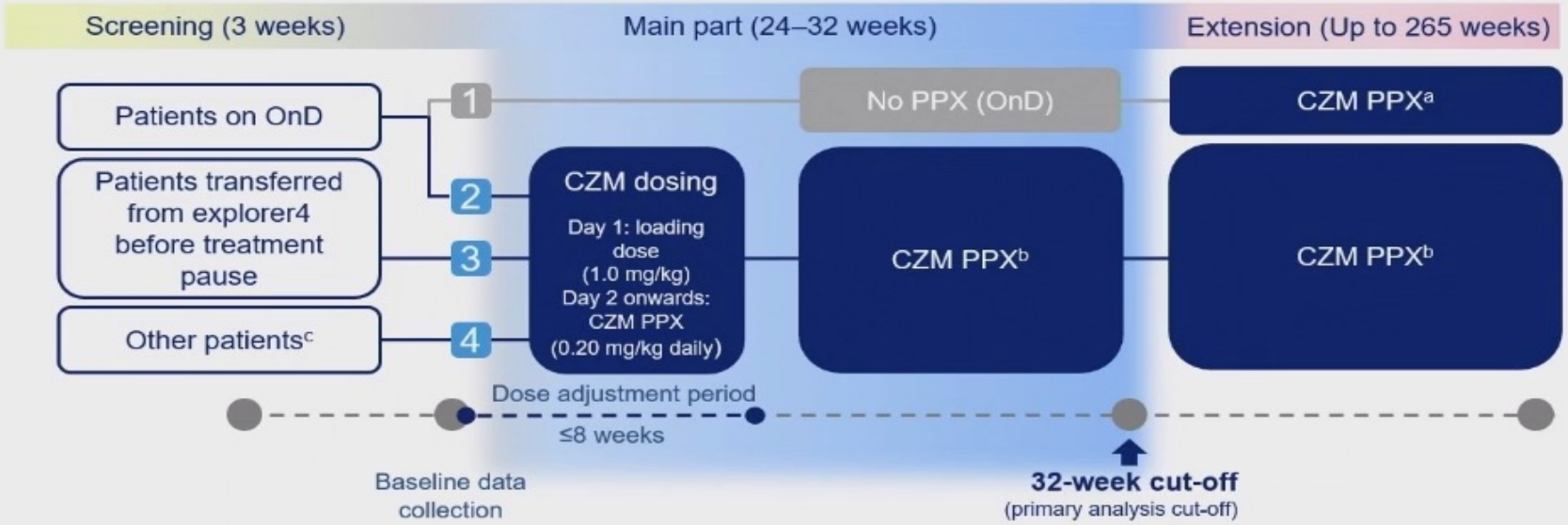
Blood (2024) 144 (supplement 1): 130.

Gli studi clinici relativi a concizumab (explorer trial)

explorer7 study design: 32-week cut-off

Male patients **≥12 years** with HAwI/HBwI in 4 arms

- Arm 1 received concizumab PPX after 24 weeks of on-demand treatment
- Arms 2–4 received concizumab PPX from study onset



explorer7 (NCT04083781). Treatment paused (2020/03–2020/08) due to non-fatal thromboembolic events; restarted after implementation of new dosing regimen and guidance on mild and moderate breakthrough bleed management with lowest dose of factor product or bypassing agent while on concizumab. [a]Dose adjustment period followed by maintenance dose. [b]The individual maintenance doses were 0.15, 0.20 or 0.25 mg/kg concizumab. [c]Patients on PPX and additional patients on OnD treatment.
CZM, concizumab; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; OnD, on-demand; PPX, prophylaxis.
Matsushita T et al. NEJM 2023; 389(9):783–94.

Annualized bleeding rates in patients with hemophilia A or B and inhibitors with and without target joints at baseline: Results from the concizumab phase 3 explorer7 study

Shapiro A, Apte S, Bodsan A, Brown Frandsen R, Linari S, Mahlangu J, Martins Mazini Tavares C, Matsushita T, Nekkal St, Sathar J, Chan AKC

Low median ABRs were maintained with concizumab prophylaxis in arms 2-4 at the 56-week cut-off in explorer7

	With target joints at baseline (arms 2–4)		Without target joints at baseline (arms 2–4)	
	32-week cut-off	56-week cut-off	32-week cut-off	56-week cut-off
n	59	59	55	55
Weeks of exposure (min; max)	2.0; 64.4	2.0; 88.7	3.6; 64.1	3.6; 87.4
Median ABR (IQR)				
Treated spontaneous and traumatic bleeding episodes	0.9 (0.0–4.7)	1.2 (0.0–3.9)	0.0 (0.0–2.6)	0.0 (0.0–2.0)
Treated spontaneous and traumatic joint bleeding episodes	0.0 (0.0–3.9)	0.7 (0.0–3.6)	0.0 (0.0–1.3)	0.0 (0.0–1.3)
Treated spontaneous and traumatic target joint bleeding episodes	0.0 (0.0–1.3)	0.0 (0.0–1.4)	0.0 (0.0–0.0)	0.0 (0.0–0.0)

explorer7 (NCT04083781). Bleeding endpoints are analyzed using a negative binomial regression model with the logarithm of the length of the observation period included (in years) as offset with treatment, type of hemophilia and bleeding frequency prior to screening as factors. Target joint is defined as having three or more spontaneous bleeds into a single joint within a consecutive 6-month period. ABR, annualized bleeding rate; IQR, interquartile range; n, number of patients.

La profilassi con concizumab risulta, ad analisi a 32 settimane, efficace nel ridurre gli ABR sia in presenza che in assenza di target joint

Un basso ABR viene osservato fino a 52 settimane

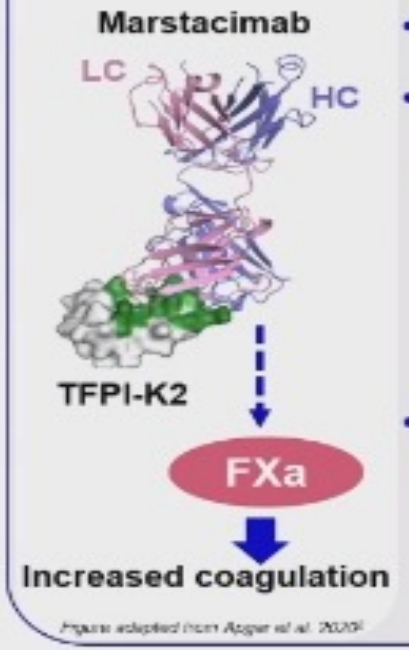
Concizumab risulta sicuro e ben tollerato

Blood (2024) 144 (Supplement 1): 715

Gli studi clinici relativi a Marstacimab (BASIS study)

Marstacimab (PF-06741086)

Marstacimab[1-3]



- A monoclonal IgG1 antibody
- Targeting the K2 domain of tissue factor pathway inhibitor
  - Reduce inhibition of the extrinsic coagulation pathway and rebalance hemostasis independently of FVIII and FIX activity
- A prophylactic treatment for people with severe HA (FVIII <1%) or moderately severe to severe (FIX ≤2%) HB, with or without inhibitors

Phase 1 and Phase 2 Studies[1,4]

For adults with HA or HB, with or without inhibitors

- **Marstacimab 150–450 mg SC QW:** safe and reduced bleeding events

The BASIS Study[5]

- Ongoing pivotal phase 3 study (NCT03938792)
- Participants with severe HA (FVIII <1%) or moderately severe to severe HB (FIX ≤2%) with or without inhibitors
- **Marstacimab 150 mg SC QW:** reduced treated bleeds in those without inhibitors

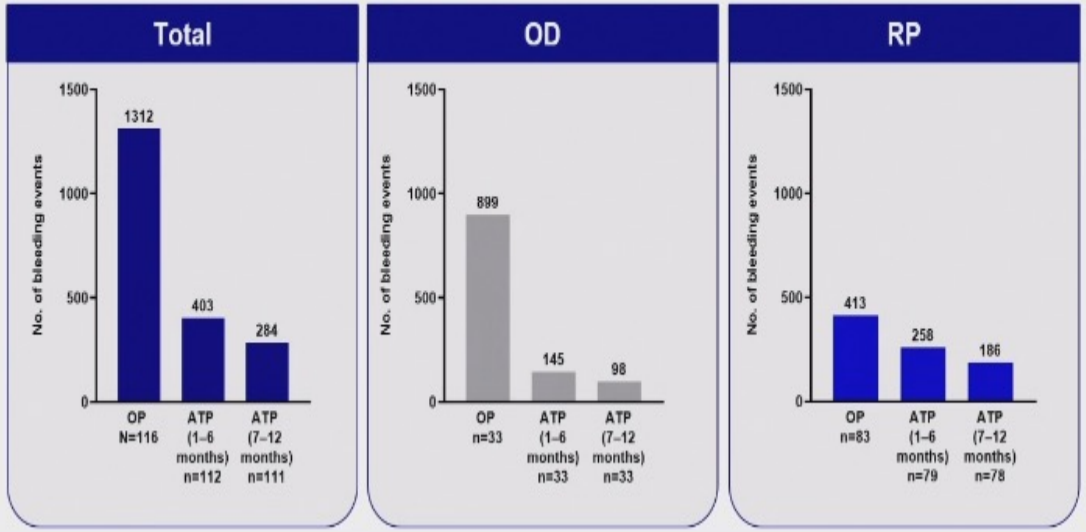
FVIII=factor VIII; FIX=factor IX; FXa=activated factor X; HA=hemophilia A; HB=hemophilia B; HC=heavy chain; IgG1=immunoglobulin G1; LC=light chain; QW=once a week; SC=subcutaneous; TFPI=tissue factor pathway inhibitor

1. Mahlangu JN, et al. Br J Haematol 2023;200(2):229-39. 2. Apgar J, et al. Res Pract Thromb Haemost 2020;4(suppl 1) [abstract]. 3. Pittman DD, et al. Res Pract Thromb Haemost 2022;6:e12679. 4. Mahlangu JN, et al. Br J Haematol 2023;200:240-8. 5. Molano D, et al. Blood 2023;142(S1):285.

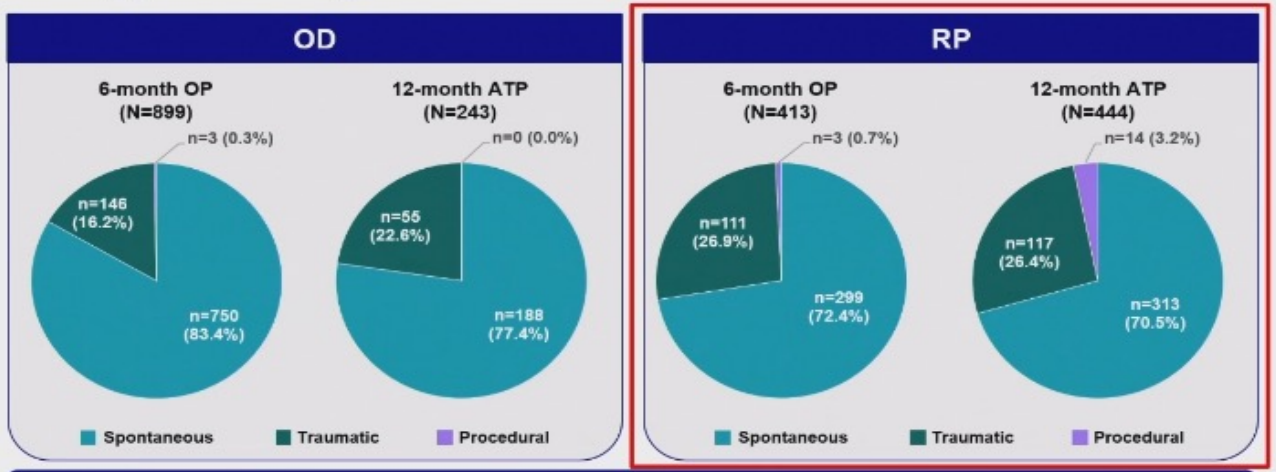
Descriptive Characterization of Bleeding Events in Participants With Severe Hemophilia A or B Without Inhibitors, Receiving Prophylactic Marstacimab Treatment

Davide Matino, Travis Gould, John Teeter, Carrie Turich Taylor, Regina McDonald, Andrew Palladino

Number of bleeding events



Etiology of bleeding events



- The majority of bleeding events were spontaneous in both OD and RP groups

ATP=active treatment phase; n=number of participants with bleeding event; N=denominator for each percentage; OD=on-demand; OP=observational phase; RP=routine prophylaxis

Il trattamento con marstacimab si associa ad una maggiore quota di «zero bleeds» per ciascun periodo di trattamento attivo (ATP, 6 mesi) vs periodo di osservazione (OP) pre terapia

Gli eventi emorragici registrati sono per lo più: Spontanei, articolari e trattati con terapia sostitutiva

Blood (2024) 144 (Supplement 1): 716.

Mim8 e gli studi FRONTIER

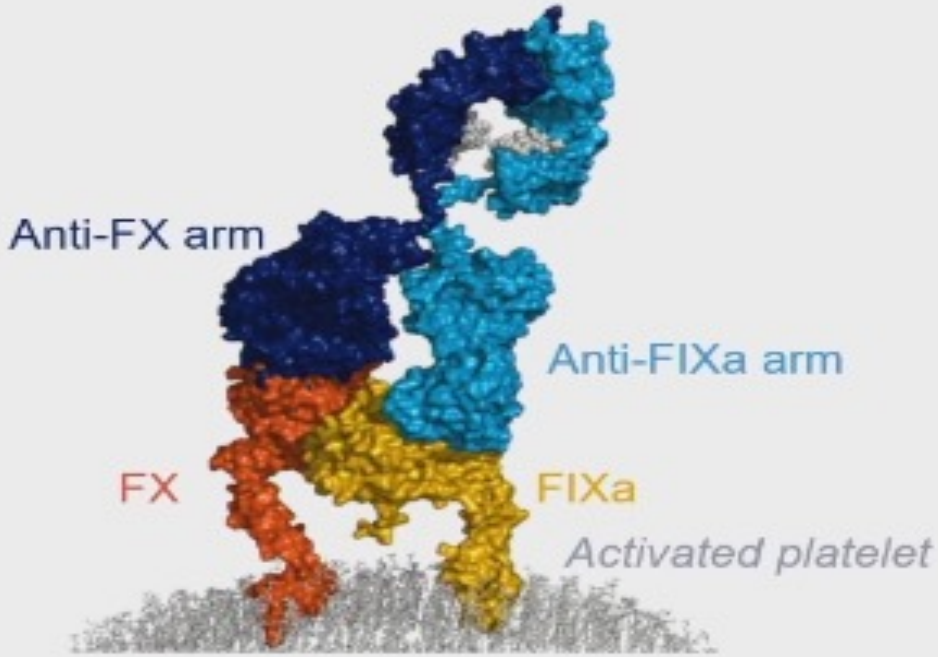
Introduction

Mim8 (denecimig) is a next-generation, activated FVIII mimetic, human bispecific IgG4 antibody. Mim8 is in clinical development as an SC prophylactic option for HA with or without FVIII inhibitors

Data from the phase 1/2 FRONTIER1 study demonstrated that Mim8 was well tolerated, and no safety concerns were observed[1,2]

The phase 3 FRONTIER2 study demonstrated superiority of QW and QM Mim8 prophylaxis for reducing ABR versus on-demand treatment and versus CFC prophylaxis during the run-in period[3]

Here we report data for Q2W dosing of Mim8 from an interim analysis of FRONTIER4* (NCT05685238)



*A phase 3, open-label extension study enrolling patients (adults and adolescents aged ≥12 years with HA with or without inhibitors) from FRONTIER1 (Arm 1) or several phase 2/3 studies of Mim8 (Arm 2).
ABR, annualized bleeding rate; CFC, clotting factor concentrate; FVIII, factor VIII; FIX, factor IX; FIXa, activated factor IX; HA, hemophilia A; IgG4, immunoglobulin G4; Q2W, once every 2 weeks; QM, once every month; QW, once every week; SC, subcutaneous. 1. Persson P, et al. Res Pract Thromb Haemost 2023;7:102181; 2. Lentz SR, et al. J Thromb Haemost 2024;22:990–1000; 3. Mancuso ME, et al. Oral presentation LB01.5 at the International Society on Thrombosis and Haemostasis Congress, Bangkok, Thailand, June 23, 2024.

Safety and Efficacy of Mim8 Prophylaxis Administered Once Every Two Weeks for Patients with Hemophilia A with or without Inhibitors: Interim Analysis of the FRONTIER4 Open-Label Extension Study

Tadashi Matsushita, Pratima Chowdary, Atanas Banchev, Kaan Kavakli, Johanna A. Kremer Hovinga, Jerzy Windyga, Victor Jiménez-Yuste, Julien Bovet, Llenalia María García Fernández, Guy Young

No treatment-emergent adverse events were related to Mim8 Q2W (26 weeks)

	Mim8 Q2W (n=37) n (%) Event [Rate]*
AEs	20 (54) 60 [3.25]
SAEs	2 (5) 3 [0.16]
SAEs considered related to trial product	
Probable/Possible	0 (0)
Severity	
Severe	1 (3) 1 [0.05]
Moderate	7 (19) 10 [0.54]
Mild	17 (46) 49 [2.65]
Injection-site reactions†	2 (5) 14 [0.76]

Total Mim8 exposure time: **18.46 years**

No AEs of special interest (TEs/TMAs) or hypersensitivity reactions were reported

Serious AEs were considered unlikely to be related to Mim8 and resolved
- 1 patient:
  - Initial report: aggression and craniocerebral injury
  - Follow up report: "physical harm" during an assault
- 1 patient: umbilical hernia‡

2 patients reported mild transient injection-site reactions, with most signs/symptoms captured as erythema and itching

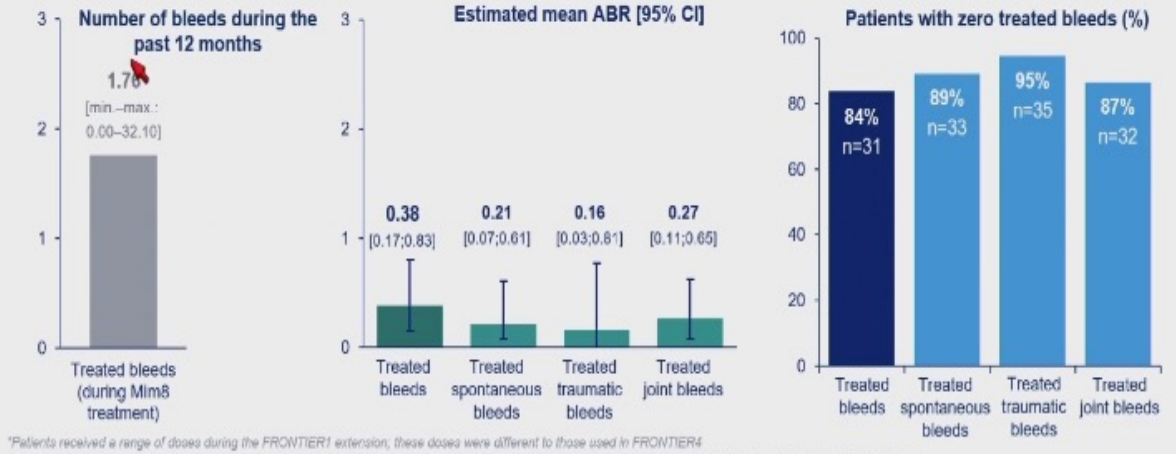
One patient (with no bleeding episodes) had a low-titer positive ADA result with no impact on Mim8 concentration or Mim8 activity

*Event: number of adverse events; rate: number of adverse events per participant-year of exposure (number of event/total time on treatment).
†Investigator's categorization following clinical study protocol. ‡The umbilical hernia (serious AE) was surgically corrected with no complications.
ADA, anti-drug antibody; AE, adverse event; n, number of patients; Q2W, once every 2 weeks; SAE, serious adverse event; TE, thromboembolic event; TMA, thrombotic microangiopathy.

Annualized bleeding rates were low during 26-week prophylaxis with Mim8 Q2W in FRONTIER4

FRONTIER1 MAD extension (N=37) Mim8 QW or QM*

FRONTIER4 (N=37) Mim8 Q2W



*Patients received a range of doses during the FRONTIER1 extension; these doses were different to those used in FRONTIER4.
ABR was estimated using a negative binomial model. The model includes historical annualized bleeding rate as a covariate and the logarithm of exposure time as offset.
ABR, annualized bleeding rate; CI, confidence interval; max., maximum; min., minimum; Q2W, once every 2 weeks; QM, once every month; QW, once every week.

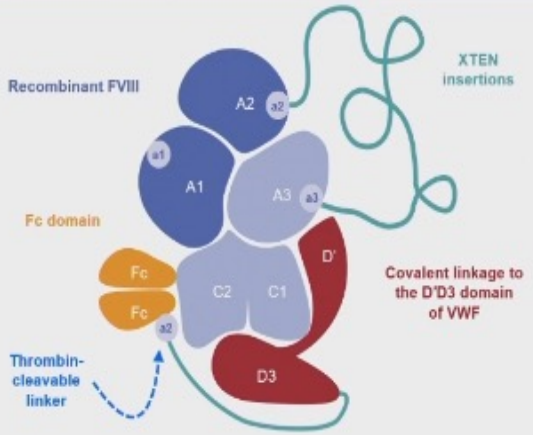
Profilassi con Mim8 ben tollerata a 26 sett nello studio FRONTIER4. Trattamento ben tollerato in assenza di eventi avversi (i.p. zero trombosi)

Blood (2024) 144 (Supplement 1): 718.

Emofilia A : terapie innovative (sostitutive)

Gli studi clinici relativi a Efanesoctocog-alfa (XTEND-ed study)

Efanesoctocog alfa is a novel fusion protein that overcomes the VWF-imposed half-life ceiling[1,2]



FVIII Replacement Therapy

- Standard half-life (SHL) factor
- Extended half-life (EHL) factor
- High-sustained factor (HSF)

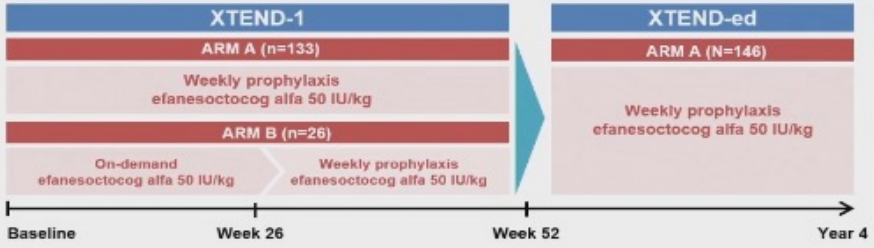
In the XTEND-1 study (NCT04161495), once-weekly efanesoctocog alfa 50 IU/kg prophylaxis[3]

- Achieved **high-sustained factor levels** in the **normal to near-normal range** (>40%) for the majority of the week
- **Provided superior bleed protection compared with prior factor prophylaxis**, with clinically meaningful improvements in physical health, pain, and joint health

FVIII, factor VIII; VWF, von Willebrand factor.
1. Chhabra ES, et al. *Blood*. 2020;135(17):1484-1496. 2. Konkle BA, et al. *N Engl J Med*. 2020;383(11):1018-1027. 3. von Drygalski A, et al. *N Engl J Med*. 2023;388(4):310-318.

XTEND-ed: An Ongoing, Multicenter, Open-Label Study of the Long-Term Safety and Efficacy of Efanesoctocog Alfa

Previously treated patients (≥12 years) **with severe hemophilia A** who completed XTEND-1, were eligible to enroll into the long-term XTEND-ed study[a]



Primary endpoint

- Occurrence of inhibitor development[b]

Secondary endpoints

- Annualized bleed rates (ABRs)
- Treatment of bleeding episodes
- Change in quality-of-life measures
- Safety and tolerability

Interim outcomes in adults/adolescents ≥12 years of age from XTEND-1 (Data cut: Feb 22, 2024)

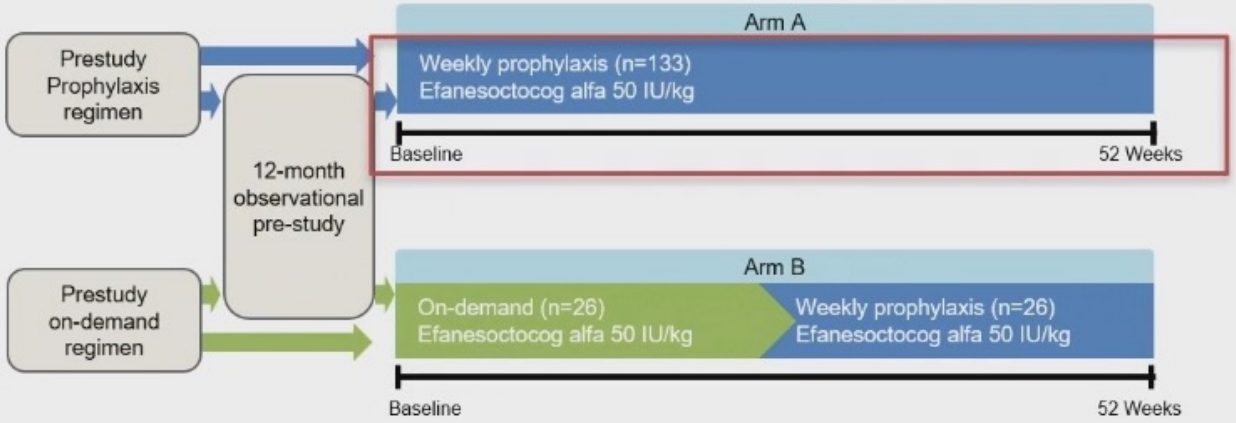
[a]Subjects <12 years who completed XTEND-Kids could enter XTEND-ed. [b]Inhibitor development was evaluated using the Nijmegen-modified Bethesda assay at the central laboratory. Inhibitor development was defined as an inhibitor result of ≥0.6 BU/mL and confirmed by a second test result from a separate sample drawn 2–4 weeks following the date of the original sample.

Association Between Hemophilia Joint Health Score and Quality of Life Using Results from the XTEND-1 Efanesoctocog Alfa Phase 3 Trial

Christoph Königs, Doris V. Quon, Cedric Hermans, Nana Kragh, Jérôme Msihid, Emilie Gerard, Duygu Bozkaya, Linda Bystricka, Cecile LeCamus, Elena Santagostino, Annemieke Willemze, and Annette von Drygalski

XTEND-1 population

Previously treated adults and adolescents aged ≥12 years with severe hemophilia A, without inhibitors[1]



Joint health endpoints

- HJHS total score change and target joint HJHS changes from baseline to Week 52
- Participants were categorized into 2 subgroups according to change from baseline in HJHS at Week 52:*
  Improvement [CFB ≤–2] or **Maintenance [–2< CFB <2]** versus **Worsening [CFB ≥2]**

PRO endpoints

Change from baseline at Week 52 for the PRO domains:†

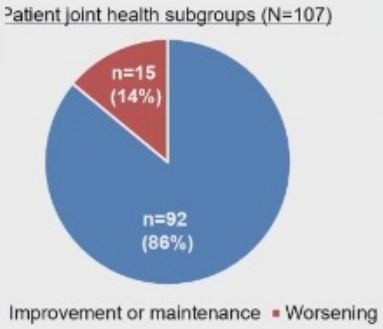
- **Overall QoL:** Haem-A-QoL total score
- **Physical function:**
  - Haem-A-QoL Physical Health domain;
  - PROMIS-SF Physical Function 6b (PROMIS PF) T-score
- **Pain Intensity:**
  - PROMIS-SF Pain Intensity 3a (PI) worst score
  - PROMIS-SF Pain Intensity 3a (PI) T-score

Blood (2024) 144 (Supplement 1): 719.

Association Between Hemophilia Joint Health Score and Quality of Life Using Results from the XTEND-1 Efanesoctocog Alfa Phase 3 Trial

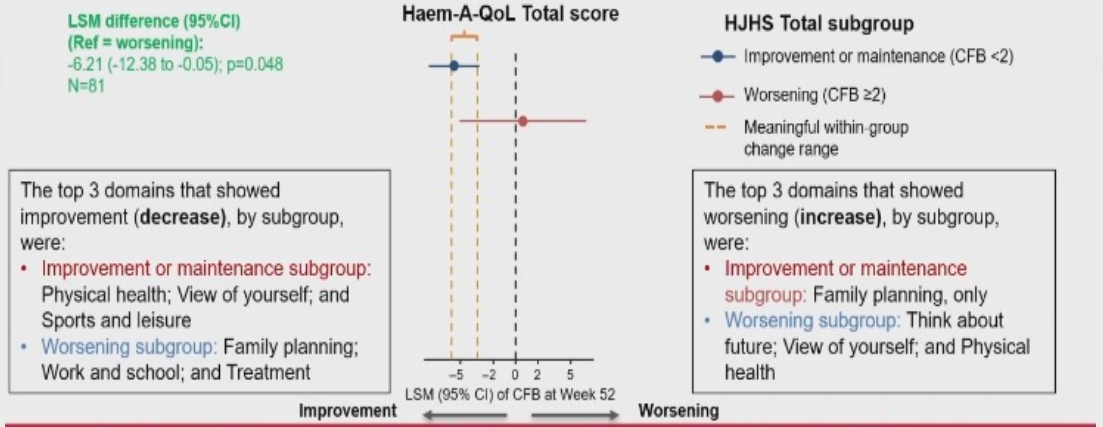
Christoph Königs, Doris V. Quon, Cedric Hermans, Nana Kragh, Jérôme Msihid, Emilie Gerard, Duygu Bozkaya, Linda Bystrická, Cecile LeCamus, Elena Santagostino, Annemieke Willemze, and Annette von Drygalski.

Changes in HJHS total score after 52 weeks of once-weekly efanesoctocog alfa prophylaxis



HJHS total score*	Patient joint health subgroup: Improvement or maintenance (CFB <2) (n=92)	Worsening (CFB ≥2) (n=15)	All (N=107)
Baseline			
Mean (SD)			18.14 (18.67)
Median			12.00
Min; max			0.0; 98.0
Week 52			
Mean (SD)			16.62 (17.79)
Median			12.00
Min; max			0.0; 98.0
Change from baseline at Week 52			
Mean (SD)			-1.52 (6.41)
Median			0.00
Min; max			-26.0; 24.0

Improvement in **overall QoL** at Week 52 was significantly higher in patients with improvement or maintenance vs those with worsening joint health



La salute articolare correla con QoL

I pazienti che hanno un miglioramento della salute articolare presentano una più alta quota di cambiamenti statisticamente significativi in QoL, dolore e funzionalità fisica

Blood (2024),144(Supplement 1):719

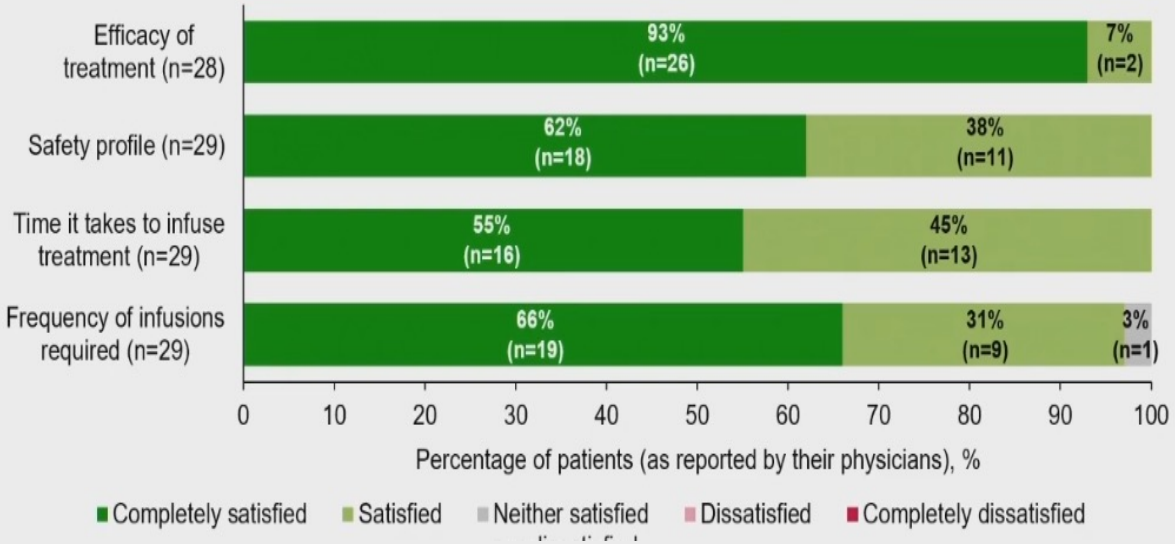
Real-world Experience of Switching to Prophylactic Efanesoctocog Alfa in Patients with Moderate and Severe Hemophilia A: An Analysis of the Adelphi Hemophilia Wave III Disease Specific Programme™

Maissaa Janbain, Miguel A. Escobar, Manuel Carcao, Andrew Wilson, Jennifer Dumont, Nathan Ball, Ella Morton, Duygu Bozkaya, Anne-Laure Tardy and Sylvie Bozzi

Estimated mean ABR was low for patients after switching to efanesoctocog alfa treatment

Outcome	
Time since initiating efanesoctocog alfa, days	n=29
Mean (SD)	268.1 (71.7)
Median (IQR)	265.0 (200.0–313.0)
Range	170–420
Dose per injection, IU/kg	n=28
Mean (SD)	49.3 (3.8)
Range	30–50
Frequency of treatment, days	n=28
Mean (SD)	6.9 (0.4)
Range	5–7
Estimated ABR after switching to efanesoctocog alfa treatment*	n=28
Mean (95% CI)	0.2 (–0.01; 0.41)
Median (IQR)	0 (0–0)

Physicians were satisfied with efanesoctocog alfa, mostly with its efficacy



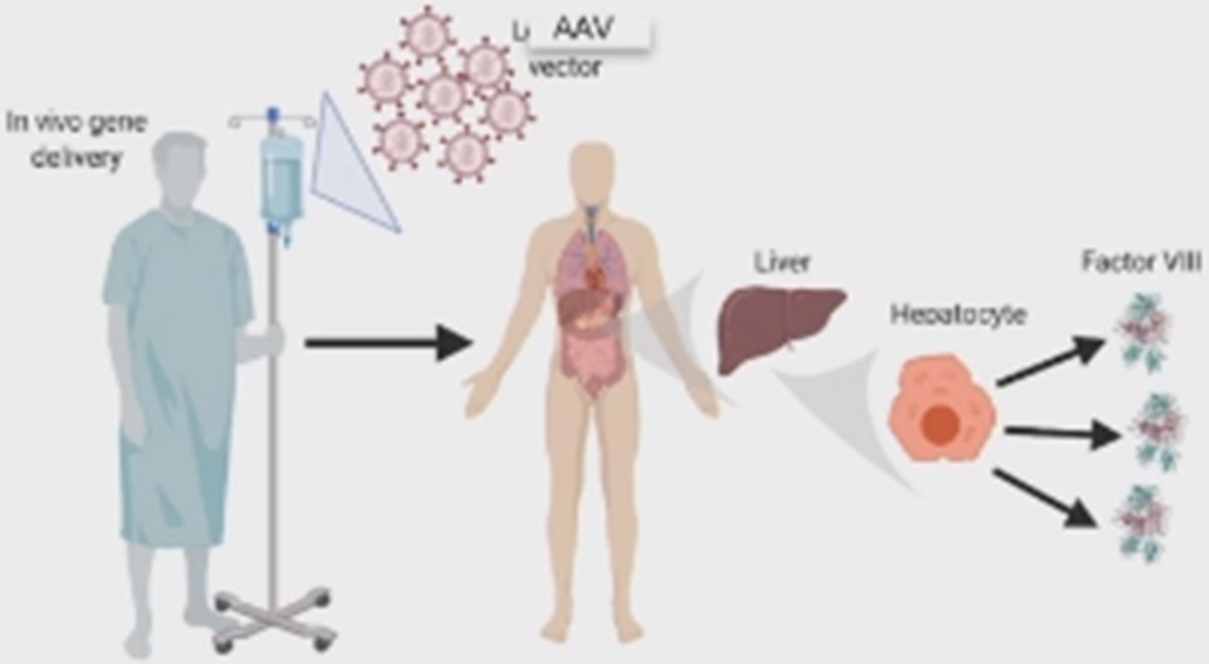
Blood 2024, 144(Supplement 1):131

Emofilia A : terapia genica

Factor VIII Expression from a Novel F8 Transgene through a Lentiviral Vector Transduced CD34+ Autologous Hematopoietic Stem Cells for Gene Therapy of Severe Hemophilia A: Final Results from a Phase 1 Clinical Trial Alok

Srivastava Aby Abraham, Fouzia Aboobacker, Gurbind Singh, Tulasi Geevar, Uday Kulkarni, Sushil

Adeno-associated virus vector based gene therapy for Hemophilia



Pros:

i. Bulk manufacturing of drug product
ii. Treatment as a peripheral vein infusion
iii. High initial expression in most patients
iv. Good safety profile so far

Cons:

i. Unpredictable initial levels of expression
ii. Progressive drop of expression after 6-12 months – particularly in hemophilia A – often associated with transaminitis, requiring immunosuppression
iii. Exclusion of many patients due to pre-existing anti-AAV antibodies (>50% in some parts of the world)
iv. Exclusion of children <12 years (liver maturity issues)

Blood (2024),144(Supplement 1):1052

Factor VIII Expression from a Novel F8 Transgene through a Lentiviral Vector Transduced CD34+ Autologous Hematopoietic Stem Cells for Gene Therapy of Severe Hemophilia A: Final Results from a Phase 1 Clinical Trial

Alok Srivastava, Aby Abraham, Fouzia Aboobacker, Gurbind Singh, Tulasi Geevar, Uday Kulkarni, Sushil Selvarajan et al.

Lentiviral gene therapy with CD34+ Hematopoietic Cells for Hemophilia A
A Phase 1 Clinical Trial

➢ ***Primary Objectives:*** ***To assess the safety and feasibility of*** CD68-ET3-LV vector transduced ***autologous hematopoietic stem cell transplantation*** in persons with severe hemophilia A

➢ ***Secondary Objective:*** ***To assess efficacy of this therapy through changes in plasma FVIII activity*** and its **impact on clinical bleeding phenotype**

Inclusion Criteria	Exclusion Criteria
Severe hemophiilia A with no inhibitors (FVIII activity <1%)	Presence of FVIII inhibitors (>0.6 BU/ml) or history of high titer inhibitor >5 BU/ml
Age: >18 to <45 years	Active hepatitis B or C infection
>100 exposures to FVIII products	
Able to provide required informed consent	

Lentiviral gene therapy with CD34+ Hematopoietic Cells for Hemophilia A
A Phase 1 Clinical Trial –

Stem cell mobilisation for HSCT

- G-CSF 5µg/kg/day x bd x 5 days + Plerixafor 0.24mg/kg

Stem Cell Dose - >2x10^6 CD34+/kg after transduction

→ An aliquot of unmodified CD34+ HSCs will be cryopreserved for rescue, if needed

HSCT – Conditioning Protocol

- Treosulfan - 14g/m^2 x 3 days (Days -5 to -3)
- Fludarabine - 30mg/m^2 x 4 days (Days -5 to -2)

→ Autologous transduced HSC infusion (Day 0)

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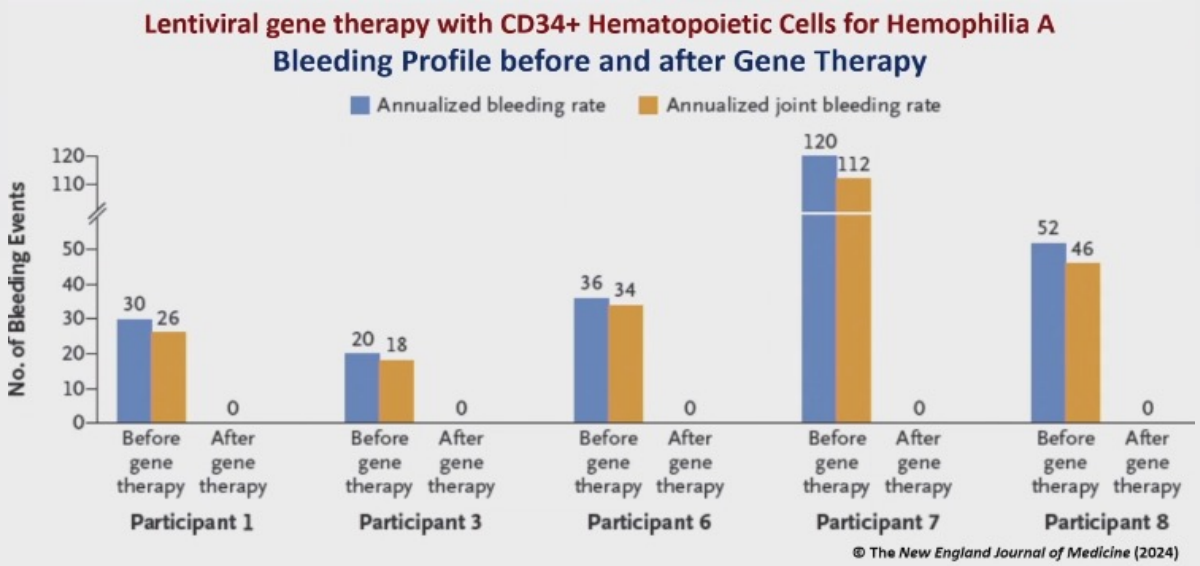
Lentiviral gene therapy with CD34+ Hematopoietic Cells for Hemophilia A
HSC Transplantation: Engraftment, Toxicities & FVIII expression

	P1	P3	P6	P7	P8
Age (years)	33	31	34	22	41
Weight (kg)	47	53.5	59.2	45.8	76.7
Engraftment Day – Neutrophil	+12	+10	+10	+12	+11
Engraftment Day – Platelet	+15	+12	+12	+15	+15
Severe neutropenia (days)	11	7	7	10	8
Severe thrombocytopenia (days)	1	3	2	4	7
Last FVIII CFC infusion day	+15	+20	+11	+17	+16
FVIIIC (%) – Median (range) Day +28 to last f/u	5.2 (3.0-8.7)	1.7 (1.0-4.0)	37.1 (18.3-73.6)	19.3 (6.6-34.5)	39.9 (20.6-55.1)
Follow-up (months)	27	19	14	12	9

*Conditioning related mucositis: <Grade 2
-All participants maintained oral intake through-out HSCT
*No clinically relevant hepatic, renal or other organ toxicities

→Semen examination (first 4 participants at >6 months post GT)
*Sperm count – Normal range: 4 / 4 (1 with reduced motility)



Sicurezza e tollerabilità di terapia con CD68-ET3-LT3-CD34+ in emofilia stabilite
Condizionamento e trapianto sono stati ben tollerati
La espressione di FVIII è risultata elevata e stabile
La risposta clinica è stata stabile ed eccellente con «zero» sanguinamenti spontanei

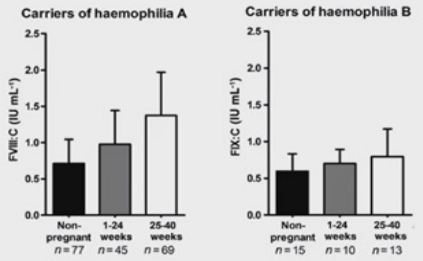
Blood (2024),144(Supplement 1):1052

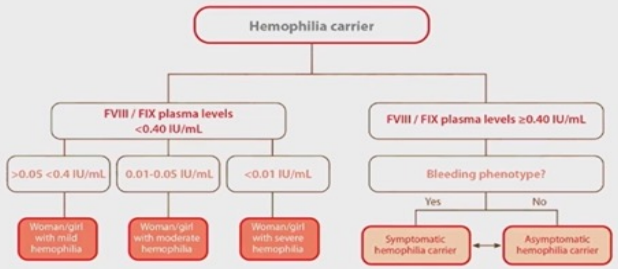
Haemophilia carriers

Postpartum Hemorrhage in Hemophilia A and B Carriers After Enhanced Prophylactic Clotting Factor Suppletion

The PRegnancy and Inherited Bleeding DisordErS Study

Hemophilia carriers and pregnancy



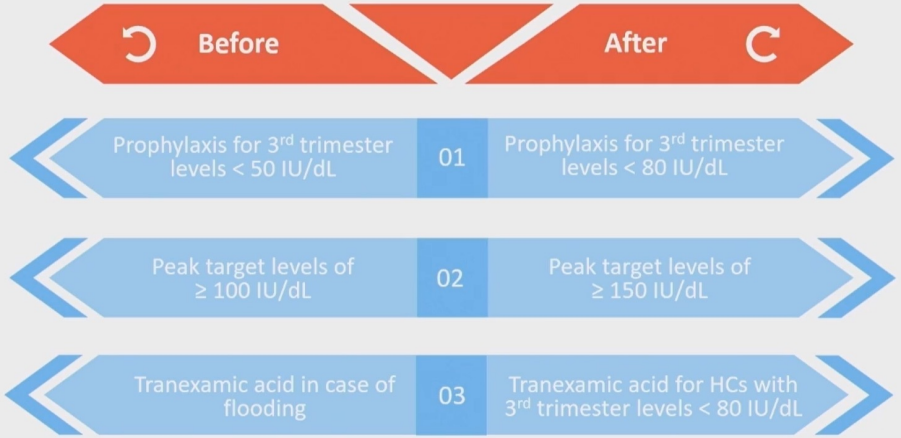


UMC Utrecht

Stoof et al. 2015, van Galen et al. 2021

1 IU/mL = 100%

Guideline revision (2018)



UMC Utrecht

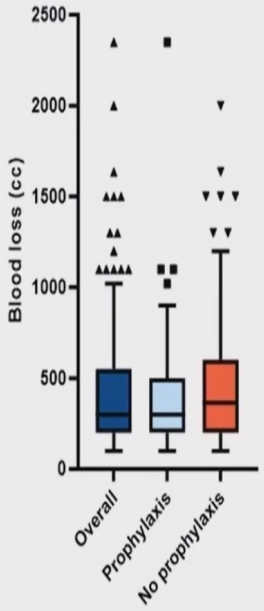
HC hemophilia carriers

Studio su portatrici di emofilia A e B. Schema decisionale basato sui livelli FVIII/FIX
Aumento soglia profilassi nel terzo trimestre da 50 a 80 IU/dL
Incremento livelli target da 100 a 150 IU/dL
Nuovo approccio con acido tranexamico per livelli < 80 IU/dL
Le modifiche indicano un approccio più preventivo nella gestione delle portatrici durante la gravidanza.

Blood (2024) 144 (Supplement 1): 129.

Postpartum Hemorrhage in Hemophilia A and B Carriers After Enhanced Prophylactic Clotting Factor Suppletion

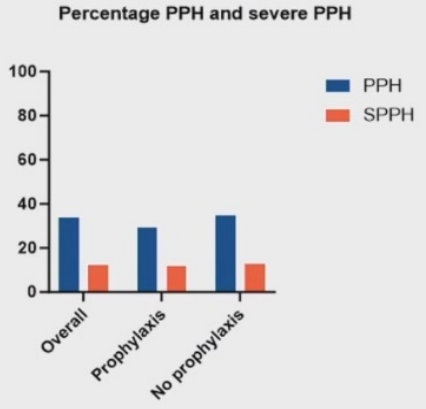
The PRegnancy and Inherited Bleeding DisordErS Study



	Prophylaxis (n=34)	No prophylaxis (n=136)	P-value
	N (%)	N (%)	
Blood loss±	300 (200-500)	365 (200-580)	0.27
Prophylaxis	25 (73.5)	3 (2.2)	<0.05
Caesarian section	5 (14.7)	36 (26.5)	0.23
Episiotomy	6/29 (20.7)	18/100 (18.0)	0.95
Tranexamic acid	28 (82.4)	77 (56.6)	<0.05
Perineal laceration	15 (44.1)	56 (41.2)	0.91
Placental retention	1 (2.9)	10 (7.4)	0.70

± Median (interquartile range)

Results – Postpartum hemorrhage incidence



	Overall	Prophylaxis (n=34)	No prophylaxis (n=136)	P-value
PPH (≥ 500 ml)	33.5%	29.4%	34.6%	0.71
Severe PPH (≥ 1000 ml)	12.4%	11.8%	12.5%	1.00

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(S)PPH (severe) postpartum hemorrhage [16]

Blood (2024) 144 (Supplement 1): 129.

MANAGEMENT AND OUTCOMES OF PREGNANCY AND CHILDBIRTH IN KNOWN AND UNKNOWN HEMOPHILIA CARRIERS: 10 YEARS RETROSPECTIVE EVALUATION FROM SOUTHERN ITALY

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INTRODUCTION

Women carriers of hemophilia (HC) or affected by haemophilia (HW) are often asymptomatic, but they may experience bleeding, in particular during menses, pregnancy, childbirth, and the postpartum period, when management may be particularly challenging if HC status is unknown or not adequately addressed before. Data regarding the correlation between bleeding symptoms and coagulation FVIII/FIX levels in HCs are conflicting, mainly due to considerable phenotypic variability. There are no specific guidelines, scientific societies still debate on the optimal mode of delivery and treatment

AIM

This retrospective, observational study, conducted in Italy in 2022, aims to describe how known and unknown HC were managed during pregnancy and delivery, by evaluating clinical, laboratory parameters and the need for any replacement therapy (RT). The study aims to collect data to understand the most commonly adopted diagnostic and therapeutic measures for women with hemophilia during pregnancy, childbirth, and postpartum.

METHOD

This study is national, and we here report the analysis performed on two regions of Southern Italy, in detail from two Haemophilia Centers in Palermo and Catanzaro. Following the approval of the Ethics Committee, HC were enrolled through Informed Consent from January 2022 to December 2022. HC and HW were defined according to the new nomenclature from ISTH. The following data were collected: age, ISTH bleeding score, genetic testing, complete blood cell count, age of menarche, awareness of HC status and age of diagnosis, prenatal diagnosis, number of pregnancies, type of delivery, FVIII and FIX levels, post-partum bleeding, and pregnancy-related complications

RESULTS

Twenty women were recruited, median age 37 y.o (22;48), at diagnosis 30 y.o (18;41), 13 from Palermo and 7 from Catanzaro, totaling 11 HC and 6 HW with Hemophilia A and 2 HC and 1 HW with Hemophilia B (Table). The hemorrhages reported were secondary to abnormal menstrual blood loss (9/20; 45%) and the postpartum period. Data were collected on 48 pregnancies, mean 2.4 (1;5), delivered to term with a total of 36 vaginal deliveries and 12 cesarean deliveries. HC status was previously known only in 4 of the 20 women. Delivery and postpartum bleeding requiring medical intervention (pRBC transfusions and antifibrinolytic agents) was observed in 2(15%) HC and 3(43%)HW. Contrasting data were found when comparing the two centers' populations. In Palermo's cohort delivery and postpartum bleeding was observed in 2(20%) HC and 1(33%) HW. In the cohort from Catanzaro delivery and postpartum bleeding was observed in 0 HC and 2(50%) HW. Peripartum anesthesia was performed in 24(50%) deliveries. Episiotomy was performed in 13(27%) deliveries. No significant differences were observed between HC and HW regarding the incidence of bleeding. However, a difference between the two centers was observed: incidence of hemorrhages was different in Palermo, where HC experienced more hemorrhages during pregnancy and postpartum than HW, while in Catanzaro, HW experienced more bleeding than HC. A single HC enrolled with a BMI30 and FVIII/IX levels above 100% had a higher incidence of bleeding compared to other HC and HW, presenting severe hemorrhages that require treatment. In women with more than one pregnancy, the management did not change after the discovery of their HC status. Interestingly 17 women out of 20 were managed outside their referral haemophilia centers and haematologist was not consulted. Only 3 women were followed during pregnancy; prenatal diagnosis was not performed, but in agreement with the gynecologist, deliveries were managed a cesarean section to avoid a potential instrumental delivery.

Demographic data,pregnancies and deliveries in the enrolled

Characteristic	Data
Median age (years)	37 (22;48)
Age at diagnosis (years)	30 (18;41)
Recruitment location	13 Palermo, 7 Catanzaro
Hemophilia type (A/B)	11 HC A, 6 HW A, 2 HC B, 1 HW B
Hemorrhages (abnormal menstrual blood loss)	9/20 (45%)
Number of pregnancies	48 pregnancies, mean 2.4 (1;5)
Type of delivery (vaginal/cesarean)	36 vaginal, 12 cesarean
Known HC status before pregnancy	4/20
Delivery and postpartum bleeding requiring intervention	2 HC, 3 HW
Peripartum anesthesia	24/48 (50%)
Episiotomy	13/48 (27%)
BMI > 30 with FVIII/IX > 100%	1 HC with severe hemorrhages
Management by referral centers	17/20 managed outside referral centers

CONCLUSIONS

The management of HC and HW during pregnancy and childbirth in the last ten years is quite variable, however pregnancy related complications occur in a not neglegible number of patients, this mirrors the absence of specific guidance on haemophilia

ACKNOWLEDGEMENT

Thanks to all haemophila carriers enrolled

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Karanth L, Abas AB. Maternal and foetal outcomes following natural vaginal versus caesarean section (c-section) delivery in women with bleeding disorders and carriers. Cochrane Database Syst Rev. 2021 Dec 9;12(12):CD011059.

CONTACT

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Grazie!