POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

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Malattie emorragiche su base costituzionale

Mariasanta Napolitano

Topics

Malattia di von Willebrand

Haemophilia carriers

Emofilia A e B: terapie innovative

Emofilia A e B: terapia genica

The Impacts of Genetic Polymorphisms on the Von Willebrand Factor Level in Type 1 Von Willebrand Disease

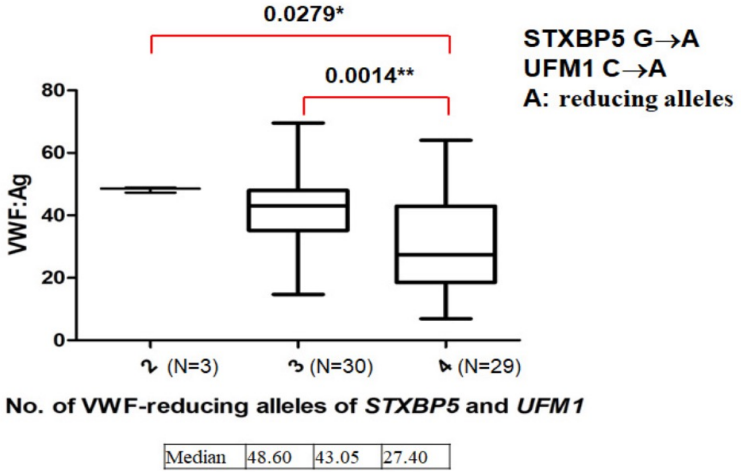
Yeu-Chin Chen

Blood 142 : 286

Table 1. The gender age, VWF antigen, VWF:Act and FVIII:C in the 62 patients with von Willebrand disease

Age median, range	32, 5-67
Blood type: O type (%)	81.7%
Bleeding Score*, median	5 (0-20)
VWF:Ag, median	39.6 (6.9-69.6)
VWF:Ag, mean±SD	36.4±14.35
VWF:Act**, median	27.4 (1.4-48.8)
VWF:Act, mean±SD	27.1±12.74
FVIII:C, median	52.3 (4.9-129.5)
FVIII:C, mean±SD	53.6±21.52

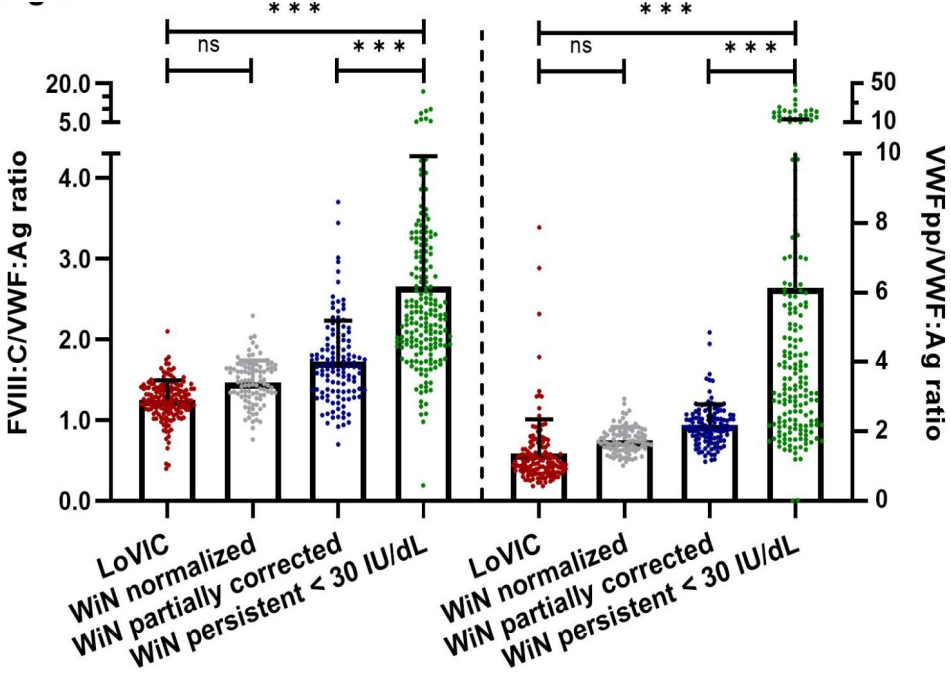
*Available in 43 patients
**VWF activity: 24 VWF:RCo and 38 VWF:ACL.



Le varianti A dei geni UFM1 (G>>A) e STXBP5 (C>>A) sono associate a ridotti livelli di vWF: Ag . Quattro varianti alleliche combinate di UFM1 e STXBP5 genes esercitano il massimo effetto di riduzione VWF: Ag

The Relationship between Low Von Willebrand Factor, Type 1 Von Willebrand Disease and Ageing – Novel Insights from the Lovic and Win Cohort Studies

Ferdows Atiq, Blood 142 : 509



Prevalenza sovrapponibile di mutazione gene *VWF* (36.4% vs 22.6% p=1.000), FVIII:C/VWF:Ag ratio (1.24 ±0.24 vs 1.46 ±0.27 , p=0.444) e VWFpp/VWF:Ag ratio (1.36 ±0.99 vs 1.75 ±0.38 , p=1.000) tra le coorti LoVIC e WiN.

Pazienti dalla coorte WiN con livelli persistenti di VWF <30 IU/dL presentano più spesso varianti genetiche di *VWF* (93.0%), più elevato FVIII:C/VWF:Ag (2.65 ±1.62) e VWFpp/VWF:Ag ratio (6.14 ±7.05) rispetto agli altri gruppi

Age Regulates Desmopressin Responses in Patients with Low Von Willebrand Factor and Type 1 Von Willebrand Disease in the Lovic and Win Studies

Ferdows Atiq, Blood 124:510

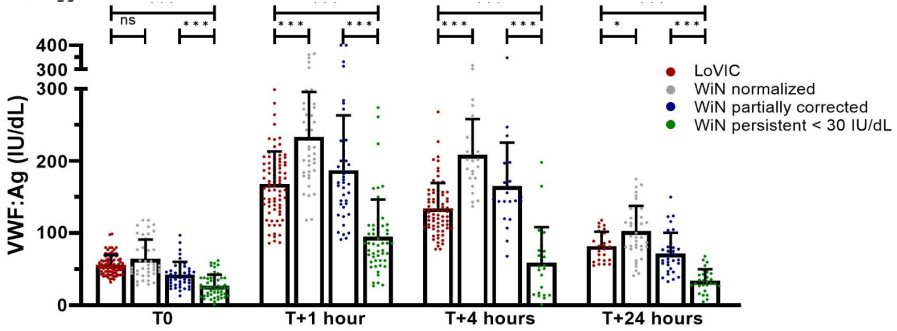
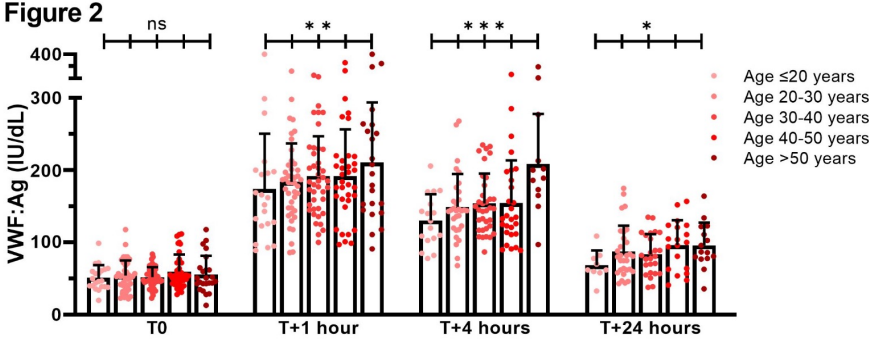


Figure 2



Desmopressina determina incremento significativo di vWF in pazienti con vWD e bassi livelli di VWF durante invecchiamento.

Effetto età-correlato su incremento di vWF 1, 4 e 24 ore dopo desmopressina

Soggetti anziani presentano sia una migliore risposta iniziale (a 1 h) a desmopressina che un incremento di emivita di vWF a 4 ore dopo desmopressina

Characterization of Joint Disease in Women with Hemophilia: The Carriers Ultrasound Project (CUP) Study

Rachel S. Kronenfeld, Blood 142:29

Table 2: Comparison of Carriers by Factor Activity

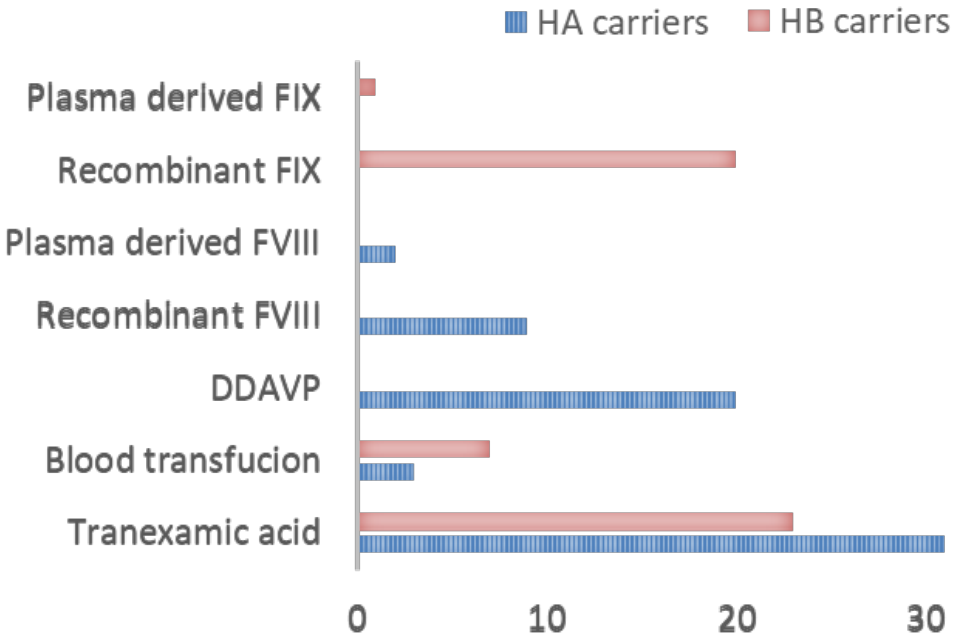
Characteristic	Factor Activity >40% (n=23)	Factor Activity <40% (n=5)	P Value
Age (years)			
Mean Age (SD)	31.1 (5.9)	32.6 (7.8)	P=0.63
Median Age (95% CI)	33.0 (29-36)	35 (34-39)	P=0.33
BMI			
Mean BMI (SD)	26.9 (5.3)	21.4 (2.7)	**P=0.03**
Median BMI (95% CI)	24.8 (23.4-30.1)	20.8 (20.3-26.1)	P=0.33
Factor Activity (%)			
Mean (SD)	61 (18)	30 (8)	P=0.001
Median (95% CI)	58 (53-71)	29 (27-39)	P=0.001
Bleeding Tendency (N, %)			
Any Bleeding Tendency	19 (82.6%)	4 (80%)	P=0.89
Heavy Menses	16 (69.6%)	2 (40%)	P=0.21
Epistaxis	6 (26.1%)	1 (20%)	P=0.78
Gingival Bleeding	6 (26.1%)	1 (20%)	P=0.78
Easy bruising	11 (47.8%)	3 (60%)	P=0.62
Joint Symptoms (N, %)			
Joint Pain	10 (43.5%)	3 (60%)	P=0.14
Joint Swelling	5 (21.7%)	4 (80%)	P=0.09
Joint Bleeding	3 (13%)	0 (0%)	P=0.39
Medications Prescribed (N, %)			
Factor Replacement	4 (17.4%)	3 (60%)	**P=0.046**
On-Demand	4 (17.4%)	3 (60%)	
Prophylaxis	0 (0%)	0 (0%)	
DDAVP	3 (13%)	2 (40%)	P=0.15
Anti-Fibrinolytic	4 (17.4%)	3 (60%)	**P=0.046**
HJHS Score			
Mean HJHS (SD)	4.3 (3.4)	6.6 (2.6)	P=0.16
Median HJHS (95% CI)	4.0 (3-6)	6 (6-10)	P=0.06
Abnormal HJHS (N, %)	19 (82.6%)	5 (100%)	P=0.31
HEAD-US Score			
Mean HEAD-US (SD)	0	0.2 (0.5)	P= 0.31
Median HEAD-US (95% CI)	0	0	N/A
Abnormal HEAD-US (N, %)	0	1 (20%)	P=0.06

Donne con emofilia sono a rischio maggiore di eventi emorragici e sintomi correlati a danno articolare, a prescindere dai livelli di Fattore.

Salute articolare valutata a HJHS e HEADUS peggiore rispetto alle non carriers.

Follow-up a lungo termine necessario per valuare alterazioni articolari,anche tramite RMN.

Proactive Systematic Hemophilia Carrier Screening: A Step Towards Gender Equity in Hemophilia Care



Evelien Krumb, Blood 142:288

Screening effettuato nel 44% della intera coorte di donne HC, status di carrier confermato geneticamente nel 73% delle madri, sorelle e figlie di pazienti con emofilia in età fertile.

Difficoltà nel fornire screening adeguato a tutte le donne geneticamente correlate con uno o più pazienti con emofilia.

PB1531

Management and outcomes of pregnancy and childbirth in known and unknown haemophilia carriers: a retrospective analysis from a reference Center in Italy

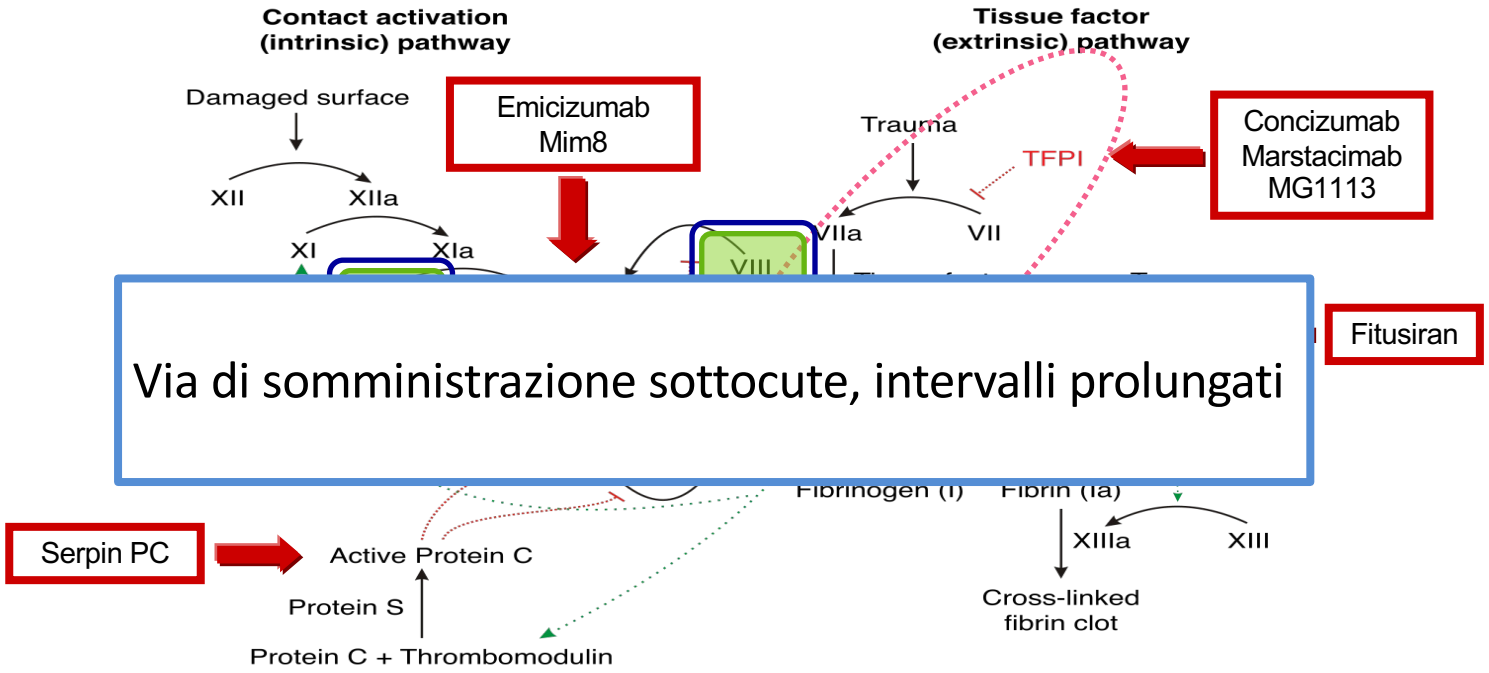
HC status is a still inadequately addressed condition, a more accurate report of pregnancy outcomes in HCis needed, a multicenter Italian study on this issue is currently ongoing.

Napolitano M, Siragusa S

Gestione di gravidanza, parto e post-partum in donne portatrici di emofilia A e B in Italia: studio osservazionale multicentrico retrospettivo.

AICE study group MEC donna

Le terapie non sostitutive in emofilia



Emicizumab Prophylaxis in Infants with Severe Hemophilia A without Factor VIII Inhibitors: Results from the Primary Analysis of the HAVEN 7 Study

Steven Pipe, Blood 142:505

Table 1. Bleeding outcomes in participants

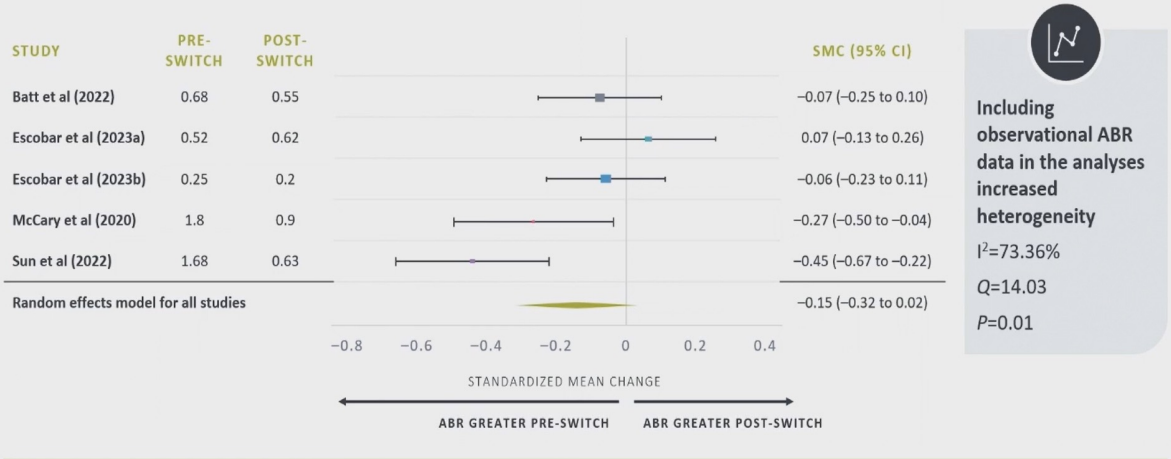
	Participants (N=55)
Model-based ABR (95% CI)	
All bleeds	2.0 (1.49–2.66)
Treated bleeds	0.4 (0.30–0.63)
Treated spontaneous bleeds	0.0*
Treated joint bleeds	0.0 (0.01–0.09)
Participants with zero bleeds, n (%)	
Zero all bleeds	9 (16.4)
Zero treated bleeds	30 (54.5)
Zero treated spontaneous bleeds	55 (100.0)
Zero treated joint bleeds	52 (94.5)
Participants with ≥1 bleed, n (%)	46 (83.6)
Total number of bleeds,† n	207
Cause/type of bleed, n (%)	
Spontaneous	**18 (8.7)**
Joint	0 (0.0)
Muscle	0 (0.0)
Other	18 (100.0)
Traumatic	**182 (87.9)**
Joint	4 (2.2)
Muscle	5 (2.7)
Other	173 (95.1)
Procedural/surgical‡	**7 (3.4)**
Muscle	1 (14.3)
Other	6 (85.7)
Participants with ≥1 treated bleed, n (%)	25 (45.5)
Total number of treated bleeds, n	42
Cause/type of treated bleed, n (%)	
Spontaneous	**0 (0.0)**
Traumatic	**42 (100.0)**
Joint	3 (7.1)
Muscle	5 (11.9)
Other	34 (81.0)

207 episodi emorragici (trattati o meno) per lo più traumatici, in 46 partecipanti.
Nessun soggetto con >3 sanguinamenti trattati.
37 partecipanti con 0–3 sanguinamenti,
9 con zero eventi emorragici
Emicizumab sicuro e ben tollerato in neonati e infanti (<12 mesi) con HA senza inibitori

Clinical Outcomes of Noninhibitor Patients with Hemophilia a Switching from Prophylaxis with Factor VIII to Emicizumab: A Meta-Analysis of Real-World Evidence Studies

Michael D. Tarantino, Blood 142:283

Results: Billed and Observational ABR Meta-analysis (Sensitivity Analysis)



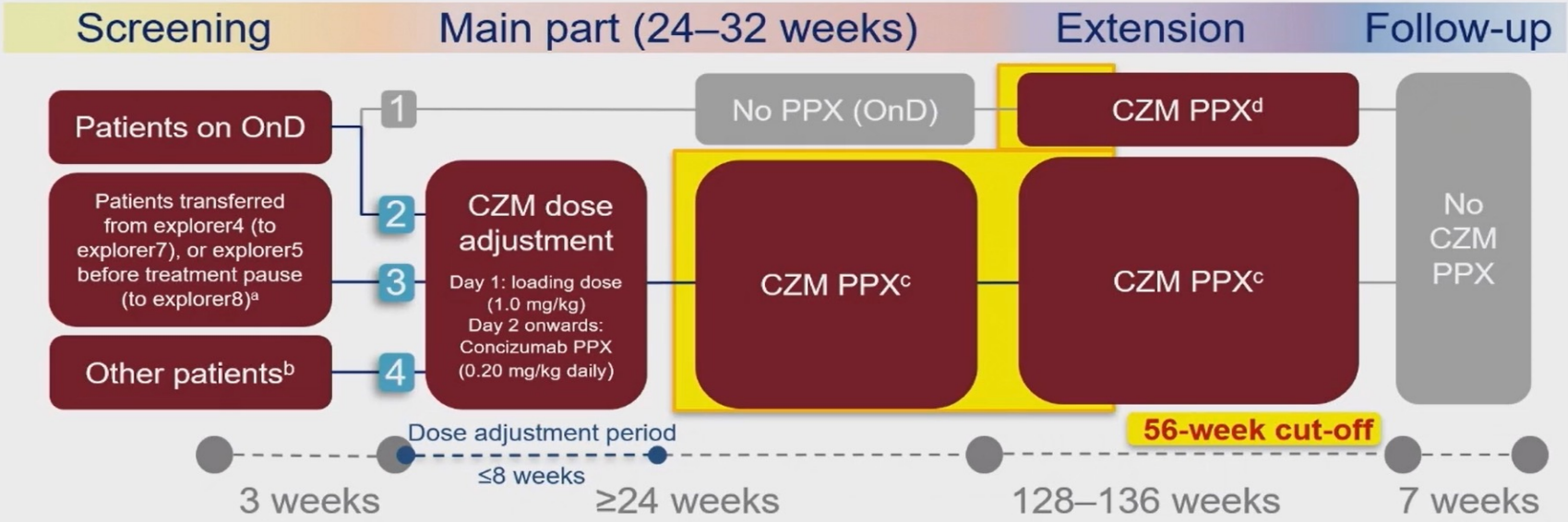
The pooled estimate indicates a statistically non-significant decline in ABR post-switch to emicizumab, with evidence of considerable heterogeneity across the studies

ABR, annualized bleeding rate; SMC, standardized mean change.

NON riduzione significative di ABR dopo switch a emicizumab, in particolare per bambini di età 3-6 aa

L'età potrebbe influire su variazioni in ABR dopo switch a emicizumab. Entità di azione di emicizumab comunque ridotta all'avanzare dell'età.

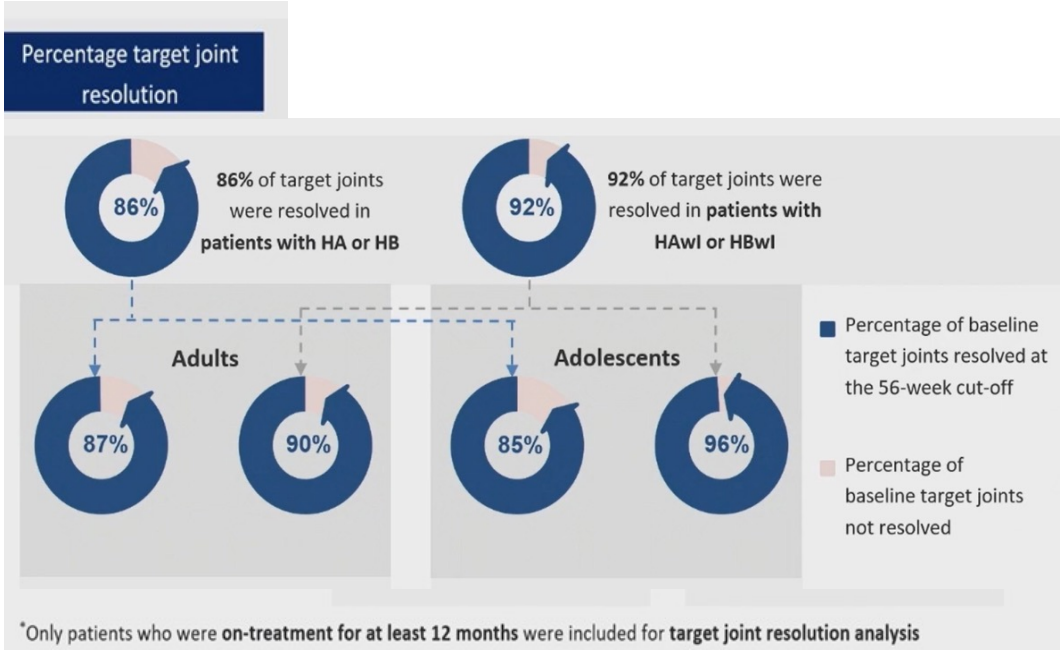
explorer7 and explorer8 trial design



[a]Arm 3 consists of patients who transferred from explorer4 to explorer7, and patients who transferred from explorer5 before the treatment pause into explorer8. [b]Additional patients on OnD treatment or patients on PPX with factor replacement, as well as patients from explorer5 who enrolled after treatment pause and patients from explorer5 randomised to arms 1 or 2 before the treatment pause. [c]The individual maintenance doses were 0.15, 0.20 or 0.25 mg/kg concizumab. [d]Dose adjustment period followed by maintenance dose.
CZM, concizumab; OnD, on demand; PPX, prophylaxis.

The Effect of Concizumab Prophylaxis on Target Joints, Resolution and Joint Bleeds in Patients With Hemophilia A or B With or Without Inhibitors in Phase 3 Clinical Trials

Guy Young , Blood 142:284



Concizumab risolve 86.3% delle target joints in pazienti con HA o HB e 91.8% delle target joints in pazienti con HAwI o HBwI, entro 12 mesi dall'inizio della profilassi.

ABRs mediano pari a ZERO per sanguinamenti spontanei o traumatici di target joint a 56 settimane in tutti i pazienti (HA,HB,HAwI,HBwI)

Surgical Procedures and Hemostatic Outcome in Patients with Hemophilia Receiving Concizumab Prophylaxis during the Phase 3 explorer7 and explorer8 Trials

Anthony KC Chan, Blood 142:30

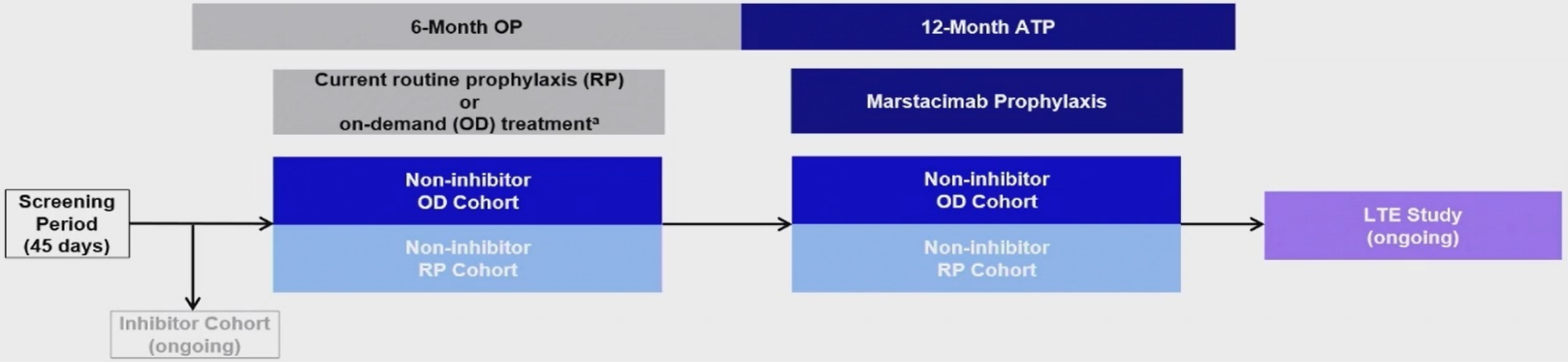
	Minor surgery			
	HA	HAwI	HB	HBwI
Pts who underwent surgical procedure, n	9	7	10	4
Total number of surgical procedures	13	10	11	4
Dental procedure	6	5	7	2
Arthrodesis	0	0	1	0
Colonoscopy	2	0	0	0
Other*	1	2	2	2

*Other surgeries included port removal, embolization, tongue mucus membrane injury, phimosis, venesection, pyoderma, urethral augmentation and hyaluronic acid infiltration. HA, hemophilia A without inhibitors; HAwI, hemophilia A with inhibitors; HB, hemophilia B without inhibitors; HBwI, hemophilia B with inhibitors; Pts, patients.

Procedure chirurgiche minori effettuate durante regolare profilassi con concizumab in ~11% dei pazienti arruolati nei due trials.
Prevalenti le procedure odontoiatriche con sanguinamenti lievi/moderati (gestiti con anti-fibrinolitici).
Procedure chirurgiche minori “safe” in corso di profilassi con concizumab.

BASIS: Study design

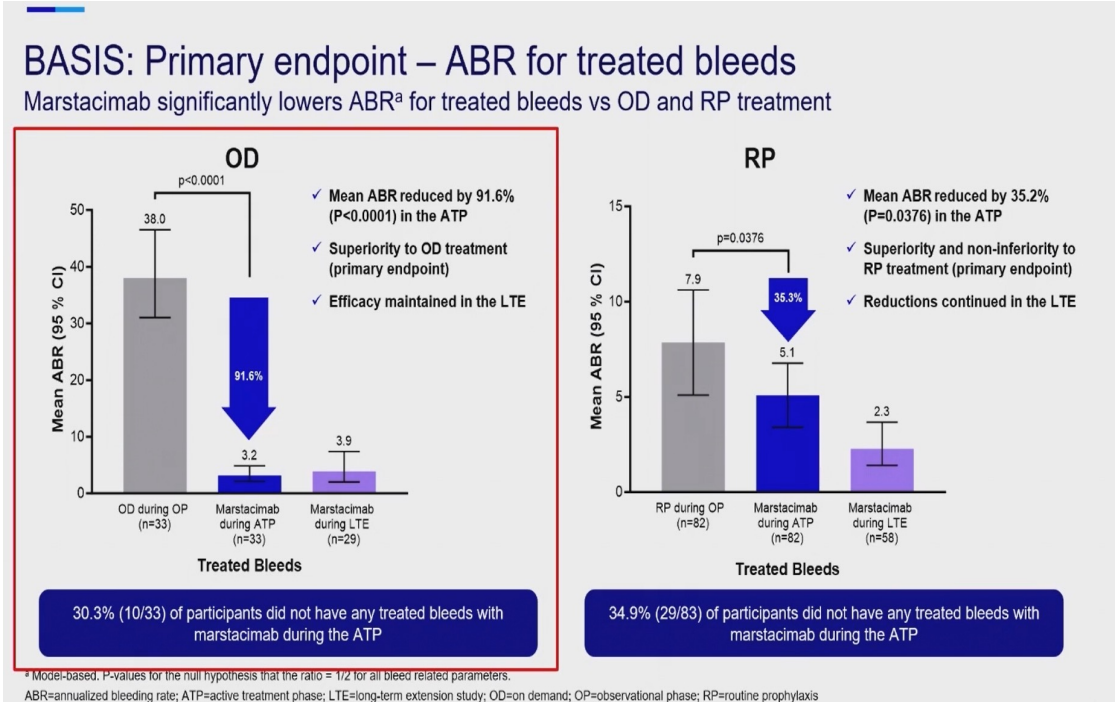
- Single arm, pivotal phase 3 trial to compare efficacy and safety of marstacimab in people with severe HA or moderately severe to severe HB, with or without inhibitors, over a 12-month active treatment phase (ATP) vs prior replacement therapy during a 6-month observational phase (OP)
- Participants received a single SC loading dose of 300 mg followed by once weekly 150 mg marstacimab
- Data are presented for the non-inhibitor cohort (complete) and is ongoing for the inhibitor cohort
- Participants who successfully completed BASIS could enroll in the long-term extension (LTE) study



[a] eg, factor replacement therapy.
ATP=active treatment phase; HA=hemophilia A; HB=hemophilia B; LTE=long-term extension study; OD=on demand; OP=observational phase; RP=routine prophylaxis; SC=subcutaneous

Efficacy and Safety of the Anti-Tissue Factor Pathway Inhibitor Marstacimab in Participants with Severe Hemophilia without Inhibitors: Results from the Phase 3 Basis Trial

Davide Matino, Blood 142: 285

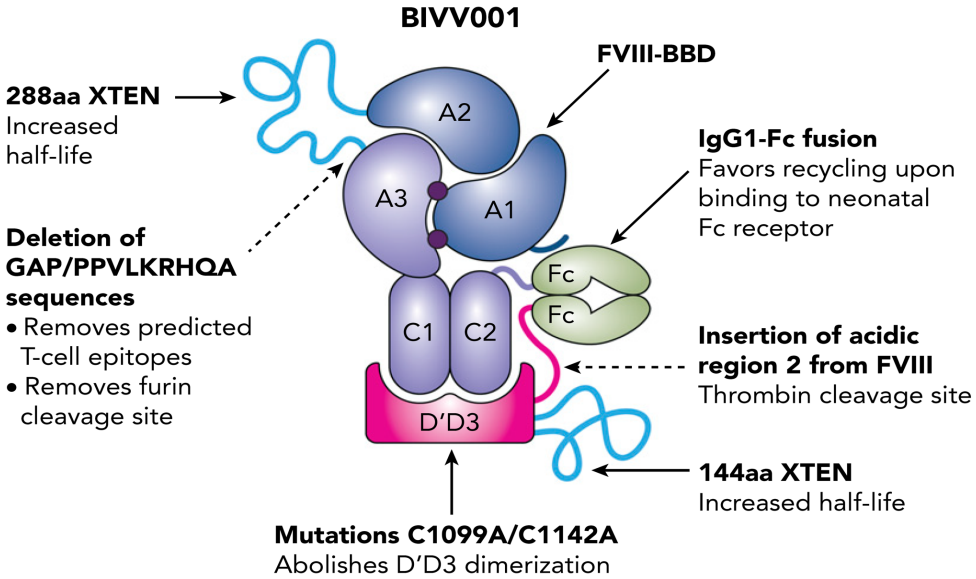


Riduzione significativa di ABR con marstacimab durante ATP

Marstacimab risulta sicuro ed efficace nel ridurre gli episodi emorragici ,comparato con precedente terapia OD o RP i.p. in HA e HB grave, fino a 12 mesi (in trial) e 16 mesi (in LTE)

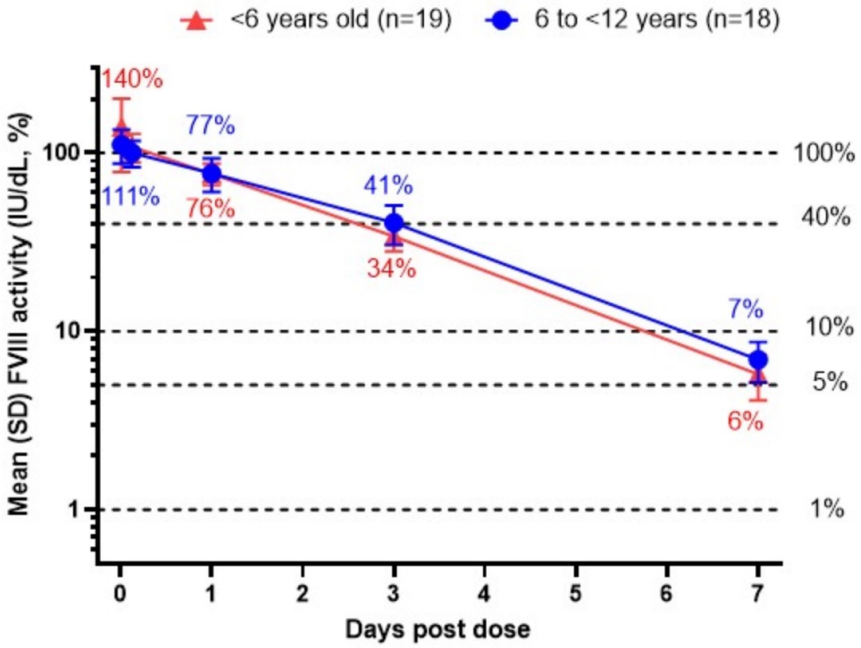
ULTRA-LONG FVIII

BIVV001 : a new FVIII fusion protein (FVIII-Fc/ D'D3 VWF / XTEN linkers)



- Absence of binding to endogenous VWF
- Extended half-life in mice (25–31 h) and monkeys (33–34 h)
- Reduces acute and prolonged bleeding in hemophilia A mice

Once-Weekly Efanesoctocog Alfa Prophylaxis Provided High Sustained Factor VIII Activity Levels, Independent of Blood Group, in Children <12 Years of Age with Severe Hemophilia A



Flora Peyvandi, Blood 142:506

Sette giorni dopo infusione di rFVIIIFc-VWF-XTEN,livelli medi di attività di FVIII pari 5.73 IU/dL in bambini <6 aa e 6.93 IU/dL in bambini ≥6–<12aa

FVIII:c circola a livelli normali (>40 IU/dL) per 3 gg e rimane >10 IU/dL per ~7 gg dopo infusione di 50 IU/kg di efanesoctocog alfa

Four-Year Follow-up of the Alta Study, a Phase 1/2 Study of Giroctocogene Fitelparvovec (PF-07055480/SB-525) Gene Therapy in Adults with Severe Hemophilia A

Leavitt DA, Blood 142:1054

Table. Factor VIII Activity Levels by 1-Stage and Chromogenic Assay for the Giroctocogene Fitelparvovec 3e13-vg/kg Cohort

FVIII Activity, % Normal, Mean, Median [min, max]	Study Week								
Assay	Week 12	Week 24	Week 52	Week 78	Week 104	Week 130	Week 156	Week 182	Week 208
1-stage clotting	110.9, 93.7 [82.7, 167.7]	107.5, 104.8 [30.5, 212.6]	66.4, 31.1 [12.0, 191.3]	65.7, 57.5 [3.8, 144.2]	38.9, 27.5 [4.1, 99.1]	54.1, 23.3 [5.4, 164.5]	40.5, 22.9 [3.3, 129.0]	40.8, 21.2 [7.2, 113.9]	66.8, 66.8 [14.7, 118.8]
Chromogenic	71.7 (62.1) [51.8, 109.5]	68.9 (70.1) [20.4, 123.8]	42.6 (20.1) [7.8, 122.3]	48.9 (40.1) [0.9, 114.7]	25.4 (16.3) [0.9, 71.6]	34.7 (12.3) [0.9, 113.2]	25.5 (11.8) [0.9, 91.1]	23.1 (12.7) [3.1, 64.0]	48.5 (48.5) [6.8, 90.1]
Participants, n	5	5	4[a]	4[a]	5	4[a]	5	4[b]	2[c]

[a] There was 1 participant each who was unable to attend visits at Weeks 52, 78, and 130.
[b] One participant left the study after Week 156.
[c] Two participants had not yet reached Week 208 at the time of the data cutoff.
FVIII=factor VIII; min, max=minimum, maximum

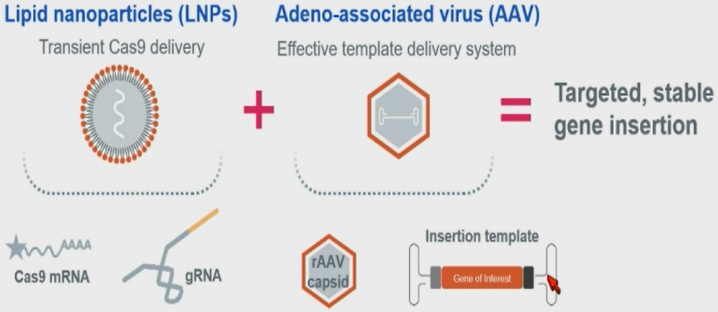
Una infusione di giroctocogene fitelparvovec in pazienti affetti da emofilia A grave è ben tollerata in un periodo di 4 anni dopo infusione, con livelli di FVIII moderati/normali senza AEs, anche epatici a 58 w

CRISP-Cas based editing for stable gene insertion in Haemophilia B

Leah Sabin, Scientific programme

CRISPR/Cas9-based gene insertion as a novel therapeutic modality

Regeneron and Intellia are partnering to jointly develop a CRISPR-based gene insertion approach for the treatment of Hemophilia B

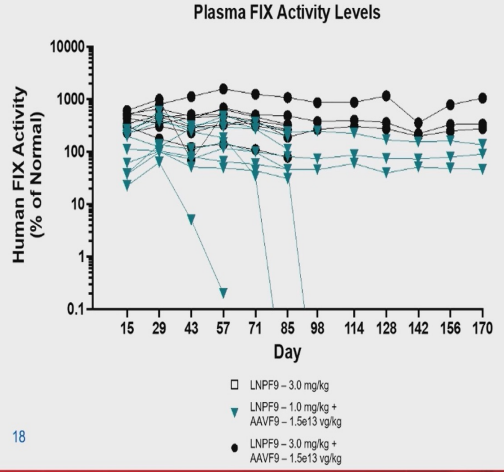


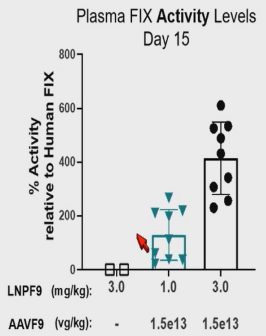
Potential advantages over AAV liver episome gene therapy:

- Higher protein expression
- Better durability
- Potential to treat pediatric populations
- Promoterless insertion cassette

AAVF9-LNPF9 mediates hFIX expression in non-human primates in an LNP dose-dependent manner

Robust expression of hFIX achieved in NHPs enables the use of wildtype FIX rather than Padua variant





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Grazie!