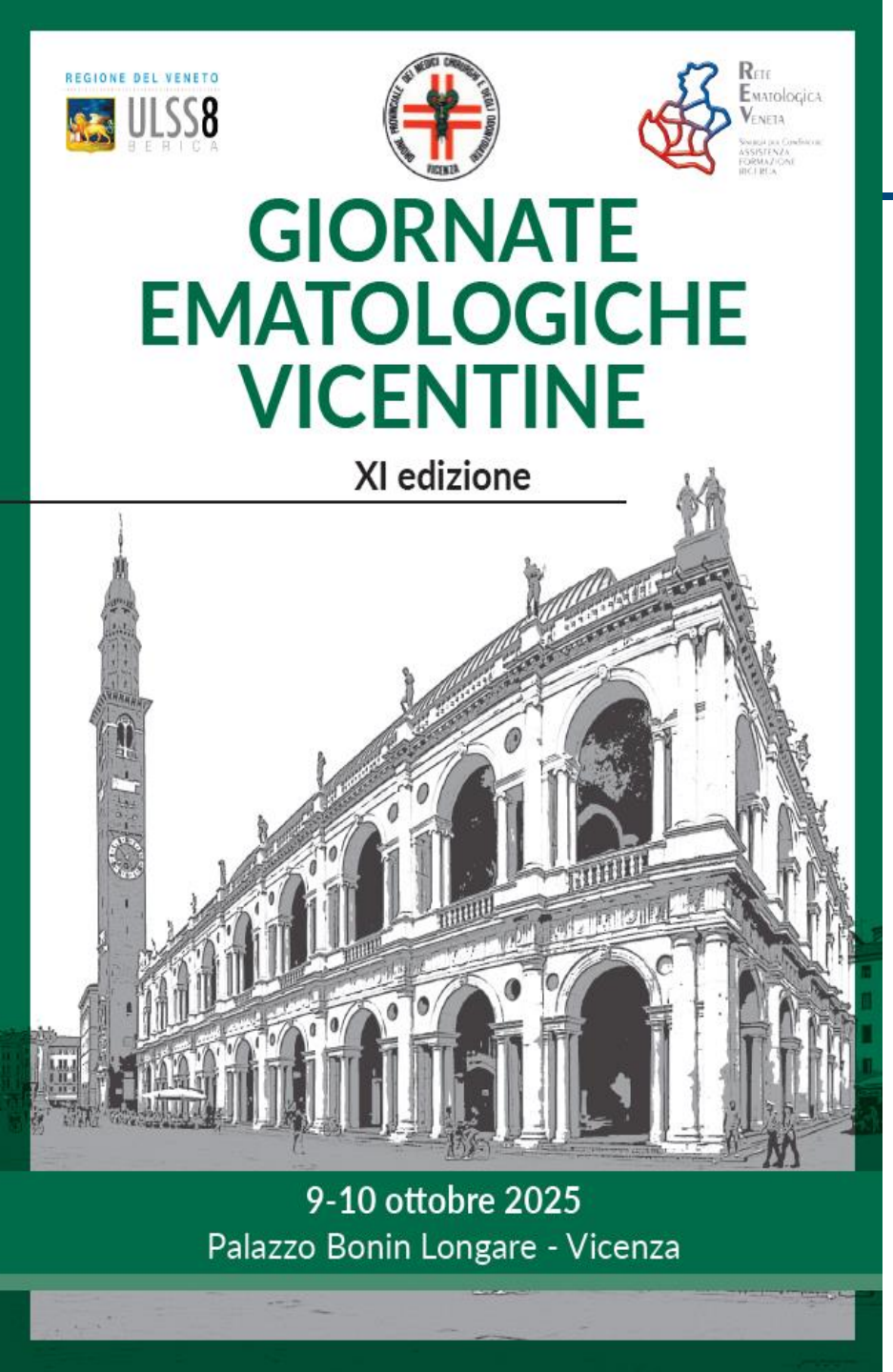


La terapia genica nell'emofilia

Giancarlo Castaman

SODc Malattie Emorragiche e della Coagulazione,
Dipartimento Cardiotoracovascolare,
AOU Careggi, Firenze

Disclosures

Giancarlo Castaman

Employment	*NONE*
Research support	*NONE*
Scientific advisory board	*BIOMARIN-CSL-BEHRING, KEDRION-LFB, SHIRE-TAKEDA, NOVO NORDISK, PFIZER, ROCHE, UNIQURE, BAYER, SOBI*
Consultancy	*CSL BEHRING ROCHE - BIOMARIN*
Speakers bureau	*CSL-BEHRING, GRIFOLS, KEDRION-LFB, SHIRE-TAKEDA, WERFEN-IL, SOBI*
Major stockholder	*NONE*
Patents	*NONE*
Honoraria	*NONE*
Travel support	*NONE*
Other	*NONE*

Hemophilia is an appropriate target for gene therapy

Hemophilia A and B are monogenic diseases[1]

Well suited for correction by gene therapy[1]

- Large phenotypic improvement following modest factor increase
- Precise regulation not necessary

Efficacy readily assessable via factor level measurements and bleeding rates[2]

1. Perrin GQ, *et al. Blood* 2019; 133:407–414. 2. Arruda VR, Doshi BS. *Mediterr J Hematol Infect Dis* 2020; 12:e2020069.

Types of viral vectors

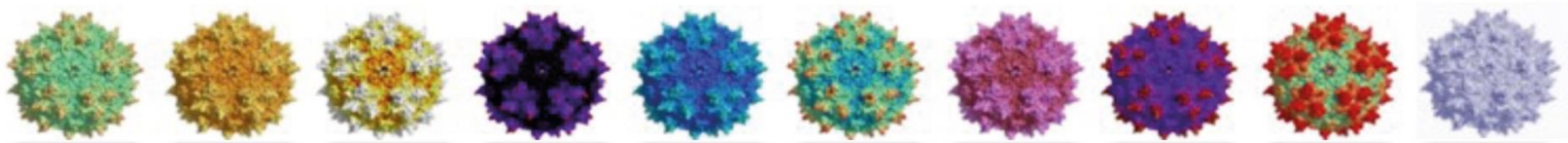
	Adenovirus	Adeno-associated virus (AAV)	Alphavirus	Herpesvirus	Retrovirus/ Lentivirus	Vaccinia virus
Cell types affected[1]	Broad low neuron transduction	Broad, dividing and non-dividing cells	Broad, neuron and glial cell-specific strains	Broad, neurons, stem cells, muscle cells	Lentivirus: Dividing and non-dividing cells Retrovirus: Dividing cells	Broad host range
Host genome integration[2]	Low level integration	Low level integration	Unknown	Low level integration	Integrating	Unknown
Transgene expression[1]	Transient	Potentially long-lasting	Transient	Potentially long-lasting	Potentially long-lasting	Unknown
Packaging capacity (kb)[3,4]	<7.5	<4.7	8	>30	8	>30

kb, kilobases.

1. Lundstorm K. *Trends Biotechnol* 2003;21:117–22; 2. Walther W *et al. Drugs*. 2000;60:249–71; 3. Lundstrom K. *Diseases* 2018;21;6. pii: E42; 4. Srivastava A *et al. J Virol* 1983;45:555–64

Tropismo tissutale del sierotipo AAV

Gli AAV hanno un'ampia diversità naturale e hanno dimostrato di essere in grado di raggiungere diversi tipi di tessuto (tropismo); questo può influenzare il profilo di sicurezza ed efficacia di un prodotto di terapia genica.



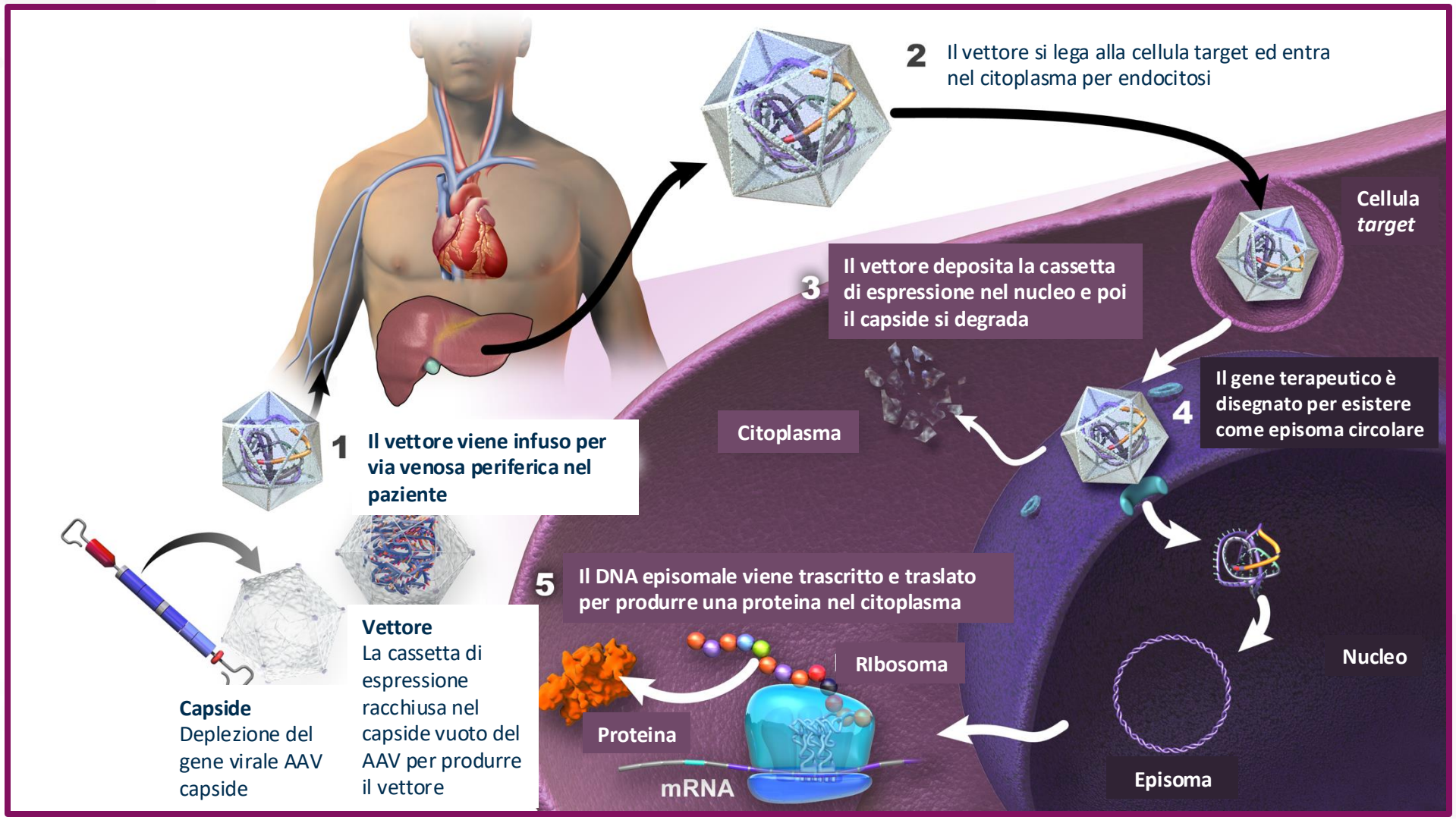
Tropismo	AAV1	AAV2	AAV3	AAV4	AAV5	AAV6	AAV7	AAV8	AAV9	AAV10
Fonte	NHP	Umano	NHP	NHP	Umano	Umano	NHP	NHP	NHP	NHP
Fegato		●			●			●	●	●
Cuore						●		●	●	
Muscoli	●	●	●		●	●	●	●	●	
Polmoni	●				●	●			●	
Retina	●			●	●		●	●		
SNC	●	●		●	●		●	●	●	
Pancreas	●							●	●	

- Sono state notate **differenze nel tropismo degli AAV nei topi, negli esseri umani e nei primati non umani** (NHP). I dati che dimostrano i profili di tropismo negli esseri umani non sono ancora ampiamente disponibili
- Per questo motivo, **nella cassetta di espressione vengono incorporati promotori specifici per ogni tessuto**, in modo da guidare l'espressione del transgene nel tessuto di destinazione

AAV: virus adeno-associato; NHP: primate non umano; SNC: sistema nervoso centrale.

Vance MA, et al. From Gene Therapy – Principles and Challenges. InTech, 2015; Verdera HC, et al. Mol Ther. 2020;28(3):723-746; Zincarelli C, et al. Mol Ther. 2008;16(6):1073-1080; Pipe S, et al. Mol Ther. 2019;15:170-178.

Meccanismo d'azione di trasferimento genico AAV-mediato



AAV: virus adeno-associato; mRNA: acido ribonucleico messaggero.

Castaman G, et al. Int J Mol Sci. 2022;23:10228.

Sieropositività ad AAV

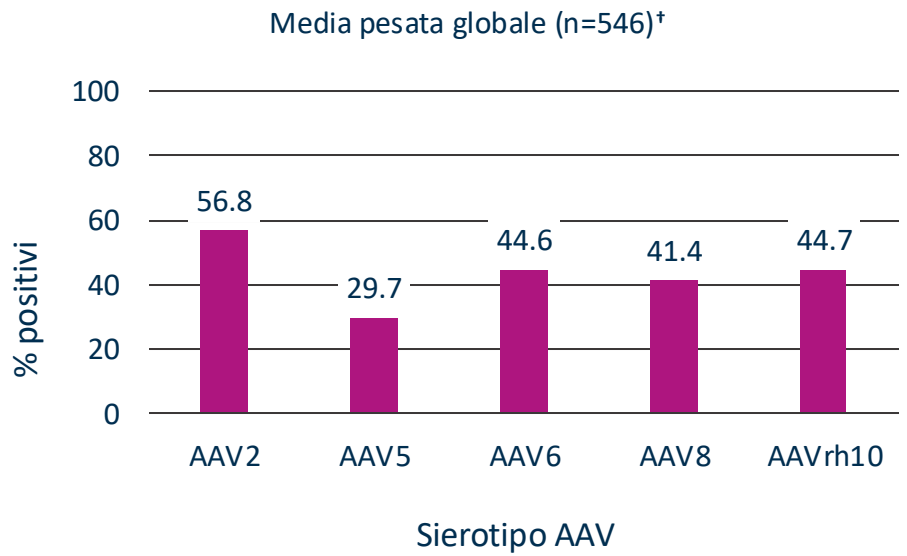
L'immunità pre-esistente a un sierotipo di AAV può influire sulla sicurezza/efficacia di qualsiasi terapia genica che utilizzi quel sierotipo

- A causa della variazione dei sierotipi di AAV, la sieropositività a un sierotipo di AAV non è necessariamente associata a una risposta immunitaria a un altro sierotipo di AAV
- La **ricerca di anticorpi neutralizzanti** contro il vettore AAV è una **componente importante dello *screening*** dei pazienti per l'eleggibilità con alcune terapie geniche AAV in fase di sperimentazione e commercializzazione

Sieroprevalenza di AAV nei pazienti con emofilia A in Italia*

AAV5	AAV6	AAV2	AAV8	AAVrh10
40%	40%	45%	40%	50%

Il tasso globale di sieropositività per AAV5 è il più basso rispetto ad altri AAV**



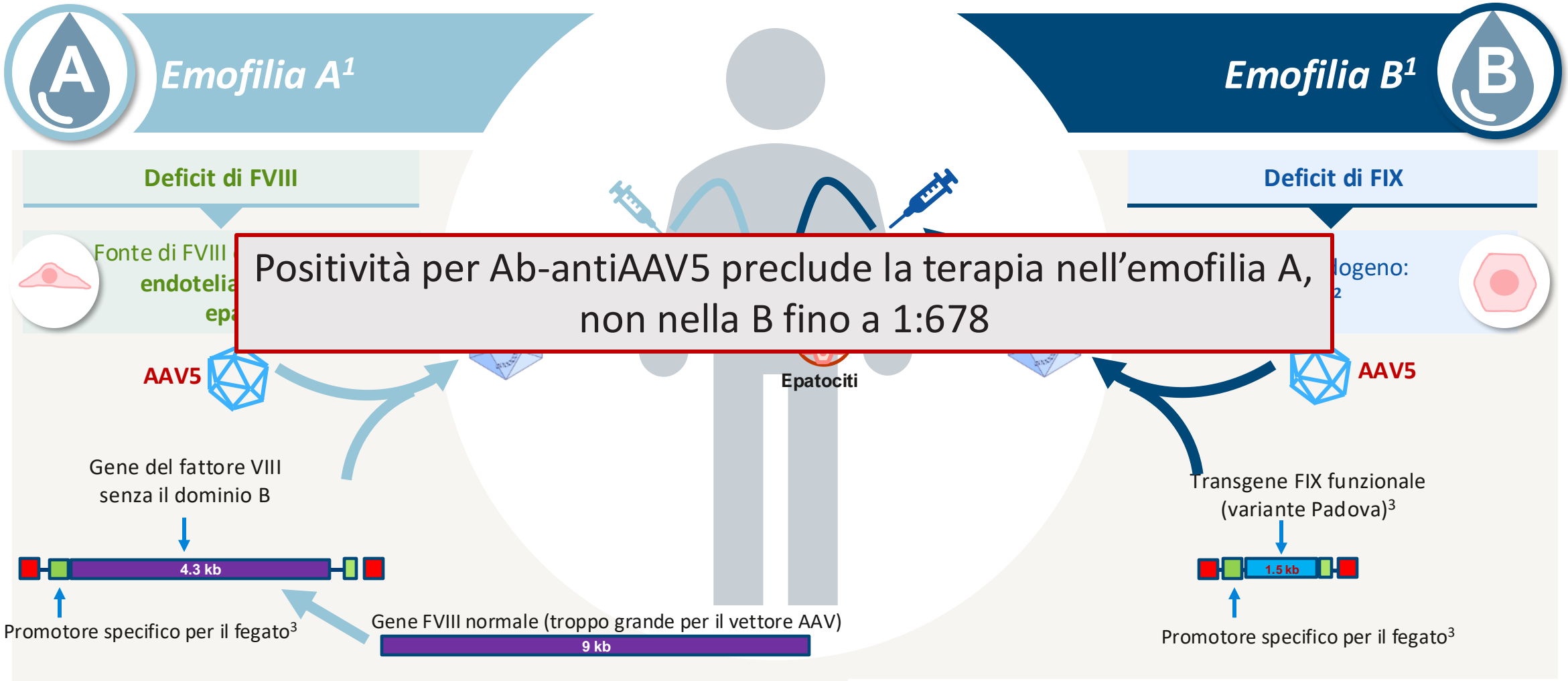
*% AAV TAb positivi.

**Tasso di sieropositività calcolato utilizzando la media ponderata dell'emofilia globale.†3 persi al *follow-up* e 1 interrotto per decisione del medico.

AAV: virus adeno-associato; AAV2: virus adeno-associato di sierotipo 2; AAV5: virus adeno-associato di sierotipo 5; AAV6: virus adeno-associato di sierotipo 6; AAV8: virus adeno-associato di sierotipo 8; AAVrh10: virus adeno-associato di sierotipo 10 rhesus-derivato.

Daya S, Berns K. Clin Microbiol Rev. 2008;21:583-593; Klamroth R, et al. Hum Gene Ther. 2022;33:432-441; Verdera HC, et al. Mol Ther. 2020;28:723-746; Wang D, et al. Nat Rev Drug Discov. 2019;18:358-378.

Gli stessi approcci di terapia genica sono stati usati sia per l'emofilia A che per l'emofilia B

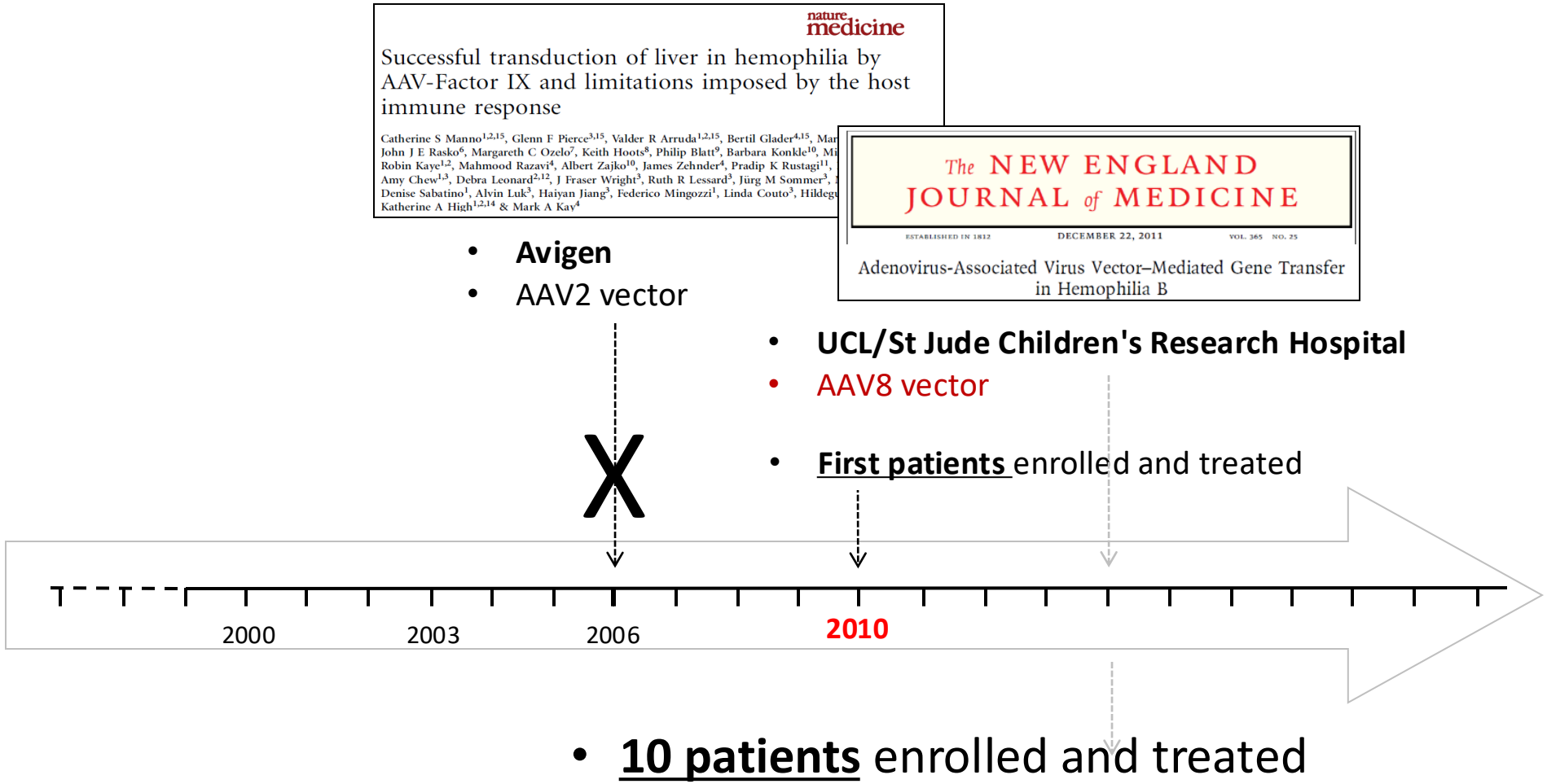


1. Arruda VR, Doshi BS. *Mediterr J Hematol Infect Dis* 2020; 12:e2020069. 2. Perrin GQ, *et al. Blood* 2019;133:407–414. 3. Batty P, Lillicrap D. *HemaSphere* 2021;5:3(e540)

Hemophilia B gene therapy: general aspects

- Four-fold lower prevalence compared to hemophilia A
- The 1.5 kb FIX cDNA is easily packaged into a range of viral vectors, with expression mediated by liver-specific regulatory elements targeting the native site of FIX production.

Primo trial clinico nell'emofilia B (2011)



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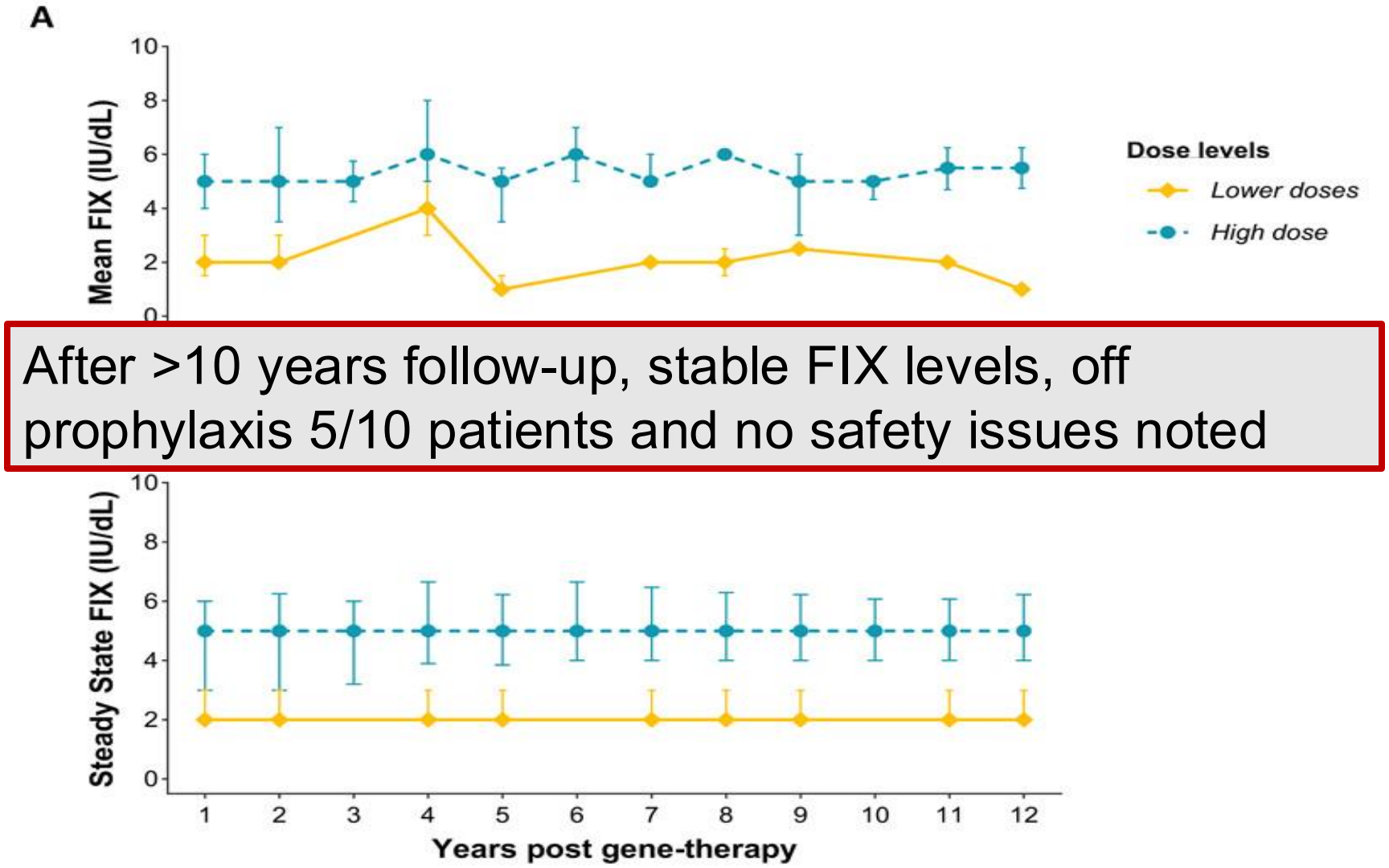
Sustained Clinical Benefit of AAV Gene Therapy in Severe Hemophilia B

Ulrike M. Reiss et al. **N Engl J Med 2025;392:2226-2234**



After >10 years follow-up, stable FIX levels, off prophylaxis 5/10 patients and no safety issues noted

Hemophilia B gene therapy: general aspects

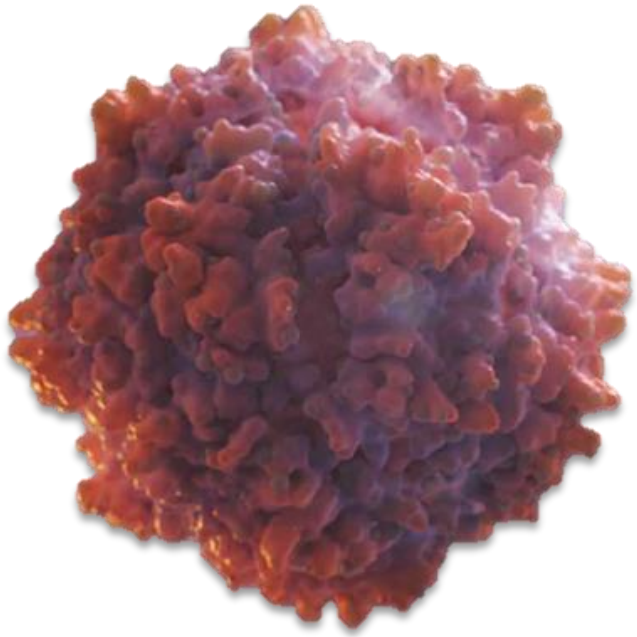
- The 1.5 kb FIX cDNA is easily packaged into a range of viral vectors, with expression mediated by liver-specific regulatory elements targeting the native site of FIX production.

- *The discovery of a gain-of-function FIX variant (FIX Padua, p.R338L)* has further enhanced the potential for attaining therapeutic FIX activity levels with moderate vector doses

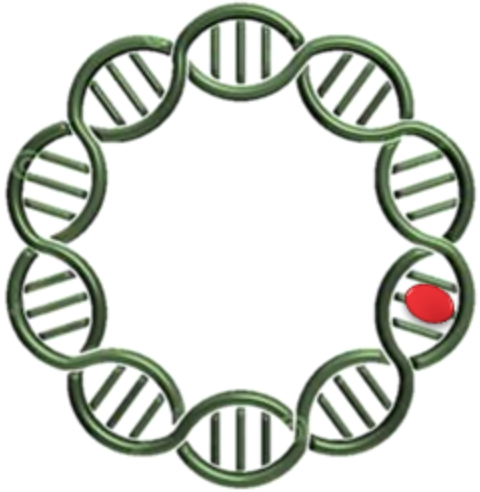
- This R338L missense mutant increases the specific activity of the molecule approximately 7-fold, *without evidence of increased immunogenicity*

AMT-060/AMT-061
Etranacogene dezaparvovec

AAV5 capsid



Liver-specific promoter & human FIX gene[3]



AMT-061
AGG to CTG in gene resulting in **R338L** in protein

- Low prevalence of pre-existing neutralizing antibodies able to impact clinical outcomes[1,4]
- Previously tested in humans without sign of cellular immune activation[2]

AMT-060 – wildtype
AMT-061 – Padua variant
(expected 6-7x increase in activity)

[1]Boutin et al, *Human Gen Ther* 2010; 21(6):704-12. [2]D'Avola et al, *Journal of Hepatology* 2016; doi: http://dx.doi.org/10.1016/j.jhep.2016.05.012.
[3]Nathwani et al. *NEJM* 2014; 371:1994-2004. [4]Majowicz et al, ASGCT 2018

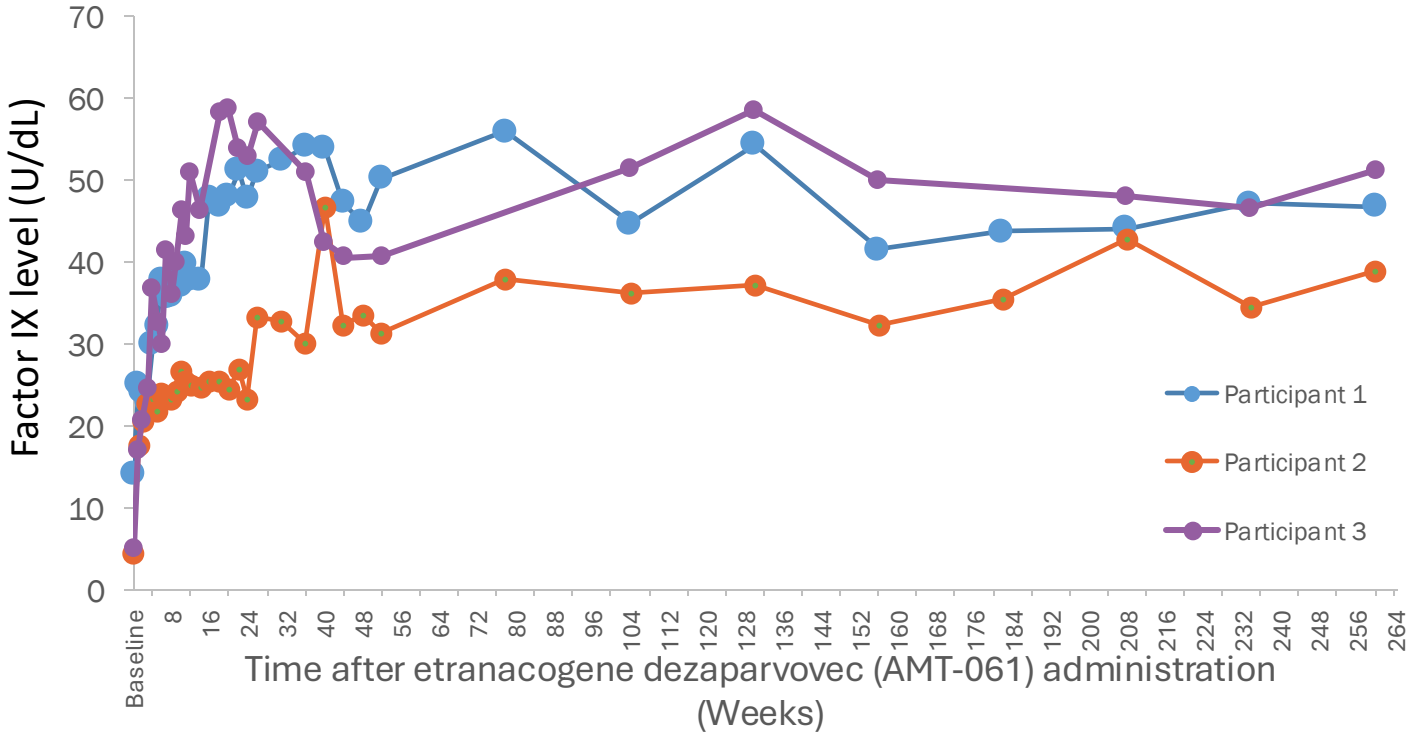
REGULAR ARTICLE

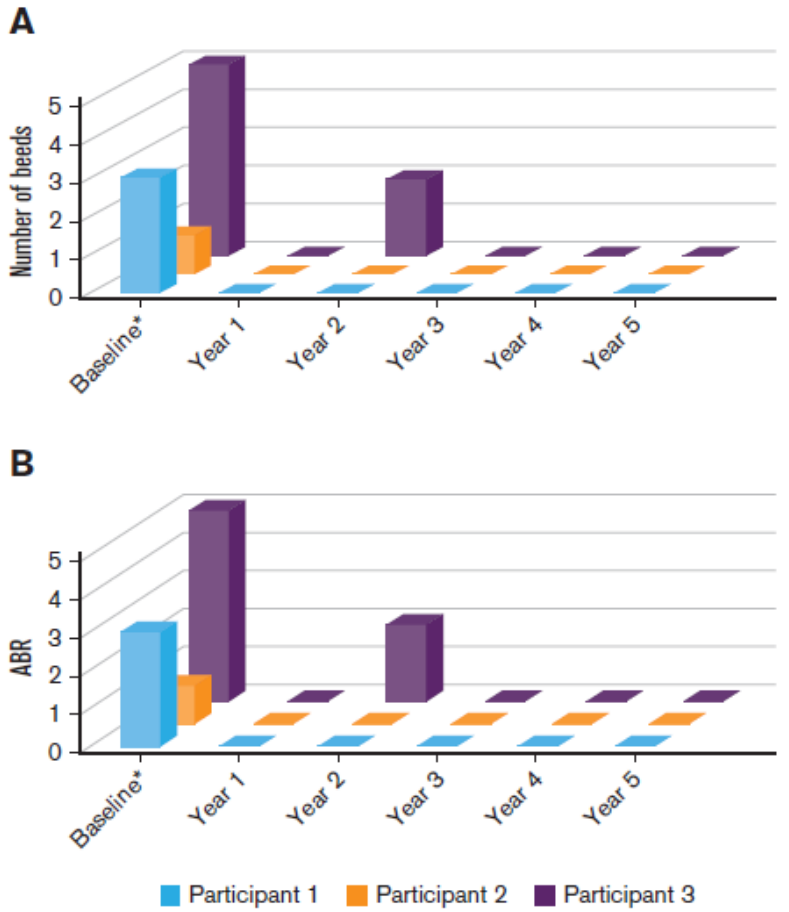
blood advances

Completion of phase 2b trial of etranacogene dezaparvovec gene therapy in patients with hemophilia B over 5 years

Annette von Drygalski,[1] Esteban Gomez,[2] Adam Giermasz,[3] Giancarlo Castaman,[4] Nigel S. Key,[5] Susan U. Lattimore,[6] Frank W. G. Leebeek,[7] Wolfgang A. Miesbach,[8] Michael Recht,[9,10] Paul E. Monahan,[11] Sandra Le Quellec,[11] and Steven W. Pipe[12]

Blood Adv 9: 3543, 2025



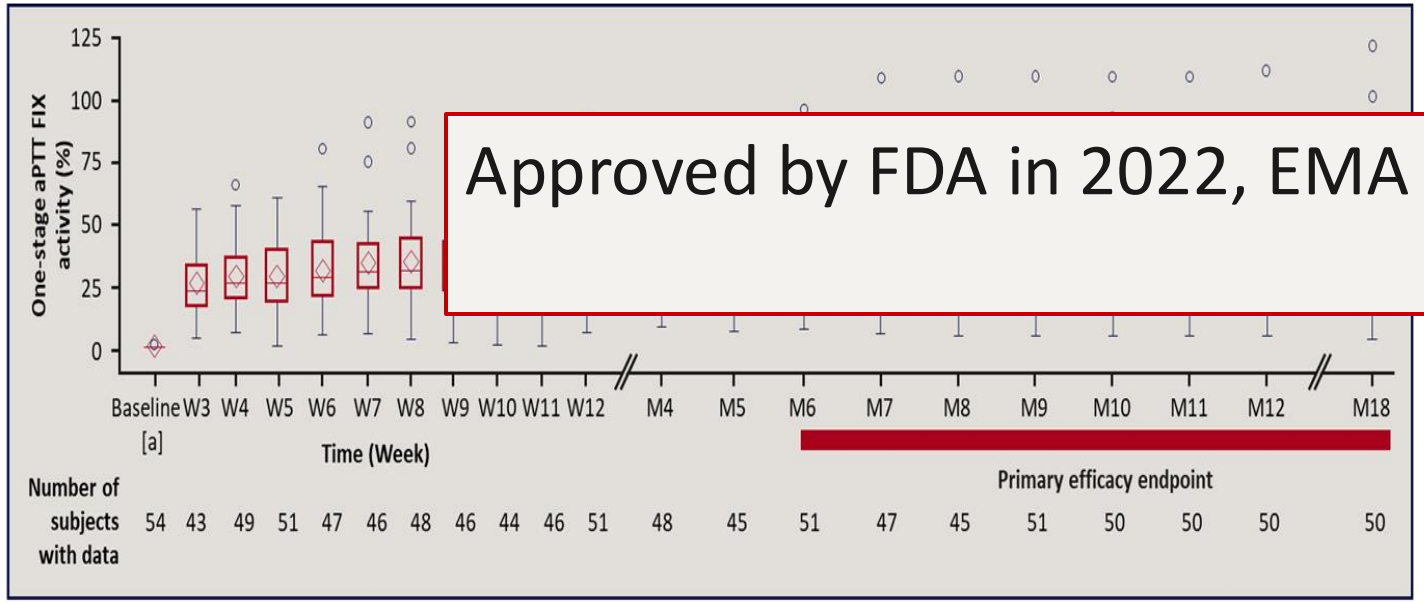


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B

S.W. Pipe, F.W.G. Leebeek, M. Recht, N.S. Key, G. Castaman, W. Miesbach, S. Lattimore, K. Peerlinck, P. Van der Valk, M. Coppens, P. Kampmann, K. Meijer, N. O'Connell, K.J. Pasi, D.P. Hart, R. Kazmi, J. Astermark, C.R.J.R. Hermans, R. Klamroth, R. Lemons, N. Visweshwar, A. von Drygalski, G. Young, S.E. Crary, M. Escobar, E. Gomez, R. Kruse-Jarres, D.V. Quon, E. Symington, M. Wang, A.P. Wheeler, R. Gut, Y.P. Liu, R.E. Dolmetsch, D.L. Cooper, Y. Li, B. Goldstein, and P.E. Monahan



Uncontaminated central laboratory data (the visit did not occur within 10 days of exogeneous FIX use). FIX levels beginning with the Week 3 assessment were used in the analysis. Subjects with 0 uncontaminated central-laboratory post-AMT-061 values had change from baseline assigned to zero for this analysis and had their post-baseline values set equal to their baseline value. Baseline FIX was imputed based on subject's historical haemophilia B severity documented on the case record form. If the patient had documented severe FIX deficiency (FIX plasma level <1%), their baseline FIX activity level is imputed as 1%. If the subject had documented moderately severe FIX deficiency (FIX plasma level ≥1% and ≤ 2%), their baseline FIX activity level was imputed as 2%.

Mean (SD; min, max) FIX activity was 39.0 IU/dL (±18.7; 8.2, 97.1) at 6 months and 36.9 IU/dL (±21.4; 4.5, 122.9) at 18 months

At 6 months, mean (SD) change from baseline was 37.77 (18.78) with a p-value <0.0001; at 18 months the change from baseline was 35.72 (21.46) with a p-value <0.0001.

aPTT, activated partial thromboplastin time; FIX, factor IX; M, month; SD, standard deviation; W, Week.

Approved by FDA in 2022, EMA 2023 and AIFA 2025

54 patients with FIX ≤ 2 U/dL

Also patients with pre-existing AAV5 Nabs responded

HOPE-B results showed less variability, with more stable factor expression

77%

6.3%

- Significant reduction in annualized FIX consumption by **97%(p<0.001)**

AEs:

- **Transaminase elevations requiring steroid treatment in 17%**
- Other common TRAEs: headache (**15%**), and influenza-like illness (**13%**)

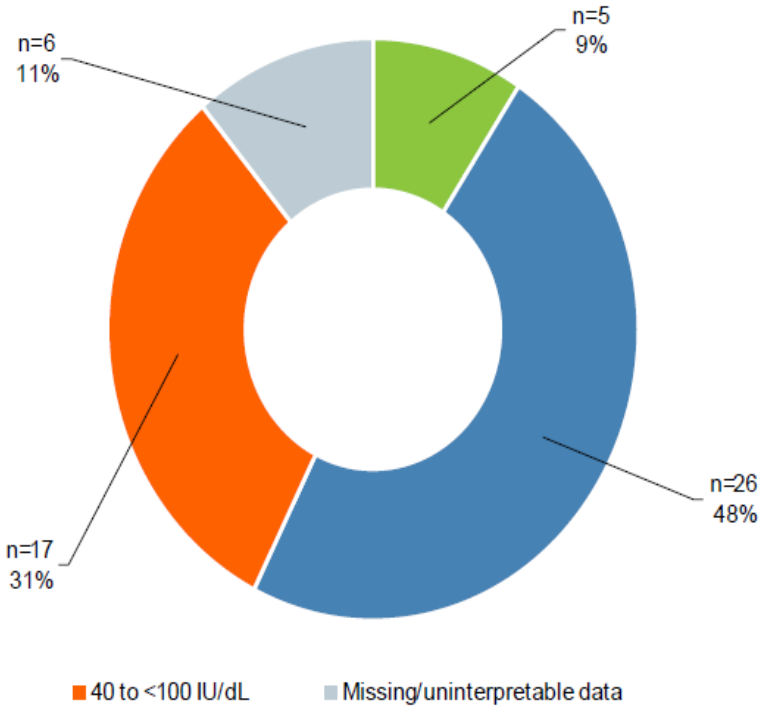
One SAE of **HCC**; occurred after the 6-month data cut and was determined **unlikely to be treatment related**

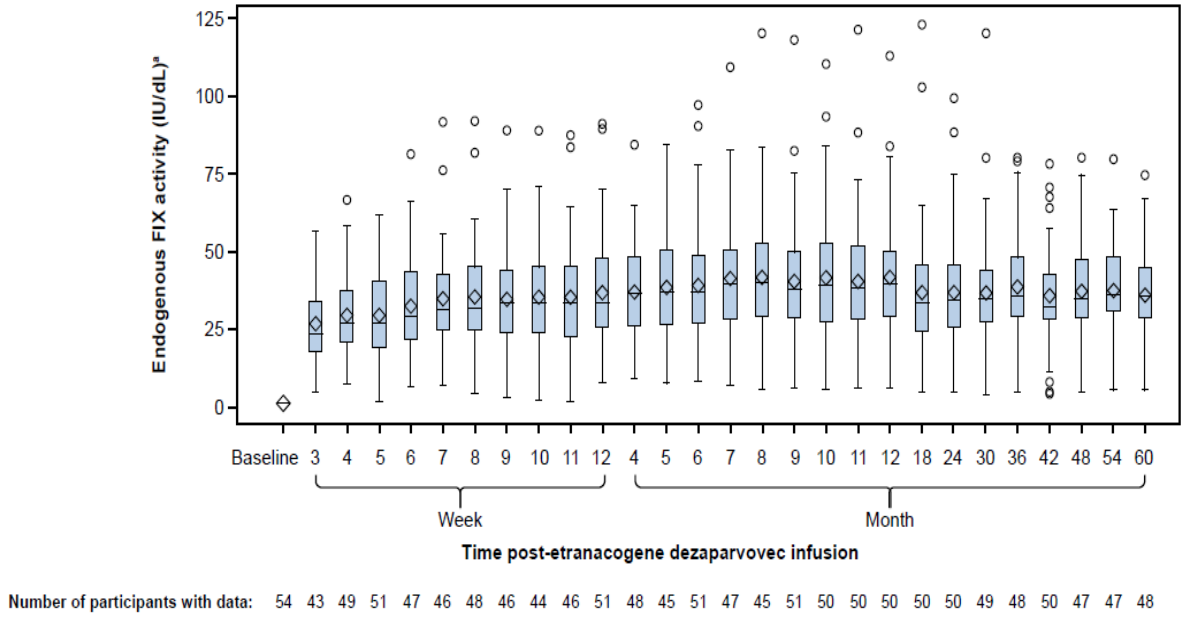
Etranacogene Dezaparvovec for Hemophilia B: Final Analysis of the HOPE-B Trial

Pipe SW, Miesbach W, Recht M, Leebeek FWG, Key NS, Castaman G, Lattimore S, Coppens M, Le Quellec S, Mahajan V, Gill S, Drelich D, Monahan P, on behalf of the HOPE-B Trial Group investigators

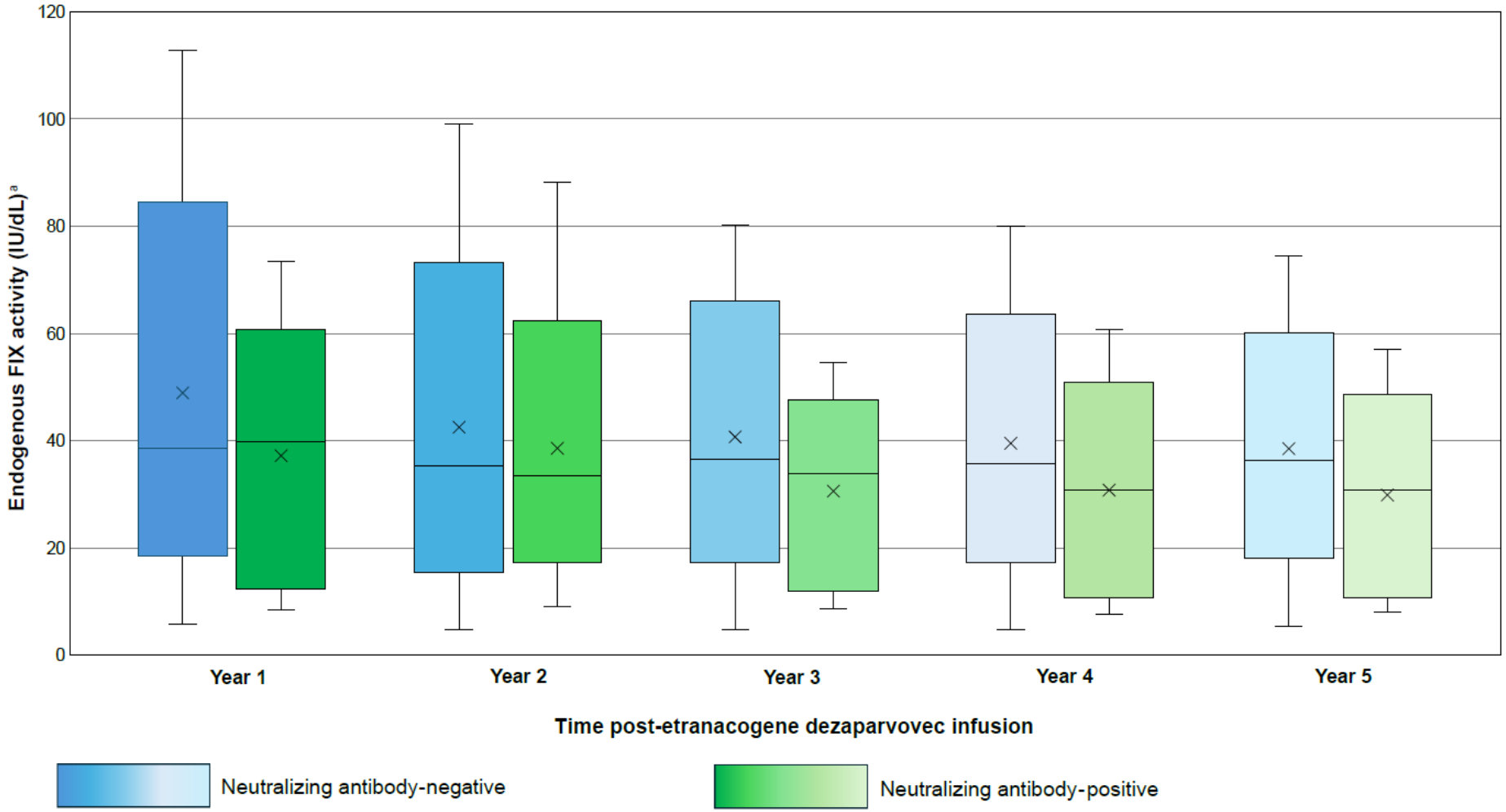
NEJM, in press

Reason for missing/uninterpretable data	Last available uncontaminated FIX activity (IU/dL)
Only received ~10% of etranacogene dezaparvovec dose and withdrew efficacy consent	1.7
Did not respond to treatment, like due to a high baseline AAV5 neutralizing antibody titer (3212) and withdrew efficacy consent	1.5
Death at month 15 (unrelated to treatment)	43.7
Liver transplant (HCC unrelated to treatment)	36.7
Returned to FIX prophylaxis at month 30	4.2
Death at month 54 (unrelated to treatment)	33.1





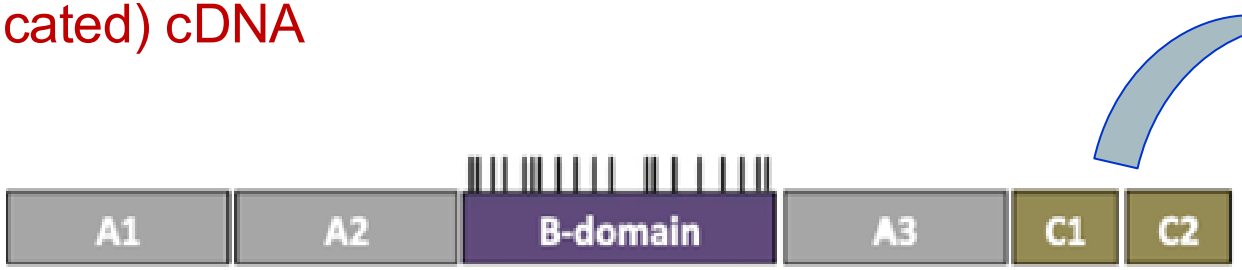
No difference in outcome between those AAV5-Ab positive vs AAV5-Ab negative



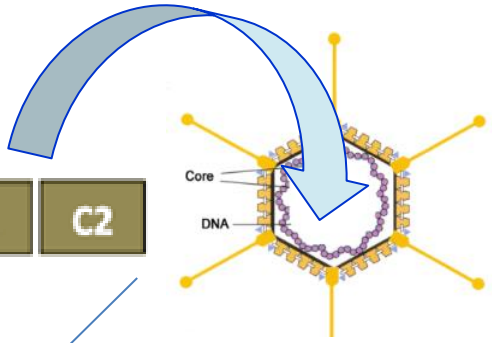
Pipe et al, 2025

Hemophilia A gene therapy: general aspects

- The size of the native FVIII cDNA of ~9 kb precludes packaging into clinically applicable vectors, and thus all current FVIII transgene constructs utilize a B domain-deleted (or truncated) cDNA

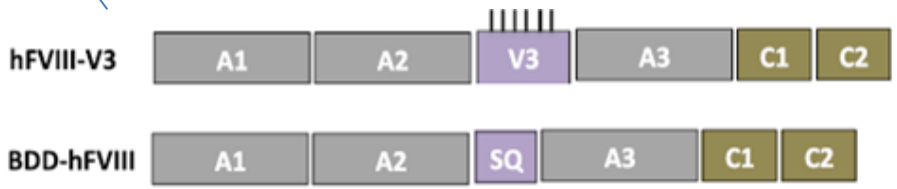


FVIII

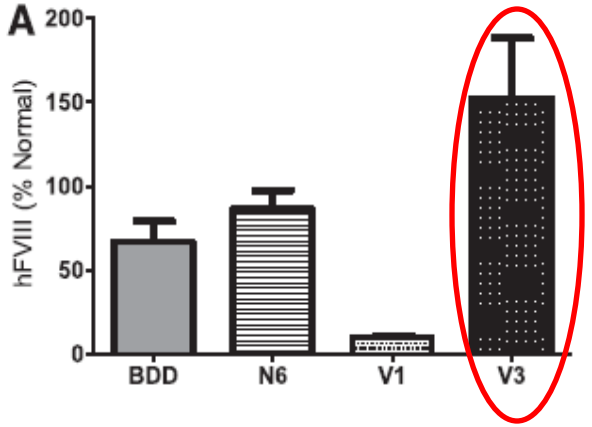


Viral vector

Codon optimized



The animal models showed an increase in FVIII expression levels

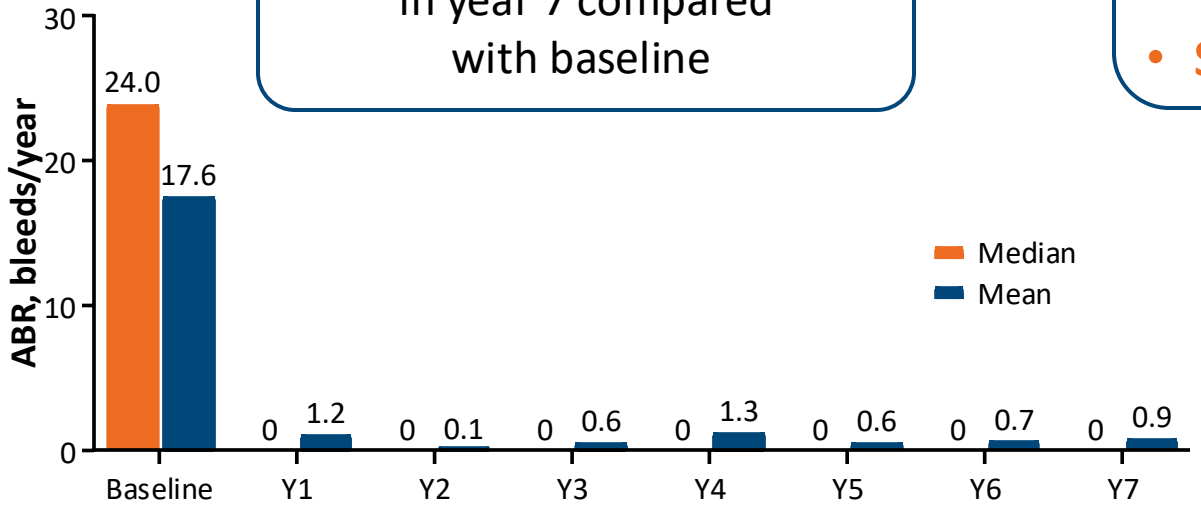


- Replacement of the FVIII B domain with a 17 amino acid peptide containing 6 glycosylation sequences has also been demonstrated to enhance FVIII trafficking and secretion

Haemophilia A: phase 1/2 clinical trial, year 7 outcomes

High dose cohort (N=7)*

96% reduction in mean ABR in year 7 compared with baseline



- **71.4%** remained **off prophylaxis** after 7 years
- **95% reduction** in annualised **FVIII infusion rate**
- **Safety** remains **consistent** with previous data

FVIII activity (IU/dL) (N=5)		
CSA	Mean	**16.2**
	Median	**10.3**
OSA	Mean	**23.9**
	Median	**19.4**

Majority of participants maintained haemostasis with continued therapeutic FVIII expression and sustained clinical benefit

Results from 270-201 study
*Dose: $6x10^{13}$ vg/kg
Symington E et al. PO124 EAHAD 2024 Congress, February 6-9, Frankfurt, Germany

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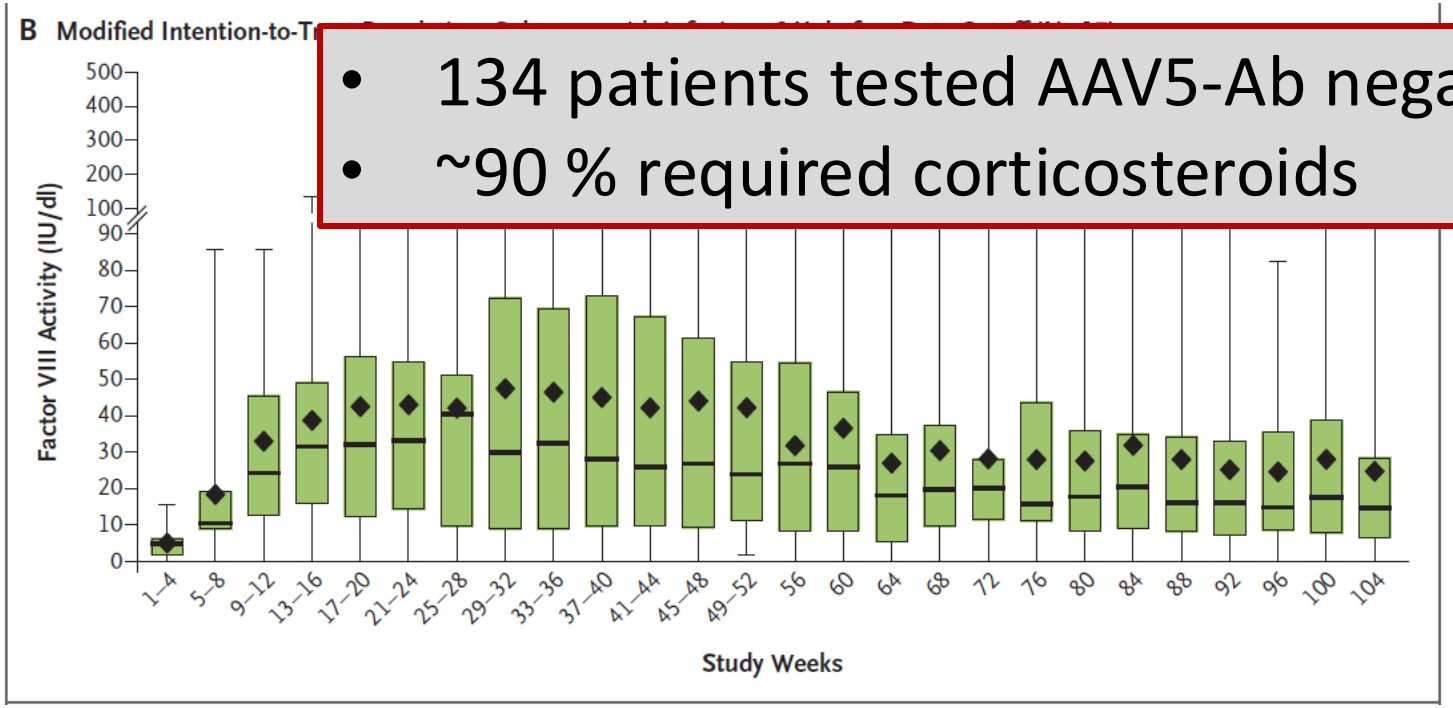
ESTABLISHED IN 1812 MARCH 17, 2022 VOL. 386 NO. 11

Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A

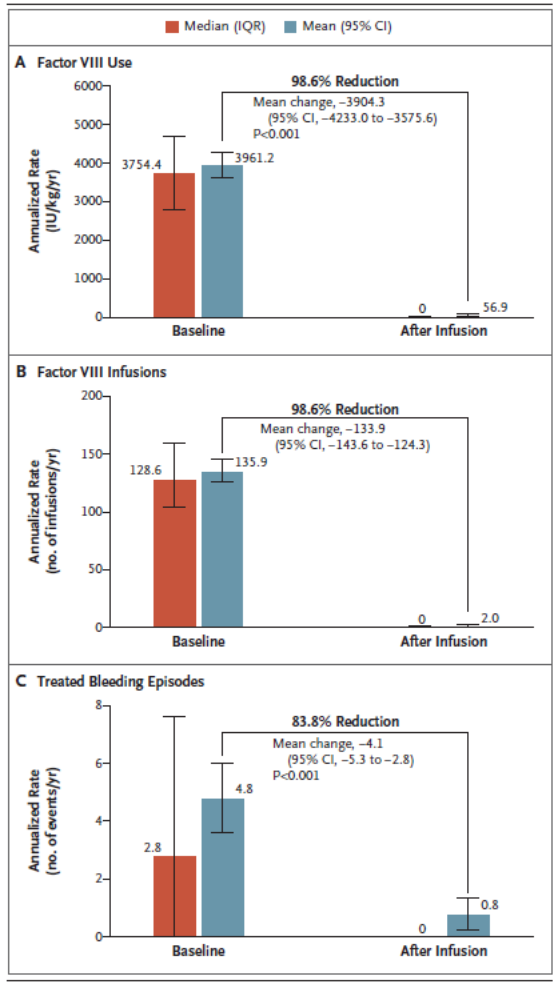
M.C. Ozelo, J. Mahlangu, K.J. Pasi, A. Giermasz, A.D. Leavitt, M. Laffan, E. Symington, D.V. Quon, J.-D. Wang, K. Peerlinck, S.W. Pipe, B. Madan, N.S. Key, G.F. Pierce, B. O'Mahony, R. Kaczmarek, J. Henshaw, A. Lawal, K. Jayaram, M. Huang, X. Yang, W.Y. Wong, and B. Kim, for the GENEr8-1 Trial Group*



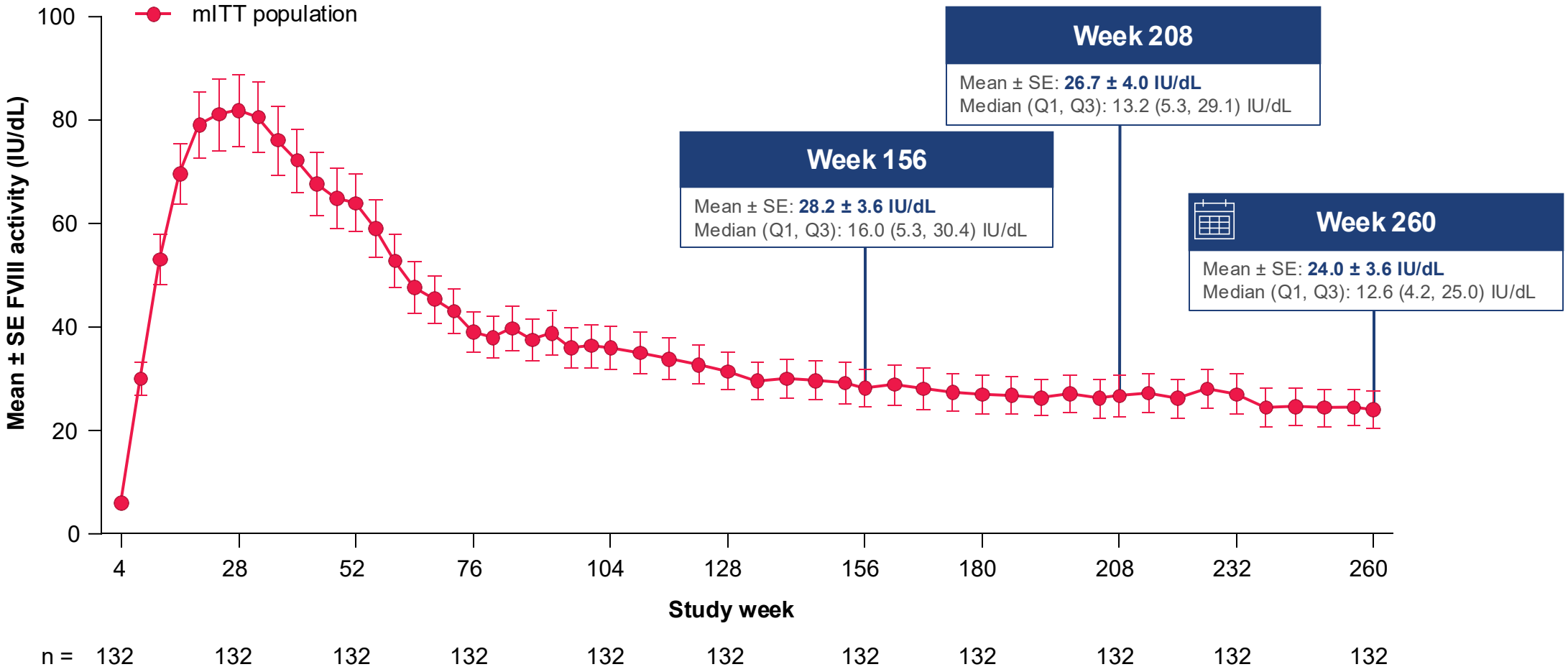
- 134 patients tested AAV5-Ab negative
- ~90 % required corticosteroids

Mean

Median



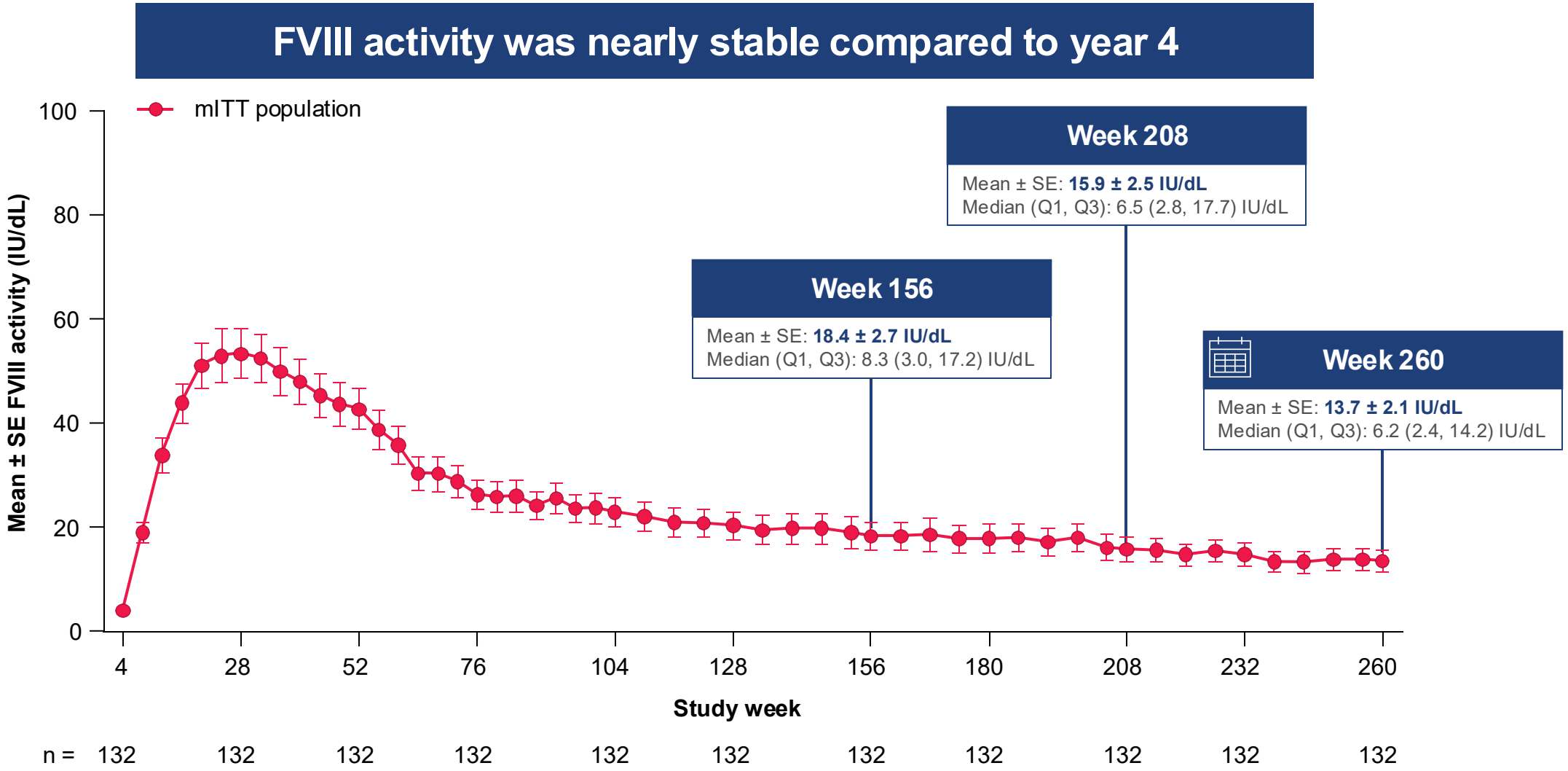
FVIII activity across the trial (OSA)



For participants who discontinued the study, missing FVIII values post-discontinuation were imputed as 0 IU/dL through the data cutoff date.
FVIII, factor VIII; mITT, modified intention-to-treat; Q, quartile; OSA, one-stage assay; SE, standard error.

mITT population (N = 132)

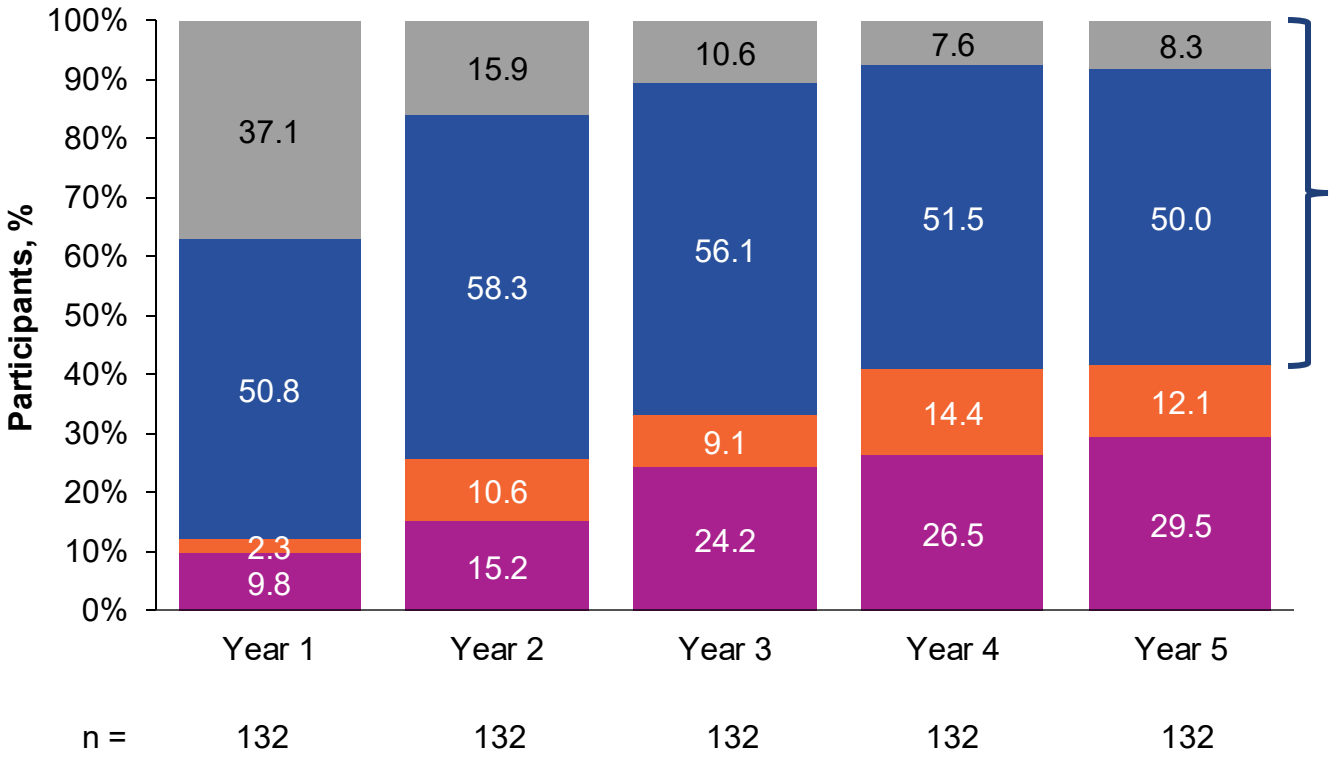
FVIII activity across the trial (CSA)



For participants who discontinued the study, missing FVIII values post-discontinuation were imputed as 0 IU/dL through the data cutoff date.
CSA, chromogenic substrate assay; FVIII, factor VIII; mITT, modified intention-to-treat; Q, quartile; SE, standard error.

mITT population (N = 132)

FVIII activity (CSA) at the end of year 5



58.3% of participants remain in the mild to non-hemophilic range

Median FVIII activity per CSA

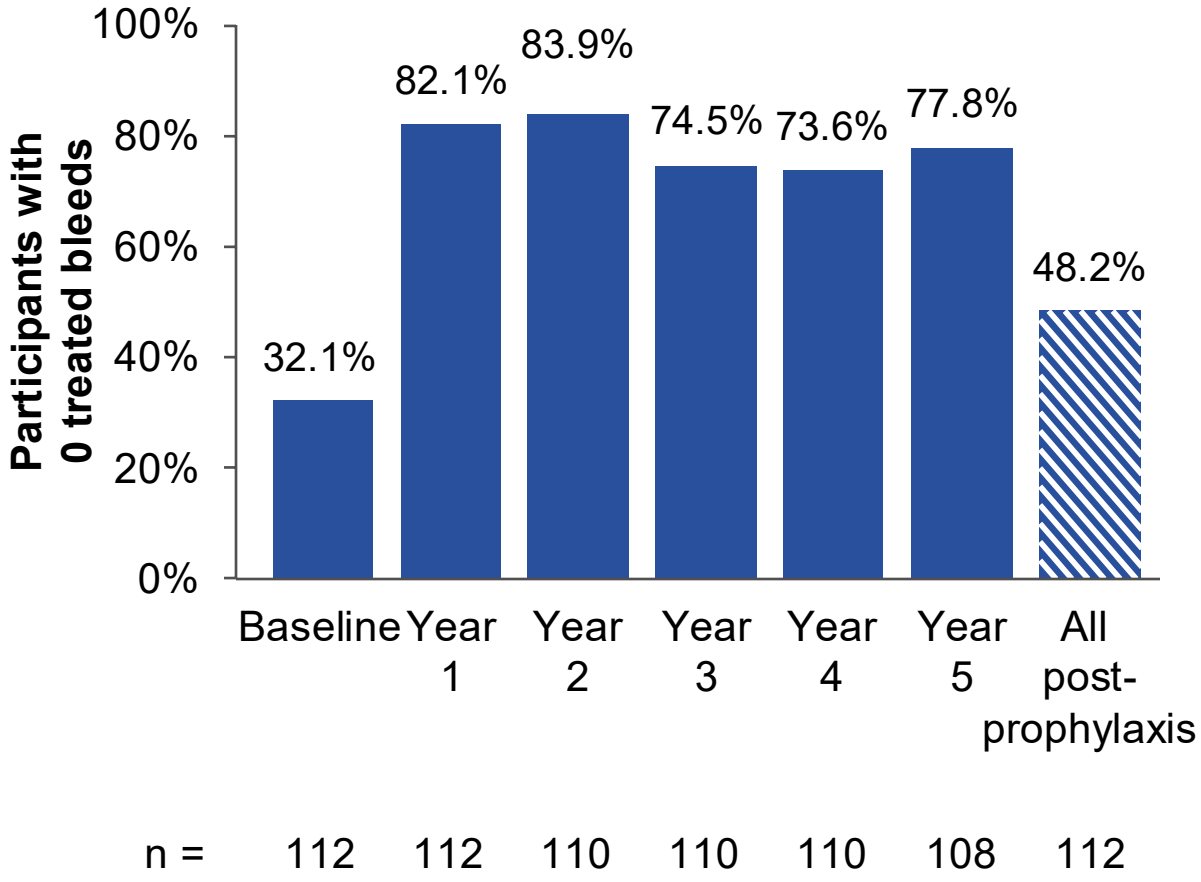
- ≥40 IU/dL
- ≥5 to <40 IU/dL
- ≥3 to <5 IU/dL
- <3 IU/dL (LLOQ)

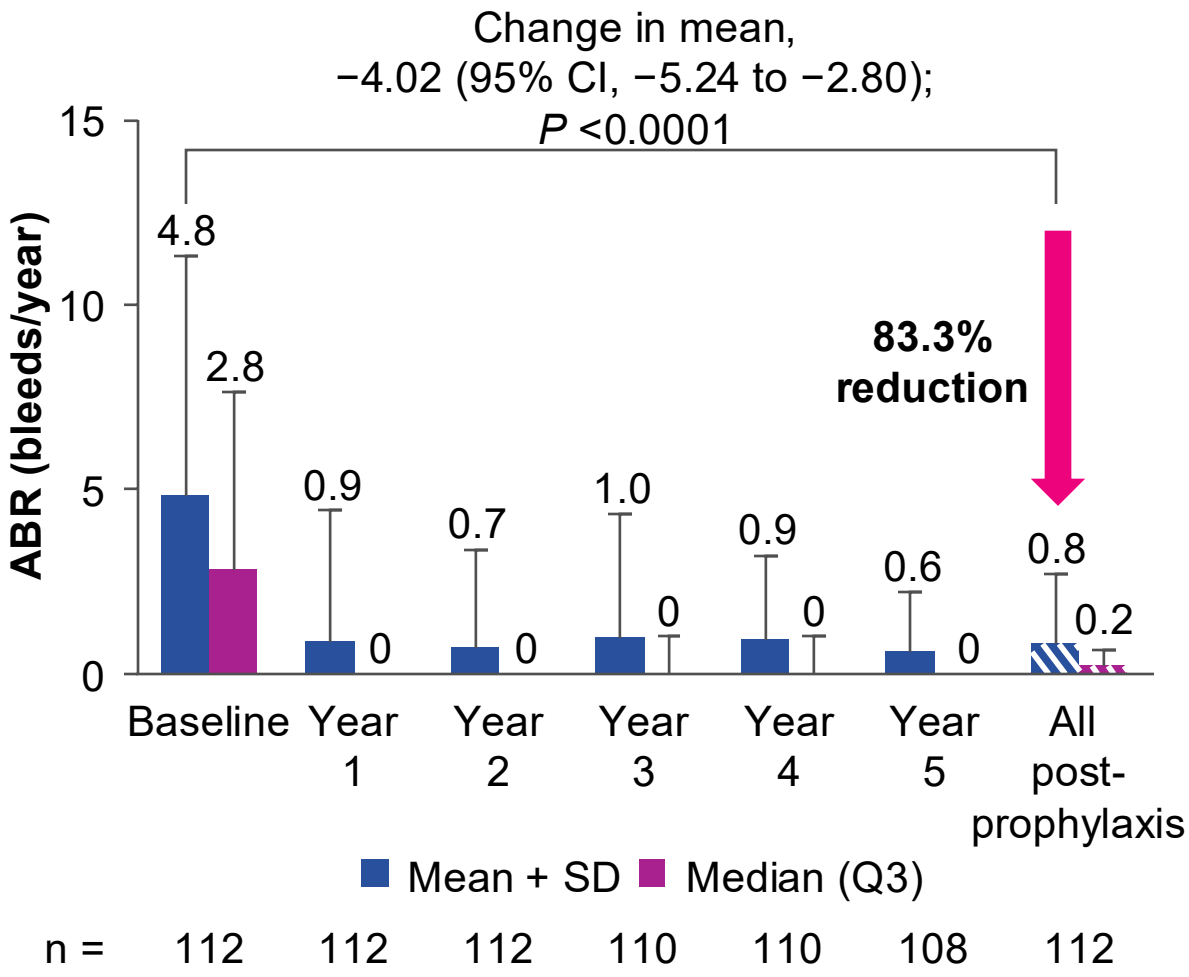
For participants who discontinued the study, missing FVIII values post-discontinuation were imputed as 0 IU/dL through the data cutoff date.
CSA, chromogenic substrate assay; FVIII, factor VIII; LLOQ, lower limit of quantification; mITT, modified intention-to-treat.

mITT population (N = 132)

Annualized bleeding rate (rollover population)

Reduction in treated bleeds was maintained over 5 years

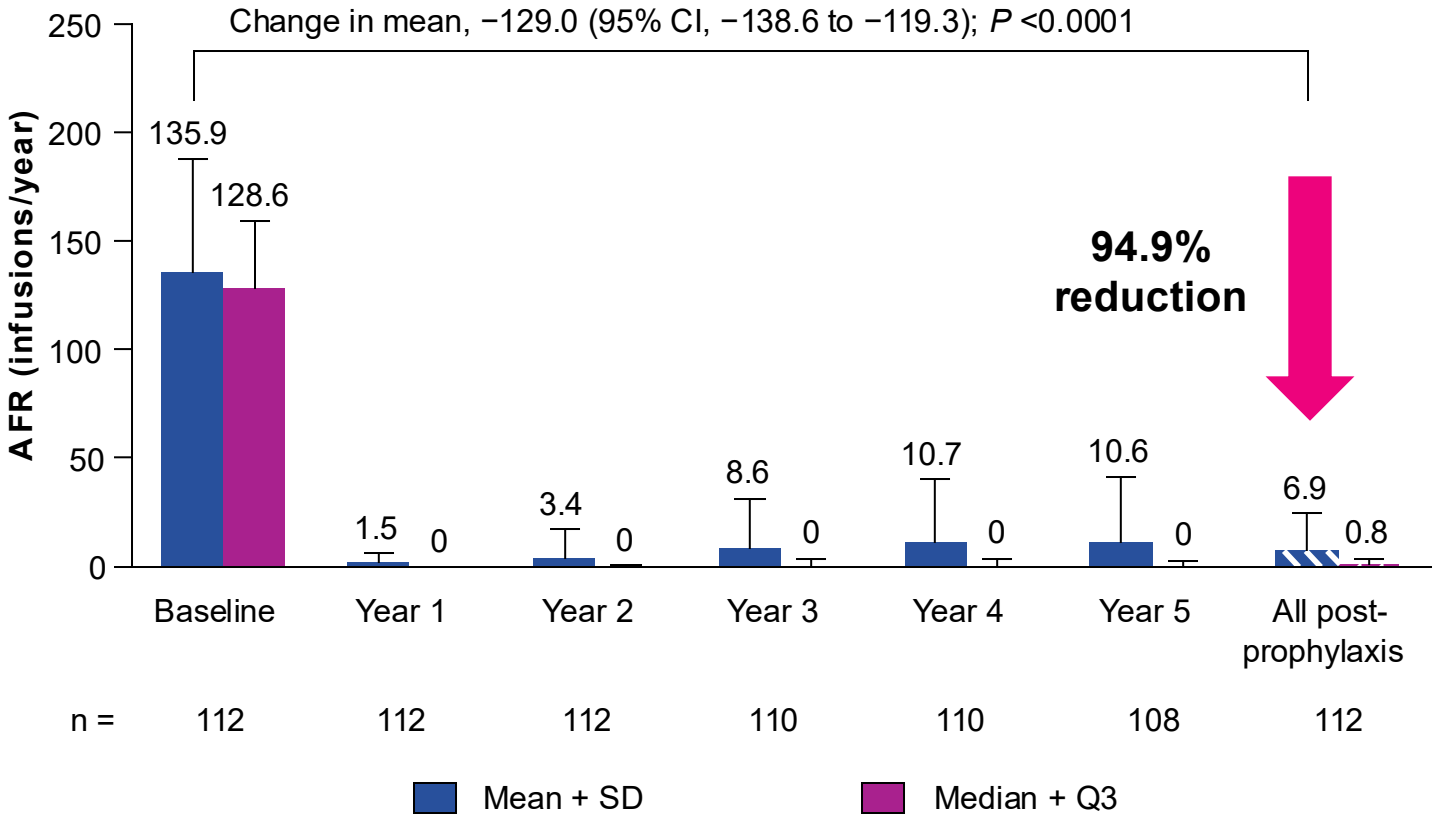




Missing data were not imputed.
ABR, annualized bleeding rate; CI, confidence interval; Q, quartile; SD, standard deviation.

Annualized FVIII infusion rate (rollover population)

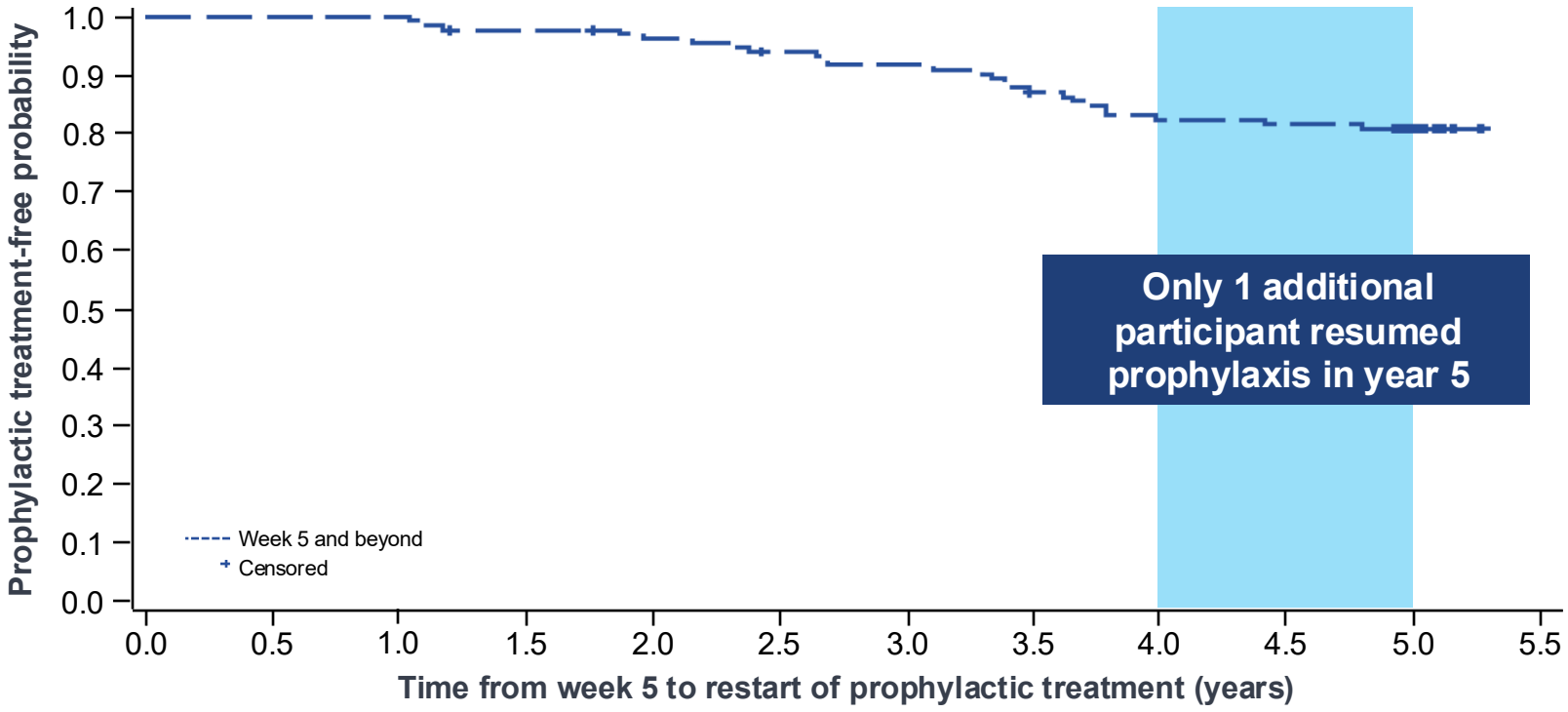
Reduction of FVIII infusion rate was maintained over 5 years



Missing data were not imputed.
AFR, annualized FVIII infusion rate; CI, confidence interval; FVIII, factor VIII; Q, quartile; SD, standard deviation.

Most participants continue to remain off prophylaxis at year 5

81.3% (109/134) of participants remain off prophylaxis



Of 25 participants who resumed prophylaxis, 68% had a lower treated annualized bleeding rate before resuming vs baseline

Missing data were not imputed.
ITT, intention-to-treat.

ITT population (N = 134)

Safety: Likelihood of Transaminitis After Gene Therapy

Manifestations[1-3]

- Transient increases in ALT and/or AST levels that usually occur within the first 4 to 12 weeks after infusion
- May be accompanied by reductions in FVIII level
- Commonly reported in trials of AAV-based hemophilia A gene therapy:
  - **Valoctocogene: 86%**[1]
  - **Giroctocogene: 82%**[2]
  - **Dirloctocogene: 52%**[3]
  - **Etranacogene Dezaparvovec 20 %**

Possible Mechanisms[4]

- Anti-AAV cytotoxic T-cell response
- Hepatocyte apoptosis induced by high factor expression/ER stress
- Direct effect of vector particle load

Typical Management[1-4]

- Oral corticosteroids for 2 to 3 months, tapering the dose as transaminase levels normalize
- Therapy course may be longer depending on response

1. Ozelo MC, et al; GENEr8-1 Trial Group. N Engl J Med. 2022;386:1013-1025; 2. Leavitt AD, et al. Blood. 2024;143:796-806; 3. Croteau SE, et al. Presented at: ISTH 2024 Congress; June 22-26, 2024; Bangkok, Thailand. Presentation OC 02.4; 4. Batty P, et al. Hemasphere. 2021;5:e540.

Transaminitis in hemophilia A gene therapy

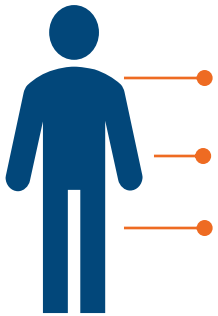
Participants, n (%)		Year 1 (N = 134)	Year 2 (N = 134)	Year 3 (N = 132)	Year 4 (N = 131)	Year 5 (N = 129)	All follow-up
AEs		134 (100.0)	112 (83.6)	104 (78.8)	98 (74.8)	102 (79.1)	134 (100.0)
SAEs		21 (15.7)	6 (4.5)	9 (6.8)	11 (8.4)	4 (3.1)	37 (27.6)
Treatment-related AEs[a]		124 (92.5)	27 (20.1)	15 (11.5)	10 (7.6)	5 (3.9)	124 (92.5)
Glucocorticoid-related AEs[a]		81 (60.4)	10 (7.5)	1 (0.8)	1 (0.8)	0	82 (61.2)
AEs of special interest	ALT elevation	116 (86.6)	39 (29.1)	31 (23.7)	49 (37.4)	52 (40.3)	125 (93.3)
	ALT elevation ≥grade 3	10 (7.5)	1 (0.7)	0	0	0	10 (7.5)
	Potential Hy's law case	0	0	0	0	0	0
	Infusion-related reactions[b]	12 (9.0)	0	0	0	0	12 (9.0)
	Systemic hypersensitivity	7 (5.2)	0	0	0	0	7 (5.2)
	Anaphylactic or anaphylactoid reactions	3 (2.2)	0	0	0	0	3 (2.2)
	Thromboembolic events	0	0	0	0	0	0
	Anti-FVIII neutralizing antibodies	0	0	0	0	0	0
	Malignancy (except nonmelanoma skin cancer)	0	0	1 (0.8)	0	0	1 (0.7)

[a]Treatment-related and glucocorticoid-related AEs were assessed by the investigator.
[b]Infusion-related reactions were defined as AEs occurring during valoctocogene roxaparvovec infusion or within 6 hours post-infusion.
AE, adverse event; ALT, alanine aminotransferase; FVIII, factor VIII; ITT, intention-to-treat; SAE, serious AE.

Integration analysis reveals no evidence of a causal relationship to cancer

- **Six incidental cancer cases** identified in haemophilia gene therapy clinical trials

Case of HCC 1 year after HB gene therapy[1]



- 69-year-old patient
- History of hepatitis B and C
- Family history of cancer

Other cases[2-4]:

Following HA gene therapy:

- Parotid acinic cell carcinoma
- B-cell acute lymphoblastic leukaemia

Following HB gene therapy:

- Tonsillar carcinoma
- Localised prostate adenocarcinoma
- Non-mucinous lung adenocarcinoma in situ

- **Robust analyses** submitted to regulatory agencies conclude that a causal relationship between gene therapy and these cancer cases is **very unlikely**
- Current evidence shows an **acceptable safety profile**
- **Long-term follow-up** of PwH receiving gene therapy continues[5,6]

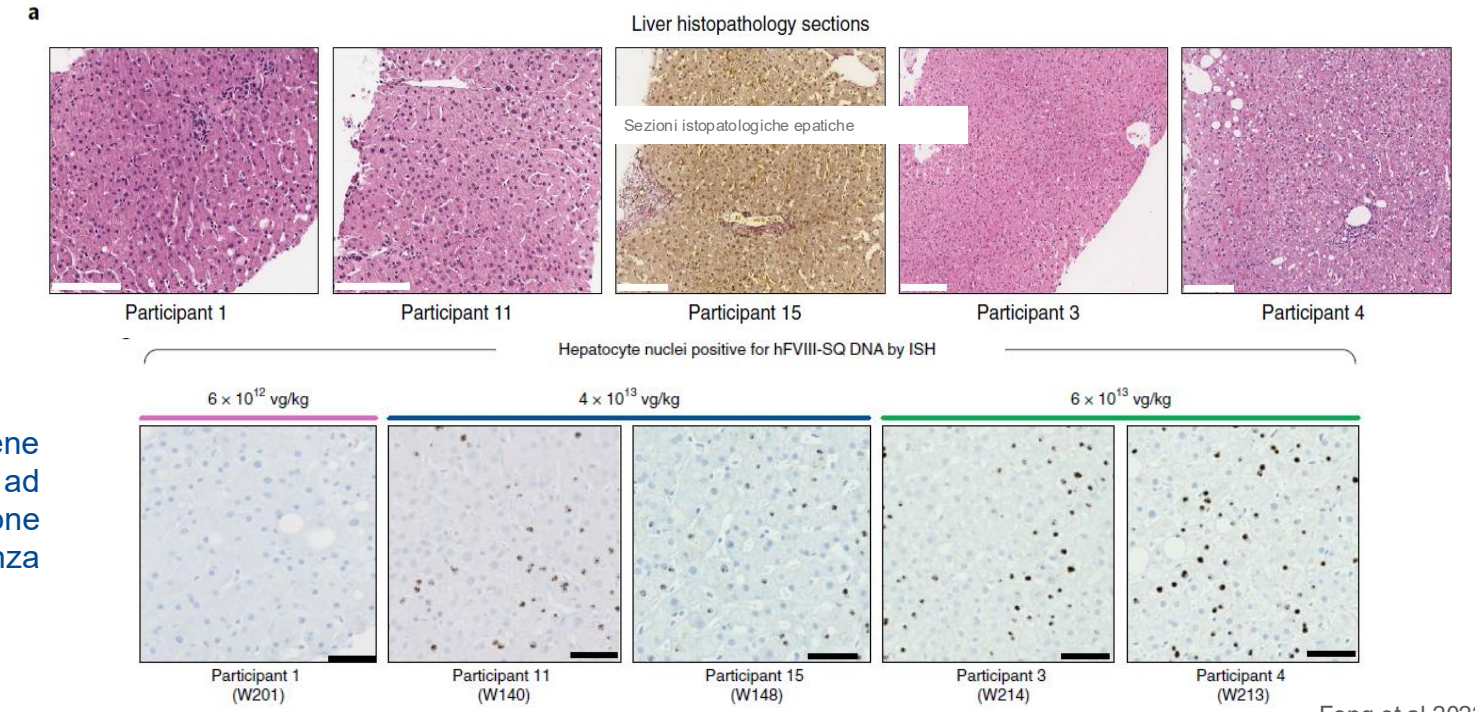
1. Schmidt M et al. Blood Adv 2023;7:4966-9; 2. Castaman G et al. Exp Rev Hematology 2023;1-14; 3. Konkle BA et al. Blood 2021;137:763-74;
4. Reiss UM et al. Abstract 1056 ASH 2023 Annual Meeting and Exposition, December 9-12, San Diego, CA, USA;
5. Samelson-Jones BJ et al. Annu Rev Med 2023;74:231-47; 6. Nathwani AC. Hematology Am Soc Hematol Educ Program 2022;2022:569-78

Studio BMN 270-201 | Espressione post-infusione di valoctocogene roxaparvovec nel fegato

In un sotto-studio dello studio clinico di fase 1/2, **sono stati raccolti campioni di biopsia epatica 2,6-4,1 anni dopo il trasferimento genico da 5 partecipanti**.

L'istopatologia non ha rivelato displasia, anomalie strutturali, fibrosi o infiammazione cronica e non è stato rilevato stress del reticolo endoplasmatico negli epatociti che esprimono la proteina hFVIII-SQ.

Una singola infusione endovenosa di valoctocogene roxaparvovec (AAV5-hFVIII-SQ), somministrata ad adulti con emofilia A grave, ha portato alla trasduzione del fegato umano in tutti i tessuti campionati senza distorsioni zonali all'interno dei lobuli epatici.



Fong et al 2022

Nel complesso, questi risultati dimostrano la persistenza di strutture vettoriali episomali dopo la somministrazione di AAV5-hFVIII-SQ e contribuiscono a chiarire i possibili meccanismi che mediano la variabilità interindividuale.

AAV5: virus adeno-associato di sierotipo 5; DNA: acido desossiribonucleico; ISH: ibridazione in-situ; hFVIII-SQ: forma SQ del fattore di coagulazione umano VIII; W: settimana; vg/Kg: genomi del vettore per chilogrammo.

Fong SA., et al. Nat Med. 2022 Apr;28(4):789-797.

How are factor levels associated with clinical outcomes of gene therapy?

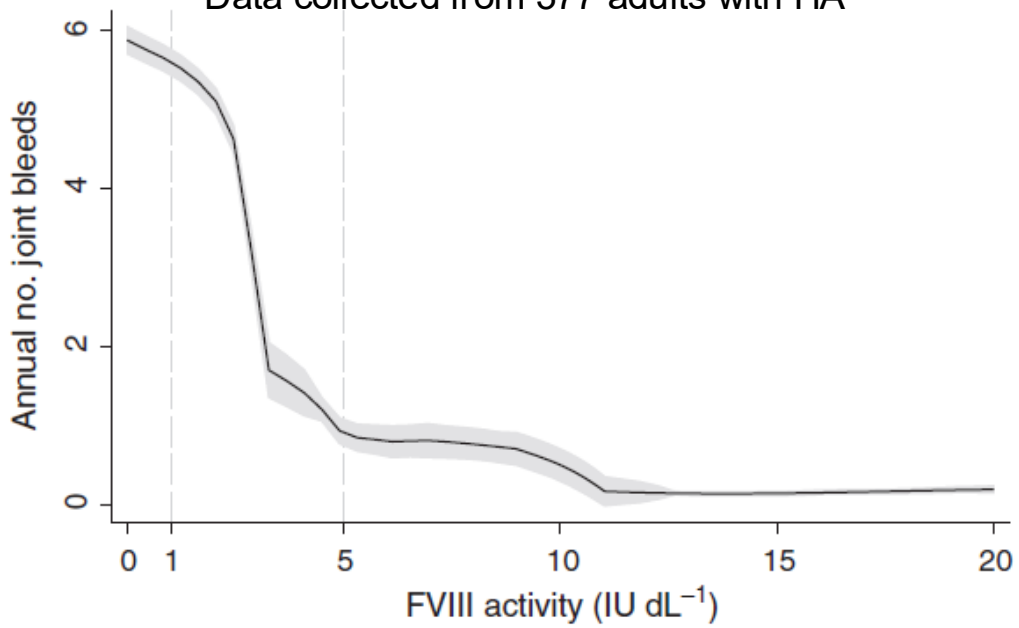
Haemophilia A

Results from several studies indicate that number of joint bleeds approaches to near-zero with **FVIII activity levels 15-50%**[1]

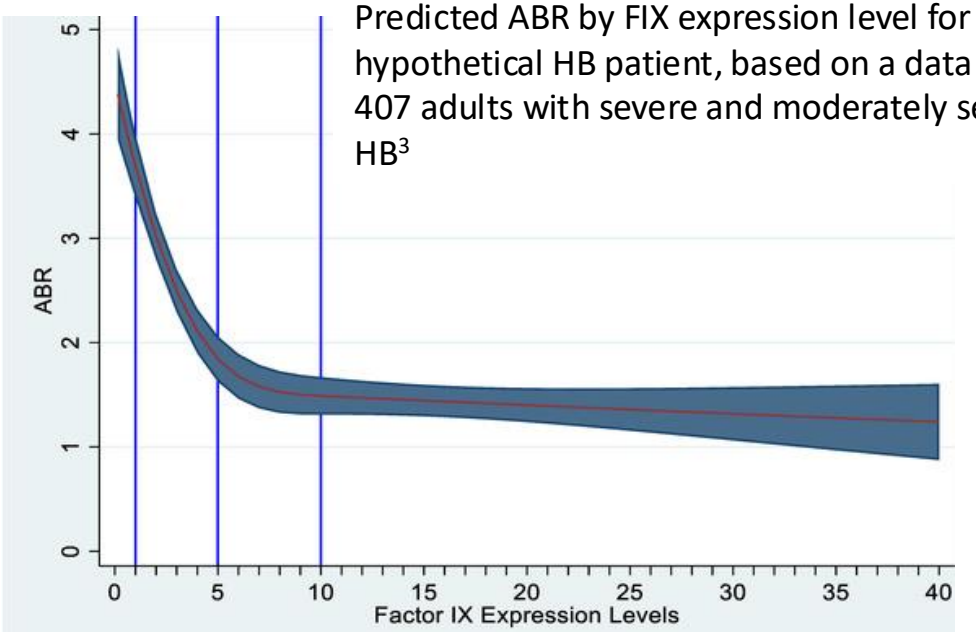
Haemophilia B

Data suggest that **FIX activity levels >25%** could be sufficient to eradicate all bleeding events[3]

Data collected from 377 adults with HA[2]



Predicted ABR by FIX expression level for a hypothetical HB patient, based on a data from 407 adults with severe and moderately severe HB[3]



1. Malec L & Matino D. Haemophilia 2023;29:1419-29; 2. Den Uijl I et al. Haemophilia 2011;17:849-53; 3. Burke T et al. Haemophilia 2023;29:115-22

Clinical trial data: key take-aways

Long-term durability of gene therapy:

- **HA**: **>80%** of participants remain **off prophylaxis** after 4 years and **>70%** after 7 years
- **HB**: **>90%** of participants remain **off prophylaxis** after 5 years and **>50%** after 10 years

Gene therapy has the potential to **positively impact** the patient's **quality of life**

- **Short-term tolerability profile is manageable**
- No new short- or long-term safety signals identified in ongoing trials

- **Consistent long-term safety profile** with monitoring beyond 7 years ongoing
- Causal relationship between gene therapy and malignancies is very unlikely

Limits for AAV-based gene therapy

- Adjunctive, non-corrective
- Expression outcome unpredictable
- Not for pediatric age
- [illegible]
- Antibodies against the vector
- Role of «transaminitis»; vector dose
- Liver disease
- Long-term durability
- Genotoxicity

At present, it is expected no more than 20-25 % of HA and
~ 30-40 % HB patients are eligible

Conclusions

- Big step forward, potential for cure, still limited follow-up
  - Available clinical trials provided information for transgene expression likely at therapeutic levels long-term for hemophilia B, medium for hemophilia A
  - Abolition of bleeding events in most, with ↓concentrate consumption
  - Population eligible limited, transaminitis in hemophilia A
  - Other technologies in development (e.g., Lentivirus, CRISPR/Cas9…)
  - Careful evaluation within the available therapeutic landscape

Conclusions…

- Hemophilia treatment is approaching new therapeutic paradigms , with rapidly evolving scenario, mainly aimed at enhancing prophylaxis and eventually providing cure

- These novel approaches open new perspectives which require teaching, learning, education, and experience to manage all the aspects of novel treatments in the «real-life»:

- Laboratory monitoring
- Effects and role in PUPS
- Which role vs ITI in patients with inhibitors
- Treatment of breakthrough bleeds
- Management of elective major surgery
- Management of post-trauma/emergency surgery

…on the way

Predictability of transgene expression level and durability

- Probably the most critical questions that patients will ask about potential outcomes of hemophilia gene therapy are:

- **what level of factor will I achieve with gene therapy?**

- **how long will the effect last?**

a) In human trials to date, there is significant variability in the factor levels that in some instances is as high as >10-fold (0.20 to >2.00 IU/mL)

b) In terms of durability of transgene expression,Human FIX gene therapy studies in adult patients are now ~ 10 years post-single administration, with minimal evidence of a decline in plasma FIX levels

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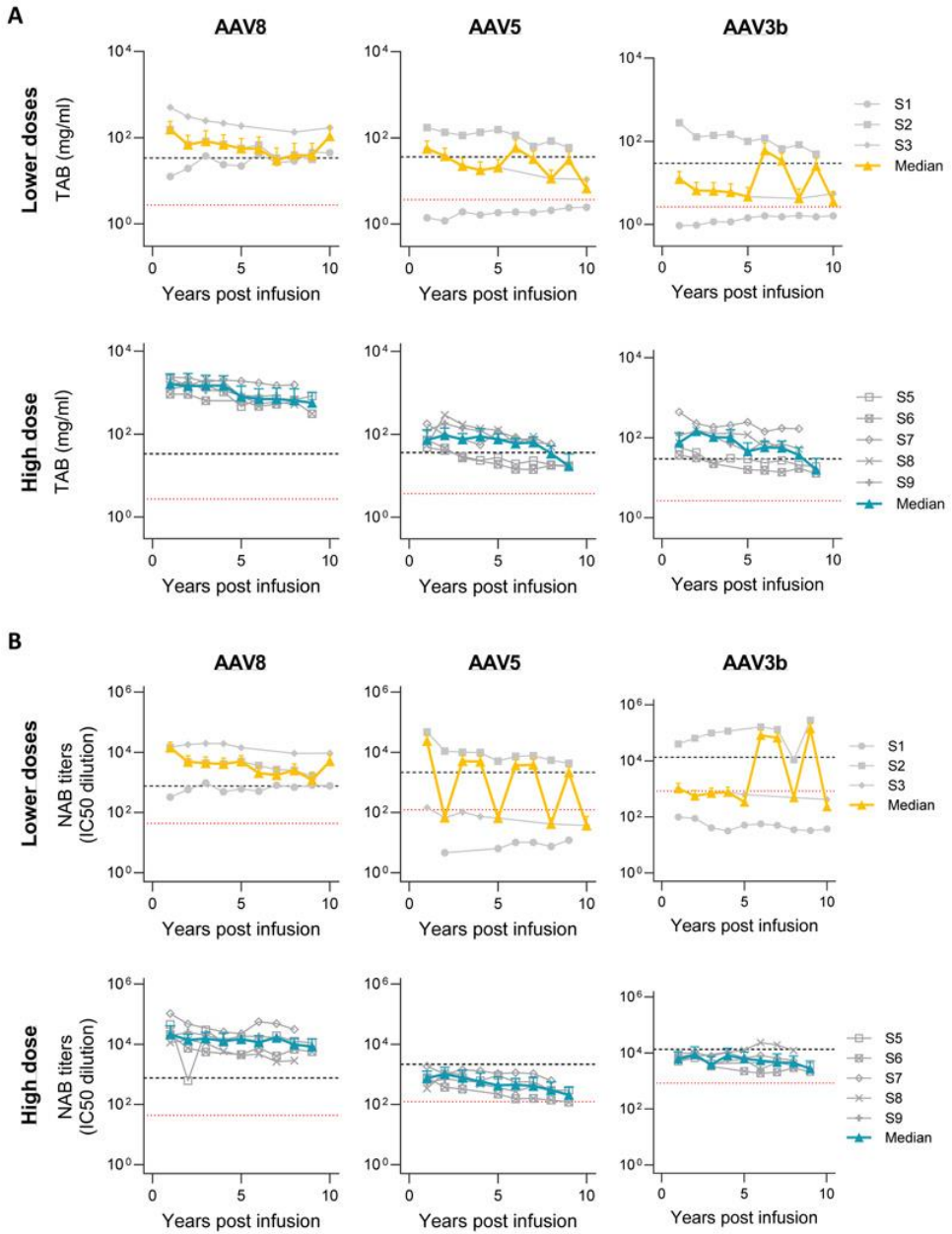
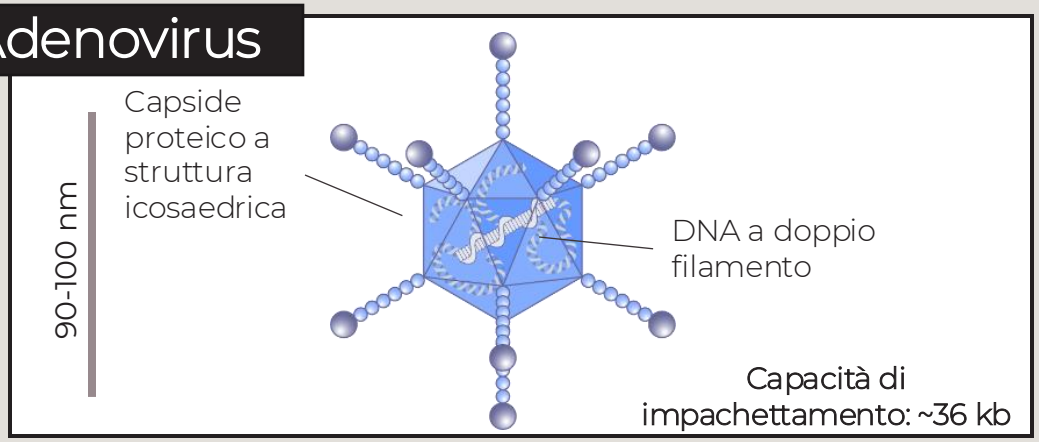


Differenze tra Adenovirus e Virus Adeno-Associati [1-2]

Adenovirus



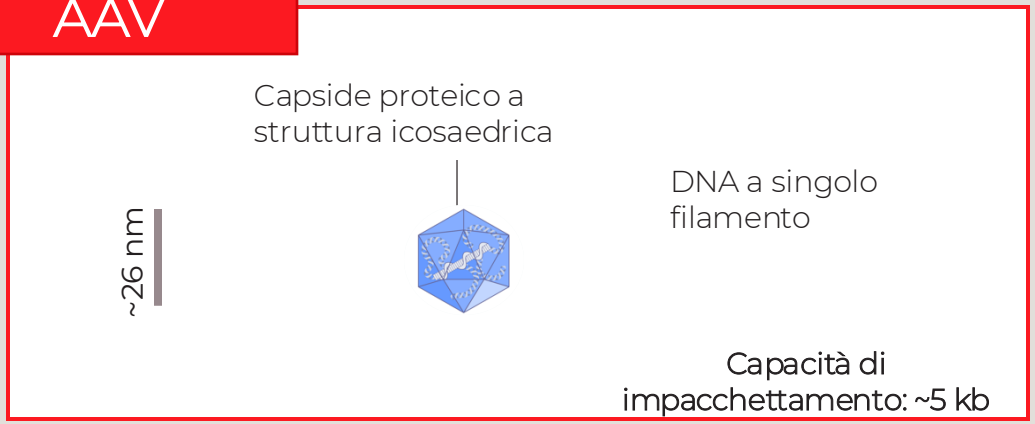
Virus

- Patogeno; noto per causare infezioni nell'uomo (es. infezioni del tratto respiratorio superiore)
- Può replicarsi nelle cellule ospiti senza un virus helper

Vettore

- Grande capacità di impacchettamento
- Altamente immunogenico e infiammatorio
- Candidato ideale per l'immunoterapia dei tumori e per i nuovi vaccini (es. Ebola, influenza)

AAV



Virus

- Non patogeno e non associato ad alcuna malattia
- Non può replicarsi nelle cellule ospiti senza un virus helper

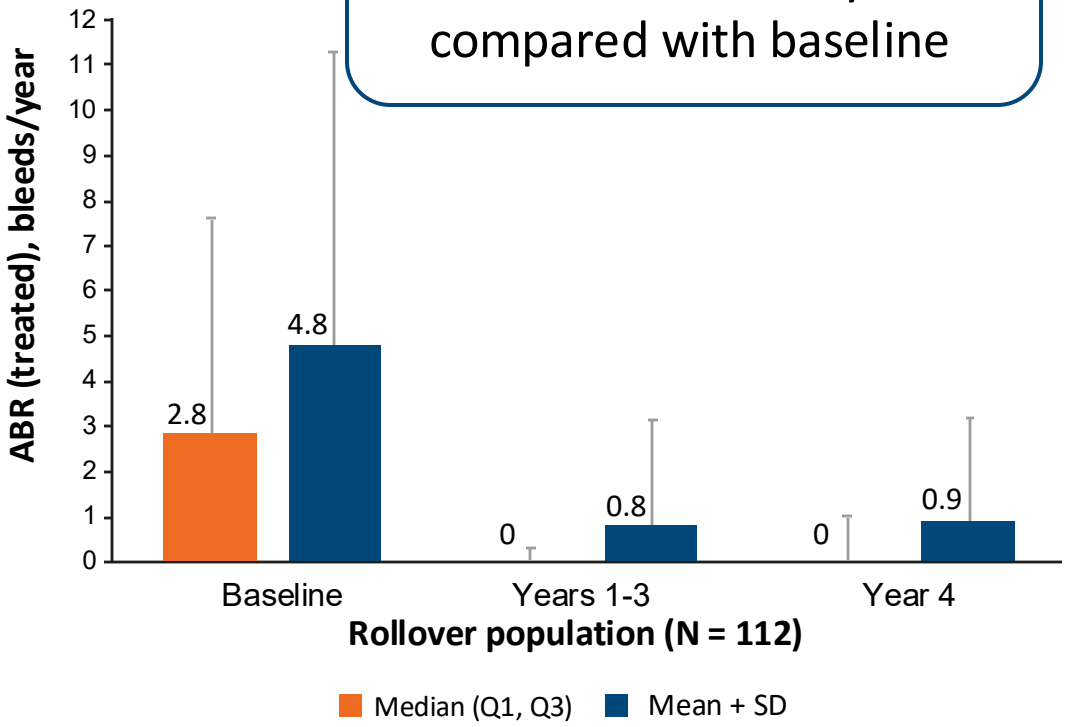
Vettore

- Ridotta capacità di impacchettamento
- Non stimola la risposta infiammatoria e non è tossico
- Persiste nei tessuti, consentendo l'espressione a lungo termine del transgene

1. Bulcha JT, et al. *Signal Transduct Target Ther* 2021; 6(1):53. 2. Wang D, et al. *Nat Rev Drug Discov* 2019; 18(5):358–378.

Haemophilia A gene therapy: phase 3, year 4 outcomes

81.3% reduction in treated bleeds in year 4 compared with baseline



- **82.1%** remained **off prophylaxis** in year 4
- **73.6%** had **no treated bleeds** during year 4
- **92.2% decrease** in mean annualised FVIII **infusion rate** compared with baseline
- **HRQoL improved** 6.2 points over baseline*
- **Consistent safety profile** maintained over 4 years post-administration

FVIII activity (IU/dL) after 4 years (N=130)		
CSA	Mean ± SD Median (Q1,Q3)	**16.1** ± 28.9 **6.7** (2.8, 17.8)
OSA	Mean ± SD Median (Q1, Q3)	**27.1** ± 45.7 **13.5** (5.3, 29.1)

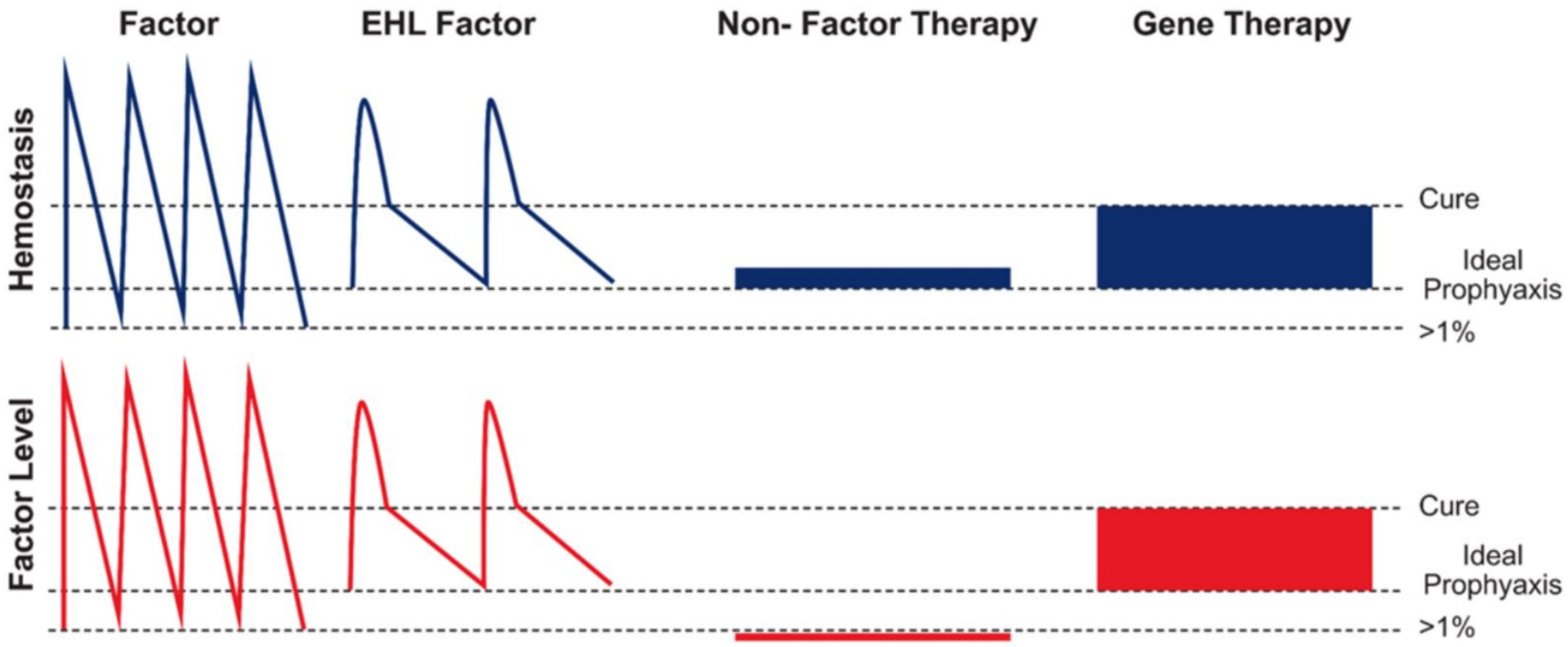
Results of the GENER8-1 trial

*As measured by mean Haemo-QOL-A Total Score. A difference of 5.5 points is considered clinically important.

CSA: chromogenic substrate assay; OSA: one-stage clotting assay; SD: standard deviation

Leavitt AD et al. Abstract THSNA 2024 Congress, April 4-6, Chicago, IL, USA; Madan B et al. J Thromb Haemost. 2024;S1538-7836(24)00184-3; Mahlangu J et al. N Engl J Med. 2023;388:694-705; Mahlangu J et al. Oral presentation at GTH 2023, February 21-24, Frankfurt, Germany

The Benefits of Gene Therapy



From: Arruda et al., Blood, 2017

jth

Invasive procedures and surgery following etranacogene dezaparvovec gene therapy in people with hemophilia B

Niamh O'Connell[1,2] | Paul van der Valk[3] | Sandra Le Quellec[4] | Esteban Gomez[5] | Paul E. Monahan[4] | Shelley E. Crary[6] | Michiel Coppens[7,8] | Richard Lemons[9] | Giancarlo Castaman[10] | Robert Klamroth[11] | Emily Symington[12] | Doris V. Quon[13] | Peter Kampmann[14]

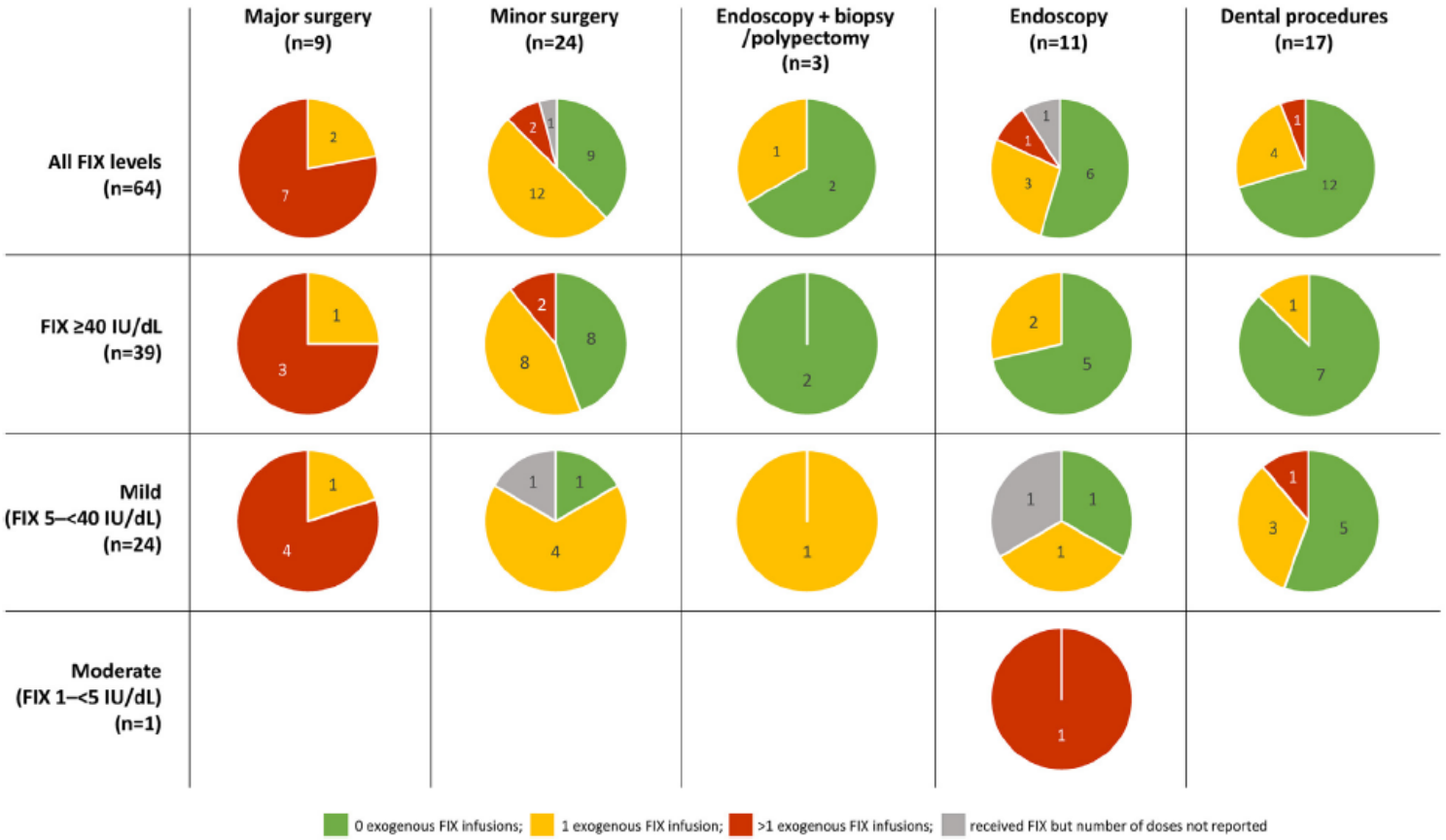
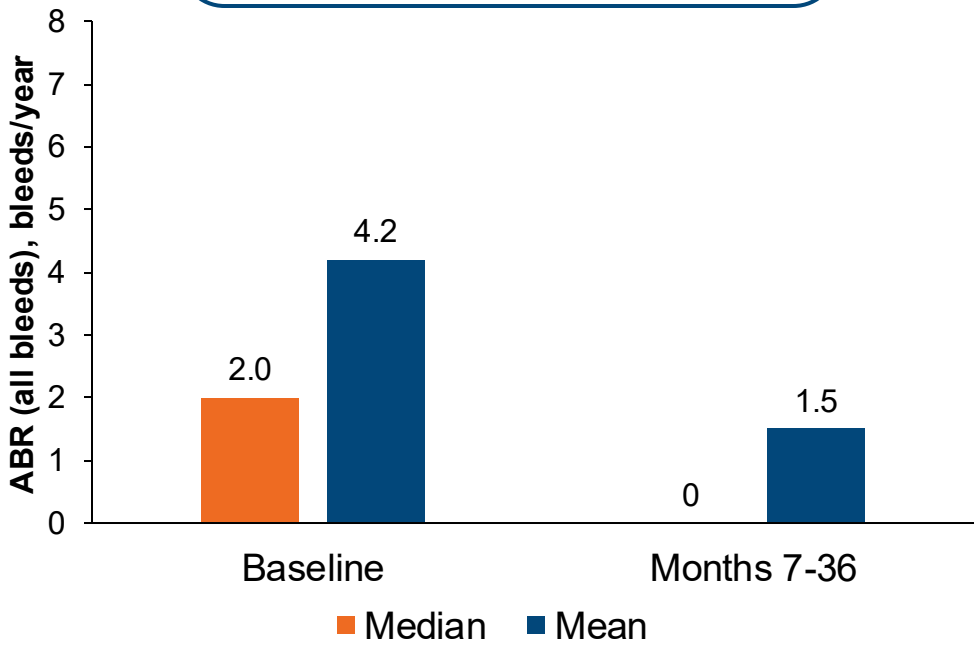


FIGURE 3 Procedures (elective and emergency) without exogenous factor (F)IX infusion, 1 exogenous FIX infusion, or more than 1 exogenous FIX infusion overall and by last recorded central laboratory FIX activity corresponding to moderate HB (FIX, 1 to <5 IU/dL), mild HB (FIX, 5 to <40 IU/dL), or nonhemophilia levels (FIX, ≥40 IU/dL).

Haemophilia B gene therapy: phase 3, year 3 outcomes
(HOPE-B with FIX Padua)

64% reduction in mean ABR in year 3 compared with baseline



- Mean annualised **FIX consumption decreased** **96%** compared with baseline
- **94%** remained **off continuous FIX prophylaxis** in year 3
- **Favourable safety profile** maintained over 3 years post-administration

FIX activity (IU/dL) (N=48)		
OSA	Mean ± SD Median (Q1, Q3)	38.6 ± 17.8 36.0 (4.8, 80.3)

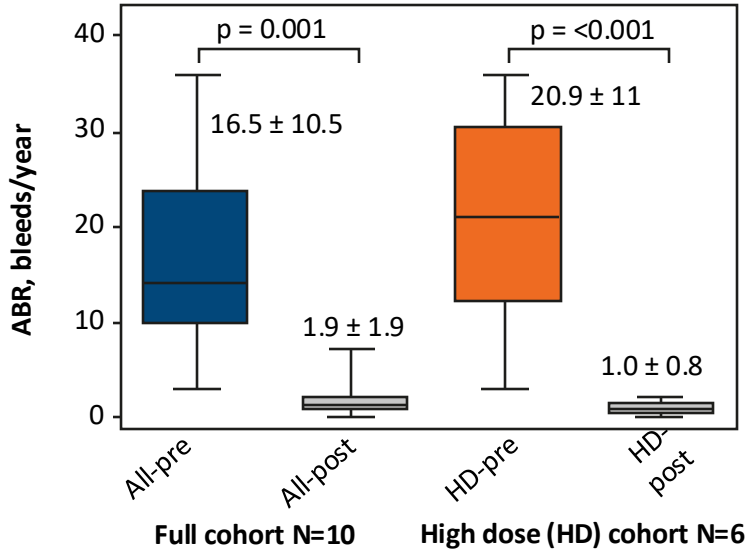
*Dose: $2x10^{13}$ vg/kg

Pipe SW et al. Blood 2023;142(Suppl1):1055; Pipe SW et al. N Engl J Med 2023;388:706-18

(1) lung adenocarcinoma in situ, detected incidentally after bullectomy for recurrent pneumothorax 5 years post-therapy in a 44-year-old with an approximately 10 pack-year smoking history over 27 years, and (2) prostate adenocarcinoma in a 74-year-old 11.6 years post-therapy.

Haemophilia B: phase 1/2 clinical trial, year 10 outcomes

95% reduction in ABR in year 10 compared with baseline in high dose cohort*,**



More outcomes in high dose cohort (N=6):

- **93%** reduction in annualised **FVIII infusion rate*****
- **No** new **safety concerns**
- Mean ± SD **FIX activity**§: **4.9 ± 2.2** IU/dL

5/10 participants of **all dose cohorts** remained **off prophylaxis**

Stable therapeutic FIX levels with durable reduction in ABR and factor concentrate use

Results from St Jude-UCL gene therapy trial
*Dose: $2x10^{12}$ vg/kg; **88% reduction in full-dose cohort (N=10); ***89% reduction in full-dose cohort (N=10);
§wild-type FIX
Reiss UM et al. Abstract 1056 ASH 2023 Annual Meeting and Exposition, December 9-12, San Diego, CA, USA

Short-term safety data of AAV gene therapy

- Most commonly-reported AE remain:[1,2]

Mild infusion-related reactions

ALT increases

- Mostly **asymptomatic** and **transient**, with no reports of recurrence beyond a 2-year interval[3]
- May be associated with a decline in factor expression
- Treatment with corticosteroids may help to save factor expression
- Data suggest increases happen more frequently in haemophilia A gene therapy

AE: adverse event; ALT: alanine aminotransferase

1. Samelson-Jones BJ et al. Annu Rev Med 2023;74:231-47; 2. Castaman G et al. Exp Rev Hematology 2023;1-14;
3. Nathwani AC. Hematology Am Soc Hematol Educ Program 2022;2022:569-78

Long-term safety data of AAV gene therapy at a glance

Study with AAV-cFVIII in HA dogs (median follow-up of >10 years)[1]

- **No** evidence of chronic liver disease
- **No** liver malignancy

Haemophilia A and B gene therapy clinical trials

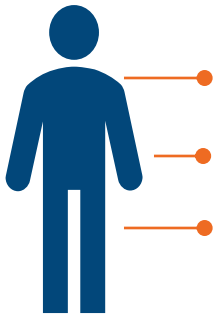
- **No** persistent, or late, liver toxicities observed[2,3]
- Data up to 7 (HA) and 15 years (HB) reveal **no new safety signals**[4,5]

1. Batty P et al. Blood 2022;140:2672-83; 2. Samelson-Jones BJ et al. Annu Rev Med 2023;74:231-47; 3. Nathwani AC. Hematology Am Soc Hematol Educ Program 2022;2022:569-78; 4. Symington E et al. Abstract 1381 EAHAD 2024 Congress, February 6-9, Frankfurt, Germany;
5. George LA et al. Mol Ther 2020;28:2073-82

Integration analysis reveals no evidence of a causal relationship to cancer

- **Six incidental cancer cases** identified in haemophilia gene therapy clinical trials

Case of HCC 1 year after HB gene therapy[1]



- 69-year-old patient
- History of hepatitis B and C
- Family history of cancer

Other cases[2-4]:

Following HA gene therapy:

- Parotid acinic cell carcinoma
- B-cell acute lymphoblastic leukaemia

Following HB gene therapy:

- Tonsillar carcinoma
- Localised prostate adenocarcinoma
- Non-mucinous lung adenocarcinoma in situ

- **Robust analyses** submitted to regulatory agencies conclude that a causal relationship between gene therapy and these cancer cases is **very unlikely**
- Current evidence shows an **acceptable safety profile**
- **Long-term follow-up** of PwH receiving gene therapy continues[5,6]

HCC: hepatocellular carcinoma; PwH: people with haemophilia

1. Schmidt M et al. Blood Adv 2023;7:4966-9; 2. Castaman G et al. Exp Rev Hematology 2023;1-14; 3. Konkle BA et al. Blood 2021;137:763-74;
4. Reiss UM et al. Abstract 1056 ASH 2023 Annual Meeting and Exposition, December 9-12, San Diego, CA, USA;
5. Samelson-Jones BJ et al. Annu Rev Med 2023;74:231-47; 6. Nathwani AC. Hematology Am Soc Hematol Educ Program 2022;2022:569-78

Short-term efficacy of gene therapy: improved factor levels

Clinical trial data have shown that gene therapy can result in **protective factor levels** in the weeks following infusion[1,2]

- Shift to mild - or even normal - bleeding phenotype[1]
- Improved protection against bleeds compared with prophylaxis with FVIII/FIX[3,4]

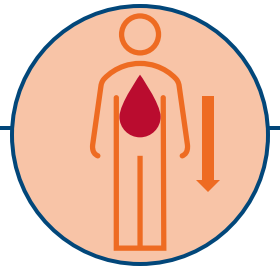
Current predictability of gene therapy response[1,5]

- Inter-individual variability in patient response
- Ongoing research to determine predictive factors for inter-individual variability

1. Ozelo MC and Yamaguti-Hayakawa GG. Res Pract Thromb Haemost 2022;6:e12695; 2. Leebeek F and Miesbach W. Blood 2021;138:923-31;
3. Ozelo MC et al. N Engl J Med 2022;386:1013-25; 4. Pipe SW et al. N Engl J Med 2023;388:706-18; 5. Bolous N et al. J Blood Med 2022;13:559-80

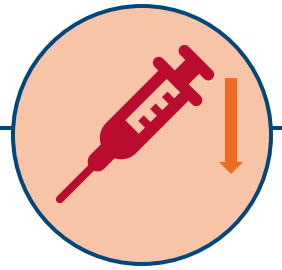
Impact of gene therapy on clinical outcomes and quality of life

Data from AAV-gene therapy trials shows
improved outcomes in most trial participants with sustained factor activity levels:



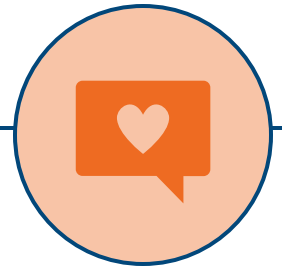
Reduced bleeding episodes

- **Significant reduction** in treated bleeds
- Many participants **achieve an ABR of 0** treated bleeds



Decreased factor concentrate use

- Majority of participants **discontinue prophylaxis**



Improved quality of life

- Likely reflective of **reduced burden of disease** and **reduced use of frequent prophylaxis**
- **Improvements post-infusion** in phase 3 trials up to 1 year (HB) and 3 years (HA)

Leebeek F and Miesbach W. Blood 2021;138:923-31; Nathwani AC. Hematology Am Soc Hematol Educ Program 2022;2022:569-78; Mahlangu J et al. N Engl J Med. 2023;388:694-705; Mahlangu J et al. Oral presentation at GTH 2023, February 21-24, Frankfurt, Germany; Madan B et al. J Thromb Haemost. 2024;S1538-7836(24)00184-3; Pipe SW et al. N Engl J Med 2023;388:706-18

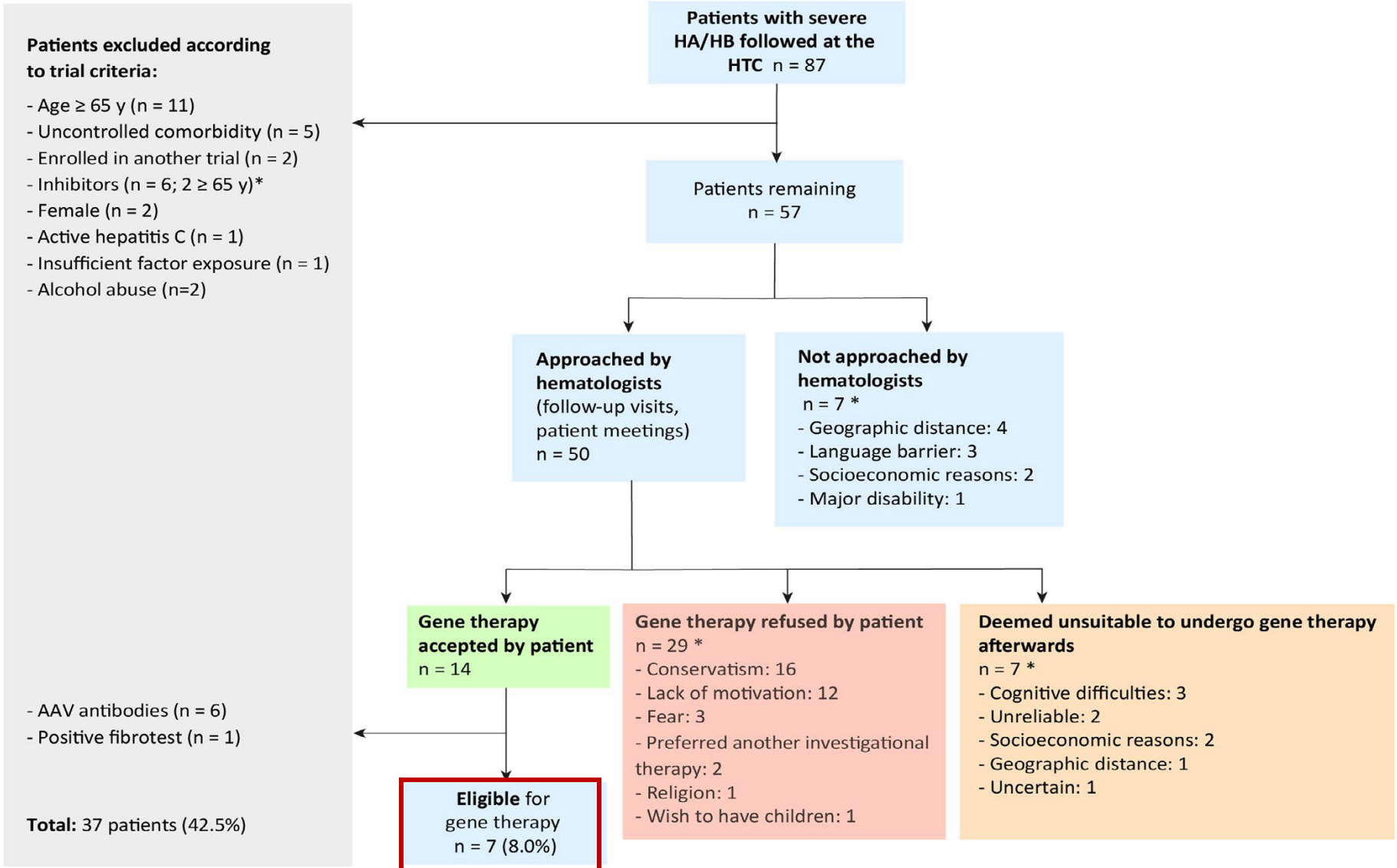
From Clinical trials to Real World…

- The first licensed hemophilia *gene therapy products are available*, and the uptake of this new treatment will then depend upon a complex combination of :
- *payment options*
- *patient satisfaction with current therapies*
- *uncertainties surrounding long-term gene therapy outcomes*

Implementing gene therapy

Patient selection for hemophilia gene therapy: Real-life Data from a single center

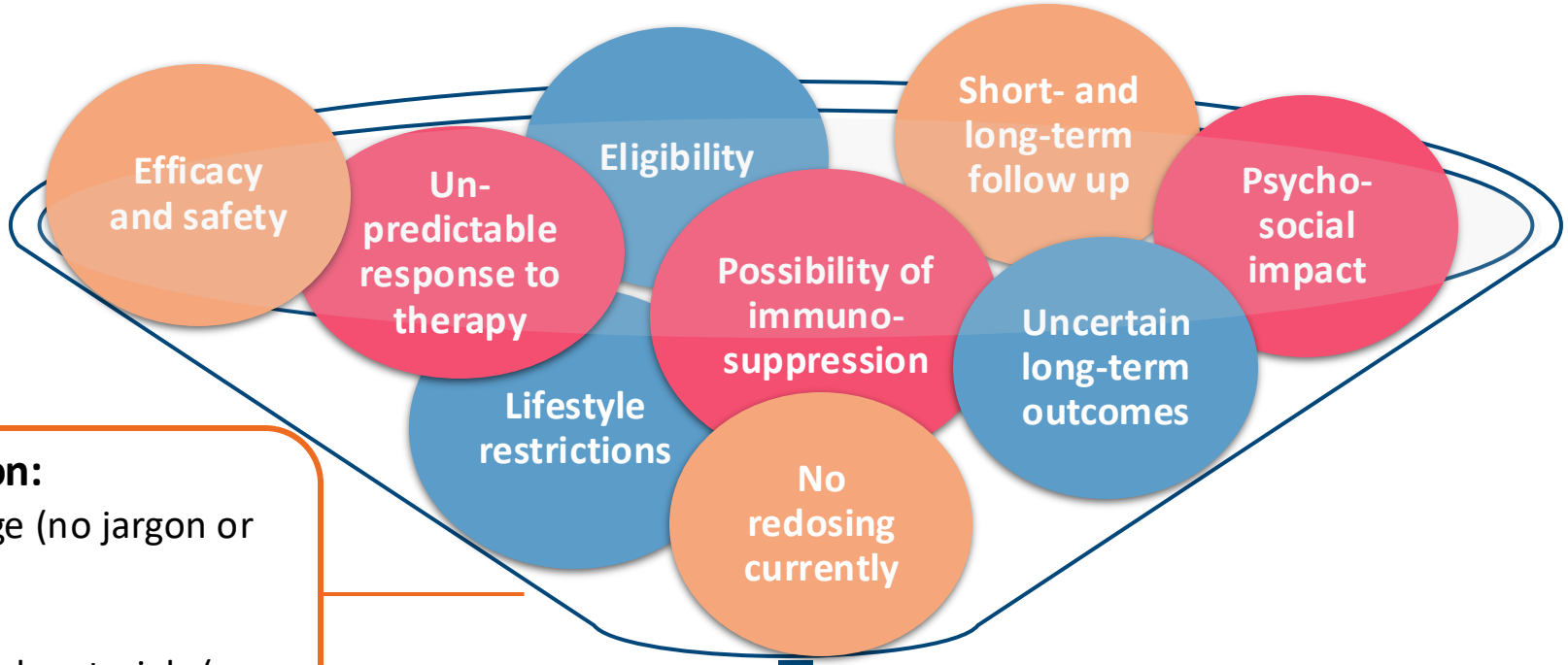
Evelien Krumb MD | Catherine Lambert MD, PhD |Cedric Hermans MD, FCRP (Lon, Edin), PhD



29/57 refused (52 %)
14/57 accepted (25%)
7/57 eligible (13 %)

DOI: 10.1002/rth2.12494

Patient-centred education on gene therapy: distilling complex information to individual needs



Adapt communication:

- Appropriate language (no jargon or too many details)
- Teach-back method
- Written and graphical materials (e.g., videos, infographics)

Informed patient with ***realistic*** treatment **expectations**

Pipe SW et al. Haemophilia 2023;29:1430-41; Wang M et al. Patient Prefer Adherence 2022;16:1439-47; Hermans C et al. Ther Adv Hematol 2023;14:20406207221145627; Boyce S et al. Orphanet J Rare Dis 2023;18:366; Limjoco J & Thornburg CD. Patient Prefer Adherence 2023;17:1093-105

WFH Shared Decision-Making Tool (SDM) facilitates patient-provider conversations

Discussing gene therapy with patients requires:

a) **Multiple** comprehensive, engaging and individualised **conversations**

b) Balancing **risks vs benefits** to set realistic expectations

c) Comparison with **other treatment options**

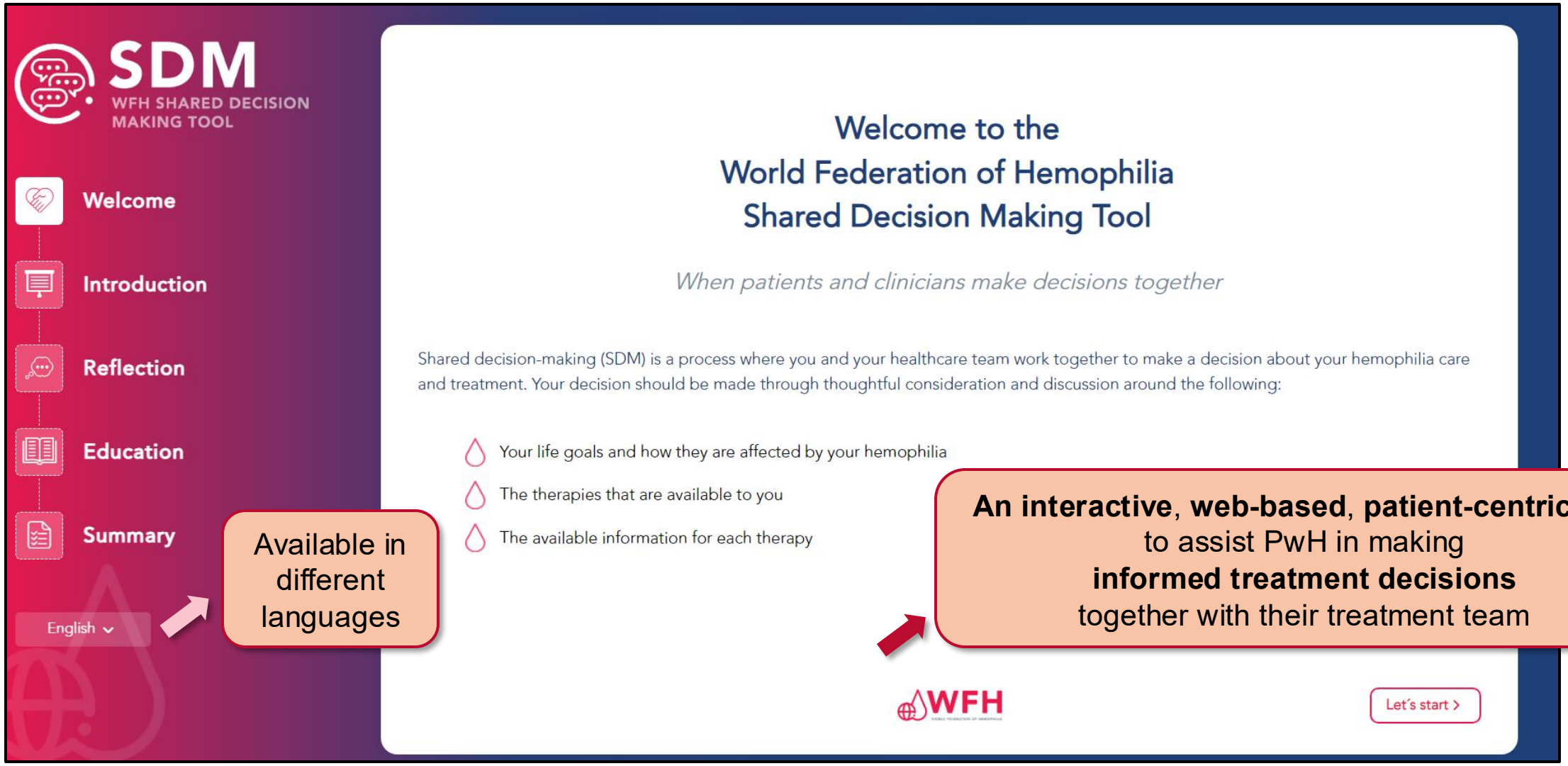
How to structure your conversations?

WFH Shared Decision-Making Tool

- **Step-by-step approach guiding patients and healthcare providers towards a treatment decision**
- **Straightforward to apply in daily practice**
- **Available at: https://sdm.wfh.org/**

Pipe SW et al. Haemophilia 2023;29:1430-41; Wang M et al. Patient Prefer Adherence 2022;16:1439-47; Hermans C et al. Ther Adv Hematol 2023;14:20406207221145627; Boyce S et al. Orphanet J Rare Dis 2023;18:366; Limjoco J & Thornburg CD. Patient Prefer Adherence 2023;17:1093-105

The WFH SDM tool



Available in different languages

An interactive, **web-based**, **patient-centric tool** to assist PwH in making **informed treatment decisions** together with their treatment team

WFH Shared Decision Making Tool. Accessible from: https://sdm.wfh.org/; Pipe SW et al. Haemophilia 2023;29:1430-41

Embarking on the SDM journey

1. Reflect on your life goals and current treatment

2. Learn about your **treatment options**

3. Compare your treatment options

4. Have **conversations** with **others**

5. Prepare for visits with your healthcare provider

6. Have an **open and meaningful conversation** with your healthcare team

7. Take time to consider your options

8. Meet with your healthcare team to **make or confirm a decision** about your treatment

WFH Shared Decision Making Tool. Accessible from: https://sdm.wfh.org/

WFH tool: setting treatment goals (1/3)

1. Reflect on your life goals and current treatment

2. Learn about your treatment options

3. Compare your treatment options

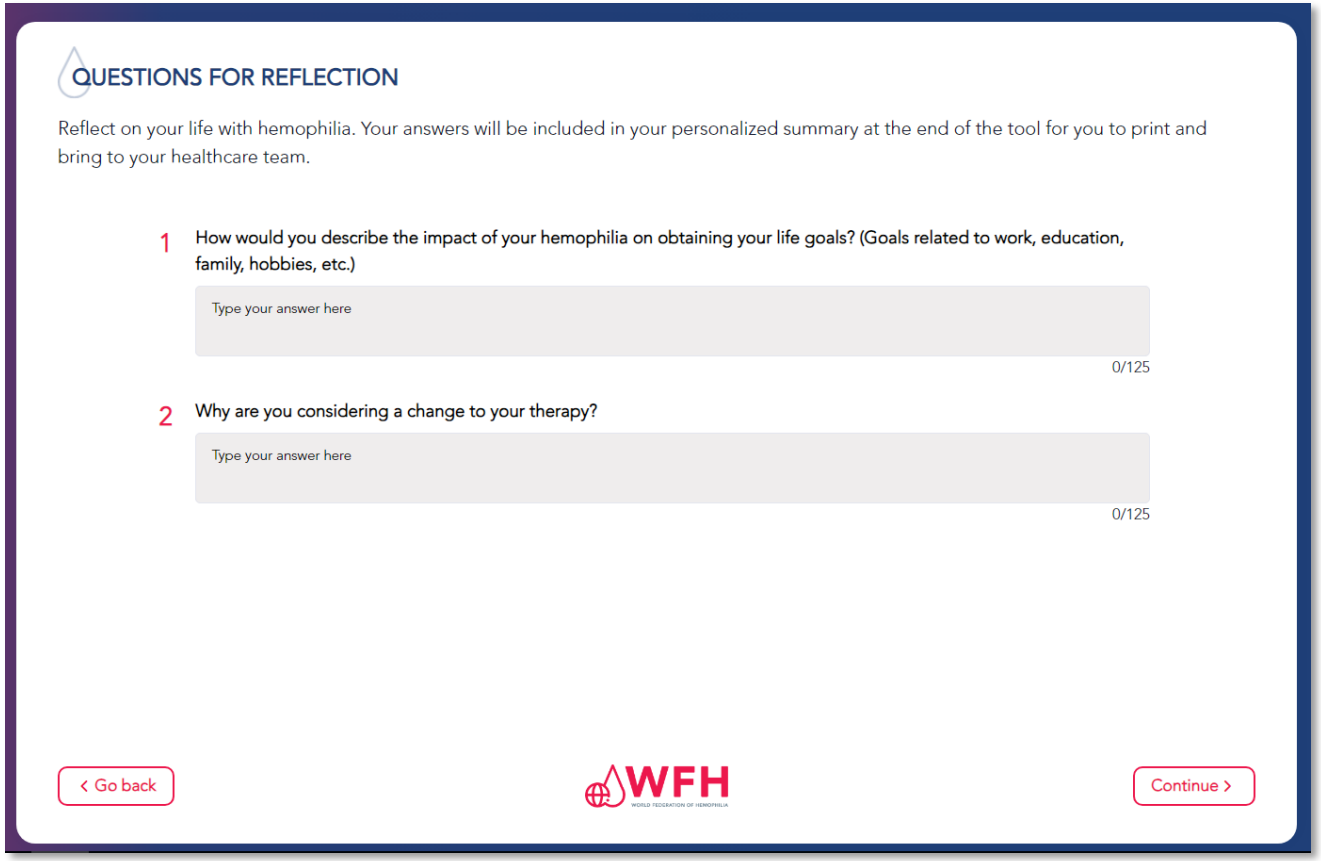
4. Have conversations with others

5. Prepare for visits with your healthcare provider

6. Have an open and meaningful conversation with your healthcare team

7. Take time to consider your options

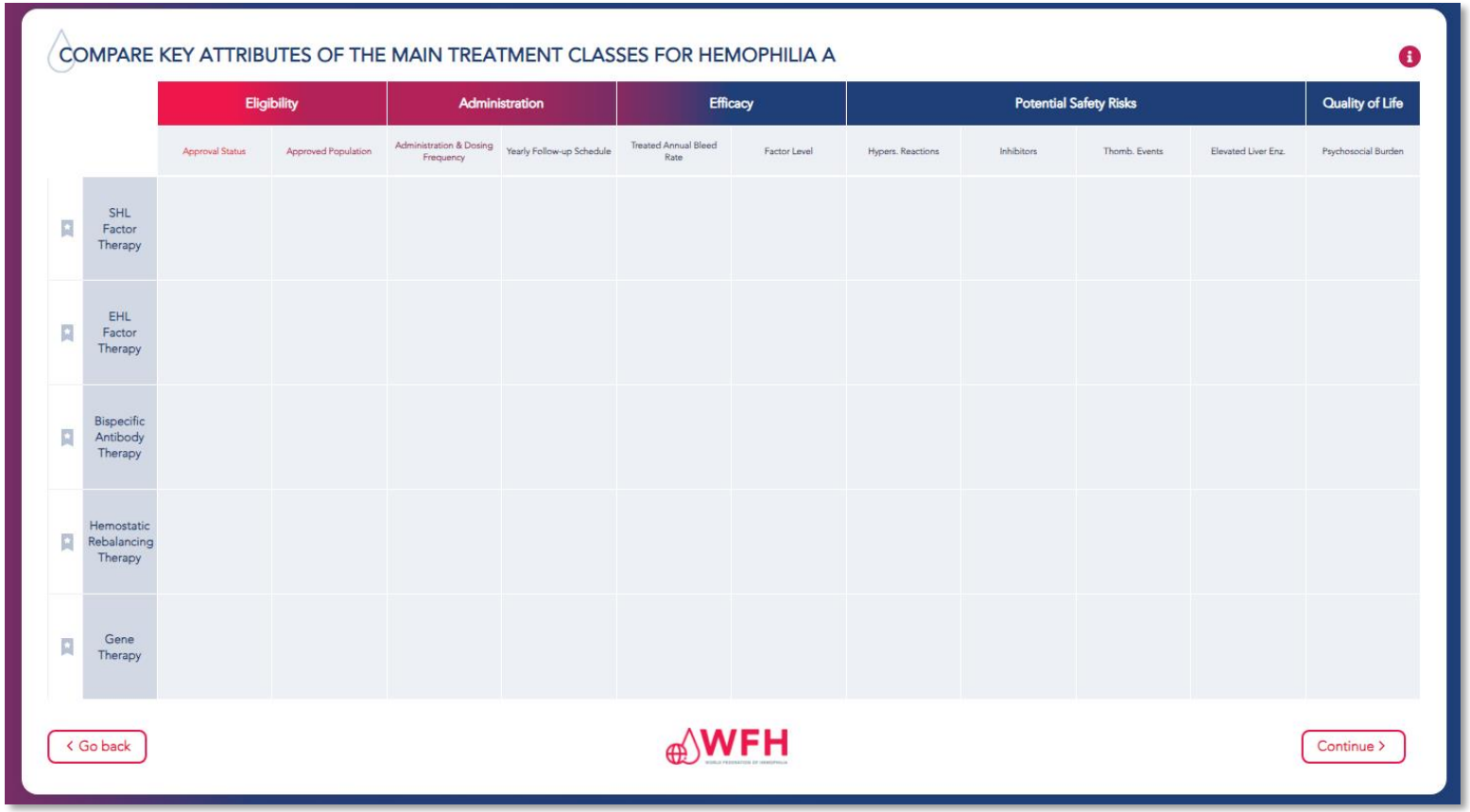
8. Meet with your healthcare team to make or confirm a decision about your treatment



WFH Shared Decision Making Tool. Accessible from: https://sdm.wfh.org/

WFH tool: comparing treatment options (2/3)

1. Reflect on your life goals and current treatment
2. Learn about your treatment options
3. **Compare** your treatment options
4. Have conversations with others
5. Prepare for visits with your healthcare provider
6. Have an open and meaningful conversation with your healthcare team
7. Take time to consider your options
8. Meet with your healthcare team to make or confirm a decision about your treatment



WFH Shared Decision Making Tool. Accessible from: https://sdm.wfh.org/

WFH tool: questions to discuss with the treatment team (3/3)

1. Reflect on your life goals and current treatment
2. Learn about your treatment options
3. Compare your treatment options
4. Have conversations with others
5. Prepare for visits with your healthcare provider
6. Have an **open and meaningful conversation** with your healthcare team
7. Take time to consider your options
8. Meet with your healthcare team to make or confirm a decision about your treatment

WFH Shared Decision Making Tool. Accessible from: https://sdm.wfh.org/

Shared decision making: key take-aways

Shared decision-making is a crucial **collaborative process** between

- The patient
- The healthcare team
- The patient's support network (e.g., family)

Shared-decision making:

- Is **multi-staged**
- Is **individualised** to the patient
- Should emphasise setting **realistic treatment expectations**

The **WFH SDM tool** is:

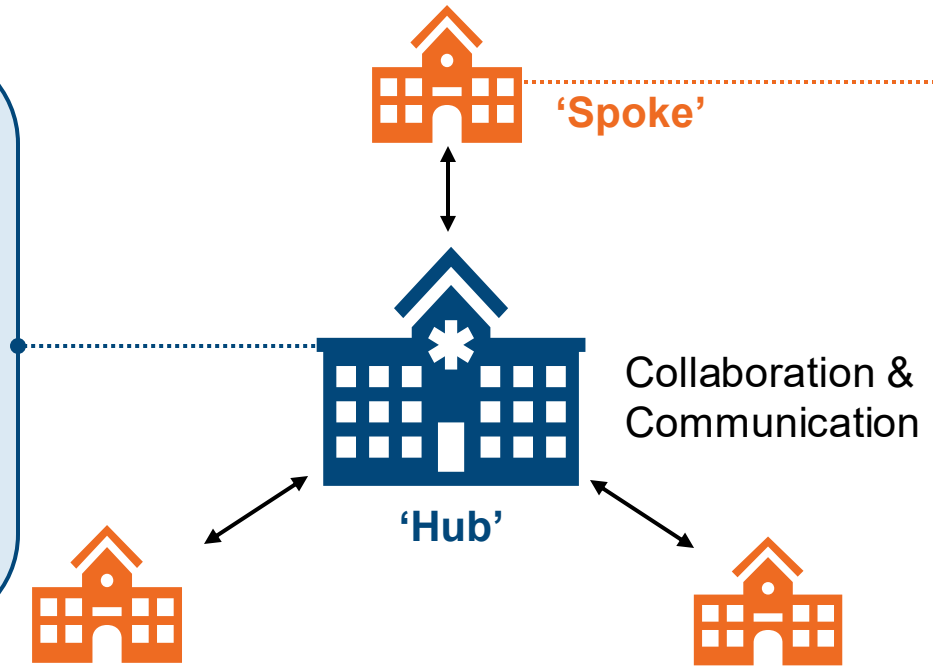
- **Recommended** (and not just limited to gene therapy)
- **Straightforward** to apply
- Designed to make the SDM process as **seamless and informative** as possible

WFH Shared Decision Making Tool. Accessible from: https://sdm.wfh.org/

The hub-and-spoke model for delivery of gene therapy proposed by EAHAD and EHC

Dosing centre: 'Hub'

- Usually a HTC with **more experience** in haemophilia gene therapy
- Responsible for **preparation** and **administration of treatment**



Referral/Follow-Up centre: 'Spoke'

- Usually a HTC with **less experience** with gene therapy trials
- Likely to be the **patient's local** hospital/centre
- Responsible for **monitoring** of patient

- Patients **treated** in dosing centres
- Then **followed up** by their own **local hospital/centre**
- To obtain **best outcomes for patients**

EAHAD: European Association for Haemophilia and Allied Disorders; EHC: European Haemophilia Consortium; HTC: haemophilia treatment centre

Miesbach W et al. Haemophilia 2021;27:967-73; Boban A et al. Haemophilia 2023;29:1442-9; Hermans C et al. Ther Adv Hematol 2023;14:1-14; Ay C et al. Haemophilia 2024;30:5-15
EAHAD-EHC Joint Statement. Published May 2020. Available at: https://www.ehc.eu/wp-content/uploads/EHC-EAHAD-Position-Statement-on-GT.pdf

DOI: 10.1111/hae.14420

Haemophilia WILEY

ORIGINAL ARTICLE

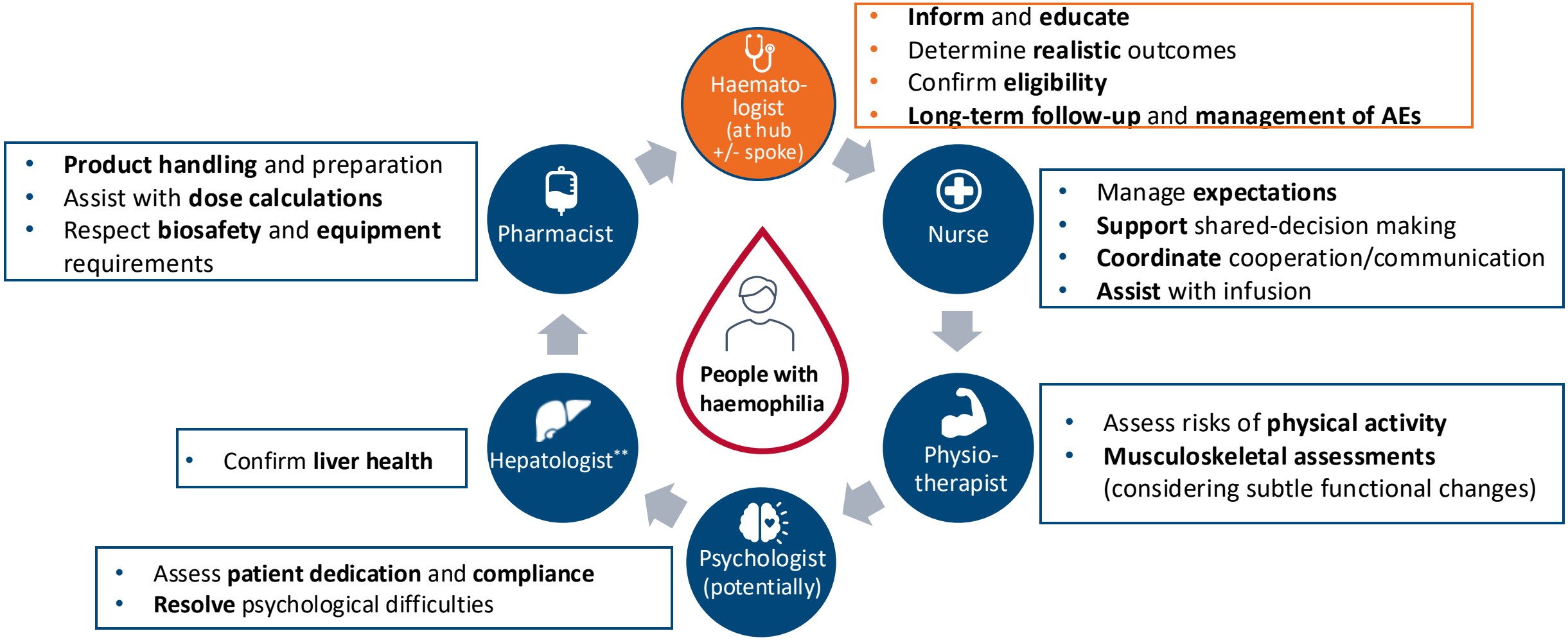
Clinical haemophilia

Delivery of AAV-based gene therapy through haemophilia centres—A need for re-evaluation of infrastructure and comprehensive care: A Joint publication of EAHAD and EHC

TABLE 1 Challenges of gene therapy for haemophilia centres

- Patient informed consent and eligibility tests
- Administration of a gene therapy construct and managing infusion related reactions
- Monitoring variability of factor expression and deciding when to stop prophylactic treatment
- Close cooperation with hepatologists and immunologists
- Monitoring of short-, medium- and long-term adverse events
- Retaining patient engagement for follow up
- Long-term follow-up by an accurate surveillance system
- Direct and indirect costs reimbursement for administration of gene therapy and follow-ups

How does gene therapy change the roles in the multidisciplinary team?



*May also help to monitor and manage liver health

Miesbach W et al. Haemophilia. 2022;28:e12-4; Miesbach W et al. Haemophilia 2021;27:511-4; Miesbach W et al. Haemophilia 2021;27:967-73; Pipe SW et al. Haemophilia 2023;29:1430-41; Speaker's view

Road to gene therapy: pre-dosing day procedures

Patient journey at spoke centre[1-3]

- **Information** seeking
- **Eligibility** testing
  Assessment of pre-existing **AAV antibodies**
- **Shared decision-making** between patient and spoke
- Post-infusion treatment **plan**

MDT journey at hub centre[1,4]

- **Shared decision-making** between patient and hub *(face-to-face visit)*
- **Review** patient's eligibility, informed consent and understanding and expectations
- Confirmation of **payer/reimbursement**
- Identification and storage of **equipment** for product preparation and administration (responsibility pharmacy in real-world setting)
- Review pre-existing **AAV antibody status**
  Post-infusion treatment **plan**

MDT: multidisciplinary team

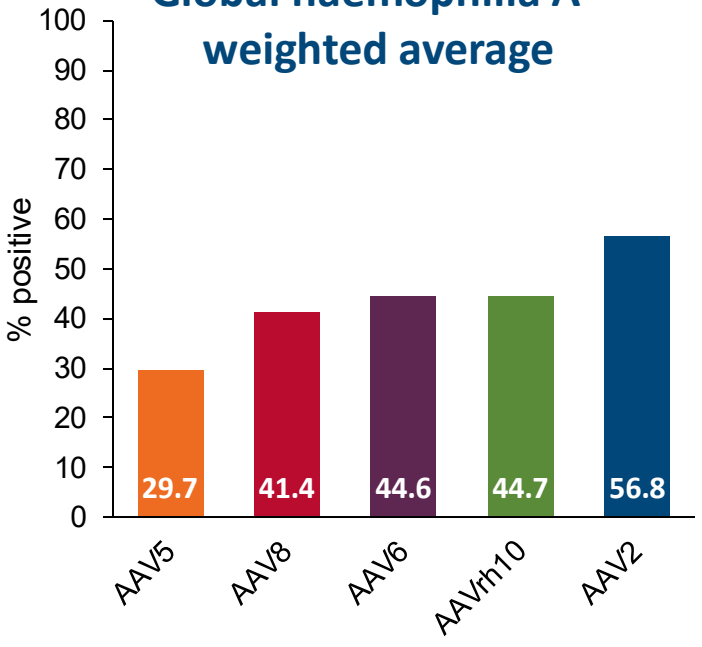
1. Pipe SW et al. Haemophilia 2023;29:1430-41; 2. Wang M et al. Patient Prefer Adherence 2022;16:1439-47; 3. Ay C et al. Haemophilia 2024;30:5-15;
4. Miesbach W et al. Haemophilia 2021;27:967-73; Speaker's view

Assessment of pre-existing AAV antibodies

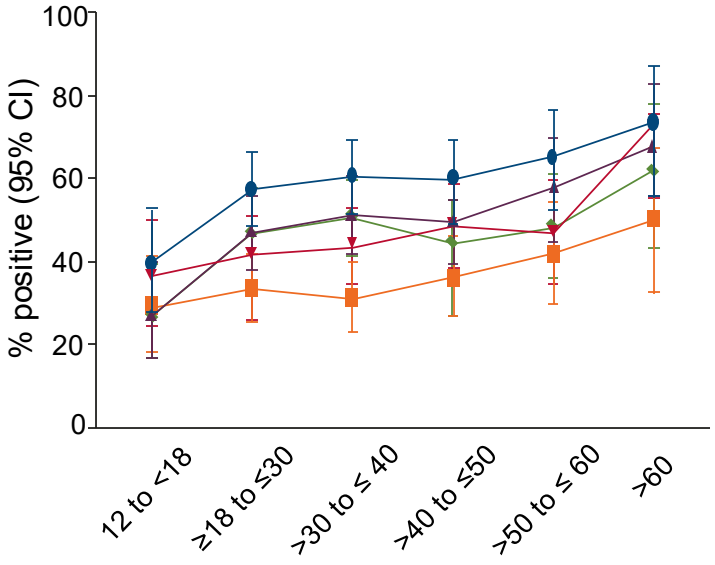
Prospective study

N=546 participants with HA across 9 countries (19 sites)[1]

Global haemophilia A - weighted average



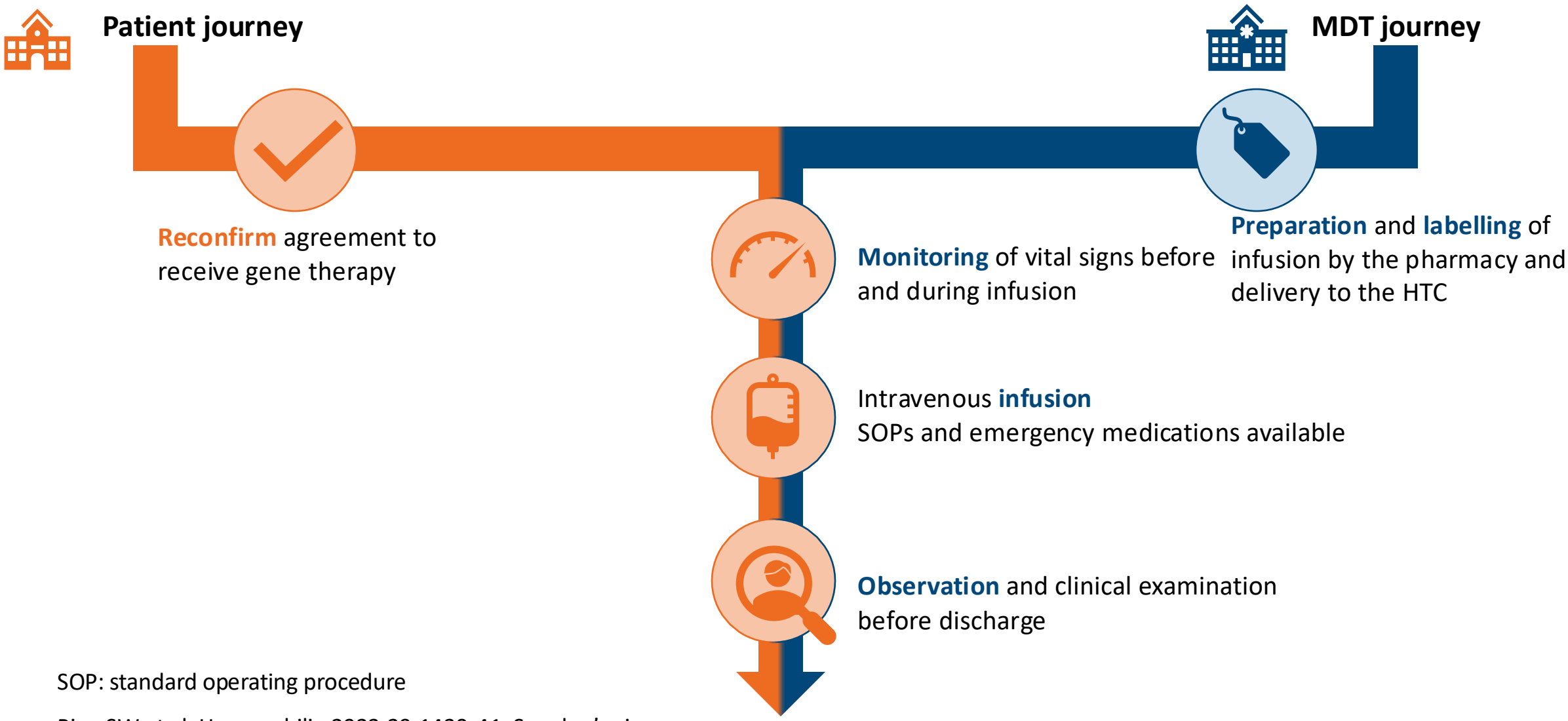
AAV serotype positivity by age group (years)



- ✓ Considerable **geographic variability** in the prevalence of pre-existing antibodies against each serotype[1,2]
- ✓ **AAV5** consistently the **lowest seroprevalence** across countries[1,3]
- ✓ **Seropositivity** tends to **increase** with **age**[1,2]
- ✓ Evidence suggests PwHA *without* AAV antibodies likely to remain AAV-negative over a 6-month period[3]
- ✓ Therefore, preferable to **dose promptly after a favourable result**

1. Klamroth R et al. Hum Gene Ther 2022;33:432-41; 2. Pabinger I et al. Gene Ther 2024;doi: 10.1038/s41434-024-00441-5;
3. Shapiro A et al. Abstract THSNA 2024 Congress, April 4-6, Chicago, IL, USA

What happens on the dosing day in the hub centre?



SOP: standard operating procedure

Pipe SW et al. Haemophilia 2023;29:1430-41; Speaker's view

After dosing day: what happens next?

Patient journey at spoke centre

Short- and long-term **follow-up:**

- Safety, efficacy, physical and mental health
  - Year 1: weekly to monthly
  - Year 2 onwards: every 3-6 months

Adhere to:

- **Lifestyle** guidelines
- **Corticosteroids** (if necessary)

MDT journey at hub centre

Coordinate follow-up with spoke centre:

- Weekly reporting from spoke to hub on safety, efficacy, physical and mental health

Enrolment into gene therapy **registry***

*Enrollment in registry can be a mandatory requirement to receive gene therapy in specific countries

Pipe SW et al. Haemophilia 2023;29:1430-41; Miesbach W et al. Haemophilia 2021;27:967-73; Ay C et al. Haemophilia 2024;30:5-15

Practical considerations to prepare your centre and team for delivery of gene therapy

Multidisciplinary treatment team[1,2]

- Staff education and training
- Establish roles and responsibilities
- Regular assessment of staff capacity
- Regular assessment of training needs
- Close collaboration (e.g., regular meetings)

Product SOPs[2]

Procurement, handling, storage and preparation (responsibility of pharmacy)

Therapy protocols and guidance documents[2]

- Infusion protocol (optimal delivery)
- Protocol for infusion-related reactions
- Safe handling
- Post-infusion management
- Follow-up

Collaboration between HTCs[2]

Process to exchange health information (e.g., regular phone calls, software solutions)

Checklist of necessary documents

1. Miesbach W et al. Haemophilia 2021;27:511-4; 2. Pipe SW et al. Haemophilia 2023;29:1430-41

Offering gene therapy in the real world: strategies to optimise patient care

Keeping patients connected to the clinic:

- Regular planned visits
- Patient support service (e.g., for regular blood draws)

Coping with unexpected scenarios:

- Emergency phone number
- Contacting clinic in case of any adverse event

Manage expectations throughout the process

Setting up your centre: key take-aways

Gene therapy dosing in clinical practice will take **effort** and **teamwork** and requires **training**, with the ultimate aim to benefit patients

Setting up a gene therapy centre is **feasible,** and has been done by several centres in different geographies

Perceived barriers to gene therapy can be **addressed** by implementing SOPs, conducting regular monitoring and developing post-treatment plans

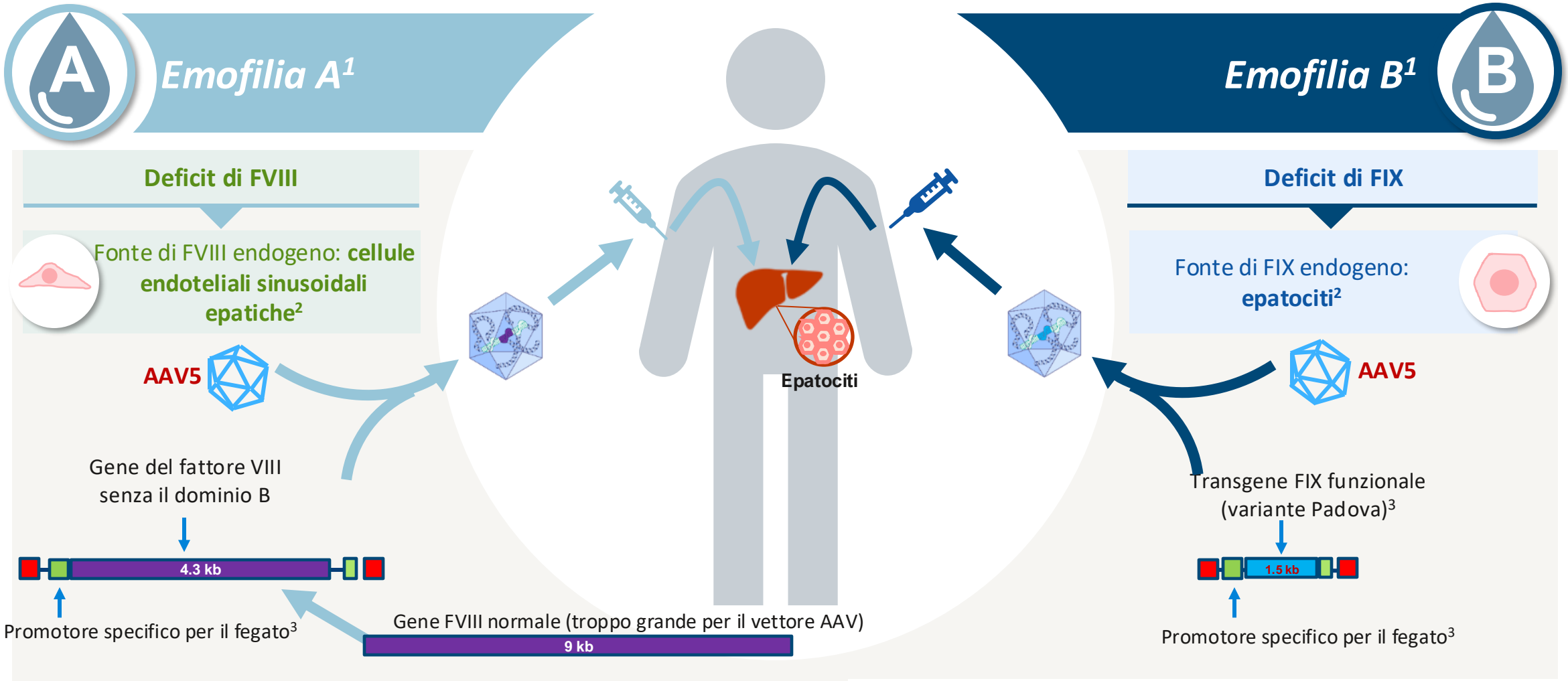
Gene Therapy in Haemophilia: From Decision to Dosing

Clinical evidence to date supports **favourable risk-benefit profile** of gene therapy

The **WFH Shared Decision-Making tool** is recommended to progress your patient conversations

Setting up a gene therapy centre is **feasible** in a **multidisciplinary** setting, to aim at **improving the lives of PwH**

Gli stessi approcci di terapia genica sono stati usati sia per l'emofilia A che per l'emofilia B

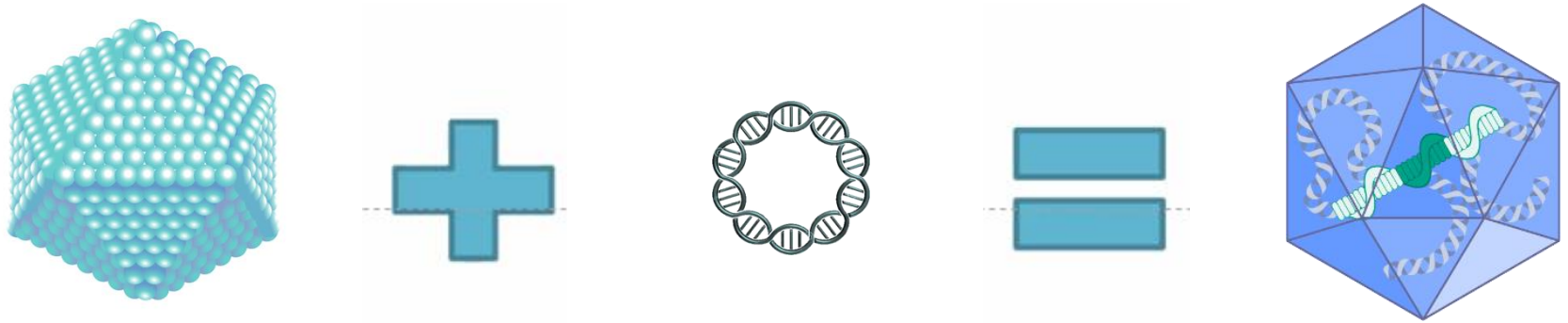


1. Arruda VR, Doshi BS. *Mediterr J Hematol Infect Dis* 2020; 12:e2020069. 2. Perrin GQ, *et al*. *Blood* 2019;133:407–414. 3. Batty P, Lillicrap D. *HemaSphere* 2021;5:3(e540)

Cosa sono i vettori ricombinanti AAV?

I vettori AAV sono stati sviluppati a partire da AAV normalmente presenti in natura e non patogeni e sono stati ampiamente studiati per il rilascio *in vivo* della terapia genica[1-3]

Capside + Cassetta genica = Vettore AAV



Le proprietà dei diversi capsidi AAV influenzano la capacità del vettore di dirigersi verso determinati tessuti

I componenti della cassetta di espressione di AAV influenzano l'espressione del transgene

I vettori AAV possono essere usati per ottenere l'espressione di un gene in cellule e tessuti target

1. Carter BJ. *Mol Ther* 2004; 10(6):981–989. 2. Mitchell AM, et al. *Curr Gene Ther* 2010; 10(5):319–340. 3. Bulcha JT, et al. *Signal Transduct Target Ther* 2021; 6(1):53.