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- Head of **Hemophilia Outpatient Clinic**
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- Clinical & research focus: **Haemophilia • Coagulation • Thrombosis**
- Principal Investigator in **international clinical trials**
- Contributor to **international treatment guidelines & consensus recommendations**

Gene Therapy for Haemophilia: Where Are We Today?

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Disclaimer

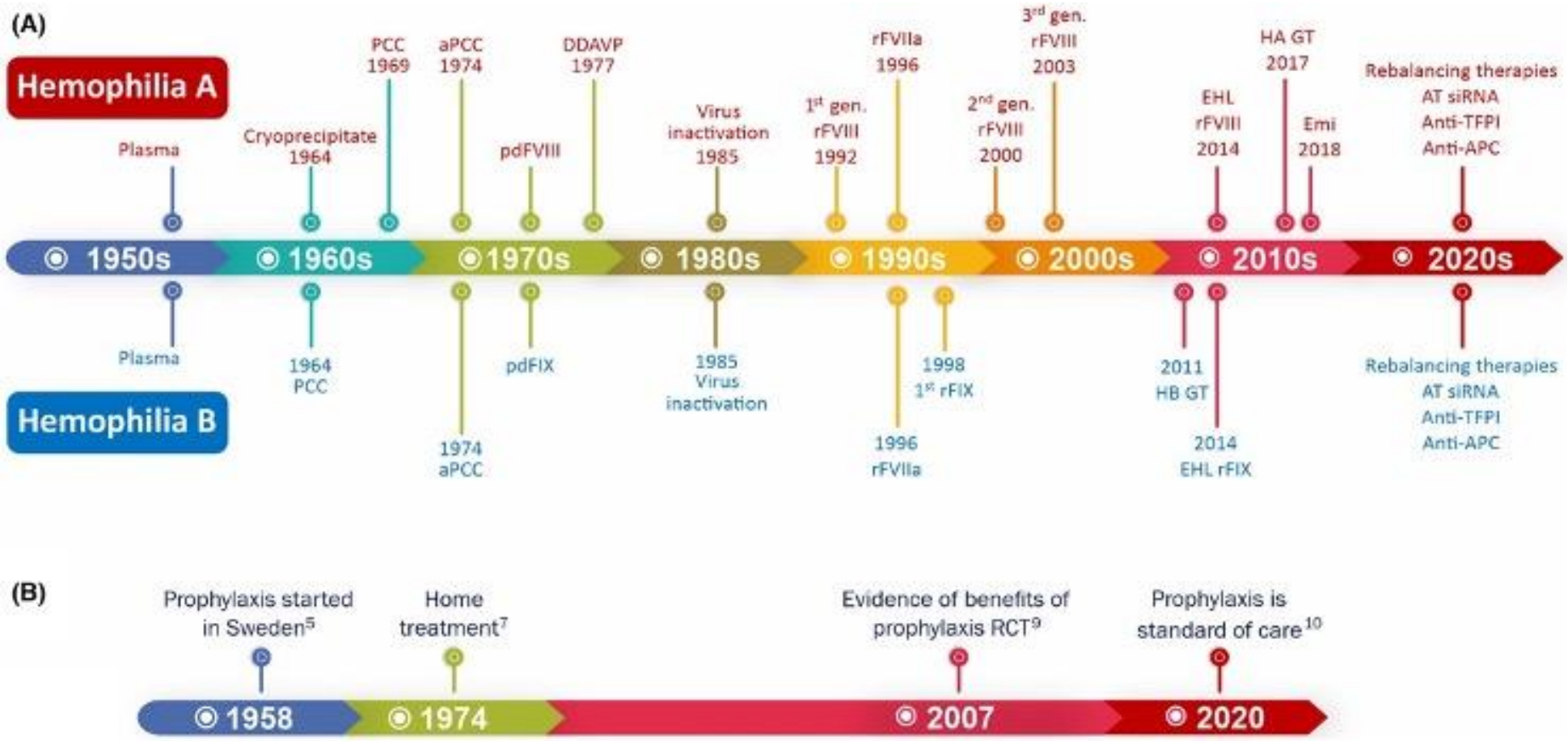
- The views shared by the speakers are their own and may not reflect those of CSL.
- This presentation is intended for educational purposes only and is not a substitute for medical advice.
- Please consult your healthcare professional regarding your individual care and treatment.

Content

- Introduction of myself and my center
- General introduction into haemophilia treatment
- The overview and clinical value of hemophilia gene therapy
- Austrian Experience
  - Coordinating a multifunctional team in hub centers for hemophilia gene therapy (cases sharing)
  - Managing the patient before and after receiving hemophilia gene therapy

Evolution Hemophilia Therapy

Development of new therapies & Improvements of hemophilia ma



Ozelo et al., Res Pract Thromb Haemost. 2022 Apr 12;6(3): e12695

Treatment Goals in Haemophilia

Provide optimal protection to avoid bleeds and subclinical changes early on[1,2]

Allow long-term joint health and engagement in physical activity[2,4]

Ensure all patient's needs are met regardless of bleeding phenotype or lifestyle choices[1,3]

Achieve optimised QoL, freedom from pain and full social participation[5]

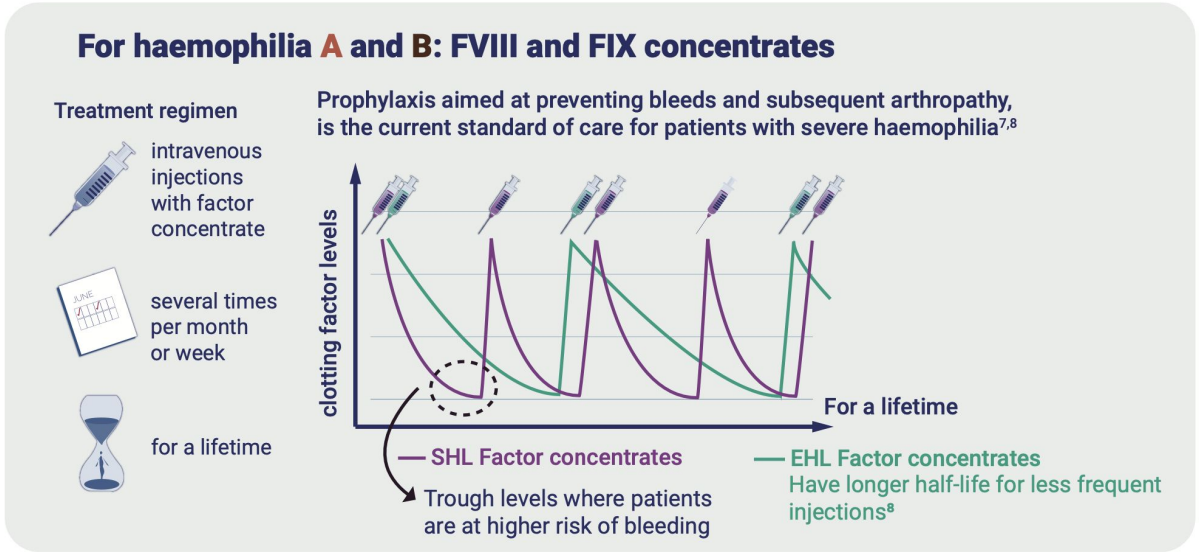
QoL: quality of life.

1. Srivastava et al. Haemophilia. 2020. **2.** Manco-Johnson et al. J Thromb Haemost. 2017. **3.** Iorio et al. Haemophilia. 2017. **4**. von Mackensen et al. Haemophilia. 2016. **5.** Skinner et al. Haemophilia. 2020.

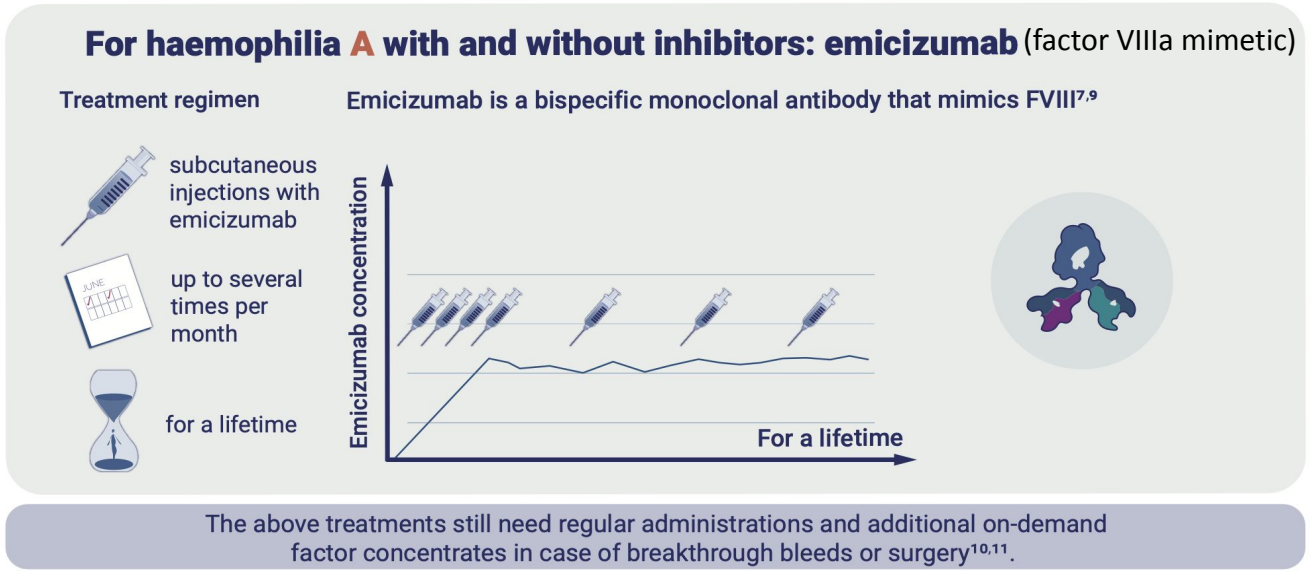
Current Treatments in Hemophilia A and B

Challenges and burden

Factor therapies (i.v. replacement therapies)



Non-factor therapies (subcutaneous)



The above treatments still need regular administrations and additional on-demand factor concentrates in case of breakthrough bleeds or surgery[10,11].

Other non-factor therapies for hemophilia A an B:

Rebalancing agents: anti-TFPI, AT siRNA

Some treatments shown may not be available in Singapore. Please speak with your healthcare professional for local treatment information.

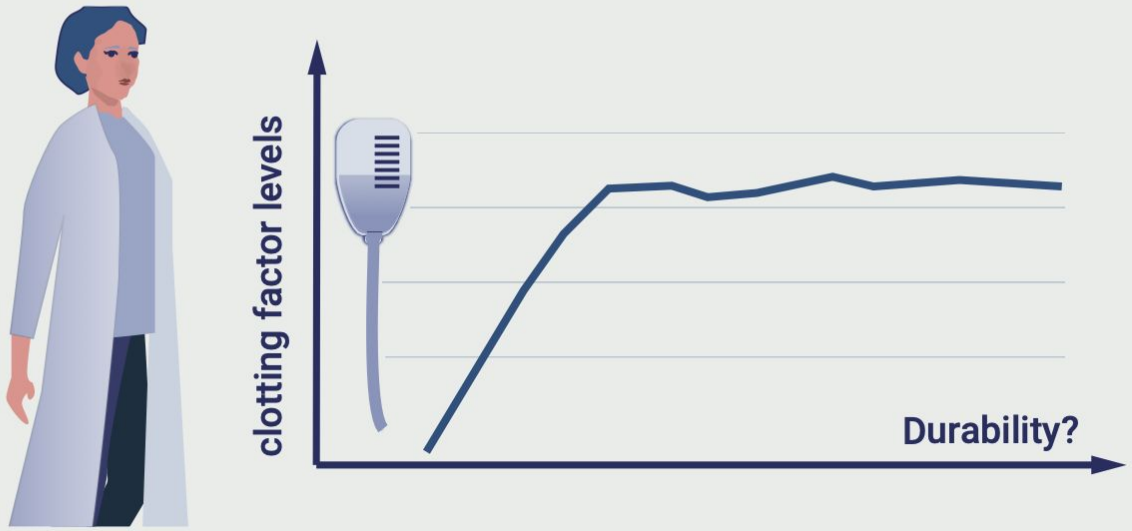
Ay C et al. Haemophilia. 2024 Jan;30(1):5-15.

TFPI, tissue factor pathway inhibitor; AT, anti-thrombin

Gene Therapy in Hemophilia – Current Status

For haemophilia A and B without inhibitors: AAV-based gene therapy

With only one infusion, gene therapy may have advantages for the treatment of patients with haemophilia by producing stable factor VIII and IX activity levels, providing better bleeding protection and subsequent increased quality of life.



Approved gene therapy products for haemophilia

Haemophilia A: FDA approval (Jun/23) and EC approval (Aug/22), for valoctocogene roxaparvovec ROCTAVIAN® (Biomarin)[12,13]

Haemophilia B: FDA approval (Nov/22) and EC approval (Feb/23) for etranacogene dezaparvovec HEMGENIX® (CSL Behring)[14,15]

Other gene therapies are in various stages of clinical development for haemophilia A and B.

*The graphs are for illustrative purposes only. The efficacy and the durability of gene therapy for haemophilia A and B are shown in Capsule 4 and Capsule 6, respectively.
AAV, adeno-associated virus; EC, European Commission; EHL, extended half-life; FDA, Food and Drug Administration; FVIII, factor VIII; FIX, factor IX; SHL, standard half-life

Capsule 2

Ay C et Ay C et al. Haemophilia. 2024 Jan;30(1):5-15.

Some treatments shown may not be available in Singapore. Please speak with your healthcare professional for local treatment information.

Why is haemophilia well suited for gene therapy?

- Monogenic, recessive disease
- Large ‘normal range’ of affected protein level
- Bleeding phenotype is responsive to a wide range of factor levels

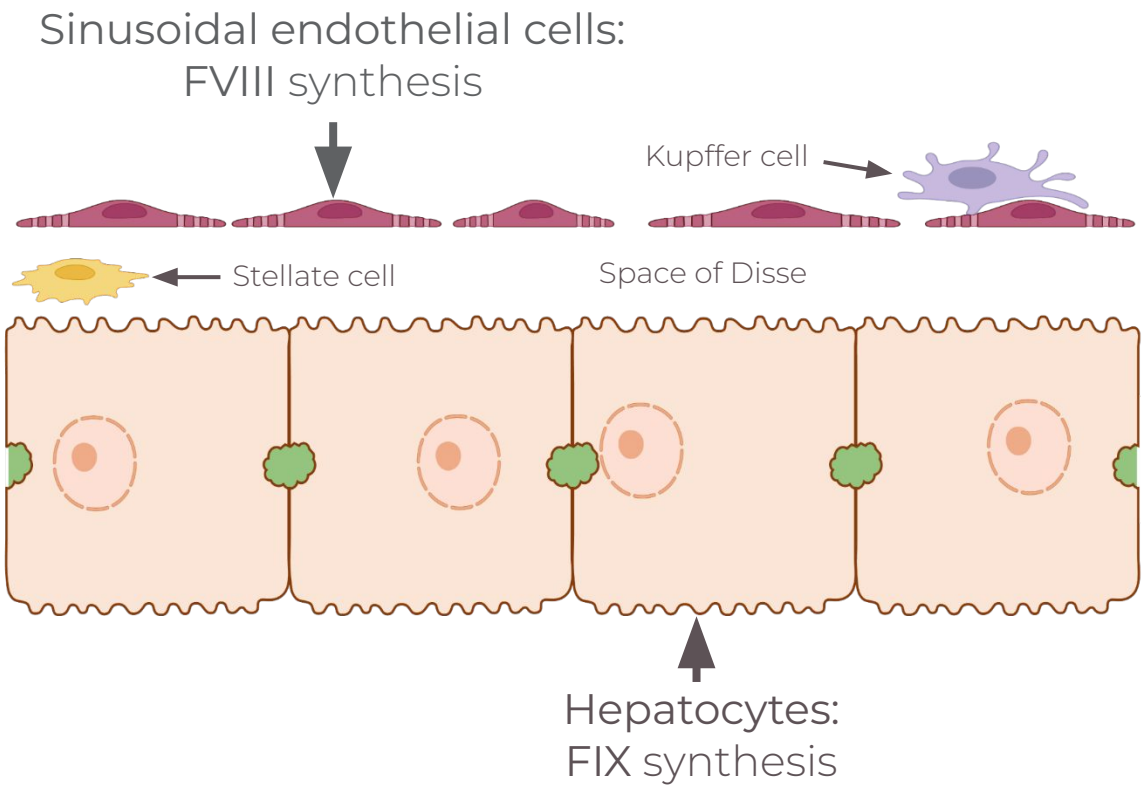


Figure made at biorender.com.

Berntorp E, *et al. Nat Rev Dis Primers*. 2021 Jun 24;7:45. Perrin GQ, et al. *Blood*. 2019 Jan 31;133:407-414.

How is gene therapy administered?

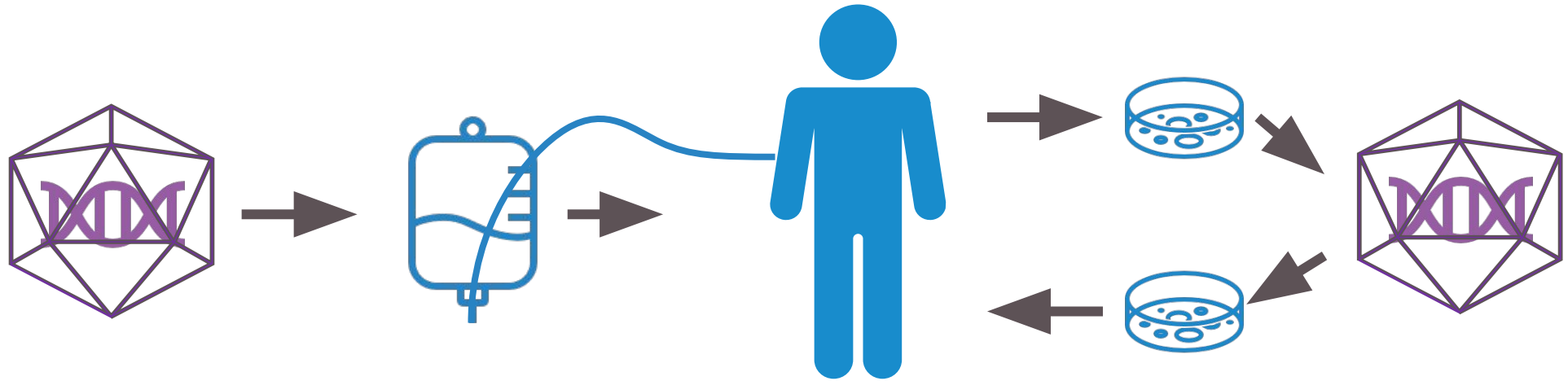
Currently, gene therapy can only be administered as a one-time treatment[1]

In vivo

Vector containing fully functional gene is directly delivered into the body. There is **no need for conditioning treatment** prior to administration.[2]

Ex vivo

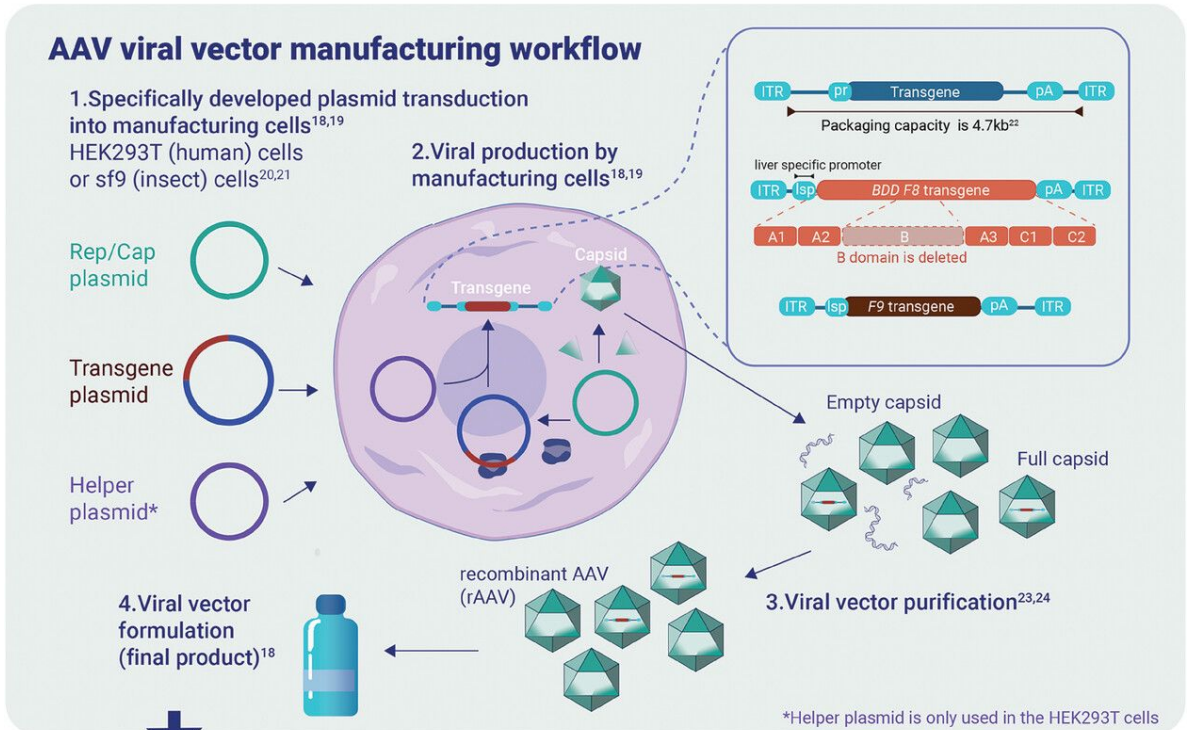
Vector containing fully functional gene is inserted into cells taken from the patient, which are returned to the patient after the **use of conditioning agents**.[2]

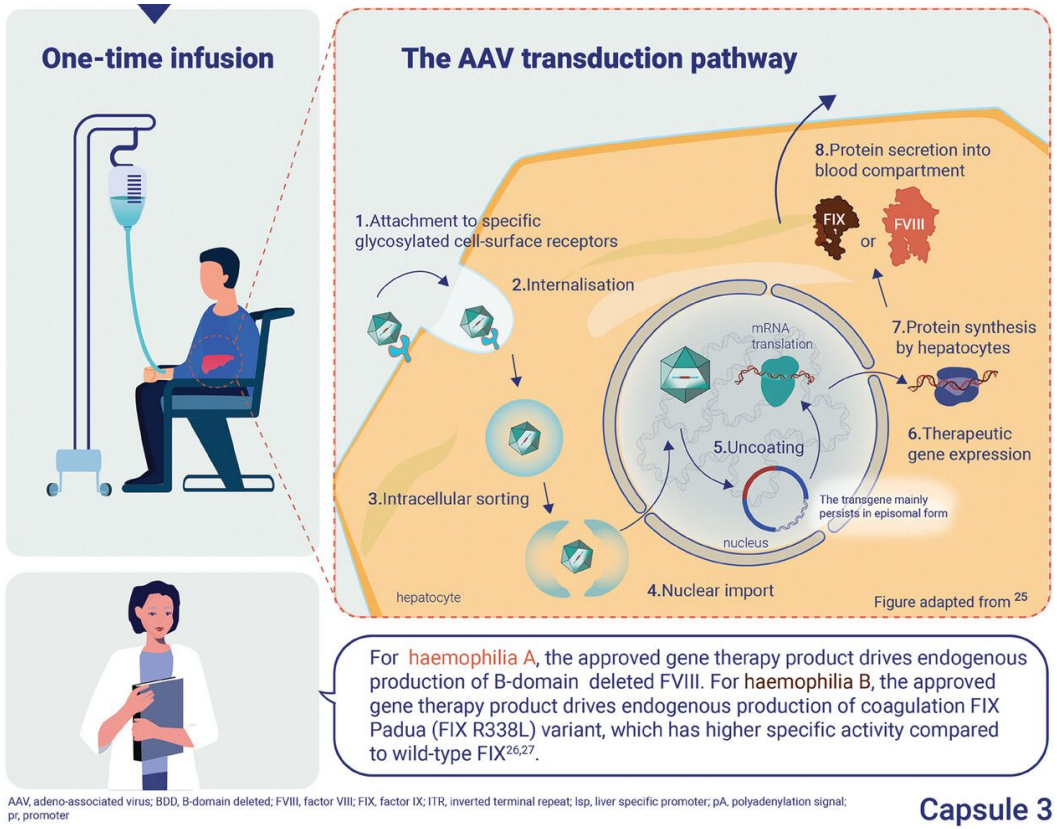


1. Muhuri M, *et al. Mol Ther*. 2022;30(4):1364–1380. 2. Anguela XM & High KA. *Annu Rev Med*. 2019;70:273–288.

Principles of Gene Therapy for Haemophilia

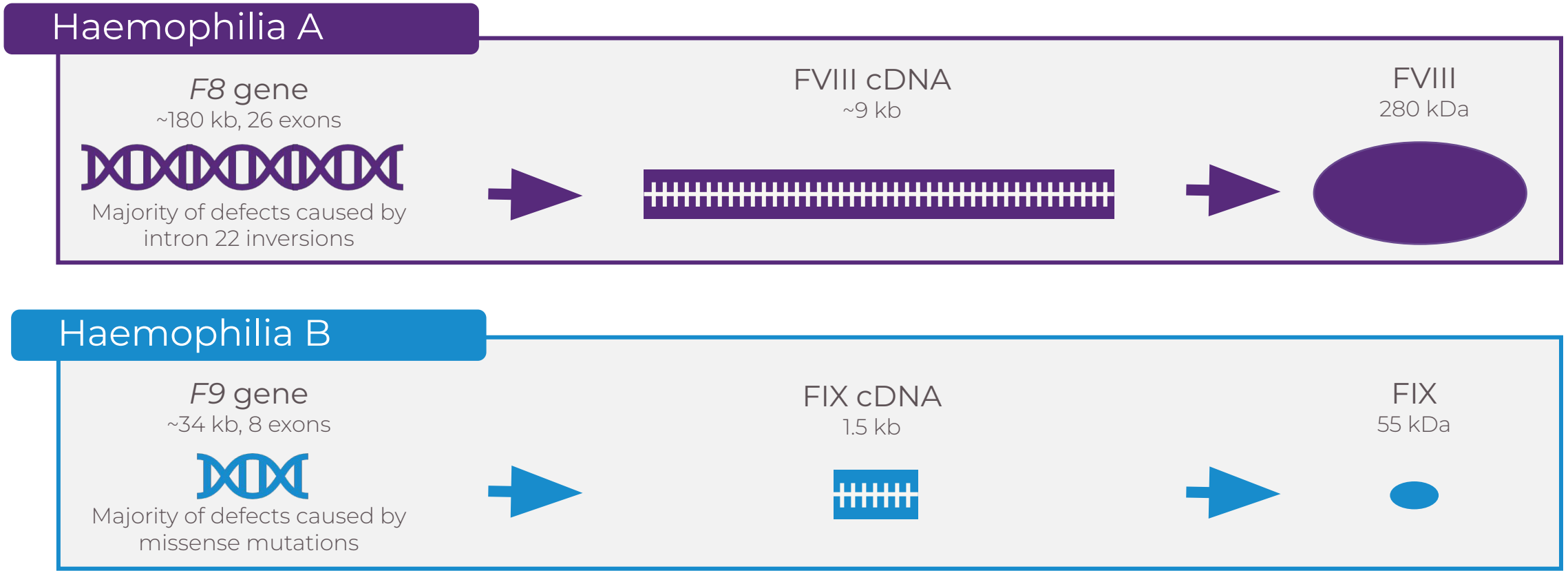
(1) Vector-based (2) Non-integrating (episomal) (3) In-vivo





Ay C et al. Haemophilia. 2024 Jan;30(1):5-15.

Haemophilia A and B molecular basis



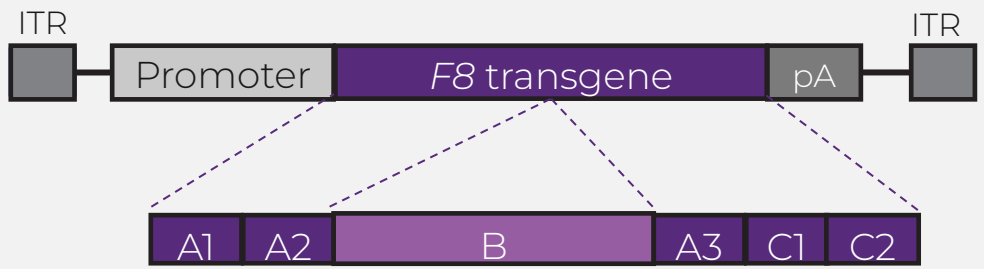
cDNA, complementary DNA; FIX, factor IX; FVIII, factor VIII.

Castaman G, Matino D. *Haematologica.* 2019; 104:1702–1709. Batty P, Lillicrap D. *HemaSphere.* 2021; 5:3(e540).

AAV vector gene therapy for haemophilia A and B

Expression cassette is ~5 kb

Haemophilia A



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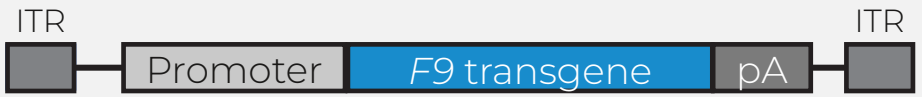
Haemophilia B



Often a natural but more active variant of factor IX is used (**Padua variant**)

AAV, adeno-associated virus; FIX, factor IX; FVIII, factor VIII; ITR, Inverted Terminal Repeat; pA, polyadenylation signal.

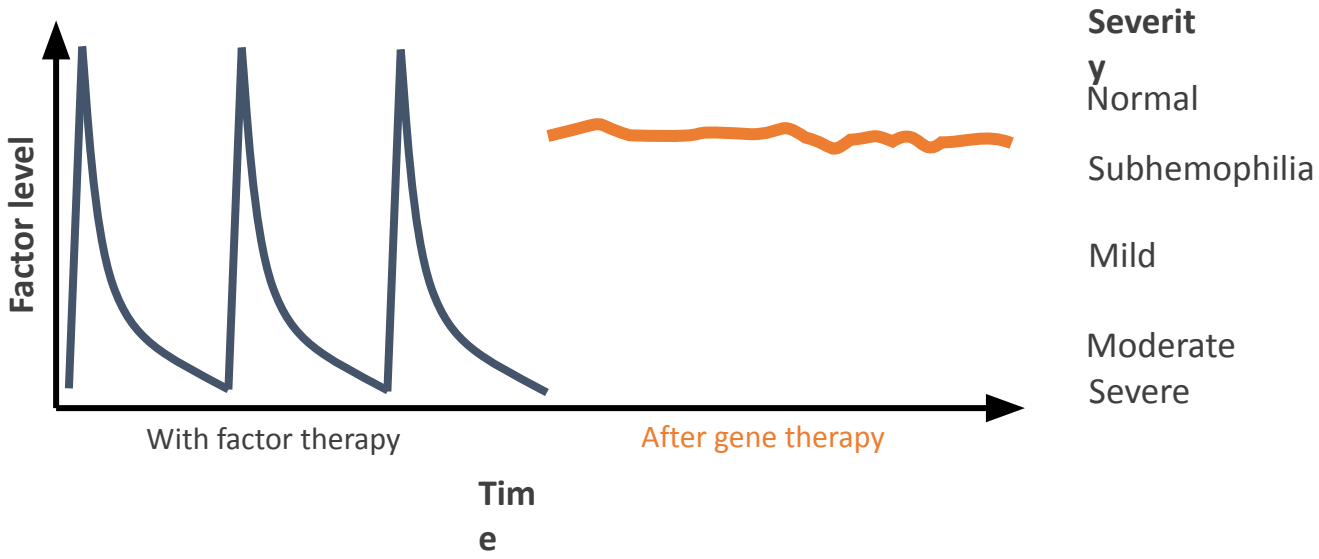
Castaman G, Matino D. *Haematologica.* 2019; 104:1702–1709. Batty P, Lillicrap D. *HemaSphere.* 2021; 5:3(e540). High KA, Anguela XM. *Hum Mol Genet.* 2016 Apr 15;25(R1):R36–41.

Goals of Gene Therapy in Hemophilia

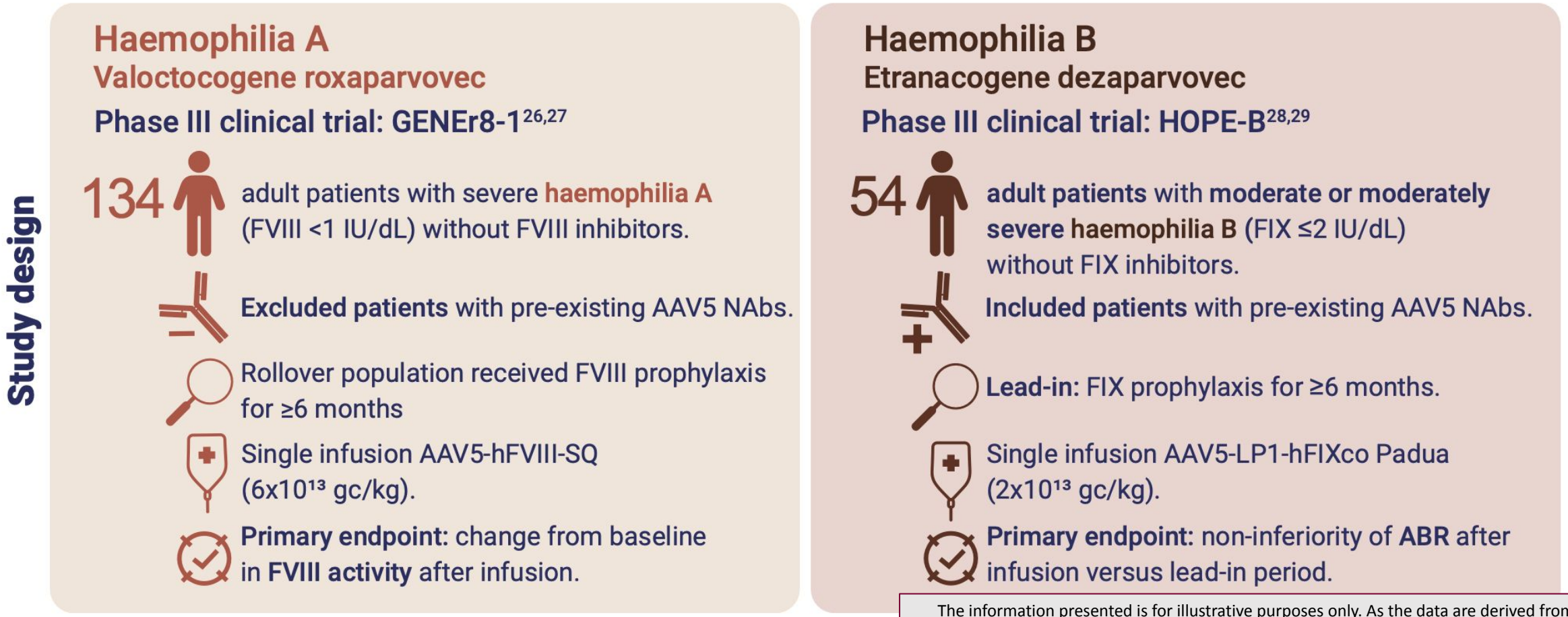
Transforming Disease Severity

Sustained, long-term endogenous factor expression after a single infusion

- Effective control of bleeding episodes
- Elimination of regular prophylactic replacement therapy
- Significant improvement in quality of life



Hemophilia Gene Therapy – Study designs



The information presented is for illustrative purposes only. As the data are derived from separate clinical studies, direct comparisons should not be made.

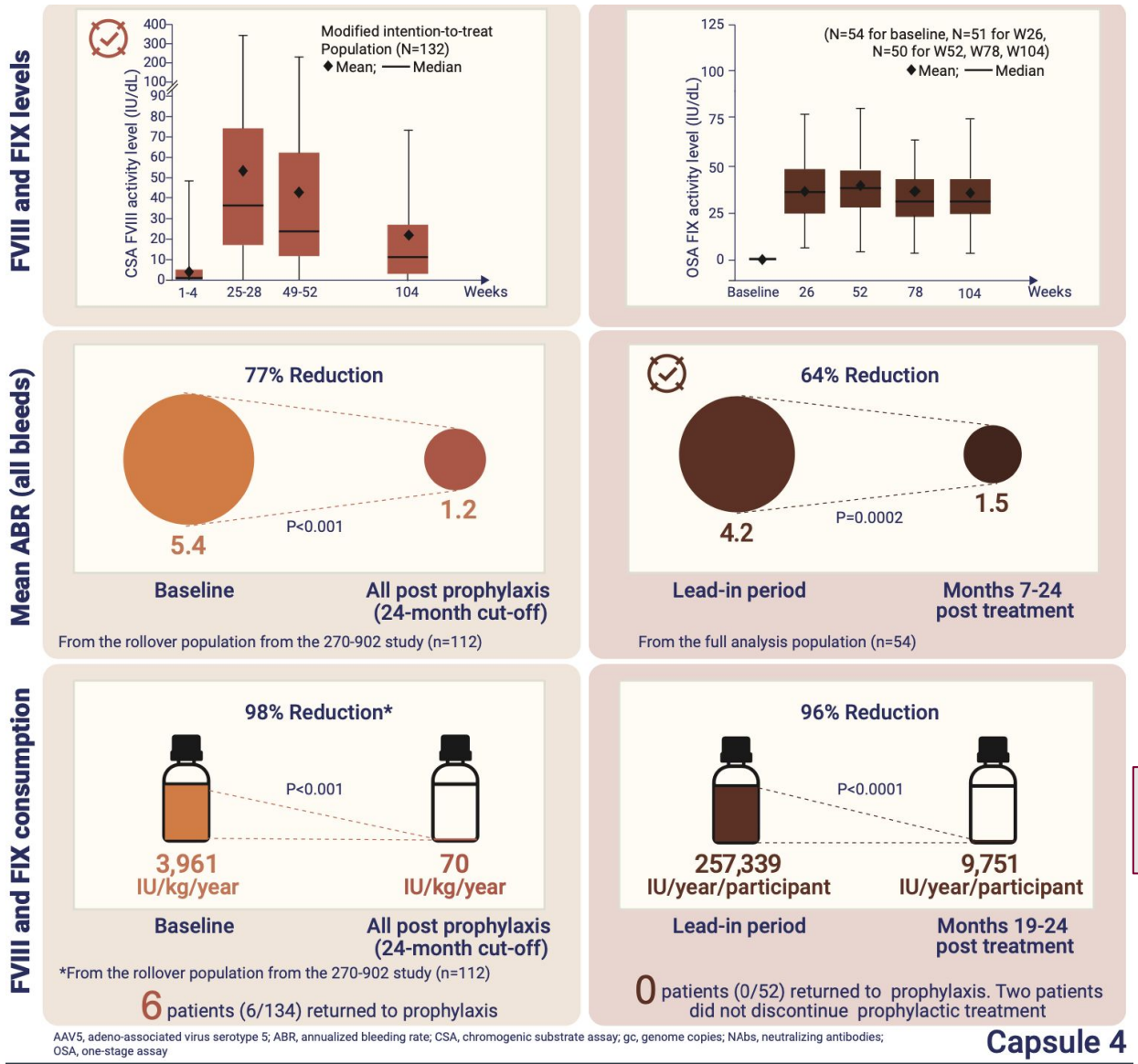
26. Ozelo MC et al. N Engl J Med. 2022;386(11):1013-1025. 27. Mahlangu J et al. N Engl J Med. 2023;388(8):694-705.
28. Pipe SW et al. N Engl J Med. 2023;388(8):706-718. 29. Coppens M et al. 16th Annual Congress of European Associa﷽on for Haemophilia and Allied Disorders 2023, 7–10 February 2023, Manchester (PO156).

Ay C et al. Haemophilia. 2024 Jan;30(1):5-15.

Hemophilia Gene Therapy – Study Results

Haemophilia A: Valoctocogene roxaparvovec
Phase III clinical trial: GENEr8-1

Haemophilia B: Etranacogene dezaparvovec
Phase III clinical trial: HOPE-B



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Ozelo MC et al. N Engl J Med. 2022;386(11):1013-1025.
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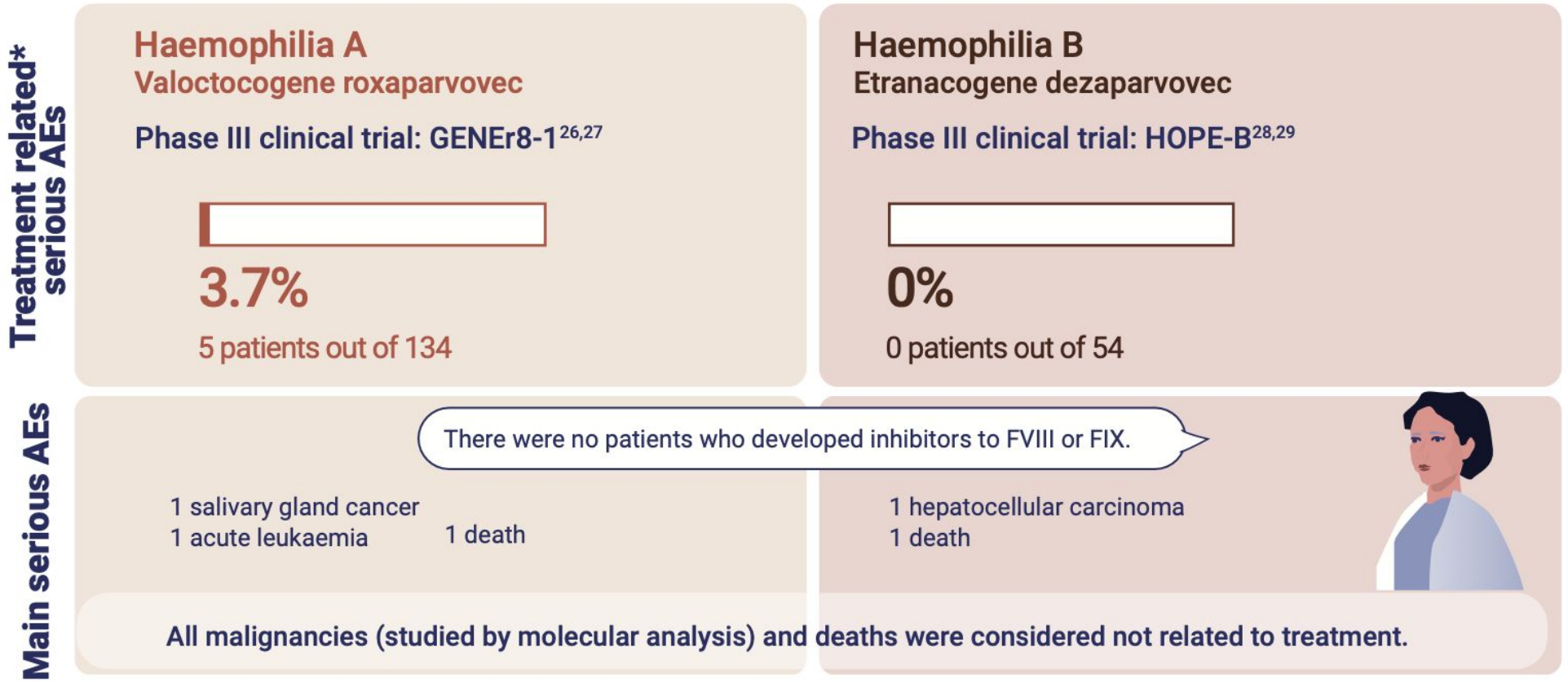
Pipe SW et al. N Engl J Med. 2023;388(8):706-718.

Ay C et al. Haemophilia. 2024 Jan;30(1):5-15.

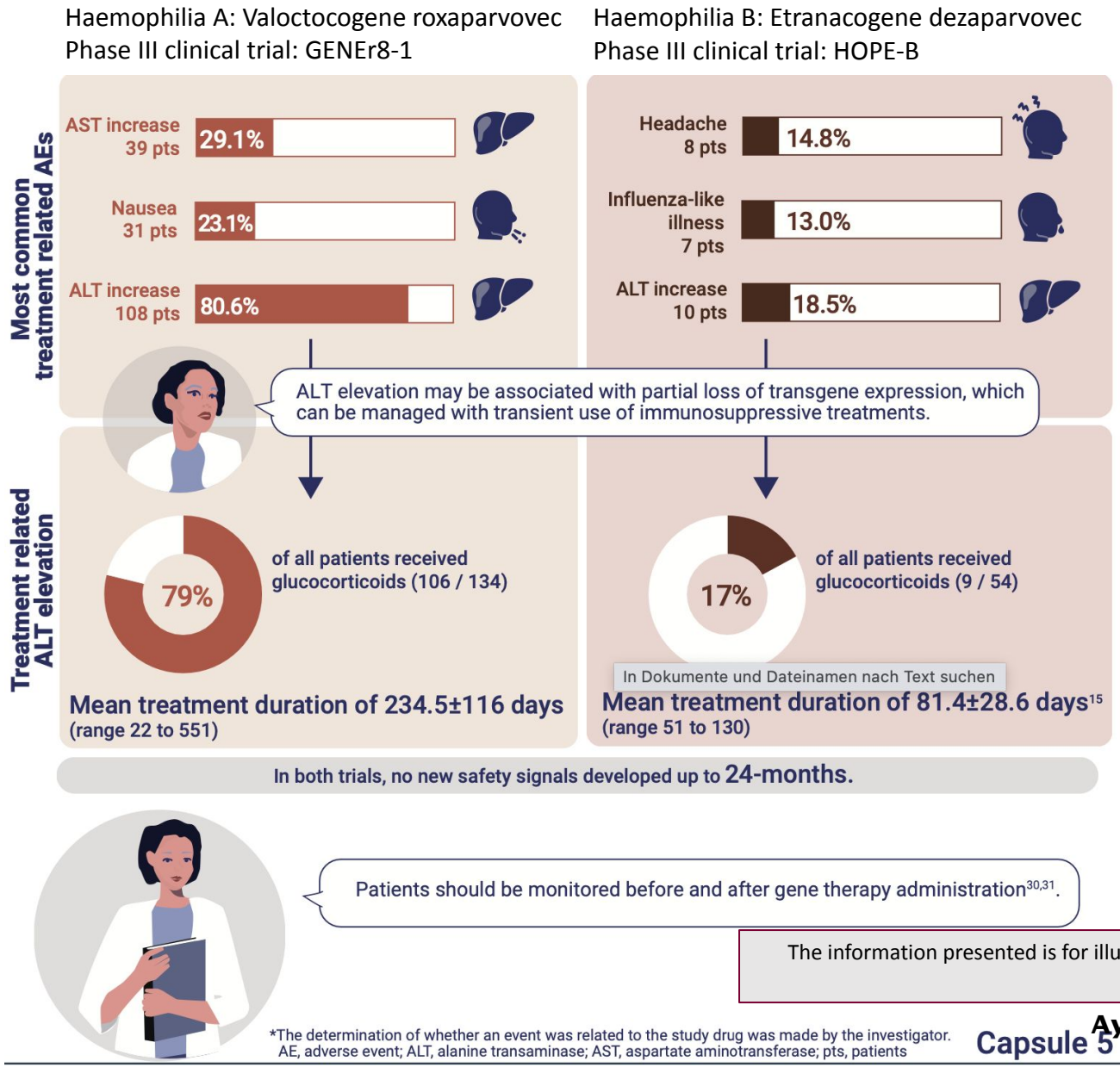
Hemophilia Gene Therapy - Safety



The information presented is for illustrative purposes only. As the data are derived from separate clinical studies, direct comparisons should not be made.

Ay C et al. Haemophilia. 2024 Jan;30(1):5-15.

Hemophilia Gene Therapy - Safety



The information presented is for illustrative purposes only. As the data are derived from separate clinical studies, direct comparisons should not be made.

Ay C et al. Haemophilia. 2024 Jan;30(1):5-15.

HOPE B - Study design

Haemophilia B
Etranacogene dezaparvovec
Phase III clinical trial: HOPE-B[28,29]

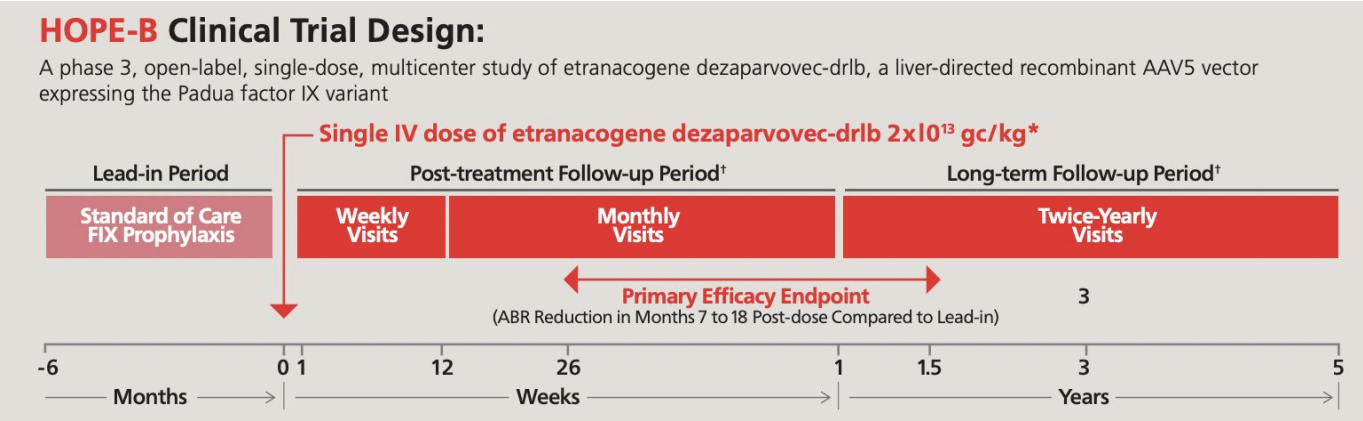
54 **adult patients** with **moderate or moderately severe haemophilia B** (FIX ≤2 IU/dL) without FIX inhibitors.

Included patients with pre-existing AAV5 NAbs.

Lead-in: FIX prophylaxis for ≥6 months.

Single infusion AAV5-LP1-hFIXco Padua ($2x10^{13}$ gc/kg).

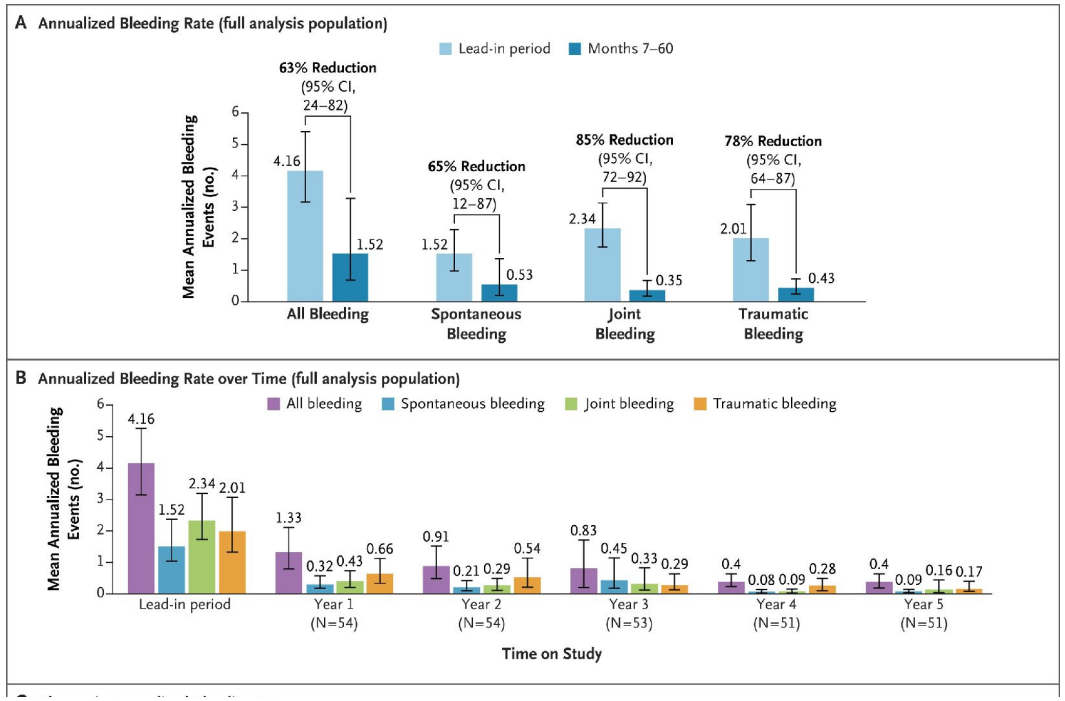
Primary endpoint: non-inferiority of **ABR** after infusion versus lead-in period.

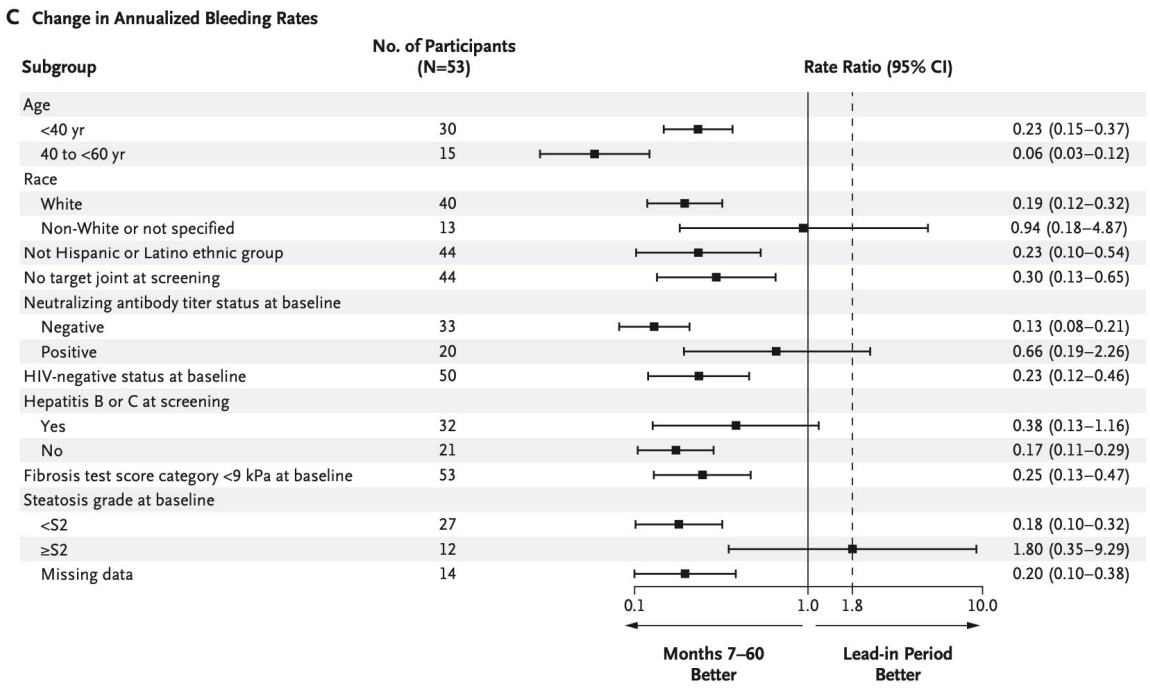


Pipe SW et al. N Engl J Med. 2026 Jan 29;394(5):463-474.

HOPE B Study – FINAL Results (5 Years)

Efficacy of Hemgenix®: Significant reduction of all types of bleeds





Pipe SW et al. N Engl J Med. 2026 Jan 29;394(5):463-474.

Hemophilia Gene Therapy - Safety

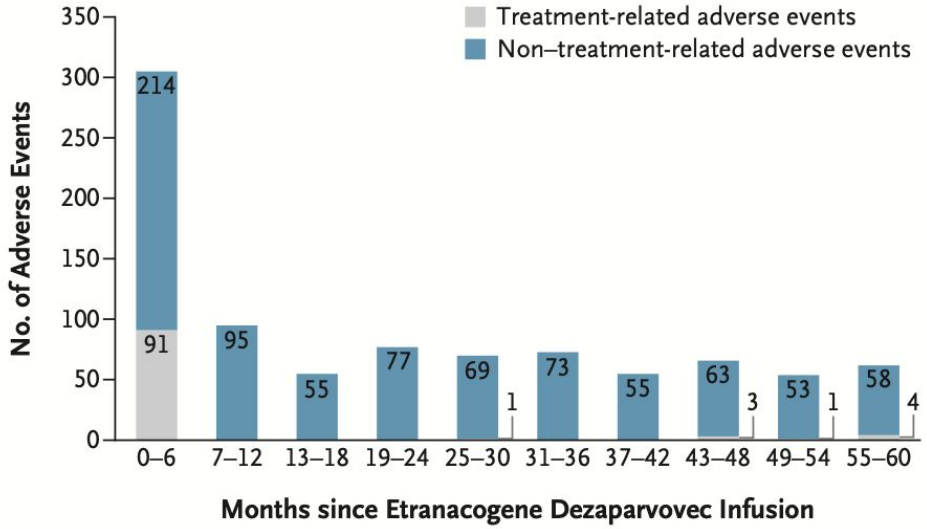


Figure 3. Adverse Events during the 5-Year Follow-up Period (Safety Analysis Population).

Shown is the number of adverse events, including those considered by the investigators to be related to treatment (in gray) and unrelated to treatment (in blue), that occurred in the safety population (54 participants) during the 5-year follow-up period after the etranacogene dezaparvovec infusion. Of the 91 treatment-related adverse events that occurred during the first 6 months after gene therapy, 89 occurred during the first 3 months and 2 occurred during months 4 through 6. The total number of adverse events during months 0 through 6 were imputed with a cutoff date of June 1, 2020, which led to two events being mapped to the period of months 7 through 12 instead of months 0 through 6.

Table 1. Adverse Events (Safety Analysis Population).*

Event	Months 0 through 6 after Gene Therapy (N=54)		Months 7 through 60 after Gene Therapy (N=54)	
	no. of participants (%)	*no. of events*	*no. of participants (%)*	*no. of events*
Any adverse event	53 (98)	307†	53 (98)	605
Adverse events occurring in ≥5% of participants				
Covid-19	NA	NA	18 (33)	20
Fatigue	13 (24)	14	5 (9)	6
Arthralgia	13 (24)	18	19 (35)	36
Headache	13 (24)	23	11 (20)	12
Nasopharyngitis	13 (24)	16	8 (15)	10
Hepatic steatosis	NA	NA	13 (24)‡	13
ALT Alanine aminotransferase increased	11 (20)	12	NA	NA
Pain in extremity	NA	NA	8 (15)	9
Influenza-like illness	7 (13)	11	3 (6)	4
Blood creatine kinase increased	7 (13)	9	5 (9)	5
Aspartate aminotransferase increased	6 (11)	7	5 (9)	5
Cough	6 (11)	6	4 (7)	4
Oropharyngeal pain	6 (11)	6	NA	NA

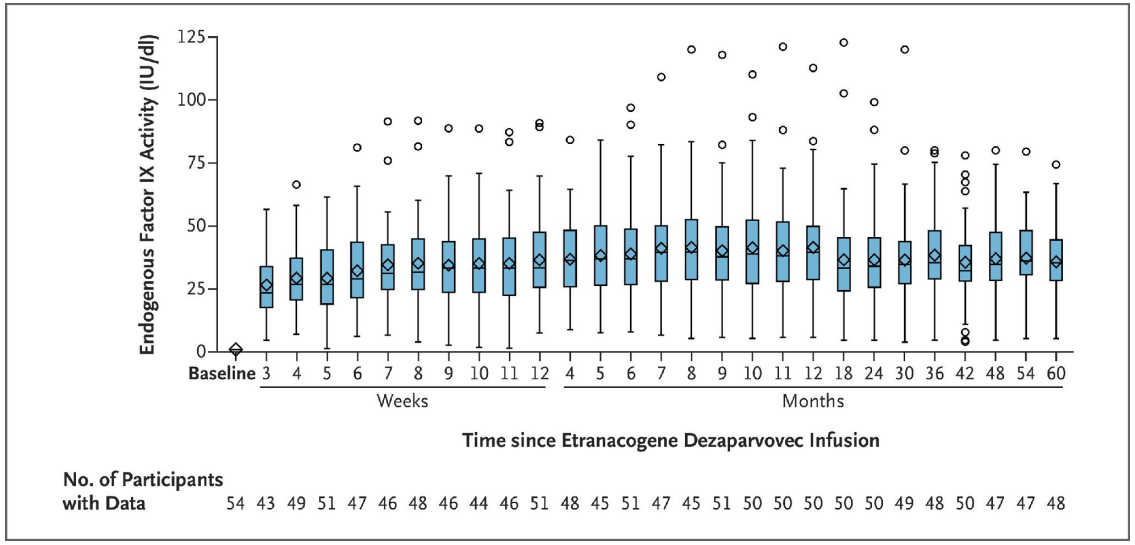
NO TRETEMENT-RELATED SERIOUS ADVERSE EVENT.

Pipe SW et al. N Engl J Med. 2026 Jan 29;394(5):463-474.

HOPE B Study – FINAL Results (5 Years)
Endogenous Factor IX Activity and Factor IX Categories

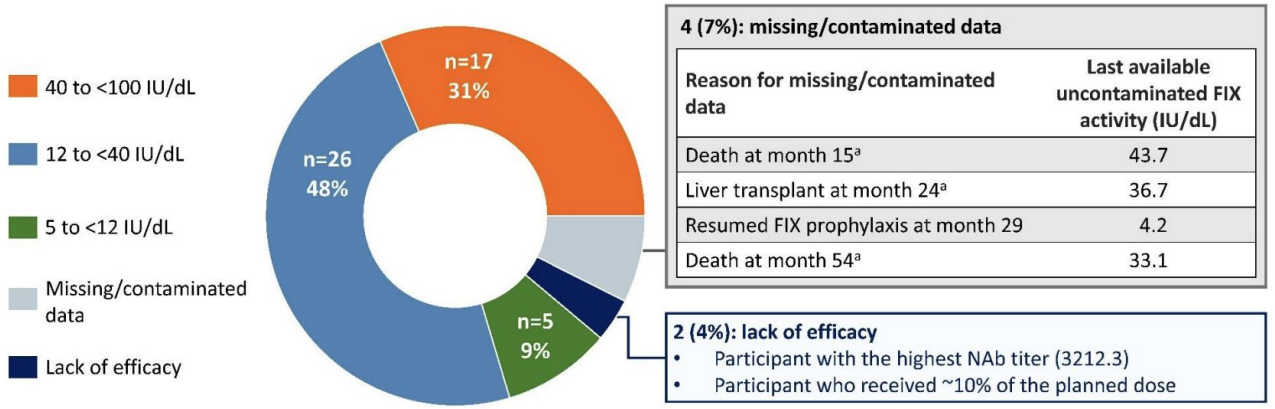
During months 7 through 60 after gene therapy:

- 51 participants (94%) discontinued and did not restart continuous factor IX prophylaxis.



During the 5-year follow-up period, endogenous factor IX expression remained stable; at 5 years, the mean (±SD) factor IX activity level was 36.1±15.7 IU per deciliter.

Proportions of participants in specific endogenous FIX categories at 5 years in the full analysis set (A; N=54) and a box plot showing endogenous FIX activity (IU/dL) over 5 years post-etranacogene dezaparvovec infusion (n=54).



4 (7%): missing/contaminated data

Reason for missing/contaminated data	Last available uncontaminated FIX activity (IU/dL)
Death at month 15[a]	43.7
Liver transplant at month 24[a]	36.7
Resumed FIX prophylaxis at month 29	4.2
Death at month 54[a]	33.1

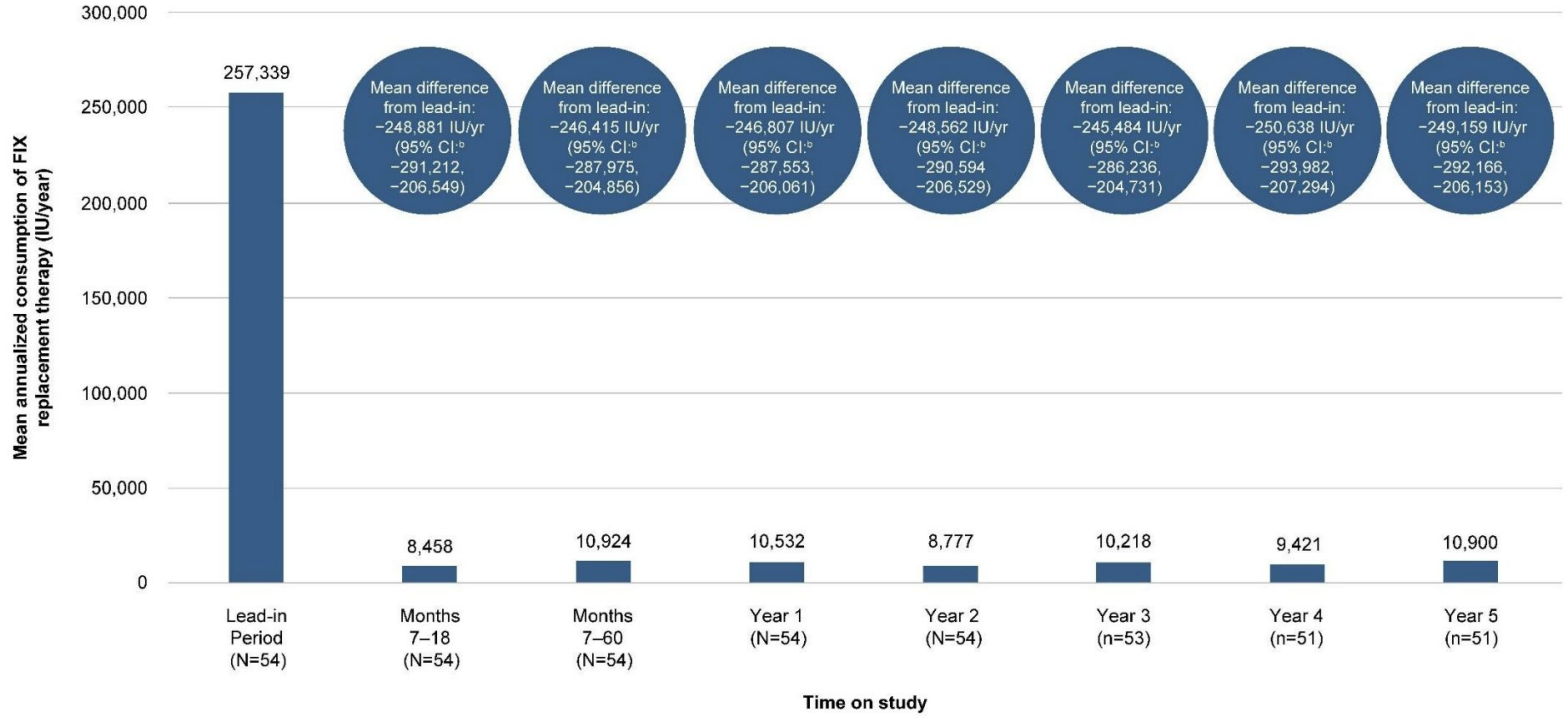
2 (4%): lack of efficacy

- Participant with the highest NAb titer (3212.3)
- Participant who received ~10% of the planned dose

Pipe SW et al. N Engl J Med. 2026 Jan 29;394(5):463-474.

Mean annualized consumption of FIX replacement therapy (IU/year)[a] in the full analysis set (N=54)

>95% Factor IX Consumption

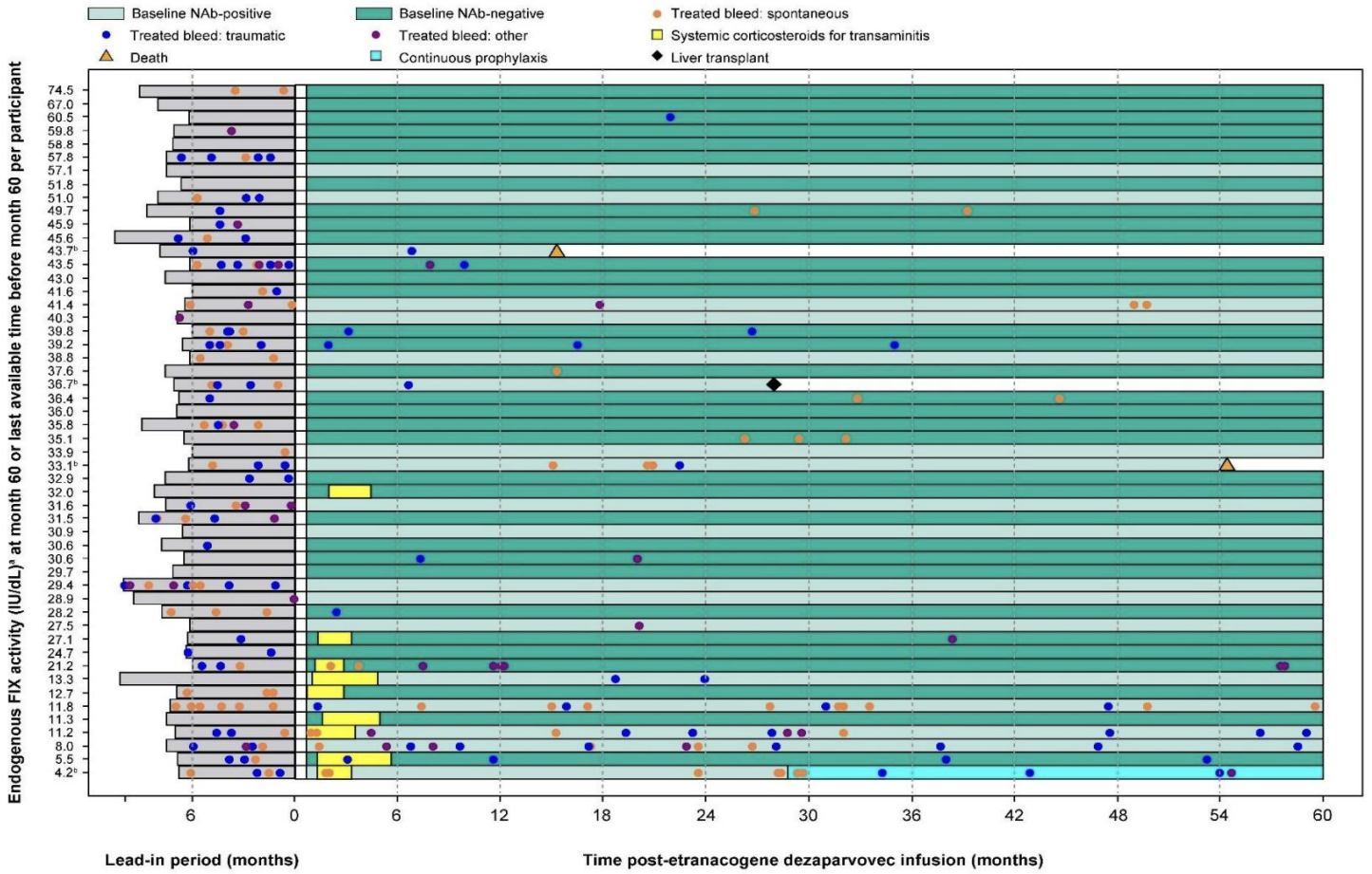


[a]Excluding use for invasive procedures. [b]The 95% CI of the mean difference is shown. Please note that confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

CI, confidence interval; FIX, factor IX.

Pipe SW et al. N Engl J Med. 2026 Jan 29;394(5):463-474.

Bleeding events for each participant during lead-in and at 5 years according to FIX activity in the responder analysis set (n=52)

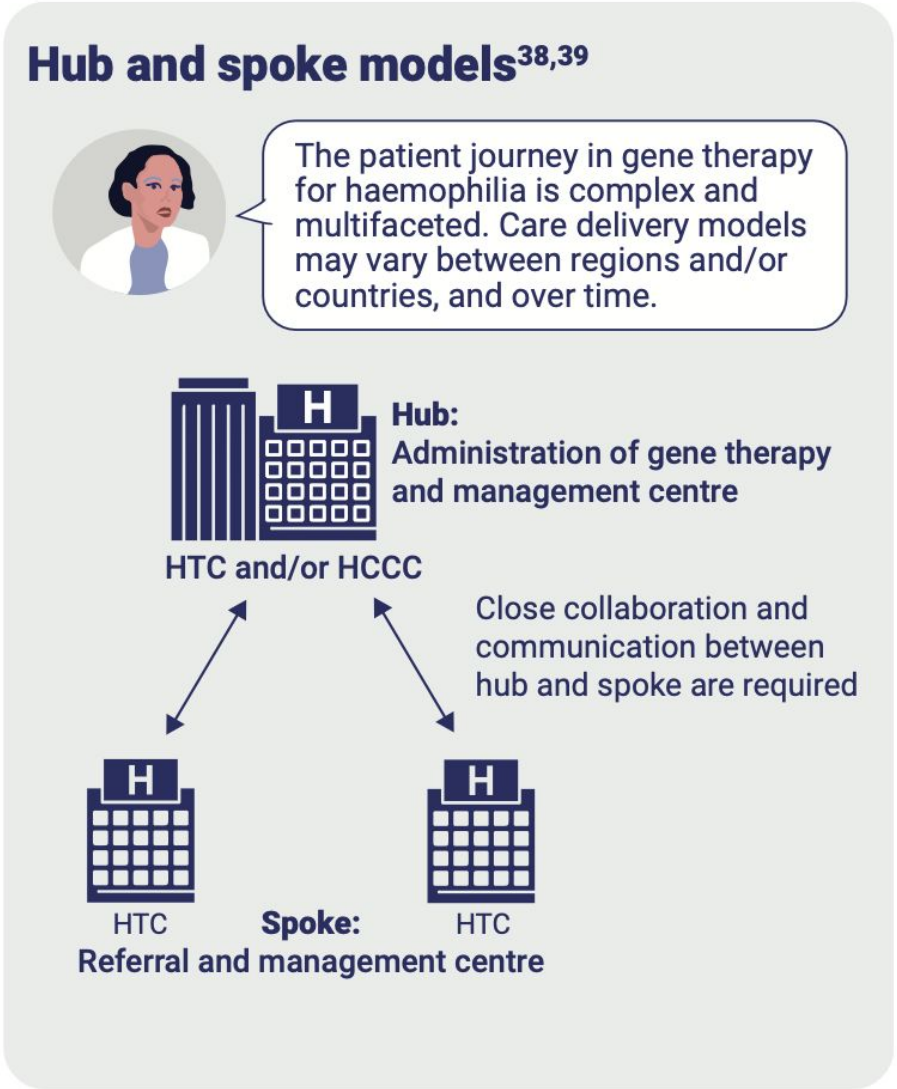


[a]Assessed by one-stage assay; [b]Most recent uncontaminated value. Please note that bleeding events within the first 21 days are not represented, per the predefined approach of the SAP.

FIX, factor IX; NAb, neutralizing antibody; SAP, statistical analysis plan.

Pipe SW et al. N Engl J Med. 2026 Jan 29;394(5):463-474.

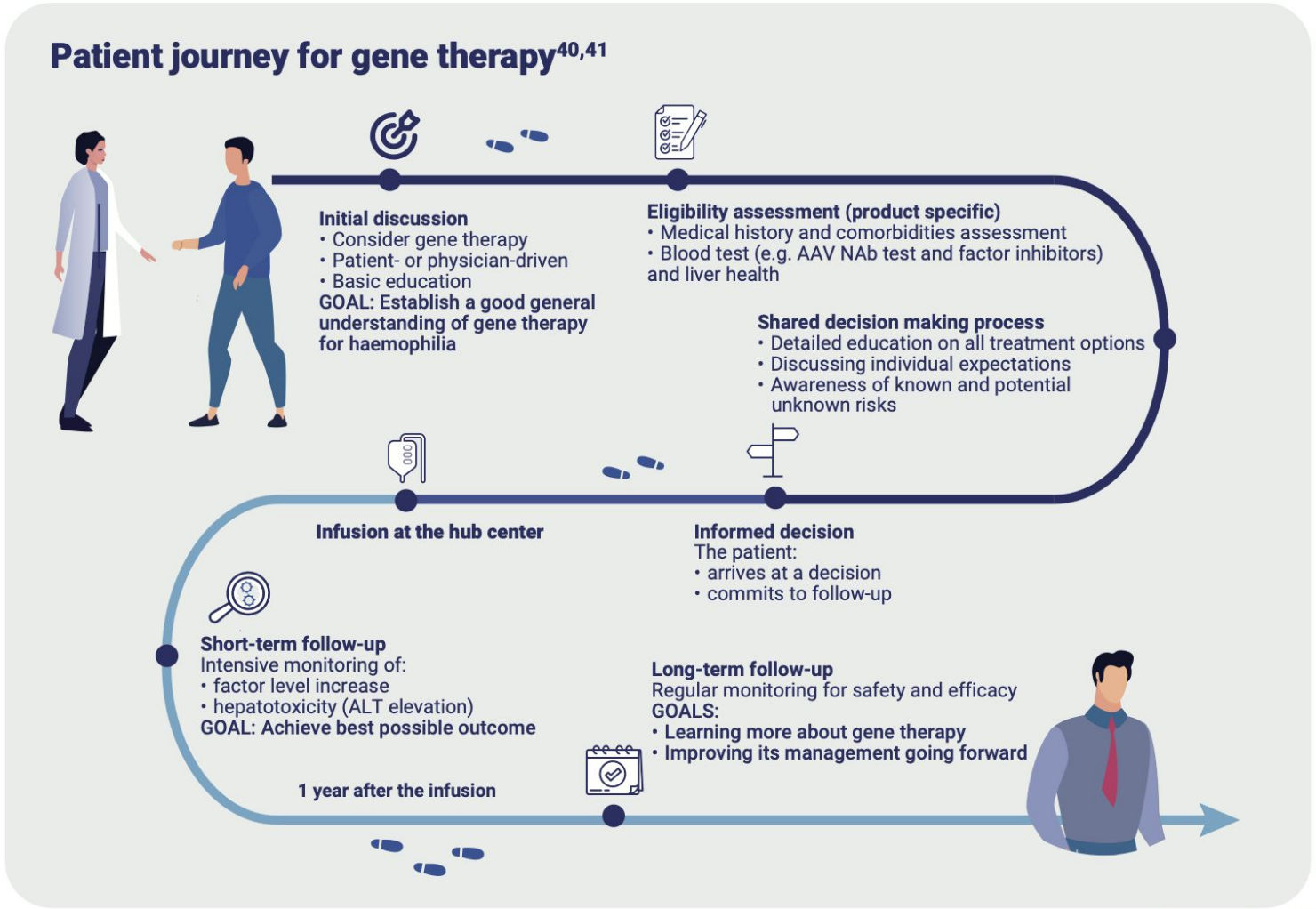
Implementation of Gene Therapy in Clinical Practice



38. Miesbach W et al. *Haemophilia.* 2021;27(6):967-973.
39. Miesbach W et al. *Haemophilia*. 2022;28(3):e86-e88.

Ay C et al. Haemophilia. 2024 Jan;30(1):5-15.

Conversations with patients



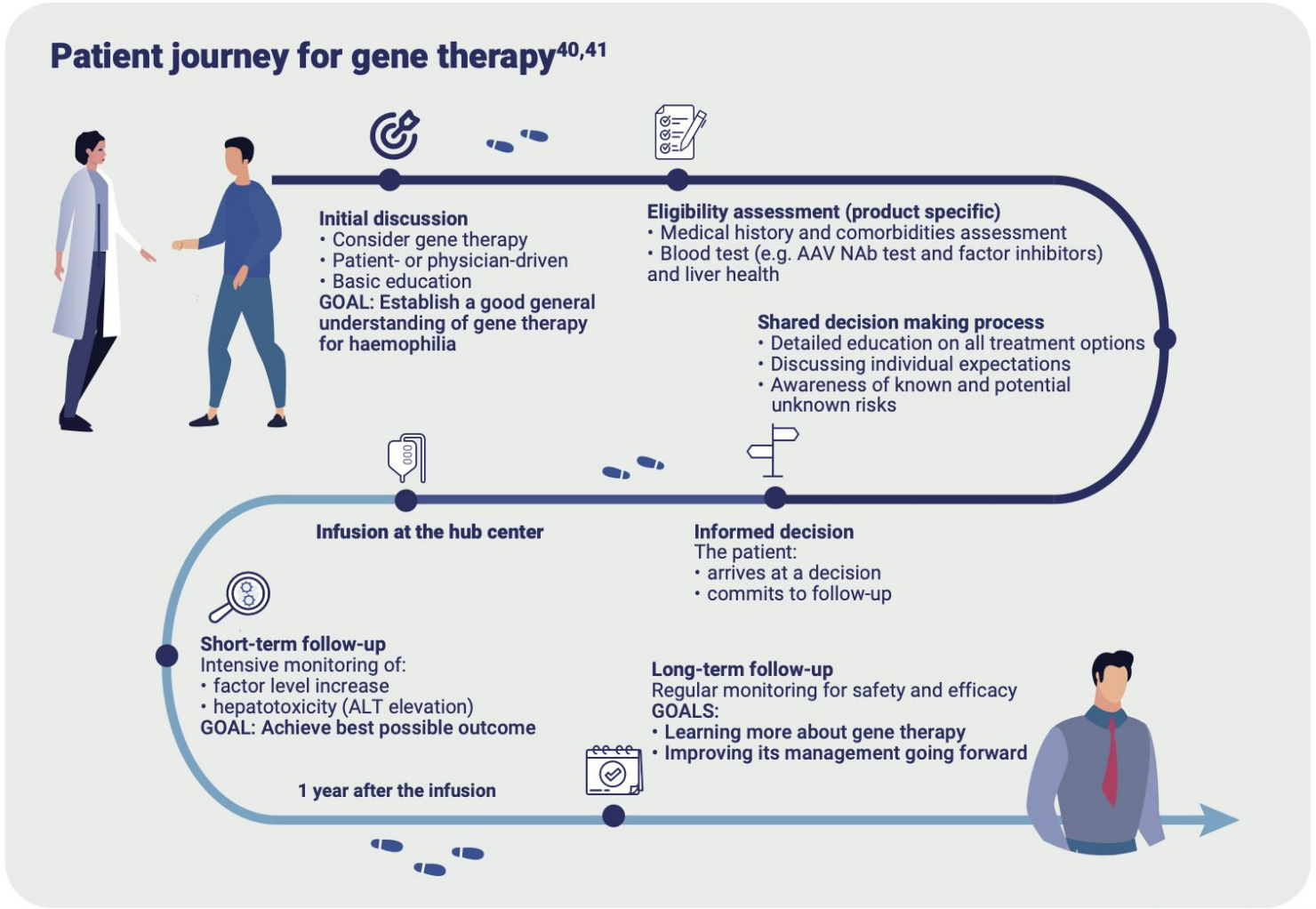
AAV NAbs, adeno-associated virus neutralizing antibodies; ALT, alanine transferase; HCCC, haemophilia comprehensive care centre; HTC, haemophilia treatment centre.

Capsule 7

- Active information about new/future treatment options and gene therapy in hemophilia during regular visits
- Patients need a lot of information (also sometimes their relatives)
- Handing out written information
- Directing to dedicted online sources for further information (patient and scientific organisations)

Ay C et al. Haemophilia. 2024 Jan;30(1):5-15.

Eligibility Assessment & Shared Decision Making Process



AAV NAbs, adeno-associated virus neutralizing antibodies; ALT, alanine transferase; HCCC, haemophilia comprehensive care centre; HTC, haemophilia treatment centre.

Capsule 7

- Reasons for decline or delay
- Written documentation of the decision process
  - Consent form

Ay C et al. Haemophilia. 2024 Jan;30(1):5-15.

Take-Home Messages – Hemophilia Gene Therapy

1. Gene therapy for hemophilia works in real-world clinical practice

2. Hemophilia B □sustained FIX expression & discontinuation of prophylaxis are achievable (individual

3. Implementation requires structured preparation & multidisciplinary collaboration

4. Safety is manageable with close monitoring & reactive steroid management

Hemophilia care is entering a new era:
Transformation from chronic management to long-term disease modification.

Thank you so much for your attention!

Q & A

First experiences with using gene therapy in Vienna, Austria

Key learnings from patient and HTC perspectives

„Prime Time“ for Gene Therapy for Hemophilia B in Austria

Fernsehen ORF ON KIDS Sound Topos Debatte Österreich Wetter Sport News ORF.at im Überblick

wien ORF.at

Wien-News Radio Wien Fernsehen Studio Wien Volksgruppen Ganz Österreich

ORF.at/Christian Öser

MEDIZIN

Premiere für Gentherapie gegen Hämophilie

Erstmals in Österreich ist an der MedUni Wien im AKH eine Gentherapie gegen Hämophilie (Bluterkrankheit) eingesetzt worden. Der Vorteil dieser Methode liegt darin, dass nur einmal eine Infusion verabreicht werden muss, um jahrelange Wirkung zu erzeugen.

13. April 2025, 10.35 Uhr Teilen

Die intravenöse Infusion wirkt gegen die schwere Form der Hämophilie B. Diese ist eine erbliche Blutgerinnungsstörung, bei der das Blut nicht richtig gerinnt. Dies führt dazu, dass Betroffene nach Verletzungen länger bluten als gesunde Menschen. Sie können auch spontane

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Neuartige Gentherapie

Neue Therapie für Bluterkrankheit am Wiener AKH

Die Behandlung für Hämophilie B muss nur einmal in Form einer intravenösen Infusion durchgeführt werden und wirkt auf Jahre hinaus.

Von **Heute Life**
09.04.2025, 13:47

Teilen Kommentare

Practical Experience
&
Real-world Observations

Pre-infusion

29-year-old with severe haemophilia B

(Studied Business Administration and Business Law; works in an office)

Medical history

FIX level: <1%

Treatment: FIX EHL prophylaxis, 4000 IU once weekly

Joint history: Pain in both ankle joints (left > right) after prolonged walking (bleeding? arthropathy?)

- Occasional use of celecoxib
- MRI: osteoarthritis of the ankle joints (left > right)
- Stopped playing basketball

Bodyweight/height: most recently 75 kg/194 cm

Liver status: Liver/Abdomen Sonography Fibroscan

- No signs of fibrosis or steatohepatitis

ABR: Bleeding episodes despite prophylaxis – ABR ~4 (however, no regular documentation)

AAV5 antibodies: <18.5 (lower limit of quantification)

Patient motivation: Independence and freedom from prophylaxis, better protection of bleeds

- Presented to the outpatient clinic in Sept. 2024 due to interest in gene therapy; received information and counseling
- Gene therapy with HEMGENIX® recommended („Hemophilia Gene Therapy Board“)

Patient case provided by the expert. Individual patient experiences may vary.

AAV5, adeno-associated virus serotype 5; ABR, annualised bleeding rate; EHL, extended half-life; FIX, factor IX; MRI, Magnetic Resonance Imaging.

Blood tests – Virology and chemistry

Geb. Datum : 21.12.1996
Geschlecht : M
Auftrags-Nr. : 7013346976
Abnahmedatum :
Erfassungsdatum : 11.09.2024 12:35

0EAICYBS0

7013346976

Klinische Angaben: schwere HB

Virologie

	Akt. Auftrag				
Erfassungsdatum	**11.09.2024**	21.10.2022	08.07.2022	06.07.2022	07.04.2022
Auftragsnummer	**7013346976**	7001774309	9015573415	9015558667	7006534764
Serum					
Hepatitis: virale Antigene und virusspezifische Antikörper					
CMIA Hepatitis-A-Virus IgG §	positiv	positiv			positiv
CMIA Hepatitis-A-Virus IgM §	negativ	negativ			negativ
CMIA Hepatitis-B-Virus HBs Ag §	negativ	negativ			negativ
CMIA Hepatitis-B-Virus HBs Ag quant.(IU/mL) §		n.d.			
CMIA Hepatitis-B-Virus HBs Ak §	positiv	positiv			positiv
CMIA Hepatitis-B-Virus HBs Ak quant. (mIU/mL) §	365				401
CMIA Hepatitis-B-Virus HBc Ak §	negativ	negativ			negativ
CMIA Hepatitis-B-Virus HBc IgM §		n.d.			
CMIA Hepatitis-B-Virus HBe Ag §		n.d.			
CMIA Hepatitis-C-Virus Ak §	negativ	negativ			negativ
CMIA Hepatitis-E-Virus IgG	negativ				
CMIA Hepatitis-E-Virus IgM	negativ				
HIV: virales Antigen und virusspezifische Antikörper					
CMIA HIV-1/2 Ag/Ak §	negativ	negativ			negativ

Klinische Chemie

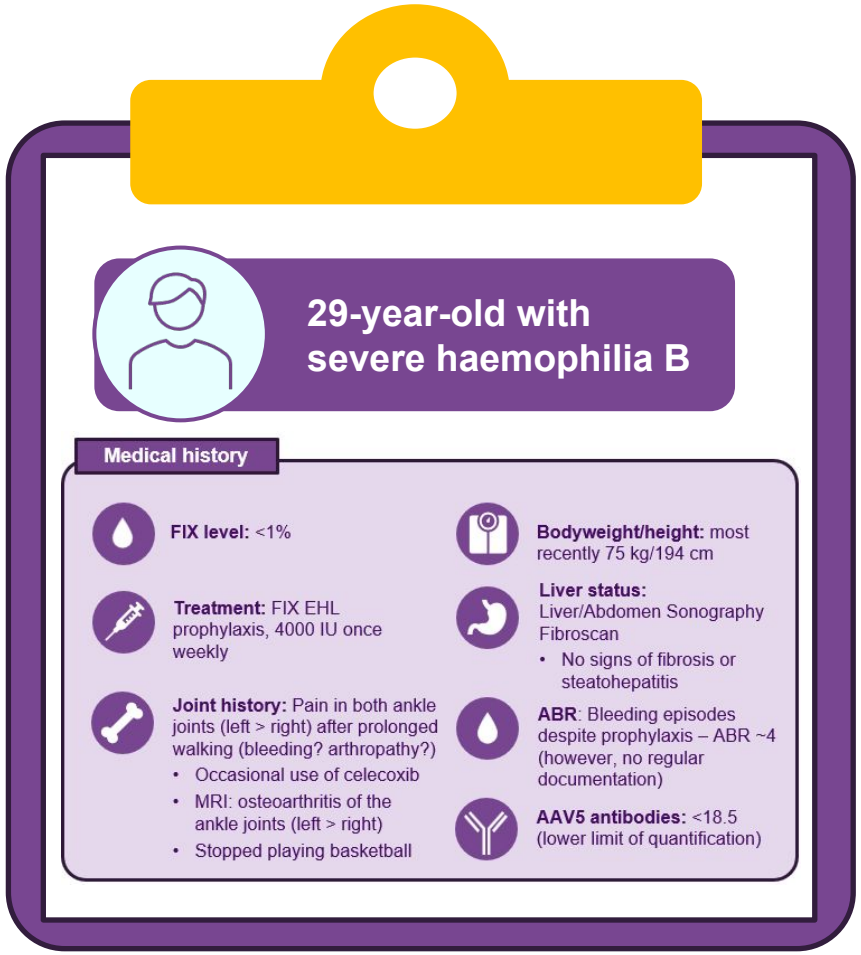
Natrium	**140**	136 - 145	mmol/L
Kalium	**4.16**	3.5 - 5.1	mmol/L
Chlorid	**104**	98 - 107	mmol/L
Kalzium	**2.41**	2.15 - 2.50	mmol/L
Anorganisches Phosphat	**0.94**	0.81 - 1.45	mmol/L
Magnesium	**0.78**	0.66 - 1.07	mmol/L
Eisen	**121**	33 - 193	µg/dL
Kalzium - Phosphat - Produkt	**2.27**		mmol^2/L^2
Kreatinin	**0.80**	0.70 - 1.20	mg/dL
Harnstoff - N	**8.9**	6 - 20	mg/dL
Harnsäure	**4.0**	3.4 - 7.0	mg/dL
Gesamt Bilirubin	**0.60**	0.0 - 1.2	mg/dL
Hämolyseindex	**4**		
Eiweiß, gesamt	**77.8**	64 - 83	g/L
Albumin	**50.5**	35 - 52	g/L
Cholinesterase	**6.67**	5.32 - 12.92	kU/L
Alkalische Phosphatase	**68**	40 - 130	U/L
ASAT (GOT)	**21**	< 50	U/L
ALAT (GPT)	**16**	< 50	U/L
Gamma - GT	**24**	< 60	U/L
LDH	**153**	< 250	U/L
STOFFWECHSELDIAGNOSTIK			
Triglyceride	**106**	< 150	mg/dL
Cholesterin, gesamt	**113**	< 200	mg/dL
HDL - Cholesterin	**65**	> 55	mg/dL
Cholesterin/HDL Quotient	**1.7**	<4	
LDL - Cholesterin errechnet	**26.80**	Zielwert bei niedrigem Risiko mg/dL	< 116
		Zielwert bei mäßig erhöhtem Risiko mg/dL	< 100
		Zielwert bei hohem Risiko mg/dL	< 70
		Zielwert bei sehr hohem Risiko mg/dL	< 55

Immunologie

Laborbefund vom 11.09.2024 13:23 Seite 2 vor

Patient case provided by the expert. Individual patient experiences may vary.

Prof. Ay Infusion



Infusion: 01.04.2025

- Contact with pharmacists to prepare the therapy; delivery of the therapy to the ward within 1 hour
- Continuous infusion over 1 hour
- Regular monitoring of vital signs (blood pressure, pulse rate, respiration rate, body temperature) and oxygen saturation
- Well tolerated (no infusion-related reactions)
- Post-infusion observation for ~ 3 hours
- Hospital discharge in the afternoon (with detailed discharge letter and prescription for corticosteroid and antipyretic)

Patient case provided by the expert. Individual patient experiences may vary.

AAV5, adeno-associated virus serotype 5; ABR, annualised bleeding rate; EHL, extended half-life; FIX, factor IX; ICU, Intensive care unit; MRI, Magnetic Resonance Imaging.

Prof. Ay
Post-infusion follow-up - weekly for 12 weeks

Infusion: 01.04.2025
Last prophylaxis: 03.04.2025

- After 7 days „flu-like“ symptoms (for 3 to 4 days)
  - Symptoms improved after Metamizole

		11.09.2024	05.03.2025	31.03.2025
Parameter	Einheit	12:11	14:34	10:29
Faktor IX Aktivität	%	11	6	9
Faktor IX Aktivität (chromogen)	%	42	36	

Last FIX prophylaxis on 26/March at 8:00 pm

- On 3/April, patient again performed FIX prophylaxis for the last time because of „concerns“.
- Prophylaxis then terminated.

No bleeds!
No need of pain killer (celecoxib) since gene therapy!
Started regular sport activities (gym and playing basketball)!

Patient case provided by the expert. Individual patient experiences may vary.
FIX, factor IX.

Prof. Ay
Post-infusion follow-up – transaminases

Start Aprednislone

Stop Aprednislone

Watch & Wait

		11.09.2024	05.03.2025	31.03.2025	01.04.2025	08.04.2025	14.04.2025	22.04.2025	29.04.2025	06.05.2025	13.05.2025	20.05.2025	27.05.2025	03.06.2025
Parameter	**Einheit**	**12:11**	**14:34**	**10:13**	**10:25**	**12:59**	**11:29**	**10:56**	**11:13**	**11:17**	**11:40**	**11:40**	**11:16**	**11:06**
ASAT (GOT)	*U/L*	21	16	24	21	20	39	12	14	16	20	23	35	39
ALAT (GPT)	*U/L*	16	20	25	25	18	**73**	25	21	20	24	32	44	42

ASAT (GOT) reference range: <50 U/L
ALAT/GPT reference range: <50 U/L

Patient case provided by the expert. Individual patient experiences may vary.
ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; GOT, Glutamate Oxaloacetate Transaminase; GPT, Glutamate Pyruvate Transaminase.

Prof. Ay
Post-infusion follow-up – 2nd Phase

- **FIX Activity levels during follow-up**

								Referenzbereich	Einheit
Abnahme (lt. Beleg)				17.07.25 11:40			01.10.25 11:10		
Erfassung(Labor)	**17.06.25 11:11**	**24.06.25 10:59**	**10.07.25 11:08**	**17.07.25 12:15**	**24.07.25 11:40**	**20.08.25 11:37**	**01.10.25 12:15**		
Auftragsnummer	1219566916	1219569935	1219569326	1219568800	1224236181	1224236594	**1224238008**		
Gerinnung - Einzelfaktoren									
Faktor IX Aktivität #	↓ **28**	↓ **30**	↓ **29**	↓ **31**	↓ **36**	↓ **34**	↓ **31**	60 - 140	%
Faktor IX Aktivität (chromogen) #	↓ **26**	↓ **20**	↓ **25**	↓ **19**	↓ **25**	↓ **22**	↓ **29**	70 - 130	%

9-Month Follow-Up

No bleeds!

12-Month Follow-Up

Patient case provided by the expert. Individual patient experiences may vary.

FIX, factor IX.

Prof. Ay
Post-infusion follow-up – 2nd Phase

- **Transaminases during follow-up**

Re-start Aprednislone for 1 month

9-Month Follow-Up

12-Month Follow-Up

Abnahme (lt. Beleg)	10.06.25 10:40						17.07.25 11:40		01.10.25 11:10		
Erfassung(Labor)	**10.06.25 11:04**	**17.06.25 11:11**	**24.06.25 [*] 10:59**	**24.06.25 10:59**	**10.07.25 11:08**	**10.07.25 11:08**	**17.07.25 12:15**	**20.08.25 [*] 11:37**	**01.10.25 12:15**		
Auftragsnummer	1225185390	1222900271	1225052076	1220735699	1225051239	1224557178	**1225050964**	1224743533	**1222341186**		
ASAT (GOT)	47	37	36		32		18	21	26	< 50	U/L
ALAT (GPT)	↑ **52**	↑ **53**	48		↑ **63**		35	25	36	< 50	U/L

20 29

24 46

Patient case provided by the expert. Individual patient experiences may vary.

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; FIX, factor IX; GOT, Glutamate Oxaloacetate Transaminase; GPT, Glutamate Pyruvate Transaminase.

Patient E.L., born 1991

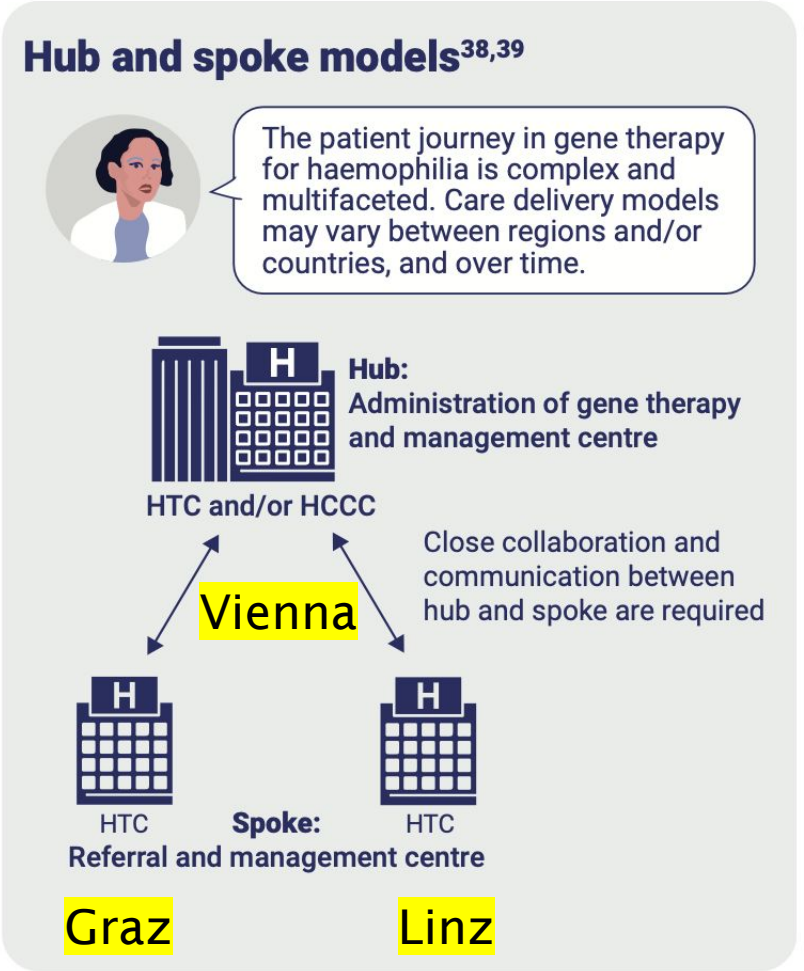
- moderate hemophilia B (F IX <2%), severe bleeding phenotype, signes of arthropathy in the ankles

Patient motivation: Independence and freedom from prophylaxis

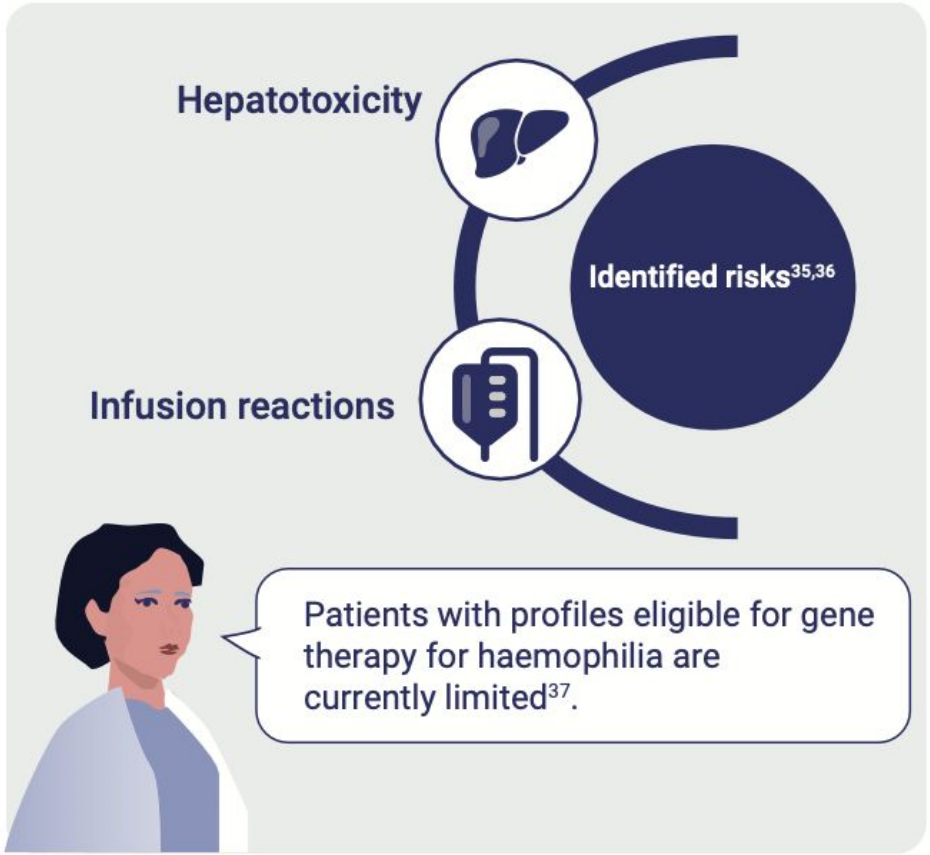
- AAV-5 NAb test positive (43.3)
  - Nab titer below the recommended cut-off (<678)
- Received Hemgenix® on 04/SEP/2025
- No ALT elevation – no steroids needed
- Faktor IX (after 3 months): 31%

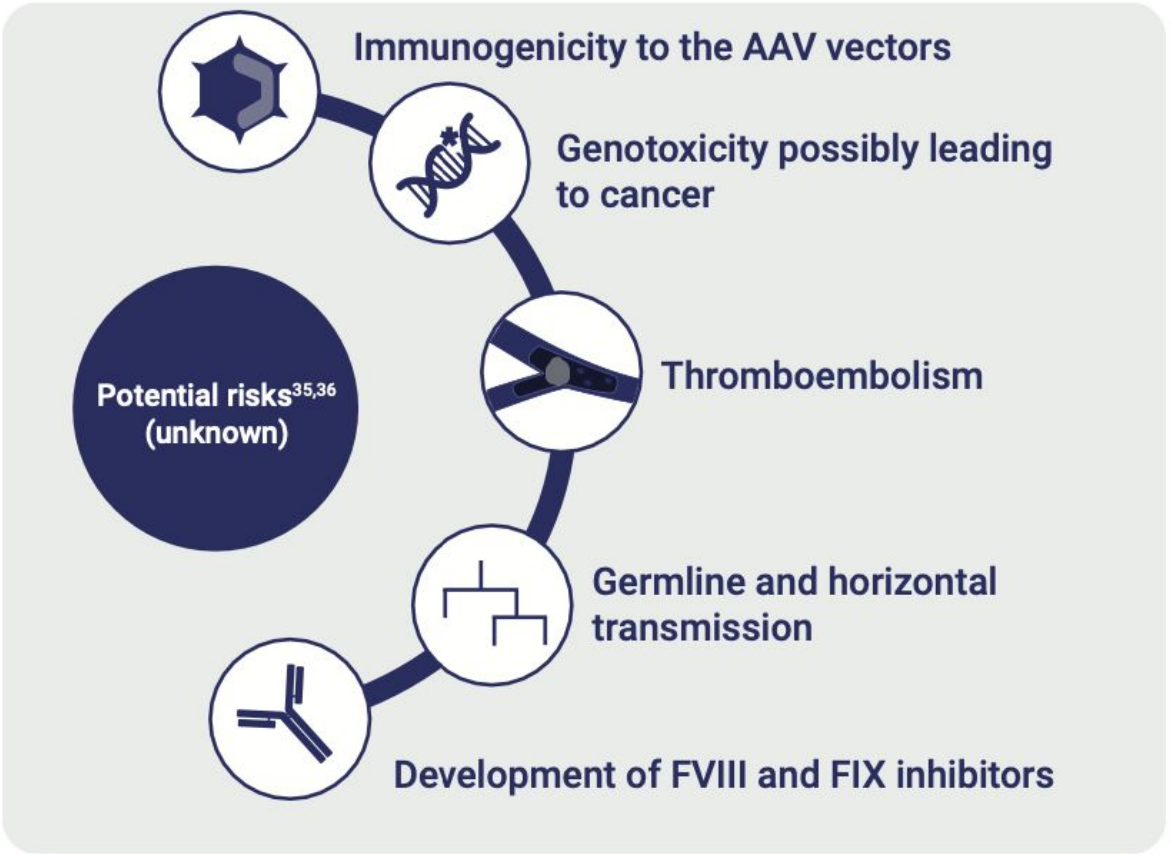
  (after 6 months): 25%

  (after 9 months): 37%



Short-term and long-term follow-up of patients is needed to determine long term efficacy and safety of gene therapy for haemophilia.

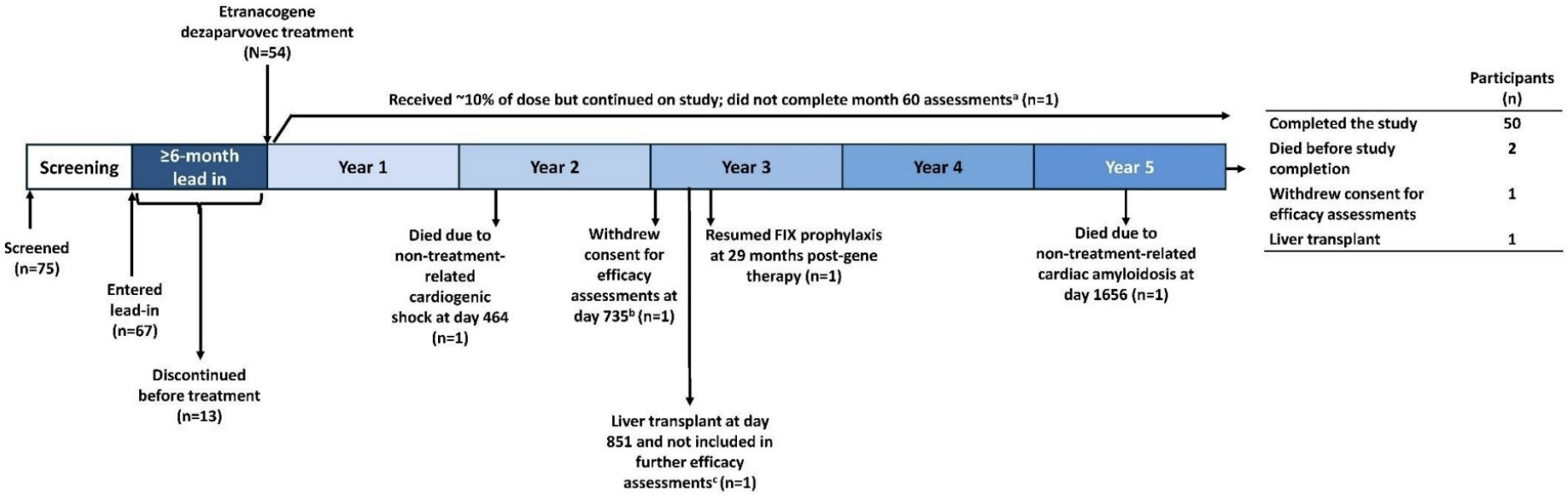




AAV, adeno-associated virus; NAb, neutralizing antibody

Capsule 6

PARTICIPANT DISPOSITION IN HOPE-B



	Participants (n)
Completed the study	50
Died before study completion	2
Withdrew consent for efficacy assessments	1
Liver transplant	1

[a]One participant received approximately 10% of the planned dose after prematurely discontinuing the infusion due to a treatment-emergent adverse event of hypersensitivity. This participant continued on study and attended the month 60 visit but did not complete all study assessments and was reported to have not completed the study in the clinical database. However, the sponsor considered this participant to have completed the study despite the missing assessments because he did not withdraw consent.

[b]This participant had the highest neutralizing antibody titer of 3212.3 at baseline and did not respond to treatment. He withdrew consent for efficacy assessments immediately after the month 24 assessment but consented to continued safety follow-up through review of medical records.

All malignancies (studied by molecular analysis) and deaths were considered not related to treatment.