ACCESS TO GENE THERAPY FOR HEMOPHILIA B PATIENTS

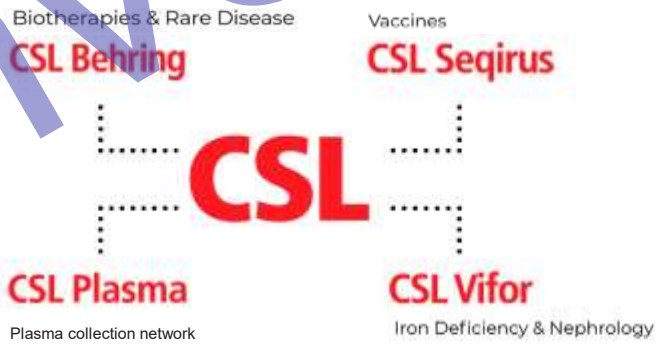
Innovation Day – November 14, 2023

Charlene Chorao – Field Medical Advisor

CSL BEHRING

Who we are ?

- A **leading international biopharmaceutical company.**
- Dedicated to developing and delivering innovative treatments for patients suffering from **rare and serious diseases.**
- With a presence in 4 areas : **immunology, haematology, respiratory, critical care**.
- CSL Behring belongs to the CSL group.



The CSL group in some figures.

32,000+ **employees** worldwide

50 **Specialities** commercialised worldwide

serving patients and people in 100+ **countries**

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CSL

A significant investment in R&D

2,000+
R&D employees
worldwide

18
R&D centres
in 10 countries

$4.6 billion
CSL R&D investment in last 5 years

30 specialities
Under development

Driven by Our Promise

More than 50 commercialized specialities

Among them, the first gene therapy in haemophilia B

Immunology

15 specialities

Respiratory

2 specialities

Hematology

26 specialities

Etranacogene dezaparvovec (HEMGENIX®) : the first gene therapy in Haemophilia B

Critical care

8 specialities

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https://www.csl.com/research-and-development/product-pipeline

Haemophilia

A coagulation problem

Hemostasis.

- All the physiological processes that allow bleeding to stop.

The 3 stages of hemostasis.

- **Primary hemostasis** : formation of the platelet plug.
- **Coagulation** : setting up of the coagulation **cascade** to form fibrin strands, which strengthen the platelet plug.
- **Fibrinolysis** : regulation of coagulation to prevent thrombus.

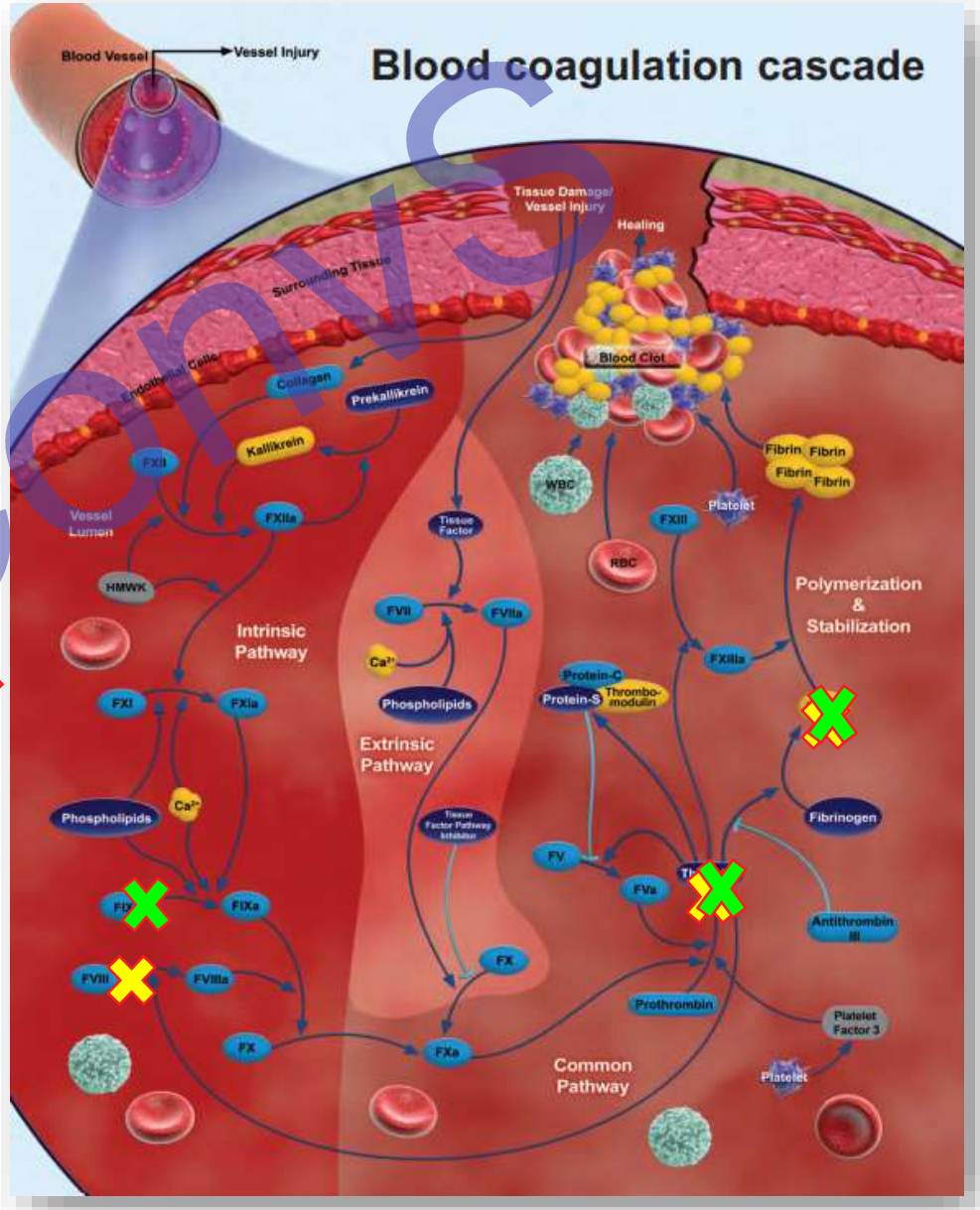
Haemophilia.

- **Haemophilia A :** FVIII deficiency
- **Haemophilia B :** FIX deficiency

No coagulation

↓

Bleeds



https://docs.abcam.com/pdf/cardiovascular/blood_coagulation.pdf

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Berntop, 2021.

Haemophilia

Clinical manifestations

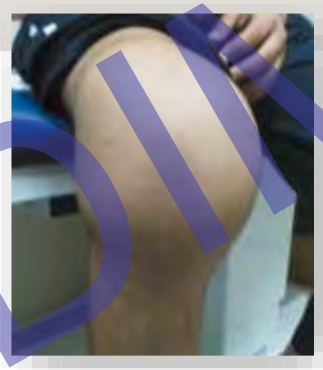
Bleeds.

- Traumatic and **spontaneous**.
- 70 to 80% are **hemarthroses**.
- 10-20% are muscular hematomas.
- **Intracranial bleeding** (<5%) that may be fatal.
- The **risk of bleeding is inversely correlated with the level of circulating factor**.

From hemarthrosis to arthropathy.

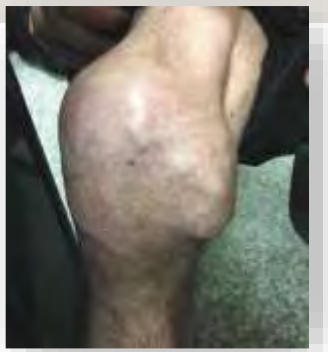
Hemarthrosis

- Effusion of blood in a joint.



Arthropathy

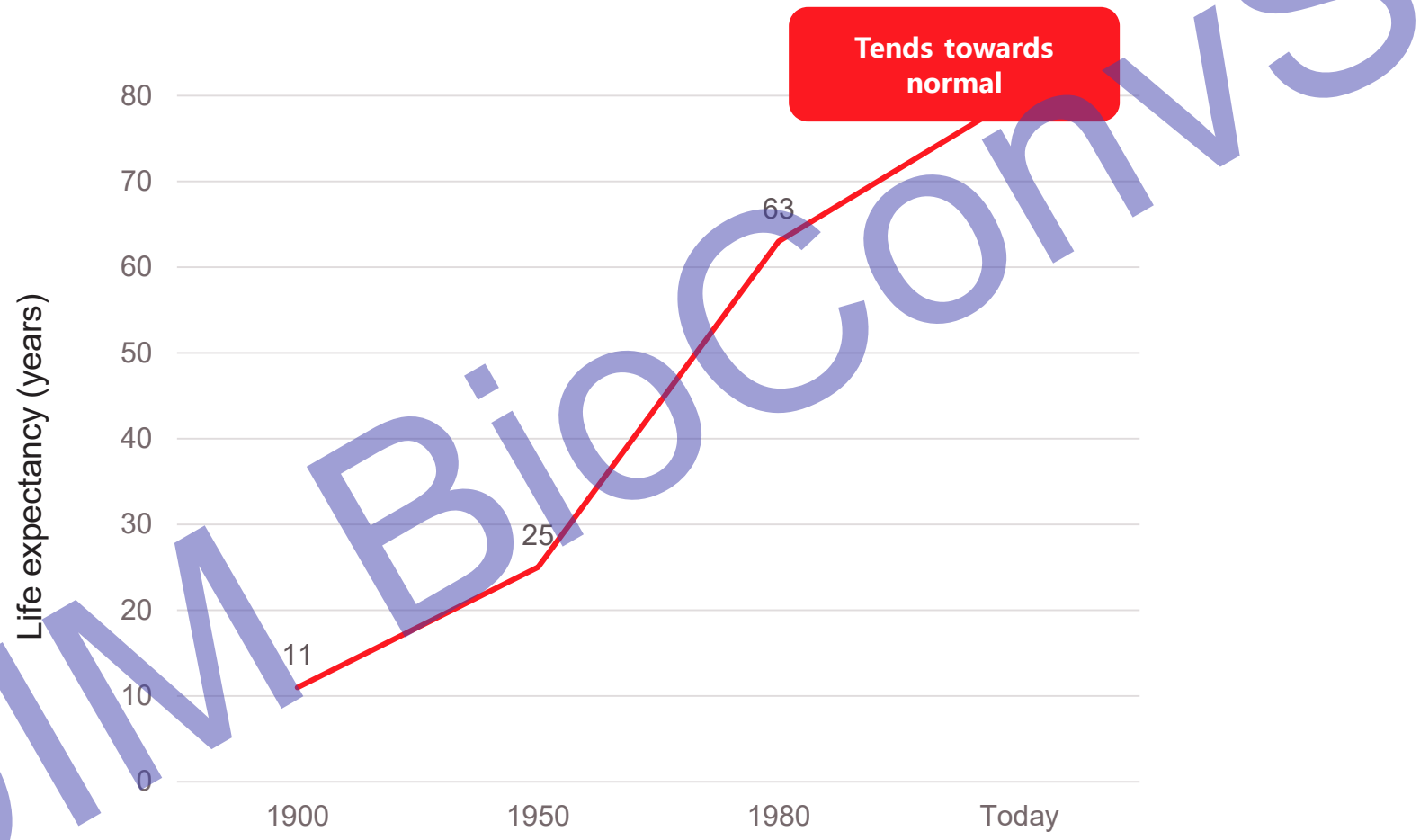
- Consequence of repeated hemarthroses.
- Very advanced formed are associated with **major disability**.



WFH guidelines, 2020.
PNDS, 2019.

Haemophilia

Life expectancy



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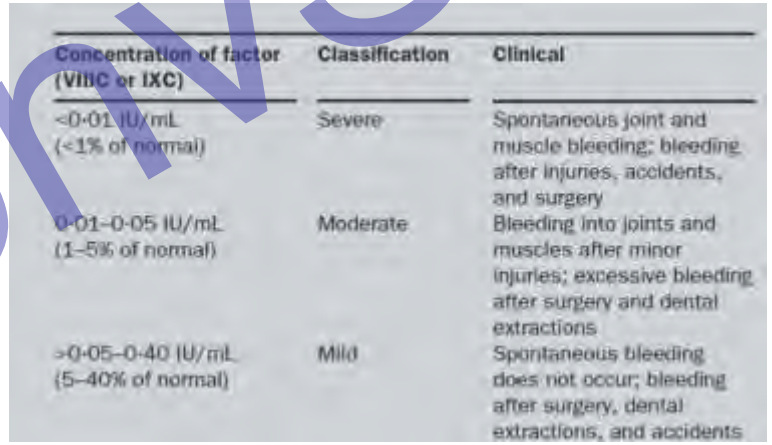
https://mhemo.fr/les-pathologies/lhemophilie/

Haemophilia

Why and how many patients ?

Etiology.

- Caused by a **mutation in the F8 or F9 gene** which can result in reduced amounts of FVIII or FIX.
- F8 and F9 genes are positioned on the X chromosome.
- **Recessive X-linked disorder.** Men are haemophiliacs. Women are carriers.
- *De novo* mutations in 30-50% of cases.
- Severity of the disease depends on the reduction of levels of FVIII or FIX.



Concentration of factor (VIIIC or IXC)	Classification	Clinical
<0·01 IU/mL (<1% of normal)	Severe	Spontaneous joint and muscle bleeding; bleeding after injuries, accidents, and surgery
0·01–0·05 IU/mL (1–5% of normal)	Moderate	Bleeding into joints and muscles after minor injuries; excessive bleeding after surgery and dental extractions
>0·05–0·40 IU/mL (5–40% of normal)	Mild	Spontaneous bleeding does not occur; bleeding after surgery, dental extractions, and accidents

Epidemiological data.

Haemophilia is a **rare disease** (< 5 people out of 10,000).

Haemophilia A (80%)

	Sévère	Modérée	Mineure	Total
Total, n	2135	889	4266	**7290**

Francecoag.org (consultation on 09/21/23)

Haemophilia B (20%)

	Sévère	Modérée	Mineure	Total
Total, n (%)	419	421	892	**1732**

Francecoag.org (consultation on 09/21/23)

The Royal Disease.

Queen Victoria of England was a carrier. Following the union of her descendants, the disease spread to other royal families (Spanish and Russian).

Bolton-Maggs, 2003.
Berntop, 2021.

Haemophilia

What is the current treatment ?

Two regimens.

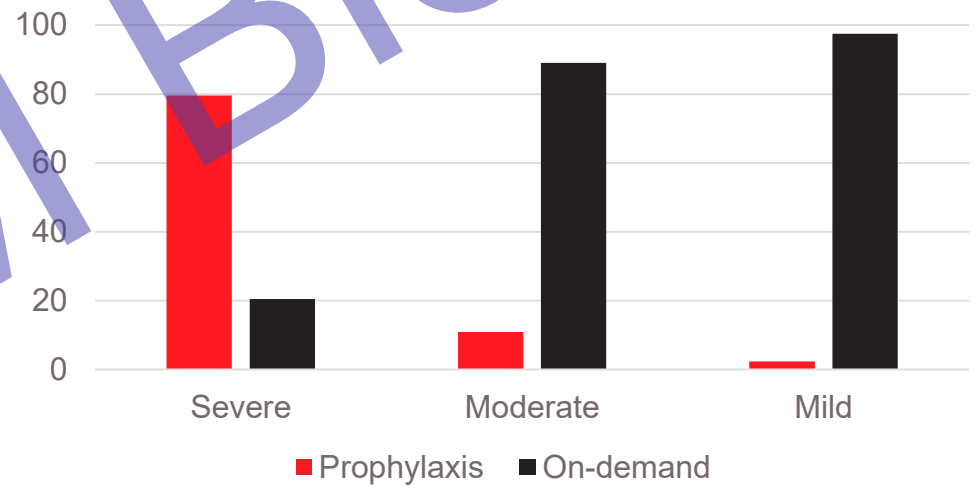
Patients with severe haemophilia

- The standard of care is **prophylaxis to prevent bleeding**.
- **Prophylaxis =** regular injections of a replacement therapy (clotting factor) or of other hemostasis products.

Patients with moderate or mild haemophilia

- **On-demand treatment to treat bleeding episodes**.
- **On-demand treatment =** treatment of a declared bleeding episode by administering the deficient factor.

In haemophilia B



Adapted from Francecoag data (2022)

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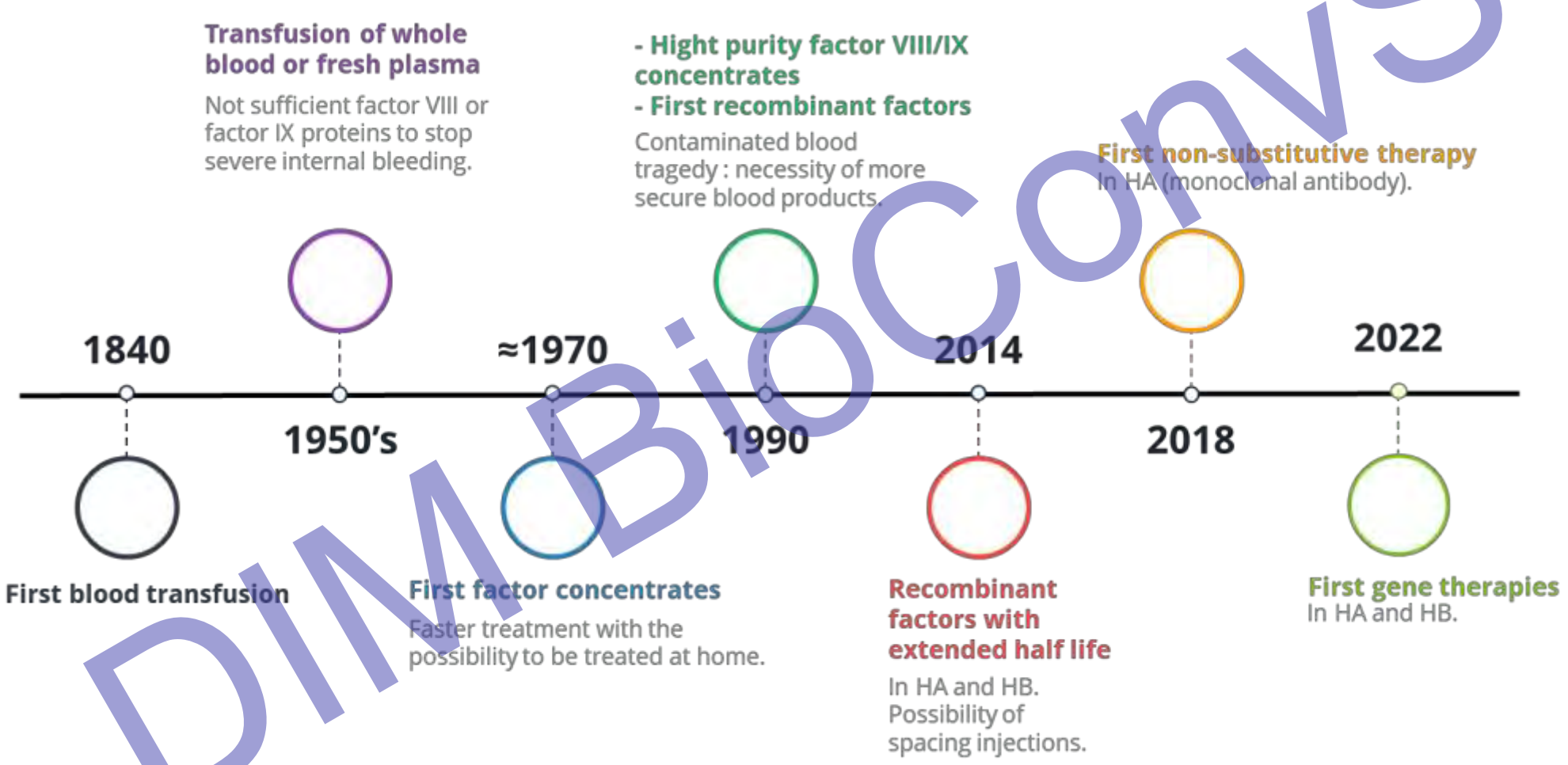
WFH guidelines, 2020.
PNDS, 2019.

Haemophilia

Treatment history



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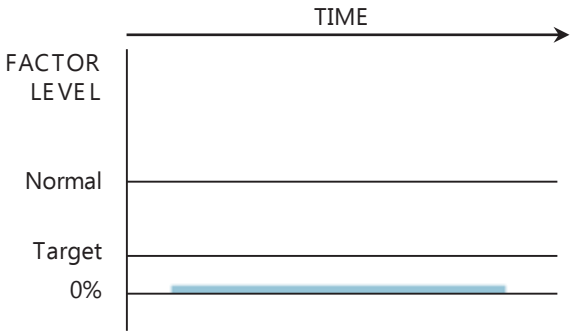
https://mhemo.fr/les-pathologies/lhemophilie/
Ozelo, 2022.

Haemophilia

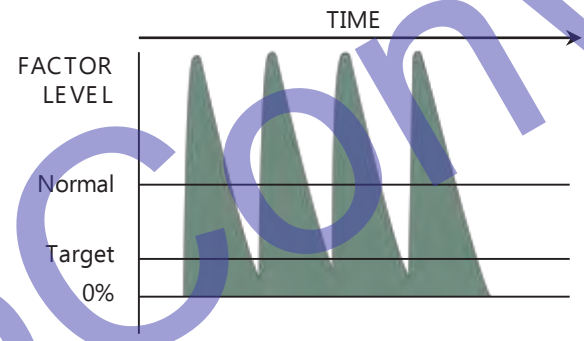
Factor levels by type of treatments in patient with severe disease

The goal of the prophylaxis is to maintain the clotting factor trough levels above a target level of 3% to 5%.



No treatment

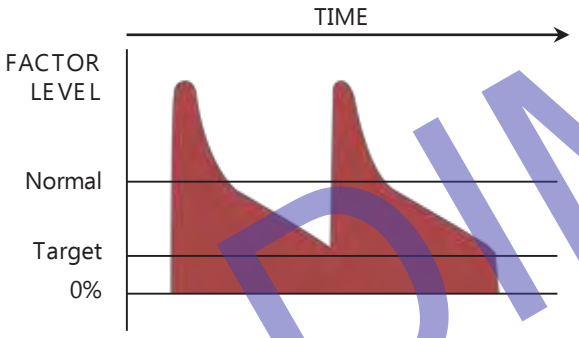
Inadequate factor levels at all times.



Standard factor therapy

Short-acting factor therapy requiring 2-3 IV injections/week.

Factor levels spike with every dose, often dipping below the target.



Long-acting factor therapy

It requires less frequent dosing.

It maintains levels at or above the target.

But it still requires regular administrations and it results in fluctuating factor levels over time.

Unmet needs

Maintain factor trough levels of 3% to 5% requires frequent infusions[2].

Burden of Treatment

High treatment burden of FIX prophylaxis may impact QoL and adherence of patients[3,4].

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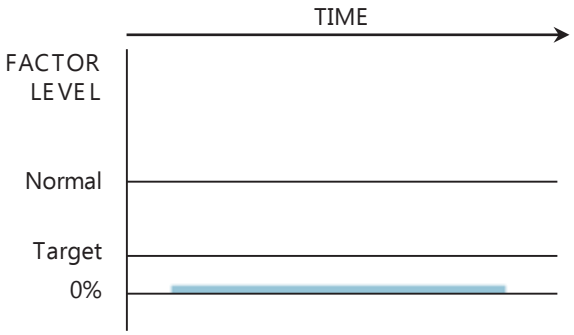
1.Arruda, 2017. 2. Peyvandi, 2020. 3. Vasquez-Loarte, 2020. 4. Wiktop, 2015.

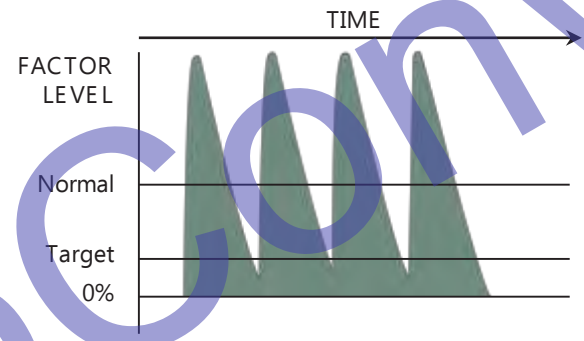
Haemophilia

Factor levels by type of treatments in patient with severe disease[1]



No treatment

Inadequate factor levels at all times (severe haemophilia).



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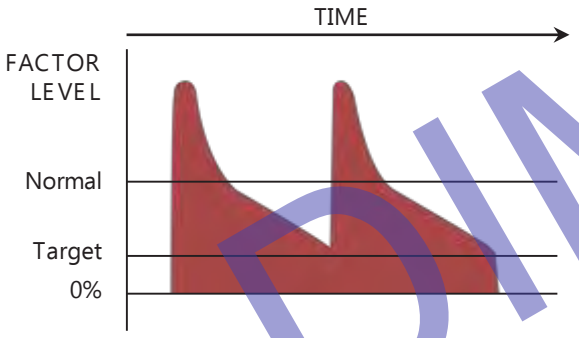

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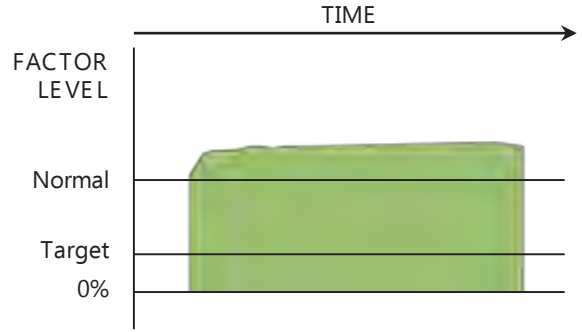

Gene therapy

A single administration holds the potential to sustain above-target factor levels for months or years at a time.

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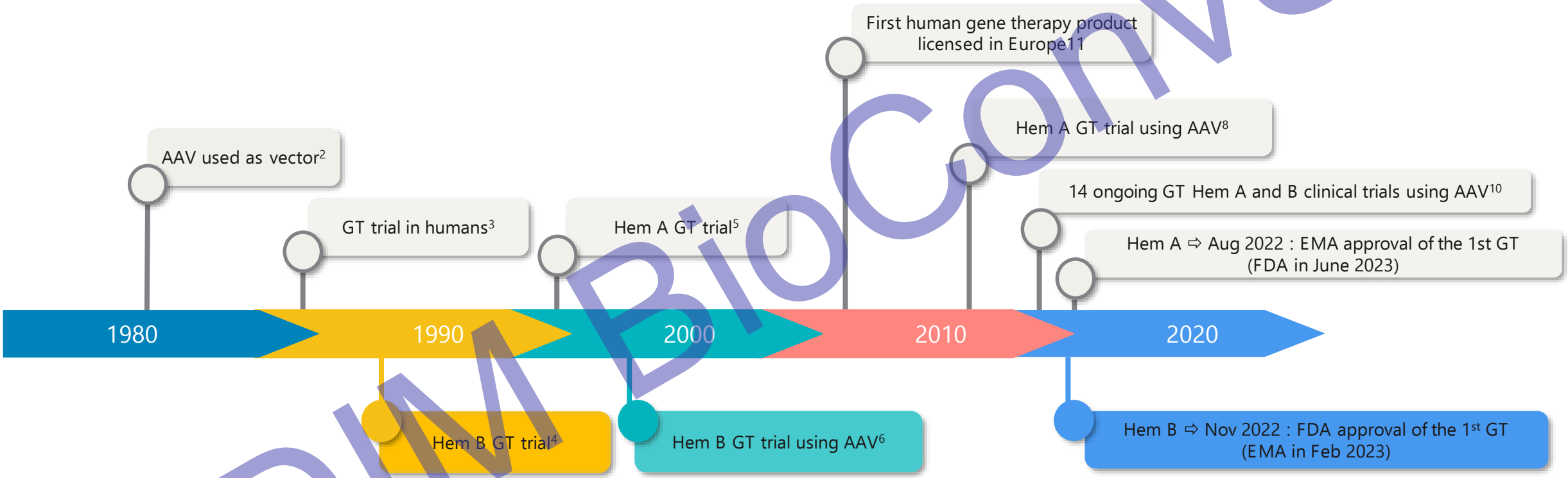
Arruda, 2017.

Haemophilia

AAV-based gene transfer therapy was investigated as a novel treatment option



AAV : adeno-associated virus.

1. ASH 2022. Available here. 2. Tratschin,1984. 3. Rosenberg, 1990. 4. Lu, 1993. 5. Roth,. 2001. 6. Manno, 2003. 7. Simioni 2009. 8. Rangarajan, 2017. *9. George,* 2017. 10. ClinicalTrials.gov search results. Accessed May 2021. 11. Keeler, 2017.

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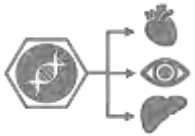
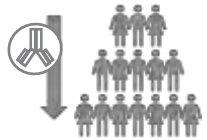
AAV-based gene transfer therapy

Why with an AAV vector ?

What is an ideal gene therapy vector ?



Delivers therapeutic gene to the appropriate organ[2]



Favourable immunologic profile to enable treatment of the largest possible population[3]

Minimal off-target effects[2]

Allows one-time administration with durable effect[1,2]

Characteristics of different vectors used in GT[4].

	AAV	Adenoviral	Lentiviral	Retroviral
Host genome integration	**Non integrating**	Non integrating	Integrating	Integrating
Viral genome	**DNA**	DNA	RNA	RNA
Gene packaging capacity	**~5 kb**	~8–30 kb	~8 kb	~8 kb
Immune response to vector	**Low**	Extensive	Low	Low
Long-term expression	**Yes**	No	Yes	Yes

1. High 2019. 2. Kay , 2001. 3. Wec 2021. 4. Anguela, 2019.

AAV-based gene transfer therapy

What is WT AAV ?

AAV vectors are derived from wild-type (WT) AAV

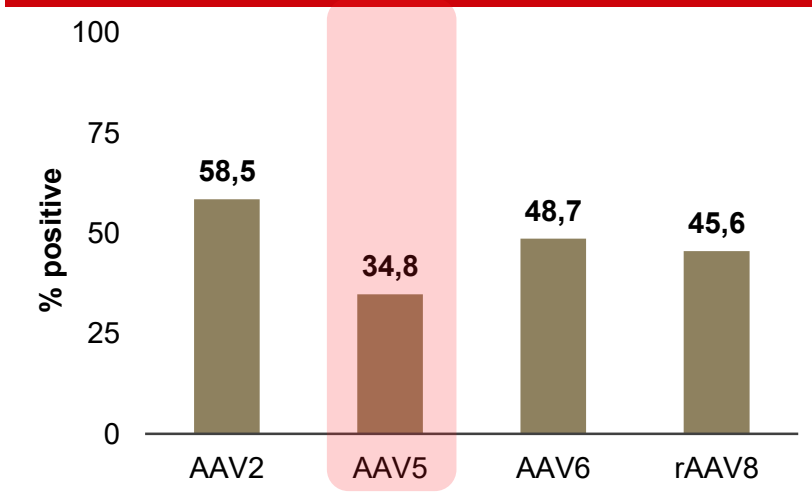
What is WT AAV?

- WT AAV is a naturally occurring, **non-pathogenic**, replication-deficient member of the parvovirus family[1]
- WT AAV **cannot replicate** without a helper virus such as an adenovirus or herpes simplex virus[2]
- Most individuals experience asymptomatic exposure to WT AAV during childhood and develop **AAV antibodies[2]**

Seroprevalence of AAV Neutralizing antibodies (NAbs).

- The seroprevalence of AAV NAbs varies by age, geographic location, and serotype[3].
- **AAV5 has a lower prevalence of preexisting immunity (NAbs)** compared with other serotypes[3].

Global seropositivity for all serotypes[3]

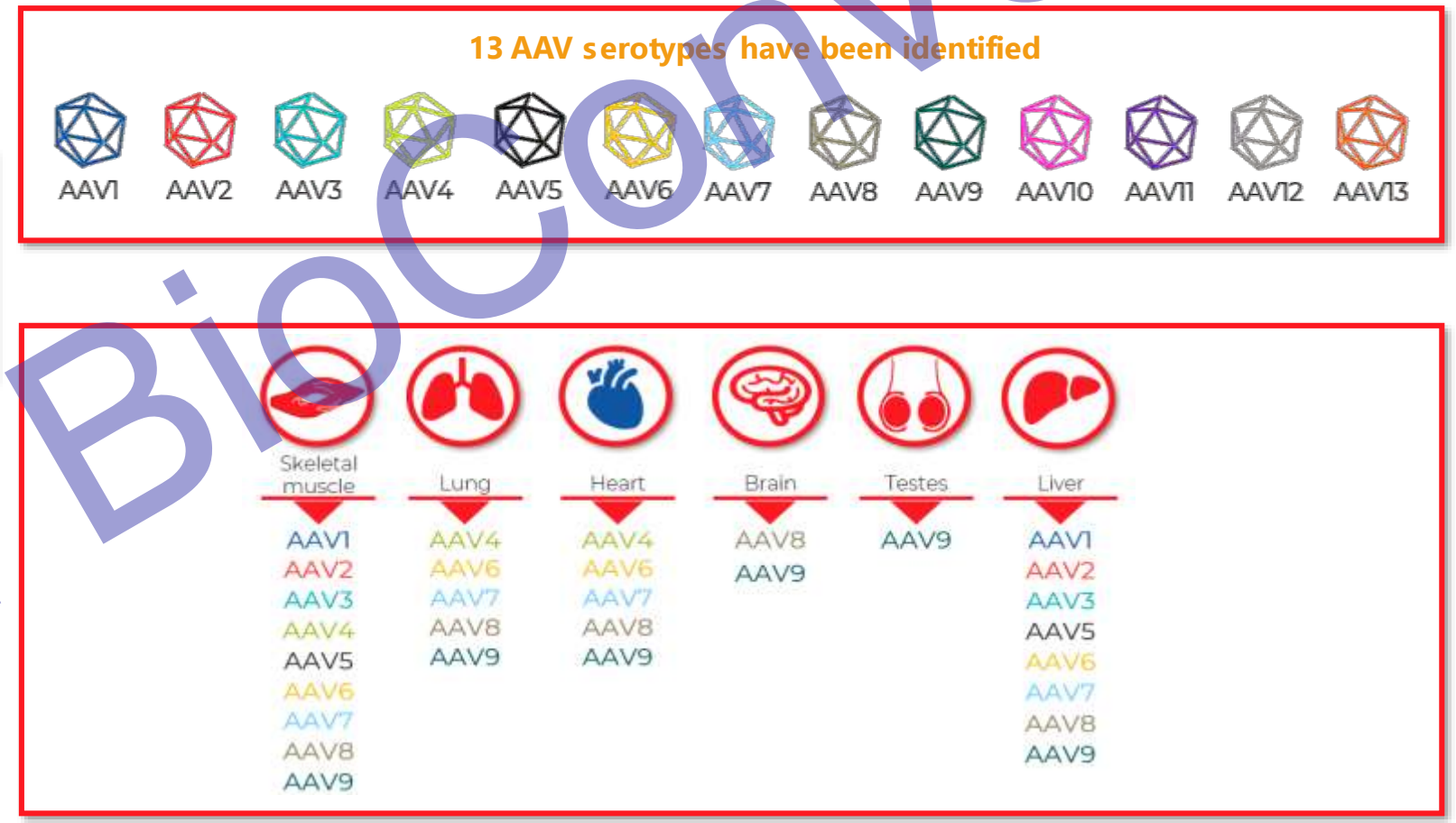


1. Arruda, 2020, 2. Nidetz, 2020. 3. Klamroth, 2022..

AAV-based gene transfer therapy

Different properties of the AAV according to the serotype

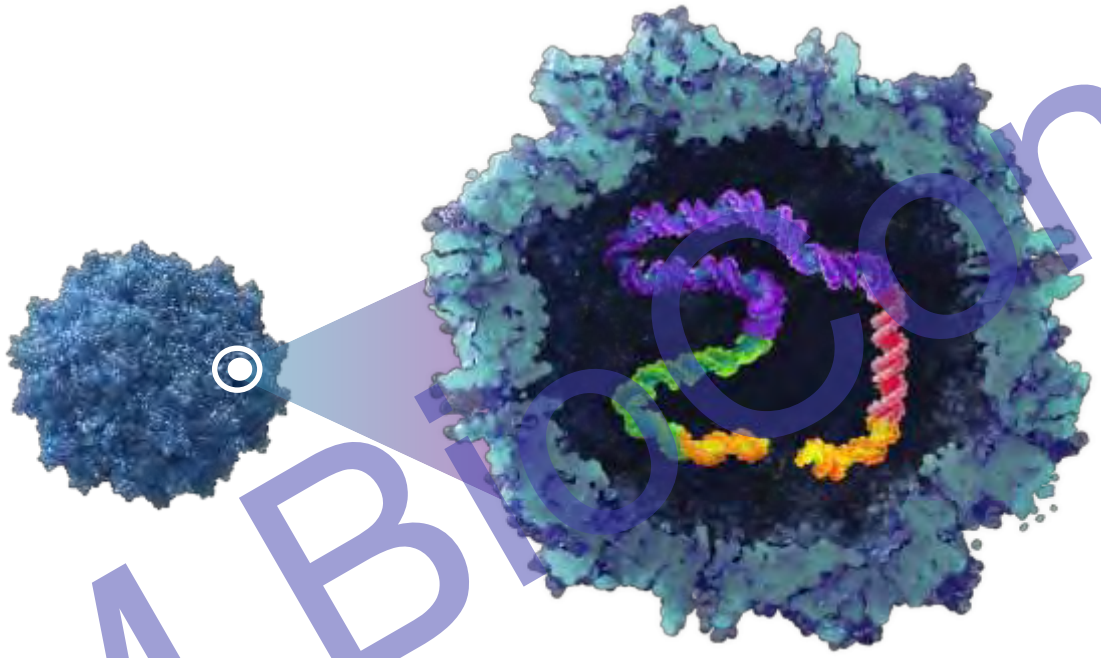
- AAV serotypes differ in terms of their capsid properties including surface antigen expression.
- This means they have **different immunologic properties** and **tropism** for different organs and tissues[1]



1. Pipe, 2019.

AAV-based GT in haemophilia B

Etranacogene dezaparvovec – Hemgenix®



rAAV5 capsid

Transgene.
Padua human variant of *F9*

Padua variant = gain-of-function mutation leading to an 6-8–fold increase in FIX protein activity over WT FIX[3].

Promoter.
LP-1 which is **liver-specific**[2].

Why serotype 5 ?

- Especially **effective in targeting liver tissue**[1]
- **Lower AAV5-NAbs prevalence**[4].
- **Lower titre of AAV5-Nabs** compared to AAV2, AAV6, AAV8, AAVrh10[4].
- Significantly **lower avidity of AAV5-specific IgG antibodies than for AAV2 and AAV8**[5].

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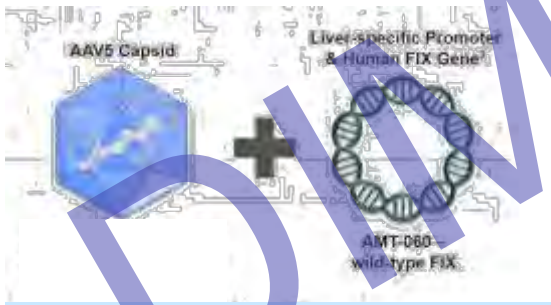
1. Vance, 2015. 2,Von Drygalski, 2019. 3. Pipe, 2023. 4. Klamroth 2022. 5. Majowicz, oral presentation, ISTH 2021.

Etranacogene dezaparvovec - Hemgenix®

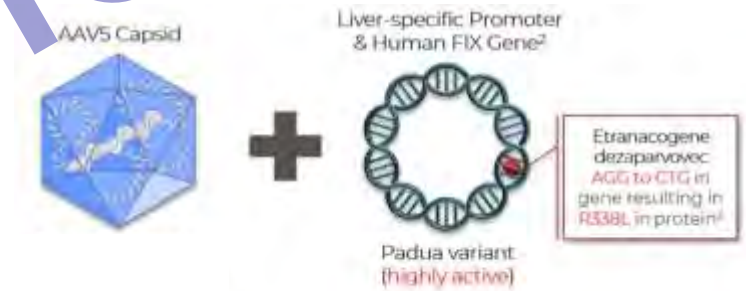
Clinical development programme in severe/moderately severe haemophilia B

Etranacogene dezaparvovec/ Hemgenix®

AMT-060 Phase 1/2[1] (2015 – 2021)	AMT-061 Phase 2b[2] (2018 - 2024)	AMT-061 Phase 3[3] HOPE B (2018 – 2025)
Cohort 1 (n=5) 5.10^{12} gc/kg	Cohort (n=3) **2.10^{13} gc/kg**	Cohort (n=54) **2.10^{13} gc/kg**
Cohort 2 (n=5) **2.10^{13} gc/kg**		



Patients with pre-existing AAV5 NAbs were **not included**.



Patients with pre-existing AAV5 NAbs were **included.**

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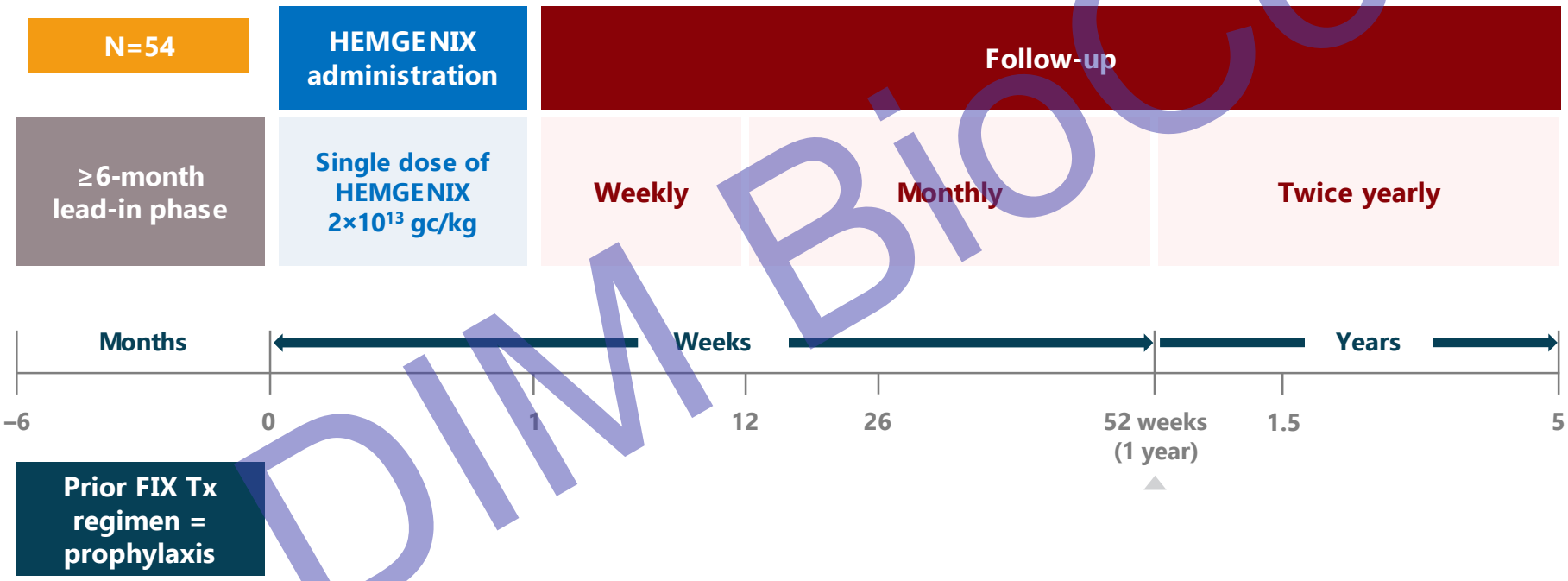
1. Miesbach, 2018. 2. Von Dryglaski, 2019. 3. Pipe, 2023.

Etranacogene dezaparvovec - Hemgenix®

An approval based on the results of the phase 3 Hope-B trial

Health Outcomes with Padua gene : Evaluation in haemophilia B (HOPE-B).

- Phase 3, open-label, single-dose, multicentre, multinational study.
- To determine efficacy and safety of HEMGENIX in patients with severe or moderately severe haemophilia B



Primary endpoint.

Annualized bleeding rate (ABR) measured from Week 26 to Week 78 after infusion compared to lead-in

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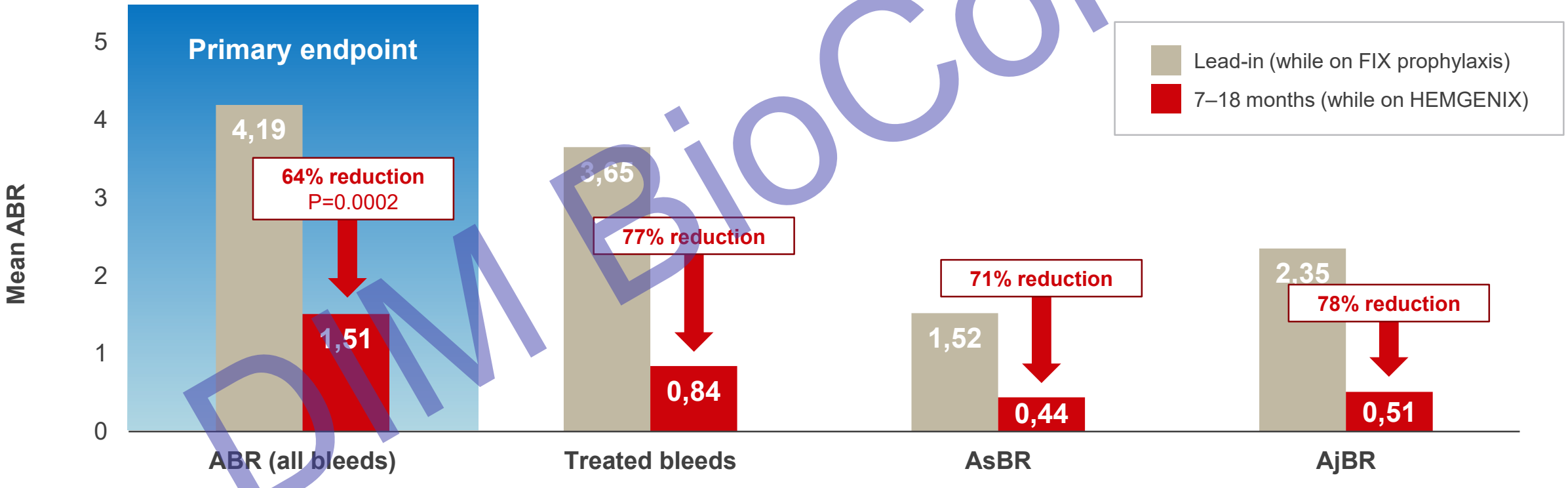
Pipe, 2023.

HOPE B trial

Superior and sustained bleed protection with Hemgenix *vs* routine FIX prophylaxis

- Hemgenix **achieved primary endpoint of reduced ABR (64%, P=0.0002) versus routine FIX prophylaxis** during the lead-in period.
- This was sustained at 24 months.



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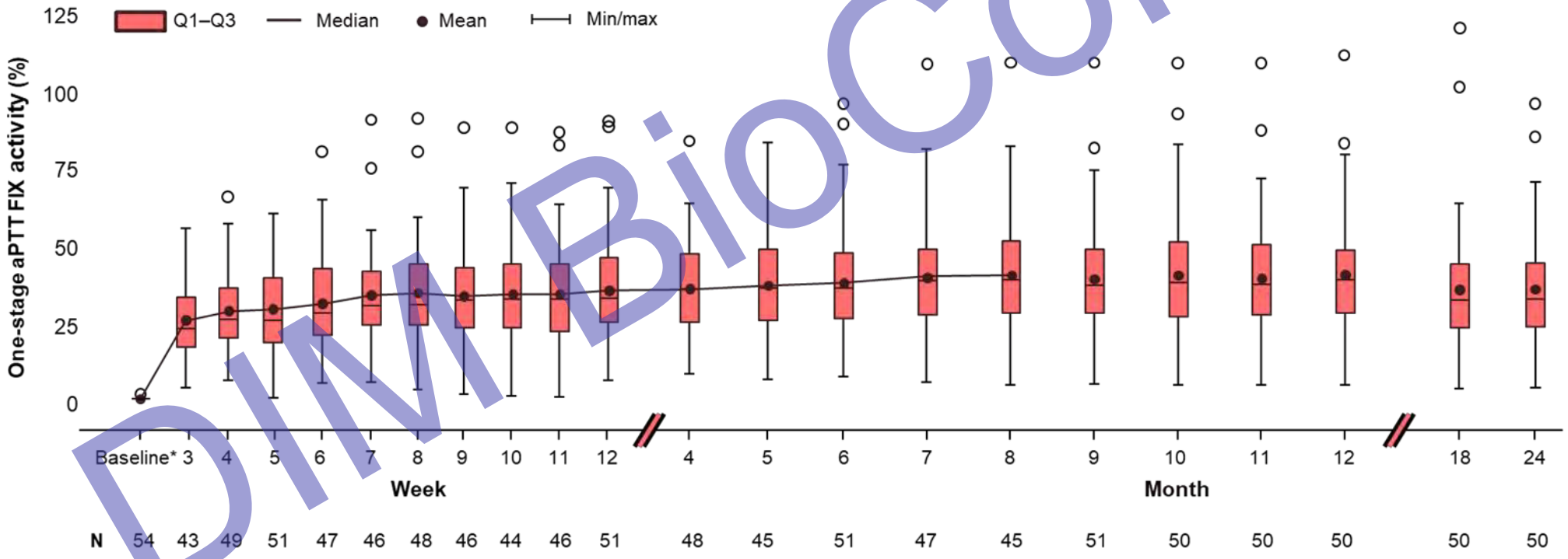
Pipe, 2023.
Pipe, Poster 2141, ASH congress, 2022

HOPE B trial

Treated patients had elevated and sustained FIX activity

After HEMGENIX, mean FIX activity levels were :

- **At Month 18 : 36.9 IU/dL** (SD ± 21.4; range, 4.5–122.9).
- **At Month 24 : 36.7 IU/dL** (SD ± 19.0, range 4.7–99.2).



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Pipe, 2023.
Pipe, Poster 2141, ASH congress, 2022

HOPE B trial

A proven safe treatment with no reported treatment-related serious adverse events

Most frequent TRAEs	n (%) N=54
ALT increased	9 (17)
Headache	8 (15)
Influenza-like illness	7 (13)
Infusion-related reactions	7 (13)
AST increased	5 (9)
Fatigue	4 (7)
Blood CPK increased	4 (7)
Nausea	4 (7)
Dizziness	4 (7)
Arthralgia	3 (6)

AEs

Mild: 78%

Moderate: 19%

Severe: 3%

Transaminase increases

- Observed in 9 patients
- All patients were treated with corticosteroids (mean duration 80 days)

FIX expression was maintained

- 1 death reported, unrelated to study treatment
- 1 case of hepatocellular carcinoma reported, unrelated to study treatment

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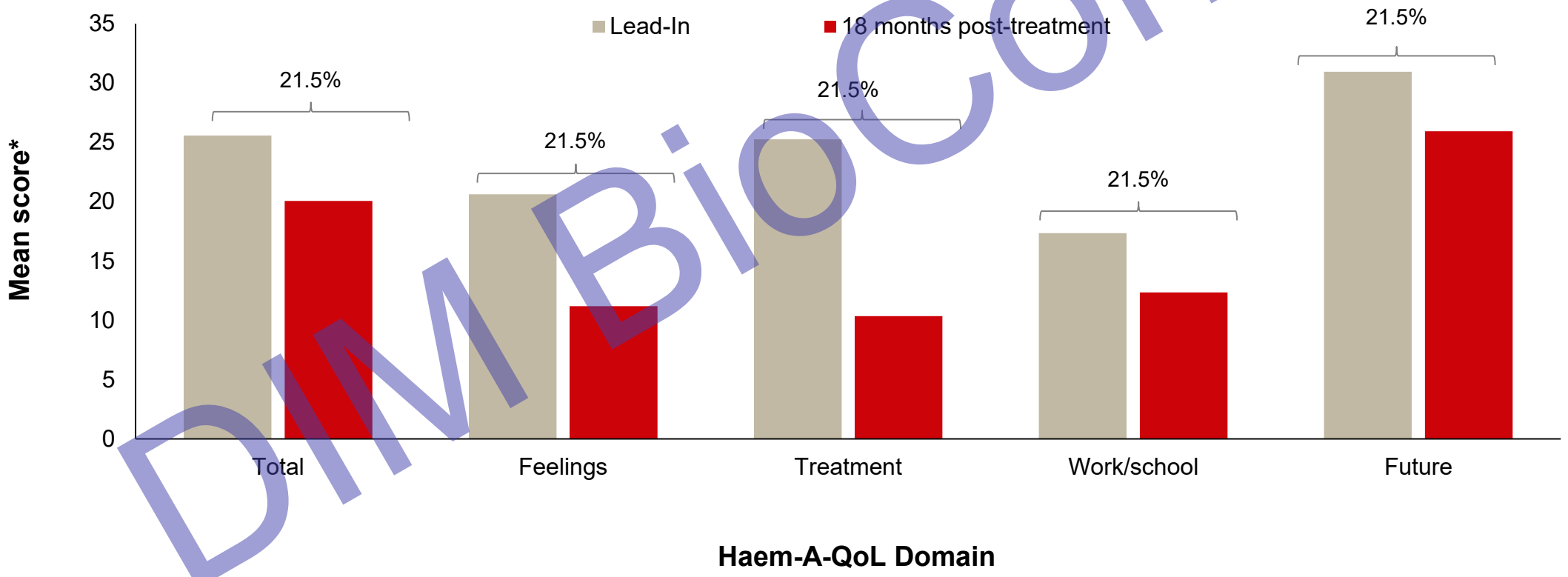
Pipe, 2023.
Miesbach, oral presentation, EAHAD 2022

HOPE B trial

Improvement in quality of life

- Patients experienced a statistically significant improvement in overall quality of life and in the domains of feelings, treatment, work/school and future.



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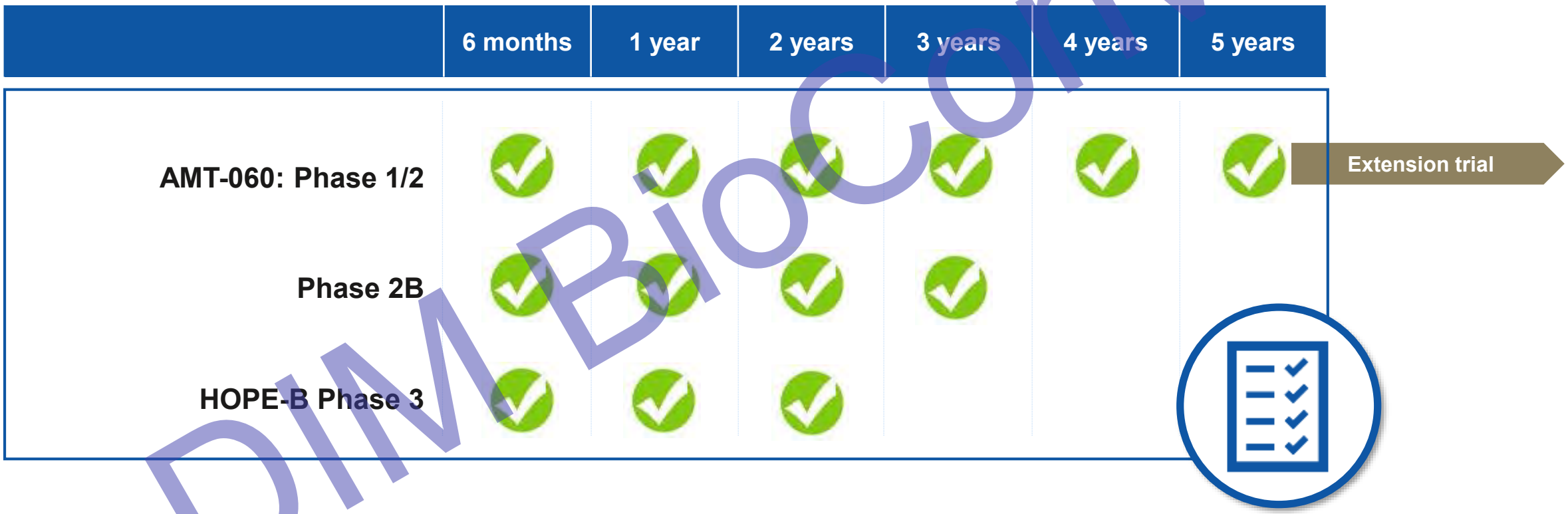
Pipe, 2023.

Hemgenix clinical development

Where do we stand now ?



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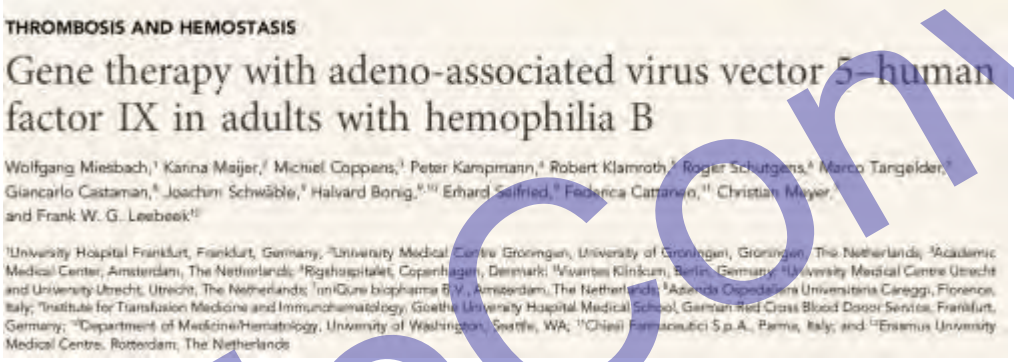
Hemgenix clinical development

Published articles

Phase 1/2.

- **Blood - March 1st, 2018.**



THROMBOSIS AND HEMOSTASIS

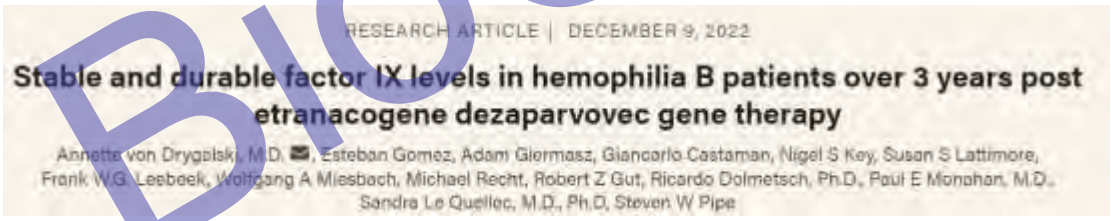
Gene therapy with adeno-associated virus vector 5–human factor IX in adults with hemophilia B

Wolfgang Miesbach,[1] Karina Meijer,[2] Michiel Coppens,[3] Peter Kampmann,[4] Robert Klamroth,[5] Roger Schutgens,[6] Marco Tangelder,[7] Giancarlo Castaman,[8] Joachim Schwäble,[9] Halvard Bonig,[9,10] Erhard Seifried,[9] Federica Cattaneo,[11] Christian Mayer,[11] and Frank W. G. Leebeek[12]

[1]University Hospital Frankfurt, Frankfurt, Germany; [2]University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands; [3]Academic Medical Center, Amsterdam, The Netherlands; [4]Rigshospitalet, Copenhagen, Denmark; [5]Vivantes Klinikum, Berlin, Germany; [6]University Medical Centre Utrecht and University Utrecht, Utrecht, The Netherlands; [7]uniQure biopharma B.V., Amsterdam, The Netherlands; [8]Azienda Ospedaliera Universitaria Careggi, Florence, Italy; [9]Institute for Transfusion Medicine and Immunohematology, Goethe University Hospital Medical School, German Red Cross Blood Donor Service, Frankfurt, Germany; [10]Department of Medicine/Hematology, University of Washington, Seattle, WA; [11]Chiesi Farmaceutici S.p.A., Parma, Italy; and [12]Erasmus University Medical Centre, Rotterdam, The Netherlands

Phase 2b.

- **Blood advances – December 9, 2022.**



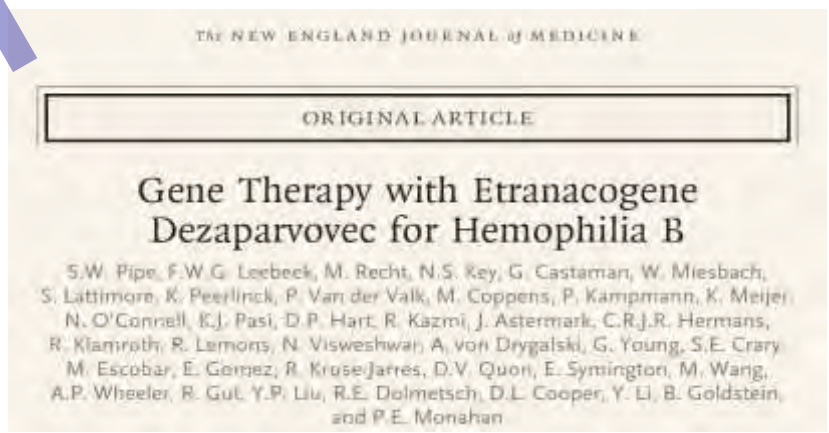
RESEARCH ARTICLE | DECEMBER 9, 2022

Stable and durable factor IX levels in hemophilia B patients over 3 years post etranacogene dezaparvovec gene therapy

Annette von Drygalski, M.D. ✉, Esteban Gomez, Adam Giermasz, Giancarlo Castaman, Nigel S Key, Susan S Lattimore, Frank W.G. Leebeek, Wolfgang A Miesbach, Michael Recht, Robert Z Gut, Ricardo Dolmetsch, Ph.D., Paul E Monahan, M.D., Sandra Le Quellec, M.D., Ph.D, Steven W Pipe

Phase 3.

- **The New England Journal of Medicine – February, 2023.**



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

Interim results are communicated at congresses.

Hemgenix : From the bench to the bedside (Europe/France)

Research	Pre-clinical trials	Clinical trials	Marketing authorization	Pricing and reimbursement	Industrial production	Availability

UniQure
Internal research and development of etranacogene dezaparvovec

- A **company specialized in gene therapy**.
- Owner of an **innovative AAV-based platform** and of a **commercial-scale manufacturing process** compliant with current good manufacturing practices (**GMP**).
- Other research programs : Huntington disease, temporal lobe epilepsy, amyotrophic lateral sclerosis, Fabry disease, Alzheimer's disease, Parkinson's disease.
- **Collaboration** with international **pharmaceutical leaders**, **innovative early-stage companies** as well as **academic institutions** and **other research organizations**.

Driven by Our Promise

https://www.uniqure.com/

CSL Behring

Hemgenix : From the bench to the bedside (Europe/France)

Research	Pre-clinical trials	Clinical trials	Marketing authorization	Pricing and reimbursement	Industrial production	Availability

UniQure
Internal research and development of etranacogene dezaparvovec

In 2021
A **licensing transaction** gives CSL Behring exclusive worldwide commercialization rights of etranacogene dezaparvovec.

UniQure
Responsible for the global commercial supply and manufactures the product at its GMP facility in Lexington (US).

CSL Behring
Solely responsible for the further development, registration, and commercialization of the therapy.

Driven by Our Promise

https://www.uniqure.com/programs-pipeline/hemophilia
https://uniqure.gcs-web.com/news-releases/news-release-details/uniqure-announces-fda-approval-first-gene-therapy-adults

CSL Behring

Hemgenix : From the bench to the bedside (Europe/France)

Research	Pre-clinical trials	Clinical trials	Marketing authorization	Pricing and reimbursement	Industrial production	Availability
UniQure					UniQure	
		CSL Behring				
			FDA : Nov. 2022			
			EMA : Feb. 2023	Submission of the Marketing Authorization to the High Health Autority Transparency Commission, which gives its opinion on the: - Medical service rendered (MSR) : **important** - Improved medical service rendered (IMSR) : **IV**		
				Price negociation with ECHP (Economic Committee for Health Products)		
				Reimbursement rates fixed by UNCAM.		

CSL Behring

THANK YOU FOR YOUR ATTENTION