Changing Haemophilia - for active people

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Novo Nordisk Europe North and Central

changing haemophilia™

For more than three decades, Novo Nordisk has been committed to Changing Haemophilia™. In addition to the discovery and development of effective and safe biological medicines, we work with our global partners to advocate for and create better access to diagnosis and multidisciplinary care with a focus on joint health.

We aim for a future where all people living with haemophilia can live a life with as few limitations as possible.

KEY INITIATIVES:

WORLD HEMOPHILIA DAY / APRIL 17

HERO
Haemophilia Experiences Results Opportunities

novo nordisk haemophilia foundation

TalkingJoints®
feel something, do something

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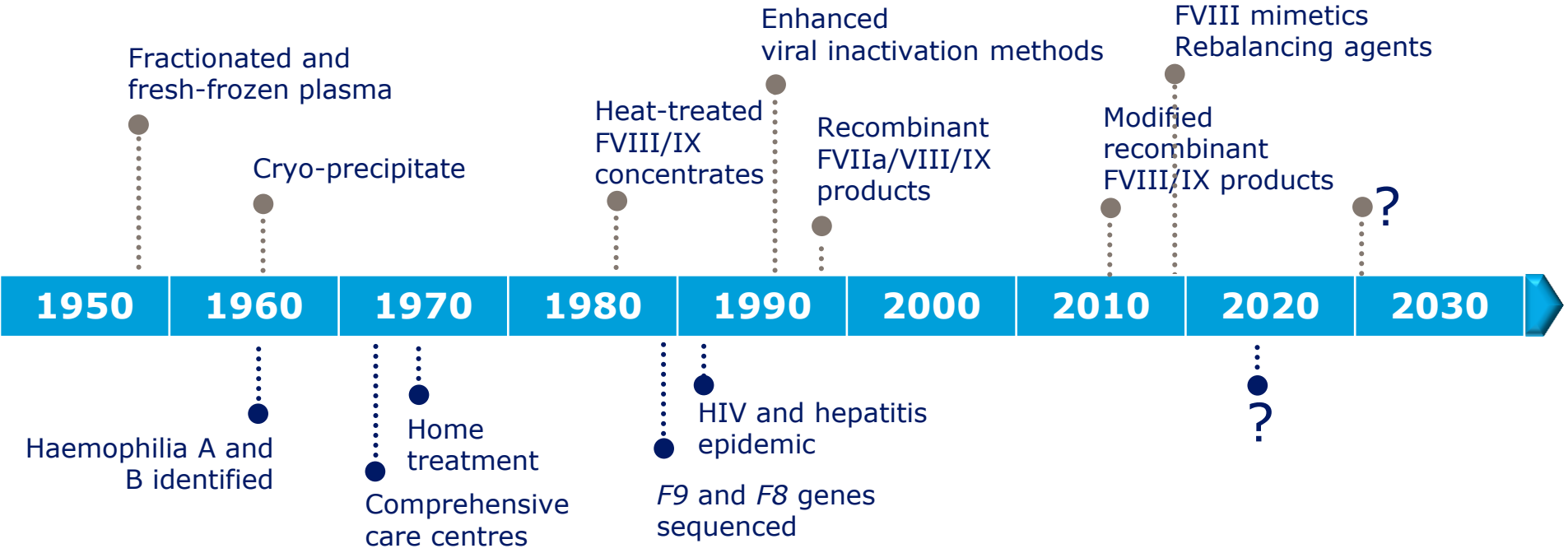
The changing landscape of haemophilia treatment



References: Kingdon HS & Lundblad RL. *Biotechnol Appl Biochem* 2002; 35:141–148
Shapiro AD *Hematology Am Soc Hematol Educ Program*. 2013;2013:37–4

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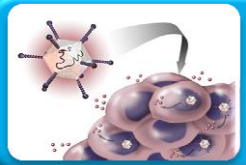
Recent innovations within treatment of genetic disorders



Gene and cell therapy

- AAV based gene therapy
- Genome editing – CAS9-Crispr

Antibody based therapies

- Conventional mAbs
- Bi-specific mAbs

New molecular formats

- RNA based therapies
- Nano-bodies

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The haemophilia treatment paradigm outlines unmet patient needs and directs new innovations

Improve treatment outcomes

- Induce fast bleed control and minimise pain
- Eliminate bleeding
- Improve joint health
- Improve quality of life

Reduce the burden of treatment

- Simplify treatment
- Reduce dosing frequency
- Pursue less invasive administration
- Reduce risk of immunogenicity
- Provide increased portability

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Novo Nordisk has been changing lives for 95 years…

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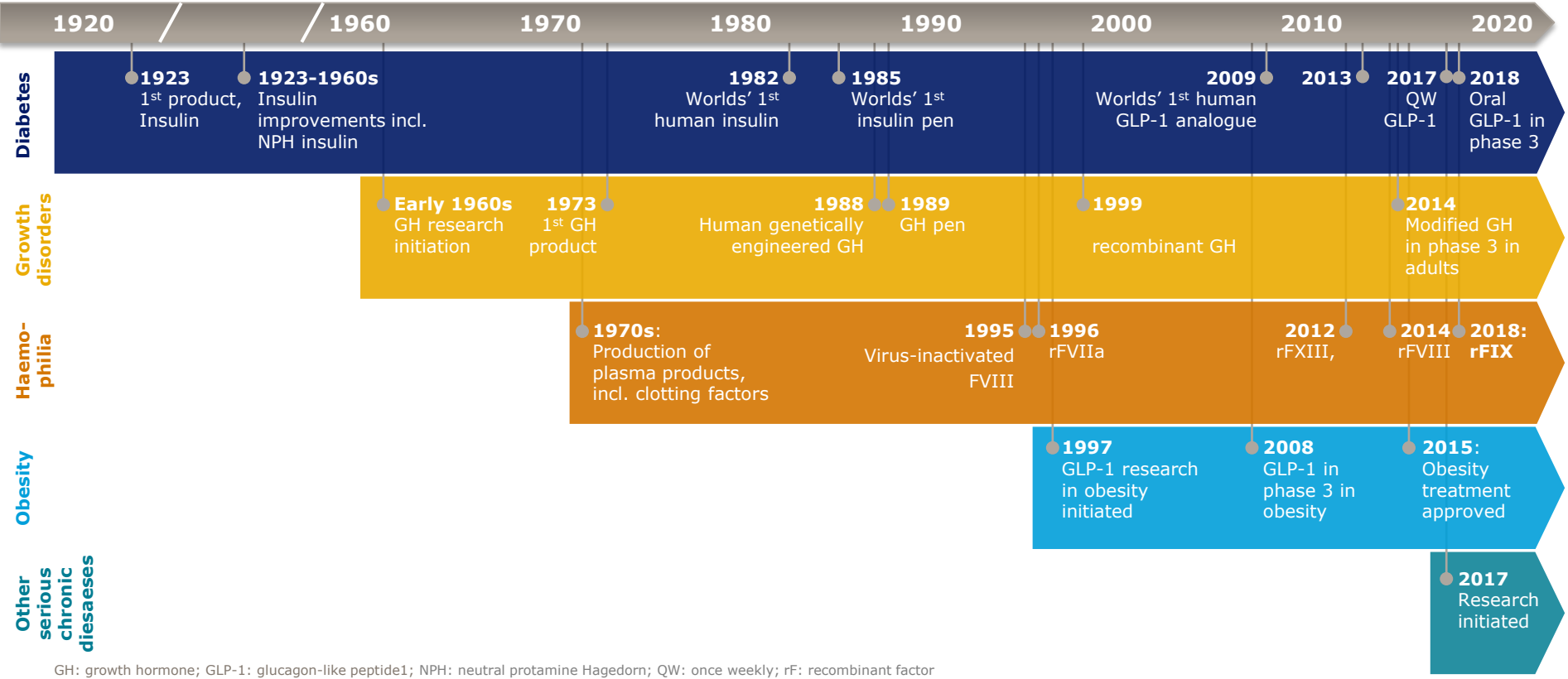
… by developing new innovative treatments for people living with serious chronic diseases



GH: growth hormone; GLP-1: glucagon-like peptide1; NPH: neutral protamine Hagedorn; QW: once weekly; rF: recombinant factor

Novo Nordisk at a glance

Novo Nordisk is a global healthcare company with more than 90 years of innovation and leadership in diabetes care.

This heritage has given us experience and capabilities that also enable us to help people defeat other serious chronic diseases: haemophilia, growth disorders and obesity.

PRODUCTS MARKETED IN
165 COUNTRIES

AFFILIATES IN 77 COUNTRIES

R&D CENTRES
IN CHINA, DENMARK, UK AND US

EMPLOYS APPROXIMATELY
41,400 PEOPLE

DKK 111.8 BILLION
IN TOTAL REVENUE

STRATEGIC PRODUCTION SITES
IN BRAZIL, CHINA, DENMARK, FRANCE AND US

APPROXIMATELY
210,000
SHAREHOLDERS

SUPPLIER OF NEARLY
HALF OF THE WORLD'S INSULIN

28,000,000
PEOPLE USE OUR PRODUCTS

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9 R&D CENTRES

4 in Denmark; 2 in US; 1 in UK, China & India

R&D AMBITION

Innovate to improve patient outcomes and drive growth

2017 R&D spend

~1.8 BILLION EUR

R&D employs approximately

>5,600 PEOPLE

in

6 R&D areas

5 STRATEGIC PRIORITIES

- Diabetes
- Obesity
- Haemophilia
- Growth disorders
- Other serious chronic diseases

Novo Nordisk R&D at a glance

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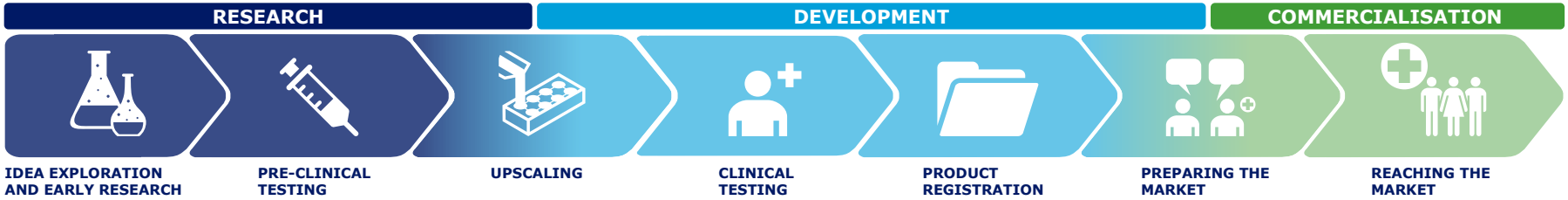
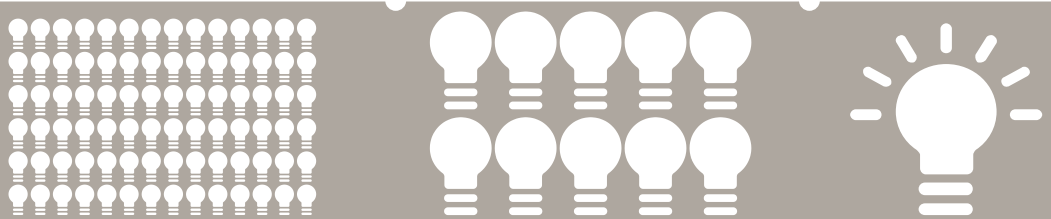
Taking a new medicine from idea to patient is a long and costly process



Generally in the pharmaceutical industry:

OUT OF **10,000** IDEAS **10** WILL BE TESTED IN HUMANS **1** MAY REACH MARKET



- In general it takes 10-15 years to reach the market[1]
- The average estimated development cost of an approved medicine is USD 2.6 billion[1]

Reference: 1. Tufts Center for the Study of Drug Development, Nov. 18, 2014

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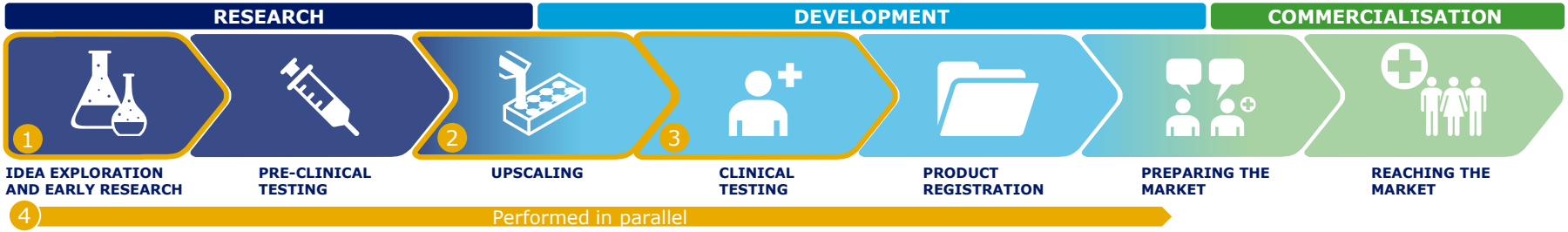
In Novo Nordisk, we have the ability to perform the entire R&D value chain in-house…



…and historically, R&D has leveraged four core competencies

1 **Rational design & biological insight**

2 **Expression & formulation**

3 **Clinical trial execution**

4 **Device innovation**

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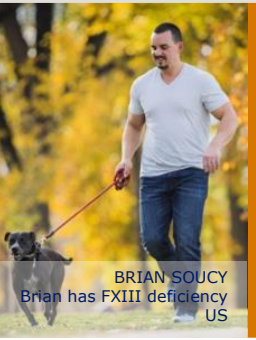
Haemophilia



Haemophilia at a glance

- Around 450,000 people worldwide live with haemophilia A or B[1,2]
- Only 25% are being treated*
- Around 3,250 have clinically identified inhibitors[3]

Haemophilia is an inherited or acquired bleeding disorder that prevents blood from clotting due to:

- Haemophilia A: clotting factor VIII deficiency
- Haemophilia B: clotting factor IX deficiency

Without treatment, uncontrolled internal bleeding can cause stiffness, pain, severe joint damage and even death.

R&D priorities are based on unmet needs

Unmet need	R&D priority
Treatment convenience	• Long-acting, subcutaneously injectable therapies
Treatments for inhibitor patients	• Bypassing agents for prophylaxis

Ambition **We will improve patient outcomes and broaden our presence in haemophilia**

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[1]Stonebraker JS et al, Haemophilia 2010; 16(1):20-32; [2]Stonebraker JS et al, Haemophilia 2012; 18(3):e91-e94; [3]WFH Annual Global Survey 2015 (published November 2016 on the WFH website);
*The treated patients are calculated based on 25% estimate of treatment access, WFH website estimate 2016, http://www.wfh.org/en/page.aspx?pid=642

Changing Haemophilia™ is Novo Nordisk's commitment to address the unmet needs in haemophilia care

Raising awareness and access to care

Joint outcomes

Science

novo nordisk®

Changing Haemophilia™ is Novo Nordisk's commitment to address the unmet needs in haemophilia care

GOING BEYOND MEDICINE

Raising awareness and access to care

We want to help **raise awareness and increase support for haemophilia** where it is needed the most.

With the **vision that all people with haemophilia have access to care and treatment wherever they live,** the Novo NNHF represents a cornerstone of our commitment to change haemophilia.

NNHF | HERO study | Advocacy | Partnerships

Joint outcomes

We want to **reduce the limitations** for people living with haemophilia.

Through our **TalkingJoints®**, HERO research grants and other initiatives, we want to **support a better understanding of joint health and care**.

HERO grants | Joint function

PROVIDING TREATMENT

Science

We are committed to **invest in the discovery and development of advanced, safe, and innovative biological treatments** for people living with haemophilia and rare bleeding disorders.

Science | Product portfolio

GHN, Global Haemophilia Network; HCP, healthcare professional; NNHF, Novo Nordisk Haemophilia Foundation.

Learn more at **novonordisk.com/changinghaemophilia**

HERO
Haemophilia Experiences Results Opportunities

HERO study

Raise awareness and access to care

- **HERO** study has provided evidence of the **psychosocial challenges** affecting people living with haemophilia
- Largest ever psychosocial study

1,386
participants

11
countries


LIAM CLEMENS
Liam has haemophilia A and lives in the US

novo nordisk haemophilia foundation

Novo Nordisk Haemophilia Foundation

Raise awareness and access to care

- **Non-profit organisation** founded in 2005
- Dedicated to defining and funding sustainable programmes which **improve access to quality care** in developing and emerging countries
- Partnering with local community members and renowned experts within three focus areas: **capacity building**, **diagnosis and registry** and **education and empowerment**

NNHF achievements as of December 2017[1]:

36,000 HCPs trained

22,750 Patients re-tested or newly diagnosed

38,150 Patients and family members educated

230 programmes

[1]Novo Nordisk Haemophilia Foundation activity report, 2017.
HCP, healthcare professional; NNFH, Novo Nordisk Haemophilia Foundation.

Find out more at nnhf.org

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The Global Haemophilia Network

Raise awareness and access to care

- GHN is a worldwide **peer support network** for HCPs and nurses that aims to improve the quality and efficiency of Novo Nordisk haemophilia-related clinical trials

GHN activities:

Global meeting held every 18–24 months

Face to face study nurse and investigator **training** sessions

Provide information and **educational material** for clinical trial staff, carers, patients and their families

Facilitate the GHN Portal, a validated online tool for **document exchange**, knowledge sharing, e-learning and electronic investigator trial file

GHN, Global Haemophilia Network; HCP, healthcare professional.

Find out more at: https://globalhaemophilianetwork.com

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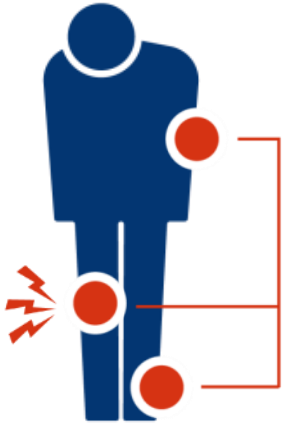
TalkingJoints®

Joint outcomes

- We work to raise awareness of the impact haemophilia has on **joint function**
- Through our Joint Function programmes, such as **TalkingJoints®**, we work to **empower patients and HCPs** to detect damages to joints early

Improving joint health and mobility is essential to reduce the limitations for people living with haemophilia



Bleeding into the joints (**haemarthrosis**) and subsequent joint damage (**arthropathy**) **are the most common complications seen in haemophilia**[1,2]

By adulthood,

23.5%

of all people with severe haemophilia will have developed one or more **'target joints'** that carry an increased risk of recurrent bleeds and are functionally impaired[3]

The knees, elbows and ankles account for

80%

of all **joint bleeds**[4]

Despite advances in treatment and care, **joint bleeding and arthropathy remain among the most common complications** of haemophilia and are **major concerns** of both healthcare professionals and people with haemophilia[2]

References: 1. Mulder K and Llinas A. *Haemophilia* 2004; 10(4):152-6.**2**. Valentino LA. *J Thromb Heamost* 2010; 8(9):1895-902. **3.** Summary Report of UDC Activity National. Treatment Clinical Characteristics (Hemophilia), accessed 30 March 2015: https://www2a.cdc.gov/ncbddd/htcweb/UDC_Report/UDC_Report.asp **4.** Rodriguez-Merchan EC. *Haemophilia* 2012; 18(1): 8–16.

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The Haemophilia Experiences, Results and Opportunities (HERO) initiative

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Most PWH experience pain that impacts on their daily lives

Impact of pain on daily lives	PWH (n=675)

PAIN	PWH experiencing pain that interfered with daily life[1]	89%
CHRONIC PAIN	PWH experiencing chronic pain[2]	43%

References: 1. Garrido et al. Haemophilia (2012); 18 (Suppl. 3), p177 - *Poster PO-TU-218* Presented at the XXX International Congress of the World Federation of Haemophilia; **2.** Forsyth A et al. Haemophilia 2014;20(1):44–51

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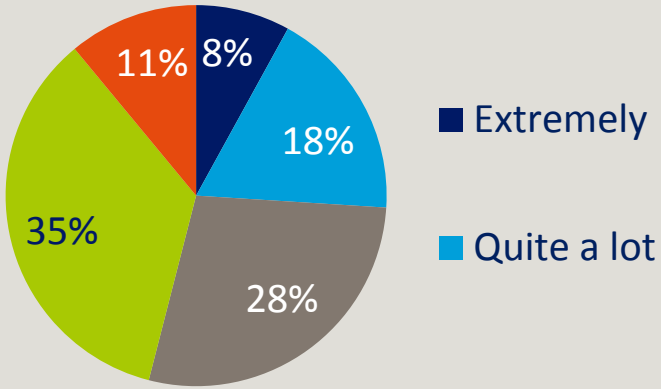
Most PWH experience pain that impacts on their daily lives

Impact of pain on daily lives	PWH (n=675)



How much has pain interfered with your daily life in the past 4 weeks?

References: 1. Garrido et al. Haemophilia (2012); 18 (Suppl. 3), p177 - *Poster PO-TU-218*
Presented at the XXX International Congress of the World Federation of Haemophilia

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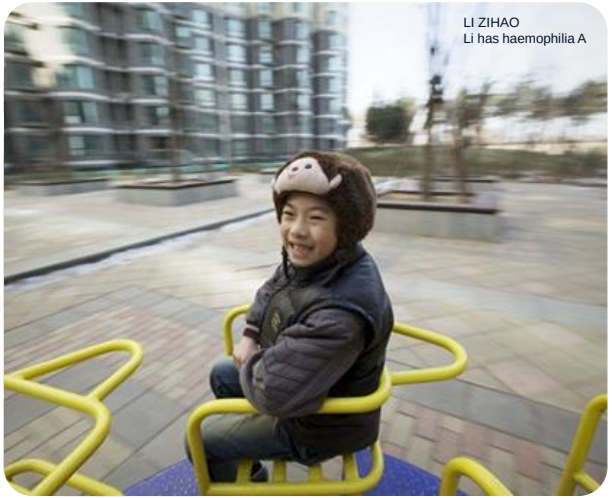
Haemophilia has a physical impact on PWH

Impact of physical conditions on PWH	PWH (n=675)



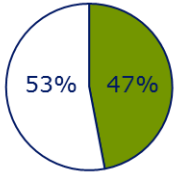
ACTIVITIES

PWH have limited mobility

59%

MOBILITY

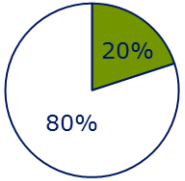
Usual activities



Some problems

No problems

Self-care



References: 1. Garrido C et al. Haemophilia 2012; 18 (Suppl. 3), p177 - *Poster PO-TU-218*
Presented at the XXX International Congress of the World Federation of Hemophilia, Paris, France, July 2012

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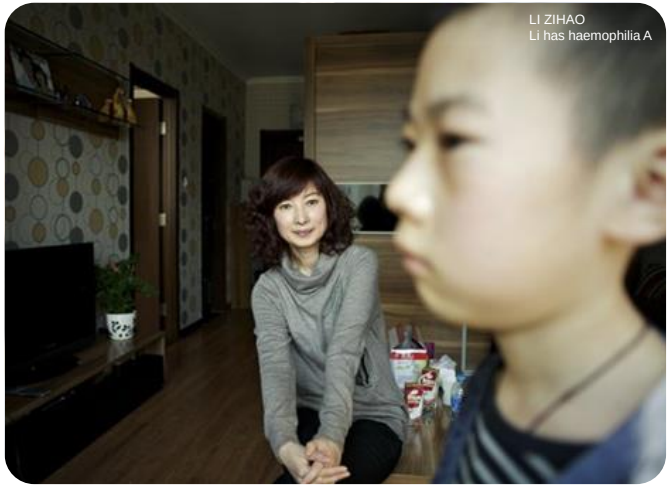
PWH report psychological/psychiatric conditions

Impact of psychological conditions on PWH	PWH (n=675)



CONDITIONS

PWH report psychological/ psychiatric conditions[1]

(stress, anxiety, depression, insomnia, fatigue)

47%

TREATMENT

PWH have received treatment for their psychological/ psychiatric conditions[2]

22%

References: 1. Forsyth A et al. Haemophilia 2014;20(1):44–51; **2.** Garrido C et al. Haemophilia 2012; 18 (Suppl. 3), p177 - *Poster PO-TU-218* Presented at the XXX International Congress of the World Federation of Hemophilia, Paris, France, July 2012

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Parents want psychological support to help them cope

Impact of psychological conditions on parents	Parents (n=561)

TREATMENT RECEIVED

Parents have received psychological support to help them cope with their son's haemophilia

24%

NTREATMENT WANTED

Parents would have liked to receive psychological support to help them cope with their son's haemophilia

33%

References: 1. Garrido C et al. Haemophilia 2012; 18 (Suppl. 3), p177 - *Poster PO-TU-218*
Presented at the XXX International Congress of the World Federation of Hemophilia, Paris, France, July 2012

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PWH are educated and working but the impact of haemophilia limits options

Haemophilia affects employment	PWH (n=626)

EDUCATION	PWH received formal education	85%
EMPLOYMENT	PWH are working*	60%
	PWH reported a negative impact of haemophilia on employment*	80%

*n=605 PWH (excludes those in full-time education)

Reference:. Forsyth A et al. Haemophilia 2014;20(1):44-51

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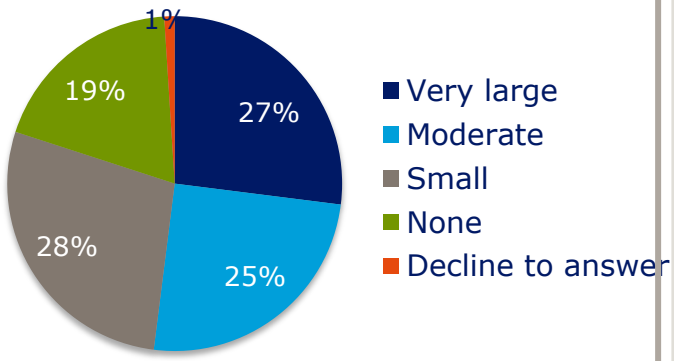
Many PWH have issues in relation to employment

To what extent has haemophilia had a negative impact on your working life?

PWH no longer in full-time education
(n=605)*



*Excludes those in full-time education

EMPLOYMENT

Selected their job/ training to take into account needs relating to haemophilia **40%**

Reported that current treatment allows them to work in most situations **30%**

Have had to voluntarily leave a job because of haemophilia **24%**

Believe that they have lost a job in the past because of their haemophilia **22%**

References: Forsyth A et al. Haemophilia 2012; 18 (Suppl. 3), p169 - *Poster PO-MO-199*
Presented at the International Congress of the World Federation of Haemophilia, Paris, France

~~limited~~ *increased*
mobility

Joint outcomes

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The importance of physical activity

- Exercise can improve not only physical well-being, but also the emotional and social well-being of people with haemophilia[1,2]
- When carried out properly, regular activity can help prevent bleeds and joint damage[3] by:
  - Helping to preserve and protect joints[4,5]
  - Improving joint stability, strength and range of motion[5,6,7]
  - Helping to maintain a healthy weight, thus reducing stress on the joints
  - Helping to get mobile again after a bleed[8]

References: 1. Negrier C, Seuser A, Forsyth A, *et al*., Haemophilia, 2013; 19(4): p. 487-98 **2.** von Mackensen S, Haemophilia, 2007; 13 Suppl 2: p. 38-43
3. Mulder K. Exercises for people with haemophilia. 2006, Montreal, Quebec, Canada: World Federation of Hemophilia.
4. Gilbert MS. Musculoskeletal complications of hemophilia: the Joint. 1997, Montreal, Quebec, Canada: World Federation of Hemophilia
5. Mulder K and Llinás A. Haemophilia 2004; 10: 152 – 156. **6.** Negrier C *et al.* Haemophilia 2013; 19(4): 487 – 986
7. Srivastava A *et al.* Haemophilia 2013; 19(1): e1– 47. **8.** Blamey G *et al.* Haemophilia 2010; 16 Suppl 5: 136 – 45.

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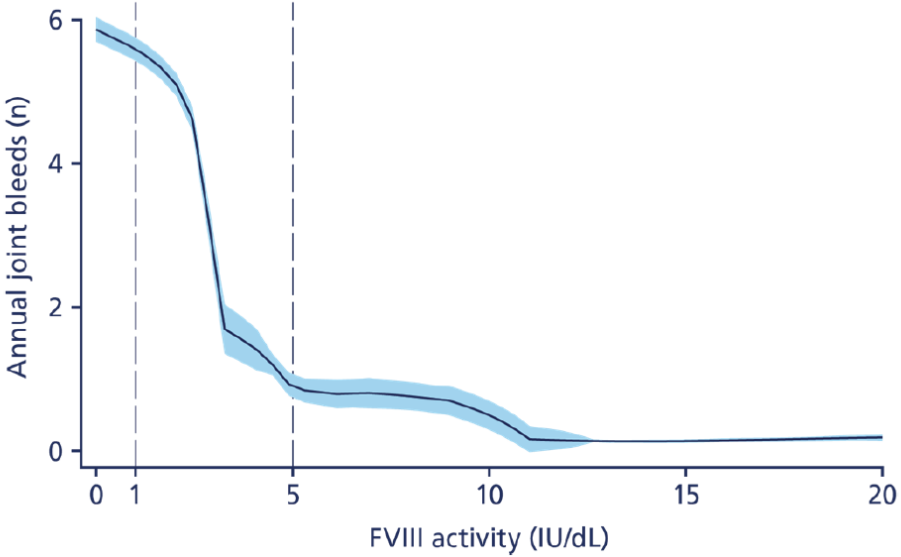
Activity levels of > 12 IU/dl are needed to avoid bleeds

Annual number of joint bleeds according to FVIII activity



Black line: median; shaded area: interquartile range

Reference: Den Uijl IE, *et al*. *Haemophilia* 2011;17:849–853.

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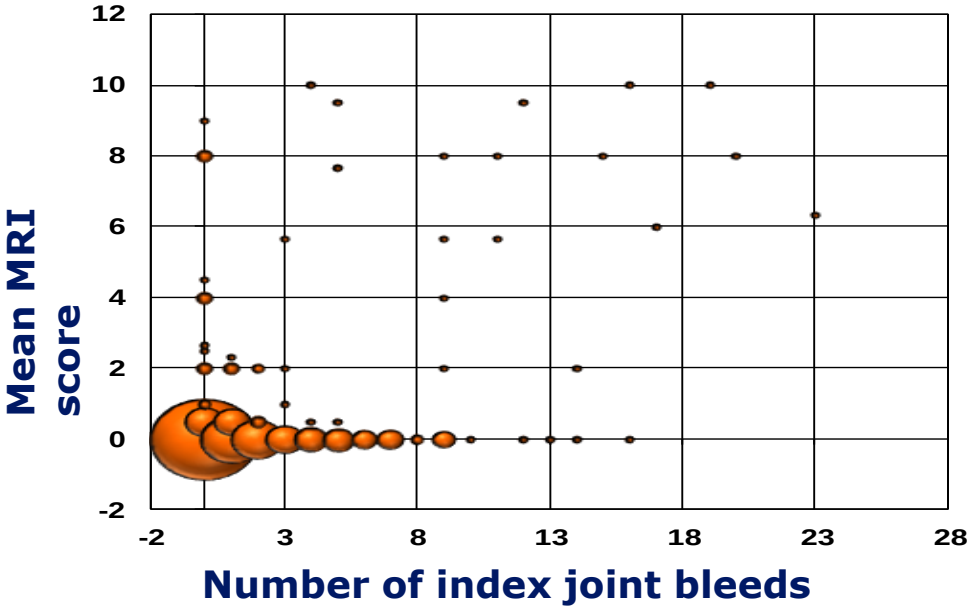
Joint damage can occur without clinical evidence of bleeds



- Some joints with no clinically evident haemorrhages had high MRI scores.
- Some joints with more than 10 haemorrhages did not show abnormal MRI outcome.
- Pathophysiology of joint damage is complex. Once joint bleeding occurs, consequences are highly variable.

Reference: Manco-Johnson MJ et al. *N Engl J Med* 2007;357:535–44.

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Haemophilia

Haemophilia (2012), 18 (Suppl. 4), 1–12 DOI: 10.1111/j.1365-2516.2012.02822.x

ORIGINAL ARTICLE

WFH: Closing the global gap – achieving optimal care

MARK W. SKINNER
World Federation of Hemophilia, Washington, DC, USA

- *"...it may be time to consider whether a 1% target is sufficient to prevent bleeding or if it is simply conveniently based on existing economics and treatment protocol burdens (frequency of dosing and venous access)*

- *Although it may seem impossible to imagine, based on currently available therapies, the paradigm may shift to a point were treatment goals could more closely mimic a normal state."*

Skinner M. *Haemophilia* 2012. 18(Suppl. 4)1-12.

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~~limited~~ *more* independence

Science

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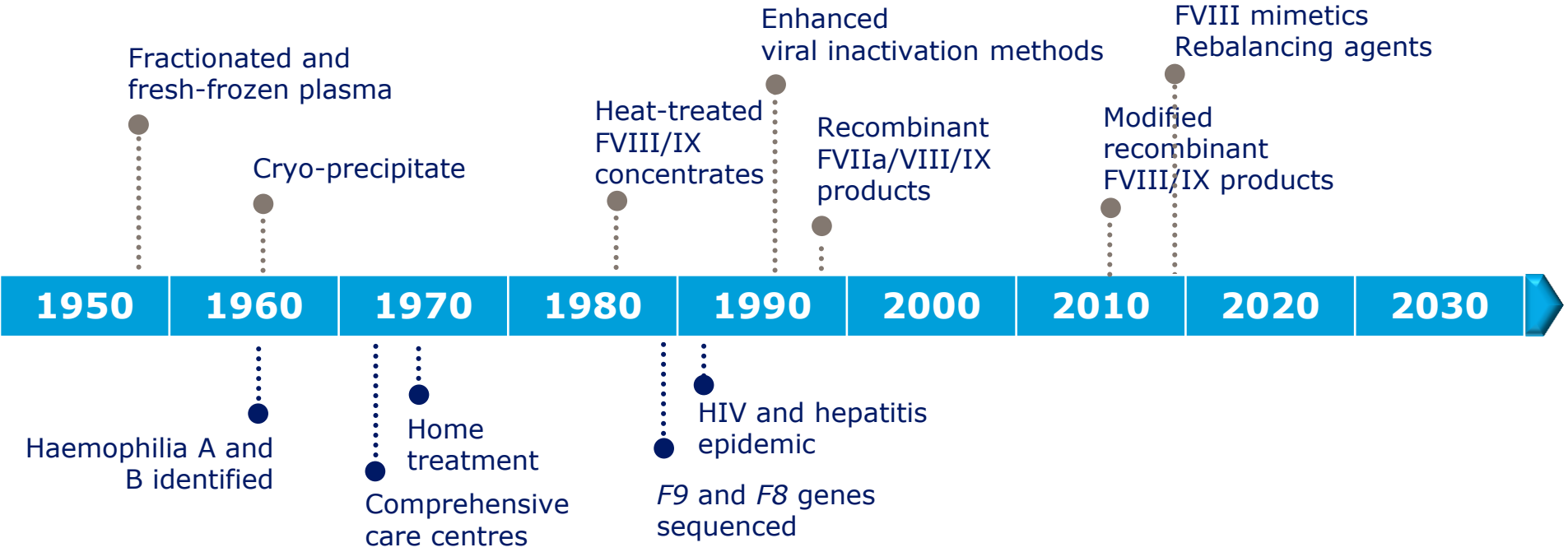
The changing landscape of haemophilia treatment



References: Kingdon HS & Lundblad RL. *Biotechnol Appl Biochem* 2002; 35:141–148
Shapiro AD *Hematology Am Soc Hematol Educ Program*. 2013;2013:37–4

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The ‘paradigm shift’ is coming closer

- Modified FVIII and FIX products are available
- Treatment to higher activity levels is practiced
- Alternative routes of administration
- Rebalancing agents and mimetic antibodies

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Treating to higher activity levels is part of the changing haemophilia landscape

Blood Reviews 32 (2018) 52–60

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

Review

Haemophilia B: Where are we now and what does the future hold?

Gerry Dolan[a,*], Gary Benson[b], Anne Duffy[c], Cedric Hermans[d], Victor Jiménez-Yuste[e], Thierry Lambert[f], Rolf Ljung[g], Massimo Morfini[h], Silva Zupančić Šalek[i,j,k]

[a] Centre for Haemostasis and Thrombosis, St Thomas' Hospital, London, UK
[b] Haemophilia and Thrombosis Centre, Belfast City Hospital, Belfast, Northern Ireland, UK
[c] World Federation of Hemophilia (WFH) Psychosocial Committee, Ireland
[d] Haemostasis and Thrombosis Unit, Division of Haematology, Cliniques Universitaires Saint-Luc, Brussels, Belgium
[e] Unidad de Hemostasia, Servicio de Hematología y Hemoterapia, Hospital Universitario La Paz, Universidad Autónoma, Madrid, Spain
[f] Hemophilia Care Center, Bicêtre AP-HP Hospital, Faculté de Médecine Paris XI, Paris, France
[g] Department of Paediatrics, Lund University, Malmö Centre for Thrombosis and Haemostasis, Skåne University Hospital, Malmö, Sweden
[h] Italian Association of Haemophilia Centres (AICE), Florence, Italy
[i] National Haemophilia and Thrombophilia Centre, Department of Haematology, University Hospital Centre Zagreb, Rebro, Zagreb, Croatia
[j] School of Medicine, University of Zagreb, Zagreb, Croatia
[k] School of Medicine, University of Osijek, Osijek, Croatia

ARTICLE INFO

Keywords:
Haemophilia B
FIX concentrates
Pharmacokinetics
Inhibitors
Gene therapy
Prophylaxis

ABSTRACT

Research has been lacking on the natural history, complications, and treatment of haemophilia B, which is less common than haemophilia A and was recognized as a distinct clinical entity in 1947. Although the two diseases share the same clinical manifestations, they differ in causative mutation, risk of inhibitor development, and patient quality of life. Frequently debated is whether haemophilia B is as clinically severe as haemophilia A, with much of the published data on overall and haemophilia-specific health outcomes suggesting that haemophilia B may have a less severe clinical phenotype. However, although fewer haemophilia B than haemophilia A patients appear to experience bleeding, bleeds are just as severe. We review distinguishing characteristics of haemophilia

"For younger, more active patients [the treatment strategy involves] a higher target FIX trough level (approximately 15% or higher)."

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Non-factor replacement treatments is part of the changing haemophilia landscape

REVIEW

Non-factor replacement therapy for haemophilia: a current update

Massimo Franchini[1], Pier Mannuccio Mannucci[2]

[1]*Department of Transfusion Medicine and Haematology, "Carlo Poma" Hospital, Mantua;* [2]*Scientific Direction, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico and University of Milan, Milan, Italy*

Abstract

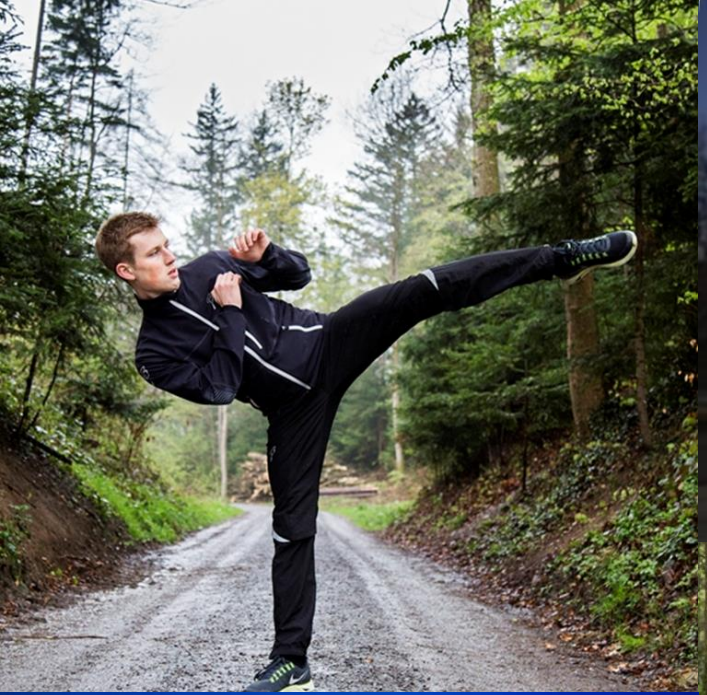
One of the most challenging issues facing us in the treatment of haemophilia is the development of alloantibodies against infused factor VIII (FVIII) or factor IX (FIX). Inhibitors render f
therapy ineffective, exposing patients
high risk of morbidity and mortality
known bypassing agents (i.e. activ
complex concentrate and recombina
VII) used to treat or prevent bleedi
patients with inhibitors, there is gro
new class of therapeutic agents whic
coagulation (i.e. emicizumab) or inhib
pathways (i.e. fitusiran and concizu
will focus on these innovative therapies, providing an

or treat bleeding episodes, and inhibitor eradication[5]. Regarding the former type of treatment, the introduction of agents that bypass the functional activity of FVIII and FIX, such as activated prothrombin complex

Technology	Chimeric bispecific humanised antibody	siRNA	Humanised monoclonal antibody
Mechanism of action	FVIIIa-mimetic	Antithrombin inhibition	TFPI inhibition
Dosing frequency	Weekly	Weekly to monthly	To be determined
Route of administration	SC	SC	SC
Stage of development	FDA approved	Phase II-III	Phase II

siRNA: short interfering RNA; TFPI: tissue factor pathway inhibitor; SC: subcutaneous; IV: intravenous; FDA: Food and Drug Administration.

Blood Transfus 2018; 16: 457-61 DOI 10.2450/2018.0272-17



JAY LUCKEY
Jay has haemophilia Bb

CHRIS BOMBARDIER
Chris has haemophilia B
US

LEANDRO KUSTER
Switzerland
Leandro has haemophilia A

Team Novo Nordisk and the Vasalopp team are Changing Diabetes

Changing Haemophilia through R&D in Novo Nordisk

Aim: A future where all people with haemophilia can live a life with as few limitations as possible

We use our extensive experience in R&D to develop advanced, safe and innovative biological treatments within the haemophilia therapy area

We work with our global partners to advocate for and create better access to diagnosis and multidisciplinary care of haemophilia with a focus on joint health

novo nordisk®

changing haemophilia®