Novel treatments in haemophilia and other bleeding disorders: A periodic EHC Review

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FOREWORD

Welcome to a new edition of the European Haemophilia Consortium's (EHC) periodic review of novel treatments in haemophilia and other rare bleeding disorders.

In this edition, we primarily cover news from the 2021 virtual Congress of the International Society on Thrombosis and Haemostasis (ISTH), held in July 2021, and the BIC Conference, held in September 2021 as well as other industry updates and news in general. You will find a direct link to the ISTH abstracts in the articles below, while the BIC abstracts can be accessed online here. For your convenience, we also include a table on all treatments covered in this newsletter as well as other novel treatments under development. We hope this will facilitate your understanding of the changing therapeutic landscape.

The purpose of this newsletter is to provide both up-to-date information to EHC National Member Organisations (NMOs), and a general overview and understanding of a rapidly evolving landscape of medicinal product developments in rare bleeding disorders. The EHC encourages its NMOs to adapt this newsletter to their national needs but takes no responsibility for any changes. This newsletter provides information by specific type of disorder: haemophilia A and B; inhibitors in haemophilia, von Willebrand disease, and other rare bleeding disorders.

The EHC wishes to thank its New Products Working Group, which has overseen the content and production of this newsletter. Its members include:

- Dr. Mariëtte Driessens, EHC volunteer,
- Dr. Radoslaw Kaczmarek, Medical and Scientific Advisory Group (MASAG) member,
- Dr. Dan Hart, EHC MASAG member,
- Dr. Ilmar Kruis, EHC volunteer,
- Prof. Mike Makris, EHC Medical Advisory Group (MAG) Chair,
- Mr. Declan Noone, EHC President,
- Asst. Prof. Brian O'Mahony, MASAG member,
- Mr. David Page, Canadian Hemophilia Society,
- Prof. Flora Peyvandi, EHC Medical Advisory Group (MAG) member,
- Ms. Laura Savini, EHC Public Policy and Communications Officer,
- Dr. Uwe Schlenkrich, EHC volunteer.

The EHC welcomes all treatment developments that may benefit patients in the future. The EHC takes no position on any product type or class reported in this newsletter. This document does not intend to replace the medical advice provided by healthcare professionals.

We hope that the information contained herein is useful and are available for any questions.

Sincere regards,

Declan Noone
EHC President

Amanda Bok
EHC CEO

ABBREVIATIONS

>	Greater than
≥	Greater or equal to
<	Smaller than
≤	Smaller or equal to
AAV	Adeno-associated virus
ABR	Annualised bleeding rate
ADAs	Anti-drug antibodies
AE	Adverse events
AjBR	Annualised joint bleeding rate
aPCC	Activated prothrombin complex
aPTT	Activated partial thromboplastin clotting time
AT	Anti-thrombin
BE	Bleeding episode
BMI	Body mass index
BPA	Bypassing agents
BU/ml	Bethesda units per millilitre
CFC	Clotting factor concentrates
CI	cumulative incidence
CL	Clearance
Cmax	Maximum plasma concentration
EAHAD	European Association for Haemophilia and Allied Disorders
ED	Exposure days
EHL	Extended half-life
EQ-5D-5L	Standardised measure of health-related quality of life
F	Factor
FISH	Functional Independence Score in Haemophilia
FVII	Factor VII
FVIIa	Factor VII activated
FVIID	Factor VII deficiency
FVIII	Factor VIII
gc/kg	Genome copies per kilogram
HA	Haemophilia A
Haem-A-QoL	Haemophilia-Specific Quality of Life Questionnaire for Adults
HAwI	Haemophilia A with inhibitors
HB	Haemophilia B
HBwI	Haemophilia B with inhibitors
HCV	Hepatitis C virus
HEAD-US	Haemophilia early arthropathy detection with ultrasound
HJHS	Haemophilic joint health score
HRQoL	Health-related quality of life
HTC	Haemophilia treatment centre
IDR	Intradermal regimen
ISTH	International Society on Thrombosis and Haemostasis
ITI	Immune tolerance induction
IQR	Interquartile range
IV	Intravenous

IU	International units
IU/dL	International units per decilitre
Kg	Kilograms
mg/kg/week	Milligrams per kilograms per week
n=	Number
NAbs	Neutralising antibodies
ng/ml	nanogram per millilitre
OD	On-demand
Pd	Plasma-derived
PD	Pharmacodynamics
PK	Pharmacokinetics
PPX	Prophylaxis
Pop	Population
PRO	Patient-reported outcomes
PTP	Previously treated patients
PUP	Previously untreated patients
PWHi	People with haemophilia and inhibitors
QM	Every month
QW	Once a week
R	Recombinant
rFVIIa	Recombinant factor VII activated
RNA	Ribonucleic Acid
rTKA	Revision knee arthroplasty
sABR	Spontaneous ABR
SAE	Serious adverse event
SD	Standard deviation
SHL	Standard half-life
SQ	Subcutaneous
T ½	Half-life
TE	Thromboembolic events
TG	Thrombin generation
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
TMA	Thrombotic Microangiopathy
ug/mL	Micrograms per milliliter
vg/kg	Vector genomes per kilogram
VAS score	Visual analogic scale
VWD	Von Willebrand Disease
VWF:Ag	Von Willebrand Factor antigen
VWF:RCo	Von Willebrand factor ristocetin cofactor (assay)
WAPPS-Hemo	Web Accessible Population Pharmacokinetic Service-Hemophilia
µg/ml	Microgram per kilogram

Executive summary

Reflection pieces

A group of Greek researchers reflected whether the **zero-bleeds goal** is achievable in haemophilia in a real-world setting (pg 12).

Staff members from the German regulatory authority, Paul-Ehrlich-Institut, reflected on whether new haemophilia therapies are **altering haemophilia treatment** (pg 12).

We report on the presentation given by Prof Michael Makris during the EHC 2021 Virtual Conference on **haemophilia and thrombosis** (pg 12).

We report on the presentation from Prof Flora Peyvandi at the EHC 2021 Virtual Conference on **liver health and haemophilia** (pg 13).

Haemophilia A

Replacement therapies

Results from **clinical trials**

A group of researchers explored the effects of **potency difference** in individual FVIII pharmacokinetic parameters and the prediction of FVIII trough levels on the dosing regimen (pg 14).

Novo Nordisk presented the **results for its clinical trial pathfinder™ 3** (pg 14). This trial studies **surgeries** in patients enrolled in the **pathfinder™ 2 trial** looking at the safety and efficacy of **Esperoct®** in people with haemophilia A. Researchers looked at AjBR and mobility. Novo Nordisk also presented the **results of the pathfinder™ 6 trial** investigating the use of Esperoct® in severe haemophilia A **previously untreated patients** (pg 14). The primary endpoint was FVIII inhibitor incidence.
Novo Nordisk also described a **temporary decrease of incremental recovery** in the absence of FVIII inhibitors in a subset of patients treated in the pathfinder™ 6 trial (pg 15).

Bayer reported on the **long-term safety of Jivi® prophylaxis** in previously treated patients with data from the **extension studies of PROTECT VIII and PROTECT VIII Kids** (pg 15). Researchers assessed safety outcomes such as adverse events, inhibitor development, anti-PEG antibodies, renal biomarkers and quantitative plasma levels free of PEG every six months.

Sanofi reported on the second **interim analysis of the FACTs study** (pg 16) looking at the use of **Elocta®** in the **Japanese haemophilia A paediatric population** (part one) and for immune tolerance induction use in Japan (part two). In part one, the authors looked at treatment frequency, ABR and inhibitor development. Sanofi and Sobi also presented the results from the **ReITIrate study** to evaluate **rescue ITI with Elocta®** in previously failed ITI (16).

Octapharma presented the results from the **NuProtect study** for the use of **Nuwiq® in previously untreated patients** with haemophilia A (pg 16). The study looked at the use of

Nuwiq® for the management of different types of bleeding episodes (occurring while on prophylaxis, on-demand, spontaneous and surgery).
Octapharma presented the **GENA clinical trial programme results** looking at **Nuwiq®'s immunogenicity and safety in previously treated patients** (pg 17). Researchers looked at inhibitor development and adverse events.
Octapharma also presented results from the GENA trial on safety and efficacy for the **use of Nuwiq® in previously treated and untreated paediatric patients**. The authors look at treatment regimens and ABR (pg 17).

Takeda presented data on the **impact of pre-study treatment regimen and ABR on the efficacy of Adynovi® prophylaxis** targeting 1-3% or 8-12% during the **PROPEL study**. The authors looked at ABR, AjBR and injury-related ABR (pg 17).

Band Therapeutics presented the results from **a phase II trial for BT200**, a pegylated aptamer with the **potential to extend the half-life of FVIII and VWF** (pg 18).

Researchers involved in the **HAVEN 3 and 4** studies presented the results of the **EmiPref survey** asking trial participants about treatment preferences (pg 18).

Results from **real-world** and **non-interventional studies**

A group of **Brazilian researchers** looked at the **inhibitor rate between PUPs** with severe or moderately severe HA **treated with third-generation recombinant- or plasma-derived factor VIII** for the first 50 ED (pg 19).

Bayer calculated **weekly FVIII consumption** of different prophylactic regimens using **Jivi®, Kogenate-FS®, Elocta® and Adynovi®** (pg 19)**.**

Bayer presented the **interim safety analysis of HEM-POWR**, a phase IV trial to study routine clinical **use of Jivi® in real-world settings** (pg 19). Researchers look at dosing frequency, previous FVIII treatment, adverse events and inhibitor development.

Researchers presented data on the **PK properties of Jivi® in a real-world setting** using data from **WAPPS-Hemo** (pg 19). The researchers looked at clearance, the volume of distribution and terminal half-life.

Non-replacement therapies
FVIII mimetics
EAHAD presented data on the **adoption of Hemlibra® in Europe** (pg 19). The **UKHCDO** reported on the **use of Hemlibra® in adults** with haemophilia A in the UK (pg 20). **Irish researchers** presented data on their experience of **introducing Hemlibra® prophylaxis** in **Ireland** (pg 20).

Sanofi presented **data** from the **US-based OM1® Real-World Data Cloud database** to **compare males with HA treated with SHL, EHL, SHL and EHL and/or Hemlibra®** (pg 19). The authors looked at factor consumption and ABR. **Dutch researchers** presented data on

Hemlibra® plasma concentrations and bleeding control on a maintenance dosing strategy using **entire vials** at seven to 28-days intervals (pg 21).

Researchers presented data from the **PedNet registry** to **evaluate the safety and efficacy of Hemlibra® prophylaxis in children** (pg 21). Data included the number of bleeds, treatment for bleeds, trauma and surgery and adverse events. A group of **Mexican researchers** presented on the **use of Hemlibra® in paediatric patients with special needs** (pg 22). A case study reported using **Hemlibra® to treat neonatal intracranial haemorrhage** (pg 22).

Roche presented data on the **use of Hemlibra® in obese patients** with data from phase III of **HAVEN 1,3 and 4 studies** (pg 22). They look at ABR and trough concentration. Data from **HAVEN 3 and 4 trials** is also presented in relation to **physical health** (pg 22). A group of researchers looks at **real-world evidence** on the **effects of Hemlibra® on sports capacity** (pg 23). Finally, researchers looked at the **impact of Hemlibra® to support bone metabolism** (pg 23).

Roche reported on data on **anti-Hemlibra® antibodies** from seven clinical studies (pg 23); a group of **Italian researchers** describes the case of **a man developing anti-Hemlibra® antibodies** (pg 23).

Gene Therapy

BioMarin looked at the **prevalence of pre-existing immunity against different AAVs** (pg 24). **BioMarin** presented data on **phase III of the GENEr8-1 trial** (pg 25)**,** and the **five-year follow-up of phase I/II trial** (pg 25) looking at the **efficacy of valoctogene roxaparvovec** for the treatment of HA.

Bayer reported on the **phase I/II trial of BAY 2599023** (pg 24); and **Spark** reported on **phase I/II of SPK-8011** (pg 24).

The **FDA put the AFFINE clinical programme on hold** due to high (150%) levels of FVIII. The trial is on hold until a new clinical protocol can be defined (pg 26).

Haemophilia B

Replacement therapies

Sobi presented an **interim analysis of the B-sure study** looking at the **real-world effectiveness and usage of Alprolix®** (pg 27).

Catalyst Biosciences reported **halting the clinical programmes for DalcA** due to a change in business strategy (pg 31).

Gene Therapy

UniQure reported on the **five-year data on safety and efficacy** for the **phase I/II of the clinical trial of AMT-060**. Endpoints included FIX activity, ABR, FIX replacement use and treatment-

related adverse events (pg 27).
The company also reported on the **phase III HOPE-B trial** looking at the safety and efficacy of **etranacogene dezaparvovec (AMT-061)**. The report includes data on neutralising antibodies and adverse events. In May, **CSL Behring** announced the closing of its commercialisation and license agreement with UniQure for this AMT-061 (pg 27).
UniQure also reported on the **phase IIb trial for AMT-061**. The trial endpoints are FIX activity at week six, bleeds, use of FIX replacement, laboratory parameters, joint health and adverse events (pg 28).

Pfizer presented **data on liver health** following treatment with **PF-06838435 (fidanacogene elaparvovec)** (pg 29).

Freeline describes a multicentre field study to **characterise FIX-R338L (FIX Padua) activity** across 15 commonly used FIX activity assays (pg 29).

Haemophilia A and B with and without inhibitors

Bypassing agents

LFB and Hema Biologics reported on the **efficacy and safety of eptacog beta** (US brand name Sevenfact®). The companies presented data from the **PERSEPT1 phase III study** in which they tested the treatment in **adults with HA and HB and inhibitors** (pg 30). The authors looked at bleeding episodes, the number of administrations, bleeding recurrence, the response at 24h and pain assessment at 12h. These companies also assessed the **safety and efficacy of eptacog beta in the paediatric population with HA and HB and inhibitors in the PERSPEPT2 phase III study** (pg 30). Endpoints included bleeding episodes, time to response, number of administrations, pain relief at 12h and bleeding recurrence within 24h and responses at 24h. Finally, the companies **pooled safety data** from the **PERSPEPT1, 2 and 3 studies in adult, paediatric and peri-surgical settings in people with HA, HB and inhibitors** (pg 31).

Catalyst Biosciences reported **halting the clinical programmes for MarzAA** due to a change in business strategy (pg 31).

FVIII mimetics

A US group of researchers reported on a study to **determine thrombin generation of *in vitro* and *in vivo* administration of activated prothrombin complex concentrate (aPCC) at escalating concentrations/doses in people with HA and inhibitors on Hemlibra®** (pg 32).

On the use of **Hemlibra® prophylaxis for people with inhibitors**, Roche reported on the final analysis from the **STASEY phase III clinical trial** assessing the safety and efficacy of Hemlibra® prophylaxis in people with haemophilia A and inhibitors (pg 33). A group of Brazilian researchers presents the case study of a **woman with mild haemophilia and inhibitors treated with Hemlibra®** (pg 33). A group of researchers presented a study on the efficacy and safety of longitudinal Hemlibra® **prophylaxis and laboratory monitoring** in people with **haemophilia A with and without inhibitors** (pg 34).

A group of **UK researchers** presented results of the **'Emi and Me' study** on experiences of patients and their families on **quality of life** while on **Hemlibra®** (pg 34).

A group of **Italian researchers** reported on the experience of **major orthopaedic surgeries** in people with HA and inhibitors using **Hemlibra®** (pg 34).

A group of **Brazilian researchers** compared the **cost-effectiveness and outcomes of the Brazilian ITI protocol** using different treatments, including **rFVIIa, bypassing agents and Hemlibra®** (pg 34).

Croatian researchers reported on a case study of **laboratory issues** in a boy **switching to Hemlibra®** (pg 35).

Rebalancing agents

Sanofi presented an analysis to characterise the **antithrombin dynamics** by population pharmacokinetic and pharmacodynamic model to **predict dosing regimens and mitigate the risk of thrombosis with fitusiran** (pg 35).

Centessa Pharmaceuticals and ApcinteX Limited presented results from the **phase IIa trial of AP-0101 trial** to evaluate the safety and efficacy of **Serpin-PC in people with HA and HB** (pg 36).

Researchers presented **results from the combined main and extension parts of the concizumab explorer4 and explorer5 phase II clinical trials** (pg 37). These trials assessed the efficacy and safety of concizumab in people with HA and HB with inhibitors. **Novo Nordisk** also presented the **explorer4 data** in relation to people with HA or HB and inhibitors **switching from on-demand rFVIIa treatment to the trial with concizumab** (pg 37). **Novo Nordisk** also presented their investigation into **concizumab anti-drug antibodies clinical impact** in their **phase II explorer4 and 5 clinical trials** (pg 37).

Pfizer evaluated the **long-term safety and efficacy of marstacimab** in patients with **severe HA and HB** by presenting data from their open-label study (pg 38).

Von Willebrand Disease

Replacement therapies

Takeda presented the evaluation of **pharmacokinetics and pharmacodynamics parameters** following a year of **prophylaxis with Vonvendi®** (pg 39). **Takeda** also reported on the results of a **phase III** prospective, open-label, non-randomised, multicentre **trial to evaluate the safety and efficacy of Vonvendi® prophylaxis** (pg 39).

Researchers from the University of Pittsburgh presented the **feasibility and trial design** for a clinical trial to compare the **use of Vonvendi® and tranexamic acid versus Vonvendi®** alone to manage **postpartum haemorrhage in women with VWD** (pg 40).

Non-replacement therapies

A group of **US researchers** presented a case report on **two female patients with VWD type 3** on **Hemlibra® prophylaxis** (pg 40).

Other rare bleeding disorders

Replacement therapies

Catalyst Biosciences reported **halting the clinical programmes for MarzAA** due to a change in business strategy (pg 31).

A group of **Italian researchers** assessed different **pharmacokinetic profiles of rFXIII** (**NovoThirteen**) in **20 patients** (pg 41).

Non-replacement therapies

Sigilon reported on **pre-clinical *in vivo* results** for the development of **SIG-009**, a novel cell-based product for **FVII deficiency** (pg 42).

REFLECTION PIECES

Considerations on the 'zero bleeds' objective of modern haemophilia care

In an abstract (PB0484) presented at the 2021 ISTH Congress, a group of Greek researchers (Adramerina et al.) reflects on whether achieving zero bleeds in haemophilia is a realistic goal in real-world settings. To evaluate this, they took records of severe paediatric haemophilia patients on prophylaxis from 2018 to 2020 and looked at annualised bleeding rates (ABR) and joint ABR (AjBR).

In 2018, 21 patients with a mean age of 12.4 (5-18) years were evaluated. Sixteen (76.2%) were on standard half-life products (SHLs) while two (9.5%) were on extended half-life (EHL) products. During the year, three patients (14.3%) switched from SHL to EHL. Mean ABR was 4.5 (0-13) and mean AjBR 3.2 (0-11). Two patients (9.5%) reported zero bleeds.

In 2019, 22 patients with a mean age of 11.9 (3-18) years were evaluated. Thirteen (59%) were on SHLs, five (22.7%) on EHLs. Two patients (9%) switched during the study year from SHL to EHL. Hemlibra® was administered to two (9%) patients. Mean ABR was 4 (0-10) and mean AjBR 3 (0-9). Zero bleeds were reported in four patients (18.3%).

In 2020, 26 patients with a mean age of 10.5 (1-18) years were evaluated. In total, 14 (53.8%) were on SHLs, eight (30.7%) on EHLs. One patient (3.84%) switched from SHL to EHL. Three received Hemlibra® (11.5%). Mean ABR was 1.8 (0-8) and mean AjBR 1.1 (0-8). Zero bleeds were reported in six patients (23%).

Researchers concluded that although novel therapies improved ABR and AjBR, the goal of zero bleeds is still difficult to attain in real-world settings.

Do new therapies alter the treatment of haemophilia patients?

In an abstract (PB0686) presented at the 2021 ISTH Congress, staff members from the German regulatory body, Paul-Ehrlich-Institut, reflect on whether new haemophilia therapies alter the treatment of haemophilia patients. To do this, researchers analysed specific aspects of data in the German Haemophilia Registry (Deutsches Hämophilieregister, dhr) to identify the impact of these new therapies on the treatment of German haemophilia patients. The researchers analysed data parameter changes in total factor consumption or shifts in product class preferences. They also calculated the per-capita factor consumption of relevant patient groups and correlated it with the past decade's market access to novel therapies.

The preliminary results suggest a shift in selected aspects of haemophilia care. Authors note that registry data should support the investigation of real-time data to elaborate patient-oriented supply.

Haemophilia and thrombosis

During the 2021 EHC Conference, Prof Mike Makris gave a presentation on thrombosis and haemophilia. In his talk, Prof Makris noted that thrombosis in haemophilia is a recent phenomenon that appeared with the advent of modern clotting factor concentrates in the 1970s. From then on, thrombotic events in people with haemophilia were mainly reported in people with HB who used old prothrombin complex concentrates (PCC) that contained other clotting factors. Thrombotic events were also observed in patients with haemophilia and inhibitors using activated PCC (aPCC). Currently, thrombotic events have been observed in clinical trials with novel non-replacement therapies. In addition, the haemophilia population is getting older, and thrombotic events are a common co-morbidity of older populations.

It is important to note that thrombosis in haemophilia remains a rare phenomenon with the current estimated incidence of one per 1,000 patient-years. Last year, Roche reported on the incidence of thrombosis in people with haemophilia using Hemlibra®. The incidence was 20 thromboses in 6,000 people. It is important to note that this is 6,000 people and not patient-year. These patients were followed over several years. In terms of rebalancing agents, such as fitusiran, anti-TFPI agents (concizumab and marstacimab) and SerpinPC, we know of five episodes of thrombosis with fitusrian, and five episodes in three patients with concizumab, whose trial has re-started. It is important to note that this data comes from clinical trials, where conditions are stable. It will be critical to see data coming from stress situations with a higher risk of thromboses, such as surgery, infection, inflammation and cancer. In data from EUHASS, 286 thromboses were reported for inherited bleeding disorders in the last eleven years. These were within 30 days of having a concentrate, and the main ones included heart attacks, deep vein thrombosis and strokes. Doctors face thrombotic issues with arterial and venous thrombosis, which are difficult to manage because they require anti-thrombotic drugs. In conclusion, although the risk of thrombosis in haemophilia is rare, the risk is real and increases as the population ages. Some rebalancing agents may carry a higher risk of thrombosis. However, the dosing has been modified to reduce the risk, and we will have to see whether this change will be effective.

Liver health and haemophilia

During the 2021 EHC Conference, Prof Flora Peyvandi presented the importance of monitoring liver cancer in people with haemophilia who have cleared HCV infections. Despite clearing the HCV infection, patients may already suffer from liver damage such as fibrosis or cirrhosis, which remains a risk factor for liver cancer.

Several causes have been reported and analysed for the development of liver cancer. One of them is viruses such as HBV, HCV and past infections with viruses, which lead to inflammation, tissue necrosis, tissue damage, fibrosis and cirrhosis. Metabolic syndrome (the combination of diabetes, high blood pressure and obesity), diabetes, obesity, NASH syndrome (non-alcoholic fatty liver disease) and alcohol use also increase the risk of hepatocellular carcinoma. It is important to note that liver cancer can also occur in patients without cirrhosis. Eradication of HCV is critical to reducing the risk of developing cancer. However, it is also crucial to monitor these patients following eradication because they may already present liver damage.

To do this, clinicians should have a comprehensive approach that considers the disease history, risk factors (as mentioned above), the risk of cirrhosis, and other liver lesions. This assessment can be performed with several tools, such as hepatological first assessment, liver ultrasound, and non-invasive evaluation using fibroscan. For patients showing liver lesions, the visits with hepatologists should be more frequent (every six or three months), and they may need more imaging such as MRI. If patients exhibit signs of liver damage, they need to be addressed through a multidisciplinary approach, including haematologists, hepatologists, liver transplant surgeons and radiologists. The type of treatment, management and investigation should be patient-centred.

In the Q&A, there was a reference to the case of a hepatocellular carcinoma that developed during a gene therapy trial. The trial sponsor investigated whether the cancer was related to the treatment and it was determined that it was not. This presentation underscores the importance of continuing to monitor liver health even after HCV eradication.

AN UPDATE ON NOVEL TREATMENTS IN HAEMOPHILIA A

Factor replacement therapies

Difference between the label and actual potency of FVIII affecting PK-guided dosing of replacement therapy in HA

In an abstract (PO 07) presented at the 2021 BIC Congress, a group of researchers, led by Goedhart, presented a study exploring the effects of potency difference on individual FVIII PK parameters and the prediction of FVIII trough levels of the dosing regimen. The authors analysed individual preoperative PK profiling data from severe and moderate HA patients included in the OPTI-CLOT randomised controlled perioperative trial. Actual potency of administered (batches of) standard half-life FVIII concentrates was provided by pharmaceutical companies to determine potency difference. Two individual PK parameter estimations and concentration-time curves were constructed by nonlinear mixed-effects modelling using both label and actual potency. Finally, the authors explored the effect of both the identified and the maximum legislated potency difference on predicted FVIII trough levels when infused in a low and high dose regimen.

In 44 of 50 included patients, actual potency was higher than label potency. The median potency difference was 6.0% (range -9.2% to 18.4%) and resulted in varying PK estimations. This difference, however, resulted in almost identical FVIII concentration-time curves. Importantly, predicted FVIII trough levels were linearly correlated to the actual dose when calculating dosing regimens. The authors concluded that potency differences linearly affect predicted FVIII trough levels of dosing regimens. Therefore, their study indicates that it is not necessary for clinicians and pharmacologists to take potency into account when applying PK guidance of FVIII concentrates in HA patients.

Clinical outcomes after joint surgery in pathfinder™3 study

During the 2021 ISTH Congress, Tiede et al. presented (PB0508) the results of pathfinder™3 (NCT01489111), a study on surgeries in patients enrolled in the pathfinder™2 (NCT01480180) clinical trial. Novo Nordisk sponsored both trials and studied the efficacy and safety of **Esperoct®** in people with haemophilia A (HA). In pathfinder™3, researchers investigated the effects of joint surgery on clinical outcomes (joint bleeding rates and patient-reported outcomes). The authors analysed data from 41 joint surgeries in 30 patients. After assessing data from both trials, the authors concluded that mean AjBR significantly declined post-surgery and mobility parameters improved in patients whose pre-and post-surgery AjBR was 0. However, these findings should be interpreted with caution. The researchers observed a general decline in AjBR in the pathfinder™2 cohort, whose patients were on Esperoct® prophylaxis.

Results from the pathfinder™ 6 trial for the use of Esperoct® in severe HA PUPs

In an abstract (PO 06) presented at the 2021 BIC Congress, Novo Nordisk presented pathfinder™ 6 (NCT02137850) clinical trial results. This study is an ongoing, open-label, single-arm, phase IIIa trial investigating the use of **Esperoct®** in severe HA PUPs, enrolling male children, <6 years old, with no exposure to FVIII concentrates and no FVIII inhibitors. The primary endpoint was the FVIII inhibitor incidence. For this analysis, ≥50 patients had ≥50 EDs to Esperoct®. Patients with ≥10 EDs or inhibitors were included in the inhibitor incidence

analysis. Patients <24 months old were treated with pre-prophylaxis or prophylaxis. Patients ≥24 months old were treated with prophylaxis.
Eighty patients received ≥1 Esperoct® dose and were included in this analysis. Of the 67 patients eligible for FVIII inhibitor analysis, 20 developed inhibitors (ten high-titre), resulting in an incidence rate of 29.9% (14.9% high-titre). Seven patients began immune tolerance induction therapy; five were successful, one withdrew, and one has ongoing therapy. Sixty-five patients received Esperoct® prophylaxis for an average of 2.17 years. In these patients, the median ABR (IQR) was 1.42 (0.76; 3.13), 91.3% of bleeds were treated with ≤2 injections, and the haemostatic success rate was 90.5% (Table). No unexpected AEs were observed.

Temporary decrease of incremental recovery during pathfinder™ 6 trial

In an abstract (PO 16) from the BIC Congress, Novo Nordisk describes a temporary decrease of incremental recovery (IR) in the absence of FVIII inhibitors in a subset of patients treated with **Esperoct®** during the pathfinder™6 trial ((NCT02137850). This study is an ongoing, multinational, phase IIIa trial investigating Esperoct® treatment in male PUPs (<6 years old) with severe HA. We present a post-hoc analysis of the observed temporarily decreased IR – defined as two consecutive measurements of IR <0.6 (IU/dL)/(IU/kg) without inhibitors. Decreased IR was observed in 17 patients (without inhibitors) within five exposure days. IR returned to expected range in 13 patients with continued Esperoct® dosing (nine patients within 30 exposure days), and four patients withdrew from study. Temporarily decreased IR had a strong temporal correlation with anti-PEG IgG. Although anti-PEG IgM and anti-Esperoct® binding antibodies were observed, anti-PEG IgG accounted for 58.4% of the within-patient IR variance (the explained variation of titres was 62.3%). During the temporary decreased IR period, the success rate for treatment of bleeds (83.2%) was similar to the overall population (86.5%) and the ABR was higher (4.14 [2.45; 7.00]) within a relatively brief period. When evaluated from the total observational period, patients with observed temporary decreased IR had an estimated ABR (95% CI) of 2.41 (1.64; 3.52), compared with 2.75 (1.97; 3.84) in other non-inhibitor patients without temporary decreased IR.

Report from the extension studies of PROTECT VIII and PROTECT VIII Kids for the use of Jivi® in people with HA

In an abstract (PO 08) presented at the 2021 BIC Congress, Bayer reported on the long-term safety of **Jivi®** prophylaxis in PTPs treated for ≥5 years from the extension studies of PROTECT VIII (NCT01580293; 12–65 years old) and PROTECT VIII Kids (NCT01775618; <12 years old).
Throughout the PROTECT VIII and PROTECT VIII Kids extension studies, safety outcomes were assessed every six months and at the last study visit, including adverse events (AEs), inhibitor development (titre, ≥0.6 Bethesda units/mL), anti-PEG antibodies, renal biomarkers and quantitative plasma levels of free PEG.
At extension completion, 75 patients completed ≥5 years of Jivi® prophylaxis (median [range], years: PROTECT VIII [n=36], 6.2 [5.0–7.0]; PROTECT VIII Kids [n=39], 6.1 [5.2–6.6], respectively). FVIII consumption (IU/kg/year) was 3332 in PROTECT VIII and 4160 in PROTECT VIII Kids using infusion schedules twice-weekly, every five days or every seven days. Nine patients experienced non-serious study-drug-related AEs; two patients experienced study-drug-related serious AEs (both were suspected, but not confirmed, FVIII inhibitors). No renal AEs were reported; renal biomarkers remained within normal levels at the last study visit. Three patients had low, unconfirmed anti-FVIII antibody titres (range: 0.6–1.5 BU/mL), negative at the second test; none developed anti-PEG antibodies. No deaths or thrombotic

events were reported. Free PEG in plasma was detectable in 14 (18.7%) patients (maximum value: 0.152 mg/L), confirming the predicted range based on simulations from preclinical studies.

Interim analysis of the FACTs study evaluating the use of Elocta® in adolescents and children in Japan

During the 2021 ISTH Congress, an abstract (PB0578) from Sanofi reported on the second interim analysis of the FACTs study. This study is prospective and multicentre, designed to evaluate the effectiveness of **Elocta®** in HA adolescents and children (part 1), and summarise the experience of immune tolerance induction (ITI) in Japan (part 2).

Ninety-one patients from 62 centres were included in this interim analysis. Sixteen (18%) were PUPs, 81 had >6 months' follow-up, and 35 completed two-years' follow-up. Before the study, five out of ten patients with a history of inhibitors underwent ITI with factor VIII (FVIII). Sixty-five (71%) patients had received prophylactic treatment with FVIII; of those, 29 (45%) received FVIII treatment at least three times/week. During the study, 49 patients on prophylaxis received Elocta® twice a week. Overall, injection frequency was maintained or lowered in the study with Elocta® compared with the pre-study. The median spontaneous ABR in the study was 0 (interquartile range (IQR)=0–0). Three patients developed inhibitors (previously untreated patients (PUPs), n=2; minimally treated patient, n=1) with titres of 3.0, 0.8, and 5.2 BU/mL, respectively, and started ITI with Elocta®.

In FACTs part 1, the authors concluded that prophylaxis with Elocta® was associated with reduced infusion frequency and low ABR in young Japanese patients. These results were consistent with findings from previous global studies with Elocta®.

Results of ReITIrate, a prospective study of ITI with Elocta® in patients who previously failed ITI

In an abstract (PB0522) from Sobi and Sanofi presented at the 2021 ISTH Congress, authors presented ReITIrate (NCT03103542), a prospective, interventional, multicentre, open-label study designed to evaluate rescue ITI with **Elocta®** in previously failed ITI. The study enrolled severe HA inhibitor patients who failed previous ITI attempts. The primary objective was ITI outcome with Elocta® (200 IU/kg/day) within a 60-week time limit. Sixteen patients enrolled in the study. They had multiple risk factors for poor ITI outcomes and a long duration of previous ITI. Seven patients (43%) withdrew prematurely (due to adverse events [n=2], physician/patient decision [n=3], other [n=2]). Of nine patients completing the ITI period, four reached confirmed negative inhibitor titres (<0.6 BU/mL) within 19 (11-60) weeks (median [range]). Three of these also reached an incremental recovery >66 % of expected, two of which reached a T½ >7 hours (one did not meet all criteria simultaneously). One patient maintained all three success criteria and experienced no relapse. No unanticipated safety concerns were identified.

The final results of the NuProtect study presented

In an abstract (PB0590) presented at the 2021 ISTH Congress, Neufield et al. presented the final results of the NuProtect study, sponsored by Octapharma. This phase III study was prospective, multinational, open-label, non-controlled of 108 PUPs of any age and ethnicity with severe HA. Patients received **Nuwiq®** for 100 exposure days (ED) or up to five years of prophylaxis, surgical prophylaxis or on-demand treatment. In PUPs who received continuous prophylaxis for ≥24 weeks (n=50), the mean (standard deviation (SD) ABR was 0.54 (1.07) for

spontaneous bleeding episodes (BEs) and 3.61 (3.82) for all BEs. One hundred per cent of patients rated continuous prophylaxis as excellent or good in 100% for spontaneous BEs and 96% for all BEs. A total of 808 BEs in 85 patients were treated during inhibitor-free periods, of which 502 (62.1%) occurred in 51 patients during on-demand treatment. Participants rated efficacy in treating BEs as excellent or good in 92.9% of 804 rated BEs. The majority of BEs (92.3%) were controlled with one or two infusions. Efficacy in surgical prophylaxis was rated as excellent or good in 94.7% (18/19) of procedures.

Safety and immunogenicity of Nuwiq®: Findings from the GENA clinical trial programme

During the 2021 ISTH Congress, Manco-Johnson et al. presented (PB0549) the findings from Octapharma's GENA clinical trial programme for the study of **Nuwiq®**. Findings looked at Nuwiq® immunogenicity and safety in previously treated patients (PTPs). This included all participants in the GENA clinical programme who had previously received FVIII for at least 50 exposure days. Pooled immunogenicity and safety data were analysed. A total of 310 paediatric or adult PTPs were switched to Nuwiq® and received treatment. Of the 310 individuals, 119 (38.4%) switched from plasma-derived FVIII (pdFVIII) products, 151 (48.7%) from rFVIII, 36 (11.6%) had received both pdFVIII and rFVIII, and 4 (1.3%) switched from an unknown FVIII. Patients received a total of 54,112 infusions during the studies. FVIII inhibitors did not develop in any patient after switching to Nuwiq®. The researchers recorded a total of 15 treatment-related adverse events in nine (2.9%) patients. Only one (0.3%) patient had an adverse event (mild fever that resolved) classified as serious because the patient was hospitalised.

Safety and efficacy of long-term prophylaxis with Nuwiq® in children

During the 2021 ISTH Congress, Klukowska et al. presented (PB0535) an assessment of the efficacy and safety of long-term prophylaxis with **Nuwiq®** in children. To do so, they pooled data on children with severe HA enrolled in the prospective GENA-15 and GENA-13 studies. GENA-15 and GENA-13 were long-term extension studies of the GENA-05 (NuProtect) and GENA-03 studies in previously untreated and previously treated children, respectively. The extension studies enrolled 97 children, and 96 were included in these analyses. The researchers excluded one child who had undergone ITI. The median (IQR) age at prophylaxis start was three (1–6) years, and the median (IQR) duration of prophylaxis was 359 (300–509) exposure days over 36.4 (31.6–40.9) months. The median (IQR) ABR was 0.31 (0–1.08) for spontaneous bleeds and 1.81 (0.58–3.94) for all bleeds; 44.8% of patients experienced no spontaneous bleeds over a median of three years. A total of 763 bleeds were treated with Nuwiq®. Most (86.5%) were managed with one or two infusions, and 85.7% (649/757) of rated bleeds were treated successfully. None of the 96 patients on long-term prophylaxis withdrew from the studies due to an adverse event, and no thrombotic events. Authors from this abstract include representatives from Octapharma.

Post Hoc Analysis of PK-guided regimens from the PROPEL phase III study

In an abstract (**PB0542**) presented at the 2021 ISTH Congress, Takeda showed the results of a study to explore the impact of pre-study treatment regimen (on-demand - OD - versus prophylaxis - PPX) and ABR on the efficacy of **Adynovi®** prophylaxis targeting 1-3% or 8-12% FVIII trough levels. During the PROPEL study, patients aged 12-65 years with ABR ≥2 were randomized to 12 months' pharmacokinetic (PK)-guided prophylaxis targeting 1-3% or 8-12% FVIII troughs (first six months: treatment adjustment). In the 8-12% arm, total, spontaneous,

and spontaneous joint ABRs were lower in all subgroups versus the 1-3% arm. Injury-related ABR was lower in the 8-12% arm among previous OD patients and patients on previous PPX with ABR <5, but similar between arms in patients on previous PPX with ABR ≥5. In the 8-12% arm, the proportion of patients with zero total ABR was higher versus the 1-3% arm, regardless of pre-study regimen or ABR.

Phase II trial for BT200

In an abstract (LB 02.1) from Band Therapeutics Inc. presented at the 2021 ISTH Congress, authors presented on **BT200**, a pegylated aptamer targeting the A1-domain of VWF shown to increase plasma levels of VWF-FVIII ≤4-fold by competing for its clearance in healthy volunteers. Authors hypesised that BT200 mediated prolongation of FVIII half-life (i) increased post infusion trough levels in severe haemophilia A patients and (ii) increased circulating FVIII levels in mild/moderate haemophilia A patients. In a phase II trial, 3mg of BT200 were administered subcutaneously on days 1, 4 and 7, followed by 4-9 mg every week until day 28. Eighteen patients (eight with severe, two with moderate, eight with mild haemophilia A, age 42; 20-62y) received six doses of BT200 without any relevant adverse events. BT200 rapidly increased circulating VWF:Antigen from 97% (51-172%) to 294% (129-421%, p<0.001), whereas VWF:RCo remained stable at ~80% in all patients. Median FVIII activity increased from 24% to 53% in mild haemophilia A (p<0.001), from 3 to 7.5% in moderate haemophilia A, and trough levels increased during regular substitution/prophylaxis intervals from 0-1% to >15% in haemophilia A. The half-lives of five different FVIII products increased two to seven-fold from a median of 11 to 38 hours (p<0.01).

Results from the EmiPref survey

In a letter to the editor published in the scientific journal *Haemophilia*, authors including representatives from Genentech and Roche, present the results of the EmiPref study conducted in participants of the HAVEN 3 and 4 trials. The EmiPref survey asked trial participants about their treatment preference. A total of 95 HAVEN 3 participants took the survey. Eighty-nine participants (94% of respondents) reported preferring **Hemlibra®** to their previous treatment. In HAVEN 4, all 41 (100%) participants completed the EmiPref survey, with all (100%) reporting a preference for Hemlibra® over their prior treatment. The most important factors influencing participants' preferences were related to the convenience of treatment administration, in terms of less frequent and easier route of administration, but also in terms of less concerns over bleeds and improvement of quality of life.

Real-world data & non-interventional studies

Inhibitor incidence in Brazilian PUPs using pdFVIII vs third-generation rFVIII

A group of Brazilian researchers looked at the inhibitor incidence rate between PUPs with severe or moderately severe HA treated **with third-generation recombinant factor VIII** (**rFVIII**) or **plasma-derived factor VIII** (**pdFVIII**) concentrates for the first 50 exposure days (EDs). These findings (OC 55.4) were presented at the 2021 ISTH Congress. They analysed 271 patients' records. Ninety-six (35.4%) were treated with pdFVIII, and 175 (64.6%) received rFVIII. Inhibitors developed in 93 of the 271 patients (cumulative incidence (CI), 34.3%); 70 had high-titres (25.8%). Twenty-nine of 96 (30.2%) patients treated with pdFVIII developed inhibitors, with 21 (21.9%) developing high-titre inhibitors. Sixty-four of 175 (36.6%) patients treated with rFVIII developed inhibitors, with 49 (28%) developing high-titre inhibitors.

Predicted FVIII consumption in Jivi® and other rFVIII therapies

In an abstract (PB0559) presented by Bayer at the 2021 ISTH Congress, authors used population pharmacokinetic (PK) modelling from available head-to-head studies to predict weekly FVIII consumption of different regimens of **Jivi®**, **Kogenate-FS®**, **Elocta®** and **Adynovi®**. Overall, 49 patients were included in this analysis (n=14, Kogenate®; n=17, Elocta®; n=18, Adynovi®). Targeting a threshold of 3 IU/dL in patients on a prophylaxis regimen of twice a week required lower median doses by approximately 58%, 33% and 35% for treatment with Jivi® compared to treatment with Kogenate®, Elocta® and Adynovi® respectively.

Interim analysis of phase IV HEM-POWER trial for the use of Jivi® in real-world setting

In an abstract (PB0570) from Bayer presented at the 2021 ISTH Congress, authors report on the six-month interim safety analysis of HEM-POWR (NCT03932201), a multicenter, non-interventional, open-label, prospective phase IV trial investigating routine clinical use of **Jivi®**. Planned enrollment is ≥200 PTPs with mild, moderate, or severe haemophilia A.

At data cut-off (21 October), 39 PTPs were enrolled; the safety analysis set included 38 patients (one patient withdrew consent), including eight mild/moderate patients. Most patients (n=32) had received Jivi® within 12 months of baseline for variable time periods (mean [SD]=354.6 [614.02] days). The median (Q1;Q3) dose was 3000 (2000;3650) IU/infusion; the most common dosing regimen being twice-weekly prophylaxis (44%). Twenty-six out of 32 patients provided information about FVIII treatment within 12 months prior to initiation of Jivi®. In this group, the most common dosing frequency was three times weekly (data available for 24 patients). A group of six Jivi®-naïve patients had a comparatively worse bleeding history. There were no study-drug-related treatment-emergent adverse events, nor inhibitor development. Two patients discontinued. Remote follow-up visits were made due to Covid-19; initial visits may now be conducted remotely.

Real-world use of Jivi®: Real-world data from WAPPS-Hemo

During the 2021 ISTH Congress (OC 08.4), researchers led by Mancuso presented data on the pharmacokinetic properties of **Jivi®** in the real-world setting. The researchers extracted data on patient demographics, PK estimates and current prophylaxis regimen from the Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo). One-hundred seventy-six PK studies were retrieved in the database: 160, 15 and one performed in severe, moderate and mild patients. The median (range) age at PK assessment was 34.9 years (12-74), bodyweight 78.5 kg (36-200), dose injected 35.6 IU/kg (8.5-70.5), and dosing interval 3.5 days (1-7). Of the 84 patients with current treatment regimen information available, twice weekly, every five days and every seven days, regimens were used in 57%, 7%, and 5% cases, respectively. PK parameters resulted as follows: mean (SD) clearance was 1.73 ml/h/kg (0.60), mean (SD) volume of distribution was 36.96 ml/kg (7.43) and mean (SD) terminal half-life was 15.94 hours (4.00).

Non-replacement therapies

FVIII mimetics

EAHAD data on the adoption of Hemlibra® for haemophilia A in Europe

The European Association for Haemophilia and Allied Disorders (EAHAD) reported (PB0530) on 2020 data on the adoption of **Hemlibra®** as a treatment for people with HA in Europe. These findings were presented during the 2021 ISTH Congress. Forty-six physicians from 21

countries responded to the EAHAD questionnaire with a total of 3420 patients with severe HA under their care. Hemlibra® is reimbursed for all patients with inhibitors and the majority (88%) of patients without inhibitors. Reducing treatment burden was the main reason to switch both inhibitor and non-inhibitor patients to Hemlibra®. An ABR of zero could be achieved in most patients with inhibitors on Hemlibra® (72.9%). Haemostasis was satisfactory in the majority of the minor (93.7%) and major (90.7%) surgical procedures performed while on Hemlibra®. No major adverse event was reported. In the 35 centres that responded to the question, a total of four patients on Hemlibra® have died to date, although none of these deaths was directly linked to Hemlibra®. The Covid-19 pandemic did not have a considerable impact on the adoption of Hemlibra® in most centres (64.9%). These results are also available in an article published in *Haemophilia*.

Efficacy and safety of prophylaxis with Hemlibra® in people with HA in the UK: A report from the UKHCDO

Researchers from the UK Haemophilia Centre Doctors Organisation (UKHCDO) published data on the safety and efficacy of **Hemlibra®** in people with haemophilia A without inhibitors in an abstract (PB0511) presented at the 2021 ISTH Congress. Authors analysed data from 378 adult patients. Within-person comparison in 179 with ≥6 months pre/post switching data demonstrated significant reduction in bleeding rates with Hemlibra®. The overall bleed-free proportion increased from 37% to 75% in the 36 weeks before and after switching (P<0.001). A sub-analysis of the 44/179 who reported bleeding after switching showed a higher median (IQR) pre-switch ABR of 5.21 (2.20; 16.0) reducing to 1.90 (1.52; 3.67) post; a change of -3.22 (-10.0; -0.36), (p< 0.001). Adverse events, reported in 9/378 (2.4%), occurred predominantly during the loading phase and included: grade 1-2 cutaneous reactions in three, severe headaches in three (resulting in drug cessation in one) and poor efficacy, unrelated to anti-drug antibodies, in one person who reverted to Elocta® prophylaxis. Recurrence of a FVIII inhibitor was reported after six months emicizumab therapy without factor VIII exposure. One death, unrelated to Hemlibra®, was reported. No thrombotic or microangiopathic events occurred.

Real-world experience in introducing Hemlibra® prophylaxis for adults with HA without inhibitors in Ireland

In an abstract (PB0537) from an Irish group of researchers led by Larkin, the authors presented how they tackled the introduction of **Hemlibra®** for patients with HA without inhibitors. They informed 91 people with severe HA by letter of the availability of Hemlibra® as a prophylaxis option. Then, they set up dedicated clinics to enable adequate time for in-depth clinical review and collaborative discussion about the potential benefits or risks of switching. The authors developed a standardised process to support patients and the multi-disciplinary team. This was done to ensure a seamless and safe transition to Hemlibra® for those who chose to change the prophylaxis regimen. To date, 35 patients have been reviewed at the dedicated clinic, and 25 have switched to Hemlibra® prophylaxis. Of the remaining ten patients, seven chose not to switch following the consultation, two were non-compliant with the recording of home treatment (an exclusion for switching), and one is due to start Hemlibra® shortly. Of the patients who switched to Hemlibra®, 24/25 have severe HA. One patient has moderate HA with a severe bleeding phenotype. Fortnightly maintenance doses are the most common treatment frequency (21/25 patients), with the remaining four patients on weekly

maintenance doses. Since switch-over, seven breakthrough bleeds were reported, with five requiring factor replacement (three trauma and two spontaneous bleeds).

US real-world data on treatment patterns and clinical outcomes in patients with HA

During the 2021 ISTH Congress, Sanofi presented (PB0518) the results of a longitudinal, retrospective, observational study of males with HA treated with SHL, EHL, both SHL and EHL factor, and/or **Hemlibra®** (January 2013–May 2020). Data originated from the US-based OM1® Real-World Data Cloud (OM1, Inc., Boston, MA, USA), derived from patient-level healthcare claims and electronic medical records. Most patients with HA on SHL (74% of 457), EHL (Elocta® and other EHLs; 70% of 321), Elocta® (EHL subgroup; 65% of 205), and Hemlibra® (63% of 118) were aged ≥12 years. In patients receiving Elocta® or Hemlibra®, the mean monthly all-factor consumption post-index date was 55% and 65% less, respectively, compared with pre-index consumption. For EHLs overall, the mean all-factor consumption was unchanged. Limited pre-index data presented a challenge in comparing factor consumption in the SHL group. FVIII consumption was reported in 47% (n=56) of Hemlibra®-treated patients. Use of Elocta®, EHLs, or Hemlibra® was associated with decreased ABR (ABR; 34%, 35%, 26%). ABR did not improve with SHL.

Real-world experience of Hemlibra® treatment using entire vials only

A group of Dutch researchers led by Fischer presented during the 2021 ISTH Congress (PB0677) data on **Hemlibra®** plasma concentrations and bleeding control on a maintenance dosing strategy using entire vials at seven to 28-day intervals. In this single-centre study, all patients received maintenance treatment for >two months with Hemlibra® through concentrations available. Loading doses were exactly dosed according to the label. Maintenance treatment was six mg/kg/four weeks using entire vials at seven-28-day intervals. During the study period, 33 patients received a median of 157 days (P25-P75 (IQR) 112-391) of Hemlibra® maintenance treatment. The median age at treatment start was 17 years (IQR 6-51), the median weight 66 kg (IQR 22-83), 30% had inhibitors and 88% severe HA. Median Hemlibra® dose was 5.9 mg/kg/4 weeks (IQR 5.6-6.2), administered in intervals of 7-28 days, with 42% using other intervals than once every week or two weeks. The median Hemlibra® concentrations were 73 µg/ml (IQR 47-82). Only five out of 33 patients (15%) had concentrations <35µg/ml, including three confirmed non-adherent patients. Seventy-nine per cent had zero bleeds during follow-up, independent of Hemlibra® concentrations. The authors stated that this dosing strategy was efficacious and that it led to avoid wastage.

Report from the PedNet Registry on the use of Hemlibra® in paediatric HA Patients

A group of researchers led by Kenet presented data from the PedNet Registry to evaluate the safety and efficacy of **Hemlibra®** prophylaxis in children. This data was presented in an abstract (PB0504) at the 2021 ISTH Congress. The PedNet Registry includes all children with haemophilia born from 1 January 2000 (NCT02979119), diagnosed and treated in one of the 33 participating centres in Europe, Canada and Israel. For this analysis, data were collected from the moment children switched to Hemlibra® until 1 January 2021. Data collected included the total number of bleeds, additional treatment for bleeds, trauma and surgery, as well as adverse events (AE). A total of 141 patients with HA (134 severe, six moderate and one mild) were included, of whom 79 (56%) had inhibitors. Twenty-eight children were below two years of age. The median treatment period in months (IQR) was 17.9 (7.9-28.1) for children with inhibitors and 3.8 (2.3-9.0) months for those without inhibitors. A total of 82 patients

(58%) reported zero bleeds. Major bleeds were more frequent in inhibitor patients; this might be due to longer follow-up for inhibitor patients. Three adverse events were reported: one patient had a local skin reaction, one developed antibodies against Hemlibra®, and one child died from unrelated problems.

Real-world experience with Hemlibra® in paediatric patients with HA and special needs in Mexico

A group of Mexican researchers led by Pompa Garza presented at the 2021 ISTH Congress (PB0637) data on real-world experience with **Hemlibra®** prophylaxis in ten people with HA with special characteristics. The patients were male with median age of eight years. All of them received Hemlibra® for more than four months. The first nine patients switched from FVIII to Hemlibra®, and patients eight and nine were on prophylaxis or ITI with either rFVIII or pdFVIII. Patient ten was a PUP and received FVIII secondary to bleeding. He started treatment with Hemlibra® afterwards. Patient one received ITI for a year without success, he is currently on Hemlibra® and ITI, and he reported zero bleeds since then. Patient four has obesity and autism, and patients six to eight are siblings. All of their caregivers reported improved adherence with the subcutaneous (SQ) therapy started. Patient eight had previously been treated with cryoprecipitates, and has HIV, HCV, and chronic arthropathy. All patients improved their bleeding rate. Eighty per cent had zero bleeds. No significant adverse events were observed. Hemlibra® was well-tolerated in PwHA with special characteristics.

Hemlibra® treatment for neonatal intracranial haemorrhage

During the 2021 ISTH Congress, Dunn reported (PB0632) how **Hemlibra®** was used safely and successfully to treat intracranial haemorrhage in an infant with severe HA who was at increased risk of inhibitor development.

Efficacy of Hemlibra® in obese adults: Results from the phase III HAVEN 1, 3 and 4 studies

In an abstract (PB0495) from Roche Genetech presented at the 2021 ISTH Congress, authors compare ABR and **Hemlibra®** trough concentrations among obese and non-obese adults with HA in HAVEN 1, 3, and 4 in a post-hoc analysis.

At database cut-off (15 May 2020), 44 (17%) and 216 (83%) adults with HA with BMI ≥30 kg/m^2 and BMI <30 kg/m^2 were included and had 94.29 and 522.97 patient-years of Hemlibra® exposure, respectively. Across the study period, adjusted ABRs were 1.48 (95% CI: 0.82–2.68) and 1.40 (95% CI: 1.06–1.85) for adults with BMI ≥30 kg/m^2 and <30 kg/m^2, respectively. ABRs were consistent across the two groups over time. Efficacious trough concentrations were sustained in both groups regardless of the dosing regimen, with concentrations >30 µg/mL. In the once-weekly dosing cohort, mean Hemlibra® trough concentration was 51.47 (3.04) µg/mL and 53.21 (1.18) µg/mL at week five following loading dosing, for adults with BMI ≥30 kg/m^2 (n=27) and <30 kg/m^2 (n=137), respectively.

Effects of Hemlibra® on physical health: Results from the HAVEN 3 and 4 trials

In an article published in *Haemophilia* in June 2021, a group of researchers, including representatives from Roche and Genentech, presented an assessment of the impact of **Hemlibra®** on health-related quality of life (HRQoL) in people with severe HA without FVIII inhibitors in the phase III HAVEN 3 and 4 studies. Among 176 evaluable participants, 96 (55%) had received prior episodic treatment and 80 (45%) prophylaxis; 70% had ≥ 1 target joint, and 51% had experienced ≥ 9 bleeds in the previous 24 weeks. The mean Haemophilia-Specific

Quality of Life Questionnaire for Adults (Haem-A-QoL), physical health and total score improved after Hemlibra® initiation. Fifty-four per cent of participants reported a clinically meaningful improvement in physical health scores (≥ 10 points) by week 73. Subgroups with poorer HRQoL prior to starting Hemlibra® (i.e. receiving episodic treatment, ≥ 9 bleeds, target joints) had the greatest improvements in physical health scores and corresponding reductions in missed workdays; a change was not detected among those previously taking prophylaxis. No change over time was detected by the EQ-5D-5L questionnaire.

Data on Hemlibra® regarding haemostasis, bleeding and sport capacity

A group of researchers led by Boulden sought to determine real-world data on haemostatic, physical activity participation and bleeding outcomes of **Hemlibra®** in people with HA. Their findings were presented at the 2021 ISTH Congress (PB0602). This was a retrospective analysis of clinical and laboratory data. Forty-six people with HA used Hemlibra® for a mean of 9.3 (SD 7) months. People with severe HA had a greater increase in FVIII compared with mild (p=0.006), but both achieved similar levels. The absolute change in thrombin generation was greater for severe (p<0.001) than moderate (p=0.01) or mild (p=.36), but all achieved similar results. People with severe HA engaged actively in physical activities but experienced a lower bleeding rate compared with mild or moderate.

The impact of novel therapies on bone metabolism

A group of researchers led by Manco-Johnson is looking (ISTH 2021 – OC 49.2) at whether the use of **Hemlibra®** will support bone metabolism, as evidence suggests that FVIII is required and it is unknown whether the FVIII effect on bones is mediated by thrombin, factor Xa or FVIII itself. Researchers' results showed that bone biomarkers on Hemlibra® are at least no worse than with factor VIII prophylaxis and may be slightly better. They warn that future research must address long-term bone and joint health in PwHA using novel factor and non-factor therapeutics.

Immunogenicity of Hemlibra®: Analysis of seven clinical trials

In an article published in *Haemophilia* in September 2021, Roche reports on data from seven completed or ongoing phase III clinical trials to evaluate the development of anti-**Hemlibra®** antibodies and their impact on PK, PD, efficacy and safety in people with HA.

Of 668 people with HA evaluable for immunogenicity analysis, 34 (5.1%) developed anti-drug antibodies (ADAs) after exposure to Hemlibra®. ADAs were transient in 14/34 people with HA (41.2%). ADAs were neutralising *in vitro* in 18/34 people with HA (52.9%) and associated with decreased Hemlibra® concentration in four out of 668 evaluable people with HA (0.6%); of those, one (.1%) discontinued Hemlibra® due to loss of efficacy. ADAs without decreased exposure did not impact Hemlibra® efficacy. The proportion of people with HA who had injection-site reactions (ISRs) was higher in ADA-positive people with HA (29.4% vs 20.8%). However, the safety profile was similar between ADA-positive and ADA-negative people with HA, overall. No cases of anaphylaxis or hypersensitivity were reported in ADA-positive participants.

Single-case report on functional transitory anti-Hemlibra® antibody creating bleeding episodes

In an abstract (PB0666) presented at the 2021 ISTH Congress, an Italian group of researchers led by Peyvandi described a new case of partially neutralizing anti-**Hemlibra®** antibody,

developed in a HA patient with no FVIII inhibitor treated with Hemlibra®, which disappeared with continuous use of the drug. This case report regards a 33-years-old male with severe HA without FVIII inhibitor. His replacement therapy was switched to Hemlibra®, receiving the initial four standard loading doses with three mg/kg/week followed by the 1.5 mg/kg/week regimen. After receiving the fifth dose, the patient developed an acute bleeding episode in his right elbow. This acute bleeding required additional treatment of FVIII. Hemlibra® plasma level and development of anti-drug antibodies were controlled. This bleeding episode was associated with a reduction of Hemlibra® concentration and the presence of anti-Hemlibra® antibodies. Since the neutralization was not complete, the patient continued his regular administration using Hemlibra® and a reduced dose of FVIII. The intensity of the anti-drug antibody was reduced at the seventh dose and completely disappeared at the eighth dose with a gradual recovery of Hemlibra® concentration.

Gene Therapy

Global seroprevalence of pre-existing immunity against AAV serotypes in people with haemophilia A

In an abstract from BioMarin (LPB0022) presented at the 2021 ISTH Congress, authors looked at the **prevalence of pre-existing immunity against AAV2, AAV5, AAV6, AAV8 and rh10 capsids** among people with HA in nine countries. Pre-existing immunity may limit treatment success with gene therapy. BioMarin conducted a prospective study in PwHA in Brazil, France, Germany, Italy, Japan, Russia, South Africa, the UK, and the USA. The study enrolled 546 participants: 478 adults (aged ≥18 years) and 68 adolescents (<18 years). Considerable geographic variability was observed in the prevalence of pre-existing antibodies against each serotype, but the percentage of participants positive for AAV5 was consistently the lowest among serotypes and across the countries studied. A greater percentage of adult participants was positive for AAV5 antibodies (36%) compared with adolescents (29%).

Reports from the phase I/II trial of BAY 2599023

During the 2021 ISTH Congress, authors of abstract PB0652 reported on the safety and FVIII activity achieved to-date in the first-in-human, dose-finding study of experimental gene therapy **BAY 2599023**. This experimental therapy is an adeno-associated virus vector with capsid serotype hu37 (AAVhu37) and codon-optimized, B-domain deleted human FVIII. Bayer is developing this treatment.

The phase I/II open-label study (NCT03588299) included males aged ≥18 years with severe HA, >150 exposure days to FVIII products, no history of FVIII inhibitors, and no detectable pre-existing neutralizing antibodies to AAVhu37. Patients received a single intravenous infusion of BAY 2599023. The primary endpoints were adverse events (AEs), serious AEs (SAEs) and AEs/SAEs of special interest (AESIs). The secondary endpoint was FVIII activity over time. Three cohorts of ≥two patients each (n=8) were enrolled sequentially.

At data cut-off (January 2021), FVIII activity data were available for the first six patients. BAY 2599023 delivered sustained FVIII expression levels for up to 21 months, with evidence of bleed protection. Of these six patients, three (cohorts 2 [n=1] and 3 [n=2]) developed AESIs: asymptomatic elevations in alanine aminotransferase, managed reactively with corticosteroids. No SAEs have been reported. Two additional patients recently enrolled in cohort three are being treated prophylactically with corticosteroids.

Results of the phase I/II trial investigating gene therapy SPK-8011

During the 2021 ISTH Congress, data (OC67.2) on cohorts from the ongoing phase I/II trial investigating **SPK-8011** for HA were presented. Spark is developing this experimental gene therapy. Seventeen men (aged 34-52) with HA were infused with adeno-associated viral (AAV) vector (SPK-8011) in four dose cohorts ranging from 5×10^{11} to 2×10^{12} vg/kg, and followed for expression, safety and preliminary efficacy after vector administration. Six participants experienced vector-related adverse events (one with an infusion reaction; five with transient liver transaminase elevations). Two participants lost all FVIII expression due to a presumed cellular immune response to the AAV capsid unresponsive to immunosuppression. The remaining 15 participants maintained FVIII expression; eleven of these were followed for >two years (median 132 weeks, range: 107-182) and demonstrated no significant decrease in FVIII activity over time (mean 12.6 ± 7.3% of normal at 26-52 weeks versus 11.8 ± 7.2% of normal at >52 weeks post vector; 95% CI: [-1.9, 0.3]). The 15 participants with sustained FVIII expression stopped baseline prophylaxis and demonstrated a 93% reduction in ABR (median rate, 12 [range: 0-43] events/year before versus 0.0 [range: 0.0-5.2] after vector administration; 95% CI: [89.0, 96.4]).

Efficacy and safety of valoctocogene roxaparvovec for severe HA: Results from the phase III GENEr8-1 trial

In an abstract (OC 26.1) from the 2021 ISTH Congress, BioMarin presented data from the phase III single-arm, open-label trial (GENEr8-1, NCT03370913) to assess the efficacy and safety of **valoctocogene roxaparvovec** for severe HA. This trial enrolled 134 adult men with severe HA on FVIII prophylaxis negative for FVIII inhibitors. Participants received a single 6×10^{13} vg/kg valoctocogene roxaparvovec infusion. The primary endpoint was a change from baseline in median FVIII activity during weeks 49–52 in HIV-negative participants. The secondary endpoints were changes from baseline in annualised treated bleeds and FVIII infusion rates for participants rolling over from a non-interventional study.

In 132 HIV-negative participants (primary endpoint), chromogenic FVIII activity increased by a mean (95% CI)/median of 41.9 (34.1–49.7)/22.9 IU/dL at weeks 49–52.

In 112 rollover participants (secondary endpoint), mean ABR and FVIII infusion rates decreased after week four by 84% ($p<0.001$) and 99% ($p<0.001$), respectively, from baseline.

After week four, 89/112 (79.5%) participants experienced zero treated bleeds vs 36/112 (32.1%) at baseline; 2/134 (1.5%) resumed prophylaxis. All 134 participants reported an AE, and 22 (16.4%) reported serious AEs. Alanine aminotransferase elevations occurred in 115/134 (86%) participants; of these, 106 and 39 received corticosteroids and/or other immunosuppressants, respectively, per protocol, and 95.6% of events resolved. Other common AEs (≥30%) were headache (38%), nausea (37%), and aspartate aminotransferase elevation (35%). No participants developed FVIII inhibitors or thromboembolism.

Data on the five-year follow-up of valoctocogene roxaparvovec treatment for severe HA

In an abstract (OC 67.1) presented by BioMarin at the 2021 ISTH Congress, the company reported on the safety, tolerability, and efficacy of **valoctocogene roxaparvovec** up to five years after administration among participants in a phase I/II clinical study. The abstract reported on adult male participants with severe HA who had previously been treated with FVIII and received a single intravenous dose of valoctocogene roxaparvovec at 6×10^{13} vg/kg (n=7) or 4×10^{13} vg/kg (n=6). ABR declined from the pre-treatment mean by 95% at year five in the 6×10^{13} vg/kg cohort and 92% at year four in the 4×10^{13} vg/kg cohort. Median (mean) FVIII

activity levels per chromogenic substrate assay were 8.2 (11.6) IU/dL at year five (6×10^{13} vg/kg cohort; n=7) and 4.8 (5.6) IU/dL at year four (4×10^{13} vg/kg cohort; n=six), continuing the decline seen previously.
All participants demonstrated clinical FVIII activity levels associated with reductions in bleeds and FVIII usage. Participants remained off prophylaxis with FVIII concentrates.
After up to five years, there was no inhibitor development and few adverse events. The overall safety profile remains unchanged since previous reports.

FDA puts AFFINE clinical programme on hold

Following the observation of FVIII levels greater than 150% in some study participants, Pfizer voluntarily paused screening and dosing in its phase III AFFINE programme investigating the use of gene therapy **giroctogene fitelparvovec** for the treatment of haemophilia A. This investigational gene therapy is being development in partnership with Sangamo. On 3rd November, the FDA informed Pfizer that the clinical programme has been placed on clinical hold.
To date, no participant receiving this gene therapy has experienced thrombotic events, and some participants with factor levels >150% are being treated with an oral anticoagulant to reduce the risk of thrombosis.
The EHC, together with the National Hemophilia Foundation and the World Federation of Hemophilia released a statement available here.

Spark Therapeutics Updated SPK-8011 Data from Phase 1/2 Study Shows Multi-Year, Durable Factor VIII (FVIII) Expression that Significantly Reduced Bleeding in Haemophilia A Patients

Spark Therapeutics, a member of the Roche Group, reported data from its phase 1/2 clinical trial of investigational **SPK-8011** in haemophilia A (cut-off May 3, 2021 NCT03003533 and NCT03432520. The trial contained 18 men with haemophilia A. Four dose cohorts were enrolled; the lowest-dose cohort received a dose of 5×10^{11} vg/kg, and the highest-dose cohort received 2×101^{2} vg/kg. Some participants received steroids within 52 weeks after vector administration either to prevent or to treat a presumed AAV capsid immune response.

The median safety observation period was 36.6 months (range, 5.5 to 50.3). Two participants lost all factor VIII expression because of an anti–AAV capsid cellular immune response that was not sensitive to immune suppression. In the remaining 16 participants, factor VIII expression was maintained; 12 of these participants were followed for more than two years. Using a one-stage factor VIII assay showed no apparent decrease in factor VIII activity over time (mean [±SD] factor VIII activity, 12.9±6.9% at 26 to 52 weeks when the participants were not receiving steroids vs. 12.0±7.1% at >52 weeks after vector administration. The participants had a 91.5% reduction (95% CI, 88.8 to 94.1) in the annualized bleeding rate (median rate, 8.5 events per year [range, 0 to 43.0] before vector administration vs. 0.3 events per year [range, 0 to 6.5] after vector administration). A 96.4% reduction (95% CI: [95.7, 97.1]) in annualized number of FVIII infusions was also demonstrated.

A total of 33 treatment-related adverse events occurred in eight participants; 17 events were vector-related, including one serious adverse event, and 16 were steroid-related.

AN UPDATE ON NOVEL THERAPIES FOR PEOPLE WITH HAEMOPHILIA B

Replacement Therapy

First interim analysis of a 24-month the French B-SURE study with Alprolix®

During the 2021 ISTH Congress, Sobi presented (OC 081) the interim analysis of the ongoing B-SURE study (NCT03655340). This is a prospective study that evaluates the real-world effectiveness and usage of **Alprolix®** over 24 months. In this analysis, the company presented data on patients with ≥1 follow-up visits after nine months. ABR, dose and injection frequency with on-demand and prophylactic Alprolix® were described and compared to previous FIX therapy. Patient- and clinician-reported satisfaction with Alprolix® was evaluated.

The interim analysis included 59 of 91 enrolled patients. The mean age was 31.1 years (range: 4-67, 13 patients <12 years). Fifty-four patients had severe, three moderate and two mild haemophilia B (HB). At Alprolix® initiation, the prescribed injection frequencies in 56 patients on prophylaxis were: every seven days (n=41), every ten days (n=7), >ten days (n=6) and other (n=2). Last documented dosing frequency was every seven days (n=35), every ten days (n=12), >ten days (n=8) and other (n=1). The median (range) follow-up since Alprolix® initiation was 22 (9.5-107.7) months. In patients on prophylaxis before and after Alprolix® initiation, the ABR on Alprolix® was low with less injection frequency than the previous FIX treatment. Most physicians (92%) and patients (76%) were satisfied or highly satisfied with Alprolix® treatment at the latest assessment.

Halting of clinical development of DalcA

On 12 November, Catalyst Biosciences announced the decision to halt the clinical development of **DalcA** (engineered), report data to date and seek a buyer for its haemophilia programme. The decision reflects a change in business strategy, noting that enrolment for clinical trials had been negatively impacted by the pandemic and competition for participants and increased availability of prophylaxis therapy globally. You can read the full press release here.

Gene Therapy

Report from the HOPE-B phase III trial

During the 2021 ISTH Congress, UniQure reported (OC 67.3, PB0653 and PB0659) on the phase III HOPE-B trial looking at the safety and efficacy of **etranacogene dezaparvovec (AMT-061**) in people with HB at the dose of 2×10^{13}gc/kg. The trial enrolled adult males with HB (FIX≤2%) receiving routine FIX prophylaxis, with/without AAV5 neutralising antibodies (NAbs), following a ≥six-month lead-in. The primary endpoint of the trial is the ABR comparison between etranacogene dezaparvovec and prophylaxis between the lead-in phase and the 52 weeks following stable FIX expression (months 6-18 post-treatment).

Fifty-four participants were dosed and completed 52 weeks of follow-up. During lead-in, 38 patients (70%) had 123 bleeds (42 spontaneous; 66 traumatic; 15 other), despite prophylaxis. Following treatment with etranacogene dezparvovec, FIX activity increased rapidly to a mean 39.0 IU/dl at week 26 and 41.5 IU/dl at week 52. Fifty-two out of 54 participants had successfully discontinued routine prophylaxis. Relative to lead–in, total bleeds reduced by 66.6% and treated bleeds reduced by 80% at 52 weeks. The treatment-related AEs occurred in 39 participants, most of which (81.5%) were mild. Post six-month data cut, a serious AE of hepatocellular carcinoma (HCC) in a subject with multiple pre-existing risk factors was

reported. Integration analyses determined HCC was unlikely to be related to the treatment with etranacogene deaparvovec. No deaths and no inhibitors to FIX were reported.

With regard to AAV5 neutralising antibodies (Nabs), of the 54 participants 23 (42.6%) had AAV5 Nabs at baseline with a median titre of 56.9 and a distribution representative of the general population. One participant (titre 198) received a partial dose and was excluded from efficacy assessments. One participant (titre 3212) did not respond and remained on prophylaxis. All other participants (n=52) discontinued prophylaxis. No correlation of pre-existing NAbs with FIX activity was observed up to a titre of 678. The mean FIX activity at 26 weeks was 32.7 IU/dl in participants with NAbs versus 41.3 IU/dl in those without.

With regard to adverse events, seven of 54 (13%) participants experienced a total of nine infusion-related reactions. Of the nine reactions, five were mild and four were moderate, and they occurred in participants with AAV5 NAbs at baseline (5/7; titer range 23-3212) and in those without (2/7). All events were reported on the day of infusion and most (8/9) resolved on the same day. The first occurrence (a moderate suspected hypersensitivity reaction) occurred after approximately 10% of the dose of etranacogene dezaparvovec was administered; the drug was withdrawn and the participant received intravenous corticosteroids and antihistamines. Subsequent occurrences were managed through a combination of temporarily interrupting or slowing the etranacogene dezaparvovec infusion and/or supportive treatment with steroids/antihistamines. Three mild reactions (e.g. hives, itchiness, headache and dizziness) in three participants required no supportive treatment; this included one participant with a baseline AAV5 NAb titer of 3212. In May 2021, CLS Behring announced the closing of **its global commercialisation and license agreement** with uniQure for etranacogene dezaparvovec.

Data from the AMT-061 phase IIb trial

During the 2021 ISTH Congress, UniQure reported (LPB0020) on the phase IIb clinical trial (NCT03489291) for their Padua-variant gene therapy (**AMT-061**). During this trial, three participants received a single intravenous dose of etranacogene dezaparvovec (2×10^{13} gc/kg) and were to be followed for five years. The primary endpoint was FIX activity at week six, while the secondary endpoints include bleeds, use of FIX replacement, laboratory parameters, joint health, and adverse events (AEs).

Participants had FIX ≤1%, required routine FIX prophylaxis, and had neutralising antibodies (Nabs) to AAV5 at baseline. Following treatment with etranacogene dezaparvovec, FIX activity rapidly increased to a mean of 31% at week six. By two years, mean FIX activity further increased to 44.2%, with FIX activity levels of 45%, 36% and 52% in participants 1-3, respectively. No relationship between treatment response and the presence of anti-AAV5 neutralising antibodies at baseline was observed. One participant experienced a spontaneous mild bleed and self-administered a single infusion of FIX replacement in year two. No clinically significant elevations in liver enzymes occurred, and no participant required steroids related to treatment. As reported previously, one participant experienced two mild AEs possibly related to treatment shortly after dosing, and one participant underwent hip surgery. No participant developed inhibitors to FIX.

Five-year data for AMT-060 phase I/II trial

In an abstract presented (OC 26.3) at the 2021 ISTH Congress, UniQure reported on the phase I/II (NCT02396342) results on the safety and efficacy of **AMT-060**. This experimental therapy was evaluated in ten participants with severe to moderately severe haemophilia B (HB) over

five years. Participants were split into two cohorts, cohort 1, receiving 5×10^{12} gc/kg (n=5) or cohort 2, receiving 2×10^{13} gc/kg (n=5). Endpoints included FIX activity, ABR, FIX replacement use, and treatment-related adverse events (TRAE). Mean FIX activity through five years was 5.2% in cohort 1 (versus 4.4%; 6.8%; 7.3%; 7.0% through years 1-4 respectively) and 7.2% in cohort 2 (versus 7.1%; 8.4%; 7.9%; 7.4% through years 1-4, respectively). Mean ABR during the last 12 and six months of observation was 6.5 for cohort 1 and 0.0 for cohort 2 (55% and 100% reduction vs. the year prior to treatment, respectively). In the same period, FIX replacement therapy consumption declined 84% (cohort 1) and 99% (cohort 2). All participants who discontinued prophylaxis remained prophylaxis-free through five years. No participants developed FIX inhibitors or signs of sustained AAV5 capsid-specific T-cell activation. TRAE were mainly reported in the first 3.5 months after treatment, including three cases of transient mild elevations in alanine aminotransferase.

Evaluation of liver health after fidanacogene elaparvovec gene therapy

In an abstract presented by Pfizer (PB0532) during the 2021 ISTH Congress, authors presented data on liver health following treatment with **PF-06838435 (fidanacogene elaparvovec)**, an AAV-based investigational gene therapy for haemophilia B. The therapy was administered to 15 adult males with moderately severe to severe haemophilia B as part of a phase I/IIa study. Patients with a history of HCV and/or HBV were eligible for study entry if liver health parameters were met. After completing the phase I/IIa study, 14/15 patients were enrolled in the long-term follow-up study for an additional follow-up of five years. One participant withdrew from long-term follow-up study three years post-infusion. Ten of the 14 participants who continued into the long-term follow-up study had a history of resolved HCV, and seven participants also had prior HBV. With follow-up ranging from 32 to 60 months, abnormalities on annual liver ultrasound included fatty liver in one participant. There were no significant elevations in plasma alfa-fetoprotein. Most common findings have been mild sustained elevations of alanine aminotransferase of uncertain aetiology. FIX activity levels have remained relatively stable in these patients.

Comparison of FIX:C results across AAV gene therapy trials

Authors of an abstract (LPB0021) from Freeline describe an international multicentre field study conducted to characterise **FIX-R338L (factor IX-Padua)** activity across 15 commonly used FIX activity assays. Results showed greater than three-fold variation in FIX-R338L activity depending on the assay used. The authors developed a 'calculator' based on SynthASil™ FIX ratios with commonly used FIX assays. Abstract authors claim that FIX:C ratios derived from the FIX-R338L field study permit direct, reliable comparison of FIX:C assay results. Their 'calculator' enables the estimation of activity results facilitating a meaningful comparison of different investigational FIX-R338L-based HB gene therapies. These results were presented at the 2021 ISTH Congress.

AN UPDATE ON NOVEL NON-FACTOR REPLACEMENT THERAPIES FOR PEOPLE WITH HAEMOPHILIA A and B with or without INHIBITORS

Bypassing agents

Efficacy and safety of Sevenfact® in adults with HA and HB and inhibitors: Results from the PERSEPT 1 study

In an abstract (PB0544) presented at the 2021 ISTH Congress, LFB And HEMA Biologics reported on the evaluation of the efficacy and safety of **eptacog beta** (US brand name **Sevenfact®**) for the treatment of bleeding episodes (BEs) in adult/adolescent (≥12 years of age) people with HA and HB and inhibitors. Eptacog beta is a human activated recombinant FVII (rFVIIa) isolated from the milk of genetically engineered rabbits.

The PERSEPT 1 study was a randomised, crossover, phase III study. Patients received either an initial dose (ID) of 75 or 225µg/kg of eptacog alfa followed by per-protocol dosing of 75µg/kg at prespecified intervals (determined by clinical response). The primary efficacy endpoint was the proportion of BEs of all severities (mild, moderate and severe) with 'good' or 'excellent' responses at 12h. Other efficacy endpoints were time to response, the number of administrations, bleeding recurrence, responses at 24h and pain assessments at 12h (Visual Analogue Scale).

Four hundred and sixty-five mild/moderate and three severe BEs were treated in 27 people with HA and HB and inhibitors. The haemostatic response was achieved in 94% of BEs in the 225µg/kg initial dose regimen (IDR; n=216) and 86% in the 75µg/kg IDR (n=252) within 12h. The median time to response was three hours and six hours, respectively, in mild/moderate BEs. Haemostasis was achieved at 12h for the three severe BEs. A single dose of 225µg/kg achieved response in 81.3% of BEs compared to 29% with the 75µg/kg dose regardless of bleed severity.

Pain was relieved in ≥89% of cases by 12h for both IDRs. The success proportion at 24h was >98%; most BEs had no recurrence or need for alternative treatment. No thromboembolic, allergic, or anti-drug antibodies were observed.

Treatment of bleeding episodes with Sevenfact® in children with HA and HB and inhibitors: Results from the PERSPEPT 2 phase III study

In an abstract (PB0536) presented at the 2021 ISTH Congress from LFB and HEMA Biologics, authors assessed the efficacy and safety of **eptacog beta** (US brand name **Sevenfact®**) in treating bleeding episodes (BEs) in the paediatric population with HA and HB and inhibitors.

The PERSEPT 2 study was a randomised, crossover, international, phase III study of eptacog beta in the paediatric population with HA and HB and inhibitors. Patients received either an initial dose (ID) of 75 or 225µg/kg of eptacog beta followed by per-protocol dosing of 75µg/kg at prespecified intervals (determined by clinical response).

The primary efficacy endpoint was the proportion of BEs of all severities (mild, moderate and severe) with 'good' or 'excellent' response at 12h after the initial dose. The secondary and tertiary efficacy endpoints included time to response, number of administrations, pain relief at 12h, bleeding recurrence within 24h, and responses at 24h.

Twenty-five patients (range 1-11 years; median 5.0 years) received eptacog beta treatment for 549 BEs (546 mild/moderate, three severe). Of these, 239 BEs (67%) treated with 75µg/kg initial dose regimen (IDR) and 310 BEs (63%) treated with 225µg/kg IDR achieved haemostatic response within 12h; median time to response was 9h and 12h, respectively. A response was

achieved with a median of three doses with 75µg/kg IDR and two doses with the 225µg/kg IDRs. Pain was relieved within 12 hours in the vast majority of cases (>90%). Most BEs (>98%) had no recurrence, and the success proportion at 24h was >97% for both IDRs.
Eptacog beta was well tolerated. No thromboembolic, allergic, or treatment-related AEs were reported. No neutralising antibodies to eptacog beta were observed.

Safety of Sevenfact® for the treatment of people with HA and HB and inhibitors, including in peri-surgical settings

In an abstract (PB0547) presented at the 2021 ISTH Congress, LFB and HEMA Biologics reported on the overall pooled safety data from three pivotal prospective phase III studies (PERSEPT 1, 2, and 3) using **eptacog beta** (US brand name **Sevenfact®**) in adult, paediatric, and peri-surgical settings in people with HA and HB and inhibitors. The results were also published in an article in *Haemophilia*.
The trials included 27 people in PERSEPT 1 (ages 12-54) and 25 in PERSEPT 2 (ages 1-11) treated BEs with an initial dose of 75 or 225 µg/kg EB followed by per-protocol dosing of 75 µg/kg at prespecified intervals (determined by clinical response). Twelve PERSEPT 3 subjects (ages 2-56) received initial peri-operative dosing of 75 µg/kg (for minor procedures) or 200 µg/kg (for major surgeries) with subsequent 75 µg/kg doses given intraoperatively and post-operatively as per protocol. The primary efficacy endpoint success proportion was 100% for minor procedures and 66.7% for major procedures; 81.8% of the procedures were considered successful using eptacog beta. The results of the PERSPECT 3 trial are also published in an article in *Haemophilia*.
Sixty people with HA and HB and inhibitors received 3,388 doses of eptacog beta during 1,087 exposure episodes (associated with BEs, invasive procedures, post-operative treatments, or pharmacokinetic assessments). Of 133 AEs, ten were treatment-related, and seven were serious AEs (SAEs). None of those seven SAEs were considered treatment-related. They included acute tonsillitis, subarachnoid haemorrhage, intracranial bleed, paresis (weak or impaired muscle movement), bloody stool/dysentery, blood loss anaemia, and gastrointestinal haemorrhage. One death occurred due to blood loss anaemia deemed unlikely related to eptacog beta treatment by the independent PERSEPT 3 Data Monitoring Committee. Overall, eptacog beta was well-tolerated; no allergic, hypersensitivity, anaphylactic, or thrombotic events occurred. No neutralising anti- eptacog beta antibodies were detected.

Halting of clinical development of MarzAA

On 12 November, Catalyst Biosciences announced the decision to halt the clinical development of **marzeptacog alfa (activated) (MarzAA)**, report data to date and seek a buyer for its haemophilia programme. The decision reflects a change in business strategy, noting that enrolment for the MarzAA clinical trials had been negatively impacted by the pandemic and competition for participants and increased availability of prophylaxis therapy globally. You can read the full press release here.

Report from the phase II trial for the use of MarzAA in people with haemophilia and inhibitors

In an article published in June in *Haemophilia*, Catalyst Biosciences reports on the results of the phase II trial to investigate if daily SQ administration of **marzeptacog alfa (activated) (MarzAA)** in people with inhibitors can provide effective prophylaxis. This multicentre, open-

label phase II trial (NCT03407651) enrolled men with severe congenital haemophilia with an inhibitor. All subjects had a baseline ABR of ≥12 events/year. Subjects received a single 18 µg/kg intravenous dose of MarzAA to measure 24-hour PK/PD, a single 30 µg/kg SC dose to measure 48-hour PK/PD, then daily SQ 30 µg/kg MarzAA for 50 days. If spontaneous bleeding occurred, the dose was sequentially escalated to 60, 90, or 120 µg/kg, with 50 days at the final effective dose without spontaneous bleeding to proceed to a 30-day follow-up. The primary endpoint was a reduction in ABR. Secondary endpoints were safety, tolerability, and anti-drug antibodies (ADA) formation.
In the eleven subjects, the mean ABR significantly reduced from 19.8 to 1.6, and the mean proportion of days with bleeding significantly reduced from 12.3% to 0.8%. Of a total of 517 SQ doses, six injection site reactions in two subjects were reported. No ADAs were detected. One fatal unrelated serious adverse event occurred: intracerebral haemorrhage due to untreated hypertension.

FVIII mimetics

Safety of aPCC and Hemlibra® in a dose-escalating study

In an abstract (PO 12) at the 2021 BIC Congress from a US group of researchers led by Kizilocak, reported on a study to determine thrombin generation (TG) of *in vitro* spiking and *in vivo* administration of **activated prothrombin complex concentrate (aPCC)** at escalating concentrations/doses in patients with HA and inhibitors on **Hemlibra®**. People on Hemlibra® can still experience breakthrough bleeds and may need treatment with aPCC. A concomitant drug reaction between Hemlibra® and aPCC resulting in thrombotic events was noted in the HAVEN 1 study which led to a reduction in the use of aPCC. Previous *in vitro* studies demonstrated excess thrombin generation (TG) when aPCC was spiked into simulated haemophilia inhibitor plasma with Hemlibra®.
Nine patients with severe HA and inhibitors currently on Hemlibra® were enrolled in the study. This study demonstrates that spiking experiments of aPCC and Hemlibra® may be misleading. The *in vitro* portion of the study demonstrated that clinically relevant concentrations of aPCC resulted in excessive TG, however *in vivo* administration of aPCC to the same patients demonstrated significantly different results, with most of the patients (66%) having normal (not excessive) TG at the approved doses of aPCC. In conclusion, this data suggests that a single licensed dose of aPCC is safe for most patients on Hemlibra® and importantly calls into question the validity of *in vitro* spiking studies using TG in this setting.

Final analysis of the STASEY trial to evaluate the safety and efficacy of Hemlibra® in people with HA and inhibitors

In an abstract presented by Roche (PB0521), authors reported on the final analysis from STASEY (NCT03191799), a phase III trial assessing the safety of **Hemlibra®** prophylaxis in PwHA with FVIII inhibitors. At the date of the last participant's last visit (19-November-2020), 193 PwHA (median age [range]: 28.0 [12–80] years) had received ≥one dose of Hemlibra®, thus forming the safety-evaluable population. The median (range) treatment duration was 103.1 (1.1–108.3) weeks. Hemlibra® was well-tolerated. The most common AEs were joint stiffness (n=33, 17.1%), cold (n=30, 15.5%), and headache (n=29, 15.0%). No new thrombotic events (TEs) were reported since the two in the interim analyses (myocardial infarction; hypertrophic clot). Hemlibra®-related AEs were reported in 35 (18.1%) participants; most frequently, injection-site reactions (n=19, 9.8%). Further to the fatality reported at the first interim analysis, one death was reported (abdominal compartment syndrome; deemed unrelated to

Hemlibra®). Five people with HA received aPCC, with no associated TMAs or TEs. Ten (5.2%) participants developed anti-drug antibodies (ADAs), five (2.6%) were neutralizing *in vitro*, which had no effect on the pharmacokinetics. Mean ABR for treated bleeds was 0.5, with 82.6% of participants having zero treated bleeds.

Report of Hemlibra® prophylaxis in a woman with mild haemophilia

A group of Brazilian investigators reported (PB0683) during the 2021 ISTH Congress on the first Brazilian woman with mild haemophilia (FVIII activity was 10.0%) treated with **Hemlibra®**. The patient suffered from Melnick-Needles syndrome, which made venous access difficult. On-demand intravenous FVIII was started (peripheral venous access was difficult to provide due to her body structure). She developed a high-response inhibitor two years later, but ITI was not tried because central venous access could not be performed. She was kept on self-infused intravenous activated recombinant factor VII (rFVIIa) as episodic treatment. Between Jan/28/2019 and Jan/28/2020 her ABR was 11.0. Her Functional Independence Score in Hemophilia (FISH) was 21. Total rFVIIa consumption was 375mg. On Jan/28/2020, at 28 years, she received a subcutaneous Hemlibra® loading dose of 3.0mg/kg once weekly for four weeks and 1.5mg/kg weekly as maintenance. She self-infused Hemlibra® at home. From Jan/28/2020 to Jan/28/2021, ABR was 0.0, and her FISH increased to 30, although she did not receive Hemlibra® during five consecutive weeks from May-Jun/2020 and two consecutive weeks on Jul/2020. Her estimated annual consumption of Hemlibra® was 2,520mg (loading dose and maintenance during the first year), or 2,340mg, for each additional year without loading doses.

Real-world data on Hemlibra® prophylaxis

In an abstract (OC 32.2) presented at the 2021 ISTH Congress, researchers led by Barg, presented a study on the efficacy and safety of longitudinal **Hemlibra®** prophylaxis and to assess laboratory monitoring in a large patient cohort.

A total of 109 adults (n=49) and children with severe HA composed the study's cohort, with follow-up for up to 2.5 years. Remaining bleeds among children were mostly trauma-related, whereas adults sustained spontaneous joint bleeds. A fatal outcome was observed in one infant, who also presented with central venous line thrombosis. A significant decrease of FVIII inhibitor levels was noted among the patients with FVIII inhibitors ($p<0.001$). Thrombin generation increased and was sustained in all patients, yet it did not correlate with patients' bleeding risk.

Impact of Hemlibra® on quality of life

A group of UK researchers led by Fletcher presented (PB0684) at the 2021 ISTH Congress the 'Emi and Me' study results on experiences with **Hemlibra®** for PWHi and their families. Fifteen participants participated in a single qualitative interview. Six themes emerged: a reduction in bleed frequency; a reduction in treatment burden; an increased sense of freedom (for both PWHi and family members); decreased pain; enhanced wellbeing; and decrease in unachieved potential. Despite this, some participants felt that pre-existing physical disabilities and a lack of physiotherapy support have prevented them from achieving the levels of functional ability they expected these improvements to facilitate.

Use of Hemlibra® and rFVIIa for major orthopaedic surgeries in patients with HA and inhibitors

A group of Italian researchers led by Carulli presented (LPB0117) at the 2021 ISTH Congress on the first experience with major orthopaedic surgery with several procedures at a single haemophilia centre in people with HA and inhibitors. Between 2018 and 2020, three PWHA with high titre inhibitors underwent five major orthopaedic surgeries: one above-the-knee amputation and total knee arthroplasty (TKA) in a 56-year-old subject; a total hip arthroplasty (THA) in a 59-year-old patient; a partial revision knee arthroplasty (rTKA) and an acetabular revision (i.e., extracting failed implants with minimal host tissue and bone destruction) on a failed THA in a 49-year-old subject. Visual Analogic Scale (VAS), Haemophilic Joint Health Score (HJHS), and a post-operative radiologic study were used to evaluate patients. The prophylaxis was performed by a regimen of weekly **Hemlibra®** and bolus infusions of rFVIIa.

A single surgeon successfully treated all patients, without any intra- or post-operative complications and with effective bleeding control. No signs of hypercoagulability or thrombotic microangiopathy were observed clinically and using specific laboratory markers. All patients were regularly rehabilitated at the same hospital. The mean follow-up is 15.7 months (range: 5-24). No adverse event was recorded at the latest evaluation. All patients reported satisfaction, pain reduction, and improved VAS and HJHS scores.

Cost-effectiveness analysis of ITI with bypassing agents or Hemlibra® for bleed prevention

A group of Brazilian researchers led by Camelo compared costs and outcomes of the Brazilian ITI protocol (BIP) looking at various treatments including **rFVIII**, **bypassing agents** and **Hemlibra®**.

The Brazilian ITI protocol recommends starting ITI at a low-dose rFVIII regimen (50IU/kg 3x/week) for all people with HA and inhibitors and, upon a poor response, increasing rFVIII dose to 100IU/kg/day. BPA can be prescribed to treat or prevent bleeding during ITI. The ITI outcomes were either success (inhibitor titre <2 BU/mL and FVIII responsiveness) or failure. The success rate of the BIP was 71%. ITI+BPA resulted in 8.25 bleeds over ITI+ Hemlibra®, and each additional bleed cost US$20,799.28. By deterministic sensitivity analysis, the most impactful variable to the incremental cost was the Hemlibra® price: if the incorporation proposed price was used, the savings generated using Hemlibra® could reach US$254,319.20 for each person with haemophilia and inhibitors on ITI. These findings were presented at the 2021 ISTH Congress (PB0678).

Laboratory issues when switching from Hemlibra® to ITI: A case report

In an abstract (PO 13) from the BIC 2021 Congress, Croatian researchers led by Herak presented a study on the laboratory long-term follow-up results of a nine-year-old boy with severe HA and inhibitors treated with **Hemlibra®** and switched to ITI. Authors note that Hemlibra® has a huge influence on standard laboratory assays and can lead to a misleading interpretation of coagulation results in Hemlibra®-treated patients. As quantification of inhibitors is the prerequisite for the successful immune tolerance induction (ITI), when switching from Hemlibra® prophylaxis to ITI, laboratory follow-up must be adequate due to the long- term effect of Hemlibra®.

The boy received an Hemlibra® loading dose (3 mg/kg) once weekly for four weeks, followed by maintenance with lower doses (1.5 mg/kg) once weekly for four weeks. One month after the last dose, the boy was switched to ITI with daily administration of plasma-derived FVIII concentrate (Octanate® 2500 IU/L). Laboratory results obtained during a four-month period

showed remarkable shortening of aPTT results and high FVIII:C activities measured with clot-based assay up to two months after Hemlibra® discontinuation. Even low Hemlibra® activity (1.6 IU/ dL) resulted in falsely low inhibitor titre (3.9 BU/mL) using a clot-based assay, compared to chromogenic Bethesda assay with human and bovine reagents (57.6 and 58.9 BU/mL, respectively). In conclusion, the authors note that residual Hemlibra® activity after discontinuation needs to be considered when performing clot-based coagulation assays in the further follow-up of patients. Regarding inhibitor testing, unlike clotting assays, both chromogenic methods enabled reliable quantification.

Rebalancing agents

Population pharmacokinetic and pharmacodynamic modelling for dosing regimens with fitusiran

In an abstract (PB0526) presented by Sanofi Genzyme at the 2021 ISTH Congress, researchers gave an analysis aimed to characterise the antithrombin (AT) dynamics by population pharmacokinetic and pharmacodynamic (PopPK/PD) model and predict dosing regimens to mitigate the risk of thrombotic events. This model will help to perform simulations for dosing selection in clinical trials with **fitusiran**. This investigational product is an SQ-administered, small interference RNA therapeutic targeting AT and restoring thrombin generation sufficient to rebalance haemostasis in people with HA or HB with or without inhibitors.

AT activity data from phase I (NCT02035605) and phase II (NCT02554773) studies in healthy subjects and people with HA or HB, with or without inhibitors, were used to develop the PopPK/PD model. The model was externally validated using AT activity data from phase III studies (NCT0341710, NCT03417245 and NCT03549871). The PopPK/PD model was used to simulate AT activity at various dosing regimens in 1000 virtual patients.

The validated model used in simulations assuming 1000 virtual patients with haemophilia receiving possible fitusiran dosing regimens (50 mg monthly [QM], 50 mg once every two months [Q2M], and 80 mg QM) to maintain AT activity levels ≥15% and ≤35% within each dosing interval. The simulation showed a starting dose of 50 mg Q2M caused the majority of patients to maintain AT activity above 15%. Patients with peak AT activity >35% at steady state with 50 mg Q2M would be considered to switch to 50 mg QM, with a subset needing escalation to 80 mg QM. The model will be used to confirm the proposed dosing regimens and adjust as necessary.

Results from the phase IIa trial for the use of SerpinPC in people with HA or HB

In a press release from Centessa Pharmaceuticals plc, together with ApcinteX Limited, the companies announced in September results from the phase IIa trial of AP-0101, the six-month repeat dose portion of its ongoing first-in-human proof-of-concept study evaluating **SerpinPC** in people with severe HA and HB.

AP-0101 is a phase I/IIa proof-of-concept study evaluating SerpinPC, an inhibitor of activated protein C (“APC”), in 23 male subjects with either severe HA or HB who were not on prophylaxis. The phase IIa part of the study assessed the safety, tolerability and pharmacokinetics across three dose cohorts (0.3 mg/kg, 0.6 mg/kg and 1.2 mg/kg) of SerpinPC administered as a subcutaneous (SC) injection every four weeks over 24 weeks (six total doses). Reduction in the ABRs were exploratory outcomes. Although eligible, none of the patients in the study had inhibitors.

SerpinPC was well-tolerated. As previously disclosed, one subject with a history of a skin disorder discontinued treatment on SerpinPC due to an injection site reaction. No other

SerpinPC-related adverse events have been recorded. There was no reported sustained elevation in D-dimer, a sensitive measure of excess thrombin generation, throughout the 24-week study. Two subjects had anti-drug antibodies and remained on treatment without apparent impact on ABRs.
In the highest dose cohort, SerpinPC reduced the self-reported all bleeds ABR by 88% during the last 12 weeks of treatment (pre-specified primary assessment period) compared to the all bleeds ABR prospectively measured during the pre-exposure observation period. Five out of eight subjects had zero or one bleed in the highest dose cohort during the 12-week pre-specified primary assessment period. Self-reported spontaneous joint bleeds ABR was reduced by 94% in the highest dose cohort. ABR reductions were similar between patients with either HA or HB. The median number of target joints (joint with >3 bleeds in any six month) was reduced to zero at the end of the study from a pre-exposure baseline of 2.5. All subjects had target joints at the start of the study, and 15 subjects had zero target joints at the end of the study. These results were also presented during the 2021 BIC Congress.
All 22 patients who completed the phase IIa portion of the study have elected to enrol into the 48-week open-label extension ("OLE") portion of the study in which a single flat 60 mg subcutaneous dose of SerpinPC will be administered every four weeks over 48 weeks (13 doses total). Centessa expects to report results from the OLE portion of this study in the second half of 2022.

Results from the main and extension phase II trials with concizumab

In an abstract (PB0514) presented at the 2021 ISTH Congress, researchers led by Astermark presented the results from the combined main and extension parts of the **concizumab** explorer4 (NCT03196284) and explorer5 (NCT03196297) phase II trials. Concizumab is an anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody in phase III clinical development as once-daily subcutaneous prophylaxis for HA and HB with and without inhibitors. Novo Nordisk is developing this investigational product.
The objective of the extension part of the trials was to assess the long-term efficacy and safety of concizumab in HA/HB with inhibitors (HAwI/HBwI) (explorer4) and in severe HA (explorer5). Both trials comprised a main (≥24 weeks) and an extension part (up to 102 weeks in total). Patients were treated with 0.15 mg/kg concizumab with potential dose escalation to 0.20 and 0.25 mg/kg if they experienced ≥3 treated spontaneous bleeds within 12 weeks. The study endpoints included ABR, change in coagulation-related parameters, number of AEs and ADA occurrence during the trial.
During the trials, 36 HA, 15 HAwI and ten HBwI patients were exposed to concizumab. Concizumab efficacy was maintained in HA, HAwI and HBwI patients in the trial extension parts. D-dimer and prothrombin fragment 1+2 increases were observed with increasing concizumab concentrations in some patients, reflecting concizumab's haemostatic effect. The majority of ADAs observed were low-titre and transient, with no observed clinical effect. There were no AEs leading to withdrawal, no thromboembolic events, and no deaths during the trial's either main or extension parts.

Safety and efficacy of concizumab for patients switching from on-demand rFVIIa: Results from the phase II explorer4 trial in people with HA or HB and inhibitors

In an abstract (PB0503) from Novo Nordisk presented at the 2021 ISTH Congress, authors reported on the assessment of safety and efficacy in patients who switched from recombinant

activated FVII (rFVIIa) on-demand treatment in the main part of the explorer4 study to daily **concizumab** prophylaxis in the extension.
The patients were randomized 2:1 and received daily concizumab prophylaxis/rFVIIa on-demand during the explorer4 main part (≥24 weeks). During the extension (56–94 weeks), on-demand patients switched to 0.15 mg/kg concizumab prophylaxis (following a loading dose of 0.5 mg/kg), with the possibility to escalate to 0.20 and 0.25 mg/kg (if ≥3 spontaneous treated bleeds occurred within 12 weeks).
Eight patients (six HAwI; two HBwI) were included in this sub-analysis. Two patients remained on 0.15 mg/kg concizumab; three escalated to 0.20 mg/kg and three to 0.25 mg/kg. One patient fulfilled protocol-defined lack of efficacy criteria on 0.25 mg/kg and was withdrawn. Estimated mean ABR (95% CI) was 19.2 (10.7; 34.2) vs 4.9 (2.4; 10.0) for on-demand treatment and concizumab prophylaxis, respectively. The estimated mean spontaneous and joint bleed ABR (95% CI) decreased from 17.0 (9.7; 29.8) to 2.5 (1.1; 5.7), and from 14.8 (8.1; 26.9) to 3.0 (1.3; 6.9), respectively. Three patients experienced zero bleeds on their last concizumab dose level (exposure time: 212, 115, 303 days). There were no safety signals following concizumab switching.

Immunogenicity in the concizumab phase II clinical trials: Clinical impact of ADA

In an abstract (OC 32.3) from Novo Nordisk presented at the 2021 ISTH Congress, authors present their investigation into **concizumab** ADA clinical impact in phase II clinical trial.
Binding ADA analysis was performed in explorer4 (HA/HB with inhibitors) and explorer5 (HA without inhibitors). Confirmed positive samples were further characterized for neutralizing activity using a modified TFPI functionality assay. Immunogenicity data were assessed in relation to the bleeding pattern, concizumab concentrations, free TFPI and safety parameters. Results from the trial main and extension parts were presented (≥76 weeks of treatment).
In explorer4, six out of 25 patients developed concizumab-binding ADAs; five patients had low-titer binding antibodies with no significant changes in bleeding pattern, concizumab and free TFPI levels, AEs or coagulation laboratory parameters. In three out of five patients, antibodies were transient and decreased to below detection during the trial. One patient with low-titre ADAs, after experiencing trauma, developed high-titre ADAs with *in vitro* neutralizing activity. This patient continued to receive concizumab, despite free TFPI restoration, reporting two bleeding episodes over a period of >7 months.
In explorer5, transient, low-titre binding antibodies against concizumab developed in nine out of 36 patients, with no significant changes in bleeding pattern, concizumab levels, free TFPI, AEs or coagulation laboratory parameters. In one patient, a positive *in vitro* neutralizing result was recorded at one visit, with subsequent visits negative.
In conclusion, in concizumab phase II trial, 25% of patients developed ADAs; the vast majority had low-titre, transient ADAs with no observed clinical effect. Only in one patient with trauma-induced high-titre ADAs, a correlation to clinical impact could be made due to free TFPI restoration; however, the clinical effect remains inconclusive.

Safety and efficacy of marstacimab in HA and HB: Results from the phase II study

In an abstract (OC32.4) presented at the 2021 ISTH Conference, Pfizer evaluated the long-term safety and efficacy of **marstacimab** in patients with severe HA or HB. Marstacimab is a monoclonal antibody targeting tissue factor pathway inhibitor (TFPI) to augment clotting activity. Patients who completed a previous short-term, phase I/II dose-escalation study of

marstacimab (NCT02974855) or who were enrolling *de novo* could participate in this open-label study (NCT03363321).

This long-term study (treatment up to 365 days) enrolled male patients with severe (factor VIII or factor IX ≤1%) HA or HB (with/without inhibitors) aged ≥12 to <75 years. Patients were assigned to either a 300-mg subcutaneous loading dose of marstacimab followed by 150 mg once weekly (QW) or 300 mg QW. Safety parameters included AEs, vital signs, laboratory, physical examination, and electrocardiograph assessments. Efficacy was assessed using ABR.

Eighteen patients from the previous dose escalation study and two *de novo* patients with severe HA and inhibitors were enrolled, ten in the 150-mg dose group (HA, n=7; HA with inhibitors, n=2; HB, n=1); ten in the 300-mg group (HA, n=5; HA with inhibitors, n=5). Mean durations of marstacimab exposure were 318 and 335 days, respectively. Twenty-four AEs (one treatment-related) occurred in seven (70.0%) patients in the 150-mg cohort; 15 AEs (two treatment-related) occurred in seven (70.0%) patients in the 300-mg cohort. Treatment-related AEs were injection-site reactions (n=2) and haematoma (n=1); one patient had two serious non-treatment-related AEs (traumatic cerebral haemorrhage; generalised tonic-clonic seizure). No patients discontinued because of AEs, and none developed ADAs. No thrombotic events were reported. Mean ABR decreased by 92.6% and 84.5% in the 300-mg QW cohort and 150-mg QW cohort, respectively, versus the pre-treatment period.

AN UPDATE ON NOVEL THERAPIES FOR PEOPLE WITH VON WILLEBRAND DISEASE

Replacement therapies

Pharmacokinetics/pharmacodynamics of Vonvendi® prophylaxis in adult VWD patients

In an abstract (PB0917) presented by Takeda during the 2021 ISTH Congress, authors report on the evaluation of the pharmacokinetic (PK) and pharmacodynamic (PD) parameters following one year of prophylaxis with **Vonvendi®**, a recombinant VWF.

Authors collected PK/PD samples from a phase III, open-label, international, multicentre study of Vonvendi® prophylaxis in adult patients with severe VWD (NCT02973087). Patients transitioning from on-demand (OD) treatment with any VWF (prior OD arm) or prophylaxis with plasma-derived VWF (switch arm) received Vonvendi®, prophylaxis for ≥1 year. Most trial participants had type 3 VWD.

In prior OD patients (n=12), following a single intravenous dose after washout (50±5 IU/kg VWF:RCo), maximum plasma concentration (C_{max}) was 72.7 IU/dL, and area under the curve (AUC_{inf}) was 1113 IU*h/dL. Following one year of twice-weekly prophylaxis (50±10 IU/kg VWF:RCo), C_{max} and AUC over 96 h ($AUC_{tau,96h}$) for VWF:RCo were 83.9 IU/dL and 1218 IU*h/dL, respectively. The corresponding FVIII:C GeoLSMeans were: 85.6 IU/dL (C_{max}) and 4466 IU*h/dL ($AUC_{0\text{-}tlast}$) initially, and 93.6 IU/dL (C_{max}) and 5453 IU*h/dL ($AUC_{tau,96h}$) at study completion. Trough FVIII:C levels increased from 3.83 IU/dL (baseline) to 18.7 IU/dL after one year prophylaxis. In switch patients (N=10), VWF:RCo and FVIII:C were generally comparable between initial steady state and following one year of Vonvendi® prophylaxis.

Pharmacokinetic data for VWF:RCo were stable over one year of Vonvendi® prophylaxis. In Prior OD patients, FVIII:C trough levels increased almost five-fold from baseline to steady state. Following long-term prophylaxis, increases in FVIII:C trough levels were maintained for one year in Vonvendi®-treated patients.

Results of the phase III trial for the study of Vonvendi® in people with severe VWD

In an abstract (LPB0128) presented by Takeda at the 2021 ISTH Congress, authors report on the efficacy and safety of **Vonvendi®** prophylaxis. The data comes from a prospective, open-label, non-randomized, multicentre, phase III study (NCT02973087) in which eligible patients aged ≥18 years had severe VWD and required VWF therapy to manage BEs in the past year either with OD treatment (prior OD arm) or with pdVWF prophylaxis (switch arm). Participants had no VWF or factor VIII inhibitors or history of thromboembolic events. The planned Vonvendi® prophylaxis duration was ≥one year: prior OD patients started with 50±10 IU/kg twice weekly; starting dose for switch patients was based on prior pdVWF weekly VWF dose and dosing frequency (one to three times weekly; maximum 80 IU/kg/infusion). The primary endpoint was ABRs for treated, spontaneous BEs during Vonvendi® prophylaxis.

Twenty-three patients enrolled and received rVWF prophylaxis (prior OD arm: n=13; switch arm: n=10). Eighteen out of 23 (78.3%) patients had type 3 VWD. Over the 12-month study period, 11/13 (84.6%) prior OD patients and 7/10 (70.0%) switch patients had a treated, spontaneous ABR (sABR) of zero, whereas, historically, 13/13 prior OD and one out of ten switch patients had a sABR >2. The sABR was reduced by 91.5% on the study compared with historical sABR in prior OD patients and 45.0% in switch patients. A benefit-risk profile was maintained, with no newly identified risks.

Presenting a trial on the management of post-partum haemorrhage in women with VWD

In an abstract (PB0944) presented at the 2021 ISTH Congress, researchers from the University of Pittsburgh, led by Machin, presented a single-centre pilot study to establish the feasibility to conduct a future multicentre randomised trial comparing the use of **Vonvendi®** and tranexamic acid versus Vonvendi® alone to manage postpartum haemorrhage in women with VWD. The trial (NCT04344860) is currently recruiting.

Non-replacement therapies

Case-report on Hemlibra® prophylaxis in adult and paediatric patients with VWD type 3

A group of US-based researchers led by Pawar presented in an abstract (PB0919) at the 2021 ISTH Congress data on the use of **Hemlibra®** prophylaxis in people with type 3 von Willebrand Disease (VWD). The premise for the use of Hemlibra® in people with type 3 VWD is that they exhibit FVIII deficiency due to an almost total or total lack of von Willebrand Factor (VWF) which has a protective effect on FVIII. Researchers report significant improvement in symptoms in four patients (two children and two adults) with type 3 VWD after starting a prophylactic regimen with Hemlibra®. The patients were two adult female patients with type 3 VWD who suffered from a lifetime of complications associated with severe haemorrhagic events requiring multiple hospitalisations, infusions of factor concentrate, and blood transfusions. They started prophylaxis with Hemlibra® in the spring/summer of 2019. The two paediatric patients aged two and six years had been hospitalised multiple times for significant bleeding after minor childhood traumas. They had been treated with multiple doses of factor VIII/VWF concentrates and even recombinant FVIIa. Initiated prophylaxis with Hemlibra®. All patients exhibited significant improvement in the symptoms, and the adults improved their perception of quality of life.

Authors note that as more substituting and rebalancing therapies in haemostasis become available, guidelines for prophylaxis in bleeding disorders like type 3 VWD will change. Multicentre trials on efficacy and safety and patient-reported outcomes (PRO) will greatly help in formulating the guidelines.

AN UPDATE ON NOVEL THERAPIES FOR PEOPLE WITH OTHER RARE BLEEDING DISORDERS

Replacement therapies

Halting of clinical development of MarzAA

On 12 November, Catalyst Biosciences announced the decision to halt the clinical development of **marzeptacog alfa (activated) (MarzAA)**, report data to date and seek a buyer for its haemophilia programme. The decision reflects a change in business strategy, noting that enrolment for the MarzAA clinical trials had been negatively impacted by the pandemic and competition for participants and increased availability of prophylaxis therapy globally. You can read the full press release here.

Italian data on the real-world use of NovoThirteen

In an abstract (PO 20) presented at the BIC Congress, a group of Italian researchers, led by Zanon, presented a study to assess the different pharmacokinetics (PK) profiles of rFXIII (**NovoThirteen**) for each patient using a population statistics model and to evaluate the clinical outcomes of prophylaxis. This study enrolled all patients presenting FXIII deficiency treated with NovoThirteen at ten Italian haemophilia centres. Overall data from 20 patients with FXIII deficiency were collected, 75% presenting severe disorder. Eleven out of 20 were female. The mean age at diagnosis was 15 years (range birth-74 years). Sixty per cent had a known family disorder. Pharmacokinetics were assessed in 18/20 cases before starting prophylaxis. The mean age at PK-evaluation was 36.4 years (6-74 years), the mean dose of drug-infused for PK was 33.9 IU/kg (25-50 IU/kg). Prophylaxis was subsequently started on 65% of patients at a mean dosage of 33.8 IU/kg (range 25.0-80.0 IU/kg), on average every 4.0 weeks (range 3.0-8.0 weeks). The following events were reported during a mean follow-up of 43 months: one ileo-psoas haematoma, which quickly resolved, one muscular haematoma, and two minor surgeries. One severe patient who remained on-demand treatment experienced a severe intracranial haemorrhage.

Cell based therapies

Pre-clinical *in vivo* data for SIG-009 for the treatment of FVII deficiency

In an abstract (OC 59.2) presented by Sigilon during the 2021 ISTH Congress, authors report on pre-clinical *in vivo* results for the development of **SIG-009**, a novel cell-based product for FVII deficiency. Researchers found in a one-month study in mice that SIG-009 showed sustained human FVII production and plasma levels in a potentially therapeutic range. Researchers also conducted experiments in FVII deficient human plasma where they demonstrated that human FVII produced by SIG-009 was sufficient to activate FX and FXa *in vitro*.

REPLACEMENT THERAPIES IN-DEVELOPMENT					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Replacement FVIII	**Haemophilia A**	BIVV001	Efanesococog alfa (rFVIIIFc-VWFD'D3-XTEN)	Sanofi and Sobi co-development	**Phase 3**
Replacement FIX	**Haemophilia B**	Dalcinonacog alfa (DalcA)	Subcutaneous coagulation factor IX variant	Catalyst Bioscience	**Halting of clinical development**[1]

BYPASSING AGENTS IN DEVELOPMENT					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Bypassing agent	**Haemophilia A or B w/ inhibitors**	Sevenfact®	Recombinant FVIIa- jncw	LFB	**Licensed in the US** **EMA accepted MAA filing (expected outcome in mid-2022)**[2]
Bypassing agent	**Haemophilia A or B w/ or w/o inhibitors**	marzeptacog alfa (activated) MarzAA	Subcutaneous coagulation rFVIIa variant	Catalyst Bioscience	**Halting of clinical development**[3]

NON-REPLACEMENT THERAPIES IN DEVELOPMENT					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
NRT Bispecific antibody	**Haemophilia A**	Mim8	Bispecific antibody	Novo Nordisk	**Phase 2**

[1] Text in red indicates a change from the last issue.
[2] Idem
[3] Idem

NRT Bispecific antibody	**Haemophilia A**	F1049	Bispecific antibody	Kymab	**Pre-clinical studies**
NRT bispecific antibody	**Haemophilia A**	NXT004 to NXT007	Bispecific antibody	Chugai	**Phase 1/2**
NRT Anti-TFPI	**Haemophilia A or B w/ or w/o inhibitors**	Concizumab	Anti-TFPI	Novo Nordisk	**Phase 3**
NRT Anti-TFPI	**Haemophilia A or B w/ or w/o inhibitors**	BAY 1093884	Anti-TFPI	Bayer	**Phase 2 trial terminated due to thrombosis**
NRT Anti-TFPI	**Haemophilia A or B w/ or w/o inhibitors**	PF-06741086 Marstacimab	Anti-TFPI	Pfizer	**Phase 3**
NRT Anti-TFPI	**Haemophilia A or B w/ or w/o inhibitors**	MG1113	Anti-TFPI	Green Cross	**Phase 1**
NRT siRNA	**Haemophilia A or B w/ or w/o inhibitors**	Fitusiran	Antithrombin Small interfering (si)RNA	Sanofi Genzyme	**Phase 3**
NRT		SerpinPC	Activated Protein C inhibitor	Apcintex	**Phase 1/2**

Activated Protein C inhibitor	**Haemophilia A or B w/ or w/o inhibitors**				

GENE THERAPY IN DEVELOPMENT					
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Developer / manufacturer**	**Development stage**
Gene Therapy	**Haemophilia A**	Roctavian® Valoctocogene roxaparvovec BMN-270	AAV5-huFVIII-SQ Valoctocogene roxaparvovec	BioMarin	**Phase 3**
Gene Therapy	**Haemophilia A**	PF-07055480 giroctocogene fitelparvovec (formerly SB-525)	Gene therapy using a rAAV2/6 vector, encoding the B-domain deleted human FVIII	Pfizer (originally Sangamo)	**On clinical hold**[4]
Gene Therapy	**Haemophilia A**	BAY2599023 / DTX 201	Gene therapy using AAVhu37FVIII	Bayer	**Phase 1/2**
Gene Therapy	**Haemophilia A**	SPK-8011	AAV-LK03 (AAV-Spark200) encoding BDD-FVIII	Spark	**Phase 1/2**
Gene Therapy	**Haemophilia A**	TAK-754 (formerly BAX 888/SHP654)	AAV8-based gene therapy using B-domain deleted (BDD)-FVIII-X5 variant	Takeda	**Clinical trial suspended**

[4] Information in red means a change from the previous issue.

Gene Therapy	**Haemophilia A**	AAV2/8-HLP-FVIII-V3	AAV2/8-based gene therapy encoding FVIII-V3 variant	UCL/St. Jude	**Phase 1**
Gene Therapy	**Haemophilia A**	ET3	Gene therapy using a combination of haematopoietic stem cells and lentiviral vectors	Expression Therapeutics	**Phase 1**
Gene Therapy	**Haemophilia A**	SPK-8016	Recombinant AAV composed of a liver-tropic bio-engineered capsid and a codon optimised B-domain deleted FVIII expression cassette	Spark	**Phase 1/2**
Gene Therapy	**Haemophilia A**	YUVA-GT-F801	autologous HSC/MSC modified with lentivirus encoding FVIII	SGIMI	**Phase 1**
Gene Therapy	**Haemophilia A**	AMT-180	Gene therapy using an AAV5-based gene therapy using a FIX variant (FIX-FIAV)	uniQure	**Pre-clinical programme suspended**
Gene Therapy	**Haemophilia A**		Non-viral technology using closed-ended DNA (ceDNA) delivered via a cell-targeted lipid nanoparticle (ctLNP) system	Generation Bio	**Pre-clinical development**
Gene Therapy	**Haemophilia B**	PF-06838435 fidanacogene elaparvovec (formerly SPK-9001)	Padua variant (AAV-Spark100) (fidanacogene elaparvovec)	Pfizer (Originally developed by Spark Therapeutics)	**Phase 3**

Gene Therapy	**Haemophilia B**	AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	**CSL Behring [5] (Formerly uniQure)**	**Phase 3**
Gene Therapy	**Haemophilia B**	AMT-060	Gene therapy using AAV5 vector encoding FIX	**CSL Behring [6] (Formerly uniQure)**	**Phase 1/2**
Gene Therapy	**Haemophilia B**	SB-FIX	AAV6-delivered ZFN integrating corrective FIX transgene into albumin locus	Sangamo	**Phase 1/2**
Gene Therapy	**Haemophilia B**	FLT180a	AAVS3 encoding FIX Padua variant	Freeline	**Phase 1/2**
Gene Therapy	**Haemophilia B**	AAV2/8-LP1-FIX	AAV2/8-LP1-FIX vector	SJCRH	**Phase 1**
Gene Therapy	**Haemophilia B**	YUVA-GT-F901	autologous HSC/MSC, modified with lentivirus encoding FIX	SGIMI	**Phase 1**
Gene Therapy	**Haemophilia B**	CB2679d-GT	Novel chimeric AAV vector Delivering an enhanced potency FIX	Catalyst Biosciences	**Pre-clinical studies**
Gene Therapy	**Haemophilia B**	TAK-748	AAV8-based gene therapy using FIX Padua variant	Takeda	**Clinical trial suspended**

[5] Text in red indicates changes from the previous edition.
[6] Idem

		(formerly SHP648/ AskBio009/BAX 335)			

CELL-BASED THERAPIES IN DEVELOPMENT					
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Developer / manufacturer**	**Development stage**
Cell-based therapy	**Haemophilia A**	SIG-001	Two-compartment spheres encapsulating human FVIII-expressing human cells	Sigilon Therapeutics	**Phase 1/2 Recruiting**
Cell-based therapy	**FVII deficiency**	SIG-009	Cell-based product for FVII deficiency	Sigilon Therapeutics	**Pre-clinical**[7]

[7] Text in red indicates changes from the previous edition.

LICENSED REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Replacement VWF recombinant	**VWD**	Veyvondi® Vonvendi®	rVWF (vonicog alfa)	Takeda	**Licensed**
Replacement VWF plasma-derived	**VWD Haemophilia A**	Voncento®	human coagulation factor VIII & human von Willebrand factor	CSL Behring	**Licensed**
Replacement VWF plasma-derived	**VWD Haemophilia A**	Haemate P®	human coagulation FVIII & human von Willebrand factor	CSL Behring	**Licensed**
Replacement FVIII	**Haemophilia A**	Advate®	human coagulation factor VIII (rDNA), octocog alfa	Takeda	**Licensed**
Replacement FVIII	**Haemophilia A**	Adynovi® Adynovate® BAX855 TAK-660 SHP-660	PEGylated recombinant factor VIII (rurioctocog alfa pegol)	Takeda	**Licensed**
Replacement FVIII	**Haemophilia A**	Afstyla® CSL627	rVIII-Single Chain	CSL Behring	**Licensed**
Replacement FVIII	**Haemophilia A**	Elocta® Eloctate®	rFVIIIFc (efmoroctocog alfa)	Sobi	**Licensed**

Replacement FVIII	**Haemophilia A**	Esperoct® N8-GP NNC 0129-0000-1003	rFVIII (turoctocog alfa pegol)	Novo Nordisk	**Licensed**
Replacement FVIII	**Haemophilia A**	Jivi® BAY 94-9027	rFVIII (damoctocog alfa pegol)	Bayer	**Licensed**
Replacement FVIII	**Haemophilia A**	Kogenate® FS	Recombinant FVIII	Bayer	**Licensed**
Replacement FVIII	**Haemophilia A**	Kovaltry® BAY 81-8937	unmodified full-length rFVIII (octocog alfa)	Bayer	**Licensed**
Replacement FVIII	**Haemophilia A**	Novoeight®	rFVIII (turoctocog alfa)	Novo Nordisk	**Licensed**
Replacement FVIII	**Haemophilia A**	Nuwiq®	human-cell-line-recombinant-human-FVIII (simoctocog alfa human-cl-rhFVIII)	Octapharma	**Licensed**
Replacement FVIII	**Haemophilia A**	Refacto AF®	moroctocog alfa	Pfizer	**Licensed**
Replacement FIX	**Haemophilia B**	Alprolix®	rFIXFc (eftrenonacog alfa)	Sobi	**Licensed**
Replacement FIX	**Haemophilia B**	BeneFIX®	nonacog alfa	Pfizer	**Licensed**
Replacement FIX	**Haemophilia B**	Idelvion®	rFIX-FP / recombinant factor IX albumin fusion protein	CSL Behring	**Licensed**

Replacement FIX	**Haemophilia B**	Refixia® / Rebinyn®	recombinant FIX glycopegylated / rFIX-GP (nonacog beta pegol)	Novo Nordisk	**Licensed**
Replacement FIX	**Haemophilia B**	RIXubis®	Nonacog gamma	Takeda	**Licensed**
Replacement FXIII	**Factor XIII deficiency**	NovoThirteen	catridecacog	Novo Nordisk	**Licensed**

LICENSED BYPASSING AGENTS					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Bypassing agent	**Haemophilia A or B w/ inhibitors**	Sevenfact®	Recombinant FVIIa- jncw	LFB	**Licensed in the US** **EMA accepted MAA filing** **(expected outcome in mid-2022)**[8]

LICENSED NON-REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Non-replacement therapy (NRT) Bispecific antibody	**Haemophilia A w/ or w/o inhibitors**	Hemlibra® emicizumab ACE-910	Bispecific antibody	Roche	**Licensed**

[8] Text in red indicates a change from the last issue.