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

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Inhibitors Only

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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 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.

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.