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 2020 virtual Congress of the American Society of Hematology (ASH), held in December 2020, and the virtual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD), held in February 2021 as well as other industry updates and news in general. You will find a direct link to the ASH abstracts in the articles below, while these EAHAD 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 viral
AJBR	Annualised joint bleeding rate
ABR	Annualised bleeding rate
ADA	Anti-drug antibodies
AE	Adverse events
ALT	Alanine aminotransferase
ASH	American Society of Hematology
AST	Aspartate aminotransferase
AUC	Area under the curve
aPCC	Activated prothrombin complex concentrate
BL	Baseline
BMI	Body mass index
BPA	Bypassing agents
ceDNA	Close-ended DNA
CT	Clinical trial
ctLNP	Cell-targeted lipid nanoparticle
CVAD	Central venous access device
DNA	Deoxyribonucleic acid
E7D	Every seven days
EAHAD	European Association for Haemophilia and Allied Disorders
ED	Exposure days
EHL	Extended half-life
EMA	European Medicines Agency
EOD	Every other day
EOS	End of study
EQ-5D	EuroQol 5 Dimensions
ETP	Endogenous thrombin potential
FDA	Food and Drug Administration
FIX	Factor IX
FVIII	Factor VIII
h	Human
HA	Haemophilia A
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
HAwI	Haemophilia A with inhibitors
HB	Haemophilia B

HBwI	Haemophilia B with inhibitors
HCC	Hepatocellular carcinoma
HCV	Hepatitis C
hFVIII	Human factor VIII
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of Life
IQR	Interquartile Range
ITI	Immune tolerance induction
IU	International units
IU/dl	International units per decilitre
IU/kg	International units per kilogram
MAA	Marketing authorisation application
MAIC	Matching-adjusted indirect comparison
mg/kg	Milligram per kilogram
mITT	Modified intent-to-treat
MTP	Minimally treated patients
n=	Number
NAb	Neutralizing antibodies
NHD	National Haemophilia Database
OR	Odds ratio
p	Significance
PBMC	Peripheral blood mononuclear cells
PEG	Polyethylene glycol
PK	Pharmacokinetics
PPAS	Protocol per analysis set
PRO	Patient-reported outcomes
PTP	Previously treated patients
PUP	Previously untreated patient
PwHA	Person with haemophilia A
PwHAI	Person with haemophilia A and inhibitors
PwHB	Person with haemophilia B
PwHABI	Person with haemophilia B and inhibitors
PwI	People with inhibitors
r	Recombinant
rFVIIa	Recombinant activated factor VII
RNA	Ribonucleic acid
SAE	Serious adverse events
SD	Standard deviation
SHL	Standard half-life
TFPI	Tissue factor pathway inhibitor

TG	Thrombin generation
TGA	Thrombin generation assay
THL	Terminal half-life
UK	United Kingdom
USA	United States
vs	versus
VWD	von Willebrand disease
VWF	von Willebrand factor
w	with
w/o	without
W	week
WAPPS-Hemo	Web Accessible Population Pharmacokinetic Service-Hemophilia
WFH	World Federation of Hemophilia
µg/kg	microgram per kilogram

EXECUTIVE SUMMARY

Dear Reader, in this section we give you a quick overview of the information we report on in this publication. Please note that the reporting in this executive summary should allow you to quickly see what reporting is of interest to you and allow you to swiftly go to the main section of the report for more detailed information. Please note that we do not take any position on any of the treatments reported here below and that you should always discuss your treatment options with your healthcare professional.

Haemophilia A

Replacement therapies

Results from **clinical trials**

Sanofi and Sobi were reporting data on their **A-LONG** and **PUP A-LONG clinical trials** for the study of **Elocta®**. Concerning the A-LONG study, the authors were reporting data from **phase III** about pain and physical functioning. The phase III PUP A-LONG study looked at inhibitor development at ten or more exposure days (pp 13-14).

Bayer reported on its **PROTECT VIII extension and post-marketing study**; as well as its **PROTECT VIII Kids** study for the use of **Jivi®**. For the PROTECT VIII extension study, authors reported on a cohort of patients who had been on prophylaxis with Jivi for six years or more. Authors looked at factor consumption, ABR and adverse events. For the PROTECT VIII post-marketing study, authors were reporting on dosing regimens, inhibitor development, PEG antibody development and ABR in previously treated patients in normal clinical settings.
In the PROTECT VIII Kids study, authors looked at long-term safety and efficacy in previously treated children between six and 12. The authors reported on ABR and PEG antibody development (pp 14-15).

In the **phase III extension study**, **NuProtect**, Octapharma collected data on ABRs and inhibitor development when using **Nuwiq®** in previously untreated patients (pg 15).

Sobi dosed its first participant in the **XTEND-Kids phase III** trial studying the use of **efanesoctocog alfa** (**BIVV001)** in previously treated children aged 12 and above (pg 16).

Reports from **non-interventional studies**

The American Thrombosis and Haemostasis Network (ATHN) reported on the **ATHN2** study, in which **Adynovi/Adynovate®** is used in previously treated patients. The study looked at dosing regimens, patient satisfaction and the impact on health status and productivity (pg 16).

Data from the **Web Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo)** showed changes in terminal half-life in individuals switching to **extended half-life products** (pg 16)**.**

Findings from a **small retrospective review** looking at **medical records of children with haemophilia A or B from one haemophilia centre switching to EHL** were analysed. Authors reported on ABR, AJBR, factor consumption, dosing regimens, trough levels, and inhibitor development (pg 16).

Adult patients with severe haemophilia A were analysed in a **retrospective, observational, single centre study**. Patients were either on **SHL** or **EHL,** and authors looked at mean half-life, dosing regimens, ABR and AJBR (pg 17).

Novo Nordisk reported on the safety and efficacy of **NovoEight®** in previously treated patients in its **Guardian 5** trial. This trial follows patients in a normal clinical setting (pg 17).

An **Italian study** looked at real-world ABRs and factor consumption with prophylactic use of **Afstyla®** compared to other factor VIII products. Authors from this study included representatives from CSL Behring (pg 18).

In **another study**, the authors looked at patients switching to prophylaxis with **Afstyla®**. The study looked at dosing regimens, factor consumption and ABR. Authors from this study include representatives from CSL Behring (pg 18).

Reports from **indirect-comparison studies**

Sobi reported on an **indirect comparison study** of **Elocta®** and **Jivi®**. This study is based on data of two clinical trials **A-LONG** (Elocta® - phase III) and **PROTECT VIII** (Jivi® - phase II/III). This indirect comparison looked at evaluating ABR in patients exposed to these products (pg18). Sobi is also reporting on an **indirect comparison** of **Elocta®** and **Hemlibra®** with data from the **A-LONG** and **HAVEN** investigational programmes. Data looked at ABR and adverse events (pg 19).

Bayer presented an **indirect comparison** of **Jivi®**, **Elocta®**, **Adynovi/Adynovate®** and **Esperoct®** to assess factor use and ABR (pg 19).

Takeda developed a **microsimulation model** to calculate bleeding risk when on 8-12% versus 1-3% trough levels with **Adynovi/Adynovate®** compared to **Hemlibra®** prophylaxis when performing different types of activities (pg 19).

Non-replacement therapy

Reports from **clinical trials**

Roche presented pooled data from paediatric and adult patients with haemophilia A with and without inhibitors enrolled in **phase III** of **HAVEN1**, **HAVEN2**, **HAVEN3** and **HAVEN4** studies on the use of **Hemlibra®**. The data looked at ABR and target joints across the four trials (pg 20).

Roche presented data on anti-drug antibodies in people with haemophilia A enrolled in the **HAVEN 1 to 5** trials studying the use of **Hemlibra** (pg 20).

Genentech presented the results of a **phase IV multicentre study** to evaluate the safety and efficacy of **Hemlibra®** in people with severe haemophilia A with or without inhibitors undergoing minor surgical procedures without additional prophylaxis with by-passing agents (pg 21).

Reports from **non-interventional studies**

Roche presented data on fatalities from its **Emicizumab Global Safety Database,** collecting data on deaths in people with haemophilia on **Hemlibra®** from clinical trials, pre-market access and spontaneous post-marketing reports (pg 21).

The **European Haemophilia Safety Surveillance (EUHASS)** database presented data on the use of **Hemlibra®** in people with haemophilia A. The data looked at concurrent treatments and adverse events. Authors from this study included representatives from Genentech (pg 22).

Two abstracts presented data from the **UK National Haemophilia Database.** The first one showed ABR and ABJR in patients with severe haemophilia A on **Hemlibra®**. The second looked at the use of Hemlibra® in children under 12 with severe haemophilia A without inhibitors, including age of first exposure (pg 22).

Data from a single centre in the US reported on using **Hemlibra®** in previously untreated patients and minimally treated patients. Reported data included reasons for initiation, bleeding events and adverse events (pg 23).

Data were reported from a **single centre** on the use of **Hemlibra®** in paediatric and adult patients with and without inhibitors. The data looked at dosing regimens, ABR, use in surgery and concomitant treatments (pg 23).

Data on patients with and without inhibitors using **Hemlibra®** in **Slovenia** were reported. The authors looked at the patient profiles and reasons for switching to Hemlibra, bleeding episodes, use in surgery and FVIII equivalency (pg 24).

Cell therapy

Reports from **clinical trials**

Sigilon is initiating its **phase I/II clinical trial** for **SIG-001** (pg 25).

Gene Therapy

Reports from **clinical trials**

BioMarin announced data from its **phase III gene therapy trial** with **Roctavian®** in people with haemophilia A. The data looked at ABR and mean FVIII expression. The company also reported on its investigational therapy regulatory status. BioMarin also reported on its **five- and four-year post-treatment follow-up of two cohorts** (6e13 vg/kg and 4e13 vg/kg) of its **phase I/II study** of Roctavian®. Data looked at ABR and factor VIII activity levels (pp 25-27).

Recruitment is ongoing for the Pfizer **phase III AFFINE study** to evaluate the efficacy of **PF-07055480** (pg 28).

Pfizer reported on its **phase I/II ALTA study** for the use of **PF-07055480**. The study reported on adverse events, factor VIII activity and bleeding events (pg 28).

Data on the study of Takeda's **AAV8 phase I/II** gene therapy **TAK-754** for people with severe haemophilia A was presented. The data looked at ABR and adverse events. This investigational program has been closed (pg 28).

Spark presented the preliminary results of its **phase I/II trial** for **SPK-8016**. This investigational therapy was administered to four patients including one HIV positive (pg 29).

A study was presented on persistent **AAV-FVIII vectors in haemophilia dogs**. The study also looks at DNA integrations in these dogs (pg 29).

Reports on **seroprevalence of AAV antibodies**
Data was presented on the seroprevalence of neutralising antibodies and anti-drug antibodies against the AAVhu37 vector used in **BAY2599023** (pg 29).

BioMarin announced the development of a **companion diagnostic** for the standardised assessment and controlled investigation of pre-existing adeno-associated virus 5 (pg 30).

Haemophilia B

Factor replacement therapies

A study evaluated the **pharmacokinetic properties** of three **EHL-FIX** concentrates for the treatment of haemophilia B. The authors compared them to SHL products and looked at half-life, the area under the curve, time above 10% FIX trough levels, required weekly dose for 1% trough levels and mean recovery (pg 31).

Sanofi and Sobi presented ata from the **phase III B-LONG** study in relation to the impact of **Alprolix®** on pain and physical activity in patients aged 12 or older (pg 31).

A study from Sobi compared the efficacy of **Alprolix®** and **Idelvion®** for the prophylactic treatment of haemophilia B using a matching adjusted indirect comparison. Data for the comparison came from the **B-LONG** and **PROLONG-9FP** studies. The authors looked at trough levels and ABR as endpoints (pg 32).

Gene therapy

Denise Sabatino reported on a case of hepatocellular carcinoma in one of the patients undergoing uniQure **phase III** gene therapy **HOPE-B** trial for haemophilia B with **AMT-061** (pg 32).

Steven Pipe reported on the latest data from **phases II and III** of uniQure **AMT-061** and the earlier **AMT-060 trials**. These trials looked at factor expression and adverse events (pg. 32)

Recruitment is ongoing for **phase III study** to evaluate the efficacy and safety of factor IX gene transfer with Pfizer's **PF-06838435** in adult males with severe haemophilia B. A Pfizer **study** presented data on **PF-06838435** clearance from the DNA (pg 33).

The **B-AMAZE** study investigated the use of Freeline **FLT180a** to achieve normal factor IX levels in people with haemophilia B. The study tested four dosing regimens and looked at resulting factor levels, adverse events and the use of exogenous factor. Freeline is anticipating the launch of a phase IIb/III trial in the second half of 2021. The company is also looking to request accelerated approval by the FDA (pg 34).

Considerations in gene therapy

We reported from the **WFH Gene Therapy Webinar on the Robustness of Data** held in December 2020. During this webinar, speakers considered aspects of gene therapy such as eligibility, predictability, tolerability, durability, transparency and affordability (pp 35-36).

Non-replacement therapies for people with haemophilia A and B with or without inhibitors

Bypassing agents

The LFB **phase III PERSEPT3** study reported on the use of **Sevenfact®** in people with haemophilia A or B with inhibitors undergoing major or minor surgeries. The study looked at dosing, safety and efficacy (pg 37-38).

The LFB **phase III PERSEPT1** trial looked at bleed management in adults and adolescents with haemophilia A or B with inhibitors using **Sevenfact®**. This study evaluated efficacy and safety on bleeding episodes in the first 12 hours after bleed onset (pg38).

The **European Medicines Agency (EMA)** has agreed to review the application by LFB for the licensing of **Sevenfact®** in Europe (pg 38).

Catalyst Bio **phase I MAA-102 study** presented data on **MarzAA** safety profile. Catalyst Bio dosed its first patient in **phase III Crimson study** to demonstrate the non-inferiority of MarzAA compared with intravenous standard of care. Catalyst Bio also initiated dosing for its **phase I/II MAA-202** study to look at pharmacokinetics and pharmacodynamics of MarzAA in patients with inhibitors using Hemlibra®, in factor VII deficiency and in Glanzmann thrombasthenia (pg 38).

Non-replacement therapies

An abstract from a **single centre in Portugal** reported on using **Hemlibra®** for prophylaxis in adult and paediatric patients with haemophilia A and inhibitors. This study reports on concomitant use of other treatments and bleeding episodes (pg 39).

In a Novo Nordisk ***in vitro*** **experiment**, thrombin generation was measured in the presence or absence of **concizumab** in haemophilia A and B plasma together with rFVIII and rFIX, respectively (pg 39).

Novo Nordisk presented an update on its **explorer4**, **explorer5**, **explorer7** and **explorer8** trials.
Explorer4 looked at the efficacy of **concizumab** in people with haemophilia A and B with inhibitors. This was measured by evaluating ABRs.
The **phase II explorer5** trial looked at the efficacy and safety of concizumab in people with haemophilia A without inhibitors. This was also done by observing ABRs.
Explorer7 and **explorer8** looked at the safety and efficacy of concizumab prophylaxis in patients with HA or HB with or without inhibitors. These trials reported on dosing regimens and adverse events. The trials had to be paused due to thrombotic events. Novo Nordisk developed a risk mitigation plan approved by the relevant regulatory authorities, who allowed the company to resume the trials.
Novo Nordisk also presented on data generated from the **phases I and II** of the concizumab trials to develop a population pharmacokinetic model to support dose selection for the phase III trials (pp 40-41).

A report was presented on a **patient undergoing minor surgery** while enrolled in a **concizumab trial** (pg 42).

Pfizer reported on its **phase II** trial for **PF-06741086** (**marstacimab)** for routine prophylaxis treatment to prevent or reduce the frequency of bleeding episodes in patients with haemophilia A or B with or without inhibitors. The authors reported on changes in biomarkers after receiving marstacimab, dosing regimens and concomitant treatment regimens (pg 42).

Pfizer dosed its first patient in the **phase III BASIS study** with **PF-06741086** (**marstacimab)**. The objective of the study is to evaluate ABR in patients with haemophilia A or B with or without inhibitors with PF-06741086 prophylaxis (pg 42).

Sanofi reported an update on the **investigational programme of fitusiran**. The investigational programme (**phase I and II studies**) had to be paused due to thrombotic events. Sanofi reported on these events as well as on a revised dosing plan during the EAHAD congress. This plan will be applied to **phase III**, currently in clinical development.
Sanofi also presented health-related quality of life data in patients in **phase II** clinical trial investigation with the use of fitusiran. Sanofi is also reporting data from its **phase I** trial on the impact of fitusiran on the **quality of life of people with inhibitors** (pg 43-45).

An update on treatments for Von Willebrand Disease

A study reported on the potential role of **Hemlibra®** in **Von Willebrand Disease** (pg 46).

A presentation reported on the French experience of using **Vonvendi®** in people with **VWD** during **surgery** (pg 46).

Other news

Takeda entered a strategic partnership to develop **at-home monitoring assays** (pg 47).

CONSIDERATIONS IN GENE THERAPY

Report from the WFH Gene Therapy Webinar on the robustness of data

In this newsletter, we also report on the discussions held during a webinar organised by the World Federation of Hemophilia (WFH) on 11 December 2020 on Gene Therapy and Robustness of Data. The webinar had a panel discussion on various aspects of gene therapy including eligibility, predictability, tolerability, durability, transparency and affordability.

On eligibility

Currently the following are excluded from gene therapy trials:

- Children due to:
    - A growing liver, which could remove the vector due to cellular renewal,
    - Ethical questions regarding informed consent and availability of other therapies,
- People with inhibitors,
- People with active hepatitis B and C.

Predictability

It is not possible to accurately predict gene therapy's response as it varies from person to person. This means that the same viral vector dose will result in a wide range of factor VIII or IX expression. Reducing this uncertainty will not be possible. This variability may result in:

- A very high expression of factor VIII or IX that can put individuals at risk of thrombosis, or
- A low expression that may need supplementation with traditional factor replacement therapy.

This variability is not solely vector-dose related but seems to result from a number of genetic differences in individuals receiving the treatment. The conclusion is that more research is needed on this aspect.

Tolerability

This aspect pertains to the safety of gene therapy. In general, the safety record in haemophilia treatment has been very good, with a few exceptions. There are currently three areas of concern for safety in gene therapy:

- The first area regards a small but definitive risk of having an acute reaction within 24 hours of receiving gene therapy. This reaction resembles acute influenza symptoms, and it is triggered by the trillions of vectors given to the patient. More genome copies of the vector are given during a gene therapy infusion than we have cells in our body. Fortunately, the acute reactions have been well controlled and limited.
- The second area regards liver enzyme elevation. This parameter indicates that hepatocytes (liver cells) are dying. We know that the vector infusion can cause this; however, it is still unclear what causes this elevation. There is probably a contribution from the adaptive immune response, which is designed to destroy viruses. Although enzyme elevation is generally not high, it has gone to 10-20 times the upper limit of normal in a few trials. Usually, this elevation goes one to two times the upper limit of normal, and this may still cause damage.

- The third area regards long-term safety. We do not yet know whether there is a safety risk in the long-term. This is because clinical trials have only been running for less than a decade, and we have not been able to collect long-term data. As noted above, we are talking about millions of vector integrations going into the liver cells. Currently, there have not been any negative effects either in haemophilia or other disease trials. However, we need to understand and collect data for long-term effects.

Durability

There are questions on the long-term durability of haemophilia A gene therapy. Currently, if a gene therapy fails, it cannot be re-dosed because the individual will have created an antibody to the vector. However, there are currently theories on whether the use of plasmapheresis, immunosuppression or immunoadsorption could allow re-dosing. These are theories that will need further testing. The panel noted that patients look for a cure in gene therapy and that a gene therapy that does not last comes into comparison with other therapeutic options that are available.

Transparency

The irreversible nature of gene therapy requires the greatest transparency so that patients, in combination with clinicians, can compare what various therapies offer. Therefore, consistent communication of clinical trials is of utmost importance. This communication should pertain to data free from commercial bias and at a level of detail that allows comparison.

The Core-HEM dataset sets endpoints for haemophilia gene therapies efficacy and safety, including liver toxicity, the immune response to the transgene and the capsid, potential integration, duration of vector neutralising response and death. Finally, the WFH World Gene Therapy Registry will play an important role in capturing real-world evidence, collecting efficacy and safety data and allowing patients and clinicians to compare different therapies over time.

Affordability

Payers and health systems need to have confidence in the therapies they are paying for. Unfortunately, just because a medicine is cost-effective, does not mean that it is affordable. Also, the uncertainties in the data will be an important part of making drugs affordable. The panel called for new health technology assessments (HTA) that capture the value of haemophilia therapies beyond what is traditionally captured.

In 2020, the US Institute for Clinical and Economic Review (ICER) reviewed haemophilia gene therapy. The report had to put many placeholders for safety and efficacy endpoints as these were not available, even though manufacturers were asked to collect this type of data during clinical trials. This lack of data and resulting uncertainty highlights the need and importance for collecting longitudinal data. Patients and healthcare professionals need more data to look at these questions and make a fair assessment of these therapies. Unfortunately, at the moment, this data is not being collected, and therefore, cannot answer the questions asked above.

AN UPDATE ON NOVEL NON-REPLACEMENT THERAPY FOR PEOPLE WITH HAEMOPHILIA A AND B WITH OR WITHOUT INHIBITORS

Bypassing agents

LFB data on the use of Sevenfact® in surgery

At the Congresses of ASH 2020 (ASH1790) and EAHAD 2021 (ABS124**)**, Escobar M. A. et al. and Hermans C. et al. respectively, presented data on the newest by-passing agent, Eptacog beta (US brand name **Sevenfact®),** a recombinant coagulation factor VIIa developed by LFB. This product is a human rFVIIa licensed in the US for the treatment and control of bleeding events (BEs) in adults and adolescents with haemophilia A or B with inhibitors. Sevenfact® has not yet been approved in the US for use in surgery. Therefore, a phase III trial (PERSEPT 3, NCT02548143) was initiated to evaluate the prevention of excessive bleeding and achievement of haemostasis in persons with haemophilia A or B with inhibitors (PwHABI) undergoing major and minor, elective surgery or other invasive procedures.

Immediately prior to the start of the procedure, patients undergoing minor invasive procedures were administered an initial dose of 75 µg/kg and those undergoing major invasive procedures were administered an initial dose of 200 µg/kg. For major procedures, additional Sevenfact® doses (75 µg/kg) were administered during the procedure and post-operatively every two hours for the first two days. The administration interval increased up to four hours on days 3-4, up to 6h on days 5-6, up to 8h in days 7-10 and then up to 12h. The minimum duration of Sevenfact® infusion for minor procedures was two days (75 µg/kg every 2h for the first two days, then every 24h).

Efficacy was assessed during the procedure, immediately following the procedure, at regular post-operative intervals, and 48 hours following the last dose of Sevenfact® (recorded as excellent, good, moderate and poor). The primary efficacy endpoint was the percentage of good and excellent responses (i.e., successes) at 48 (±4) h following the final dose.

Twelve male patients with severe haemophilia A and inhibitors (aged 2-56 years; median 20 years) were enrolled. There were six minor procedures (circumcision [n=3] and tooth extraction [n=3]), and six major procedures (left transtibial amputation, hip replacement, orthopaedic knee surgery, amputation of the left leg, left knee joint endoprosthesis removal, and left ankle achilloplasty).

The good and excellent proportion was 67% for major procedures, (with two surgeries not meeting the criteria; these two surgeries were orthopaedic knee surgery (n=1) and hip replacement surgery [n=1]) and 100% for minor procedures. The intraoperative efficacy of Sevenfact® was rated as good or excellent in all 12 procedures. Efficacy 24 hours following procedure completion was rated as good or excellent in all procedures where data were reported (major, 4/4; minor, 6/6).
One patient (major procedure) was withdrawn from the study due to an adverse event (postprocedural hematoma). This patient subsequently received activated Prothrombin Complex Concentrate and non-steroid anti-inflammatory drugs and experienced blood loss anaemia and gastrointestinal haemorrhage. Other non-treatment-related adverse events included post-operative anaemia, post-procedural haemorrhage, procedural pain, wound

secretion and haemorrhage. No allergic, hypersensitivity or anaphylactic events were reported; no anti-Sevenfact® antibodies were observed, and no thromboembolic events occurred. *Authors of both abstracts included representatives from LFB and HEMA Biologics.*

Results from LFB phase III PERSEPT1 trial

Additionally, at the Congresses of ASH in 2020 (ASH 2699) and EAHAD in 2021 (ABS123), data were reported on bleed management in adult and adolescent patients with haemophilia A or B with inhibitors during the PERSEPT 1 trial. This phase III study evaluates the efficacy and safety of **Sevenfact®** (US brand name) on bleeding episodes in the first 24h after bleed onset. Twenty-seven (27) patients with haemophilia A or B with inhibitors (22 adults / 5 adolescents) were randomised to receive an initial dose of Sevenfact® either 75 µg/kg followed by a subsequent dose every three hours or 225 µg/kg, followed by 75 µg/kg every three hours after nine hours, if necessary, for mild or moderate bleeding episodes.

This regimen occurred for the first three months of the trial. Then patients were crossed over to the alternate treatment options. For severe bleeding episodes, the initial dose of 75 µg/kg, every two hours or the initial dose of 225 µg/kg followed, if necessary, by 75 µg/kg every two hours from six hours after initial dose with 75 µg/kg every two hours. Four hundred sixty-eight (468) bleeding episodes (465 mild/moderate, three severe) were treated. A good/excellent response was achieved at 12hours for 94% (95% CI = 88.9%, 98.6%) of bleeding episodes in the high initial dose regimen of 225 µg/kg (n=216) and 86% (95% CI = 75.0%, 96.4%) in the lower 75 µg/kg (n=252). The median time to good clinical response was 3h and 6h and the median duration of bleeding episodes was 4.5h and 6.5h, respectively. A single dose of 225 µg/kg was sufficient to achieve response in 81.3% of bleeding episodes compared to 29% with the 75 µg/kg dose (3h). No anti-Sevenfact® antibodies were observed.
Both regimens for Sevenfact® achieved successful resolution of bleeding episodes. The regimen with a larger initial dose (225 µg/kg) may provide a higher success with a single administration, early onset of action, and timely resolution of symptoms.

The US Food and Drug Administration (FDA) approved Sevenfact® for the treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with haemophilia A or B with inhibitors in April 2020. The European Medicines Agency (EMA) has agreed to review an application by LFB, and a decision on the licence is expected by mid-2022.

An update on Catalyst Bio's MarzAA

An update on Marzeptacog alfa (activated) (**MarzAA**) program was presented at ASH (ASH 1795). This product is an activated recombinant factor VII (rFVIIa) administered subcutaneously. Data from the phase I study, MAA-102, demonstrated that subcutaneous MarzAA is quickly absorbed and can achieve and maintain plasma levels in the desired range with an acceptable safety profile.
In May 2020, the company dosed its first patient in the Crimson 1 phase III study. The company announced that the phase III study will enrol approximately 60 patients to treat 244 eligible bleeding episodes with each treatment. The primary endpoint for the trial is the percentage of treated bleeds resulting in effective haemostasis at the 24-hour timepoint. The objective of the trial is to demonstrate the non-inferiority of MarzAA compared with intravenous standard of care. *This study is being carried out by Catalyst Bioscience.*

In May 2021, dosing initiated in the phase I/II MAA-202 pharmacokinetics/ pharmacodynamics study and thereafter the treatment of episodic bleeding in patients with inhibitors using Hemlibra® prophylaxis, factor VII deficiency or Glanzmann thrombasthenia.

In December 2020, Catalyst Biosciences announced that the U.S. Food and Drug Administration (FDA) had granted Fast Track Designation for MarzAA based on the Crimson 1 study for the treatment of episodic bleeding in patients with haemophilia A and B with inhibitors.

Non-replacement therapies

Single centre experience with Hemlibra® in inhibitor patients

During the 2021 EAHAD Congress, an abstract (ABS166) from Portugal reported on the use of **Hemlibra®** for prophylaxis in patients with haemophilia A and inhibitors. Three patients started prophylaxis with Hemlibra®: one adult patient (aged 42) since December 2017 and two paediatric patients (aged five and six); one since December 2019 and the other since May 2018. They were previously on on-demand treatment with by-passing agents (BPA). Both children had unsuccessful immune tolerance induction (ITI). In contrast, the adult patient had longstanding inhibitors, and ITI was never tried. He experienced a significant number of bleedings interfering with his quality of life and had been submitted to total joint replacement of both hips. These patients were followed up for a median period of 24 months after starting Hemlibra®. One child received BPA on two occasions after traumatic bleedings of the knee and ankle, treated with a single infusion (90 µg/kg) of recombinant FVIIa (rFVIIa). The adult patient required a single infusion of rFVIIa once due to bleeding after a skin biopsy. No spontaneous bleedings were reported during this time in any patient. Hemlibra® prophylaxis resulted in a 100% reduction in bleeding rate in two patients and a 90% reduction in the other. No target joints were identified during the study period, and no adverse events were reported.

In vitro effect on thrombin generation of adding rFVIII or rFIX to haemophilia A or B plasma in the absence or presence of concizumab

Concizumab, a humanized recombinant monoclonal antibody directed against the tissue factor pathway inhibitor, is under investigation as a subcutaneous prophylactic treatment for patients with haemophilia A or B (HA/HB) with and without inhibitors.

In an experiment on thrombin generation of concizumab and FVIII and FIX presented at ASH 2020 (ASH 1777), the concomitant effect was measured *in vitro*. The aim of the study was to compare the effect of recombinant FVIII (rFVIII) and FIX (rFIX) in HA and HB plasma, respectively, in the absence or presence of concizumab. rFVIII/rFIX was added to haemophilia A/B pooled plasma at 0.25, 0.5 or 1 IU/mL (corresponding to post-administration plasma concentrations of 12.5, 25 and 50 IU/kg rFVIII and 12.5−25, 25−50 and 50−100 IU/kg rFIX) in the absence or presence of concizumab (1,500, 4,500 or 15,000 ng/mL). In a separate experiment, 33 plasma samples from eight HA patients, who were on concizumab prophylaxis as part of phase II explorer5 trial (NCT03196297), were spiked with 0.5, 1 and 1.5 IU/mL rFVIII. rFVIII/rFIX increased the thrombin peak in haemophilia A and B plasma, respectively, both in the absence and presence of concizumab. The combined effects of rFVIII/rFIX with concizumab were mainly additive, with an up to 20% additional effect caused by drug-drug interaction with rFVIII and a 10% reduction with rFIX. No signs of exaggerated thrombin

generation were observed by combining concizumab with rFVIII or rFIX as rFVIII/rFIX, and concizumab have additive effects in thrombin generation capacity. Data suggest that clinical effectiveness could be achieved with rFVIII/rFIX doses in the lower range recommended for such products. *This product is in development by Novo Nordisk and authors of this abstract included representatives from this company.*

An update on Novo Nordisk's explorer4 trial

At the 2020 ASH Congress (ASH2696), updated results from the combined main and extension parts (at least 76 weeks) of the phase II **concizumab** explorer4 trial (NCT03196284) were presented. The study assessed the safety and longer-term efficacy of concizumab in patients with haemophilia A with inhibitors (HAwI) and haemophilia B with inhibitors (HBwI).

The explorer4 trial included the main part of the study, which lasted at least 24 weeks for all patients, and an extension part, which lasted at least 52 weeks. The primary objective of the main part of explorer4 was to assess the efficacy of concizumab in preventing bleeds in patients with HAwI/HBwI, evaluated as annualized bleeding rate (ABR) at the last dose level after at least 24 weeks. This objective has been addressed in the previous reporting of the main part of the trial (Shapiro A, et al. Blood 2019; 134[22]:1973–1982). During the main part of the trial, patients were randomized 2:1 to receive either concizumab prophylaxis or on-demand treatment with recombinant activated factor VII (rFVIIa). At the end of the main part, patients in the rFVIIa on-demand arm were switched to 0.15 mg/kg concizumab for the extension part. The concizumab dose was escalated to 0.20 and 0.25 mg/kg in both the main and extension parts if a patient experienced ≥3 treated spontaneous bleeding episodes within 12 weeks and if deemed safe by the investigator.

Twenty-five patients with inhibitors were treated with concizumab (n=15 with HAwI; n=10 with HBwI). Eight of these patients received on-demand treatment with rFVIIa during the main part of the trial before receiving their first concizumab dose in the extension phase. The estimated annual bleeding rate (ABR) at the last dose level for all patients treated with concizumab during the main and extension parts was 4.8 (95% CI: 3.2–7.2), while during the trial, this was 5.7 (95% CI: 4.2−7.8). During the main and extension parts, four (16%) patients had zero treated bleeding episodes on their last dose level. Increased concizumab concentration was observed in patients who received concizumab at 0.20 mg/kg. These patients also had lower concentrations of free TFPI. There were no AEs leading to withdrawal, no thromboembolic events and no deaths during the main and extension parts of the trial. Anti-drug antibodies (ADAs) developed in six patients. Elevated D-dimer levels were observed in some patients treated with concizumab.

Results from the combined main and extension studies provided further details on the safety and longer-term efficacy of subcutaneous prophylactic treatment with concizumab for at least 76 weeks in patients with HAwI and HBwI. *The explorer4 trial was conducted by Novo Nordisk.*

An update on Novo Nordisk's explorer5 trial

At EAHAD 2021, (ABS139) data were presented on results from the combined main and extension parts (≥76 weeks [w]) of the phase II explorer5 **concizumab** trial (NCT03196297) in severe haemophilia A (HA) patients without inhibitors.

Explorer5 comprised a main (≥24 w) and an extension part (≥52 w). During the single-arm trial, 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 bleeding episodes within 12 weeks. Thirty-six patients were treated with concizumab during explorer5 (32/36 entered the

extension part). The estimated annualised bleeding rate (ABR) for all patients treated with concizumab during the main and extension parts was 6.4 (95% CI: 4.1–9.9) at each patient's last dose level. During the main and extension parts, six (17%) patients had zero treated bleeding episodes (at their last dose level). Similar to explorer4, increased concizumab plasma concentrations were observed in patients who received concizumab 0.25 mg/kg. These patients also had lower free TFPI concentrations. There were no adverse events (AEs) leading to withdrawal, no thromboembolic events and no deaths during the main and extension parts of the trial. ADAs developed in nine patients, with no observed clinical effect. Elevated prothrombin fragment 1+2 and D-dimer levels were observed, reflecting the haemostatic activity of TFPI inhibition.

An update on Novo Nordisk's explorer7 and 8 trials

At the Congresses of ASH 2020 (ASH 1796) and EAHAD 2021 (ABS188), an update was presented on risk mitigation strategy as a result of non-fatal thrombotic serious adverse events (SAEs) that occurred in three patients during the phase III trials, explorer7 (NCT04083781) and explorer8 (NCT04082429).

These trials were initiated in late 2019 to assess the efficacy and safety of **concizumab** prophylaxis in patients with haemophilia A or B with (explorer7) or without inhibitors (explorer8). Patients received a subcutaneous loading dose of 1.0 mg/kg concizumab, and from the second day onwards, all patients received a daily subcutaneous maintenance dose of 0.25 mg/kg. Patients from the phase II trials who consented to transfer to phase III received concizumab 0.25 mg/kg daily (no loading dose). In March 2020, the explorer 7 and explorer 8 trials were temporarily paused because two patients with haemophilia A and one patient with haemophilia B with inhibitors, and baseline thrombotic risk factors, experienced two arterial and three venous thrombotic SAEs. All patients had received concomitant by-passing agents on the day of the event onset. In two cases, haemostatic medication had also been administered in the days leading up to the event. Two of the patients were among those with the highest concizumab exposure in the phase III trials. Novo Nordisk developed a risk mitigation plan based on in-depth, cross-functional analysis of available data from phase II and III clinical trials. This included data from the three patients who experienced thrombotic events. Novo Nordisk amended the phase III explorer trial protocols. Relevant authorities approved the risk mitigation plan allowing re-initiation of the explorer7 and explorer8 trials. The risk mitigation plan includes guidelines for managing bleeding episodes with concomitant haemostatic agents in patients treated with concizumab and updates to the concizumab prophylactic dosing regimen. *The explorer7 and 8 trials are conducted by Novo Nordisk.*

PK models to predict dosing in Novo Nordisk's phase III concizumab trials

Understanding the pharmacokinetic properties of treatments is becoming increasingly relevant in the management and care of patients using non-replacement therapies. At the 2020 ASH congress (ASH 2701), data generated from phases I and II of the **concizumab** trials were used to develop a population pharmacokinetic (PK) model to support dose selection for phase III trials.

The developed model described the PK of concizumab delivered at a wide dose range by either subcutaneous or intravenous administration to non-haemophilic patients and patients with haemophilia A or B with and without inhibitors. The model was subsequently used for simulations to select the dosing regimen for subsequent phase III studies. *Concizumab is an experimental medicinal product in development by Novo Nordisk.*

Case study on concizumab used during a minor surgery

During the 2021 EAHAD Congress (ABS154), a report was presented on a patient undergoing surgery while enrolled in a **concizumab** clinical trial.

The individual was a 46-year-old male with severe haemophilia A (FVIII <1%) with no personal or family history of inhibitors or thrombotic events. In October 2017, he was enrolled in the phase II concizumab trial (explorer5, NCT03196297) and used daily concizumab treatment at a dose of 0.15 mg/kg. In October 2019, the patient decided to undergo a minor surgical procedure (hair implant). Rurioctocog alfa pegol (Adynovate®) at 20 IU/kg was administered one hour before surgery and was repeated at 24 and 48 hours, maintaining the daily prophylaxis with concizumab. The course proved satisfactory, with a good haemostatic response and no bleeding or infectious complications. At control one week after surgery, a mild increase in D-dimer was noted (702 ng/ml), with normalization at follow-up two months later. The patient experienced no thrombotic events or inhibitor development.

The case-study data indicates that concizumab combined with low-dose FVIII is effective.

Update on the findings of Pfizer's phase II study investigating marstacimab

PF-06741086 (**Marstacimab**) is a fully human monoclonal antibody against tissue factor pathway inhibitor (TFPI)α and (TFPI)β and is currently in phase III development. The intended indication is routine prophylaxis treatment to prevent or reduce the frequency of bleeding episodes in patients with haemophilia A or B (with or without inhibitors). At the 2020 ASH Congress (ASH1789), a post hoc analysis of data from a phase II study was presented on patients with haemophilia with and without bleeding episodes. Investigators looked at peak thrombin and D-dimer levels to assess changes in these biomarkers' levels after bleeding episodes in patients receiving prophylactic PF-06741086 treatment.

Patients in phase II (NCT02974855) received subcutaneous (SC) PF-06741086 at doses of (1) 150 mg once weekly, with a loading dose of 300 mg, (2) 300 mg once weekly, or (3) 450 mg once weekly. Treatments permitted for bleeding episodes included activated coagulation factor VIIa, FVIII, or FIX. The use of activated prothrombin complex concentrate was prohibited. D-dimer and peak thrombin data collected within three days after each bleeding episode were used for this analysis. Biomarker profiles were compared between patients with and without bleeding episodes, as well as with the data from healthy volunteers (n=41). A total of 15 bleeding episodes were reported in eight of 26 patients during the study.

No transient increases in D-dimer could be attributed to the administration of bleeding episode treatment. The transient increases in peak thrombin levels following on-demand treatment for bleeding episodes did not exceed peak thrombin levels seen in patients without bleeding events or the levels seen in healthy volunteer controls receiving single doses of PF-06741086. *The study was funded by Pfizer*.

First patients dosed in Pfizer's phase III BASIS study

In November 2020, Pfizer announced dosing its first patient in the phase III BASIS study with **PF-06741086** (**marstacimab),** an investigational product evaluated for the treatment of people with severe haemophilia A or B, with or without inhibitors.

The BASIS phase III (NCT03938792) study will evaluate annualized bleed rate through 12 months on treatment with PF-06741086, in approximately 145 adolescent and adult participants between ages 12 to <74 years with severe haemophilia A or B (defined as factor VIII or factor IX activity <1%, respectively), with or without inhibitors. Approximately 20% of participants will be adolescents (ages from 12 to <18 years old). This study compares

treatment with a run-in period on patients' prescribed factor replacement therapy or bypass therapy during a six-month observational phase with a 12-month active treatment phase. During the latter phase, participants will receive prophylaxis (a 300 mg subcutaneous loading dose of PF-06741086, followed by 150 mg subcutaneously once weekly) with the potential for dose escalation to 300 mg once weekly.

An update on Sanofi's fitusiran

Fitusiran is an investigational small interfering RNA (siRNA) therapeutic, that targets and reduces antithrombin and promotes thrombin generation, sufficient to rebalance haemostasis in people with haemophilia A or B, with or without inhibitors. It is prophylactically administered subcutaneously every other month *or* once a month.

Patients who completed the phase I study were able to roll over to the phase I/II open-label study. The phase III study is currently in clinical development in adult and adolescent patients. A dose-confirmation study in the paediatric group has been initiated.

All fitusiran investigations were paused in October 2020 due to reports of non-fatal thrombotic events. An investigation was initiated, including the analysis of antithrombin (AT) levels and other available data, as well as pharmacokinetic and pharmacodynamic modelling.

As of November 5 2020, 259 patients had received at least one dose of fitusiran in the clinical trial programme, with an estimated total of 293 patient-years of exposure. Five thrombotic events were included in the analysis:

- Cerebral vascular accident,
- Cerebral infarct,
- Spinal vascular disorder,
- Atrial thrombosis, and
- Cerebral venous sinus thrombosis.

Four of the five events happened in patients with haemophilia A, three of which in those without inhibitors. The fifth event occurred in a patient with haemophilia B and inhibitors.

For each patient AT levels in which each patient spent the most time were shared. Patients with cerebral vascular accident, cerebral infarct, and spinal vascular disorders were <10%, while patients with atrial thrombosis and cerebral venous sinus thrombosis were at levels between 10 and 20%. It is important to note that patients between 10 and 20% were also using concomitant factor or bypassing agents in excess of the current bleed management guidelines in fitusiran clinical studies.

The incident rate of vascular thrombotic events in 100 patient-years in AT categories of <10%, 10-20% and >20% was 5.91, 1.49 and 0, respectively.

The data suggest that the risk of thrombotic events may be greater with AT levels of <10%. Based on intra-patient variability in AT levels, a therapeutic window was defined where a lower AT threshold of 15% was selected to minimise the occurrence of AT levels <10% in patients exposed to fitusiran. In addition, an upper AT threshold of 35% was chosen as a target based on intra-patient variability and blinded fitusiran efficacy data. The aim of the proposed

revision of the fitusiran dose regimen in adults and adolescents is to minimise AT reduction and, therefore, to mitigate the risk of vascular thrombosis.

During the EAHAD 2021 Congress, Sanofi gave an oral presentation on its proposed revision of fitusiran dose and regimen as risk mitigation to vascular thrombosis, seen in 2020 and described above. Based on PK and PD modelling in clinical data, the following revised dosing plan is proposed.

1. Patients will start with an SQ dose of fitusiran at 50 mg every other month. If patients have two AT levels <15% at this step, they will need to be discontinued from fitusiran dosing.
   To escalate patients to higher doses, they will need to have achieved two AT levels >35% once the patient has achieved steady-state at a given dose regimen. The next two escalating dosing regimens are:
   a. 50 mg monthly based on AT levels, and
   b. 80 mg monthly based on AT levels.

An update on Sanofi's fitusiran clinical studies

As of January 2021, the revised plan came under review by the global health authorities (HA), and **fitusiran** dosing has resumed. Following HA and Institutional Review Board (IRB) review as well as patient re-consent, resuming of fitusiran dosing in patients is underway on a country-by-country basis. As of January 2021, patients have begun re-dosing in the fitusiran study. There is no change to the guidance for breakthrough bleed management guidelines (updated in 2017) during fitusiran prophylaxis, and patients will continue to use these guidelines to treat breakthrough bleeds.

During the ASH 2020 Congress, an abstract (ASH511) reported on phase I (NCT02035605) and phase II extension studies (NCT02554773). This study included male patients, >18 years, with moderate or severe haemophilia A and B, with or without inhibitors. Patients received monthly fixed doses of fitusiran 50 mg or 80 mg subcutaneously.

Thirty-four patients (haemophilia A, n=27 [13 with inhibitors and 14 without inhibitors]; haemophilia B, n=7 [two with inhibitors and five without inhibitors]) were enrolled in the phase II open-label extension study. They were treated for up to 4.7 years with a median exposure of approximately 2.6 years (as of March 10, 2020). Once-monthly subcutaneous dosing of fitusiran prophylaxis lowered antithrombin (a reduction of between 85% to 72% from baseline) across patients over a sustained period. An exploratory analysis of bleeding events showed an overall median annualized bleed rate of 0.84 during the observation period. Breakthrough bleeds were managed successfully in accordance with the reported bleed management guidelines for reduced doses of bypassing agents and replacement factors.
Fitusiran is an investigational medicinal product in development by Sanofi.

Sanofi's data on the impact of fitusiran on the quality of life of people with inhibitors

During the 2020 ASH congress, data (ASH877) were presented on health-related quality of life (HRQoL) in patients in the phase I clinical trial investigating the use of **fitusiran**. The report evaluated changes in patient-reported outcomes (PRO) in terms of patient-relevant

improvements in people with haemophilia with inhibitors (PwHI) on prophylactic fitusiran treatment.
HRQoL was assessed using the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) and the EuroQol 5 Dimensions (EQ-5D) questionnaires at baseline and at the end of the study in a cohort of 17 PwHI (haemophilia A, n=15; haemophilia B, n=2) from the phase I study.

Patients previously treated on-demand or prophylactically had a mean (standard deviation [SD]) age of 34.6 (10.3) years and a mean (SD) number of bleeding episodes in the six months before baseline of 16.6 (10.7). Mean (SD) changes from baseline to end of study (day 84 or later) in Haem-A-QoL total (–9.2 [11.2]) and physical health (−12.3 [15.1]) domain scores suggest a clinically meaningful improvement (lower scores indicate better HRQoL). Numeric reduction (i.e., improvement) in all other domains appeared to be dose-dependent (greater improvement in the 80 mg group) (Table 1). Changes in EQ-5D utility and EQ-VAS scores were not clinically meaningful. Further analyses in people with haemophilia with and without inhibitors from phase II will be presented. *Fitusiran is an investigational medicinal product in development by Sanofi.*

OTHER NEWS

Enzyre and Takeda enter strategic partnership to develop at-home monitoring assays

In March 2021, Enzyre and Takeda entered a strategic partnership to develop assays for the diagnosis and monitoring of congenital bleeding disorders. The partnership builds on the existing research collaboration agreement signed in December 2019.The Hemophilia Enzycard, a product using Enzyre's proprietary Enzypad platform technology will enable patients to test in a home setting, immediately transferring coagulation status results to the patient's treating physician through a mobile phone app. It is hoped that this will further allow personalisation of therapies and improved outcome.

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 facto r	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 FVIII	**Haemophilia A**	BIVV001	Efanesococog alfa (rFVIIIFc-VWFD'D3-XTEN)	Sanofi and Sobi co-development	**Phase 3**
Replacement FIX	**Haemophilia B**	Alprolix®	rFIXFc (eftrenonacog alfa)	Sobi	**Licensed**

Replacement FIX	**Haemophilia B**	BeneflX®	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 FIX	**Haemophilia B**	Dalcinonacog alfa (DalcA)	Subcutaneous coagulation factor IX variant	Catalyst Bioscience	**Phase 2**

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 May [1]2022)**
Bypassing agent		Marzeptacog alfa (activated) MarzAA	Subcutaneous coagulation rFVIIa variant	Catalyst Bioscience	**Phase 3**

[1] Text in red highlights changes from the last edition.

	Haemophilia A or B w/ or w/o inhibitors				**Recruiting**[2]

[2] Text in red highlights changes from the last edition.

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**
NRT Bispecific antibody	**Haemophilia A**	Mim8	Bispecific antibody	Novo Nordisk	**Phase 2**
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**[3]
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**

[3] Text in red highlights changes from the last edition.

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	**Dosing resumed Phase 3[4]**
NRT Activated Protein C inhibitor	**Haemophilia A or B w/ or w/o inhibitors**	SerpinPC	Activated Protein C inhibitor	Apcintex	**Phase 1/2**

GENE THERAPY					
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[5]**
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)	**Phase 3**
Gene Therapy	**Haemophilia A**	BAY2599023 / DTX 201	Gene therapy using AAVhu37FVIII	Bayer	**Phase 1/2**

[4] & [4] Text in red highlights changes from the last edition.

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**
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**[6]
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)	uniQure	**Phase 3 (FDA removed the clinical hold in April 2021**[7]**)**
Gene Therapy	**Haemophilia B**	AMT-060	Gene therapy using AAV5 vector encoding FIX	uniQure	**Phase 1/2 (FDA removed the clinical hold in April 2021)**[8]
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	AAV encoding FIX Padua variant	Freeline	**Phase 1/2**

[6] Text in red highlights changes from the last edition.
[7] Idem
[8] Idem

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 (formerly SHP648/ AskBio009/BAX 335)	AAV8-based gene therapy using FIX Padua variant	Takeda	**Clinical trial suspended**

CELL-BASED THERAPIES					
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**[9]

[9] Text in red highlights changes from the last edition.