NOVEL TREATMENTS IN HAEMOPHILIA & OTHER BLEEDING DISORDERS: A PERIODIC REVIEW

2021 – ISSUE 1

IRISH HAEMOPHILIA SOCIETY

JUNE 2021

haemophilia.ie

Contents

Issue 1 of 2021, Issue 6 of Series

Foreword

Welcome to the Irish Haemophilia Society 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 (*https://onlinelibrary.wiley.com/doi/10.1111/hae.14236*). 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,

Brian O'Mahony,	**Declan Noone**	**Amanda Bok,**
Chief Executive, Irish Haemophilia Society	**EHC President**	**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 disorder
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.

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.

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

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.

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.

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**.

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.

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.

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.

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.

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.

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. 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.

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

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.

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.

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®**.

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.

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.

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.

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.

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.

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.

Cell therapy

Reports from clinical trials

Sigilon is initiating its p**hase I/II clinical trial** for **SIG-001**.

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.

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.

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.

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

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**.

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

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.

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.

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.

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**.

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.

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.

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.

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.

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.

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.

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

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.

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.

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.

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.

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

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.

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.

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 q**uality of life of people with inhibitors**.

An update on treatments for Von Willebrand Disease

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

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

Other news

Takeda entered a strategic partnership to develop **at-home monitoring assays**.

Factor replacement therapies

Results from the phase III Sanofi/Sobi A-LONG study

During the 2021 EAHAD Congress, an abstract (ABS128) presented an analysis examining pain and related physical functioning from the phase III A-LONG study (NCT01181128), **Elocta®**. This analysis included adult and adolescent patients (≥12 years) who completed the Haem-A-QoL and EQ-5D-3L questionnaires at baseline (BL) and end of study (EoS). A significantly greater proportion of patients reported they never/rarely experienced painful swellings (n=87; 66% vs 46%, p=0.001) or pain in their joints (n=89; 42% vs 27%; p=0.012) at EoS compared with BL. The number of patients who never/rarely found it painful to move increased at EoS (n=86; 47% vs 38%); however, the change was not significantly different (p=0.194). A significantly greater proportion of patients reported no pain/discomfort at EoS compared with BL (n=116; 45% vs 34%; p<0.05). The mean change from BL in EQ-5D-3L index and VAS scores was significant at EoS (0.04 and 4.45, respectively; both p<0.05). The results show statistically significant improvements in pain-related QoL over time with Elocta® prophylaxis, and that effective pain management in haemophilia is, therefore, a key component of patient care.

Final results of Sanofi/Sobi PUPs A-LONG study

During the 2020 ASH Congress, in an abstract (509) authors presented the final results of the PUPs A-LONG study, which evaluated an extended half-life (EHL), **Elocta®** (rFVIIIFc), in previously untreated patients (PUPs) with haemophilia A. This phase III study (NCT02234323) enrolled male PUPs <6 years of age with haemophilia A (<1 IU/dL endogenous FVIII) to receive Elocta®. The primary endpoint was inhibitor development (incidence rate=number of patients with inhibitor/number of patients reaching ≥10 exposure days [ED] milestone or developing an inhibitor). Of 103 patients receiving ≥1 dose, 80 (77.7%) were <1 year of age; 20 (19.4%) had a family history of inhibitors, and 82 (79.6%) had a high-risk haemophilia genotype. Eighty-one patients started with on-demand treatment; of these, 69 switched to prophylaxis. Twenty patients started on prophylaxis, and two were not assigned a regimen. Eighty-seven (84.5%) patients completed the study. Eighty-seven (84.5%), 85 (82.5%), and 81 (78.6%) patients had ≥10, ≥20, ≥50 EDs to Elocta®, respectively. Total and high-titre (≥5.00 BU/mL) inhibitor rates were 31.1% (28/90) and 15.6% (14/90), respectively, for patients with ≥10 EDs (three inhibitor patients with <10 EDs were included). The median time to inhibitor development was nine EDs (range: 1–53). Twenty-eight (27.2%) patients had 32 adverse events assessed as related by the investigator: FVIII inhibition (n=28); soft tissue haemorrhage (n=1); deep vein thrombosis (n=1); device-related thrombosis (n=1); rash papular (n=1). There was one non–treatment-related death due to an intracranial haemorrhage. Overall inhibitor development was in the expected range, although the high-titre incidence was lower than that reported in the literature. *This abstract included in its authors representatives from Sanofi and Sobi.*

Findings from Bayer's PROTECT VIII extension study

Data on phase II/III PROTECT VIII extension study were presented in an abstract (ABS088) at the EAHAD 2021 Congress. During this study, **Jivi®** was tested for its efficacy and safety as a prophylactic or on-demand treatment in PTPs with severe haemophilia A aged 12-65. Patients who completed the PROTECT VIII main study could enrol in the open-label extension and receive either on-demand or prophylaxis (30-40 IU/kg twice weekly; 45-60 IU/kg every five days or 60 IU/kg every seven days). Patients who switched regimen after the first seven days in the extension were assessed in a variable frequency group (VAR). In addition, patients with ≥6 years of prophylaxis with BAY 94-9027 were assessed for bleeding and safety outcomes.

During the main and extension study, 22 patients (median age 43.5 years) received Jivi® prophylaxis for ≥six years (twice weekly, n=two; every five days, n=four, every seven days, n=five; VAR, n=11). The median (Q1; Q3) annualised bleeding rate (ABR) for the full extension period was 0.9 (0.4; 2.2) compared with an ABR of 3.0 (1.0; 15.0 pre-study). Median joint ABR was also reduced (0.6 [0.4; 1.7]) compared with pre-study joint ABR (3.0 [0.0; 12.0]). Median (range) total time in extension was 5.6 (5.3–6.3) years, and median FVIII consumption was 3413 IU/kg/yr. During the extension, study-drug-related adverse events (AEs) were reported in four (18.2%) patients and were either mild (two AEs in two patients: elevated alanine aminotransferase and arthralgia) or moderate (bone marrow oedema and meniscal degeneration [in one patient), and osteoarthritis). No study-drug-related serious AEs, deaths or thrombotic events were reported. No patients developed FVIII inhibitors.

Results from Bayer's PROTECT VIII Kids study

During the 2020 ASH Congress, an abstract (1797) presented the findings of the PROTECT VIII Kids study. As a reminder, at present (June 2021), **Jivi®** is not licenced for children under 12 years by the European Medicines Agency. In the PROTECT VIII Kids main study (NCT01775618), Jivi® was assessed for long-term efficacy and safety in patients aged <6 and 6 to <12 years at study entry. Male previously treated patients (PTPs) aged <12 years with severe haemophilia A were enrolled in two age cohorts: <6 and 6 to <12 years. Patients received Jivi® prophylaxis twice weekly (25–60 IU/kg), every five days (E5D, 45–60 IU/kg), or every seven days (E7D, 60 IU/kg). Patients completing ≥50 exposure days and ≥6 months in the main study, or a 12-week safety expansion study that enrolled additional PTPs aged <6 years, could continue in the optional extension phase. Seventy-three previously treated patients were enrolled in the main or expansion study, 59 continued in the extension phase (n=32 aged <6 years; n=27 aged 6 to <12 years). The median age at enrolment was 5.0 years, and the median age at the end of the extension was 12.0 years. Median time in the extension study was 4.7 years in patients aged <6 years and 5.5 years in those aged 6 to <12 years; median exposure was 354.5 and 424.0 days, respectively. Fifty-two patients completed ≥3 years of treatment, and 39 patients completed ≥5 years. At the end of the extension, 29 patients were treated twice weekly, 20 patients were treated every five days, and ten patients were treated every seven days. The median annualized bleeding rate (ABR) for total bleeds was 1.54 for all patients aged <6 years and 1.89 for those aged 6 to <12 years. Total ABR improved compared to the main study and was maintained during the extension. In the last 12 months of treatment, the median spontaneous ABR was 0.0 in both age groups. However, trauma ABR was higher in patients aged <6 years. In the last 12 months, 19 patients (33.3%) had zero bleeds, and 27 patients (47.4%) had zero joint bleeds. Overall, joint bleeds comprised 49.2% and 46.5% of total bleeds in younger and older patients, respectively, and predominantly affected ankle, knee and elbow joints. A total of 11 patients (18.6%) had detectable PEG in plasma during the extension (n=6 aged <6 years; n=5 aged 6 to <12 years). PEG was detected at only a single time point in 6 patients and at repeated time points in 5 patients; in all cases, PEG levels were just above the detection limit (0.1 mg/L) and did not change over time, indicating a steady-state was reached. Levels of renal biomarkers were consistent over time, demonstrating normal renal function.

The post hoc analysis of the children aged 12 at the end of the extension study was presented during the 2021 EAHAD Congress (ABS055). This analysis included 30 previously treated patients (PTPs) PTPs aged 12–18 years (median 15 years). The total study time was 6.1 years (5.6;6.3) and 5.5 years (4.9;5.7) in the extension. The cumulative number of **Jivi®** exposure days was 482.5 (429;602). The number of infusions per year was 89.7 (73.6;104.3) at a dose of 45.4 (37.2;57.2) IU/kg/infusion. The median (Q1; Q3) FVIII consumption was 3945.8 (3134.3;4331.5) IU/kg/year. The total annualised bleeding rate (ABR) was 1.8 (0.5;3.3); ABR was 0.4 for spontaneous, 0.7 for traumatic and 0.7 for joint bleeds. In the last 12 months, most patients were treated twice weekly (n=15) or every five days (n=10). This study was financed by Bayer.

Findings from Bayer's PROTECT VIII post-marketing study

During the EAHAD 2021 Congress (ABS191), the results of the post-marketing, interventional phase IV of the PROTECT VIII trial were presented. This study included previously treated patients (≥150 exposure days [ED]) with severe haemophilia A (FVIII:C <1%) aged ≥18 years. The eligible patients received **Jivi®** prophylaxis for 100 exposure days (EDs). The recommended starting dose was every five days (E5D, 45 IU/kg) until the next planned visit (visit three after 10–15 EDs) with an option to continue or increase the dose, or switch regimen to either twice-weekly, every five days, or every seven days. The change in the regimen should be based on patient needs and bleeding events. Patients could also start on a twice a week regimen. By 1 September 2020, 32 patients were enrolled (dropouts, n=3; one due to perceived lack of efficacy), and 18 patients have received Jivi® prophylaxis for ≥24 weeks (2×W, n=2; E5D, n=7; E7D, n=5; VAR, n=4). No patients developed FVIII inhibitors, PEG antibodies or anti-drug antibodies. At data cut-off, the median (range) total time in the study was 235.2 (185–293) days with a median (range) of 48 (34–80) exposure days.

The median (Q1; Q3) total, spontaneous and joint ABRs were 1.76 (0.0; 3.80), 1.59 (0.0; 3.80) and 0.0 (0.0; 3.80), respectively. The authors of this abstract included Bayer representatives.

Findings from Octapharma's NuProtect study and extension study

In the NuProtect study, previously untreated patients, PUPs with severe haemophilia A treated with **Nuwiq®** for 100 exposure days (EDs) showed a 17.6% cumulative incidence of high-titre inhibitors [Liesner RJ, Neufeld EJ. Blood 2019; 134 (Suppl. 1): 903], while the SIPPET study showed a cumulative incidence of 28.4% (Peyvandi F et al. New Engl J Med 2016; 374:2054-34). In the NuProtect study, children who received continuous prophylaxis had a median spontaneous annualised bleeding rate (ABR) of 0 [mean (SD): 0.54 (1.07)]. Forty-eight patients continued into the NuProtect extension study at 15 centres in nine countries. One patient was lost to follow-up after one ED. The remaining 47 patients received prophylax-

is for a mean (SD) of 20.6 (6.5) months and 179 (72) exposure days. By the end of the study, 85% of patients were on a twice-weekly infusion schedule. During prophylaxis, the median (IQR) spontaneous ABR was 0 (0–0.5). The median (IQR) total ABR was 1.0 (0–1.95). Of the 47 patients, 34% were bleed free, and 72% experienced no spontaneous bleeds. No children developed FVIII inhibitors during the NuProtect extension study. Most patients received twice-weekly prophylaxis.

These findings were presented in an abstract (2681) at the 2020 ASH Congress.

First patient dosed in Sobi's XTEND-Kids study

In April 2021, Sobi announced that it had dosed its first patient in the phase III, open label, interventional XTEND-Kids study of **Efanesoctocog alfa (BIVV001)**. This study investigates the efficacy, safety and pharmacokinetics of once-weekly prophylaxis with efanesoctocog alfa in some 65 PTPs aged 12 or over for 52 weeks. Efanesoctocog alfa (rFVIIIFc-VWF-XTEN) is a novel fusion protein designed to overcome the von Willebrand factor-imposed half-life ceiling.

Findings from ATHN 2 study on dosing, patient satisfaction and other patient-reported outcomes

The ATHN 2 study on factor switching sponsored by the American Thrombosis and Hemostasis Network (ATHN) in the US reported longitudinal data on previously treated haemophilia patients switching to **Adynovi® /Adynovate®** to identify dosing regimens, patient satisfaction, impact on health status and productivity. This study enrolled children and adults with moderate or severe haemophilia A or B (factor VIII or IX clotting activity ≤5% of normal) who were previously treated with factor concentrates with more than 50 exposure days. Fifty-nine patients with haemophilia A were enrolled into the Adynovi® /Adynovate® sub-study by May 1, 2020. Mean (± standard deviation [SD]) age was 25 ± 18 years (range = 4–77 years); 72.9% (n=43) were in a prospective arm and 27.1% (n=16) in a retrospective arm; 11.9% (n=7) had moderate haemophilia A and 88.1% (n=52) had severe haemophilia. All were taking prophylaxis. At study end, the most common treatment regimen was twice weekly (45.1%, n=23), and the mean nominal dose was 50 ± 10 IU/kg. Patients were highly adherent with a mean total VERITAS-Pro score of 31.4 ± 8.4, which improved slightly over time (32.6 ± 9.0 at baseline vs 29.2 ± 4.2 at month 12). Patients strongly preferred bleeding control and convenience for this EHL. These findings were presented in an abstract (870) during the 2020 ASH Congress. Authors of this abstract include representatives from Takeda.

Real-world data on half-life extension with EHL treatment

An abstract (ASH 2020 Congress; 234) was presented from the database of the Web Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo) to assess individual changes in terminal half-life (THL) after switching from standard half-life (SHL) to extended half-life (EHL) concentrates in patients with severe haemophilia. Data were collected from 649 patients (1298 infusions) with severe haemophilia (89% haemophilia A; median age: 21.7 (11.5-37.7); weight: 66.0 kg (43.6-80.0) BMI: 22.5 (18.9-25.3); positive inhibitor history: 11.7%). All patients had received both SHL and EHL infusions.

THL increased by a median factor of 1.4 (1.2-1.7) in FVIII, leading to an absolute median increase of 4.1 hours (IQR: 2.0-6.7). However, THL was extended by less than 20% in 157 (27,2%) patients with haemophilia A after switching to EHL factor concentrate, leading to less than 48 minutes of extension of THL. The study showed decreased THL in 57 (9,9%) patients with haemophilia A after switching. For patients switching to EHL FIX, THL increased by a median factor of 3.1 (2.4-3.6), leading to a median extension of 70.3 (52.5-90.8) hours in THL of FIX. All patients with haemophilia B showed an extension of THL after switching, with a minimum increase of 25%.

Both the absolute and the relative increase in THL were similar for children and adults for both FVIII and FIX. These findings indicate that although an increased THL was observed at a group level, this was not the case for all individual patients. These findings support the use of individualized pharmacokinetic assessment in patients with haemophilia to guide clinical decisions on switching from SHL to EHL concentrates. These findings were presented during the 2020 ASH Congress.

Real-world data on the use of EHL in children

During the 2021 EAHAD Congress (ABS067), the findings of a small retrospective review were presented. Existing medical records of children with haemophilia A (HA) and B (HB) from one haemophilia treatment centre who had switched from SHL to EHL were analysed. A total of 25 male patients enrolled in the study (20 HA; 3-6 years old: n=4; 7-12 years old: n=8; and 13-18 years old: n=13). The reasons given for switching from SHL to EHL were to "improve quality of life" (75%), to "improve compliance" (25%) and to decrease the frequency of bleedings (38%). Overall, treatment with EHL lengthened

the median dosing interval from 2.3 to 3.5 days for HA (p=0.018) and from 3.5 to 7 days for HB. For HA, mean trough levels were 4.0% on EHL and 3.1% on SHL (p=0.019). For HB, mean trough levels were 13.25% on EHL and 6.7% on SHL (p>0.05). For HA on EHL, the mean FVIII half-time was 16.4 hours for children 13-18 years old (n=10) and 13.0 hours for children 3-12 years old (n=10). For HB on EHL, the mean FIX half time was 109.16 hours, according to WAPPS-Hemo. People with HA reduced their ABR and annual joint bleed rate (AJBR) from 1.1 and 0.7 to 0.7 and 0.3, respectively, following treatment with EHL (AJBR: p=0.048). For HB, the ABR and AJBR changed from 0.75 and 0.2 to 2.4 and 1.0, respectively, following treatment with EHL (p>0.05). Also, the EHL factor IX consumption level (49 IU/kg/week) used for prophylaxis was statistically significantly lower (p =0.0431) than the corresponding SHL factor IX consumption (66.2 IU/kg/week). Finally, there was no inhibitor development.

Retrospective PK evaluation of SHL and EHL FVIII

In a retrospective, observational, single-centre study of adult patients with severe haemophilia A, without inhibitor, 16 patients were analysed. All were male with severe haemophilia A, of which 11 patients (68.75%) were being treated with an EHL and five (31.25%) with a SHL.

For SHL, the mean half-life was 13.25 hours of half-life and a mean of 83.9 hours until reaching 1%. For EHL, the mean half-life was 18.95 hours, and the mean time until reaching one per cent of 130.89 hours. After dose adjustment based on PK, 31.25% (five patients) reduced the FVIII dose, 43.75% (seven patients) maintained it, and 25% (four patients) required an increase of it. Annualised bleeding rate (ABR) was reduced, from the mean of 1.94 (0-6) bleeding episodes before the PK adjustment to 1.75 (0-5) after this adjustment (p= 0.366). A reduction was noted in the mean of annualized joint bleeding rate (AJBR): 1.81 (0-6) vs 1.75 (0-5) after PK adjustment (p= 0.705). These findings were presented in an abstract (ABS160) during the 2021 EAHAD Congress.

Findings from Novo Nordisk's Guardian 5 study

The Guardian 5 (NCT02035384) study assessed the safety and efficacy of **NovoEight®** in previously treated patients (>150 exposure days [EDs]) of any age with severe/moderately severe haemophilia A (FVIII ≤2%) and a negative inhibitor test prior to first dosing. They received prophylaxis or on-demand treatment. In total, 70 patients were screened and 68 exposed to NovoEight® (median [range] age: 26.5 [5–76] years). At inclusion, 63 (92.6%) patients were on prophylaxis (<12 years, n=14; ≥12 years, n=49), of which 55 had severe haemophilia and eight moderately severe. Six (8.8%) patients reported a history of inhibitors. Among prophylaxis patients, median (range) annual bleeding rate (ABR) was 1.97 (0.0–25.5) bleeds/year; estimated ABR (negative binomial model) was 3.65 (95% CI: 2.53, 5.25). Overall, mean (SD) consumption per month was 157.6 (137.9) IU/kg. These findings were presented during the 2021 Congress of the European Association for Haemophilia and Allied Disorders (EAHAD; abstract ABS210). *Authors of this abstract include representatives from Novo Nordisk.*

Retrospective analysis comparing prophylaxis treatment regimens in patients in Italy

During the EAHAD 2021 Congress, an abstract (ABS186) presented data from an Italian study of 290 patients, which evaluated real-world annualised bleed rates (ABR) and factor consumption associated with prophylactic use of **Afstyla®** compared to other FVIII products. De-identified patient data were collected for patients on one of the following four rFVIII products for at least eight weeks, Afstyla® (n=60), **Elocta®** (n=73), **Advate®** (n=83) and **Kovaltry®** (n=74). Patients were matched for age and disease severity across the four patient groups. In patients treated with Afstyla® and Elocta®, 56.7% and 76.7%, respectively, were dosed ≤2 times per week, while most patients on Advate® (83.1%) or Kovaltry® (63.5%) infused more frequently than twice per week. Mean ABR was 0.4 with Elocta®, 0.7 with Afstyla®, 0.8 with Kovaltry® and 1.2 with Advate®. The median annualised spontaneous bleed rate (AsBR) was 0.0 for all products with 88.3%, 87.7%, 82.4% and 71.1%, of patients reporting zero spontaneous bleeds for Afstyla®, Elocta®, Kovaltry® and Advate®, respectively. The mean factor consumption was lowest with Afstyla® (92.7 IU/kg/week); 10.7%, 17.7% and 24.3% below Elocta®, Kovaltry® and Advate®, respectively. *The authors of this study included representatives from CSL Behring.*

Study looking at patients switching to Afstyla®

In a study looking at switching to **Afstyla®**, the authors obtained data for 60 patients (mean [standard deviation, SD] aged 33.1 [18.5] years) on prophylaxis. Of these, 50.9% were dosed ≤2× per week. On their previous FVIII therapy, 53/60 (88%) patients were treated prophylactically, with 54.7% of patients dosing at least three times per week. In these 53 prophylaxis-to-prophylaxis switch patients, mean (SD) prophylactic factor consumption was similar to the previous regimen, 94.6 (38.5) IU/kg/week, or Afstyla®, 95.0 (37.1) IU/kg/week. Mean (SD) ABR decreased in this group from 1.8 (1.7) with the

prior drug to 0.5 (1.2) with Afstyla®. The percentage of patients with zero spontaneous bleeds increased from 45.3% to 90.6% after switching. These findings were presented in an abstract (ABS074) at the 2021 EAHAD Congress. The authors from the abstract include representatives from CSL Behring.

Sobi's indirect comparison of Elocta® and Jivi™

An article in the *Journal of Advances in Therapy* recently published a matching-adjusted indirect comparison (MAIC) study evaluating **Elocta®** compared to **Jivi™**. The indirect comparison builds on data from the individualised prophylaxis arm of the A-LONG phase III clinical trial evaluating Elocta® in 117 people and from the pooled prophylaxis population of the PROTECT VIII phase II/III study evaluating Jivi® in 110 people with haemophilia A. Once matched, the effective sample size for A-LONG was 81 people. The report was based on an indirect comparison of pivotal clinical trial data in adults. The mean annualised bleeding rate (ABR) was lower in the Elocta® individualised prophylaxis group versus the Jivi® pooled prophylaxis population (3.0 vs 4.9, p=0.02). The proportion of patients with zero bleeds was numerically higher for Elocta® (45.5%) than for Jivi® (38.2%), although the difference was not statistically significant. The authors of this article include representatives from Sobi.

Sobi's indirect comparison of Elocta® and Hemlibra™

In an article in the Journal of Blood Medicine, Klamroth et al. published in February 2021 a matching-adjusted indirect comparison (MAIC) study evaluating **Elocta®** compared to **Hemlibra™**. The aim of the indirect comparison was to compare the approved dosing regimens for each product, Elocta® individualized prophylaxis and Hemlibra™ administered once every week (Q1W), every 2 weeks (Q2W) or every 4 weeks (Q4W), based on clinical trial evidence. Individual patient data for Elocta® (A-LONG) were compared with data for Hemlibra™ (HAVEN trial program) for mean annualized bleeding rate (ABR) and proportion of patients with zero bleeds. Safety data reported across the analysed treatment arms were tabularized but not formally compared. After matching, no significant differences were observed between mean ABR for Elocta® and Hemlibra™ administered Q1W, Q2W or Q4W. The proportion of patients with zero bleeds was significantly higher with Elocta® compared with Hemlibra™ administered Q4W (51.2% versus 29.3%, respectively). The mean number of adverse events expressed per participant was 1.9 for individualized prophylaxis with Elocta® and 3.7–4.0, 4.1 and 3.6 for Hemlibra™ administered Q1W, Q2W or Q4W, respectively. This indirect treatment comparison suggests that Elocta® individualized prophylaxis is more efficacious than Hemlibra™ Q4W, and at least as effective as more frequent Hemlibra™ regimens, for the management of severe haemophilia A.

ABR and factor consumption of Jivi, Elocta, Adynovate and Esperoct in matching-adjusted indirect comparison from Bayer

During the 2021 EAHAD Congress, an analysis (ABS132) of **Jivi®, Elocta®, Adynovate®** and **Esperoct®** was presented to compare bleeding rates and factor consumption in prophylaxis regimens using matching-adjusted indirect treatment comparison (MAIC). This is a method for comparing outcomes in interventions in the absence of head-to-head trials. The comparison was conducted using data from PROTECT VIII (patient-level; Jivi®), A-LONG (aggregated; Elocta®), PROLONG-ATE (aggregated; Adynovate®) and pahtfinder2 (aggregated; Esperoct®) studies. Patient data from PROTECT VIII were weighted to match baseline characteristics in each comparator trial, including age, race, weight, prior treatment, region (Elocta® only), and bleeding events in the preceding year (Elocta® and Esperoct®). In additiona, annualised bleeding rate (ABR), percentage of patients with no bleeds, and annual rFVIII consumption were compared.

After matching, Jivi had a similar mean ABR as the comparators: 3.77 vs 3.90 Elocta®; 3.95 vs. 3.70 Adynovate®; 4.10 vs 3.70 Esperoct®. Jivi® had a similar percentage of patients with zero bleeds as the comparators: 34.1% vs 40.7% Elocta®; 38.9% vs 39.6% Adynovate®; 41% vs 40% Esperoct®. However, the mean annual consumption for Jivi® was 20% significantly lower than Elocta® (3469.88 vs 4289.08 IU/ kg/year) and 27% significantly lower than Esperoct® (3552.43 vs 4845.0 IU/kg/year). The median annual consumption for Jivi® was 26% lower than Adynovate® (3355.08 vs 4560.41 IU/kg/year). Authors from the abstract include a representative from Bayer.

Bleed risk simulation using Takeda's PROPEL study data

In an abstract (ABS190) from the 2021 EAHAD Congress, authors presented a microsimulation model developed to examine the proportion of patients achieving zero bleeds with 8-12% versus 1-3% FVIII trough levels with **Adynovate®** versus prophylaxis with **Hemlibra®** This simulation was done by creating six hypothetical patient profiles and calculating their bleeding risk for low, moderate or high-risk activities while on either of the regimens noted above. While these results are

modelled with significant limitations on assumptions, they indicate that, given access to a regimen of frequent and/or high doses of coagulation factor concentrate, PK-tailored prophylaxis may offer reduced bleed risk during physical activities, which may be a decision-making component for active patients.

Non-replacement therapies

Pooled data from the phase III Roche's HAVEN studies

Abstracts presented at the ASH 2020 Congress (1800) and the EAHAD 2021 Congress (ABS192) presented pooled data from patients with haemophilia A with and without inhibitors enrolled in the phase III HAVEN 1 (NCT02622321), HAVEN 2 (NCT02795767), HAVEN 3 (NCT02847637) and HAVEN 4 (NCT03020160) studies. The studies enrolled paediatric and adult patients who received **Hemlibra®** prophylaxis (1.5 mg/kg weekly, 3 mg/kg every two weeks, or 6 mg/kg every four weeks). The analysis included all participants assigned to receive Hemlibra® (including those assigned to the control arms who later switched).

Overall, the study included 400 people with haemophilia A (PwHA) in HAVEN 1, 2, 3 and 4 (n=113, 88, 151, and 48, respectively) at the cut-off date (15 May 2020). The median age at baseline was 28.5 (range 1–77) years, and 52.3% had FVIII inhibitors. In the 24 weeks prior to study entry, 60.9% had target joints. Across all studies, the model-based treated bleed annual bleeding rate (ABR) was 1.4 (95% confidence interval 1.1–1.7); treated bleed ABRs remained low throughout and were seen to decrease with successive 24-week treatment intervals. During weeks 121–144 (n=170), 82.4% of participants had zero treated bleeds, and 15.3% of participants had 1–3 treated bleeds. During the same period, 91.8% and 90.0% had zero treated spontaneous/joint bleeds, respectively. The proportion of participants with target joints reduced from 60.9% prior to study entry to 4.6% at weeks 1–24, then <1.5% in all subsequent treatment intervals. The authors from these abstracts included representatives from Genentech and Roche, respectively.

Data from Roche's HAVEN studies on antidrug antibodies with Hemlibra®

In an abstract (ABS141) presented at the 2021 EAHAD Congress, data was presented on the anti-drug antibodies (ADAs) in people with haemophilia A (PwHA) enrolled in HAVEN 1–5 (NCT02622321, NCT02795767, NCT02847637, NCT03020160 and NCT03315455, respectively, run by Roche), HOHOEMI (JapicCTI-173710) and STASEY (NCT03191799) who had ≥1 ADA assessment post-Hemlibra® exposure. Cut-off dates were 15 May 2020 (HAVEN 1–4 and STASEY), 21 June 2019 (HAVEN 5), and 3 July 2019 (HOHOEMI). Of 668 participants included in this analysis, the median [IQ] exposure time was 103 [82–148] weeks.

Thirty-four (5.1%) tested positive for ADAs (2/111, 6/88, 6/151, 2/48, 8/64, 0/13 and 10/193 in HAVEN 1–5, HOHOEMI and STASEY, respectively). ADAs reported in 14/34 (41.2%) participants were detected only once. Four ADA-positive participants (HAVEN 1, n=1; HAVEN 2, n=2; HAVEN 5, n=1) were classified as having ADAs with neutralising potential (0.6% of the total population), only one of which was not previously reported. Of these four, one participant in HAVEN 2 discontinued Hemlibra® due to a lack of efficacy and resumed pre-study treatment without complication. ADAs without neutralising potential had no impact on efficacy. No differences in the safety profile were detected between those with and without ADAs, including the frequency or severity of injection-site reactions. No cases of anaphylaxis or systemic hypersensitivity were reported in ADA-positive participants. Overall, ADAs with neutralising potential occurred in <1% of participants. ADAs did not impact safety. The authors of this abstract included representatives from Roche.

Genentech's post-marketing data on the use of Hemlibra® in minor surgeries

In an abstract (1786) presented at the 2020 ASH Congress, a phase IV, multicentre study (NCT03361137) evaluating the safety and efficacy of **Hemlibra®** in severe haemophilia A with or without inhibitors undergoing minor surgical procedures without additional prophylaxis with by-passing agents (BPAs; for patients with FVIII inhibitors) or FVIII (for patients without FVIII inhibitors) was reported. Patients were followed for 28 days following discharge from surgery. Between June 28, 2018, and March 13, 2020, 14 people with haemophilia A (PwHA) undergoing minor surgeries were enrolled (with FVIII inhibitors n=11; without FVIII inhibitors n=3). One PwHA with FVIII inhibitors enrolled but did not have surgery and discontinued prematurely. Therefore, the surgery analysis population comprised 13 patients (with FVIII inhibitors n=10; without FVIII inhibitors n=3). The majority (78.6%) of those enrolled were aged <18, and all surgeries were either central venous access device (CVAD) removal (n=11) or dental procedures (n=2).

Of the ten patients with inhibitors, one CVAD removal led to excessive bleeding during surgery with a need for by-passing

agent (BPA) therapy, and two patients received BPA therapy during surgery without reported excessive bleeding. Three (two CVAD removals, one dental extraction) had post-operative bleeding that required the use of a BPA. Seven patients with inhibitors had zero bleeds after discharge from surgery. None of the three without FVIII inhibitors had excessive bleeding necessitating FVIII treatment during surgery or until discharge. Two CVAD removals resulted in zero bleeds post-operatively, and one dental extraction led to a post-operative bleed that did not require treatment. The study was terminated early due to low enrolment and the limited variety of surgery types. The majority of surgeries were performed without additional prophylactic coagulation factor. However, the small sample size should be considered here. Authors of this study included representatives from Genentech.

Report from the Roche Emicizumab Global Safety Database

In an article from the *Journal of Thrombosis and Haemostasis,* a report was presented from the Roche Emicizumab Global Safety Database. This database includes all fatalities in people with haemophilia, from clinical trials, pre-market access, and spontaneous post-marketing reports. These fatalities are categorized into: associated with haemophilia A (HA) (e.g., haemorrhagic; thrombotic; human immunodeficiency virus (HIV)/hepatitis C virus (HCV)), hepatic (non-HCV); associated with the general population (e.g., trauma/suicide; non-HA-associated conditions; or, unspecified. The reported cause of death was not reassessed. As of the cut0off date of May 15, 2020, 31 fatalities were reported. The median age at death was 58 years; 51% had factor VIII inhibitors. Fifteen (15/31) fatalities were considered associated with HA. Overall, the most frequent category was haemorrhage (11/31). Of these, six had a history of life-threatening bleeds, and four had a history of intracranial haemorrhage. The remaining HA-associated fatalities were related to HIV/HCV (3/31) and other hepatic causes (1/31). No cases were categorized as thrombotic. Of 10 cases considered not associated with HA, two were classified as cardiovascular (non-thrombotic), five as infection/sepsis, and one each as trauma/suicide, pulmonary, and malignancy. Six cases were unspecified. No unique risk of death was associated with **Hemlibra®** prophylaxis. The data reveal that mortality was primarily associated with haemorrhage or non-HA-associated conditions and was not reported by treaters to be related to Hemlibra® treatment. The authors from this article include representatives from Genentech.

EUHASS data on side-effects of Hemlibra®

An abstract (2685) presented at the ASH 2020, Congress reported on the use of **Hemlibra®** in people with haemophilia A (PwHA). The EUHASS registry comprises 86 participating centres in 27 countries, which reported on the use of Hemlibra® in a broad, representative PwHA population. The analysis included data from 148 PwHA treated in 2018. Concurrent treatments included recombinant activated factor VII (rFVIIa; **NovoSeven®**; n=23), factor VIII (FVIII products other than **Obizur®**; n=9) and activated Prothrombin Complex Concentrate (aPCC; **FEIBA®**; (n=1).

Two adverse events were reported in 2018. One event was an acute reaction (rash), reported 48 hours after dosing of a PwHA treated with Hemlibra® only. The person recovered from the rash; the frequency was 0.7% (1/148; 95% confidence interval [CI] 0.02–3.71%). The second event was a thrombotic event (myocardial infarction) that occurred ten hours after Hemlibra® dosing in a PwHA age >65 years receiving Hemlibra® and aPCC (FEIBA®). The frequency of thrombotic events was calculated as 0.7% (1/148; 95% CI 0.02–3.71%). No thrombotic microangiopathy (TMA) or anaphylaxis events were reported. However, this analysis was limited by the low numbers, especially in those without FVIII inhibitors, and relatively short exposure time to Hemlibra®. The authors of this abstract included representatives from Genentech.

Real World Data on the use of Hemlibra® from the UK National Haemophilia Database

During the 2021 EAHAD Congress, an abstract (ABS176) presented the UK experience using **Hemlibra®** with data from the National Haemophilia Database (NHD). The study included data on patients with severe haemophilia A (PwHA) starting 01/08/2019 until 30/06/2020. Annualised bleed rates (ABR) and joint bleed rates (AJBR) were calculated in people with ≥6 months on Hemlibra® based on Haemtrack (HT) home treatment data. Of the 263 people eligible, 92 had ≥ 6 months post-switching HT data with a median (IQR) age of 24.5 (4.76; 40.8), including 38 under 18 years old. ABR and AJBR were both 0.0 (0.0;0.0) over 33.3 (28.8;35.0) weeks treatment. A within-person comparison in 64 people showed a pre-switch ABR 2.61 (0.99;8.83), AJBR 1.78 (0.55;5.19) and 12 (19%) with zero-treated bleeds using FVIII prophylaxis (including 23 using rFVIIIFc) over 94 (89;97) weeks. After switching to Hemlibra® this reduced to ABR 0.0 (0.0;0.0) (P<0.001) and AJBR 0.0 (0.0) (P<0.001). Zero treated bleeds were recorded in 51 (80%) people. However, the duration of the follow up was significantly shorter at 32.0 (29.0;34.0) weeks than in the pre-switch period. Within-person comparison of FVIII and Hemlibra® prophylaxis in the subset of 14/17 people reporting bleeds on Hemlibra® showed a pre-switch ABR of 4.08 (1.91;10.8) and post-switch 2.89 (1.63;3.55); a change of -1.55 (5.42;0.54) (P<0.001). Hemlibra® was stopped in 5/263 subjects due to death (n=1) (ischaemic heart disease), poor efficacy (n=1), severe headaches (n=2) and unknown reasons (n=1). This real-world evidence suggests that Hemlibra® prophylaxis is associated with significantly fewer bleeds than FVIII prophylaxis in severe

PwHA without inhibitors. Those reporting frequent bleeds on FVIII prophylaxis are less likely to be bleed-free post switch but nevertheless achieve significant bleed reduction. Longer follow-up is required to fully evaluate the effect of Hemlibra® on haemophilic arthropathy.

UKHCDO real-world data on the usage of Hemlibra®

During the 2021 EAHAD Congress, another study from the UK (ABS206) presented data on prophylaxis from the UKHCDO National Haemophilia Database. Data were reported on 391 children under 12 receiving prophylaxis for severe haemophilia A without inhibitors at 20 UK Comprehensive Care Centres. Two hundred and thirty-four (70%) patients were receiving FVIII, and 157 (30%) were on **Hemlibra®**. There were significant differences in the proportion of children receiving Hemlibra® between centres (range: 0-78%), likely reflecting variations in practice. A total of 39 children had started Hemlibra® aged ≤2. The median age at first exposure in this sub-group was 11 months (range 4-24 months). In this sub-group of children, 15/39 (38%) were previously untreated with FVIII (PUPs), and 33/39 (85%) had received <20 exposure days to FVIII. Sixteen out of twenty (80%) of centres recorded the ability to measure Hemlibra® levels as part of monitoring.

Data on Hemlibra® use in PUPs or minimally treated patients

In an abstract (1787) presented at the 2020 ASH Congress, data was reported on the use of **Hemlibra®** in previously untreated patients (PUPs) and minimally treated patients (MTPs). These data included six patients between 1-23 months of age with severe HA at Rady Children's Hospital-San Diego (RCHSD) from November 2017 to April 2020. The cohort included 1 PUP and 5 MTPs with less than 20 FVIII exposure days (ED) prior to the initiation of Hemlibra® prophylaxis. All MTPs were previously treated with on-demand treatment before the initiation of Hemlibra®. The median age and weight at initiation were eight months (range: 1 to 23 months) and 9.5 kg (range: 4.4 to 11.8 kg). One patient treated on-demand was diagnosed with a high-titre FVIII inhibitor in the setting of a mouth bleed and started Hemlibra® prophylaxis after bleed management. The most common reason for initiation in non-inhibitor patients was the ability to administer medication without reliable venous access.

Following four once-weekly loading doses with Hemlibra®, five patients continued weekly maintenance dosing, and one patient continued 28-day maintenance dosing. Patients were followed for a median of nine months (range 3-24 months) after Hemlibra® initiation. Four patients, including the patient with a known FVIII inhibitor, had zero treated bleeds. Two patients were diagnosed with high-titre FVIII inhibitors on routine inhibitor surveillance after initiation of Hemlibra® and were the only patients who experienced treated bleeds during the study period. The majority (6/8) of treated bleeds were traumatic. The patient with the highest FVIII inhibitor titre experienced a disproportionately high number of total treated bleeds, though three of the seven bleeds were prior to FVIII inhibitor diagnosis. No patients required central venous catheter placement. One patient underwent circumcision with peri-operative FVIII replacement and did not have post-op bleeding. In terms of medication safety, one patient reported injection site bruising. No patient experienced severe adverse reactions, including thrombotic microangiopathy, thrombosis, or clinical evidence of anti-drug neutralizing antibodies. All patients continued Hemlibra® prophylaxis during the study period.

Single centre experience with Hemlibra® prophylaxis

In an abstract (1791) presented at the ASH 2020 Congress, another single-centre report on the use of **Hemlibra®** was presented. In this report, 38 patients, both children and adults with haemophilia A with and without inhibitors, were included. Of these, 35 patients (92.1%) had severe and three (7.9%) had moderate haemophilia A. Eleven patients (28.9%) had a FVIII inhibitor. The mean age was 16.4 with 18 patients (47%) below 12 (age limit used in HAVEN trials). Fifty-four point one per cent of patients were Caucasian, 18.9% were Asian, and 16.2% were African American.

Thirty patients (78.9%) were on prophylaxis with either rFVIII (71.5%) or FEIBA (21.4%) before starting Hemlibra®. All 38 patients were started on Hemlibra® with a loading dose of 3 mg/kg weekly for four weeks, followed by a weekly maintenance dose of 1.5 mg/kg. The annual bleed rate (ABR) decreased by 52% for inhibitor patients (3.6 prior and 1.7 after initiation of Hemlibra®). Similarly, there was a 70.6% reduction for non-inhibitor patients (1.5 before and 0.44 after initiation of Hemlibra®).

Patients on Hemlibra® prophylaxis experienced 35 bleeding events over the 24 months. Nine of these 35 events occurred in one patient with a high titre FVIII inhibitor. Fifty-six point five per cent of these events were joint bleeds, 26.1% muscle bleeds, 13% soft tissue bleeds, and 4.4% were mucocutaneous bleeds. Barring two events, all episodes (93.9%) were managed in outpatient care. A majority of bleeds (72.1%) in inhibitor patients were treated with recombinant factor VIIa (rFVIIa, 16-24 doses for documented hemarthroses), and 3.4% were treated with FEIBA after non-response to rFVIIa (9-15 doses)

due to delayed treatment.

The remaining non-inhibitor patients were treated with rFVIII (2-5 doses) with a good response. Fifty-two per cent of these bleeds were trauma-related. Five surgeries were conducted in the inhibitor patients, and none experienced perioperative bleeding. rFVIIa was used as a by-passing agent for two of these surgeries: a hemispherectomy and a port removal. No by-passing agents were used for the remaining three port removals.

Five surgeries (one total knee arthroplasty and four port removals) were performed in patients without FVIII inhibitors. Recombinant factor VIII was used as the replacement agent, and the patient with knee arthroplasty experienced post-operative bleeding. There were no thrombotic episodes or deaths, and all but one continued on Hemlibra®. The patient post knee arthroplasty discontinued Hemlibra® after recurrent bleeds into the replaced joint despite aggressive replacement with rFVIII and absence of an inhibitor. The investigators highlighted the need for ongoing patient education for early bleed recognition, prompt treatment of breakthrough bleeds and the possible need for pre-sports prophylaxis with FVIII or by-passing agents.

Real-world data on the usage of Hemlibra® in Slovenia

During the 2021 EAHAD Congress, an abstract (ABS096) reported on the use of **Hemlibra®** in patients with haemophilia A (PwHA), with and without inhibitors, in Slovenia. The study reports from the time Hemlibra® was licensed and reimbursed in Slovenia (August 2019). In 14 consecutive months, 19 out of 83 severe PwHA and one mild PwHA who turned into a severe phenotype due to inhibitor development were switched to Hemlibra® prophylaxis; three PwHA with inhibitors (two adults, one child) and 17 severe PwHA without inhibitors (16 adults, one child). The median age of adult patients was 54 (32-69) years. The children were nine and seven years old. All adult patients and one child (non-inhibitor) had haemophilic arthropathy. Two adult patients with inhibitors were previously receiving rFVIIa on demand, and one child was unsuccessfully treated with ITI. The ABR of inhibitor patients ranged from 6-26. Non-inhibitor patients were switched to Hemlibra® due to poor compliance (four patients treated on-demand with ABR 16-40), others were switched due to difficult venous access and at their request. Thirteen patients previously receiving regular prophylaxis with FVIII had median ABR 3 (0-6). After switching to Hemlibra®, two patients (one with inhibitors and one without inhibitors) reported one spontaneous joint bleed. A total of four major orthopaedic surgeries (two in patients with inhibitors and two in patients without), a urologic intervention (in a patient without inhibitors), and port removal (in a patient with inhibitors) were performed with concomitant use of rFVIIa or rFVIII without complications. FVIII equivalent activity of Hemlibra® ranged from 9-28% in inhibitor patients and 9-38% in non-inhibitor patients.

Cell Therapy

Description of Sigilon's phase I/II of SIG-001

SIG-001 is a buffered suspension of alginate spheres encapsulating hFVIII-expressing human cells, which can produce functionally active hFVIII in a dose-dependent manner, and has demonstrated efficacy in preclinical studies. The phase I/II trial (SIG-001-121, EudraCT 2019-004210-33) will assess the safety, tolerability, and preliminary efficacy of SIG-001. This multi-centre, open-label study with sequential, dose-escalating cohorts will enrol up to 18 participants. The study will include adult males (≥18) with severe or moderately severe haemophilia A (≤2% FVIII activity) who have had ≥150 exposure days to FVIII product(s). The key exclusion criteria include patients with a current or past history of FVIII inhibitors.

SIG-001 will be administered into the abdomen and patients will be followed for five years. The study will be conducted at sites located in the UK, US and Germany. This information was presented during the 2020 ASH Congress in abstract 860. *Authors of this abstract included representatives from Sigilon.*

Gene therapy

BioMarin announces phase III clinical trial results for valoctogene roxaparvovec

In an article published in January 2021, BioMarin announced data from the phase III gene therapy trial in patients with haemophilia A. In short, it announced:

- Significantly reduced mean annualized bleeding rate by 84% (p-value <0.0001) compared to factor VIII (FVIII) prophylaxis and reduced mean annualized FVIII infusion rate by 99% (p-value <0.0001).
- The mean FVIII Expression of 42.9 IU/dL at one year in the full study population.

- The subset dosed more than two years ago showed a slower rate of decline in FVIII expression compared to the prior study. The mean ABR in this population was 0.9 over these two-plus years.
- BioMarin plans to meet with the European Medicines Agency (EMA) to discuss submission of one-year data and the Food and Drug Administration (FDA) to review the two-year data request.

At the 2021 EAHAD Congress, Biomarin announced topline results from its ongoing global phase III GENEr8-1 study of valoctocogene roxaparvovec (ROCTAVIAN®) with 134 patients. All participants in the study received a single dose of valoctocogene roxaparvovec and completed a year or more of follow-up.

Data from the GENEr8-1 phase III study with a mean follow-up of 71.6 weeks showed that in the pre-specified primary analysis for annualized bleeding rate (ABR), a single dose of valoctocogene roxaparvovec reduced ABR by 84% from a prospectively collected 4.8 (median 2.8) at baseline to 0.8 (median 0.0) bleeding episodes per year ($p < 0.0001$), among a pre-specified group of prior participants in a non-interventional baseline observational study (rollover population; n=112). Eighty per cent of participants were bleed-free starting at week five after treatment.

Table 1: Mean/Median Annualized Bleeding Rate (ABR) and FVIII Infusion Rate in Phase 3 GENEr8-1 Study

	Phase 3 Rollover Population[1] **On factor VIII prophylaxis, before valoctocogene roxaparvovec infusion** **N=112**	**Phase 3 Rollover Population[2]** **After valoctocogene roxaparvovec infusion** **N=112**
	Mean (SD) **Median (IQR)**	**Mean (SD)** **Median (IQR)**
Annualized **Bleeding Rate** (Bleeding episodes per year)	4.8 (6.5) 2.8 (0.0, 7.6)	0.8 (3.0) 0.0 (0.0, 0.0)
Annualized **FVIII Infusion Rate** (Infusions per **year)**	135.9 (52.0) 128.6 (104.1, 159.9)	2.0 (6.4) 0.0 (0.0, 0.9)

Rollover Population (n=112) from Week 5 Through Week 52 at Nov. 2020 Cut Off

At the end of the first-year post-infusion with valoctocogene roxaparvovec, participants in the modified intent-to-treat (mITT) population (n=132) had a mean endogenous factor VIII expression level of 42.9 (SD 45.5, median 23.9) IU/dL, as measured by the chromogenic substrate (CS) assay.

In a subset of the mITT population that had been dosed at least two years before the data cut date (n=17), factor VIII expression declined from a mean of 42.2 (SD 50.9, median 23.9) IU/dL at the end of year one to a mean of 24.4 (SD 29.2, median 14.7) IU/dL at the end of year two with continued haemostatic efficacy with a mean ABR of 0.9 (median 0.0) bleeding episodes per year.

Table 2: Factor VIII Activity Levels in 6-Month Intervals

Median Factor VIII Activity, IU/dL	**Phase 3 Rollover Population (n=112)** **Mean (SD)** **Median**	**Phase 3 mITT Subset Population (n=17[3])** **Mean (SD)** **Median**	**Phase 1/2 6e13 vg/kg Cohort** **(n=7)** **Mean (SD)** **Median**	**Phase 1/2 4e13 vg/kg Cohort** **(n=6)** **Mean (SD)** **Median**
Week 26	55.1 (57.4) 38.6	43.9 (42.1) 33.8	71.0 (41.6) 61.2	18.0 (8.7) 18.0
Week 52	43.6 (45.3) 24.2	42.2 (50.9) 23.9	63.6 (36.5) 60.3	21.1 (12.3) 23.8
Week 76		27.9 (30.6) 15.8	53.9 (31.2) 50.2	20.6 (15.4) 21.3
Week 104		24.4 (29.2) 14.7	36.4 (26.3) 26.2	12.3 (8.2) 11.6

1. See study descriptions for patient population information.

2. Idem

3. Includes only HIV-negative subjects dosed two or more years prior to November 2020 data cut date. One participant was lost to follow-up at 66.1 weeks and was henceforth imputed to have a factor VIII activity of 0 IU/dL through 104 weeks.

Overall, in the phase III study, valoctocogene roxaparvovec has been well tolerated by the 134 participants who received a single 6e13 vg/kg dose. No participants developed inhibitors to FVIII or thromboembolic events. One participant was lost to follow-up. Infusion-related reactions were effectively mitigated by managing infusion rates.

Alanine aminotransferase (ALT) elevation (115 participants, 86%) remained the most common adverse event (AE). Other common adverse events were headache (51 participants, 38%), nausea (50 participants, 37%), aspartate aminotransferase (AST) elevation (47 participants, 35%), arthralgia (38 participants, 28%) and fatigue (37 participants, 27%). Twenty-two (16.4%) participants experienced a total of 43 serious adverse events (SAEs), and all SAEs resolved.

Common steroid-related side effects can occur with the temporary use of corticosteroid (or alternative immunosuppressants) to manage ALT elevation. These side effects have generally been graded 1/2 in intensity, manageable and reversible. Isolated grade 3 steroid-related sides effects (e.g., diabetes, hypertension, weight gain, bone fractures) were observed with longer-term higher dose corticosteroid administration. Corticosteroid-related grade 3 SAEs emerged as a safety issue with extended use of corticosteroids which were reversible with only one event of weight gain ongoing.

Regulatory Status

In a press release from May 2021, BioMarin announced that it planned to submit a marketing authorisation application (MAA) for valoctogene roxaparvovec for the treatment of severe haemophilia A with one-year results from the phase III GENEr8-1 study to the European Medicines Agency (EMA) in June. In the USA, BioMarin plans to submit two-year follow-up safety and efficacy data on all study participants from the GENEr8-1 study in response to the FDA's request for these data to support their benefit-risk assessment of valoctogene roxaparvovec. BioMarin is targeting a Biologics License Application submission in the second quarter of 2022. The FDA granted Regenerative Medicine Advanced Therapy (RMAT) designation to valoctogene roxaparvovec in March 2021.

BioMarin provides highlights of five years of clinical data from ongoing phase I/II study of Valoctocogene Roxaparvovec
In May 2021 BioMarin reported on its five-year and four-year post-treatment follow-up of the 6e13 vg/kg and 4e13 vg/kg cohorts, respectively. The data show that participants in both cohorts remain off prophylactic FVIII treatment. Mean cumulative ABR remains less than one in the 6e13 vg/kg cohort and below pre-treatment baseline levels. The mean ABR in year five for the 6e13 vg/kg cohort was 0.7 with an ABR reduction of 95% and FVIII use reduction of 96% through five years compared to pre-infusion. The mean ABR in year four for the 4e13 cohort was 1.7 with a mean cumulative ABR reduction of 92% and FVIII use reduction of 95%, compared to pre-infusion. FVIII activity levels declined commensurate with the most recent years observations and continue to remain in a range to provide homeostatic efficacy.

Ongoing recruitment for Pfizer's phase III AFFINE trial

Recruitment is ongoing for the phase III, open-label, single-arm study to evaluate the efficacy and safety of **PF-07055480** (Recombinant AAV2/6 Human Factor VIII Gene Therapy) in adult male participants with moderately severe to severe haemophilia A(FVIII:C≤1%) (AFFINE).

Results from Pfizer's phase I/II Alta study

The Alta study is a phase I/II dose-ranging, single-dose study of **giroctocogene fitelparvovec** (also known as **SB-525** and **PF-07055480**), a recombinant AAV serotype 2/6 (rAAV2/6) vector encoding a modified F8 gene. Giroctocogene fitelparvovec was infused into patients in four cohorts of two patients each across four ascending doses (9e11, 2e12, 1e13, and 3e13 vg/kg). The 3e13 vg/kg dose cohort was expanded with three additional patients. Eleven male patients participated in the study (mean [SD] age: 30.3 [7.8] years; white: 81.8%). As of the cut-off date, patients have been followed for 35 to 144 weeks; one patient in the 1e13 vg/kg cohort discontinued from the study. Overall, the most commonly reported adverse events (AEs; n) included increased alanine aminotransferase (ALT; 8 [72.7%]), increased aspartate aminotransferase (AST; 5 [45.5%]), upper respiratory tract infection (4 [36.4%]), and pyrexia (4 [36.4%]). Treatment-related serious AEs were reported in one patient (in the 3e13 vg/kg cohort) who experienced hypotension and fever ≈6 hours after giroctocogene fitelparvovec infusion; the events fully resolved with treatment and did not delay post-infusion discharge. In the three lower-dose cohorts, no ALT elevation requiring more than seven days of corticosteroid treatment was observed. Of the five patients in the 3e13 vg/kg cohort, four had elevations in ALT that were managed with a tapering course of corticosteroids (ranging from 10–134 days) without loss of clinically relevant FVIII activity through 40 weeks. Increases in FVIII activity from baseline were generally dose-dependent. Patients in the 3e13 vg/kg cohort achieved a mean normal range of FVIII activity within five weeks post-infusion, with a mean (SD) FVIII activity of 63.5 (55.6) % at 40 weeks. Following the initial prophylactic period of up to ≈3 weeks after giroctocogene fitelparvovec administration, no bleeding events occurred in any patient treated in the

3e13 vg/kg cohort. These findings were presented during the 2020 ASH Congress in abstract 671. Authors of this abstract included representatives from Pfizer.

Data from Takeda's phase I/II data of TAK-754

In an abstract (ABS185) presented at the 2021 EAHAD Congress, authors reported on the study of the AAV8 based phase I/II gene therapy, **TAK-754** (formerly **BAX 888, SHP654**) for patients with severe haemophilia A (HA) (NCT03370172). Men aged 18-75 years with severe HA and no history of inhibitors were eligible if they had an annualized bleeding rate (ABR) of ≥3 or were using FVIII prophylaxis and had >150 exposure days. Four patients received intravenous infusions of TAK-754 (n=2 in each cohort). All four were using FVIII prophylaxis before enrolment (ABRs of 0-2). At the time of analysis, all patients had ≥10 months' follow-up. A total of 61 AEs were recorded: 14 related to corticosteroid use and eight related to TAK-754. One severe adverse event of severe hypophosphatemia was reported one month after infusion. Peak FVIII activity occurred 4-9 weeks after infusion and was dose-dependent (cohort one [n=2]: 3.8% and 11%; cohort two [n=2]: 54.7% and 69.4%). All patients developed minor transaminase elevations and received corticosteroids (n=3) or corticosteroid prophylaxis (n=1). FVIII expression declined significantly during corticosteroid tapering, and three of the four patients have resumed FVIII replacement. The program was subsequently closed. Authors of this abstract included representatives from Takeda.

An update on Spark phase I/II trial with SPK-8016

In an abstract (ABS197) presented at the 2021 EAHAD Congress, Spark presented the preliminary results of the phase I/II open-label, dose-escalation trial (NCT03734588) to evaluate the safety and efficacy of SPK-8016 in adults with haemophilia A. Since September 2020, four subjects received a starting dose of 5x1011 vg/kg.

Trial participants were males with severe haemophilia and no AAV neutralising antibodies. No SAE or increase in liver transaminases were observed. Subjects 1, 2 and 4 (age 18-36) were HIV negative. Patient 3 (age 63) was HIV positive with CD4 count > 200/mm3. At weeks 52-66 after the infusion, FVIII levels were 6.7%, 6.2%, 21.8% and 6.9%. Patients 1, 2, 4 discontinued prophylaxis, with ABR pre- and post-gene therapy of 5 pre- 2.4 post-; 1 pre-,2.4 post-; and 5 pre-, 0 post-. Patient 3 infused FVIII on-demand with ABR of 18 in the year before SPK-8016 and 0 post-gene therapy.
Participants 1, 2, 4 required initiation of daily oral steroids at weeks 3-7. These three patients received courses of oral steroids for 43-48 weeks. Immunosuppressants (azathioprine or tacrolimus) was added for patient 1 & 2 to limit steroid exposure. Steroid use was discontinued for 2-6 months in all patients at the time of data cut-off. Patient 3 did not require immunosuppressive therapy.

Long-term follow-up of vector persistence in haemophilia dog model

In a study to characterise how AAV-FVIII vectors persist and also to identify common integration sites (CIS) and evaluate their effects, eight severe haemophilia A dogs were treated with a canine FVIII-AAV vector (AAV-BDD-cFVIII) at a median (range) dose of 1.25e13 (6e12 – 2.7e13) vector genomes (vg)/kg. AAV-FVIII genomes were detected in the liver of all dogs at a median of 10.8 (8.2–12.0) years following vector infusion. Intra-hepatic regional differences were seen in AAV-FVIII DNA distribution and mRNA expression. Episomal AAV-FVIII was the predominant AAV form detected (mean episomal = 95.4% & integrated = 4.6%). Median integration frequencies of 9.55e-4 (1.62e-4 – 34.8e-4) integration sites (IS)/cell were seen, with the majority (93.8%) of IS occurring in intergenic regions of the dog genome. Despite integration events occurring in all animals, no tumours were found within the liver at post-mortem. Overall, episomal AAV-FVIII is the predominant vector form detected ten years after a single portal-vein infusion. Low integration frequencies, several orders of magnitude lower than the natural human mutation rate, were seen with some sites of non-random integration. Intra-hepatic regional differences in AAV-FVIII distribution requires further investigation in studies evaluating long-term gene therapy outcomes. These findings were presented at the 2021 EAHAD Congress in abstract ABS021. Authors of the abstract included representatives from BioMarin.

Study on the prevalence of AAVhu37 antibodies

During the 2021 EAHAD Congress, an abstract (ABS057) presented the analysis of a seroprevalence study of neutralising antibodies (NAbs) and anti-drug antibodies (ADAs) against the AAVhu37 vector used in **BAY2599023** in 100 US patients with haemophilia A. In the same analysis, NAbs against AAV5 and AAV8 were also determined. Low seroprevalence of NAbs and ADAs with low maximum titres for NAbs (26) and ADAs (182) against AAVhu37 was identified in the study. Based on the study results, 86% of patients would be eligible for AAVhu37-based treatment. Authors of the abstract included representatives from Bayer.

BioMarin announces companion diagnostic for BMN-270

BioMarin announced that a companion diagnostic is being developed in partnership with ARUP Laboratories to enable the standardised assessment and to allow for the controlled investigation of the clinical relevance of pre-existing adeno-associated virus 5 (AAV5) antibodies for **valoctocogene roxaparvovec**. The FDA has accepted the premarket approval application for this assay.

An Update On Novel Treatments In Haemophilia B

Factor replacement therapies

Comparing PK properties of three EHL FIX products

A study by Preijers T. et al. **(EAHAD - ABS130)** evaluated the pharmacokinetic (PK) properties of three EHL-FIX concentrates for the treatment of haemophilia B. These were A PEGylated FIX (N9-GP, **Rebinyn®**), FIX linked with human albumin (rIX-FP, **Idelvion®**), FIX coupled to human IgG1 Fc-domain (rFIXFc, **Alprolix®**). The authors compared them to a standard half-life (SHL) recombinant FIX.

Activity-time profiles were simulated for 10,000 patients during steady-state dosing of 40 IU/kg once weekly (EHL-FIX) and biweekly (rFIX) using published concentrate specific population PK models. Results were:

	SHL rFIX	N9-GP, Rebinyn®	rIX-FP, Idelvion®	rFIXFc, Alprolix®
Half-life	22 hours	80 hours	104 hours	82 hours
Area under curve (AUC)		78.5 IUhmL^{-1}	49.6 IUhmL^{-1}	12.1 IUhmL^{-1}
Time above 10% FIX		168 hours	168 hours	36 hours
Required weekly dose for 1% trough		40-fold lower than rFIX	27-fold lower than rFIX	4.1-fold lower than rFIX
Mean recovery	1.05	1.70	1.18	1.00

Researchers concluded that the study *"provides insight into the different PK properties of these EHL-FIX concentrates and may aid in the determination of dosing regimens of EHL-FIX concentrates in real life."* However, to fully unravel the effects of these concentrates on haemostatic efficacy, further research evaluating associations between the dose, PK and pharmacodynamics is urgently needed.

Results from the phase III Sanofi/Sobi B-LONG study

During the 2021 EAHAD Congress, an abstract (ABS127) presented an analysis examining pain and physical activity levels from the phase III B-LONG study (NCT01027364), **Alprolix®**. This analysis included adult and adolescent patients (≥12 years) who completed the Haem-A-QoL or Haemo-QoL questionnaires at baseline (BL) and end of study (EoS). A significantly greater proportion of patients reported they never/rarely/seldom experienced painful swellings (n=73; 64% vs 44%, p=0.004) or pain in their joints (n=78; 44% vs 28%; p=0.003) at EoS compared with BL. The number of patients who never/rarely/seldom found it painful to move increased at EoS (n=76; 54% vs 41%, p=0.026). A statistically significant greater proportion of patients were never/rarely/seldom likely to avoid participating in sports like soccer (n=50; 30% vs 8%), avoid sports that they like due to their haemophilia (n=62; 47% vs 27%) or have trouble walking as far as they wanted to (n=76; 63% vs 43%) at EOS vs BL.

The results show statistically significant improvements in patient-reported outcomes related to pain and physical activity with Alprolix® prophylaxis, indicating that Alprolix® may be clinically useful to improve HRQoL.

Efficacy of Alprolix® and Idelvion® in matching-adjusted indirect comparison from Sobi

A study by Astermark J. et al. from Sobi (EAHAD - ABS092) used an established method (matching-adjusted indirect comparison [MAIC]) to compare the efficacy of rFIX Fc fusion protein (rFIXFc, **Alprolix®**) and rFIX albumin fusion protein (rIX-FP, **Idelvion®**), two EHL therapies approved for prophylactic treatment of patients with haemophilia B.

Data for rFIXFc were extracted from the weekly- and interval-adjusted prophylaxis groups of B-LONG (n=92) and from the overall rIX-FP-treated population of PROLONG-9FP (N=63). Data were split according to treatment regimen prior to study entry (prior prophylaxis [rFIXFc, n=48; rIX-FP, n=40] or prior on-demand [n=43; n=23, respectively]) and

compared using MAIC. Individual patient data for rFIXFc were matched to aggregated characteristics of patients from PROLONG-9FP, including age, weight, prior bleeds and ethnicity, and compared regarding estimated annualised bleeding rate (ABR) using a Poisson regression model with adjustment for overdispersion. Relative treatment effects are presented as incidence rate ratios (IRR) with 95% confidence intervals (CI).

After adjustment for baseline characteristics, no significant differences were observed between rFIXFc and rIX-FP in estimated ABR in patients who received prior prophylaxis (1.87 vs 1.58; IRR 1.18; 95% CI 0.67–2.10) or prior episodic (2.25 vs 2.22; IRR 1.01; 95% CI 0.40–2.57) regimens. The effective sample sizes for B-LONG were 26 and ten patients for analysis of patients receiving prior prophylaxis or episodic treatment, respectively.

Researchers concluded that "results of this analysis did not demonstrate a significant difference in efficacy between rFIXFc and rIX-FP when used for prophylaxis, as determined by ABR." This conclusion is despite the large difference in trough levels between the two products (1–3% [targeted] vs 20%, [mean], respectively) indicating trough level is not a relevant indicator of treatment efficacy in haemophilia B when comparing these FIX products.

Gene Therapy

uniQure's etranacogene dezaparvovec AMT-060 and AMT-061 trials (HOPE-B) trials

In an oral presentation at EAHAD, Denise Sabatino from the University of Pennsylvania reported on the December 2020 report of a case of hepatocellular carcinoma (HCC) in one of the 54 subjects in uniQure's phase III trial of gene therapy in haemophilia B (**AMT-061**, HOPE-B). The tumour was discovered during routine ultrasound monitoring one year after vector administration. The individual had other risk factors for HCC, including previous infection with HCV and HBV, non-alcoholic fatty liver disease and advanced age. While recruitment in this phase of the trial was already complete, no additional administration of the gene therapy took place until conclusion of the investigation. In April 2021, the U.S. FDA removed its hold in the program. According to uniQure, the FDA found it was "very unlikely" that AMT-061 had contributed to a case of liver cancer in a patient who had received the therapy during the phase III HOPE-B trial. More than 70 subjects have been ad ministered **AMT-060** and AMT-061 in the different phases of the research over the last decade.

In another oral presentation at EAHAD, Steve Pipe from the University of Michigan reported the latest data from phases II and III of uniQure's AMT-061 trial and the earlier AMT-060 trial. The AMT-060 trial, which does not employ the Padua gene to increase FIX expression, nevertheless demonstrated stable levels of FIX expression four to five years after vector administration (mean of 5.1%) with no safety signals. (See also the following abstracts: December 2020 ASH abstract 3373 and the February 2021 EAHAD abstract ABS043.) Results from phase II of the AMT-061 trial, with the Padua mutation, revealed mean FIX levels of 44% after two years, which also appear to be stable. (See also ASH abstract 672.)

The phase III results were reported as follows:

- Antibodies to the AAV vector were not an exclusion.
- Fifty-four patients (19-75 years) were dosed.
- Forty-two per cent of them had antibodies to AAV.
- The mean FIX levels were 37% at 26 weeks.
- Treated bleeds decreased by 91%.
- Ninety-eight per cent of subjects did not need FIX prophylaxis.
- Nine out of 54 subjects required steroids to treat an immune system reaction to the AAV vector.
- One person developed hepatocellular carcinoma (HCC) one year after vector administration (see above).
- One patient received 10% of the dose; the administration had to be stopped because of an allergic reaction.
- A second patient with a very high level of antibody to AAV did not respond to the treatment.

(See also ASH abstract LBA-6 and EAHAD abstract ABS100.)

Pfizer fidanacogene elaparvovec (PF-06838435) haemophilia B gene therapy

Recruitment is ongoing for the phase III, open-label, single-arm study to evaluate efficacy and safety of factor IX (FIX) gene transfer with **PF-06838435** (rAAV-Spark100-hFIX-Padua) in adult male participants with moderately severe to severe haemophilia B (FIX:C <=2%) (BENEGENE-2).

In an abstract (ABS064) from the February 2021 EAHAD meeting, Chhabra A. et al. presented data on the clearance of **fidanacogene elaparvovec (PF-06838435)** vector DNA from a Pfizer study. Fidanacogene elaparvovec is a hepatotropic

bioengineered AAV-based vector that delivers a high-activity FIX transgene that has shown durable FIX expression and low mean annualized bleeding rate (ABR)/annualized infusion rate (AIR) up to the four-year time point at the 5e11 vg/kg dose. Clearance of viral vector DNA was assessed following a single infusion of fidanacogene elaparvovec at a dose of 5e11vg/kg, using quantitative real-time PCR analysis of five body fluids. Peripheral blood mononuclear cells (PBMCs), saliva, urine and serum samples were collected at screening or day 0 and every scheduled visit from week one post-vector infusion. Semen samples were collected at screening or day 0, week one, every four weeks starting from week four, and every visit after week 16. All samples were collected until three consecutive samples were negative. Time to clearance was defined as time to reach the first negative of three consecutive samples per matrix. Results showed that urine, saliva, and semen were the quickest to be cleared, with urine by week seven, saliva by week eight, and semen by week twelve in all patients. Serum and PBMCs were the longest to clear, with serum clearing at week 22 and PBMCs at week 52 post-infusion. The median (range) time to first clearance was one (1-7) week in urine, four (3-8) weeks in saliva, four (1-12) weeks in semen, seven (3-22) weeks in serum, and 32 (17-52) weeks in PBMCs. There were no adverse events reported that appeared attributable to systemic vector distribution. *This experimental gene therapy is in phase III development by Pfizer.*

An update on Freeline's FLT180a (B-AMAZE)

In an abstract (ABS114) from the February 2021 EAHAD meeting, Chowdary P. et al. presented data on a novel adeno associated virus (AAV) gene therapy (**FLT180a**), achieving normal factor IX (FIX) activity levels in severe haemophilia B (HB) patients (B-AMAZE study). FLT180a consists of a novel, engineered capsid (AAVS3) containing an expression cassette that encodes for a FIX protein variant with a gain-of-function 'Padua' mutation. B-AMAZE is a phase I/II clinical trial designed to identify a dose of FLT180a that normalises FIX activity (50-150%) in patients with severe HB who were negative for neutralising AAVS3 antibodies in an escalating/descending adaptive design. Prophylactic immunosuppression was given to mitigate vector-related transaminitis and associated reduction in FIX expression.

Ten patients were enrolled and received a single dose of FLT180a and prophylactic corticosteroids and/or tacrolimus to decrease the risk/severity of transaminitis. Four dose levels from 3.84e11vg/kg to 1.28e12vg/kg (previously reported as 4.5e11vg/kg to 1.5e12vg/kg) were assessed, with follow-up of eight months to two and half years. There was evidence of gene transfer in all patients with FIX activity levels increasing from baseline (<1%) to a range between 24-168% at week three. In seven of ten patients, FIX activity levels were ≥50% (the lower limit of normal) at six months. At the highest dose of 1.28e12vg/kg, steady-state expression of approximately 250% was observed in one patient, whilst a second patient who experienced severe transaminitis had steady-state FIX activity levels of 70%. No patients required administration of exogenous FIX for the treatment of bleeds, and only one returned to routine prophylaxis due to delayed identification of transaminitis-mediated reduction in transgene expression. Safety assessments indicated that FLT180a did not cause any infusion or allergic reactions. Temporary transaminitis (high levels of liver enzymes) was the most common serious side effect.

In conclusion, this HB gene therapy clinical trial achieves normal levels of FIX activity using relatively low doses of the vector. Results support further work to achieve and maintain normal levels of FIX activity in a larger number of patients.

Freeline is now anticipating the launch of a pivotal phase IIb/III trial in the second half of 2021 to confirm FLT180a's safety and effectiveness. The phase IIb portion of the upcoming trial will confirm the dose to be used in phase III. Freeline then plans to request the therapy be given accelerated approval by the FDA, provided six-month data demonstrate that FLT180a has a strong effect at raising FIX activity levels in around 20 participants. The company also plans to submit data showing a correlation between FIX activity levels at six months post-dosing and annual bleed frequency in a subset of these patients. This trial will enrol up to 30 more patients to generate data on the annual bleed frequency that will potentially support the therapy's full approval. Enrolment is ongoing in ECLIPSE (NCT04272554), a six-month run-in study in Australia to gather data on patients' FIX activity levels, bleed frequency, and eligibility for gene therapy clinical trials.

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:
    - o A growing liver, which could remove the vector due to cellular renewal,
    - o 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 end-point 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.*

An Update On Novel Treatments For People With Von Willebrand Disease

The potential role of Hemlibra® prophylaxis in severe VWD

In an oral presentation (ASH-575) at the 2020 ASH Congress, Barg et al. reported on the potential role of **Hemlibra®** in severe von Willebrand disease (VWD) as an alternative to prophylactic treatment in a cohort of patients with severe VWD. Researchers presented a thrombin generation (TG) model evaluating patients' haemostasis following ex vivo spiking of their plasma samples with Hemlibra®. They also reported 24 weeks of successful Hemlibra® prophylaxis in a child with severe VWD and repeated joint bleeds.-

A cohort of 24 VWD patients was included in the study: 54% were male, 14 were children (≤18 years), and 10 were adults, with 96% of Caucasian origin. Hemarthrosis was encountered in most type 3 VWD patients, whereas none of the type 2 VWD patients had any joint bleeds. Prophylactic treatment was previously administered in the majority of type 3 VWD patients, whereas type 2 VWD patients largely required only intermittent on-demand therapy applied for bleeding episodes or surgical interventions.

An improvement in peak height was demonstrated following spiking with both Haemate P concentrations (p=0•001 for both) and higher Hemlibra® concentration (p=0•011). Notably, whereas spiking with both Haemate P concentrations increased peak height to near-normal level, spiking with higher Hemlibra® concentration increased it to a lesser extent (the median was still lower than in normal controls (p=0•005).

Following the decision to treat the patient with Hemlibra® prophylaxis, TG analyses were performed in the patient's plasma before and during Hemlibra® loading and maintenance. As expected, the patient's initial TG was extremely low and improved following the first administration of the Hemlibra® loading dose (at week two after therapy initiation). Further significant improvement of TG was noted following loading period completion. The patient has been treated with Hemlibra® for more than six months altogether and has not encountered any joint bleeds since the commencement of therapy. During this period, a single dose of Haemate P® was administered following tooth exfoliation.

The successful prophylaxis of the patient and the ex vivo laboratory findings should set the ground for further collaborative multicentre studies and suggests that some severe VWD patients could be safety and efficiently treated with Hemlibra®.

The use of recombinant VWF in surgery

In an oral presentation at the EAHAD meeting in February 2021, Nicolas Drillaud presented data (ABS230) on recombinant von Willebrand factor (**Vonvendi®**) used in surgery in seven French haemostasis centres. rVWF contains no FVIII but has a high amount of high molecular weight VWF multimers. Fifty-five individuals underwent 63 procedures: 33 minor and 30 major. During minor surgeries, the median (range) number of infusions was one (1–8) with a preoperative loading dose of 35 (19–56) rVWF IU/kg and a total median dose of 37.5 IU (12–288). During major surgeries, the median (range) number of infusions was three (1–14) with a median preoperative loading dose of 36 IU (12–51) rVWF IU/kg, and a total median dose of 108 IU (22–340) rVWF IU/kg. The overall clinical efficacy was qualified as excellent/good in 61 of the procedures (97%), moderate in one (1.5%) and poor in one (1.5%). There was no accumulation of VWF or FVIII during postoperative monitoring. No thromboembolic events, anti-VWF antibodies or adverse events were reported. The study concluded that no additional FVIII is needed when FVIII levels are maintained above 40%. These articles were also published in an article in the *Haemophilia Journal.*

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.

Table of Treatments

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 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**	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 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 2022)[5]**
Bypassing agent		Marzeptacog alfa (activated) MarzAA	Subcutaneous coagulation rFVIIa variant	Catalyst Bioscience	**Phase 3**
	Haemophilia A or B w/ or w/o inhibitors				**Recruiting[6]**

[6] 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[7]**
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**

[7] 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**[8]
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**[9]
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**

[8] & [8] 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**[10]
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**[11]**)**
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)**[12]
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**

[10] Text in red highlights changes from the last edition.
[11] Idem
[12] 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**[13]

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

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**

IRISH HAEMOPHILIA SOCIETY

First Floor
Cathedral Court
New Street
Dublin 8

Tel: 01 657 9900
Fax: 01 657 9901

Email: info@haemophilia.ie
Website: www.haemophilia.ie

@HaemophiliaIRL