

**NOVEL TREATMENTS IN HAEMOPHILIA &
OTHER BLEEDING DISORDERS:
A PERIODIC REVIEW
2023 - ISSUE 1**



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Disclaimer:

This publication is produced by the Irish Haemophilia Society based on a publication by the European Haemophilia Consortium (EHC), produced primarily as an education tool for National Member Organisations (NMOs). With the constantly changing therapeutic environment, it is our intention to publish updates on a periodic basis. The information contained, and the views expressed herein constitute the collective input of the EHC New Products Working Group. The EHC does not engage in medical practice and under no circumstances recommends particular treatment for specific individuals. The EHC makes no representation, express or implied, that drug doses or other treatment recommendations in this publication are correct. For these reasons it is strongly recommended that individuals seek the advice of a medical adviser and/or consult printed instructions provided by the pharmaceutical company before administering any of the drugs referred to in this publication. The EHC does not endorse treatment products or manufacturers; any reference to a product name is not an endorsement by the EHC.

Forward

Welcome to the latest 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 2022 Congress of the World Federation of Hemophilia (WFH), held in May 2022, and the 2022 Congress of the International Society for Thrombosis and Haemostasis (ISTH), held in July 2022, as well as other industry updates and news in general. You will find a direct link to the WFH ISTH abstracts in the articles below. For your convenience, we also include a table (pg 52) 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 Paul Batty, EHC volunteer,
- Dr Mariëtte Driessens, EHC volunteer,
- Dr Radoslaw Kaczmarek, Medical and Scientific Advisory Group (MASAG) member,
- Dr Ilmar Kruis, EHC volunteer,
- Prof David Lillicrap, 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,
- Dr Suthesh Sivapalaratnam, EHC Volunteer,
- 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
Chief Executive,
Irish Haemophilia Society

Declan Noone
EHC President

Amanda Bok
EHC CEO

Abbreviations

>	Greater than	ECLA	Electrochemiluminiscent
≥	Greater or equal to	ED	Exposure days
<	Smaller than	EHL	Extended half-life
≤	Smaller or equal to	ELISA	Enzyme-linked immunoassay
Ab	Antibodies	EMA	European Medicines Agency
AAV	Adeno-associated virus	EQ-5D-5L	Standardised measure of health-related quality of life
ABR	Annualised bleeding rate	F	Factor
ADAs	Anti-drug antibodies	FDA	Food and Drug Administration
AE	Adverse events	FVII	Factor VII
ALT	Alanine transaminase	FVIIa	Factor VII activated
AjBR	Annualised joint bleeding rate	FVIID	Factor VII deficiency
AsBR	Annualised spontaneous bleeding rate	FVIII	Factor VIII
ASH	American Society of Hematology	FIX	Factor IX
aPCC	Activated prothrombin complex	gc/kg	Genome copies per kilogram
aPTT	Activated partial thromboplastin time	h	Hours
AST	Aspartate transaminase	HA	Haemophilia A
AT	Antithrombin	Haem-A-QoL	Haemophilia-Specific Quality of Life Questionnaire for Adults
ATHN	American Thrombosis and Hemostasis Network	HAL	Haemophilia activity list
AUCinf	Area under the curve extrapolated to infinity	HAwI	Haemophilia A with inhibitors
BDD	B-domain deleted	HB	Haemophilia B
BE	Bleeding episode	HBwI	Haemophilia B with inhibitors
BLA	Biologics License Application	HCRU	Healthcare resources utilisation
BP	Bodily pain	Hemo-TEM	Hemophilia Treatment Experience Measure
BPA	Bypassing agents	HCV	Hepatitis C virus
BU/ml	Bethesda units per millilitre	HIV	Human immunodeficiency virus
CFB	Change from baseline	HJHS	Haemophilic joint health score
CFC	Clotting factor concentrates	HRQoL	Health-related quality of life
CHMP	Committee for Human Medicinal Products	HTC	Haemophilia treatment centre
CI	Cumulative incidence	HTI	High titre inhibitors
CID	Clinically important difference	IDR	Initial dosing regimen
CL	Clearance	IND	Investigational new drug
Cmax	The peak plasma concentration after drug administration.	IR	Incremental recovery
CSA	Chromogenic substrate assay	ITI	Immune tolerance induction
CV	Cardiovascular	IQR	Interquartile range
CVAD	Central venous access device	ISTH	International Society for Thrombosis and Haemostasis
CWA	Clot waveform activity	IV	Intravenous
DNA	Deoxyribonucleic acid	IU	International units
DMC	Data Monitoring Committee	IU/dL	International units per decilitre
DVT	Deep vein thrombosis	IU/kg	International units per kilograms
EAHAD	European Association for Haemophilia and Allied Disorders	kg	Kilograms
EC	European Commission	LTI	Low-titre inhibitors
		mg/kg	Miligrams per kilograms

mg/kg/week	Milligrams per kilograms per week	UK	United Kingdom
mHJH	Modified hemophilia joint health score	UKHCDO	United Kingdom Haemophilia Doctors' Organisation
mITT	Modified intent to treat		
MoA	Mode of action	US	United States
MOI	Multiplicity of infection	vg/kg	Vector genomes per kilogram
n=	Number	VAS score	Visual analogue scale
NAbs	Neutralising antibodies	vs	Versus
NATEM	Non-activated thromboelastometry	VWD	Von Willebrand disease
ng/ml	Nanogram per millilitre	VWF	Von Willebrand factor
OD	On-demand	W	Week
OSA	One-stage assay	WAPPS-Hemo	Web Accessible Population Pharmacokinetic Service-Hemophilia
Pd	Plasma-derived		
PD	Pharmacodynamics	WFH	World Federation of Hemophilia
PE	Pulmonary embolism	µg	Microgram
pedHAL	Paediatric haemophilia activity list	µg/kg	Microgram per Kilogram
PEG	Polyethylene glycol	µL	Microlitre
PF	Physical function		
PK	Pharmacokinetics		
PKP	Pharmacokinetics-guided prophylaxis		
PROs	Patient Reported Outcomes		
psHA	People with severe haemophilia A		
PTP	Previously treated patients		
PUP	Previously untreated patients		
PwHA	People with haemophilia A		
PwHB	People with haemophilia B		
PwHI	People with haemophilia and inhibitors		
Q&A	Questions and answers		
QM	Every month		
QW	Once a week		
R	Recombinant		
rFVIIa	Recombinant factor VII activated		
ROTEM	Rotational thromboelastometry		
RNA	Ribonucleic Acid		
SAE	Serious adverse event		
SC	Subcutaneous		
SD	Standard deviation		
SHL	Standard half-life		
siRNA	Silencing RNA		
SP	Standard prophylaxis		
SQ	Subcutaneous		
T ½	Half-life		
TE	Thromboembolic events		
TEAE	Treatment emergent adverse events		
TFPI	Thrombin factor pathway inhibitor		
TG	Thrombin generation		
TGA	Thrombin generation assay		
TMA	Thrombotic microangiopathy		
Tmax	The time to reach Cmax		
TSQM-9	Treatment satisfaction questionnaire for medication		
ug/mL	Micrograms per millilitre		

Executive Summary

Welcome to the executive summary of this report!

This section will highlight some trends in the novel treatment landscape for rare bleeding disorders. We also give you a shorter summary of the content of the newsletter.

We would like to remind you that this newsletter is not designed to be read from cover to cover, but instead, it is a compendium of the latest information on novel therapies.

For your convenience, you will find at the end of the document tables summarising licensed and unlicensed therapies and their clinical development status.

As noted in the foreword, this document does not give you basic scientific knowledge about rare bleeding disorders and their treatment. For this, we advise you to download the EHCucate app (available on IOS and Google Play), which provides simple and comprehensive scientific information in lay language on rare bleeding disorders and their treatment options.

We wish you good reading.

Report Highlights

Update on recent marketing authorisations and indication expansion

Since our last issue in May 2022, several new products have been either licensed or received positive opinions from the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA) for licensing or indication expansion:

1. **Cevenfacta®**, a recombinant-activated FVII developed by LFB, received a European marketing authorisation from the European Commission in July 2022. The treatment has been approved for treating bleeding episodes and for preventing bleeding episodes in surgery or other invasive procedures in patients with haemophilia A or B and inhibitors. Concretely this marketing authorisation means that the product is considered safe and effective for the European market. It will now be up to LFB to submit reimbursement requests in each European country.
2. In August 2022, **Roctavian®**, gene therapy for haemophilia A developed by BioMarin, received a positive opinion from the EMA CHMP for conditional marketing authorisation. The condition for marketing authorisation is that the company collects 15-year post-marketing data on the safety and efficacy of the product. The therapy received marketing authorisation in November 2022. The product also received orphan drug designation granting ten years of marketing exclusivity. Roctavian® is indicated in the treatment of severe haemophilia A in adult patients without a history of FVIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5.
3. In December 2022, **Hemgenix®**, gene therapy for haemophilia B, developed by UniQure/CSL Behring, received a positive opinion from the EMA CHMP for conditional marketing authorisation in Europe. This product is indicated for the treatment of severe and moderately severe haemophilia B in adult patients without a history of FIX inhibitors. This decision needs to be adopted by the European Commission, after which CSL Behring can start submitting requests for reimbursement in individual European Member States.
4. In December 2022, the EMA CHMP adopted a positive opinion to extend the marketing authorisation of **Hemlibra®**, licensed by Roche, to include routine prophylaxis of bleeding episodes in patients with moderate haemophilia A without inhibitors. This opinion needs to be approved by the European Commission.

Clinical trials on the horizon

- ASC Therapeutics announced its plans for a clinical trial for **ASC618**, an experimental gene therapy to treat haemophilia A.

- Pfizer and Sangamo announced that it would resume recruitment for its clinical programme to investigate its gene therapy **giroctocogene fitelparvovec** for the treatment of haemophilia A.
- TeraImmune announced that the US FDA cleared their proposal to start a phase I/IIa clinical trial to evaluate **TI-168** cell therapy in patients with haemophilia A and inhibitors.
- Hemab dosed its first patient with **HMB-001**, a bispecific antibody that binds and accumulates endogenous FVIIa in circulation. This therapy is currently being tested in people with Glanzmann Thrombasthenia.

Phase III clinical trials updates

In this document you will find updates on phase III clinical trials (the more advanced stage of clinical development) for various products, including:

- **efanesoctocog alfa**, a novel extended half-life factor VIII replacement therapy for haemophilia A,
- **Elocta®**, an extended half-life recombinant FVIII for use in children (<6 years old),
- **Hemlibra®**, a bispecific antibody for use in people with haemophilia A. We have updates from the HAVEN 1-4 trials and HAVEN 6 trial in people with non-severe haemophilia A without inhibitors.
- **Roctavian®**, a gene therapy for haemophilia A,
- **Refixia®**, an extended half-life recombinant FIX for use in children (<6 years old),
- **FLT-180a**, gene therapy for haemophilia B,
- **Cevenfacta®**, a recombinant activated FVII for the treatment of people with haemophilia A and B and inhibitors,
- **Marzeptacog alfa**, a recombinant activated human FVII variant for the treatment of people with haemophilia A and B and inhibitors,
- **Fitusiran**, an investigational silencing RNA therapy that targets antithrombin to rebalance haemostasis in people with haemophilia A or B irrespective of their inhibitor status, and
- **Concizumab**, an anti-tissue factor pathway inhibitor, to rebalance haemostasis in people with haemophilia A or B with or without inhibitors.

Interrupted clinical programmes

This report contains information regarding the discontinuation of clinical trials for the following treatments:

- **OCTA 101**, a subcutaneous recombinant FVIII,
- **TAK-754**, a gene therapy for haemophilia A,
- **FLT-180**, a gene therapy for haemophilia B, and
- **Marzeptacog alfa**, a recombinant activated human factor VII variant.

Updates on treatments in rare bleeding disorders

This report describes some preclinical studies on the potential use of **Hemlibra®** in people with haemophilia B, people with Von Willebrand Disease type 2N and 3, and people with Glanzmann Thrombasthenia.

We also note some new therapies that could benefit people with rare bleeding disorders with limited treatment options, such as **BT200** for the treatment of type 2B von Willebrand Disease, **HMB-001** for the treatment of Glanzmann Thrombasthenia, **gene therapy** for people with von Willebrand Disease and **two repurposed cancer drugs** for FVII deficiency. We would like to stress that all of these developments are in the preclinical or very early clinical stage and that their safety and efficacy will need further study and testing.

An update on novel therapies in haemophilia A

In this section, we cover updates on replacement therapies, non-replacement therapies and gene therapy for people with haemophilia A.

Replacement therapies

We start our report on novel therapies in haemophilia A with updates on replacement therapies. These are therapies that consist of coagulation FVIII that directly replaces the missing factor in people with haemophilia A. In this section we cover efanesoctocog alfa, Elocta®, Jivi® and OCTA101.

Efanesoctocog alfa (BIVV001)

During the 2022 ISTH Congress, Drygalski A. gave an update on efanesoctocog alfa (also known informally as BIVV001 or 'efa'). This treatment is a novel molecule consisting of an Fc-linked B-domain deleted-FVIII combined with a D'D3 region of the von Willebrand Factor. The modifications to this molecule are meant to remove the half-life limit imposed on FVIII by the von Willebrand Factor. This therapy is in development by Sobi and Sanofi. Currently, the product is in its third phase of the clinical study (XTEND-1) for its use in prophylaxis in adult males with haemophilia A. The trial participants were put either on prophylaxis or on-demand treatment with BIVV001. The primary outcome that investigators were looking at was annualised bleeding rate. The mean half-life of BIVV001 is 47 hours, and in the trial, a single injection of BIVV001 resulted in FVIII activity within normal to near normal (>40%) levels.

During the WFH Congress, Sanofi presented a study on the pharmacokinetics of efanesoctocog alfa, Advate® and Adynovi®. This small (13 participants) study looked at the elimination half-life for each product as the main outcome, and the characterisation of additional PK parameters, the evaluation of safety and tolerability of efanesoctocog alfa as secondary outcomes. Based on this research, researchers concluded that BIVV001 had a three- to four-fold longer half-life and four- to six-fold greater area under the curve extrapolated to infinity than the other two products.

Elocta®

Elocta® is an extended half-life coagulation factor concentrate marketed in Europe by Sobi.

At the 2022 ISTH Congress, we heard reports on inhibitor incidence in previously treated patients, comparative real-world effectiveness compared to standard half-life products, and real-life experiences of managing surgeries with Elocta®.

Carcão M. gave a descriptive analysis of the inhibitor incidence in previously untreated male patients (under six years) with severe haemophilia A on prophylaxis with Elocta®. This data came from the PUP A-LONG study. This analysis aimed to identify factors that predispose individuals to inhibitors. The analysis shows that half of the high-titre inhibitor patients initially develop low-titre inhibitors. The frequency of inhibitor development was comparable following intense factor exposure or the placement of a central venous access device, although this analysis is based on limited patient numbers (n=24).

Oldenburg J. reported on the comparative real-world effectiveness of Elocta® prophylaxis versus matched treatment groups on standard half-life. This report was based on the A-SURE study. The study showed lower ABR, injection frequency and factor consumption in those on Elocta® compared to those on standard half-life treatment.

French and Irish researchers presented their experiences in managing surgeries with Elocta®. The French group concluded that Elocta® is safe and well tolerated in patients with haemophilia A undergoing invasive procedures. The Irish group noted that preoperative surgical haemostasis with Elocta® was effective and safe in real-world conditions.

Jivi®

Jivi® is a licensed PEGylated recombinant factor VIII marketed by Bayer.

During the ISTH Congress, Reding M. presented an interim analysis of HEM-POWR, a post-marketing study looking at the real-world effectiveness of Jivi. Researchers looked at data on annualised bleeding rates. In the presentation, Reding M. describes a reduction in ABR and improvements in joint health in patients with all severities of haemophilia A. HEM-POWR is a study funded by Bayer.

OCTA 101

In an abstract presented at the ISTH 2022, Octapharma gave data on phase I/II clinical trial of OCTA101, a subcutaneous recombinant factor VIII. The study had to be terminated due to the occurrence of inhibitors. The authors speculated that this may have occurred due to the subcutaneous route of administration.

Non-replacement therapies

In this section, we include therapies that are not coagulation factor VIII but that mimic its effect or rebalance the coagulation system by targeting other parts of the coagulation cascade. In this section, we cover updates on Hemlibra® and Mim8. Both products mimic the role of FVIII.

Hemlibra®

Hemlibra® is a non-replacement therapy for the treatment of haemophilia A with or without inhibitors. It is a bispecific antibody that acts in replacement of factor VIII. It is administered subcutaneously. Hemlibra® is marketed by Roche.

We begin our update by informing you that in December 2022, the **European Medicines Agency recommended extending Hemlibra®'s marketing authorisation's indication to people with moderate (FVIII \geq 1% and \leq 5%) haemophilia A**. Concretely, this means that once this recommendation is adopted, the use of Hemlibra® in people with moderate haemophilia A will become an official (on-label indication), which should facilitate its use in this patient population.

We continue with a series of reports on the **use of Hemlibra® in a real-world setting**.

The **UK Haemophilia Doctors Organisation (UKHCDO)** presented data on the use of Hemlibra® in non-inhibitor patients. Their data came from their database and covered a period from August 2019 to September 2021. They concluded that Hemlibra® improved bleed control in all age groups and that in 65% to 80% of patients included in the analysis, no bleeds were reported. Target joints resolved more frequently than in those who continued factor VIII prophylaxis. Anti-drug antibodies were uncommon, and recurrent FVIII inhibitors occurred in ~5% of those at risk.

At the ISTH Congress, Escuriola-Ettinghausen C. reported on the **real-life data on the efficacy of Hemlibra® in people with severe haemophilia A in Germany**. This was based on data collected with smart medication eDiary. These data show a decrease in bleeding episodes for people with severe haemophilia A switching from FVIII concentrates to Hemlibra.

The **American Thrombosis and Hemostasis Network (ATHN)** presented, at the ISTH Congress, **data on the safety, effectiveness and practice of treatment for people with haemophilia with current therapies, including Hemlibra®**. The study looked at data across four years from 26 ATHN-affiliated sites. Researchers did not identify any new safety signal.

During the WFH 2022 Congress, **Genentech** presented, in an abstract, **data from a one-year retrospective study looking at the persistence and adherence to Hemlibra® prophylaxis in people with haemophilia A**. Authors concluded that most individuals had high rates of adherence and persistence to the treatment.

Finally, we hear an update on a **Dutch study looking at the use of entire vials of Hemlibra® in order to avoid treatment waste**. We first reported on this study in the EHC New Product Newsletter 2021 Vol. 2. Researchers note that the Hemlibra® dose administered to individuals often does not match the Hemlibra® vial content, and this can lead to product waste. They looked at alternative dosing regimens and intervals that would match entire Hemlibra® vials.

In an abstract at the ISTH Congress, researchers led by Mancuso M.E. presented data on the **effectiveness of Hemlibra® in a real-world setting using the bleed data on all bleeds from the Cost of Haemophilia in Europe: A Socioeconomic Survey II (CHESS II) study**. Their analysis showed that annualised bleeding rates decreased after switching to Hemlibra® in both people who were previously on either FVIII prophylaxis or on-demand. This was based on clinician-reported data.

In terms of updates from **Hemlibra® clinical trials**, we give an **update from the HAVEN 1-4 and 6 studies as well as the CHESS II study**.

At ISTH, Hermans C. reported the primary analysis of the **phase III HAVEN 6 study**, supported by Roche. This is a study assessing the **safety and efficacy of Hemlibra® prophylaxis in people with non-severe (FVIII levels between >5% and <40%) haemophilia A without FVIII inhibitors**. The data showed efficacy and a favourable safety profile for the use of Hemlibra® in this patient population.

In an article published in the scientific journal *Haemophilia* Roche presented data from the **HAVEN 3 clinical trial to assess the effect of Hemlibra® on bone and joint health in people with severe haemophilia A without inhibitors**. Authors note improvements in the haemophilic joint health score in younger people with haemophilia A and those with target joints. They also do not see any changes in bone biomarkers, suggesting that the use of Hemlibra® does not hinder bone density.

Data on major and minor surgeries collected during the phase III of the HAVEN 1-4 clinical trials are published in the scientific journal *Blood Advances*. The HAVEN 1-4 trials were conducted in people with severe haemophilia A with or without inhibitors. The data show that surgeries can be performed safely on people on Hemlibra® prophylaxis.

We also included a few abstracts on **‘special’ populations or cases on the use of Hemlibra®**. As Hemlibra® is used in a wider population in the real world, we start to hear about ‘special’ clinical cases that we think you will find relevant.

Regarding the use of **Hemlibra® in paediatric patients**, Chugai presented at the ISTH 2022 a study looking at the coagulation potential of Hemlibra® in plasma samples collected in **children aged 0 to 42 months with haemophilia A**. Data from the study showed that Hemlibra® improved the coagulant potential in the plasma of children with haemophilia A. They evaluated the samples with global coagulation assays. In another ISTH abstract, Portuguese patients described the treatment protocols with Hemlibra® in four paediatric patients aged over 21 months.

Danish researchers presented a **case study of a patient with end-stage renal disease undergoing dialysis on Hemlibra®**. This single-patient experience showed that Hemlibra® in standard dosing remained stable and effective during progressive renal failure and haemodialysis.

Japanese researchers looked at **reasons for Hemlibra® discontinuation in ten patients**. They note that patients who had discontinued had experienced more bleeding before and during the use of Hemlibra®. Researchers underscore the importance of patient education prior to switching treatment.

French researchers carried out **tests to look at the potential interference of Hemlibra® on the anticoagulant effect of anticoagulant therapy**. The tests were done *in vitro*, and researchers note that, to their knowledge, this is the first study of its kind. They conclude from their tests that Hemlibra® at a therapeutic dose does not impact the anticoagulant effect of anticoagulant medication. However, they note that further studies are needed to confirm this data.

This information will be particularly relevant as Hemlibra® is used more widely in an ageing population.

In this report, we also include a series of abstracts on **anti-Hemlibra® antibodies**. From these abstracts, we should take away that **anti-Hemlibra® antibodies are rare**. **The clinical signs are increased breakthrough bleeds and prolonged times for activated partial thromboplastin clotting time** (a laboratory test). We also learn that the presence of antibodies does not always equal an increase in bleeding. Finally, there are currently no commercially available laboratory assays to identify anti-Hemlibra® antibodies. These can be calculated with a modified Bethesda assay. We also included a series of abstracts on laboratory assays and Hemlibra® to highlight that researchers are still testing the best parameters to correctly

calibrate commercially available laboratory tests to evaluate Hemlibra® activity in patients.

Mim8

Mim8 is a novel bispecific antibody in phase III clinical development by Novo Nordisk. The administration of Mim8 is via subcutaneous injection. The bispecific antibody replaces the missing FVIII.

At the 2022 ISTH Congress Chowdary presented **results from phase I/II of FRONTIER1**, a clinical trial investigating **the safety, tolerability, pharmacokinetics and pharmacodynamics of Mim8 in healthy participants and people with haemophilia A with or without inhibitors**. Participants with haemophilia A were given ascending doses of Mim8. The researchers concluded that Mim8 was well tolerated with no occurrence of anti-Mim8 antibodies and the pharmacokinetic properties were consistent with dose-proportionality and supported weekly or monthly dosing approaches.

In another oral presentation at the 2022 ISTH Congress, Wyndiga J. reported on **phase II of FRONTIER1** with regard to **peak thrombin generation and laboratory markers**. He concluded that thrombin generation depended on the dose of Mim8 and that Mim8 reached a higher peak thrombin level compared to people receiving Hemlibra®. The laboratory parameters did not show any signs of potential thrombosis.

In another abstract from ISTH, Novo Nordisk presented a **study to evaluate the effects of using FVIII to treat breakthrough bleeds in people on Mim8**. They concluded that Mim8 does not affect FVIII function in haemophilia and can be used according to label instructions.

Finally, we included three abstracts on **laboratory assays and Mim8**. As this is a novel agent, it will be important to identify laboratory assays that adequately measure Mim8 activity.

Gene therapy

Gene therapy is a technology that is used to correct genetic disorders. It uses a virus as a vector to carry a 'healthy' version of the patient's faulty gene. It is administered via a single infusion. Once infused, the virus travels towards the organ that requires the healthy gene (in the case of haemophilia, the virus travels to the liver) delivering the modified 'healthy' gene. Following this process, the patient starts to produce its own 'missing' factor.

In this section, we give an update on the following gene therapies: Roctavian™, giroctocogene fitelparvovec, ASC618 and TAK-754. We also give an update on laboratory assays, psychological aspects and haemophilia centres' accreditations.

Roctavian™

Roctavian™ is a gene therapy marketed by BioMarin for the treatment of haemophilia A.

In August 2022, the **European Commission granted conditional marketing authorisation to Roctavian™**, a gene therapy licensed by BioMarin.

At the 2022 WFH Congress, BioMarin presented the **phase III data from the GENER8-1 study on the efficacy of Roctavian™**. The data came from a **52-week analysis** of 134 clinical trial participants. Researchers noted that immune responses to Roctavian™ were predominantly directed to the AAV5 vector. The response was characterised by the production of anti-AAV5 binding and neutralising antibodies as well as transient AAV5 capsid-specific immune response. The capsid-specific immune response showed a moderately positive correlation with plasma levels of the liver enzyme ALT suggesting these responses may be a contributing factor to transient elevations in ALT in some participants. There was no clinical evidence of FVIII inhibitor formation.

During the 2022 WFH Congress, **BioMarin presented data on changes in quality of life at 104 weeks post-infusion with Roctavian™**. The data came from the **GENER8-1 phase III clinical trial**. Researchers concluded that the health-related quality of life observed at week 52 post-infusion was maintained at week 104 post infusion.

BioMarin presented at the 2022 ISTH **data on the characterisation of vector DNA biodistribution and shedding following the administration of Roctavian™**. Concretely this means that researchers studied where the gene therapy vectors distributed in the body and how they were removed from the body following the infusion. They noted that vector DNA and capsid were steadily cleared from the blood and that the risk of transmission to untreated individuals was extremely low.

In an oral presentation at the 2022 ISTH Congress, BioMarin presented the *post hoc* **analysis on the efficacy of Roctavian™ by comparing 112 participants of the GENER8-1 clinical trial** who rolled over into the trial from a non-interventional study to 73 participants receiving replacement therapy in a non-interventional study. Researchers concluded that people who received Roctavian™ had lower annualised bleeding rates and higher rates of ‘zero bleeds.’

In an oral presentation at the 2022 ISTH Congress, Laffan M. reported on the **six-year post-infusion safety and efficacy of Roctavian™ in patients enrolled in phase I/II clinical trial** to determine the safety and efficacy of Roctavian™.

Giroctocogene Fitelparvovec

Giroctocogene fitelparvovec is a gene therapy for haemophilia A in development by Pfizer and Sangamo.

In 2021, Pfizer and Sangamo voluntarily paused the clinical study following the observation of FVIII levels greater than 150% post-infusion in some trial participants. In September 2022, the companies announced that the **trial would resume recruitment following the amendment of their clinical protocol**. The companies expect to share the first trial results in the first half of 2024.

ASC618

ASC Therapeutics presented at the 2022 ISTH Congress their **plans for a clinical trial for ASC618**, a gene therapy for haemophilia A. The trial is currently recruiting patients.

TAK-754

At the ISTH Congress 2022, Takeda presented **data on the immunogenicity of TAK-754**, an experimental gene therapy whose clinical development has been discontinued.

Psychological aspects of gene therapy

At the 2022 WFH Congress, Israeli researchers presented **data on the psychological aspects of gene therapy**. The researchers surveyed 40 people on their feelings and attitudes towards gene therapy. The study conclusion was that most haemophilia patients surveyed felt they needed more information before considering gene therapy.

Organisation of care

Finally, gene therapy's arrival raises questions on how it will change the organisation of haemophilia care. Boban A. presented at the 2022 ISTH Congress, **a novel accreditation method for haemophilia centres dispensing gene therapy**. The hope is that this accreditation system will improve multidisciplinary care delivery.

Cell therapy

Cell therapy uses cells delivered to the body for a therapeutic effect.

TI-168

In October 2022, TeraImmune Inc. announced that the **US FDA granted clearance to start a phase I/IIa clinical trial to evaluate TI-168**, cell therapy in patients with haemophilia A and inhibitors.

An update on novel therapies in haemophilia B

Replacement therapies

These are therapies that consist of coagulation FIX that directly replaces the missing factor in people with haemophilia B. In this section we cover Refixia®, Alprolix® and Idelvion®.

Refixia®

Refixia® is a licensed extended half-life replacement factor IX therapy for the treatment of haemophilia B. This product is marketed by Novo Nordisk.

During the 2022 ISTH Congress, Novo Nordisk reported on **the main and extension phase III of paradigm6, a clinical trial evaluating Refixia® prophylaxis in previously untreated children under six years of age**. This data analysis gives an overview of up to six years of outcomes with Refixia® prophylaxis. Researchers noted low inhibitor incidence, favourable annualised bleeding rates for prophylactic treatment, no target joint development and high adherence.

Alprolix®

Alprolix® is a licensed extended half-life replacement factor IX therapy for haemophilia B. Alprolix® is marketed by Sobi.

At the 2022 ISTH Congress, Sobi reported on the interim data of **B-MORE, a prospective study on patients either on prophylaxis or on-demand Alprolix®**. The data shows that Alprolix® provides bleed protection, including in paediatric patients and that the median annualised bleeding rate is close to zero with low factor consumption.

Idelvion®

Idelvion® is a licensed extended half-life replacement factor IX for haemophilia B. This product is marketed by CSL Behring

At the ISTH 2022 Congress, CSL Behring reported on the **dosing frequency, efficacy and safety of Idelvion® during routine clinical practice in Italy**. They concluded that treatment with Idelvion® reduced infusion frequency while providing higher trough levels, reducing target joints and chronic pain while showing a good safety profile.

Non-replacement therapies

In this section, we include therapies that are not coagulation factor VIII but that mimic its effect or rebalance the coagulation system by targeting other parts of the coagulation cascade. In this section, we cover updates on Hemlibra®.

Hemlibra®

Hemlibra® is a non-replacement therapy for the treatment of haemophilia A with or without inhibitors. It is a bispecific antibody that acts in replacement of factor VIII. It is administered subcutaneously. Hemlibra® is marketed by Roche.

In a presentation at the 2022 ISTH Congress, Samuelson-Jones B. described **the potential use of Hemlibra® in people with haemophilia B presenting specific missense variants**. The data was based on laboratory tests with patients' blood samples. The authors concluded that FVIII mimetic treatment products, like Hemlibra®, could improve coagulation in people with haemophilia B and FIX missense variants with dysfunctional FIXa/FVIIIa interactions.

Gene therapy

Gene therapy is a technology that is used to correct genetic disorders. It uses a virus as a vector to carry a 'healthy' version of the patient's faulty gene. It is administered via a single infusion. Once infused, the virus travels towards the organ that requires the healthy gene (in the case of haemophilia, the virus travels to the liver), delivering the modified 'healthy' gene. Following this process, the patient starts to produce its own 'missing' factor.

In this section, we give an update on the following gene therapies: Hemgenix®, FLT-180a, BBM-H901 and fidanacogene elaparvovec. We also describe a study on the effects of growth on gene therapy-induced FIX.

Hemgenix®

Hemgenix® is a gene therapy developed by UniQure/CSL Behring for the treatment of haemophilia B.

In November 2022, the **US FDA approved Hemgenix®**, a gene therapy for haemophilia B developed by UniQure/CSL Behring. In December 2022, the **EMA granted conditional marketing authorisation for this medicine**. The results from UniQure/CSL Behring phase III trial for Hemgenix® presented at ASH will be included in the next edition of this report.

FLT-180a

In an article published in the *New England Journal of Medicine*, Chowdary P. presented **data on phase I/II trial to assess the safety and efficacy of varying doses of FLT180a**, an experimental gene therapy for haemophilia B in development by Freeline Therapeutics.

In November 2022, **Freeline Therapeutics** issued a financial statement noting that it would **stop investing in the therapeutic programme of FLT180a**.

BBM-H901

In May 2022, BioMed reported in the *Lancet Haematology* **data on phase I clinical trial of BBM-H901**, an investigational gene therapy for haemophilia B. The phase one trial looked at the safety, factor activity and bleeding frequency. In their conclusions, the authors suggest that one year after infusion, BBM-H901 is safe and that the vector-derived FIX concentration is sufficiently high to prevent bleeding events and minimise the need for replacement therapy. These early findings will require further research for confirmation.

Fidanacogene elaparvovec

Fidanacogene elaparvovec is an experimental gene therapy for haemophilia B in development by Pfizer.

At the 2022 WFH Congress, Pfizer presented a **small study on plasma samples to assess if the FIX Padua derived from the infusion of fidanacogene elaparvovec interfered with the detection of factor IX from replacement therapy**. This is important as patients receiving this gene therapy may require additional replacement therapy prior to surgical events or in case of breakthrough bleeds. The authors concluded that the FIX variant provided by fidanacogene elaparvovec did not interfere with the detection of replacement factor IX therapy.

In another abstract from the 2022 WFH Congress, data from the **phase I/IIa study of fidanacogene elaparvovec in relation to laboratory assay variability**. The authors concluded that, as shown in prior data, the SynthAsil assay shows consistently higher FIX activity levels. Laboratory assays are a critical tool for monitoring patients' coagulation levels.

Effects of growth on gene therapy in dogs

During the 2022 ISTH Congress, Pfizer presented data on the **effects of growth on FIX levels in male juvenile haemophilia B dogs, following gene therapy**. This small study shows that in dogs there was a durable efficacy of gene therapy despite liver growth and blood volume expansion.

An update on novel therapies for people with haemophilia A or B with or without inhibitors

This section looks at therapies that do not replace the missing factor. They consist of the following:

- **Bypassing agents:** These products go around (bypass) the factors blocked by the inhibitor to help the body form a normal clot.
- **Non-replacement therapies** help rebalance haemostasis by working on different parts of the coagulation cascade.

The products included in this section are Cevenfacta®, marzeptacog alfa, fitusiran, concizumab, marstacimab and serpinPC.

Bypassing agents

Cevenfacta®

Cevenfacta® is a recombinant activated FVII marketed by LFB.

In July 2022, the **European Commission granted marketing authorisation to Cevenfacta®** for licensing in Europe. In an abstract presented at the 2022 ISTH Congress, the American Thrombosis and Hemostasis Network (ATHN) with the support of LFB presented the study design of a **post-marketing study to evaluate the safety of Cevenfacta® for the treatment of breakthrough bleeds** in people with haemophilia A or B with inhibitors.

Still at the 2022 ISTH Congress, Windyga J. presented the results from the **phase III PERSPEPT 1 trial to evaluate the treatment of bleeding episodes using Cevenfacta®**. Researchers concluded that Cevenfacta® achieved safe resolution of spontaneous and traumatic bleeds at 12 and 24 hours post-bleed in both adults and adolescents with haemophilia A or B with inhibitors.

In another 2022 ISTH Congress abstract, Hart D. reported on **the efficacy of Cevenfacta® in treating bleeding episodes according to low or high inhibitor titres**. Researchers concluded that Cevenfacta® achieved bleed resolution in people with haemophilia A or B with inhibitors irrespective of inhibitor titre. No safety issues were reported.

Marzeptacog alfa

Marzeptacog alfa is a recombinant activated human factor VII variant. This product was developed by Catalyst Biosciences. Marzeptacog alfa development was halted due to difficulties in clinical trial recruitment brought about by the COVID-19 pandemic.

At the 2022 ISTH Congress, Rangarajan S. presented the **phase III Crimson 1 study on marzeptacog alfa for on-demand treatment of bleeds in people with haemophilia A or B and inhibitors**. The primary endpoints were efficacy and safety of marzeptacog alfa versus standard of care. Researchers concluded that although the trial was interrupted early, the data suggests that it could have the potential for safe and effective treatment of bleeding episodes in people with haemophilia A and B and inhibitors.

Rebalancing agents

Fitusiran

Fitusiran is an investigational silencing RNA therapy that targets antithrombin to rebalance the haemostasis in people with haemophilia A or B, irrespective of their inhibitor status. Fitusiran is an investigational product in development by Sanofi.

During the 2022 ISTH Congress, Kenet G. presented the results of the **phase III ALTAS-PPX looking at the efficacy and safety of fitusiran prophylaxis versus prior factor or bypassing agents prophylaxis in people with haemophilia A or B with or without inhibitors**. Researchers reported that fitusiran achieved statistically significant reductions in estimated ABR, AsBR and AjBR versus factor/BPA prophylaxis. Fitusiran improved HRQoL versus factor/BPA. Serious adverse events (SAEs) occurred in 5/65 participants (7.7%) with factor/BPA and 9/67 (13.4%) with fitusiran prophylaxis, including thromboembolic events. These were already reported by the EHC in two statements¹. Kenet G. explained that the mechanisms behind these adverse events are still being evaluated and currently remain unknown. During the congress, there were questions on whether this therapy should be administered to patients with increased risks of cardiovascular problems (such as older patients).

During the ISTH 2022 Congress, Srivastava A. presented on **two randomised, open-label, phase III trials (ATLAN-**

1) <https://www.ehc.eu/wfh-ehc-nhf-joint-statement-on-global-dosing-hold-in-fitusiran-trials-initiated-by-sanofi-genzyme-to-investigate-new-adverse-events/>

<https://www.ehc.eu/joint-statement-on-fitusiran-update-following-cahad-2021-congress/>.

INH and ATLAS-A/B), including patients with haemophilia A and B with or without inhibitors. Patients were randomised to either fitusiran or on demand bypassing agents (BPA, for inhibitor patients) or replacement therapy (CFC, for non-inhibitor patients). Investigators assessed annualised treatment consumptions, number of treated bleeds and infusions per bleed. Researchers noted that from these data, fitusiran prophylaxis reduced total BPA/CFC consumption by reducing the number of treated bleeds, injections and BPA/CFC doses required to treat breakthrough bleeds in people with haemophilia A or B with and without inhibitors by ~95% or more thereby reducing treatment burden.

In an oral communication at the 2022 ISTH Congress, Pipe S. presented the analysis of the **phase III ATLAS A/B study on the use of fitusiran in males with haemophilia A or B without inhibitors who had previously been treated on-demand**. The objective of the study was to assess the changes in antithrombin levels and thrombin generation over time in the patient cohort described above. Results show a reduction in estimated ABR by 89.9% versus on-demand treatment with factor concentrates. Pipe S. also presented the revised dose and dose regimen targeting antithrombin, range from 15-35% to reduce the risk of vascular thrombotic events.

In a poster presented at the WFH 2022 Congress, Kavakli K. presented the results of the **ATLAS-A/B trial with regard to health-related quality of life in people with haemophilia A or B without inhibitors either on fitusiran prophylaxis or on-demand replacement therapy**. The authors noted that fitusiran prophylaxis scored better than on-demand with the Haem-A-QoL questionnaire.

Finally, during the 2022 ISTH Congress, Sanofi presented an **assessment of changes over time in antithrombin activity levels and thrombin generation in people with haemophilia A or B with inhibitors on fitusiran prophylaxis**. They concluded that fitusiran has the potential to reduce ABR and provide bleed protection by rebalancing the haemostasis.

Concizumab

Concizumab is an anti-tissue factor pathway inhibitor antibody developed by Novo Nordisk for the treatment of people with haemophilia A or B with or without inhibitors.

During the 2022 ISTH Congress, Jiménez Yuste V. presented the results from the **phase III explorer7 trial to assess the safety and efficacy of concizumab in people with haemophilia A or B and inhibitors**. Researchers randomised patients to concizumab prophylaxis or no prophylaxis. Results showed a lower ABR rate for the prophylaxis arm and a higher proportion of zero-treated bleeds. No thromboembolic events were reported. There was no significant difference between the two arms for key secondary endpoints such as bodily pain and physical functioning. The presentation also highlighted some of the adverse events that occurred during the trial, but none was deemed related to concizumab.

In another presentation at the 2022 ISTH Congress, Mancuso M.E. presented the results of the **phase II clinical trials explorer4 and 5**. These trials looked at the treatment burden of daily concizumab subcutaneous injection. Researchers used a questionnaire designed to evaluate treatment burden and concluded that questionnaire scores improved at or after 24 weeks of concizumab subcutaneous prophylaxis during the explorer4 and 5 trials in patients with or without inhibitors.

Marstacimab

Marstacimab is a human monoclonal antibody targeting tissue factor pathway for the treatment of people with haemophilia A or B with or without inhibitors. This product is in development by Pfizer.

In an article in the *British Journal of Haematology*, Mahlangu J. reported on the results of the **phase Ib/II study on the use of marstacimab in people with haemophilia A or B with or without inhibitors**. Participants were assigned to four dose cohorts and received escalating weekly doses based on their inhibitor status. The article concludes that marstacimab was well tolerated and had an acceptable safety profile. Clinically meaningful reductions in annualised bleeding rates and treatment-related changes for all pharmacodynamics biomarkers indicated effective targeting of TFPI.

In November 2022, Pfizer announced a **new clinical trial on the study of marstacimab in paediatric patients with haemophilia A or B**.

SerpinPC

SerpinPC is an inhibitor of activated protein C in development by Centessa Pharmaceuticals.

In September 2022, Centessa pharmaceuticals announced that **SerpinPC received Orphan Drug Designation from the US FDA.**

An update on novel therapies in von Willebrand Disease and other rare bleeding disorders

Non-replacement therapies

Non-replacement therapies help rebalance haemostasis by working on different parts of the coagulation cascade. The products included in this section are BT200, Hemlibra® and HMB-001.

BT200

Rondoroptivon pegol, or BT200 is a pegylated aptamer that binds the A1 domain of von Willebrand factor with a novel mechanism of action. It enhances VWF/FVIII levels by decreasing their clearance. This treatment is being developed and tested by the Medical University of Vienna.

In an article published in *Blood Advances*, Ay C. described a **prospective phase II clinical trial on the prospective benefits of BT200 in patients with type 2B von Willebrand Disease.** The study included five patients. BT200 rapidly tripled platelet count, and circulating von Willebrand Factor antigen increased, which doubled FVIII activity levels. This data provides the basis for a phase IIb/III trial.

Hemlibra®

Hemlibra® is a non-replacement therapy for the treatment of haemophilia A with or without inhibitors. It is a bispecific antibody that acts in replacement of factor VIII. It is administered subcutaneously. Hemlibra® is marketed by Roche.

In an abstract presented at the 2022 ISTH Congress, Roche presented an *in vitro* **investigation on the efficacy of the haemostatic-promoting mechanisms of Hemlibra® in people with haemophilia A and von Willebrand Disease.** This preliminary data suggest that Hemlibra® promotes higher thrombin generation in von Willebrand disease (VWD) type 2N plasma compared to haemophilia A and VWD type 3 plasma. These data provide early insight into Hemlibra® mode of action in these diseases and support the notion of efficacy in VWD type 2N and 3.

French researchers presented results at the ISTH 2022 Congress from an assessment of **the effects of Hemlibra® on the bleeding profile of a von Willebrand disease mouse model.** The authors concluded that, as observed in patients, Hemlibra® improved the bleeding phenotypes in a mouse model of VWD type 3, suggesting that Hemlibra® assists in restoring primary clot formation in the absence of von Willebrand factor (VWF). However, no amelioration was observed in VWD type 2A mice, suggesting degraded VWF, even at low concentrations. These preclinical findings need to be viewed with caution and require further investigation.

HMB-001

HMB-001 is an investigational product in development by Hemab. It is a bispecific antibody that binds and accumulates endogenous FVIIa in circulation. Upon vessel injury, HMB-001 promotes local FX activation and thrombin generation by placing FVIIa on the surface of activated platelets via binding to the TREM-like transcript 1 (TLT-1) receptor. The activity of HMB-001 thus builds on the mechanism of action (MoA) of recombinant FVIIa (rFVIIa) and can potentially prevent bleeds in multiple haemostatic disorders, of which Glanzmann Thrombasthenia is the primary focus. This treatment had promising results in animal models and in vitro studies but further studies will be required to confirm these findings in humans.

In January 2023, Hemab announced that it had **dosed its first patient with HMB-001 for the treatment of Glanzmann Thrombasthenia.**

Gene therapy

A group of Dutch researchers presented at the 2022 ISTH Congress a study on a **potential personalised gene therapy for von Willebrand Disease using CRISPR/Cas9 technology**. This study is in its preclinical stage.

An Update on Novel Therapies for Haemophilia A

In this section we update on novel therapies in people with haemophilia A without inhibitors. For an update on the use of these therapies in people with haemophilia A and inhibitors please go to pg 42.

Factor replacement therapies

Results from the phase III XTEND-1 study for the use of Efanesoctocog alfa (BIVV001) prophylaxis in previously treated patients with severe haemophilia A

In a late-breaking presentation (LB 01.4) at the 2022 ISTH Congress, von Drygalski A. presented data from the phase III XTEND-1 study (NCT04161495) assessing the efficacy, safety and pharmacokinetics (PK) of **efanesoctocog alfa (BIVV001)** as a prophylactic treatment in previously treated people (PTP ≥ 12 years) with severe haemophilia A.

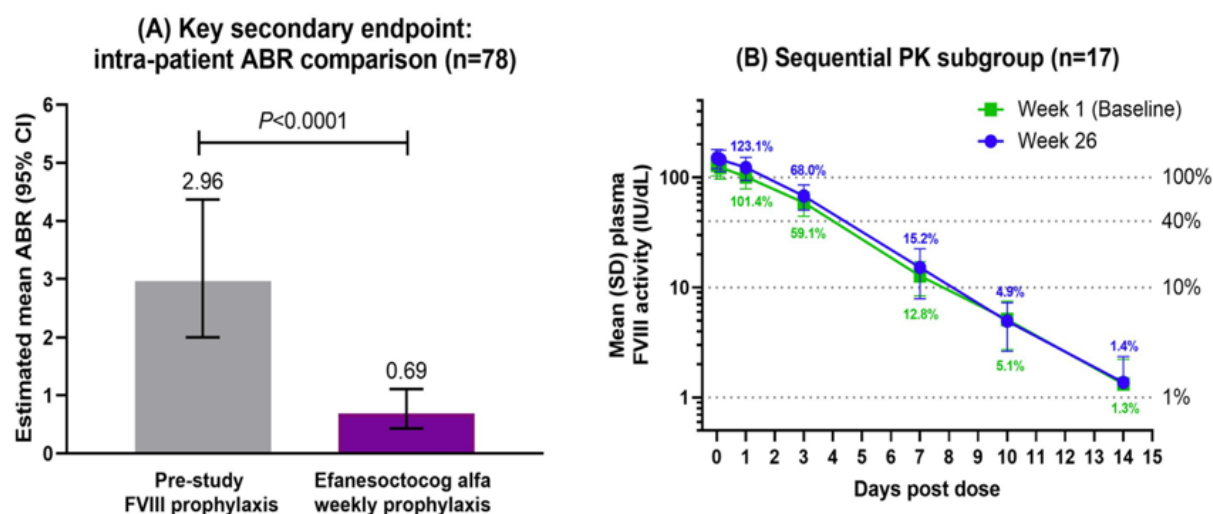
Efanesoctocog alfa is a new class of recombinant FVIII replacement, consisting of an Fc linked B-domain deleted (BDD)-FVIII combined with the D'D3 region of von Willebrand factor. The rationale for this approach is to overcome the von Willebrand factor-imposed half-life ceiling of current recombinant FVIII concentrates. BIVV001 is in development by Sobi (Europe) and Sanofi (US).

The study consisted of two arms:

- Arm A: Patients on prior prophylaxis. Prophylactic treatment with once-weekly intravenous efanesoctocog alfa (50 IU/kg) for 52 weeks.
- Arm B: Patients who were previously on-demand. On-demand intravenous efanesoctocog alfa (50 IU/kg) for 26 weeks, followed by a switch to efanesoctocog alfa prophylaxis for 26 weeks.

The primary endpoint was annualised bleed rate (ABR) in arm A. Secondary endpoints included pre-study versus on-study intra-patient ABR comparison (key secondary), bleed treatment, physical health, pain, joint health, PK, and safety.

One hundred and thirty-two patients (males, $n=131$; females, $n=1$) were enrolled in arm A; 26 males in arm B. Arm A mean standard deviation (SD) and median interquartile range (IQR) ABR were 0.71 (1.43) and 0.00 (0.00–1.04), respectively. Intra-patient ABR comparison demonstrated superior bleed protection with efanesoctocog alfa versus prior FVIII prophylaxis ($P < 0.001$). Most bleeds (96.7%) resolved with one efanesoctocog alfa injection, and 94.9% of responses were rated excellent/good. Once-weekly efanesoctocog alfa provided high sustained factor VIII activity consistent with earlier PK studies. efanesoctocog alfa prophylaxis was associated with significant improvements from baseline in physical health ($P=0.0001$), pain ($P=0.0276$), and joint health ($P=0.0101$) at week 52. No FVIII inhibitors were detected. The most common treatment-emergent adverse events ($>5\%$ of participants overall) were headache, arthralgia (joint pain), fall, and back pain.



During the presentation, von Drygalski reported a mean half-life of 47 hours. This resulted in FVIII activity within normal to near-normal levels (>40%) for most of the week with a mean of 15% FVIII level after seven days (figure B). During ISTH, a member of the audience asked von Drygalski A. whether efanesoctocog alfa was more immunogenic compared to other extended half-life (EHL) or standard factor VIII due to the more extensive manipulation of the molecule. The reply was that currently, the product had only been tested in PTPs but that studies in previously untreated patients (PUPs) were planned and they would hopefully help to clarify this issue.

In August, the US Food and Drug Administration (FDA) granted priority review for the approval of efanesoctocog alfa. Priority review aims to shorten the time to possible approval.

Pharmacokinetic profile of Efanesoctocog alfa

During the 2022 WFH Congress, Sanofi presented (FP-LB-03 (1227074)) a study evaluating the pharmacokinetics (PK) profiles of **Efanesoctocog alfa (BIVV001)**, **Advate®** and **Adynovi®**.

Thirteen previously treated adult males with severe haemophilia A were enrolled in this phase I study (NCT05042440). After appropriate washout periods, each patient sequentially received single 50 IU/kg doses of Advate®, Adynovi®, and Efanesoctocog alfa. The primary objective was to assess the elimination half-life ($t_{1/2}$) for each product. Secondary objectives were characterisation of additional PK parameters and evaluation of safety and tolerability of Efanesoctocog alfa. Geometric mean $t_{1/2}$ of Advate®, Adynovi®, and Efanesoctocog alfa were 11.0, 15.4, and 43.3 hours, respectively. Corresponding values for area under the curve extrapolated to infinity (AUC_{inf}) were 1670, 2820, and 10,100 IU × h/dL. Efanesoctocog alfa maintained mean FVIII activity levels >40 IU/dL for up to four days and □ 10 IU/dL at day seven. Corresponding times >40 IU/dL and >10 IU/dL were <1 and <2 days for Advate® and □ 1 day and < 3 days for Adynovi®. No serious or severe treatment-emergent adverse events were reported.

Based on these data, researchers concluded that a single-dose Efanesoctocog alfa had a 3–4-fold longer $t_{1/2}$ and 4–6-fold greater AUC_{inf} than the other two products.

Post hoc analysis from the PUP A-LONG study on the occurrence of inhibitors in PUPs < 6 years old with severe haemophilia A using Elocta

In an oral presentation (OC 47.4) from the 2022 ISTH Congress, Carcao M., supported by Sanofi, described the *post hoc* analysis of inhibitor incidence in patients treated in the PUP A-LONG study. This is an open-label multicentre phase III study (NCT02234323) evaluating the safety and efficacy of **Elocta®** in male previously untreated patients (PUPs) < 6 years old with severe haemophilia A. The primary endpoint was the occurrence of inhibitor development. Inhibitors occurred in 27% (28/103) patients who received Elocta® on the PUPs A-LONG study. Twenty-four of the study participants were on prophylaxis as their final treatment regimen. Of 14 patients with high-titre inhibitors (HTI), half (n=7) had prior low-titre inhibitors (LTI). Inhibitor development followed central venous access device (CVAD) placement in 17% of those who underwent the procedure (n=7/42) and in 20% of those who had intense factor exposure (n=9/44). Five of nine patients (56%) experienced intense factor exposure due to CVAD placement. Matching inhibitor-positive and -negative patients with intense factor exposure by exposure days indicated no significant difference between groups in cumulative dose (IU/kg) administered until inhibitor development, nor was there a correlation between groups (unmatched) for total consumption over time.

Results from the A-SURE study on the use of Elocta in a European real-world setting

In an oral presentation (OC 27.4) at the ISTH Congress, Oldenburg J. et al., supported by Sobi, reported on the direct comparative real-world effectiveness of **Elocta®** prophylaxis versus (vs) a matched treatment group on standard half-life FVIII. The report was based on the A-SURE study (NCT02976753), a 24-month prospective non-interventional European study. Three hundred and fifty-six people with haemophilia A were enrolled (n=186, Elocta® group; n=170, standard half-life FVIII (SHL FVIII) group). The primary endpoints were annualised bleeding rates (ABR), injection frequency and annualised factor consumption. All primary endpoints were lower (see table below) in the Elocta® group compared to the SHL FVIII group during the study.

	rFVIII Fc (N=184) ^a	SHL FVIII (N=170) ^a	rFVIII Fc vs SHL FVIII	
Observation time in the treatment group (months), Median (IQR; range)	21.4 (19.4-24.3; 5.5-38.6)	21.0 (18.6-24.6; 5.0-40.3)	Not applicable	
Endpoint	Mean (95% CI)	Mean (95% CI)	Effect (Mean Difference)	p-value
ABR ^b	1.5 (1.0;1.9)	2.3 (1.8;2.8)	-0.8 (-1.5; -0.2)	0.0147
Annualised injection frequency ^c	114.4 (100.6;128.2)	169.2 (155.2;183.2)	-54.8 (-64.6;-45.0)	<.0001
Annualised factor consumption (IU) ^c	243 024 (210 178;275 871)	288 719 (255 261;322 176)	-45 695 (-70 415;-20 974)	0.0003
^a Patients with <3 months on study treatment were excluded from analysis of annualised endpoints (SHL FVIII n=0, rFVIII Fc n=2) to support an accurate estimation of annualised outcomes. ^b ABR estimated with a generalized linear mixed model (GLMM) adjusted for propensity score, age and ABR during the 12-month retrospective period. The predefined negative binomial regression model for ABR which was rejected due to poor model fit showed a mean (95% CI) ABR of 0.9 (0.6;1.2) for rFVIII Fc and 1.2 (0.9;1.6) for SHL FVIII, with an effect ratio of 0.7 (0.5;1.0) (p=0.0548). ^c Estimated with a predefined GLMM adjusted for propensity score, age and ABR during the 12-month retrospective period. rFVIII Fc: recombinant factor VIII Fc; SHL: standard half-life; FVIII: factor VIII; IQR: interquartile range; CI: confidence interval; ABR: annualised bleeding rate; IU: international units				

Real-world evidence of Elocta® use in surgery

In two abstracts from the 2022 ISTH Congress, researchers from France (VPB 1190) and Ireland (PB1145) presented their experience of managing major and minor surgeries with **Elocta®**.

The first abstract described a retrospective analysis of 39 major and 31 minor surgeries performed in 49 haemophilia A patients (severe n=33, moderate n=2, and mild n=14). The authors describe peri-, during- and post-operative dosage. The authors adjusted dosage based on FVIII chromogenic assay results (instead of the one-stage assay), in line with local guidelines. In doing so, Elocta® consumption decreased, and savings were generated.

The second abstract presented data on 24 major and 225 minor procedures managed with Elocta® on 105 people with haemophilia A (96 male and 9 female). Surgeries were performed in people with different haemophilia severities. The authors presented data on pre-operative dosage and factor level as well as post-operative factor level.

Haemostasis was rated as excellent in the major surgeries. In the minor surgeries, a transient low-titre inhibitor (< 0.5 BU) was detected in one patient four weeks post-procedure but was not present on repeat testing.

Interim analysis of the HEM-POWR study looking at the effectiveness of Jivi® in previously treated patients

In an abstract (PB 1123) from the 2022 ISTH Congress, authors led by Reding M. presented a second interim analysis of the HEM-POWR (NCT03932201) study, funded by Bayer. This is an ongoing, multicentre phase IV study evaluating the real-world effectiveness and safety of **Jivi®**, a PEGylated recombinant FVIII, in previously treated patients (age ≥12 years) with haemophilia A. The primary endpoints include total bleeding events and annualised bleeding rate (ABR). At the data cut-off date (31 August 2021), 162 patients were enrolled, with 78 patients included in the full analysis set (FAS; mild n=3; moderate n=9; and severe n=99).

Mean age at enrolment was 35.4 years with 91% (71/78) on prophylaxis before enrolment. The median (mean, SD) difference in ABR between the observation period and prior to Jivi® initiation was -0.11 (-1.01, 9.94). Joint health was assessed by the number of pre-treatment joint bleeds compared with the number of bleeds at the first follow-up. The number of patients with any affected joint decreased from 59.7% (37/62) to 14.3% (8/56).

Clinical trial for the study of subcutaneous FVIII terminated due to inhibitor development

In an abstract (PB0672) presented at the 2022 ISTH Congress, Octapharma presented data on the phase I/II study (NCT04046848) to assess the safety, pharmacokinetics (PK), and bioavailability of subcutaneous **OCTA101**, a recombinant FVIII with a recombinant VWF factor fragment dimer.

The study included previously treated (≥ 150 exposure days to FVIII) male patients (≥ 18 years) with severe haemophilia A. This was a single centre prospective, open-label, dose-escalation study. Patients in the dose-escalation cohorts received a single injection of OCTA101 for PK assessment followed by three-month daily prophylaxis. Assessment by an independent Data Monitoring Committee (DMC) was performed before escalating to the next higher dose tier. The primary outcome measures included FVIII and VWF fragment PK, dose-linearity, adverse events (AEs), dose-limiting toxicities, thromboembolic events, local injection site reactions, and FVIII inhibitor formation.

Twenty patients were enrolled in the PK part of the study. The factor half-life and recovery were as expected from pre-clinical studies, and trough plasma FVIII levels $\geq 10\%$ were achieved. Two patients developed inhibitory antibodies to OCTA101, and the trial was put on hold during discussion with the DMC. The trial resumed with an amended protocol, including a lower dose and the integration of additional safety steps, and ten patients started OCTA101 treatment. Another two patients subsequently developed inhibitors while on daily prophylaxis. In accordance with the amended protocol and in agreement with the DMC, the study was terminated. Other than the development of FVIII inhibitors, no serious treatment-related AEs were reported. The occurrence of inhibitors despite dose reduction suggests this is related to the subcutaneous route of administration. Similarly, development of another subcutaneous recombinant FVIII product (turoctocog alfa pegol) was terminated due to antibody development in previously treated patients.

Non-replacement therapies

FVIII mimetics

EMA recommends to extend Hemlibra®'s indication to people with moderate haemophilia A

On 15 December 2022, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for Hemlibra®. The CHMP adopted an extension to an existing indication to include routine prophylaxis of bleeding episodes in patients with haemophilia A without factor VIII inhibitors who have moderate disease with severe bleeding phenotype. The European Commission needs to officially validate this recommendation before it is implemented.

Report from the UK Haemophilia Doctors Organisation (UKHCDO) on the use of Hemlibra® in people with severe haemophilia A without inhibitors

In a presentation (OC 30.1) from the 2022 ISTH Congress, Wall C. presented data on the use of **Hemlibra®** in non-inhibitor haemophilia patients collected by the UKHCDO database since 2019.

Hemlibra® was prescribed to 673 non-inhibitor people with severe haemophilia A, 36.9% of the UK-registered cohort, including 85 (12.6%) with an inhibitor history. An analysis of 144 people who had reported data on their bleeds, showed that 73% (105/144) reported reduced bleeds after switching to Hemlibra®.

Relatively few subjects had target joints using ISTH criteria; 35 switchers had 51 target joints and 45 non-switchers had 69 target joints. After a median 21 months follow-up, 74% of Hemlibra® switchers experienced fewer and 6% more target joints versus 42% fewer and 33% more target joints in non-switchers ($p=0.004$). Recurrent FVIII inhibitors were reported in 4.7% (4/85) people at 4-15 years post-tolerization. FVIII inhibitors occurred between two and six months after starting

Hemlibra®. One person (1/673; 0.15%) developed a low-level anti-drug antibody to Hemlibra®. The person stopped Hemlibra®.

Efficacy of Hemlibra®: Real-world data from Germany

In a presentation (OC 30.2) from the 2022 ISTH Congress, Escuriola-Ettinghausen C. reported on real-life data on the efficacy of **Hemlibra®** treatment in patients with severe haemophilia A in Germany. The data was collected using the smart medication eDiary. Data was reported from 39 people with severe haemophilia A in seven German treatment centres. The data showed a significant bleed reduction in those who switched to Hemlibra®, however, they were still experiencing low levels of bleeds, which the authors concluded meant Hemlibra® did not achieve zero bleeds.

Data from the ATHN 7 study on the use of Hemlibra® in a real-world setting

During the ISTH 2022 Congress, Recht M. presented (OC 40.4) the results from the ATHN 7, a natural history study on the safety, effectiveness and practice of treatment for people with haemophilia with current therapies, including **Hemlibra®**. ATHN 7 is a longitudinal, prospective, observational cohort study being conducted at 26 American Thrombosis and Hemostasis Network (ATHN)-affiliated sites.

Researchers collected data on the safety and effectiveness of Hemlibra® for four years.

Baseline inhibitor status was available for 236 individuals (59 with inhibitor, 177 without inhibitor). For the entire cohort, median (range) duration of Hemlibra® exposure was 77.2 (0.14–141.00) weeks. Fifteen adverse events (AEs) were reported in nine participants, including six injection-site reactions in one participant. There was one death due to haemorrhagic shock, which was deemed unrelated to Hemlibra®. No thrombotic events or thrombotic microangiopathies were reported. Mean (standard deviation) annualised bleeding rates were 1.30 (2.78) for treated bleeds and 0.73 (2.07) for treated joint bleeds, with similar values for the participants with moderate or severe haemophilia A.

In conclusion, no new safety signals were identified in relation to the use of Hemlibra® in a real-world setting in people with haemophilia A with or without inhibitors.

The monitoring of safety and effectiveness of treatment in bleeding disorders in US haemophilia centres will continue with the ATHN Transcend (NCT04398628) study that plans to enrol 3000 patients and monitor them over 15 years.

Real-world persistence and adherence to Hemlibra® prophylaxis

In an abstract (LR-10.03) presented at the WFH 2022 Congress, authors from Genentech led by Kharinar R. presented data from a retrospective study of one-year persistence and adherence to **Hemlibra®** prophylaxis in people with haemophilia A. The authors also describe the concomitant use of FVIII.

The study data came from the commercial insurance claims data from IQVIA PharMetrics® Plus (P+; Nov-17/Dec-20) and IBM® MarketScan® Commercial Research (IBM; Nov-2017/Sep-2020) databases. The authors identified 184 and 105 individuals who met the inclusion criteria from the P+ and IBM databases, respectively. All were male; the mean (\pm SD) age was 24 ± 16 years for P+ and 22 ± 17 for IBM. Twelve per cent of patients in each database had inhibitors. Most individuals (P+: 87%; IBM: 92%) were persistent with Hemlibra® prophylaxis during the one-year period. Among the 24 (13%) and 8 (8%) PwHA in P+ and IBM, respectively, who discontinued Hemlibra®, 54% and 75% restarted, with mean (\pm SD) times to restart of 127 ± 55 and 110 ± 37 days. Adherence and persistence with Hemlibra® were high regardless of inhibitor status. Data from the databases indicate that within the non-inhibitor population ($n=129$), 49 (38%) and 49 (62%) PwHA in P+ and IBM, respectively, used FVIII in the one year period, with means (\pm SD) of 3 ± 4 and 4 ± 6 claims. The highest proportions of FVIII use was in the first month after Hemlibra® initiation.

Real world experience using Hemlibra® entire vial-based dosing regimen for people with haemophilia A: An Update

During the 2022 ISTH Congress, Van der Zwet K. gave an update (OC 30.4) on a study first presented at the 2021 ISTH and reported in the EHC New Product Newsletter 2021 Vol. 2.

The study was focused on dosage of **Hemlibra®** given to an individual, as prescribed doses often did not match with vial content, leading to medication wastage. To avoid wasting doses, a Dutch centre started to give entire-vial-based-dosing-regimen of Hemlibra® in patients with haemophilia A. The loading doses were given according to the label and the maintenance dose was 6mg/kg/4 weeks using entire vial regimens by varying intervals between seven and 28 days.

A total of 89 patients were included with a median age of 18.5 years. Patients received a median of 115 days Hemlibra® maintenance treatment. The median Hemlibra® dose of 5.9 mg/kg/4 weeks administered in seven to 28 days intervals, with 31% of patients using intervals >12 days. Median plasma concentration of Hemlibra® was 61.7 µg/ml with no differences observed between adults and children. A total of 74 patients (83%) demonstrated Hemlibra® concentration ≥ 40 µg/ml during maintenance therapy using the entire-vials-based dose regimen. This dosing resulted in effective concentrations of Hemlibra® in both children and adults. Based on these results, using entire vials may avoid treatment waste.

Results from the HAVEN 6 Study on the use of Hemlibra® in people with moderate or mild haemophilia A without inhibitors

During the ISTH 2022 Congress, Hermans C. presented (OC 30.5) the primary analysis of phase III HAVEN 6 (NCT04158648) study assessing safety and efficacy of **Hemlibra®** prophylaxis in people with non-severe HA without FVIII inhibitors. The HAVEN 6 study is supported by Roche.

Participants received subcutaneous Hemlibra® 3mg/kg weekly for four weeks, then 1.5mg/kg weekly, 3mg/kg every two weeks, or 6mg/kg every four weeks. Safety endpoints included adverse events (AEs), serious AEs (SAEs) and AEs of special interest, including thromboembolic events (TEs) and thrombotic microangiopathies (TMAs). Efficacy endpoints include negative binomial regression model estimates of annualized bleed rates (ABRs).

As of 30-Oct-2021, 72 participants (70.8% [n=51] moderate; 29.2% [n=21] mild; 95.8% [n=69] male; 4.2% [n=3] female) received Hemlibra®. The median follow-up was 55.6 weeks. At baseline, 37 participants (51.4%) were on FVIII prophylaxis; 24 (33.3%) had target joints. Within 24 weeks prior to study entry, participants had a median (range) of 2.0 (0–96) bleeds and a model-based ABR (95% CI) of 10.1 (6.93–14.76). Sixty participants (83.3%) had ≥ 1 AE and 15 (20.8%) had ≥ 1 Hemlibra®-related AE; no AEs led to treatment withdrawal/modification/interruption. Ten SAEs were reported by eight participants (11.1%), none were Hemlibra®-related. There were no deaths or TMAs. One participant experienced a grade 1 thrombosed haemorrhoid unrelated to Hemlibra®, classified as a TE. Model-based ABRs (95% CI) were 0.9 (0.55–1.52) for treated bleeds, and 2.3 (1.67–3.12) for all bleeds. Forty-eight participants (66.7%) had zero treated bleeds.

Impact of Hemlibra® on bone/joint health: Data from the HAVEN 3 studies

In an article published in *Haemophilia* in July 2022, Roche presented data from the HAVEN 3 trial (NCT02847637) to assess the effect of **Hemlibra®** prophylaxis on bone/joint health in people with haemophilia A (PwHA) without inhibitors. Authors evaluated the haemophilia joint health scores at baseline and at weeks 49 and 97 in people with haemophilia A who switched to Hemlibra® after 24 weeks of no prophylaxis (n=17). Bone and joint biomarkers were measured in 117 PwHA at baseline and at weeks 13, 25, 49 and 73.

Haemophilic joint health score (HJHS) was lower for PwHA who were previously on FVIII prophylaxis, aged <40 years or had no target joints at baseline compared with PwHA who were receiving no prophylaxis, aged ≥ 40 years or with target joints. Clinically significant improvements from baseline of -2.13 (-3.96, -0.29) in HJHS joint-specific domains were observed at week 49 in PwHA with at least one target joint at study entry (n=71); these changes were maintained through week 97. Improvements in HJHS from baseline were also observed for PwHA aged 12-39 years. Biomarkers of bone resorption/formation, cartilage degradation/synthesis, and inflammation did not change significantly during Hemlibra® prophylaxis.

Surgical outcomes from the HAVEN 1-4 clinical trials in people with haemophilia A with or without inhibitors on Hemlibra® prophylaxis.

In an article published in Blood Advances Kruse-Jarres R. presented the data from the HAVEN 1-4 phase III clinical studies on the surgical outcomes in people with haemophilia A with or without inhibitors taking **Hemlibra®** prophylaxis.

Overall, 233 surgeries were carried out during the HAVEN 1-4² trials: 215 minor surgeries (including minor dental and joint procedures, central venous access device placement or removal, and endoscopies) in 115 people with haemophilia A (PwHA) (64 with FVIII inhibitors) and 18 major surgeries (including arthroplasty and synovectomy) in 18 PwHA (10 with FVIII inhibitors). Peri-operative haemostatic support was at the discretion of the treating physician. Overall, the median (interquartile range [IQR]) age was 33.5 (13.0-49.0) years and the median (IQR) Hemlibra® exposure time before surgery was 278.0 (177.0-431.0) days. Among the 215 minor surgeries, 141 (65.6%) were managed without additional prophylactic factor concentrate, and of those, 121 (85.8%) were not associated with a postoperative bleed. The majority (15 of 18 [83.3%]) of major surgeries were managed with additional prophylactic factor concentrate. Twelve (80.0%) of these 15 surgeries were associated with no intra-operative or postoperative bleeds. The data demonstrate that minor and major surgeries can be performed safely in PwHA receiving Hemlibra® prophylaxis.

Efficacy of Hemlibra®: An analysis of data from the CHESS II study

In an abstract (PB0674) from Roche presented at the 2022 ISTH Congress, Mancuso M. E. and colleagues examined the effectiveness of **Hemlibra®** in a real-world setting by using the bleed data on all bleeds from the Cost of Haemophilia in Europe: A Socioeconomic Survey II (CHESS II). This is a retrospective burden of illness questionnaire-based study. Overall, 146 people with severe haemophilia A (PwHA) (Italy n=81; Germany n=26; Spain n=26; France n=10; UK n=3) were included in the analysis. Of these, 78 adults received Hemlibra® for ≥12 months, including 49 (62.8%) previously treated with FVIII prophylaxis, 28 (35.9%) treated on demand, and one who previously received gene therapy; 22/78 (28.2%) had either a history of, or current, FVIII inhibitors. The mean all-bleeds annualised bleed rate (ABR) in the 78 participants decreased from 3.37 at last treatment pre-Hemlibra® to 1.42 post-Hemlibra®. Median ABR decreased from 3.00 to 1.19. In the 49 participants previously on prophylaxis, mean ABR decreased from 3.49 to 1.40 after switching to Hemlibra®. A sensitivity analysis including 123 PwHA who received Hemlibra® for ≥6 months showed a decrease in mean ABR from 4.33 pre-Hemlibra® to 1.91 post-Hemlibra®; median ABR decreased from 3.00 to 1.33 (all p < 0.001).

Efficacy of Hemlibra® in children up to 42 months of age

During the 2022 ISTH Congress, researchers from Chugai led by Takeyama M. presented data (VPB0208) from a study looking at the coagulation potential of **Hemlibra®** *in vivo* or *ex vivo* in plasma collected from children aged 0 to 42-month old with haemophilia A.

Plasma from 27 children with haemophilia A up to 42 months of age, receiving Hemlibra®, FVIII, or neither Hemlibra® nor FVIII (median age; 19 months) were enrolled. FVIII activity in people with haemophilia A (PwHA) receiving FVIII agents was reduced to < 1 IU/dL by the addition of anti-FVIII A2 monoclonal antibody. Samples of Hemlibra®-spiked plasma (*ex vivo*) or Hemlibra®-treated plasma (*in vivo*) were analysed. Untreated plasma or Hemlibra®-treated plasma supplemented with anti-Hemlibra® antibody were used as reference samples, respectively. Global coagulation activity was measured and adjusted for maximum coagulation velocity (Ad|min1|) in a clot waveform analysis (CWA) and peak thrombin was measured using thrombin generation assay (TGA). Ad|min1| in 24 of the 27 cases was improved in the presence of Hemlibra®. Three children with haemophilia A, which did not respond were one, 23, and 31 months of age. Although 20 of the 27 cases showed an age-dependent increase in peak thrombin with Hemlibra®, seven cases (0, 1, 1, 2, 8, 19, and 36 months) did not. A Hemlibra®-dependent increase in coagulant potential was shown in 18 cases by both Ad|min1| and peak thrombin, and in eight cases by one parameter but not the other. Only one case (one month of age) did not respond with either Ad|min1| or peak thrombin. Currently the HAVEN7 clinical trial, which includes children up to 12 months of age with haemophilia A and inhibitors on Hemlibra® is ongoing.

2) #NCT02622321, #NCT02795767, #NCT02847637, and #NCT03020160.

Hemlibra® in paediatric patients

A group of Portuguese researchers led by Urbano M. describe their treatment protocol with **Hemlibra®** in four paediatric patients aged over 21 months. Treatment is administered monthly at the hospital, which allows clinicians to reduce usage and contain costs while ensuring optimal treatment. You can further read about this case study in abstract VPB0230 from the 2022 ISTH Congress.

Use of Hemlibra® in end stage renal disease

A case study (PB0661) from Denmark was presented at the 2022 ISTH Congress on the use of **Hemlibra®** in a patient with end stage renal disease and undergoing dialysis. This is of interest as patients with this particular comorbidity were excluded from clinical trials. In this case, researchers (led by Funding E.) found that Hemlibra® in standard dosing remained stable and effective as prophylaxis during progressive renal failure and haemodialysis.

Analysis of Hemlibra® discontinuation in ten patients in a Japanese centre

In an abstract (VPB0694) from the 2022 ISTH Congress, a group of Japanese researchers led by Nagao A. looked at factors contributing to **Hemlibra®** discontinuation and how to promote this medicine's safe use.

Researchers collected data from medical records in their hospital until the analysis in September 2021. Of 64 patients (including nine with inhibitors), ten discontinued Hemlibra® (median, 23 months until discontinuation). The age range of these ten patients was seven-69 years. None of the patients who discontinued had FVIII inhibitors. Thereafter, only non-inhibitors were examined because the bleeding nature is different between inhibitors and non-inhibitors. The disease severity was severe (n=43 continued, n=8 discontinued), moderate (n=2, continued; n=1, discontinued), and mild (n=1 discontinued). Researchers looked at the adherence to prophylaxis and changes in annual bleeding rates, which can be found here. No patient in the discontinued group achieved zero bleeding. Reasons for discontinuation included poor bleeding control (n=5), possible side effects (n=2), prolonged dosing intervals due to poor understanding of the treatment (n=1), and concerns about medical costs (n=1). Four patients with poor bleeding control experienced frequent joint pain and bleeding sensation, and haemorrhagic synovitis was detected using joint ultrasound. Hemlibra® blood levels were measured in several patients; none had low Hemlibra® levels. Six patients initiated prophylaxis with standard half-life products (SHLs), two with extended half-life products (EHLs), and two with SHLs before switching to EHLs.

***In vitro* tests on the effects of Hemlibra® on anticoagulant medication**

In an abstract (PB1154) presented at ISTH 2022, a group of French researchers led by Leroy looked at the potential interference of **Hemlibra®** on the anticoagulant effect of anticoagulant therapy. To assess this, they used laboratory assays on both FVIII-deficient and normal plasma in the presence of anticoagulant medicines alone or in the presence of Hemlibra®. In the tests performed, the addition of Hemlibra® did not alter the anticoagulant action of the anticoagulant medicines tested. This data needs to be confirmed with further studies.

A literature review of neutralising antibodies in Hemlibra®

A group of Californian researchers led by Kizilcok H. conducted a literature review (PB0221) to identify previously reported anti-**Hemlibra®** anti-drug antibodies (ADA) from around the world. The cases found were supplemented by additional patients tested in their laboratory. Authors developed a Bethesda-like assay using the human chromogenic FVIII activity to determine the presence of ADA from patients' plasma with a known concentration of Hemlibra® in control plasma. They presented their findings in an abstract at the 2022 ISTH Congress.

In total, five people with haemophilia A with and without inhibitors with a median age of seven (2-62) have been identified with anti-Hemlibra® ADA. According to the manufacturer, ~12,000 individual people with haemophilia A have been treated with Hemlibra®. The clinical presentation of ADA was unexpected/excessive bleeding and a prolonged activated partial thromboplastin clotting time (aPTT) in all cases. Four of the five cases had FVIII inhibitors and one did not. Four of the five were found to have a neutralizing ADA and one had a non-neutralizing ADA, which resulted in increased/rapid clearance of Hemlibra®. Interestingly, all the cases presented in the first year and 4/5 in the first 24 weeks after Hemlibra® initiation. Authors note that breakthrough bleeding and aPTT prolongation are the first signs of ADA to Hemlibra®, which should prompt further evaluation. There currently are no commercially available assays to determine ADA to Hemlibra®. Authors

suggest identifying them with a modified Bethesda assay with commercially available reagents and calculate an approximate level of ADA.

Characterisation of anti-Hemlibra® antibodies

In an abstract (VPB0206) from Chugai, Matsumoto N. and colleagues presented research at the 2022 ISTH Congress to characterise **Hemlibra®** anti-drug antibodies (ADA) using repository samples from Hemlibra® ADA-positive patients in phase I, I/II and bioavailability studies conducted in Japan. Neutralizing activity of ADAs against Hemlibra® was measured in ten patients who tested positive for ADAs in the clinical studies. An epitope analysis was performed in eight of these. Neutralising activity was assessed by a modified Bethesda assay using FVIII-deficient plasma spiked with Hemlibra®, and epitope analysis was assessed by an electrochemiluminescence immunoassay. This research confirmed the neutralising activity of ADAs in three out of ten ADA-positive patients. The epitopes of ADAs in these three patients included regions of the common light chain of Hemlibra® that is important to exert the pharmacological activity.

Coagulation assays in people on Hemlibra® with and without partially neutralising antibodies

During the 2022 ISTH Congress, a group of Italian researchers presented data (PB0173) on the ability of non-activated thromboelastometry (NATEM) and thrombin generation assay (TGA) to reflect the biological effect of the presence of **Hemlibra®** anti-drug antibodies (ADA).

The researchers looked at two patients with persistent partially neutralising ADA occurring after their ninth exposure and 14 patients without ADA. After six months of follow-up, the two patients with ADA and decreased Hemlibra® plasma concentration reported no bleeding. Mean Hemlibra® plasma concentration was 62.6 ug/ml in patients without ADA and 25.9 ug/ml in patients with ADA. When analysing the coagulation with global assays in ADA patients, NATEM showed a delay in clot activation but the clotting formation was sustained and within the control range. When the TGA was carried out, the lag time was not prolonged in comparison to controls, and again the endogenous thrombin potential and peak height were within control range. Authors conclude that despite decreased Hemlibra® level and prolonged activated partial thromboplastin clotting time (aPTT), the coagulation of these patients was comparable to the controls when assessed with global coagulation tests, reflecting the absence of bleedings in vivo in two patients with ADA.

Laboratory assays and Hemlibra®

During the 2022 ISTH Congress several abstracts were presented in relation to laboratory assays for Hemlibra.

In abstract PB0219, researchers led by Dargaud Y. presented a study in which they compared **different analytical conditions in order to make thrombin generation more sensitive to the procoagulant effect of Hemlibra®**. To this end they measured thrombin generation in platelet rich and platelet poor plasma samples from people with haemophilia A and inhibitors receiving Hemlibra®. Coagulation was triggered with tissue factor or FIXa and tissue factor.

They noted that thrombin generation in platelet rich plasma or the use of tissue factor in combination with FIXa with platelet poor plasma may be more appropriate for evaluating the procoagulant effect of Hemlibra® compared to tissue factor alone. The use of appropriate analytical conditions to measure thrombin generation is important because it may help to monitor the efficacy of bypassing agents or recombinant porcine FVIII in inhibitor patients on prophylaxis with Hemlibra.

A group of Italian researchers also looked (PB0224) at methods to **measure Hemlibra® levels through thrombin generation assay (TGA) in severe haemophilia A with and without inhibitors**. They tested ten patients (non-inhibitor, n=6; inhibitor, n=4) who received Hemlibra®. They observed that although there was variability among patients as regards Hemlibra® concentration and TGA, the medicine was efficacious in all. It has to be explored if variables such as inhibitors, body mass index, patients age, adherence to treatment, time period from the last infusion, influence Hemlibra® concentration and/or TGA.

A group of French researchers led by Lanais A. presented a study (PB0220) to evaluate **the reliability of the CK-Prest®, Cephasceen® and STA-PTT Automate® reagent (Stago) on the analyzer STAR MAX® (Stago) and Actin FS® (Siemens) on the analyser ATELLICA® COAG 360 (Siemens) for Hemlibra® dosing in real life conditions**. Their

research in 21 patients showed that the four techniques seem to be acceptable for the measurement of Hemlibra® on the coagulation analysers STAR MAX® (Stago) and Actin FS® (Siemens) on the analyser ATELLICA® COAG 360 (Siemens). However further studies need to confirm these findings.

A group of Argentinian researchers led by Sueldo R. presented their research (PB0229) on a **modified one-stage assay to quantify Hemlibra® in plasma**. Although this is not routinely done, it could be required to verify adherence and suspected anti-Hemlibra® antibodies.

Report from the phase I/II FRONTIER1 trial on the use of Mim8 in people with haemophilia A

During the ISTH 2022 Congress, Chowdary P. presented (OC 40.1) on the phase I/II FRONTIER1 (NCT04204408) clinical trial investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of single ascending doses of Mim8 in healthy participants and multiple ascending doses of **Mim8** in people with haemophilia A (PwHA) with or without inhibitors.

Mim8 is a subcutaneous factor IXa/X bispecific antibody in development by Novo Nordisk.

Mim8 was well tolerated following both single and multiple dosing, and no thromboembolic events or related serious adverse events were reported. No occurrences of anti-Mim8 antibodies were reported. The increases in the area under the curve (AUC) and C_{max} with increasing dose were consistent with dose-proportionality. Data from the single ascending dose section suggests that half-life was 30.4 days, and T_{max} was 9.1 days. During the 12-week observation period, 15 treated bleeds were reported in eight patients, of which 13 bleeds (nine traumatic) were observed in six patients from the lowest dose cohort. The two bleeds in patients from cohorts 2 and 3 were traumatic, thus neither treated joint nor spontaneous bleeds were observed beyond cohort 1.

Pharmacokinetic properties were consistent with dose-proportionality and support weekly and monthly dosing approaches.

Results from the phase II FRONTIER1 study on the use of Mim8 in people with haemophilia A with and without inhibitors

In an oral presentation (OC 50.5) at the 2022 ISTH Congress Windyga J. reported from the phase II FRONTIER1 (NCT04204408) clinical trial with regard to peak thrombin generation and laboratory markers in response to **Mim8** or **Hemlibra®**. Mim8 is an investigational medicinal product in development by Novo Nordisk.

In this trial, Mim8 is administered subcutaneously over 12 weeks across four multiple ascending dose cohorts, targeting average plasma exposure of 1–9 µg/ml, through dosing weekly (cohorts 1–3) or every four weeks (cohort 4); cohorts 3/4 targeted the same plasma exposure. FRONTIER1 is ongoing with a fifth ascending dose cohort. An additional cohort of patients treated with Hemlibra® was included for comparison. Thirty-two patients on Mim8 (cohorts 1 [n=7], 2 [n=9], 3 [n=8], and 4 [n=8]) and ten on Hemlibra® were included. Peak thrombin levels increased with Mim8 dose, at lower plasma concentrations than with Hemlibra®, indicating higher potency for Mim8. Mean peak thrombin levels were comparable between patients on Hemlibra® and Mim8 in cohort 2. No dose-dependent changes in D-dimer, fibrinogen, platelets, or FIXa/FX antigen levels were observed; most values remained within the normal range. A relative increase in prothrombin fragments 1 and 2, with stabilisation at steady state, was seen for both Mim8- and Hemlibra®-treated patients, in correlation with the respective thrombin peak increase.

Concomitant use of Mim8 and FVIII

During the ISTH 2022 Congress, researchers from Novo Nordisk led by Lund J. presented (PB0223) investigations to evaluate the effect of **Mim8** and FVIII over a broad range of concentrations in severe haemophilia A plasma using tissue factor and factor XIa as activators in thrombin generation tests.

Mim8 is a factor IXa/factor X bispecific antibody.

Haemophilia A patients without inhibitors treated with Mim8 may require concomitant use of factor VIII to treat

breakthrough bleeds or surgeries. Therefore, the authors evaluated the haemostatic potential of Mim8 and FVIII combined. The authors concluded that Mim8 does not affect FVIII function in haemophilia A. Thus per-label FVIII doses can be used with Mim8 treatment when necessary.

Impact of Mim8 on laboratory assays

During the 2022 ISTH, Congress Novo Nordisk presented research on the impact of Mim8 on laboratory assays.

In abstract PB0217 Fauconnier L. and colleagues describe **the effects of Mim8 on routine coagulation assays (prothrombin time test (PT) and activated partial thromboplastin clotting time (aPTT)) on one-stage and chromogenic intrinsic pathways coagulation factor assays** and thrombophilia coagulation tests using stage reagents. They conclude, as it has been described for Hemlibra®, that Mim8 interferes with aPTT and aPTT-based one-stage factor VIII, IX, XI and XII assays. Mim8 has a limited effect on PT measurement.

In abstract PB0226 Wilmot H. and colleagues investigate **the suitability of FVIII one-stage clotting assays for measuring Mim8**. They concluded that Mim8 should not be assayed against the FVIII international standard nor the Hemlibra® calibrator. For accurate measurement of Mim8, a specific reference material must be used. With this, no aPTT reagent discrepancy was observed. Therefore inter-laboratory discrepancy would be reduced.

In a third abstract (PB0218), Martineau N. and colleagues **evaluate the use of a Stago-modified one-stage assay (OSA) and chromogenic substrate assay (CSA) to determine the plasma levels of Mim8**. They conclude that a modified method using either aPTT or chromogenic reagents from Stago can be used to quantify Mim8 concentration in haemophilia plasma samples using Mim8 as reference material as a calibrator.

Rebalancing agents

There are currently several rebalancing agents being studied to treat haemophilia A. For conciseness, we have included updates on these products in the section ‘An update on novel non-factor replacement therapies for people with haemophilia A and B with or without inhibitors’ on page 42. We invite you to consult this section for further updates on these products.

Gene therapy

BioMarin granted marketing authorisation in Europe for its haemophilia A gene therapy, Roctavian™

In August, the European Commission (EC) granted conditional marketing authorisation to its haemophilia A gene therapy **Roctavian™** (valoctocogene roxaparvovec). The product is licensed for the treatment of adults with severe haemophilia A without a history of FVIII inhibitors and detectable antibodies to adeno-associated virus serotype 5.

The EC also endorsed the European Medicines Agency’s (EMA) recommendation for Roctavian™ to maintain orphan drug designation, thereby granting a ten-year period of market exclusivity. The EMA recommendation noted that, even in light of existing treatments, Roctavian™ may potentially offer a significant benefit to those affected with severe haemophilia A.

In September, BioMarin resubmitted a Biologics License Application (BLA) to the US Food and Drug Administration (FDA) for Roctavian™. The resubmission incorporates BioMarin’s response to the FDA Complete Response Letter for valoctocogene roxaparvovec issued in August 2020 and subsequent feedback, including two-year outcomes from the global GENE8-1 phase III study and supportive data from five years of follow-up from the ongoing phase I/II dose escalation study.

Interim 52-week analysis of immunogenicity to the vector capsid and transgene-expressed human FVIII in GENE8-1 study

In an abstract (FP-01.02 (1160263) presented at the 2022 WFH Congress, BioMarin reports on the clinical immunogenicity monitoring data from up to one year of follow up from GENE8-1 (NCT03370913), a phase III, single-arm, open-label study to evaluate the safety and efficacy of **Roctavian™** (valoctocogene roxaparvovec) in 134 male participants with severe

haemophilia A.

Prospective patients were required to test negative for anti-AAV5 total antibody (AAV5 TAb) utilising a bridging electrochemiluminescent (ECLA) screening assay being developed as a companion diagnostic. Additionally, all participants were required to have had at least 150 exposure days to FVIII replacement products without previous clinically detectable FVIII inhibitor development.

Immune responses to valoctocogene roxaparvovec were predominantly directed toward the AAV5 capsid, characterised by the production of anti-AAV5 binding and neutralising antibodies as well as transient AAV5 capsid-specific cellular immune responses. A moderately positive correlation between AAV5 capsid-specific IFN γ ELISpot responses and plasma levels of the liver enzyme ALT was detected, suggesting these responses may be a contributing factor to transient elevations in ALT in some participants. There was no significant association between AAV5-specific cellular immune responses and FVIII activity, and no association between FVIII-specific cellular immune response and ALT or FVIII activity was detected. There was no clinical evidence of inhibitor formation in subjects dosed with Roctavian™.

Changes in quality of life 104 weeks post infusion with Roctavian™

During the 2022 WFH Congress, BioMarin reported (FP-LB-01 (1206065) changes in health-related quality of life for men with severe haemophilia A in their phase III GENER8-1 trial (NCT03370913) looking at the safety and efficacy of Roctavian™ (valoctocogene roxaparvovec) at 104 weeks post-treatment.

Data was collected with the Haemo-QoL-A questionnaire at baseline week 52 (W) and at W104. Total and domain scores range from 0–100; higher values indicate better HRQOL. An anchor-based clinically important difference (CID) of 5.5 was used for Total Score.

For the modified intent-to-treat population (N=132), mean±standard deviation (SD) Haemo-QOL-A Total Score increased from 75.7±16.7 at baseline to 82.1±15.4 at W52 and 82.8±15.3 at W104 (Table 1). Mean±SD change from baseline was 6.3±12.0 at W52 and 7.0±12.6 (P <0.0001) at W104, exceeding the anchor-based CID of 5.5 at both time points. The domain with the greatest improvement was Consequences of Bleeding (CoB), which includes anxiety around bleeding. In the CoB domain, baseline mean±SD score was 73.6±21.7 and improved by 9.7±15.5 at W52 and 10.3±17.7 at W104 (P <0.0001). Reductions in bleeding and FVIII infusions in this study are provided for context.

Table 1. Change from baseline in mean±SD Haemo-QOL-A Total Score and domain scores in the mITT (N=132)

	Baseline	Week 52	CFB to week 52	Week 104	CFB to week 104
Total score	75.7 ± 16.7	82.1±15.4	6.3±12.0^d	82.8±15.3	7.0±12.6^e
n	130	129	127	128	126
Physical Functioning	70.3±20.8	77.5±20.7	7.2±15.3^d	75.1±20.3	4.9±13.8 ^e
n	132	130	130	129	129
Role Functioning	78.2±17.8	84.4±15.7	6.2±13.5^d	85.7±15.6	7.4±15.2^e
n	131	130	129	129	128
Consequences of Bleeding	73.6±21.7	83.1±19.1	9.7±15.5^d	83.6±18.6	10.3±17.7^e
n	132	130	130	129	129
Worry	78.4±22.7	84.2±20.2	5.8±20.1^b	85.7±20.7	6.9±19.8^c
n	131	130	129	129	128
Emotional Impact	78.1±16.5	81.1±16.7	2.9±15.5^a	81.5±18.6	3.2±14.7^a
n	131	130	129	129	128
Treatment Concern	76.2±25.4	82.7±24.5	6.3±18.5^c	84.9±22.8	8.8±20.5^d
n	130	129	127	128	126

^aP <0.05, ^bP <0.01, ^cP <0.001, ^dP <0.0001 were based on a two-sided t-test of CFB vs 0 without controlling for multiplicity.

^cP <0.0001 based on two-sided t-test of CFB vs 0 performed as part of a hierarchical testing sequence controlling overall Type 1 error. Data presented as mean ± SD. Boldface indicates that CFB had a P-value <0.05. CFB, change from baseline; Haemo-QOL-A, haemophilia-specific quality of life questionnaire for adults; mITT, modified intent-to-treat; SD, standard deviation.

Relationship between the transgene-produced FVIII and bleeding rates after two years of infusion with Roctavian™

In a late-breaking presentation (LB 01.3) at the 2022 ISTH Congress, Mahlangu J. presented an analysis of bleeding rates in participants from the phase III GENEr8-1 clinical trial to evaluate the safety and efficacy of **Roctavian™** in people with severe haemophilia A. The objective was to assess the relationship between factor VIII produced by study participants over two years following gene therapy and bleeding rates.

The phase III GENEr8-1 trial (NCT03370913) included 112 participants rolling over from a non-interventional study used to provide baseline data and 22 patients directly enrolled in the study.

A median follow-up was done for 110.9 weeks (n=134). Overall, 83 (61.9%) participants reported 450 bleeds; 39 (29.1%) participants reported 268 treated bleeds. Of treated bleeds, 56.0% were joint bleeds. In the rollover population, the proportion of participants with no bleeds, regardless of treatment, increased each year. Using data from 134 participants, the negative binomial model predicted increasing bleeds with decreasing FVIII; 1.4 (95% CI, 0.9–2.2) and 1.0 (95% CI, 0.7–1.5) treated joint bleeds/year were predicted with FVIII of 5 IU/dL per one-stage (OSA) and chromogenic assay (CSA), respectively.

Estimates of treated joint bleeding rates per FVIII activity, particularly using the one-stage assay, align with those using epidemiological data in people with haemophilia A on standard therapy, suggesting transgene-derived FVIII provides similar protection as native or exogenous FVIII.

Table. Participants in the rollover population (N = 112) with no bleeds at baseline and during each year of follow-up

	Rollover population (N = 112) ^a		
	Baseline ^b	Year 1 ^c	Year 2 ^d
Participants with no bleeds	34 (30.4)	65 (58.0)	75 (67.0)
Participants with no treated bleeds ^e	36 (32.1)	92 (82.1)	94 (83.9)
Participants with no treated joint bleeds ^e	49 (43.8)	99 (88.4)	99 (88.4)
Annualized treated joint bleeding rate, bleeds/yr			
Mean ± SD	2.8 ± 4.3	0.5 ± 2.0	0.5 ± 2.4
Median (Q1, Q3)	1.4 (0, 3.9)	0 (0, 0)	0 (0, 0)

Data are n (%), unless otherwise noted.

Vector viral biodistribution and clearance in participants from the GENEr8-1 study

During the 2022 ISTH Congress, BioMarin presented (PB0210) on the characterisation of vector DNA biodistribution and shedding following the administration of **Roctavian™**. These data come from the phase III GENEr8-1 clinical trial (NCT03370913). The median peak vector DNA levels were observed one to eight days after dosing and were highest in blood, followed by saliva, semen, stool, and urine; concentrations then declined steadily. Encapsidated vector DNA was cleared more rapidly than total vector DNA, with the maximum time to clearance ≤12 weeks in both plasma and semen. Vector genomes transitioned from initial non-contiguous forms into full-length forms over time; the fraction of inverted terminal repeat fusions, indicating formulation of circularised episomes, steadily increased. Vector DNA and vector capsids were steadily cleared from the blood and shedding matrices of people with severe haemophilia A treated with Roctavian™. The replication-incompetent nature of Roctavian™ and the rapid clearance of encapsidated vector make the risk of transmission

to untreated individuals extremely low.

ABR and zero bleed comparison in people who underwent gene therapy vs those on prophylaxis with standard replacement FVIII

During a presentation (OC 21.5) at the 2022 ISTH Congress, BioMarin presented a post hoc analysis of 112 participants who rolled over from a prospective non-interventional study into the GENER8-1 study on the efficacy and safety of **Roctavian™**, a haemophilia A gene therapy. The analysis compared bleeding outcomes among adults with severe haemophilia A treated with Roctavian™ vs prophylactic FVIII replacement therapy using propensity scoring³.

The *post hoc* analysis looked at 112 participants who rolled over into GENER8-1 (intervention cohort) compared to 73 participants in the non-interventional study. Comparable cohorts were generated and compared regarding mean annualised bleeding rate (ABR) and the proportion of participants with zero bleeds. Data showed that mean treated and all bleeds ABR were significantly lower in the intervention (i.e., gene therapy) vs control cohorts. The proportions of participants with zero treated and all bleeds was significantly higher in the intervention vs control cohorts.

Six-year follow-up data from the phase I/II clinical trial for Roctavian™

In a presentation (abstract OC 21.2) from the 2022 ISTH Congress, Laffan M. reported on the six-year post-infusion safety and efficacy of **Roctavian™** (valoctogene roxaparvovec) in patients who were enrolled in the phase I/II clinical trial (NCT02576795) to determine safety and efficacy of Roctavian in people with severe haemophilia A.

Adult males with severe haemophilia A who had previously been treated with replacement therapy received a single intravenous dose of Roctavian at 6E13 vg/kg (n=7) or 4E13 vg/kg (n=6).

One serious adverse event (AE) of a salivary gland mass occurred, but was not associated with the treatment (see EHC New Product Newsletter 2022 Vol. 1). Over the six-year follow-up, participants sustained reduction in the annualised bleeding rate (ABR). The number of patients who were bleed-free increased compared with baseline. Improvements in ABR and use of replacement FVIII were noted even in patients with low FVIII transgene expression. Twelve out of 13 participants did not require FVIII prophylaxis at year six, and patients either improved or maintained their quality of life for up to six years following treatment.

Pfizer and Sangamo Therapeutics announce the phase III trial of the investigational gene therapy giroctocogene fitelparvovec has re-opened recruitment

In a press release from September 2022, Pfizer and Sangamo Therapeutics announced that the phase III AFFINE study evaluating **giroctocogene fitelparvovec**, an investigational gene therapy for patients with moderately severe to severe haemophilia A, has re-opened recruitment.

In November 2021, the US Food and Drug Administration (FDA) placed the Pfizer/Sangamo haemophilia A gene therapy programme on clinical hold until a review of a proposed protocol amendment. This decision subsequently came to Pfizer's voluntary pausing of the study following the observation of FVIII levels greater than 150% in some trial participants.

The press release announced that trial sites were to resume enrolment in September, with dosing expected to resume in October. All trial sites are anticipated to be active by the end of 2022, and a pivotal readout is expected in the first half of 2024.

The phase III AFFINE (NCT04370054) study is an open-label, multicentre, single-arm study to evaluate the efficacy and safety of a single infusion of giroctocogene fitelparvovec in more than 60 adult (ages 18-64 years) male participants with

3) Propensity score matching (PSM) is a quasi-experimental method in which the researcher uses statistical techniques to construct an artificial control group by matching each treated unit with a non-treated unit of similar characteristics. Using these matches, the researcher can estimate the impact of an intervention. Matching is a useful method in data analysis for estimating the impact of a program or event for which it is not ethically or logistically feasible to randomize. Source World Bank.

moderately severe to severe haemophilia A. Eligible study participants will have completed at least six months of routine

FVIII prophylaxis therapy during the lead-in phase III study (NCT03587116) in order to collect pre-treatment data for efficacy and selected safety parameters.

The primary endpoint is the impact on annualised bleeding rate (ABR) through 15 months following treatment with giroctocogene fitelparvovec. This will be compared to ABR on prior FVIII prophylaxis replacement therapy. The secondary endpoints include FVIII activity level after the onset of steady-state and through 15 months following infusion of giroctocogene fitelparvovec.

The FDA granted Orphan Drug, Fast Track, and regenerative medicine advanced therapy (RMAT) designations to giroctocogene fitelparvovec, which also received Orphan Medicinal Product designation from the European Medicines Agency.

Giroctocogene fitelparvovec is being developed as part of a collaboration agreement for the global development and commercialization of gene therapies for haemophilia A between Sangamo and Pfizer.

In late 2019, Sangamo transferred the manufacturing technology and the Investigational New Drug (IND) application to Pfizer.

Recruitment is underway for phase I/II clinical trials for the use of gene therapy ASC618 in people with haemophilia A

In an abstract (PB0662) from ASC Therapeutics presented at the 2022 ISTH Congress, the company presented its prospective clinical trial to study gene therapy ASC618 in people with moderately severe to severe haemophilia A. **ASC618** is a highly potent and minimally sized vector containing a hepatic combinatorial bundle promoter, liver-specific codon optimisation, and a highly expressing bioengineered human FVIII (ET3) transgene, designed to express FVIII protein in people living with haemophilia A.

The prospective clinical study (NCT04676048) will assess the safety, tolerability and preliminary efficacy of ASC618. The decision of dose escalation vs dose expansion in each cohort will be based on FVIII levels and safety evaluations such as Liver Function Tests, enzyme-linked immunospot (ELISpot), bleeding episodes and adverse events.

Following the infusion, patients will be closely monitored for FVIII levels and ALT/AST for up to five years post-infusion. The trial is currently in phase I/II and recruiting patients in the United States.

Report on immunogenicity biomarkers of TAK-754

During the 2022 ISTH Congress, Takeda reported (PB0211) on the clinical immunogenicity biomarkers from patients treated with **TAK-754** (NCT03370172) and presented an immunogenicity transcriptomics analysis from peripheral blood.

TAK-754 is an experimental AAV8-based gene therapy using B-domain deleted FVIII-X5 variant whose clinical development programme was discontinued by Takeda.

Research into laboratory assay discrepancies for transgene-derived FVIII

Sternberg A. presented (OC 01.3) at the 2022 ISTH Congress research into **discrepancies in laboratory assay results for FVIII expression in people who have undergone gene therapy**. Namely, discrepancies in FVIII expression have been observed between the one-stage clotting assay (OSA) and the chromogenic assay (CSA). The research was conducted in mice, and researchers concluded that the OSA/CSA discrepancy is observed in humans and mice, and therefore it is not species specific.

The discrepancy was maintained in the absence of the von Willebrand factor (vWF), supporting that it is not related to interactions with vWF. Interestingly, FVIII concentration by two-stage clotting assay is higher for transgene-derived versus

recombinant FVIII, suggesting gene therapy-derived FVIIIa has enhanced function relative to rFVIII.

Psychological impact of gene therapy

An abstract from Israeli researchers at the 2022 WFH Congress presented data (FP-05.01) on the **psychological aspects of gene therapy**. To understand this, the investigators ran a questionnaire to understand the fears and concerns of patients or patients' parents regarding gene therapy use and the patients or parents' expectations of gene therapy treatment.

A total of 40 patients/caregivers (mostly with severe Haemophilia A, four with FVIII inhibitors) whose median age was 35 years (age range of patients: 0.5–73 years) answered the questions. Interestingly four patients who were already delivered gene therapy within a company-sponsored trial also provided responses. Most patients/caregivers felt that additional data regarding gene therapy would be of value to them and preferred to wait before enrolling on a currently running gene therapy trial. Half the patients stated that the existence of curative options would change their perspective regarding future family planning.

A novel accreditation system for European haemophilia treatment and gene therapy centres

In an abstract (PB1127) from EAHAD and EHC, authors led by Boban A. describe the development of a **novel accreditation system for haemophilia treatment centres dispensing gene therapy** and other novel therapies for rare bleeding disorders. This accreditation process will help haemophilia centres to improve the delivery of care by a multidisciplinary integrated, comprehensive care model and provide more equal access to all novel therapies and multidisciplinary services to all patients.

Cell therapy

Clinical trial to start for the use of cell therapy to eradicate refractory inhibitors in haemophilia A

In October, TeraImmune, Inc. announced that the US Food and Drug Administration (FDA) had granted Investigational New Drug (IND) clearance to start a phase I/IIa clinical trial to evaluate **TI-168** in congenital haemophilia A (HA) patients with refractory inhibitors.

TI-168 is a next-generation, autologous FVIII TCR-Treg cell therapy candidate to eliminate FVIII inhibitors in HA patients. The multi-centre, open-label, phase I/IIa study is designed to assess the safety and efficacy of TI-168 in up to 18 congenital HA patients with refractory inhibitors. All patients will continue to receive mandatory prophylactic Hemlibra® and standard-of-care treatment with their usual episodic agents to treat breakthrough bleeds, as needed.

The primary objectives are to evaluate the safety and feasibility of TI-168 and determine the maximum tolerated dose. The secondary objectives are to evaluate the efficacy of TI-168 and the characteristics of engrafted TI-168.

An Update on Novel Therapies for Haemophilia B

Factor replacement therapies

Report from the paradigm6 trial for the use of Refixia® in children under six years of age

In an abstract (PB0657) from the 2022 ISTH Congress, Novo Nordisk reported on the ongoing main and extension phases of paradigm6 (NCT02141074), an open-label phase III trial evaluating **Refixia®** prophylaxis in previously untreated children with haemophilia B. The study included previously untreated males aged < 6 years with haemophilia B (FIX activity level $\leq 2\%$); up to three exposure days (EDs) to FIX-containing products prior to enrolment. Patients received Refixia® 40 IU/kg once weekly (prophylaxis) with an optional on-demand or slow start-up of prophylaxis up to 24 months of age or 20 EDs, whichever came first (pre-prophylaxis). Key treatment outcomes were incidence of anti-FIX inhibitory antibodies (≥ 0.6 Bethesda units), annualised bleeding rates (ABRs), treatment consumption, haemostatic response for the treatment of bleeds, FIX trough levels, and patient adherence. In total 47 patients were in the prophylaxis arm of the study. The inhibitor incidence rate was 8%. Adherence to Refixia® prophylaxis was 96.1%. The overall haemostatic success rate was high at 96.4%. Notably, overall and spontaneous ABRs were low (medians of 0.25 and 0.00, respectively), and most bleeds (88.3%) required only one injection. Furthermore, mean FIX trough levels (15.6 IU/dL) were within the range of mild haemophilia; no patients developed target joints.

Interim results from the B-MORE study on the use of Alprolix® in a real-world setting in people with haemophilia B

In an abstract (PB1153) from the 2022 ISTH Congress, Sobi reported on the interim data for people treated with **Alprolix®** in the ongoing B-MORE study (NCT03901755). This is a prospective, multi-centre non-interventional study including patients on either prophylaxis or on-demand Alprolix® before or at the study enrolment. The study includes 117 patients (including two female patients and 60 patients aged <18 years). Interim data indicate that Alprolix® prophylaxis can provide and maintain bleed protection in people with haemophilia B, including paediatric patients. These real-world data show a median ABR close to zero on Alprolix® prophylaxis (median 0.0; 0.0-0.5; in 72 patients with prior prophylaxis) and a low factor consumption (median 47.6 IU/Kg/week; 37.6-52.3 in 104 patients regardless pre-study treatment) mainly based on a once-weekly regimen.

Results from the IDEAL study on the use of Idelvion® in people with moderate to severe haemophilia B in Italy

In an abstract (VPB1165) from the 2022 ISTH Congress, CSL Behring described the dosing frequency, consumption, efficacy and safety of **Idelvion®** during routine clinical practice in Italy in patients with moderate/severe haemophilia B on prophylaxis with Idelvion® for ≥ 6 months. This observational study lasted from March 2017 to February 2019 and followed up for two years. Data were collected from 59 male patients (median age 30.1 years) enrolled in 23 Italian centres. Of them, 50 were on prophylaxis during the entire observation period and completed the study. The infusion frequency changed from every 2-3 times/week in 86.0% of patients with previous treatment to less than once a week in 84.0% of patients treated with Idelvion® at the second-year follow-up. The annual number of infusions decreased by about 70%. However, the mean FIX activity trough level increased from 3.8% to 14.4%. A median ABR of 0.00 was achieved across all prophylaxis regimens. Subjects with zero bleeds increased with Idelvion® from 66.0 % to 78.0%. In the two-year follow-up, the rate of patients with chronic joint pain decreased from 44.0% at baseline to 16.0%, while that of patients with target joints from 30.0% to 8.0%. No safety concerns were identified and no patient developed inhibitors.

Non-replacement therapies

FVIII mimetics

In vitro clotting tests on the use of Hemlibra® in haemophilia B samples

During the 2022 ISTH Congress, Samuelson-Jones B. gave an oral presentation (OC 50.3) on the potential use of **Hemlibra®** in patients with haemophilia B presenting specific missense variants. The authors tested if FVIII mimetics can rescue the procoagulant activity of FIX variants.

To test this hypothesis, the procoagulant activity of recombinant FIX protein and patient samples were assayed by either activated partial thromboplastin time (aPTT) assay, one-stage FIX activity, thrombin generation assay (TGA), and rotational thromboelastometry (ROTEM).

The recombinant protein of high-prevalence HB-causing FIX variants with dysfunctional FIXa/FVIIIa interactions (G93S, R338P, E387K, and I397T) and severe-to-mild HB phenotypes demonstrated increased FIX activity with the addition of therapeutic amounts (300 nM) of Hemlibra®. The FIX activities of these recombinant FIX variants without Hemlibra® are comparable to the clinical data. Hemlibra® also corrected the thrombin generation of these variants. In contrast, HB-causing FIX variants with missense mutations outside FVIIIa-interacting motifs (R248Q and A390V) had no improvement in FIX activity or thrombin generation. In samples from patients with FIX-I397T, Hemlibra® normalised the aPTT-based clotting time in plasma and substantially improved the ROTEM clot time in whole blood. It is important to note that these tests were not done in humans but in human whole blood samples. The authors note that the effect of Hemlibra® is only limited to certain mutations and that, currently, it is difficult to determine how many patients could benefit from this.

Rebalancing agents

There are currently several rebalancing agents being studied to treat haemophilia B. For conciseness, we have included updates on these products in the section 'An update on novel non-factor replacement therapies for people with haemophilia A and B with or without inhibitors' on page 42. We invite you to consult this section for further updates on these products.

Gene therapy

Hemgenix® gene therapy for haemophilia B approved by the FDA

In November 2022, the US Food and Drug Administration (FDA) granted approval to **Hemgenix®** (etranacogene dezaparvovec-drlb) from UniQure/CSL Behring as a one-time gene therapy treatment for adults of 18 years of age and older living with haemophilia B. The product is licensed for patients with haemophilia B who are currently on FIX prophylaxis, have current or historical life-threatening haemorrhage, or have repeated serious spontaneous bleeding episodes.

Further updates on Hemgenix clinical trials were given at the 2022 Congress of the American Society of Hematology. We will report on these updates in the next issue of this newsletter.

EMA recommends granting conditional marketing authorisation to Hemgenix®, a gene therapy for haemophilia B

The European Medicines Agency (EMA) has recommended granting a conditional marketing authorisation for Hemgenix® (etranacogene dezaparvovec) for the treatment of severe and moderately severe haemophilia B in adults without inhibitors. The EMA recommendation is based on two prospective, open-label, single-dose, single arm studies in which 57 adult male patients with moderately severe or severe haemophilia B were enrolled. In the first study, the three patients sustained positive treatment effects up to three years following the infusion. In the second study, 52 patients sustained positive treatment effects up to two years following the infusion. It is yet unknown how long the benefits of this one-time treatment will last.

Efficacy data show that the treatment significantly reduces the frequency of bleeding compared to standard care (annualised bleeding rate reduced from 4.19 to 1.51 bleedings per year after the infusion), achieves clinically relevant levels of factor IX

activity, and minimises the need for prophylactic factor IX replacement therapy (96 % of subjects treated with Hemgenix discontinued use of routine prophylaxis).

The majority of reported adverse events were considered mild. Hepatotoxicity (liver damage), a common side effect due to immune reaction induced by these AAV-based gene therapies and characterised by an increase in the levels of liver enzymes called transaminases, has been reported with Hemgenix. The condition can be treated successfully with corticosteroids. Patients should also be monitored for infusion-related reactions. Other common side effects include headache and flu-like symptoms.

Patients treated with Hemgenix® will be followed up for 15 years, to monitor the long-term efficacy and safety of this gene therapy.

The opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorisation. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role or use of this medicine in the context of the national health system of that country.

Results from the phase I-II trial of FLT180a for gene therapy in people with haemophilia B

In July, Chowdary P. et al. published an article in the *New England Journal of Medicine* (NEJM) on the phase I-II trial (NCT03369444) to assess the safety and efficacy of varying doses of **FLT180a** in people with severe or moderately severe haemophilia B. All patients received glucocorticoids (i.e., a class of steroid hormones) with or without tacrolimus (i.e., an immunosuppressive drug) for immunosuppression to decrease the risk of the vector-related immune response. After 26 weeks, patients were enrolled in a long-term follow-up study (NCT03641703). The primary endpoints were safety and efficacy as assessed by factor IX (FIX) levels at week 26.

Ten patients received one of four FLT180a doses of vector genomes (vg) per kilogram of body weight: 3.84×10^{11} vg, 6.40×10^{11} vg, 8.32×10^{11} vg, or 1.28×10^{12} . After receiving the infusion, all the patients had dose-dependent increases in FIX levels. At a median follow-up of 27.2 months (range 19.1–42.4 months), sustained FIX activity was observed in all the patients except one, who resumed FIX prophylaxis. As of the data-cut-off date (September 20, 2021), five patients had normal FIX levels (range 51 to 78%), three patients had levels from 23 to 43%, and one had a level of 260%. Of the reported adverse events, approximately 10% were related to FLT180a and 24% to immunosuppression. Increases in liver alanine aminotransferase levels (a biomarker for liver inflammation) were the most common FLT180a-related adverse events. Late increases occurred in patients who had received prolonged tacrolimus beyond the glucocorticoid taper. A serious adverse event of arteriovenous fistula thrombosis occurred in the patient with high FIX levels above the normal range. The patient also received anticoagulation medication. These trials are funded by Freeline Therapeutics.

Freeline announces pausing investment in FLT180a clinical programme

In a financial statement released in November 2022, Freeline announced that it will stop investing in the clinical programme for **FLT180a**, an investigational gene therapy for the treatment of haemophilia B. The company is seeking a partner to bring this therapy into phase III as clinical data support continuing the development of this therapy.

Results of the phase I clinical trial for the study of gene therapy BBM-H901

In May, Belief BioMed reported in the *Lancet Haematology* data on phase I clinical trial (NCT04135300) for a novel engineered, liver-tropic adeno-associated virus vector expressing a hyperactive Padua factor IX (FIX) protein (**BBM-H901**) for the treatment of haemophilia B. The phase I study looked at the safety, factor activity and bleeding frequency.

Ten adult Chinese patients were enrolled in a single-centre, single-arm, phase I pilot trial. Participants were intravenously infused with a single dose of 5×10^{12} vector genomes (vg)/kg of BBM-H901 after one week of prophylactic prednisone treatment (1 mg/kg per day). The primary endpoints were the incidence of treatment-related adverse events, change in liver biomarkers alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and development of antibodies against vector capsid within one year of infusion. The authors report on the one-year analysis results.

After a median follow-up of 58 weeks (IQR 51·5–99·5), mean FIX:C reached mean 36·9 IU/dL (SD 20·5). No serious adverse events, no grade 3–4 adverse events were observed. Grade 1–2 adverse events related to BBM-H901 include fever (1 [10%]) and AST elevation (1 [10%]). No FIX inhibitors were observed. All participants developed antibodies against vector capsid after infusion. Two (20%) participants had an elevation of ALT and AST accompanied by a decrease of FIX:C, which remained at 7 IU/dL and 11·8 IU/dL, respectively. The authors estimated that these findings support further study.

Study on the effect of FIX Padua on laboratory assays

In an abstract (PP-LB-03) from Pfizer presented at the 2022 WFH Congress, authors led by Pittman D. presented on a small study (five plasma samples in total) to assess if the presence of FIX Padua (FIX-R338L, a high-activity variant of human FIX) in plasma provided by **fidanacogene elaparvovec** (an experimental gene therapy for haemophilia B) alters the determination of FIX activity. The authors performed this study because data emerging from clinical trials suggest that FIX activity varies between different one-stage and chromogenic assays. Patients who received fidanacogene elaparvovec may still require exogenous FIX before surgery or to treat breakthrough bleeds. The authors conclude that their study showed the FIX-R338L variant did not interfere with the detection of FIX activity from plasma-derived, recombinant, or recombinant-extended half-life FIX products added to a study participant's plasma. The details of the study can be read in the abstract.

Preliminary study on differences in FIX activity based on assay from gene therapy patients expressing FIX Padua

In another abstract from the WFH (LR-09.03) Pittman D. and colleagues showed an international multisite field study, leveraging samples from the phase I/IIa study of **fidanacogene elaparvovec** (an experimental gene therapy for haemophilia) and its long-term follow-up study to assess assay variability. This study supported prior data showing consistently higher FIX activity levels for the SynthASil assay.

Effects of growth on gene therapy mediated FIX expression in juvenile dogs

During the 2022 ISTH Congress, authors from Pfizer presented (OC 21.4) a small study on **the effects of growth on FIX levels in male juvenile haemophilia B dogs following gene therapy**. The human liver doubles in mass at 8-9 months from birth and again by 3-4 years. It is hypothesised that liver growth and expanding blood volume may reduce FIX levels in paediatric recipients of haemophilia B (HB) gene therapy, based on the current AAV viral vectors. HB dogs exhibit a similar phenotype and have proven to be highly predictive of the human experience with gene therapy. HB dogs with severe spontaneous bleeding can be monitored post-gene therapy to assess the effect of normal growth on FIX transgene levels and bleeding phenotype.

Researchers gave gene therapy to twelve HB dogs at age three or six months to model two-to-six-year- or six-to-12-year- old children, respectively. Dogs were followed for ≥12 months, during a period of liver growth and blood volume expansion. Treatment was well tolerated. To date, no spontaneous bleeds have occurred post-treatment. Increasing vector dose was associated with progressive shortening of clotting times. Laboratory tests indicated FIX activity.

An Update on Non-Replacement Therapies for People with Haemophilia A and B with and without Inhibitors

Bypassing agents

Cevenfacta® licensed by the European Commission

In July 2022, following the positive opinion from the European Medicines Agency (EMA) Committee for Human Medicinal Products (CHMP), the European Commission granted marketing authorisation to **Cevenfacta®**, a recombinant activated factor VII. Cevenfacta® is indicated in adults and adolescents (aged 12 and above) for the treatment of bleeding episodes and prevention of bleeding in those undergoing surgery or invasive procedures in people with congenital haemophilia A or B and inhibitors.

LFB presents plans for phase IV study for the use of Cevenfacta® in people with inhibitors on Hemlibra

In an abstract (VPB 1189) presented at the 2022 ISTH Congress, the American Thrombosis and Hemostasis Network (ATHN) with support from LFB presented a phase IV study design to evaluate the safety of **Cevenfacta®** (US brand name Sevenfact®, a recombinant activated factor VII) to treat breakthrough bleeds in people on Hemlibra®. ATHN 16 (NCT04647227) will be rolled out in the United States across 22 participating sites. It will enrol people with haemophilia A or B with inhibitors aged 12 to 65 years.

Results from the PERSEPT 1 trial looking at efficacy and safety of Cevenfacta® in people with inhibitors

During the 2022 ISTH Congress, a group of researchers led by Windyga J. presented an abstract (PB1188) evaluating **Cevenfacta®**'s safety and efficacy for treating spontaneous versus traumatic bleeding episodes in people with haemophilia A or B and inhibitors (PwHABI). Cevenfacta® is a licensed medicinal product manufactured by LFB.

The PERSEPT 1 trial is a randomised, cross-over, phase III trial (NCT02020369) in which PwHABI aged ≥ 12 -75 years received Cevenfacta® for treatment of bleeding episodes using an initial dose regimen (IDR) of either 75 or 225µg/kg followed by 75µg/kg at predefined intervals over 24 hours. The primary endpoint, per EMA definition, was the proportion of successfully treated bleeding episodes (BEs; i.e., 'good'/'excellent' response), irrespective of BE severity, 12 hours after the initial dose.

Among the 27 patients in PERSEPT 1, 27 had spontaneous BEs (197 BEs treated with 75µg/kg IDR and 184 BEs treated with 225µg/kg IDR), and 21 had traumatic BEs (53 BEs treated with 75µg/kg IDR and 32 BEs treated with 225µg/kg IDR). A similarly high proportion of spontaneous and traumatic BEs achieved successful resolution at 12 (95.8% and 100% respectively) and 24 hours (99.4% and 100% respectively). Two patients experienced seven treatment-related adverse events [infusion site discomfort (n=4), infusion site haematoma (n=2) and body temperature increase (n=1)] during two spontaneous and three traumatic BEs. There were no thromboembolic events, hypersensitivity reactions, or deaths; no neutralising antibodies to Cevenfacta® were detected.

Efficacy of Cevenfacta® to treat bleeding episodes in people with inhibitors: Results from the PERSEPT 1 study

In abstract PB1174, Hart D. and colleagues reported on the efficacy of **Cevenfacta®** to treat bleeding episodes (BE) according to low (<5BU) or high (≥ 5 BU) inhibitor titres. The analysis came from the PERSEPT 1 study. This is a phase III study sponsored by LFB in people with haemophilia A or B and inhibitors aged ≥ 12 years.

Twenty-seven patients with 468 BEs were analysed (low-titre subgroup, 218 BEs; high-titre subgroup, 250 BEs). The proportion (95%CI) of successfully treated BEs at 12 hours with 75 and 225µg/kg initial dose regimens (IDRs), respectively, was 75.2% (63.6–86.8) versus 87.1% (79.8–94.5) in the low-titre subgroup ($p=0.006$), and 94.6% (88.2–100) versus 100% (100–100) in the high-titre subgroup ($p=0.034$). Corresponding results at 24 hours were 96.4% (91.5–100) versus 99.0% (97.1–100) in the low-titre subgroup ($p=0.118$) and 96.9% (92.4–100) versus 100% (100–100) in the high-titre subgroup ($p=0.125$). Two patients in the low-titre subgroup experienced seven treatment-related adverse events (infusion site discomfort

[n=4]; infusion site haematoma [n=2]; body temperature increase [n=1]). None occurred in the high-titre subgroup. No thromboembolic events, hypersensitivity reactions, or deaths were reported. No Cevenfacta® neutralising antibodies were detected.

Report on the phase III Crimson 1 trial (trial halted in November 2021 due to the pandemic)

During the 2022 ISTH Congress, Rangarajan S. presented (OC 40.5) on the Crimson 1 phase III study to investigate the safety and efficacy of **marzeptacog alfa** (activated - MarzAA) for on-demand treatment of bleeds events in people with haemophilia A or B and inhibitors. MarzAA is an activated FVII developed for subcutaneous administration. Unfortunately, the study was terminated due to the pandemic, which impacted patient recruitment and Catalyst Biosciences discontinued its clinical programme, also citing issues with trial completion, the competition for trial participants, and the increasing availability of prophylaxis globally.

Nonetheless, the results of the trial were presented. At the time of the trial halt, 18 subjects had been randomised and enrolled, with an observation of 74 eligible bleeds (30 and 44 bleeds in eight and 11 subjects treated with MarzAA and standard of care, respectively). The proportion of effective treatment at 24 hours post-initial dose was 86.2% versus 86.5% for subjects treated with MarzAA versus standard of care, respectively. One subject treated with standard of care reported a serious adverse event of ureterolithiasis (i.e. kidney stones) unrelated to treatment. No thromboembolic events were reported. One subject treated with MarzAA was found to have low-titer cross-reactive anti-drug antibodies (ADAs) with neutralising antibody assessments pending.

Rebalancing agents

An update on the results of the ATLAS-PPX study for people who have switched to fitusiran from prophylaxis

During a late-breaking presentation at the 2022 ISTH Congress, Kenet G. presented abstract LB 01.1 on the results of the phase III ATLAS-PPX looking at the efficacy and safety of **fitusiran** versus prior factor or bypassing agents (BPA) prophylaxis in people with haemophilia A or B with or without inhibitors.

Fitusiran is a subcutaneous (SQ) investigational siRNA therapeutic that targets antithrombin to rebalance haemostasis in people with haemophilia A or B, irrespective of their inhibitor status.

During ATLAS-PPX, participants continued factor or bypassing agents (BPA) prophylaxis (for six months) before switching to once-monthly 80 mg SQ fitusiran prophylaxis (for seven months; one month onset period and six months efficacy period). The primary endpoint was annualised bleeding rates (ABR) in the factor/BPA prophylaxis period (day -168 to day -1) and fitusiran efficacy period (day 29 to day 190). The secondary endpoints included spontaneous ABR (AsBR), joint ABR (AjBR), and health-related quality of life (HRQoL). Safety and tolerability were also assessed.

Of 80 enrolled participants, 65 (inhibitor/non-inhibitor, n=19/46; haemophilia A/haemophilia B, n=50/15) were eligible for ABR analyses. The median observed (IQR) ABRs (based on statistical models) were 4.4 (2.2; 10.9) with factor/BPA and 0.0 (0.0; 2.3) with fitusiran prophylaxis. These data were for HA/HB patients without inhibitors. Forty-one participants (63.1%) experienced zero-treated bleeds with fitusiran. Fitusiran achieved statistically significant reductions in estimated ABR, AsBR and AjBR versus factor/BPA prophylaxis. Fitusiran improved HRQoL versus factor/BPA as measured by Haem-A-QOL total score (LS mean difference -4.6 [95% CI: -7.6; -1.5; p< 0.01]). Serious adverse events (SAEs) occurred in 5/65 participants (7.7%) with factor/BPA and 9/67 (13.4%) with fitusiran prophylaxis. In the fitusiran prophylaxis period, two participants (3.0%) experienced suspected or confirmed thromboembolic events. One of the participants reported a cerebral vascular event and stopped participation in the study. This patient had a history of deep-vein thrombosis and cardiovascular disease that he did not disclose to investigators prior to enrolment in the study. One participant experienced a suspected thrombosis of the papilla of the eye; the AE resolved, and the participant stayed in the study, although he did not participate in the extension study. Seventeen participants (25%) experienced increased ALT and AST in some doses. This is only considered significant if it reaches three times the upper normal limit. This was achieved by 3% of the study participants. ALT and AST elevation was resolved in some patients by withholding a dose of fitusiran, while in others, they continued their normal regimen (without withholding the therapy). These were not sustained and resolved within a median

time of two to three months. All participants with ALT and AST elevation remained in the study. As previously reported in this newsletter, five participants experienced cholecystitis (i.e., an inflammation of the gallbladder) and five experienced cholelithiasis (a gallstone). Kenet G. explained that the mechanisms behind these adverse events are still being evaluated and currently remain unknown. During the ISTH presentation Q&A, a member of the audience noted that the study population age was quite young (the mean SD age for the inhibitor population was 27.8 years and the mean SD age of the non-inhibitor population was 23.5 years of age) and asked the presenter whether she had concerns of administering this product to older patients and Kenet G. replied that, indeed, she would have concerns in patients with an increased risk of cardiovascular problems (such as older people with bleeding disorders). She emphasised that more data were needed.

Management of breakthrough bleeds in people on fitusiran: Analysis of two phase III studies

During the 2022 ISTH Congress, Srivastava A. presented (OC 40.3) on two randomised, open-label, phase III trials (NCT03417102 and NCT03417245), which enrolled males ≥ 12 years with severe haemophilia A/B with inhibitors (ATLAS-INH) and without (ATLAS-A/B). Eligible participants were randomised 2:1 to once-monthly 80 mg subcutaneous **fitusiran** or on-demand BPA (ATLAS-INH) or CFC (ATLAS-A/B) for nine months. Annualised weight-adjusted BPA/CFC consumption, numbers of treated bleeds and infusions per bleed were assessed.

Overall, 118 participants were randomised to fitusiran, 19 to on-demand BPA and 40 to on-demand CFC. The total consumption of activated prothrombin complex (aPCC) and rFVIIa was 97.5% and 98.2% lower in the fitusiran arm vs the on-demand BPA arm. Overall, the mean consumption of FVIII and FIX was lower in the fitusiran arm vs the on-demand CFC arm (95.9% and 94.7%, respectively). The total number of treated bleeds was lower in the fitusiran arm vs the on-demand BPA and CFC arms by 82.0% and 79.2%, respectively. In ATLAS-INH, participants who received fitusiran required fewer mean injections (1.2 vs 3.7) and lower mean BPA doses per bleed vs participants who received on-demand BPA. In ATLAS-A/B, participants in both arms required a mean of 1.2 injections per bleed. Participants who received fitusiran required lower mean CFC doses vs participants who received on-demand CFC.

From these data, we note that fitusiran prophylaxis reduced total BPA/CFC consumption by reducing the number of treated bleeds, injections and BPA/CFC doses required to treat breakthrough bleeds in PwHA/B with and without inhibitors, by ~95% or more thereby reducing treatment burden.

Report from the phase III analysis of ATLAS A/B on the study of fitusiran in people with haemophilia A or B without inhibitors

In an oral communication (OC 50.2) presented at the 2022 ISTH Congress, Pipe S. presented the analysis of phase III, multinational, randomised, open-label study ATLAS A/B (NCT03417245) on the use of **fitusiran** in males aged 12 or above with severe haemophilia A or B without inhibitors who were previously treated on-demand.

The objective of the study was to assess the changes in antithrombin levels and thrombin generation over time in the patient cohort described above. Participants were randomised 2:1 to receive once-monthly 80 mg of subcutaneous fitusiran prophylaxis (fitusiran arm) or on-demand (OD) factor concentrate for nine months. The primary endpoint was annualised bleeding rate. Exploratory endpoints included changes in antithrombin levels and mean peak height assessed by thrombin generation over time.

Overall, 120 participants were randomised. Seventy-nine (98.8%) in the fitusiran arm and 37 (92.5%) in the OD arm completed the study. On day 15, there was a 71.6% mean reduction from baseline in antithrombin levels in the fitusiran arm, with a further reduction to 79.8% on day 29 and maintained at 85.3%–88.6% from day 43 onwards. There was a mean increase in thrombin generation of 17.1 nM from baseline in the fitusiran arm on day 15, increasing to 24.4 nM on day 29 and maintained at 29.8.1–43.1 nM from day 43 onwards. These results corresponded with an 89.9% reduction in estimated ABR with fitusiran vs OD factor concentrates.

Pipe S. also presented the revised dose and dose regimen targeting antithrombin range from 15-35% to reduce the risk of vascular thrombotic events. The regimen was modified based on the mode of action of fitusiran and observation of antithrombin levels lower than 10% in participants with reported vascular thrombotic events in the fitusiran clinical

development programme. Data suggests that the risk of serious vascular thrombotic events may be greater with antithrombin levels lower than 10%, therefore a lower antithrombin threshold of 15% was selected. In addition, antithrombin levels lower than 25% may lead to a desirable ABR and therefore an upper antithrombin threshold of 35% was chosen based on fitusiran efficacy data.

In the revised dose regimen, participants will be started on fitusiran 50mg every two months.

- Participants are eligible for dose escalation if: at least four doses of fitusiran have been administered at the current dose level, and they experienced at least two pre-dose antithrombin activity levels >35% (as per central laboratory) after their second dose at the current dose, and fitusiran administration and antithrombin activity assessments occurred as per schedule at the current dose level. In this case participants are moved to a regimen of monthly 50mg of fitusiran.
 - If, following the regimen change described above, participants continue to experience at least two pre-dose antithrombin activity levels >35% (as per central laboratory) after their second dose at the current dose, and fitusiran administration and antithrombin activity assessments occurred as per schedule at the current dose level. In this case participants are moved to a regimen of monthly 80mg of fitusiran.
- If participants experience one antithrombin activity level of <15% then they are moved to a regimen of 20mg of fitusiran every two months.
 - If, at this dose regimen, they experience at least two pre-dose antithrombin activity levels >35% (as per central laboratory) after their second dose at the current dose, and fitusiran administration and antithrombin activity assessments occurred as per schedule at the current dose level. In this case participants are moved to a regimen of monthly 20mg of fitusiran.
 - If, on the other hand, they experience one antithrombin level below 15%, they are discontinued from the clinical programme.

Start of dosing after de-escalation from higher dose is to occur only after centrally measured antithrombin levels $\geq 22\%$. Participants receiving fitusiran at a dose of 20 mg every two months who experience ≥ 1 antithrombin activity level <15% (as per central laboratory) within a 12-month period must permanently discontinue fitusiran treatment. Participants previously escalated to a dose of monthly 20mg, 50mg or 80mg due to antithrombin >35% who experience >1 antithrombin activity level <15% within a 12-month period must either permanently discontinue fitusiran prophylaxis, or in consultation with the Study Medical Manager may have the option to be de-escalated to their prior dose level.

Dose escalation despite an antithrombin level $\leq 35\%$ may be considered if, at the current dose level:

- ≥ 2 doses of fitusiran have been administered, and
- The investigator judges suboptimal bleeding control (≥ 2 bleeds treated with CFC or BPA within a 12-week period).

However, participants with monthly dosing bleeding episodes during the first eight weeks at the current dose level or every two months dosing bleeding episodes during the first 12 weeks at the current dose level will not be considered for this judgement.

Quality of life with fitusiran in the ATLAS A/B trial

In a poster presented during the 2022 WFH Congress, Kavakli K. presented on the results of the phase III ATLAS-A/B trial with regard to health-related quality of life in people with haemophilia A or B without inhibitors either on **fitusiran** prophylaxis or on on-demand replacement therapy. Fitusiran is an investigational product in development by Sanofi. One hundred and twenty male patients aged 12 or older with severe haemophilia A or B without inhibitors and having six or more bleeding episodes treated with coagulation factor concentrate within the six months prior to enrolment were included in the trial. The trial consisted of two arms, a fitusiran prophylaxis where participants received fitusiran 80mg monthly (n=80; HA, n=62; HB, n=18) or an arm where 40 participants received on-demand treatment with coagulation factor concentrates. The

primary endpoints was ABR and secondary endpoints were total score and physical health domain scores of the Haem-A-QoL.

A total of 79 people with haemophilia A and B completed the fitusiran arm for an exposure of 8.09 months. A total of 40 (50.6%) participants in the fitusiran arm had zero treated bleeds compared with 2 (5%) in the on-demand arm. Eight out of ten domains in the Haem-A-QoL questionnaire favoured fitusiran prophylaxis.

Analysis of antithrombin levels in people with inhibitors on fitusiran – Results from the phase III ATLAS-INH

In an abstract (PB1152) presented at the 2022 ISTH Congress, Sanofi presented a longitudinal assessment of changes over time in antithrombin activity levels and thrombin generation in people with haemophilia A or B with inhibitors (PwHI) with **fitusiran** prophylaxis to prevent bleeding. These data came from an analysis of the phase III ATLAS-INH (NCT03417102), including males aged ≥ 12 years with severe haemophilia A or B with inhibitors, previously treated on-demand with bypassing agents (BPA). Participants were randomized 2:1 to receive once-monthly 80 mg subcutaneous fitusiran prophylaxis (fitusiran arm) or on-demand BPA (BPA arm) for nine months. The primary endpoint was annualised bleeding rate (ABR). Exploratory endpoints included changes in antithrombin levels and thrombin generation over time.

Overall, 60 participants were included in the exploratory analysis. On day 15, there was a 76.8% mean reduction from baseline in antithrombin activity levels in the fitusiran arm, with a further reduction to 84.1% on day 29 and maintained at 87.6%–89.9% from day 43 onwards. There was a mean increase in peak thrombin generation of 21.9 nM from baseline in the fitusiran arm on day 15, with a further increase to 30.8 nM on day 29 and maintained at 36.8–47.5 nM from day 43 onwards. These results translated into a 90.8% reduction in estimated ABR with fitusiran prophylaxis vs on-demand BPA.

Results from the phase III explorer7 trial on the use of concizumab in patients with haemophilia A and B and inhibitors

During a late-breaking presentation (LB 01.2) at the 2022 ISTH Congress, Jiménez Yuste V. presented the results from phase III explorer7 (NCT04083781). **Concizumab** is an anti-tissue factor pathway inhibitor (TFPI) antibody in development by Novo Nordisk for the treatment of people with haemophilia A and B. Explorer7 assessed the efficacy and safety of concizumab in people with haemophilia A/B and inhibitors.

Patients in the trial (133 enrolled) were randomised 1:2 to no prophylaxis (arm 1, n=19) or daily concizumab prophylaxis (arm 2, n=33). These two arms contributed towards the primary analysis for efficacy by comparing the number of treated spontaneous and traumatic bleeding episodes between arms 1 and 2. These patients were also included in the secondary analysis for safety, patient-reported outcomes (PROs), pharmacokinetics (PK) and pharmacodynamics (PD). Another 81 patients were assigned to concizumab in arms 3 and 4, and contributed to the secondary analysis (safety, etc.).

Of the 19 assigned to arm 1, four withdrew, and one died due to pneumonia. After 24 weeks, another patient withdrew. In arm 2, four did not restart, and one died due to a road traffic accident. After 32 weeks, another patient died of COVID-19. Investigators found no relation between COVID-19 and concizumab, as when the patient was infected, he stopped the treatment and had very low concizumab activity at the time of death.

The estimated mean annualised bleeding rate (ABR) was 1.7 (95% CI, 1.0–2.9) for concizumab versus 11.8 (95% CI, 7.0–19.9) for no prophylaxis (ABR ratio, 0.14 [95% CI, 0.07–0.29]; $P < 0.001$). The median ABR on concizumab was 0. Twenty-one (63.6%) concizumab patients had zero treated bleeds at 24 weeks (including those who discontinued before 24 weeks) versus two (10.5%) on no prophylaxis. No thromboembolic events were reported after the treatment restart. Positive trends were observed across 36-Item Short-Form Health Survey (SF-36v2) domains with concizumab. There was no significant difference between the two randomised arms for key secondary endpoints such as bodily pain and physical functioning. Concizumab exposure was stable over time.

As a reminder, the concizumab trial had to be paused due to a non-fatal renal infarct.

Results from the phase II explorer4 & 5 clinical trials on the treatment burden in people with and without inhibitors with concizumab

During the 2022 ISTH Congress, Mancuso M.E. presented (OC 30.3) the results of the explorer4 and 5 studies. Explorer4 was a phase II clinical trial assessing the impact of **concizumab** subcutaneous prophylaxis on treatment burden in people with haemophilia A and B with inhibitors. Explorer5 was a phase II clinical trial assessing daily concizumab prophylaxis in patients with severe haemophilia A without inhibitors. The objective of the studies was to assess the impact of concizumab subcutaneous prophylaxis on treatment burden through the Hemophilia-Treatment Experience Measure (Hemo-TEM) questionnaire.

Twenty-five and 29 patients completed explorer4 and 5, respectively. In explorer4, mean baseline Hemo-TEM total scores were similar between concizumab (25.0) and on-demand arms (26.2). After 24 weeks of treatment, the concizumab arm demonstrated a change from baseline in mean Hemo-TEM total score of -15.3, indicating a lower treatment burden versus baseline, with no change in the on-demand arm. Similarly, the change in mean Hemo-TEM total score from baseline (21.9) was -12.8 for patients in explorer5 after 24 weeks. Improved scores were observed for all Hemo-TEM domains, with sustained improvements at the last observational visit in both trials.

Results from the phase Ib/II trial for the use of marstacimab in people with haemophilia A or B with or without inhibitors

In an article published in the *British Journal of Haematology* in August 2022, authors, led by Mahlangu J., presented the results of the phase Ib/II study (NCT02974855) on the use of **marstacimab**, a human monoclonal antibody targeting tissue factor pathway inhibitor (TFPI), in people with haemophilia A or B, with or without inhibitors. This product is in development by Pfizer.

Participants assigned to four cohorts received escalating weekly doses based on inhibitor status (without inhibitors: 300 mg, a single 300-mg loading dose with subsequent 150-mg doses, or 450 mg; with inhibitors: 300 mg). Safety outcomes were treatment-emergent adverse events (TEAEs), injection site reactions, and clinical and laboratory parameter changes.

The authors assessed efficacy by looking at annualised bleeding rates (ABRs). Pharmacokinetics and pharmacodynamics (PD) were also evaluated.

Among 26 treated participants were: HA without inhibitor, n=16 (61.5%); HA with inhibitor, n=7 (26.9%); and HB, n=3 (11.5%). Twenty-four participants completed the study. Overall, 80.8% experienced TEAEs. ABR during treatment was significantly reduced versus an external on-demand control group ($p < 0.0001$) and versus pre-treatment ABR ($p < 0.0001$), with significant reductions observed across all dose cohorts. Marstacimab exposure generally increased in a dose-related manner, with steady-state concentration reached by day 57. Changes in PD biomarkers occurred across all dose cohorts. Fifty-six adverse events were reported in 21 (80.8%) participants. The most common were injection site pain, injection site swelling and hypertension. Four (15.4%) participants experienced serious adverse events (appendicitis, physical assault, cholelithiasis, i.e. gallstones in the gallbladder, and tooth socket haemorrhage), but none were treatment-related. No thrombotic events occurred.

Marstacimab was well tolerated and had an acceptable safety profile. Clinically meaningful reductions in ABR and treatment-related changes for all PD biomarkers indicated effective targeting of TFPI.

Phase II study results on safety and efficacy of marstacimab

In an article published in October 2022 in the *British Journal of Haematology*, authors led by Mahlangu J. presented the findings from the phase II clinical trial (NCT03363321) looking at long-term safety and efficacy for the use of **marstacimab** in people with haemophilia. This is an investigational human monoclonal antibody targeting tissue factor pathway inhibitor.

This multicentre, open-label study investigated the safety, tolerability, and efficacy of long-term weekly prophylactic marstacimab treatment in participants with severe haemophilia A and B, with or without inhibitors. Adult participants were enrolled from a previous phase Ib/II study or *de novo* and assigned to one of two subcutaneous (SC) marstacimab doses:

once-weekly 300 mg or a 300-mg loading dose followed by once-weekly 150-mg doses, for up to 365 days. The study endpoints included safety assessments and annualised bleeding rates (ABRs). Of the 20 enrolled participants, 18 completed the study. Overall, 70% of participants had treatment-emergent adverse events, including injection site reactions, injection site haematoma, and haemarthrosis. No treatment-related serious adverse events or thrombotic events occurred. Across all treatment cohorts, the mean on-study ABR ranged from 0 to 3.6 bleeding episodes/participant/year (median ranged from 0 to 2.5), compared with a mean pre-treatment ABR of 14.0 to 22.0 bleeding episodes/participant/year (median ranged from 14.0 to 20.0). No treatment-induced anti-drug antibodies were detected. Once-weekly SC marstacimab prophylaxis was well tolerated, with an acceptable safety profile, and maintained long-term efficacy for up to 365 days.

Pfizer announces clinical programme for the study of marstacimab in children

In November, Pfizer announced a new clinical trial on the study of **marstacimab** in paediatric patients with haemophilia A or B (BASIS KIDS - NCT05611801). The trial is not yet recruiting. This study will enrol participants aged one to 17 in a sequential opening enrolment to older children and progressively moving to younger patients. Primary outcome measures will be annualised bleeding rates of treated bleeding events, incidence of adverse events and serious adverse events. Secondary outcomes will look at the impact on quality of life.

SerpinPC granted Orphan Drug Designation for haemophilia B by the FDA

In a press release from September 2022, Centessa Pharmaceuticals announced that the US Food and Drug Administration had granted Orphan Drug Designation to **SerpinPC**, a novel inhibitor of activated protein C for the treatment of haemophilia B. The treatment is currently in phase I/IIa trial for the evaluation of its safety, tolerability and pharmacological properties.

An Update on Novel Therapies for Von Willebrand and Other Rare Bleeding Disorders

Non-replacement therapies

Data from the phase II trial on the use of BT200 in people with type 2B von Willebrand Disease

In an article published in September in *Blood Advances*, Ay C. and colleagues described a prospective phase II trial (NCT04677803) on the potential benefits of **rondoroptivon pegol (BT200)** in patients with type 2B von Willebrand Disease (vWD). BT200 is a pegylated aptamer binding to the A1 domain of VWF with a novel mechanism of action: it enhances VWF/factor VIII (FVIII) levels by decreasing their clearance.

Patients with type 2B VWD received 3 mg BT200 subcutaneously on study days one, four, and seven, followed by six to nine mg every week until day 28. The study included five patients (male: female ratio = 3:2). BT200 rapidly tripled platelet counts from a median of 60 to $179 \times 10^9/L$ ($P < .001$). Circulating von Willebrand factor (vWF) antigen increased from a median of 64% to 143%, which doubled FVIII activity levels from 67% to 134%. In all thrombocytopenic patients, plasma levels of VWF:GPIbM (a laboratory assay using gain-of-function glycoprotein Ib without ristocetin) normalised, VWF ristocetin cofactor and VWF collagen-binding activity increased, and high molecular weight multimers appeared. These improvements reversed during the washout of the drug, thus demonstrating causality. The A1 domain binding aptamer directly corrects the underlying defect of type 2B VWD, thus providing a novel potential option for prophylaxis and treating patients with this VWD type. These data provide the basis for a phase IIb/III trial in such patients.

In vitro research into the use of Hemlibra® for the treatment of von Willebrand Disease

In an abstract (PB0816) from Roche presented at the 2022 ISTH Congress, Locke M. and colleagues reported on an *in vitro* investigation on the efficacy and mechanisms by which **Hemlibra®** promotes haemostatic activity in people with haemophilia A and von Willebrand Disease. Efficacy and Mode of Action (MoA) data were generated in multiple lots of HA and VWD patient plasmas and reconstituted blood using platelet aggregation/activation assays, thrombin generation (TG) assays and fibrinolysis assays. Hemlibra® had no effect on platelet activation or aggregation but promoted TG in HA and VWD type 3 plasmas. Higher baseline TG was measured in reconstituted VWD type 2N plasmas (5-40% residual FVIII) compared to type 3 plasma, which increased a further 2.4 to 3.3-fold by adding 50 ug/ml Hemlibra®. In tissue plasminogen activator (tPA)-induced fibrinolysis assays, Hemlibra® promoted surprisingly high anti-fibrinolytic activity in VWD type 3 and HA samples (2.2 and 1.6-fold extension to clot lysis times, respectively) compared to the anti-fibrinolytic activity of FVIII.

In conclusion, Roche's preliminary data suggest that Hemlibra® promotes higher TG in VWD type 2N plasma when compared to HA and type 3 plasmas. Overall, these data support the notion of Hemlibra® efficacy in VWD type 2N and 3 patients and provide early insight into its MoA.

Hemlibra® use in VWD – results from mice models

A group of French researchers led by Mc Cuskey G. presented (PB0817) at the 2022 ISTH Congress results from an assessment of the effects of **Hemlibra®** on the bleeding profile of a von Willebrand Disease (VWD) mouse model following reports of the successful off-label use of Hemlibra® in people with type 3 VWD. The authors applied a tail-vein-transection (TVT) bleeding assay to mouse models of VWD-type 3 and VWD-type 2A. Hemlibra® was administered in conjunction with human factors IX and X or FVIII. The authors concluded that, as observed in patients, Hemlibra® improved the bleeding phenotypes in a mouse model of VWD type 3, suggesting that Hemlibra® assists in restoring primary clot formation in the absence of VWF. However, no amelioration was observed in VWD type 2A mice, suggesting that degraded VWF, even at low concentrations, has a negative effect on clot formation in a TVT bleeding model. These pre-clinical findings need to be viewed with caution.

Pre-clinical data on the therapeutic potential of HMB-001 in Glanzmann Thrombasthenia and haemophilia A.

During the 2022 ISTH Congress, researchers led by Ostergaard H. presented pre-clinical data (OC 78.3) on the therapeutic potential of **HMB-001** in Glanzmann Thrombasthenia (G Thromb), and haemophilia A. HMB-001 is a bispecific antibody that binds and accumulates endogenous FVIIa in circulation. Upon vessel injury, HMB-001 promotes local FX activation and thrombin generation by placing FVIIa on the surface of activated platelets via binding to the TREM-like transcript 1 (TLT-1) receptor. The activity of HMB-001 thus builds on the mechanism of action (MoA) of recombinant FVIIa (rFVIIa) and can potentially prevent bleeds in multiple haemostatic disorders, of which G Thromb is the primary focus. Multiple-dose subcutaneous administration of HMB-001 in cynomolgus monkeys resulted in the accumulation of endogenous FVIIa to low nM levels. Upon supplementation of corresponding levels of rFVIIa to ex vivo models of G Thromb and HA, HMB-001 was shown to potentiate the activity of FVIIa by 6-14-fold in a TLT-1 dependent manner reaching activity levels in the therapeutic range by comparison to rFVIIa. A similar enhancement of the haemostatic activity of FVIIa by HMB-001 was demonstrated in the mouse TVT injury model upon co-administration of rFVIIa and HMB-001. It is important to note that this bispecific antibody has not yet been tested in humans. HMB-001 is an investigational product in development by Hemab.

Pre-clinical results of the use of HMB-001 for the treatment of Glanzmann Thrombasthenia

During the 2022 ISTH Congress, researchers led by Zikovic M. presented pre-clinical data (PB0719) on the potentiation of FVIIa activity by **HMB-001** on platelets in Glanzmann Thrombasthenia (G Thromb). The authors determined with *in vitro* studies that HMB-001 potentiates FVIIa-dependent formation on platelets in G Thromb. HMB-001 is an investigational medicinal product in development by Hemab.

First patient dosed with HMB-001

In January 2023 Hemab announced in a press release that the first patient was dosed in the phase I/II of the **HMB-001** study to treat Glanzmann Thrombasthenia.

Research into repurposing of existing medicines to treat FVII deficiency

In an abstract (PB0700) from the 2022 ISTH Congress, Norwegian researchers led by Andresen M. presented the results of their investigation into the dose-response effect of FDA-approved medicines **abexinostat** and **tyloxapol** in plasma from people with factor VII deficiency. They screened >1500 FDA-approved drugs and identified the orally available histone deacetylase inhibitor abexinostat (an investigational medicine for cancer) and the inhaled surfactant tyloxapol as enhancers of FVII p.Q160R variant activity. They then tested them in the patient's plasma in an *in vitro* pilot study. The authors note that these results showed that treatment with the FDA-approved drugs abexinostat and tyloxapol increased FVII activity by about 20% in the patient's plasma *ex vivo*. It is important that a modest increase in FVII activity can ameliorate the bleeding phenotype in patients. This proof-of-concept study demonstrates that drug repurposing may be feasible for the novel treatment of FVII deficiency. Further research will need to be carried out to validate this hypothesis and preliminary results.

Gene therapy

Pre-clinical data on gene therapy in VWD

A group of Dutch researchers led by Bär I. presented at the 2022 ISTH Congress a study (PB0805) to set a ground for personalised gene therapy in von Willebrand Disease (VWD) by developing CRISPR/Cas9 gene correction methods in VWD using patient derived endothelial colony forming cells (ECFCs). The Willebrand in the Netherlands (WiN) cohort study characterised >800 VWD patients. ECFCs were isolated from venous blood of selected VWD patients who enrolled in the BOEC-MK study. VWD mutations will be corrected using a Cas9-based cytosine base editor in conjunction with specific guide RNAs directed against the site of mutation. Single cell sorted ECFCs will be clonally expanded and will be evaluated for rescue of the disease phenotype. Correction of the mutation will be confirmed using DNA sequencing. A panel of causative VWF mutations has been selected for gene correction. Corresponding patient ECFCs have been isolated and their baseline disease phenotypes are being characterised using morphological and biochemical assays. ECFCs are currently being immortalised to overcome their limited proliferation ability. This study is at a preclinical stage and further research will be needed to determine whether this will be a viable treatment technique. Funding was received from the Netherlands Organization for Scientific Research (NWO), Domain Applied and Engineering Sciences (TTW), 'Connecting Innovators' Open Technology Programme, Project#18712.

Table of Treatments

REPLACEMENT THERAPIES IN DEVELOPMENT						
Type of product	Indication / treatment of	Product name(s)	Mechanism of action	Mode of administration	Developer / manufacturer	Development stage
Replacement FVIII	Haemophilia A	BIVV001	Efanesococog alfa (rFVIIIIFc-VWFD'D3-XTEN)	Intravenous	Sanofi and Sobi co-development	Phase 3
Replacement FVIII	Haemophilia A	OCTA 101	Subcutaneous FVIII with VWF fragment dimer	Subcutaneous	Octapharma	Phase 1/2 terminated due to serious adverse events
Replacement FIX	Haemophilia B	Dalcinonacog alfa (DalcA)	Subcutaneous coagulation factor IX variant	Subcutaneous	Catalyst Bioscience	Halting of clinical development

BYPASSING AGENTS IN DEVELOPMENT						
Type of product	Indication / treatment of	Product name(s)	Mechanism of action	Mode of administration	Developer / manufacturer	Development stage
Bypassing agent	Haemophilia A or B w/ inhibitors	eptacog beta (activated) Sevenfact® Cevenfacta®	Recombinant FVIIa- jncw	Intravenous	LFB	Licensed in the US and Mexico (under the brand name SevenFact®) Licensed in Europe and the UK (under the brand name Cevenfacta®)
Bypassing agent	Haemophilia A or B w/ or w/o inhibitors	marzeptacog alfa (activated) MarzAA	Subcutaneous coagulation rFVIIa variant	Subcutaneous	Catalyst Bioscience	Halting of clinical development

Text highlighted in red indicates change from last edition.

NON-REPLACEMENT THERAPIES IN DEVELOPMENT						
Type of product	Indication / treatment of	Product name(s)	Mechanism of action	Mode of administration	Developer / manufacturer	Development stage
NRT	Haemophilia A	Mim8	FVIIIa-mimetic, bispecific antibody	Subcutaneous	Novo Nordisk	Phase 3
NRT bispecific antibody	Haemophilia A	F1049	Bispecific antibody	-	Kymab	Pre-clinical phase
NRT bispecific antibody	Haemophilia A	NXT004 to NXT007	Bispecific antibody	Subcutaneous	Chugai	Phase 1/2
NRT bispecific antibody	Glanzmann Thrombasthenia	HMB-001	Bispecific antibody	-	Hemab	Pre-clinical phase
NRT Aptamer	Haemophilia A type 2B VWD	rondoroptivon pegol BT200	Pegylated aptamer	Subcutaneous	Medical University of Vienna	Phase 2
NRT Anti-TFPI	Haemophilia A or B w/ or w/o inhibitors	Concizumab	Anti-TFPI	Subcutaneous	Novo Nordisk	Phase 3
NRT Anti-TFPI	Haemophilia A or B w/ or w/o inhibitors	BAY 1093884	Anti-TFPI	Subcutaneous	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	Subcutaneous	Pfizer	Phase 3 (Recruitment is ongoing)
NRT Anti-TFPI	Haemophilia A or B w/ or w/o inhibitors	MG1113	Anti-TFPI	Subcutaneous	Green Cross	Phase 1
NRT siRNA	Haemophilia A or B w/ or w/o inhibitors	Fitusiran	Antithrombin Small interfering (si)RNA	Subcutaneous	Sanofi	Phase 3
NRT Activated Protein C inhibitor	Haemophilia A or B w/ or w/o inhibitors	SerpinPC	Activated Protein C inhibitor	Subcutaneous	Apcintex	Phase 1/2 Received FDA Orphan Drug Designation for HB

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GENE THERAPIES IN DEVELOPMENT						
Type of product	Indication / treatment of	Product name(s)	Name(s) of active ingredient	Mode of administration	Developer / manufacturer	Development stage
Gene Therapy	Haemophilia A	Roctavian™ Valoctocogene roxaparvovec BMN-270	AAV5-huFVIII-SQ Valoctocogene roxaparvovec	Single intravenous infusion	BioMarin	Conditional licensing in Europe (under the brand name Roctavian™)
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	Single intravenous infusion	Pfizer (originally Sangamo)	Phase III trial has re-opened recruitment
Gene Therapy	Haemophilia A	BAY2599023 / DTX 201	Gene therapy using AAVhu37FVIII	Single intravenous infusion	Bayer	Phase 1/2
Gene Therapy	Haemophilia A	SPK-8011	AAV-LK03 (AAV-Spark200) encoding BDD-FVIII	Single intravenous infusion	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	Single intravenous infusion	Takeda	Clinical trial suspended
Gene Therapy	Haemophilia A	AAV2/8-HLP-FVIII-V3	AAV2/8-based gene therapy encoding FVIII-V3 variant	Single intravenous infusion	UCL/St. Jude	Phase 1
Gene Therapy	Haemophilia A	ET3	Gene therapy using a combination of haematopoietic stem cells and lentiviral vectors	Single intravenous infusion	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	Single intravenous infusion	Spark	Phase 1/2
Gene Therapy	Haemophilia A	YUVA-GT-F801	autologous HSC/ MSC modified with lentivirus encoding FVIII	Single intravenous infusion	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

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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 phase
Gene Therapy	Haemophilia A	ASC618	Vector containing a hepatic combinatorial bundle promoter, liver specific codon optimisation, and highly expressing bioengineered human FVIII (ET3) transgene	Single intravenous infusion	ASC Therapeutics	Phase 1/2
Gene Therapy	Haemophilia A	Pleightlet (MUT6)	Auto CD34+PBSC, transduced with a lentiviral vector encoding the B domain deleted from of coagulation factor VIII	Single intravenous infusion	Medical College of Wisconsin	Phase 1
Gene Therapy	Haemophilia A	CD68-ET3-LV-CD34+	CD34+ hematopoietic stem cells transduced with CD68-ET3 lentiviral vector (encoding human factor VIII gene) is administered by IV infusion following conditioning regimen	Single intravenous infusion	Christian Medical College, Vellore, India	Phase 1
Gene Therapy	Haemophilia B	PF-06838435 fidanacogene elaparvovec (formerly SPK-9001)	Padua variant (rAAV-Spark100) (fidanacogene elaparvovec)	Single intravenous infusion	Pfizer (Originally Spark)	Phase 3
Gene Therapy	Haemophilia B	Hemgenix® AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	Single intravenous infusion	CSL Behring (Formerly uniQure)	Licensed in the US
Gene therapy	Haemophilia B	AMT-060	Gene therapy using AAV5 vector encoding FIX	Single intravenous infusion	CSL Behring (Formerly uniQure)	Phase 1/2
Gene Therapy	Haemophilia B	SB-FIX	AAV6-delivered ZFN integrating corrective FIX transgene into albumin locus	Single intravenous infusion	Sangamo	Phase 1/2

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Gene Therapy	Haemophilia B	FLT180a	AAVS3 encoding FIX Padua variant	Single intravenous infusion	Freeline	Clinical programme paused due to lack of commercial partnership to bring forward the development of the drug
Gene Therapy	Haemophilia B	AAV2/8-LP1-FIX	AAV2/8-LP1-FIX vector	Single intravenous infusion	SJCRH	Phase 1
Gene Therapy	Haemophilia B	YUVA-GT-F901	autologous HSC/ MSC, modified with lentivirus encoding FIX	Single intravenous infusion	SGIMI	Phase 1
Gene Therapy	Haemophilia B	CB2679d-GT	Novel chimeric AAV vector Delivering an enhanced potency FIX	Single intravenous infusion	Catalyst Biosciences	Pre-clinical phase
Gene Therapy	Haemophilia B	TAK-748 (formerly SHP648/ AskBio009/BAX 335)	AAV8-based gene therapy using FIX Padua variant	Single intravenous infusion	Takeda	Clinical trial suspended
Gene Therapy	Haemophilia B	BBM-H901	Engineered liver-tropic AAV vector expressing a hyperactive Padua FIX	Single intravenous infusion	Belief BioMed	Phase 1
Gene Therapy	von Willebrand Disease		CRISPR/Cas9 gene correction method using patient-derived endothelial colony forming cells	Single intravenous infusion	Dutch researchers with funding from Netherlands Organization for Scientific Research (NWO), Domain Applied and Engineering Sciences (ITW), 'Connecting Innovators' Open Technology Programme, Project#18712	Pre-clinical phase

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CELL-BASED THERAPIES IN DEVELOPMENT						
Type of product	Indication / treatment of	Product name(s)	Name(s) of active ingredient	Mode of administration	Developer / manufacturer	Development stage
Cell-based therapy	Haemophilia A	SIG-001	Two-compartment spheres encapsulating human FVIII-expressing human cells	Placed under the skin	Sigilon Therapeutics	Suspended Temporary Enrolment Halt
Cell-based therapy	FVII deficiency	SIG-009	Cell-based product for FVII deficiency	Placed under the skin	Sigilon Therapeutics	Pre-clinical
Cell-based therapy	Haemophilia A with inhibitors	TI-168	Autologous FVIII TCR-Treg cell therapy	-	TeraImmune Inc.	Phase 1/2a clinical trial

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

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Replacement FVIII	Haemophilia A	Esperoct® N8-GP	rFVIII glycoPEGylated (turoctocog alfa pegol)	Novo Nordisk	Licensed
Replacement FVIII	Haemophilia A	Jivi® BAY 94-9027	rFVIII (damoctocog alfa pegol)	Bayer	Licensed
Replacement FVIII	Haemophilia A	Kogenate® FS	Recombinant FVIII	Bayer	Licensed
Replacement FVIII	Haemophilia A	Kovaltry® BAY 81-8937	unmodified full- length rFVIII (octocog alfa)	Bayer	Licensed
Replacement FVIII	Haemophilia A	Novoeight®	rFVIII (turoctocog alfa)	Novo Nordisk	Licensed
Replacement FVIII	Haemophilia A	Nuwiq®	human-cell-line- recombinant-human- FVIII (simoctocog alfa human-cl-rhFVIII)	Octapharma	Licensed
Replacement FVIII	Haemophilia A	Refacto AF®	moroctocog alfa	Pfizer	Licensed
Replacement FIX	Haemophilia B	Alprolix®	rFIXFc (eftrenonacog alfa)	Sobi	Licensed
Replacement FIX	Haemophilia B	BeneFIX®	nonacog alfa	Pfizer	Licensed
Replacement FIX	Haemophilia B	Idelvion®	rFIX-FP / recombinant factor IX albumin fusion protein	CSL Behring	Licensed
Replacement FIX	Haemophilia B	Refixia® / Rebinyn® rFIX-GP / N9-GP	recombinant FIX glycopegylated / rFIX-GP (nonacog beta pegol)	Novo Nordisk	Licensed
Replacement FIX	Haemophilia B	RIXubis®	Nonacog gamma	Takeda	Licensed
Replacement FXIII	Factor XIII deficiency	NovoThirteen®/ Tretten	Recombinant FXIII (catridecacog)	Novo Nordisk	Licensed

LICENSED BYPASSING AGENTS					
Type of product	Indication / treatment of	Product name(s)	Mechanism of action	Developer / manufacturer	Development stage
Bypassing agent	Haemophilia A or B w/ inhibitors	Sevenfact® / Cevenfacta®	Recombinant FVIIa-jncw	LFB	Licensed in the US and Mexico (under brand name Sevenfact®) Licensed in Europe and the UK under brand name Cevenfacta®
Bypassing agent	Haemophilia A or B w/ inhibitors	NovoSeven® / NovoSeven® RT	Recombinant FVIIa (eptacog alfa)	Novo Nordisk	Licensed

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

LICENSED GENE THERAPIES					
Type of product	Indication / treatment of	Product name(s)	Mechanism of action	Developer / manufacturer	Development stage
Gene Therapy	Haemophilia A	Roctavian™ Valoctocogene roxaparvovec BMN-270	AAV5-huFVIII-SQ Valoctocogene roxaparvovec	BioMarin	Conditional licensing in Europe
Gene Therapy	Haemophilia B	Hemgenix® AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	CSL Behring	Licensed in the US

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IRISH HAEMOPHILIA SOCIETY

First Floor
Cathedral Court
New Street
Dublin 8

Tel: 01 657 9900

Email: info@haemophiliaie
Website: www.haemophilia.ie
Twitter handle: @HaemophiliaIRL

