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

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TABLE OF CONTENTS

FOREWORD

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

In this edition, we primarily cover news from the 2022 virtual American Society of Hematology (ASH), held in December 2021, and the 2022 virtual Conference of the European Association for Haemophilia and Allied Disorders (EAHAD), held in February 2022, as well as other industry updates and news in general. You will find a direct link to the ASH abstracts in the articles below, while the EAHAD abstracts can be accessed online here. For your convenience, we also include a table (pg 43) 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. Dan Hart, EHC 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,
- Ms. Laura Savini, EHC Public Policy and Communications Officer,
- Dr. Uwe Schlenkrich, EHC volunteer.

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

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

Sincere regards,

Declan Noone
EHC President

Amanda Bok
EHC CEO

ABBREVIATIONS

>	Greater than
≥	Greater or equal to
<	Smaller than
≤	Smaller or equal to
Ab	Antibodies
AAV	Adeno-associated virus
ABR	Annualised bleeding rate
ADAs	Anti-drug antibodies
AE	Adverse events
AjBR	Annualised joint bleeding rate
AsBR	Annualised spontaneous bleeding rate
ASH	American Society of Hematology
aPCC	Activated prothrombin complex
AT	Anti-thrombin
BDD	B-domain deleted
BE	Bleeding episode
BP	Bodily pain
BPA	Bypassing agents
BU/ml	Bethesda units per millilitre
CFC	Clotting factor concentrates
CI	Cumulative incidence
CL	Clearance
CV	Cardiovascular
CVAD	Central venous access device
Cmax	Maximum plasma concentration
DVT	Deep vein thrombosis
EAHAD	European Association for Haemophilia and Allied Disorders
ED	Exposure days
EHL	Extended half-life
ELISA	Enzyme-linked immunoassay
EQ-5D-5L	Standardised measure of health-related quality of life
F	Factor
FVII	Factor VII
FVIIa	Factor VII activated
FVIID	Factor VII deficiency
FVIII	Factor VIII
gc/kg	Genome copies per kilogram
h	Hours
HA	Haemophilia A
Haem-A-QoL	Haemophilia-Specific Quality of Life Questionnaire for Adults
HAL	Haemophilia activity list
HAwI	Haemophilia A with inhibitors
HB	Haemophilia B
HBwI	Haemophilia B with inhibitors
HCRU	Healthcare resources utilisation
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HJHS	Haemophilic joint health score
HRQoL	Health-related quality of life
HTC	Haemophilia treatment centre

IR	Incremental recovery
ITI	Immune tolerance induction
IQR	Interquartile range
IV	Intravenous
IU	International units
IU/dL	International units per decilitre
kg	Kilograms
mg/kg/week	Milligrams per kilograms per week
mHJH	modified hemophilia joint health score
MOI	multiplicity of infection
n=	Number
NAbs	Neutralising antibodies
ng/ml	nanogram per millilitre
OD	On-demand
Pd	Plasma-derived
PD	Pharmacodynamics
PE	Pulmonary embolism
pedHAL	Paediatric haemophilia activity list
PEG	Polyethylene glycol
PF	Physical function
PK	Pharmacokinetics
PKP	Pharmacokinetics-guided prophylaxis
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
QM	Every month
QW	Once a week
R	Recombinant
rFVIIa	Recombinant factor VII activated
RNA	Ribonucleic Acid
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SHL	Standard half-life
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
TMA	Thrombotic Microangiopathy
TSQM-9	Treatment satisfaction questionnaire for medication
ug/mL	Micrograms per milliliter
UK	United Kingdom
UKHCDO	United Kingdom Haemophilia Doctors' Organisation
vg/kg	Vector genomes per kilogram
VAS score	Visual analogic scale
vs	Versus

VWD	Von Willebrand disease
VWF	Von Willebrand factor
WAPPS-Hemo	Web Accessible Population Pharmacokinetic Service-Hemophilia
µg	Microgram
µL	Microlitre

Executive summary

We start the newsletter with a reflection piece on whether it is possible to achieve the much-sought-after 'zero bleeds' with available therapies. Hermans C. describes a Belgian example (pg 11).

An update on novel treatments in haemophilia A

In this section we only describe novel therapies for haemophilia A used in people without inhibitors. A detailed reporting on their use in people with haemophilia A and inhibitors is given below.

Replacement therapies

An update on BIVV001

- Investigators reported on the safety, tolerability and pharmacokinetics of repeat dose BIVV001® in a phase I study in previously treated adults with severe haemophilia A (pg 12).

An update on Adynovi®

Baxalta and Takeda reported on:

- The incidence of inhibitor development, safety and efficacy for the use of Adynovi® in previously untreated patients (<6 years of age) with severe haemophilia A and their use during surgery and immune tolerance induction (pg 12).
- Adynovi®'s haemostatic effectiveness with data from the German Antihemophilic factor Haemophilia A outcome database (AHEAD) (pg 13).
- The impact of Adynovi® on joint health (pg 14).

An update on Esperoct®

- Researchers presented the results from the pathfinder8 trial on long-term satisfaction with Esperoct® (pg 14).
- During EAHAD, Oldenburg J. reported on cases of lower-than-expected FVIII expression with Esperoct® (pg 14).
- French researchers reported on their experience using Esperoct® in surgeries (pg 15).

An update on Elocta®

- Sanofi presented a post hoc analysis of data from the A-LONG study and its extension study ASPIRE to assess healthcare resource utilisation and changes in joint health in people with haemophilia A using Elocta® (pg 15).
- Pasi J. and colleagues reported on changes in pain-related quality of life in people with severe haemophilia A treated with Elocta®, also with data from the A-LONG study (pg 16).
- Taiwanese researchers reported on real-world evidence of bleeding outcomes, weekly factor dose and factor costs for adult non-inhibitor patients who switch to Elocta® (pg 16).
- UK researchers reported on a case study on the use of Elocta® in a pregnant woman with severe haemophilia A (pg 16).

An update on Jivi®

Investigators supported by Bayer reported on:

- FVIII inhibitor development, treatment-emergent adverse events, PEG-antibodies and ABR with Jivi® in adults with severe haemophilia A with data from a post-marketing interventional study (pg 16).
- Real-world safety and effectiveness with Jivi® with data from a post-marketing study (HEM-POWR) (pg 17).

Non-replacement therapies - FVIII mimetics

An update on Hemlibra®

- Roche presented data on:
    - The safety of Hemlibra® from its Global Safety Database (pg 17).
    - The impact of Hemlibra® from the Canadian Haemophilia Bleeding Disorders Registry (pg 18).
    - The phase III HAVEN 6 clinical trial on the safety, efficacy, pharmacokinetics and pharmacodynamics of Hemlibra® in prophylaxis in people with mild or moderate haemophilia A without FVIII inhibitors (pg 19).
    - Real-world data on the use of Hemlibra® in non-severe haemophilia A patients (pg 19).
    - The safety and efficacy of Hemlibra® in people aged >50 with co-morbidities with data from the HAVEN and STASEY clinical trials (pg 20).
- Takeda compared ABR and care costs for people without inhibitors switching from FVIII replacement therapies to Hemlibra® (pg 21).
- Doctors from the UKHCDO presented data from an observational study on the use of Hemlibra® in non-inhibitor haemophilia A people (pg 18).
- Dutch researchers reported on the use of Hemlibra® in non-inhibitor patients with data from the Dutch Haemophilia Registry 'HaemoNed' (pg 18)
- Russian and Israeli researchers compared breakthrough bleeding risks in people on Hemlibra® (pg 20).
- Slovenian researchers reported on the use of Hemlibra® in invasive surgeries (pg 20).
- Thai investigators reported on their experience of low-dose prophylaxis with Hemlibra® in people with haemophilia A without inhibitors (pg 21).

An update on Mim8

- Researchers presented data on the cross-reactivity of Hemlibra® anti-drug antibodies against Mim8 (pg 21).
- Novo Nordisk presented a study to determine which assay could monitor FVIII activity in the presence of Mim8 (pg 22).

An update on NXT007

- Chugai examined the *in vitro* effect of bypassing agents in the co-presence of NXT007 to determine its safety (pg 22).

Non-replacement therapies – Rebalancing agents

An update on the rebalancing agents for the use in haemophilia A patients is provided below (pg 10).

Gene therapy

An update on valoctocogene roxaparvovec

BioMarin:

- Presented an update on its phase III clinical trial for valoctocogene roxaparvovec in adults with severe haemophilia A (pg 22), including an update on the gene therapy use in HIV positive people (pg 24).
- Reported on the genomic analysis of a serious adverse event, a salivary gland mass, in one of the participants from the phase I/II study with valoctocogene roxaparvovec (pg 25).
- Presented on the impact of valoctocogene roxaparvovec on quality of life (pg 25).

An update on giroctocogne fitelparvovec

- Pfizer presented an update from a two-year follow-up of its phase I/II dose-ranging ALTA study for giroctocogene fitelparvovec in men with severe haemophilia A (pg 25).

- Pfizer/Sangamo Inc. reported on a deep vein thrombosis in one trial participant dosed with giroctocogene fitelparvovec (pg 27).

An update on BAY2599023
Bayer presented an update on its phase I/II dose-finding study with BAY 2599023 (pg 26).

An update on SPK-8011
Spark Therapeutics reported on phase I/II trial with SPK-8011 (pg 27).

An update on novel treatments in haemophilia B

Replacement therapies

An update on Idelvion®
CSL Behring presented data from the ATHN2 study on real-world data of people with haemophilia B switching to Idelvion® (pg 28).

An update on Alprolix®
Researchers presented an update on the B-LONG study describing changes in patient-reported outcomes associated with pain and physical activity in people on Alprolix® (pg 28).

Non-replacement therapies – Rebalancing agents

An update on the rebalancing agents for the use in haemophilia B patients is provided below (pg 10).

Gene therapy

An update on fidanacogene elaparvovec
Pfizer reported on the five-year follow-up study of patients treated with fidanacogene elaparvovec (pg 28).

An update on FLT180a
Freeline gave an update on the phase I/II dose-finding study, B-AMAZE, and the ongoing long-term follow-up study for the use of FLT180a in people with moderate to severe haemophilia B (pg 29).

An update on etranacogene dezaparvovec
CSL Behring/UniQure:

- Presented the final analysis of the HOPE-B trial for the use of etranacogene dezaparvovec in people with haemophilia B (pg 30).
- Announced submitting a marketing authorisation application review for this product with the EMA (pg 30).
- Presented the multi-year data on durable FIX expression from the phase IIb clinical trial with etranacogene dezaparvovec in people with haemophilia B (pg 30).

Gene therapy assays

The EHC NPR committee considers issues in current assays to measure factor expression during gene therapy trials (pg 32).

An update on novel non-factor replacement therapies for people with haemophilia A and B with or without inhibitors

Bypassing agents

An update on eptacog beta
LFB and Hema Biologics presented data on the use of eptacog beta (US brand name Sevenfact®) to relieve pain (pg 35).

Immune Tolerance Induction with replacement factor

An update on Elocta®
Sanofi and Sobi described:

- The use of Elocta® in first time immune tolerance induction with data from the VerITI-8 study (pg 35).
- An interim analysis of real-world use of Elocta® in immune tolerance induction (pg 36).

FVIII mimetics

An update on Hemlibra®
Roche presented the use of Hemlibra® during surgeries in people with haemophilia A and inhibitors with data from the phase IIIb STASEY study (pg 36).

Rebalancing agents

An update on fitusiran
Sanofi presented:

- The results from the phase III study ATLAS A/B on the efficacy and safety of fitusiran in people with haemophilia A or B without inhibitors (pg 37).
- The results from the phase III study ATLAS-INH on the safety and efficacy of fitusiran prophylaxis in people with inhibitors (pg 37).
- Changes in health-related quality of life in people with haemophilia A with or without inhibitors with fitusiran (pg 38).
- A study to evaluate the interference of antithrombin reduction in routine clinical coagulation assays to monitor patients treated with fitusiran (pg 39).

An update on concizumab
Novo Nordisk reported on:

- Surgeries on people with haemophilia A or B with or without inhibitors while on concizumab. Data comes from the phases II explorer4 and explorer5 clinical trials evaluating the safety and efficacy of concizumab (pg 39).
- Long-term impact of concizumab on health-related quality of life in people with haemophilia. Data comes from the phase II explorer4 and explorer5 clinical trials analysis (pg 40).
- Risk mitigation plan developed to re-initiate the phase III clinical trial for concizumab. The trial had been placed on voluntary hold following the observation of non-fatal thrombotic events in three patients with distinct thrombotic risk factors (pg 40).

An update on marstacimab
Pfizer described a bioequivalence study to support the bridging of clinical results between using a marstacimab prefilled syringe and prefilled pen devices (pg 40).

An update on SerpinPC
Researchers supported by Centessa Pharmaceuticals presented data from the dose-finding phase IIa study to use SerpinPC in people with haemophilia A or B (pg 41).

An update on novel therapies for people with von Willebrand Disease

Replacement therapies

An update on Veyvondi®
UK researchers reported on the obstetric management of two pregnant women with von Willebrand disease and Veyvondi® (pg 42).

Non-replacement therapies

An update on Hemlibra®
Authors performed a scoping review on the use of Hemlibra® in von Willebrand Disease (pg 42).

REFLECTION PIECES

Achieving zero bleeds with novel haemophilia therapies: the Belgian experience

In our previous issue, we reported on an abstract presented by a group of Greek researchers reflecting on their clinical practice in relation to the objective of achieving zero bleeds for their patients and whether that was a realistic goal in the real-world setting with novel therapies.

During EAHAD 2022, Hermans C. and his team (Belgium) also address (PO109) this question by assessing the impact of the adoption of novel haemophilia therapies in their centre. They included in their analysis 106 adult patients with severe or moderate haemophilia A or B (HA, n=81; HB, n=20; male, n=99; female, n=2) as well as five HA patients with persistent inhibitors.

All patients had their treatment reviewed and therapeutic alternatives or protocols offered. Following this, 97 out of the 99 non-inhibitor patients were on prophylaxis with standard half-life FVIII (SHL, n=16), extended half-life FVIII (EHL, n=23), EHL-FIX (n=18), Hemlibra® (n=40) and BIVV001 (n=2).

All these patients currently have an annualised spontaneous joint bleeding rate close to zero and a very good adherence as assessed by 80 % between recommended and administered treatments.

One patient persistently refused prophylaxis, one is poorly adherent, 13 well-controlled HA patients on SHL-FVIII (including three patients on plasma-derived FVIII) are reluctant to switch to EHL-FVIII. All patients with a persistent inhibitor (n=5) are treated with Hemlibra®. After excluding two patients treated with gene therapy, all patients with haemophilia B (including six patients with moderate HB and a severe phenotype) are on EHL-FIX.

In conclusion, investigators experienced that the wide range of current treatment options as well as the multidisciplinary selection of a personalized treatment modality allowed patients to achieve the adoption of and adherence to highly effective prophylaxis in nearly all adults with severe HA or HB.

AN UPDATE ON NOVEL TREATMENTS IN HAEMOPHILIA A

In this section we update on novel therapies in people with haemophilia A without inhibitors. For an update on these therapies' use in people with haemophilia A and inhibitors please go to pg 35.

Factor replacement therapies

Efanesoctocog alfa (BIVV001®): Results from the phase I repeat-dose study

In an article published in *Blood Advances*, published in February 2022, investigators led by Lissitchkov T. reported on the safety, tolerability and pharmacokinetics of repeat-dose **BIVV001®** in a phase I study in previously treated adults with severe haemophilia A. Efanesoctocog alfa is a new class of FVIII replacement (BIVV001®) that breaks the von Willebrand factor-imposed FVIII half-life ceiling.
Participants received four once-weekly doses of BIVV001® (cohort one, 50 IU/kg; cohort two, 65 IU/kg). All enrolled participants (cohort one, n=10; cohort two, n=14) completed the study. Investigators did not detect inhibitor development to FVIII. After the last dose of BIVV001®, mean FVIII activity half-life, area under the activity-time curve, and maximum steady-state concentration for cohort one and two were 41.3 and 37.3 hours, 8290 and 11 200 hours × IU/dL, and 131 and 171 IU/dL, respectively. There was minimal accumulation after four doses. Mean FVIII activity for cohorts one and two, respectively, was 46% and 69% on day three post-dose and 10% and 12% on day seven post-dose.
Overall, four once-weekly doses of BIVV001® were well tolerated, no safety concerns were identified, and no bleeds were reported during the treatment period.

Immunogenicity of Adynovi® in previously untreated patients, its efficacy and safety in ITI and in surgeries

During ASH 2021, Baxalta and Takeda presented two abstracts with data from an open-label, prospective multi-centre phase III study (NCT02615691)[1] in patients aged <6 years with severe haemophilia A. Patients were either previously untreated or had <3 exposure days (EDs) to **Adynovi®**, Advate® or plasma transfusion. The study did not include patients with detectable FVIII antibodies or a history of antibodies. Patients received Adynovi® as prophylaxis (25-50 IU/kg, up to 80 IU/kg ≥1 × weekly) and/or on-demand therapy (10-50 IU/kg, up to 80 IU/kg depending on bleed severity). Prophylaxis was started before three years of age or after a maximum of two joint bleeds. The primary endpoint was the incidence of FVIII inhibitor development, and the secondary endpoints included safety and efficacy (annualised bleeding rate (ABR) and haemostatic efficacy).
In abstract 3184, Sidonio R. F. and colleagues used data from the study to evaluate the safety, immunogenicity and haemostatic efficacy of Adynovi® in previously untreated patients (PUPs) with severe haemophilia A. Adynovi® is an extended half-life recombinant FVIII. As of the data cut-off, 59 of the 80 enrolled patients had received ≥1 dose of Adynovi®. Twenty-one patients did not meet the eligibility criteria or were discontinued prior to treatment. Fifty-four patients received prophylaxis, and 35 received on-demand treatment at any time during the study period. Fifty-two patients qualified for the interim analysis. Ten of them developed an inhibitory antibody to Adynovi® during the study. The total ABR rate was 3.2 in both the on-demand and prophylaxis population. At bleed resolution, haemostatic efficacy was rated "excellent" for 88/269 bleeds (32.7%) and "good" for 73/269 bleeds (27.1%). Overall, 52 (88.1%) patients receiving Adynovi® experienced a total of 283 adverse events (AEs), and 13 patients experienced 14 Adynovi®-related AEs (including ten severe AEs). SAEs occurred in 24 patients, ten of whom experienced ten treatment-related SAEs of FVIII inhibitor development.
In abstract 3185, Sidonio R. F. and colleagues evaluated the safety and efficacy of immune therapy induction (ITI) with Adynovi®. In the study referred to above (NCT02615691), patients who developed a high-titre FVIII inhibitor (>5.0 BU) or low-titre FVIII inhibitor (≥0.6 BU to ≤ 5.0 BU) plus poorly controlled bleeding despite increased FVIII doses and/or bypassing agents were eligible for ITI therapy. At the investigators' discretion, dosing for ITI therapy ranged between 50 IU/kg 3 × weekly (low dose)

[1] A study of PEGylated recombinant FVIII (BAX855) in previously untreated young children with severe haemophilia A.

and 100-200 IU/kg daily (high dose). The primary endpoint of this study was the success rate of ITI with Adynovi®. The secondary endpoints included the rates of partial success and failure of ITI and ABR during ITI.
As noted above, of the 52 patients who qualified for the interim analysis, ten developed an inhibitor to Adynovi® (high titre, n=5; low titre, n=5), of these, six patients were enrolled to receive ITI, and only five of these (83.3%) actually received ≥1 dose of Adynovi® for the treatment of FVIII inhibitors (low dose, n=3; high dose, n=2). Of these five patients, one completed high-dose ITI therapy, which was successful. The remaining four patients continued the study at the time of the data cut-off. Of the five patients who received ≥1 dose of ITI, four (80.0%) had a total of 17 AEs, three (60.0%) experienced eight SAEs, and one experienced a treatment-related SAE of FVIII inhibition. It is important to note that the onset date of FVIII inhibitor development in this patient occurred prior to initiation of ITI. One patient experienced two catheter-related AEs, both of which resolved, and no patients experienced thrombotic AEs, study procedure-related AEs, or AEs leading to discontinuation of treatment.
In an abstract (PO050) at EAHAD, researchers led by Peyvandi F. and supported by Takeda presented data from a prospective phase III study (NCT02615691 – see above) in children <6 years old who underwent one or more invasive procedures. Participants had <3 exposure days to **Adynovi®**, Advate®, or plasma transfusion.
At the data cut-off date (August 2019) 26 minor invasive procedures were conducted in 16 patients. Most procedures were port insertion. No patient experienced post- or perioperative blood loss. The mean average postoperative dose per invasive procedure was 257.6 IU/kg. Eleven adverse events were reported by six patients undergoing invasive procedures. Three events (rash, drug hypersensitivity, FVIII inhibitor development) were considered to be related to study treatment.

Haemostatic effectiveness of Adynovi®

In an abstract (3187) from ASH 2021, Klamroth R. and colleagues, supported by Takeda, describe the haemostatic effectiveness of **Adynovi®** as standard prophylaxis (SP) and individualised pharmacokinetic-guided prophylaxis (PKP) in adult patients with severe haemophilia A. The authors are using data from the German Antihaemophilic factor Haemophilia A outcome database (AHEAD) study, which evaluates the real-world, long-term effectiveness and safety of recombinant factor VIII, Advate® and Adynovi®. The AHEAD study is non-interventional, prospective and multicentre and includes patients who switched to Adynovi® or enrolled on Adynovi® during seven years of follow-up. Key outcomes included annualised bleeding rates (ABR), annualised joint bleeding rates (AjBR), factor consumption, factor VIII trough levels (expressed in patient years). The data cut-off date for this analysis is June 2020.
Of 382 patients, 62 (severe HA, n=55; moderate HA, n=7; SP, n=35; PKP, n=27) were enrolled in the study. Median ABRs were lower in patients receiving PKP with Adynovi® vs SP. Similar median AJBRs were observed between the PKP and SP groups. A higher proportion of patients receiving PKP vs SP had an ABR or AJBR of zero (ABRs, 60% vs 50%; AJBRs, 80% vs 75%, respectively). The mean annualised total dose for Adynovi® was 4154 IU/kg for SP and 4662 IU/kg for PKP. Mean target FVIII trough levels for patients with severe HA receiving Adynovi® PKP were 6.0%. Adverse events occurred in nine out of 62 patients treated with Adynovi®. Four were serious adverse events, and none were treatment-related. These results were also presented during EAHAD in abstract PO105.
During the EAHAD 2022 Congress, Ozelo M. C. and colleagues, supported by Takeda, presented (abstract PO045) another interim analysis of the AHEAD Database with data cut-off date of July 2021. The authors presented two-year data on the secondary efficacy endpoints in patients receiving Adynovi® prophylaxis and included ABR and AjBR.
In this analysis, 25 (severe HA, n=17; moderate HA, n=8) people were on Adynovi® prophylaxis. In the twelve months before screening, median ABR and AjBR were 1.0 and 0.0. In year one median ABR and AjBR were 0.0 and 0.0. In year two median ABR and AjBR were 0.9 and 0.0. In terms of the number of patients achieving zero ABR and AjBR bleeds, the percentage increased following uptake of Adynovi® prophylaxis. The mean annualised Adynovi® dose was 3893 IU/kg during year one and 3803 during

year two. Fourteen patients experienced adverse events, and three experienced serious adverse events, but none were related to treatment, and no patient developed an inhibitor.

The impact of Adynovi® on joint health using collagen formation and degradation biomarkers

In an abstract (2102) from ASH 2021, Takeda and Baxalta presented data from the PROPEL study (NCT0285960)[2] to examine the relationship between collagen biomarkers for joint health and factor replacement therapy targeting two different FVIII trough levels in patients with severe haemophilia A. Collagen is a major structural component of the highly vascular synovium and is essential for vascular mechanical stability.

Patients with haemophilia A were randomised to 12 months' pharmacokinetic-guided prophylaxis targeting FVIII trough levels of 1-3% or 8-12%. Longitudinal biomarkers (including various types of collagens) were collected at five time points (baseline and month three, six, nine and twelve).

Biomarkers were measured in 98 patients. Fifty patients were randomized to the 1-3% and 48 to the 8-12% FVIII trough level treatment arms. Before normalization, collagen biomarkers associated with joint damage and disease, were elevated by an average of 38% compared with healthy controls.

These biomarkers significantly and consistently decreased in both arms of the study after six months. The data suggest that FVIII prophylaxis leads to a normalization of joint remodelling. This is further supported by primary data from PROPEL, which demonstrated that targeting FVIII 8-12% vs 1-3% results in a lower annualized bleeding rate. This novel biomarker data is the first to demonstrate the importance of FVIII prophylaxis for joint health in patients with haemophilia A from a randomized clinical trial.

Long-term satisfaction with Esperoct®: Results from the pathfinder8 trial

In an abstract (PO088) presented at the 2022 EAHAD Congress, a group of researchers led by Nagao A. et al. and supported by Novo Nordisk analysed the maintenance of long-term treatment satisfaction with **Esperoct®** in patients of all ages with severe haemophilia A from the non-randomised phase III pathfinder8 trial (NCT03528551)[3]. Treatment satisfaction was assessed with the Haemophilia Treatment Satisfaction (Hemo-SAT) questionnaire for adult- and parents of patients. Score baselines were taken from the beginning of the pathfinder2 and 5 trials from which the patients were enrolled.

One hundred and fifty-four patients from pathfinder8 (96.3%) answered at least one question in the Hemo-SAT. In patients of all ages with severe haemophilia A, long-term improvements in treatment satisfaction, or maintenance of treatment satisfaction benefits, were observed with Esperoct®. Efficacy, burden, ease and convenience domains showed the largest benefits.

Cases of lower-than-expected FVIII expression with Esperoct®

During the 2022 EAHAD Congress, Oldenburg J. presented data on decreased factor VIII activity of Esperoct® in previously treated patients, in absence of inhibitor development. **Esperoct®** is a recombinant pegylated extended half-life FVIII product. These cases arose from a single report of less than expected FVIII activity when the patient switched to Esperoct®. Following this single event, researchers searched the Esperoct® post-marketing safety database for other similar reports.

Between the Esperoct® launch in 2019 and October 2021 (cut-off date), researchers found 15 cases, which possibly could be associated with decreased factor VIII activity in previously treated patients. These cases tended to present early between exposure days (ED) one and five and in all severities of haemophilia. Most were detected during routine FVIII measurements, which is routinely performed when a patient is switched to a different therapy.

Some patients were positive for anti-PEG antibodies, although they had wide variations in antibody levels, which does not clearly correlate with an impact on FVIII activities or bleeding profile.

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[2] BAX855 PK-guided dosing (PROPEL)

[3] A research study looking at how a factor VIII medicine called turoctocog alfa pegol (N8-GP) works in people with haemophilia A (pathfinder8).

Of these 15 cases, two had unknown outcomes. Nine patients were switched to an alternative product, one patient died for reasons unrelated to haemophilia. One remained on Esperoct® for 37 ED before switching to another product on parents' request. Two patients continued treatment with Esperoct®. Due to the nature of post-marketing surveillance data collection, the available data was limited, and investigators were not able to contact some treaters for further questions. Therefore, it was difficult to determine the cause of this lower-than-expected FVIII expression. Investigators looked at clinical trial data of Esperoct® in previously treated patients (pathfinder 2 and 5) and were not able to observe similar reduction in FVIII activity. There was no evidence that anti-Esperoct® antibodies had any clinical impact in this study population.

Surgery experience in a real-world setting with Esperoct®

A group of French researchers led by Bertho P.-O. reported at EAHAD 2022 (PO051) their experience using **Esperoct®** in 59 surgeries (major, n=39; minor, n=20; male patients, n=36; female patients, n=2; severe HA, n=5; moderate HA, n=2; mild HA, n=31).

For patients who underwent major surgeries, baseline levels of FVIII plasma coagulant activity were 12 IU/dL. The number of infusions was seven with a preoperative loading dose of 41.7 IU.kg and a total dose of 242.2 IU/kg. In patients who underwent minor surgeries, the baseline level of FVIII was 28 IU/dL. The number of infusions was two with a preoperative loading dose of 33.3 IU/kg and a total dose of 56.6 IU.kg. The duration of hospitalization was six days for major surgeries and one day for minor surgeries. The overall clinical efficacy was qualified as excellent/good in 51 procedures (86%) and fair in eight (14%). Of this latter population representing six patients (minor HA, n=5; severe HA, n=1), four procedures involved urological surgery, two dermatological interventions, one haematoma the day after heart surgery despite normal FVIII levels and one bleeding episode after dental avulsions (i.e., displacement of teeth from their socket) for the patient with severe haemophilia. Therefore, two out of six patients received antiplatelet therapy. FVIII levels were maintained at acceptable physiological values in the days following major and minor surgeries. No thromboembolic events, anti-FVIII antibodies or adverse events were reported.

No adverse events were observed.

Impact of Elocta® on joint health: Results from the A-LONG and ASPIRE trials

In an abstract (PO132) from the EAHAD 2022 Congress, Sanofi presented a post hoc analysis with data from A-LONG (NCT01181128)[4] and its extension ASPIRE (NCT01454739)[5] to assess healthcare resource utilisation (HCRU) over time with changes in joint health in people with haemophilia A using **Elocta®**.

The analysis included 106 adult patients with severe haemophilia A and no history of inhibitors, followed for a median time of 52.5 months. Participants received as treatment individualised prophylaxis (67.9%), weekly dosing (14.2%) or on-demand treatment (17.9%).

Investigators concluded that Elocta® improved joint health over time. This was evaluated using the modified Haemophilia Joint Health Score (mHJH). They also noted that people who began treatment with individualised prophylaxis had fewer HCRU events (i.e., instances of using healthcare resources to treat joint bleeds and damage) than those on weekly dosing or on-demand treatment, but this was non-significant.

Finally, people with target joints at the beginning of the study had more HCRU than those without.

Changes in pain-related quality of life in patients with haemophilia A treated with Elocta® individualised prophylaxis: post hoc analysis from the A-LONG study

A manuscript by Pasi J. et al. published in the scientific journal *Therapeutic Advances in Haematology* (*Ther Adv Hematol.* 2022, Vol. 13: 1–9) in February 2022, presents the post hoc analysis of data from

[4] Study to evaluate the safety, pharmacokinetics and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in previously treated subjects with severe haemophilia A.

[5] Long-term safety and efficacy of rFVIIIFc in the prevention and treatment of bleeding episodes in previously treated participants with haemophilia A (ASPIRE).

the A-LONG study (NCT01181128)[6], to assess change over time in pain-related quality of life in patients with severe haemophilia A treated prophylactically with Elocta®, a recombinant factor VIII Fc fusion protein (rFVIIIFc).
A greater proportion of patients reported they did not experience painful swellings (n=87; 66% versus 46%, p < 0.01) or pain in their joints (n=89; 42% versus 27%; p < 0.05) at end of study (EoS) versus baseline (BL). A greater proportion of patients reported no pain/discomfort at EoS versus BL (n=116; 45% versus 34%; p < 0.05). The proportion of patients who did not find it painful to move numerically increased at EoS versus BL (n = 86; 47% versus 38%; p = NS).

Real-world data of Elocta® use in adults and children in Taiwan

In an abstract (3198) from ASH 2021, Taiwanese researchers compared pre-and post-switch to **Elocta®** in a real-world setting. Their analysis included bleeding outcomes, weekly factor doses and factor costs. In total, they enrolled 51 non-inhibitor patients (adults, n=43; children, n=8) enrolled in two haemophilia treatment centres from November 2018 to July 2019. Pre-switch and post-switch prophylaxis rates were 62.7% (32/51) and 94.1% (48/51), respectively. Only 48 patients treated prophylactically were included in the analysis. For comparison of pre-switch and post-switch outcomes: median annualised bleeding rate (ABR) decreased from 48, 12, and 4 to 1.15, 1.9, and 1.5 for on-demand (n=16), irregular prophylaxis (n=7), and regular prophylaxis (n=25) groups. Median joint ABR (AjBR) decreased from 32, 11, and 4 to 0.95, 0.7, and 1.2 for on-demand, irregular prophylaxis, and regular prophylaxis groups, respectively. Median weekly dose increased in all groups, as did annualise factor costs. Zero ABR accounted for 5.9% (3/51) for all patients with pre-switch SHL rFVIII treatment and 20.8% (10/48) with post-switch Elocta® prophylaxis. Zero AjBR accounted for 9.8% (5/51) with SHL rFVIII treatment and 33.3% (16/48) with Elocta® prophylaxis.

Case study of severe HA pregnant woman managed with Elocta®

UK researchers report (EAHAD 2022, abstract PO119) on a case study on the use of **Elocta®** in a pregnant woman with severe haemophilia A. Prophylaxis was established at 30 IU/kg every four days to achieve FVIII level of >5% with no reported adverse events. Complications arose following birth due to retained placental products, which resolved through surgery. Fifty IU/kg of Elocta® successfully facilitated the haemostasis achieving FVIII levels >100%. Elocta® prophylaxis was recommenced through breastfeeding without observed breakthrough bleeds or adverse events, including thrombosis to mother and child.

Safety of Jivi®: Results from a post-marketing study

In an abstract from the EAHAD 2022 Congress, investigators led by Holme P. A. and supported by Bayer presented the results of a preliminary report (PO121) of a post-marketing, interventional study (NCT04085458)[7] for the use of **Jivi®** in adult people with haemophilia A. Jivi® is a licensed PEGylated extended half-life FVIII product.
Eligible patients received Jivi® for 100 exposure days (ED), initially at 45 IU/kg every five days (recommended) or at 40 IU/kg twice weekly until visit three after 10-15 ED. At this point, patients either continued the same regimen or switched regimens. In the proposed switch, patients could also choose to infuse every seven days.
The primary endpoint was FVIII inhibitor development. The secondary endpoints were treatment-emergent adverse events (TEAE), anti-PEG (polyethene glycol) antibody (Ab) development, and annualised bleeding rate (ABR).
Thirty patients were eligible for inclusion at the data cut-off date of June 2021. None developed FVIII inhibitors. TEAE were observed in 16 (53.3%) patients, 12 were mild in severity (40%). Three patients

[6] Study to evaluate the safety, pharmacokinetics and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in previously treated subjects with severe haemophilia A.
[7] Study to gain more information on how safe and effective Jivi is in patients with severe haemophilia A (post-marketing investigation).

(10%) had mild or moderate TEAE considered as study-drug-related by the investigator. Pre-study median total ABR was 3.0. At the data cut-off date, (2xW, n=7; E5D, n=8; E7D, n=9; variable, n=6), median total and joint ABR were 1.82 and 0.37, respectively. Pre-study median ABR was 3.0.

Post-marketing study for the safety and effectiveness of Jivi® in the real-world setting: Second interim analysis from the HEM-POWR study

Investigators led by Reding M. T. and supported by Bayer presented during the 2022 EAHAD Congress an abstract (PO124) with data on the second interim analysis of HEM-POWR (NCT03932201)[8], a post-marketing study to evaluate the real-world safety and effectiveness of **Jivi®**. This is a licensed PEGylated extended half-life FVIII.

The HEM-POWR primary outcomes were total bleeding events and annualised bleeding rate (ABR). The secondary outcomes included safety.

At the data cut-off date (August 2021), 162 previously treated patients (PTPs) were enrolled, mostly from Germany (28.4%), Japan (23.5%) and the United States (14.2%). The full analysis set included 78 PTPs (mild, n=3; moderate, n=9; severe, n=66). The mean number of observation days was 189. Most patients (62/78, 79.5%) were pre-treated with Jivi® within 12 months of enrolment. The median dose per infusion was 3000 IU; twice-weekly was the most common prophylaxis regimen (32.5%). Within 12 months of enrolment, 16 Jivi®-naïve patients generally had worse bleeding history compared to pre-treated patients. Common comorbidities included pain (16.7%) and hypertension (14.1%). The median total ABR was 0.0, and 56 (71.8%) patients reported no bleeds during the study. The corresponding values for joint ABR were 0.0, and 64 (82.1%) patients reported no joint bleeds during the study. No inhibitor development or deaths were reported.

Non-replacement therapies

FVIII mimetics

Safety reporting of Hemlibra® from Roche Global Safety Database

During the 2021 ASH Congress, Roche reported (3186) on the safety evaluation of **Hemlibra®** prophylaxis focusing on thrombotic events (TEs) and thrombotic microangiopathies (TMAs). The abstract authors took all individual safety reports for Hemlibra® from clinical trials, registries, expanded access programs, compassionate use and the post-marketing setting with a data cut-off date of May 2021. Authors estimated that Hemlibra® had been used by >11,400 people from across the world.

In total, 52 cases (56 events) were identified on the Roche Global Safety Database. Thirty-nine cases were reported in people with haemophilia A. Six cases occurred with concomitant use of activated prothrombin complex concentrate (aPCC), of which four were TMAs. No new TE or TMA associated with aPCC were reported since the last update (Lee, et al. *Haemophilia,* 2020).

For the remainder 37 TEs and not associated with aPCC, 17 occurred in people with haemophilia A and inhibitors. Seven were associated with central venous access devices (CVADs), of which four were reported to be resolving/recovering. All except for two non-aPCC associated TEs in PwHA were associated with ≥1 cardiovascular risk factors (e.g., previous myocardial infarction, ischemic heart disease, coronary artery disease, hypertension, hyperlipidaemia, smoking and advanced age) or other risk factors for thrombosis (e.g., sepsis/bacteraemia, device use, coinciding injury, hepatitis C).

Of the non-aPCC and non-CVAD associated events reported, six (20.0%) TEs led to the discontinuation of Hemlibra®. Across all non-aPCC associated events, an evaluation of latency or duration of treatment did not reveal any patterns or trends. In total, four TEs were fatal: two myocardial infarctions, both in medically complex patients, and two disseminated intravascular coagulation events in patients >70 years of age with pneumonia. Where reported, 20/31 (64.5%) TEs were recovered/resolving at the

[8] Evaluating effectiveness and long-term safety of damoctocog alfa pegol in patients, who have been diagnosed with hemophilia A (HEM-POWR).

time of this analysis, with the majority of these cases reporting no change to Hemlibra® prophylaxis as a result of the event.

Impact of Hemlibra® on Canadian patients

In an abstract from Roche (347) from the 2021 ASH Congress, authors reported results from an analysis of the Canadian Haemophilia Bleeding Disorders Registry with regard to people with haemophilia A using **Hemlibra®**. The authors identified 73 patients who had received Hemlibra® at least once up to December 2021. There were 64 PwHA with severe disease, seven with moderate disease and two with mild disease; both cases with mild disease had current FVIII inhibitors. Forty-nine PwHA had current FVIII inhibitors, 12 had a history of FVIII inhibitors, and 12 had no FVIII inhibitors. Five out of 73 (6.8%) received immune tolerance induction (ITI) treatment while on Hemlibra®. Two cases of rash (allergic or acute reactions) were reported (2/73, 2.7%) of which one (reported six days after administration) was possibly related to Hemlibra® according to the reporting haemophilia treatment centre. No thromboembolisms or thrombotic microangiopathies were observed.
Median ABR (IQR) for the entire study population was 0.0 (0, 0) and 59/73 (80.8%) had no recorded bleeds. In the 14/73 (19.2%) with recorded bleeds, median ABR (IQR) was two (1, 3); eight of those 14 had joint bleeds and seven had spontaneous bleeds.

UKHCDO study of non-inhibitor people with haemophilia A using Hemlibra®

Doctors from the UK Haemophilia Centre Doctors' Organisations (UKHCDO) led by Hay C. presented at the EAHAD 2022 Congress (PO054) an observational 19-month study of 543 people with severe haemophilia A (pSHA) without inhibitors using **Hemlibra®**. Clinical practice with this novel treatment in non-inhibitor patients is starting to increase and rates of patients switching to Hemlibra® for prophylaxis are variable between UK centres[9]. The analysis was conducted in patients with ≥ six months pre-switch Haemtrack home-therapy diary data.
Hemlibra® was prescribed to 543 non-inhibitor pSHA, 30% of potentially eligible pSHA. A within-patient comparison with previous recombinant FVIII prophylaxis was conducted in 259 pSHA with sufficient factor usage data and was broken down by age. In the period after switching, the zero treated bleed rate increased from 36% to 80% in those aged <18 and from 30% to 68% in patients aged ≥18. The median (IQR) ABR and joint ABR (AjBR) reduced from 2.9 and 1.2 to 0.3 and 0.0 respectively in those aged <18 and from 6.6 and 2.7 to 0.8 and to 0.0 respectively in those aged ≥18s. Annualised spontaneous bleeding (ASBR) for both groups decreased from 0.6 to 0.0. A within-person sub-analysis of 78 people reporting bleeding after switching to Hemlibra® showed a median (IQR) change in ABR of -0.7 in <18 and -3.4 in ≥18, and overall 72% (56/78) bled less. All subjects used prophylaxis and few, consequently, had active target joints. Comparing the 27 switchers with 44 target joints with 58 non-switchers with 88 target joints, after a median of 15 months of factor usage, 41% of non-switchers had fewer and 34% more target joints compared to switchers, of whom 67% had fewer and only 7% more target joints.
In conclusion, switching to Hemlibra® was associated with improvement in bleed control in all age groups of pSHA without inhibitors. Spontaneous bleeding was largely eliminated - those who continued to bleed had a significant reduction in ABR, AjBR and ASBR. Target joints settled significantly more frequently than in people who continued rFVIII prophylaxis.

Data from the Dutch HemoNED registry on the use of Hemlibra®

Dutch researchers led by Taal E. presented during the 2022 EAHAD Congress data (abstract PO096) on using **Hemlibra®** in non-inhibitor patients in the Netherlands. Their data came from the Dutch Haemophilia Registry 'HemoNED.' This registry includes the Netherlands' six haemophilia comprehensive care treatment centres, and most severe patients are included (following informed consent). At the cut-off data date, 1333 patients with haemophilia A (severe, n=572; on prophylaxis, n=575) were in the database. One hundred and sixty-two patients were treated with Hemlibra®. Forty-

[9] UKHCDO Annual Report 2021.

three per cent were <18, and the majority (92%) had severe HA. Over 80% of patients took Hemlibra® either every one or two weeks. The mean prescribed dose was 1,60 mg/kg/week. People on Hemlibra® reported starting the treatment due to venous access problems (16%), inhibitor with a bleeding tendency (12%) or recurring bleeds despite regular prophylaxis (9%). However, more than half (52%) of the patients started for non-specific reasons, most likely patient preference. Seventy-seven per cent reported no bleeds during the treatment with Hemlibra®.
In terms of side effects, three patients reported rash and joint pain in the digital infusion log while two patients stopped Hemlibra® treatment.

Results from the HAVEN 6 trial: Use of Hemlibra® in mild and moderate haemophilia A

In an abstract (343) from ASH 2021, Roche presented the phase III HAVEN 6 trial (NCT04158648)[10] to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of **Hemlibra®** prophylaxis in people with mild or moderate haemophilia A without FVIII inhibitors.
Participants received Hemlibra® loading doses of three mg/kg once weekly for four weeks, followed by a maintenance dose of either 1.5 mg/kg every week, three mg/kg every two weeks or six mg/kg every four weeks. The safety endpoints included adverse events (AEs), serious AEs (SAEs) and AEs of special interest, including thromboembolic events (TEs) and thrombotic microangiopathies (TMAs). The efficacy endpoints included ABR and Hemophilia Joint Health Score (HJHS), health-related quality of life and treatment preference. Seventy-one (males, n=69; females, n=2; mild, n=21; moderate, n=51) participants were included in the analysis. Thirty-seven participants were on FVIII prophylaxis at baseline.
In terms of safety results, 49 participants had ≥1 AE. Headache was the most common (14.1%). The majority of AEs (84.5%) were not Hemlibra®-related. Nine participants experienced Hemlibra®-related local injection-site reactions. One participant experienced two grade-≥3 AEs, neither Hemlibra®-related. Four participants reported a total of six SAEs; none were considered Hemlibra®-related by the investigator. There were no deaths, AEs leading to treatment withdrawal, modification or interruption, TEs, or TMAs.
In terms of efficacy, investigators looked at ABR for treated bleeds, all bleeds, treated joint bleeds and treated spontaneous bleeds. The calculated median ABR were zero in all categories except 'all bleeds.' Zero bleeds were reported for 80.3% (treated bleeds), 46.5% (all bleeds), 90.1% (treated joint bleeds), 95.8% (treated spontaneous bleeds), and 94.4% (treated target joint bleeds) of participants. Two participants developed anti-drug antibodies (ADAs). One of these had ADAs neutralizing *in vitro*; however, no clinical impact or impact on Hemlibra® PK was observed. Hemlibra® trough concentrations were 10%–15% higher than HAVEN 1–4 (Callaghan et al., *Blood*, 2021).
A mean improvement in HJHS total score from the baseline of –1.77 (2.94) was observed at week 25 (n=47). The trend for improvement from baseline in the treatment burden domain for the Comprehensive Assessment Tool of Challenges in Haemophilia (CATCH)[11] was consistent across age groups. Except for a small improvement in 'social activity risk perception' among adolescents, the remaining CATCH domains were stable. Improvements were observed in 'treatment burden,' and 'preoccupation' domains among caregivers, but due to the small sample number, trends should be interpreted with caution. Overall, 48 out of 50 respondents preferred Hemlibra® over their previous therapy.

Impact of Hemlibra® on ABR in a real-world setting in non-severe HA patients

In an ASH 2021 abstract (1961), Roche presented data on the use of Hemlibra® in non-severe haemophilia A patients in a real-world setting. They aimed to describe the changes in annualised

[10] A study to evaluate the safety, efficacy, pharmacokinetics and pharmacodynaimcs of emicizumab in participants with mild or moderate haemophilia A without FVIII inhibitors (HAVEN 6).
[11] CATCH is a questionnaire developed to assess the impact of haemophilia and its treatment on PwHA and their families. Markowitz JT, et al. Presented at the American Thrombosis and Hemostasis Network Data Summit. Chicago, Illinois. October 25–26, 2018.

bleeding rate (ABR) in these patients after initiating Hemlibra®. The researchers collected data via the Adelphi HA Disease-Specific Programme™, a point-in-time survey of physicians treating people with haemophilia A collected in the United States from February 2020 to April 2021. Nineteen patients (severe, n=14; mild/moderate n=5) were included in the survey. Following initiation with Hemlibra® (average time of use was 20.8 months), a large proportion of patients (79%) experienced zero bleeds compared to their pre-Hemlibra® time (21%). ABR during pre-Hemlibra® was 2.1 compared to 0.3 post-Hemlibra® initiation. In particular, for mild/moderate patients, ABR was 3.2, and it decreased to 0.57 following Hemlibra®.

Real-world bleeding risk assessment for people on Hemlibra®

A group of Russian and Israeli researchers led by Levy-Mendelovich S. compared breakthrough bleeding risks for patients on Hemlibra® (EAHAD 2022, PO113). This observational study included 70 HA patients from an Israeli haemophilia treatment centre and looked at spontaneous and traumatic bleeds during selected time points. The percentage of traumatic and spontaneous bleeding episodes was not significantly different among "bleeding periods." Most trauma-related treated bleeds resulted from either hemarthrosis (53%) or head trauma (33%). Spontaneous bleeding episodes were mostly hemarthroses (80%). Potential associations of the patients' age, annualised bleeding rate before Hemlibra® treatment, and the presence of inhibitor with spontaneous bleed occurrence were analysed. The odds of bleeding while on Hemlibra® increased by a factor of 1.029 (P = 0.034) for every one year of age. No difference was found with regards to inhibitor existence. This data revealed that the risk of bleeding while on Hemlibra® persists, especially in older patients.

Report of invasive surgeries with Hemlibra® in Slovenia

A group of clinicians led by Rener K. reported surgical experiences in people with haemophilia A on Hemlibra® in Slovenia (EAHAD 2022, abstract PO082). These surgeries occurred between August 2019 and September 2021. Seven procedures were performed in six people with haemophilia A (with inhibitors, n=2; without inhibitors, n=4) while on Hemlibra® prophylaxis. These included three minor surgeries, four major orthopaedic surgeries and one percutaneous coronary intervention with stent implantation performed in a patient with ST-elevation myocardial infarction (a type of heart attack leading to a greater risk of complications and death). Patients with inhibitors received rFVIIa (mean consumption 7.1 mg/kg), and those without inhibitors received standard half-life rFVIII (mean consumption 437 IU/kg). In inhibitor patients, no additional laboratory monitoring was performed during the procedure, while in non-inhibitor patients, bovine and human chromogenic assays were used. No thromboembolic events or new inhibitors developed.

Data on the use of Hemlibra® in people aged ≥50 with co-morbidities

In an abstract (2103) from the 2021 ASH Congress, Jimenez-Yuste V. and colleagues, supported by Roche, presented an analysis based on data from four phase III studies (the HAVEN studies 1[12],3[13] and 4[14], and STASEY[20] - see above) to evaluate the safety and efficacy of **Hemlibra®** in people with haemophilia A aged ≥50 years with cardiovascular (CV) risk factors, HIV and/ or prior or current HCV infection. These studies included people with and without FVIII inhibitors and no clinical signs or history of cirrhosis. In the HAVEN studies, potential participants were excluded if they had severe hepatic disease, HIV infection with a CD4 count <200 cells/µL, or concurrent disease.

Ninety-six patients were ≥50 years and eligible for this analysis. The median Hemlibra® treatment duration was 2.02 years. Participants included people with CV risk factors (≥1 CV risk factor, n=70; ≥2 CV risk factors, n=24) and viral infections (HIV, n=1; HCV infection, n=48; HCV+HIV co-infection, n=22).

[12] A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Participants With Inhibitors (HAVEN 1).

[13] A Clinical Trial to Evaluate Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Participants Without Inhibitors (HAVEN 3).

[14] A Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Emicizumab Given Every 4 Weeks in Participants With Hemophilia A (HAVEN 4).

The mean annualised bleeding rate (ABR) for this population was 1.82 and was consistent in participants with CV risk factors and HIV or HCV infection. Participants aged ≥50 years with HIV+HCV co-infection had a higher treated ABR of 2.72 (95% CI: 0.5–8.34).
Adverse events (AEs) and serious AEs occurred in 89 (92.7%) and 23 (24.0%) participants ≥50 years, respectively. Grade 3-4 AEs and injection site reaction rates were similar among participants in the overall study population and participants ≥50 years. Thrombotic events (Tes) and thrombotic microangiopathies occurred in two participants ≥50 years (2.1%); both had ≥1 CV risk factor, and one also had HCV infection.
In conclusion, ABRs for PwHA ≥50 years with CV risk factors, or with HIV or HCV infection, receiving Hemlibra® prophylaxis were similar to the overall study populations. Higher ABRs were observed for PwHA with HIV+HCV co-infection; however, authors hypothesise that these may have been skewed by a minority of PwHA with unexpectedly high ABRs. Furthermore, given the small sample size and wide confidence intervals, they stated that it was difficult to draw conclusions. HIV and HCV infections have been associated with increased bleeding risk in PwHA (Chen, et al. Value Health 2015), which may have had a cumulative effect in this subpopulation. Safety outcomes were similar to the overall study populations; Hemlibra® prophylaxis was well tolerated in PwHA ≥50 years with comorbidities.

Comparison of ABR and costs of FVIII prophylaxis and Hemlibra® treatment in people without inhibitors

In an abstract (3028) from ASH 2021, Takeda presented a comparison for annualised bleeding rates (ABR and all-cause costs (ACC)) for patients with haemophilia without inhibitors switching from FVIII replacement and **Hemlibra®**. It should be noted that this comparison only considered 'billed' bleeds, those are bleeds that required medical assistance. It left out bleeds that patients were able to home-treat. The investigators used the IQVIA PharMetrics® Plus database (2015-2020) - a large longitudinal US commercial health plan database with over 190 million patient records.
The study included 121 patients. In 42% patients, ABR remained unchanged from pre-switch to post-switch, while in 38% patients, there was an improvement. Twenty per cent of patients experienced worsening of ABR. Investigators noted an increase in ACC post-switch. This study is specific to US healthcare costs, and its results cannot be easily transferred to a European setting.

Low-dose Hemlibra® prophylaxis experience in Thai patients

In an abstract (2116) from ASH 2021, a group of Thai investigators led by Chuansumrit A. detailed their experience of low-dose prophylaxis with **Hemlibra®**. Investigators aimed to achieve the equivalent of FVIII levels of 1-3%. To do so, they enrolled five haemophilia A non-inhibitor patients (severe, n=3; moderate, n=2) and one inhibitor patient. They all behaved in low bleeding risk circumstances (avoiding contact sports). All patients received one whole vial of Hemlibra® at 30,75, 105 mg per month. Three patients received 60 mg per month, equalling 1.1 to 1.6 mg/kg. The monthly trough levels of Hemlibra® determined by a modified one-stage factor VIII assay using Hemlibra® calibrator were maintained at 3.8 to 9.8 µg/ml, which were equivalent to the levels of FVIII at 1 to 3%. The bleeding rate was markedly decreased from 4-8 episodes monthly to 0-1 episode monthly. Four patients experienced monthly zero bleeds. The swollen target joint gradually dissolved. Their quality of life markedly improved evaluated by the Hemo-QoL and CHO-KLAT questionnaires. Participants were able to resume regular activities such as attending school and work.

Cross-reactivity of Mim8 and anti-Hemlibra® antibodies

In an abstract (3193) at ASH, Gualtierotti R. and colleagues presented data on cross-reactivity of **Hemlibra®**-anti-drug antibodies against **Mim8**, a novel experimental FVIII-mimetic human bispecific antibody (as is Hemlibra), currently in phase II development by Novo Nordisk. Investigators developed an in-house detection method. They studied serum from three patients who developed anti-Hemlibra® antibodies. Patients' plasma was collected during treatment, thus containing Hemlibra® at steady-state levels. One patient had neutralising persistent antibodies, while the other two had non-neutralising transient antibodies.

Investigators showed that anti-Hemlibra® antibodies did not react with Mim8 *in vitro*. Further studies are needed to confirm that Mim8 can be safely used in patients with anti-Hemlibra® antibodies.

Use of chromogenic assays with Mim8

In an abstract (PO004) presented at the 2022 EAHAD Congress, Novo Nordisk presented a study to determine which chromogenic substrate assay (CSA) could monitor FVIII in the presence of Mim8. This product is a factor IXa/X bispecific antibody in phase II clinical developments. No Mim8 interference was seen with bovine CSAs for all FVIII concentrations. However, human CSAs cannot measure FVIII in samples containing Mim8. With bovine/human CSAs, the interference observed at high Mim8 concentrations diminished as FVIII concentrations increased, and the interference disappeared at 100 IU/dL of FVIII.

Use of bypassing agents with NXT007

In an abstract (2114) from ASH 2021, Ogiwara K. and colleagues supported by Chugai examined the *in vitro* effect of bypassing agents (BPAs) in the co-presence of **NXT007** to determine its safety. NXT007 is a bispecific antibody which increases tissue factor-triggered thrombin generation potential of FVIII-deficient plasma.
The authors concluded that when considering concomitant use of BPA with NXT007-prophylaxis, a dose of activated prothrombin complex (aPCC) should be more carefully determined than that of rFVIIa. In this non-clinical study, the combined effect of ~0.13 U/mL aPCC (equivalent to ~10 U/kg infusion) and ~15 µg/mL NXT007 did not exceed that of 0.65 U/mL aPCC (50 U/kg infusion) under Hemlibra®-prophylaxis situation corresponding to the upper limit of initial concomitant dose recommended by the National Hemophilia Foundation (NHF) Medical and Scientific Advisory Council. This data might give rough indicators in future clinical settings.

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 37. We invite you to consult this section for further updates on these products.

Gene Therapy

Results from the phase III GENEr81 trial for valoctocogene roxaparvovec

In an abstract (3972) from ASH 2021, Pipe S. and colleagues supported by BioMarin presented the post-hoc analyses of the gene therapy-derived FVIII activity and bleeds in their phase III GENEr81 (NCT03370913)[15] clinical trial. This study evaluated factor VIII activity and annualised bleed rate (ABR) following one infusion of their experimental gene therapy **valoctocogene roxaparvovec** in 134 adult males with severe haemophilia A. Participants received one $6x10^{13}$ vg/kg infusion of valoctocogene roxaparvovec. As of the cut-off date, investigators had followed participants for 71.6 weeks. A summary of factor VIII expression in participants at week 49-52 is shown. The authors chose this timepoint because it was the last time all participants had their FVIII activity levels measured.

[15] Single-arm study to evaluate the efficacy and safety of valoctocogene roxaparvovec in haemophilia A patients (BMN-270-301).

Achieved factor activity range at weeks 49-52 of the GENEr81 trial (measured by chromogenic assay)	Number of trial participants reaching the values in the left column against the total number of trial participants. In brackets is their proportion compared to the total number of trial participants.
<3 IU/dL	12/134 (9%)
3–5 IU/dL	4/134 (3%)
5–15 IU/dL	23/134 (17%)
≥15 IU/dL	95/134 (71%)

While on FVIII prophylaxis, prior to gene transfer, 32% of participants (43/134) had an ABR of zero. After gene transfer, 75% of participants (101/134) were bleed-free through their last follow-up prior to the data cut. The remaining 33 participants reported a total of 149 treated bleeds total, with 62% (93/149) being traumatic and 38% (56/149) as spontaneous. Most bleeds occurred in the joints (53%) followed by muscle, soft tissue and other unspecified locations. Most treated bleeds (54%) occurred when FVIII activity levels were below 3 IU/dL (measured with chromogenic assay). Only 16/149 bleeds occurred in the ≥15 IU/dL FVIII range, with 13 of these being traumatic. The same pattern was seen in treated joint bleeds, where 51% of bleeds occurred when FVIII activity levels were <3 IU/dL. In BioMarin's mathematical modelling of these data, it was predicted that individuals treated with valoctocogene roxaparvovec who reached a chromogenic FVIII activity ≥15 IU/dL would have less than one bleed in two years.

In this abstract, BioMarin notes that the chromogenic assay used to measure factor VIII activity is limited by its own lower limit of quantitation (LLOQ) of 3 IU/dL. This means that 3 IU/dL is the lowest amount of FVIII that the assay can distinguish from the absence of FVIII with certainty. The abstract tells us that nine out of 12 participants with FVIII activity less than the LLOQ by the chromogenic assay at 49-52 weeks had either improved or maintained the same ABR after gene therapy compared to prophylaxis. To gain more granularity in the factor VIII expression levels in these participants, BioMarin also tested samples using a one-stage assay (OSA) with a LLOQ of 1 IU/dL. Of the twelve participants in the lower spectrum of FVIII expression as measured by chromogenic assay, one had levels less than 1 IU/dL using the OSA assay. Five had levels between 1 and 5 IU/dL, and three had levels ≥5 IU/dL. The three remaining participants, who had increased ABR after gene therapy, had levels of 0, 2.1, and 4.8 IU/dL measured with OSA.

During the 2022 EAHAD Congress, Mahlangu J. presented during a Congress session the results of the two-year analysis (median 110.9 weeks) of the phase III GENEr8-1 clinical trial for investigational gene therapy valoctocogene roxaparvovec for haemophilia A. As mentioned above, all participants in this phase III study received a single $6x10e^{13}$ vg/kg dose of valoctocogene roxaparvovec. A summary of factor VIII expression in participants at week 104 is shown below:

Achieved factor activity range at week 104 of the GENEr81 trial (measured by chromogenic assay)	The number of trial participants reaching the values in the left column against the total number of trial participants. In brackets is the proportion compared to the total number of trial participants.	Percentage of patients with no treated bleeds in the past year of follow-up and not on prophylaxis.
<3 IU/dL	18/134 (14%)	28% (4 reinitiated prophylaxis)
3–5 IU/dL	13/ 134 (10%)	77% (1 reinitiated prophylaxis)
5–15 IU/dL	46/134 (35%)	85% (1 reinitiated prophylaxis)
15-40 IU/dL	35 /134 (26%)	97%
>40IU/ml	20 / 134 (15%)	100%

The ABR was significantly reduced by 4.1 treated bleeds per year (p-value <0.0001), or by 85% from a baseline mean of 4.8 (median 2.8), in the prespecified primary analysis in participants from a prior non-interventional study. The percentage of participants with zero treated bleeds increased from 32% on prophylaxis at baseline to 82% during year one and 84% during year two. The mean post-treatment ABR was 0.8 (median 0.0) through the entire efficacy evaluation period, 0.9 (median 0.0) during year one, and 0.7 (median 0.0) during year two. Across all participants in the rollover population (n=112), the mean annualised factor VIII infusion rate was reduced by 133 infusions per year (p-value <0.0001) or 98% from baseline. As of the two-year data cut, 95% of participants remain off FVIII prophylactic therapy. No participant developed inhibitors to FVIII, malignancy or thrombotic event linked to the investigational gene therapy. During year two, no new safety signals emerged, and no treatment-related serious adverse events (SAE) were reported.

Overall, the most common adverse events (AE) associated with valoctocogene roxaparvovec occurred early and included transient infusion associated reactions and mild to moderate rise in liver enzymes with no long-lasting clinical sequelae. Alanine aminotransferase (ALT) elevation (119 participants, 89%), a laboratory test of liver function, remained the most common AE. Most patients had discontinued any corticosteroid (CS) use in year one, and there were no CS-related SAEs in the remaining patients being tapered off CS in year two. Other common adverse events included headache (41% of participants), arthralgia (40% of participants), nausea (38% of participants), aspartate aminotransferase (AST) elevation (35% of participants), and fatigue (30% of participants). During year one another serious adverse event of suicide occurred in an individual taking part in the study. The individual had an underlying history of depression and mental health issues and was not taking immunosuppressant therapy at the time. The adverse event was deemed unrelated to the treatment. In November 2021, during the phase 1/2 study, an SAE of a salivary gland mass was identified in one study participant, who was treated more than five years prior with the gene therapy and was reported as unrelated to valoctocogene roxaparvovec by the investigator. The relevant health authorities were notified in late 2021, and all studies remain ongoing without modification. The independent Data Monitoring Committee (DMC) have further reviewed the case. Genomic analysis is being conducted as pre-specified in the clinical trial protocol.

In an article in the *New England Journal of Medicine*, published in March 2022, Ozelo M. C. et al. report on the results of the phase III clinical trial [16]to evaluate the safety and efficacy of valoctocogene roxaparvovec in men with severe haemophilia A. Participants included adults with no pre-existing anti-AAV5 antibodies or a history of development of FVIII inhibitors. They received a single infusion of 6×1013 vg/kg of valoctocogene roxaparvovec. The primary endpoint was the change from baseline of FVIII activity (measured with a chromogenic substrate assay) during weeks 49 through 52 after infusion. The secondary endpoints included the change in annualised FVIII concentrate use and bleeding rates. Safety was assessed as adverse events and laboratory tests results.

One hundred and thirty-four participants received an infusion as described above and completed more than 51 weeks of follow-up. Among the 132 HIV negative participants, the mean FVIII activity level at week 49 through 52 had increased by 41.9 IU per dL (95% CI). Among the 112 participants who enrolled from a prospective non-interventional study, the mean annualised rate of FVIII concentrates use and treated bleeding after four weeks had decreased after infusion by 98.6% and 83.8% respectively. All the participants had at least one adverse event, 22/134 reported serious adverse events. Elevations in alanine aminotransferase (ALT) levels occurred in 115/134 participants (85.8%) and were managed with immune suppressants. The other most common adverse events were headache (38.1%), nausea (37.3%), and elevations in aspartate aminotransferase levels (AST, 35.1%). No development of factor VIII inhibitors or thrombosis occurred in any of the participants. This article was supported by BioMarin Pharmaceuticals.

Valoctocogene roxaparvovec reported adverse event and update

During the 2022 EAHAD Congress, Mahlangu J. presented during a session the two-year analysis of the phase III GENEr8-1 clinical trial for investigational gene therapy valoctocogene roxaparvovec for haemophilia A, where a serious adverse event (SAE), of a salivary gland mass, deemed unrelated to the treatment was reported. In November 2021, during the phase 1/2 study, an SAE of a salivary gland mass was identified in one study participant who was treated more than five years prior with the gene therapy. The relevant health authorities were notified in late 2021, and all studies remain ongoing without modification. The SAE was monitored by an independent Data Monitoring Committee (DMC).

In April 2022, BioMarin reported that the patient was reported successfully treated. A genomic analysis from a tissue sample containing the mass was conducted. The findings from the completed analysis showed a comparable pattern of integration between healthy and tumour containing tissues, with no evidence emerging that vector integration contributed to the salivary gland mass. These data will be presented both in a workshop at the annual American Society of Gene & Cell Therapy meeting and the World Federation of Hemophilia 2022 World Congress and supplied to the EMA as part of the ongoing review of the marketing application authorisation (MAA).

Valoctocogene roxaparvovec in people with HIV

In an abstract from the EAHAD 2022 Congress (PO146), investigators led by Ragni M. described the outcomes of people with HIV receiving BioMarin's experimental gene therapy, **valoctocogene roxaparvovec**, in the phase III trials 301 (NCT03370913 – see above) and 302 (NCT03392974)[17].

Two HIV positive participants took part in trial 301 where they received $6x10^{13}$ vg/kg valoctocogene roxaparvovec. Patient 1 (P1) received Eviplera (emtricitabine, rilpivirine, tenofovir) and dolutegravir for HIV treatment. P1 had six mild adverse events with no liver-related adverse events. Patient 2 (P2) received darunavir, dolutegravir, and ritonavir for HIV treatment. He had 50 minor adverse events and two serious ones (upper respiratory tract infection and traumatic haematoma). P2 reported elevated

[16] Single-arm study to evaluate the efficacy and safety of valoctocogene roxaparvovec in haemophilia A patients at a dose of $4x10^{13}$ vg/kg (BMN270-302).

[17] Single-arm study to evaluate the efficacy and safety of valoctocogene roxaparvovec in haemophilia A patients at a dose of $4x10^{13}$ vg/kg (BMN270-302).

liver biomarkers (aspartate aminotransferase, AST) on day 85 and day 107. P2 initiated corticosteroids (prednisone) on day 109 at 60 mg/day and liver adverse events were resolved.

In the 302 trial, one HIV positive patient (P3) received a $4x10^{13}$ vg/kg of valoctocogene roxaparvovec. P3 was receiving efavirenz, lamivudine, and tenofovir disoproxil fumarate for HIV treatment and had negative HIV RNA PCR and normal liver function tests (LFTs) at baseline. Five weeks post gene therapy infusion, his LFT began to increase. On day 34, he developed moderate liver biomarkers elevation (AST and alanine transaminase, ALT) and was started on corticosteroids (prednisone) at 60 mg/day. These liver biomarkers worsened, and on day 41, he developed hepatocellular injury (peaking at an ALT of 807U/L on day 51, AST of 408U/L on day 49 and gamma-glutamyl transferase at 437 U/L on day 49). On day 65, following discussions between the patient, a hepatologist and the investigator, his HIV treatment was replaced with raltegravir and emtricitabine/tenofovir alafenamide. Afterwards LFTs declined continuously, with complete resolution on day 105. The patient (P3) was asymptomatic throughout.

Post-infusion, P1 and P2 had a reduction in treated bleeds (2.8 to 0.9 and 5.8 to 3.5 bleeds/year, respectively) and increased FVIII (weeks 49–52, 24.3 and 6.1 IU/dL) and remained off prophylaxis.
P3 gained FVIII (day 22, 11.5 IU/dL), which was lost (along with protection from bleeds) concurrent with the LFT AEs. He resumed prophylaxis at week 49. Investigators believe that the high liver biomarkers elevation in P3, which was unresponsive to corticosteroids, was due to an interaction between gene therapy and efavirenz, a known liver-toxic agent.

Impact of valoctocogene roxaparvovec on quality of life

In an abstract (PO077) presented at EAHAD 2022, researchers led by O'Mahony B. and supported by BioMarin presented the impact of **valoctocogene roxaparvovec** on health-related quality of life. This experimental gene therapy is in development by BioMarin. Investigators looked at data from baseline and compared it to 26- and 52-weeks post-gene therapy. Health-related quality of life was analysed using Haemo-QoL-A, EQ-5D-5L visual analogue scale (VAS) and the Utility Index Score. One hundred and thirty-two male participants without a history of inhibitors and who previously were on prophylaxis reported their quality of life. Improvements in core outcomes of mental health, pain and discomfort, and the ability to perform daily activities were seen compared to baseline on FVIII prophylaxis following treatment with valoctocogene roxaparvovec.

Two-year follow-up data from the ALTA study

In abstracts presented at ASH 2021 (564) and at EAHAD 2022 (PO043), Visweshwar N., Rupon J. and colleagues supported by Pfizer presented the two-year follow-up data from the phase I/II dose-ranging ALTA study (NCT03061201)[18]. In this study men with severe haemophilia A were infused with giroctocogene fitelparvovec. Participants were infused with this experimental gene therapy in four cohorts of two patients each across four ascending doses 9e11, 2e12, 1e13, and 3e13 vg/kg. The 3e13-vg/kg dose cohort was then expanded to include three additional patients, resulting in a total of eleven patients reported in this trial.

The most commonly reported treatment adverse events (AEs) were elevated liver enzymes (alanine aminotransferase (ALT), n=5; aspartate aminotransferase (AST), n=3), fever (n=3), and tachycardia (n=2). The majority of adverse events occurred in the 3e13 vg/kg cohort of five patients.
Treatment-related serious AEs were reported in one patient (3e13-vg/kg cohort) who experienced hypotension and fever with onset ≈6 hours after giroctocogene fitelparvovec infusion. These events fully resolved with treatment and did not delay post-infusion discharge on the next day.

[18] A study of recombinant AAV2/6 human factor 8 gene therapy SB-525 (PF-07055480) in subjects with severe haemophilia A.

ALT elevations requiring more than seven days of corticosteroid treatment were observed in four of the five patients in the 3e13-vg/kg cohort. These elevations in ALT were managed with a tapering course of corticosteroids, with the maintenance of efficacious levels of FVIII activity, as evidenced by a lack of bleeding events around the time of corticosteroid treatment and minimal bleeding events afterwards. No patient in the study developed a FVIII inhibitor, and there were no thrombotic events and no hepatic masses were detected (i.e., liver cancer or tumours). Four of the five patients in the 3e13-vg/kg cohort had data available at week 104 and they had mean FVIII activity maintained in the mild haemophilia to normal range. In this cohort, the annualised bleeding rate (ABR) was zero for the first-year post-infusion and 0.9 throughout the total duration of follow-up. In the 3e13-vg/kg cohort, two patients experienced a total of three bleeding events (two traumatic; one unknown), requiring treatment with replacement FVIII treatment. One of these events occurred in a target joint. No patients in cohort 4 (3e13 vg/kg) have needed to resume prophylaxis.

Investigators assessed clearance of viral vector DNA in saliva, urine, plasma, stool and semen following vector infusion. Vector shedding levels across all cohorts (n=11) were generally the highest during the first two weeks post-infusion and gradually declined in all specimen types. In the 3e13-vg/kg dose cohort, the median time (range) to first clearance was two (1–4) weeks in urine (n=5), four (2–12) weeks in semen (n=5), eight (6–12) weeks in saliva (n=4), and eight (4–26) weeks in the stool. In plasma (n=3), the median clearance was eight (8–20) weeks, except for one participant whose last positive sample was at week 64. There was a dose-dependent increase in peak vector values in plasma and saliva. Detectable levels of vector were only seen in cohort four for urine.

Pfizer/Sangamo reported a deep vein thrombosis (DVT) in one trial participant dosed with giroctocogene fitelparvovec

In March 2022, the US Food and Drug Administration (FDA) lifted the clinical hold placed on the phase III AFFINE study in November 2021 following the observance of factor VIII levels greater than 150% in some study participants. At the time of this report going to print, the initial voluntary pause by Pfizer/Sangamo remains in place until all necessary conditions are met, including approval of updated study protocols by regulatory authorities. In a recent investor report (page 12), an event of below-the-knee deep vein thrombosis in one trial participant with elevated Factor VIII levels. The patient had a history of thrombotic events prior to participation in the study, a known risk factor for subsequent events. The case was assessed to understand all potential contributing factors, including missed doses of investigator-prescribed direct oral anti-coagulants. The patient is reported to be doing well.

Reports from the phase I/II study of BAY 2599023

In an abstract (3971) presented at ASH 2021, Pipe S. and colleagues supported by Bayer presented an update on the phase I/II trial (NCT03588299)[19] of the experimental gene therapy, **BAY 2599023**. Patients were enrolled in this dose finding study to three dose cohorts (cohort 1: 0.5×10^{13}genome copies (gc)/kg, cohort 2: 1.0×10^{13} gc/kg and, cohort 3: 2.0×10^{13} gc/kg), each comprising at least two patients. The investigators plan to enrol two or more patients into a fourth dosing cohort to receive a single infusion of 4×10^{13}gc/kg.

In our last issue, we reported the data on this trial with a cut-off data date of January 2021. In this abstract, the data cut-off date was May 2021. Patients in cohorts 2 (n=2, $1.0\text{x}10^{13}$ gc/kg) and 3 (n=5, $2.0\text{x}10^{13}$ gc/kg) have been off prophylaxis with FVIII products since approximately 6-12 weeks after the gene therapy infusion. To date, no spontaneous bleeds requiring treatment have been reported once FVIII levels >11 IU/dL were achieved. Since our last newsletter, an additional patient has been included in the study (total participants, n=9). Changes from the previous reporting include sustained factor VIII

[19] Study to test the safety and how well patients with severe haemophilia A respond to treatment with BAY 2599023 (DTX 201), a drug therapy that delivers a normal FVIII gene into the nucleus of liver cells using an altered non-infectious virus (AAV) as a 'shuttle'.

expression levels for up to >23 months (vs 21 months) with evidence of bleed protection. Five out of nine patients developed adverse events of special interest: mild/moderate alanine aminotransferase (ALT) elevations. This includes two additional patients who have developed ALT elevation, since our last reporting. Both participants were in cohort 3 (2.0×10^{13} gc/kg). One patient developed mild to moderate ALT; the other ALT elevation was reported as a study-drug-related serious adverse event but returned to normal a few weeks after interruption of the H2 blocker famotidine.

Report from the phase I/II clinical trial for SPK-8011

In an article published in November 2021 in the *New England Journal of Medicine*, George L. and colleagues reported on phase I/II trial (NCT03003533)[20] with **SPK-8011**, an experimental gene therapy for people with haemophilia A in development by Spark Therapeutics.

Investigators infused 18 men split into four dose cohorts. The lowest dose cohort received $5x10^{11}$ vector genomes (vg)/kg, and the highest dose cohort received $2x10^{12}$ vg/kg. The trial was set up to test the safety, efficacy, expression and durability of SPK-8011.

In the November 2021 EHC New Product Newsletter, the ISTH 2021 presentation was featured. The data cut-off was also May 2021.

Participants were observed for safety for a median of 36.6 months (range 5.5-50.3 months). A total of 33 treatment-related adverse events occurred in eight participants. Seventeen adverse events were vector-related, including one serious adverse event, and 16 were glucocorticoid-related. Some participants received corticosteroids within 52 weeks of gene therapy infusion either to prevent or treat a presumed AAV capsid immune response. Two participants lost all factor VIII expression as a result of an anti–AAV capsid cellular immune response that was not responsive to immune suppression. In the remaining 16 participants, factor VIII expression was maintained; 12 of these participants were followed for more than two years, and the one-stage factor VIII assay showed no apparent decrease in factor VIII activity over time. Among the 15 participants in whom factor VIII expression was maintained and who were followed for more than 52 weeks, the mean factor VIII activity more than 52 weeks after vector administration was 11.0±6.8% of the normal value (range, 3.2 to 24.8) in a one-stage factor VIII assay and 6.9±3.8% of the normal value (range, 3.0 to 14.3) in a chromogenic factor VIII assay. However, it should be noted that these participants were on different dosing levels. After vector administration, the participants had a 91.5% reduction in the annualised bleeding rate. These results were also presented at the 2021 ISTH Congress in abstract OC 67.2.

[20] A gene transfer study for haemophilia A.

AN UPDATE ON NOVEL THERAPIES FOR PEOPLE WITH HAEMOPHILIA B

Replacement Therapy

Report from the ATHN 2 study on people switching to Idelvion®

In an abstract (1039) from the 2021 ASH Congress, investigators led by Journeycake J. and supported by CSL Behring presented data from the ATHN 2 study in which they switched patients to **Idelvion®**, an extended half-life recombinant FIX. The ATHN 2 study was sponsored by the American Thrombosis and Hemostasis Network (ATHN) and conducted on participants in the US haemophilia treatment centre network. The study had two arms, a prospective one that followed participants who had switched for up to one year and a retrospective one that followed participants who had switched in the 50 previous weeks of joining the study.
Forty-one participants were included in the analysis (prospective arm, n=27; retrospective arm, n=14). Sixty-three per cent (n=26) participants had severe haemophilia B. Following the treatment switch, 89% of participants remained on prophylaxis with once-weekly or less frequent dose intervals. Seventy per cent of participants were able to extend their dosing interval compared to prior joining the study. Thirty-three out of 37 participants responding to a satisfaction survey said they were somewhat or very satisfied.

Effects of Alprolix® on physical activity: post hoc analysis from the B-LONG study

In an article published in *Haemophilia* in January 2022, Astermark J. and colleagues presented a post hoc analysis of the B-LONG study describing change over time in patient-reported outcomes associated with pain and physical activity. Patients aged 12 or above received weekly dose-adjusted or interval adjusted prophylaxis with Alprolix® and completed the Haemophilia-Specific Quality of Life questionnaire at baseline and end of the study.
At the end of the study, 64% (vs 44% at baseline) of participants did not experience painful swelling, 44% (vs 28% at baseline) did not experience painful joints, and 54% (vs 41% at baseline) did not experience pain when moving. Additionally, patients were less likely to avoid sports. The authors of this abstract included Sobi representatives.

Non-Replacement Therapy

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 37. We invite you to consult this section for further updates on these products.

Gene Therapy

Five-year reporting post-infusion with fidanacogene elaparvovec

In an abstract (3975) presented at the 2021 ASH Congress, Samelson-Jones B. and colleagues gave an overview of the five-year follow-up of patients treated with Pfizer's experimental gene therapy fidanacogene elaparvovec at a dose of 5e11 vg/kg as part of their phase I/IIa study. The authors of this abstract included representatives from Pfizer. Patients taking part in that study could register for a long-term follow-up (LTFU) of up to five years. At the data cut-off date (December 2020), thirteen patients were enrolled in the LTFU study with follow-up ranging from >2.5 years to >five years following vector administration. No patient required treatment or re-treatment with corticosteroids in the LTFU study. Three patients reported serious adverse events in the LTFU study, none of which were considered treatment-related. No patient developed an inhibitor or reported thrombotic events,

and no patient developed hepatic masses or elevation in alpha-fetoprotein (AFP), a biomarker for liver cancer. A report specifically on the liver health post-fidanacogene elaparvovec infusion was presented at ISTH 2021 Congress, and we reported it in the 2021/2 issue of this publication.
The annual liver ultrasounds revealed only hepatic steatosis (fatty liver disease) in one patient. The mean FIX activity levels by year remained in the mild haemophilia severity range: 22.8%, year one (n=15); 25.4%, year two (n=14); 22.9%, year three (n=14); 24.9%, year four (n=9); and 19.8%, year five (n=7) when evaluated centrally using one-stage assay. These levels have been associated with the mean annualised bleeding rates (ABR) ranging from 0–0.9 throughout follow-up, and no patients have resumed FIX prophylaxis. Four patients have undergone six surgical procedures during the LTFU study. There were no bleeding complications with these procedures, and two of these procedures (appendectomy and lumbar discectomy) were performed without the need for additional FIX. Fidanacogene elaparvovec remains generally well tolerated over up to five years post-infusion. While encouraging, more long-term data in a larger cohort of patients are needed to characterise further the safety and durability of fidanacogene elaparvovec, which is underway in an ongoing phase III study.

Results from the dose-finding phase I/II study to evaluate the safety and efficacy of FLT180a

In an abstract (3967) from ASH 2021, Chowdary P. and colleagues presented the results from the phase I/II dose-finding study, B-AMAZE (NCT03369444)[21], and the ongoing long-term follow-up study (NCT03641703)[22]. In these studies, sponsored by the University College London (UCL) and Freeline, investigators looked at the use of experimental gene therapy FLT180a to treat people with moderately severe to severe haemophilia B (HB).
Ten HB patients received a single dose of FLT180a ranging from 3.84e11 vg/kg to 1.28e12 vg/kg. As of the data cut-off date, all patients were followed for ≥16 months.
FLT180a did not elicit any inhibitors or allergic reactions. The most common treatment-related adverse event was a transient elevation in alanine aminotransferase. An event of arteriovenous fistula thrombosis occurred in a 67-year-old patient who received the highest dose of 1.28e12 vg/kg (total dose of 1.15e14 vg) and had supranormal FIX levels. This patient was treated with anticoagulants. This dose will not be used in future haemophilia studies.
At week 26 after FLT180a administration, a dose-response relationship was observed with mean FIX activity of 45.0%, 35.5%, 141.5%, and 175.5% for 3.84e11, 6.4e11, 8.32e11, and 1.28e12 vg/kg doses, respectively. FIX activity levels ≥50% were achieved in seven of eight patients treated with the three highest doses. One patient who received 6.4e11 vg/kg, lost transgene expression early due to transaminitis and resumed routine factor prophylaxis. The 8.32e11 vg/kg cohort received an extended immune management regimen (nine to 18 weeks) with prophylactic tacrolimus (i.e., an immunosuppressant) in addition to prednisolone (steroid treatment) to prevent breakthrough vector-related transaminitis. However, after cessation of the immune management regimen, transaminitis with concomitant reductions in FIX activity were observed in all patients in the 8.32e11 vg/kg cohort. The combination of prophylactic tacrolimus and prednisolone appeared to have suppressed immune-mediated transaminitis while administered, but recurrence of transaminitis developed soon after cessation. This unique and previously unreported observation suggests that the longer-duration prophylactic immune management regimen may have prevented tolerisation to the vector because this was not observed in earlier cohorts where a brief course of tacrolimus was given reactively for breakthrough transaminitis. All patients (including the 8.32e11 vg/kg cohort) have achieved a steady state. Patients in the earliest cohort who received the lowest dose (3.84e11 vg/kg) have shown stable FIX activity for >three years. There were no spontaneous bleeds that required FIX supplementation in patients who remained off prophylaxis.
Patient 4 in the 6.4e11 vg/kg cohort experienced two bleeds (cause unknown) after losing transgene expression, which were treated with exogenous FIX. One patient received exogenous FIX for treatment of a traumatic bleed, but his FIX activity level was 57% at the time of the event.

[21] A factor IX gene therapy study (FIX-GT).
[22] A long-term follow-up study of haemophilia B patients who have undergone gene therapy.

In an abstract (PO049) presented at EAHAD 2022, investigators led by Young G. presented the B-LIVE study, a phase I/II trial of FLT180a using commercial-scale vector production to confirm the dose of FLT180a and immune management (IM) approach to be used in the FLT180a phase III study. A dose of $7.7x10^{11}$ vg/kg with a dose cap of $6.93x10^{13}$ vg/kg was selected for the first three patients in B-LIVE. A data monitoring committee will advise on any dose modification for the second cohort of three patients and enrol up to nine total patients if further dose adjustments are required. The prophylactic IM regimen will consist of a tapering course of prednisolone (steroid treatment) combined with a short course of tacrolimus (an immunosuppressant).

Results from the phase III HOPE-B trial for the use of etranacogene dezaparvovec in people with haemophilia B

During the 2022 EAHAD Congress, Miesbach W. presented the final analysis of the HOPE-B trial for the use of etranacogene dezaparvovec in people with haemophilia B. This is an experimental gene therapy in development by CSL Behring/uniQure.

Fifty-four male patients with severe or moderately severe haemophilia B took part in the HOPE-B phase III trial. Participants were dosed at $2X10^{13}$ gc/kg and expressed mean FIX activity of 39.0 IU/dL at six months and 36.9 IU/dL at 18 months post-infusion.

Post-gene therapy results were compared with six-month lead-in period before gene therapy administration, where patients were all under FIX well conducted prophylaxis by their usual factors.

The adjusted annualised bleeding rate (ABR) (1.51) for all bleeds was reduced by 64%(p=0.0002), and all FIX-treated bleeds were reduced by 77% (3.65 to 0.83; p<0.0001) over months seven to 18, as compared with prophylaxis. In addition, 98% of participants treated with a full dose of etranacogene dezaparvovec discontinued use of prophylaxis, with an overall 97% reduction in mean unadjusted annualised FIX consumption of 257338.8 IU/year/participant to 8486.6 IU/year/participant (from lead-in period to months 13-18).

Pre-existing neutralising antibodies against the AAV5 vector were assessed, but not used as an exclusion criterion. Twenty-one out of 54 patients had detectable anti-AAV5 antibodies at baseline.

Eighty per cent of adverse events in people taking etranacogene dezaparvovec were considered mild. One death resulting from urosepsis (untreated urinary tract infection) and cardiogenic shock in a 77-year-old patient at 65 weeks following dosing was considered unrelated to treatment by investigators and the company sponsor. One individual had a serious adverse event of hepatocellular carcinoma. An independent molecular tumour characterization and vector integration analysis determined a this to be unrelated to treatment with etranacogene dezaparvovec. No inhibitors to FIX were reported.

CSL Behring announced on 28 March 2022 that the European Medicines Agency (EMA) started the Marketing Authorisation Application review for etranacogene dezaparvovec under its accelerated assessment procedure, based on the above-mentioned positive findings from HOPE-B pivotal phase III trial, presented at EAHAD 2022.

Results from the phase IIb for etranacogene dezaparvovec

In an abstract (PO098) presented at EAHAD, investigators led by Gomez E. and supported by CSL Behring/UniQure presented the findings from the phase IIb clinical trial etranacogene deaparvovec (NCT03489291)[23], an experimental gene therapy for people with haemophilia B. In this abstract, researchers presented the multi-year data on durable FIX expression.

Participants received a single intravenous dose of $2x10^{13}$ gc/kg of etranacogene dezaparvovec. The primary efficacy endpoint was FIX activity ≥ 5% six weeks after infusion. Participants were also monitored for bleeding rates, FIX replacement, and safety over five years.

Three participants were dosed having AAV5 neutralising antibodies at baseline. All participants discontinued routine FIX prophylaxis. FIX activity increased from ≤1% to a mean of 31% at week six

[23] Dose confirmation trial of AAV5-hFIXco-Padua.

(primary efficacy endpoint met) and continued to rise to 54.4%, 37.1% and 58.6% in participants one to three, respectively (mean=50%) at 2.5 years.
A sustained reduction in bleeds and FIX replacement was demonstrated at 2.5 years follow-up. Only one participant experienced any bleeds (one traumatic and one spontaneous/mild) each requiring a single dose of FIX replacement. Two treatment-related adverse events (AEs) were resolved without intervention in one participant, with no new treatment-related AEs over the last two years of follow-up, including no clinically significant transaminase elevations. No participant developed inhibitors to FIX. There was no requirement for immunosuppression.

GENE THERAPY ASSAYS

Interpreting data coming from gene therapy trials may be challenging. The ongoing gene therapy studies use several different assays to look at three aspects:

- Pre-existing immunity against the adeno-associated viral (AAV) vector,
- Immune response to the therapy, and
- Therapeutic response (measured by coagulation assays).

Many individuals have pre-existing immunity against adeno-associated virus (AAV). Thirty to sixty percent of the general population may have neutralizing anti-AAV antibodies, with this frequency depending on the AAV serotype and geography. Pre-existing antibodies against the AAV capsid may be an issue because they may reduce transduction efficiency. Clinical gene therapy trials use two assay types to measure pre-existing immunity: Enzyme-Linked Immuno-Sorbent Assay (ELISA)-based total antibody assay and transduction inhibition assay.

The total antibody (ELISA) assay measures the concentration of all antibodies that recognise AAV. This includes neutralising anti-AAV antibodies and antibodies that bind but do not neutralise AAV. In a blood serum sample from an individual with pre-existing immunity, this assay produces a colour product, so that the more anti-AAV antibody present in the serum, the more colour will be produced. Therefore, by measuring the amount of colour generated, one can estimate the anti-AAV antibody titre. This is a fairly standard and reliable test, but does not tell much about the effects of these antibodies.

In contrast, the Transduction Inhibition Assay measures the amount of neutralising AAV antibodies in a blood sample. These antibodies can prevent the AAV vector from entering the target cell, so they prevent (or inhibit) transduction. The assay uses a reporter AAV vector containing the code for a protein that produces light. This reporter AAV is similar to the therapeutic vector except for its genetic cargo. The reporter AAV is first mixed with different serial dilutions of an individual's test serum, and these mixtures are then added to cultured cells, such as Human Embryonic Kidney cells. If the individual's serum contains neutralising anti-AAV antibodies, these bind to the AAV reporter vector, blocking cellular entry. Otherwise, the reporter AAV vector will enter the cells and make it synthesise the reporter protein that it encodes. This protein will produce a measurable amount of light. The higher the neutralising effect of AAV antibodies in the test serum, the less light one will see. This is due to the reporter AAV needing to enter the cell to generate light, which it cannot accomplish when antibodies block it. Typically, we define the neutralising titre in this assay as the highest dilution that reduces transduction by ≥50%. For example, if a 20-times diluted serum reduces the amount of produced light by 50%, we have an anti-AAV titre of 20. This assay is more specific than the total antibody assay because it only measures the antibodies that block cell entry. It does however have several weaknesses including lack of standardisation and no clear definition of a positive and negative result. Furthermore, this assay is hard to perform due to the living cells and infection processes involved. Also, individuals can have anti-AAV antibodies against several serotypes, which will cross-react and confound the titre measured for one specific serotype. Additionally, test AAV used in the assays and gene therapy are still different, despite the capsid similarity. Finally, titres are not comparable between studies because they all use different assay conditions, such as multiplicity of infection (MOI) and the number of reporter AAV particles per cell. Even if all other conditions were perfectly the same, variation of MOI used in clinical trials would show as high as over 60-fold[24][25] difference in anti-AAV titres.

[24] Majowicz A., et al. Therapeutic hFIX Activity Achieved after Single AAV5-hFIX Treatment in Hemophilia B Patients and NHPs with Pre-existing Anti-AAV5 NABs. *Mol Ther Methods Clin Dev*. 2019 May 28;14:27-36.
[25] Falese L., et al. Strategy to detect pre-existing immunity to AAV gene therapy. *Gene Ther*. 2017 Dec;24(12):768-778.

Assays measuring the immune response after gene therapy look at two different aspects. One is the antibody response to the transgene product (FVIII or FIX), known as inhibitor formation, which has not been seen in gene therapy trials so far. The other aspect is the cellular immune response to gene therapy, which is measured by a specific assay called interferon-gamma Enzyme-Linked Immunosorbent Spot (ELISpot) and less specific liver function tests (e.g., alanine aminotransferase, ALT). The latter measures damage to the liver, which might not be immune-related. Here is also the case of a fairly reliable but generic assay (the ALT) and a very specific, but technically less reliable partner-assay (ELISpot). Treatment with gene therapy, which results in transduction of cells, resembles a natural viral infection insofar that the vector capsid gets shredded to pieces upon entry into the host cell, and this cell displays these pieces on the surface. Such pieces of foreign agents may be recognized by specialized immune cells called cytotoxic T cells, which may then go on to kill the transduced cell and release cytokines (signalling molecules that control immune responses) to bring more killer cells. ELISpot measures the number of such activated cytokine-secreting cytotoxic T cells in the blood. The test requires collecting peripheral blood mononuclear cells, a fraction of blood cells that contains T cells. Exposure of the cells to a specific antigen (in this case, AAV capsid peptides or FVIII or FIX fragments) stimulates specific cytotoxic T cells (if they are present in the sample) to release interferon-gamma (a cytokine), which can be detected using a colour reaction similarly to the aforementioned ELISA-based total antibody assay. Development of colour spots means that the sample contained activated cytotoxic T cells, which can be enumerated based on the amount of colour spots. The more colour spots seen, the more cytotoxic T cells, and the stronger the therapy's cellular response. In gene therapy for haemophilia, these responses may cause a loss of factor expression. ELISpot also needs standardisation because it is technically demanding, requires specialised skills, and correct sample collection and processing are crucial for reliability.

We assess therapeutic response to gene therapy by measuring factor levels using one-stage or chromogenic substrate assays. The fundamental difference between them is that one-stage measures clotting time, while chromogenic assay measures the number of reaction products generated by coagulation factors. Blood coagulation is a fine-tuned and concerted process. Individual events take time, from initiation to amplification to clot formation, and glitches in any of these steps delay clot formation. FIX needs to form a complex with FVIII to activate factor X, which activates thrombin. When FVIII or FIX are missing or inactive (in haemophilia A or B), factor X activation is inefficient, delaying clot formation. The one-stage assay measures the time for a plasma sample to clot from initiation to clot formation. Clotting is measured in seconds and proceeds in one uninterrupted reaction, hence the name one-stage. Comparing test plasma clotting times to clotting times of a serial dilution of the reference plasma (with normal coagulation factor levels) allows quantitating the level of clotting factor VIII or IX in a patient's plasma sample. The chromogenic assay evaluates the part of the clotting process we are the most interested in, which is the activation of FX by FIX in a complex with FVIII. First, FIXa and FX or FVIII and FX are added in excess to test plasma to generate activated FX. The next stage adds a chromogenic substrate that can be cleaved by activated FX, which releases a colour product. The amount of the colour product will be proportional to the amount of activated FX generated in the first reaction, proportional to the amount of FVIII or FIX in the test plasma.

These different assays for measuring coagulation factor activity are set up in different ways, showing different limitations in estimating coagulation. This means that either assay can overestimate or underestimate coagulation when an exogenous (e.g., concentrate) or transgene-expressed FVIII or FIX is not identical to the natural (wild-type) molecule. Therapeutic clotting factors differ from normal factors in several ways: they may be missing non-function parts of the protein (e.g., Factor VIII B-domain), be fused to another protein to prolong half-life or come from different cellular sources. The assays were initially optimized for measuring standard half-life wild-type or minimally different FVIII and FIX molecules, not truncated, fused, or hyperactive proteins varying in their cellular origins. These differences may affect coagulation assay performance unexpectedly, so it may be challenging to determine which one most accurately represents true therapeutic level, necessitating a reappraisal

and adjustments in monitoring FVIII and FIX activities. In haemophilia A gene therapy trials, a one-stage assay has consistently shown higher FVIII levels by ~1.6-fold due to the transgene-expressed B-domain deleted (BDD)-FVIII speeding up early activation of factor X, but without increasing overall thrombin generation. Hence, the chromogenic assay seems more reliable. Haemophilia B trials have seen even more significant discrepancies, but these appear to be inherent to the FIX-Padua enhanced kinetics and unrelated to *in vivo* transgene expression.

In summary, the evaluation of gene therapies involves multiple specialised laboratory assays, which have differing considerations and limitations. In the long term, clarity on these matters will be necessary for optimal care. At the current state of the art, these uncertainties may complicate the interpretation and comparison of trial results and should be kept at the forefront in these discussions.

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

Bypassing agents

Pain relief with Sevenfact®: Results from the PERSEPT1 and 2 studies

In an abstract (PO099) presented at the 2022 EAHAD Congress, investigators led by Hermans C. and supported by LFB and Hema Biologics presented data on the use of **eptacog beta** (US brand name **Sevenfact®)** to relieve pain. Investigators looked at two phase III clinical trials. PERSEPT1 (NCT02020369)[26] was conducted in adults and adolescents, while PERSEPT2 (NCT02448680)[27] was conducted in children. Eptacog beta is a recombinant factor VIIa, currently only marketed in the United States.

Of 52 patients evaluated, 27 were ≥12 years old, and 25 were <12 years old. The majority of 1017 bleeding episodes were successfully treated at 12 hours and 24 hours in both age groups. The proportion of bleeding episodes with successful pain relief was approximately 90% in both age groups, irrespective of bleeding episode severity. From baseline until 24 hours after eptacog beta administration, the visual analogue scale (VAS) pain score consistently decreased at all time points in both age groups. The median time to pain relief was three hours in the older groups and above five hours in the younger. The concomitant analgesic requirement was less common among older vs younger patients (29.6% vs 48%, respectively).

Immune Tolerance Induction with replacement factor

Results from the VerITI-8 study looking at ITI with Elocta®

In an abstract (LBA-5) from ASH 2021, Malec L. and colleagues, supported by Sanofi and Sobi, describe the VerITI-8 (NCT03093480)[28] study, looking at the use of **Elocta®** in first time immune tolerance induction (ITI) over 48 weeks in people with severe haemophilia A and high-titre inhibitors. This study follows the reITIrate (NCT03103542)[29] study looking at the use of Elocta® in rescue ITI.

Initial screening was followed by an ITI period in which all patients received 200 IU/kg/day of Elocta® until tolerization or 48 weeks had elapsed. The primary endpoints were time to tolerization (successful ITI) with Elocta®, incremental recovery (IR) ≥66%, and half-life ($t_{½}$) ≥seven hours (h) within 48 weeks. The secondary endpoints included the number of patients achieving ITI success, annualised bleed rates (ABR), and adverse events (AEs).

Sixteen patients were enrolled and received ≥one dose of Elocta®. Twelve (75%), eleven (69%), and ten (63%) patients, respectively, achieved a negative inhibitor titre, an IR >66%, and a t½ ≥ seven hours (i.e., tolerance) within 48 weeks. One patient achieved partial success (negative inhibitor titre and IR ≥66%), and five subjects failed ITI, of which two had high inhibitors throughout, two experienced an increase in inhibitor levels, and one recorded a negative inhibitor titre at 282 days. Most bleeds occurred in the ITI period when median ABRs (n=13) were 3.8 overall, zero for spontaneous, one for traumatic, and zero for joints. During tapering, median (IQR) ABRs (n=10) were overall, zero; spontaneous, zero; traumatic, zero; and joint, zero. All 16 subjects experienced ≥1 treatment-emergent AE (TEAE), the most frequent of which was fever (pyrexia) in seven patients (44%). One patient reported ≥1 related TEAE (injection site pain). Nine patients (56%) experienced ≥1 treatment-emergent serious AE (TESAE). TESAEs occurring in ≥2 patients included vascular device infection, contusion, and hemarthrosis.

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[26] Phase III study of coagulation FVIIa (recombinant) in congenital haemophilia A or B patients with inhibitors.

[27] A phase III study on the safety, pharmacokinetics and efficacy of coagulation factor VIIa (PERSEPT2).

[28] A study to evaluate efficacy of rFVIIIFc for immune tolerance induction (ITI) in severe haemophilia A participants with inhibitors undergoing the first ITI treatment (verITI-8 Study).

[29] Study of rFVIIIFc for immune tolerance induction (ITI) in haemophilia A patients with inhibitors who have failed previous ITI therapies (ReITIrate).

No treatment-related TESAEs, discontinuations due to AEs, or deaths were reported.

Real-world use of Elocta® in ITI

In an abstract (PO081) presented at EAHAD 2022, researchers led by Klamroth R. and supported by Sobi reported on the second interim data analysis from a chart review of real-world use of **Elocta®** in immune therapy induction (ITI) (NCT03951103)[30]. This analysis includes 39 haemophilia A patients (severe, n=38; moderate, n=1) who went through ITI with Elocta® in 17 haemophilia treatment centres in eight countries.

First-time ITI was initiated in 22 patients. Of these patients, 21 had high-titre inhibitors. At the data cut-off date (July 2021), twelve out of 22 patients had reached a negative inhibitor titre. Ten of these were deemed ITI successes by the investigator with a median (range) ITI duration of 359 days, and four of them received a weekly dose of ≤300 IU/kg. ITI was ongoing in ten patients, and two patients were ITI failures.

Seventeen rescue ITI patients had two prior ITI attempts and a total prior ITI duration of 62 months. At the data cut-off date, five patients had ITI success, two partial success, six failures, whereas rescue ITI was ongoing in four patients. Median ITI duration in patients with ITI success or partial success was 472 or 408 days. In 13 completed ITI cases, Elocta® weekly dose was ≤300 IU/kg in three out of five ITI successes. ITI with Elocta® was well tolerated, no unexpected adverse events (AE) were observed, no AE led to treatment discontinuation.

FVIII mimetics

Surgical experiences with Hemlibra® in people with inhibitors: Results from the phase IIIb STASEY study

In an abstract (344) from ASH 2021, Roche presented the surgical experience of people with haemophilia A and inhibitors during the phase IIIb STASEY study (NCT03191799)[31]. This study was designed to assess the safety and efficacy of **Hemlibra®** prophylaxis in people with haemophilia A and inhibitors.

Forty-six people with haemophilia A aged ≥12 years with FVIII inhibitors reported on ≥1 on-study surgery. Patients received three mg/kg/week Hemlibra® for four weeks (loading dose), then 1.5 mg/kg/week for the remaining two-year treatment period.

Thirty-seven patients had 56 minor surgeries (central venous access device [CVAD], n=9; dental, n=20; joint, n=4; other, n=23), one of which (skin laceration and suture insertion on day nine) was performed during the loading phase. Forty-two per cent of surgeries were managed with additional prophylactic medications. Of these, 11/24 (45.8%) resulted in postoperative bleeds, of which 6/11 were treated (54.5%). Of surgeries managed without additional prophylactic medications, 15/32 (46.9%) resulted in postoperative bleeds, of which 5/15 (33.3%) were treated.

A total of 13 patients had 22 major on-study surgeries (arthroplasty, n=13; other, n=9). Eighteen (81.8%) major surgeries, including all arthroplasties, were managed with additional prophylactic medications. Of these, 12/18 (66.7%) resulted in postoperative bleeds (including 10/13 arthroplasties), of which six (50.0%) were treated (all arthroplasties). Four (18.2%) major surgeries were managed without additional prophylactic medication.

No thrombotic events (TEs) or thrombotic microangiopathies (TMAs) related to surgeries were observed.

[30] rFVIIIFc (Elocta®) ITI chart review in patients with haemophilia A.

[31] A study to evaluate the safety and tolerability of prophylactic emicizumab in people with haemophilia A with inhibitors (STASEY).

Rebalancing agents

Results from Sanofi's phase III ATLAS-A/B trial for the use of fitusiran in people without inhibitors

In an abstract (LBA-3) presented at the 2021 ASH Congress, investigators led by Srivastava A. and supported by Sanofi presented the results of the phase III study (ATLAS-A/B; NCT03417245) on **fitusiran** prophylaxis' efficacy and safety compared to on-demand treatment with factor concentrates in people with haemophilia A or B without inhibitors.

Fitusiran is a subcutaneous administered investigational product that uses siRNA technology targeting antithrombin to enhance thrombin generation potential to rebalance haemostasis in people with haemophilia.

This study included 120 males aged ≥12 years with severe haemophilia A (n=93) or B (n=27) without inhibitors previously treated on-demand. Participants were randomised to receive either once-monthly 80 mg fitusiran prophylaxis (fitusiran study arm; n=80; HA=62 and HB=18) or on-demand factor concentrates to treat bleeding episodes (on-demand study arm; n=40; HA=31 and HB=9) for nine months. The primary endpoint was annualised bleeding rate (ABR), and the secondary endpoints included annualised spontaneous bleeding rate (AsBR), annualised joint bleeding rate (AjBR) and health-related quality of life.

A similar percentage of patients in both arms completed the study, and both groups had similar demographics and characteristics. Patients in the fitusiran arm experienced a significant reduction in treated bleeds for all measures (ABR, AjBR and AsBR), including 50.6% of participants in the fitusiran-arm experienced zero treated bleeds. There was also a significant improvement in the physical health score in the fitusiran arm.

	Fitusiran arm	On-demand arm
Median ABR	0.0	21.8
Median AsBR	0.0	16.1
AjBR	0.0	15.9

Close to eighty per cent of the patients in the fitusiran arm experienced ≥1 treatment-emergent adverse events. A total of five treatment-emergent serious adverse events were reported in five patients (6.3%) in the fitusiran arm. These included gallstones (cholelithiasis; n=2), gallbladder inflammation (cholecystitis, n=1), lower respiratory tract infection (n=1), and asthma (n=1). These serious adverse events resulted in two patients (2.5%) discontinuing fitusiran (for the gallbladder infection and increased alanine aminotransferase, a liver enzyme served as a marker for liver damage). No thrombosis or fatal treatment-emergent adverse events were reported.

Investigators are currently evaluating a revised regimen with reduced dose and frequency to improve the benefit-risk profile of fitusiran.

Results from Sanofi's phase III ATLAS-INH trial for the use of fitusiran in people with inhibitors

During the 2021 ASH Congress, Young G. presented the results of the phase III study ALTAS-INH (NCT03417102), looking at the safety and efficacy of **fitusiran** prophylaxis in people with haemophilia and inhibitors.

Fitusiran is an investigational subcutaneous medicinal product using siRNA technology to restore thrombin generation and rebalance haemostasis in people with haemophilia A or B with or without inhibitors. This product is in development by Sanofi.

Fifty-seven people (males ≥12 years) took part in the ATLAS-INH study. Participants received on-demand treatment with bypassing agents (BPA) before the study. They were then randomised in a 2:1 ratio to receive once monthly 80 mg of fitusiran (fitusiran arm; n=38; HA=29 and HB=9) or to continue with their on-demand BPA treatment (on-demand arm; n=19; HA=16 and HB=3). The primary endpoint

was annualised bleeding rate (ABR), and the secondary endpoints included annualised spontaneous bleeding rate (AsBR), annualised joint bleeding rate (AjBR) and quality of life measured with Haem-A-QoL.
A significant reduction in treated bleeds were observed in patients in the fitusiran arm. Here below is a table showing the bleeding events in the ATLAS-INH study (in the efficacy period). Investigators define the efficacy period from day 29 to day 246, or the last day of bleeding follow up, whichever is the earliest.

	Fitusiran arm	On-demand arm
Median ABR	0.0	16.80
Median AsBR	0.0	13.40
AjBR	0.0	11.70

A total of 25 patients in the fitusiran arm (65.8%) had zero treated bleeding events. Efficacy of fitusiran prophylaxis treatment was seen in both haemophilia A and haemophilia B patients with inhibitors. Improvements were also noted for general physical health and quality of life for people in the fitusiran arm.
One patient discontinued fitusiran after serious adverse events (suspected spinal vascular disorder and thrombosis, assessed by investigators as possibly related to fitusiran). There were no fatal adverse events reported.
Investigators are currently evaluating a revised regimen with reduced dose and frequency to improve the benefit-risk ratio of fitursiran.

Changes of health-related quality of life in patients with haemophilia A with or without inhibitors treated with fitusiran prophylaxis

Research (abstract 3197) presented at ASH 2021 by Sanofi describes the changes of health-related quality of life (HRQoL) in people with haemophilia A with or without inhibitors who took part in phase I study (NCT02035605)[32] and continued in phase II open-label extension study (NCT02554773)[33].
Twenty-seven people with HA (severe=26 and moderate=1; with inhibitors=13 and without inhibitors=14) received subcutaneous fixed monthly doses of 50 mg (n=9) or 80 mg (n=18) of **fitusiran**. Quality of life data were collected in three-month lapse periods. As of February 2021, participants were treated for up to mean 33.32 months. Improvements in quality of life were observed in nine out of ten domains in participants with the exception of sport & leisure, a domain that was higher in the non-inhibitor group. Results suggest a modest trend of higher improvement in quality of life in non-inhibitor patients. Investigators note that the small sample size may limit the results.
Further research will be carried out in the phase III study.

Quality of life with fitusiran prophylaxis: Analysis of the phase III ATLAS-INH study

During the 2022 EAHAD Congress, investigators led by Négrier C. and supported by Sanofi presented (PO067) data on health-related quality of life in people with haemophilia A (PwHA) or B (PwHB) with inhibitors receiving **fitusiran** prophylaxis during the phase III ATLAS-INH study.
This analysis included 60 participants (PwHA, n=48; PwHB, n=12; fitusiran arm, n=41; OD arm, n=19). Health-related quality of life was assessed at baseline and end of the study (nine months) using the Haemophilia Quality of Life Questionnaire (Haem-A-QoL [adults], Haemo-QoL [adolescents]),

[32] A phase I study of an investigational drug, ALN-AT3SC (fitusiran), in healthy volunteers and haemophilia A or B patients.
[33] An open-label extension study of an investigational drug, fitusiran, in patients with moderate or severe haemophilia A or B.

Haemophilia Activity List (HAL [adults], pedHAL [adolescents]), EuroQoL-5 Dimension 5-Level (EQ-5D-5L) and the Treatment Satisfaction Questionnaire for Medication (TSQM-9).
The primary endpoint was met with a 91% reduction in annualised bleeding rate (ABR) for the fitusiran vs the OD BPA arm.
The secondary endpoint demonstrated statistical improvement in the fitusiran arm showing that nine out of ten domains of the Haem-A-QoL improved, including total score and physical health domains. The fitusiran arm also showed higher and more favourable scores for HAL, EQ-5D-5L and TSQM-9. Finally, HRQoL outcomes in all two adolescent-specific instruments (Haemo-QoL and pedHAL) favoured the fitusiran arm.

Impact of AT reduction on coagulation assays in people on fitusiran

In an abstract (PO007) presented at EAHAD 2022 Sanofi presented a study to evaluate the interference of antithrombin (AT) reduction in routine clinical coagulation assays critical to monitor patients treated with fitusiran. This is an investigational therapy using silencing RNA technology. It targets and lowers the natural anticoagulant antithrombin, so it is important to determine whether AT fluctuations disrupt routine haemophilia assays.
Investigators concluded that AT reduction did not interfere with routine FVIII/FIX inhibitors coagulation assays. They determined that plasma containing different levels of FVIII or FIX displayed comparable clotting potential at 15% and normal AT levels.

Use of concizumab in surgeries: results from phase II explorer 4 and 5

In an abstract (345) presented at the 2021 ASH Congress, Wheeler A.P. and colleagues, supported by Novo Nordisk, released information on minor surgeries and diagnostic procedures performed during the phase II explorer4 (NCT03196284)[34] and explorer5 trials (NCT03196297)[35] on patients taking **concizumab**.
Concizumab is an anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody in phase III clinical development as once-daily subcutaneous prophylaxis for the treatment of haemophilia.
The trials mentioned above were carried out to investigate the safety and efficacy of this investigational therapy. Both trials consisted of a main and extension part with patients receiving concizumab at an initial maintenance dose of 0.15 mg/kg (with an additional loading dose of 0.5 mg/kg as a first dose in explorer4). Both trials offered participants the option to dose escalate to maintenance doses of 0.20 and 0.25 mg/kg in case of ≥3 spontaneous treated bleeds within the previous 12 weeks. Concomitant treatment with systemic antifibrinolytics was not allowed in either trial, while local/topical use was permitted.
In explorer4, seven of 25 patients treated with concizumab had a total of 17 surgeries (1 surgery n=5; 2 surgeries n=1; 10 surgeries n=1). The majority of procedures were dental surgery but also included port-a-catheter removal, hordeolum removal, knee replacement and laser eye surgery. At the time of surgery, except for one patient on concizumab at 0.20 mg/kg, all patients were on 0.15 mg/kg. Five out of six recorded mild to moderate surgery-related bleeds, while one was severe.
In explorer5, thirteen of 36 patients treated with concizumab had 33 surgeries. The majority of patients (8/13) were receiving concizumab at 0.15 mg/kg, one patient at 0.20 mg/kg, two patients at 0.25 mg/kg at the time of surgery, and two patients were on 0.15 mg/kg concizumab for their first surgeries and switched to 0.20 mg/kg for later surgeries. Dental procedures constituted most surgeries, and other procedures included vaccinations and cataract surgery, diagnostic procedures such as biopsy, endoscopy and gastroscopy, and a hair graft. A total of nine surgery-related bleeds were recorded during explorer5, all of which were classified as mild or moderate. These data were also presented during EAHAD in abstract PO129.

[34] A trial evaluating the efficacy and safety of prophylactic administration of concizumab in haemophilia A and B patients with inhibitors.
[35] A trial evaluating efficacy and safety of prophylactic administration of concizumab in patients with severe haemophilia A without inhibitors

During EAHAD 2022, Spanish researchers led by Mena-Santano A.-M. and supported by Takeda presented (abstract PO095) two case studies of two minor surgeries (hair transplant and tooth extraction) in two patients from the phase II explorer5 and phase III explorer8 (NCT04082429)[36] clinical trials. Both patients were supplemented with Adynovate® prior to the surgery. In the case of the tooth extraction, the patient had to take another dose of Adynovate® to treat a surgery-related bleed. No thrombosis or inhibitors were reported.

Impact of long-term concizumab use on health-related quality of life: Results from phase II explorer4 and explorer5 trials

During the 2021 ASH Congress, Novo Nordisk presented (1041) the impact of long-term **concizumab** in the health-related quality of life in people with haemophilia. The data for this analysis came from phase II explorer4 (NCT03196284) and explorer5 (NCT03196297). Concizumab is an anti-tissue pathway inhibitor (TFPI) investigated as a subcutaneous treatment for haemophilia.

Both trials had a main (≤24 weeks) and extension part (explorer4: ≤94 weeks; explorer5: ≤102 weeks). At an individual level, a responder analysis was conducted to identify the proportion of patients who had improved scores in the physical component summary (PCS), physical function (PF) and bodily pain (BP) domains.

For explorer4, 22 patients (HAwI, n=14; HBwI, n=8) were included in the analysis, which showed improvement for PCS as a group. At an individual level, the analysis also showed positive improvement in most patients for PCS, PF and BP scores.

The improvement was lower in the explorer5 trial. Although a large standard deviation is reported, the authors note a PCS improvement across all haemophilia subgroups, suggesting better functional health. Further research on this matter is being carried out in phase III of both trials.

Presenting the risk mitigation plan for the phase III clinical trial to assess the safety and efficacy of concizumab

In an abstract (PO005) presented at the 2022 EAHAD Congress by Novo Nordisk, a group of investigators led by Chowdary P. presented on the risk mitigation plan developed to re-initiate the phase III clinical trial for **concizumab**.

The phase III trial had been placed on hold following the observation of non-fatal thrombotic events in three patients with distinct thrombotic risk factors. The risk mitigation plan includes updated breakthrough bleed guidance stipulating using the lowest approved dose for additional haemostatic agents and closer monitoring of bleed treatment. An expert panel was established. Furthermore, a new concizumab dosing regimen was adopted, with a 1 mg/kg loading dose followed by daily dosing of 0.2 mg/kg concizumab, supported by the updated target-mediated drug disposition-PK model. Based on concizumab exposure measured at week 4 (using a concizumab-ELISA), patients below 200 ng/mL exposure can be adjusted to daily 0.25 mg/kg, and patients above 4,000 ng/mL exposure can be adjusted to daily 0.15 mg/kg within the initial five-to-eight-week dose adjustment period.

This new dosing regimen was also presented in an abstract (PO091) at the 2022 EAHAD Congress.

Bioequivalence of administration of marstacimab prefilled pens (PFP) and prefilled syringes (PFS) devices in healthy volunteers

An abstract (PO036) presented at EAHAD 2022 from Pfizer described a bioequivalence study to support the bridging of clinical results between using a **marstacimab** prefilled syringe and prefilled pen devices (NCT04832139)[37].

Marstacimab is a fully human monoclonal antibody directed against tissue factor pathway inhibitor under development for the treatment of severe haemophilia A and B.

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[36] Research study to look at how well the drug concizumab works in your body if you have haemophilia without inhibitors (explorer8).

[37] A study of marstacimab to compare prefilled pen (PFP) device to prefilled syringe (PFS) device.

A first-in-human study conducted in healthy adult males and a proof-of-concept study conducted in patients with haemophilia A or B characterized the pharmacokinetics, pharmacodynamics, safety, and efficacy of single and weekly subcutaneous (SC) marstacimab dose using the vial formulation. A prefilled pen (PFP) device is being used in the ongoing phase III study in adults and adolescents with severe haemophilia A or B with or without inhibitors receiving weekly SC doses of 150 or 300 mg. The PFP device, a pen device assembled around a staked needle prefilled syringe (PFS), is the anticipated commercial presentation.
The study in healthy volunteers had to be terminated prematurely due to thrombotic events of deep vein thrombosis/ pulmonary embolism (DVT/PE), which occurred in one participant.
Results from the study in healthy volunteers showed that marstacimab PFP and PFS devices demonstrated bioequivalence with a smaller than anticipated sample size. The observed DVT/PE events in one healthy adult male participant creates an unfavourable benefit/risk profile for further marstacimab administration in the healthy (non-haemophilic) population.

Phase IIa evaluating three dose levels of SerpinPC in people with haemophilia A or B

During the 2022 EAHAD Congress, Baglin T. presented the findings of a phase IIa study evaluating three dose levels of **SerpinPC** in people with haemophilia A or B.
Investigators chose three doses of SerpinPc to evaluate its tolerability, safety and pharmacokinetics. Reductions in annualised bleeding rates (ABR) were an exploratory objective, and the study was not designed to be dose-finding. Twenty-three male patients with severe HA or HB who were not on factor prophylaxis were divided into three cohorts to receive subcutaneously one of the following doses of SerpinPC: 0.3 mg/kg (n=8), 0.6 mg/kg (n=7) or 1.2 mg/kg (n=8) every four weeks over a 24 weeks period for a total of six doses. All participants from the phase I study chose to take part in phase II.
There were no serious adverse reactions or adverse events of interest. There was only one adverse event related to SerpinPC, which was a moderate skin reaction that led to the withdrawal of a patient with a history of skin disorder. Anti-drug antibodies were detected in two patients (one at week 16 and another one at week 20) with no apparent impact on ABR. There were no instances of sustained elevation in D-dimer (a biomarker for thrombosis). The elimination of half-life was approximately four to five days. Following five months of subcutaneous doses once every four weeks, accumulation ratios for Cmax (i.e., a measurement of pharmacokinetics to define the peak concentration of a medicine in the body) suggest none to minimum accumulation for this ratio.
There was a reduction in all bleeds ABR at all doses. In the highest dose cohort (1.2 mg), there was an 88% reduction in all bleeds ABR with median ABR reduction from 36 to 4.4. Patients that experienced breakthrough bleeds during the SerpinPC trial were treated with usual factor replacement therapy at a normal dose. Concomitant use of factor replacement therapy was not associated with any adverse events or elevation of D-dimer. Investigators noted a reduction in spontaneous joint bleed ABR in all dose cohorts. As an example, spontaneous joint bleed ABR (AjBR) was reduced by 94% in the highest dose cohort, corresponding in a reduction in the median spontaneous AjBR from 21.1 to 2.2. All subjects had target joints at baseline with a median of 2.5 joints and, at the end of study, 15 of the participants had no target joints, including six of the participants in the highest group.
Phase III of the trial is currently ongoing.

AN UPDATE ON NOVEL THERAPIES FOR PEOPLE WITH VON WILLEBRAND DISEASE

Replacement therapies

Pregnancy management with Veyvondi®

In an abstract from EAHAD 2022 (PO164), UK researchers led by Quinn D. reported the obstetric management of two pregnant women with von Willebrand disease (VWD) with **Veyvondi®**.
One patient was 30 years old and had type 1 VWD and she was in her second pregnancy (patient A). The second patient was 29 years old and had type 2B VWD, and for her, it was her first pregnancy.
In their third trimester, patient A had 37.7% VWF and 143% FVIII. Patient B had 45% VWF and 159% FVIII. A trial of Veyvondi® at 35 IU/kg in patient B did not induce thrombocytopenia upon correction of VWF.
Both patients received doses of Veyvondi® peripartum, achieving VWF >100%. Patient A underwent an uncomplicated elective caesarean section under regional anaesthesia, with post-surgical VWF maintained >75% for 72 hours post-partum. Patient B underwent induction of labour complicated by post-partum haemorrhage due to uterine atony. Here, satisfactory management was supported by maintaining VWF >100% for 120 hours post-partum. There were no thrombotic or neonatal complications.

Non-replacement therapies

Scoping review of off-label use of Hemlibra® in VWD

In an article by Vinay M. T. and colleagues, published in *Haemophilia* in November 2021, authors conducted a scoping review on the use of Hemlibra® in acquired haemophilia and von Willebrand disease (VWD). They searched medical databases (PubMed, EMBASE and Scopus) and found 17 studies with a total of eight type 3 VWD patients, all of which were started on Hemlibra® for active or recurrent bleeds. All patients had a clinical response to Hemlibra®. No specific adverse events were reported for the VWD patients.

REPLACEMENT THERAPIES IN DEVELOPMENT					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Replacement FVIII	**Haemophilia A**	BIVV001	Efanesococog alfa (rFVIIIFc-VWFD'D3-XTEN)	Sanofi and Sobi co-development	**Phase 3**
Replacement FIX	**Haemophilia B**	Dalcinonacog alfa (DalcA)	Subcutaneous coagulation factor IX variant	Catalyst Bioscience	**Halting of clinical development**[38]

BYPASSING AGENTS IN DEVELOPMENT					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Bypassing agent	**Haemophilia A or B w/ inhibitors**	Eptacog beta	Recombinant FVIIa- jncw	LFB	**Licensed in the US (under the brand name Sevenfact®) EMA accepted MAA filing (expected outcome in mid-2022)**[39]
Bypassing agent	**Haemophilia A or B w/ or w/o inhibitors**	marzeptacog alfa (activated) MarzAA	Subcutaneous coagulation rFVIIa variant	Catalyst Bioscience	**Halting of clinical development**[40]

NON-REPLACEMENT THERAPIES IN DEVELOPMENT					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
NRT Bispecific antibody	**Haemophilia A**	Mim8	FVIIIa-mimetic, bispecific antibody	Novo Nordisk	**Phase 2**
	Haemophilia A	F1049	Bispecific antibody	Kymab	**Pre-clinical studies**

[38] Text in red indicates a change from the last issue.
[39] Idem
[40] Idem

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

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

GENE THERAPY IN DEVELOPMENT					
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Developer / manufacturer**	**Development stage**
Gene Therapy	**Haemophilia A**	Roctavian® Valoctocogene roxaparvovec BMN-270	AAV5-huFVIII-SQ Valoctocogene roxaparvovec	BioMarin	**Phase 3**
Gene Therapy	**Haemophilia A**	PF-07055480 giroctocogene fitelparvovec (formerly SB-525)	Gene therapy using a rAAV2/6 vector, encoding the B-domain deleted human FVIII	Pfizer (originally Sangamo)	**On clinical hold**[41]
Gene Therapy	**Haemophilia A**	BAY2599023 / DTX 201	Gene therapy using AAVhu37FVIII	Bayer	**Phase 1/2**
Gene Therapy	**Haemophilia A**	SPK-8011	AAV-LK03 (AAV-Spark200) encoding BDD-FVIII	Spark	**Phase 1/2**
Gene Therapy	**Haemophilia A**	TAK-754 (formerly BAX 888/SHP654)	AAV8-based gene therapy using B-domain deleted (BDD)-FVIII-X5 variant	Takeda	**Clinical trial suspended**

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

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

Gene Therapy	**Haemophilia B**	AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	**CSL Behring [42] (Formerly uniQure)**	**Phase 3**
Gene Therapy	**Haemophilia B**	AMT-060	Gene therapy using AAV5 vector encoding FIX	**CSL Behring [43] (Formerly uniQure)**	**Phase 1/2**
Gene Therapy	**Haemophilia B**	SB-FIX	AAV6-delivered ZFN integrating corrective FIX transgene into albumin locus	Sangamo	**Phase 1/2**
Gene Therapy	**Haemophilia B**	FLT180a	AAVS3 encoding FIX Padua variant	Freeline	**Phase 1/2**
Gene Therapy	**Haemophilia B**	AAV2/8-LP1-FIX	AAV2/8-LP1-FIX vector	SJCRH	**Phase 1**
Gene Therapy	**Haemophilia B**	YUVA-GT-F901	autologous HSC/MSC, modified with lentivirus encoding FIX	SGIMI	**Phase 1**
Gene Therapy	**Haemophilia B**	CB2679d-GT	Novel chimeric AAV vector Delivering an enhanced potency FIX	Catalyst Biosciences	**Pre-clinical studies**
Gene Therapy	**Haemophilia B**	TAK-748 (formerly SHP648/	AAV8-based gene therapy using FIX Padua variant	Takeda	**Clinical trial suspended**

[42] Text in red indicates changes from the previous edition.
[43] Idem

		AskBio009/BAX 335)			

CELL-BASED THERAPIES IN DEVELOPMENT					
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Developer / manufacturer**	**Development stage**
Cell-based therapy	**Haemophilia A**	SIG-001	Two-compartment spheres encapsulating human FVIII-expressing human cells	Sigilon Therapeutics	**Suspended Temporary Enrolment Halt**[44]
Cell-based therapy	**FVII deficiency**	SIG-009	Cell-based product for FVII deficiency	Sigilon Therapeutics	**Pre-clinical**[45]

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

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

Replacement FVIII	**Haemophilia A**	Esperoct® N8-GP	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®	Recombinant FVIIa- jncw	LFB	**Licensed in the US** **EMA accepted MAA filing** **(expected outcome in mid-2022)**[46]
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**

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