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

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FOREWORD

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

In this edition, we primarily cover news from the 2020 World Federation of Hemophilia (WFH) Virtual Summit, held in June 2020, and the International Society on Thrombosis and Haemostasis (ISTH) Virtual Congress, held in July 2020 as well as other industry updates and news in general. The abstracts of the WFH and ISTH meetings can be accessed online. For your convenience, we also include a table on all treatments covered in this newsletter as well as other novel treatment under development. We hope this will facilitate your understanding of the 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:

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- Dr. Radoslaw Kaczmarek, Medical and Scientific Advisory Group (MASAG) member,
- Dr. Dan Hart, EHC MASAG member,
- Dr. Ilmar Kruis, EHC volunteer,
- Prof. Mike Makris, EHC Medical Advisory Group (MAG) Chair,
- Mr. Declan Noone, EHC President,
- Asst. Prof. Brian O'Mahony, MASAG member,
- Mr. David Page, Canadian Hemophilia Society,
- Prof. Flora Peyvandi, EHC Medical Advisory Group (MAG) member,
- Geneviève Piétu, PhD, EHC volunteer,
- Ms. Laura Savini, EHC Public Policy and Communications Officer,
- Dr. Uwe Schlenkrich, EHC volunteer.

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

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

Sincere regards,

Declan Noone
EHC President

Amanda Bok
EHC CEO

ABBREVIATIONS

AAV:	Adeno-associated viral
ABD:	Albumin binding domains
ABR:	Annualised bleeding rate
AE:	Adverse events
AUC:	Area under the curve
aPCC:	Activated prothrombin complex concentrate
BPA:	Bypassing agents
BU/ml:	Bethesda units per millilitre
CBDR:	Canadian Bleeding Disorders Registry
CT:	Clinical trial
EMA:	European Medicines Agency
FDA:	Food and Drug Administration
FIX:	Factor IX
FVIII:	Factor VIII
gc/Kg:	Genome copies per kilogram
h:	Human
HA:	Haemophilia A
HAwI:	Haemophilia A with inhibitors
HB:	Haemophilia B
HBwI:	Haemophilia B with inhibitors
HCP:	Healthcare professionals
HJHS:	Haemophilia Joint Health Score
IQR:	Interquartile Range
ISTH:	International Society on Thrombosis and Haemostasis
IU:	International units
IU/dl:	International units per decilitre
IU/kg:	International units per kilogram
n=:	Number
NAb:	Neutralizing antibodies
NHP:	Non-human primates
pd:	plasma-derived
PK:	Pharmacokinetics
PPX:	Prophylaxis
PwHA:	Person with haemophilia A
PwHB:	Person with haemophilia B
r:	recombinant
rFVIIa:	recombinant activated factor VII
RNA:	Ribonucleic acid

SAE:	Serious adverse events
SQ:	Subcutaneous
UK:	United Kingdom
US:	United States
vg/Kg:	Vector genomes per kilogram
vs:	versus
VWD:	von Willebrand disease
VWF:	von Willebrand factor
WFH:	World Federation of Hemophilia
µg/kg:	microgram per kilogram

HIGHLIGHTS

Haemophilia A

- In a phase I/IIa trial, a single intravenous injection of **BIVV001** (rFVIIIFc-VWF-XTEN), an extended half-life FVIII for the treatment of haemophilia A, results in high sustained factor VIII activity levels, with a half-life up to four times the half-life of standard rFVIII, raising the potential for weekly infusions. (See page 7.)

- On August 18, the U.S. FDA announced that it required more data to support regulatory assessment of BioMarin's gene therapy for haemophilia A, **ROCTAVIAN® (valoctocogene roxaparvovec**). In its complete response, the FDA requested two years' worth of follow-up data on safety and efficacy in the 134 patients in the phase 3 trial to support the benefit-risk evaluation. On November 5, BioMarin announced its withdrawal of its marketing authorisation application (MAA) from the European Medicines Agency (EMA) following a request by the EMA to provide full 12 months' data for all participants in the phase 3 study (See page 10.)

Haemophilia B

- Final efficacy and safety data from the phase IIb trial of **dalcinonacog alfa (DalcA)**, a next generation, subcutaneously (SQ) administered factor IX (FIX) developed by Catalyst Bioscience, showed that 28 days of daily SQ dosing of DalcA achieved protective target FIX levels of >12% in all participants, with FIX levels of up to 27% and a half-life of 2.5 to 5.1 days with no bleeds. (See page 12.)

- Researchers from uniQure reported on a study to explore the impact of pre-existing anti-adeno-associated viral (AAV) serotype 5 vector neutralizing antibodies (NAbs) on the efficacy of AAV5-based gene therapies, in trials for **AMT-060 and AMT-061**. No relationship was observed between the presence of pre-treatment anti-AAV5 NAbs and therapeutic efficacy. Consequently, patients are currently not excluded from *HOPE-B* (phase III clinical trial (CT) of AMT-061) based on anti-AAV5 NAbs levels. (See page 13.)

- Freeline announced results in its phase I/II trial *B-AMAZE* of **FLT180a**. A dose between 7.5 to 9.75e11vg/kg can potentially create sustained, normal FIX activity levels in patients with severe haemophilia B (HB). Freeline has announced plans to launch a pivotal trial for FLT180a. (See page 14.)

Haemophilia A, B with and without inhibitors

- Novo Nordisk announced in August that its *Explorer 6, 7* and *8* trials investigating the use of **concizumab** will re-start after the U.S. FDA lifted the study hold. The trials were halted in March 2020 following cases of non-fatal thrombotic complications in three patients. (See page 18.)

- Pfizer announced the dosing of its first patient with **marstacimab** for its phase III BASIS clinical trial.

AN UPDATE ON NOVEL TREATMENTS IN HAEMOPHILIA A

Factor replacement therapies

Report from clinical trial data for BIVV001

An article published in the September 10 edition of the *New England Journal of Medicine* (N Engl J Med 2020; 383:1018-1027 - DOI: 10.1056/NEJMoa2002699) by Konkle et al reported on the trial (NCT03205163) funded by Sanofi and Sobi, of **BIVV001** (rFVIIIFc-VWF-XTEN), a novel fusion protein designed to overcome the von Willebrand factor-imposed half-life ceiling.

In this phase I/IIa open-label trial, 16 previously treated men (18 to 65 years of age) with severe haemophilia A (FVIII activity, <1%) received a single intravenous injection of BIVV001 at a dose of 25 IU/kg (lower-dose group) or 65 IU/kg (higher-dose group). This injection was followed by a washout period of at least three days. The patients then received a single intravenous injection of BIVV001 at the same corresponding dose of either 25 IU/kg or 65 IU/kg. No inhibitors to FVIII were detected and no hypersensitivity or anaphylaxis events were reported up to 28 days after the injection of single-dose BIVV001. The geometric mean half-life of BIVV001 was three to four times as long as that of rFVIII (37.6 hours vs. 9.1 hours in the lower-dose group; and 42.5 vs. 13.2 hours in the higher-dose group). After the injection of BIVV001 in the higher-dose group, the mean FVIII level was in the normal range (≥51%) for four days; and 17% at day seven, which suggested the possibility of a weekly interval between treatments.

In this phase I study, a single intravenous injection of BIVV001 resulted in high sustained FVIII activity levels, with a half-life that was up to four times the half-life of standard rFVIII, an increase that could signal a new class of factor VIII replacement therapy with a weekly treatment interval. No safety concerns were reported during the 28-day period after administration.

Cross-over studies of extended half-life products

In a two-way crossover study that compared the pharmacokinetics (PK) of **Jivi®** and **Elocta®** in patients with severe haemophilia aged 18-65 years were randomized to receive an intravenous single-dose of Jivi® 60 IU/kg followed by rFVIIIFc (Elocta®) 60 IU/kg or vice versa, with ≥7-day wash-out between doses. FVIII activity was measured by one-stage assay. The area under the curve (AUC) was significantly higher for Jivi® versus Elocta®, which represented a median time to 1 IU/dL of approximately 13h longer for Jivi® using a population PK model. In a second study using similar methodology, Jivi® was compared to **Adynovate®**, using 50 IU/kg. One additional component to this study was differences in batch specific dosing, resulting in reported actual administered median doses of 54.3 IU/kg for Jivi® and 61.4 IU/kg for Adynovate®. Based on population PK modelling, median time to reach 1 IU/dL was 16 h longer for Jivi® compared with Adynovate®. *Both of these trials were funded by Bayer.*

Ingenza announces progress towards low-cost FVIII

In a press release from the company, Ingenza announced it has reached an important milestone in its work to develop a low-cost rFVIII production process to make materials for ProFactor Pharma Ltd (PFP). Ingenza is now working to finalise the manufacturing process and generate material for PFP's pre-clinical toxicology studies later in 2020, ahead of CTs in 2021.

Biotest presents pre-clinical data on novel rFVIII

In an abstract (PB1144) at the ISTH Virtual Congress, Biotest presented pre-clinical results for a novel rFVIII protein containing four albumin-binding domains (FVIII-ABD). It was injected intravenously and subcutaneously into ten haemophilia A mice and three Göttingen minipigs with moroctocog alfa (**Refacto®**) used as comparison. Blood samples taken at defined time points (0-240 h) after administration were analysed for chromogenic FVIII activity and/or FVIII antigen levels. A subcutaneous bioavailability of 15.3% (mean) and 18.6% (median) was determined for FVIII-ABD in haemophilia A mice. Moroctocog alfa was not detectable. In the Göttingen minipig model, which provides a dermal structure closer to the human setting, subcutaneous bioavailability of up to 50% was observed for FVIII-ABD, depending on the dose and formulation. The abstract concluded that a next generation rFVIII molecule fused to four albumin-binding domains resulted in a feasible treatment option allowing SQ haemophilia A prophylaxis with the benefit of a substantial half-life extension.

Biotest presents pre-clinical data on lower immunogenicity FVIII

In an abstract (PB0223) at the ISTH Virtual Congress, Biotest presented results from *in vitro* studies aimed at developing FVIII with lower immunogenicity by reducing the number of FVIII-peptides presented on immune cells leading to a reduction of FVIII-specific naïve T cell maturation, and hence a reduction in the production of high-affinity inhibitory antibodies. Functional and structural analyses of this deimmunized FVIII variant revealed similarity to a non-modified FVIII reference and other registered rFVIII products. An *in vitro* DC-T cell assay was used to examine the immunogenicity of the deimmunized FVIII variant, which demonstrated its significantly reduced immunogenicity. Researchers concluded that this molecule has the potential to reduce the risk of inhibitor development in haemophilia A patients.

Non-replacement therapies

Novo Nordisk presents characteristics of Mim8

In an abstract (PB1147) presented at the ISTH Virtual Congress, researchers from Novo Nordisk described a next generation anti-FIXa/anti-FX bispecific antibody, **Mim8**, which demonstrated haemostatic properties *in vitro* as well as in bleeding models in HA mice. In preclinical models, Mim8 shows 15-fold increased potency as compared to **Hemlibra®**. The abstract concluded that Mim8 has an efficacious haemostatic effect in preclinical studies. The activity of Mim8 is derived from efficient assembly with FIXa and FX on the procoagulant membrane surface and a strong stimulation of FIXa's proteolytic activity. The physiological function of FIXa is activation of FX by proteolytic cleavage (cutting off a piece of the protein).

Factor VIII level equivalency of Hemlibra®

In an abstract (PB1149) at the ISTH Virtual Congress, researchers presented data on the degree to which **Hemlibra®** corrects the clotting defect and how it corresponds to FVIII activity levels. Twenty-five patients with mild/moderate haemophilia (group one) and eleven severe haemophilia patients with inhibitors on Hemlibra® (group two) participated in the study. Blood drawn from both groups was assayed for FVIII activity (group one) and thrombin generation (both groups). All the patients on Hemlibra® had predicted FVIII activity levels above 10% with most having levels above 20%. The wide variability in the predicted FVIII activity level was tightly correlated to weight with the heaviest patients having the lowest FVIII predicted levels. Further data will be collected to assess this relationship. Moving forward,

understanding the correction of the clotting defect of non-replacement therapies is an important goal.

Real world joint health and physical activity data with Hemlibra®

In an abstract (PB1161) at the ISTH Virtual Congress, researchers explored joint physical exam outcomes and physical activity in a cohort of people with haemophilia A (PwHA) on **Hemlibra®.** Data regarding age, inhibitor status, prior treatment, physical activity, ABR, and Hemophilia Joint Health Scores (HJHS) of PwHA on Hemlibra® for >6 months were extracted from a consented, single-centre cohort study (*HemoPICS*). Joint ABR and HJHS progression for each participant were compared before and after starting Hemlibra®. Data from 58 PwHA, with baseline FVIII levels < 1% to 6%, were analysed. Median age at the start of the study was 12.8 (range 0.6-79.8) years. Median time on Hemlibra® was 10.9 (range 6.2-44.2) months. Nine participants had active inhibitors, and 49 did not, including 39 (80%) on FVIII prophylaxis. Joint ABR improved in all patients (p=0.03), including in patients without an inhibitor. HJHS progression slowed in the overall group (p=0.03), but this was not significant in subgroup analyses.

The impact of Hemlibra® on societal burden: an Australian study

An article published in *Haemophilia* (Haemophilia. 2020;26(Suppl. 5): 21–29) in May 2020 by the Institute for Governance and Policy Analysis at the University of Canberra with funding by Roche, modelled the societal costs of the introduction of **Hemlibra®** on haemophilia A (HA) in Australia. Overall, the model estimates 64.2% reduction in the cost of FVIII blood products and 92% reduction in the cost of bypassing agents (BPA). The modelling also found 30.7% reduction in non-treatment direct costs; and 19.1% reduction in indirect costs (AUD$2.732M) including disability pensions, lost productivity, and work and school absenteeism.

Adverse events reporting in UK patients using Hemlibra®

In an abstract (PB0962) at the ISTH Virtual Congress, the Co-morbidity Working Party of the UK Haemophilia Centres Doctors´ Organisation (HCDO) reported on adverse events (AEs) reported to the National Haemophilia Database in UK patients treated with **Hemlibra®** from February 2018 to January 2020. There were 101 inhibitor and 71 non-inhibitor HA patients treated with Hemlibra® for a median (IQR) of 13.1 (range 4.6-194) months; total 969 months and a median 2.0 (range 1.3-2.7) months, total 1080 months, respectively. Thrombotic microangiopathy and anti-drug antibodies were not reported. Three possible thrombotic events and two deaths were reported; the first in a 51-year-old from multi-organ failure with complicating viral infection, and the second from intra-abdominal bleeding in a 27-year-old man with significantly delayed presentation to hospital, hypovolaemic shock and multiorgan failure. Eight (4.5%) patients reported skin reactions: mild localised reactions in five (2.9%): systemic rash in two and increasingly severe, recurrent reactions leading to cessation of Hemlibra® in one (0.6%). Small joint arthralgia was reported in two (1.2%) and gastro-intestinal symptoms in three (1.7%). Five (2.9%) reported headaches occurring soon after dosing: mild and self-limiting in two; more severe requiring imaging in a further two and severe enough to require hospitalisation and drug cessation in one. Other reports included appendicitis (n=1) and osteonecrosis (n=1). They concluded that continued follow-up is required to establish long-term safety, particularly in relation to thrombotic events. Headaches severe enough to require imaging are reported for the first time. Robust pharmacovigilance is required for all HA treatments to avoid reporting bias.

Influence of Hemlibra® on patient lifestyle

Researchers at the University of Colorado (WFH Virtual Summit abstract MED-PP-010 (616)) surveyed PwHA treated at the Hemophilia and Thrombosis Center (UCHTC) who had been treated with **Hemlibra®** for >1 month as part of a quality improvement effort to identify care delivery challenges, and to monitor closely for adverse effects or unexpected complications shortly after its regulatory approval. Scripted phone surveys lasting 5-10 minutes on adverse effects, bleeding, physical activity, pain medications, and travel were administered to adult patients, or to paediatric patients' guardians. Sixty-nine patients were eligible as of September 1, 2019. Forty-seven patients aged 6 months to 79 years (mean age 18.3 years, median 13.1 years) had taken Hemlibra® for 1.2 to 40.5 months (mean 9.4 months, median 6.6 months) and had survey results. Hemlibra® was associated with improvement in joint health (23/29, 79%), less pain medication use (13/20, 65%), decreased work/school absences (23/33, 70%), and increased physical activities (26/47, 55%). Several PwHA reported missing doses of Hemlibra®, suggesting imperfect adherence.

Pre-clinical studies in new FVIII-mimetic bispecific antibody

In an abstract (PB1145) at the ISTH Virtual Congress, researchers from Chugai in Japan presented results of work to develop new generations of emicizumab to achieve improvement in dosing frequency/volume and/or haemostatic activity to achieve a non-haemophilic status. They developed four-chain asymmetric bispecific antibodies, termed **NXT004** to **007**, which increased in vitro FVIII-equivalent activity of plasma thrombin generation to levels similar to those of standard FVIII (100%). The haemostatic activity was also confirmed in non-human primates (NHPs) with acquired haemophilia A at low dose of the antibody. NXT004 had an approximate three-week half-life in NHPs. From these results, they simulated that the engineered antibody may have a potency to keep a non-haemophilic range of FVIII-equivalent thrombin generation activity by SQ doses every four weeks clinically. A phase I/II clinical study with healthy volunteers and PwHA is underway.

Gene therapy

FDA withheld approval of ROCTAVIAN® (valoctocogene roxaparvovec) pending provision of data on the full cohort of patients in the phase 3 clinical trial

On August 18, the U.S. FDA issued a complete response letter (CRL) to BioMarin requesting further information to enable robust evaluation of BioMarin's gene therapy for haemophilia A, **ROCTAVIAN®.** In the CRL, the FDA requested that BioMarin provide two years' safety and efficacy data for all 134 patients in the phase III study (*GENEr8-1*, NCT03370913). On November 5, BioMarin announced withdrawal of its EMA marketing authorisation application (MAA) following a request by the EMA to provide full 12 months' data for all participants in the phase III study, which will be available at the end of November 2020. BioMarin expects the new MAA to the EMA to be made in the second quarter of 2021.

The aforementioned request for additional data likely concerns the durability of FVIII expression. In the phase I/II trial FVIII activity levels dropped from a mean of 64.3 IU/dL one year after high-dose treatment to a mean of 24.2 IU/dL at four years post-treatment, a 63% decline.

The four-year update for the 6e13 vg/kg and three-year update for the 4e13 vg/kg cohorts demonstrated that all patients remain off prophylactic FVIII treatment since receiving their single dose of valoctocogene roxaparvovec. Cumulative mean ABR remains <1 in both cohorts and below pre-treatment baseline levels. The mean ABR in year four for the 6e13 vg/kg cohort

was 1.3, and the mean ABR in year three for the 4e13 vg/kg cohort was 0.5. Over the past year, six of the seven participants in the 6e13 vg/kg cohort and five of the six participants in the 4e13 vg/kg cohort remain free of spontaneous bleeds. At the end of four years' post-infusion with valoctocogene roxaparvovec, the mean FVIII activity level in all patients in the 6e13 vg/kg cohort was measured at 24.2 IU/dL by the chromogenic substrate (CS) assay and at 35.4 IU/dL as measured by one-stage (OS) assay. The median FVIII activity levels at the end of the fourth year was 16.4 IU/dL as measured by the CS assay and 23.4 IU/dL as measured by the OS assay. These measurements are based on six of the seven participants, as an evaluable sample for the seventh study participant was not available.
No major safety issues have been reported.

Updated results for SB-525 in ALTA study and dosing of first patient in AFFINE study

Updated results for Pfizer's (previously Sangamo's) gene therapy trial *Alta* phase I/II (NCT03061201) for **SB-525 (**giroctocogene fitelparvovec) for the treatment of haemophilia A were presented at the WFH Virtual Summit. Up to 14 months after a one-time infusion of SB-525, durable increases in the activity of clotting FVIII are continuing in all five severe haemophilia A patients treated at the highest dose. As of March 2020, five patients at the highest dose (3×10^{13} vg/kg) were followed between 33-65 weeks and showed increases in FVIII activity levels, with a median increase of 64.2% using a chromogenic assay. Only one patient had one-year data available. There were no bleeding events recorded and no additional FVIII infusions have been required past the initial use of prophylactic factor.
The Alta trial is assessing the safety, tolerability, and effectiveness of a one-time infusion of four increasing doses of SB-525 — 9×10^{11} vg/kg, 2×10^{12} vg/kg, 1×10^{13} vg/kg, and 3×10^{13} vg/kg — in eleven men with severe haemophilia A. Patients' average age is 30 (range 18-47).
Pfizer and Sangamo announced in October that the first participant had been dosed in the phase III *AFFINE* study with SB-525. AFFINE is a global phase III, open-label, multicentre study to evaluate the efficacy and safety of SB-525 in patients with moderately severe to severe haemophilia A. The primary endpoint is impact on ABR through 12 months following treatment compared to ABR on FVIII replacement therapy.

Update from SPK-8011 phase I/II trial data

At a presentation at the ISTH Virtual Congress, researchers from Spark (part of the Roche group) presented an update on the phase I/II trial of **SPK-8011**, a novel bio-engineered AAV vector utilizing the AAV-LK03 capsid, also referred to as Spark200. Fourteen participants in the phase I/II trial received a single administration of investigational SPK-8011, two at a dose of 5×10^{11} vg/kg, three at a dose of 1×10^{12} vg/kg and nine at a dose of 2×10^{12} vg/kg.
As of the June 3, 2020 data cut-off, results from the five total participants in the 5×10^{11} vg/kg and 1×10^{12} vg/kg dose cohorts and seven participants in the 2×10^{12} vg/kg dose cohort show an acceptable safety profile for progression towards phase III, 91% reduction in ABR, 96% reduction in FVIII infusions, and stable and durable factor FVIII expression after 2 (n=5) to 3.3 (n=1) years of follow-up. As previously reported, two of nine participants in the 2×10^{12} vg/kg dose cohort lost FVIII expression, likely due to a capsid-based immune response and required steroids and also immunosuppressive medication. Optimal vector dose and immune suppression regimens, including alternatives to daily oral steroid use, are being studied in the phase I/II to optimise predictable, safe, efficacious and durable FVIII expression.

A long-term study of AAV gene therapy in dogs with haemophilia A showing integration of viral vector

In October, a long-term study of adeno-associated viral (AAV) gene therapy in nine dogs with haemophilia A, which were treated with AAV gene therapy and followed for up to ten years was reported. The dogs were administered AAV8 or AAV9 vectors expressing canine factor VIII (AAV-cFVIII) that corrected the FVIII deficiency to 1.9-11.3% of normal FVIII levels. In two of nine dogs, levels of FVIII activity increased gradually starting about four years after treatment. This data suggests that the increase in FVIII protein expression in two dogs may have been due to clonal expansion of cells harbouring integrated vectors. The results support the clinical development of liver-directed AAV gene therapy for haemophilia A, while emphasizing the importance of long-term monitoring for potential genotoxicity. None of the dogs showed evidence of tumours or altered liver function.

Data from first in-human gene therapy study of BAY 2599023

In a presentation by Dr. Steven Pipe from the University of Michigan at the ISTH Virtual Congress, results from the first six patients receiving a single dose in the phase I/II trial of **BAY 2599023** show that that the gene therapy safely promotes a sustained production of FVIII, effectively preventing spontaneous bleeds in people with severe haemophilia A. Patients treated to date in this clinical study, are showing durable FVIII activity at more than one year post-treatment, its investigators report. This gene therapy trial for haemophilia A (NCT03588299) is being developed by Bayer in collaboration with Ultragenyx Pharmaceuticals. BAY 2599023 uses the AAVhu37 serotype, selected for its efficient liver-directed FVIII gene transfer and sustained, long-term FVIII expression. Dr. Pipe also presented preliminary seroprevalence data, which suggests a broad base of patients may be eligible owing to a low rate of pre-existing neutralizing antibodies against the AAVhu37 vector compared to other AAV based gene therapy. The phase I/II study aims to recruit 30 eligible patients at various sites across the U.S. and Europe. Enrolled patients are being assigned to one of four increasing doses of BAY 2599023 — 0.5 x 10^{13} gene copies per kilogram (gc/kg), 1.0 x 10^{13} gc/kg, 2.0 x 10^{13} gc/kg, and 4.0 x 10^{13} gc/kg.

Pre-clinical safety and efficacy data for SIG-001

In an abstract (PB1153) at the ISTH Virtual Congress, researchers from Sigilon Therapeutics assessed the preclinical safety and toxicology of **SIG-001**, a cell therapy with genetically engineered human cells expressing hFVIII.

SIG-001 is a candidate product consisting of a two compartment 1.5 mm alginate sphere containing the cells, which can produce functionally active hFVIII in a dose-dependent manner, correct the bleeding phenotype in haemophilia A mice, and maintain viable cells for at least six months in model animals (Carmona ASH 2019). The cells are contained in an inner compartment that is surrounded by an outer layer of alginate conjugated to a proprietary compound selected to avoid foreign body immune response. Six months after placement into mice, SIG-001 spheres remained intact, with viable cells, without safety or toxicological findings. They also conducted a broken sphere study in immunocompetent mice and none of the intentionally broken sphere components raised any safety concerns for up to one-month post-administration. Finally, no toxicologically relevant effects were observed 6 months after empty spheres were placed laparoscopically into the peritoneal cavity of NHPs. They concluded that these safety studies, combined with the *in vivo* efficacy data reported

previously, indicate that preclinical evaluation of SIG-001 did not identify any safety/toxicology signal and results in sustained, long-lasting FVIII levels.
The first-in-human trial of SIG-001 started recruiting in September 2020.

uniQure announces deprioritisation of clinical programme investigating AMT-180

In a press release uniQure announced that it planned to deprioritise its research programme of AMT-180 for patients with haemophilia A. AMT-180 is a novel AAV5 gene therapy clinical candidate that encodes a transgene for a variant of FIX, FIX-FIAV, which possesses four amino acid substitutions under the control of a proprietary primate-specific liver promoter. Upon activation of FIX-FIAV to activated FIX-FIAV, haemostasis is induced through FVIII-independent activation of FX making AMT-180 a strong candidate to treat both inhibitor and non-inhibitor haemophilia A patients.
The AMT-180 research programme was in the pre-clinical stage.

AN UPDATE ON NOVEL TREATMENTS IN HAEMOPHILIA B

Factor replacement therapies

Survey of Japanese HB patients treated with Idelvion®, Alprolix® or standard rFIX

Researchers associated with CSL Behring assessed the experience among patients receiving prophylaxis with either extended half-life rIX-FP (**Idelvion®**), rFIXFc (**Alprolix®**), or standard half-life rFIX (WFH Virtual Summit abstract MED-PP-009 (382)).

Seventy-four haemophilia B patients ≥ 18 years of age, 66 of whom had FIX levels <1%, who had been treated with rIX-FP, rFIXFc, or rFIX for at least six months participated in this cross-sectional study. They completed a survey to gather personal details (age, disease severity, weight), number of spontaneous and trauma-related bleeds in the previous 12 months, and current infusion frequency and dosage. The mean (median) ABR for patients who had received the current brand for ≥ 1 year was 3.1 (2.0, n=17) for rIX-FP, 6.3 (4.5, n=18) for rFIXFc, and 13.8 (13.0, n=19) for rFIX, while the spontaneous ABR (AsBR) was 1.6 (1.0, n=17), 3.4 (2.0, n=18), and 4.4 (4.0, n=19) for rIX-FP, rFIXFc, and rFIX, respectively. All rFIX-FP patients and 69.6% of rFIXFc patients received prophylaxis once-weekly or longer dosing intervals; all rFIX patients received prophylaxis every four days or more often. Mean (median) consumption was 31.7 (31.5) IU/kg/week for rIX-FP, 58.9 (54.5) IU/kg/week for rFIXFc, and 90.3 (89.7) IU/kg/week for rFIX.

Researchers concluded that EHL products such as rIX-FP can reduce consumption and dosing frequency while maintaining and potentially improving efficacy.

Real-world data of Canadian haemophilia B patients

During the ISTH Virtual Congress, data from the Canadian Bleeding Disorder Registry (CBDR; abstract PB0905) was presented on a non-interventional, retrospective study, capturing infusion reports collected from haemophilia treatment centres and directly from patients. These were used to assess real-world outcomes in Canadian haemophilia B patients receiving **Rebinyn®/Refixia®** for ≥3 months in any setting (prophylaxis, on-demand treatment, treatment of breakthrough bleeds). For comparison with previously used products, only patients for whom data existed in the CBDR for the 6-month period pre-switch to Rebinyn®/Refixia® were included.

At the data cut-off (September 30, 2019), 40 patients were included in the analysis, with a median age of 44 years. Distribution of disease severity was 2.5% mild, 40% moderate, 55% severe, and 2.5% unknown. At study start, ten target joints, as per ISTH definition, were present in five patients. Most patients had previously received **Alprolix®** (55% versus 40% rFIX), with most previously receiving prophylactic treatment (85% versus 15% on-demand). No patients had present or previous inhibitor development. During a median treatment period of 11.11 months on Rebinyn®/Refixia®, 106 breakthrough bleeds were reported in 22 patients; 42% of patients reported zero bleeds. Annualised bleeding rate (ABR) was lower after switching to Rebinyn®/Refixia® than for previous products. ABR for patients who switched from Alprolix® to Rebinyn®/Refixia®, decreased from 4.8 to 2.7. Median time from last recorded prophylactic injection to start of bleeding was 7.1 days and the mean number of injections required to treat a bleed was 1.23.

Initial data suggest improved bleeding outcomes with lower factor consumption after switching to Rebinyn®/Refixia®, regardless of whether patients previously received standard

or extended half-life products. *Authors of this abstract include representatives from Novo Nordisk.*

Final results of phase II DLZ-201 trial

Final efficacy and safety data from the phase IIb trial of **dalcinonacog alfa** (**DalcA**), a SQ administered FIX therapy being developed for the treatment of haemophilia B by Catalyst Biosciences, were presented at the World Federation of Hemophilia Virtual Summit in June 2020.

The trial was designed to evaluate daily SQ dosing and the ability to maintain protective steady state FIX levels above 12% in six individuals with severe haemophilia B. Each patient received a single intravenous dose, followed by daily SQ doses of DalcA for 28 days. Pharmacokinetics, pharmacodynamics, safety, tolerability and anti-drug antibody formation were monitored. Data from the trial showed that 28 days of daily SQ dosing of DalcA achieved protective target FIX levels of >12% in all participants, with FIX levels of up to 27% and a half-life of 2.5 to 5.1 days with no bleeds, demonstrating prophylaxis and the potential for lower or less frequent dosing. Injection volumes were less than 1 mL. One patient withdrew on day seven after reporting injection site reactions from the first 3 SQ doses. No neutralizing inhibitors were detected, and no serious adverse events (SAEs) were reported. Some patients reported mild pain and/or redness, primarily with the initial injections. No thrombotic events occurred and blood coagulation markers of d-dimer, prothrombin fragment 1+2, thrombin-antithrombin and fibrinogen did not show any prothrombotic signals.

Gene Therapy

Experience with surgery in patients that underwent gene therapy with fidanacogene elaparvovec (formerly SPK-9001)

In an abstract (PB1096) at the ISTH Virtual Congress, researchers from Spark-Pfizer assessed the safety and efficacy in patients with haemophilia B undergoing surgery and having been exposed to gene therapy using **fidanacogene elaparvovec** (formerly **SPK-9001**).

This gene therapy utilises a bioengineered hepatotropic AAV vector capsid and a transgene cassette that expresses a high-activity variant of hFIX-Padua transgene via a liver-specific promoter. Fifteen patients with moderately severe to severe haemophilia B (FIX activity ≤2%) received fidanacogene elaparvovec in a phase I/IIa study and ongoing long-term follow-up study. Fidanacogene elaparvovec demonstrated sustained efficacy over a period of up to four years, as assessed by steady-state FIX activity, ABR, and annualised infusion rate. It has been well tolerated, with no related SAEs reported to date. Two patients had non-related SAEs of appendicitis and emergent lumbar discectomy. Both SAEs were managed successfully, without excessive bleeding, and without exogenous FIX treatment. FIX activity levels were in the mild range (26.3% and 11.8%) at last measurement available before the event (measured via a central laboratory one-stage assay).

These are the first reported cases of surgical procedures in patients with haemophilia B who received FIX-Padua via AAV-based gene therapy.

Recent progress in the development of AMT-061

Researchers presented an overview of results (WFH Virtual Summit abstract MED-FP-010 (258)) from ongoing **AMT-060** (5e12 gc/kg and 2e13 gc/kg; n=5 per dose) and **AMT-061** (2e13 gc/kg; n=3) studies in patients with severe/moderately severe haemophilia B. AMT-060/AMT-061 are AAV5 vectors containing a codon-optimized hFIX gene (AMT-060: wildtype; AMT-061:

2 nucleotide substitution resulting in highly active Padua variant) with a liver-specific promotor.
All participants are adult males with FIX ≤2% and a severe bleeding phenotype. All phase I/II study participants stably expressed FIX 3-3.5 years post-dose (mean FIX activity at 1, 2, and 3 years, respectively: 4%, 6.8%, 7.3% with low-dose AMT-060; 7.1%, 8.4%, 7.9% with the higher dose). Eight out of nine participants discontinued prophylaxis post-treatment and remained prophylaxis-free at last follow-up. Three participants experienced transient asymptomatic elevations in liver enzymes at 4-16 weeks with no impact on FIX expression. A single treatment related AE (joint swelling) has been reported in the years since the initial 3.5 months of follow-up. Three lower-dose participants were retrospectively found to have AAV5 NAbs at baseline. NAbs had no impact on AMT-060 safety or efficacy. In the phase IIb study, mean FIX activity increased to 31% at six weeks and 45% at 36 weeks, despite low AAV5 NAb titres at baseline. There were no bleeds post-treatment, no requirement for FIX replacement excluding surgery, and no clinically significant elevations in liver enzymes. One participant experienced two mild AEs possibly related to treatment (headache and slightly elevated C-reactive protein, CRP – an inflammation marker). No participant in either trial developed FIX inhibitors.
Researchers concluded that one-time AMT-060 treatment led to stable, long-term FIX activity without late-emergent safety events. AMT-061 led to sustained elevations of FIX activity into the mild-to-normal range 36 weeks post-treatment. Both constructs were safe and well tolerated. Results from these studies support the ongoing phase III *HOPE-B* study in which all 54 patients have completed 26-week follow-up visits.

HOPE-B primary endpoint of FIX activity at 26 weeks achieved, irrespective of pre-existing NAbs

On November 19, 2020, uniQure announced top-line data from its pivotal, phase III *HOPE-B* gene therapy trial of **AMT-061** (etranacogene dezaparvovec), for the treatment of patients with severe and moderately severe haemophilia B. This is the first data set to be reported from a phase III gene therapy study in haemophilia; it has enrolled 54 patients. These clinical data were published as a late-breaking abstract in the upcoming 62nd Annual Meeting of the American Society of Hematology (ASH). The abstract is available here.
Patients received a single intravenous infusion of etranacogene dezaparvovec gene therapy at $2x10^{13}$ gc/kg, including 23 patients who had pre-existing NAbs to AAV5. FIX activity in the 54 patients increased to a mean of 37.2% at 26 weeks. During the 26-week period after dosing, 72% of patients reported no bleeding events. Fifteen patients reported a total of 21 bleeds[1]. Mean annualized usage of FIX replacement therapy declined by 96%.
There was no correlation between pre-existing NAbs and FIX activity found in patients with NAb titres. One patient with a NAb did not show an increase in FIX activity. Adverse events were classified as mild (81.5%). Most common events included transaminase elevation treated with steroids per protocol (nine participants; 17%), infusion-related reactions (seven participants; 13%), headache (seven participants; 13%) and influenza-like symptoms (seven participants; 13%). Liver enzyme elevations resolved with a tapering course of corticosteroids and FIX activity remained in the mild range in the steroid treated patients. No relationship between safety and NAbs titres was observed.

[1] Total bleeds include any bleeding event reported after the treatment of etranacogene dezaparvovec, including spontaneous, traumatic, and those associated with unrelated medical procedures, whether or not FIX treatment was required.

Based on interactions with the FDA and EMA, the company is aiming to have a pre-biologic licensing application meeting with the FDA and to completing the last patient's 52-week follow-up visit in the first quarter of 2021.

Results for phase I/II gene therapy trial in HB with FLT180a

Freeline is currently investigating the safety and efficacy of single, increasing doses of **FLT180a** in its phase I/II trial *B-AMAZE* (NCT03369444) and announced results at the ISTH Virtual Congress (abstract LB/C001.1).

Ten patients with severe HB were treated across four dose levels, with FIX activity levels at week 3 ranging between 24 and 168%. The first two patients, receiving the 4.5e11vg/kg dose, have stable, therapeutic FIX activity levels through week 104. No patient has had a bleeding episode requiring FIX concentrates. The most common drug-related SAE was transient transaminitis (in four patients) requiring supplemental immunosuppression. FIX activity levels well above 150% have been observed, which were individually assessed for risk of thrombosis, and this patient is being treated with direct oral anticoagulants. Refinement of the immunosuppression regimen for the latest three patients (9.75e11 vg/kg dose) prevented transaminitis during the critical phase (4-16 weeks). FLT180a achieves clinically meaningful, durable FIX activity levels in patients with HB, associated with independence from FIX replacement therapy and zero treated bleeds. Transient transaminitis was largely averted by prophylactic immunosuppression. A dose between 7.5 to 9.75e11vg/kg can potentially create sustained, normal FIX activity levels in patients with severe HB.

Freeline has announced plans to launch a pivotal trial (NCT03641703) for FLT180a.

FIX activity after a single treatment with AMT-060 or AMT-061 in patients with pre-existing AAV5 immunity

Researchers from uniQure (WFH Virtual Summit abstract MED-FP-008 (583)) reported on a study to explore the impact of pre-existing anti-AAV5 NAbs on the efficacy of AAV5-based gene therapy. Previously, NAbs against AAV serotypes were shown to decrease the efficacy of systemically administered AAV-based gene therapies, both in humans and NHPs. Consequently, individuals with pre-existing anti-AAV NAbs above a titre of five have been excluded from most systemic AAV-based CTs.

Pre-treatment serum samples from ten haemophilia B patients from CTs with AAV5-FIX (**AMT-060**) and three patients from the phase IIb CT with AAV5-hFIX-Padua (**AMT-061**) were analysed for anti-AAV5 NAbs. Results were correlated with hFIX activity after treatment with AMT-060/AMT-061, AAV5-specific T-cell response, and transaminase levels. Additionally, pre-treatment serum samples from 14 NHPs were analysed for anti-AAV5 NAbs and results were correlated with hFIX protein expression after treatment with AAV5-hFIX. Three out of ten AMT-060 CT patients and all three AMT-061 patients returned positive pre-existing anti-AAV5 NAb titres. No relationship was observed between the presence of pre-treatment anti-AAV5 NAbs and therapeutic efficacy.

Regarding AMT-060 CT, the patient with the highest anti-AAV5 NAb titre (340) presented the highest mean hFIX activity (6.8%) in this dose cohort. The other two positive patients had titres of 210 and 21, with a mean hFIX activity of <2% and 3.0%, respectively. Three patients participating in the phase IIb AMT-061 CT presented pre-existing anti-AAV5 NAbs of 48, 44 and 25 while demonstrating mean hFIX activity at nine months at 45% of normal. None of the patients experienced relevant elevations in transaminases and no clinically relevant T-cell responses to the capsid were detected. Further NHP studies showed that AAV5 transduction

efficacy was similar following high-and low-dose AAV5-hFIX treatment, irrespective of the level of pre-existing anti-AAV5 NAbs. Circulating hFIX protein was detected in NHPs at level therapeutic in humans, with pre-existing anti-AAV5 NAb titres up to 1030.
These results demonstrate efficacious systemic gene delivery with AAV5 targeting the liver in presence of pre-existing anti-AAV5 NAbs. Consequently, patients are currently not excluded from *HOPE-B* (phase III CT of AMT-061) based on anti-AAV5 NAb levels.

Pre-clinical findings for CB 2679D-GT

Catalyst Biosciences presented data from preclinical studies of its haemophilia B gene therapy **CB 2679d-GT** at the WFH Virtual Summit. The oral presentation "Combination of a Novel Chimeric AAV Capsid and Potency Enhanced FIX Variant for Hemophilia B Gene Therapy" provided preclinical results of CB 2679d-GT, the company's novel FIX gene therapy.
CB 2679d-GT was designed to achieve clinically relevant FIX levels at a reduced viral vector load by combining engineered AAV capsids with Catalyst's novel high potency FIX transgene. Studies of CB 2679d-GT in haemophilia B mice have demonstrated a four-fold reduction in blood loss and an eight-fold reduction in bleeding time when compared with the same dose of the Padua variant of FIX. Furthermore, when packaged in a proprietary chimeric AAV capsid, CB 2679d-GT demonstrated a clear dose response of high stable FIX levels across the three dose levels in haemophilia B mice. A pilot NHP study compared the expression and tolerability of CB 2679d-GT in the novel chimeric capsid KP1 with the LK03 capsid.
The study demonstrated that CB 2679d-GT was well tolerated with high FIX expression that stabilized to approximately 25% to 50% FIX above baseline levels at the six-week interim data cut-off. The novel chimeric capsid had differentiated and superior response to anti-capsid NAbs than that observed for the LK03 comparator during the screening of NHP for the study.

AN UPDATE ON NOVEL TREATMENTS FOR PEOPLE WITH HAEMOPHILIA A AND B AND INHIBITORS

Bypassing agents

Treatment of acute bleeds with MarzAA

Catalyst Biosciences presented two posters at the ISTH Virtual Congress on their new recombinant FVIIa product. The first poster, "Phase I study to evaluate the PK, pharmacodynamics, and safety of ascending doses of subcutaneous (SQ) **marzeptacog alfa** (**activated**) (**MarzAA**) in adult patients with haemophilia" included the final data from *MAA-102*. This study was conducted in adults with haemophilia A or B, with or without inhibitors, to evaluate the PK, pharmacodynamics, and safety of a single intravenous dose and ascending SQ (single and multiple) doses of MarzAA. The final data demonstrated the potential of SQ MarzAA to rapidly achieve and maintain therapeutic levels to treat acute bleeding events in haemophilia and confirm the dosing regimen chosen for the upcoming phase III trial, *Crimson 1*.

The second poster: "Marzeptacog alfa (activated) population PK: Simulations for dose selection in Phase 3 trials" was a population PK model developed and used for simulations of clinical trials. Based on simulating PK for SQ MarzAA in 1000 patients, the model confirmed that target levels for haemostasis may be rapidly achieved and sustained for over 24 hours in the upcoming phase III *Crimson 1* trial using 60 µg/kg dosed SQ once, and 36-48 hours when dosed twice or three times at 3-hour intervals.

Additionally, Catalyst Biosciences announced the design for the pivotal phase III *Crimson 1* ("Subcutaneous Marzeptacog Alfa (Activated) For On Demand Treatment and Control of Bleeding Episodes in patients with Haemophilia A or Haemophilia B with Inhibitors") study that will enrol individuals who experience episodic bleeding (NCT04489537). *Crimson 1* will be a cross-over, open-label global trial, evaluating the safety and efficacy of SQ MarzAA in the treatment of approximately 244 bleeding episodes in approximately 60 patients, compared with standard of care in a similar number of bleeding episodes. The study will assess the effectiveness of SQ MarzAA, using up to three doses to treat a bleeding episode. The primary endpoint will be haemostatic efficacy at 24 hours using a standard four-point assessment scale.

Non-replacement therapies

Comparison of bypassing agents in patients using Hemlibra®

In an abstract (PB1148) at the ISTH Virtual Congress, researchers aimed to assess the effect on thrombin generation by spiking various concentrations of BPAs on plasma taken from patients on **Hemlibra®**. Management of breakthrough bleeding events in inhibitor patients on Hemlibra® involves episodic treatment with activated prothrombin complex concentrate (aPCC) and recombinant activated FVII (rFVIIa). A concomitant drug reaction between Hemlibra® and aPCC resulting in thrombotic events was noted as a SAE in the *HAVEN* CTs. Eleven patients with severe HA and inhibitors currently on Hemlibra® for at least six weeks were enrolled in the study. The thrombin generation assay parameters were assessed.

In conclusion, it was demonstrated that lower doses of aPCC could potentially be used safely and effectively in inhibitor patients on Hemlibra®. It would be important to test this hypothesis in a clinical study.

Inhibitor status of patients with haemophilia A who transitioned to Hemlibra® after ITI

Researchers from Emory University (WFH Virtual Summit abstract MED-FP-011 (139)) evaluated the inhibitor status of patients with haemophilia A and a history of inhibitors successfully or partially tolerized after immune tolerance induction (ITI) who have switched from FVIII prophylaxis to **Hemlibra®.** The medical records of paediatric patients with haemophilia A and inhibitor history (N.B. duration of inhibitor not specified) on Hemlibra® were evaluated. Half of the eight patients evaluated in this study had a history of a high titre inhibitor (range 1.7-819 BU/mL). Three patients had been successfully tolerized and five patients achieved partial tolerance after ITI. Six patients (75%) transitioned to Hemlibra® alone while two patients (25%) transitioned to Hemlibra® with intermittent FVIII dosing. In the group of six patients on Hemlibra® alone, one patient had a peak inhibitor titre at 2.5 chromogenic BU/mL five months after starting Hemlibra®. However, three of the five patients with a negative inhibitor titre had positive anti-FVIII IgG4 antibodies. Both of the patients on Hemlibra® and intermittent FVIII dosing were partially tolerized and had negative inhibitor titres, but positive anti-FVIII IgG4 antibodies. FVIII dosing regimens for patients on Hemlibra® and intermittent FVIII exposure was prescribed as 50 IU/kg twice weekly or once every other week infusions. None of the patients had detectable anti-FVIII IgG1 antibodies.

The majority of patients maintained negative inhibitor titres after switching to Hemlibra® with or without intermittent FVIII exposure. However, the persistence of anti-FVIII IgG4 antibodies raises concern for an underlying inhibitor that could result in a re-occurrence of the inhibitor following intense factor exposure for example due to a catastrophic bleed and major surgery.

Preliminary report from major orthopaedic surgeries with Hemlibra® and rFVIIa

Researchers from Florence, Italy (WFH Virtual Summit abstract MED-PP-025 (101)) reported their experience in major orthopaedic surgery in PwHA and inhibitors on **Hemlibra®.**

For many years, PwHA and inhibitors needing surgery have been treated by using aPCC or rFVIIa. Hemlibra® was used together with rFVIIa because of the thrombotic risk associated with the use of aPCC and Hemlibra®. Between 2018 and 2019, three PwHA and high titre inhibitors underwent four major orthopaedic surgeries: one amputation above the knee and a total knee arthroplasty in a 56-year-old patient; a total hip arthroplasty in a 59-year-old patient; and a partial revision knee arthroplasty in a 49-year-old patient. All patients were previously managed for surgery by rFVIIa prophylaxis. Parameters of evaluation were: pain visual analogue scale (VAS), HJHS, and radiologic study. Hemlibra® was continued once weekly and they were treated before and after surgery by bolus infusions of rFVIIa (90 µg/kg) every four hours during the first two days, every six hours the next two days after surgery, every eight hours for an additional two days, and then with longer intervals, up to two weeks.

All patients were successfully managed by a single surgeon, without any complications during surgery, the postoperative period, and at the latest follow-up. The mean follow-up was 15.3 months (range: 5-22). Effective bleeding control was confirmed during surgery. No AEs were observed for the haematological prophylaxis, and in particular, no significant changes of markers of thrombophilia/microangiopathy were observed. All patients were regularly discharged after early rehabilitation with a mean hospital stay of 12.1 days (range: 12-13); they were then admitted to the rehabilitative ward at the same hospital.

All patients reported satisfaction for pain reduction and improved joint and global function as per VAS and HJHS scores.

Researchers concluded that major orthopaedic surgery with a regimen of Hemlibra® and rFVIIa in PwHA and inhibitors has been efficaciously performed with successful clinical outcome and effective bleeding control. This represents the first series of major orthopaedic surgeries ever reported in this setting. However, a larger number of procedures are required in order to validate this haematological protocol for orthopaedic surgery.

AN UPDATE ON NOVEL TREATMENTS FOR PEOPLE WITH HAEMOPHILIA A AND B

Non-Replacement therapies

Novo Nordisk resumed concizumab trial

Novo Nordisk announced in August that its *Explorer 6*, *7* and *8* trials investigating the use of **concizumab**, a TFPI-inhibiting antibody, will re-start after the U.S. FDA lifted the hold.
The trials were halted in March 2020 following cases of non-fatal thrombotic complications in three patients. In collaboration with regulatory authorities, new safety measures and guidelines were established. *Explorer 6* (NCT03741881) is an observational study to collect data on bleeding and quality of life in people with severe congenital haemophilia A and B, with or without inhibitors on their usual local treatment. Data from this study are used to make within-patient comparisons with data from the phase III *Explorer 8* clinical trial. *Explorer 7* (NCT04083781) is investigating the use of concizumab in patients with haemophilia A or B with inhibitors toward FVIII or FIX. *Explorer 8* (NCT04082429) is investigating concizumab in patients with haemophilia A or B without inhibitors.

Survey results on patients and HCP clinical trial experience with concizumab

Researchers from Novo Nordisk presented results from an electronic survey of HCPs who participated in the phase II **concizumab** trials (*Explorer4* [NCT03196284]; *Explorer5* [NCT03196297]).
Concizumab is in clinical development for the once-daily, subcutaneous (SQ) prophylactic treatment of haemophilia patients with/without inhibitors. The survey was conducted in January/February 2019 and comprised 22 questions: 12 on the HCPs' impression of patient experience with concizumab administration (preference, adherence, concerns); five on the impact of concizumab on patients' daily life (social/physical activities, emotional well-being); three on demographics; and two on HCP experience with concizumab administration. There were 30 respondents from Europe (n=18), North America (n=3) and Asia (n=9) including 16 physicians, 13 nurses, and one unknown, with >75% of HCPs having seen one/two patients during the concizumab phase II trials. HCPs selected the SQ administration mode (47%) and treatment efficacy (40%) as the two main differentiating factors for patients. Concizumab injections were well received according to respondents, with 94% and 84% of physicians and nurses, respectively, describing patients' injection experience as completely/quite painless. There were limited concerns regarding the use of a SQ self-injection (87% of HCPs reported that their patients had no concerns). Seventy-three percent of HCPs reported some to large improvement in patients' ability to participate in physical activities/sports and social activities while on concizumab.

Overview of clinical development of fitusiran

In an abstract (MED-FP-002 (598)) at the WFH Virtual Summit, researchers from Sanofi reported on trials with **fitusiran**, a once-monthly SQ administered investigational therapy that harnesses the natural RNA interference mechanism to reduce antithrombin, enhancing thrombin generation and rebalancing haemostasis in haemophilia A or B, with or without inhibitors. Of 42 patients with haemophilia treated with fitusiran in the phase I study, 34 rolled over into the phase I/II open label extension study. As of September 30, 2019, the median exposure in the phase I/II open label extension study was 2.1 years, the maximum exposure

was 3.3 years, and the total exposure was 68.6 patient-years. As of November 1, 2019, 162 patients were enrolled in the *ATLAS program* (ATLAS-INH, 35 patients; ATLAS-A/B, 66; ATLAS-PPX, 61). Data to-date show that monthly fitusiran enables steady-state AT lowering and increased levels of thrombin generation, promoting rebalance of haemostasis in haemophilia patients. Ongoing evaluation of the efficacy and safety of fitusiran will clarify its therapeutic potential for haemophilia A or B, with or without inhibitors.

Global dosing hold in fitusiran trials initiated by Sanofi Genzyme to investigate new adverse events

In a statement released in November by the WFH, EHC and National Hemophilia Foundation (NHF), these organizations announced that they had learned of and subsequently confirmed a decision by Sanofi Genzyme to initiate a voluntary sponsor-led global dosing hold on its full clinical development program for **fitusiran** due to the identification of new adverse events. Read the full statement.

Pfizer doses first patients with marstacimab in phase III trial

In November, Pfizer dosed its first participant in the phase III *BASIS* study of **marstacimab** (PF-06741086) for people with severe haemophilia A and B with or without inhibitors (NCT03938792). Marstacimab is an anti-tissue factor pathway inhibitor (anti-TFPI). The *BASIS* study will evaluate annualized bleed rate (ABR) through 12 months on prophylactic treatment with marstacimab, in adolescents and adults with haemophilia A or B compared to a run-in period on replacement therapy with FVIII, FIX clotting factor, or bypassing agents. The study will be in approximately 145 adolescent and adult participants between ages 12 to <75 years with severe haemophilia A or B (defined as factor VIII or factor IX activity <1%, respectively), with or without inhibitors. Approximately 20% of participants will be adolescents.

Perioperative management of patients with haemophilia receiving fitusiran

In an e-Poster at the ISTH Virtual Congress, researchers reported on successful perioperative haemostatic management of patients in the context of antithrombin regulation with **fitusiran**. Six patients, aged 27 to 53 years, with HA (four with inhibitors) underwent a total of seven surgical procedures including a thoracotomy/partial lung segmentectomy and a total knee joint replacement. Patients were managed with reduced or standard supplemental factor or BPA for six procedures; no additional haemostatic agent was used for one procedure. All procedures were rated by the respective investigators as resulting in minimal blood loss or blood loss similar to that for patients without haemophilia. No thromboprophylaxis was used in any procedure.

These cases suggest that haemostatic capacity conferred by fitusiran may allow reduced dosing of factor or BPA for perioperative management.

AN UPDATE ON NOVEL TREATMENTS FOR PEOPLE WITH VON WILLEBRAND DISEASE

Comparison of recombinant vs plasma-derived VWF

Researchers from Takeda presented an abstract at the ISTH Virtual Congress (abstract PB1545) to compare the structural and functional comparison of plasma-derived concentrates (**HAEMATE P®/HUMATE-P®, VONCENTO®, WILATE®/EQWILATE®, WILFACTIN®/WILLFACT®**) and recombinant VWF concentrates (**Vonvendi®/ Veyvondi®**)**.** In all pdVWF concentrates the ratio between measurements of biological function of VWF and VWF antigen content was < 1, indicating the presence of not fully active VWF between 5 and 30%. Corresponding ratios for rVWF were > 1. Thus, rVWF has higher specific activity by all biological measurements. Only rVWF contained the full spectrum of ultra-large and high molecular weight multimers. While pdVWF showed varying satellite band structures indicative of different degrees of proteolysis, rVWF had an intact multimeric pattern. VWF:GpIbM measurements were, for all products, higher than those obtained with the VWF:RCo assay. Thus, VWF products differ in their contents, multimer size and structure of functional VWF. These differences may translate into improved biological activity of rVWF in clinical settings and influence the treatment regimen of individuals with VWD.

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 FVIII	**Haemophilia A**	Advate	human coagulation factor VIII (rDNA), octocog alfa	Takeda	**Licensed**
Replacement FVIII	**Haemophilia A**	Adynovi Adynovate BAX855 TAK-660 SHP-660	PEGylated recombinant factor VIII (rurioctocog alfa pegol)	Takeda	**Licensed**
Replacement FVIII	**Haemophilia A**	Afstyla CSL627	rVIII-Single Chain	CSL Behring	**Licensed**
Replacement FVIII	**Haemophilia A**	Elocta Eloctate	rFVIIIFc (efmoroctocog alfa)	Sobi	**Licensed**
Replacement FVIII	**Haemophilia A**	Esperoct N8-GP NNC 0129-0000-1003	rFVIII (turoctocog alfa pegol)	Novo Nordisk	**Licensed**

Replacement FVIII	**Haemophilia A**	Jivi BAY 94-9027	rFVIII (damoctocog alfa pegol)	Bayer	**Licensed**
Replacement FVIII	**Haemophilia A**	Kovaltry BAY 81-8937	unmodified full-length rFVIII (octocog alfa)	Bayer	**Licensed**
Replacement FVIII	**Haemophilia A**	Novoeight®	turoctocog alfa	Novo Nordisk	**Licensed**
Replacement FVIII	**Haemophilia A**	Nuwiq	human-cell-line-recombinant-human-FVIII (simoctocog alfa human-cl-rhFVIII)	Octapharma	**Licensed**
Replacement FVIII	**Haemophilia A**	Refacto AF	moroctocog alfa	Pfizer	**Licensed**
Replacement FVIII	**Haemophilia A**	BIVV001	rFVIIIFc-VWFD'D3-XTEN	Sanofi and Sobi co-development	**Phase 3**
Replacement FIX	**Haemophilia B**	Alprolix	rFIXFc (eftrenonacog alfa)	Sobi	**Licensed**
Replacement FIX	**Haemophilia B**	BeneflX	nonacog alfa	Pfizer	**Licensed**
Replacement FIX	**Haemophilia B**	Idelvion	rFIX-FP / recombinant factor IX albumin fusion protein	CSL Behring	**Licensed**

Replacement FIX	**Haemophilia B**	Refixia / Rebinyn	recombinant FIX glycopegylated / rFIX-GP (nonacog beta pegol)	Novo Nordisk	**Licensed**
Replacement FIX	**Haemophilia B**	RIXubis	Nonacog gamma	Takeda	**Licensed**
Replacement FIX	**Haemophilia B**	Dalcinonacog alfa (DalcA)	Subcutaneous coagulation factor IX variant	Catalyst Bioscience	**Phase 2**

BYPASSING AGENTS					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Bypassing agent	**Haemophilia A or B w/[2] inhibitors**	Sevenfact	Recombinant FVIIa- jncw	LFB	**Licensed in the US**
Bypassing agent	**Haemophilia A or B w/ or w/o[3] inhibitors**	Marzeptacog alfa (activated) MarzAA	Subcutaneous coagulation rFVIIa variant	Catalyst Bioscience	**Phase 3**

[2] w/: with

[3] w/o: without

NON-REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Non-replacement therapy (NRT) Bispecific antibody	**Haemophilia A w/ or w/o inhibitors**	Hemlibra emicizumab ACE-910	Bispecific antibody	Roche	**Licensed**
NRT Bispecific antibody	**Haemophilia A**	Mim8	Bispecific antibody	Novo Nordisk	**Phase 2**
NRT Bispecific antibody	**Haemophilia A**	KY1049	Bispecific antibody	Kymab	**Pre-clinical studies**
NRT bispecific antibody	**Haemophilia A**	NXT004 to NXT007	Bispecific antibody	Chugai	**Pre-clinical studies**
NRT Anti-TFPI	**Haemophilia A or B w/ or w/o inhibitors**	Concizumab	Anti-TFPI	Novo Nordisk	**Phase 3 trials resumed**[4]
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 dosing started**

[4] Text in red indicates changes in the table since the last issue.

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	**global dosing hold**
NRT Activated Protein C inhibitor	**Haemophilia A or B w/ or w/o inhibitors**	SerpinPC	Activated Protein C inhibitor	Apcintex	**Phase 1/2**

GENE THERAPY					
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Developer / manufacturer**	**Development stage**
Gene Therapy	**Haemophilia A**	Roctavian® Valoctocogene roxaparvovec BMN-270	AAV5-huFVIII-SQ Valoctocogene roxaparvovec	BioMarin	**Withheld approval**
Gene Therapy	**Haemophilia A**	SB-525 giroctocogene fitelparvovec	Gene therapy using a rAAV2/6 vector	Pfizer (originally Sangamo)	**Phase 3**
Gene Therapy	**Haemophilia A**	BAY-2599023 / DTX 201	Gene therapy using AAVhu37FVIII	Bayer	**Phase 1/2**
Gene Therapy	**Haemophilia A**	Spark-8011	AAV-LK03 (AAV-Spark200) encoding BDD-FVIII	Spark	**Phase 1/2**

Gene Therapy	**Haemophilia A**	TAK-754 (formerly BAX 888/SHP654)	AAV8-based gene therapy using B-domain deleted (BDD)-FVIII-X5 variant	Takeda	**Clinical trial suspended**
Gene Therapy	**Haemophilia A**	AAV2/8-HLP-FVIII-V3	AAV2/8-based gene therapy encoding FVIII-V3 variant	UCL/St. Jude	**Phase 1**
Gene Therapy	**Haemophilia A**	ET3	Gene therapy using a combination of haematopoietic stem cells and lentiviral vectors	Expression Therapeutics	**Phase 1**
Gene Therapy	**Haemophilia A**	Spark-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	**Clinical programme deprioritised**
Gene Therapy	**Haemophilia B**	PF-06838435 fidanacogene elaparvovec	Padua variant (AAV-Spark100) (fidanacogene elaparvovec)	Pfizer (Originally developed by Spark Therapeutics)	**Phase 3**

		(formerly SPK-9001)			
Gene Therapy	**Haemophilia B**	AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	uniQure	**Phase 3**
Gene Therapy	**Haemophilia B**	AMT-060	Gene therapy using AAV5 vector encoding FIX	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	AAV 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/ AskBio009/BAX 335)	AAV8-based gene therapy using FIX Padua variant	Takeda	**Clinical trial suspended**

CELL-BASED THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Developer / manufacturer**	**Development stage**
Cell-based therapy	**Haemophilia A**	SIG-001	Two-compartment spheres encapsulating human FVIII-expressing human cells	Sigilon Therapeutics	**Phase 1/2**