

Novel Treatments in Haemophilia & Other Bleeding Disorders: A Periodic Review

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Disclaimer:

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



Foreword

Welcome to the third edition of the European Haemophilia Consortium's (EHC) periodic review of novel treatments in haemophilia and other bleeding disorders. We are very grateful to the European Haemophilia Consortium who produce this publication as a valuable information tool for their National Member Organisations. We are reprinting this for our Irish readers.

This review is meant to provide an overview in the haemophilia therapeutic landscape from January to September 2019. Therefore this issue will solely offer quick snapshots of notable advances in existing clinical trials, initiation of new clinical trials and development of novel molecules/treatments in the area of rare bleeding disorders. An additional addendum will follow, in which these advances will be presented specifically from a Quality of Life perspective.

The purpose of this newsletter is to provide up-to-date information to EHC National Member Organisations (NMOs) and to provide their members with a general overview and understanding of a rapidly-evolving landscape of medicinal product developments in rare bleeding disorders. The EHC encourages its NMOs to use and 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, and other rare bleeding disorders. The next newsletter will be issued in early 2020. This edition heavily draws from the information presented at the last Congress of the International Society of Thrombosis and Haemostasis (ISTH).

The EHC wishes to thank its New Products Working Group, which has overseen the content and production of this newsletter. Its members include:

- Dr. Mariëtte Driessens, EHC volunteer,
- Dr. Radoslaw Kaczmarek, EHC Steering Committee member,
- Dr. Dan Hart, EHC Medical and Scientific Advisory Group (MASAG) member,
- Prof. Mike Makris, EHC Medical Advisory Group (MAG) member,
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- Dr. Geneviève Piétu, EHC volunteer,
- Ms. Laura Savini, EHC Public Policy Officer,
- Dr. Uwe Schlenkrich, EHC volunteer, and
- Ilmar Kruis, EHC volunteer.

The EHC also wishes to thank Dr Yvonne Brennan, University of Sydney, for her contribution towards this issue.

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

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

Sincere regards,

Brian O'Mahony,

Chief Executive of Irish Haemophilia Society

Amanda Bok,

EHC CEO

Abbreviations

ABR:	Annualised bleeding rate
ADA:	Anti-drug antibodies
AE:	Adverse events
ALT:	Alanine aminotransferase
BPA:	Bypassing agents
CT:	Clinical trial
ED:	Exposure days
EHL:	Extended half-life
F:	Factor
FDA:	Food and Drug Administration
FIX:	Factor IX
FVIII:	Factor VIII
gc:	genome copies
GT:	Gene therapy
h:	Human
HA:	Haemophilia A
HB:	Haemophilia B
hrs	Hours
ISTH:	International Society of Thrombosis and Haemostasis
ITI:	Immune tolerance induction
IU:	International units
IV:	Intravenous
kDA:	Kilodalton
LFT:	Liver function test
NHF:	National Hemophilia Foundation
PEG:	Polyethylene glycol
PWH:	People with haemophilia
r:	recombinant
SAE:	Serious adverse events
SHL:	Standard half-life
SQ:	Subcutaneous
TGA:	Therapeutic Goods Administration
UK:	United Kingdom
US:	United States
vg/kg:	vector genomes per kilogram
VWD:	von Willebrand disease
VWF:	von Willebrand factor
wk:	week
vs:	versus

An Update on Novel Treatments in Haemophilia A

Replacement Therapies

During the Congress of the International Society of Thrombosis and Haemostasis (ISTH), several abstracts were presented on updates on extended half-life (EHL) factor VIII products.

A survey of physicians' treatment switching practice in five European countries

In a poster (PB0692) from *Sanofi/Sobi*, authors described an on-line questionnaire completed by physicians ($n = 37$) in Germany, France, UK, Italy and Spain in which they report experience of switching patients to **Elocta®**. Physicians provided information on 113 patients, in total. They reported a mean weekly dose reduced from 103.3 international units (IU)/kg to 86.0 IU/kg after the switch, while median injection frequency decreased from three times to twice per week.

Real-life experience of switching to Elocta®

In a poster (PB0722), a Portuguese study from the Centro Hospitalar Lisboa Norte – Hospital de Santa Maria described nine patients switching to **Elocta®**. This switch resulted in a 23% reduction of the IU consumed and a decrease of 22% in infusions annually. Similarly, in an abstract (PB0740) from a *Spanish study from the University Hospital Val d'Hebron*. Twenty-two patients (61%) were on prophylactic treatment before the switch to **Elocta®**. Seventy-three per cent of these had a decrease in monthly infusions and a 51% reduction in bleeding episodes. Two patients (5.5%) were children and the remainder adults

Update on A-LONG and ASPIRE clinical trials

In an update (PB1410) on phase III *A-LONG study* (NCT01181128) and *ASPIRE extension study* (NCT01454739), long-term outcomes for patients that switched from on-demand to prophylaxis with **Elocta®** were analysed. The median overall annualised bleeding rate (ABR) for on-demand was 30.0 (18.0-42.0) versus 1.5 (0.4-3.5) for prophylaxis, and 29% of patients had a reduction in reported joints with pain. Three of the co-authors of the poster are representatives from *Sanofi* and *Sobi*.

A retrospective observational study on the use of Adynovate® in the United States

In another poster (PB0702) from *Takeda*, data were presented from 82 patients using **Adynovate®** from Takeda. Eighty-three per cent of the patients had severe haemophilia. After the switch to **Adynovate®**, the number of weekly administrations decreased by 25.5% (2.8 vs 2.1), and the weekly factor consumption decreased by 4.1% (98.0 vs 94.0 IU/Kg/week). ABR data were available from 47 patients and showed a decrease of 47.2% (3.3 vs 1.7; $n=40$) in patients who had switched from a standard half-life (SHL) factor concentrate and 19.4% (1.8 vs 1.4, $n=7$) in patients who switched from another EHL factor concentrate.

Use of lower dose EHL for prophylaxis

Another poster (PB0688) showed a study from the *Ajou University Medical Centre* in which 12 patients switched to **Adynovate®** from SHL. Although the mean dose remained the same per infusion (29.7 ± 6.8 vs 29.0 ± 1.0 IU/kg/infusion), the frequency reduced (3.0 ± 1.0 vs 1.8 ± 0.2 /week (wk)) and the monthly factor usage decreased by 27%. Bleeding during the first three months was none. The satisfaction score improved due to the decreased infusion frequency.

Prophylactic use and clinical outcomes with Afstyla®

In one *study in Germany (PB0733)*, 40 patients switched from SHL FVIII to **Afstyla®**. In 21 patients, mean prophylactic factor consumption was reduced by 32% while mean bleeding rate was decreased from 0.7 ± 1.0 from SHL to 0.2 ± 0.5 with Afstyla®. One of the co-authors of the abstract is a representative from *CSL Behring*.

Target joint resolution in patients with haemophilia A

In an overview of phase III *PROTECT VIII* clinical trial (CT) data for **Jivi®** (PB1450), data were presented on 82 patients who were on pre-study prophylaxis and continued to receive prophylaxis throughout the trial. These patients were analysed concerning target joints. The study showed that target joints (historic or new) resolved in 90% (56/62) of patients. New target joints developed in 11% (9/82) within the median time range of 1402 days of the study. Authors of this poster include a representative from *Bayer*.

Jivi five year PROTECT VIII Extension Study

In an update on the PROTECT VIII extension study (OC 70.2), data were presented on 36 patients who had completed ≥ 5 years of prophylaxis as of 31 August 2018. In the study, patients received 25 IU/kg twice weekly for a 10-week run-in period. Patients with more than one breakthrough bleed during this period were randomized to 45-60 IU/kg every five days or 60 IU/kg every seven days, or assigned to 30-40 IU/kg twice per week for the 26-week study period. The median ABR was 1.2 and joint ABR was 0.8. The median dose and infusion rate per year was 3,343 IU/kg/year and 70.7, respectively. Co-authors of the abstract are representatives from *Bayer*.

Pharmacokinetics crossover study of EHL

In a crossover study comparing the pharmacokinetics (PK) of **Jivi®** and **Elocta®/Eloctate®**, patients with severe haemophilia A were randomized to receive an intravenous single-dose 60 IU/kg of Jivi® and Elocta®/Eloctate®. After a ≥ 7 -day wash-out period between doses, patients were crossed over to the alternate product using the same dose. Data in this study indicated that Jivi® had a half-life of 16.3 (34.1) hrs compared to 15.2 (33.1) hrs for Eloctate®/Elocta® ($p < 0.05$). However, FVIII activity of both products was measured by one-stage assay and measurement data using chromogenic assay were not reported in full. Co-authors of the paper are representatives from *Bayer*.

Update on investigational FVIII therapy to break through the VWF ceiling

During ISTH, *Sanofi/Sobi* presented an update (OC11.1) on **BIVV001**. This treatment uses the Fc technology of rFVIII-Fc plus the addition of XTEN polypeptides and a linkage to the D'D3 domain of von Willebrand factor (VWF) to extend the half-life of FVIII above the VWF half-life ceiling. Treatment with BIVV001 resulted in a half-life of three- to four-fold higher than SHL. Sixteen patients were treated in two dose groups (25 IU/kg & 65 IU/kg); both groups sustained higher levels of rFVIII. FVIII activity at post-treatment days five and seven in the 65 IU/kg dosing group was 38% and 17%, respectively.

During the National Hemophilia Foundation (NHF) Workshop on Novel and Gene Therapies held in Washington DC in September, additional data were presented on a repeat dose study of ten patients from the original 16 at 50 IU/kg. Factor levels at the end of seven days were 10% (range 5-16%) with factor levels in the normal range for the first three days post-infusion and troughs maintained above 10% at seven days. The trial will be commencing with once-weekly dosing.

Comparison of pharmacokinetic parameters of two EHL FVIII in haemophilia A patients

A Canadian study (PB0237) examined patients ($n=21$) who switched from **Eloctate®/Elocta®** to **Adynovate®/Adynovi®**. The mean and median half-lives were 16.3 and 16 hrs for Elocta®, and 15.6 and 16 hrs for Adynovate®. The half-life was longer for Eloctate® in eleven patients and Adynovate® in ten. Mean and median intra-individual differences were 2.8 hrs and 2.5 hrs. The difference exceeded three hrs in seven patients, and five hrs in two - with substantial inter-individual differences (6-24.5 hrs for Eloctate® and 10.5-21.5 hr for Adynovate®).

Comparison of FVIII prophylaxis treatment regimen and associated clinical outcomes

At ISTH, a survey (PB0282) was presented of patient-collected data from 225 German patients who had switched from SHL to EHL products, for at least eight weeks. Data showed that infusion rates ranged from two or less doses per week for **Afstyla®** and **Elocta®** and three or more doses per week for SHL products. The median bleeding rates for both SHL and EHL products was 0. The mean bleeding rate ranged from 0.4-0.5 on EHL and 0.6-1.2 on SHL. One of the co-authors of the poster is a representative from *CSL Behring*.

Switching from SHL to EHL in patients with haemophilia A

In a study (PB1442) from the Netherlands, 28 patients switched from SHL to EHL. There was a reduction in the ABR from 1.0 to 0.96, with a corresponding clotting factor consumption decrease from 68.6 to 61.4 IU/kg/week. The mean half-life of FVIII rose from 10.6 to 15.4 hours.

Comparison of patients using EHL in the US

In a US study (PB1456), 120 patients switched to EHL and were treated with either **Afstyla®** (n=40), **Elocta®** or **Adynovate®** for more than eight weeks. Sixty-five per cent in **Afstyla®**, 70% in **Elocta®**, and 72.5% in **Adynovate®** were dosed ≤ 2 /per week (pw), while most patients treated with SHL rFVIII infused at least three times/pw. Mean ABR ranged from 2.6 - 3.9 compared to 2.8-4.4 in standard rFVIII. Mean FVIII consumption ranged from 91.1-111.0 IU/kg/week for EHL products compared to 103.6-100.8 IU/kg/week for the SHL products.

Physical activity and treatment adherence: SHL vs EHL therapies

In a poster (PB0210) on the HemACTIVE patient survey, authors examined the impact of EHL vs SHL on physical activity, treatment satisfaction and adherence. The study demonstrated an increase in the quantity and type of physical activity. People with haemophilia (PWH) were also more likely to infuse as directed using EHL products than SHL products (55% vs 34%). Adherence was higher in patients using EHL compared to SHL, with 2% of EHL users missing/changing infusion schedules compared with 16% of SHL users.

Update on Esperoct® and EMA license

Esperoct® is the brand name for **turoctocog alfa pegol, N8-GP**. The European Medicines Agency (EMA) licensed **Esperoct®** in June 2019 with an indication for prophylaxis and on-demand treatment of bleeding as well as for surgical procedures in adolescents (>12years) and adults with haemophilia A. At ISTH, data (poster PB0239) were reported on the 254 patients included in the *Pathfinder* clinical trials. In the initial *Pathfinder 2* study, adolescents/adults who were previously treated with prophylaxis and on-demand had a median ABR of 1.18 and 30.87, respectively. In the main phase, before patients were randomised to the extension phase, median ABR was 0.98 and 0.00 for patients randomised to receive 50 IU/kg every four days and 75 IU/kg every seven days, respectively. At the end of the extension phase, median ABR was 0.00 for both cohorts. A total of 65 children who received prophylaxis prior to N8-GP treatment experienced a median reduction in ABR of 2.01.

Other developments in replacement therapies

Update on NuPreviq and NuProtect studies

Robert Klamroth presented data from the NuPreviq study (OC 42.1) at ISTH on the use of pharmacokinetic (PK) information to personalise prophylaxis with **Nuwiq®** (simoctocog alfa). An individualised dosing approach enabled over half (57%) of patients to reduce dosing with Nuwiq® to twice weekly or less, whilst providing effective bleed protection. Eighty-three per cent of patients did not report spontaneous bleeds during the six months of personalised prophylaxis.

Ri Liesner also presented for the first time the final data from the *NuProtect study* (PB1448), which investigated the development of inhibitors in 108 previously untreated patients (PUPs) treated with Nuwiq®. The cumulative

incidence of high-titre inhibitors was 17.6%.

Subcutaneous injections of FVIII

Data was presented (OC 11.5) on the *Alleviate 1 trial* by Novo Nordisk on subcutaneously injected **N8-GP** for prophylactic use. The study (NCT02994407) comprised two parts. In part A, 24 patients received a single subcutaneous dose of SQ N8-GP 12.5-100 IU/kg, and no FVIII inhibitors were detected. In part B, 26 patients received a fixed daily dose of 2000 or 4000 IU for three months and five patients, including a patient with detectable inhibitors, developed anti-drug-binding antibodies (42-91 exposure days (EDs)). Although SQ N8-GP demonstrated clinically relevant FVIII levels, the immunogenicity findings in part B, which may relate to the subcutaneous route of administration, made Novo Nordisk decide not to continue the development of SQ N8-GP.

SubQ-8 is a recombinant factor VIII (rFVIII) under development by Octapharma for subcutaneous treatment. It is comprised of simoctocog alfa and a recombinant VWF fragment dimer.

The safety and PK of SubQ-8 at different doses is being investigated in a phase I/II study (SubQ-8-01 study) in five cohorts. Sixteen patients (4, 4 and 8) in total will be involved in cohorts one to three, where they will be receiving daily **SubQ-8** prophylactic dosing of 40-60IU/kg for three months after a single injection of 50, 100 and 200IU/kg (the latter one as cross-over after 50 IU/kg iv Nuwiq to evaluate bioavailability). Cohort four will examine PK with subcutaneous dosing of 400IU/kg. The final cohort is a single dosing cross-over regimen that will examine dose-linearity of 50IU/Kg SubQ-8 vs 100IU/kg and 200 IU/kg in 8 individuals.

Non-replacement therapies

There were several updates on the use of **Hemlibra®** presented at the 2019 Congress of the International Society of Thrombosis and Haemostasis (ISTH).

Data pooled from HAVEN 1-4 clinical trials

In one update given during the ISTH Congress, authors pooled data from all clinical trials (CT) for emicizumab in patients with and without inhibitors (OC60.2). This efficacy analysis included data from 400 participants from CTs *HAVEN 1, 2, 3, and 4*. The median usage was 82.4 weeks. Seventy-seven per cent of participants were treated for ≥ 74 weeks. Authors used a methodology that created a model to estimate the annualised treated bleed rate. The annualised treated bleeding rate (AtBR) rate was calculated to be 1.5 (95% C.I 1.20-1.84). More important, however, is the increasing use of these types of models to look at ABR. This approach is being used as the mean bleeding rate over each subsequent 24-week period decreased. Using this approach will indicate the added benefits of avoiding even one or two bleeding episodes within three months and the potential downstream effects for further bleeding and potentially some sub-clinical bleeds damaging the joint. Across the studies, those with no treated joint bleeds were over 87% after 25 weeks. Over 92% did not report a spontaneous bleeds after 25 weeks. Authors of this poster include representatives from the pharmaceutical industry.

Data on surgical procedures

During the ISTH Congress, there was a report on surgical procedures (214 minor and 19 major surgeries, performed in 113 and 19 patients respectively) from the clinical trials Haven 1-4 with patients with or without inhibitors using **Hemlibra®**. The majority of minor surgeries (n=141; 65.9%) such as dental and central venous access device (CVAD) procedures were managed without the use of prophylactic factor concentrate. There was no reported information on the use of tranexamic acid and it is unclear if this was used, in particular, for dental procedures. Of these, 128 (90.8%) did not result in treated postoperative bleeds. Of the 19 major surgeries, 16 (84.2%) were managed with prophylactic coagulation factor. Only one of these resulted in a treated postoperative bleed.

Emicizumab monitoring and ADA issue

The increase in the use of **emicizumab** means that clinicians, patients and regulators need to be increasingly cautious about monitoring coagulation factor levels in preparation of surgery and in case of trauma. This information will also be needed in case of using additional treatment products as well as monitoring for adherence issues. Another issue that will need to be tackled is the monitoring of anti-drug antibodies (ADA), which are currently reported as low (5% incidence rate). Clinicians and regulators will need to work towards getting a better understanding of ADA prevalence and their potential impact on efficacy. Finally, a company-independent assay must be developed.

To this end, there is reporting of several laboratories in France (PB0323) developing methods to characterize the performance of, and study the correlation with, FVIII chromogenic assays to assess emicizumab activity. So far, the performance of the FVIII chromogenic assay is showing good precision and reproducibility, and this will be useful in case of clinical suspicion of ADA or poor compliance. Similar approaches for the detection of ADA are also being examined in several other European centres.

An update on fitusiran

Prof. John Pasi presented an update at the ISTH Congress on *Sanofi's* **fitusiran** phase II study for patients with haemophilia A or B with or without inhibitors from the most recent data cut in May 2019. This study administers fitusiran once-monthly, subcutaneously (SQ) and aims to improve thrombin generation (TG) by rebalancing haemostasis. The dataset evaluated 34 enrolled patients (haemophilia A (HA) n=27; haemophilia B (HB) n=7; inhibitors, n=14), followed for up to three years, with a median exposure of approximately 23 months. Of the 33 patients examined, the overall median ABR was of 1.08, without the development of antibodies to fitusiran.

To compare pre-study ABR, authors examined 19 patients without inhibitors. Those patients who were previously on either on-demand or prophylaxis reported an ABR of 12 or 2 respectively; reduced to a mean ABR of 1.08. In the inhibitor cohort (n=14), the pre-study ABR was 42 reducing to a median ABR of 1.04. Fourteen patients (all anti-HCV antibody positive) reported increases in alanine aminotransferase (ALT) tests >3 times the upper limit of normal. All were asymptomatic and resolving, with no elevations of bilirubin twice the upper limit of normal.

In a poster presented during the ISTH Congress, authors presented data (PB0324) on the **bleed management guidelines** developed to mitigate the risk of thrombosis during breakthrough bleeds treated with either replacement factors or bypassing agents (BPA). The guidelines provide information on maximum dosing and frequency of repeated dosing. At the time of ISTH with these revised treatment guidelines, there had been no related thrombotic events as of the data cutoff. The treatment guideline recommends avoiding antifibrinolytics in conjunction with either factor replacement or BPA.

Subsequently there was a report of a thrombotic event in phase II open-label extension trial in a patient with inhibitors. The event has been reported to regulators.

Update on Pfizer's anti-TFPI (marstacimab)

During the ISTH Congress, there was an update (OC 11.2) on the data from *Pfizer's* phase I/II clinical trial using a subcutaneous (SQ) anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody **marstacimab** (PF-06741086). The trial enrolled 26 patients with severe (FVIII or FIX $\leq 1\%$) HA or haemophilia B (HB) with or without inhibitors. All received on-demand treatment and had ≥ 6 bleeding episodes in the six months before starting the trial.

Patients were assigned to one of four cohorts:

- Cohort 1 received 300mg SQ once weekly;
- Cohort 2 received a 300mg SQ loading dose and then 150 mg SQ weekly;
- Cohort 3 received 450mg SQ weekly; and
- Cohort 4 of inhibitor patients received 300mg SQ weekly.

A model-based ABR was used to compare to historic controls. The mean ABR was 27.6 for all patients pre-treatment. Authors reported a decrease across all patient groups after treatment. In the non-inhibitor cohort, mean

ABR decreased to between 1.5-4.2. In the inhibitor cohort, the mean ABR decreased to 0.7. This reduction equals a decrease of mean ABR of 85-95% in the non-inhibitor group and 98% in the inhibitor group.

No thrombotic events occurred. Three patients discontinued the trial because of adverse events (AEs). The most common treatment-related AEs were reactions at the injection site. Three patients had anti-drug antibodies (ADA), with no impact on either safety or efficacy.

Update on concizumab from Novo Nordisk

In a late-breaking session at the ISTH Congress, authors presented information on phase II clinical trial data for the use of **concizumab** from *Novo Nordisk* in haemophilia A patients (explorer 5). The trial examines a once-daily SQ treatment that inhibits TFPI. The explorer 5 trial involved 36 adults with severe haemophilia A without inhibitors who were started on concizumab. If they experienced three or more spontaneous bleeds during that time, they were escalated through two more dose regimens.

So far there were a total of 70 treated bleeding episodes in 23 patients (63.9%), with an estimated ABR of 7.0 and a median ABR of 4.5. There was a lower proportion of spontaneous vs traumatic bleeds (37% vs 61%). Most bleeds (63%) occurred in joints, and the estimated joint ABR was 4.9. A total of three bleeding episodes were assessed as severe. All patients chose to continue in the extension phase and no adverse events led to withdrawal.

Update on SerpinPC from Apcintex

SerpinPC by *Apcintex* targets the anticoagulant enzyme of activated Protein C (aPC), in its approach to rebalancing the coagulation system. The company is due to start phase I/II trials (NCT04073498) at the end of October 2019 for healthy volunteers and March 2020 for patients with haemophilia. The study will be split into three parts: Part 1a will be conducted in healthy male volunteers in the UK (up to 15) and Parts 1b and 2 will be conducted in haemophilia A & B patients in Moldova and Georgia. Part 1a will look at safety and pharmacokinetics is when given as a single dose to healthy volunteers at different strengths and via two different routes of administration (via IV and SQ), with a reduction in ABR being an exploratory endpoint. Part 2 will be a once monthly SQ treatment for 6 months in 20-25 patients.

Other developments in non-replacement therapies

Korea GreenCross has administered the first dose of **MG1113**, an anti-TFPI, to a patient participating in a phase I clinical trial for the drug. The company plans to evaluate the safety of MG1113 in 49 healthy adult and haemophilia patients.

Bayer's escalating dose study of **BAY1093884**, another anti-TFPI, has currently stopped recruiting for its clinical trial (NCT03597022).

Sigilon presented preclinical data demonstrating the feasibility of cellular therapies for bleeding disorders developed with the company's *Shielded Living Therapeutics™* platform. The **SIG-001** implants - small spheres containing engineered human cells optimized for human (h)FVIII, hFIX and hFVII proteins - were placed into the abdomens of wild-type mice. This implant resulted in therapeutic levels of blood clotting factors to treat haemophilia A. The first clinical studies of Sigilon's SIG-001 are expected to begin in the first half of 2020.

Takeda conducted some pre-clinical studies to identify **bispecific antibody (bsAbs)** targeting FIXa and FX to increase thrombin generation in the plasma of HA patients. This treatment could potentially provide in the future a differentiated antibody-based therapy for HA with and without inhibitors.

During the ISTH Congress, an abstract (OC 60.5) reported the development of **oral delivery of FVIII via a robotic pill**. The key injectable element of the robotic pill is its drug payload (FVIII). A solid micro tablet containing FVIII is sealed inside a hollow, dissolvable microneedle. In multiple, consecutive batches of micro tablets and microneedles, FVIII activity was consistently retained (>90%) with little or minimal loss. Results showed that FVIII could be successfully formulated with no impact on activity. In-life proof-of-concept studies in appropriate animal models are in progress.

Gene therapy

Since the last issue of this newsletter, there have been several reports on the development of FVIII gene therapy. There is still limited but increasing information on the expectations from these treatments in terms of factor levels and bleeding rates. Furthermore, we are now starting to see indications on duration of expression.

An update on Biomarin's FVIII gene therapy clinical trials

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) granted *BioMarin's* **valoctocogene roxaparvovec** their PRiority MEdicine (PRIME) scheme and Breakthrough Therapy designation, respectively. These programs are generally for therapies that show, based on early clinical data, their potential to benefit patients with unmet medical needs. Regulators made these decisions based on three-year data from the phase I/II clinical trial, and an interim analysis of the initial patient cohort enrolled in the phase III trial (GENEr8-1).

BioMarin will be submitting an application for marketing authorisation both in the US and the EU in Q4/2019. This could mean that HA gene therapy (GT) could be commercially available for the first time in 2020/2021.

Currently, BioMarin has three clinical studies in HA GT:

- There were previously two phase III clinical trials (GENEr8-1[301] and GENEr8-2[302]) evaluating two dose levels. These doses showed positive results in Study 201 initiated in Q4 2017 (see below). Biomarin have since announced they are restricting the phase III trial to GENEr8-1[301], which is the the highest dose trial and have discontinued the lower dose GENEr8-2[302].
- One phase I/II clinical trial assessing **valoctocogene roxaparvovec's** safety in patients with pre-existing antibodies to AAV5;
- The original phase I/II clinical trial (BMN 270-201), which is now fully enrolled. This study evaluates the safety and efficacy of gene therapy and is monitoring all 15 patients for safety and durability of effect for five years.

Review of BMN 270-201 data

During the ISTH Congress, *BioMarin* reported an update on their phase I/II data (LB01.2) on two different cohorts:

- an interim analysis of 104-week data of 6 x 10¹³ vector (vg)/kg, and
- the 52-week data of 4 x 10¹³ vg/kg

This data indicated a reduction both in factor levels and efficacy three years post-treatment (see Table 1). Although the decrease has been consistent over time for the group as a whole, it should also be noted that there is a widening gap between the mean and median values over time which comes from a greater range of factor level measurements at each time point. This indicates there is a difference in drop-off rates between individuals, suggesting some people respond better than others in terms of factor expression activity and/or duration of the response which raises questions about the general unknowns in gene therapy. Data on the impact on quality of life was also reported demonstrating a clinically relevant increase in quality of life.

In relation to the high-dose cohort in the Phase I/II study, the ABR decrease seen from pre-infusion to end of year one from a mean [standard deviation] of 16.3 [15.7] to 0.9 [2.2], and those with zero bleeds, increased from 14% to 71% with a reduction in total factor usage of 98%. By year three, the mean ABR was 0.7 [1.6] with 86% of patients having zero bleeds and a 96% reduction in factor use compared to pre-infusion.

For the lower-dose cohort, these patients started with a smaller increase in initial factor levels and experienced a similar drop-off in factor level and efficacy. The results of this low-dose cohort are comparable to their high-dose counterpart with the critical difference of fewer patients experiencing a zero-bleed rate. However, despite these results, GT effects are well established, and despite a decrease in factor levels, the cohort reports almost no bleeds.

It is essential to put these data in context. These results affect only a small patient cohort (n=7 in the high-dose, and n=6 in the low-dose cohort). In such small numbers, a single bleed has the potential to alter results considerably. We should note that bleeds are dependent on their location, disease type and severity as well the weight of the patient. It is critical going forward to better understand what is happening to these patients.

During the ISTH presentation, authors also updated delegates on other relevant information such as raised ALT levels, the need for corticosteroids treatment and vector shedding.

Liver function tests were monitored to ensure safety and to protect against loss of FVIII activity expression. Eleven out of the 15 participants reported ALT elevations. Patients were treated with prophylactic corticosteroids after ALT elevation reached 1.5 fold above their own baseline (not upper limit of normal range). The median time at the start of the ALT elevation occurred at 7.6 weeks with a duration <25.3 weeks. All instances resolved, and the requirement for prophylactic corticosteroids has since been removed for all newly enrolled patients. However, steroids are still used in patients experiencing an ALT elevation of 1.5 times above baseline.

The vector DNA was detected in blood, semen, saliva, urine and faeces within 72 hours after infusion with levels peaking in weeks 1 through 4 and decreasing over time. The highest clearance of vector DNA from biologic fluids was from urine, which occurred by week 28, and from semen, which occurred by week 36. Vector DNA remained persistent in seminal fluid but not in sperm in a few patients. This result suggests that the risk of inadvertent germline modification (i.e. the potential to pass the gene mutation to progeny) is minimal, and the risk of horizontal and vertical transmission is negligible.

Table 1: BMN 270-201 Factor level after three years

		Year 1	Year 2	Year 3
High-Dose 6 x 10 ¹³ vg/kg Cohort, N=7	Median (mean) FVIII activity levels with chromogenic assay	60.3 (64.3)	26.2 (36.4)	19.9 (32.7)
	Median (mean) FVIII activity levels with one stage assay	88.6 (103.8)	45.7 (59.0)	29.8 (52.3)
Low-Dose 4x 10 ¹³ vg/kg Cohort, N=6	Median (mean) FVIII activity levels with chromogenic assay	22.9 (21.0)	13.1 (14.7)	
	Median (mean) FVIII activity levels with one stage assay	31.7 (31.4)	23.5 (23.2)	

An update on phase III (GENEr8) study

As mentioned above BioMarin had two phase III clinical trials (GENEr8-1[301] and GENEr8-2[302]) evaluating two-dose levels. GENEr8-2[302] which was looking at the lower dose cohort has been discontinued and the data below is only in relation to the GENEr8-1[301], the high-dose cohort.

In the GENEr8-1, inclusion and exclusion criteria are similar to the phase I/II BMN 270-201 study. However, for phase III clinical trials, the inclusion criteria were restricted to exclude both HIV-positive patients and patients with mild liver disease. This change was the result of two patients whose liver function test (LFT) elevations were higher than in the phase I/II study. Both patients’ laboratory values recovered without sequelae, and both patients have been asymptomatic of liver damage.

Sixteen patients reached 26 weeks post-treatment in data cut-off in April 2019. Of those 16 patients:

- Seven achieved >40 International Units (IU) FVIII/dL;
- One patient has since reached the same levels; and
- Another three patients still need to be evaluated.

In weeks 23 to 26, the mean FVIII level using chromogenic substrate assays (CSA) was 36 (SD=28) IU/dL, and

the median was 33 IU/dL. The mean ABR decreased from 0.92 (9.88) at baseline to 0 (1.48), representing a mean reduction of 85% from baseline, where all patients were on prophylaxis. Seventeen patients had an ALT elevation.

Initial results of Sangamo / Pfizer SB-525

During the ISTH Congress, *Sangamo* and *Pfizer* presented (OC 01.2) updated phase I/II-ALTA study results for **SB-525** in haemophilia A using an AAV6 vector. The study has so far included ten patients who were treated in sets of two patients each at different dose-escalation studies to determine the most effective dose moving forward. The study data examined four ascending dose cohorts:

- 9e11 vg/kg (two patients);
- 2e12 vg/kg (two patients);
- 1e13 vg/kg (two patients); and
- 3e13 vg/kg (four patients).

The first two patients treated at the 3e13 vg/kg dose level achieved normal (mean 79%), sustained factor VIII levels with no reported bleeding events and no factor usage. However, these data are very preliminary at 24 weeks of follow-up. The second two patients are reported as following a similar profile; however, no data is currently available. In patients who had reached three weeks post gene therapy, there were no bleeding events and there was only one infusion of FVIII in a patient who received his prescribed prophylactic dose the day after receiving gene therapy.

The two patients more recently treated at the 3e13 vg/kg dose level demonstrated FVIII activity seemingly consistent with the first two patients in this dose cohort at similar early time points. The study did not use prophylactic steroids; however, in the 3e13 vg/kg cohort, two patients experienced a 1.5 times increase in ALT compared to their normal baseline. A tapering course of oral steroids was used to manage this ALT elevation, and it appears that this elevation did not cause loss of FVIII expression.

There were also two reported treatment-related serious adverse events (SAE), hypotension and fever. These events occurred six hours after completion of the infusion, but they both fully resolved with treatment. The patient was discharged as planned within 24 hours. No similar events were observed in other patients. The poster's authors include representatives from the pharmaceutical industry.

Initial results of UCL/St. Jude AAV8 FVIII V3

UCL/St. Jude are conducting clinical trials in an **AAV8 Codon optimised human FVIII (FVIII-V3)**. This vector is optimised to meet the size constraints of the AAV vector, and significantly improves the efficiency of FVIII expression and secretion. This is a phase I/II dose escalation trial. In data presented at the NHF Workshop on Novel and Gene Therapies held in Washington DC in September, seven patients received treatment. The first patient received a dose of 6x10¹¹vg/kg and after two years has maintained an expression of 11%. Patients two to four received a dose of 2x10¹²vg/kg, and with between one and one-and-one-half years of follow-up have expression levels of 8-29%. The last three patients received a dose of 4x10¹²vg/kg in the last two to five months, and FVIII activity levels are 45-74%. Two more dose-escalation cohorts are planned within the current phase I/II trial.

Other gene therapy updates

UniQure's **AMT-180** (OC 22.3) concept is of an optimised FIX, delivered via AAV-based gene therapy, that does not require the presence of FVIII to activate FX. This has the benefit of "by-passing" FVIII in the clotting cascade and as a result is not impacted by FVIII inhibitors. Normally, when bleeding occurs, FIX activates factor X, and FVIII helps in two ways: by changing the shape of FIX, making it far more active, and linking it to FX. AMT-180 uses a modified FIX, that, when activated as a regular FIX would be, is able to activate FX in the absence of FVIII because it already has the shape change. Preclinical studies with FVIII-depleted human plasma with and without inhibitors as well as studies in haemophilia A mice have demonstrated up to 29% of Factor VIII-independent mimetic activity.

Takeda reported re-introducing gene therapy in their haemophilia A pipeline with **TAK-754**. This product is

an AAV8 FVIII gene therapy vector currently under investigation in a phase I/II trial. **TAK-754/SHP654/BAX 888** uses an AAV8 vector to drive expression of codon-optimized human B-domain-deleted-FVIII (AAV8. BDD-FVIIIopt). Takeda's phase I/II CT is recruiting patients, with four patients currently dosed in two dose cohorts.

There were no additional updates on gene therapy trials from *Spark* **SPK-8001** or *Bayer* **DTX201** on their respective clinical trials.

At the NHF Workshop on Novel and Gene Therapies, Sanofi presented on the use of lentiviral vectors as an alternative to AAV vectors. These have the potential benefit of delivering a life-long expression of the FVIII proteins; however, the way in which this is achieved is using the properties of the lentivirus, which integrates itself into the cell. So far the lack of integration has been the preferred approach by companies developing gene therapy, and this is partly why AAV vectors have been prominent so far. These lentiviral vectors may be an option for the future. Sanofi also presented the concept of using their **EHL FVIIIXTEN** in the lentiviral vector, with the concept that, if the FVIII that is produced is long-acting, high levels may not be required and this would potentially reduce the requirement to increase the amount of the actual vector.

So far, gene therapy has been focused on gene replacement, which causes cells to produce rFVIII. On the horizon is gene editing with **CRISPR/Cas9** technology, which fixes the defective gene and the body produces its own protein. The first abstract (OC 40.2) in haemophilia on the use of this technology in mice was presented at ISTH with the result being low frequency generated therapeutic levels of FVIII in mice. This technology is developed by Casebia Therapeutics in a joint venture with Bayer.

Paul Batty and David Lillicrap presented data at ISTH (OC 22.5) analysing the long term impact of gene therapy in different tissues of the dog colony at Queens University, Kingston, Canada. This presentation suggested that there was persistence of the viral vector in the liver and a low level in the spleen. This evidence is reassuring that there is only gene persistence in the target organ, albeit the explanation for splenic detection is not clear.

Company news

Roche and *Spark* Therapeutics announced entering into a definitive merger agreement so that Roche can fully acquire Spark Therapeutics. The merger, initially due to take place in Q2/2019, has been pushed back to provide the U.S. government additional time to complete its review of the proposed transaction.

A Comment on Gene Therapy

As noted earlier in this section, regulators in Europe and the US have granted gene therapy clinical trials fast track processes to determine safety and efficacy. In light of these developments, we are now seeing patients and clinicians asking questions such as *“What is the duration of this treatment? What is the rate of factor level loss on an annual level? At what factor levels are patients starting to re-bleed or need treatment in the event of a trauma/surgery? At what activity level are bleeds occurring?”*

While one clinical trial in haemophilia A has shown loss of expression over time, this has not been reported in other trials. However, only one trial has the duration data after three years, and there is a much shorter follow-up to date in the others. It is too early to question whether a specific vector is responsible for this decrease of factor level and efficacy. Nevertheless, data available from factor IX (FIX) GT clinical trials, which have been running for longer, do not show a similar reduction in factor level. One hypothesis advanced during the NHF Workshop on Novel and Gene Therapies related to cell-stress in hepatocytes during and after gene therapy. In fact, FIX is naturally produced in hepatocytes, unlike FVIII, which is naturally produced in the endothelial cells. As a result, it was considered during the meeting that the impact of stress on hepatocytes over time could be greater for FVIII gene therapy than FIX and that this could be part of the reason for the reduction in FVIII activity over time.

On the other hand, FIX gene therapy does not show an increase in factor level activity as significant as in FVIII trials. Therefore, this leads us to ask two additional questions. First, once patients reach a certain factor level that is lower than the desired normal range, does factor level plateau? The second question is whether there will be a considerable difference, in terms of peak and durability of factor expression, between GT in FVIII and FIX.

In addition, increasing information is being analysed concerning the causes and timing of ALT increase in the liver after gene therapy. It is hypothesised that ALT may impact factor expression.

An Update on Novel Treatments in Haemophilia B

Replacement Therapies

Treatment patterns and clinical outcomes after switching to Alprolix®

In one study (PB0284) using data from the *UK National Haemophilia Database*, authors analysed treatment patterns and clinical outcomes for patients (n=60) post-switching from rFIX to rFIXFc (**Alprolix®**, Sanofi/Sobi). Within-patient comparison showed that switching to Alprolix® was associated with a significant reduction in factor use (66 vs 45 IU/kg/wk), reduction in infusion frequency (1.83 vs 1.06/wk), reduction in ABR (4.23 vs 2.27) and a reduction in annual joint bleeding rates (1.18 vs 0.73).

Long-term outcomes after switching to Alprolix®

In an update (PB0693) on the phase III B-LONG and B-YOND extension studies, data was evaluated in those who switched to **Alprolix®** prophylaxis from on-demand. Thirty-three patients received weekly prophylaxis with dosing ranging from 20-100 IU/kg and 17 received individualised interval prophylaxis, with dosing of 100 IU/kg on regimens between 8-16 days. The median duration of prophylaxis was 3.6 years. Overall the median ABR in the entire patient cohort was 24.2 (16.0-33.0) on on-demand treatment compared to 2 (0.5-4.3) after the switch to rFIXFc prophylaxis. The ABR remained low between the first 6 months (2.0 [0.0-6.0]) and last 6 months (2.0 [0.0-4.0]) on any rFIXFc prophylaxis.

It should be noted that 70% of the cohort reported target joints prior to the switch and, in the most recent six months prior to data collection cut-off, the annual joint bleeding rate had reduced to a median of 0 (0-2). Authors of the poster include representatives from Sobi and Sanofi.

A physicians' survey on switching patients to Alprolix®

Another abstract (PB0208) reported that a survey of 25 physicians from five western European countries was conducted to explore their experience of switching patients with haemophilia B to **Alprolix®**. Physicians reported perceived reductions in treatment burden (72%), pain (68%), disease burden (68%), improved quality of life (68%) and adherence (68%) in patients following the switch, with the median physician-estimated ABR being three before and one after switch. This poster's authors are representatives from Sobi.

Real-world use of Idelvion® (Europe)

In a poster (PB0691) on patients switching to **Idelvion®** from *CSL Behring*, a study examined dosing frequency and ABR in patients (n=84) from their previous FIX product in three European countries. The duration of treatment on Idelvion® ranged between 29-46 weeks. A reduction in mean ABR of 67.7-94.3% with Idelvion® was reported compared to their prior FIX concentrate. Compared with the previous FIX product, Idelvion® was associated with a reduction in mean weekly FIX consumption of 56-73%. Authors of this poster include representatives from *CSL Behring*.

Idelvion® phase 3b extension study

In an abstract (PB1453) on the use of **Idelvion®** in the US, data were collected on 83 previously treated patients with haemophilia B for 36 months. They were receiving either 7-, 10-, 14- or 21-day regimens. Of the 11 patients that extended their dosing intervals to 21 days, two switched back to a 14-day regimen to reduce bleeding frequen-

cy. Four previously treated paediatric patients who started a dosing interval of 14 days switched back to shorter intervals. Low spontaneous bleeding rates were achieved with all regimens. Mean steady-state trough levels were over 5% across all regimens.

EHL FIX comparison

In a study from four US haemophilia treatment centres (OC 70.4), 71 patients with severe haemophilia B used two different types of EHL FIX. This included 55 who used **Idelvion®** (n= 24) and **Alprolix®** (n=31). Unexpected and poorly controlled bleeding was reported in 13 patients, all using Idelvion® prophylaxis. Five patients switched from Idelvion® to another FIX EHL, one patient switched from Alprolix® to a different EHL and, six patients switched from Idelvion® back to FIX SHL. It remains unclear whether the extravascular distribution and/or collagen binding of FIX is important to long term efficacy. Measurement of intra-vascular FIX levels does not inform treaters about the ability of the FIX to escape the blood vessels to work like native FIX. Different technologies to extend FIX half-life may behave differently in this respect. Greater understanding and work is needed in terms of monitoring when patients are switched to ensure that it is a beneficial improvement for the patients. However no information was presented on bleeding rates or dosing regimens.

An update on Rebinyn®/Refixia® in children

In an update (PB0242) on the **Rebinyn®/Refixia®** extension study, 22 children were enrolled. After five years on study, median ABR measures decreased to 0.66 compared to the first year on treatment of 1.0 ABR. Five patients (20.0%) were bleed-free, and 16 (64.0%) had experienced no spontaneous bleeds. No intracranial haemorrhage occurred, and bleeds were controlled with one to two injections. Authors of this poster included representatives from Novo Nordisk.

Non-replacement therapies

Please refer to the section on the treatment of haemophilia A, non-replacement therapies for an update (page 8).

Please note that **Hemlibra®** from *Roche* is only applicable to those with haemophilia A. Currently **concizumab** from *Novo Nordisk* is being tested in all types of haemophilia (A and B) in patients with and without inhibitors. All other non-replacement therapies are being trialled in haemophilia B without inhibitors.

Gene therapy

An update on AMT-061 (etranacogene dezaparvovec)

UniQure presented data (OC 01.1) on their phase IIb study of **AMT-061 (Padua FIX)** during the ISTH Congress. Three patients were enrolled received a single intravenous infusion of 2x10¹³ vc/kg. Before the administration of AMT-061, all three patients showed low levels of pre-existing neutralizing antibodies to AAV5 used for the delivery of the FIX gene. Interestingly, this trial did not exclude these patients because of their pre-existing antibodies. After 36 weeks, data showed that all three patients had sustained increases in FIX levels with a mean of 45% FIX activity levels. More specifically:

- the first patient achieved FIX activity of 54 IU/dL;
- the second patient achieved FIX activity of 30 IU/dL; and
- the third patient achieved FIX activity of 51 IU/dL.

No patient experienced a material loss of FIX level. Additionally, there were no reports of any bleeding events or need for prophylactic or on-demand FIX replacement therapy. One patient did require hip surgery due to a pre-existing condition and was treated post-surgery for a short duration. Authors of the abstract included representatives from the pharmaceutical industry.

UniQure announced in September that they have now recruited all 56 patients to their phase III CT (HOPE-B).

An update on AMT-060

In an update (abstract 0C01.4) on the initial phase I/II study of **AMT-060** (wild-type FIX) from *UniQure*, after 3.0 years of follow-up, five patients in the second dose cohort of 2×10^{13} genome copies (gc)/kg have not required routine FIX replacement therapy. During the last 12 months of observation, the mean ABR was 0.7 bleeds, representing an 83% reduction to the year before treatment. During this same period, the usage of FIX replacement therapy declined by 96% compared to the year before treatment. The mean yearly FIX activity at three years was 7.9%, as compared to 7.1% in the first year and 8.4% in the second year demonstrating no loss in efficacy over the timeframe.

An update on fidanacogene elaparvovec (SPK-9001)

Spark/Pfizer have not reported additional information on phase I/II or updates on the advancement to phase III trial (NCT03587116) recruiting a total of 110 male patients, ages 18 to 64. The first part of the study, a lead-in phase III trial, will investigate the effectiveness of the current standard of care for factor IX replacement therapy taken by patients in their usual care setting. Data collected will serve as a control for the next part of the study in which **fidanacogene elaparvovec (SPK-9001)** treatment will be administered.

An update on FLT180a

Freeline presented further follow-up data on **FLT180a** at the third International Conference on Inhibitors held in September 2019. Pratima Chowdary presented the latest data from the first cohort of two patients who were treated with the lowest study dose (4.5×10^{11} vg/kg). A single infusion at this low dose was given to two patients (one was previously on on-demand treatment, and the other was previously on prophylaxis). FIX activity remained stable and consistent post steady state at 40 ± 5.5 over 66 weeks and 74 weeks post-administration, respectively, with no evidence of transaminitis. Both patients remained free of spontaneous bleeding episodes and did not require any FIX supplementation. The Freeline FLT180a programme uses the company's AAVS3 capsid and a gain of function variant of human factor IX. The therapy is being evaluated in collaboration with UCL in a phase I/II trial known by Freeline as B-AMAZE, with the goal of normalising FIX activity in patients with moderate and severe haemophilia B.

An update on SB-FIX

Sangamo's **SB-FIX** is now recruiting patients for a clinical trial, which is based on in vivo genome editing, a type of targeted gene therapy. The trial is known as the *FIXtendz* study.

FIX gene editing

So far, gene therapy has been focused on gene replacement, which causes cells to produce a rFIX. On the horizon is gene editing with **CRISPR/Cas9** technology, which fixes the defective gene and the body produces its own protein. A presentation at the NHF Workshop on Novel and Gene Therapies held in September by *Intellia Therapeutics* demonstrated the application in mice and reported a durable effect after 12 months of observation.

Other developments in FIX gene therapies

Low and middle-income countries (LMIC) trial

About 75% of the haemophilia patients in low- and middle-income countries have limited access to factor concentrates due to cost, and therefore face a lack of supply of haemophilia treatment. In this regard, gene therapy has the potential to dramatically impact the life of patients in these countries. A phase II trial, based on the original

work of Nathwani et al. 2011, and the further development of this work using their Padua variant, will be carried out in LMIC countries. The results of this trial will help create pathways for making these new technologies available to underserved patients in the haemophilia community. In the initial stages, a single dose range will be identified, and the vector will be infused at St. Jude. The monitoring will occur in the LMIC countries. In later stages, vector infusion and monitoring will be carried out in the LMIC countries.

Catalyst Biosciences are taking their **CB-2679d (DalcA)** molecule that was previously being assessed for subcutaneous administration into gene therapy and presented at the NHF Workshop on Novel and Gene Therapies. CB-2679d GT has the potential for greater expression than the Padua variant that has been adopted by all current gene therapy approaches.

At the NHF Workshop on Novel and Gene Therapies, *Sanofi* presented on the use of lentiviral vectors as an alternative to AAV vectors. These viruses have the potential benefit of delivering a life-long expression of the FIX proteins; however, the way in which this is achieved is by using the properties of the lentivirus, which integrates itself into the cell. So far, the lack of integration has been the preference. This is partly why AAV vectors have been more prominent, but these lentiviral vectors may be an option for the future. Data from dog models initially peaked at between 15-30% but dropped to 3-5% after 3.5 years.

Comment - PEG: Same Data, Same Discussions, Different Regularity Decisions

Polyethylene glycol (PEG) is a chemically inert polymer of ethylene that comes in various sizes and molecular weights. PEG has been used as an excipient in many pharmaceuticals, cosmetics, and consumer products for decades. PEG was first used as a conjugate in a medicinal product in a drug called Adagen, which received FDA approval in 1990. In medicines, PEG extends the half-life of therapeutic proteins, hence prolonging the medicine's effects.

The first PEGylated product used in haemophilia patients was Peginterferon alfa-2a (Pegasys) for the treatment of hepatitis C and B. Prior to PEGylation, the therapy required multiple injections per week. The PEGylation reduced the frequency of injections to once a week, making this year-long treatment somewhat more tolerable for patients.

In haemophilia, the idea is similar; attaching a PEG molecule to FVIII or FIX proteins extends the half-life. There are currently four haemophilia replacement products that utilise PEGylation (Table 2 and Table 3). The approved indication for these products differs between regions, with the EMA consistently limiting its approval to patients ≥ 12 years. The FDA has been more variable in its approvals. When **Adynovate® /Adynovi®** by *Takeda* came to market in 2015, the FDA licensed it for patients of 12 years of age and above. In 2016, the FDA extended its license to children. In 2017, the FDA approved **Rebinyn®** (recombinant coagulation factor IX, glycoPEGylated) by *Novo Nordisk* for all ages for on-demand treatment and control of bleeding episodes and perioperative management of bleeding. In 2018, the FDA licensed **Jivi®** by *Bayer* for patients of ≥ 12 years. The most recent FDA approval of **Esperoct®** by *Novo Nordisk* has been for all ages and routine prophylaxis despite it being the same PEG molecule as **Refixia®/Rebinyn®**. In Australia, Switzerland and Canada, as in a few other regions, **Adynovate®/Adynovi®** has been approved for all ages for prophylaxis; however, there is practice variability among paediatric haemophilia specialists, with some choosing to limit its use to children >6 years. These disparities have created questions with arguments and counter-arguments, leading to a variety of opinions on the use of PEG.

The differences in approvals between regions and the limitations to specified ages is not something new, nor is the situation in which a product does not have a specific indication for prophylactic use. The approval is merely a response to the current view based on the best available data.

However, questions remain on the long-term safety of PEGylated products. It is still unclear whether the PEG molecule is eliminated from the body or whether it accumulates in the body over time. It is also unclear whether the molecule causes harm if it accumulates in the body. For example, in animal models, there have been reports of increased cellular vacuolation, which is thought to be associated with the presence of intracellular PEG. Vacuolation is a process by which the cell tries to remove foreign entities. In animal cells, these vacuoles are not usually present or are very small but can grow spontaneously when exposed to bacteria, viral pathogens and various naturally-occurring or artificial small molecule compounds.

Increased vacuolation has been detected in various tissues, including the kidney, liver and choroid plexus epithelial cells (ependymal cells) in the brain. However, despite research on the mechanism of vacuolation, its effects remain

unclear. There are limited data on the overall impact of vacuolation, and there are no long-term surveillance data.

So, while PEG has been used in therapeutics for almost 30 years, decisions on its use so far have been based on a balance between the accumulation of the PEG and its inert properties weighed against the advancement of the condition, the duration of the treatment, the benefit of the treatment in a specific timeframe and the other available treatments. This is not unusual in the licencing of any product; however, when the risk vs benefit argument becomes more finely balanced, opinions begin to diverge.

In haemophilia, the critical question regards accumulation due to the repeated and long-term exposure to the PEGylated factor. An individual is put on a PEGylated treatment with multiple infusions per month (2-15) for routine prophylaxis and likely to be on the PEGylated product for years. Moreover, because a child may receive more frequent infusions due to shorter half-life, accumulation may be a slightly more significant concern. There are also questions on the impact of vacuolation on the developing brain that have little data and are unanswered. The counter-argument to this is that in very high dosing trials in animal models, accumulation does not cause harm unless the exposure to PEG is multiples of the lifetime amount an individual would get on routine prophylaxis. A further complication is that AE profiles are difficult to identify. Also, the likelihood of an individual being on the same product for a lifetime is lower than in the past given the rapid advances in treatments and product switching. Another argument is that PEG is not a naturally occurring molecule in the body, unlike other EHL half-life extension techniques; the counter argument being that, while the individual components may be naturally occurring in the body, their combinations with FVIII or FIX are not naturally occurring.

Although PEGylated drugs have been used safely for almost 30 years, this is the first time they have been used in people with haemophilia and are being scrutinised in the same manner as all other products. Currently with very little long-term follow-up data in children with haemophilia (and enough data will not be available for some time), some regulators have chosen a cautious approach to licensing. Whether this is warranted or overly cautious will only become apparent with the availability of more information over time.

Table 2: Summary of PEGylated recombinant factor VIII and factor IX products

Trade name Company Name	Generic name	PEG size	PEG attachment	Half-life in adults (hours)
Adynovi®, Adynovate® (BAX 855) Takeda	Rurioctocog alfa pegol	20 kDa	Lysine residues of rFVIII	14.7
Esperoct® (N8-GP) Novo Nordisk	Turoctocog alfa pegol	40 kDa	O-glycan moiety of the B domain of rFVIII	21.7
Jivi® (BAY 94-9027) Bayer	Damoctocog alfa pegol	60 kDa (branched PEG, 2 x 30 kDa)	Cysteine amino acid position 1804 (within the A3 domain)	17.4
Refixia®, Rebinyn® (N9-GP) Novo Nordisk	Nonacog beta pegol	40 kDa	Specific-N-linked glycans in the rFIX activation peptide	83

Table 3: Approval dates of PEGylated factors

PEGylated factor	Australia (TGA)	Europe (EMA)	US (FDA)
Adynovi®, Adynovate® (Bax 855) Takeda	Registered March 2017 for adults / children	Approved Jan 2018 for adults and chil- dren ≥12 yrs	Approved Nov 2015 for adults and children ≥12. Approved Dec 2016 for children <12
Esperoct® (N8-GP) Novo Nordisk	Not registered	Approved June 2019 for adults and chil- dren ≥12 yrs	Approved Feb 2019 for adults and children
Jivi® (BAY 94-9027) Bayer	Not registered	Approved Nov 2018 for adults and chil- dren ≥12 yrs	Approved Aug 2018 for previously treated adults and children ≥12
Refixia®, Rebinyn® (N9-GP) Novo Nordisk	Approved April 2019 for adults / children ≥12 yrs	Approved June 2017 for adults and chil- dren ≥12 yrs	Approved May 2017 for adults and children

Update on Novel Therapies for Inhibitor Treatment

By-passing Therapies

An update on MarzAA

Catalyst Biosciences updated their phase II trial of its SQ factor VIIa (FVIIa) **variant marzeptacog alfa (activated) (MarzAA)** for prophylaxis. In the daily SQ administration for 50 days of MarzAA in nine patients, there was a reduction in the pre-study ABR from 19.8 to 1.6 during treatment. Additionally, the proportion of days with bleeding (PDB), was significantly reduced from a six-month pre-treatment mean of 12.3% to 0.8% during treatment ($p < 0.01$). The median ABR and PDB were both reduced to zero during treatment, with seven of nine patients experiencing no bleeds, either traumatic or spontaneous, at their final dose level. There were no anti-drug antibodies or inhibitors to MarzAA detected after administration of a total of 517 SQ doses. SQ administration prolonged the half-life of MarzAA to 16.6 hours, so that trough levels of MarzAA before the next SQ dose were sufficient to provide bleed prevention. MarzAA has been granted orphan drug designation by the US FDA and the EMA for routine prophylaxis to prevent bleeding episodes in individuals with haemophilia A or B with inhibitors.

Non-replacement therapies

Please see further updates for the use of **Hemlibra®** in inhibitor patients in the Haemophilia A non-replacement section of this issue.

¹ Further information on this is also available in abstract LB01.1, available at on ISTH Congress 2019 website.

Additional data from original bi-specific antibody clinical trial cohort

In another related abstract (PB1416) presented at the Congress, data on bleeding symptoms and daily life were collected from seven patients Haemophilia A with inhibitors. These patients were on prophylaxis using **emicizumab** and belonged to the original cohort of the phase I/II trial in Japan. The median observation period for these patients was 3.6 years. Bleeding rates had reduced in all patients. These patients' joints were affected by chronic historic bleeds, which caused pain, joint swelling, limited mobility and range of motion. The treatment only led to slight improvement or unchanged status concerning joint health. However, patients reported an increase in daily activities and an overall decrease in anxiety.

Safety and tolerability of prophylactic emicizumab in people with inhibitors

Victor Jiménez-Yuste presented interim data (OC60.3) on the safety and tolerability of prophylactic **Hemlibra®** in people with haemophilia A (PwHA) with FVIII inhibitors (STASEY) trial. The trial looked at 88 patients, median age 28 (12-80), receiving emicizumab every week for a median duration of 39.2 (range 4.4-57.1) weeks. Authors calculated the mean ABR using a statistical model, and it resulted in 0.5 ABR for treated patients, 1.4 ABR for all patients, 0.2 ABR spontaneous bleeds, 0.3 ABR joint bleeds and very low target joint bleeds. Seventy-one patients had zero treated bleeds (80.7%). Of 17 patients who received treatment for a spontaneous or traumatic bleed, 16 received rFVIIa, and one received FVIII. Eighteen (20.5%) patients reported an emicizumab-related AE, of which injection-site conditions were the most common.

ITI while on Hemlibra®

Within the haemophilia community, there have been many discussions on the need to continue to tolerate FVIII patients with inhibitors, even when managed with **emicizumab**, as treatment with emicizumab may only defer development of inhibitors rather than prevent them. Therefore, it was interesting to see some data on this topic presented during the ISTH Congress.

The use of a low-dose immune tolerance induction (ITI) regimen with a long-acting rFVIII was described in three case studies from Japan (PB0236). In two cases, the doses, as well as the dosing interval of **Eloctate®/Elocta®**, decreased after starting the patients on **Hemlibra®**. The inhibitor titers decreased in all three cases, and there were no AE observed. The authors suggest that the use of low-dose (less than 50IU/kg) EHL products and twice-weekly ITI under emicizumab, may be an option for the future. It has been suggested that this treatment could be called the Tokyo protocol.

Although the patient cohort is very small, it is useful to consider the concept of tolerising the inhibitor for better bleeding control in the event of bleeding and surgical procedures using lower doses of FVIII.

Carmen Escuriola Ettingshausen also introduced the investigator-initiated MOTIVATE study (PB1406), which will investigate the efficacy and safety of “standard of care” ITI vs novel approaches combining FVIII (**Nuwiq®**) and emicizumab, or emicizumab prophylaxis alone, in people with inhibitors.

An update on concizumab in patients with inhibitors

In a late-breaking session at the ISTH Congress, authors presented phase II clinical trial data for the use of concizumab in HA and HB patients with inhibitors (explorer 4).

The trial examines a once-daily subcutaneous treatment that inhibits tissue factor pathway inhibitor (TFPI). This clinical trial enrolled 16 HA patients and 10 HB adults, all with inhibitors. Patients in Explorer 4 were randomised 2:1 to either prophylaxis with concizumab or on-demand treatment with recombinant activated factor VII [rFVIIa]. Initial data suggests mean ABR for all bleeds declined from 20.4 to 4.5 bleeds, spontaneous bleeds declined from 18.5 to 2.5, and joint bleeds declined from 15 to 3.2. Optimised dose and trial design were identified, and concizumab initiated phase III pivotal trials. Some patients showed anti-concizumab antibodies, but these were transient and did not appear to have any effect on clinical outcomes. Most patients also reached a normal level of thrombin generation, and there were no thromboembolic events, and no significant safety concerns emerged during the study. All patients chose to continue in the extension phase and no adverse events led to withdrawal.

Sigilon presented preclinical data demonstrating the feasibility of cellular therapies for bleeding disorders developed with the company's *Shielded Living Therapeutics*TM platform. More information is provided in the 'non-replacement' section for FVIII and the attached link. This may be an interesting possibility for inhibitors for a few reasons. Firstly, they can be implanted, and if there is an issue or a reaction, they can be removed, which may have a distinct advantage in those few patients with anaphylactic inhibitor reactions. Secondly, it may be able to produce a dose respondent, constant supply of rFVIIa and overcome the issues of short half-lives for constant prophylaxis.

Please see the 'haemophilia A' section above for further updates on other non-replacement therapies.

Gene therapy

This review has discussed in the past the theories about gene therapy in patients with inhibitors, and while there is currently a trial that accepts patients with previous inhibitors, there is still a gap for those with current inhibitors. In basic terms, ideas related to gene therapy in inhibitors are that gene therapy would create FVIII proteins (other considerations are important in FIX) and the inhibitor may not recognise it as a foreign protein. If the body does not see the protein as foreign, the continuous production of FVIII protein would eventually lead to immune tolerance and rather than getting a response of increased factor expression in the first few weeks, it might take longer. *UniQure's AMT-180* takes a different approach to this problem to hopefully accelerate access for patients with inhibitors without the potential unknown additional risks associated with a current inhibitor. The concept (poster OC 22.3) uses an optimised FIX delivered via AAV vector, which does not require the presence of FVIII to activate FX. This has the benefit of "by-passing" FVIII in the clotting cascade and as a result, is not impacted by FVIII inhibitors. Normally, when bleeding occurs, FIX activates factor X, and FVIII helps in two ways: by changing the shape of FIX, making it far more active, and linking it to FX. AMT-180 uses a modified FIX, that, when activated as a regular FIX would be, is able to activate FX in the absence of FVIII because it already has the shape change. Preclinical studies with FVIII-depleted human plasma with and without inhibitors as well as studies in haemophilia A mice have demonstrated up to 29% of factor VIII-independent mimetic activity.

An Update on Novel Therapies for von Willebrand Disease

Update on rVWF

Takeda received marketing authorisation for **Veyvondi®** (**Vonvendi®** in the US), a recombinant von Willebrand factor (rVWF). The product is licensed for the treatment of bleeding events, as well as the treatment and prevention of surgical bleeds, in adults (18 years of age and older) with von Willebrand disease (VWD) when desmopressin alone is ineffective or not indicated. Regulators licensed the product based on the outcomes of three clinical trials with a total of 80 patients with VWD. These included:

- a phase I dose-escalation study of the safety, tolerability and PK of rVWF:rFVIII in subjects 18 to 60 years of age with severe VWD;
- a phase III study to assess the PK, safety and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in adult subjects with severe VWD; and
- a phase III study to assess the efficacy and safety of rVWF with or without rFVIII in 15 adult subjects with severe VWD undergoing major, minor, or oral elective surgical procedures.

The rVWF prophylaxis study (NCT02973087), is still ongoing, and expected to close in 2020.

Differences between rVWF and pdVWF

Regarding differences between rVWF and plasma-derived (pd)VWF, one ISTH poster (PB0803) presented data on a comparison of the number of infusions needed to stop a bleed, adjusting for the daily dose. The comparison found that overall, the indirect treatment comparison indicates fewer infusions of rVWD compared to pdVWF

may be needed to stop a bleed.

It is important to note that the analysis has several assumptions and limitations; for example, the assessments and treatment decisions in different studies were assumed to be comparable. However, despite this, this analysis may indicate that there is a potential additional value of treating VWD bleeds with rVWF.

An Update on Therapies for Rare Bleeding Disorders

There are few updates for patients with rare bleeding disorders, which is disappointing for a patient population that have little access to safe and effective treatments. However, in this document, we outline some therapies in the non-replacement section of the 'haemophilia A' that may apply to patients with rare bleeding disorders. While the descriptions are specific to FVIII or FIX, the potential to treat using these therapies is a possibility. The products that may benefit people affected by rare bleeding disorders are:

1. Rebalancing agents - there are six rebalancing agents that could benefit patients with rare bleeding disorders depending on where the deficiency occurs in the clotting cascade. These agents are **fitusiran** by *Sanofi*, **concizumab** by *Novo Nordisk*, **marstacimab** by *Pfizer*, and **SerpinPC** by *Apcintex*, **BAY1093884** by *Bayer* and **MG113** by *GreenCross*. These agents rebalance the clotting cascade by reducing the signals that tell the body to stop clotting. In this way, the body balances out this signal by telling the body to clot.
2. With the recent licensing of rFVIIa for use in Glanzmann's thrombasthenia, there are two products that could in the future help people affected by rare bleeding disorders. The first is **MarzAA** by **Catalyst Biosciences**, which is a daily subcutaneous injection of a long-acting rFVIIa, and **SIG-001** by *Sigilon*, which are implantable spheres that contain cells that could produce rFVIIa and release it consistently into the body.

The biggest issue in product development for patients with rare bleeding disorders is the small number of patients, which limits data development for understanding safety and efficacy of these products in this patient population. Unfortunately, this will lead to a slower access to novel technologies. The EHC is committed to advocate for expanding the development of these products to people affected by rare bleeding disorders. However, the community should not compromise on the safety and risk/benefit analysis of these novel therapies in patient populations that have not been studied as extensively as haemophilia A and B.



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