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 2019 Congress of the American Society of Hematology (ASH) and the 2020 Congress of the European Association for Haemophilia and Allied Disorders (EAHAD) as well as other news from the industry and from the news in general. The abstracts of the EAHAD congress can be accessed online here. For your convenience, we have also decided to 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 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, von Willebrand disease, and other rare bleeding disorders.

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

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

AJBR:	Annualised joint bleeding rate
ABR:	Annualised bleeding rate
AE:	Adverse events
aPCC:	Activated prothrombin complex concentrate
aPTT:	Activated partial thromboplastin time
ASH:	American Society of Hematology
BPA:	Bypassing agents
BU/ml:	Bethesda units per millilitre
CI:	Confidence interval
ED:	Exposure day
EHL:	Extended half-life
ER:	Emergency room
EU:	European Union
F:	Factor
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
HCV:	Hepatitis C
HEAD-US:	Haemophilia early arthropathy detection with ultrasound
Hemo-QoL-A:	Haemophilia specific quality of life questionnaire
HIV:	Human Immunodeficiency Virus
Hrs:	Hours
IQR:	Interquartile Range

ITI:	Immune tolerance induction
IU:	International units
IU/dl:	International units per decilitre
IU/kg:	International units per kilogram
n=:	Number
N/A:	Not applicable
OD:	On-demand
PD:	Pharmacodynamics
PEG:	Polyethylene glycol
PK:	Pharmacokinetics
PPX:	Prophylaxis
PTP:	Previously treated patient
PUP:	Previously untreated patient
r:	recombinant
RNAi:	Ribonucleic acid interference
SAE:	Serious adverse events
SD:	Standard deviation
SHL:	Standard half-life
TE:	Thromboembolic events
TMA:	Thrombotic microangiopathy
UK:	United Kingdom
US:	United States
vs:	versus
VWD:	von Willebrand disease
VWF:	von Willebrand factor
wk:	week
WPAI:	Work productivity and activity impairment questionnaire

AN UPDATE ON NOVEL TREATMENTS IN HAEMOPHILIA A

Highlights of this section

In this section, you will find a summary of developments in treatments for haemophilia A. We cover replacement, non-replacement and gene therapies.

Extended half-life (EHL) replacement therapies for haemophilia A have now been on the market in Europe and North America for six years and this issue gives an insight into post-marketing data from both post-marketing surveillance (phase IV trials) and real-world experience. The main focus is on personalisation of treatment and trying to understand which treatment offers the better therapeutic solution to which patient and which medical situation.

With regards to clinical trials for non-replacement therapies, Novo Nordisk has announced a pause of clinical trials of concizumab, due to thrombotic events in three patients. Although these were not observed in the phase II trial, they occurred when moving to phase III. Novo Nordisk is currently reviewing data to assess the potential causes and a decision on continuation will be made in collaboration with regulators. We give you an update on real-world use of Hemlibra® in people without inhibitors, with additional information in the inhibitor section. Additionally, preclinical data for three new bispecific antibodies and further development of a cell based implantable therapy are also included in this section.

For gene therapy, we report on a *New England Journal of Medicine* article detailing a three-year follow-up of BMN-270, a gene therapy for haemophilia A developed by BioMarin. In December 2019, BioMarin announced that the EMA had validated a marketing authorisation application. This could mean that the first gene therapy could be licensed either this year or next. We also see a number of prevalence studies that have been carried out to determine pre-existing immunity to the most common viral vectors used to deliver gene therapy (AAV5, AAV6 and AAV8) in order to understand who may be eligible for gene therapy. Immunity to these vectors may prevent patients accessing these technologies.

As a reminder, the abstracts of the EAHAD congress can be accessed online here.

Replacement Therapies

Reports from clinical trials

Data on the use of Afstyla in PUPs and inhibitor treatment

In an abstract of the 2019 ASH Congress, data were presented on a multicentre, open-label, phase III extension study investigating the use of **Afstyla®** in 50 previously untreated patients (PUPs) for at least 50 exposure days (EDs). An immune tolerance induction (ITI) sub study was also implemented for those PUPs who developed an inhibitor to FVIII. As of March 2019, 23 PUPs were treated with Afstyla® with a median age: 1 y (range 0-5). Mean (SD) time on study was 21.6 (12.6) months. Twelve patients (52%) were diagnosed with an inhibitor to FVIII: 6 (26%) high titre (≥5 BU/mL), and 6 (26%) low titre. The median ED for inhibitor development (initial result) was 10, range 4-23. All PUPs enrolled had ≥1 risk factor for inhibitor development including genetic mutation, age at first exposure, initial treatment reason and assigned regimen, as well as bleeding events and infections; inhibitor positive and negative patients were comparable.

Of the 12 inhibitor positive patients, 11 continued treatment, 7 were treated with low dose ITI, 3 with an increased prophylaxis regimen, 1 with no change in regimen. Eight of 11 (73%) inhibitor positive

patients (2 high titre, 6 low titre) achieved eradication. The clinically relevant inhibitor patients (2 high titre, and 1 persistent low titre) achieved eradication in a median of 15.7 months. Patients who eradicated the inhibitor were negative for a median of 13.6 months, and no inhibitor relapse was observed. Three remaining inhibitor positive patients still are undergoing treatment.

Italian experience on switching to Afstyla®

A poster (P042) presented at the 2020 EAHAD congress showed the results from an online survey and interviews of 91 patients switching to **Afstyla®** for ≥12 months across 14 haemophilia treatment centres in Italy. Patients reported a reduction in infusion frequency, product consumption and a reduction in spontaneous annual bleeding rate (ABR). *Authors of this poster were representatives of the pharmaceutical industry.*

Results from the ASPIRE extension study

A total of 150 patients from *A-LONG* and 61 patients from *Kids A-LONG* enrolled in *ASPIRE* (NCT01454739), an open-label extension study of **Elocta®** as an extended half-life treatment . Most patients received the prophylactic regimen (A-LONG: n=110; Kids A-LONG: n=59). Median (range) treatment duration in ASPIRE for patients from A-LONG and Kids A-LONG was 3.9 (0.1-5.3) years and 3.2 (0.3-3.9) years, respectively. No inhibitors were observed (0 per 1000 subject-years; 95% confidence interval, 0-5.2) and the overall Elocta® safety profile was consistent with prior studies. For patients on the prophylactic regimen, annualised bleed rates (ABR) remained low (median overall ABR for adults and adolescents was <1.0).

Results of the NuProtect study

Results of the *NuProtect* study presented PUP data in an abstract during the 2019 ASH congress. In this open-label, non-controlled phase III study using **Nuwiq®**, 105 PUPs with a median age of 12 months (range 0-146) at ED 1 were evaluable for inhibitor development. They were treated for a median of 101 EDs, with 96 patients treated for ≥100 EDs (or until inhibitor development). Cumulative inhibitor incidence was 17.6% (95% CI: 10.0%, 25.3%) for high-titre inhibitors and 27.9% (95% CI: 19.1%, 36.7%) for all inhibitors. No PUPs with non-null FVIII mutations developed inhibitors.

Results of the pathfinder™ 2,3 and 5 trials

During the 2019 ASH congress, an abstract presented the results of the *pathfinders 2,3 and 5 trials*. These trials evaluated routine prophylaxis and bleed treatment in previously treated adolescents/adults (*pathfinder 2*) and children (*pathfinder 5*) with severe haemophilia using **ESPEROCT®**, also known as N8-GP**,** an extended half-life recombinant FVIII product.

Pathfinder 2 enrolled 186 adolescents/adults, with 128 (69%) completing the second extension phase, with 2,758 treated bleeds. On-demand patients (n=12) treated for a total of 37 patient-years of exposure reported 1,270 (46%) bleeds. In the main phase, 105 of 175 patients on prophylaxis, receiving 50 IU/kg every 4 days, experienced 436 bleeds with a median ABR of 1.2. Through the study (mean 3.5 years), 177 adolescents/adults on doses of more than 52 IU/kg had a median ABR of 0.99 and mean (95% CI) FVIII trough levels of 3.1 (2.6-3.4) IU/dL. The median dose for mild/moderate bleeds was 42 IU/kg. For on-demand patients, the median initial dose was 28 IU/kg, with 88.4% of bleeds treated with a single dose. In patients receiving prophylaxis, the median initial dose matched the prophylaxis dose (52 IU/kg), and 76% of bleeds received a single dose. For 15 severe bleeds, the median total dose was 111 IU/kg per episode.

Pathfinder 5 enrolled 68 children (34 aged 0-5 y, 34 aged 6-11 y), 95% previously on prophylaxis, 62 completed the extension, amounting to 306 patient-years with mean exposure of 4.5 years. Overall, 55 patients (81%) reported 330 bleeds; most were traumatic (67%). Median ABR in the main phase (0.48 years) was 2.0 and through the entire study was 0.8 with mean (95% C.I.) FVIII activity trough level of 1.9 (1.6-2.5) IU/dL. The mean prophylaxis dose was 64.7 IU/kg at a mean interval of 3.5 days,

likely reflecting rounding the targeted 60 IU/kg twice weekly dose. For 70 bleeds, median utilisation for bleeds was 68 IU/kg.

Results of the PROTECT VIII trial and extensions study

Data on the clinical trial *PROTECT VIII* and its extension study for **Jivi®** were presented in two abstracts at the 2019 ASH congress. The first abstract focused on patients with comorbidities. This looked at 104 patients who received Jivi® prophylaxis during the main study and the extension. The mean age of patients was 34.3 years with a median of 7 (IQR:2-15) bleeds in the 12 months before enrolment. Most patients (72.1%) had target joint(s) at baseline. Before the study, 22 (21.2%) patients were receiving on-demand treatment; the remaining 82 were on regular prophylaxis. Most patients (n=66, 63.5%) had ≥1 comorbidity of interest, such as HCV, HIV or cardiovascular. In the pre-study, the median ABR was 6.0 and 7.0 in patients with and without comorbidities of interest respectively, which decreased to 2.9 and 1.5 respectively during the main study, and further to 1.8 and 1.2 respectively during the extension. In all patients with comorbidities of interest, improvements in median ABR were observed between the 12-month pre-study period and the main study period and were maintained or improved in the extension.

A second abstract focused on patients who were previously on on-demand treatment switching to Jivi® on a regimen of either on-demand or prophylaxis treatment. Of 43 patients on prior on-demand therapy, 20 selected on-demand (OD) [OD→OD] and 23 selected prophylaxis (PPX) [OD→PPX]. Thirty-nine patients continued into the extension study; 14 continued OD, and 25 switched to PPX [OD→PPX]. A total of 89 patients on prior PPX therapy received PPX during the main study [PPX→PPX] and 82 continued to receive PPX during the extension.

At the end of the main study, median ABR was 23.43, 2.7 and 2.1 in the OD→OD, OD→PPX and PPX→PPX groups, respectively. During the extension, median ABR was 33.5, 1.3 and 1.6 in the OD→OD, OD→PPX and PPX→PPX groups, respectively. Robust improvements in median ABR were observed for patients previously on OD treatment in both the main study and extension, irrespective of which PPX regimen they received. The Hemo-QoL-A score was maintained or improved from baseline during the main study for all prophylaxis regimens with greater benefit among those who switched from on-demand to prophylaxis, particularly those who could switch to a once-a-week regimen. Patients who were on on-demand prior to study entry also saw improvements in activity and work impairment using the WPAI instrument.

Jivi® has been approved in the US, EU, Japan and Canada for previously treated patients ≥12 years old.

Interim results of the TAURUS study on patients aged <12

During the 2020 EAHAD congress, the interim results of the *TAURUS* (phase IV - post-marketing) study on the use of **Kovaltry®** in patients aged <12 as prophylactic treatment for moderate to severe haemophilia A were presented (poster P165). In the poster, 40 patients were included in the analysis set with a median age of 8 (2-11) years. All patients entering the study had previously received prophylaxis with FVIII. Most patients were assigned prophylaxis with Kovaltry® either twice or three times per week. At data cut-off the median spontaneous ABR and trauma ABR were 1.5 (0.0;2.4) and 0.9 (0.0;4.0) respectively.

Comparing efficacy and consumption of three factor concentrates using clinical trials data

During the 2020 EAHAD congress data (poster 063) were presented comparing the efficacy and consumption of **Afstyla®**, **Advate®** and **Elocta®**. This was performed through a comparison of outcomes and population of published trials using these products. Despite being limited to published information for comparator trials, this study suggests that Afstyla® has comparable prophylactic treatment efficacy, superior on-demand treatment efficacy and lower FVIII consumption than Advate® and equivalent consumption to Elocta®. *One of the authors of this abstract is an employee of CSL Behring.*

Indirect comparison of efficacy of EHL FVIII products

In a poster (P132) presented at the 2020 EAHAD congress, authors presented the results of a systematic literature review to compare the efficacy of EHL Factor VIII products. Authors identified five articles and extracted and summarised their data for indirect comparison. Reported consumption was comparable among all EHL products. *One author of the poster is a CSL Behring employee.*

	Afstyla®	**Esperoct®**	**Elocta®**	**Adynovi®**	**Jivi®**
Treatment Regimen	every second day or 2-3 times weekly,	every four days	twice weekly followed by every 3-5 days	twice weekly	twice weekly
ABR (IQR)	1.14 (0.0, 4.2)	1.18 (0.00-4.25)	1.6 (0.0, 4.7)	1.9 (00, 5.8)	1.9 (0.0, 5.2)
AJBR (IQR)		0.85 (0.00, 2.84)	0.0 (0.0, 1.7)	0.0 (0.0, 2.0)	

Results from PK-guided prophylaxis in PROPEL study

In an oral presentation (OR09) at the 2020 EAHAD congress an analysis of the clinical trial *PROPEL* (NCT02585960) was presented in which the relationship between patient factor VIII half-life and efficacy and consumption of prophylactic **Adynovi®/Adynovate®** (rurioctocogalfa pegol); was evaluated. Patients were randomised to PK-guided prophylaxis targeting FVIII troughs of 1-3% (Reference) or 8-12% (Elevated) independent of their PK profile. Results suggest patients with the shortest FVIII half-life appeared to benefit most from 8-12% vs 1-3% FVIII troughs regarding bleed prevention. Patients with shorter FVIII half-life required higher Adynovi®/Adynovate® doses and more frequent infusions to achieve higher target FVIII troughs vs those with longer FVIII half-life. The results demonstrate the heterogeneity of patients' PK profiles and reinforce the importance of individualized treatment to achieve a certain FVIII level for adequate bleed protection.

Report on the results of phase I/II of the BIVV001 trial

In an abstract presented during the 2019 congress of the American Society of Hematology (ASH), data were presented on the phase I of the first in-human trial (NCT03205163) of **BIVV001**[1] (rFVIIIFc-VWFD'D3-XTEN) (Konkle et al, Blood, 2018).

Patients received 4 once-weekly doses of BIVV001 (days 1, 8, 15, and 22) at either 50 IU/kg (cohort 1) or 65 IU/kg (cohort 2). The mean (range) half-life for 50 IU/kg and 65 IU/kg BIVV001 was 41.3 (34.2-50.1) hours and 37.3 (28.9-43.8) hours, respectively. At 5 and 7 days after the final BIVV001 infusion, mean steady-state FVIII activity was 22% and 10% for cohort 1 and 27% and 12% for cohort 2, respectively. These results support the continued development of BIVV001 in a phase III clinical trial program.

In an abstract (P057) presented at EAHAD (Lissitchkov et al.) further data were presented demonstrating a mean steady-state FVIII activity was 46% 50IU/kg group and 69% for 65IUI/kg cohort after 3 days respectively.

Real-world experience

Clinical experience of the use of prophylaxis Elocta® in Taiwan

In an abstract presented at the 2019 ASH congress, experience from Taiwan in switching 49 patients to extended half-life **Elocta®** was outlined, including 44 severe, 3 moderate and 2 mild patients. The

[1] See EHC New Product Newsletter Issue 1/2018, pg 9.

rates of routine prophylaxis elevated markedly from 47.5% to 90% after switching from SHL FVIII to Elocta®. The frequency of ER visits due to bleeding reduced during 6 months after switching. More than 60% of PTP with routine prophylaxis reported improved morning stiffness, rheumatic joint pain, chronic joint pain, and increased ability to exercise. Within the study, 36 patients completed a pharmacokinetics analysis with a mean (range) trough level of 3.2 (<1-8.5%). Those with a history of transient inhibitors and O-blood type had a lower half-life.

Real-world experience of switching to Elocta® presented at EAHAD 2020

A poster presented the Swedish experience (P138) of 351 patients with moderate or severe haemophilia; 80% were on prophylaxis. Ninety-six patients received **Elocta®** and 93 were on prophylaxis. In the within-patient comparison (n=83), mean prescribed weekly dose was 10% lower on Elocta®. The median ABR (n=62) was 0 (IQR 0-0) on FVIII and 0 (IQR 0-0.8) on Elocta®. *One of the authors of this abstract is a representative of Sobi.*

Data were also presented from the UK at the 2020 EAHAD congress (P073) on 81 UK patients who switched from SHL to Elocta® prophylaxis between September 2016 and March 2019. A within-patient comparison showed a reduction in infusion frequency, clotting factor consumption and ABR. This change was maintained over a period of > 52 weeks.

In France data were presented on the real-world use of Elocta® in North-Western France (P155) in 121 patients on prophylaxis in 7 centres who were followed for two 1-year periods. The use of Elocta® led to a decrease both in prescription (-8.8% IU/kg/week) and in the number of infusions (-0.4 injections/week).

A single centre experience was also reported on 15 teenage patients (P066) (13 severe, 2 moderate) switching to Elocta® with the interval between infusions being able to be prolonged to every 3 days in 14 out of 15 patients. In 1 patient the former treatment schedule was maintained. No adverse events (AEs) or inhibitor development were detected. Despite this being a single centre study with limited population, it shows a reduction of infusion frequencies in a cohort of patients in which it is not easy to reduce the number of weekly infusions. Clinical outcomes were maintained and quality of life improved.

Real-world use of Adynovi®/ Adynovate® in the US

In an abstract presented during the 2019 ASH congress, patient data from US specialty pharmacies on the real-world utilisation of **Adynovate®** (**Adynovi®** in Europe) were presented. The data describe patients' clinical profile before and after switching (from November 2015 to September 2018) to Adynovate®.

Data were collected from 82 patients, 44% were <18 years old, 80% had severe haemophilia and 88% had received prior SHL-FVIII treatment. Compared with any prior FVIII therapy, switching to Adynovate® increased the weekly FVIII consumption in patients aged <18 years (+11.2%) and decreased consumption in those aged ≥18 years (-12.8%). Meanwhile the switch decreased weekly administration frequency (-21.4% and -28.1%, respectively). ABR data before and after switching were available in 47 patients. Compared with any prior FVIII therapy, mean ABR decreased in patients aged <18 years (-39.5%; 2.8 to 1.7) and ≥18 years (-50.3%; 3.4 to 1.7). The observed differences in FVIII consumption between patients <18 and ≥18 years old may have been in part a result of age-related changes in bleeding patterns, prior treatment regimens and other factors. *This abstract was written by representatives of the pharmaceutical industry.*

Clinical use in the US for Adynovi®/Adynovate®

In a recent paper on real-world consumption, for patients switching from prophylaxis with standard half-life (SHL) to EHL rFVIII (**Adynovate® / Adynovi®),** data was collected from 56 patients. The age

was 24 years (IQR 14-34); 20% were aged < 12 years; and 89% (50/56) had severe haemophilia. All patients had ≥12 months of rFVIII treatment before switching to Adynovate® / Adynovi®. Before the switch, patients had a mean 1.8 target joints and a subjective pain assessment was mild to moderate for 68% (38/56) of patients. Before switching most patients received prophylaxis (73%, 41/56). Mean dose and infusion frequency for prior prophylaxis was 109.8IU/kg x 2.8/week for SHL rFVIII and 83.8IU/kg x 1.8 per week for EHL rFVIII, and 101IU/kg x 2.2 per week for all after switching to prophylaxis. Mean ABRs on prior prophylaxis were 5.9 for SHL rFVIII (n = 35) and 4.7 for EHL rFVIII (n = 3). After switching to rurioctocog alfa pegol, the overall mean ABR reduced by 71% (5.8 to 1.7, P < 0.001) and 20 patients had no bleeding events. The proportion of patients with good/complete treatment adherence increased from 68% (38/56) on any prior rFVIII to 80% (45/56) post switch. The most common reason to switch was to reduce infusion frequency. *Two authors of the poster are employees of Baxalta, a Takeda company.*

Inhibitors or PEG antibodies formation with Adynovi®: Results from 6 clinical studies

During the 2020 EAHAD congress, data (P187) were presented analysing 6 clinical studies using **Adynovate®/Adynovi®** to evaluate the potential of immune response against FVIII or PEG and assess the impact on treatment efficacy and safety. None of the unique 360 participants developed a persistent binding antibody response against FVIII, PEG-FVIII or PEG. However, 54 patients tested positive at single time points. Of these patients, 34 had pre-existing antibodies to FVIII, or PEG or PEG-FVIII prior to their first exposure. These disappeared during the study. Transient antibodies to FVIII, PEG-FVIII or PEG after exposure to Adynovi®/Adynovate® developed in 22 patients who were negative at screening. No causal relationship was observed between the appearance of binding antibodies against FVIII, PEG or PEG-FVIII and severe adverse events (SAEs) and no impact on haemostatic efficacy was seen. *The authors of this abstract are representatives from Baxalta, a Takeda company.*

PEG steady state in humans

In a poster (P049) presented at the 2020 EAHAD congress, authors describe a simulation performed to assess time to reach the steady state of PEG distribution in plasma and different organs in humans. Times to reach a steady state of PEG distribution in different organs were simulated in patients receiving **Jivi®**. Plasma PEG levels were measured in 120 adults/adolescents (*PROTECT VIII*, NCT01580293) and 59 children <12 years (*PROTECT VIII Kids*, NCT01775618) at baseline and for up to 5 years during the ongoing extension studies. The predicted time to reach a steady state was 1 year for plasma and 1.5 years for kidney. PEG concentrations in human plasma were below quantifiable levels for most samples. Six patients presented borderline, transient, positive results with negative follow-up samples, confirming that the predicted plasma levels were at the detection limit. There were no AEs indicative of renal dysfunction. Creatinine levels and calculated creatinine clearance remained stable over time. Biomarker results did not indicate kidney injury.

PEG levels reach steady state following repeated treatment with Esperoct

In a another paper, PEG levels were examined in rats and humans who were repeatedly treated with **Esperoct®** (N8-GP) for periods of up to 5 years. Human plasma samples from children, adolescents and adults treated as part of the pathfinder programme were also examined (NCT01731600; NCT01480180). These data were then compared with steady-state PEG levels predicted by pharmacokinetic modelling from rat data. The timing and degree of PEG increase to steady state were in line with or below model predictions. Steady-state plasma PEG concentrations in patients were predicted to be reached within 6 months. This gives an indication that initial pharmacokinetic models from rat data can be used to estimate human plasma PEG levels.

Comparison of EHL prophylactic regimens in Germany

In a poster (P163) at the 2020 EAHAD congress, data were presented from 225 German patients, 76 with severe haemophilia, receiving prophylaxis for at least eight weeks with **Afstyla®** (n=40), **Elocta®** (n=47), **Advate®** (n=58), **Kovaltry®** (n=40) and **Refacto AF®** (n=40). Patients with Afstyla® and Elocta®

received treatment twice a week or less and those on SHL products were infused 3 times a week or more.

Mean ABR with Afstyla® was 0.4 and 0.3 in those with severe. For other products mean ABR ranged from 0.5 (Elocta®) to 1.5 (Advate®) for severe patients. Mean consumption across all patients was also lowest with Afstyla® (59.2 IU/kg/week), followed by Elocta® (81.1 IU/kg/week).), Kovaltry® was the product with the highest consumption (91.4/IU/kg/week). *Authors from this abstract were representatives of the CSL Behring.*

Preliminary data on Swedish real-world experience of switching to EHL

During the EAHAD 2020 congress aggregate data from the Swedish National Board of Health and Welfare (NBHW) were presented on diagnoses and filled prescriptions from 2012-2018 for 492 patients (P080). The number of patients on EHL increased from 2 in 2016 to 48 in 2018 resulting in an average monthly dosing higher for people on EHL compared to SHL. More analysis is being carried out to examine the reasons for the differences, especially considering data presented at the same conference on a reduction in prescriptions doses. *One of the authors of this abstract is a representative of Pfizer.*

UK issues new prophylaxis guideline

In May 2020, the British Society of Haematology published a new guideline on the use of prophylactic factor replacement for children and adults with haemophilia A and B.

Non-Replacement Therapies

Bi-Specific Antibodies

Real-world data on the use of Hemlibra®

In an abstract presented during the 2019 ASH congress, clinicians presented the data from 89 patients on prophylactic **Hemlibra®** from three centres in the US. There were 3 moderate patients and 19 had an active inhibitor prior to the start of the study. Patients were followed for a duration of 6 months approximately. Overall, the experience of patients was favourable with no SAEs. The proportion of patients whose ABRs were zero increased in both inhibitor (from 46% to 74%, p=0.06) and non-inhibitor patients (from 60 to 78%, p=0.015). Patients with inhibitors were more likely to receive weekly dosing and there were no SAEs.

In another abstract, real-world data were presented from 42 patients who switched from replacement therapy to Hemlibra® between November 2017 and May 2019. Overall, patients reported fewer bleeds (lower ABR), infrequent surgical bleeding and subjective improvement to health. Postoperative thrombosis/thrombotic microangiopathy suggests that FEIBA should be avoided for at least 6 months after Hemlibra® discontinuation.

In relation to adherence, results were presented from a retrospective cohort study looking at 48 patients using Hemlibra® for 7 months. Almost 80% were on a weekly administration. Adherence was close to 90% in patients (n=12) who had previously received on-demand treatment while patients who had been receiving routine FVIII prophylaxis prior to the study had an adherence of close to 100%. Other variables that were significant predictors for decreased adherence were the age (young adults), active inhibitor and prior non-adherence to factor. Differences were reported as small.

FVIII consumption to treat breakthrough bleeds during HAVEN 3 trial

At the ASH congress, data were presented on the dose and frequency of the use of replacement factor VIII to treat breakthrough bleeds during the *HAVEN 3* clinical trial for **Hemlibra®.** This analysis compared the use of FVIII to treat breakthrough bleeds in 48 patients who were previously on FVIII prophylaxis and then switched in the study to Hemlibra®. The number of patients treating bleeds reduced from 29 to 27 post switch. The total number of bleeds also reduced from 137 treated bleeds over a median time of 0.58 years pre-switch to 71 treated over a median of 1.7 years post-switch. The median number of infusions per bleed were 1.0 pre-switch and 2 post-switch, with a corresponding cumulative increase in doses from 43.5 (IQR=35.1) versus 50.0 (IQR=72.7) IU/kg, respectively. However, the overall annualised infusion rate (15.3 vs 7.2; median 3.6 vs 0.6) and dose reduced (602.4 IU/kg vs 209.0 IU/kg; median 75.5 IU/kg vs 19.1 IU/kg, respectively) post-switch. At the individual bleed level, the amount of FVIII used per bleeding episode was comparable between FVIII prophylaxis period and HAVEN 3 exposure periods.

Patient and clinician preferences regarding Hemlibra®

During the 2019 ASH congress, results were presented on a survey regarding the knowledge and opinion of haemophilia A patients with regard to **Hemlibra®.** One hundred and twenty-six respondents took the survey. Regardless of inhibitor status, patients with higher ABR and worse compliance with prophylaxis are more likely to use Hemlibra®. From the non-inhibitor patient perspective, ease of administration with dosing ≤1 time per week was at least as important as effectiveness and safety of the drug in their decision to switch, whereas this was much less important to inhibitor patients. Patients choosing not to switch were concerned about safety, unknowns with a new treatment, and lack of lab monitoring. Although 1/3 of patients felt they lacked the information to decide whether to use it.

In another survey presented at ASH, 79 US clinicians were asked about the use of Hemlibra® in previously untreated patients (PUPs) since there is limited real-world data available. Forty-nine per cent were either unsure or stated that they wouldn't prescribe Hemlibra® to a 2-month-old PUP. Those providers, however, would become more likely to prescribe if the PUP had gone through 50 exposure days without inhibitor development. Overall, there is still significant debate and there is no standardised or defined approach for the use of Hemlibra® in PUPs. Patient preferences and individual bleeding risk were top reasons for which switching was considered. This pattern reflects the current trend of individualization of treatment.

At the EAHAD congress, a poster (P205) showed the results of an online survey of 50 US clinicians to understand disease management and treatment, including immune tolerance induction and surgery management in patients treated with Hemlibra®. Clinicians reported less frequent testing for FVIII activity (52%) and inhibitors (28%). Thirty-four per cent reported changed guidance on breakthrough bleed treatment and 42% advised Hemlibra® users to keep 3-4 doses of bypassing agent/FVIII at hand for treatment of breakthrough bleeds. Most clinicians reported that physical activity levels remained the same or increased. Over half of haematologists reported treating patients on Hemlibra® with ITI or considering it in the future and amongst those treating with ITI, 73% reported treating with a lower dose of FVIII or shortening ITI duration (n=5/11). *Authors of this abstract are representatives of the pharmaceutical industry including Genentech.*

Clinical Trials

Pre-clinical development of novel bispecific antibodies

In an abstract from the 2019 ASH congress, Novo Nordisk presented the development and pre-clinical characterisation of **Mim8**, a new FVIII mimetic human bispecific antibody. Later at the EAHAD congress (P028), dose/response studies indicated Mim8 potency relative to Hemlibra® was significantly elevated by 9- to 14-fold in cynomolgus monkeys and in mice with human components. Mim8 was also

efficacious in the tail clip model and in the cynomolgus tail bleeding model. Mim8 is in development for subcutaneous treatment of people with haemophilia A with and without inhibitors. A phase II clinical trial was started in January 2020 for further development.

Pre-clinical data for KY1049

In a poster presented at the 2019 ASH congress, preclinical data were presented on **KY1049**, a FVIII mimetic bispecific antibody. KY1049 was tested in mice.

Re-balancing Agents

Management of breakthrough bleeds with fitusiran

In an abstract at the 2019 ASH congress, results from phase I and II clinical trials on the management of breakthrough bleeds in patients on **fitusiran** were presented. This therapy is a once-monthly subcutaneously administered investigational small interference RNA (siRNA) therapeutic targeting antithrombin. During the trial, bleed management guidelines supporting the use of lower dose and reduced-frequency factor or bypassing agent (BPA) were developed and implemented to manage breakthrough bleeds in patients participating in clinical trials of fitusiran. Since implementation of these guidelines, all treated bleeding events in patients with HA or HB with or without inhibitors were successfully managed with factor or by-passing agents, and most have been managed using reduced and less frequent dosing of factor or by-passing agents in compliance with the guidelines.

Concizumab trials have been suspended

In an abstract presented at the 2019 ASH congress, results from the phase II *explorer 5 trial* were reported. In this trial, once-daily subcutaneous infusion of **concizumab** was used in 36 patients with severe haemophilia A without inhibitors. The estimated ABR at the last dose level was 7.0, the median ABR was 4.5 and the estimated ABR for spontaneous bleeds was 2.5. Concizumab concentration varied considerably between patients on the same dose level. No deaths, thromboembolic events or AEs related withdrawals occurred in this trial. Three patients had anti-drug antibody positive (low titres) tests with one being neutralizing in vitro in a single but not subsequent test, and with no apparent clinical effect.

Subsequently in March 2020, Novo Nordisk indicated that it had paused **concizumab** treatment in *explorer 5,7 and 8* clinical trials. This means that the trials have temporarily stopped recruitment and dosing around the world. This decision was based on three patients experiencing non-fatal thrombotic events in phase III studies. These side effects were not observed in the phase II trials and hence phase III trials could commence. The company is currently reviewing the data and is in discussions with regulators.

Laboratory Monitoring

Monitoring factor VIII (FVIII) activity has traditionally been complicated by different types of assays and reagents. The advent of novel non-factor therapies (bi-specific antibodies, anti-thrombin RNAi, and anti-tissue factor pathway inhibitor antibodies) in haemophilia poses a new level of difficulty on the laboratory monitoring of patients. A recent publication by Lenting, which was also presented at EAHAD, highlights the importance of using the correct assays and also the proper interpretation of their results. It is pertinent to understand the mode of action of these non-replacement agents. The findings in animal models, which are not always directly relatable, indicate that **Hemlibra®** provides a FVIII comparison of ~10% to 20%. Unfortunately, FVIII calibrators are lacking in reports assessing

fitusiran and **concizumab**. However, based on their capacity to fully correct the bleeding in these models, it seems fair to assume that their FVIII comparison is ≥20% FVIII.

Data were presented at EAHAD on the real-world laboratory monitoring of use of Hemlibra® in Israel. In total 50 patients with haemophilia A, median age 11 years (1 month-76 years) including 31 children and 19 adults of whom 22 had FVIII inhibitors were enrolled. Patients were clinically followed for 8 months (2-21 months). Overall, aPTT values normalized at week 2 with significant shortening at week 5. Endogenous thrombin potential peak height increased after 5 weeks although thrombin generation did not reach levels observed in normal controls. No differences were found between adults and children or between inhibitor and non-inhibitor patients after the loading period. Lower thrombin generation was observed in very young infants, thus interpretation of laboratory results needs caution. These data were also presented during the 2019 ASH congress on prospective laboratory monitoring.

An update on cellular therapy for bleeding disorders

During the 2019 ASH congress, Sigilon Therapeutics presented pre-clinical data on **SIG-001**. As a reminder, this is a product consisting of two-compartment spheres encapsulating human FVIII-expressing human cells. These spheres were placed in the abdomens of wild-type mice and stable FVIII production and good cell viability was shown for spheres retrieved after long-term placement in immunocompromised mice (up to 6 months). Furthermore, data showed FVIII activity and the correction of the bleeding phenotype in immunocompetent haemophilia A mice. In March 2020, the company announced it had secured funding to start a clinical trial in 2020.

Gene Therapy

Three-year follow-up of gene therapy in patients with haemophilia A

In January 2020, the three-year follow-up results of the 'Gene Therapy Study in Patients with Severe Haemophilia A' were published in an article in the *New England Journal of Medicine.* This trial (**BMN 270-201,** Valoctocogene roxaparvovec) used AAV5-hFVIII-SQ vector. The results reported in the article are as follows:

- One participant received a dose of $6x10^{12}$ vg/kg
- One participant received a dose of $2x10^{13}$ vg/kg
    - Both of these participants had factor VIII expression of less than 1 IU/dL.

- Seven participants who received $6x10^{13}$ vg/kg had a median FVIII expression of 20 IU/dL (range 4-100 IU/dl), as measured via the chromogenic assay. Factor VIII levels sustained over 3-year period were sufficient to achieve haemostatic efficacy. The annualised treated bleeding events rate was zero and the median use of factor VIII was reduced from 138.5 infusions per year to 0. Bleeding in all target joints resolved.

- Six participants who had received $4x10^{13}$ vg/kg had a median factor VIII expression of 13 IU/dL, as measured by chromogenic assay. The median ABR was 0 and the median use of factor VIII was reduced from 155.5 infusions to 0.5 infusions per year. Bleeding in target joints resolved in 5 of 6 participants.

No inhibitor development, thromboses, deaths, or persistent changes in liver-function tests were observed. In conclusion, gene therapy within participants with haemophilia A resulted in sustained clinically relevant improvement.

As a reminder, BioMarin decided to only continue its *GENEr8-1* phase III study evaluating the $6x10^{13}$ vg/kg dose of valoctocogene roxaparvovec, and has stopped further recruitment into the GENEr8-2 study of the lower $4x10^{13}$ vg/kg dose. One-hundred and thirty-four patients have received the one-time dose for the GENEr8-1 trial.

BioMarin submitted a Marketing Authorisation Application (MAA) for valoctocogene roxaparvovec to the European Medicines Agency (EMA) on 21 November 2019. On 23 December 2019, the EMA announced that the EMA had validated the MAA and that the review will begin in January 2020 under an accelerated assessment.

On May 31, 2020 BioMarin announced a 4-year update for the $6x10^{13}$vg/kg and 3-year update for the $4x10^{13}$ vg/kg cohorts. All patients in both cohorts remain off prophylactic factor VIII treatment. The mean ABR remains less than 1 in both cohorts and below pre-treatment baseline levels. The mean ABR in year 4 for the $6x10^{13}$vg/kg cohort was 1.3, and the mean ABR in year 3 for the $4x10^{13}$ vg/kg cohort was 0.5. Factor VIII activity levels declined in proportion with the most recent years' observations and remain in a range to provide efficacy. No patients developed inhibitors and there have been no thrombotic events. The most common adverse events occurred early and mild to moderate rise in the levels of certain proteins and enzymes measured in liver function tests do not appear to have long-lasting clinical effects. Further detailed information will be presented in a late-breaking abstract to the World Federation of Hemophilia (WFH) Virtual Summit to be held June 14-19, 2020.

The Food and Drug Administration (FDA) is reviewing the biologics license application with an action date of August 2020 under the Breakthrough Therapy designation. The European Medicines Agency (EMA) validated the company's Marketing Authorization Application (MAA) using the PRIME designation so far but there is a possibility that the MAA will revert to the standard review procedure, as is the case with most filings that initially receive accelerated assessment. Combining this with and combined with COVID-19 delays, an opinion is expected in late 2020/early 2021.

Data on Bayer's AAVhu37FVIII gene therapy

During the last ASH congress data were presented on **BAY-2599023** (AAVhu37FVIII), based on the AAV serotype hu37, which contains DNA encoding a B-domain deleted FVIII. This is the first clinical-stage AAV gene therapy vector based on the AAV serotype hu37. The data from the phase I/II dose finding trial was presented showing safety and FVIII activity following a single intravenous infusion, at the starting dose of 0.5×10^{13} GC/kg in 2 patients. Following the infusion, evidence of FVIII expression was observed in both patients with stable values of ~5% and ~17%. The first patient has successfully halted prophylaxis for 6 weeks, while the second one treated on-demand prior to the infusion had been bleed-free for 5.5 months to date of the presentation.

During the last EAHAD congress data (P190) were presented on BAY-2599023 (AAVhu37FVIII), based on the AAV serotype hu37, which contains DNA encoding a B-domain deleted FVIII. This is the first clinical-stage AAV gene therapy vector based on the AAV serotype hu37. The data from the phase I/II dose finding trial was presented showing safety and FVIII activity following a single intravenous infusion. Following 52 weeks of safety observation of the first cohort (0.5×10^{13} GC/kg), no SAEs, study-drug-related AEs or S/AESIs were reported. Clear evidence of FVIII expression was observed. Since June 2019, 2 patients were enrolled into the second cohort, with a dose of 1.0×10^{13} GC/kg. Both patients are expressing FVIII (~8–40%) and are currently off prophylaxis. Besides inter-patient variability a dose response could be shown. Following 12-weeks safety review of Cohort 2 data, escalation to 2.0×10^{13} GC/kg (cohort 3) was recommended. Currently, two patients have been treated with this dose with a favourable safety profile.

Update on the results of the ALTA study

During the 2019 ASH congress, Pfizer presented results on the *ALTA study* phase I/II, a dose-ranging single-dose study of **SB-525** gene therapy using rAAV6 vector. In the last newsletter we reported on the results of the single injection in ten patients. Patients were split amongst 4 cohorts and since our last reports an additional patient was included in cohort 4 (3e13 vg/kg):

- 9e11 vg/kg (2 patients);
- 2e12 vg/kg (2 patients);
- 1e13 vg/kg (2 patients); and
- 3e13 vg/kg (**5 patients**).

Dosing in the fourth cohort is ongoing and additional analyses of the trial data including FVIII levels, bleeding rate and factor usage will be presented as available. Four to 11 months follow-up data on all patients in the fourth cohort will also be presented.

In December, Sangamo Therapeutics announced the completion of the transfer to Pfizer of the SB-525 haemophilia A gene therapy investigational new drug application. Recruitment is ongoing for the phase III six-month lead-in study to evaluate prospective efficacy and safety data of current FVIII prophylaxis replacement therapy in adult haemophilia A patients (FIX:C≤1%), prior to the phase III gene therapy study.

Preclinical studies for AMT-180

In preclinical studies, presented in a poster at the 2019 ASH congress, UniQure is developing an AAV5-mediated gene therapy (**AMT-180**) for haemophilia A using a FIX variant (named FIX-FIAV) that is independent from FVIII, with the aim of the FIX being able to work unaided by FVIII. FIX-FIAV has demonstrated mimicking 30% activity of FVIII and AMT-180 has shown promise in preclinical studies with animal models of haemophilia A.

Pre-clinical studies of BDD-FVIII-X5

In a poster presented at the 2019 ASH congress, data were presented on pre-clinical studies of a B-domain deleted **(BDD)-FVIII-X5** variant delivered by AAV8 vector. Authors believe that this type of FVIII could overcome the secretion challenges of high level FVIII expression that are currently faced by other gene therapies targeting the liver. In other gene therapies under development, very high doses of vectors are needed to achieve therapeutic factor levels. In pre-clinical studies, this fully active BDD-FVIII-X5 demonstrated improved secretion in vitro and in vivo, resulting in higher FVIII levels in a haemophilia A mouse model, which may potentially reduce the overall vector dose required to deliver the therapy. No signs of enhanced immunogenicity were noted in a comparative immunogenicity study. Further exploration of BDD-FVIII-X5 variant is continuing.

Green light for phase I gene therapy with ET3

On 27 May, the US FDA has approved Expression Therapeutics' request to open a phase I trial of **ET3,** an investigational gene therapy for people with haemophilia A. Patient enrolment in the phase 1, called *ET3-201*, is expected to start soon at Emory University. ET3 is an investigational gene therapy that uses genetically modified blood cell progenitors, called hematopoietic stem cells, derived from patients' white blood cells. Investigators use a recombinant lentiviral vector to force blood cell progenitors to produce an altered version of factor VIII. The modified cells are then returned to patients, so that they may generate new blood cells able to produce a functional form of FVIII. During the ET3-201 trial, patients will first be treated at low-dose agents that suppress stem and immune cells, followed by a single intravenous infusion of ET3. In addition, Expression Therapeutics, a US-based company, is developing gene therapies for haemophilia B.

Understanding the prevalence of pre-existing immunity against commonly used vectors

There are a number of trials that are currently looking at the prevalence of pre-existing immunity against commonly used AAV2, AAV5 and AAV8 capsid in adult patients with haemophilia. This will help in identifying those eligible for gene therapy and how cross-reactive antibodies may impact treatment and outcomes. Takeda's co-prevalence study in haemophilia presented data at ASH 2019, showing 50% of patients with haemophilia have neutralizing antibodies to AAV2, AAV5 or AAV8 capsid with 40% demonstrating co-prevalence to all three evaluated serotypes (see table below). As a result, these patients are not likely to respond to gene therapies based on AAV vectors.

Table 1. Prevalence/co-prevalence of neutralizing antibodies (NAbs) and binding antibodies to (BAbs)

Prevalence/co-prevalence	NAbs (%)	BAbs (%)
AAV2	54.4	30.9
AAV5	54.4	20.3
AAV8	49.4	30.1
AAV2 & AAV8	41.8	25.8
AAV5 & AAV8	43.9	16.5
AAV2 & AAV5	40.9	17.8
AAV2, AAV5 & AAV8	39.7	16.1

During the 2020 EAHAD congress, additional results were presented from the same study for 5 European countries (Austria, France, Germany, Italy and Spain) (P149). Of 168 patients, 135 had haemophilia A and 33 had haemophilia B. Overall, 55.4, 51.2 and 51.8% had pre-existent neutralizing antibodies to AAV2, AAV5 or AAV8 respectively. Co-prevalence of responses to all 3 serotypes was 41.6% and 17.8% had binding antibodies. *This abstract was written by a representative of Baxalta, a Takeda company.*

UniQure also has conducted a study on pre-existing immunity, the results of which were presented at the EAHAD congress (P054). In total, 300 healthy human donors were sampled for their antibodies to AAV1, AAV2, AAV5 and AAV8. The highest prevalence of AAV antibodies was against AAV1 and AAV2. This also showed that 50% of the cohort had antibodies to AAV5 and 50% had antibodies to AAV8, both vectors that are used in haemophilia gene therapy trials.

Dealing with pre-existing AAV immunity

The studies above indicate potential hurdles for gene therapy to provide treatment options for those with pre-existing immunity. One interesting poster presented at ASH in 2019 presented pre-clinical data on one investigational approach to overcoming pre-existing AAV immunity. In the study, an AAV8-specific immune adsorption column (IAC) was used to remove anti-AAV8 antibodies from the plasma. In other studies, pre-existing anti-AAV5 neutralizing antibodies measured in vitro do not interfere with the AAV5-based in vivo transduction as much as pre-existing antibodies against other serotypes do.

Follow-up analysis of gene therapy in dogs with haemophilia A

In a presentation at ASH 2020, authors report on the long-term (10 years) follow-up of haemophilic A dogs that received gene therapy. This particular report looks at the integration of the vector in the dogs' DNA. In fact, while recombinant AAV primarily remains in the episome, meaning that it generally does not integrate into the host DNA, integration events in mouse models and liver cancer have been observed. In these dogs, however, while AAV integration and clonal expansion were observed, the dogs had no evidence of tumorigenesis or any other AE. Meanwhile FVIII expression remained sustained for 10 years or increased but it remains unclear if that was due to the clonal expansion.

AN UPDATE ON NOVEL TREATMENTS IN HAEMOPHILIA B

Highlights of this section

In this section we cover replacement and gene therapy. For an update on non-replacement therapies, please refer to the haemophilia A section. We also have some reports from real-world experience with EHL FIX.

There is also an update on the clinical trial reports on DalcA, a subcutaneous recombinant FIX variant developed by Catalyst Biosciences. Interestingly, that FIX variant is also being considered as a molecule for gene therapy approach. Delivering it as a gene therapy could mean a lower viral load but with similar levels of factor IX activities than gene therapies using the wild-type FIX gene. The approach of using a molecule with a higher activity has also been tried with the Padua FIX variant and the DalcA has an even higher activity. However, gene therapy developments are still in the pre-clinical phase.

Continuing on gene therapy, UniQure announced that it achieved its targeted dosing for the HOPE-B trial using etranacogene dezaparvovec (AMT-061). This is a gene therapy that uses a Padua variant of FIX, which has also a greater activity of FIX. In addition, we have a 1-year follow-up data for fidanacogene elaparvovec, a gene therapy developed by Pfizer. Finally, Takeda presents its pre-clinical data for TAK-748.

As a reminder, the abstracts of the EAHAD congress can be accessed online here

Replacement therapies

Reports from clinical trials and real-world experience

Efficacy and outcome of Alprolix® in haemophilia B in the UK

During the 2020 EAHAD congress, data (P074) were presented on a within-patient comparison of SHL and **Alprolix®** after 2 years of follow-up in the UK. Patients were non-randomly switched to Alprolix® between 2016 and 2019. The study looked at infusion frequency, clotting factor consumption, ABR and annualised joint bleed rate (AJBR) before and after the switch was conducted. Forty-four patients were included, median age was 25 (11;47) years with 59 (46;73) weeks pre and 95 (80;103) weeks post switch follow-up. The weekly median infusion rate for the whole group pre-switch was two and post-switch was one with a 47% within-patient reduction. The median clotting factor consumption was 61 IU/kg/week pre-switch and 43 IU/kg/week post switch with a median reduction of consumption of 38%. The median ABR fell from 3.2 pre-switch to 1.8 post-switch. For patients with a pre-switch ABR of > 10 (n=6), a greater decrease in ABR was observed. There was a modest but statistically significant reduction in AJBR (from median 0.9 to 0.7). Overall the data shows a reduction in infusion rate and treatment consumption with maintained bleed protection. There was also a moderate reduction in ABR and AJBR in patients switching to Alprolix® and the suggestion that those with higher bleeding rates may benefit the most, although the numbers of frequent bleeders were limited.

Real-world data on the use of Idelvion® in three European countries

During the 2020 EAHAD congress data (P160) was presented on a study of patients switching to **Idelvion®** in Italy, Belgium and the United Kingdom. In total 84 patient records were examined. The majority of patients in all 3 countries had severe haemophilia and were on prophylactic regimens (Italy, 44/49; Belgium 7/10; UK 22/25) with prior FIX therapy. All patients were switched to prophylaxis with Idelvion®. The mean ABR reduced between 67.7% and 94.0%. The proportion of patients with zero spontaneous bleeds was higher than in prior FIX. The majority of patients had a reduction in dosing

frequency after switching and this was associated with a reduction in mean weekly FIX consumption of 54-71% compared to prior FIX prophylaxis.

Efficacy of EHL-FIX to prevent breakthrough bleeds

There have been previous reports of issues with spontaneous bleeding and poorly controlled bleeding events in patients with haemophilia B receiving extended half-life products. In a survey presented at the 2019 ASH congress, 90 patients with haemophilia B from haemophilia centres across the US and Canada were surveyed. Sixty-seven utilized EHL, including 26 using **Idelvion®**, 37 **Alprolix®** and 4 **Refixia®/Rebinyn®**. All patients had severe haemophilia B except for one smaller centre also contributing data regarding moderate patients on prophylaxis. All centres reported having patients with unexpected spontaneous/minimally traumatic bleeding with factor levels >10% and poorly controlled bleeding which did not seem to be dependent on age (median age 14.5 years, range 1.4-44). This occurred in 18 patients on prophylaxis, including 16 of 26 (62%) patients using Idelvion®, and 2 of 4 (50%) of patients using Refixia®/Rebinyn®. None of these events were observed with patients on Alprolix® prophylaxis.

Although plasma FIX activity levels have driven prophylaxis and bleed management decisions, clinical experience suggests novel properties of EHL-FIX may potentially have some impact on haemostasis. Although achieving seemingly adequate FIX plasma troughs (>10%), limited clinical experience suggests patients may have a differential response to EHL-FIX. Successful bleed prevention or control may be predicted by the distribution of FIX in circulation and extravascular space, and the presence of FIX in tissues at time of injury. The data demonstrate the importance of real-world monitoring of efficacy of novel FIX products and suggest the need for more robust mechanisms to understand the haemostatic performance of products and the potential importance of extravascular distribution of FIX.

Results from the CHESS US study for patients with haemophilia B

During the 2019 ASH congress, a poster presented the results from the 'Cost of Hemophilia Across the USA: a Socioeconomic Survey' (CHESS US). This retrospective cross-sectional dataset of adults with severe haemophilia in the US gathered information on patient cost via patient record form. The study looked at data on the following parameters: FIX consumption, ABR, the presence of chronically damaged joints, as well as costs associated with factor consumption and hospitalisation.

Of 576 patients profiled by the study, 132 had severe haemophilia B. The results showed substantial costs and resource utilisation for patients on prophylaxis with severe haemophilia B and although ABR was low, bleed-related hospitalisation comprised a significant non-drug cost to the healthcare system and a proportion of patients still experienced joint arthropathy. This led the authors to conclude that such substantial clinical and economic burden highlights that unmet need remains for patients with severe haemophilia B on prophylaxis in the US.

Interim results of DLZ-201 trial

During an oral presentation at the 2020 EAHAD congress, interim data from the DLZ-201 trial was reported. This trial was set-up to assess the safety, FIX activity levels and immunogenicity of daily subcutaneous infusions of **Dalcinonacog alfa (DalcA),** a recombinant FIX variant. The patients (n=6) enrolled received an IV dose of DalcA of 50 IU/kg and 35 minutes later the first of 28 daily SQ doses of 100 IU/kg. Factor IX activity, anti-drug antibodies and safety assessment were performed weekly throughout the study and at follow-up 30 days after the last treatment. FIX activity levels were measured daily during the washout period from day 29 to 33 to assess DalcA terminal half-life. All participant activities have been completed. To date FIX activity levels were between 16 and 27% at Day 29. One subject withdrew after 6 days due to injection site redness and swelling. DalcA half-life ranged from 84 to 112 hours. Final results will be presented at the WFH virtual meeting.

Gene Therapy

Reports from clinical trials

UniQure's HOPE-B trial update

During the 2019 ASH congress, UniQure presented an abstract on its 1-year data from phase IIb of the tranacogene dezaparvovec **(AMT-061)** trial. All participants (n=3) sustained normal range of FIX (between 30.1 and 54.1 % of FIX activity measured with one stage aPTT) at 36 weeks after treatment, which was well-tolerated and did not require any immunosuppression. The pivotal phase III *HOPE-B trial* of (AMT-061), follows this phase IIb trial and in March 2020, UniQure announced that it had achieved full enrolment in the study. The targeted number of patients to be dosed per clinical trial protocol was 50. In total, 54 patients have received the one-time dose of AMT-061. UniQure is hoping to submit for FDA Biologics License Application (BLA) in 2021.

Additionally, in the original ongoing phase I/II trial of **AMT-060**[2], UniQure's initial generation gene therapy treatment for haemophilia B, all 10 patients continued to show sustained and stable increases in FIX activity (mean FIX activity was 5.1 IU/dl in cohort 1 and 7.5 IU/dl in cohort 2), improved disease phenotype and substantial reduction in spontaneous bleeds at up to 4 years of observation.

Update on Pfizer's fidanacogene elaparvovec (SPK-9001) initiated by Spark

During the 2019 ASH congress data on **fidanacogene elaparvovec** were presented on the ≥ 1 year of follow-up (phase I/IIa dosing study) of 15 patients with haemophilia B dosed (5 x 10^{11} vg/kg) with the therapy. The mean post-infusion steady state was 22.9% ±9.9% at one-year post vector infusion as measured in a central laboratory by one-stage assay utilizing Actin-FSL. Mean ABR during the first 52 weeks following infusion was 0.4±1.1 compared to 8.9±14.0 in the 52 weeks preceding infusion ($p<0.001$). Twelve out of 15 patients reported zero bleeds in the 52 weeks post-vector infusion. Five patients infused factor for a total of 20 infusions and 3 patients were treated with corticosteroids for elevations in hepatic transaminases. There were no other treatment-related AEs. During the 2020 EAHAD congress, health-related quality of life (HRQoL) data on fidanacogene elaparvovec were presented on the ≥ 1 year of follow-up (phase I/IIa dosing study) of 15 patients with haemophilia B dosed (5 x 1011 vg/kg) with the therapy.

Pre-clinical findings for CB 2679D-GT

In a poster (P030) presented at the 2020 EAHAD congress, Catalyst Biosciences announced testing **CB 2679D-GT**, which is a combination of AAV/DJ8 vector with DalcA (dalcinonacog alfa / CB 2679D) transgene to see whether it would significantly enhance expression of FIX activity and achieve superiority over the Padua variant in a preclinical proof of concept study in haemophilia B mice. Additional rodent and non-human primate studies are underway using a novel chimeric AAV-based vector.

Vector clearance in gene therapy for haemophilia B

In a poster during the 2020 ASH congress, data on clinical trials of **AMT-060** (NCT02396342) and **AMT-061** (NCT03489291) were presented examining the amount and duration of vector DNA in participants. Post-AMT-060 treatment, vector DNA was undetectable in all participants in the high dose group by 10 months and considered cleared by 16 months in all bodily fluids except blood. AMT-060 was cleared from the blood in all participants in the low dose group at 3 years and 80% of participants in the high dose group by 2.5 years. As expected, AMT-061 vector DNA was detectable at 36 weeks in blood and in the semen of 1 of 3 participants, although clearance had not yet been established in the remaining

[2] Also see https://ashpublications.org/blood/article/134/Supplement_1/2059/428128/Stable-FIX-Expression-and-Durable-Reductions-in

participants. The presence of vector DNA in bodily fluids assessed was not associated with any adverse safety or efficacy findings.

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

Highlights of this section

In this section we have reports from clinical trials as well as real-world experience on non-replacement therapies.

We saw some preclinical data on the use of MarzAA, a subcutaneous rFVIIa variant, to treat acute bleeds in people with inhibitors and we were given more information regarding the phase III clinical trial for this product. SevenFact ®, a recombinant FVIIa was approved in the US for the treatment of patients with inhibitors.

With regard to patients on Hemlibra®, recommended treatment for acute bleeding in patients with haemophilia A with inhibitors is rFVIIa. There are two interesting studies, one on low dose aPCC and another one in vitro on the use of FIX as alternatives in the potential lack of response to other options. Depending on the results of further clinical studies, these could potentially become alternatives for acute bleeds in inhibitor patients on Hemlibra®. It is important to keep in mind that there is no in vivo evidence to support the use of FIX. Furthermore, it is important to stress that currently the agreed clinical recommendation is to avoid aPCC (unless there is no alternative) in people using Hemlibra® because it can increase their risk of thrombosis. Therefore, the information presented below has to be viewed with caution.

Until recently there were 4 anti-tissue pathway inhibitor (TFPI) molecules in clinical trials. The clinical trial assessing BAY 109388 has stopped due to thrombotic events. We also report on the phase II trial data with regard to the use of concizumab, another anti-TFPI, in patients with inhibitors. The phase III trial of this product has now been paused, after 3 non-fatal thrombotic events.

As a reminder, the abstracts of the EAHAD congress can be accessed online here.

Bypassing agents

Treatment of acute bleeds in patients with haemophilia A and B with inhibitors using MarzAA

In a poster published at the 2019 ASH congress, authors looked at the use of subcutaneous **Marzeptacog alfa (activated) (MarzAA**) for treatment of acute bleeds in people with haemophilia A. To do so, authors used an animal model giving the treatment to mice with haemophilia A and then using a tail clip model to assess efficacy. The experiment showed that MarzAA was efficacious when administered subcutaneously both before and after injury and that this resulted in reduced bleeding in haemophilia A mice similar to non-haemophilia mice and similar to intravenous NovoSeven when dosed one minute after the tail clip. More information was provided at EAHAD 2020 (P128) regarding the phase I of the *MAA-102* study to further determine the pharmacokinetics, pharmacodynamics and safety of a single intravenous dose to treat acute bleeding in haemophilia. The study will enrol at least 8 patients with haemophilia with or without inhibitors to assess 7 dose levels of MarzAA. The investigators in these studies also presented an abstract during the ASH congress in which authors assessed in-vitro thrombin generation of MarzAA, when spiked into haemophilia A plasma containing Hemlibra® at clinically relevant concentrations. Results suggest that, based on these data, MarzAA and NovoSeven are expected to behave similarly when dosed to achieve equipotent plasma concentrations. Additionally, Catalyst Biosciences announced the design of the pivotal phase III *Crimson-1* study will enrol individuals who experience episodic bleeding. Crimson-1 will be an open-label global trial, evaluating the safety and efficacy of subcutaneous MarzAA in the treatment of approximately 230 bleeding episodes in approximately 75 patients, compared with their prior standard of care in a similar number of bleeding episodes. The study will assess the effectiveness of

subcutaneous MarzAA, using up to 3 doses to treat a bleeding episode. The primary endpoint will be the haemostatic efficacy using standard 4-point assessment scale.

Sevenfact approved by the US FDA

The US Food and Drug Administration (FDA) approved in April 2020 **Sevenfact®,** manufactured by the Laboratoire Français du Fractionnement et des Biotechnologies (LFB)**.** This is a recombinant coagulation factor VIIa recombinant, for the treatment and control of bleeding episodes occurring in adults and adolescents (>12 years) with haemophilia A or B with inhibitors. Sevenfact® contains an active ingredient expressed in genetically engineered rabbits, a first for haemophilia treatment.

The safety and efficacy of Sevenfact® were determined using data from a clinical study that evaluated 27 patients with haemophilia A or B with inhibitors, which included the treatment of 465 mild or moderate, and 3 severe bleeding episodes. The proportion of mild or moderate bleeding episodes treated successfully requiring no further treatment for the bleeding episode, no administration of blood products and no increase in pain beyond 12 hours from the initial dose, was approximately 86%. The study also included 3 severe bleeding episodes that were treated successfully with the higher dose. Sevenfact is contraindicated in patients with known allergy or hypersensitivity to rabbits or rabbit proteins.

Bispecific antibodies

Real-world data from the UK on the use of Hemlibra®

During the 2020 EAHAD congress (P075), data were reported on the first year of use of **Hemlibra®** in the UK. All UK non-trial patients with haemophilia A and inhibitors using Hemlibra® between 1/04/2018 and 30/06/2019 were identified. There were 62/202 patients with an active inhibitor (56 severe haemophilia A, 5 moderate and 1 mild) who switched to Hemlibra®. The median age of switchers was 32 (13;48) and non-switchers was 7 (3;18) years old. The median (IQR) historical peak inhibitor titre (BU) for switchers and non-switchers was 19.8 (4-48) and 6.5 (1.2-17.9). The median ABR and AJBR for switchers was 12.5 (3.7;17.2) and 5.8 (1.8;11.4), whilst for non-switchers was 0.8 (0;3.6) and 0 (0;0.9).

A comparison of 21 patients who had ≥ 6 months data, pre- and post- switch was also carried out. This showed a significant reduction in ABR from a median 14.3 to 0 and AJBR reduced from 7.4 to 0. One patient was bleed-free before switching compared with 86% (n=18) bleed free post-switching. One non-fatal adverse event was reported in a patient with established, symptomatic ischemic heart disease, who continued Hemlibra® without further episodes. One patient died from multi-organ failure unrelated to Hemlibra®. There were 5 localized skin reactions reported in 3 patients and there were no reports of loss of efficacy.

Management of breakthrough bleeds in inhibitor patients on Hemlibra®

Mild to moderate bleeding phenotypes are seen in patients on prophylaxis with **Hemlibra®**, thus treatment with factor concentrates will be required to control breakthrough bleeds. In those with inhibitors to haemophilia A, the therapeutic options have been rFVIIa or in the event of a low titre inhibitor FVIII concentrate in some situations. Early in the clinical trials for Hemlibra®, activated Prothrombin Complex Concentrates (aPCC) were contraindicated for the treatment of breakthrough bleeding as there were a number of thrombotic events and fatalities associated with the combination of the two therapies. The mechanism of interaction was that the FIXa present in the aPCC was enhancing the effect of Hemlibra® and accelerating thrombin generation. The recommendation was that, if aPCC was necessary, a low dose would be used not exceeding a defined amount (100 IU/Kg) in a 24-hour period.

In that context, the following 3 studies are interesting. Firstly, in a poster presented at the 2019 ASH congress on the use of aPCC, 3 patients with a history of inhibitors presented with 4 breakthrough bleeds, despite being given prophylaxis with Hemlibra®. Three of the bleeds were the result of trauma and 1 was spontaneous. One of the bleeds was treated with recombinant factor VIII; however, the remaining 3 bleeds were treated with a low dose (15IU/kg) of aPCC as a result of a lack of response to rFVIIa. No patient experienced thrombosis. This case study suggests that low dose aPCC or a continuous infusion of FVIII may be feasible options to treat acute bleeds in patients with inhibitors and on Hemlibra® prophylaxis. This was also investigated in another study at the same congress reporting even lower dose concentrations of aPCC equating doses of ~5 and ~10 IU/kg in order to reach normal thrombin levels.

Then at EAHAD 2020 (P017), investigators presented data on treating bleeds in patients with haemophilia A with inhibitors currently using Hemlibra® by raising levels of FIX. Five patients with inhibitors on prophylaxis with Hemlibra® and 20 healthy controls took part in the study. Therapeutic doses of rFVIIa, aPCC and rFIX were tested. In the results, increments of 25 IU/dL FIX had procoagulant effect similar to what would be obtained after 1 dose of 90 mcg/kg of rFVIIa. Regarding aPCC in ROTEM, increments of FIX levels up to 200 IU/dL were necessary to achieve procoagulant effect similar to a dose of 2.5 IU/kg of aPCC. Thrombin generation was normalized in all patients with increments of 25 IU/dL of FIX. It should be noted that these are in vitro studies and pre-clinical studies are necessary to test the in vivo clinical efficacy and thrombotic risk for concomitant use of FIX and Hemlibra®.

Summary of adverse events with Hemlibra®

During the 2020 EAHAD congress data (P131) was presented on thromboembolic (TE) or thrombotic microangiopathy (TMA) events in people taking **Hemlibra®.** Data on more than 5,200 people having received Hemlibra® between November 2017 and September 2019 were reviewed. Among those with congenital haemophilia A, there were 8 TE events in 7 people and 4 TMA events in 4 people. All but 1 TE event occurred in people with FVIII inhibitors. Overall 2/8 TE events were reported in people receiving concomitant aPCC; of the remaining 6 TEs, 4 were arterial events associated with cardiovascular risk factors, and 2 were venous events associated with venous thromboembolism risk factors. All TMA events were associated with concomitant aPCC use on average 100 IU/kg/24hrs for 24 hours or more. Among all events, all TEs and TMAs were reported as resolved/resolving; none was contemporaneous with fatalities beyond 1 due to rectal haemorrhage reported in the *HAVEN 1* trial. *This abstract was presented by representatives from Genentech and Hoffman La Roche.*

Pre-clinical development of novel bispecific antibodies

There are also 3 new bi-specific antibodies being tested, **Mim8, NXT007** and **KY1049**. Please see Haemophilia A non-replacement section for a short description or click the attached links.

Rebalancing Agents

Please also look at the Haemophilia A section for further information on these products.

Antithrombin

Anti-tissue factor pathway inhibitor antibodies (TFPI)

Concizumab

At ASH 2019, results of the *explorer 4* phase II trial were presented on **concizumab**. This trial tested the use of concizumab, an anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody in development for the subcutaneous treatment of haemophilia patients with inhibitors. Twenty-six

patients were randomized to concizumab (9 HAwI and 8 HBwI) prophylaxis or rFVIIa (7 HAwI and 2 HBwI) on-demand treatment. Twenty-five patients completed the main 24-week part of the trial. The estimated ABR at the last dose level for concizumab prophylaxis was 4.5 and for rFVIIa on demand 20.4. There was a 78%, 88% and 79% reduction in all treated bleeds, spontaneous and joint bleeds, respectively with concizumab prophylaxis compared to on-demand treatment. Concizumab concentration varied considerably between patients on the same dose level. No deaths, thromboembolic events or AEs-related withdrawals occurred. No safety concerns with concomitant use of concizumab and rFVIIa were identified. Three patients had positive (very-low to medium-titer) anti-drug antibody tests but with no apparent clinical effect. Elevated D-dimers were observed across all concizumab dose levels. In addition improvements on quality of life for patients was demonstrated using the SF-36 tool in other reports from this study.

Data was also presented at the ASH congress, on the investigation of the in vitro effect of rFVIIa and aPCC on haemophilia A plasma containing concizumab. This was done to investigate treatment for breakthrough bleeds in haemophilia A inhibitor patients while on concizumab prophylaxis. Addition of rFVIIa or aPCC to haemophilia A plasma with or without inhibitors increased peak thrombin generation both in the absence and presence of concizumab. The effect of concizumab and rFVIIa or aPCC was mainly additive.

A poster at the 2020 EAHAD congress (P196) described a meta-analysis of the phase II clinical data evaluating pharmacokinetics dosing regimen of a loading dose of 1 mg/kg followed by a daily prophylactic dose of 0.25 mg/kg in phase III of *explorer 7* and *explorer 8*.

Subsequently in March 2020, Novo Nordisk indicated that it had paused concizumab treatment in *explorer 5,7 and 8* clinical trials. This means that the trial has temporarily stopped recruitment and dosing around the world. This decision was based on 3 patients experiencing non-fatal thrombotic events in phase III studies. These side effects were not observed in the phase II trials and hence phase III trials could commence. The company are currently reviewing the data and in discussions with regulators.

Clinical studies with BAY 1093884 stopped due to thrombotic events

In another study **BAY 1093884**, another anti-TFPI for non-replacement prophylaxis treatment for patients with haemophilia A or B with or without inhibitors, was also stopped. A phase II study was initiated in July 2018 with a multiple dose, dose-escalating study designed to evaluate the safety of BAY 1093884 in patients with haemophilia A or B with or without inhibitors in 3 dose cohorts (100, 225 and 400 mg). Unfortunately, the study was stopped prematurely after 3 serious adverse thrombotic events (2 at 225 mg dose and 1 at 400 mg dose) - all study-drug related. All occurred in the absence of concomitant use of replacement factors or bypassing agents. An initial evaluation of the pharmacokinetic/pharmacodynamic (PK/PD) data showed that none of the patients who experienced thrombosis had higher levels of BAY 1093884 following subcutaneous administration, or a stronger degree of TFPI inhibition, than patients who did not experience thrombotic events. This absence of specific laboratory findings or any differentiating characteristics in those patients raises concerns about the predictability of thrombosis during the treatment with BAY 1093884. These findings were reported in a poster (P099) during the 2020 EAHAD congress.

Highlights of this section

In this section we see a few reports from clinical trials, in particular a randomised clinical trial to compare the use of tranexamic acid and rVWF for the management of heavy menstrual bleeding in women with type 1 VWD. We also see two studies looking at the efficacy of two different FVIII/VWF products for people with VWD.

In addition, we present you with a few real-world experiences in relation to delivery, management of menorrhagia, the economic burden of VWD and a report on Spanish patients using FVIII/VWF treatment.

As a reminder, the abstracts of the EAHAD congress can be accessed online here.

Results from clinical trials

Randomised trial for the management of heavy menstrual bleeding in VWD

The National Heart, Lung and Blood Institute in the US has funded *a phase III trial* to compare the use of **tranexamic acid** and **recombinant von Willebrand factor** for the management of heavy menstrual bleeding in women with mild to moderate type 1 VWD. This is a randomised, crossover trial that will include a total of 442 potential participants across 19 haemophilia treatment centres.

Natural history study on VWD type 3

The American Thrombosis and Hemostasis Network (ATHN) together with Takeda have initiated a natural history study to assess the safety of various von Willebrand factor (VWF) regimens for different indications (on-demand, surgery and prophylaxis) in adult and paediatric patients with clinically severe congenital VWD. The study aims to enrol 130 patients. The study was described in a poster presented during the 2019 ASH congress.

Results of the Opale study

During the 2020 EAHAD congress, data (poster P220) were reported on the *OPALE study*, which aims to describe the haemostatic efficacy and tolerance of hFVIII/VWF concentrate (**Voncento®**) in patients with VWD on prophylaxis. This is a French national prospective multicentric observational study. Ninety patients (60% female; mean age 39.3 (range 3-86)) were included in the study between May 2016 and May 2019. The distribution of VWD type was type 1 (n=24), type 2 (n=51) and type 3 (n=15). Twelve patients received Voncento in prophylaxis. The clinical efficacy of prophylactic treatment with Voncento® was evaluated by the investigators as either excellent or good for 10 out of 12 patients. No thrombosis episodes were observed. *Authors of this abstract include representatives from CSL Behring.*

Results from real-world experiences

Economic burden of surgeries in patients with VWD

During the 2019 ASH congress, a poster was presented on a large retrospective study that analysed health economic burden data from a US healthcare database looking at 2972 patients with and 2972 patients without VWD that had 1 or more major surgeries in 2018. This analysis showed that patients with VWD were significantly more likely to have inpatient, outpatient or emergency room admissions than patients without VWD. They also had significantly higher total health care costs than patients without VWD (USD 50,733.89 vs USD 30,154.84).

Management of delivery in VWD

In a poster (P215) presented at the 2020 EAHAD congress, authors report on the management of 2 c-sections in women with type 2 VWD with plasma-derived VWF or rVWF. Authors found that lower doses and better in-vitro recovery were observed with rVWF, suggesting that because of an improved multimeric profile, rVWF may be useful in type 2 VWD bleeding management. However, authors caution that further studies are needed to confirm these results.

Efficacy of rVWF for managing menorrhagia

During the 2020 EAHAD congress, a post-hoc analysis (poster P218 – NCT01410227) aimed to determine the efficacy and safety of on-demand treatment of bleeding episodes with recombinant von Willebrand factor (rVWF**; VEYVONDI®)** in patients with severe VWD and menorrhagia. Six patients with VWD (type 2A: n=1, type 3: n=5; median age 29 years) had 45 menorrhagia bleeds (3 to 15 bleeds per patient) treated only with rVWF. Menorrhagia episodes were rated either as minor (n=27), moderate (n=17) or severe (n=1). Median rVWF dose was 50.6 IU/kg with one (1-4) infusion per bleeding episode. The median time to resolution was 24.3 hours. Haemostatic efficacy was rated subjectively within 8 hours after first infusion by patients as excellent in 39 out of 43 bleeding episodes and as good in 3 out of 43 bleeding episodes. Concomitant treatments for menorrhagia included iron replacement therapy (n=6), oral contraceptive (n=3) and tranexamic acid (n=3). *Authors of this abstract include representatives of Baxalta, a Takeda company.*

AN UPDATE ON NOVEL TREATMENTS FOR PEOPLE WITH RARE BLEEDING DISORDERS

During the 2019 ASH congress, a poster was presented with the results of an analysis of clinical trials and registry databases utilizing recombinant factor FVIIa for the treatment of bleeding episodes and surgeries in women with Glanzmann Thrombasthenia or congenital factor VII deficiency. This report looks at the outcomes and safety of the use of rFVIIa in these women. The study includes 118 females with Glanzmann Thrombasthenia and 10 female patients with FVII deficiency. Authors concluded that without therapy patients with rare bleeding disorders may have high rates of bleeding and considerable risk of morbidity and mortality.

OTHER NEWS

Development of diagnostic tool to monitor coagulation status at home

Takeda and Enzyre have announced a collaboration to develop a diagnostic tool that will enable patients with haemophilia to track their coagulation status at home. The idea is that the data collected at home would be immediately transferred to the patient's treating physicians via an app and that this would further facilitate personalized care.

REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Replacement VWF recombinant	**VWD**	Veyvondi / Vonvendi	rFVIII (vonicog alfa)	Takeda	**Licensed**
Replacement VWF plasma-derived	**VWD Haemophilia A**	Voncento	human coagulation factor VIII / human von willebrand factor	CSL Behring	
Replacement FVIII	**Haemophilia A**	Adynovi / Adynovate / BAX855 / TAK-660 / SHP-660	PEGylated recombinant factor VIII (rurioctocog alfa pegol)	Takeda	**Licensed**
		Afstyla / CSL627	rVIII-Single Chain	CSL Behring	
		Elocta / Eloctate	rFVIIIFc (efmoroctocog alfa)	Sobi	
		Esperoct / N8-GP / NNC 0129-0000-1003	rFVIII (turoctocog alfa pegol)	Novo Nordisk	
		Jivi / BAY 94-9027	rFVIII (Damoctocog alfa pegol)	Bayer	
		Kovaltry / BAY 81-8937	unmodified full-length rFVIII (octocog alfa)	Bayer	
		Nuwiq	human-cell-line-recombinant-human-FVIII (simoctocog alfa / human-cl-rhFVIII)	Octapharma	

		BIVV001	rFVIIIFc-VWFD'D3-XTEN	Sanofi and Sobi co-development	**Phase 3**
Replacement FIX	**Haemophilia B**	Alprolix	rFIXFc (eftrenonacog alfa)	Sobi	**Licensed**
		Idelvion	rFIX-FP / recombinant factor IX albumin fusion protein	CSL Behring	
		Refixia / Rebinyn	recombinant FIX glycopegylated / rFIX-GP (nonacog beta pegol)	Novo Nordisk	
		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 with inhibitors**	Sevenfact	Recombinant FVIIa- jncw	LFB	**Licensed in the US**
	Haemophilia A or B with or without inhibitors	Marzeptacog alfa (activated) MarzAA	Subcutaneous coagulation rFVIIa variant	Catalyst Bioscience	**Phase 3**

NON-REPLACEMENT THERAPIES					
Type of product	**Indication / treatment of**	**Product name(s)**	**Mechanism of action**	**Developer / manufacturer**	**Development stage**
Non-replacement therapy **Bispecific antibody**	**Haemophilia A with or without inhibitors**	Hemlibra / emicizumab / ACE-910	Bispecific antibody	Roche	**Licensed**
	Haemophilia A	Mim8	Bispecific antibody	Novo Nordisk	**Phase 2**
		KY1049	Bispecific antibody	Kymab	**Pre-clinical studies**
		NXT007	Bispecific antibody	Chugai	
Non-replacement therapy **Anti-TFPI**	**Haemophilia A or B with or without inhibitors**	Concizumab	Anti-TFPI	Novo Nordisk	**Phase 3** **trial paused**
		BAY 1093884		Bayer	**Phase 2** **Trial terminated due to thrombosis**
		PF-06741086 Marstacimab		Pfizer	**Phase 3**
		MG1113		Green Cross	**Phase 1**
Non-replacement therapy	**Haemophilia A or B with or**	Fitusiran	Antithrombin Small interfering (si)RNA	Genzyme, a Sanofi Company	**Phase 3**

siRNA	**without inhibitors**				
Non-replacement therapy	**Haemophilia A or B with or without inhibitors**	SerpinPC	Activated Protein C inhibitor	Apcintex	**Phase 1**
GENE THERAPY					
Type of product	**Indication / treatment of**	**Product name(s)**	**Name(s) of active ingredient**	**Developer / manufacturer**	**Development stage**
Gene Therapy	**Haemophilia A**	Valoctocogene roxaparvovec/ BMN-270	AAV5-huFVIII-SQ (Valoctocogene roxaparvovec)	BioMarin	**Phase 3**
		SB-525 (giroctocogene fitelparvovec)	Gene therapy using a rAAV2/6 vector	Pfizer (originally Sangamo)	
		BAY-2599023 / DTX 201	Gene therapy using AAVhu37FVIII	Bayer	**Phase 1/2**
		Spark-8011	AAV-Spark200 encoding BDD-FVIII	Spark	
		TAK-754 (formerly BAX 888/SHP654)	AAV8-based gene therapy using B-domain deleted (BDD)-FVIII-X5 variant	Takeda	**Phase 1**
		AAV2/8-HLP-FVIII-V3	AAV2/8-based gene therapy encoding FVIII-V3 variant	UCL/St. Jude	

		ET3	Gene therapy using a combination of haematopoietic stem cells and lentiviral vectors	Expression Therapeutics	
		AMT-180	Gene therapy using an AAV5-based gene therapy using a FIX variant (FIX-FIAV)	UniQure	**Pre-clinical studies**
		Spark-8016	Modified AAV that carries a bioengineered gene whose protein product can suppress factor VIII inhibitors	Spark	**Phase 1/2**
Gene Therapy	**Haemophilia B**	SPK-9001 PF-06838435 fidanacogene elaparvovec	Padua variant (AAV-Spark100) (fidanacogene elaparvovec)	Pfizer (former collaboration with Spark Therapeutics)	**Phase 3**
		AMT-061	Gene therapy using AAV5 vector with FIX Padua variant (etranacogene dezaparvovec)	UniQure	
		AMT-060	Gene therapy using AAV5 vector encoding FIX	UniQure	**Phase 1/2**
		SB-FIX	AAV6-delivered ZFN integrating corrective FIX transgene	Sangamo	

			into albumin locus		
		FLT180a	AAV encoding FIX Padua variant	Freeline	
		AAV2/8-LP1-FIX	AAV2/8-LP1-FIX vector	SJCRH	**Phase 1**
		TAK-748 (formerly SHP648/ AskBio009/BAX 335)	AAV8-based gene therapy using FIX Padua variant	Takeda	**Pre-clinical studies**
		CB2679d-GT	Novel chimeric AAV vector	Catalyst Biosciences	
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**	YUVA-GT-F801	autologous HSC/MSC modified with lentivirus encoding FVIII	SGIMI	**Phase 1**
		SIG-001	Two-compartment spheres encapsulating human FVIII-expressing human cells	Sigilon Therapeutics	**Pre-clinical development**

	Haemophilia B	YUVA-GT-F901	autologous HSC/MSC, modified with lentivirus encoding FIX	SGIMI	**Phase 1**