

**Novel Treatments in Haemophilia & Other
Bleeding Disorders:
A Periodic Review
2019 - Issue 1**



Irish Haemophilia Society
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haemophilia.ie

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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 second edition of the 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.

Unlike the first edition of this review, which was published in May 2018 and is available on the EHC website, this second review is meant to provide a short overview of advances in novel therapeutic medicinal products that occurred between May and December 2018. Therefore this issue will solely provide a quick snapshots of notable advances in existing clinical trials, initiation of novel clinical trials and development of novel molecules/treatments in the area of rare bleeding disorders.

As with the first edition, the purpose of this newsletter is to help provide people with haemophilia and related bleeding disorders, their families and indeed health care professionals with a general overview and understanding of the rapidly evolving landscape of medicinal product development in inherited bleeding disorders.

The information provided in this newsletter is divided by specific type of disorder for which there is an update to report. We anticipate the production of the next edition of this newsletter in July 2019.

The information provided in this newsletter was compiled from multiple sources, including presentations at recent scientific meetings (e.g. EHC New Technologies workshop, ASH Annual Meeting), websites (e.g. www.clinicaltrials.gov) and by writing directly to pharmaceutical companies. It was then redrafted and presented in easy-to-understand language. For this we give special thanks and recognition to Mr Declan Noone.

The EHC is also grateful to the 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
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- Dr Geneviève Piétu, EHC volunteer
- Dr Uwe Schlenkrich, EHC volunteer

The EHC greatly 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.

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

Sincere regards,

Brian O'Mahony,

EHC President,

Chief Executive of Irish Haemophilia Society

Amanda Bok,

EHC CEO

Abbreviations

ABR: Annualised bleeding rate
AIR: Annualised infusion rate
APC: Activated protein C
ASH: American Society of Hematology
AT: Antithrombin
BPA: Bypassing agents
EHL: Extended half-life
EU: European Union
F: Factor
FDA: Food and Drug Administration
ITI: Immune tolerance induction
IV: Intravenous
LFT: Liver function test
NEMJ: New England Journal of Medicine
SAE: Serious adverse events
SHL: Standard half-life
SQ: Subcutaneous
UK: United Kingdom
US: United States
vg/kg: vector genomes per kilogram
VWF: Von Willebrand Factor
wk: week

An Update on Novel Treatments in Haemophilia A

Extended half-life (EHL)

Jivi® granted marketing authorisation

Marketing authorisation has been granted for **Jivi®**, Bayer's extended half-life (EHL) product **BAY 94-9027** for previously treated patients 12 years and older in the European Union (EU), United States (US), Canada and Japan. Jivi® is a pegylated FVIII and is **indicated for both prophylaxis and treatment of bleeds**.

Bayer presented data at the 2018 American Society of Hematology (ASH) in San Diego, United States (US). Overall, median spontaneous and joint annualised bleeding rates (ABRs) were low (≤ 2) in patients who received Jivi® as prophylaxis every five days or every seven days during the PROTECT VIII phase II/III trial. Preliminary analyses suggested that best responders to every-five-day prophylaxis experienced fewer bleeds and target joints in the 12 months prior to study enrollment vs patients with $ABR \geq 1$.

An update on clinical studies and real-world data on switching patients from SHL FVIII to EHL FVIII

In the use of EHL factor (F)VIII, a joint abstract from adult (Guy and Thomas's, NHS) and paediatric centres (Evelina, London) in the United Kingdom (UK) reported their experience with switching patients from their standard factor concentrates (SHL) to EHL products. Thirty-three haemophilia A patients switched to EHL with factor usage showing a reduction in units used in 13/13 children and 19/20 with cost neutrality or savings made. Trough levels ranged from 1.8–5.9% in children and 2.3–9.2% in adults. It was reported that this was especially beneficial in patients with difficult venous access in achieving reliable levels despite fewer injections.

In a **broader report from the UK database**, 61 patients were switched from their standard treatment to EHL. Their before and after treatment regimens and annualised bleeding rate (ABRs) were compared and reported. The infusion rate fell from a median of 3.52 to 2.38 injections/week (wk), (–32%), with 91% of the patients reducing their infusion frequency. Clotting factor reduced from a median of 5,306 to 4,620 IU/wk (–12%), reducing in 73% of patients. Median ABR was 2 (0-6) pre-switch and 2 (0-4) post-switch (not statistically significant) with no significant change in the proportion bleed-free (44% pre and 45% post) incidents.

In a **first analysis of the completed ASPIRE trial**, overall median ABRs for those on prophylactic treatment with rFVIII-Fc (**Elocta®**) remained low throughout ASPIRE, with zero spontaneous joint bleeds reported in all age groups in the individualised dosing arm. The median joint ABR in this arm ranged from 0.49 to 0.66 across age groups, with 92-95% of people either lengthening or maintaining dosing intervals.

In a report from US haemophilia treatment centres, of 15 patients with a median of nine months' use of **Adynovate®**, nine patients had ≥ 1 bleed within six months pre-switch. The most frequent reason for switching was to reduce infusion frequency (14 patients). After switching, infusion frequency reduced for 13 patients, and overall weekly factor consumption decreased by 19%. Eight (53%) patients had no bleeds post switch, three (20%) had spontaneous joint bleeds (versus four pre-switch), and three (20%) had only mild traumatic bleeds.

In November, Canada and Australia authorised Adynovate® for haemophilia A patients younger than 12 based on results of phase III trial data. Of 66 patients with severe haemophilia A on prophylaxis, 73% of patients experienced no joint episodes, 67% experienced no spontaneous bleeding episodes, and 38% experienced no bleeds.

New EHL FVIII (BIVV001) announced at ASH

At the ASH annual meeting in December 2018, Bioverativ showed data on a new FVIII concentrate in development. **BIVV001 (rFVIII-Fc-VWF-XTEN)** is a novel EHL FVIII and is independent of the half-life ceiling imposed on FVIII by binding to Von Willebrand Factor (VWF). It does this by leveraging the Fc technology of rFVIII-Fc, plus the addition of XTEN polypeptides, and a linkage to the D'D3 domain of VWF. Six patients who received a single low dose (25 IU/kg) of BIVV001 showed an EHL of 37.6 hours. Average FVIII activity after a single low dose infusion was 12.2% at five days and 5.3% at seven days. The first two subjects in the high-dose cohort (65 IU/kg) had an average FVIII activity level of 39.6% at day five and 18.5% at day seven, with an average

half-life of 43.8 hours. This should allow prophylaxis in haemophilia A with one intravenous (IV) dose per week.

Non-replacement therapies

Hemlibra® (emicizumab)

An update on the NIS, HAVEN 3 & 4 studies

Roche announced full results from the **phase III HAVEN 3¹** study evaluating **Hemlibra® (emicizumab) prophylaxis** administered every week or every two weeks in people with **haemophilia A without FVIII inhibitors** and the **phase III HAVEN 4²** study evaluating **Hemlibra® prophylaxis** administered every four weeks in **people with haemophilia A with or without FVIII inhibitors**.

In HAVEN 3, adults and adolescents aged 12 years or older showed a 96% and 97% reduction in treated bleeds, respectively, compared to those who received no prophylaxis. Fifty-six per cent of people treated every week and 60% treated every two weeks experienced zero treated bleeds, compared to no people with zero treated bleeds in the no prophylaxis arm. In comparison to prophylaxis with SHL FVIII, a 68% reduction in treated bleeds was reported.

In the HAVEN 4 study, adults and adolescents aged 12 years or older with or without FVIII inhibitors receiving Hemlibra® prophylaxis every four weeks had a median ABR for treated bleeds of 0.0, with 56.1% of people experiencing zero treated bleeds and 90.2% experiencing three or fewer treated bleeds.

Hemlibra® was approved by the Food and Drug Administration (FDA) in October 2018, for **routine prophylaxis** to prevent or reduce the frequency of bleeding episodes in adults and children with **haemophilia A without inhibitors**.

At ASH 2018, Dr Michael Callaghan showed data from the Roche **NIS trial before patients received treatment with Hemlibra® in the HAVEN programme**. There were 103 patients in the inhibitor cohort and 94 in the non-inhibitor group. The inhibitor group had 1,596 total bleeds, with 58.7% treated and 41.3% untreated. In the patient group without inhibitors, there were 1,456 bleeds, of which 86.5% were treated and 13.5% were untreated.

The cause of the treated bleeds among both groups was relatively evenly split between spontaneous or traumatic reasons. Bleeds due to surgery or procedure were not considered; however, causes of untreated bleeds were a different story. Spontaneous bleeds made up two-thirds of the causes for inhibitor patients, but only one-third for non-inhibitor patients. Traumatic causes were responsible for about one-third of inhibitor patients but two-thirds of non-inhibitor patients. This suggests that future trials should report both treated and untreated bleeds and it may also be beneficial to investigate the decision-making process regarding treatment of bleeds to better understand what bleeds are not treated and what the long-term impact of that may be.

On the 1st of February 2019, the **Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA)** announced a positive opinion for **Hemlibra® for routine prophylaxis of bleeding episodes in adults and children with severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without factor VIII inhibitors**.

Fitusiran

An update on fitusiran

An update on **fitusiran** by Sanofi was also presented at ASH 2018. In September 2017, the **phase II open-label extension (OLE) study** was temporarily suspended to investigate a case of fatal cerebral venous sinus thrombosis. Following this investigation, fitusiran dosing resumed in December 2017 with protocol amendments for bleed management and safety monitoring. Before the dosing suspension, 28 patients continued treatment up to 20 months in the phase II OLE study. As of June 2018, anti-thrombin (AT) activity in patients previously receiving

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

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

fitusiran increased during the suspension. Median percentage of AT increased to >60% after a five-month period. In the gradual recovery of AT levels over time, preliminary analysis shows the median overall ABR increased from 1.43/year before the dosing interruption to 6.07/year during the dosing interruption. The **phase III (ATLAS) trials** for those with haemophilia A and B, with or without inhibitors are on-going. ATLAS-INH (NCT03417102) and ATLAS-A/B (NCT03417245) are for on-demand patients and ATLAS-PPX (NCT03549871) is for prophylaxis patients.

An update on anti-TFPI BAY1093884

Bayer has moved in to **phase II with their anti-TFPI BAY1093884**.

Gene therapy

An update on FVIII gene therapy clinical trials with valoctocogene roxaparvovec (BMN 270)

Biomarin's **valoctocogene roxaparvovec**, previously known as **BMN 270**, has **four clinical studies being conducted for haemophilia A**. The **phase III program (GENEr8-1 and GENEr8-2)** evaluating two dose levels has been initiated.

The GENEr8-1 study will now include 130 patients and is expected to be fully enrolled in the second quarter of 2019. The enrolment has slightly restricted criteria for the GENEr8 studies, to match the enrolment criteria from the phase II study; the trial will not include patients that have HIV or mild liver disease. This change was the result of one patient having higher liver function test (LFT) elevations due to interaction with efavirenz, an HIV medication that can cause liver toxicity. After a switch in medication, the LFT elevation resolved. The trial is managing LFT elevations with on demand steroids and there has been no inclusion or addition of steroid prophylaxis to the protocol as a result. Prophylactic steroids were used in the phase I/II study and were of unclear benefit.

There is now a **phase I/II study evaluating the safety of valoctocogene roxaparvovec in patients with pre-existing immunity to adeno-associated virus (AAV) 5**, which was initiated in May 2018.

In addition, there are two ongoing **non-interventional global studies**, one to **study seroprevalence of AAV in patients with severe haemophilia A** and another study to **determine the baseline characteristics of haemophilia A**. These cohorts will be eligible for subsequent enrolment into studies GENEr8-1 and GENEr8-2.

Based on the recently released US FDA Draft Guidance for Human Gene Therapy for Haemophilia, BioMarin expects that data available in 2019 could potentially allow submission of a marketing application through an accelerated approval pathway in the second half of 2019.

The data presented at the World Federation of Hemophilia's Congress in Glasgow on GENEr8-1 study, showed continued and substantial reductions in bleeding requiring FVIII infusions with a 97% reduction in mean ABR, with no spontaneous bleeds and elimination of all bleeds in target joints in the second year. Quality of life, as measured by the six-domain Haemo-QoL-A instrument, showed improvement across all domains. At 104 weeks post-infusion, mean FVIII activity level of the GENEr8-1 study is within the normal range at 59%, and the median is near normal at 46%.

The GENEr8-2 study also showed a substantial reduction in bleeding requiring FVIII infusions with a 92% reduction in ABR.

For the GENEr8-1 study, mean FVIII activity levels from week 20 through 104 have been consistently within the normal or near normal range and no participant was above the upper limit of normal at week 104, expressed as a percentage of normal factor activity in blood.

At 52 weeks post-infusion, mean and median FVIII activity levels of the GENEr8-2 study are 32%.

An update on FVIII gene therapy clinical trial with SPK-8011

In July 2018, **preliminary phase I/II data** for investigational **SPK-8011** for **haemophilia A** from Spark showed a 97% reduction in ABR and 97% reduction in annualised infusion rate (AIR) across all 12 participants in the study.

Initial evidence of stable expression, with no decline in plateau FVIII levels was observed in two participants in the 5×10^{11} vg/kg cohort who have been followed for greater than one year. A dose response was demonstrated with FVIII expression from 16-49%, with a mean of 30% post-12 weeks after vector infusion in five of the participants in the 2×10^{12} vg/kg cohort. In data presented at ASH in December 2018, there was a 94% observed reduction in bleeds and 95% observed reduction in infusions. Seven participants needed steroids for transaminitis (abnormal liver enzymes), and two of these individuals lost much of their FVIII expression, with one patient's levels dropping from 29% to <5%. FVIII levels on all 12 patients were not presented. One serious adverse event (SAE) of elevated liver transaminases that resolved with tapering course of IV and oral corticosteroids was reported. Phase III studies will start but it is anticipated that prophylactic steroids will be used in order to reduce or eliminate the transaminitis.

An update on GO-8 FVIII gene therapy clinical trial

During ASH 2018, Dr Chowdary presented data on the **UCL GO-8 (NCT03001830) gene therapy trial**.

In this trial, four patients have been treated to date, with two patients in the mid dose group achieving levels of 34 and 63%. Three of four patients developed transaminitis, which responded to steroids. This trial used a modified FVIII designed to be expressed at higher levels in the liver cells following delivery by AAV. Prophylactic steroids, however, did not prevent breakthrough transaminitis.

An update on the ALTA study

In October 2018, Sangamo's **phase I/II Alta Study evaluating SB-525 for hemophilia A** reviewed accumulated safety and efficacy data from six patients enrolled in three dose cohorts.

As of that review, SB-525 exhibited dose-dependent efficacy on serum factor levels and was generally well-tolerated with no treatment-related SAE and no use of tapering courses of oral steroids.

An independent Safety Monitoring Committee overseeing the study recommended that the study continue with escalation to an additional dose.

Get8 trial is underway

Bayer's trial, **Get8**, is underway, with two patients enrolled and dosed to date.

Pre-clinical developments of AMT-180 for gene therapy in haemophilia A with and without inhibitors

UniQure announced the pre-clinical development of AMT-180, haemophilia A gene therapy that will include those with past and current inhibitors. The gene is actually a modified FIX gene, designed to bypass the need for FVIII, thus at this stage they plan to study it in haemophilia A patients with and without inhibitors.

An Update on Novel Treatments in Haemophilia B

Extended half-life (EHL)

An update on clinical studies and real-world data on switching patients from SHL FIX to EHL FIX

In the use of **EHL FIX**, a joint abstract³ from adult (Guy and Thomas's, NHS) and a paediatric centres (Evelina, London) in the UK reported their experience with switching patients from their SHL to EHL products. Eight haemophilia B patients switched to EHL (five to **Alprolix®**, three to **Idevion®**) with factor usage showing a reduction in units in all, with cost neutrality or savings being demonstrated. Trough levels ranged from 2.3-9.2% in children and 9.3-10.3% in adults. This has been especially beneficial in patients with difficult

³ Abstract M-P-083 (354)

venous access in achieving reliable levels despite fewer injections.

In a report⁴ from the **Irish experience of an en-masse switch to EHL recombinant FIX** replacement therapy by **Dr Lavin in St James's Hospital**, 28 adults with a median age of 43.6 years were switched. Twenty-two of these were previously on prophylaxis and post switch all patients were receiving prophylactic regimens. The mean prophylactic dose reduced from 77.2 IU/kg/wk to 55.1IU/kg/wk. FIX trough levels have increased (0.05 IU/ml to 0.08IU/ml) despite a reduction in mean FIX usage. Additionally, 26 patients had improved joint scores, with the greatest improvements in gait domains.

In **Scotland**, results were similar with 11 adults and four children with haemophilia B switching to EHL factor concentrates (13 **Idelvion®** and 2 **Alprolix®**). Overall trough levels of FIX were between 0.05-0.13 IU/ml. All but one patient has less treatment days per year on EHL factor concentrates. Physical disability made SHL product prophylaxis unfeasible for this one patient.

In a first analysis of the completed **B-YOND study**, adult and adolescent patients following a weekly prophylactic regimen with rFIXFc (**Alprolix®**), joint and spontaneous joint median ABRs were 0.67 and 0.38, respectively. Spontaneous joint median ABR in paediatrics was 0.00. Additionally, 85% of adult and 93% of paediatric patients either lengthened or experienced no change in dosing intervals during the extension study, with dosing intervals up to 14 days.

An update on SQ FIX

At the 2018 **Congress of the International Society for Thrombosis and Haemostasis (ISTH)**, data on **dalcinonacog alfa (DalcA)** that is in development by Catalyst Biosciences, was presented showing that a **subcutaneous (SQ) injection of an improved FIX** with 22-fold greater potency, increased FIX levels into the high mild haemophilia range (> 30%). Data showed that neutralizing antibodies, one transient, in two cousins, do not cross-react or inhibit wild-type FIX.

A phase IIb trial 28-day subcutaneous dosing study in six patients is currently enrolling. In December 2018, Catalyst announced the results of an extensive DalcA immunogenicity risk assessment, which revealed a similar low immunogenicity potential compared with **BeneFIX®** and other commercial wildtype [natural form] FIXs.

Non-replacement therapies

Fitusiran

Please see 'Fitusiran' in Haemophilia A - NRT

Gene therapy

An update on HOPE B FIX gene therapy studies

In June 2018, UniQure enrolled its first patient in the **phase III HOPE-B** pivotal study of **AMT-061**, an investigational AAV5-based gene therapy incorporating the FIX-Padua variant for the treatment of patients with severe and moderately severe haemophilia B.

Approximately 50 patients will be enrolled in the HOPE-B trial. Patients will be tested for the presence of pre-existing neutralising antibodies to AAV5 but are not excluded from the trial based on their titers. Concurrent with the lead-in phase of the HOPE-B pivotal study, uniQure is also conducting a short, phase IIb dose-confirmation study of AMT-061 in haemophilia B patients. In the phase IIb study of AMT-061, three patients with severe haemophilia B received a single IV infusion of AMT-061 at 2×10^{13} vc/kg.

Six weeks after administration, the mean FIX activity for the three patients was 31% of normal. The first patient acquired a FIX activity of 37% of normal at ten weeks, the second patient acquired a FIX activity of 23% of normal at eight weeks, and the third patient acquired a FIX activity of 30% of normal at six weeks of administration. No patients had any significant loss of FIX activity, any reported bleeding events, or required FIX replacement therapy.

4 Abstract M-P-035 (513)

Only 1 patient had a mild, asymptomatic increase in liver enzyme levels, but it resolved quickly without treatment.

An update on fidanacogene elaparvec (SPK-9001) FIX gene therapy trial

As of May 7, 2018 data cutoff, Spark and its partner Pfizer showed data from 15 patients in the **phase I/II gene therapy trial**. FIX levels were reported in 13 participants who reached stable FIX levels of more than 12% after 12 weeks of therapy. For all 15 participants, ABR was reduced by 98% and AIR was reduced by 99%.

An update on FIX gene therapy trial with scAAV2/8-LP1-hFIXco

At **ASH 2018**, Dr Reiss presented the **latest update on the original Nathwani's** (Royal Free/ St Jude) **New England Journal of Medicine (NEJM) study of haemophilia B gene therapy study**, with FIX expression remaining stable during follow-up of up to 8.6 years. Mean FIX levels in the low, mid and high dose cohorts were 1.9, 2.3, and 5.1%, respectively.

An update on FLT180a FIX gene therapy trial

Prof Nathwani presented the new Freeline **FLT180a gene therapy preliminary data at ASH 2018**. Two patients who were treated in the lowest dose cohort achieved levels of 42 and 49% with no transaminitis; however, the patients were given prophylactic steroids.

An update on SB-FIX genome editing trial

Sangamo Therapeutics has announced treatment of the first patient in the **phase I/II clinical trial** evaluating **SB-FIX**, an investigational **in vivo genome editing therapy** for patients with **haemophilia B**. Unlike the other AAV gene therapies, SB-FIX is designed with the goal to permanently and precisely **integrate the FIX gene into the DNA**.

An Update on Novel Therapies for Inhibitor Treatment

Extended half-life (EHL)

An update on MarzAA

Catalyst Bio presented data on its trial of **Marzeptacog alfa (activated) (MarzAA)**.

In a daily **SQ FVIIa** dosing, nine patients have been enrolled with median ABR 16.25. Median SQ bioavailability was 22% and a SQ half-life of 13.1 hours compared to 3.9 hours as IV infusion. There was a fatal hemorrhagic stroke that was determined not to be related to the study drug. The patient had untreated hypertension.

Clinical trial for rFVIIa-FP is terminated

A clinical trial from CSL Behring for **rFVIIa-FP** has been terminated.

Non-replacement therapies

Fitusiran

Please see the 'Fitusiran' section in haemophilia A for details with the only modification being, the phase III trial for those with haemophilia A and B with inhibitors is **ATLAS-INH (NCT03417102)**.

Hemlibra® (emicizumab)

An update on the HAVEN 2 study

In updated results from the **HAVEN 2 (Roche)** presented at **ASH 2018**, 77% of children with inhibitors treated once weekly (n=65) experienced zero treated bleeds. Once-weekly treatment showed a 99% reduction in treated bleeds compared to prior treatment with bypassing agents (BPAs) as prophylaxis (n=15) or on-demand (n=3) in a prospective intra-patient comparison.

The new data also showed that 90% of children with inhibitors receiving treatment every two weeks (n=10) and 60% of children receiving every four weeks (n=10) experienced zero treated bleeds, demonstrating clinically meaningful bleed control at both dosing schedules.

Gene therapy

Clinical trial to start for gene therapy in people with haemophilia A and inhibitors

Spark has received FDA clearance for SPK-8016 (NCT03734588), a novel, internally developed AAV gene therapy candidate aimed at treating patients with haemophilia A inhibitors with gene therapy. Data available from animal studies suggest that gene therapy might induce immune tolerance in patients with inhibitors.

Pre-clinical developments of AMT-180 for gene therapy in haemophilia A with and without inhibitors

See section on gene therapy in haemophilia A.

Gene Therapy Comment

With gene therapy for haemophilia on the cusp of entering clinical practice and clinical trials reporting increases in FVIII or FIX activity to almost normal levels, reduced bleed frequency, and a reduced need for FVIII or FIX replacement with a positive and generally manageable safety profile of AAV-mediated vectors, patients now need to consider a world after the gene transfer. Does the individual consider their haemophilia to be ‘cured?’ This creates the need to manage expectations, particularly regarding activity levels and bleed risk in the immediate post-treatment period. Despite patients effectively now having a mild phenotype, these individuals may retain a legacy of increased bleed risk and joint damage from their years with severe haemophilia and will need different clinical management compared to a more typical individual with mild haemophilia. These are conversations that need to be addressed in the near term such as:

- How a bleed risk is likely to change (e.g. there may still be some risk of bleeding particularly traumatic bleeds);
- Contacts to discuss potential positive and challenging emotional issues resulting from changes in usual haemophilia management;
- Any precautionary requirements to avoid vertical or environmental transmission (e.g. use of appropriate barrier contraception during sex until vector has cleared).

An Update on Novel Therapies for Rare Bleeding Disorders

Novo Seven® receives license expansion for Glanzmann’s thrombasthenia

Novo Nordisk’s, NovoSeven® RT has had a licence expansion for the indication of use in patients with Glanzmann’s thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets.

Post-marketing studies for Obizur®

Obizur® (Shire), a recombinant porcine FVIII was licensed in Europe for the treatment of bleeding episodes in adults with acquired haemophilia, which is caused by the spontaneous development of antibodies that inactivate FVIII. This was based initially on 28 adult patients.

In two post-marketing studies (NCT02610127 and NCT03199794), data will be gathered to further increase data in relation to usage and dosing. Currently, this does not have a licence for use in those with congenital haemophilia.

Noteworthy News

Development of APC inhibitor

Activated protein C (APC) breaks down the complex that produces thrombin by inactivating factor Va. Defects in this mechanism (e.g. FV Leiden) are associated with thrombosis but result in less severe bleeding when co-inherited with haemophilia. Selective inhibition of APC might therefore be effective for the treatment of haemophilia. *Apcintex* has developed an **APC inhibitor** but currently does not have a clinical trial, although it could be one to watch for a number of conditions including rare bleeding disorders.

IDO 8 granted orphan drug designation in the EU and US

The **IDO 8** from Idogen program is aimed at developing a tolerogenic cell therapy for patients with inhibitors, which would be a **cell therapy alternative to immune tolerance induction (ITI)**. Idogen has been granted orphan drug designation in the EU and US.

Developments in cell therapy for haemophilia

HemAcure is an innovative idea that isolates cells from blood of the haemophilia A patient and performs a genetic (FVIII) correction of those cells. The corrected cells are expanded, meaning grown in a laboratory, and if enough cells are available to produce sufficient FVIII, corrected cells are transplanted back into the patient in a medical device designed for therapeutic cells (**Cell Pouch™**). The cells in this kind of cell bag or artificial organ are connected with the bloodstream of the patient and that allows a continuous release of FVIII into the patient's blood with the aim of maintaining steady state factor levels. This is in very early development.

Sigilon Therapeutics is also developing a similar strategy with their **SIG-003** program.

Other News

Takeda to take over Shire

Takeda, the Japanese pharmaceutical company, won EU anti-trust approval for its bid for Shire and following the agreement of both sets of shareholders is taking over Shire.



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