EHC
european haemophilia consortium

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

**Issue One**

## Inhibitors Only

**May 2018**

# Novel treatments in haemophilia and other bleeding disorders:

# A periodic EHC review

# Issue 1/2018

# May 2018

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## Disclaimer:

## EXECUTIVE SUMMARY

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

The purpose of this newsletter is primarily to help educate EHC National Member Organisations (NMOs) and help them to provide their members and caregivers with a general overview and understanding of the rapidly evolving landscape of medicinal product development 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.

The information provided in this newsletter covers recent major developments and is divided by specific type of disorder for which there is an update to report. This newsletter will be updated periodically.

The information provided in this newsletter was compiled from multiple sources, including presentations at recent scientific meetings (e.g. EHC New Technologies workshop, EAHAD Congress), 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 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:

- Asst Prof Brian O'Mahony, EHC President
- Dr Radoslaw Kaczmarek, EHC Steering Committee member
- Prof Mike Makris, EHC Medical Advisory Group (MAG) member
- Prof Flora Peyvandi, EHC Medical Advisory Group (MAG) member
- Dr Dan Hart, EHC Medical and Scientific Advisory Group (MASAG) member
- Mariëtte Driessens, EHC volunteer
- 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

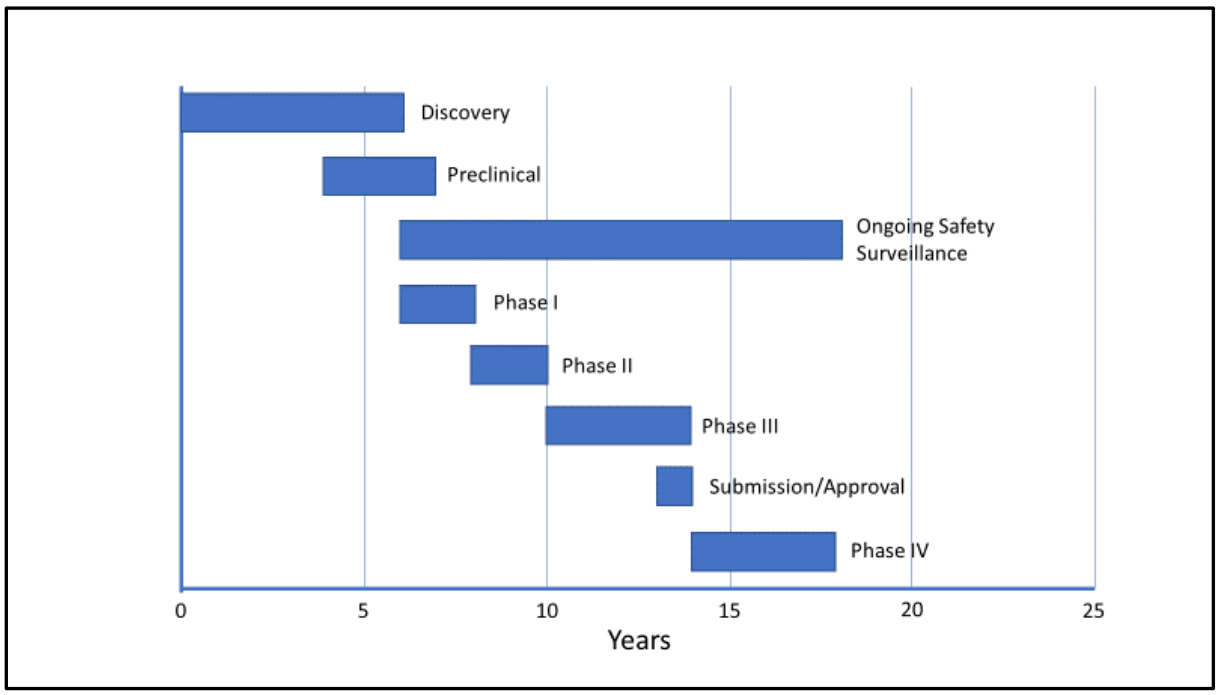
Amanda Bok
EHC CEO

**PHASES OF CLINICAL TRIALS**

## What Are the Phases of Clinical Trials?

Clinical trials are usually conducted in phases that build on one another. Each phase is designed to answer certain questions. Knowing the phase of the clinical trial is important because it can give you some idea about how much is known about the treatment being studied.

*Figure 1: Phases and approximate times from inception to clinical trial to approval*




## Phase I clinical trials: Is the treatment safe?

Phase I studies of a new drug are usually the first that involve people. The main reason for doing phase I studies is to find information about the dose of the new treatment that can be given safely, without serious side effects. Although the treatment has been tested in lab and animal studies, the side effects in people can't always be predicted. These studies also help to decide on the best way to administer the new treatment.

Key points of phase I clinical trials:

- The first few people in the study often get a very low dose of the treatment and are watched very closely. If there are only minor side effects, the next few participants may get a higher dose. This process continues until doctors find a dose that's most likely to work while having an acceptable level of side effects.
- The focus in phase I is looking at what the drug does to the body and what the body does with the drug. In haemophilia, this could be what the addition of a molecule to the factor VIII (FVIII) or factor IX (FIX) does to the protein, or how the drug gets broken down. In terms of gene therapy, this maybe looks at how the body responds to the capsid that the FVIII or FIX gene is delivered in.

- Safety is the main concern at this point. Doctors keep a close eye on participants and watch for any serious side effects. Because of the small number of people in phase I studies, rare side effects may not be seen until later.
- These studies usually include a small number of people. In haemophilia, it this could be between 5 and 20 people.

## Phase II clinical trials: Does the treatment work?

If a new treatment is found to be reasonably safe in phase I clinical trials, it can then be tested in a phase II clinical trial. The type of benefit or response the doctors look for in this phase depends on the goal of the treatment and may concern intermediate outcomes (i.e. factor level increase). In extended half-life products (EHLs), they may look for how much factor is needed to stop a bleed with one to two infusions. In gene therapy, they may look at what dose is needed to get a factor level that will provide enough protection and how many bleeds are occurring at these levels.

**Key points of phase II clinical trials:**

- Usually, a group of 15 to 50 patients with the same type of haemophilia (A, B, vWF, inhibitors) get the new treatment in a phase II study. They're treated using the dose and method found to be the safest and most effective in phase I studies.
- In phase II clinical trials, all patients usually get the same dose. But some phase II studies randomly assign participants to different treatment groups (much like what's done in phase III trials). These groups may get different doses or get the treatment in different ways to see which provides the best balance of safety and effectiveness.
- Phase II studies are often done at major haemophilia centres.

If enough patients benefit from the treatment in this phase, and the side effects are acceptable, the treatment is allowed to go on to a phase III clinical trial. Along with watching for responses, the research team continues to look for any side effects.

## Phase I/II

In haemophilia, some trials are Phase I/II. This is often seen in conditions where there are limited numbers of patients available, such as rare diseases. Usually it means that in the first, small (phase I) group of treated patients, doctors not only look at safety but also immediately at effectiveness and if the drug appears safe, a second, larger group is treated and analysed together. Combining phases I and II may allow research questions to be answered more quickly or with fewer patients.

## Phase III clinical trials: Is it better than what's already available?

Treatments that have been shown to work in phase II studies must usually succeed in one more phase of testing before they're approved for general use. Phase III clinical trials compare the safety and effectiveness of the new treatment against the current standard treatment or placebo (products without active substance).

This is usually done in randomised studies, i.e. in which it is randomly decided who receives one of the two treatments, to remove possible bias. Randomisation is not often used in haemophilia clinical trials for several reasons. The trial can follow patients on current treatment who are then switching to a new treatment, or record a period of time on the current treatment, followed by patients switching to the new treatment at different levels, e.g. on-demand patients switching to prophylaxis on new treatment, prophylaxis patients switching to the new treatment at new doses, such as from 35IU/kg to 50IU/kg, or pharmacokinetic guided dosing.

**Key points of phase III clinical trials:**

- These studies are often done in many places around the world at the same time.
- These studies tend to last longer than phase I and II studies.
- Placebos are never used in haemophilia trials. People with haemophilia always get the trial drug.
- As with other studies, patients in phase III clinical trials are watched closely for side effects and treatment is usually stopped if side effects are serious. In haemophilia, the primary side effect that has been examined is the development of inhibitors. For this reason, there are often two Phase III clinical trials, one in previously treated patients (PTPs) and one in previously untreated patients (PUPs).

## Submission for approval: New drug application

When phase III clinical trials (or sometimes phase II studies) show a new drug is effective/safe with an acceptable risk of side effects, as with current standard treatment, a new drug application (NDA) is submitted for approval. The authorities (European Medicines Agency [EMA] or the Food and Drug Administration [FDA] in the US) then review the results from the clinical trials and other relevant information.

Based on the review, the authorities decide whether to approve the treatment for use in patients with the type of illness the drug was tested on. If more evidence is needed to show that the new treatment's benefits outweigh its risks, they may ask for more information or even require that more studies be done and they can limit approval until this information is available.

## Phase IV clinical trials: What else do we need to know?

Approved drugs are often monitored over a long period of time in phase IV studies. Even after the first three phases of clinical trials, the full effects of the treatment may not be known. Some questions may still need to be answered. For example, a treatment may get approval because it was shown to reduce the number of infusions per week and decrease the number of bleeds per year. However, is the dose high enough to prevent sub-clinical bleeds? Does the new treatment do something that the old treatment does not? Are there rare side-effects? These types of questions may take many more years to answer and are often addressed in phase IV clinical trials.

**Key points of phase IV clinical trials:**

- Phase IV studies look at drugs that have already been approved. The drugs are available for doctors to prescribe for patients, but phase IV studies might still be needed to answer important questions.
- This is typically the safest type of clinical trial to participate in because the treatment has already been studied and might have already been used in many people. Phase IV studies look at safety over time.
- These studies may also look at other aspects of the treatment, such as quality of life or cost effectiveness.

## NOVEL TREATMENT IN HAEMOPHILIA AND INHIBITORS

If haemophilia had a calendar, 2018 would be the year of the inhibitor. This is highlighted by discussions at international conferences relating to prophylaxis with bypassing agents (BPAs), new products and increasing numbers of clinical trials with new or existing products so patients with inhibitors can begin to move toward a level of treatment that has been achieved in those without inhibitors.

An inhibitor is a high-affinity antibody response that specifically neutralises the procoagulant activity of the relevant clotting factor, causing difficulty in managing bleeds. Inhibitors are characterised in two ways — by the titre and by the immune response. The titre refers to the inhibitory capacity of the patient's plasma to neutralise clotting factor in normal plasma. A high-titre inhibitor is defined as having 5 Bethesda units (BU) or higher, and a low-titre one is defined between a cut off value (usually 0.6 BU) and 5 BU. Patients whose titre is less than 5 BU are divided into those in whom a rapid anamnestic response to factor infusion occurs (i.e. high responders) and those in whom such a response does not occur (i.e. low responders). This characterisation is important because patients with a low titre and low responding inhibitors can be treated with standard replacement therapy, albeit at increased doses to overwhelm the inhibitor. Patients with a high titre or high responding inhibitors can only be treated effectively with BPAs, unless the inhibitor is eradicated.

Using on-demand treatment to treat bleeding episodes in people with inhibitors can be less effective than in those without inhibitors leading to increased joint damage and a significant impact on quality of life (QoL) as well as increased rate of haemophilia-related deaths. Although prophylaxis with BPAs in those with inhibitors does improve outcomes, especially when started early, and reduce joint and other types of bleeds (45%-72%), it often does not achieve this to the same degree as prophylaxis in non-inhibitor patients. There is also a variable response to prophylaxis, which highlights the need for personalised treatment in people with inhibitors.

With the licensing by the European Medicines Agency (EMA) of Hemlibra® (emicizumab from Roche) in February 2018 for routine prophylaxis of bleeding episodes in people with haemophilia A with factor VIII inhibitors, this is a very promising time. Studies have shown a reduction of >70% in bleeding rates in inhibitor patients compared to their previous prophylaxis.

Based on the present knowledge, prophylaxis should be considered in inhibitor patients who have experienced a life-threatening bleed, frequent musculoskeletal bleeds, spontaneous bleeds causing significant impairment of QoL and in patients who have failed Immune Tolerance Induction (ITI). The treatment goal for patient suffering from longstanding inhibitors should be the same as for haemophilia patients without inhibitors.

*Table 1:On-going bypassing agents, ITI and non-replacement therapy clinical trials for inhibitors*

| NCT Number | Title | Sponsor | FVIII | FIX | Phase I | Phase II | Phase III | Completion Date |
|---|---|---|---|---|---|---|---|---|
| NCT02448680 (Wilfactin®) | A Phase III Study on the Safety, Pharmacokinetics and Efficacy of Coagulation Factor VIIa | LFB (USA) | Yes | Yes | | | | Aug-17 |
| NCT02919800 (MOD-5014) | A Single-dose, Dose-escalation Study of a Long-acting MOD-5014 in Healthy Adult Male | Opko Biologics | Yes | Yes | | | | May-18 |
| NCT02484638 (CSL689) | Study of Recombinant Factor VIIa Fusion Protein (rVIIa-FP, CSL689) for On-demand Treatment of Bleeding Episodes in Patients with Hemophilia A or B with Inhibitors | CSL Behring | Yes | Yes | | | | Jun-18 |
| NCT02571569 (BAY 1093884) | A Single Escalating Dose and Multiple Dose Study of BAY 1093884 in Subjects with Severe Hemophilia Types A or B, With or Without Inhibitors | Bayer | Yes | Yes | | | | Jul-18 |
| NCT03407651 (Marzeptacog Alfa) | Study of Coagulation Factor VIIa Variant Marzeptacog Alfa (Activated) in Adult Subjects with Hemophilia A and B | Catalyst Biosciences | Yes | Yes | | | | Jul-18 |
| NCT03417102 (Fitusiran) | A Study of Fitusiran (ALN-AT3SC) in Severe Hemophilia A and B Patients with Inhibitors | Alnylam/Sanofi | Yes | Yes | | | | Jul-19 |
| NCT03196284 (Concizumab) | A Trial Evaluating the Efficacy and Safety of Prophylactic Administration of Concizumab in Haemophilia A and B Patients with Inhibitors | Novo Nordisk | Yes | Yes | | | | Oct-19 |
| NCT03103542 (Elocta®/Eloctate®) | Study of rFVIIIFc for ITI in Haemophilia A Patients with Inhibitors Who Have Failed Previous ITI Therapies (ReITIrate) | Bioverativ (a Sanofi Company) /Sobi | Yes | | | | | Apr-20 |
| NCT03191799 (Hemlibra®) | A Study to Evaluate the Safety and Tolerability of Prophylactic Emicizumab in Hemophilia A Patients With Inhibitors | Hoffmann-La Roche | Yes | | | | | Sep-20 |
| NCT03093480 (Elocta®/Eloctate®) | A Study to Evaluate Efficacy of rFVIIIFc for Immune Tolerance Induction (ITI) in Severe Hemophilia A Participants With Inhibitors Undergoing the First ITI Treatment (verITI-8 Study) | Bioverativ (a Sanofi Company) /Sobi | Yes | | | | | Dec-20 |

## Bypassing agents

There are several activated recombinant factor VII (rFVIIa) products in clinical trials occurring internationally, with LR769 from LFB USA completing their trial at the end of 2017 and MOD-5014 by Opko Biologics expected to finish trials in May 2018 for the market in Israel. Additionally, CSL Behring are using their fusion technology to extend the half-life of rFVIIa by attaching albumin to the molecule (rFVIIa-FP), which is currently in Phase III. The half-life of rFVIIa-FP at the highest dose investigated in the study was 8.5 hours, which represents a three to four-fold half-life extension compared with rFVIIa. Marzeptacog alfa from Catalyst Bioscience, currently in Phase II trials, is a FVIIa that has a higher clot-generating activity and longer activity at the site of bleeding. It also has the potential to be infused subcutaneously for prophylactic treatment for those with inhibitors. Trial results are expected in July 2018.

## Immune Tolerance Induction (ITI)

In terms of treatment for those with an inhibitor, the best option has always been the eradication of the inhibitor, using high doses of FVIII for approximately 12-18 months. With the advent of new products and different treatment approaches, this view might change in terms of the day-to-day treatment of people with an inhibitor. However, when it comes to treating the bleeds that occur with new therapies, surgery or responding to a trauma, the most predictable response to bleeding in these cases will be treatment with FVIII. The coming years may see a significant evolution in the way Immune Tolerance Induction (ITI) is used to eradicate an inhibitor.

In the SIPPET study, patients treated with plasma-derived factor VIII containing von Willebrand Factor had a lower incidence of inhibitors than those treated with recombinant Factor VIII. One of the proposed reasons for this was that as the FVIII molecule is mostly attached to the von Willebrand Factor molecule and, as a result, the von Willebrand Factor molecule may cover the parts of the FVIII molecule that the inhibitor attaches to. This may give time for the body to become accustomed to the foreign FVIII, reduce its immune response and stop producing the inhibitor. There are some international trials further examining the impact of using FVIII products containing von Willebrand Factor to eradicate inhibitors.

With the idea of preventing the inhibitor attaching to specific sites on the FVIII molecule, the question could be theorised, could an extended half-life product be beneficial? Would a different molecule, such as Fc being attached to the FVIII molecule, provide a similar protection by covering the same parts as the von Willebrand Factor? The ReITIerate and verITI-8 trials Sobi/Bioverativ (a Sanofi Company) for patients who have failed ITI and those with first time ITI, respectively, will aim to see if there is any additional benefit of using the Fc bound Factor VIII for ITI. Results for these trials are expected in 2020.

## Non-replacement therapies (NRT)

The development of Non-(factor) Replacement Therapies (NRTs) that mimic the FVIII and/or FIX has the potential to have the biggest impact on quality of life in patients with inhibitors, especially those who have failed ITI. Of added benefit is that many of these NRTs are administered via subcutaneous infusions weekly or monthly.

Emicizumab (Hemlibra®; Hoffman-La Roche Pharmaceutical) is a bispecific antibody that bridges activated factor IX (FIXa) and factor X (FX) in order to restore the function of the missing activated FVIII (FVIIIa) that is needed for effective haemostasis. The “Factor VIII activity” of emicizumab in preclinical studies is estimated to be equivalent to 10% to 15% of normal FVIII activity levels with weekly subcutaneous injections. Emicizumab has demonstrated efficacy in preventing bleeding in FVIII patients with inhibitors, resulting in the recent approvals from the EMA and the FDA for prophylaxis of bleeding episodes in people with haemophilia A with FVIII inhibitors. However, it is not approved for

use on demand due to its formulation, so additional clotting factor treatments will be required intravenously when breakthrough bleeds occur as is the case currently with any prophylaxis regimens (BPA or FVIII).

Emicizumab is licensed for prophylaxis treatment of bleeding and not for the treatment of break through bleeding. The adult inhibitor trial (HAVEN 1), demonstrated that patients receiving emicizumab experienced an 87% reduction in treated bleeding episodes compared with patients not receiving emicizumab. 63% of all patients receiving emicizumab experienced no bleeding episodes that required treatment. Emicizumab prophylaxis demonstrated a 79% reduction in treated bleeding episodes compared to prior bypassing agent prophylaxis, which is the current best standard of care. Long term assessment of treated bleeds in 24-week intervals showed an increase in the percentage of zero treated bleeds from the first 24 weeks to the 48-72-week interval. Overall, the number of bleeds that required treatment reduced over time, possibly because damaged joints have less bleeding, built strength and were protected against further bleeding. This may be the same for haemophilia A patients without inhibitors. This will also be a consideration for potential wider spread use of emicizumab. However, the haemophilia patient population is used to an approach of “if in doubt, treat” and this approach may need to be reconsidered with the use of emicizumab. The next stage is the approval of emicizumab for patients with haemophilia A without inhibitors. This cohort is being studied in the Phase III HAVEN 3 trial with results and potential licensing expected by 2019. Additional trials are looking at extending the time between dosing to once every four weeks in patients with or without inhibitors.

In the Haven 1 trial for patients with inhibitors, three patients that received 100u/kg/24hr of aPCC (FEIBA® from Shire) for ≥ 24 hours (FEIBA® from Shire) developed thrombotic microangiopathy, one of whom continued to have serious bleeding and died of the bleed after the inability to identify the source of the bleed and the patient refusing red cell transfusion due to personal beliefs. In addition, two subjects that received 100u/kg/24hr of aPCC (FEIBA® from Shire) for ≥ 24 hours had thrombotic complications. Studies suggest that aPCC can substantially enhance the thrombin generation of emicizumab and the current hypothesis is that this is a result of presence of FIXa and FX in aPCC. It is currently thought unlikely that this problem will be seen in patients without inhibitors where FVIII concentrate is used, but these adverse events emphasize the potential complications that may arise due to different mechanisms of regulating the clotting process. How best to combine non-factor and factor therapies will likely remain an important issue requiring additional studies and widespread education amongst both clinicians and patients.

There were an additional four deaths reported recently. Three of these four cases were compassionate use requests for patients who had very serious or life-threatening conditions where every other treatment option has been exhausted. There is limited detail on all these cases as the treating clinicians want to ensure that the confidentiality of the patient is respected. However, the statement issued by Roche on March 18th, 2018, clarifies that in each of the four cases, the assessment of the treating clinician was that the cause of death was unrelated to Hemlibra®.

In April 2018, a patient with inhibitors, in the Phase III HAVEN 2 clinical trial, developed a neutralising anti-drug antibody to Hemlibra®. As with all therapeutic proteins, there is a potential for the development of anti-drug antibodies with Hemlibra®. The anti-drug antibody resulted in reduced efficacy of Hemlibra® and it was decided to discontinue treatment and the patient resumed his previous treatment. With more than 600 people treated, this is the first confirmed report of a detectable anti-drug antibody that has impacted efficacy. Monitoring for the development of anti-drug antibodies to Hemlibra® is ongoing.

A long-term extension study to evaluate the product is in Phase III trials and is expected in September 2020.

The other methods that are being investigated under the NRT category use a different approach. However, their concept is broadly similar. In normal clotting, there are factors that promote clotting, such as factor VIII or factor IX, and also molecules (anticoagulants) that prevent too much clotting (thrombosis). These two types are in a balance, which is disturbed when one type is missing, like FVIII or FIX in haemophilia. The idea of these treatments is to restore the balance at a lower level, by reducing the levels of the anticoagulants. The NRTs that are being investigated are the inhibitor of anti-thrombin (AT), tissue factor pathway inhibitor (TFPI) and activated protein C (aPC).

Fitusiran by (Sanofi Genzyme/Alnylam) is an anti-thrombin synthetic inhibitor RNA (siRNA), which is currently in Phase III trials for patients with haemophilia with and without inhibitors. Monthly subcutaneous injections of fitusiran reduce the levels of anti-thrombin to approximately 20% of normal levels and this reduction appears to be efficacious in preventing bleeding, with 33 patients (in Phase II open label extension study) experiencing median annualised bleeding rates (ABRs) of 1.0 and 48% experiencing zero bleeds.

However, in September 2017, all trials were suspended after a patient died. The patient had treated himself for a musculoskeletal injury with factor concentrate and then developed a headache. He was erroneously diagnosed with a bleed in the brain (subarachnoid haemorrhage) based on CT imaging and was treated with high intensity FVIII concentrate. He sadly passed away. After his death, expert review of the scans revealed he actually had a clot (cerebral venous sinus thrombosis), not a bleed. As a result, the clinical trial was suspended. In December 2017, the FDA agreed on the recommencement of the trial with alignment on new clinical risk mitigation measures, including protocol-specified guidelines and additional investigator and patient education concerning reduced doses of replacement factor or bypassing agents to treat any breakthrough bleeds in fitusiran studies.

There are three products using the anti-TFPI approaches: PF-06741086 from Pfizer and concizumab from Novo Nordisk, both of which are in Phase II clinical trials, and BAY 1093884 from Bayer in Phase I. Initially anti-TFPIs were considered for use in conjunction with bypassing agents for patients with inhibitors. However, results from Phase I studies demonstrated a reduction to levels of 20% of normal TFPI, which were associated with reduced clotting time and hence may be used to prophylactically treat patients with haemophilia with subcutaneous (and weekly/monthly) administration.

Another approach is inhibiting activated protein C (aPC). Targeting the anticoagulant effect of aPC has restored haemostasis in haemophilia mouse models in the pre-clinical phase and the company ApcinteX is expected to apply for Phase I trials for haemophilia in the near future.

With the significant potential in improvement in quality of life that NRTs can provide, come additional unknowns. NRTs do not prevent all bleeding and their impact on the coagulation cascade adds a great deal to the complexity in the management of bleeding events as well as to the condition of haemophilia itself. Treatment with concizumab was associated with elevated D-dimer levels (which are considered in patients with thrombotic disorders) although the clinical relevance of this observation is unknown. The experience with emicizumab and fitusiran should promote a level of caution about thrombotic consequences, especially when combining therapies.

There is an additional complexity associated with NRTs, in that current laboratory assays to measure the clotting factor levels may not be the most appropriate and additional work will need to be done in order to monitor these therapies in both comprehensive care centres and even more so outside specialist centres.

## Gene therapy

For many years the hope for those with haemophilia without inhibitors was gene therapy, which would allow people to live a life free of infusions, bleeds and progressive joint damage. The hope for those with inhibitors was the same. While the non-inhibitor population may see this by 2023, it is unlikely that this will be the case for those with inhibitors as the current clinical trials exclude people with a history of an inhibitor for now.

There are some considerations in terms of the mechanism of action of inhibitors, and how they may be affected, that currently justifies the present exclusions from the trials. In the current trials, the gene therapy is administered and then there is an initial response where the FVIII or FIX levels increase. In those without inhibitors, the calculation of the amount of FVIII and FIX that is being produced is relatively simple: the gene is injected, the body produces factor to a certain level and it is measured. In some cases, the body then produces an immune response to the capsid, the envelope that the gene is delivered in. This response is detected by raised ALT levels in the liver. If this happens, then there is a reduction in the expression of the FVIII or FIX that is being produced, which again can be measured.

The measured response of the production of FVIII or FIX and the time it takes to be detected might be different in patients with an inhibitor. There is reason to hope that gene therapy may be an effective therapeutic option for people with inhibitors in the future. However, currently no clinical trials are ongoing for patients with a current inhibitor.

One of the first steps towards the inclusion of patients with inhibitors in clinical trials is the Sangamo trial, which is not excluding patients who had a transient inhibitor in childhood. The EHC very much look forward to presenting the first gene therapy in patients with inhibitors in the future in this section. If you would like to get more detail on the current trials, please see the other articles in this newsletter.

# PHARMACEUTICAL COMPANIES LANDSCAPE

There have been a significant number of changes in the haemophilia landscape over the last five years, not just in the number and variation of new products, but in the spinning off, mergers and acquisitions by companies, which has led to a lot of changes in company names. This is a brief article that summarises some of these changes in the companies mentioned in this newsletter. Whilst this is not very useful on an individual country level, as the company that supplies the products in that country will be based on the name that is registered, it may be useful when trying to search for information on products and trials that may be carried out by one of the companies in a partnership, or one where the names may have changed during development.

In 2015, Baxter spun off a new company called Baxalta, which had a heavy focus on haemophilia products. In June 2016, Baxalta then got purchased by Shire. Shire has received a bidby Takeda.

Swedish Orphan Biovitrum (Sobi) has been involved in the process of development and manufacturing of recombinant protein drugs since the technology was first developed around 30 years ago. In 2004, Biovitrum started to manufacture Wyeth's (now Pfizer's) ReFacto® and ReFacto AF/Xyntha®. Sobi partnered with Syntonix on the development of extended half-life products. Syntonix was subsequently acquired by Biogen Idec and in 2016 Biogen Idec spun off their haemophilia business into

a company called Bioverativ. In terms of the partnership, Sobi and Bioverativ (a Sanofi company) collaborate on the development and commercialisation of Alprolix® and Elocta®/Eloctate®. Sobi has final development and commercialisation rights in the Sobi territory (essentially Europe, North Africa, Russia and most Middle Eastern markets). Bioverativ has final development and commercialisation rights in North America and all other regions in the world excluding the Sobi territory and has manufacturing responsibility for Elocta®/Eloctate® and Alprolix®.

In March 2018, Sanofi announced the acquisition of Bioverativ. Through that and two other transactions - the planned acquisition of Ablynx and the above-outlined agreement on fitusiran - they are building a franchise in the field of rare blood disorders. Chugai, the Japanese company that developed ACE910, which became emicizumab and is marketed as Hemlibra®, has a strategic alliance with Roche and Genentech. Roche will market Hemlibra® in Europe, Genentech will market it in the US and Chugai will market it in Japan.

In the gene therapy space, Spark Therapeutics haemophilia B gene therapy is being developed in collaboration with Pfizer. However, Spark Therapeutics retains global commercialisation rights for the haemophilia A gene therapy. Pfizer has partnered with Sangamo in haemophilia A. Sangamo will be responsible for conducting the SB-525 Phase I/II clinical study and certain manufacturing activities. Pfizer will be operationally and financially responsible for subsequent research, development, manufacturing and commercialisation activities for SB-525. Bayer has partnered with Ultragenix for haemophilia A gene therapy, and is scheduled to start Phase I study later this year (2018).

With so many new treatments, including gene therapy, the haemophilia landscape will undoubtedly change again over the coming months and years. Updates will be provided in this newsletter on a periodic basis.