Haemophilia

More and more people living with haemophilia A and B, and their treaters, are seeing the improvements in quality of life that treatment with Elocta and Alprolix brings. This was the key driver of continued strong growth for our Haemophilia franchise throughout 2018.

The ambition within Haemophilia continues: we will do our best to enable access to our treatments for everyone in our territories who has a need. More people are getting access to Elocta (efmoroctocog alfa) and Alprolix (eftrenonacog alfa), and more are choosing to switch to them. Sales of both products showed strong and consistent quarter-on-quarter growth throughout 2018.

The platform that we and Sanofi have developed with Elocta and Alprolix has reshaped the expectations that people with haemophilia A and B can have for their lives. Liberate life

For many people with haemophilia, the main goal of treatment over the years has been safe protection from bleeds. This is obviously a primary consideration, but replacement treatment has now progressed beyond bleed prevention. As well as protection from bleeds, extended half-life treatments are allowing people with haemophilia to expect less pain, better target joint resolution (halting repetitive bleeds into a specific joint and reversing joint damage) and fewer days when they have to worry about their treatment. The main benefit of extended half-life treatments is no longer seen simply as convenience but rather the way these treatments let people with haemophilia live well and feel confident.

In 2018, we undertook an extensive ethnographic study of people living with haemophilia. Despite advances in recent years, many people in the study told how they have to live with compromises and limitations. Younger people told of restricting their activities on non-treatment days, of missing out on opportunities to spend time with friends. Adults spoke of having to cope with everyday pain, of living with stiff joints, having to live with constraints.

This study showed us that people with haemophilia can liberate their lives when treatment delivers in four fundamental areas.

Treatment needs to:
- Allow you to feel safe
- Provide protection from all types of bleeds
- Preserve long-term joint health and reduce pain; and
- Remove the mental burden of haemophilia.

We believe that every person with haemophilia has the right to live well, to live a life free from constraints and compromises. That is why we have a vision of liberating people’s lives.

In recent years, increasing levels of understanding and experience with Elocta and Alprolix, among thousands of people of all ages, have spread throughout the haemophilia community. Patients, carers and treaters talk to each other about lower levels of pain and higher quality of life. This has created a momentum for change, and as a result, we have seen higher numbers of people switching to our treatments.

Proven safety and efficacy

The latest research1, released at the American Society of Hematology (ASH) annual meeting in December, confirms the efficacy and safety profiles of Elocta and Alprolix. Among thousands of people of all ages, haemophilia community. Patients, carers and treaters talk to each other about lower levels of pain and higher quality of life. This has created a momentum for change, and as a result, we have seen higher numbers of people switching to our treatments.

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The results from the ASPIRE and B-YOND studies demonstrate that long-term prophylactic treatment with Elocta and

1. Sobi press release: At ASH, extended half-life therapies Elocta® and Alprolix® demonstrate proven efficacy and well-characterised safety over four years, 12 January 2018 www.sobi.com
EHL factor replacement a mainstay of treatment
We remain convinced that the well-established safety and efficacy profile of both Elocta and Alprolix, confirmed by several years of real-world data from thousands of patients, and their suitability for all patient groups and ages, position them and Sobi well to withstand competition from treatments now entering the market (see box). We see replacement factor as fundamental to the wellbeing of people with haemophilia, and expect it to be the mainstay of treatment for the foreseeable future. We see significant opportunities for growth in the treatment of haemophilia A and B in our territories, notwithstanding the eventual uptake of alternative treatments.

We estimate the market value of haemophilia A treatments to be around USD 3.5 billion and USD 500 million for haemophilia B. Sobi’s market share is estimated at 15 to 20 per cent.

2018 access achievements
Elocta is now available and reimbursed in 26 countries, and Alprolix in 19 countries. Both received new reimbursement in five countries respectively during 2018. Elocta in Slovakia, Poland, Portugal, Croatia and the Czech Republic; Alprolix in Austria, France, Sweden, Slovakia and Hungary. A filing for approval for Elocta in Russia was filed in July following successful GMP inspections.

Committed to treatment for all
Every person with haemophilia should have an equal right to treatment that can liberate their lives and lead to a better tomorrow. But people in different countries face different challenges. So we are working actively to find ways to provide sustainable treatment for as many people with haemophilia as possible. Our aim is the same in each country: to provide timely and sustainable access to transformative treatment for every person with haemophilia.

Yet only 30 per cent of people diagnosed worldwide are currently receiving access to clotting factor replacement treatment. To overcome this fact, we work with stakeholders to improve access to sustainable treatment. Two key initiatives in this commitment are the World Federation of Haemophilia’s Humanitarian Donation Program and the European Haemophilia Consortium’s PARTNERS programme.

About the Sobi-Sanofi collaboration
We work together with Sanofi on the development and commercialisation of Elocta/Eloctate and Alprolix. We have final development and commercialisation rights in our territory – essentially Europe, most Middle Eastern markets, North Africa and Russia.

Sanofi has manufacturing responsibility for the products as well as final development and commercialisation rights in North America and all other regions of the world excluding the Sobi territory.

Our development and commercialisation agreement also includes BIVV001 (added 2014), an engineered factor VIII molecule that uses Fc fusion and XTEN, a half-life extension technology, and BIVV002 (added 2017), a novel factor IX fusion protein, that also uses Fc fusion and XTEN.

BIVV001 is a Sanofi development programme. Sobi has elected to add BIVV001 to its collaboration agreement with Sanofi but has not yet opted in.

1. Sobi press release: At ASH, extended half-life therapies Elocta® and Alprolix® demonstrate proven efficacy and well-characterised safety over four years, 12 January 2018 www.sobi.com
As visionary contributors to the WFH donation programme, Sobi and Sanofi Genzyme, Sanofi’s specialty care business, have committed to donate 1 billion international units of our EHL factor treatments to the haemophilia community, of which 500 million IUs has been committed to the WFH Humanitarian Donation Program over a five-year period which started in 2015. As well as treatment and the necessary transportation, we are supporting the programme’s efforts to build up infrastructure and expertise in the recipient countries. This will enable them to provide ongoing, sustainable treatment for people with haemophilia.

The impact of the donation programme so far has been extensive and rewarding:

- More than 16,800 people reported treated in 45 countries
- Nearly 2,000 surgeries including operations that have saved people’s lives and limbs
- More than 117,000 acute bleeds treated.

More than 370 million IUs of factor have already been donated to the WFH.

The EHC PARTNERS programme is designed to improve access to treatment in countries in Central and Eastern Europe that currently have insufficient budgets to provide sustainable access to the level recommended by the European Directorate for the Quality of Medicines and Healthcare (EDQM). Sobi was one of the two founding corporate partners in the programme, which aims to provide subsidised treatment to countries that commit to increasing their investment in haemophilia to ensure sustainable access to treatment. We are pleased to see other companies now agreeing to support the PARTNERS programme.

In developed countries in our territory, we work together with healthcare systems to apply a pricing strategy based on annual parity with conventional treatments available on the market. This means that our products can reach everyone with haemophilia without any significant extra cost and no additional barriers.

We work closely with the community – patients, caregivers, treaters and payers – in areas such as education and support services. This is part of our commitment to enabling people living with haemophilia to liberate their lives.

»More and more patients in France are converting to our therapies for haemophilia.«

Sofiane Fahmy,
Head of Southern and Western Europe and North Africa

**Brief facts about Sobi’s Haemophilia portfolio:**

**ELOCTA®**

Elocta (efmoroctocog alfa) is a recombinant clotting factor VIII therapy developed for haemophilia A with prolonged circulation in the body using Fc fusion technology. Elocta is approved for the treatment of haemophilia A in adults and children of all ages and marketed by Sobi in the EU, Iceland, Liechtenstein, Norway, Switzerland, Kuwait and Saudi Arabia. It is approved under the name Eloctate, for the US, Canada, Japan, Australia, New Zealand, Brazil and other countries, where it is marketed by Sanofi.

For full prescribing information, please see the EMA’s website.

- Total sales: SEK 3,261M
- Sales growth: 109%
- Number of new markets: 5

**ALPROLIX®**

Alprolix (eftrenonacog alfa) is a recombinant clotting factor therapy developed for haemophilia B using Fc fusion technology to prolong circulation in the body. Alprolix is approved for the treatment of haemophilia B in adults and children of all ages in the EU, Iceland, Liechtenstein, Norway, Switzerland, Kuwait and Saudi Arabia, where it is marketed by Sobi. Alprolix is approved for the treatment of haemophilia B in the US, Canada, Japan, Australia, New Zealand, Brazil and other countries, where it is marketed by Sanofi.

For full prescribing information, please see the EMA’s website.

- Total sales: SEK 974M
- Sales growth: 168%
- Number of new markets: 5
Therapeutic options for haemophilia A and B

Haemophilia therapy has undergone a major evolution over the past decade. Because haemophilia A and B are caused by deficiencies in factor VIII (FVIII) and factor IX (FIX) respectively, replacement of the missing factor has been and remains the standard of care for both the prevention of bleeding episodes (prophylaxis) and the treatment of breakthrough bleeds (on-demand therapy).

Factor concentrates were initially produced from plasma, but large-scale production first became possible with the development of recombinant technology, which also avoids the inherent risks of using pooled human plasma in the manufacturing process.

A more recent evolution in factor replacement therapy is the use of technologies to extend the relatively short half-life of clotting factor, which allows improved protection without increasing treatment burden. Half-life extension can be accomplished by fusion of factor to the Fc part of antibodies (IgG) or albumin, or the addition of synthetic polyethylene glycol (PEG). In contrast to FIX, the extension of the half-life of FVIII has so far been limited by the binding of FVIII to von Willebrand Factor (VWF), a problem which is circumvented by the development of the VWF-independent product candidate rVIIIIfc-VWF-XTEN (BIVV001). The long-term safety and efficacy of factor replacement therapies using Fc fusion to extend half-life have been demonstrated in trials including ASPIRE and B-YOND.

When haemophilia patients develop neutralising/inhibitory antibodies to infused factor, eradication of those inhibitors through Immune Tolerance Induction (ITI) therapy is considered a first-choice treatment. To prevent or treat breakthrough bleeds, bypassing agents such as FVIII inhibitor bypass agent and recombinant FVII can be used. Recently, a bispecific antibody mimicking FVIIa has been approved for the prevention of bleeding in haemophilia patients with or without inhibitors. These patients would however still need alternative/bypass therapy for the treatment of breakthrough bleeds.

Other non-factor replacement therapies are under development. Gene therapy has been under investigation for quite some time now for haemophilia A and B, but remains in clinical development and the long-term efficacy and safety of this potentially curative approach have yet to be established.

»Believe in yourself. You can achieve anything.«

Alexis Perdikis has a message for people with haemophilia: “Believe in yourself. You can achieve anything. This is what I feel, it comes right from my heart.”

Alexis, 33, is a sports journalist in Athens, the capital of Greece.

He also has severe haemophilia A.

Today, he lives a life full of opportunity and possibility. “I can go to work without having to worry about getting a bleed. I can go swimming, which is very important for my quality of life.”

But life hasn’t always been so free of limitations. As a boy, Alexis experienced the restrictions familiar to many who grow up with haemophilia.

“Growing up with severe haemophilia is difficult, a bit tough. It is very strange for a parent to have to explain to a little child, you cannot play, you cannot play football with your friends, you cannot run, you cannot ride your bicycle. It’s like there is a big DON’T above your head all the time. Don’t do this, don’t do that.”

“That is one part. The second part is your psychology. Haemophilia hits your self-confidence and self-esteem. You grow up and you don’t believe in yourself. You think, ‘I won’t be able to do this or that’. This is probably the biggest limitation.”

Alexis was receiving on-demand treatment until the age of 27. For five years he has been on prophylaxis, the past two years with Elocta.

“There have been many differences. The most important at first was zero bleeds – less pain in my joints and muscles, in my body in general.”

“Sober, it’s about your mental health. It’s a sense of freedom. You feel freer. You feel that you can do things you couldn’t do before.”

He emphasises the importance of self-confidence and self-esteem for people living with haemophilia. “It’s all about believing in yourself. To realise, I can have a normal job like anyone else, a girlfriend or a family. This is so, so important.”

For the past five years, Alexis has served as secretary general of the Greek Haemophilia Society. He sees national member organisations as playing an essential role in the haemophilia community: “They are a link in the chain between the patients and all the other stakeholders: government, ministry of health, hospitals, administration, the companies. Patient organisations must help bring those different parts together.”

Asked what someone with haemophilia should expect from their treatment, Alexis says people can set their own ambitions: “Be strong. Use your inner power to achieve whatever you want. Of course, good treatment is important. But in the end everything has to do with you, and with what you want to achieve.”
MEETING PATIENT NEEDS

Armin Reininger
Our Head of Global Medical and Scientific Affairs reflects on highlights from 2018, and emerging trends for the years ahead.

Background
When Armin joined Sobi in January 2017, it was the latest step in a distinguished career in medicine and research. With extensive experience in both blood research and transfusion medicine, Armin has published more than 70 scientific articles. He has also held senior positions at Harvard Medical School, Scripps Research Institute, and at Ludwig-Maximilians-Universität in Munich where he continues as a professor of anatomy. He has served on the boards and committees of several international organisations in the areas of thrombosis and haemostasis. When Armin joined Sobi, he came from a position as Head of Medical Affairs EMEA at Shire/Baxalta.

What have been the highlights for you in Haemophilia in 2018?
The most important is that more people are benefiting from our treatments. As word spreads through the patient and treater communities about the difference our treatments can bring, people are re-examining their initial hesitation about switching from conventional therapies. Key opinion leaders tell us they see significant benefits for patients on EHL treatments.

Real-world experience is showing that patients can expect more from life, and truly live well with haemophilia. Just a few decades ago, we told people with haemophilia not to move – stay at home, don’t do anything, in order to avoid bleeds. That has changed dramatically. Now we offer them EHL products that can liberate their lives.

Looking forward, we can see from the preliminary data released last year (see Haemophilia section) that BIVV001 has potential to build on where we have already taken treatment for haemophilia A. We continue to strengthen our relationship with Sanofi, and I see a very bright future here.

How do you see the haemophilia landscape developing?
There is a lot of hype about new treatments being approved. I believe strongly, and I hear constantly from the treater community, that replacing the missing clotting factor is fundamental to the wellbeing of people with haemophilia. The safety and efficacy profiles of Elocta and Alprolix have been confirmed by several years of real-world experience from thousands of patients. They have been shown conclusively to be suitable for all patient groups and ages, and provide the flexibility to truly match treatment to expected outcomes.

I hear clear feedback from physicians that they and their patients appreciate the very physiological approach of replacing the missing clotting factor: you can measure the factor level, you can increase the dose to the level needed. I remain convinced that proven and effective factor replacement that can be matched to an individual’s treatment goals in all situations will continue to be the mainstay of treatment for the future.

What do you see as some other major highlights from 2018?
One was definitely emapalumab. This is a huge step forward for Sobi, because it confirms our commitment to the immunology space and demonstrates how our success in haemophilia lets us invest in helping more children with a severe unmet medical need. Our most recent addition, Synagis, fulfils the same fundamental ambition. It helps as a prophylactic treatment so that premature babies survive better, and require fewer hospitalisations and intensive care unit admissions when exposed to RSV (respiratory syncytial virus), which causes respiratory tract infections.

Another highlight for me is the way everyone within Sobi – from the Executive Committee to the many teams throughout the organisation – works together to find innovative treatments and get them to the people who need them. This is a long-standing strength at Sobi. Our position today, as a leading player in rare diseases, is built on a lot of partnership over the years, internally and externally, as well as on our core values, which have been evolved to address the challenges we encounter on a daily basis.

We have a clear strategy on which we are delivering, and a clear path ahead of us. We really have made a mark, in haemophilia in particular, and are no longer the new kid on the block. Sobi is seen today as a major player, making a real difference to the lives of people with rare diseases. And as a physician that is my main motivation for trying to do better every day.

»Sobi is seen today as a major player, making a real difference to the lives of people with rare diseases.«

Armin Reininger
Our Head of Global Medical and Scientific Affairs reflects on highlights from 2018, and emerging trends for the years ahead.
Better meeting patient needs

We are working actively to find better ways to meet patient needs. This can entail product development and innovation driven by medical needs. New medical needs may arise when people with certain rare diseases grow up, reaching adolescence and adulthood for the first time thanks to the treatments we provide.