Making a difference

With a firm philosophy that innovation is an idea successfully commercialised, our R&D organisation is seeking to transform our new innovations into commercially available treatments for patients.

### Our innovation pipeline as per 31 December 2016

<table>
<thead>
<tr>
<th>Therapeutic area/Indication</th>
<th>Product/Project</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>Haemophilia A</td>
<td>Elocta/ASPIRE(^1)</td>
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<tr>
<td>Haemophilia A</td>
<td>Elocta/PUP(^2)</td>
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<td>Haemophilia A</td>
<td>BIVV001(^3)/XTEN</td>
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<tr>
<td>Haemophilia B</td>
<td>Alprolix/B-YOND(^1)</td>
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<tr>
<td>Haemophilia B</td>
<td>Alprolix/PUP(^2)</td>
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<tr>
<td>Acute gout</td>
<td>Kineret/anaGO</td>
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<tr>
<td>Still's disease</td>
<td>Kineret/anaSTILLS(^4)</td>
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<td>Alkaptonuria</td>
<td>Orfadin/SONIA2</td>
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<td>MPSIII</td>
<td>SOBI003</td>
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<td>CS driven diseases</td>
<td>SOBI005</td>
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<td>IL-1 driven diseases</td>
<td>SOBI006</td>
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1. Extension trial for an already approved indication.
2. PUP = Previously Untreated Patients.
3. Bioverativ development programme. Sobi has elected to add the programme to the collaboration agreement but not yet opted-in.

Our R&D model is not linear but rather cyclical, as the knowledge we gain throughout the process is continuously fed back into development. By working cross-functionally and identifying the stakeholders at each stage, we aim to streamline the time it takes to bring treatments to patients, while also ensuring optimal outcomes and sustainable access.

### Driving the portfolio forward

In 2015/2016, a number of projects aimed at developing approved products and late-stage projects, such as our haemophilia products, were successfully brought to market. These innovations will lay the foundation for building Sobi, a research-based biotech company, in the years to come.

We achieved substantial in-house accomplishments in our early-stage pipeline during the year by focusing on our capabilities in protein engineering and biologics production. We have now begun to seek collaboration with patient communities and authorities at the pre-clinical stage to ensure access to treatments once the development process has been successfully completed.
Sobi’s innovation model

Using a multi-disciplinary approach, cross-functional teams map and evaluate new R&D projects by applying the three lenses of our innovation model. This ensures that new projects are aligned with our corporate strategy, that we successfully utilise our strengths, and assures that only projects with favourable risk profiles will be pursued.

A transformational impact on rare diseases

Our innovation model revolves around the patient journey for people with rare diseases. We aim to define the real unmet needs by collaborating with patients, their families, caregivers, and the medical community; and by continuously studying treatment outcomes. By doing so, we aim to achieve a transformative impact with our programmes – to substantially improve the lives of people living with rare diseases.

Expertise in biologics and process development

Our R&D approach provides an interface between new discoveries and integrated research and development processes. The scientific/technological aspects of a proposed programme (drug molecule, processes, development plans) should be aligned with our capabilities and skill sets.

Providing sustainable access to medicines

By identifying the relevant stakeholders at each stage of the patient journey we aim to co-create and secure optimal outcomes along the development pathway. When we collaborate we believe that we are able to facilitate each step, resulting in smoother, and ideally faster development and delivery to patients.
Our R&D capabilities

Our in-house capabilities encompass the entire R&D value chain, from gene to patient, and our aim is to build a balanced portfolio of new biological entities and projects to develop our existing products according to patient insight.

Biologics development and supply – a strategic asset

The close collaboration and integration within our project teams, and with our biologics manufacturing unit in Stockholm, Sweden, is a key success factor for both the development of our candidate drug SOBI003 and our other programmes.

Our in-house competences provides an understanding of the elements needed in order to successfully scale up and prepare for commercial-scale production. A holistic view of the process, with integrated development and manufacturing approaches, supports our ability to reduce the overall time from early development to products reaching the patients, without compromising safety. In 2016, we invested in new cell culture technology, which enables greater flexibility and shorter set-up times to accelerate lead times.

Process development and optimisation of manufacturing is resource intensive, requiring high investment by drug developers throughout the process. Our end-to-end perspective on research, development, manufacturing and product maintenance is a strategic asset, and our ability to access in-house manufacturing facilities creates a competitive advantage. The combination of biologics production know-how and manufacturing under license to Pfizer generates synergies and reduces costs, which benefits Sobi as well as our partners and patients.

Protein engineering

Pharmaceutical protein engineering is the process of developing proteins that can be useful in the treatment of diseases. The aim is to optimise and tailor the key properties of new investigational leads and products, in an effort to create differentiated products in an increasingly competitive pharmaceutical landscape and, even more importantly, to design proteins that are suitable for effectively targeting rare diseases.

This technique has made it possible to develop new therapeutic proteins with improved properties. Many of the key attributes that determine the future success of a protein lead can be modulated by protein engineering. Sobi has more than 30 years of experience in protein engineering and were one of the pioneers in using recombinant technologies to develop biopharmaceuticals in the 1980s. Together with our partner companies, we use protein engineering to design and produce therapeutic proteins with the potential to transform the lives of rare disease patients.

Extending the half-life of proteins

Extending the half-life of a therapeutic protein means that it can stay in the bloodstream for longer. The advantages of extending the half-life can include increased efficacy of a single dose, as well as increased concentration of drug substance, which can lead to enhanced uptake and reduced treatment burden. The Fc-fusion technology platform is already being used in haemophilia and the IL-1 inflammation (SOBI006) and complement C5 (SOBI005) development programmes. In addition to the Fc-fusion technological platform to extend the half-life of products, we are currently exploring a number of other platforms, both our own and those of partners.

In our biopharmaceutical production, we mimic the natural process in the cell by using cells from different species as a “protein factory”. We employ recombinant DNA technology to produce an optimised protein. In the bioreactors, we grow a large number of cells – each producing our biopharmaceutical, which is then isolated and purified. Throughout, our protein is analysed and characterised to verify that the production process produces our biopharmaceutical at consistent quality, to ensure the safety and efficacy of the product. The production process must also be robust, scalable and cost-effective.
Responding to patient insights

Influenced by the patient journey and based on the needs of patient representatives and caregivers, we continuously explore the potential to further develop authorised medications for new indications.

Orfadin (nitisinone) – delivering on our promise to patients
We have developed a new dosage form and new strengths of Orfadin to meet changing needs. The two new formulations – an oral suspension and a 20 mg capsule – were authorised by the European Commission in 2015 and approved by the Food and Drug Administration (FDA) in 2016. The oral suspension formulation is a result of our commitment to the needs of infants and children diagnosed with HT-1 early in life, to provide a formula that is suited for a population that is growing and where treatment is given relative to body weight. The 20 mg capsule facilitates adherence to treatment regimens by reducing treatment burden. With a continued strong patient-centric approach we aim to improve the treatment, care and ultimately, lives of people living with HT-1 in the coming years.

Safety first
Sobi is sponsoring a long-term safety study of Orfadin treatment in HT-1 in standard clinical care (the OPAL study). The participants are using Orfadin according to normal clinical practice. The study is in response to demands from the Committee for Medicinal Products for Human Use (CHMP) who have looked at the data for approximately 400 patients and found the benefit-risk ratio to be positive.

Patient-driven development
Alkaptonuria (AKU) is a genetic disease that damages the bones and cartilage, causes severe pain and leads to health problems such as osteoarthritis, heart and kidney disease. It is extremely rare and approximately 950 people worldwide are living with AKU.

DevelopAKUre1 is a clinical development programme for the drug nitisinone, the first potential treatment for AKU, run by a European consortium, which was initiated by a patient group. Sobi is an equal partner in this consortium of 12 member organisations; hospitals, pharmaceutical companies and consultancies, universities, biotech companies and national AKU patient organisations are all working towards the development of nitisinone as a treatment for AKU.

Kineret (anakinra) – exploring the full potential
Interleukin-1 (IL-1) is a key mediator of local and systemic inflammation and a significant contributor to autoinflammatory diseases. Many autoinflammatory diseases, such as CAPS (cryopyrin-associated periodic syndrome) and NOMID (neonatal-onset multisystem inflammatory disease) one of three forms of CAPS, have symptoms that are chronic from childhood or infancy. Blocking IL-1 activity in autoinflammatory syndromes results in a rapid and sustained reduction in disease severity. We are determined to continue exploring the full potential of Kineret in auto-inflammatory diseases, such as Still’s disease, as well as other more common inflammatory diseases, such as acute gout. In 2016, we expanded our strategic development activities for the product in an effort to meet the needs of the medical and patient communities.

ABOUT STILL’S DISEASE
Still’s disease is an autoinflammatory disease that affects both children and adults, and is characterised by high spiking fevers, intermittent rash and arthritis. Still’s disease is also referred to as systemic juvenile idiopathic arthritis or adult-onset Still’s disease. For patients with Still’s disease, there remains a high unmet need for a short-acting treatment option with a quick onset of efficacy and a well-established benefit-risk profile. The total number of people in the US with Still’s disease, is an estimated 40,000.

1. This project has received funding from the EU’s Seventh Framework Programme for Research and Technological Development under grant agreement no 304985
Two new clinical programmes
Clinical programmes with Kineret have been designed with the aim of evaluating two new potential indications where a significant need for alternative treatment options exists: acute gout and Still’s disease. The clinical trials will take place in North America.

The acute gout programme – anaGO – was initiated in 2016 and will include a dose-finding phase 2 study, followed by a planned phase 3 study designed to evaluate the efficacy and safety of Kineret treatment in resolving the auto-inflammatory driven pain of acute flares.

The planned Still’s disease study – anaSTILLS – is a phase 3 study designed to evaluate the efficacy and safety of Kineret in newly diagnosed adult and paediatric patients. The trial is planned to start in the second half of 2017. Sobi received Orphan Drug Designation in the US in September 2015 for anakinra for the treatment of Still’s disease including systemic juvenile idiopathic arthritis and adult-onset Still’s disease.

Product maintenance
We are committed to addressing all kinds of patient and caregiver needs.

For the administration of Kineret, we have introduced a new syringe with a thinner, 29-gauge, needle and components not made from natural rubber latex. The new syringe was launched in all markets during the year. In addition, we have been granted both a European and US patent for a citrate-free formulation of anakinra.

Exploring unmet need

Our world-class capabilities in protein biochemistry and biologics manufacturing allow us to develop next-generation biological products. Our patient-access oriented approach from early development and onwards generates the evidence needed to support early and sustainable access to treatment.

Lysosomal storage disorders – a Sobi candidate
In 2016, the European Commission granted orphan drug status to our product candidate SOBI003, a modified human recombinant sulfamidase enzyme for the treatment of mucopolysaccharidosis type IIIA (MPS IIIA), or Sanfilippo disease.

In MPS IIIA, the body is unable to break down long chains of sugar molecules called heparan sulfate, resulting in heparan sulfate accumulation in lysosomes. MPS IIIA affects the whole body, especially the central nervous system where it causes severe progressive degeneration. SOBI003 is an enzyme replacement therapy, intended to reduce accumulated heparan sulfate in the affected cells.

Our entire approach has been built on elements that have been identified by representatives of the patient community, starting from the earliest phases. Development of SOBI003 is currently in late preclinical stage and to date, preclinical studies with repeated systemic infusions have demonstrated reduced substrate levels in the brain of mice with resulting disease-modifying effects. We are preparing for clinical studies with a planned start in 2018. In 2016, we established advisory boards with patient representatives and experts to promote a collaborative approach to clinical study design.

Rare diseases require a creative and collaborative approach to overcome the challenges along the way. Our emphasis on patient-access oriented R&D is actively guiding the SOBI003 programme and co-creation with all stakeholders is, and will remain, a critical success factor for this work. There are many decision points along the path to real patient access for a novel treatment for a rare disease, particularly when there has been no treatment available to date. Evidence is required for each decision point and our collaborative and co-creative approach with our stakeholders aims at supporting the availability of good decisions based on as solid evidence as possible at each step along the way.

Exploring a novel technological platform
We have continued to capitalise on proprietary and partner platform technology, with the aim of developing new molecules with sustained effect and improved utility.

We have been working with Affibody AB on various programmes over the years, exploring a novel technological platform. Affibody molecules are a class of
protein-targeting biological molecules that can be considered an alternative to antibodies. We have used this technology to develop highly potent inhibitors to complement factor C5. The complement system is an important part of the immune system involved in the pathology of many severe diseases. Complement factor C5 is one of the central components in the complement cascade and has a clear therapeutic potential to target diseases such as PNH (paroxysmal nocturnal haemoglobinuria) and aHUS (atypical haemolytic uraemic syndrome). In 2016, we chose a new drug candidate, SOBI005, within this programme.

In 2016, we also signed a licensing agreement with Affibody AB to exploit Affibody molecules as a potential new interleukin-1 (IL-1) pathway modulators for the development of novel treatments for inflammatory diseases where IL-1 is involved. We nominated our second new drug candidate for the year, SOBI006, within this IL-1 programme. SOBI006 is directed against a specific target in the IL-1 pathway and is aimed at further strengthening our presence in the inflammation field with the objective to provide additional opportunities to address unmet medical needs in the field of auto-inflammatory diseases.

Building next-generation treatments

BIVV001 (rFVIIIFc-XTEN) is a drug candidate developed by Bioverativ. The molecule has the potential to further extend the half-life of factor VIII for the treatment of haemophilia A. The XTEN technology is proprietary to Amunix Operating, Inc. The collaboration agreement with Bioverativ has similar terms to those of Elocta and Alprolix and we have not yet exercised our opt-in right to this programme.