BUSINESS SWEDEN

RARE- & ORPHAN DISEASE DRUG DEVELOPMENT

WHAT IS THE STATUS IN SWEDEN?

BUSINESS SWEDEN & SWEDENBIO 2019

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Pharmaceutical companies – driven primarily by increased pressure from payers and regulators – now focus their attention more or less exclusively on areas with a high and clearly unmet medical need. Technical and scientific advances within the field of genomics and precision medicine also means that the patient populations targeted by new therapeutics become smaller and more defined. Together, these trends have paved the way for a booming interest in the orphan- and rare diseases space - a development that is seen also in Sweden.

This paper describes the orphan disease pipeline of Swedish companies and presents statistics over orphan drug designations granted to Swedish companies by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In addition, five different perspectives on orphan drug development will be presented, including those of both a large and a small specialist company, a leading medical university, a venture capital investor and a company that provides regulatory services and expertise.

REPORT HIGHLIGHTS

- Swedish companies have been granted 60 orphan designations in the EU and 47 in the US from January 2000 until December 2018
- Oncology is the leading orphan drug therapy area accounting for about 38% of the total Swedish pipeline
- Neurology, immunology/rheumatology and transplantation are the next leading therapy areas, accounting for another 26% of the pipeline
- Sobi is the largest Swedish company active in this area with several approved orphan drugs
- Perspectives on orphan drug development is given by HealthCap, Immedica Pharma, Karolinska Institutet, NDA Group, and Sobi
- A list of Swedish orphan disease pipeline projects is outlined (page 10)

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INTRODUCTION

The US Orphan Drug Act of 1983 and the EU Orphan Regulation of 2000 were both created to provide incentives for companies to develop orphan drugs. This since it is often not profitable for companies to develop medicines for rare diseases under normal market conditions. Similar legislation exists in Australia and Japan.

Any disease affecting fewer than 5 people in 10,000 in the European Union is considered rare, which translates into approximately 246,000 people [1]. In the United States, a rare disease is defined as one that affects fewer than 200,000 people[2]. Most patients suffer from even rarer diseases affecting 1 person in 100,000 or fewer. About 350 million people globally are living with a rare disease. Of these, 30 million people are found in the United States and about 30 million people in the European Union [3, 1].

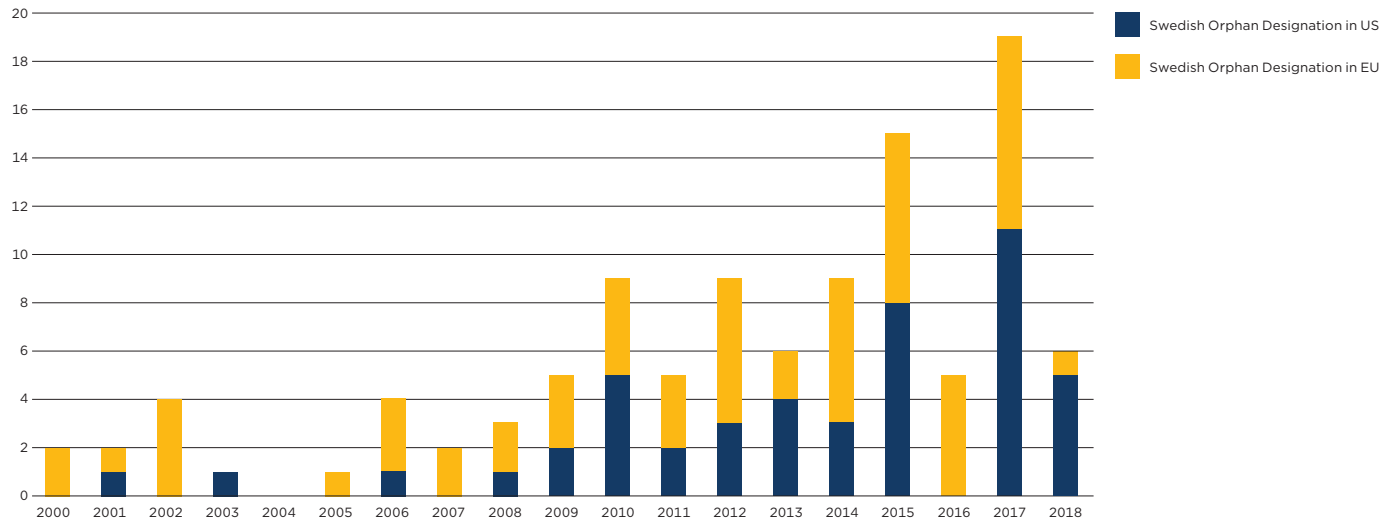
Over 7,000 distinct rare diseases exist of which approximately 80 percent are caused by faulty genes [4]. Diseases such as malaria are quite common in some parts of the world but are considered rare in the US or in the EU. Other diseases, e.g. Alzheimer's disease, are not rare diseases as a whole, but certain forms of these diseases are considered rare [4].

The grant of an Orphan Designation for a medicine will give the holder benefits such as protocol assistance, fee-reductions and tax-credits. Once an Orphan Drug is authorised it qualifies for 10-year market exclusivity in both the EU and Japan, while 7 years in the US. However, this market exclusivity does not necessarily block medicines which are used for the same rare disease but differ from the first medicine on the basis of their molecular make up, the way they work and the way they are used [6, 7, 8].

ORPHAN DRUG DEVELOPMENT ON THE RISE

During the period January 2000 to December 2018 more than 3,800 orphan designations have

ORPHAN DESIGNATIONS SWEDISH PROJECTS



been granted in the US and more than 2,000 in the EU. During this period, 547 orphan drugs have also been granted in the US and 154 in the EU [9, 10].

Pharmacia was the first Swedish company to receive an orphan designation. Their anti-trombin III product Atnativ was granted orphan designation already in 1985. It was later approved as an orphan drug in the US.

In recent years, Sobi has been the Swedish company with the highest number of approved orphan drugs. In the EU, Sobi's Orfadin (nitisinone) received approved orphan drug status in 2005. This orphan drug was later followed by Alprolix (2016), which still holds market exclusivity for the treatment of haemophilia B (congenital factor IX deficiency). Kineret has also recently (2018) been approved as an orphan drug in the EU for treatment of Still's disease.

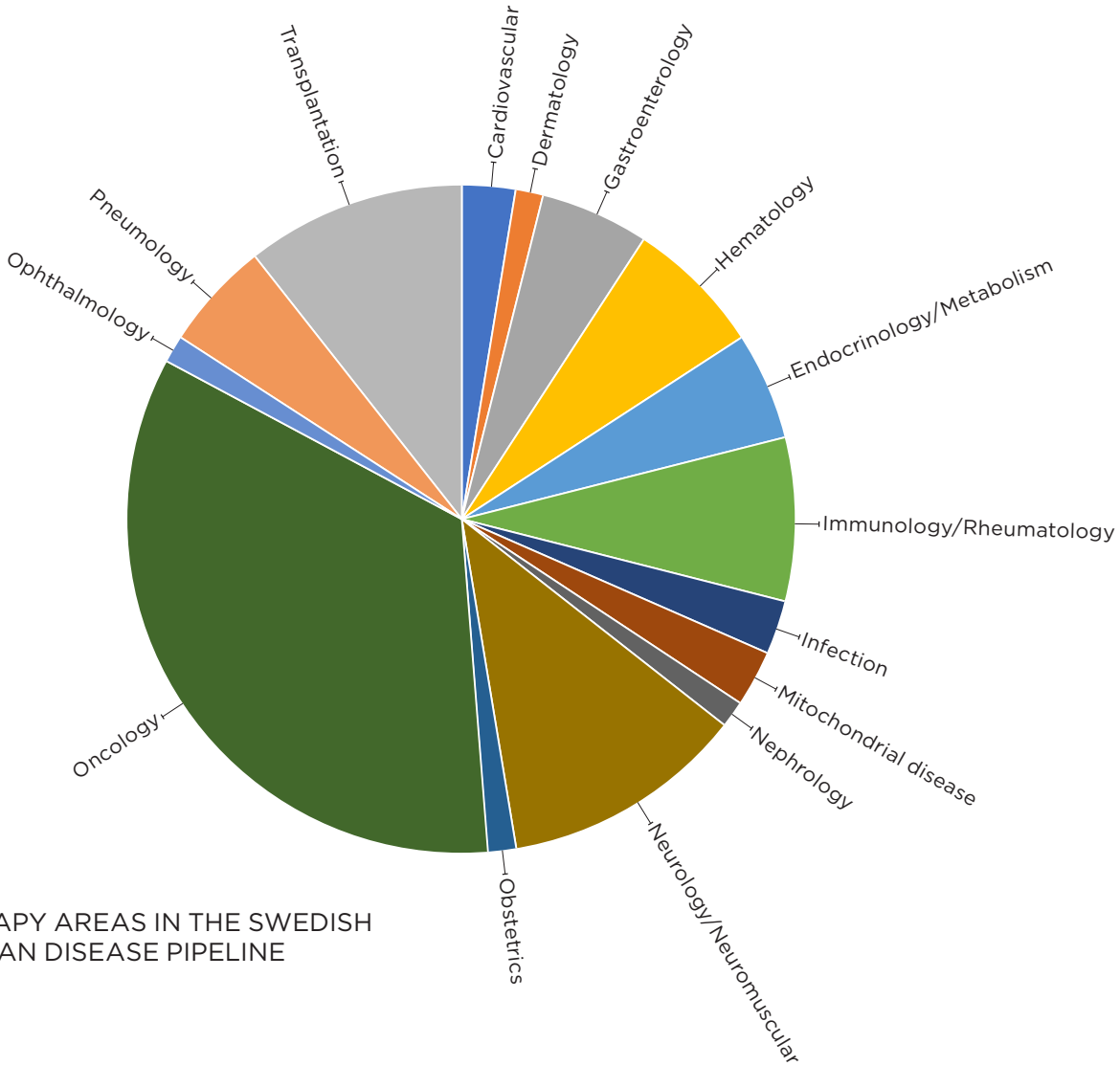
Swedish companies have been granted 60 orphan designations in the EU and 47 in the US from January 2000 until December 2018.

We see an increasing trend in the number of Swedish medicines being granted orphan designation each year, showing that this field of drug development is gaining pace.

SWEDISH ORPHAN DESIGNATIONS

To get a more comprehensive view of all the ongoing Swedish projects in rare diseases, we have used the report "Swedish Drug Discovery and Drug Development Pipeline 2016" [11], published by SwedenBIO, in addition to the orphan designation registers from EU and FDA. For classification of rare diseases into therapy areas the classification at Orphanet was used [12].

Most rare diseases projects are found within the oncology, neurology/neuromuscular and transplantation fields. There are also projects in areas such as immunology/rheumatology, hematology and pneumology. In total, 37 companies reported 66 different projects, 52 unique substances and 60 unique indications.



THERAPY AREAS IN THE SWEDISH ORPHAN DISEASE PIPELINE

FIVE PERSPECTIVES ON THE RARE DISEASE AREA

NDA GROUP

The regulatory service provider

NDA is a leading regulatory consultancy with a dedicated team of over 150 consultants. Headquartered in the northern part of Stockholm, conveniently close to Stockholm Arlanda Airport, they also have offices in four additional European countries and in the US. In this capacity they have supported over 40% of the new medicinal products approved in the EU over the last five years.

In Sweden, NDA Group is working with around 50 companies, several of them developing orphan disease products. "An orphan designation gives access to certain benefits from the European Medicines Agency and the FDA in the US. This includes reduced fees and market exclusivity when the product is launched", explains Johan Strömqvist, CEO, NDA Group.

To qualify for orphan designation in the EU the medicine must be indicated for a life-threatening or chronically debilitating disease which does not affect more than 5 in 10,000 people. In addition, there should be no satisfactory treatment already available. "Supporting companies with their applications for orphan designation is one of many things we do", he continues. "In Europe, these applications are examined by EMA's Committee for Orphan Medicinal Products (COMP) and the evaluation process takes a maximum of 90 days. The application is then granted by the European Commission."

Designated orphan medicines are also eligible for conditional marketing authorisation and may sometimes be administered to patients under a compassionate use schedule. "This gives physicians the option of treating patients using unauthorised medicine outside of clinical studies", explains Strömqvist.

NDA Group sees many good reasons for staying put at their current premises just north of Stockholm. "In Sweden we have excellent competence available at a very competitive cost. We have strong life science clusters both in the Stockholm/Uppsala area and around Malmö/Lund in the south of Sweden. It's a global business but Arlanda Airport is only fifteen minutes away." Johan Strömqvist also sees that there is a lot of innovation and many interesting biotech companies in Sweden. "Given the abundance of high quality innovation, the availability of venture capital needs to improve. We need more investors from the US or investors with an American mentality."

Another advantage for NDA Group is that the Swedish Medical Products Agency is located in Uppsala. Strömqvist sums it up: "This is very favourable for us, since the MPA truly is an internationally leading regulatory agency. There is great regulatory competence available and a rotation of people between agency and industry drives quality on both sides."

CEO JOHAN STRÖMQVIST

HEALTHCAP

The life science investor

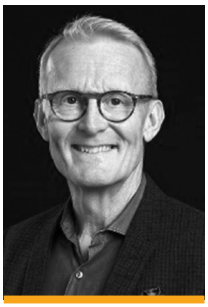
In the wake of the 2001 and 2008 financial crises several life science venture firms disappeared in Sweden and Europe. Furthermore, large pharma companies became more and more risk-averse and focused primarily on topline growth rather than pipeline opportunities. This led the Swedish-based venture capital firm HealthCap to revisit their investment strategy. Partner Dr Johan Christenson explains that the ambition was to find areas with lower capital need and shorter development lead times. "Also, we wished to focus on projects where the biology was well understood and where we could develop products all the way to the market." This led HealthCap to increase the number of investments in niche and rare disease projects – a strategy which has paid off handsomely.

With more than EUR 1 billion raised since the start in 1996, HealthCap is one of the largest specialised providers of venture capital within life sciences in Europe. The firm invests globally and has backed and built more than one hundred companies, taken more than forty of them public and done numerous trade sales. HealthCap companies have developed more than twenty pharmaceutical products to market approval, many of which are breakthrough therapies helping patients with life-threatening diseases.

Examples of successful investments in the rare disease space include Jerini AG, Oncopeptides AB and Wilson Therapeutics AB. Christenson points out that Sweden offers an attractive environment for operating smaller and partly virtual companies. "There is good access to talent and expertise and people are very collaboration-minded."

Wilson Therapeutics was founded around technology licensed from Northwestern University in Chicago. The technology was then incubated and developed in the Swedish company. It was recently sold to Alexion Therapeutics for SEK 7,100 million (~$855 million). Both Oncopeptides and Wilson Therapeutics were successfully introduced on the Nasdaq Stockholm stock exchange.

"A large number of rare diseases are still not well-characterised and diagnosed. We anticipate plenty of new opportunities in this space also in the future", concludes Christenson.



DR JOHAN CHRISTENSON

IMMEDICA PHARMA

The emerging company

Immedica Pharma offers pan-European niche specialty pharma launch, commercialisation and distribution services. The company was just recently formed through the acquisition of Medical Need Europe AB and is supported by the venture capital firm Impilo which brought in an experienced leadership team, including the CEO Dr Anders Edvell.

"Our business model is to support small and mid-size pharma companies in accessing the fragmented European market. We have the knowledge and experience to commercialise niche and orphan medicines across Europe and the Middle-East," says Edvell.

In order to do this successfully, Edvell underscores the need to know the local environment and business conditions, for example price negotiation practices, in each of the key European markets. The people at Immedica Pharma have long experience from engaging in discussions with the Swedish Dental and Pharmaceutical Benefits Agency (TLV), which is typically willing to hold direct dialogue with companies.

Edvell continues: "In Sweden, rules and regulations are stable and the system and price negotiations are predictable. This is very valuable for a company navigating in this market, but it still requires local experience and knowledge".

Immedica Pharma sources its product portfolio primarily from US companies that wish to capitalise on the European market but who lack the infrastructure and know-how for doing it in the most efficient way. "Typically, these small biotech companies will not launch a new product in Europe more than once or twice. With our experience we provide a reduced operational risk combined with significantly lower investment requirements, hence opening an attractive channel for companies that may otherwise not launch in Europe at all.

"Ultimately, this will benefit patients with rare conditions in Europe, as the likelihood of them getting access to new innovative medicines increases considerably."

DR ANDERS EDVELL

SOBI

The established specialty company

Sobi, with headquarters in Stockholm, is an international biopharmaceutical company dedicated to rare diseases. The 2017 sales of SEK 6,511 million ($700+ million) were more or less equally split between the two business areas Haemophilia and Specialty Care, with the best-selling products being Elocta® for haemophilia A, Kineret® for auto-inflammatory conditions and Orfadin® for the treatment of hereditary tyrosinaemia type 1 (HT-1).

Dr Stephen James, Vice President and Head of Research & Translational Science at Sobi recognises that an increasing number of pharmaceutical companies are attracted to the rare disease space. This might be driven by price pressure and the idea that rare disease is a safe haven from increasingly demanding payers. According to James, companies focusing on rare diseases should base their presence on a clear ambition to contribute and make a difference to patients' lives. "This is the main reward and you clearly have to demonstrate value to patients and payers," he explains.

Sobi's innovation model is built on three pillars. The first is about the patient journey and understanding the patient's situation and needs. The second is to focus on biopharmaceuticals i.e. biological drugs such as proteins and antibodies which are core skills and capabilities within Sobi. The third innovation pillar is to make sure that the products being developed provide sustainable value to patients and payers.

Sobi focuses on indication areas where patients are treated by specialists. Stephen James argues that this gives mid-sized companies the possibility of making a big difference. "Being active in the rare disease space is about credibility and having the right footprint at the most important specialist centres", says James. "This is essential in order to build trust among key opinion leaders and to get patient access. A long-term commitment is needed."

The orphan space offers some advantages in terms of market exclusivity and clinical development timelines and pathways. Often, fewer patients are needed in the clinical studies which means lower costs. "On the other hand," James points out, "patients in these indications are by definition few and may therefore be harder to find and more centres are needed for recruitment." Sometimes it will also be impossible to include a placebo group in the study design because of the severity of the disease. "Regulatory authorities are typically helpful and supportive and provide valuable discussions," he adds.

As Head of Research & Translational Sciences at Sobi, Stephen James sees some key benefits of being based in Sweden. "There is excellent access to highly innovative, well-educated and diligent researchers. It is easy to network and people are collaborative by nature." Sobi is conveniently close to Karolinska Institutet, the Karolinska University Hospital, as well as the Science for Life Laboratory (SciLifeLab*). "This, together with for example the recently opened biopharmaceutical test facility Testa Center** in Uppsala provides valuable infrastructure for supporting the development of the next generation of much needed rare disease treatments."

DR STEPHEN JAMES

*www.scilifelab.se **www.testacenter.com

KAROLINSKA INSTITUTET

Academia

"At Karolinska Institutet we do a substantial amount of research within the field of rare diseases", says Dr Richard Cowburn, Project Manager and responsible for industry collaborations.

Cowburn explains that Karolinska Institutet is perfectly positioned to accelerate research and improve treatment of rare diseases. "We bring research into the clinics through our close collaboration with the regional health authority and Karolinska University Hospital."

This close proximity means that translational and precision medicine is an area where Karolinska Institutet is particularly strong.

"We have been able to get two complex organisations, in the form of the university and the hospital, to work closely together, to develop new understanding and solutions that benefit patients. We are also supported by the excellent national infrastructure available at the SciLifeLab, and the evolving Genomic Medicine Sweden initiative," he says.

The latter is a nationwide collaborative project involving key stakeholders from the Swedish healthcare system, patient organisations, academia, SciLifeLab and industry. The initiative's aim is to bridge the gap between healthcare and research in order to provide world-leading diagnostics and precision medicine in Sweden. The initial focus is on patients with rare inherited diseases and cancer.

As one of several examples, Cowburn mentions the work by Professor Anna Wedell at the Department of Molecular Medicine and Surgery. Professor Wedell and her colleagues work with inborn errors of endocrinology and metabolism and have built a multidisciplinary team with clinical, technical and molecular competence. This enables the direct translation of genetic findings into individual treatment for affected patients. Together with the SciLifeLab Clinical Genomics facility, they are currently transforming clinical diagnostics, with huge gains for many affected patients who can now receive accurate diagnosis and suitable clinical care in early disease stages. Clinical implementation started in 2014, with dramatic consequences for large numbers of patients. Among patients who remain unexplained, they are working to discover and validate novel disease mechanisms and pathways.

Cowburn concludes: "The key to success in this field is to understand the patient. Such precision medicine initiatives are extremely interesting for the Pharma and Biotech industries since they provide a strong insight into relevant human disease mechanisms, thereby creating a high level of confidence upon which to build successful drug discovery programmes".

DR RICHARD COWBURN

Swedenbio

SwedenBIO, the trade association for the Swedish life science sector has more than 260 members operating across all sub-sectors from pharmaceutical, biotechnology, medical technology to diagnostics. SwedenBIO serves to the benefit the entire life science industry in Sweden and is a member-driven, private, non-profit organization. The main objective is to contribute to improving the conditions for the life science industry for the benefit of industry growth and business development. Sweden's life science industry accounts for 20% of Sweden's net exports.

www.swedenbio.se/information-in-english

Business Sweden

Business Sweden is the official Swedish trade and investment council.

Business Sweden's purpose is to help Swedish companies grow global sales and international companies invest and expand in Sweden. Business Sweden supports international companies to develop successful business in Sweden by providing strategic advice, information and hands-on support – from initial evaluation of growth opportunities to final establishment, strategic partnership or capital investment.

www.business-sweden.se

sweden BIO
The Swedish Life Science Industry Organization

BUSINESS SWEDEN
THE SWEDISH TRADE & INVEST COUNCIL

THE SWEDISH ORPHAN DISEASE PIPELINE*

Company	Compound	Therapeutic area	Indication	Stage
A1M Pharma	ROSgard (A1M)	Obstetrics	Preeclampsia	Preclinical
Active Biotech	Tasquinimod	Oncology	Multiple myeloma	Phase I
Active Biotech	ANYARA	Oncology	Renal cell cancer	Phase I
Active Biotech	Paquinimod	Rheumatology	Systemic Sclerosis (SSc)	Phae II
Active Biotech	Laquinimod	Neurology	Huntington's disease (HD)	Phase III
Aprea	APR-246	Oncology	Myelodysplastic Syndrome	Phase I
Aprea	APR-246	Oncology	High Grade Serous Ovarian Cancer (Platinum-Resistant)	Phase I
Aprea	APR-246	Oncology	High Grade Serous Ovarian Cancer (Platinum-Sensitive)	Phase II
Aprea	APR-246	Oncology	Esophageal Cancer	Phase I
Athera Biotechnologies	PC-mAb	Cardiovascular	AV access dysfunction in dialysis patients	Phase II
Axelar	AXL-1717	Oncology	Glioblastoma	Phase I
Beactica	USP7	Oncology	Undisclosed	Preclinical
Beactica	LSD1	Oncology	Glioblastoma	Preclinical
BioArctic	SC0806	Neurology	Complete Spinal Cord Injury	Phase I
BioInvent International	BI-1206	Oncology	Chronic lymphatic leukemia (CLL)	Phase I
BioInvent International	TB-403	Oncology	Medulloblastoma	Phase I
BioInvent International	BI-1206	Oncology	Non Hodgkins lymphoma (NHL) B-cell type	Phase I
Calliditas	Nefecon	Nephrology	Inflammatory kidney disease (IgA nephropathy)	Phase III
Camurus	CAM2029	Endocrinology	Acromegaly	Phase II
Camurus	CAM2029	Oncology	Neuroendocrine tumors	Phase II
Camurus	CAM2043	Pneumology	PAH	Phase I
CellProtect Nordic Pharmaceuticals	CellProtect	Oncology	Multiple Myeloma	Phase I
Corline Biomedical	Renaparin™	Transplantation	Kidney Transplantation	Phase I
Diamyd Medical	GAD	Immunology	Autoimmune diabetes	Phase II
Double Bond Pharmaceutical	SA-033	Oncology	Hepatoblastoma (primary liver cancer in children)	Preclincal
Double Bond Pharmaceutical	Temodex	Oncology	Operable primary brain tumors	Preclinical
Double Bond Pharmaceutical	SA-033	Oncology	Hepatocellular carcinoma (common primary liver cancer)	Preclinical
Edvince	EDV2209	Cardiovascular	Non-traumatic subarachnoid haemorrhage	Preclinical
Galecto Biotech	TD139	Pneumology	Idiopathic pulmonary fibrosis (IPF)	Phase II
Hansa Medical	Imlifidase (IdeS)	Immunology	Anti-glomerular basement membrane (anti-GBM) disease	Phase I
Hansa Medical	imlifidase (IdeS)	Neurology	Guillain-Barré syndrome (GBS)	Phase I
Hansa Medical	Imlifidase (IdeS)	Transplantation	Kidney transplants in sensitized patients	Phase III
Hansa Medical	Imlifidase (IdeS)	Transplantation	Other kidney transplant indications	Phase I
Idogen	Tolerogenic vaccine	Hematology	Haemophilia A patients with inhibiting antibodies to factor VIII	Preclinical
Immunicum	Ilixadencel	Oncology	Gastrointestinal stromal tumor (GIST)	Phase I
Immunicum	Ilixadencel	Oncology	Hepatocellular carcinoma (HCC)	Phase I
Immunicum	Ilixadencel	Oncology	Renal cell carcinoma (mRCC)	Phase II
InDex Pharmaceuticals Holding	Cobitolimod	Gastroenterology	Ulcerative colitis	Phase II
Infant Bacterial Therapeutics	IBP-9414	Gastroenterology	Prevention of necrotizing enterocolitis	Phase II
Infant Bacterial Therapeutics	IBP-1016	Gastroenterology	Gastroschisis	Preclinical

*Non-exhaustive list. Based on EMA and FDA orphan designation registers, the report "Swedish Drug Discovery and Drug Development Pipeline 2016" by SwedenBio, and information from individual company webpages.

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Company	Compound	Therapeutic area	Indication	Stage
ITB-MED AB	Siplizumab	Transplantation	Solid organ transplantation	Phase II
LipUm	BSSL mAb	Rheumatology	Juvenile Idiophatic arthritis	Preclinical
Lokon Pharma	LOAd703	Oncology	Pancreatic cancer	Phase I
Medivir	MIV-818	Oncology	Hepatocellular cancer	Phase I
Modus Therapeutics	Sevuparin (DF02)	Hematology	Vaso-occlusive crisis (VOC) in patients with sickle cell disease (SCD)	Phase II
Modus Therapeutics	Sevuparin (DF02)	Infection	Severe malaria	Phase I
NeuroVive Pharmaceutical	NVP015	Mitochondrial disease	Genetic mitochondrial diseases	Preclinical
NeuroVive Pharmaceutical	NeuroSTAT	Neurology	Traumatic Brain Injury	Phase II
NeuroVive Pharmaceutical	KL1333	Mitochondrial disease	Mitochondrial respiratory chain disease	Phase I
Oncopeptides	Melflufen	Oncology	Multiple myeloma	Phase III
OxThera	OxaBact	Metabolism	Primary Hyperoxaluria	Phase III
OxThera	Oxazyme	Metabolism	Primary Hyperoxaluria	Phase II
PledPharma	Aladote	Gastroenterology	Paracetamol (acetaminophen) acute liver failure	Phase II
Respiratorius / Valcuria	VAL-001	Oncology	Lymphoma	Phase II
Sixera Pharma	Proteases inhibitors	Dermatology	Netherton syndrome	Preclinical
Swedish Orphan Biovitrum	SOBI005	Hematology	C5 driven diseases	Preclinical
Swedish Orphan Biovitrum	XTEN-FVIII	Hematology	Haemophilia A	Phase I
Swedish Orphan Biovitrum	Orfadin (nitisinone)	Metabolism	Alkaptonuria	Phase III
Swedish Orphan Biovitrum	SOBI003	Neurology	MPS3A, Sanfilippos disease	Phase I
Tikomed	IBsolvMIR	Transplantation	Regenerative Medicine - Diabetes type 1	Phase II
Tikomed	ILB	Neurology	ALS	Phase I
Toleranzia	Tolerogen	Immunology	Myasthenia Gravis	Preclinical
Vicore Pharma	C21	Neurology	Spinal cord injuries	Preclinical
Vicore Pharma	C21	Pneumology	Idiopathic pulmonary fibrosis (IPF)	Phase I
Vicore Pharma	C21	Pneumology	Pulmonary arterial hypertension (PAH)	Phase I
Vivolux	VLX1570	Oncology	Multiple myeloma	Phase I

Data sources

[1] The European Commission
[2] The Genetic and Rare Diseases
[3] Global Genes
[4] Global Genes RARE list
[5] Rare diseases, orphan medicines - Getting the facts straight (EMA/551338/2017)
[6] Orphanet
[7] Regulations of orphan designations in the EU
[8] Regulation of orphan designation in the US
[9] All orphan designations in EU
[10] FDA: All orphan designations in US
[11] Swedish Drug Discovery and Drug Development Pipeline 2016
[12] Orphanet
[13] Annual reports EMA

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