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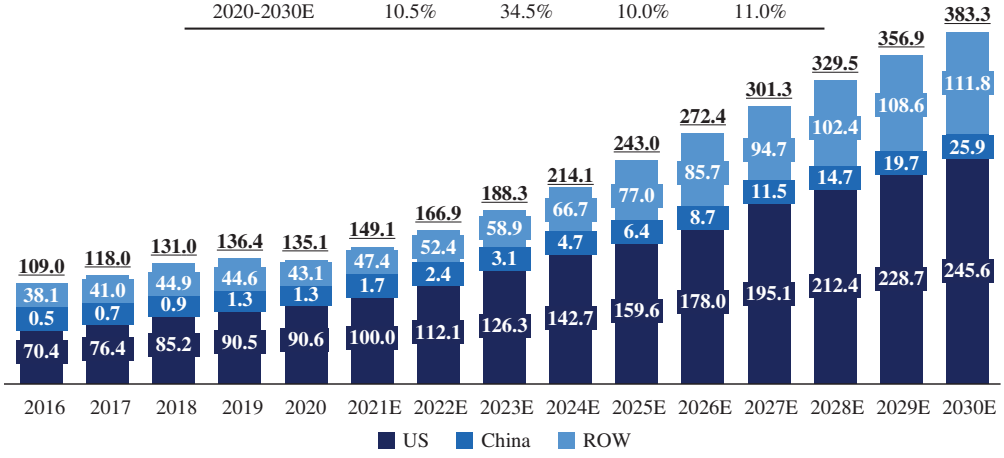
OVERVIEW OF THE GLOBAL RARE DISEASE MARKET

The global rare disease market is a sector of biopharmaceutical market focused on the discovery, development and commercialization of medicines for the treatment of diseases which affect a small number of people, compared with other prevalent diseases in the general population. According to Frost and Sullivan, approximately 80% of rare diseases are genetic, with three out of four cases starting in childhood and a mortality rate of 30% before the age of five. Collectively, rare diseases are estimated to affect 3.5%-5.9% of the world's population.

The market size of global rare disease drug market grew from US$135.1 billion in 2020 to US$383.3 billion in 2030 at a CAGR of 11.0% from 2020 to 2030. Particularly, the rare disease drug market in China is expected to dramatically grow from US$1.3 billion in 2020 to US$25.9 billion in 2030 at a CAGR of 34.5%, as compared to the market growth in the U.S. and the rest of the world in the same period at a CAGR of 10.5% and 10.0%, respectively. The China rare disease drug market accounted for 0.4% and 1.0% of the global rare disease market in 2016 and 2020, respectively, and is expected to account for 6.8% in 2030, indicating favorable rare disease market outlook, as China reforms to introduce more innovative medicines to the market and improved access/affordability. The following chart illustrates the historical and forecasted rare disease drug market in the U.S., China and the rest of the world from 2016 to 2030.

Global Rare Disease Drug Market, Breakdown by Regions, 2016-2030E

Billion USD	CAGR	US	China	ROW	Total
	2016-2020	6.5%	29.9%	3.1%	5.5%
	2020-2025E	12.0%	37.0%	12.3%	12.5%
	2025E-2030E	9.0%	32.1%	7.7%	9.5%
	2020-2030E	10.5%	34.5%	10.0%	11.0%



**Note:* Rare disease drugs in this market include drugs indicated for rare disease only and drugs obtaining orphan drug designation first but their indication expanded later of which generated most of their revenue, such as Humira. However, the part of revenue generated by expanded non-orphan indications was not included in this market.

Source: Frost & Sullivan analysis

Due to the nature of low prevalence, rare diseases were historically an infrequent target for the development of drug treatments by pharmaceutical companies. According to Frost & Sullivan, there are about 7,000 rare diseases lacking authorized or satisfactory method of treatment worldwide, reflecting the serious unmet needs for such life-threatening or chronically debilitating diseases. In addition, the majority of rare diseases are chronic and are associated with long term high medical costs and reduced quality of life. The unique nature of rare diseases resulted in a high mortality rate and significant social and economic burden on patients, which renders the development of effective treatments urgent and essential.

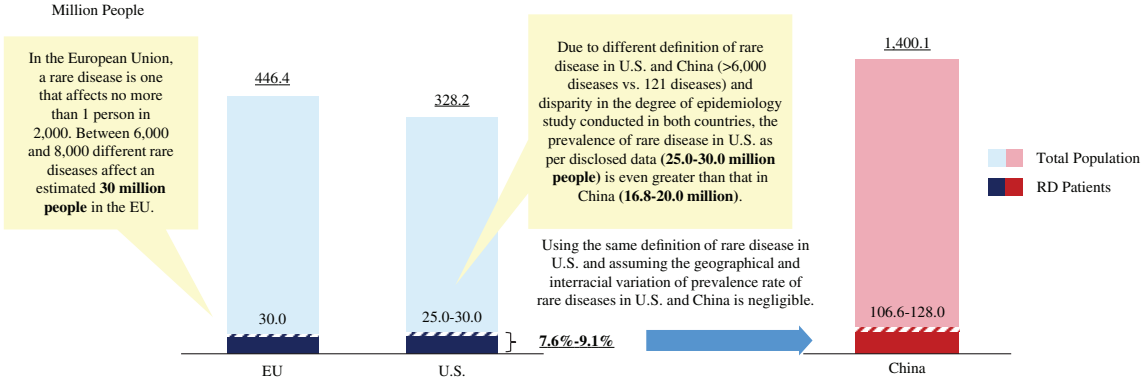
There is currently no harmonized global definition for rare diseases. The definition and classification of rare diseases and the granting of orphan drug designation may differ across regulatory authorities. Governments and respective agencies may establish separate thresholds based on local needs. The table below summarizes the respective definition of rare disease implemented in the U.S., Europe and China.

	The U.S.	Europe	China
Definition	• Rare diseases that affect fewer than 200,000 people in the United States or are of low prevalence (less than 5 per 10,000 in the community). • NIH's Office of Rare Diseases publishes a list of over 6,000 rare diseases, ranging from Aagenaes syndrome to Zuska's disease.	• A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare in Europe (Orphan Drug Regulation 141/2000). • According to EURORDIS (European Organization for Rare Diseases), the number of rare diseases numbers from about 6,000 to 8,000.	• On May 21, 2018, NHFPC and other four departments jointly formulated the first catalogue of rare diseases, include 121 rare diseases. • On June 5, 2018, NHFPC publish *Working Procedure for Rare Diseases Catalogue.* Rare disease catalogue will update every two years.

Source: FDA, EMA, CFDA, NHFPC, Frost & Sullivan Analysis

Based on different definitions for rare diseases, the number of rare diseases recognized is far lower in China (121) than the U.S. and Europe (each with over 6,000). The diagram below shows the prevalence of rare diseases in the U.S. and Europe respectively, and in China applying the broader definition of rare disease in the U.S. in 2019, which leads to an implied patient pool potentially over four times larger in China than the U.S. According to a research report published by the Economist Intelligence Unit in 2020, China is believed to be the single largest market with the world's largest population of rare disease patients. It is estimated that the first list of 121 rare diseases defined in China alone affect more than 3 million patients, therefore it is an appropriately reasonable estimate that China may have a total prevalence base which exceeds 100 million patients suffering from one or more forms of rare diseases, by way of extrapolation adopting the broader definition in the U.S. or Europe.

Prevalence of Rare Disease in U.S. & EU and Estimated Prevalence in China



Source: FDA, EMA, EC, CFDA, NHFPC, Frost & Sullivan Analysis

Evolution of the Rare Disease Market

The regulatory frameworks within the US and Europe for orphan drug designations for rare diseases are well established. While in China, the first list of rare diseases was published in May 2018, since when many major initiatives and regulatory reforms were announced, which together are expected to significantly develop and grow the Chinese rare diseases drug market and its ecosystem in the next decade.

The global rare disease drug market has grown rapidly since 1983, when the Orphan Drug Act was first promulgated by the FDA, which set standards for regulatory pathways that were followed by other jurisdictions in subsequent years. As rare diseases do not share a harmonized definition across the globe, orphan drug market is used to mirror the growth and potential of rare disease market. According to Frost & Sullivan, orphan drug market includes both targeted therapy drugs indicated for rare disease only and other drugs obtaining orphan drug designation (ODD) which may include those covering additional orphan indications and usage outside of their core prescription label for non-orphan diseases. The part of revenue generated by expanded non-orphan indications was excluded in the market analysis by Frost & Sullivan below. For the purpose of this Industry Overview section, "rare disease drug market" means the total orphan drug market excluding the revenues generated from the non-orphan indication expansions of certain non-targeted ODD drugs, such as Humira or Keytruda.

Significant Unmet Medical Needs and Market Opportunities

There remain urgent and unmet medical needs worldwide for the growing list of rare diseases. It is estimated that, worldwide, less than one-tenth of patients with rare diseases have received disease-specific treatment. The treatment of rare diseases continues to face challenges including lower priority for drug development, limited awareness and availability of targeted treatment options, and unestablished government policies. Unmet medical needs and challenges come along with significant market opportunities and commercial potential. The U.S., followed by Europe, remains as the largest rare diseases market with the most mature ecosystem. The U.S. market alone accounts for 67.1% market share of the global rare diseases market in 2020 and expected remain the world's largest market in 2030. Owing to the regulatory reforms including simplified application process, flexibility in clinical trial design, and likelihood of trial waiver on the basis of overseas clinical data and post-approval clinical trials, China is experiencing a structural shift for its rare disease market. According to Frost & Sullivan, the rare disease drug market in China is expected to grow at 34.5% CAGR from US$1.3 billion in 2020 to US$25.9 billion in 2030. The rapid growing rare disease drug market is primarily driven by the large but untapped patient population, demand for targeted treatment options and favorable regulatory path.

- ***Largely untapped patient population*:** China has a large but currently underserved patient pool with rare diseases compared to the U.S. and Europe with limited treatment options, diagnosis deficiency and under-developed market and regulations. As compared to the U.S., the market size of rare disease drugs in the U.S. was nearly 70 times larger than that of China in terms of dollar value, while the total number of patients in China is estimated to be at least four times larger than the US market given overall population size and prevalence rate. The discrepancy between patient population and market size suggests significant room for rare disease drug growth in China. In addition, as China and some other emerging markets including Latin America and Southeast Asia are building up the rare disease ecosystem, the list of rare diseases globally is expected to expand regularly with new types of rare diseases being introduced in medical literatures along with science and technology advancement for their diagnosis and treatments.

- ***Limited awareness and targeted treatment options*:** Delayed diagnosis of rare diseases is common due to lack of knowledge by both patients and doctors, especially in jurisdictions with an immature rare disease ecosystem. After diagnosis, a large number of patients still face the challenge to access effective and targeted

treatments that serve as disease-modifying therapies. According to Frost & Sullivan, there are about 7,000 rare diseases lacking authorized or satisfactory method of treatment worldwide. On the other hand, increased disposable income, improved government medical reimbursement coverage and favorable pricing policies have enhanced the accessibility of healthcare services and pharmaceutical medications for patients. As of December 2020, China has approximately 69 drugs approved for the treatment of rare diseases (among which 29 drugs are rare disease-targeted therapies), as compared to approximately 180 approved drugs in more developed markets such as the U.S., Europe and Japan for the 121 rare diseases recognized in the First National Rare Disease List, representing a highly underserved market with massive potential. However, even in established markets such as the U.S., Europe and Japan, there are still 46 diseases that are lacking treatments among the 121 rare diseases.

- ***Favorable government policies under development*:** In recognition of the urgency for effective rare disease treatment and the unique clinical challenges associated with the development of rare disease treatment, regulatory authorities in the U.S., and Europe have provided regulatory incentives and adopted specific regulatory frameworks to encourage development and commercialization of drugs to treat rare diseases. In 1983, the Orphan Drug Act was first enacted in U.S., in order to encourage the development of drugs for rare disease by granting exclusivity for orphan indication, tax credit for qualified clinical trials, and waiver of application fees. The FDA has also adopted post-approval studies in response to the limited size and duration of a pivotal trial before commercialization. Among the major pharmaceutical markets, the EU has enacted orphan drug legislation in 2000. Efforts to establish clearer pathway towards rare disease drug definition and registration are emerging in China, but the ecosystem is still at its infancy compared to those in the U.S. and EU. In 2018, China published the first edition of the Rare Disease List that include 121 rare diseases, hallmarking the transformational debut of the Chinese rare disease market. Currently 29 targeted therapies for the treatment of these 121 diseases have been approved and 16 of them are included in the National Reimbursement Drug List (NRDL) in 2020. The NMPA is making significant efforts to accelerate approval of rare disease drugs by providing favorable review and approval policies of rare disease in China. Also in 2018, the NMPA and the National Health Commission announced the Guidebook for Review and Approval Procedures of Overseas Imported New Drugs for Chinese Clinical Urgent Demand to provide a dedicated pathway for priority review and approval of overseas drugs imported into the Chinese healthcare market, which allows for an accelerated approval process for drugs with overseas clinical trial data treating serious or life-threatening diseases with clinical advantages and for an exemption of a bridging trial or additional local trial in China. Since 2018, three lists of Clinical Urgently Needed Foreign New Drugs have been announced, with a significant increase in the percentage of rare disease drugs recognized from 42% in first list to 65% in the second list in 2019. The application for marketing of varieties listed in such lists can be submitted directly in accordance with the Work Procedures for Review and Approval of Overseas New Drugs Catering to Clinical Urgent Needs, where a special channel is set up to speed up the review by the NMPA. In 2021, the initiation of formulation of the second edition of the Rare Disease List was announced by the National Health Commission of the PRC and more rare disease drugs are expected to be included.

- ***Efficient business model and attractive returns:*** The rare disease industry is a highly efficient business model. According to Frost & Sullivan, most rare diseases are caused by genetic mutations with well-defined pathology, which leads to higher probability of technical and regulatory success ("PTRS") in the research & development ("R&D") of drugs for the treatment of rare diseases. The R&D effort is also more targeted with smaller clinical trial required. In addition, certain rare disease patients are treated at a limited number of specialized hospitals, resulting in the high pricing power with a focus target patient pool, and small-scale and targeted sales efforts covering key hospitals and clinical centers and KOLs and clinicians. The unique nature of rare diseases has also created a favorable regulatory environment with increasingly well-established regulation and fast track orphan drug pathway, which helps accelerate the development and commercialization of rare disease drugs.

- ***Technology innovation and emergence of gene therapy***: Propelled by the technology advancement in the rare disease R&D and regulatory approvals across the world, there has been an increasing number of innovative rare disease treatment options to address unmet medical needs, including enzyme replacement therapy (ERT), designing new molecular entities or manipulation of gene expression. Enabled by new technologies, gene therapies such as CRISPR and RNAi have shown the potential to treat more rare diseases. Approximately 80% of rare diseases result from genetic disorders and thus gene therapies provide hope of a one-time treatment for numerous rare diseases that currently have no specific therapeutic options. Recent advances in genetic engineering and recombinant viral vector development have ignited interest in the field, with several gene therapy products gaining approval. The success of certain marketed pioneering clinical trials of gene and cell therapies has validated their efficacy and safety, such as SPINRAZA developed by Biogen and Zolgensma developed by Novartis and AveXis in treatment of Spinal Muscular Atrophy (SMA).

Rare Disease Therapies Reimbursement and Pricing

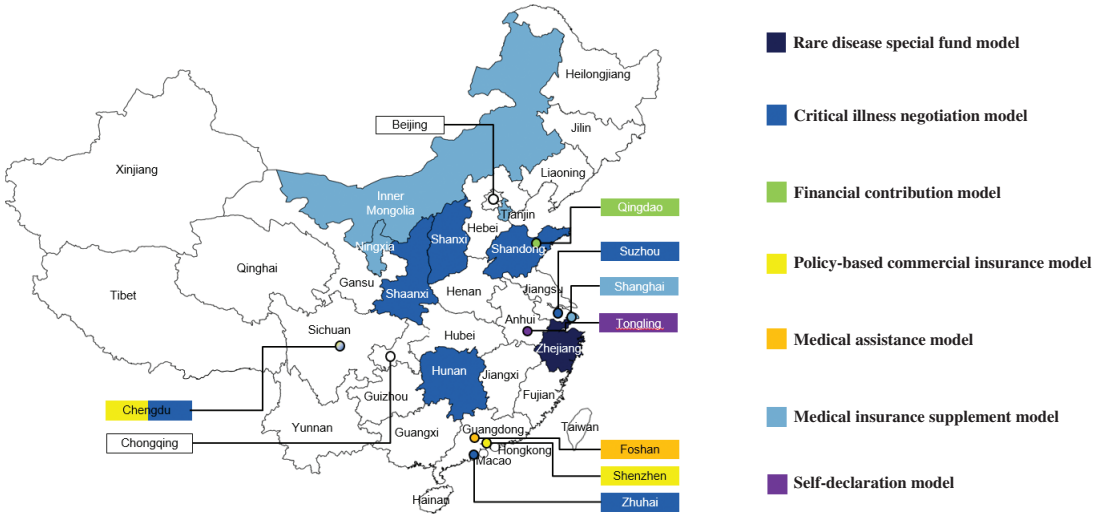
Due to the substantial R&D costs and small patient pool associated with the nature of rare diseases, the pricing for orphan drugs is generally higher than that for non-orphan disease drugs. Rare disease therapies are usually life-time chronic treatments. The annual cost for Spinraza, a targeted drug for spinal muscular atrophy (SMA), is approximately US$0.7 million for the first year and US$0.4 million in subsequent years in the U.S. New modalities of therapies are offering potential one-time treatment with substantial one-time cost. Zolgensma, an AAV-based gene therapies approved by the FDA, is priced at US$2.13 million.

Pricing and reimbursement policies, which dictate the patient access to rare disease drugs, differ greatly between countries, and sometimes even within a single country, due to variations in national policies, healthcare budgets, health insurance, and reimbursement systems. In the U.S., commercial insurance payers cover the majority of the costs of rare disease drugs for insured patients, with many pharmaceutical companies operating patient assistance programs to help offset a portion of the costs for uninsured or underinsured patients. In China, however, national or provincial public medical insurance dominates the healthcare insurance system and commercial medical insurance only plays a supplementary role.

While the Chinese rare disease market is in its infancy, China's government has rolled out several policies relating to the pricing and medical insurance, as a means to enhance the affordability and accessibility of rare disease drugs. Since rare diseases were covered in a consultation paper on national medical insurance, certain rare disease drugs such as Bosentan for the treatment of idiopathic pulmonary arterial hypertension (IPAH) has been included in the 2020 National Medical Insurance Drug Catalogue. Pricing benefits are also granted for a batch of 21 orphan drugs and 4 drug substances, where value added tax will be reduced to 3% referring to the anti-cancer drug in import process, and the domestic value added tax may choose the simple method, levied by 3%. Under the National Reimbursement Drug List in 2020, medical insurance included 40 rare disease drugs, albeit most of them are general medicines repurposed for orphan disease indication. A total of 16 medicines for specific targeted treatment of rare diseases are included, accounting for 40% of the list.

Insurance reimbursement policies significantly increase the affordability and accessibility of treatments to patients. Insurance coverage varies geographically across provinces and tiered cities, with Beijing currently covering up to 80% of the treatment cost for certain rare disease drugs. China is moving towards more established insurance environment for rare disease, where the nationwide insurance coverage will broaden and become more dynamic, providing reimbursement scheme for even ultra-rare disease drugs, along with expansion of patient assistance programs. For example, imiglucerase, a targeted drug for Gaucher disease (GD), is currently not included in the NRDL but has been included in the local reimbursement list of certain provinces and cities such as Zhejiang and Qingdao. According to Frost & Sullivan, the annual out-of-pocket expense of a GD patient in Zhejiang can be as low as approximately RMB30,000 and approximately RMB150,000 in Qingdao under different reimbursement policies, as compared to the estimated annual cost of approximately RMB3 million before reimbursement.

Over the years of China's exploration in insurance mechanism of rare diseases at the local level, an aggregate of 29 provinces have implemented insurance policies for rare disease with various reimbursement models. The graph below illustrates the coverage of rare disease drug reimbursement policies in China and their respective models:



Source: Frost & Sullivan Analysis

Among all local governments' offerings of rare disease reimbursement policies, seven major models can be concluded from regions where high level reimbursements for rare diseases are provided, including special fund model, critical illness negotiation model, financial contribution model, policy-based commercial insurance model, medical assistance model, medical insurance supplement model and self-declaration model, as elaborated in the table below. Under the reimbursement model in Zhejiang Province, for example, the total costs incurred for rare disease treatments in a year can be reimbursed by 80% for the portion below RMB300,000, 90% for the portion between RMB300,000 to RMB700,000, and 100% for the portion above RMB700,000.

Model Category	Reimbursement Policy	Representative Province/Cities
Rare disease special fund model	• The special fund model is based on the standard of 2 yuan per person per year, one-time transfer from the critical illness insurance fund of this coordinating area to the Zhejiang Province Rare Disease Drug Reimbursement Fund. • Drug coverage: Expert argumentation of drug catalogue, price negotiation, dynamic adjustment • Reimbursement depth: Cost accumulation, reimbursement in stages, capping of personal burden	Zhejiang Province
Critical illness negotiation model	• The funding comes from the basic medical insurance fund and the critical illness insurance fund. Some regions (such as Shanxi Province and Shaanxi Province) also provide a multi-level reimbursement policy supplemented by financial allocations for special assistance and social assistance. • Drug coverage: Negotiations to include the scope of medication for critical illness insurance • Reimbursement depth: Reimbursement amount: tens of thousand ~ hundreds of thousand RMB/year	Shanxi Province, Shaanxi Province, Hunan Province, Zhejiang Province, Shandong Province, Sichuan Chengdu, Jiangsu Suzhou, Guangdong Zhuhai
Financial contribution model	• The financial contribution model is mainly funded by the Ministry of Finance, supplemented by personal payment. • Drug coverage: Expert argumentation, special medicine negotiation • Reimbursement depth: Less patients' own expenses	Shandong Qingdao
Policy-based commercial insurance model	• Drugs are publicly procured by the government, while the fund is operated by a commercial insurance company, with voluntary participation and individual payment (personal account balance, or personal expense). • Drug coverage: The Medical Insurance Bureau and the commercial insurance company jointly evaluated the designated drug catalog • Reimbursement depth: Higher claims status, processing at different grades	Guangdong Shenzhen, Sichuan Chengdu
Medical assistance model	• The sources of medical assistance funds include special medical aid funds allocated by the Ministry of Finance, welfare lottery charity funds, social donations, etc. • Drug coverage: Include the diseases in the national rare disease list into the scope of assistance • Reimbursement depth: Uncertainty about whether patients can get assistance	Guangdong Foshan
Medical insurance supplement model	• The funding comes from basic medical insurance fund. • Drug coverage: Limited range of rare disease drugs included • Reimbursement depth: Consistent with basic medical insurance reimbursement policy, non-institutionalized, sustainability to be seen	Ningxia, Tianjin, Inner Mongolia, Fujian Sanming, Yunnan Kunming, Shandong Jining, Guangdong Zhongshan, Fujian Xiamen, Shanghai, etc.
Self-declaration model	• The sources of funding include basic medical insurance fund and critical illness insurance fund. • Drug coverage: No list of specific diseases and drugs established. Patients declare independently. • Reimbursement depth: Uncertainty about whether patients can get assistance	Anhui Tongling

Source: Frost & Sullivan Analysis

Rare disease drug industry offers market potential evidenced by attractive returns. The ten top-selling orphan drugs brought in a combined US$42.8 billion globally in 2020 among which four are for oncology indications while the other six are targeting rare diseases that require life-long treatments, as shown in the table below.

Global Top 10 Orphan Drug* in Terms of Sales Revenue, 2020

Brand Name	Sales Revenue, 2020	Company	Major Indication	Therapeutic Area	Pricing in US (USD)	Annual Cost (USD)**	Pricing in China (RMB)	Annual Cost (RMB)**
Revlimid (2005)	12.1	BMS	Multiple Myeloma	Anti-neoplasm	832.52/25mg	227,902.4	1,030.68/25mg (NRDL covered)	282,148.6
Ocrevus (2017)	4.6	Roche	Multiple Sclerosis	Autoimmune Disease	17,483.45/ 300mg/10ml	69,933.8	NA	NA
Darzalex (2015)	4.2	J&J	Multiple Myeloma	Anti-neoplasm	122.07/20mg/ml	123,046.6 ~ 134,765.3	985.5/20mg/ml	993,384 ~ 1,087,992
Soliris (2007)	4.1	Alexion Pharmaceuticals	PNH, aHUS, TMA	Hemoglobinuria, Paroxysmal	6,819.51/300mg/ 30ml	461,487 ~ 736,560	NA	NA
Tecfidera (2013)	3.8	Biogen, Eisai	Multiple Sclerosis	Autoimmune Disease	144.68/120mg; 144.16/240mg	105,244.1	NA	NA
Jakafi/Jakavi (2011)	3.3	Incyte, Norvartis	Myelofibrosis	Myeloproliferative Disorders, Polycythemia Vera	256.88/5mg, 10mg, 15mg, 20mg, 25mg	92,476.8	133.33/5mg	143,996.4 ~ 239,994.0
Pomalyst (2013)	3.1	BMS	Multiple Myeloma	Anti-neoplasm	947.64/1mg, 2mg, 3mg, 4mg	259,416.5	NA	NA
Gilenya (2010)	3.0	Novartis	Multiple Sclerosis	Autoimmune Disease	316.83/0.5mg	115,643.0	228/0.5mg (NRDL covered)	83,220.0
Hemlibra (2017)	2.3	Genentech Roche	Hemophilia A	Genetic Disease	16,092.21/ 150mg/ml	540,698.0	8,100/30mg/ml	1,360,800.0
Aubagio (2012)	2.3	Sanofi	Multiple Sclerosis	Autoimmune Disease	280.78/7mg, 14mg	102,484.7	282/14mg (NRDL covered)	102,930.0

Billion USD
Chemical Drug
Biologics

Notes:

* Orphan drug mentioned in this table does not include drugs obtaining orphan drug designation first but their indication expanded later of which generated most of their revenue, such as Humira.

** Patient assistance program (PAP) is not taken into consideration when calculating the annual cost, because the eligibility criteria varies among drugs and is usually determined on a case-by-case basis. Assume body weight is 60kg.

• The pricing in EU is not displayed in the table because the regulation of drug prices are different among countries and governments control prices in various ways in the EU.

Source: Annual Report, Frost & Sullivan Analysis

RARE ONCOLOGY

Glioblastoma Multiforme (GBM)

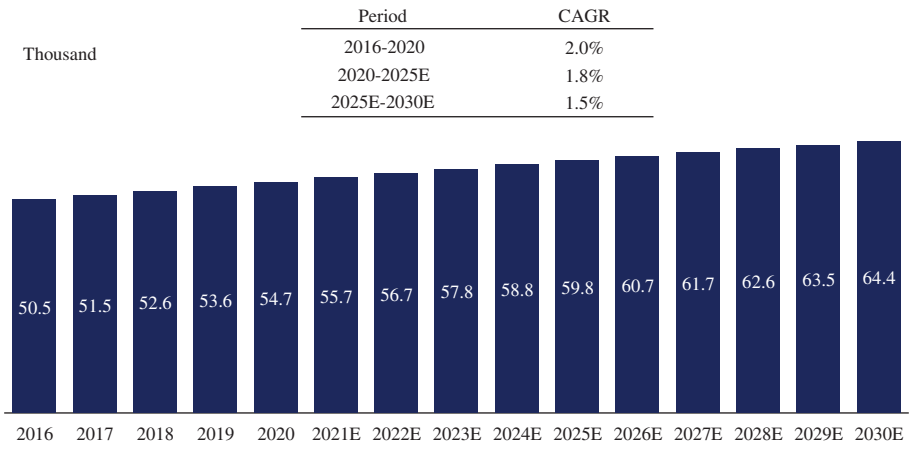
GBM is a fast-growing malignant glioma that develops from glial cells (astrocytes and oligodendrocytes) or their precursors that support the health of the nerve cells within the brain. It is the most common and malignant type of glioma in adults. About 45% of gliomas are glioblastoma multiforme, which is classified as Grade IV (most serious) astrocytoma, is the most common and aggressive brain cancer where a large portion of tumor cells are reproducing and dividing at any given time, with an estimated 5-year survival of 5.5% globally and below 5% in China. The incidence of GBM was approximately 3.9 cases per 100,000 individuals in 2020. The tumor is predominantly made up of abnormal astrocytic cells, but also contain a mix of different cell types (including blood vessels) and areas of dead cells (necrosis). GBM is infiltrative and is the most invasive type of glial tumors, rapidly growing and commonly

spreading into nearby brain tissue. It can also sometimes spread to the opposite side of the brain through connection fibers (corpus callosum). GBM is characterized as a disease with one of the highest unmet needs in oncology, with patients having a median overall survival between one and two years.

Market Overview

GBM represents 46.6% of the total incidence of brain cancer in China and has reached 54.7 thousand in 2020 with a CAGR of 2.0% from 2016 to 2020. With factors including increasing aging population, ionizing radiation and air pollution, the incidence of GBM in China is expected to grow to steadily 59.8 thousand in 2025 and 64.4 thousand in 2030 at a CAGR of 1.8% and 1.5%, respectively. The diagnostic rate of GBM in China remains low due to the complicated diagnostic process and lack of accessibility to effective diagnostic methods.

Incidence of Glioblastoma Multiforme in China, 2016-2030E



Source: Frost & Sullivan analysis

Treatment Methods

GBM grows rapidly and is the most invasive type of glioma. There are significant unmet medical needs for GBM patients in China calling for alternative options as a result of the limitations to the current available treatments.

The standard of care for GBM consists of surgical resection, adjuvant chemotherapy with temozolomide (TMZ). However, radiation and chemotherapy always come with adverse events that greatly undermine the life quality of patients. In addition, tumor cells may develop some resistance to TMZ. Current GBM therapies have limited improvement in progression-free survival (PFS) with an estimated 5-year survival of 5.5% globally and below 5% in China.

The current targeted therapy treatment options for GBM in China include surgery, radiotherapy combined with TMZ concurrent chemotherapy, tumor treating field (TTF), bevacizumab (Avastin) and a bevacizumab biosimilar. Vascular endothelial growth factor (VEGF) is an important factor in angiogenesis that is highly expressed by the endothelial cells in most human tumors, and bevacizumab biosimilar is a recombinant humanized anti-VEGF monoclonal antibody drug.

TMZ was marketed in 2004 while TTF, bevacizumab (Avastin) and the bevacizumab biosimilar were approved in 2020 in China as new treatments for GBM.

Competitive Landscape

The CAN008 fusion protein has competitive advantages in the treatment of GBM over other treatment options, including a validated novel mechanism of action, improved efficacy and the potential for combination therapy. For details, please refer to "Business – Our Portfolio – Late Stage Drug Products and Candidates – CAN008 CD95-Fc fusion protein for GBM – Market Opportunity and Competition." CAN008 has been well tolerated with a favorable safety profile and promising efficacy in multiple clinical trials, highlighting its potential to play a significant role in GBM treatment.

The following table illustrates the current status of targeted drugs for GBM marketed in China.

Classification	Generic Name/ Product Code	Company	NMPA Approved Date	Price in China, RMB	Annual Cost in China, RMB
Chemotherapy	temozolomide	Tasly Diyi Pharmaceutical	2004*	895 (100mg)	101,896
		MSD	2007	3,300 (100mg)	187,853
Chemotherapy	carmustine	Tianjin Tianyao	2015	122 (2g: 0.125g)	2,393
Biological therapy	bevacizumab	Roche	2020	1,934 (100mg)	301,704
		Innovent Bio	2020	1,188 (100mg)	185,328

Note: Generic Temozolomide manufactured by Tasly Diyi Pharmaceutical was approved by NMPA in 2004, which was earlier than the NMPA approval of original drug manufactured by MSD in 2007.

Source: Frost & Sullivan Analysis

The following table illustrates the current status of targeted drugs for GBM being developed in China and worldwide.

Classification	Generic Name/ Product Code	Company	China Clinical Status
Chemotherapy	enzastaurin	Xcelience/Denovo Biopharma/ Suoyuan Biopharm	Phase III
	elemene	Second Affiliated Hospital/Zhejiang University	Phase II
	ZSP-1602	Guangdong Zhongsheng Pharma	Phase I
Fusion Protein	asunercept/CAN008	CANbridge	Phase II
	efineptakin alfa/TJ-107	Tianjing Biotech/Binex/ Neoimmunetech	Phase II
Cell and Gene Therapy	ever supreme	Ever Supreme	Phase II
	anti/EGFRvIII-directed CAR-T cell therapy	Shenzhen BinDeBio	Phase II
	B7-H3 CAR-T cell therapy	BoYuan RunSheng Pharma	Phase II
Small Molecular Targeted Drug	ABT-414	AbbVie	Phase II/III
	RX-108	NeuPharma	Phase II
	ACT-001	Accenda	Phase II
	AT-101	Ascentage Pharma	Phase II
	bozitinib	Beijing Borunao Biotech	Phase II
	apatinib	Xijing Hospital	Phase II
	anlotinib	Shandong Cancer Hospital and Institute	Phase I/II
	zotiraciclib	Tragara Pharmaceuticals/ ZHAOKE	Phase I
Vaccine	HSP Gp96 vaccine	Cure & Sure	Phase II
	dendritic and glioma cells fusion vaccine	Hangzhou Medical Biotechnology	Phase II
Oncolytic Adenovirus	T-601	Transgene	Phase I
Antibody	camrelizumab	Jiangsu Hengrui	Phase II
	nimotuzumab	Biotech Pharmaceutical/Sun Yat-sen University	Phase II
	bevacizumab	CTTQ Pharma	Phase I

Source: Frost & Sullivan analysis

RARE DISEASES

Mucopolysaccharidosis Type II (MPS II or Hunter syndrome)

MPS II, also known as Hunter syndrome, is an X-linked recessive lysosomal storage disorder caused by deficient or absent activity of iduronate-2-sulfatase (IDS), an enzyme which cleaves O-linked sulfate moieties from two human glycosaminoglycans (GAG), dermatan sulfate and heparan sulfate. In MPS II, these GAGs accumulate in almost all body organs and tissues including the brain, heart, lung, bone, muscle, intestines, and skin. Accumulation of GAG leads to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction.

MPS II is a rare, disabling and life-threatening genetic disease. Patients appear healthy at birth, with initial symptoms appearing between 18 months and 4 years of age. Life expectancy of patients with severe MPS II (60%-80% of cases) is significantly reduced, with death occurring generally before the age of 25 as a result of CNS neurodegeneration and

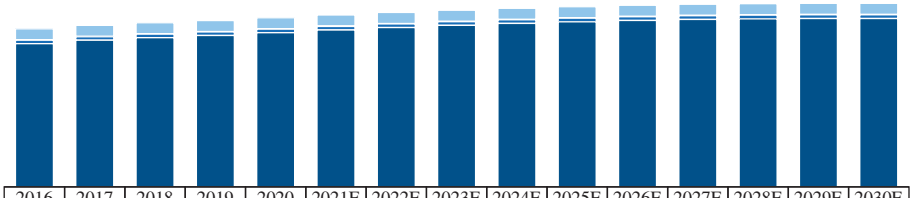
cardio-respiratory complications. The remaining patients have attenuated MPS II that may present at any age and is distinguished from the severe form by slower disease progression, lack of CNS neurodegeneration, and long-term survival. The severity of disease is attributed to the amount of residual IDS activity: patients with severe disease have little to no IDS activity, whereas those with the attenuated form have partial IDS activity.

Market Overview

In East Asian countries, MPS II is the most common form of MPS disorders. With Hunterase® as the only approved treatment in China and an estimated number of over 8,000 patients countrywide in 2020, there is a high level of unmet need and the Chinese government has included MPS II on the "National Rare Disease List" as a disease group to target. The MPS II market in China remains stable as it is a genetically-related rare disease but highly underserved. The prevalence of MPS II in Greater China mainland reached 8,005 in 2020 and is estimated to reach 8,175 in 2030.

MPS II Prevalence in Greater China, 2016-2030E

CAGR	Mainland China	Hong Kong	Taiwan	Macau
2016-2020	0.4%	0.6%	0.1%	1.7%
2020-2025E	0.3%	0.6%	0.1%	1.5%
2025E-2030E	0.1%	0.4%	0.0%	-0.1%



	2016	2017	2018	2019	2020	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Taiwan	131	131	131	131	131	132	132	132	132	132	132	132	132	132	132
Macau	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Hong Kong	41	41	42	42	42	42	43	43	43	43	44	44	44	44	44
Mainland China	7,697	7,738	7,768	7,794	7,827	7,859	7,888	7,914	7,937	7,956	7,972	7,984	7,991	7,995	7,995
Total	7,873	7,914	7,944	7,971	8,005	8,037	8,067	8,093	8,117	8,136	8,152	8,164	8,171	8,175	8,175

Source: Frost & Sullivan Analysis

Treatment Methods

Enzyme replacement therapy (ERT) is recommended as the standard of care by worldwide treatment guidelines and expert consensuses. ERT provides exogenous IDS enzyme for uptake into cellular lysosomes through the binding of mannose-6-phosphate (M6P) residues on its oligosaccharide chains to M6P receptors on the cell surface, leading to cellular internalization of the enzyme, targeting to intracellular lysosomes, and subsequent catabolism of accumulated GAG. ERT is effective in clearing accumulated GAG with resulting clinical benefits, including improved mobility, slowing disease progression, controlling symptoms and disease manifestations, such as organ enlargement, decreased cardiac, respiratory system and skeleton functions, and has been proven to improve health outcomes of patients with MPS II.

Another current therapy treatment for MPS II in China is hematopoietic stem cell transplantation (HSCT), where stem cells obtained from donor bone marrow, peripheral blood or umbilical cord blood is infused intravenously into a patient. The transplanted stem cells re-populate the patient's bone marrow with IDS-producing cells which can then migrate into various tissues and organs and then produce sufficientenzyme to alleviate symptoms. The main limitations of HSCT are the difficulty in finding matched donors, the high occurrence of transplant complications such as graft-versus-host disease, and the inability to prevent cognitive decline.

Competitive Landscape

ERT is the standard of care based on its ability to reduce GAG storage and improve, slow, or in some instances prevent the progressive tissue and organ damage associated with MPS II. Hunterase® (CAN101), as the first and only approved treatment in China, is a purified form of recombinant human iduronate-2-sulfatase (rhIDS) produced in CHO DG44 cells using a serum-free process. The IDS enzyme is specifically taken up by cells and directed into lysosomes, where itdegrades stored GAG and prevents further its accumulation. Hunterase® is currently the only targeted therapy to MPS II available in China.

The following table illustrates the targeted therapy and drugs approved and in clinical stage for MPS II globally:

Generic Name/ Product Code	Brand Name	Company	FDA Approved Date/US Clinical Status	Price, USD (Region)	Annual Cost, USD (Region)	NMPA Approved Date/China Clinical Status	Price in China, RMB	Annual Cost in China, RMB	Mechanism of Action
idursulfase	Elaprase	Shire (Acquired by Takeda)	2006 (US)*	$2,249/6mg (South Korea)	$341,046 (South Korea)	–	–	–	Iduronate sulfatase replacements
idursulfase beta	Hunterase	GC Pharma/ CANBridge	2012 (South Korea)**	$1,912/6mg (South Korea)	$289,931 (South Korea)	2020	Unknown	Unknown	Iduronate sulfatase replacements
idursulfase beta	Hunterase ICV	Clinigen/GC Pharma	2021 (Japan)	Unknown	Unknown	–	–	–	Iduronate sulfatase replacements
JR-141	Izcargo	JCR Pharma	2021 (Japan)	Unknown	Unknown	–	–	–	Iduronate sulfatase replacements
RGX-121	–	Regenxbio	Phase I/II	–	–	–	–	–	Gene transference; Iduronate-sulfatase stimulants
DNL-310	–	Denali Therapeutics	Phase I/II	–	–	–	–	–	Iduronate sulfatase replacements
adalimumab	Humira	AbbVie/Eisai/ Lundquist Institute	Phase I/II	–	–	–	–	–	Anti-TNFα monoclonal antibody
SHP-631/AGT-182	–	ArmaGen	Phase I (Completed)	–	–	–	–	–	Iduronate sulfatase replacements
GNR-055	–	AO GENERIUM	Phase I (Completed)	–	–	–	–	–	Iduronate sulfatase replacements

Note: We assume that the average weight of the patient is 35 kg.

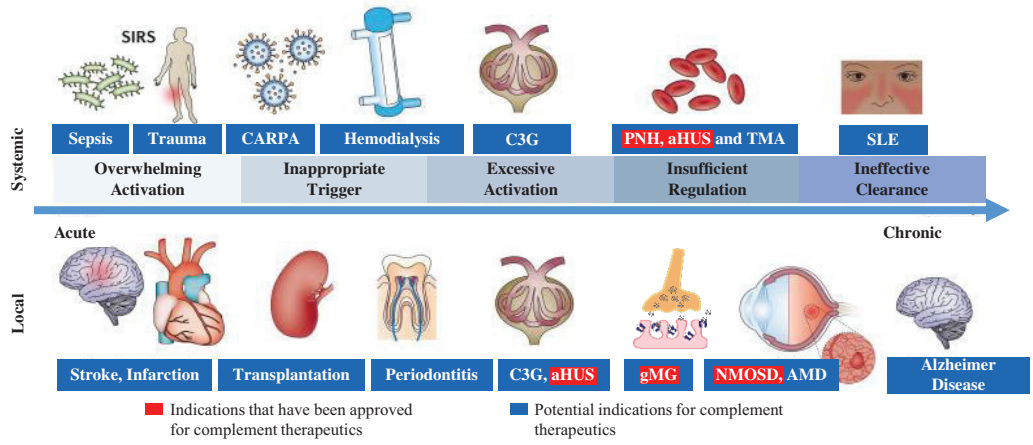
* Elaprase was firstly approved in the US in 2006, and now approved in the US, Japan and EU.

** Hunterase was firstly approved in South Korea in 2012, and now approved in South Korea and China.

Source: FDA, NMPA, Frost & Sullivan analysis

Complement Mediated Diseases

Disorders with known or suspected complement involvement cover an exceptionally broad range, including tissue- specific, systemic, acute and chronic disorders of the inflammatory, autoimmune, age-related, biomaterial-induced and neurodegenerative spectrum. Dysregulation of the complement system underlies the pathophysiology of a broad spectrum of diseases, such as Paroxysmal Nocturnal Hemoglobinuria (PNH), Atypical Hemolytic Uremic Syndrome (aHUS), generalized Myasthenia Gravis(MG) and Neuromyelitis Optica Spectrum Disorders (NMOSD). The number of potential indications for complement therapeutics, including kidney disorders, is growing owing to new genetic and molecular insights as well as clinical data, and the majority of indications currently are shown in the chart below.



Note for Abbreviations:

(1) aHUS, atypical hemolytic uremic syndrome; (2) AMD, age-related macular degeneration; (3) C3G, C3 glomerulopathy; (4) CARPA, complement activation-related pseudo allergy; (5) gMG, generalized myasthenia gravis; (6) PNH, paroxysmal nocturnal hemoglobinuria; (7) SIRS, systemic inflammatory response syndrome; (8) SLE, systemic lupus erythematosus; (9) TMA, thrombotic microangiopathy.

Source: Frost & Sullivan Analysis

The following table demonstrates the introduction of major complement mediated diseases and their respective prevalence and current treatment methods.

Indication	Introduction	Prevalence	Treatment Methods
PNH	PNH is a chronic, multi-systemic, progressive and life-threatening disease characterized by intravascular hemolysis, thrombotic events, serious infections and bone marrow failure.	The prevalence of PNH in China has experienced steady growth. From 2016 to 2020, the prevalence of PNH have increased from 23.3 thousand to 23.8 thousand, and is predicted to reach 24.3 thousand in 2025 and 24.5 thousand in 2030. From 2016 to 2020, the prevalence of PNH in the rest of the world have increased from 95.8 thousand to 100.5 thousand, and is predicted to reach 106.2 thousand in 2025 and 111.8 thousand in 2030.	PNH is a disease whose diagnosis may be delayed due to variable clinical findings and this delay increases the risk of mortality and morbidity. PNH treatment can be grouped under three main titles: Supportive Treatments; Treatment changing the course of the disease; Potential Curative Treatment.
aHUS	aHUS is a disease that primarily affects kidney function. This condition, which can occur at any age, causes abnormal blood clots (thrombi) to form in small blood vessels in the kidneys, which can cause serious medical problems if they restrict or block blood flow.	From 2016 to 2020, the prevalence of aHUS in China have increased from 9.7 thousand to 9.9 thousand, and is anticipated to reach 10.1 thousand by 2025 and 10.2 thousand in 2030. From 2016 to 2020, the prevalence of aHUS in the rest of the world has gradually increased from 20.8 thousand to 22.0 thousand. In the next 5 years, the prevalence of aHUS is anticipated to reach 23.4 thousand by 2025, and to reach 24.7 thousand in 2030.	The introduction of eculizumab, the humanized anti-C5 complement monoclonal antibody, has brought about a paradigm shift in the management of aHUS. For children with a clinical diagnosis of aHUS, the physicians propose eculizumab as first-line treatment, to avoid PE and the complications of central venous double line catheters.

Indication	Introduction	Prevalence	Treatment Methods
gMG	gMG is a rare autoimmune disease caused by antibodies directed against proteins in the postsynaptic membrane of the neuromuscular junction. Targets of antibodies include nicotinic acetylcholine receptor (AchR), muscle-specific tyrosine-kinase (MuSK), lipoprotein receptor-related protein 4 (LRP4) and agrin.	From 2016 to 2020, the prevalence of gMG in China have increased from 229.5 thousand to 233.8 thousand, and is forecasted to reach 239.1 thousand by 2025 and 241.4 thousand by 2030. From 2016 to 2020, the prevalence of gMG in the rest of the world have increased from 1,006 thousand to 1,056 thousand, and is forecasted to reach 1,115 thousand by 2025 and 1,172 thousand by 2030.	All subgroups of MG respond to acetylcholinesterase inhibition. Pyridostigmine is the preferred drug for the treatment of symptoms in all myasthenia gravis subgroups. Studies has shown positive results after early onset or thymoma MG patients conduct thymectomy. Most MG patients need immunosuppressive medication to meet the treatment goals of full or nearly full physical function and high quality of life. Prednisone or prednisolone in combination with azathioprine is used as first-line treatment.
Neuromyelitis optica (NMO)/ NMOSD	NMO/NMOSD is a group of autoimmune conditions characterized by inflammatory involvement of the optic nerve, spinal cord and central nervous system. They have garnered attention due to their high pathogenicity, high risk of relapse, and poor prognosis as an inflammatory central nervous system (CNS) syndrome.	From 2016 to 2020, the prevalence of NMOSD in China have increased from 46.6 thousand to 48.9 thousand. Driven by the increasing prevalence autoimmune disease of China, the prevalence of NMOSD in China is forecasted to reach 51.2 thousand by 2025, and to reach 52.6 thousand. There are an estimated 122.1 thousand people with NMOSD in the rest of the world in 2020. The number is expected to grow to 128.4 thousand people in 2025. From 2025 to 2030, it is expected to be 135.0 thousand people with NMOSD in 2030.	Currently there is no cure for NMOSD. The overall goal of disease management in NMOSD is to reduce the acute attack and prevent the sequential relapse. In the acute phase, current treatment strategy is to alleviate the acute symptoms, shorten the course of the disease and reduce the degree of disability. The purpose of sequential treatment is to prevent recurrence and reduce the accumulation of mental dysfunction. Patients are treated with immunosuppressants, steroids and plasmapheresis in an effort to prevent NMOSD attacks. However, these treatments are known to cause adverse events, such as upper gastrointestinal bleeding (UGIB), femoral head necrosis, progressive multifocal leukoencephalopathy, cardiotoxicity, acute leukemia and etc., which may lead to treatment discontinuation.

C5 is the protease complexes in the complement system that protect against invading organisms. C5 complement inhibitors block the complement cascade at the level of C5, so it can stop the immune responses that cause disease. C5 complement inhibitors also preserve the generation of C3b, which is essential for the clearance of circulating immune complexes and the normal phagocytosis of bacterial and fungal pathogens. Complement C5 inhibitors have massive market potential as they target a broad spectrum of indications that can be addressed as a result of dysregulation of complement system.

Competitive Landscape

The clinical and commercial value of C5 inhibitor has been validated by Alexion through its marketed products ULTOMIRIS and SOLIRIS. SOLIRIS market presented continued growth since its first approval by the FDA in 2007 and by the NMPA in 2018. The 2020 global revenue generated by SOLIRIS were US$4,064.2 million, reflecting growths of 3.0% compared to the same period in 2019. ULTOMIRIS market recorded annual sales US$1,076.7 million and US$338.9 million in 2020 and 2019, respectively, since first approved by the FDA in December 2018, although it has not been approved by the NMPA yet. SOLIRIS is the only approved product in China so far. The comparable annual cost of SOLIRIS is approximately $500,000 per patient, being one of the most expensive therapies in the world. China remains to be the largest untapped market for complement mediated diseases and more cost-efficient therapies are at urgent needs.

The following table illustrates the current status of major C5 inhibitors approved or being developed for PNH, aHUS, gMG and NMOSD globally.

Generic Name/ Product Code	Brand Name	Company	FDA Approved Date / US Clinical Status	Indication (FDA)	Price, USD (Region)	Annual Cost, USD (Region)	NMPA Approved Date/China Clinical Status	Indication (China)	Price in China, RMB	Annual Cost in China, RMB
eculizumab	Soliris	Alexion	2007	PNH	$6,820/ 300mg (US)	$545,600 (US)	2018	PNH	Unknown	Unknown
				aHUS	$6,820/ 300mg (US)	$461,487 (US)		aHUS	Unknown	Unknown
			2018	PNH/aHUS	$6,695/ 300mg (US)	$ 511,331 (US)	–	–	–	–
ravulizumab	Ultomiris	Alexion	Phase III	NMOSD	–	–	–	–	–	–
			Phase III	gMG	–	–	–	–	–	–
eculizumab biosimilar	Elizaria	AO Generium	2019 (Russia)*	PNH*	–	–	–	–	–	–
eculizumab biosimilar/BCD-148	–	Biocad	Phase III (Completed)	PNH	–	–	–	–	–	–
eculizumab biosimilar/SB-12	–	Bioepis/ AffaMed Therapeutics	Phase III	PNH	–	–	Phase III Terminated	PNH	–	–
crovalimab	–	Hoffmann-La Roche/Chugai	Phase III	PNH/aHUS	–	–	Phase III	PNH/ aHUS	–	–
eculizumab biosimilar/ABP-959	–	Amgen	Phase III	PNH	–	–	–	–	–	–
zilucoplan	–	Ra Pharmaceuticals	Phase III	gMG	–	–	–	–	–	–
			Phase II (Completed)	PNH	–	–	–	–	–	–
cemdisiran	–	Alnylam	Phase II	PNH	–	–	–	–	–	–
pozelimab	–	Regeneron	Phase II	PNH	–	–	–	–	–	–

Note:

* Elizaria was approved in Russia in 2019 and not yet approved by FDA.

Source: FDA, NMPA, Frost & Sullivan analysis

Other Lysosomal Storage Diseases (LSDs)

LSDs are a group of over 70 diseases that are characterized by lysosomal dysfunction, most of which are inherited as autosomal recessive traits, including Gaucher disease (GD), Fabry disease (FD) and Pompe Disease (PD). For details on FD and PD, please see "– Gene Therapy." LSDs typically present in infancy and childhood, although adult-onset forms also occur. While clinical trials are in progress on possible treatments for some of these diseases, there is currently no approved treatment for many LSDs.

Gaucher Disease (GD)

GD is a genetic disorder where fat-laden Gaucher cells build up in cells of the reticuloendothelial stsem, including the spleen, liver, bone marrow, and lungs, and in the most severe cases, the central nervous sytem. It is one of the most common lysosomal storage disorders. GD is a rare inherited LSD caused by autosomal recessive inheritance of mutations in the GBA gene encoding the lysosomal enzyme, acid β-glucosidase, which converts its major substrate, glucocerebroside (glucosylceramide), into glucose and ceramide, and its minor substrate, lyso-glucocerebroside (lyso-glycosylceramide), into glucose and sphingosine.

Market Overview

The prevalence of GD has experienced steady growth throughout various indications both globally and in China. From 2016 to 2020, the potential diagnosed prevalence of GD in China maintained a steady growth from 2,765 to 2,812, and is expected to reach 2,872 in 2030, representing one of the largest treatment naïve patient pools globally. From 2016 to 2020, the prevalence of GD in the rest of the world also experienced sustainable growth from 68.2 thousand to 71.4 thousand, and is expected to reach 75.1 thousand by 2025 and 78.7 thousand in 2030.

Treatment Methods

GD is a clinically heterogeneous disorder, including neuropathic and non-neuropathic variants. Optimal care may necessitate both palliative and adjunctive therapies. There are currently two specific types of treatment for GD: enzyme replacement therapy (ERT) and substrate reduction therapy (SRT).

ERT is the most accepted form of treatment for GD, and has well-established therapeutic goals (changes in liver and spleen size, improvement in blood parameters, bone pain and bone crises). ERT specifically supplements the lack of enzymes in the patient's body and reduces the accumulation of glucocerebrosides in the body and shows favorable safety performance.

In SRT a small molecule drug is used to partially inhibit the biosynthesis of the compounds, and accumulate in the absence of a specific lysosomal enzyme. The drug will reduce the number of molecules requiring catabolism within the lysosome, thus contributing to balance the rate of synthesis with the impaired rate of catabolism.

Competitive Landscape

The following table illustrates the current status of targeted drugs for GD marketed in the U.S..

Generic Name/ Product Code	Brand Name	Company	FDA Approved Date	Price, USD (Region)	Annual Cost, USD (Region)	NMPA Approved Date/China Clinical Status	Price in China, RMB	Annual Cost in China, RMB	Mechanism of Action
imiglucerase	Cerezyme	Genzyme (Acquired by Sanofi)	1994	$1,784/ 400 units (US)	$278,345 (US)	2017	20,700/ 400 units	3,229,200**	Glucosylceramidase replacements; Catalyzing the hydrolysis of glucocerebroside
miglustat	Zavesca	Actelion (Acquired by J&J)	2003	$20,263/ (100 mg*90) (US)	$246,533 (US)	–	–	–	Glucosylceramide synthase (UGCG) inhibitors
velaglucerase alfa	Vpriv	Shire (Acquired by Takeda)	2010	$1,490/ 400 units (US)	$232,440 (US)	–	–	–	Glucosylceramidase replacements; Catalyzing the hydrolysis of glucocerebroside
imiglucerase	Abcertin	ISU ABXIS	2012*	Unknown	Unknown	–	–	–	Recombinant human enzyme β-glucocerebrosidase
taliglucerase alfa	Elelyso	Protalix	2012	$852/200 units (US)	$265,824 (US)	–	–	–	Glucosylceramidase replacements; Catalyzing the hydrolysis of glucocerebroside
eliglustat tartrate	Cerdelga	Genzyme (Acquired by Sanofi)	2014	$7,474/ 84 mg*14 (US)	$194,858 ~ $389,716 (US)	Phase III	–	–	Glucosylceramide synthase (UGCG) inhibitors

Note: Assume patient body weight is 40kg.

* Abcertin was approved in South Korea in 2012, and not yet approved by FDA.

** Imiglucerase is currently not included in the NRDL, but it has been included in the local reimbursement list some province/cities, such as Zhejiang and Qingdao. The annual cost shown here is the annual cost of adequate medication for adults patient with Gaucher disease in China. Since the actual dosage amount is usually lower than the theoretical value, 2.62 million RMB is used as the calculation standard. According to calculations, the out-of-pocket expense of a GD patient in Zhenjiang can be as low as RMB30,000 after reimbursement and medical assistance, while the out-of-pocket expense of GD patient in Qingdao is approximately RMB150,000.

Source: Frost & Sullivan analysis

The following table illustrates the current status of targeted drugs for GD being developed in China and worldwide.

Generic Name/ Product Code	Company	US Clinical Status	NMPA Approved Date/China Clinical Status	Mechanism of Action
venglustat/ ibiglustat	Genzyme (Acquired by Sanofi)	Phase II/III	–	Glucosylceramide synthase (UGCG) inhibitors
afegostat tartrate/AT-2101	Amicus Therapeutics/ Shire (Acquired by Takeda)	Phase II (Completed)	–	β-glucosidase (β-Glu) inhibitors
arimoclomol	Orphazyme	Phase II	–	Amplification of Heat-Shock Proteins production
AVR-RD-02	AVROBIO	Phase I/II	–	Gene transference; Glucosylceramidase replacements
PR-001	Prevail	Phase I/II	–	Gene therapy
acetylcysteine	University Of Minnesota	Phase I (Completed)	–	Antioxidant and glutathione inducer

Source: Frost & Sullivan analysis

Gene Therapy

Approximately 80% of rare diseases result from genetic disorders. Gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use, and to achieve durable expression of the therapeutic gene or "transgene" at a level sufficient to ameliorate or cure disease symptoms with minimal adverse events. Aiming to correct or replace dysfunctional genes that are the cause of many rare disease, gene therapy serves as a one-time treatment with the potential to fundamentally address the original source of the disease, and is applicable to a broad spectrum of indications, including monogenic diseases such as muscular dystrophy, spiral muscular atrophy (SMA), hemophilia or severe combined immunodeficiency (SCID), cancer, and LSDs such as Fabry disease (FD) and Pompe Disease (PD).

Ex vivo and in vivo are the two major techniques in gene therapies. For ex vivo gene therapy, cells are extracted from the patient, followed by the transduction with the gene of interest in vitro before their subsequent transplantation back into the patient. For in vivo gene therapy, the vector containing the gene of interest is injected directly into the patient, with adeno-associated virus (AAV) being the most commonly-used vector in current studies.

Viral Vectors Used in Gene Therapy

Viral transduction has been validated for introducing genetic material into mammalian cells. Viral vectors are highly amenable for many basic research applications, such as protein overexpression, antibody production, and gene knockout, and hold promise for gene therapy. Through viral vectors, therapeutic genes can be effectively delivered to target tissues/cells of patients in vivo or ex vivo. The currently viral systems for DNA delivery include Retrovirus, Lentivirus, Adenovirus and AAV. Each viral system has its own unique features as shown below:

○ Low ● High	Retrovirus	Lentivirus	Adenovirus	AAV
Definition	A retrovirus is a virus that uses RNA as its genetic material. When a retrovirus infects a cell, it makes a DNA copy of its genome that is inserted into the DNA of the host cell.	Lentiviruses are a subset of retroviruses. Lentiviruses can deliver significant amounts of genetic information into host cells and integrate it into the cellular genome.	Adenovirus (Ad) is a non-enveloped, linear double-stranded DNA virus with 57 identified human Ad serotypes. Adenoviruses are engineered to make them safe and efficient for human use gene therapy vectors.	Adeno-associated virus (AAV) is a protein shell surrounding and protecting a small, single-stranded DNA genome, which can be engineered to deliver DNA to target cells.
Type	ssRNA	ssRNA	dsDNA	ssDNA
Host Range (Infected Cell Types)	Dividing Cells Only	Dividing and Non-dividing Cells	Dividing and Non-dividing Cells	Dividing and Non-dividing Cells
No Genome Integration Involved*	X	X	√	√**
***In vivo* Safety**	◑	◑	◑	◕
Less Immunogenicity	◑	◑	◔	◕
Insert size capacity	~8 kb	~8 kb	~7.5 kb	~4.5 kb
Able to obtain high multiplicity of infection (>25 copies per cell)	No (up to 10 copies integrated)	No (up to 10 copies integrated)	Yes	Yes
Stability of inserted gene expression	◕	◕	◔	◑

Notes:

* The integration of a viral vector may result in insertional mutagenesis that can alter the expression of chromosomal genes. Possible genotoxic effects include the inactivation of genes at the integration site and the dysregulation of neighboring genes as a consequence of enhancers and promoters present in the vector.

** Although recombinant AAV vector genomes persist within cells as episomes, random integration has been observed.

Source: Frost & Sullivan Analysis

Currently, only two AAV-based gene therapies have been approved by the FDA, including Luxturna in 2017 for a rare inherited retinal dystrophy, and Zolgensma in 2019 for spinal muscular atrophy.

Gene therapy breakthroughs have been propelled by technological advancement in gene editing tools from Zinc Finger Nucleases (ZFNs) and Transcription Activator-like Effector Nucleases (TELENs) to Clustered Regularly Interspaced Short Palindromic Repeats (CRISPRs) as next-generation gene editing tools. The CRISPR gene editing tool is a ribonucleoprotein complex in which a guide RNA recognizes and binds to a specific nucleotide sequence in the genome, which activates a Cas9 nuclease to create a double-stranded cut of the DNA. Normal cellular machinery repairs the cut strands either through non-homologous end-joining, which adds or removes a few nucleotides to inactivate a gene or splice site, or by replacing a short nucleotide sequence using homology-directed repair with a donor template. A newer adaptation of CRISPR technology called base editing uses a hybrid enzyme to chemically convert a single nucleotide-causing mutation to a non-pathogenic sequence without cutting the DNA. CRISPR is the easiest of the genome editing technologies to design and use because the genome recognition sequence is based on the complementary RNA sequence rather than a protein sequence that needs to undergo interative designs. CRISPR has the potential for exquisite specificity with no off-target genome effects.

Gene Therapy Application to LSDs

Gene therapy holds the promise to transform treatments for LSDs such as Fabry disease and Pompe disease from chronic to curative. The following table demonstrates the introduction of Fabry disease and Pompe disease, and their respective prevalence and current treatment methods.

Indication	Introduction	Prevalence	Treatment Methods
Fabry disease (FD)	FD is one of the most common LSDs which usually starts in childhood and is much more common in men than women. FD is a rare, inherited disease caused by a mutation in the alpha galactosidase (GLA) gene on the X chromosome. The *GLA* gene produces the α-GAL enzyme that helps break down a lipid molecule in the cells known as globotriaosylceramide (GL-3). When the *GLA* gene is mutated, the α-GAL enzyme has reduced or absent activity. As a result, GL-3 builds up in blood vessels and tissues and narrows blood vessels, which can damage the skin, kidneys, heart, brain, and nervous system. Significant medical problems are renal failure, cardiomyopathy, myocardial infarction, arrhythmias, painful peripheral neuropathy, diarrhea, and stroke.	From 2016 to 2020, the prevalence of FD in China maintained a steady growth from 354.0 thousand to 360.3 thousand, and is forecasted to reach 364.6 thousand by 2025 and 368.3 thousand by 2030. China has a relatively large number of patients with FD, accounting for about one fifth of patients in the world. From 2016 to 2020, the prevalence of FD in the rest of the world have increased from 1,359.6 thousand to 1,428.3 thousand, and is forecasted to reach 1,512.1 thousand by 2025 and 1,591.1 thousand by 2030.	There are four main treatment approaches considered for FD, including symptomatic therapy, enzyme replacement therapy (ERT), substrate reduction therapy and chaperone therapy. Gene therapy is considered an innovative and promising treatment for FD and is currently the clinical development stage. *Symptomatic Therapy:* As Fabry disease damages multiple tissues and organs, various methods are used to alleviate symptoms. Treatment of Fabry disease with supportive care alone is not sufficient because it does not target the underlying Fabry disease pathogenesis. Symptomatic therapy of Fabry disease includes medicine, surgery, lifestyle changes and so on. *Enzyme Replacement Therapy (ERT):* Exogenous delivery of intravenous recombinant human α-GAL can replace GAL activity in patients with decreased or absent enzyme activity, and thereby reduce GL-3 storage and slowing the progression of renal disease. ERT may cause infusion-related reactions and lead to the formation of anti-ERT antibodies. There are five approved ERTs for FD globally. *Substrate Reduction Therapy (SRT):* SRT is intended to lower GL-3 through a different mechanism than ERT by reducing the rate of substrate synthesis to match the lower rate of substrate degradation, thereby restoring metabolic balance. SRT uses small molecule drug which do not induce anti-drug antibody (ADA) development and in some cases may be capable of passing the blood-brain barrier. There are no approved SRTs for FD. *Chaperones Therapy:* Chaperone therapy uses an oral small molecule drug to help α-GAL fold correctly for normal function and increase or restore its activity. Treatment is only applicable to patients with certainmissense mutations that produce α-GAL with reduced activity. As a molecular chaperone, migalastat has shown some efficacy in FD and is increasingly being used in patients. *Gene Therapy:* Gene therapy for FD refers to the delivery of the *GAL* gene into cells, including delivery of DNA and mRNA, in which way the patient's cells can produce α-GAL consistently by DNA delivery while the effect of mRNA is transient and thus requires repeated administration. Gene therapy has the potential to induce immune tolerance in patients with FD. There are currently no approved gene therapies for FD.

Indication	Introduction	Prevalence	Treatment Methods
Pompe disease (PD)	PD, also known as acid maltase deficiency (AMD), acid alpha-glucosidase (GAA) deficiency and type II glycogen disease storage disease (GSD II), was the first identified LSD. PD is a rare genetic condition resulting from mutations in the acid α-glucosidase (*GAA*) gene, leading to the deficiency of an enzyme called GAA which breaks down glycogen in lysosomes as part of normal cell turnover. As a result, glycogen builds up inside cells, which damages organs and tissues, especially muscles.	From 2016 to 2020, the prevalence of PD in China have maintained a steady growth from 37.4 thousand to 38.2 thousand, and is forecasted to reach 38.7 thousand by 2025 and 39.3 thousand by 2030. From 2016 to 2020, the prevalence of PD in the rest of the world have increased from 125.8 thousand to 132.2 thousand, and is forecasted to reach 141.6 thousand by 2025 and 147.4 thousand by 2030.	There are two mail treatment approaches for Pompe disease, including symptomatic treatment and ERT. Gene therapy is also considered an innovative and promising treatment for Pompe disease and is currently at clinical stages. *Symptomatic Therapy:* Similar to FD, treatment of Pompe disease by symptoms alone can only alleviate the symptoms and does not target the underlying Pompe disease pathogenesis. *ERT:* ERT directly introduces a functional enzyme (recombinant human acid α-lucosidase (rhGAA)) into the body to compensate for deficiency of GAA. ERT can improve respiratory function and muscle weakness by reducing glycogen storage. ERT may cause infusion-related reactions and induce anti-ERT antibodies, particularly in infantile-onset disease with no detectable GAA. The latter requires the use of immunomodulatory drugs like rituximab,mycophenolate mofetil, methotrexate and sirolimus to try to induce immune tolerance. There is one ERT for PD approved globally, and another ERT that has completed clinical development and is awaiting regulatory decisions on approval. *Gene Therapy*: Gene therapy for Pompe disease refers to the delivery of the *GAA* gene into cells, which can provide a durable source of GAA that addresses a major convenience limitation of ERT being a chronic therapy that requires time-consuming, biweekly infusions. In addition to providing a continuous source of enzyme, gene therapy has the potential to induce immune tolerance in PD patients.

Competitive Landscape

The following table illustrates the current status of targeted drugs for Fabry disease marketed globally.

Brand name	Generic Name	Company	Approved Region	First Approved Date	Price, (USD) (Region)	Annual Cost*, (USD) (Region)	China Status	Price in China, RMB	Annual Cost* in China, RMB	Mechanism of Action
Fabrazyme	agalsidase beta	Genzyme (Acquired by Sanofi)	US, China, Japan, EU	2001	$798.3/ 5mg (US)	$312,186 (US)	Approved	39,900/ 35mg	1,778,400	glycosphingolipid hydrolysis activators; globotriaosylceramide (GL-3) hydrolysis; Alpha-galactosidase replacements
Replagal	agalsidase alfa	Shire (Acquired by Takeda)	China, Japan, EU	2001	Unknown	Unknown	Approved	Unknown	Unknown	Alpha-galactosidase replacements
–	agalsidase beta biosimilar	Isu Abxis/ GC Pharma	South Korea	2014	Unknown	Unknown	–	–	–	glycosphingolipid hydrolysis activators; globotriaosylceramide (GL-3) hydrolysis; Alpha-galactosidase replacements
Galafold	migalastat hydrochloride	Amicus Therapeutics	US, EU, Japan	2016	$1,700.0/ 150mg (US)	$310,250 (US)	–	–	–	α-Galactosidase stimulants
–	agalsidase beta biosimilar	JCR Pharmaceuticals	Japan	2018	Unknown	Unknown	–	–	–	glycosphingolipid hydrolysis activators; globotriaosylceramide (GL-3) hydrolysis; Alpha-galactosidase replacements

Note:

* Assumes 75 kg average patient weight.

Source: Frost & Sullivan Analysis

The following table illustrates the current status of targeted drugs for Fabry disease being developed in China and worldwide.

Generic Name	Company	US Clinical Stage	Start Date	Mechanism of Action	China Status
pegunigalsidase alfa/ PRX-102	Protalix Biotherapeutics Inc	NDA	2020	Alpha-galactosidase replacements	–
lucerastat	Idorsia Pharmaceuticals/ Actelion (Acquired by J&J)	Phase III	11/2018	Ceramide glucosyltransferase inhibitors	–
ibiglustat/GZ/SAR402671	Genzyme (Acquired by Sanofi)	Phase II	11/2014	Ceramide glucosyltransferase inhibitors	–
AVR-RD-01	Avrobio	Phase I/II	02/2018	Cell replacements; Gene transference; α-Galactosidase stimulants	–
FLT-190	Freeline Therapeutics	Phase I/II	07/2019	Gene transference; α-Galactosidase stimulants	–
ST-920	Sangamo Therapeutics	Phase I/II	07/2019	Gene transference; α-Galactosidase stimulants	–
4D-310	4d Molecular Therapeutics	Phase I/II	09/2020	Gene therapy	–
apabetalone/ RVX000222	Resverlogix	Phase I/II	09/2019	Bromodomain-containing protein 4 inhibitors	–
GC1119	Green Cross Corporation	Phase I (Completed)	11/2012	Recombinant human α-Galactosidase A	–
alpha galactosidase	Greenovation Biotech	Phase I (Completed)	11/2016	Alpha-galactosidase replacements	–
alpha-galactosidase A stem cell therapy	University Health Network	Phase I	07/2016	Autologous stem cell transplantation	–

Source: Frost & Sullivan Analysis

The following tables illustrate the current status of targeted drugs for Pompe disease in China and worldwide.

Brand name	Generic Name	Company	Approved Region/US Clinical Stage	First Approved Date/ Start Date	Price, USD (Region)	Annual Cost*, USD (Region)	China Status	Price in China RMB	Annual Cost* in China, RMB	Mechanism of Action
Lumizyme	alglucosidase alfa	Genzyme (Acquired by Sanofi)	US, China, Japan, EU	2006	$905/ 50mg (US)	$707,839 (US)	Approved	5,480/ 50mg	3,419,520	Alpha glucosidase replacements
–	avalglucosidase alfa	Genzyme (Acquired by Sanofi)	NDA	11/2016	–	–	–	–	–	Glycogen metabolizers Alpha glucosidase replacements
–	cipaglucosidase alfa/ ATB200	Amicus Therapeutics Inc	Phase III	12/2018	–	–	–	–	–	Alpha glucosidase replacements
–	duvoglustat hydrochloride	Amicus Therapeutics Inc	Phase II (Completed)	10/2011	–	–	–	–	–	Maltase-glucoamylase stimulants
–	AAV2/8LSPhGAA	Asklepios Biopharmaceutical, Inc; Duke University; National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)	Phase I/II	11/2018	–	–	–	–	–	GAA gene transference
–	RP-A501	Rocket Pharmaceuticals	Phase I	04/2019	–	–	–	–	–	Gene transference

Note:

* Assumes 75kg average patient weight.

Source: Frost & Sullivan Analysis

Rare Cholestatic Liver Diseases

Cholestatic liver diseases are a group of diseases caused by a primary defect in the flow of bile within the liver or from the liver to the intestines, which results in similar symptoms. Cholestasis can be caused by decreased bile production by dysfunctional hepatic or bile duct cells, inhibition of bile secretion, or blockage of bile excretion, consequently bile flows into the lymphatics and blood circulation instead of the small intestine. Cholestatic liver diseases such as Alagille Syndrome (ALGS) and Progressive Familial Intrahepatic Cholestasis (PFIC) are rare diseases with clear genetic bases, whereas Biliary Atresia (BA) is believed to have a multifactorial cause involving genetic risk factors with immune dysregulation and exposure to environmental factors such as viruses or toxins playing a variable role.

The following table demonstrates the introduction of major rare cholestatic liver diseases, and their respective prevalence, current treatment methods and approved products.

Indication	Introduction	Prevalence	Treatment Methods
ALGS	ALGS is a rare genetic disorder that can affect multiple organ systems of the body including the liver, heart, skeleton, eyes and kidneys. ALGS is an autosomal-dominant multisystem disorder caused by mutations in Jagged 1 (*JAG1*) or *NOTCH2*. Approximately 90% of ALGS patients have liver disease caused by "bile duct paucity," which means a reduction in the number of bile ducts in the liver. Bile ducts are small tube-like structures that connect the liver, gallbladder and small intestine, while extrahepatic bile ducts refer to the bile ducts outside the liver.	From 2016 to 2020, the prevalence of ALGS in China has increased from 7.2 thousand to 7.4 thousand, and is forecasted to reach 7.5 thousand by 2025 and 7.6 thousand by 2030. From 2016 to 2020, the prevalence of ALGS in the rest of the world have increased from 65.0 thousand to 68.0 thousand, and is forecasted to reach 71.6 thousand by 2025 and 75.0 thousand by 2030.	There is currently no procedure that can correct the loss of the bile ducts within the liver to cure ALGS syndrome completely. Treatments for ALGS include liver transplantation, diet & lifestyle control and medications. The emergence of inhibitors of the apical sodium-dependent bile acid transporter (ASBT) marks an innovative treatment for ALGS with the potential to cure the disease. ASBT inhibitors interrupt the enterohepatic circulation of bile acids, resulting in more bile acids being excreted in the feces and lowering the levels of bile acids systemically, thereby potentially reducing bile acid-mediated liver damage and related effects and complications.

Indication	Introduction	Prevalence	Treatment Methods
PFIC	PFIC is a liver disorder in which liver cells do not release a digestive fluid, called bile, properly, which results in bile accumulation in the cells, known as cholestasis, which causes liver disease. The condition usually progresses slowly over decades from early life.	From 2016 to 2020, the prevalence of PFIC in China has increased from 9.6 thousand to 9.8 thousand, and is forecasted to reach 10.0 thousand by 2025 and 10.1 thousand by 2030. From 2016 to 2020, the prevalence of PFIC in the rest of the world has increased from 42.7 thousand to 44.8 thousand. In the forecasted next five years, the prevalence of PFIC is forecasted to reach 47.3 thousand by 2025, and reach 49.7 thousand by 2030.	Treatments for PFIC mainly include medical and surgical approaches. Diets, medications, and nasobiliary drainage are used for medical treatment and external or internal biliary diversions are applied for surgical treatment. Surgical approaches have an important role in the relief of symptoms such as pruritus and prevention of development of cirrhosis of the liver. ASBT inhibitor is also a novel, promising investigational medication being evaluated in PFIC.
BA	BA is a rare disease of the liver and bile ducts that occurs in infants. When a baby has biliary atresia, bile flow from the liver to the gallbladder is blocked. This causes the bile to be trapped inside the liver, quickly causing damage and scarring of the liver cells (cirrhosis), and eventually causing liver failure.	From 2016 to 2020, the prevalence of BA in China have increased from 43.7 thousand to 44.6 thousand, and is forecasted to reach 45.3 thousand by 2025 and 45.9 thousand by 2030. The global prevalence rate is comparable to that of China. From 2016 to 2020, the global prevalence of BA increased from 192.6 thousand to 201.0 thousand, and is forecasted to reach 211.0 thousand by 2025 and 220.3 thousand by 2030.	There is currently no cure for BA available. The treatments for BA mainly include liver transplant and the Kasai procedure, an operation to re-establish bile flow from the liver into the intestine. ASBT inhibitor is a potential treatment for BA currently under development.

Competitive Landscape

There is currently no approved product in China or worldwide for ALGS, PFIC or BA. The following tables illustrate the current status of targeted therapies and drugs for ALGS under development in China and worldwide.

Generic Name	Company	US Status	Start Date	Mechanism of Action	China Status
maralixibat/ CAN108	Shire (Acquired by Takeda); Mirum; Canbridge	NDA	2021	Ileal bile acid transporter inhibitors	–
odevixibat	Albireo	Phase III	03/2021	Ileal bile acid transporter inhibitors	–

Source: Frost & Sullivan Analysis

The following table illustrates the current status of targeted therapy and drugs for PFIC in China and worldwide.

Generic Name	Company	US Status	Start Date	Mechanism of Action	China Status
odevixibat	Albireo	NDA	2020	Ileal bile acid transporter inhibitors	–
maralixibat/ CAN108	Shire (Acquired by Takeda); Mirum; Canbridge	Phase III	10/2018	Ileal bile acid transporter inhibitors	–

Source: Frost & Sullivan Analysis

The following table illustrates the current status of targeted therapy and drugs for BA in China and worldwide.

Generic Name	Company/ Sponsor	US Status	Start Date	Mechanism of Action	China Status
odevixibat	Albireo	Phase III	07/2020	Ileal bile acid transporter inhibitors	–
maralixibat/ CAN108	Shire (Acquired by Takeda); Mirum; Canbridge	Phase II	05/2021	Ileal bile acid transporter inhibitors	–
n-acetylcysteine	Baylor College of Medicine	Phase II	05/2018	Glutathione synthesis stimulator	–
pentoxifylline	Baylor College of Medicine	Phase II	01/2013	Methylxanthine derivative	–

Source: Frost & Sullivan Analysis

OVERVIEW OF THE CHINA ONCOLOGY MARKET

The China oncology drug market is a sector focusing on the discovery, development, and commercialization of medicines for the treatment of cancer. The China oncology drug market increased significantly from US$18.8 billion in 2016 to US$28.6 billion in 2020, representing a CAGR of 11.1%. It is expected to grow to US$60.3 billion by 2025, at a CAGR of 16.1% from 2020, and to further grow to US$99.0 billion by 2030, at a CAGR of 10.4% from 2025.

Breast Cancer

Breast cancer is the most common cancers in women, and the incidence increases year by year. Breast cancer mostly happens in women aged over 50. Human epidermal growth factor receptor (HER2) is a ligand-orphan receptor which is expressed in many human tumors, especially in breast cancers. HER2 inhibitors are either tyrosine kinase inhibitors or monoclonal antibodies that slow down or stop cell growth. The incidence of breast cancer in mainland China reached 331.6 thousand in 2020 at a CAGR of 1.7% from 2016 to 2020 and is estimated to reach 355.6 thousand in 2025 and 372.4 thousand in 2030. In Hong Kong, the incidence of breast cancer reached 5.2 thousand in 2020 and is estimated to reach 6.6 thousand in 2025 and 8.0 thousand in 2030. In Taiwan, the incidence of breast cancer was 15.7 thousand in 2020 and is estimated to reach 19.1 thousand in 2025 and 22.2 thousand in 2030. HER2 positive breast cancer accounts for approximately 25% of breast cancer types in China.

The table below illustrates the current marketed small molecular anti-HER2 drugs in China and worldwide.

Brand name	Generic Name	Company	FDA Approval	Price, USD (US)	Annual Cost, USD (US)	NMPA Approval	Price, RMB (China)	Annual Cost, RMB (China)	Indication	Combination	Treatment Line
Tykerb	lapatinib	Norvartis	2007	$58/ 250mg	$6,090 (21 days/ course)	2013	70/ 250mg	7350 (21 days/ course)	Advanced or metastatic breast cancer whose tumors overexpress HER2	Capecitabine	2L
					348 (daily cost)			420 (daily cost)	Postmenopausal women with HR+ metastatic breast cancer that over expresses the HER2 receptor for whom hormonal therapy is indicated	Letrozole	1L
Ai Rui Ni (艾瑞妮)	pyrotinib	Hengrui	–	–	–	2018	4093.6/ 160mg	12,708	Advanced or metastatic breast cancer whose tumors overexpress HER2	Capecitabine	1L/2L
Nerlynx	neratinib	Puma Biotech/ Canbridge	2017	$102/ 40mg	$223,380	2020	Unknown	Unknown	Adjuvant treatment for early stage HER2-positive breast cancer, to follow adjuvant trastuzumab based therapy	Na	2L
					$12,852 (21 days/ course)				Advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting	Capecitabine	≥2L
Tukysa	tucatinib	Seattle Genetics	2020	$172/ 150mg	$125,560	–	–	–	Advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting	Trastuzumab/ Capecitabine	2L

Notes:

- We assume that the average weight of the patient is 60 kg.
- The course of treatment for lapatinib is mainly determined according to the actual situation of the patient. Currently, there is no unified statement on how long and how many courses of treatment are needed.

Source: FDA, Frost & Sullivan analysis

The table below illustrates the current status of small molecular anti-HER2 drugs being developed in China.

Product Name/Code	Company	US Clinical Status	Indication (US)	China Clinical Status	Indication (China)
selatinib	Qilu Pharmaceutical Co Ltd	–	–	Phase II	Recurrent or metastatic breast cancer whose tumors overexpress HER2
allitinib	Allist Pharmaceuticals Co.,Ltd	–	–	Phase II	Recurrent or metastatic breast cancer whose tumors overexpress HER2
AMX3009	Arromax Pharmatech Co., Ltd	–	–	Phase I	Solid tumor with HER2+
Hemay-022	Tianjin Hemay Pharmaceutical Co Ltd	–	–	Phase I	HER2 positive breast cancer

Source: FDA, Frost & Sullivan analysis

Oral Mucositis

Oral mucositis is a frequent complication in patients receiving radiation therapy to the head and neck and chemotherapy. The incidence of oral mucositis varies between chemotherapeutic agents, the frequency and dosage of chemotherapy, as well as individual patient. Oral mucositis is a severely debilitating condition that could cause pain and restrict oral intake. It is reported that oral mucositis occurs in up to 20% to 40% of adult cancer patients receiving conventional chemotherapy for solid tumors, about 80% of patients receiving high-dose chemotherapy before hematopoietic stem cell transplantation, and almost all patients receiving radiotherapy for head and neck cancer. Drugs or medical devices for the treatment of oral mucositis is often a short-term treatment to manage the symptoms or complications as a result of patients receiving chemotherapy. Key oral mucositis treatments include mouthwash, pain control medications or other drugs.

REPORT COMMISSIONED BY FROST & SULLIVAN

In connection with the [**REDACTED**], we have engaged Frost & Sullivan to conduct a detailed analysis and to prepare an industry report on the worldwide and China oncology drug markets. Frost & Sullivan is an independent global market research and consulting company founded in 1961 and is based in the United States. Services provided by Frost & Sullivan include market assessments, competitive benchmarking, and strategic and market planning for a variety of industries.

We have included certain information from the Frost & Sullivan Report in this document because we believe such information facilitates an understanding of the rare disease and oncology drug market for potential [**REDACTED**]. Frost & Sullivan prepared its report based on its in-house database, independent third-party reports and publicly available data from reputable industry organizations. Where necessary, Frost & Sullivan contacts companies operating in the industry to gather and synthesize information in relation to the market, prices and other relevant information. Frost & Sullivan believes that the basic assumptions used in preparing the Frost & Sullivan Report, including those used to make future projections, are factual, correct and not misleading. Frost & Sullivan has independently analyzed the information, but the accuracy of the conclusions of its review largely relies on the accuracy of the information collected. Frost & Sullivan research may be affected by the accuracy of these assumptions and the choice of these primary and secondary sources.

We have agreed to pay Frost & Sullivan a fee of RMB650,000 for the preparation of the Frost & Sullivan Report. The payment of such amount was not contingent upon our successful [**REDACTED**] or on the content of the Frost & Sullivan Report. Except for the Frost & Sullivan Report, we did not commission any other industry report in connection with the [**REDACTED**]. We confirm that after taking reasonable care, there has been no adverse change in the market information since the date of the report prepared by Frost & Sullivan which may qualify, contradict or have an impact on the information set forth in this section in any material respect.