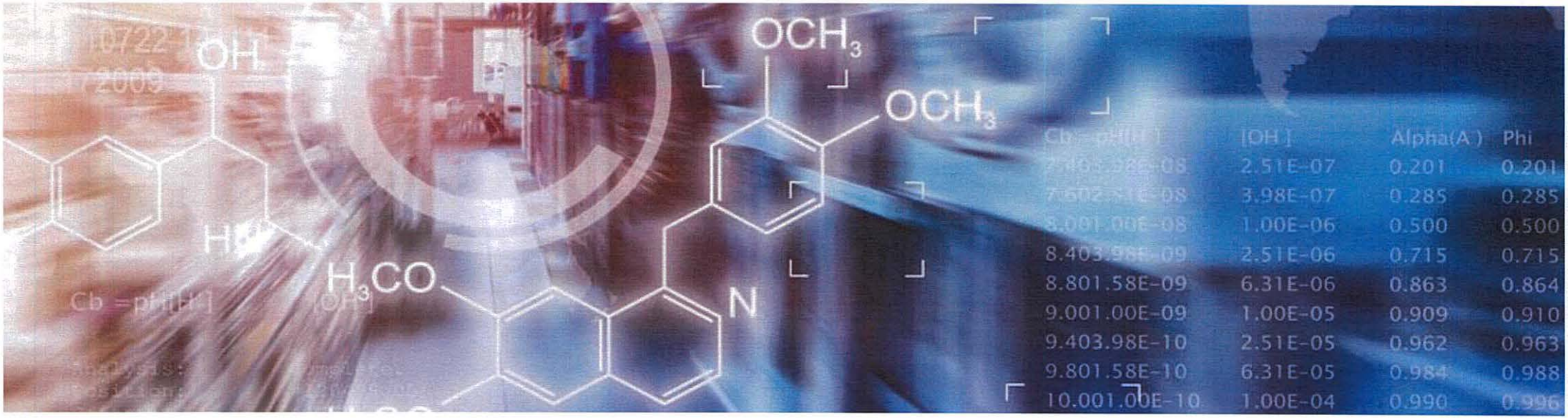


China Insights Consultancy

# Project 525- Industry Report

For and on behalf of
China Insights Industry Consultancy Limited

November 20, 2024

Name: Luke Liu
Title: Managing Director

# Introduction, methodology and assumptions

China Insights Consultancy was commissioned to conduct research and analysis of, and to produce a report on China【orthopedic diseases treatment, metabolic diseases drug, oncology drug, and hematological diseases drug】 markets. The report commissioned has been prepared by China Insights Consultancy independent of the influence of the Company and other interested parties.

China Insights Consultancy's services include industry consulting, commercial due diligence, strategic consulting, etc. Its consulting team has been tracking the latest market trends in industrial, energy, chemicals, healthcare, education, consumer goods, transportation, agriculture, internet, finance, etc., and has the most relevant and insightful market intelligence in the above industries.

China Insights Consultancy conducted both primary and secondary research using a variety of resources. Primary research involved interviewing key industry experts and leading industry participants. Secondary research involved analyzing data from various publicly available data sources, such as the National Bureau of Statistics, National Medical Products Administration, Food and Drug Association, National Health Commission of the People's Republic of China, the International Monetary Fund, World Health Organization, etc.

The market projections in the commissioned report are based on the following key assumptions: (i) the overall social, economic and political environment in China is expected to remain stable during the forecast period; (ii) China's economic and industrial development is likely to maintain a steady growth trend over the next decade; (iii) related key industry drivers are likely to continue driving the growth of the market during the forecast period, such as the increasing number of eye disease incidences mainly owing to aging population, strengthened public awareness of eye care, enhanced patient affordability, enriched drugs and therapies, etc.; and (iv) there is no extreme force majeure or industry regulation in which the market may be affected dramatically or fundamentally.

All statistics are reliable and based on information available as of the date of this report. Other sources of information, including from the government, industry associations, or market participants, may have provided some of the information on which the analysis or data is based.

All the information about the Company is sourced from the Company's audited report or management interviews. The information obtained from of the Company has not been independently verified by China Insights Consultancy.

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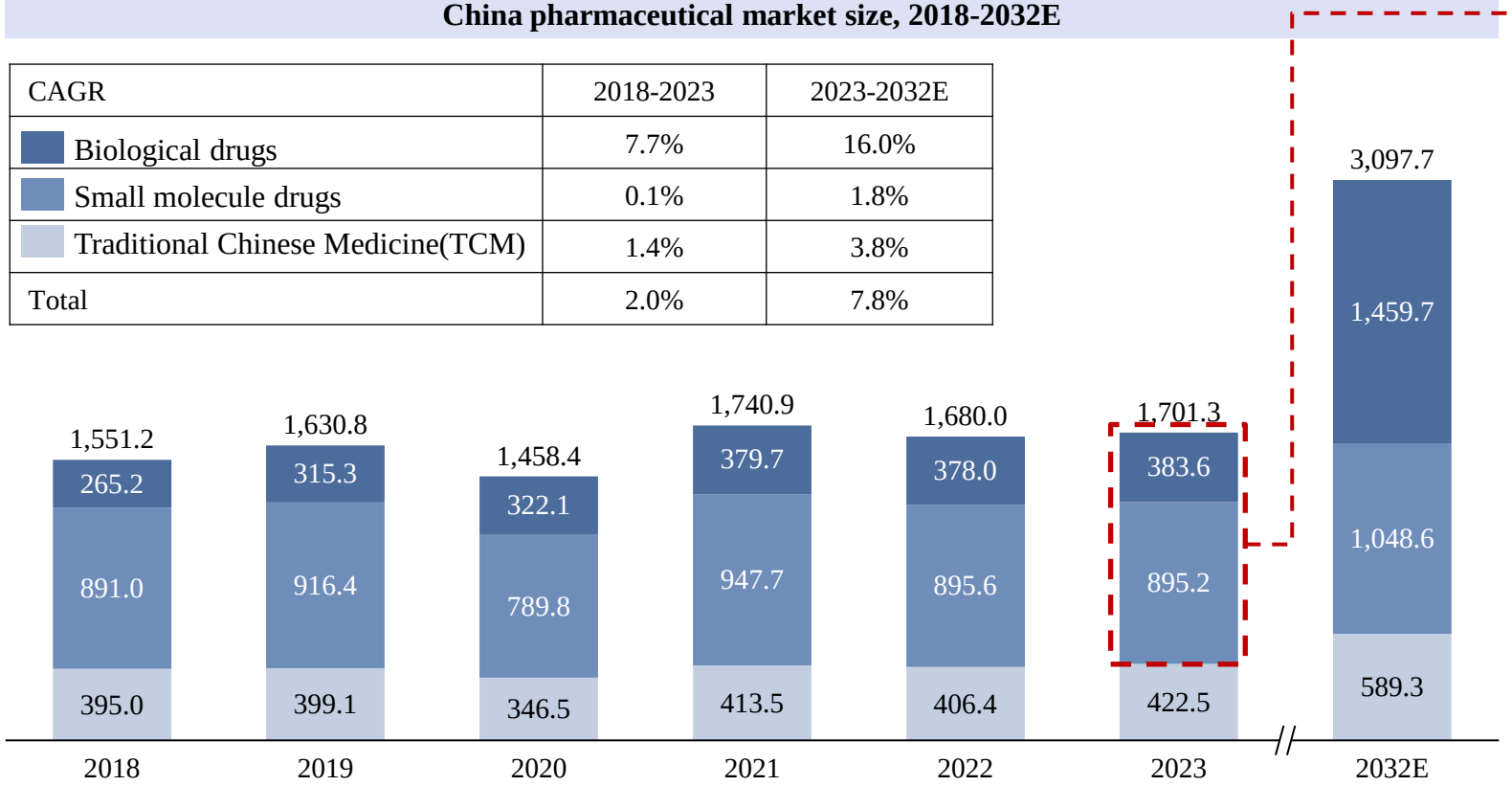
# The market size of China pharmaceutical market is expected to increase from RMB[1,701.3] billion in 2023 to RMB[3,097.7] billion by 2032 at the CAGR of 7.8%

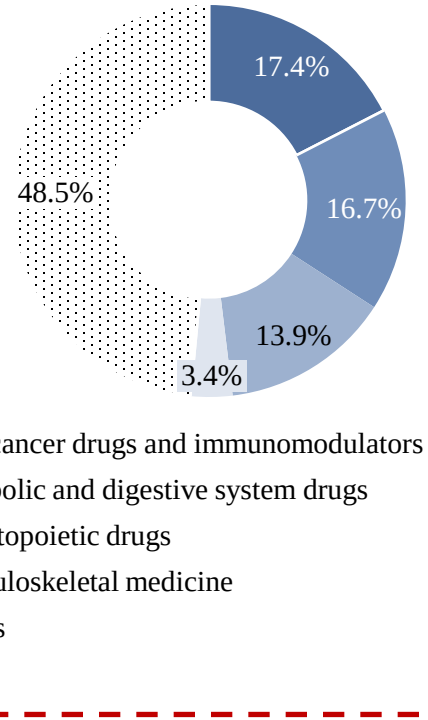


## China pharmaceutical market size, 2018-2032E

| CAGR | 2018-2023 | 2023-2032E |
|---|---|---|
| Biological drugs | 7.7% | 16.0% |
| Small molecule drugs | 0.1% | 1.8% |
| Traditional Chinese Medicine(TCM) | 1.4% | 3.8% |
| Total | 2.0% | 7.8% |




## Breakdown by market segment, 2023(excl. TCM)




**Key Analysis**

- Orthopedics, metabolic diseases, oncology, and hematology. Collectively, these four therapeutic areas accounted for [51.5]% of the total pharmaceutical sales in China in 2023, **and grew faster than the overall PRC pharmaceutical market, which grew at a CAGR of 4.3% from 2018 to 2023**, a trend which is expected to continue in the near future.



Source: IMS, Menet; China Insights Consultancy

# Summary of biosimilar regulatory policies



| Date | Institution | Document | Main content |
|---|---|---|---|
| 2015 | NMPA | Technical guidelines on the development and evaluation of biosimilars | Clarified the basic principles of biosimilar development and evaluation including comparison principle, stepwise progression principle, consistency principle and similarity evaluation principle |
| 2016 | NMPA | Measures for the Administration of Drug Registration (Revised Draft) | Tightened approval criteria for biosimilars |
| 2017 | CPC | Regulation on the Principles of Naming of Biological Products by Common Name | Standardized the generic naming method of biological products |
| 2017 | State Council | Opinions on Deepening the Reform of the Review and Approval System to Encourage Innovation in Drugs and Medical Devices | Supported the imitation of biosimilar drugs and drug and device combination products with clinical value |
| 2017 | NMPA | Questions and Answers on Biosimilar Drug Development | Clarified the scope of application of biosimilars, the overall R&D strategy, the selection and source of reference drugs, etc. |
| 2021 | CDE | Technical guidelines for similarity evaluation and indication extrapolation of biosimilar drugs | Proposed guidance for biosimilar similarity evaluation and indication extrapolation |
| 2021 | NMPA | The 14th Five-Year Plan for National Drug Safety and Quality Development | Proposed guidance for biosimilar similarity evaluation and indication extrapolation |
| 2022 | CDE | 2022 Technical guidelines for clinical pharmacology studies of biosimilars | Proposed guiding recommendations for clinical pharmacology studies of biosimilars, aiming to provide technical reference for the development of biosimilars |

- Since 2020, CDE introduces clinical study guidelines for several major biosimilar single product, including Trastuzumab, Liraglutide, Bevacizumab, Omalizumab, Tolimumab, Patuximab, and Cetuximab

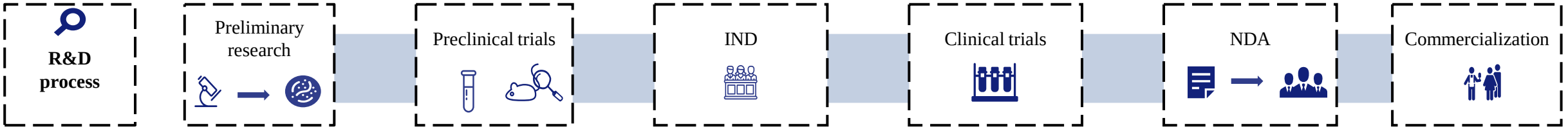
CPC refers to Chinese Pharmacopoeia Commission;
NMPA refers to National Medical Products Administration;
CDE refers to Drug Evaluation Center

Source: NMPA; China Insights Consultancy

# Overview of R&D process and approval process for biosimilars in China



## R&D process and approval process for biosimilars in China




### Preclinical trials

**Comparative quality studies**

| | |
|---|---|
| **Molecule** | Physical properties |
| | Chemical properties |
| **Function** | Biology |
| | Pharmacology |

Primarily involve the assessment of the physical, chemical, and biological properties of biosimilars, such as their molecular structure and bioactivity

**Comparative non-clinical trials**

**Pharmacology**

**Toxicology**

Mainly involves the evaluation of animal pharmacokinetics (PK), pharmacodynamics (PD), and toxicology to address the impact of quality attribute differences between biosimilars and reference drugs on the safety and effectiveness of biosimilars

### Clinical trials

**PK** + **PD**

- Efficacy
- Safety
- Immunogenicity

To confirm the comparable clinical efficacy between a biosimilar and a reference drug, this step overcomes the necessary sensitivity often lacking in many animal models to assess human immunogenicity

- In China, biosimilars do not have a separate streamlined approval pathway but instead follow the same approval route as innovative biopharmaceuticals. NMPA and CDE released the "Technical Guiding Principles for Research and Evaluation of Biosimilars (Trial)" on February 28, 2015. For the first time, it is explicitly stated that the regulatory evaluation requirements for biosimilar drug registration should progressively demonstrate pharmaceutical similarity, non-clinical similarity, clinical pharmacology similarity (PK/PD), safety and efficacy similarity (Phase III clinical trials), as well as immunogenicity similarity
- CDE also encourages pharmaceutical companies to submit detailed structural and functional characteristics of biosimilars for comparison with reference drugs. Additionally, the CDE has adopted a progressive approach similar to that of developed countries, evaluating similarity through pharmacological data, non-clinical studies, and clinical research



Source: NMPA; China Insights Consultancy

# Following NDA, access to NRDL and bid for regional or centralized VBP are two major events that could lead to drug price reduction



## National Drug Reimbursement list application and inclusion process

1. Product launch after regulatory approval
2. Preparation for NRDL listing
3. Pharma companies submit application
4. Expert review and vote for shortlist
5. Price negotiation and tendering
6. NRDL inclusion results

- Preliminary conditions and criteria for eligibility of NRDL released
- Pharmaceutical companies could prepare required qualifications and documents accordingly

- Experts assess clinical value, budget impact and cost-effectiveness of underlying drugs proposed to be included in NRDL

- Drug manufacturers present price quote and bid for NRDL inclusion
- If proposed price exceeds certain threshold, drug manufacturers may lose the bid

- Two drug groups in NRDL with different reimbursement level
- Class A: 100% reimbursed
- Class B: partially reimbursed, varies across municipalities and provinces

- In the new 2023 NRDL, 111 new drugs were added, and their prices were reduced by an average of 60.1% through negotiations and bidding. The catalog now contains a total of 2,967 drugs, including 1,586 western medicines and 1,381 traditional Chinese medicines. Some drugs for conditions like cancer, COVID-19, rare diseases, diabetes, and chronic obstructive pulmonary disease were included. Notably, COVID-19 drugs like Azvudine tablets were added

## Evolution of centralized VBP program

| | 2018.11 4+7 pilot | 2019.9 4+7 expansion | 2019.12 2nd round | 2020.7 3rd round | 2021.1 4th round | 2021.6 5th round | 2021.11 6th round | 2022.7 7th round | 2023.3 8th round |
|---|---|---|---|---|---|---|---|---|---|
| **Scale** | **11 pilot cities** | **25 provinces** | **nationwide** | **nationwide** | **nationwide** | **nationwide** | **Nationwide (for Insulin)** | **nationwide** | **nationwide** |
| **# of drugs** | 25 | 25 | 32 | 55 | 45 | 61 | 16 | 61 | 39 |
| **Avg price cut** | 52% | 59% | 53% | 53% | 52% | 56% | 48% | 48% | 56% |

- Volume-based procurement program is a series of drug procurement policies implemented in China, which aims to encourage the substitution of generic drugs and reduce the cost of drugs that have passed their exclusivities. In the pilot run of centralized VBP, the policy only covered 11 pilot cities in 2018, but fast rolled out to nationwide implementation.
- Centralized procurement for drugs has yielded cost savings by creating economies of scale and improving purchasing and negotiation power over pricing by pooling procurement process for drugs across multiple buyers. Pharma companies in turn should design market access strategies to cope with expected price cut



Source: NMPA; China Insights Consultancy

# Overview of the two-invoice system



## Overview of the two-invoice system

- **Definition:** The two-invoice system refers to the drug manufacturers selling to first-tier distributors and issuing the first invoice, while first-tier distributors selling to hospitals and issuing the second invoice. It prohibits the process of multiple intermediate invoicing and allows manufacturers to distribute drugs on their own or choose only one distributor to supply directly to hospitals. The regulatory authorities can regulate the flow of drugs and increase in price through the two invoices issued by enterprises and the listed factory price. This means that the phenomenon of multiple intermediaries marking up the price of drugs after they leave the factory will be completely changed


| Interested parties | Impact of the two-invoice system |
|---|---|
| Pharmaceutical company | • Increased pressure on capital turnover<br>• Only one level of distributors in each sales region, making overall management more difficult<br>• Large pharmaceutical companies began to build their own sales teams |
| Pharmaceutical Distributor | • Decrease in the number of drug distributors and distribution companies<br>• Large-scale mergers and acquisitions within the industry<br>• Decrease in overall profits of the pharmaceutical distribution industry |
| Hospital | • Lower drug prices due to fewer distributors, benefiting patients<br>• Strengthened capacity of medical insurance to control costs |

- In 2016, China's State Council Healthcare Reform Office, in conjunction with the National Health Planning Commission, the State Food and Drug Administration and other eight ministries and commissions, issued the Notice on the Implementation Opinions on the Implementation of the "Two-invoice System" in Drug Purchasing for Public Medical Institutions (Trial Implementation), which stipulates the implementation of the "Two-invoice System" in drug purchasing for public medical institutions. ”
  - **Background:** China's pharmaceutical distribution chain is lengthy, and its distribution system is often chaotic, plagued by issues like over-reliance, money laundering, and rebates, all of which contribute to higher drug prices. This environment fosters corruption in the pharmaceutical supply and distribution process, leading to substantial losses for the government, society, and individuals
  - **Purpose:** The two-invoice system reduces intermediary steps in pharmaceutical distribution, improving efficiency and regulating distribution practices. It also cleans up the market environment and curbs the practice of money laundering through excessive invoicing by existing pharmaceutical distribution companies. Additionally, it encourages the transformation and upgrading of pharmaceutical enterprises, resulting in a steady increase in industry concentration. Large pharmaceutical distribution companies with high standardization and extensive terminal coverage continuously enhance their market share and reputation



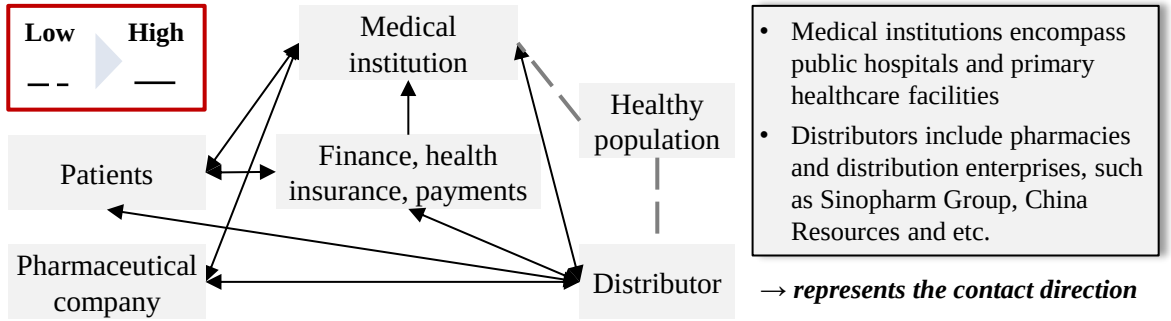
Source: NMPA; China Insights Consultancy

# Overview of the pharmaceutical circulation process in China



## Overview of the pharmaceutical circulation process in China

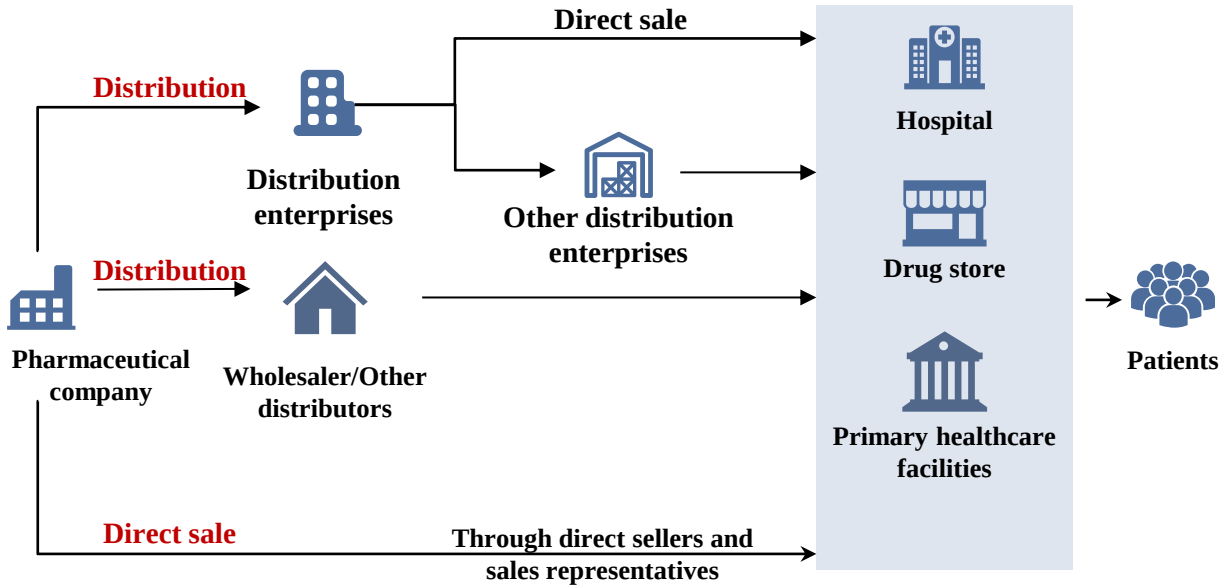
**Industry contact map**




- Medical institutions encompass public hospitals and primary healthcare facilities
- Distributors include pharmacies and distribution enterprises, such as Sinopharm Group, China Resources and etc.

→ *represents the contact direction*

**Drug circulation process chart**




### Current status of pharmaceutical circulation

- The logistics in the circulation process refer to the movement of finished pharmaceutical products from the pharmaceutical company's warehouse to the end consumers. This process involves the transportation of finished drugs from pharmaceutical companies to retail endpoints and consists of two distinct types of transport: mainline transportation and regional distribution
- In the pharmaceutical circulation, two main models exist: direct sales and distribution. Direct sales involve manufacturers delivering drugs directly to healthcare institutions, offering strong control and higher profits. In contrast, distribution involves selling drugs to other distribution companies, providing broader market coverage and faster capital turnover, but with weaker endpoint control and lower profit margins

### Reasons for the development of pharmaceutical circulation

- **Healthcare system reform, especially the "Two-Invoice System":** National healthcare reforms, notably the "two-invoice system," have streamlined the distribution process, reducing intermediaries, promoting diversity and integration of distribution companies, and increasing industry concentration
- **Removal of third-party pharmaceutical logistics approval:** Easing or removing approval requirements for third-party pharmaceutical logistics has encouraged industry integration and collaboration, injecting fresh energy into the sector



*Source: NMPA; China Insights Consultancy*

# China's pharmaceutical market is thriving with increased R&D, biological agents growth, patent expirations, and focuses on accelerated approvals, innovative SMEs, and ongoing regulation standardization in the future



## Market drivers for China pharmaceutical market

**1 Increase in pharmaceutical market R&D expenditure**

- According to data from the National Bureau of Statistics, China's pharmaceutical market research and development (R&D) expenditure is expected to grow at a compound annual growth rate of 13.6% from 2016 to 2022. The rapid increase in R&D spending in the Chinese pharmaceutical market is advantageous for enhancing R&D incentives, elevating the level of biotechnology, and promoting the commercialization of pharmaceutical products

**2 Fast development of biological agents**

- **Policy advocacy**: In 2020, the "Fourteenth Five-Year Plan" for the bioeconomy aimed to build key biotech innovation platforms and develop new biopharmaceuticals, biomaterials, and precision medicine. It emphasized speeding up innovative drug approvals and creating a safety evaluation platform for fusion protein drugs, biosimilars, and gene therapy, supporting biopharmaceutical development
- **Increased clinical demand**: WHO show that in 2020, China have 4.57 million new cancer cases, accounting for 23.7% of the world, ranked in the first. On December 6, 2021, IDF released that the number of adults with diabetes in the world reached 537 million cases in 2021, affecting about 1/10 of adults in the world[1]. Biopharmaceuticals have demonstrated excellent clinical efficacy in a range of chronic diseases, including cancer and diabetes. The vast patient population will further drive market growth

**3 Expiration of numerous patented novel drugs**

- According to the New Drug Development Monitoring Database (CPM), 38 and 29 drugs with expiring patents have been identified for 2021 and 2022, respectively. Additionally, in 2018, the General Office of the State Council issued "Opinions on Reforming and Improving Policies for Ensuring the Supply and Use of Generic Drugs," which encouraged the development of a catalog to guide orderly development, registration, and production of generic drugs. This has particularly benefited generic drugs in high clinical demand, with proven efficacy, and facing supply shortages, further boosting the Chinese pharmaceutical market

## Market trends for China pharmaceutical market

**Accelerated approval process of drugs**

- In the future, the Chinese pharmaceutical market will see an acceleration in drug research and development as well as the approval process for market entry. This is not only due to the continuous strengthening of biotechnology but also because of national policies aimed at expediting the drug approval process. In 2020, the NMPA introduced the "Priority Review and Approval Procedure for Drug Market Authorization (Trial)" and the "Procedure for Conditional Market Authorization Application for Drugs (Trial)" to streamline the drug evaluation and approval process, facilitating the timely market entry of new drugs and better meeting patient needs

**The rise of small and medium-sized innovative pharmaceutical companies**

- Innovative small and medium-sized pharmaceutical companies typically possess strong research and development capabilities in a specific therapeutic area and adopt a more flexible R&D approach. They have shifted from primarily focusing on in-house R&D to embracing various collaborative models, including partnership research, patent licensing, and outsourcing. They also actively establish commercial teams or engage in joint marketing efforts to expedite product launches in key markets. This diversified approach to both research and commercialization optimizes resource allocation along the pharmaceutical industry chain, enhances the efficiency of transferring products from the laboratory to patients, and allows innovative small and medium-sized pharmaceutical companies to concentrate on leveraging their unique R&D strengths within the industry chain

**Continuous standardization of market regulation**

- Due to the relatively late start of the pharmaceutical industry, regulatory oversight has been lacking in areas such as pre-clinical and clinical research, as well as drug production. As a result, there have been numerous instances of non-compliance by pharmaceutical companies. With regulatory agencies gradually tightening their review and approval processes and implementing routine inspections, the pharmaceutical market in developing countries is transitioning towards standardization

*SMEs refers to Small and Medium-sized Enterprises*

1. *International Diabetes Federation. IDF Diabetes Atlas, 10th ed[M]. Brussels, Belgium: 2021.*

*Source: National Bureau of Statistics; China Insights Consultancy*

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# Orthopedic diseases can be categorized into four main segments, including trauma-related, joint-related, spinal-related and sports medicine-related orthopedic diseases



## Introduction

- Orthopedic diseases refers to injuries and diseases that affect the musculoskeletal system. This body system includes the muscles, bones, nerves, joints, ligaments, tendons, and other connective tissues. Damage to any of these tissues or structures can come from chronic orthopedic diseases or from an injury.
- **Orthopedic diseases can be categorized into four main segments, including trauma-related, joint-related, spinal-related and sports medicine-related orthopedic diseases**
- Common treatments for orthopedic diseases include medication, physical therapy, and orthopedic surgery.

## Risk factors

Risk factors for orthopedic diseases include:

- Aging
- Being overweight or obese, which puts extra pressure on bones, joints, and joint structures
- Having a chronic disease, such as diabetes
- Playing sports or participating in recreational activities
- Smoking
- Working in a profession involving the same tasks every day, which increases strain on the musculoskeletal system

## Types of orthopedic diseases

- The prevalence of orthopedics disease in China reached over 260 million patients in 2023.

### 01 Trauma related orthopedic diseases

**Bone trauma:** refers to fractures, dislocations, ligament and tendon injuries in the limb parts of the humerus, radius and tibia caused by trauma

- Classified according to skin mucosal integrity of the fracture:
  - Open fracture
  - Close fracture
- Classified according degree of fracture:
  - Complete fracture
  - Incomplete fracture
  - Comminuted fracture

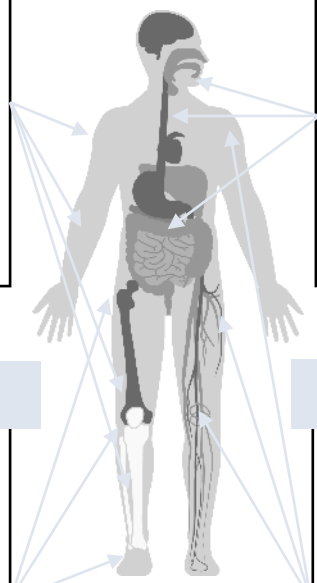
### 02 Spinal related orthopedic diseases

The Spine is one of the most important skeletal systems in the human body, consisting mainly of the small bones of the vertebrae, intervertebral discs, ligaments, muscles and joints

- Common spine related orthopedic conditions
  - Spinal degenerative disease

Include cervical spondylosis, lumbar disc herniation, lumbar spinal stenosis, osteoporosis, etc. (account for 80+% of all spinal surgeries)

- Spinal cord injury
- Spinal deformity
- Spinal tumor



### 04 Sports medicine related orthopedic diseases

**Sports medicine** related orthopedic diseases mainly study medical problems related to daily activities and sports, referring to diseases such as ligament tears and joint instability in shoulder joints, hip joints, knee joints and facet joints

Sports medicine department utilizes minimally invasive arthroscopic techniques for treatment and rehabilitation, with the features of small injury, fast recovery, good efficacy, and high safety

### 03 Joint related orthopedic diseases

**Joints** are usually composed of fibrous connective tissue, cartilage and ligaments. Joint-related orthopedic diseases usually refer to: osteoarthritis, bone tumors, and other diseases of the shoulder, hip, knee, etc. that may require artificial joint replacement

- Common joint related orthopedic conditions
  - Osteoarthritis(OA)/Degenerative arthritis
  - Rheumatoid arthritis(RA)
  - Hyperostosis
  - Bone tumor, bone defect around joint, bone necrosis, etc.



Source: China Insights Consultancy

# Overview of major orthopedic disease treatment modalities



## Overview of major orthopedic disease treatment modalities

*Incomplete statics: only demonstrate common* orthopedic *diseases here*

Diagnosis

Treatment

**Conservative treatment**
- **Basic therapy**
  - Exercise
  - Physical therapy
  - …
- **Drug therapy**

**Further treatment**
- **Biologics treatment/Targeted drug therapy**
- **Surgical treatment**
  - Restorative therapy
  - Reconstruction therapy
  - ….

| Trauma related orthopedic disease | Spinal related orthopedic disease (Degenerative diseases of the spine are the main parts | | | Joint related orthopedic disease | | |
|---|---|---|---|---|---|---|
| **Fracture** | **Cervical spondylosis** | **Lumbar spinal stenosis** | **Lumbar disc herniation** | **Osteoarthritis** | **Rheumatoid arthritis** | **Osteonecrosis** |
| X-ray | • X-ray<br>• CT<br>• MRI | • X-ray<br>• MRI | • X-ray<br>• CT<br>• MRI | • X-ray<br>• CT<br>• MRI | • Blood routine examination<br>• Autoantibody test<br>• Imaging tests: X-ray, ultrasound, MRI | • X-ray<br>• MRI<br>• CT<br>• ECT |
| Fracture reduction<br>Immobilization<br>Functional exercise | **Drug therapy:** Nonsteroidal anti-inflammatory analgesics, nutraceuticals, muscle relaxants<br>**Physical therapy:** Magnetic therapy, pulling material, electric therapy<br>**Traction therapy** | **Traction therapy**<br>**Massage therapy**<br>**Drug therapy**: Epidural steroid injection therapy | **Drug therapy:** OTC pain relievers, neuro medications, muscle relaxants, opioids, cortisone injections<br>**Physical therapy** | **Drug therapy: 1) Pain relievers** (NSAIDs, opioids, strong opioid, antidepressant, glucocorticoid); **2) DMOADs** (Chondroitin sulfate, diacerein, etc.) | **DMARDs therapy**: Methotrexate, LEF, sulfasalazine<br>**Other drug therapy:** NSAIDs, glucocorticoid, etc.<br>**Physical therapy** | **Drug therapy:** NSAIDs, Osteoporosis drugs, cholesterol-lowering drug, blood thinner, etc.<br>**Others:** Electric stimulation, etc. |
| Open reduction (surgery) | **For common spine related orthopedic diseases, surgical treatments include conventional open surgery as well as minimally invasive surgeries that have emerged in recent years**<br>• **Traditional open surgery**<br>• **Minimally Invasive Spinal Surgery, (MISS):** MISS results in similar outcomes, less trauma and more rapid recovery<br>- Microsurgical spinal surgery<br>- Percutaneous vertebroplasty（PVP）<br>- Spinal endoscopic surgery<br>- … | | | • **Joint replacement surgery**<br>• **Other surgery** (Not yet in the guide but widely used)<br>- Arthroscopic debridement<br>- Synovectomy<br>- Other knee preservation surgeries | **Targeted drug combo therapy:** TNF-α inhibitors, interleukin (IL) -6 receptor antagonists, T cell co-stimulatory signal modulators, etc.<br>**Surgical treatment:** Synovectomy, Artificial joint replacement, carpal tunnel release, etc. | **Surgical treatment:** Synovectomy、Artificial joint replacement 、joint capsule incision/dissection, carpal tunnel release |

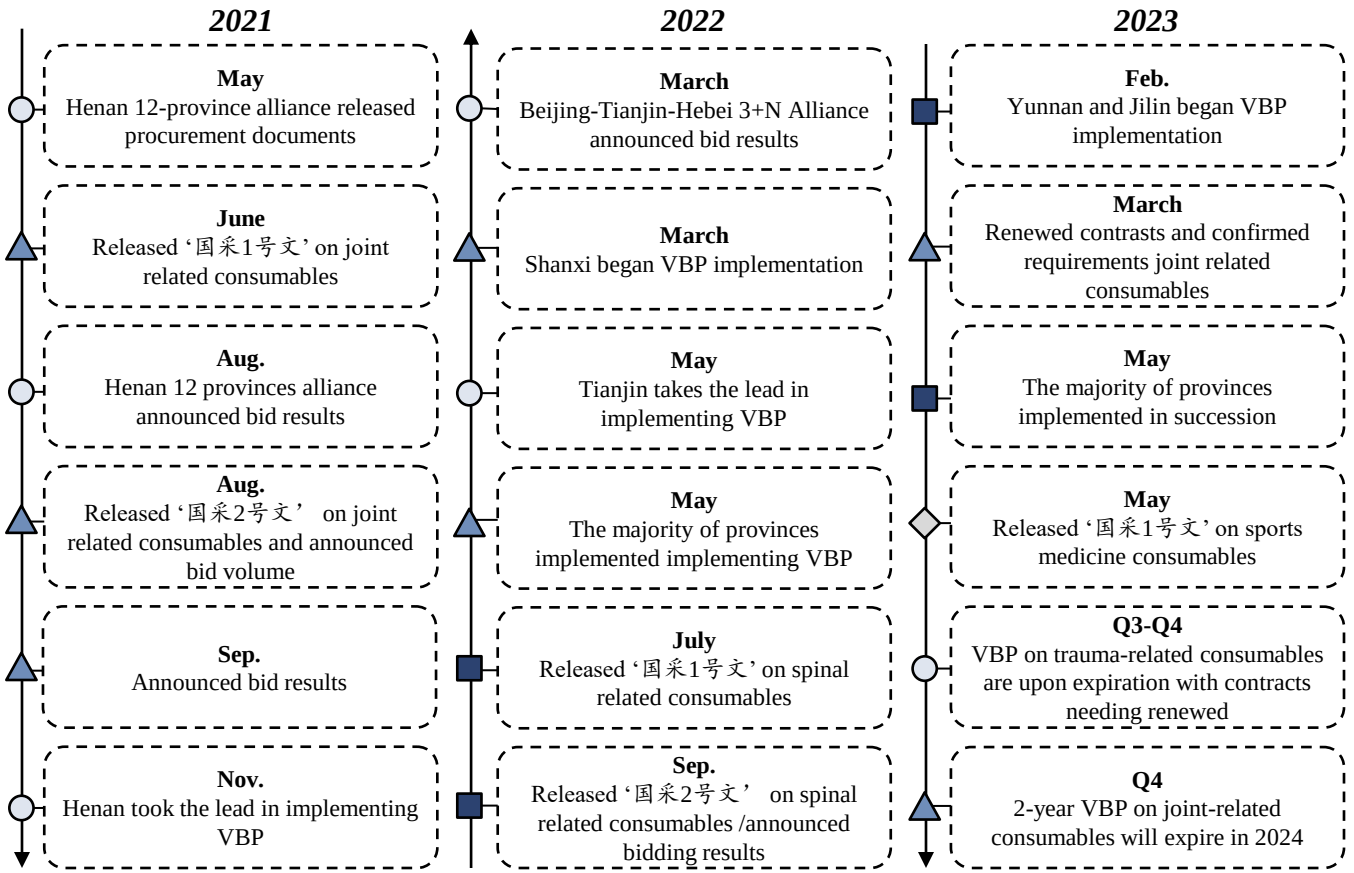
Source: Expert consensus; Diagnosis and Treatment Guidelines; China Insights Consultancy

# By the end of 2022, the three major segments of orthopedic high-value consumables (trauma, joints, and spine) have basically fulfilled VBP both on province-wide and national wide



## Analysis of VBP's influence on orthopedic high-value consumables

### Overview of the progress of VBP on major orthopedic categories




### Comparison of VBP results of three major orthopedic product categories

| Category | Implement area | VBP quantity | VBP period | Average price reduction after VBP |
|---|---|---|---|---|
| Trauma related orthopedic disease | Henan 12 Provinces Alliance | 970,000 | 1 year | -88.7% |
| | Beijing-Tianjin-Hebei 3+N Alliance (16 Provinces) | 1,080,000 | 1 year | -83.5% |
| | Jiangsu Province | - | 2 years | -73.0% |
| Joint related orthopedic disease | National-wide | 550,000 | 2 years | -83.0% |
| Spinal related orthopedic disease | National-wide | 1,210,000 (Bone cement excluded) | 3 years | -84.0% |

100%

Note: Trauma-related; Joint-related; Spinal-related; Sports medicine related

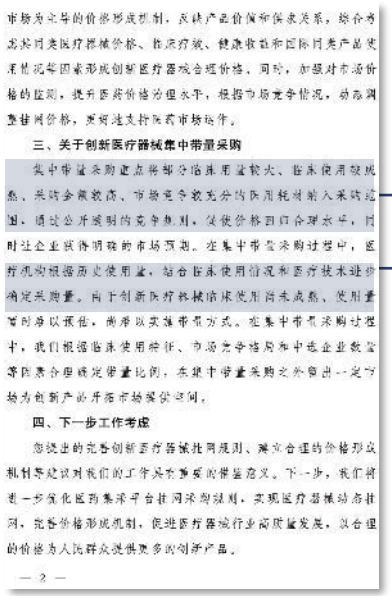
Source: China Insights Consultancy

# Analysis of VBP's influence on orthopedic high-value consumables



## Analysis of VBP's influence on orthopedic high-value consumables

### Favorable policy supports for innovative medical device



市场为主导的价格形成机制，反映产品价值和供求关系，综合考虑我国医疗保障价格、临床疗效、健康收益和国际同类产品定准情况等因素形成创新医疗器械合理价格。同时，加强对市场价格的监测，提升医药价格治理水平，根据市场竞争情况，动态调整挂网价格，更好地支持医药市场运作。

三、关于创新医疗器械集中带量采购

集中带量采购重点将部分临床用量较大、临床使用较成熟、采购金额较高、市场竞争较充分的医用耗材纳入采购范围，通过公开透明的竞争规则，促使价格回归合理水平，同时让企业获得明确的市场预期。在集中带量采购过程中，医疗机构根据历史使用量，结合临床使用情况和医疗技术进步确定采购量。由于创新医疗器械临床使用尚未成熟，使用量预测存在困难，尚难以实施带量采购。在集中带量采购过程中，我们根据临床使用特征、市场竞争格局和中选企业数量等因素合理确定带量比例，在带量采购之外给出一定市场为创新产品开拓市场提供空间。

四、下一步工作考虑

您提出的完善创新医疗器械挂网规则、建立合理的价格形成机制等建议对我们的工作具有重要的借鉴意义。下一步，我们将进一步深化医药集采平台挂网采购规则，实现医疗器械动态挂网，完善价格形成机制，促进医疗器械行业高质量发展，以合理的价格为人民群众提供更多的创新产品。

— 2 —

- **As for mature medical devices:** VBP tends to include medical consumables with relatively bulk use volume, higher maturity clinical use and higher purchasing amount, in a more competitive market
- **As for innovative medical devices:** clinical use of innovative medical devices is not mature and their use volume is hard to predict at present, hence it is yet suitable to implement VBP on them

- The NHPA will reasonably determine the VBP ratio based on factors such as clinical use characteristics, market competition pattern and the number of bid-winnings, and leave a certain market space for innovative products

#### Key Analysis

- The core of the VBP is to restructure the internal structure of the healthcare payment system, so that the space for payment can be vacated for innovative products; NHPA have shown their total support towards continuous innovation
- The standard of covering in VBP remains unchanged for mature devices and consumables, to expand payment space for innovative products: the temporary exclusion of innovative medical devices from VBP will hopefully extend their life cycle. Therefore, innovation is still the main theme in the medical device field

### Influence of 4th high-value consumables VBP on orthopedic high-value consumables

**Artificial crystal consumables**

| Intraocular lens |
|---|
| Aspheric-Monofocal-Non astigmatic |
| Aspheric-Monofocal-Astigmatism |
| Bifocal-Astigmatic |
| Bifocal-Non astigmatic |
| Trifocal-Non astigmatic |
| Trifocal-Astigmatic |
| Extended depth of focus-Non astigmatic |
| Extended depth of focus-Astigmatic |
| **Viscoelastic material** |
| Cohesive type |
| Diffuse type |
| Mixed type |

**Sports medicine consumables**

| Suture anchor |
|---|
| Ti alloy type |
| PEEK type |
| Bioabsorbable type |
| All suture anchor |
| **Knotless suture anchor** |
| Ti alloy type |
| PEEK type |
| Bioabsorbable type |
| All suture anchor |
| **Fixation nail** |
| Ti alloy type |
| PEEK type |
| Bioabsorbable type |
| Soft tissue type |

| Fixing plate |
|---|
| Adjustable type |
| Non-adjustable type |
| **Repair suture** |
| Repair suture |
| **Soft tissue reconstruction material** |
| Artificial ligament |
| Meniscus repair and suture consumables |
| Meniscus repair double needle consumables |
| **Bone reconstruction** |
| **Artificial synthetic bone** |

The 4th high-value consumables VBP covers:

**9** of classification

**31** of product categories

- In the orthopedics field, this round of VBP only covers synthetic bone. Some innovative products such as drug-device combination products with medical devices as the primary mode of action (such as rhBMP-2 artificial bone) are not included in the VBP list at this moment. For innovative device corporate and investors, policy has bottomed out and market is starting to rebound
  - For the fourth high-value consumables VBP, the average price reduction of orthopedic high-value consumables **on the VBP list**, reaches over 70%.
  - As for orthopedic high-value consumables ***not*** **on the VBP list**, they are listed on the bidding network or auction network listings with price limited, with lighter price reduction.



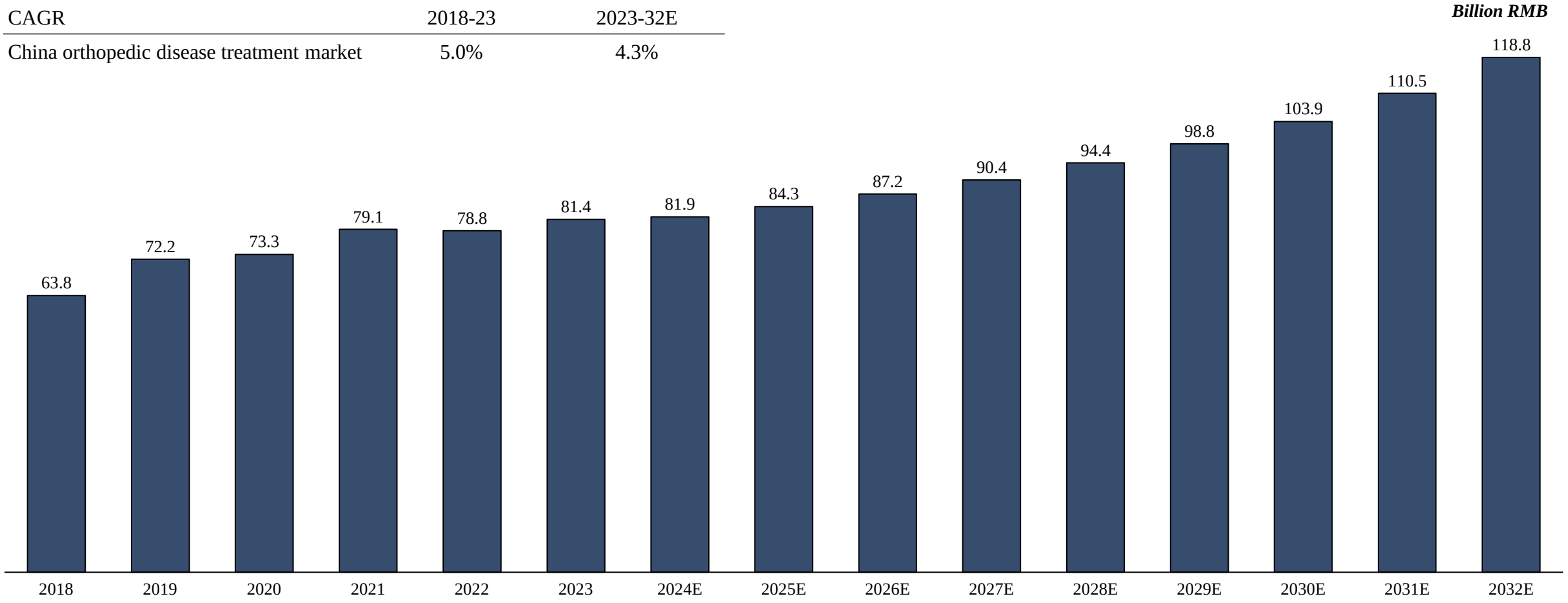
Source: National Health Care Security Administration; China Insights Consultancy

# China orthopedic disease treatment market grew from RMB[63.8] billion in 2018 to RMB[81.4] billion in 2023 at the CAGR of [5.0]%, and is projected to reach RMB[118.8] billion by 2032 at the CAGR of [4.3]%



China orthopedic disease treatment market size, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| China orthopedic disease treatment market | 5.0% | 4.3% |






Source: American Orthopaedic Society for Sports Medicine; Chinese Center for Disease Control and Prevention; American College of Rheumatology; Menet; Expert interview

# Table of contents



# Bone injury is characterized by the impairment of bone's structural integrity, resulting from a wide range of etiological factors, including both congenital and acquired factors, and giving rise to systemic symptoms



## Introduction to bone injury

- Bone injury refers to the **disruption of the structural integrity of bone**, which can arise from a variety of etiological factors including both congenital and acquired factors.
- Due to bone's regeneration capacity, particularly in younger individuals, most bone injuries, including fractures and bone defect, heal, spontaneously without major interventions. However, large bony defects, so-called critical-size defects (CSDs), lack the ability for self-regeneration and require surgical intervention.
- CSDs, defined as segmental bone deficiency of a length exceeding 2-2.5 times the diameter of the affected bone, often leads to **non-union, delayed healing, or non-healing of the bone, as well as localized functional impairments**.

## Risk factors for spontaneous bone healing

- Size of injuries or unstable biomechanical properties
- Unfavorable wound environment
- Suboptimal surgical technique
- Other factors such as metabolic factors, hormones, nutrition, and applied stress

## Causes of bone injuries

**Congenital factors:**

- **Congenital factors** such as inadequate maternal nutrition, endocrine disorders, infections, psychological stress, and genetics during pregnancy, can result in bone injury and deformities.
- **Osteoporosis** is a common disease with a strong genetic component characterized by reduced bone mass, injuriess in the microarchitecture of bone tissue, and an increased risk of fragility fractures.

**Acquired factors:**

1. **Traumatic factors:** Severe trauma, such as traffic accidents, can lead to comminuted open fractures or bone loss in the limbs, resulting in bone injuries.
2. **Infection factors:** Bone infections can cause bone necrosis, osteolysis, or bone injuries after surgical debridement for infected bones.
3. **Iatrogenic factors**: Various types of bone tumors may require the resection of extensive bone tissue due to the severity of the condition, leading to bone injuries.

## Typical symptoms

**Impaired mobility and functional loss:**
Following bone defect, the weight-bearing and conduction functions of the bone are lost, preventing normal joint movements and causing abnormal activity and functional loss.

**Pain:**
Pain occurs when the fractured ends of the bone move or during weight-bearing activities.

**Deformity and muscle atrophy:**
Unaligned fracture ends can exhibit angulation, shortening, and rotational deformities. Prolonged disuse of the limb can lead to joint contractures, deformities, and muscle wasting.

**Associated symptoms of bone infection:**
Bone defects significantly increase the possibility of bone infection which is associated with infection
Systemic manifestations include high fever, localized redness, swelling, and warmth.



Source: Acta Biomaterialia; Journal of Orthopaedic Translation; Journal of Translational Medicine; China Insights Consultancy

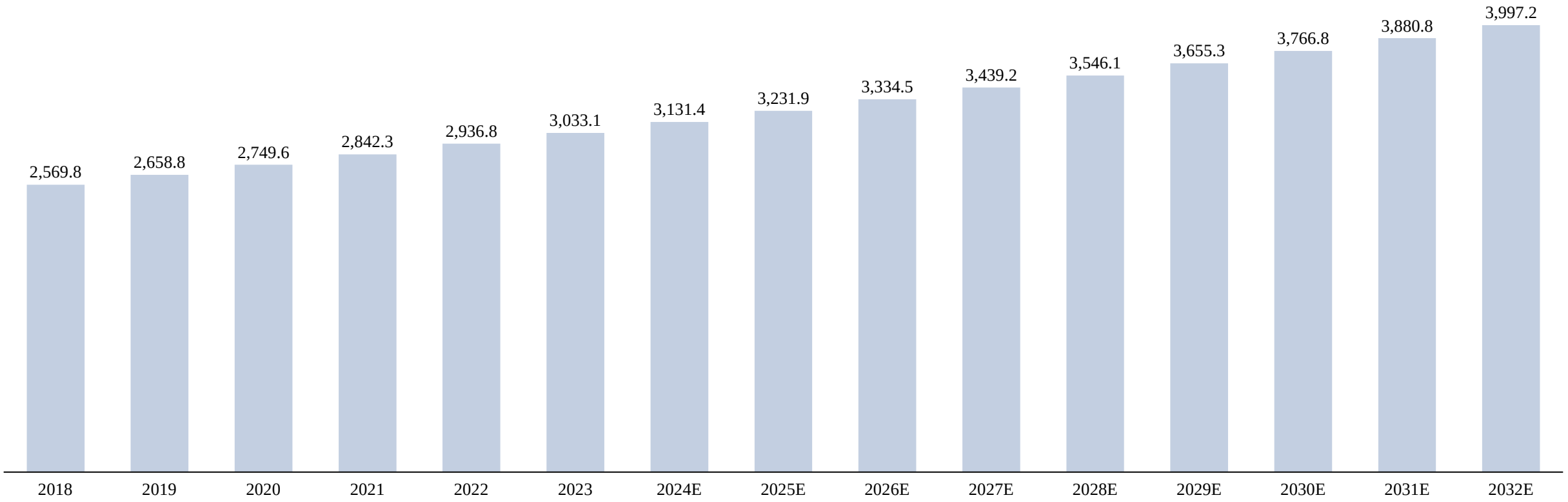
# In 2023, over 3.0 million individuals in China were diagnosed with bone injuries; with the rapid aging population, lifestyle change, etc., China is projected to have over 3.9 million bone injury incidence in 2032



**Incidence of bone injury in China, 2018-2032E**

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Incidence of bone injury in China | 3.4% | 3.1% |

Thousand patients






Source: China Insights Consultancy

# Desirable characteristics of bone repair materials in bone injury surgeries includes wide range of sources, superior biocompatibility, non-immunogenicity, safety, biodegradability, mechanical strength, flexibility and others



| | |
|---|---|
| Introduction of bone repair materials | • Bone repair materials refer to materials implanted in the human body during surgery to help repair bone injuries.<br>• The combined use of autologous cancellous bone and fracture fixation, in particular, are regarded as the gold standard for the surgical treatment of bone injuries.<br>• Bone defect repair materials are primarily used to fill in the defect areas after skeletal damage or implanted between bones that require fusion for clinical purposes.<br>• Bone repair materials can be divided into two main categories: natural bone repair materials and artificial bone repair materials.<br>• These materials play a role in promoting bone defect healing, guiding bone fusion, and accelerating the restoration of pathological bone tissue to its normal state. |

**Treatment and repair methods of bone injuries**

| Treatment and repair methods | Application condition | Methodology | Clinical benefits |
|---|---|---|---|
| Bone graft | Small bony injuries(usually shorter than 2 cm) | Allogenic platelet gel and autologous bone technique, which uses the patient's own blood and bone to stimulate healing | Well adapted to injuries |
| Bone tissue engineering technique | CSDs | Bone graft refers to the application of the principles and techniques of cell biology and materials science to construct and cultivate physiologically functional substitute materials in vitro. | Induce bone cell remodeling |
| Ilizarov technique | Complex bony injuries (usually longer than 6 cm) | Ilizarov method involves using an external fixator to gradually stretch the bone and stimulate new bone formation. | Stimulate new bone formation |
| Masquelet induced membrane technique | Small bony injuries | Masquelet induced membrane technique involves creating a membrane around the defect and filling it with a graft in a two-stage procedure. | Induced membrane generation |
| Gene technique | CSDs | Gene therapy is a method of repairing bone injuries by introducing osteogenic genes into target cells or vectors and regulating the expression of genes related to osteogenic function, thus inducing bone regeneration. | Osteoinductive; Induce bone regeneration |





Source: Regenerative Medicine and Tissue Engineering; Frontiers in Bioengineering and Biotechnology; China Insights Consultancy

# Bone repair materials can be divided into two main categories: natural bone repair materials and artificial bone repair materials, each category of which has its clinical advantages and disadvantages (1/2)



**Characteristics of natural bone repair materials**

| Category | | Source | Advantages | Disadvantages |
|---|---|---|---|---|
| Human-sourced | Same-species allograft bone | Deceased or amputated human bodies | • Excellent osteoconductive properties | • Limited source<br>• Raises legal and ethical concerns<br>• Hard to meet the demands of large-scale clinical applications<br>• Risks of immune rejection reactions, disease transmission, delayed healing, and infection as potential complications |
| | Autologous bone | Patients' own body | • A low risk of immune rejection and exhibits excellent biocompatibility<br>• Remarkable osteoconductive and osteoinductive capabilities | • Limited bone volume<br>• Hard to meet the demands of large-scale clinical applications<br>• Risks of additional blood loss and trauma for the patient, increasing surgical complexity and time costs |
| Non-human sourced | Xenograft bone | Animals such as cows and pigs | • Wide availability<br>• excellent osteoconductive properties<br>• processing methods such as high-temperature calcination can remove immunogenicity | • Risks of immune rejection reactions and disease transmission. Lower biodegradability<br>• The clinical use of xenograft bone is now extremely limited |



Source: Oral and Maxillofacial Surgery Clinics of North America; China Insights Consultancy

# Bone repair materials can be divided into two main categories: natural bone repair materials and artificial bone repair materials, each category of which has its clinical advantages and disadvantages (2/2)



**Characteristics of artificial bone repair materials**

| Category | | Source | Advantages | Disadvantages |
|---|---|---|---|---|
| Bioactive artificial bone | BMP-2 materials | Produced through nanotechnology engineering and genetic engineering techniques | • Enhanced bone repair capability<br>• Superior osteoinductive capacity and osteoconductive ability<br>• Improved bone regenerative environment<br>• Wide adaptability based on the specific bone defect of the patient | • Possible bone tissue proliferation or local lesions<br>• High clinical cost |
| Non-bioactive artificial bone | Polymer materials | Widely sourced from natural polymers such as collagen, hyaluronic acid, chitosan, as well as PMMA and polyurethane | • Wide range of sources<br>• Good biocompatibility and osteoconductivity<br>• High flexibility according to clinical needs | • The degradation rates of polymer materials may not match the rate of new bone growth.<br>• Some polymer materials degrade into acidic byproducts, which can hinder new bone formation |
| | Metal materials | Porous titanium and titanium alloys, titanium-nickel alloys, tantalum metal, stainless steel, and others | • Wide range of sources<br>• Excellent mechanical strengths | • Potential toxic effects<br>• Instability<br>• Limited plasticity in clinical use<br>• Decreasing clinical application |
| | Inorganic non-metallic materials | Hydroxyapatite ceramics, calcium phosphate ceramics and others | • Wide range of sources<br>• Good biocompatibility and osteoconductivity | • Weaker mechanical strength<br>• Unsuitable for load-bearing applications<br>• Poor degradation control |
| | Other materials | Composite materials, and tissue engineering materials | • These materials often exhibit superior application properties that meet clinical needs | • Limited clinical applications<br>• Lack of long-term clinical research data |



Source: Oral and Maxillofacial Surgery Clinics of North America; China Insights Consultancy

# Bone repair materials can be divided into 5 main types: natural bone repair materials and artificial bone repair materials, each has its clinical advantages and disadvantages



**Comparison of bone repair materials**

- **BMP-included bone repair material is among the main bioactive bone repair materials types in China.**

| Main types | BMP bone repair material[1] | Non-bioactive artificial bone | Allograft bone | Xenograft bone | Autograft bone | Advantages of BMP bone repair material |
|---|---|---|---|---|---|---|
| Osteoinductive capacity | ★★★ | ★★ | ★★ | ★ | ★★★ | • BMPs are important in formation and maintenance of bones and cartilage. Among these proteins, BMP-2 has the strongest osteoinductive ability, enabling direct stimulation of osteogenesis. |
| Post-operative healing rate | ★★★ | ★★ | ★ | ★ | ★★★ | • BMP bone repair material exhibits a higher post-operative healing rate and more rapid bone formation compared to other types of bone repair materials. |
| Repairing speed | ★★★ | ★ | ★ | ★ | ★★★ | • Multiple studies show that BMP bone repair material results in a shorter hospital stay compared to other bone materials, therefore demonstrating faster reparative speed. |
| Production scalability | ★★★ | ★★ | ★ | ★ | ★ | • Allograft, xenograft and autograft bone, sourced from cadavers, animals and people themselves respectively, have highly limited supplies. In contrast, the production of BMP bone repair material can be scaled in a controlled laboratory setting. |
| Safety | ★★★ | ★★ | ★ | ★ | ★★★ | • Allograft and xenograft bones carry the potential risk of immune rejection. BMP bone repair material has better safety profile. |



Source: Oral and Maxillofacial Surgery Clinics of North America; The American Society of Plastic Surgeons; China Insights Consultancy

# Bone morphogenetic protein-2 significantly reduces surgical revision rate, time to union, and new-onset postoperative infection.



## Introduction to BMP-2

- Bone morphogenetic proteins (BMPs) are internationally recognized as a local growth factor capable of **inducing bone tissue formation**, possessing the ability for hard tissue repair.
- Among the BMPs family, BMP-2 stands out as one of the factors with the **strongest osteoinductive ability**.
- BMP-2 can induce undifferentiated mesenchymal stem cells to orient and proliferate towards chondrocytes and osteoblasts. It also promotes the maturation and differentiation of osteoblasts, participating in the growth, development, and reconstruction of bones and cartilage. As a result, it **accelerates the repair of bone injuries**.

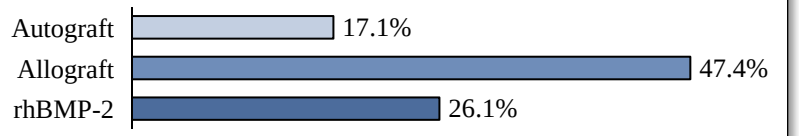
## Advantages of rhBMP-2 application in clinical settings

| | |
|---|---|
| Biological activity | RhBMP-2 possesses a high biological activity, enabling direct stimulation of osteogenesis. |
| Reduced need for bone grafts | RhBMP-2 can be applied directly to bone defect areas without the necessity to harvest bone from other parts of the patient's body. |
| Scalability | The production of rhBMP-2 can be controlled in a laboratory setting and can be produced at scale. |
| Stimulate bone healing | RhBMP-2's proliferation and differentiation of primitive bone cells and stem cells into osteoblasts, aiding the bone healing process. |

## Clinical Benefits of rhBMP-2 compared with autograft and allograft

- Studies suggest that BMP-2 exhibits comparable bone healing rates to autologous bone grafts.
- Moreover, clinical efficacy of rhBMP-2 is highlighted due to the shorter length of hospital stay after surgeries.

**Surgical revision rate**




## Clinical Benefits of rhBMP-2 compared with autograft and allograft

Studies indicate that comparing with standard care only, standard care combined with rhBMP-2 demonstrates higher efficiency for the treatment of open tibial fractures, especially in the following aspects:

1. **Shorter wound closure time**

Bone injuries treated with rhBMP-2 have a short median time from injury to definitive wound closure.

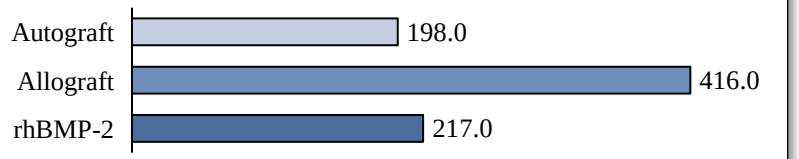
2. **Reduced secondary injuries**

Bone injuries treated with rhBMP-2 needs less secondary and subsequent interventions.

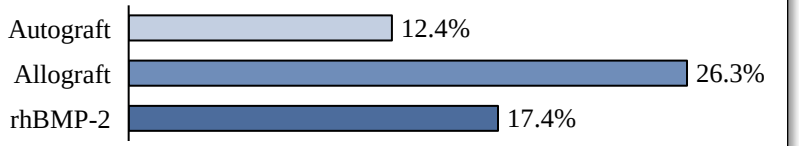
3. **High level of safety**

Bone injuries treated with rhBMP-2 are associated with lower rate of infection and hardware failure (screw breakage or bending).

**Time to union in days**




**New-onset postoperative infection**




Reference: Flierl MA, Smith WR, Mauffrey C, Irgit K, Williams AE, Ross E, Peacher G, Hak DJ, Stahel PF. Outcomes and complication rates of different bone grafting modalities in long bone fracture nonunions: a retrospective cohort study in 182 patients. J Orthop Surg Res. 2013 Sep 9;8:33.





Source: The Journal of Bone & Joint Surgery; Journal of Orthopaedic Surgery and Research; Spine; Organ Development and Regeneration; China Insights Consultancy

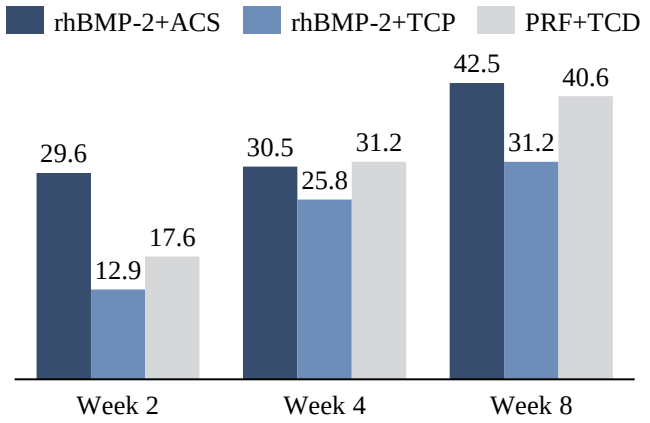
# The average price for bone repair materials in China experienced a stable decline in the past, and the non-bioactive artificial bone category is expected to experience a steeper decrease in 2023 due to VBP inclusion



## Clinical Benefits of rhBMP-2 compared with Non-bioactive artificial bone[1]

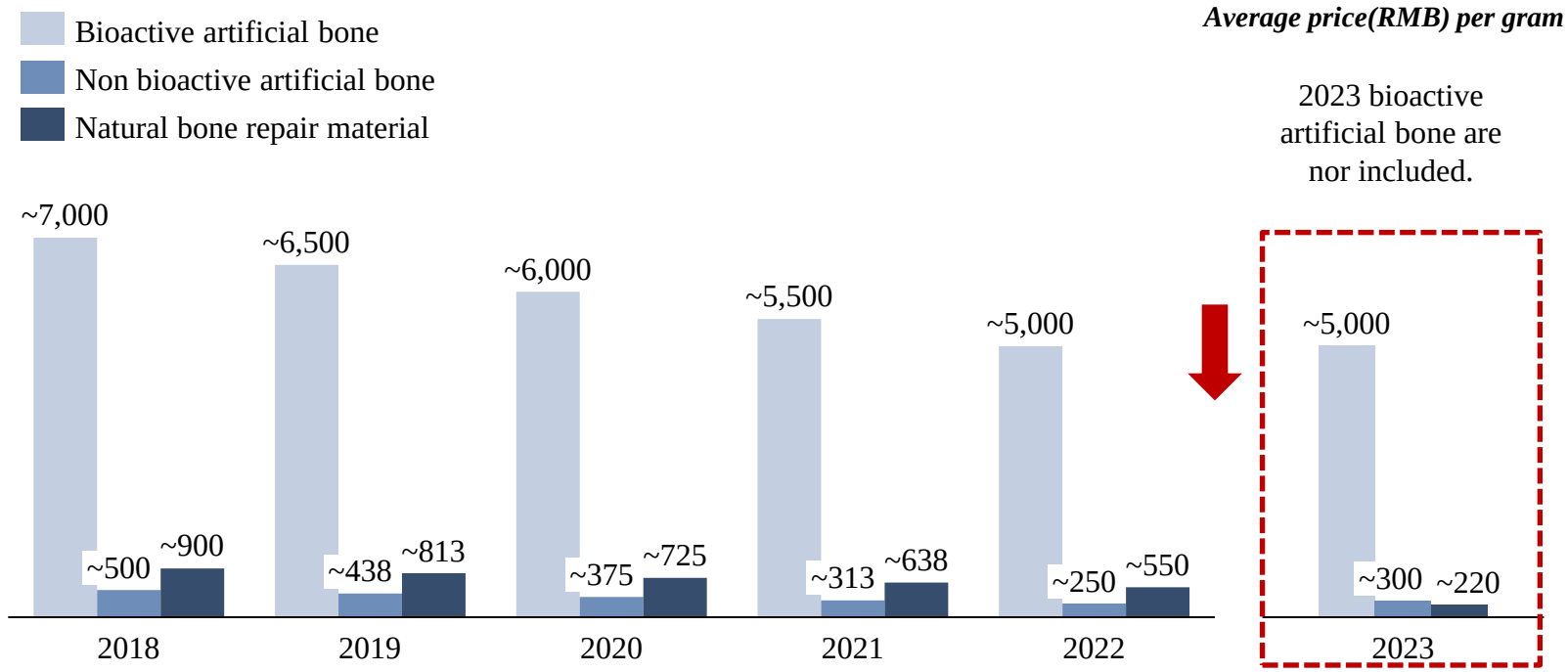
- Bioactive artificial bones have better osteoconductive ability and are less likely to cause complications
- rhBMP-2 with ACS showed a larger and more rapid bone formation area in 2 weeks and 8 weeks.

**Comparing rhBMP-2-infused ACS, rhBMP-2-TCP, and platelet-rich fibrin –mixed TCP for sinus augmentation in bone formation rate, percentage (%)**




ACS = absorbable collagen sponge; TCP = tricalcium phosphate; PRF = platelet-rich-fibrin

## Price trends of bone repair materials in China




**Key Analysis**

- The average price per gram of bioactive artificial bone decreased from approximately RMB7,000 per gram in 2018 to around RMB5,000 per gram in 2022.
- The average price per gram of non-bioactive artificial bone decreased from approximately RMB500 per gram in 2018 to around RMB250 per gram in 2022.
- The average price per gram of natural bone repair material decreased from approximately RMB900 per gram in 2018 to around RMB550 per gram in 2022.

Reference: 1. Kim CH, Ju MH, Kim BJ. Comparison of recombinant human bone morphogenetic protein-2-infused absorbable collagen sponge, recombinant human bone morphogenetic protein-2-coated tricalcium phosphate, and platelet-rich fibrin-mixed tricalcium phosphate for sinus augmentation in rabbits. *J Dent Sci*. 2017;12(3):205-212. doi:10.1016/j.jds.2017.01.003

Note: ODI =Oswestry Disability Index

Source: Clinical Orthopaedics and Related Research, Expert Interview; China Insights Consultancy

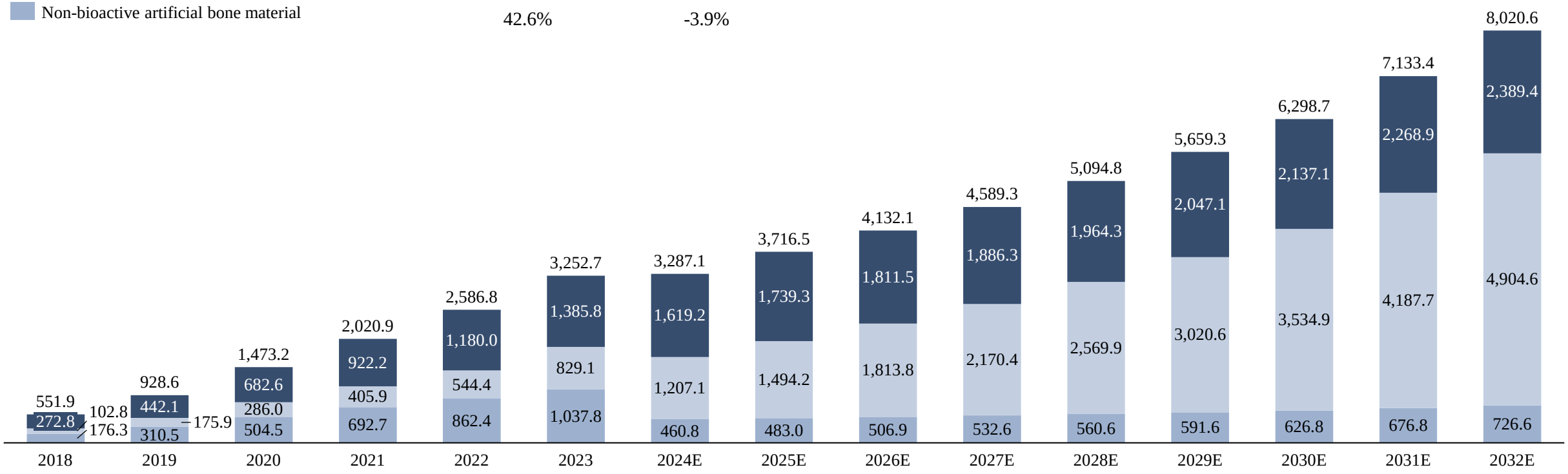
# China bone repair material market grew from RMB[551.9] million in 2018 to RMB[3,252.7] million in 2023 at the CAGR of [43.6]%, and is projected to reach RMB[8,020.6] million by 2032 at the CAGR of [10.5]%



Market size of bone repair material in China, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| China bone repair material market | 42.6% | 10.5% |
| Allograft bone material | 38.4% | 6.2% |
| Bioactive artificial bone material（including rhBMP） | 51.8% | 21.8% |
| Non-bioactive artificial bone material | 42.6% | -3.9% |

*Million RMB*






Source: The Lancet Rheumatology; Chinese Journal of Orthopaedics; Expert interview; China Insights Consultancy

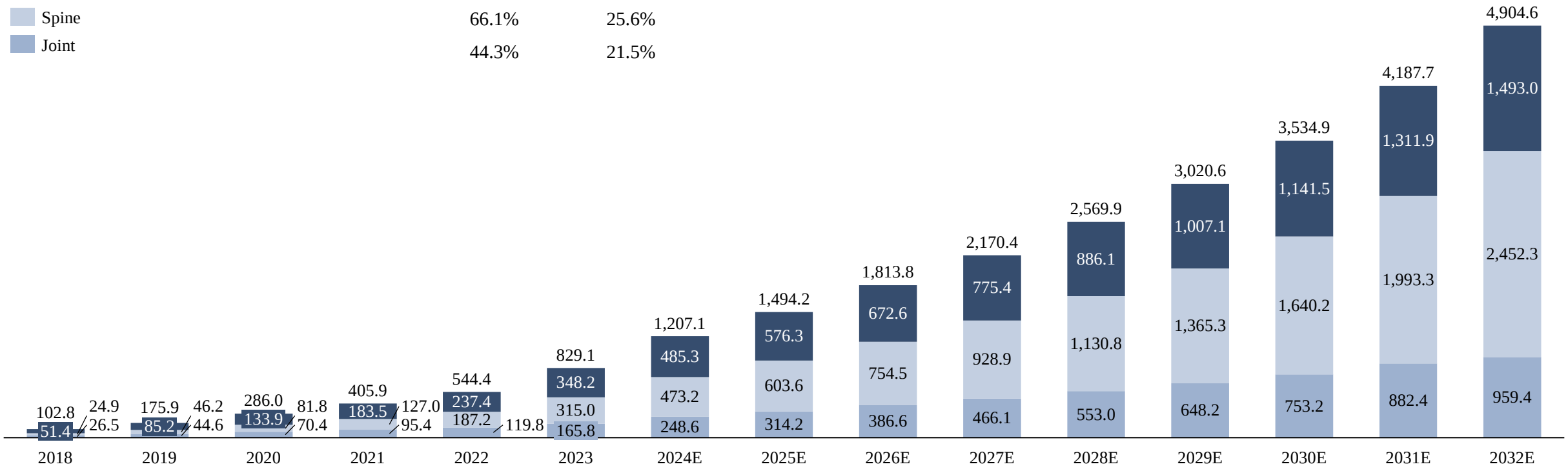
# China bioactive artificial bone material market, by indication, 2018-2032E



Market size of bioactive artificial bone repair material in China, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| China bioactive artificial bone material market | 51.8% | 21.8% |
| Trauma | 46.6% | 17.6% |
| Spine | 66.1% | 25.6% |
| Joint | 44.3% | 21.5% |

***Million RMB***






Source: The Lancet Rheumatology; Chinese Journal of Orthopaedics; Expert interview; China Insights Consultancy

# Artificial bone repair material approved from 2021 to 2023, by NMPA



**Artificial bone repair material approved from 2021 to 2023, by NMPA**

| Fisrt Approval Time | Company | Product Name | Product Composition | rhBMP-2 |
|---|---|---|---|---|
| 2023 | Medtronic Sofamor Danek USA | Infuse Bone Graft | **rhBMP-2**; Absorbable collagen sponge (ACS) | √ |
| 2023 | Ubiosis | COLTRIX CartiRegen | Collagen | ○ |
| 2023 | Shangdong Junxiu | Bone repair material | Hydroxyapatite, HAP | ○ |
| 2022 | NovaBone Products | PerioGlas Bioglass Synthetic Bone Graft Particulate | SiO2; CaO; Na2O; P2O5 | ○ |
| 2022 | Wuhan Asia Biomaterials | Artificial Bone Repair Material | HAP | ○ |
| 2022 | Yantai Zhenghai Bio-Tech | Bioactive Bone | Collagen; HAP; **rhBMP-2** | √ |
| 2021 | Naton Biotechnology (Beijing) | Porous Bioglass Ceramic Artificial Bone | β-TCP; HAP | ○ |

- **As of the end of 2023, 24 imported artificial bone repair materials had been registered with the NMPA, but only 3 of which were registered since 2021. As of the same date, 17 domestic artificial bone materials had been registered with the NMPA, 4 of which were registered since 2021.**

Imported products  Domestic products

Note: The table exclusively encompasses orthopedic artificial bone repair materials that have received their newest approval in China from the year 2021 onwards.

Source: NMPA; China Insights Consultancy

# Competitive landscape of bone repair materials in China, 2023

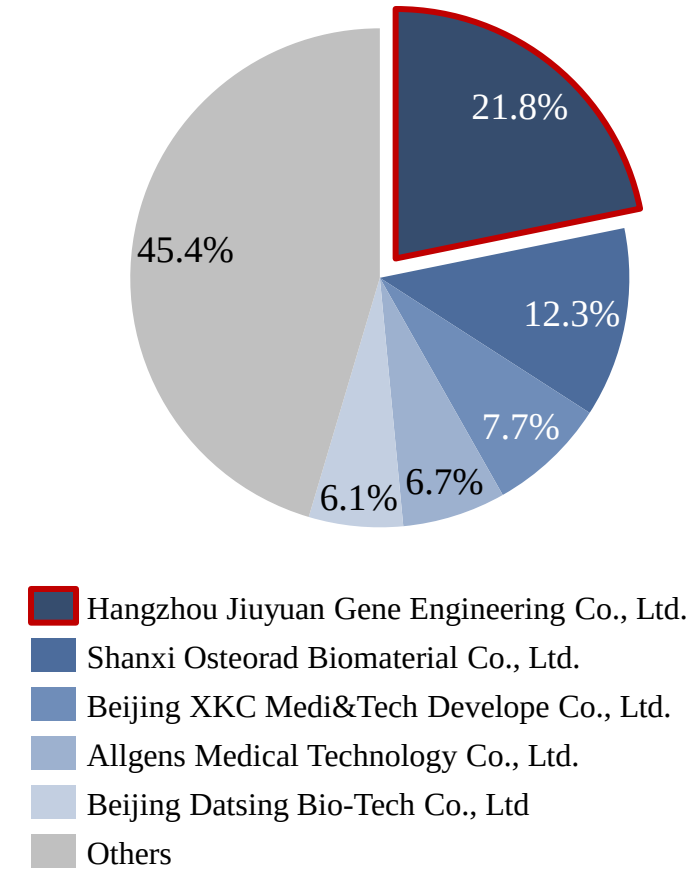


**Competitive landscape of bone repair materials in China, 2023**

| Rank | Company | Description | Material Category |
|---|---|---|---|
| 1 | Hangzhou Jiuyuan Gene Engineering Co., Ltd.<br>杭州九源基因工程有限公司 | Its businesses involves genetically engineered drugs, biochemical drugs, and medical devices. It is a modern biopharmaceutical company and one of the earliest established gene engineering pharmaceutical companies in China. | Bioactive Artificial bone |
| 2 | Shanxi Osteorad Biomaterial Co., Ltd.<br>山西奥瑞生物材料有限公司 | This company is affiliated with the China Institute of Radiation Protection. Its main business scope includes the production of medical devices and the development and research of biological tissue materials. | Allografts |
| 3 | Beijing XKC Medi&Tech Develope Co., Ltd.<br>北京鑫康辰医学科技发展有限公司 | Its has four production bases located in Beijing, Hebei, Jiangxi, and Texas, USA. Its business mainly focus on biological bone repair materials. | Allografts |
| 4 | Allgens Medical Technology Co., Ltd.<br>奥精医疗科技股份有限公司 | Its businesses involve biomedical materials and related medical devices, primarily focusing on research and development in the field of mineralized collagen artificial bone repair materials. | Artificial bone |
| 5 | Beijing Datsing Bio-Tech Co., Ltd<br>北京大清生物技术股份有限公司 | Its business scope covered the developing, manufacturing and serving products on wound management, minimally invasive surgery, stomatology and regenerative medicine. | Allografts |

Jiuyuan Gene Engineering ranks 1st

**Market share breakdown**





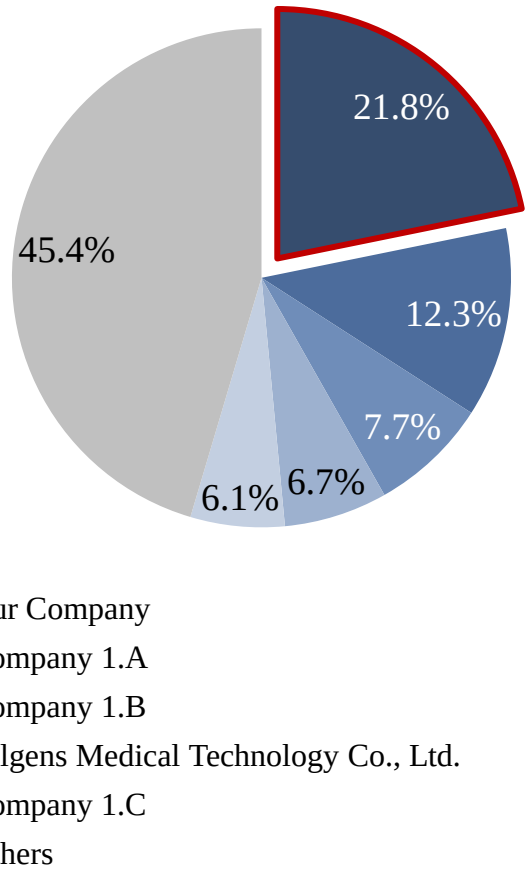

Note: This table lists the top 5 manufacturers of bone repair materials in China, 2023

Source: NMPA; China Insights Consultancy

# Competitive landscape of bone repair materials in China, 2023



**Market share breakdown**




- Company 1.A, headquartered in Shanxi, China, was founded in 1999. It focuses on the R&D, production and sales of biological tissue materials. It entered the bone repair materials sector in 2012 and currently holds one approved non-bioactive bone repair material product in China.
- Company 1.B, headquartered in Beijing, China, was founded in 2002. It is committed to the R&D, production, and sales of Class 3 medical devices (medical biomaterials). It entered the bone repair materials sector in 2016 and currently holds three approved non-bioactive bone repair material products in China.
- Allgens Medical Technology Co., Ltd. (奥精醫療科技股份有限公司), headquartered in Beijing, China, was listed on Shanghai Stock Exchange in 2021 (stock code: 688613.SH). It was founded in 2004 and is dedicated to the R&D, production and sales of implantable medical devices for tissue regeneration and repair.
- Company 1.C, headquartered in Beijing, was founded in 2001. Its business scope covered the developing, manufacturing and serving products on wound management, minimally invasive surgery, stomatology and regenerative medicine. It entered the bone repair materials sector in 2015 and currently holds one approved non-bioactive bone repair material products in China.



Source: NMPA; China Insights Consultancy

# Competitive landscape of bone repair materials in China, 2022



**Competitive landscape of bone repair materials in China, 2022**

| Company | Generic Name | Brand Name | NMPA First Approval Year | NRDL Inclusion | Revenue (Ten thousand RMB) | Market share | Indication | Key patent |
|---|---|---|---|---|---|---|---|---|
| Shanxi Osteorad Biomaterial Co., Ltd.<br>山西奥瑞生物材料有限公司 | Allografts | / | 2012 | Yes | 45,000.0 | 17.4% | Bone defect filling, repair, reinforcement, and spinal fusion | / |
| Hangzhou Jiuyuan Gene Engineering Co., Ltd.<br>杭州九源基因工程有限公司 | Bioactive Artificial bone | Guyoudao | 2009 | Yes | 44,434.0 | 17.2% | Repairing bone defects, nonunion, delayed union, or non-healing, as well as spinal fusion, joint fusion, and orthopedic bone graft repair | 1 |
| Allgens Medical Technology Co., Ltd.<br>奥精医疗科技股份有限公司 | Artificial bone | Gejin | 2011 | Yes | 24,530.5 | 9.5% | Bone defect filling, repair, reinforcement, and spinal fusion, bone defects in oral or plastic surgery | 15 |
| Beijing XKC Medi&Tech Develope Co., Ltd.<br>北京鑫康辰医学科技发展有限公司 | Allografts | Junkangzhengu | 2016 | Yes | 13,000.0 | 5.0% | Non-weight-bearing bone defects filling, fusion of the spine and joints, and reconstruction of non-weight-bearing bones | 1 |
| Wiltrom Co., Ltd.<br>台湾微创医疗器材股份有限公司 | Artificial bone | Osteocera | 2016 | Yes | 11,000.0 | 4.3% | Filling non-weight-bearing bone defects during orthopedic surgery | / |
| Yantai Zhenghai Bio-Tech Co., Ltd.<br>烟台正海生物科技股份有限公司 | Bioactive Artificial bone | Haiyu | 2022 | Yes | / | / | Bone defects caused by trauma or surgery that do not affect bone structural stability | 7 |
| Shanghai Rebone Biomterials Co., Ltd.<br>上海瑞邦生物材料有限公司 | Bioactive Artificial bone | Gutai | 2016 | Yes | 10,000.0 | 3.9% | Bone defects in non-weight-bearing or low-weight-bearing areas, and root canal filling | 2 |
| Medtronic Sofamor Danek USA, Inc.<br>美敦力枢法模丹历股份有限公司 | Bioactive Artificial bone | Infuse | 2023 | Yes | / | / | Spinal fusion surgery for a skeletally mature patient with degenerative disc disease affecting a single segment from L2 to S1 | / |

BMP-2 included

Source: NMPA; China National Intellectual Property Administration; China Insights Consultancy

# Competitive landscape of bone repair materials in China, 2023



**Competitive landscape of bone repair materials in China, 2023**

| Company | Generic Name | Brand Name | NMPA First Approval Year | NRDL Inclusion | Market share | Indication | Key patent |
|---|---|---|---|---|---|---|---|
| Hangzhou Jiuyuan Gene Engineering Co., Ltd.<br>杭州九源基因工程有限公司 | Bioactive Artificial bone | Guyoudao | 2009 | Yes | 21.8% | Repairing bone defects, nonunion, delayed union, or non-healing, as well as spinal fusion, joint fusion, and orthopedic bone graft repair | 1 |
| Shanxi Osteorad Biomaterial Co., Ltd.<br>山西奥瑞生物材料有限公司 | Allografts | / | 2012 | Yes | 12.3% | Bone defect filling, repair, reinforcement, and spinal fusion | / |
| Beijing XKC Medi&Tech Develope Co., Ltd.<br>北京鑫康辰医学科技发展有限公司 | Allografts | Junkangzhengu | 2016 | Yes | 7.7% | For filling, fusion, repair, auxiliary reinforcement and reconstruction of non-weight-bearing bones in diseases such as spinal injury, spinal degeneration, etc. | / |
| Allgens Medical Technology Co., Ltd.<br>奥精医疗科技股份有限公司 | Artificial bone | Gejin | 2011 | Yes | 6.7% | Bone defect filling, repair, reinforcement, and spinal fusion, bone defects in oral or plastic surgery | 15 |
| Beijing Datsing Bio-Tech Co., Ltd<br>北京大清生物技术股份有限公司 | Allografts | / | 2015 | Yes | 4.3% | Non-weight-bearing bone defects filling, fusion of the spine and joints, and reconstruction of non-weight-bearing bones | 1 |

BMP-2 included

Source: NMPA; China National Intellectual Property Administration; China Insights Consultancy

# Competitive landscape of rhBMP bone repair materials in China, 2023

| Brand Name | Company | NMPA First Approval Year | Indication | Average end-selling price* per surgery | Addressable market size (mn RMB) | Market share | Regional coverage of sales | MoA (Formulation) | Pros | Cons |
|---|---|---|---|---|---|---|---|---|---|---|
| 骨优导® | Hangzhou Jiuyuan Gene Engineering Co., Ltd. 杭州九源基因工程有限公司 | 2009 | • Repairing bone defects, nonunion, delayed union, or non-healing<br>• Spinal fusion<br>• Joint fusion<br>• Orthopedic bone graft repair | ~5,000 RMB | 829.1 | ~85.5% | Nationwide | Medicinal gelatin, soybean lecithin and hydroxyapatite as carrier | • A wide range of specifications to choose from | • Cold-chain logistics is required to assure rhBMP-2 activity |
| 骨泰® | Shanghai Rebone Biomterials Co., Ltd. 上海瑞邦生物材料有限公司 | 2016 | • Bone defects in non-weight-bearing or low-weight-bearing areas, and root canal filling | ~7,000 RMB | 514.0 | ~14.5% | Nationwide | Calcium phosphate cement(CPC) as carrier | • Relatively high compressive strength | • Self-setting thus hard to quantify rhBMP-2 content |
| 海昱® | Yantai Zhenghai Bio-Tech Co., Ltd. 烟台正海生物科技股份有限公司 | 2022 | • Bone defects caused by trauma or surgery that do not affect bone structural stability | ~14,000 RMB | 514.0 | ~0 | N.A | Xenogeneic bone as carrier | • A combination of rhBMP-2 and collagen may synergize | • More likely to induce immune rejection due to the Xenogeneic bone component |
| Infuse™ | Medtronic Sofamor Danek USA, Inc. 美敦力枢法模丹历股份有限公司 | 2023 | • Spinal fusion surgery for a skeletally mature patient with degenerative disc disease (DDD) affecting a single segment from L2 to S1 | ~30,000 RMB | 315.0 | ~0 | ~0 | Absorbable collagen sponge(ACS) as carrier | • Over 20-year clinical application and testimony overseas | • Highly costly |

Note: *from bid-winning side

Source: Yaozhi data; official websites; expert interview; NMPA; China Insights Consultancy

# Barriers to the bone repair material industry in China include specific entry thresholds, technological expertise, marketing channels, and brand cultivation



| Industry Barriers | |
|---|---|
| **Strict access management system in product access, production access and operation** | • In China, bone repair material falls into implantable medical devices under Class III medical devices, which are defined as high-risk and must be strictly controlled. The products need to pass the review of the medical products administration where they are located and obtain the **medical device production permit** under the law.<br>• •Class III medical devices are required to conduct clinical studies, subject to the National Medical Products Administration (NMPA) review to **obtain a registration certificate**.<br>• Generally, the time period for a bone repair material to enter the market is about **5 years**. |
| **High level of technological expertise and cultivation of research and development capabilities** | • The bone repair materials industry is a multidisciplinary and knowledge-intensive domain that integrates materials science, biology, and medicine.<br>• The accumulation of technology and the cultivation of R&D capabilities are long-term processes. The core technology level of domestic bone repair material companies is **relatively low**. The technical level of domestic enterprises in product design, raw material processing, production technology, tool manufacturing, etc., still needs to be improved. |
| **A long-term process in marketing channels building and highly affected by policies** | • Bone repair material enterprises require a large amount of capital investment and a long time period to establish complete market network channels, which also takes **long-term market accumulation** to form a marketing network of a particular scale.<br>• China encourages centralized procurement of medical devices, which will change the sales channels of bone repair material manufacturers to a certain extent. Existing companies may have well-established relationships with hospitals, clinics, and other healthcare providers, making it challenging for new entrants to gain market share. |
| **Brand awareness and economies of scale are key factors to take market share** | • Established companies such as Medtronic, Johnson & Jonhson, Stryker et al. likely have built strong brand recognition and trust among healthcare professionals and consumers. New entrants may struggle to establish comparable credibility in the market.<br>• Existing companies may benefit from economies of scale, allowing them to produce bone repair materials **at lower costs**. New entrants may find it challenging to compete on price without reaching a similar production scale. |



Source: NMPA; China Healthcare Security; China Insights Consultancy

# The growth drivers of China bone repair materials market include accelerating aging process, favorable policy environment, and unmet clinical orthopedic bone defect repair demand



| Growth drivers | |
|---|---|
|  **Population aging** | • With the development of the economy, population growth, increasing degree of societal aging, and the continuous enhancement of health awareness among individuals, there is a growing demand for healthcare in China<br>• Due to a large population and the accelerating pace of population aging, the number of individuals with orthopedic bone injuries resulting from aging continues to increase. Consequently, there is a rising number of patients requiring surgical treatment for bone injuries or functional deficiencies<br>• Moreover, with the continuous development of the national economy and the improvement of people's living standards, there is a rapid increase in the demand for high-quality bone repair materials, which offers vast market development opportunities for the industry<br>• Orthopedic artificial bone repair materials used for tissue regeneration and trauma repair have extensive market development prospects |
|  **Favorable policy environment towards innovative medical consumables** | • China's VBP policy is dedicated towards medical devices/consumables with mature, high-volume clinical usage and sufficient market competition. Due to the limited clinical use and the difficulty in estimating future clinical usage of innovative medical devices/consumables, innovative medical devices/consumables are typically not included in the scope of volume-based procurement. Instead, they are listed on online government platforms with reasonable price reduction which reflects product market value and supply-demand relationships.<br>• In the latest round of VBP for high-value medical consumables, rhBMP-2 artificial bone is grouped to be listed on online government platforms with reasonable price reduction, which leaves substantial independent pricing power for manufacturers to generate enough profit and expand R&D and sales channels to increase clinical utilization. |
|  **Unmet clinical orthopedic bone defect repair demand** | • There are over [2.8 million] new cases of bone injuries in China in 2022. However, a considerable number of bone defect patients in China still undergo orthopedic surgery using autologous bone for various reasons, or even fail to undergo specialized treatment for the bone defect, which severely affects the efficiency of bone healing and postoperative recovery.<br>• This gap in the healthcare system underscores a critical demand for innovative bone repair materials, offering a substantial opportunity for market growth in clinical orthopedics. |



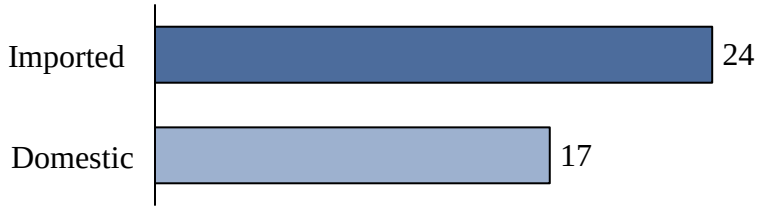
Source: NMPA; China Insights Consultancy

# The future trends of China bone repair material market include broad clinical prospects of artificial bone repair materials, increasing application of bioactive materials and domestic substitution



| Future Trends | |
|---|---|
| **Broad clinical prospects of artificial bone repair materials** | • Natural bone repair materials like allografts face several disadvantages in clinical applications, such as higher risks of immune rejection and potential transmission of diseases, limited availability of healthy donor sources and scarcity of excellent donors, and ethical concerns regarding their use.<br>• Artificial materials are increasingly preferred in clinical settings for the reasons of its wide range of sources, high flexibility according to clinical needs, and premium qualities.<br>• Additionally, these materials effectively avoid the various issues associated with allograft transplantation. For instance, bioactive materials like BMP-2 have demonstrated inducing bone regeneration and favorable prognostic characteristics. |
| **New generation of bioactive material delivering superior osteoconductivity** | • Bioactive biomaterials are a type of materials capable of inducing specific biological responses at the interface, promoting or influencing the connection between tissues and materials, as well as triggering cellular activity or regeneration of new tissue.<br>• The new generation of rhBMP2 bone repair material, combines rhBMP-2 with gelatin and bioacitve glass, can effectively induces the differentiation of mesenchymal stem cells and bone progenitor cells into osteoblasts. Compared with current generation of bioactive rhBMP-2 material, the new generation has superior sustained release and osteoconduction properties, making it more suitable for use in minimally invasive orthopedic surgeries which have become increasingly prevalent. |
| **Emerging substitution effect of imported orthopedic bone repair materials** | • There are 24 registered imported orthopedic artificial bone repair materials on NMPA, involving manufacturers such as Medtronic, while there are 17 domestically registered orthopedic artificial bone repair materials, involving manufacturers such as Jiuyuan Gene.<br>• After years of development, China has made significant progress in the technological research and development of medical materials. In recent years, the domestically registered orthopedic artificial bone repair materials have shown an upward trend, indicating an increasingly evident substitution effect for imported materials. |

**Number of Orthopedic Artificial Bone Repair Materials Registered on NMPA**




Source: NMPA; Biomaterials; China Insights Consultancy

# Competitive landscape

| Bone repair materials | The number of products approved as of LPD |
|---|---|
| Allograft bone materials | 3 |
| Xenograft bone materials | 5 |
| Bioactive artificial bone materials | 4 |
| Nonactive artificial bone materials | >50 |

| Osteoporosis | The number of products as of LPD |
|---|---|
| Approved products | 181 |
| Clinical pipelines | 162 |

| CD38+ MM | The number of products as of LPD |
|---|---|
| Clinical pipelines | 28 |

| IL-11 | The number of products as of LPD |
|---|---|
| Approved products | 6 |



Source: NMPA; China Insights Consultancy

# Competitive landscape

| Palonosetron | The number of products as of LPD |
|---|---|
| Approved products | 29 |

| Enoxaparin | The number of products as of LPD |
|---|---|
| Approved products | 15 |



Source: NMPA; China Insights Consultancy

# Undisclosed competitors

| Code | Company | Competing areas | Initial year | Number of comparable products | Comparable products |
|---|---|---|---|---|---|
| Company 1.A | Shanxi Osteorad Biomaterial Co., Ltd. (山西奥瑞生物材料有限公司) | Bone repair materials | 2012 | 1 | Non-bioactive bone materials |
| Company 1.B | Beijing Xinkangchen Medical Technology Development Co., Ltd. (北京鑫康辰医学科技发展有限公司) | Bone repair materials | 2016 | 2 | Non-bioactive bone materials |
| Company 2.A | QiLu Pharmaceutical Co., Ltd. (齐鲁制药有限公司) | Oncology drugs | 1999 | 5 | rhG-CSF/ rhIL-11/ Palonosetron/ Fuvestrant/ Fosaprepitant |
| Company 2.B | CSPC Baike (Shandong)Bio-Pharmaceutical Co., Ltd (石药集团百克(山东)生物制药股份有限公司) | Oncology drugs | 2000 | 2 | (PEG) rhG-CSF |
| Company 2.C | Kyowa Kirin Co Ltd (协和发酵麒麟株式会社) | Oncology drugs | 2017 | 1 | rhG-CSF |
| Company 2.D | Chugai Pharmaceutical Co., Ltd. (中外制药株式会社) | Oncology drugs | 2014 | 1 | rhG-CSF |
| Company 2.E | China Resources Angde Biotech Pharma Co., Ltd. (华润昂德生物药业有限公司) | Oncology drugs | 2008 | 1 | rhIL-11 |
| Company 2.F | ChiaTai Tianqing (CCTQ) (正大天晴药业集团股份有限公司) | Oncology drugs | 2015 | 3 | Palonosetron/ Fuvestrant/ Fosaprepitant |
| Company 2.G | Yangtze River Pharmaceutical Group Sichuan Hairong Pharmaceutical Co., Ltd. (扬子江药业集团四川海蓉药业有限公司) | Oncology drugs | 2013 | 1 | Palonosetron |
| Company 2.H | Helsinn Healthcare S.A (和欣保健SA有限公司(瑞士)) | Oncology drugs | 2000 | 1 | Palonosetron |
| Company 2.I | Sanofi-Aventis Deutschland GmbH (赛诺菲) | Hematology drugs | 2017 | 1 | Enoxaparin |
| Company 2.J | Techdow Pharmaceutical (深圳市天道医药有限公司) | Hematology drugs | 2005 | 1 | Enoxaparin |



Source: NMPA; China Insights Consultancy

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# Overview of osteoporosis



## Introduction to and classification of osteoporosis

- Osteoporosis is a systemic bone disease characterized by low bone mass, microstructural damage to bone tissue, increased bone fragility, and a tendency to fracture easily. In 2001, the National Institutes of Health (NIH) in the United States defined it as a skeletal disorder characterized by decreased bone strength and an increased risk of fractures. Osteoporosis can occur at any age but is more common in postmenopausal women and elderly men. Based on its etiology, osteoporosis is divided into two main categories: primary and secondary

| | | | |
|---|---|---|---|
| 1 | Primary osteoporosis | Postmenopausal osteoporosis (Type I) | Generally occurs within 5 to 10 years after menopause in women |
| | | Senile osteoporosis (Type II) | Typically refers to osteoporosis that occurs after the age of 70 |
| | | Idiopathic osteoporosis (Adolescent Type) | Primarily occurs in adolescents, and its exact causes are not yet clear |
| 2 | Secondary osteoporosis | Refers to osteoporosis caused by specific diseases, medications, or other identifiable factors that affect bone metabolism | |

## Clinical manifestations of osteoporosis

- **Pain:** In patients with osteoporosis, there may be lower back pain or generalized bone pain. Pain typically occurs when changing positions, sitting down, or after prolonged walking. Pain worsens at night or during weight-bearing activities and may be accompanied by muscle spasms, and it may even restrict mobility
- **Spinal deformity**: Severe osteoporosis patients may experience vertebral compression fractures, resulting in height loss, hunchback, or other spinal deformities. Multiple compression fractures in the thoracic vertebrae can lead to thoracic deformities and may even affect cardiovascular and pulmonary function
- **Fracture:** Fractures typically occur with minor trauma in everyday life, with common fracture sites being the vertebrae (thoracic and lumbar), hip (proximal femur), distal forearm, and proximal humerus. After an osteoporotic fracture occurs, the risk of subsequent fractures significantly increases
- **Impact on psychological well-being and quality of life:** This primarily includes psychological abnormalities brought about by the disease. In elderly patients, there is a decrease in their ability to live independently, and after a fracture, the lack of contact and communication with the outside world can impose a significant psychological burden on patients

### Characteristics of high-risk population

- Aging;
- Female menopause;
- Maternal family history (especially a family history of hip fractures);
- Low body weight;
- Low levels of sex hormones;
- Unhealthy lifestyle: Smoking, excessive alcohol or coffee consumption, and etc.

### Causes of osteoporosis

- Osteoporosis is influenced by both genetic (congenital) and acquired (postnatal) factors. Congenital factors include ethnicity, gender, age, and family history, while acquired factors encompass medications, diseases, nutrition, and lifestyle choices. Advanced age, female menopause, and reduced male sexual function are all reasons that can lead to osteoporosis



*Source: National Health Commission of the People's Republic of China; Chinese Medical Journal; China Insights Consultancy*

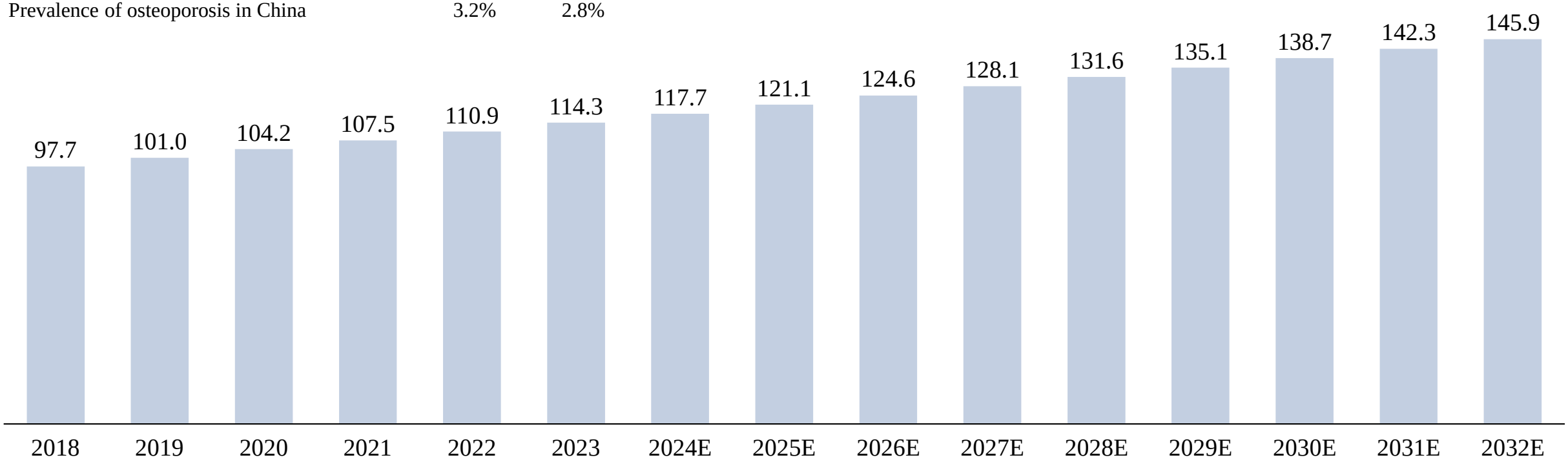
# Osteoporosis patients 2018-2032E



**Prevalence of osteoporosis in China, 2018-2032E**

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Prevalence of osteoporosis in China | 3.2% | 2.8% |

*Million patients*




- Osteoporosis is a widespread bone disease, particularly among middle-aged and elderly individuals, and is the most common chronic bone condition. Characterized by low bone mass, structural deterioration of bone tissue, and increased fragility, it often leads to easy fractures.
- From an economic perspective, the annual direct cost for a patient with an osteoporotic hip fracture is around RMB30,000. This economic burden, combined with the high prevalence and serious health implications of the disease, highlights the importance of understanding and addressing this disease.



Source: Chinese Medical Journal; China Insights Consultancy

# Diagnosis and treatment pathways of osteoporosis

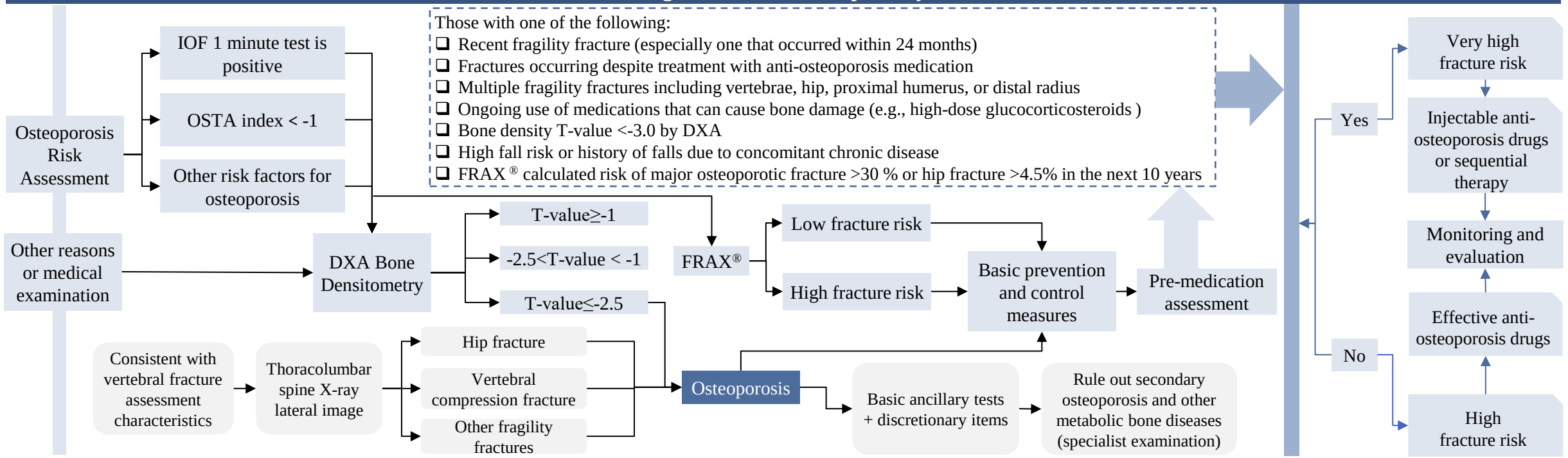


## Diagnosis and treatment pathways of osteoporosis

**Risks of osteoporosis**

- Osteoporosis is the fourth most common chronic disease and the most common bone disease amongst middle aged and elderly people. Osteoporosis has been called the silent killer. Fracture is a serious consequence of osteoporosis and is often the first symptom and reason for consultation in some osteoporosis patients. Mortality within the first year after hip fracture reaches 20-25% due to various complications. More than 50% of survivors will have varying degrees of disability. The direct economic burden of an osteoporotic hip fracture patient is over 30,000 per year[1]. This economic burden, combined with the high prevalence and serious health implications of the disease, highlights the importance of understanding and addressing this disease.

**Diagnosis and treatment pathways**




*Note: IOF = International Osteoporosis Foundation, OSTA = Osteoporosis Self-Screening Tool for Asians, DXA = Dual Energy X-ray Absorptiometry, FRAX® = Fracture Risk Assessment Tool*



*1. Notice from the Office of the Ministry of Health on the Issuance of "Key Points on the Prevention and Treatment of Osteoporosis Knowledge."*

*Source: Chinese Medical Journal; China Insights Consultancy*

# Current pharmacological treatment approaches for osteoporosis



## Current pharmacological treatment approaches for osteoporosis

**Overview**

- Currently approved drugs for treating osteoporosis can be categorized into bone resorption inhibitors, bone formation promoters, other medications, and traditional Chinese medicine. Despite significant progress in the development of drugs for the prevention and treatment of osteoporosis, clinical practice often faces challenges in the selection of anti-osteoporosis drugs, leading to misconceptions and gaps. Addressing how to avoid the pitfalls and blind spots in drug treatment, and developing individualized treatment strategies based on patients' conditions and the characteristics of the drugs, is a critical issue that warrants attention at present

### Pharmacological treatment approaches

#### Define treatment objectives

- It is crucial to select medications with evidence from evidence-based medicine that supports a reduction in the risk of fractures. Additionally, it is important to clearly define the target population for anti-osteoporosis treatment medications

#### Target population

- Individuals with a history of vertebral or hip fragility fractures
- T-score of ≤-2.5 for central bone mineral density (BMD) or distal third of the radius BMD measured by dual-energy X-ray absorptiometry (DXA)
- Meets the criteria for low bone mass and FRAX calculation indicates a higher risk of fractures (10-year risk of major osteoporotic fracture ≥20%, hip fracture risk ≥3%)

**Initiate drug therapy as early as possible**

#### Rationally select the initial treatment drugs

- The selection of initial treatment drugs should be based on stratified fracture risk

| Patients | Drugs |
|---|---|
| Patients at extremely high risk of fractures | Abaloparatide、Denosumab、Romosozumab）、Teriparatide、Zoledronic acid |
| Patients at extremely high risk of vertebral fractures | Teriparatide |
| Extremely high risk of hip fractures | Zoledronic acid、Denosumab |
| Patients diagnosed with osteoporosis, who do not have an extremely high risk of fractures, are considered to be at high risk of fractures | Alendronate sodium、Denosumab、Ibandronate sodium |
| Patients with reduced bone mineral density (BMD) only in the lumbar spine | Ibandronate sodium、Raloxifene |

#### Other key considerations during drug therapy

- **Attention to treatment duration and medication holidays:** Bisphosphonates (BPs) are usually taken for 3-5 years. However, high-risk individuals can extend oral BP treatment to 10 years, and zoledronic acid treatment to 6 years, based on guidelines from the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE). Teriparatide or abaloparatide treatment should not exceed 2 years due to potential osteosarcoma risk, and romosozumab treatment should not exceed 1 year due to potential cardiovascular risks
- **Avoid combination therapy unless necessary:** there is no evidence supporting the idea that combining two or more osteoporosis drugs is more effective in reducing fracture risk than using a single drug
- **Adhere to prolonged and systematic treatment:** For patients at extremely high fracture risk, it is recommended to follow treatment with bone-forming agents (such as teriparatide, abaloparatide, romosozumab) with either bisphosphonates (BPs) or denosumab. This helps prevent a decrease in bone mineral density (BMD) and loss of anti-fracture effectiveness



*Source: Chinese Medical Journal; China Insights Consultancy*

# In Chinese clinical guidelines, approximately 5 categories of drugs with different mechanisms of action are recommended for the treatment of osteoporosis, and the selection is based on each individual patient's condition



## Introduction to main osteoporosis drugs

| • Categories | • Mechanism of drugs | • Key Drugs |
|---|---|---|
| Bone resorption inhibitors | Primarily acts on osteoclasts, inhibits osteoclast differentiation and maturation, and reduces bone resorption | • Bisphosphonates (such as alendronate sodium, zoledronic acid, risedronate sodium, ibandronate sodium, minodronic acid)<br>• Anti-RANKL antibody (Denosumab)<br>• Calcitonin (Ecalcitonin, Salmon Calcitonin)<br>• Estrogen<br>• Selective Estrogen Receptor Modulators (SERMs) |
| Bone formation promoters | Primarily acts on osteoblasts, activates their bone-forming function, increases bone density, and reduces the risk of vertebral and non-vertebral fractures | • Parathyroid Hormone Analog, such as Teriparatide (rhPTH-34) |
| Dual-action medications | Increases bone density in osteoporosis patients and reduces the risk of vertebral and hip fractures | • Sclerostin monoclonal antibody (Romosozumab) |
| Medications with alternative mechanisms | It has the effect of increasing bone density, reducing falls, lowering the risk of fractures, and increasing bone mass | • Active Vitamin D and its analogs (Alfacalcidol, Calcitriol, Eldecalcitol)<br>• Vitamin K family (Menatetrenone) |
| Traditional Chinese medicine | Traditional Chinese medicine treatment principles for osteoporosis primarily involve nourishing the kidneys and replenishing essence, strengthening the spleen and invigorating qi, and promoting blood circulation and resolving stasis | • Bone density support with total flavonoid preparation<br>• Epimedium total flavonoid preparation<br>• Artificial tiger bone powder preparation<br>• Traditional Chinese medicine compound preparation |



Source: Chinese Medical Journal; China Insights Consultancy

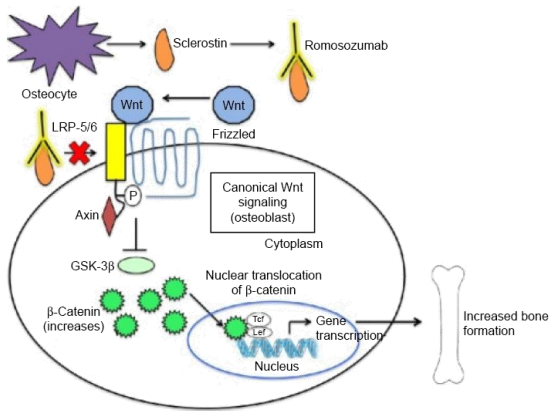
# Overview of romosozumab



## Introduction to and mechanism of action of romosozumab

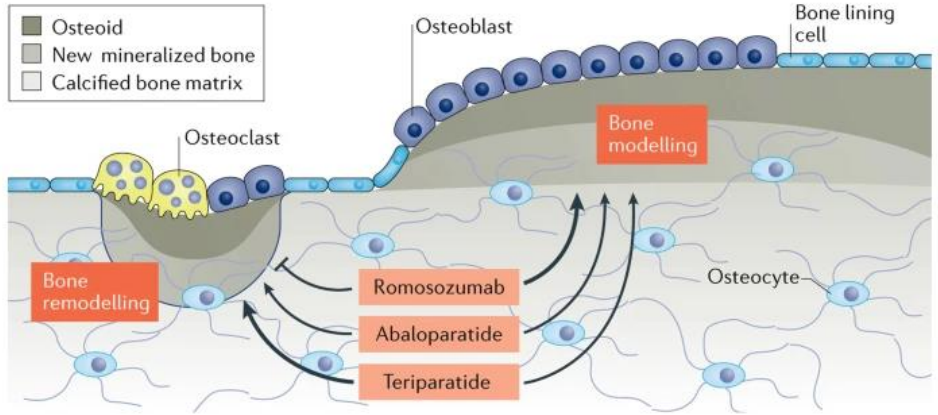
- Romosozumab is a humanized monoclonal antibody (IgG2) that can inhibit the activity of sclerostin (SOST). It functions to promote bone formation while reducing bone resorption simultaneously, thereby increasing bone density
- In April 2019, **this drug was approved in the United States for the treatment of postmenopausal women with osteoporosis who are at high risk of fractures**. Additionally, it has also been **approved in Japan for osteoporosis patients at high risk of fractures**, aiming to reduce fracture risk and increase bone density
- Several studies[1,2,3] show promising results for using romosozumab in men with osteoporosis; however, as of 2022, its use in this population is not FDA-approved. The use of romosozumab to treat osteoporosis in premenopausal women is also not FDA-approved but is currently under investigation

### Mechanism of action




- Romosozumab is a human monoclonal antibody that binds sclerostin (an inhibitor of Wnt pathway signaling). When this monoclonal antibody binds to sclerostin, sclerostin cannot bind to the LRP-5 and LRP- 6 receptors and is unable to exert its inhibitory effect. Wnt binds to LRP-5 or LRP-6 coreceptors and specific Frizzled family receptor, leading to activation of the Wnt signaling pathway and bone formation

## Differential effects of bone-forming agents on bone surfaces[4]




- Teriparatide and abaloparatide primarily function by stimulating bone formation in conjunction with bone resorption at remodeling sites, and to a lesser extent, by activating dormant bone-forming cells at modeling sites. On the other hand, **romosozumab primarily operates by enhancing bone formation based on modeling while concurrently suppressing bone resorption at remodeling sites**
- Romosozumab stands as one of the most potent bone-building agents available to date, offering substantial promise for enhancing our capacity to address osteoporosis in the future. Additional research is essential to validate its safety profile and explore strategies for maximizing the utilization of this powerful bone-building agent in osteoporosis treatment
- Romosozumab is currently under phase III trial for the treatment of osteoporosis in China and has not commenced commercial launch.



Source: Chinese Medical Journal; China Insights Consultancy

# As of 2/21/2024, there are 2 Romosozumab clinical pipelines in China for osteoporosis patients



**Pipelines of Romosozumab for osteoporosis, CDE-registered, as of 2/21/2024**

| Drug Name | Target | Company | Indications | Phase | First Posted Date | Route of Administration | Estimated Approval Year |
|---|---|---|---|---|---|---|---|
| Romosozumab | SOST | Amgen Inc./Patheon Italia S.p.A./UCB 安进/意大利培森/上海优时比 | Osteoporosis | Phase III | 2020/2/10 | s.c | 2025 |
| Romosozumab | SOST | Hangzhou jiuyuan gene engineering Co., Ltd. 杭州九源基因 | Osteoporosis | Pre IND | N/A | s.c | N/A |

- In addition to western medical treatment, osteoporosis can also be addressed through Traditional Chinese Medicine (TCM) and traditional Chinese herbal remedies. Based on the pathogenesis and clinical manifestations of osteoporosis, similar conditions in TCM include “Gu Bi” or “Gu Bi Zheng” (骨痿 or 骨痹). Some Chinese patent medicines with well-defined active ingredients include Gu Sui Bu Total Flavonoids (骨碎补总黄酮) , Yin Yang Huo Total Flavonoids (淫羊藿总黄酮), and artificial tiger bone powder (人工虎骨粉). Traditional Chinese medicine compound formulations mainly include the tonifying formula Xian Ling Gu Bao Capsules (仙灵骨葆胶囊),, the supplementing pill Zuo Gui Wan (左归丸), and the dual-purpose supplement and tonic capsules Qigubu Capsules (芪骨胶囊) and Boshu Kang Capsules (骨疏康胶囊)



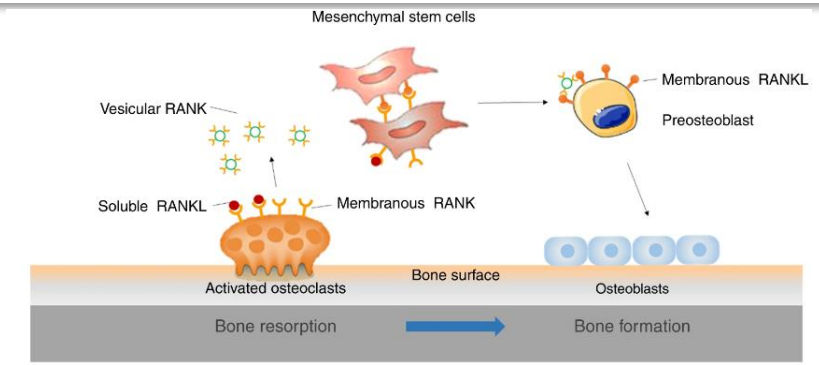
Source: Chinese Medical Journal; CDE; China Insights Consultancy

# Overview of anti-RANKL antibody



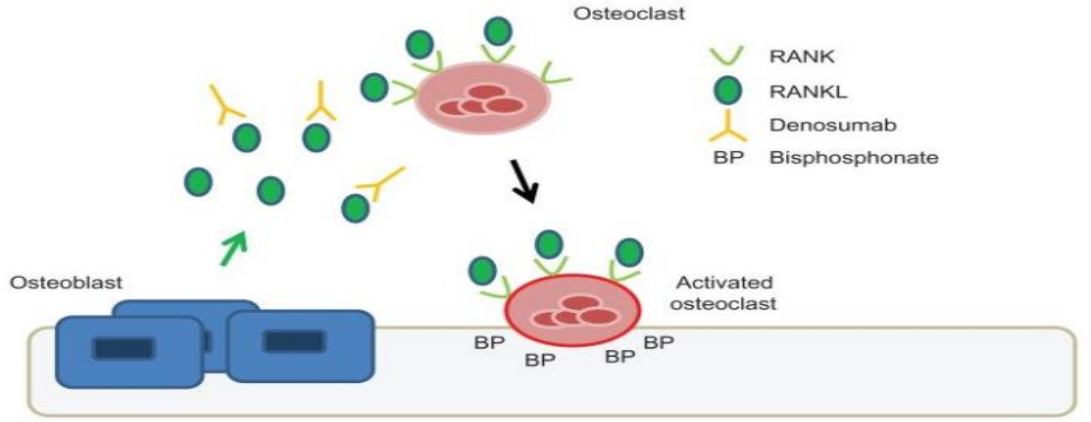
## Introduction to and mechanism of action of anti-RANKL antibody

- The RANKL-RANK signaling pathway has emerged as a central player in the control of osteoclastic bone resorption. Targeting this pathway has become a crucial therapeutic strategy in managing osteoporosis. Denosumab, an entirely human monoclonal antibody that neutralizes RANKL, has been developed as a pharmaceutical agent for osteoporosis treatment
- **Denosumab is China's first and only fully human monoclonal antibody against RANKL, making it an international frontline medication for osteoporosis**. It offers a convenient, effective, and cost-efficient treatment option for postmenopausal women with osteoporosis. As a broad-spectrum osteoporosis medication, Denosumab functions as a potent therapeutic agent by suppressing bone resorption, enhancing bone density, and mitigating the risk of osteoporosis and fractures




- RANKL signaling drives osteoclastogenesis. In BMSCs, RANKL binding to RANK activates RANKL forward signaling, which inhibits osteoblast differentiation. Maturing osteoclasts secrete vesicular RANK which activates RANKL reverse signaling in osteoblasts and promotes osteoblast differentiation. During osteoblastogenesis, the RANK expression is reduced and RANKL forward signaling on osteoblast differentiation is relieved

## Mechanism of action of denosumab compared to zoledronic acid




- RANKL is secreted by bone marrow stromal cells and osteoblasts. RANKL binds to the RANK receptor on osteoclasts and promotes osteoclast differentiation and activity. Denosumab is a fully human monoclonal antibody that binds to RANKL and thereby inhibits the activation of osteoclasts by RANKL. Bisphosphonates (for example, zoledronic acid) bind to bone, enter, and inhibit bone resorption by osteoclasts
- A study revealed the effectiveness and patients' persistence for two commonly used anti-osteoporosis agents after hip fracture. In this frail, elderly population, half-yearly **denosumab was superior to yearly zoledronic acid in bone mineral density （BMD) and demonstrated significant higher persistence rate**, indicating a potential therapeutic advantage that warrants further validation



*Source: Chinese Medical Journal; China Insights Consultancy*

# Increasing clinical demand, innovative targeted therapies, and heightened national attention drive antibody drugs' development, with a focus on combination therapies, enhanced versions, and improved affordability in the future



## Market drivers

**1 Rising clinical demand**

- The development of antibodies for the treatment of osteoporosis is driven by various factors, with population aging being a significant contributor. According to data from the Seventh National Population Census, China has a population of approximately 264 million aged 60 and above, accounting for 18.7% of the total population, and over 190 million aged 65 and above, representing 13.5% of the total population. China ranks among the countries with the largest elderly population globally. Furthermore, according to epidemiological surveys on osteoporosis in China[1], the prevalence of osteoporosis among individuals aged 50 and above is 19.2%, and it increases to 32.0% among those aged 65 and above. These statistics indicate that as the trend of population aging intensifies, the prevalence of osteoporosis continues to rise, so more patients need more effective osteoporosis medications.

**2 Development of novel high-efficiency targeted therapeutic drugs**

- The development of antibody drugs is primarily motivated by the research and introduction of a highly efficient new generation of targeted therapeutic drugs. The introduction of these innovative drugs, which exhibit more significant clinical outcomes, enhances the effectiveness of osteoporosis treatment. Consequently, patients are more willing to actively pursue treatment measures, which in turn drives the development of antibody drugs

**3 Increasing national attention**

- Increased national attention has led to greater awareness of osteoporosis, driving more people to seek effective medications. In October 2022, the Chinese Center for Disease Control and Prevention, along with other departments, launched the "National Healthy Lifestyle Action Plan (2017-2025)," focusing on the "Three Reductions and Three Enhancements" initiative. This aims to raise public awareness and self-management skills for osteoporosis, train healthcare workers and lifestyle instructors, and establish osteoporosis health centers in eligible areas

## Market trends

**Combination therapy**

- Antibody drugs are expected to be used in conjunction with other treatment modalities such as bone formation enhancers, calcium and vitamin D supplementation, physical exercise and physiotherapy, dietary and nutritional guidance, as well as personalized treatment plans. The future trend in the treatment of osteoporosis is likely to adopt a more comprehensive and diversified approach, moving away from the confinement to single-drug therapy and instead embracing the synergy of multiple drugs and treatment methods to achieve more effective disease management

**Enhanced effectiveness**

- The continuous research and innovation in the pharmaceutical field have led to the emergence of more efficient and safer antibody drugs. These new drugs typically exhibit more significant clinical effects and fewer adverse effects, thereby offering more potent treatment options. Furthermore, future developments may move towards greater personalization and precise alignment with patients' needs, further enhancing treatment effectiveness

**Improved affordability**

- There are relatively few approved antibody drugs on the market in China, however, with ongoing development, an increasing number of antibody drugs are expected to receive approval, and they may even enter medical insurance or centralized procurement programs. As prices decrease, more osteoporosis patients will have the financial means to afford the treatment. This will provide hope for more osteoporosis patients, enabling them to access more advanced treatments and improve their quality of life



1. The National Health Commission has released the epidemiological survey results of osteoporosis in China

Source: National Health Commission of the People's Republic of China; China Insights Consultancy

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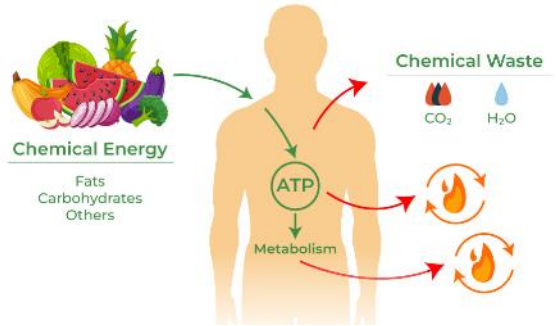
# A metabolic disorder is a disorder that negatively alters the body's processing and distribution of macronutrients such as proteins, fats, and carbohydrates



## Introduction to metabolic disorders




Metabolism is the set of biochemical reactions that take place in the cells of the human body and aim towards the sustenance of the cells and the human organism.

**A metabolic disorder is a disorder that negatively alters the body's processing and distribution of macronutrients such as proteins, fats, and carbohydrates. Metabolic disorders can happen when abnormal chemical reactions in the body alter the normal metabolic process.**

## Causes of metabolic disorders

**Genetics:** a gene that tells the body how to do a certain metabolic process or make a chemical or enzyme mutates.

**Organ dysfunction:** an organ involved in metabolism gets diseased or damaged, such as the pancreas or thyroid.

**Unknown Causes:** the causes of some metabolic disorders remains unknown, such as type 1 diabetes, which is an autoimmune disorder.

## Types of metabolic disorders

There are various types of metabolic disorders, among which diabetes, overweight and obesity are the most common ones.

**Amino acid metabolism disorders**
- Tay-Sachs disease
- Tyrosinemia
- Phenylketonuria
- Homocystinuria

**Protein metabolism disorders**
- Organic Acidemias
- Urea Cycle Defects
- Aminoaciduria

**Lysosomal Storage Disorders**
- Hurler Syndrome
- Krabbe Disease

**Fatty Acid Metabolism Disorders**
- Niemann-Pick Disease
- Medium-Chain Acyl-coenzyme A Dehydrogenase (MCAD) Deficiency
- Fabry's Disease

**Carbohydrate Metabolism Disorders**
- Diabetes
- Hereditary Fructose Intolerance
- Galactosemia
- Pyruvate Metabolism Disorders
- Von Gierke's Disease
- Insipidus
- Forbes' Disease
- Mcardle Disease
- Pompe's Disease

**Glycolipid Disorders**
- Gaucher's Disease

**Vitamin Metabolism Disorders**
- Biotinidase Deficiency

**Mineral Disorders**
- Wilson Disease
- Cystinosis
- Menkes Disease

**Peroxisomal Disorders**
- Zellweger Syndrome
- Adrenoleukodystrophy



Source: WHO; China Insights Consultancy

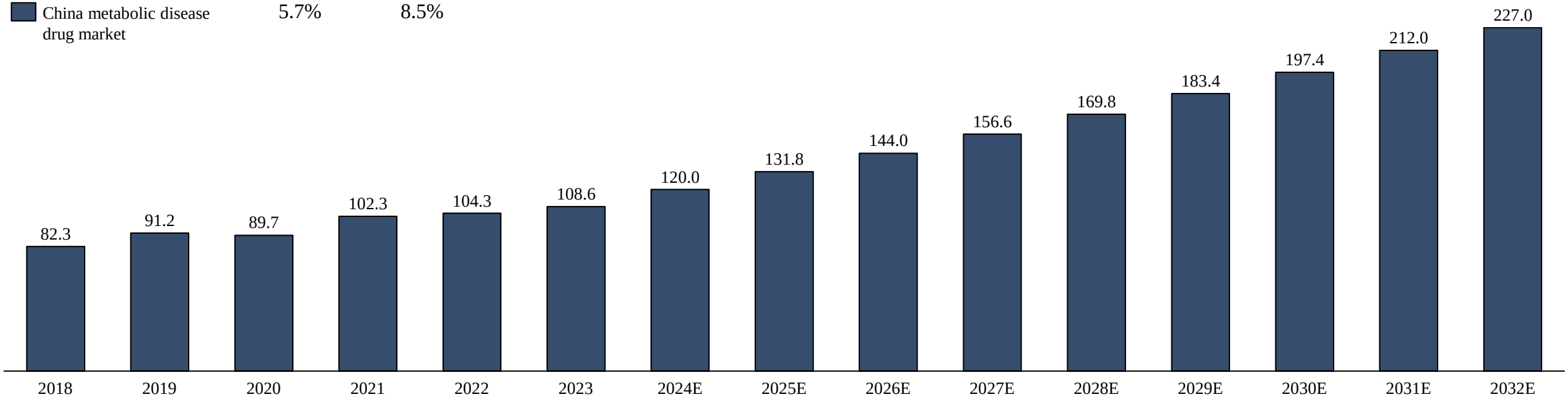
# China metabolic disease drug market increased from RMB[82.3] Billion in 2018 to[108.6] Billion in 2023, and is expected to reach [227.0] Billion by 2032 at the CAGR of [8.5] %



## China metabolic disease drug market size , 2018-2032E

*RMB Billion*

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| China metabolic disease drug market | 5.7% | 8.5% |




**Key Analysis**

- China metabolic disease drug market increased from RMB[82.3] Billion in 2018 to[108.6] Billion in 2023, and is expected to reach [227.0] Billion by 2032 at the CAGR of [8.5] %



Source: China Insights Consultancy

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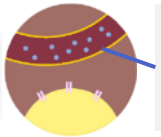
# Chronic diabetes conditions include type 1 diabetes(T1DM) and type 2 diabetes(T2DM); T2DM accounts for around 90% of all cases of diabetes



## Introduction to diabetes

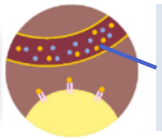
Diabetes is a chronic, metabolic disease characterized by **elevated levels of blood glucose**, which leads over time to serious damage to the heart, blood vessels, eyes, kidneys and nerves. Chronic diabetes conditions include type 1 diabetes(T1DM) and type 2 diabetes(T2DM). T2DM accounts for around **90%** of all cases of diabetes.

**T1DM**



T1DM is an autoimmune disease that leads to the destruction of insulin-producing pancreatic beta cells. In this condition, the pancreas makes little or no insulin.

**T2DM**



In T2DM, the body fails to respond properly to insulin and over time, the pancreas makes less insulin, resulting in too much sugar build-up in the bloodstream (hyperglycemia).

## Causes of diabetes

- **Increased Hepatic Glucose Production**
- **Increased Carbohydrate Intake**
- **Decreased Insulin Secretion**
- **Decreased Peripheral Glucose Uptake**

→ Blood Glucose

## Diagnosis of diabetes and prediabetes

There are several way to diagnose diabetes. Each way usually need to be repeated on a second day;

- **Hemoglobin A1C Test (HbA1c)** measures average blood sugar for the past two to three months;
- **Fasting Plasma Glucose Test (FPG)** checks fasting blood sugar levels. 8-hours fasting before the test is required;
- **Oral Glucose Tolerance Test (OGTT)** is a two-hour test that checks blood sugar levels before and two hours after drinking a special sweet drink;
- **Random Plasma Glucose Test** is a blood check at any time of the day when patients have severe diabetes symptoms.

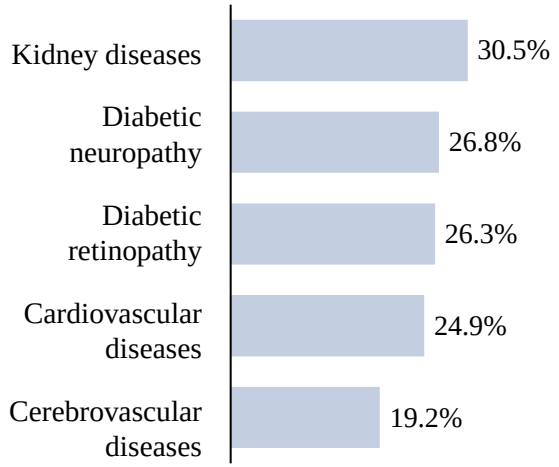
| | HbA1c Test (%) | FPG Test (mg/dL) | OGTT Test (mg/dL) |
|---|---|---|---|
| Diabetes | ≥ 6.5 | ≥ 126 | ≥ 200 |
| Prediabetes | 5.7 – 6.4 | 100 – 125 | 140 - 199 |
| Normal | ≈ 5 | ≤ 99 | ≤ 139 |

## Symptoms of T2DM

- Frequent urination, excessive thirst and fluid intake
- Fatigue, blurred vision, abnormal weight loss and increased hunger
- Sores that do not heal

## Comorbidities of T2DM

Approximately 66.8% of Chinese T2DM patients have chronic comorbid condition, and the average number of chronic complications per patients is 2.17[1].






[1]He S N, Zhang Y W, Ruan Z, et al. Study on the prevalence of chronic complications and sub-average medical costs in Chinese patients with type 2 diabetes mellitus [J] . Chinese Journal of Endocrinology and Metabolism,2019,35 (3): 200-205. doi: 10.3760/cma.j.issn.1000-6699.2019.03.004

Source: WHO, Chinese Journal of Endocrinology and Metabolism; China Insights Consultancy

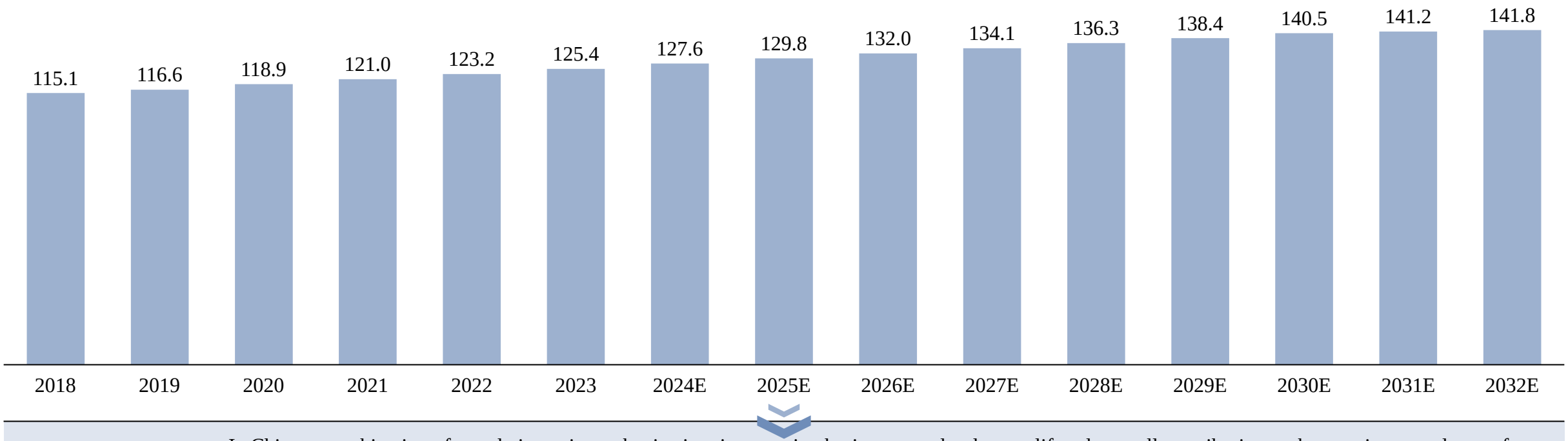
# Due to rapid population aging and lifestyle changes, the overall prevalence of T2DM in China is increasing and is expected to reach 141.8 million patients by 2032



**Prevalence of T2DM in China, 2018-2032E**

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Prevalence of T2DM in China | 1.7% | 1.4% |

*million patients*




**Key Analysis**

- In China, a combination of population aging, urbanization, increase in obesity rate and sedentary lifestyle are all contributing to the growing prevalence of T2DM, resulting in growing heavy economic burdens on China's healthcare systems.
- The overall prevalence of T2DM in China has increased from 115.1 million in 2018 to 125.4 million in 2022 and is expected to reach 141.8 million by 2032.

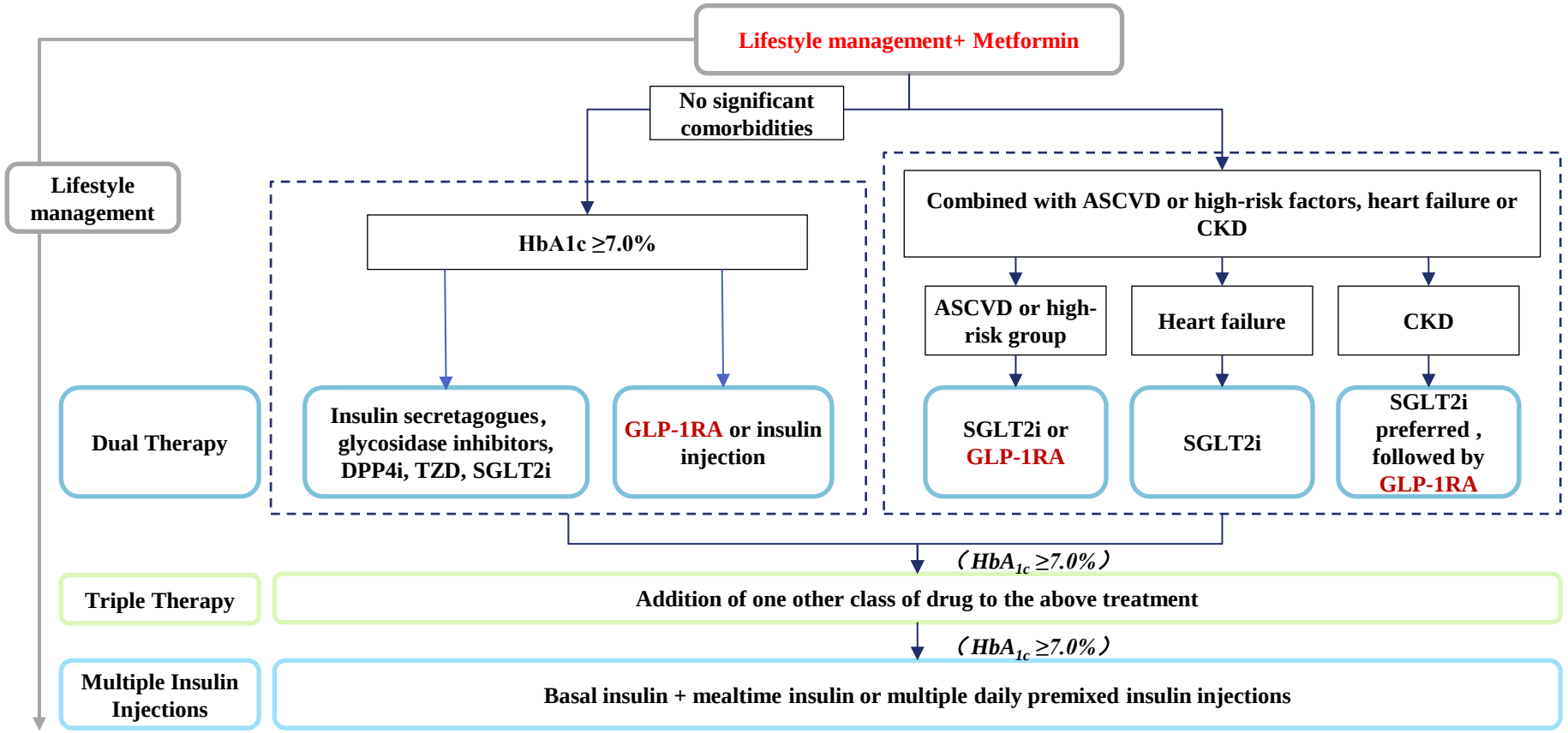


Source: IDF; China Insights Consultancy

# GLP-1RA is one of the guideline-recommended medications for dual therapy of T2DM patients with high HbA1c and comorbidities in China



## Treatment flow of T2DM in China




*Note: HbA1c, glycated hemoglobin; ASCVD, atherosclerosis cardiovascular disease; CKD, chronic kidney disease;*

- GLP-1RA is one of the guideline-recommended medications for dual therapy of T2DM patients with HbA1c ≥7.0%, or with comorbidities including ASVCD(or high-risk group), heart failure or CKD regardless HbA1c level in China;
- Currently, about 1/3 of T2DM patients still need insulin injection for glycemic control. With increasing clinical emphasis on comprehensive benefits for diabetic patients, GLP-1RA is increasingly used to reduce the occurrence of long-term complications;
- Due to the relatively high cost of GLP-1 and low patient awareness, the market share of GLP-1RA drugs in China is currently low among patients.



Source: Chinese Diabetes Society; China Insights Consultancy

# There are eight classes of drugs commonly used for the treatment of T2DM; GLP-1RAs are superior in terms of efficacy, and have beneficial effects towards weight management, cardiovascular and renal systems



| Drug Class | Mechanism of Action | Main target organ site | Efficacy | Weight change | Drug delivery method | CV effects | | Renal effects | Price level |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Effect on MACE | HF | Progression of DKD | |
| Biguanides (Metformin) | Decrease in hepatic glucose production; increase in muscle insulin sensitivity by activating AMPK | Liver and intestine | High | Neutral |  | Potential benefit | Neutral | Neutral | Low |
| Thiazolidinediones (TZDs) | Bind PPAR-γ, decrease insulin resistance and increase glucose utilization | Muscle, adipose tissue, and liver | High | Gain |  | Potential benefit: pioglitazone | Increased risk | Neutral | Low |
| Sulfonylureas | Stimulates beta cell insulin secretion | Islet cells of pancreas | High | Gain |  | Neutral | Neutral | Neutral | Low |
| DPP4 inhibitors | Prevent degradation Of GLP-1 | Intestine | Intermediate | Neutral |  | Neutral | Neutral(potential risk: saxagliptin) | Neutral | High |
| SGLT2 inhibitor | Prevent glucose reabsorption and facilitate its excretion in urine by inhibiting SGLT-2 | Kidney | Intermediate to high | Loss (Intermediate) |  | **Benefit**: canagliflozin, empagliflozin | **Benefit:** canagliflozin, Dapagliflozin, empagliflozin, ertugliflozin | **Benefit:** canagliflozin, Dapagliflozin, empagliflozin | High |
| GLP-1 receptor Agonists(GLP-1RAs) | Activate GLP-1 receptor, increase insulin secretion, decrease glucagon secretion | Islet cells of pancreas | High to very high | Loss (Intermediate to very high) |  | **Benefit**: dulaglutide, liraglutide, Semaglutide(SQ) | Neutral | **Benefit for renal endpoints CVOTs, driven by albuminuria outcomes:** dulaglutide, liraglutide, Semaglutide(SQ) | High |
| GIP and GLP-1RA | Activate GIP receptor, increase insulin secretion, improve insulin sensitivity; activate GLP-1 receptor, stimulate postprandial insulin secretion, decrease glucagon secretion | Islet cells of pancreas | Very high | Loss (Very high) |  | Under investigation | Under investigation | Under investigation | High |
| Insulin | Stimulate glycogen synthesis, increase glycolysis and glucose transport, inhibit glycogenolysis and gluconeogenesis, inhibit glucagon secretion | Muscle, adipose tissue, and liver | High to very high | Gain |  | Neutral | Neutral | Neutral | Low (Human) High (Analogs) |



Source: Diabetes Care, China Insights Consultancy

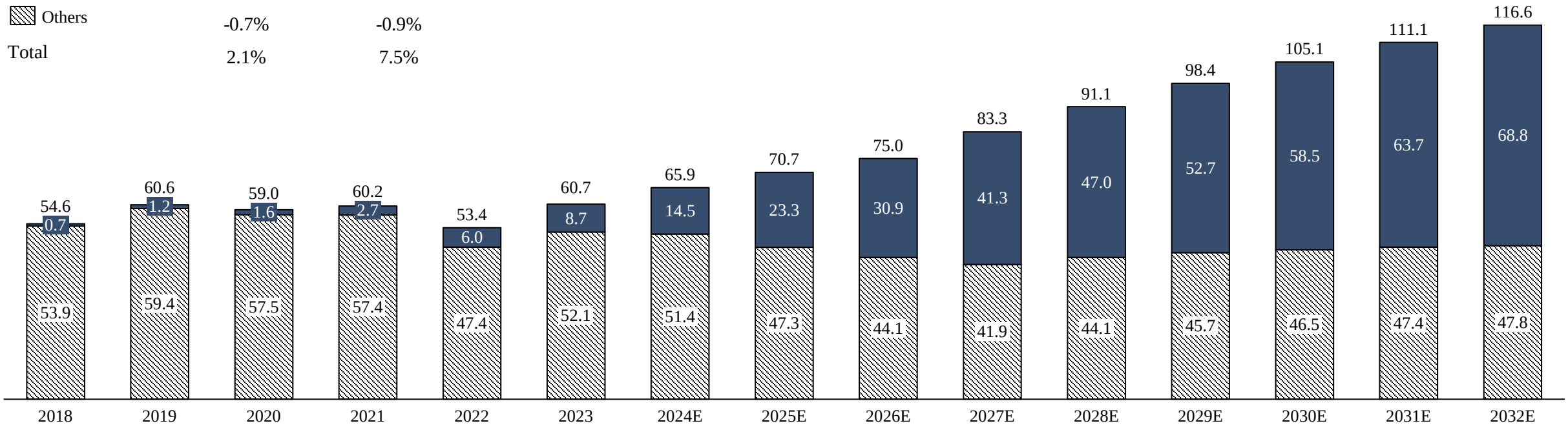
# The market size of China T2DM drug market is projected to increase from RMB[60.7] billion in 2023 to RMB[116.6] billion in 2032, with GLP-1RAs significantly outpacing the overall T2DM drug market



## China T2DM Drug Market Size, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| GLP-1RAs | 64.1% | 25.9% |
| Others | -0.7% | -0.9% |
| Total | 2.1% | 7.5% |

*RMB Billion*




- According to the Chinese Journal of Diabetes, there are primarily three currently used treatments for T2DM: lifestyle interventions, drug treatments, and metabolic surgery.
- Lifestyle interventions, encompassing blood sugar monitoring, diet control and exercise, are the cornerstone of T2DM treatment. They are safe, free from side effects, aiding in weight loss and improving insulin sensitivity at a low cost.
- When lifestyle changes alone are inadequate, drug treatment is introduced. This includes oral diabetes medications, which are effective but can have side effects. Notably, Glucagon-like peptide-1 receptor agonists (GLP-1RAs), a newer type of injectable medication, are recommended by leading diabetes guidelines due to their benefits in lowering HbA1c levels, reducing weight, and decreasing cardiovascular risks.
- The T2DM drug market in China could potentially be limited by alternative prevention and treatment methods for such indications and medication treatment is used only for a portion of the total T2DM patients.



Source：The Journal of the American Medical Association; International Diabetes Federation World Diabetes Atlas; Menet

# GLP-1RAs can regulate six out of the eight pathogenic mechanisms of T2DM simultaneously and have high efficacy in controlling T2DM hyperglycemia



## Introduction of GLP-1 peptide and GLP-1RAs

- Glucagon-like peptide-1 (GLP-1) is an **incretin secreted by the distal intestinal ileum and colon L-cells** following food intake.
- GLP-1 stimulates glucose-dependent insulin release from the pancreatic islets. GLP-1 also slows gastric emptying, regulates postprandial glucagon, and reduces food intake.
- Natural human GLP-1 has a **short half-life (around 2 min),** due to the rapid degradation by the enzyme dipeptidyl-peptidase-4 (DPP-4), a serine aminopeptidase, and because of renal clearance, due to its low molecular weight.
- Synthetic GLP-1 receptor agonists (GLP-1RAs) are **variably resistant to degradation by the enzyme DPP-4**, and therefore have a longer half-life, facilitating clinical use.
- Currently, GLP-1RAs have been approved for the treatment of **T2DM and obesity**, and ongoing clinical trials are also exploring the clinical effect of GLP-1RAs in other indications such as NASH and ASCVD.

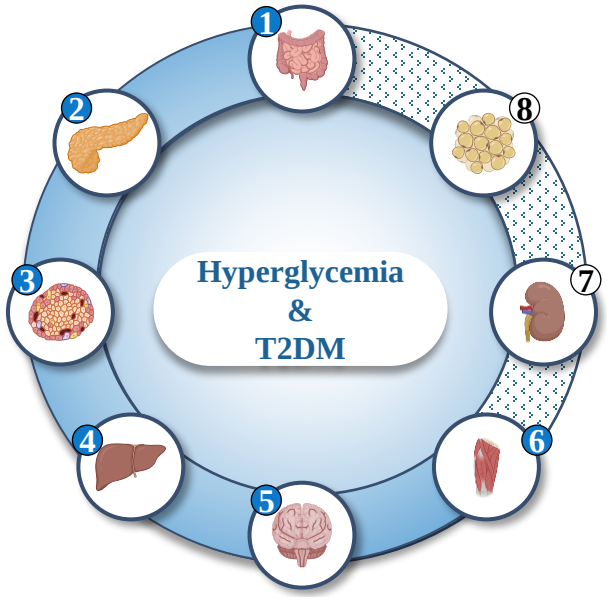
## The pathogenic mechanisms of T2DM and the therapeutic effects of GLP-1RAs

**1 Decreased incretin secretion**
GLP-1RAs are modified to be **less susceptible to rapid degradation by DPP-4 enzyme**

**2 Decreased insulin secretion**
GLP-1RAs **increase insulin synthesis, increase glucose sensitivity of glucose-resistant β-cells, stimulate β-cell proliferation and neogenesis,** and **inhibit β-cell apoptosis**

**3 Increased glucagon secretion**
GLP-1RAs **can inhibit glucagon secretion from pancreatic islet α-cells by stimulating insulin secretion**

**4 Increased glucose production**
GLP-1RAs **can inhibit hepatic glucose production (HGP) and reduce liver lipid content**




**8 Increased lipolysis rate and free fatty acids**

**7 Increased renal glucose reabsorption**

**6 Decreased glucose uptake in skeletal muscle**
GLP-1RAs **can significantly increase the uptake of glucose by muscle tissue, thus lowering blood glucose**

**5 Neurotransmitter dysfunction**
GLP-1RAs **can significantly increase the uptake of glucose by muscle tissue, thus lowering blood glucose**

**Key Analysis**

- GLP-1RAs can regulate six out of the eight pathogenic mechanisms of T2DM simultaneously and have high efficacy in controlling T2DM hyperglycemia.
- GLP-1RAs are recommended as a dual therapy medication for the treatment of T2DM by Chinese and international T2DM treatment guidelines.



Source: []; China Insights Consultancy

# GLP-1RAs can be classified into natural GLP-1RA and human GLP-1RA by origin, and short-acting and long-acting by efficacy length



## ① Classification by origin

- **Based on origin, GLP-1RAs can be categorized into natural GLP-1RA and human GLP-1RA.**
- The immunogenicity of GLP-1RA drugs and human GLP-1 homology are highly positively correlated—homology of drugs based on natural GLP-1RA modifications is lower than that of human GLP-1RA modifications.
- Therefore, drugs based on natural GLP-1RA modifications are more likely to produce anti-drug and neutralizing antibodies, resulting in **strong allergic reactions or reduced efficacy.**

## ② Classification by efficacy length

- **Based on efficacy length, GLP-1RAs can be categorized into short-acting GLP-1RAs and long-acting GLP-1RAs.**
- With modification techniques, the half-life of long- acting GLP-1RAs has gradually increased, which leads to **decreased frequency of drug administration** and **higher patient compliance.**

***Definition :***

- GLP-1RA can be divided into humanized and non-human GLP-1 structural GLP-1RA based on its molecular structure characteristics. GLP-1RA includes liraglutide, dulaglutide, benaglutide, semaglutide, etc. Human GLP-1RA is processed by partially modifying the molecular structure of human GLP-1. It has high amino acid sequence homology with human GLP-1 (≥90). The amino acid sequence of non-human GLP-1RA has low homology with human GLP-1. It is a synthetic GLP-1RA drug based on the Exendin-4 structure, including exenatide and exenatide preparations (microspheres), lixisenatide, polyethylene glycol loxenatide, and iglilinatide. Exendin-4 is a polypeptide isolated from the saliva of the American poisonous lizard. It can effectively resist the cleavage of DPP-4, has a high renal filtration rate, and has a longer half-life than natural human GLP-1.

| **Drug type** | **Non-human GLP-1RA** | | | **Humanized GLP-1RA** | | | |
|---|---|---|---|---|---|---|---|
| **Drug base** | Based on heterologous Exendin-4 | | | Based on human GLP-1 analogs | | GLP-1 fusion protein | |
| **Drug name(generic)** | Exenatide | Exenatide Microspheres | Lixisenatide | Liraglutide | Semaglutide | Albiglutide | Dulaglutide |
| **Amino acid sequence homology with human GLP-1** | 53% | 53% | ~50% | 97% | 94% | 97% | 90% |
| **Antibody positive rate (immunogenicity)** | 40% | 87.7% | 69.8% | 8.6% | 4.3% | 4% | 1.6% |
| **Modification for extended clearance time** | N/A | N/A | N/A | Fatty acid chain modification | Fatty acid chain modification | Fusion with HSA[1] | Fusion with the human IgG4-Fc heavy chain |
| **Efficacy length** | Short-acting | Long-acting | Short-acting | Short-acting | Long-acting | Long-acting | Long-acting |
| **Administration frequency** | Twice a day | Once a week | Once a day | Once a day | Once a week | Once a week | Once a week |
| **Half life** | 2.4 hrs | One-week sustained release | 3 hrs | 13 hrs | ~7 days | ~5 days | ~5 days |



*Note: 1.Human Serum Albumin， HSA*

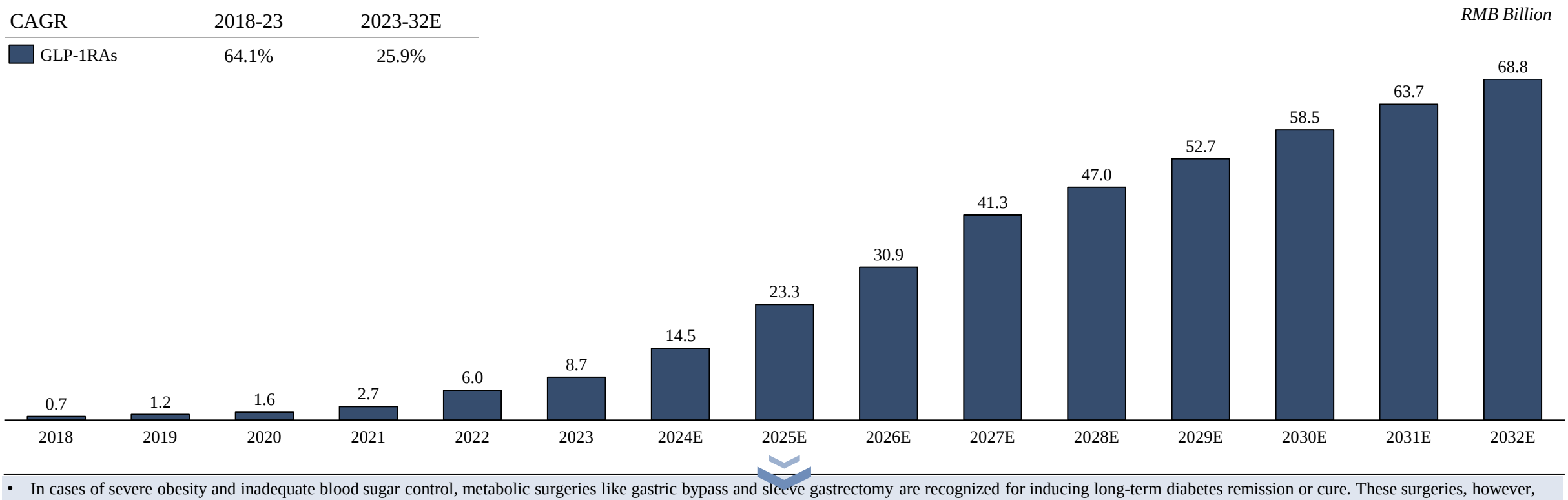
Source：Diabetes Care; China Insights Consultancy

# The market size of China GLP-1RAs for the treatment of T2DM market is projected to increase from RMB8.7 billion in 2023 to RMB68.8 billion in 2032 at a CAGR of 25.9%



## China GLP-1RAs for the treatment of T2DM Market Size, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| GLP-1RAs | 64.1% | 25.9% |




- In cases of severe obesity and inadequate blood sugar control, metabolic surgeries like gastric bypass and sleeve gastrectomy are recognized for inducing long-term diabetes remission or cure. These surgeries, however, involve certain risks, are expensive, and necessitate continued lifestyle changes to prevent relapse.
- We adjust the total number of T2DM patients in China for the diagnosis rate (around 49% in 2022) and the drug treatment rate (around 68% in 2022), as reported in studies such as Prevalence and Treatment of Diabetes in China and consider the adjusted number of T2DM patients receiving drug treatment as addressable patients for T2DM drugs. See "— Metabolic Disease Drugs Market — T2DM Drug Market — Size of T2DM drugs market in China."
- The annual expenditure on these drugs is then factored in, with unit prices sourced from NRDL files and commercial database.



Source: China Insights Consultancy

# As of LPD, there are 16 approved GLP-1RA products in China for T2DM patients, of which 7 are domestic products



**Approved GLP-1RA products for T2DM by NMPA, as of LPD**

| Drug Name | Brand Name | MoA | Indication | Company | First Approval |
|---|---|---|---|---|---|
| Exenatide | / | GLP-1R | T2DM | Hybio Pharmaceutical | 2024/9/10 |
| Liraglutide | Beilelin | GLP-1R | T2DM | Chia Tai Tianqing Pharmaceutical Group | 2024/6/18 |
| Tirzepatide | Mounjaro | GLP-1R, GIP | T2DM | Eli Lilly | 2024/5/15 |
| Semaglutide | Rybelsus | GLP-1R | T2DM | Novo Nordisk | 2024/1/26 |
| Liraglutide | Tongboli | GLP-1R | T2DM | Tonghua Dongbao Pharmaceutical | 2023/11/28 |
| Liraglutide | Liluping | GLP-1R | T2DM | Hangzhou Zhongmei Huadong Pharmaceutical /Our Company | 2023/3/28 |
| Insulin Glargine Lixisenatide | Soliqua | GLP-1R, insulin | T2DM | Sanofi | 2023/1/10 |
| Exenatide | / | GLP-1R | T2DM | Qinghai Chenfei Pharmaceutical | 2022/7/29 |
| IDegLira | Xultophy | GLP-1R, insulin | T2DM | Novo Nordisk | 2021/10/26 |
| Semaglutide | Ozempic | GLP-1R | T2DM | Novo Nordisk | 2021/4/27 |
| Polyethylene Glycol Loxenatide | Fulaimei | GLP-1R | T2DM | Jiangsu Hansoh Pharmaceutical Group | 2019/5/5 |
| Dulaglutide | Trulicity | GLP-1R | T2DM | Eli Lilly | 2019/2/22 |
| Lixisenatide | Lyxumia | GLP-1R | T2DM | Sanofi | 2017/9/29 |
| Beinaglutide | Yishengtai | GLP-1R | T2DM | Shanghai Benemae Pharmaceutical | 2016/12/13 |
| Liraglutide | Victoza | GLP-1R | T2DM | Novo Nordisk | 2011/3/4 |
| Exenatide | Byetta | GLP-1R | T2DM | AstraZeneca | 2009/5/8 |

Imported products  Domestic products



Source: NMPA; China Insights Consultancy

# Numerous completed SUSTAIN phase 3 trials investigating the effect of semaglutide in patients with type 2 diabetes show preferable results in terms of HbA1C level and bodyweight decrease(1/3)



| Clinical Trial ID | Trial Name | Trial Population | Comparator treatment | Duration of Trial (Weeks) | Results | | |
|---|---|---|---|---|---|---|---|
| | | | | | Groups | $HbA_{1c}$ Change % | Average Bodyweight Reduction KG |
| NCT02054897 | SUSTAIN 1 | Type 2 Diabetes | Placebo | 30 | 0.5 mg Semaglutide | 1.45 | 3.73 |
| | | | | | 1.0 mg Semaglutide | 1.55 | 4.53 |
| | | | | | Placebo | 0.02 | 0.98 |
| NCT01930188 | SUSTAIN 2 | Type 2 diabetes, taking metformin and/or thiazolidinediones | Sitagliptin | 56 | 0.5 mg Semaglutide | 1.3 | 4.3 |
| | | | | | 1.0 mg Semaglutide | 1.6 | 6.1 |
| | | | | | Sitagliptin | 0.5 | 1.9 |
| NCT01885208 | SUSTAIN 3 | Type 2 diabetes, taking metformin and/or thiazolidinediones and sulfonylureas | Exenatide ER | 56 | 1.0 mg Semaglutide | 1.5 | 5.6 |
| | | | | | 2.0 mg Exenatide ER | 0.9 | 1.9 |
| NCT02128932 | SUSTAIN 4 | Type 2 diabetes; insulin-naïve, taking metformin with/without sulfonylurea | Insulin glargine | 30 | 0.5 mg Semaglutide | 1.21 | 3.47 |
| | | | | | 1.0 mg Semaglutide | 1.64 | 5.17 |
| | | | | | Insulin glargine | 0.8 | 1.15 |
| NCT02305381 | SUSTAIN 5 | Type 2 diabetes, taking basal insulin with/without metformin | Placebo | 30 | 0.5 mg Semaglutide | 1.4 | 3.7 |
| | | | | | 1.0 mg Semaglutide | 1.8 | 6.4 |
| | | | | | Placebo | 0.1 | 1.4 |



Note: MACE = cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke

Source：The Lancet Diabetes & Endocrinology; Cardiovasc Diabetol; China Insights Consultancy

# Numerous completed SUSTAIN phase 3 trials investigating the effect of semaglutide in patients with type 2 diabetes show preferable results in terms of HbA1C level and bodyweight decrease(2/3)



| Clinical Trial ID | Trial Name | Trial Population | Comparator treatment | Duration of Trial (Weeks) | Results | | |
|---|---|---|---|---|---|---|---|
| | | | | | Groups | $HbA_{1c}$ Change % | Average Bodyweight Reduction KG |
| NCT01720446 | SUSTAIN 6 | Type 2 diabetes at high cardiovascular risk, excluding those using other GLP-1 analogs or dipeptidyl peptidase 4 inhibitors | Placebo | During a median of 2.1 years of follow-up, 26% reduction of MACE with treatment; Semaglutide group MACE occurrence: 6.6% Placebo group MACE occurrence: 8.9% | | | |
| NCT02648204 | SUSTAIN 7 | Type 2 diabetes on stable metformin treatment | Dulaglutide | 21 | 0.5 mg Semaglutide | 1.5 | 4.6 |
| | | | | | 0.75 mg Dulaglutide | 1.1 | 2.3 |
| | | | | | 1.0 mg Semaglutide | 1.8 | 6.5 |
| | | | | | 1.5 mg Dulaglutide | 1.4 | 3.0 |
| NCT03136484 | SUSTAIN 8 | Type 2 diabetes on stable metformin treatment | Canagliflozin (SGLT-2) | 52 | Semaglutide | 1.5 | 5.3 |
| | | | | | Canagliflozin | 1.0 | 4.2 |
| NCT03086330 | SUSTAIN 9 | Type 2 diabetes, taking SGLT-2 inhibitor with or without metformin or sulfonylurea | Placebo | 30 | Semaglutide | 1.5 | 4.7 |
| | | | | | Placebo | 0.1 | 0.9 |
| NCT03191396 | SUSTAIN 10 | Type 2 diabetes on stable treatment with up to three oral antidiabetics | Liraglutide | 30 | Semaglutide | 1.7 | 5.8 |
| | | | | | Liraglutide | 1.0 | 1.9 |



Note: MACE = cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke

Source：The Lancet Diabetes & Endocrinology; Cardiovasc Diabetol; China Insights Consultancy

# Numerous completed SUSTAIN phase 3 trials investigating the effect of semaglutide in patients with type 2 diabetes show preferable results in terms of HbA1C level and bodyweight decrease(3/3)



| Clinical Trial ID | Trial Name | Trial Population | Comparator treatment | Duration of Trial (Weeks) | Results | | |
|---|---|---|---|---|---|---|---|
| | | | | | Groups | $HbA_{1c}$ Change % | Average Bodyweight Reduction KG |
| NCT03689374 | SUSTAIN 11 | Type 2 diabetes, taking basal insulin plus metformin | Insulin Aspart | 52 | Semaglutide | 1.5 | 4.1 |
| | | | | | Insulin Aspart | 1.2 | -2.8 (weight gain) |
| NCT03989232 | SUSTAIN FORTE | Type 2 diabetes, taking metformin with/without a sulfonylurea | Semaglutide 2.0 mg | 40 | 2.0 mg Semaglutide | 2.2 | 6.9 |
| | | | | | 1.0 mg Semaglutide | 1.9 | 6.0 |
| NCT03061214 | SUSTAIN CHINA MRCT | Patients with type 2 diabetes, taking metformin | Sitagliptin | 40 | 0.5 mg Semaglutide | 1.4 | 2.9 |
| | | | | | 1.0 mg Semaglutide | 1.7 | 4.2 |
| | | | | | Sitagliptin | 0.9 | 0.4 |
| NCT02207374 | SUSTAIN Japan | Japanese type 2 diabetes patients on stable oral antidiabetic medication | Oral antidiabetic (OAD) | 56 | 0.5 mg Semaglutide | 1.7 | 1.4 |
| | | | | | 1.0 mg Semaglutide | 2.0 | 3.2 |
| | | | | | OAD | 0.7 | -0.4 (weight gain) |
| NCT02254291 | SUSTAIN Japan, sitagliptin | Japanese patients with type 2 diabetes treated with lifestyle management or monotherapy | Sitagliptin | 30 | 0.5 mg Semaglutide | 1.9 | 2.2 |
| | | | | | 1.0 mg Semaglutide | 2.2 | 3.9 |
| | | | | | 100mg Sitagliptin | 0.7 | 0.4 |



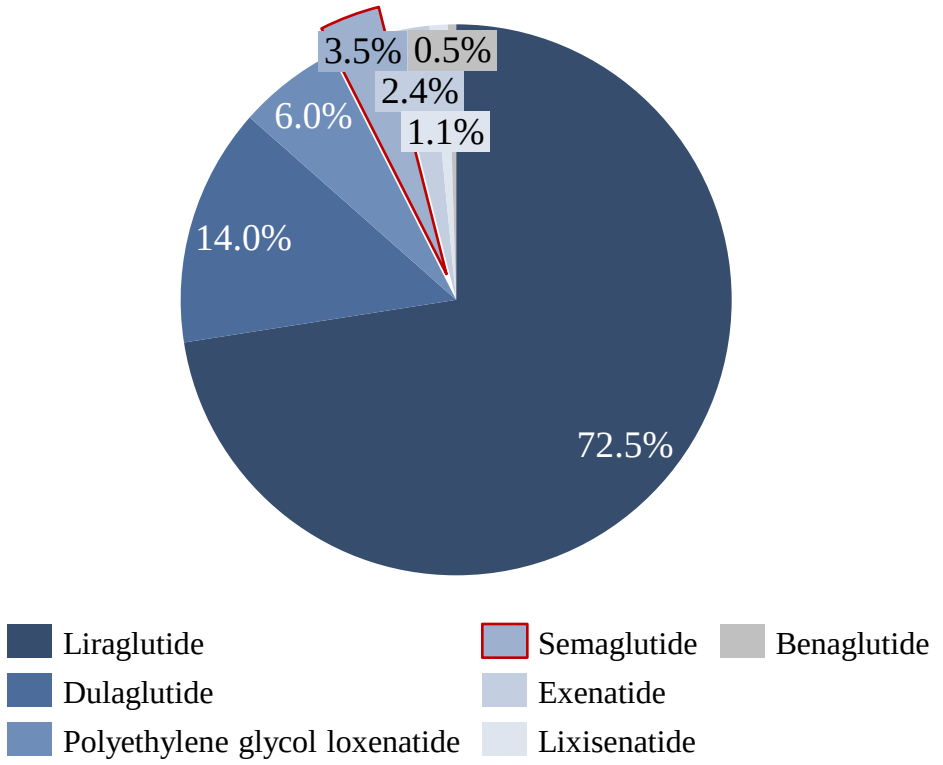
Note: MACE = cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke

Source：The Lancet Diabetes & Endocrinology; Cardiovasc Diabetol; China Insights Consultancy

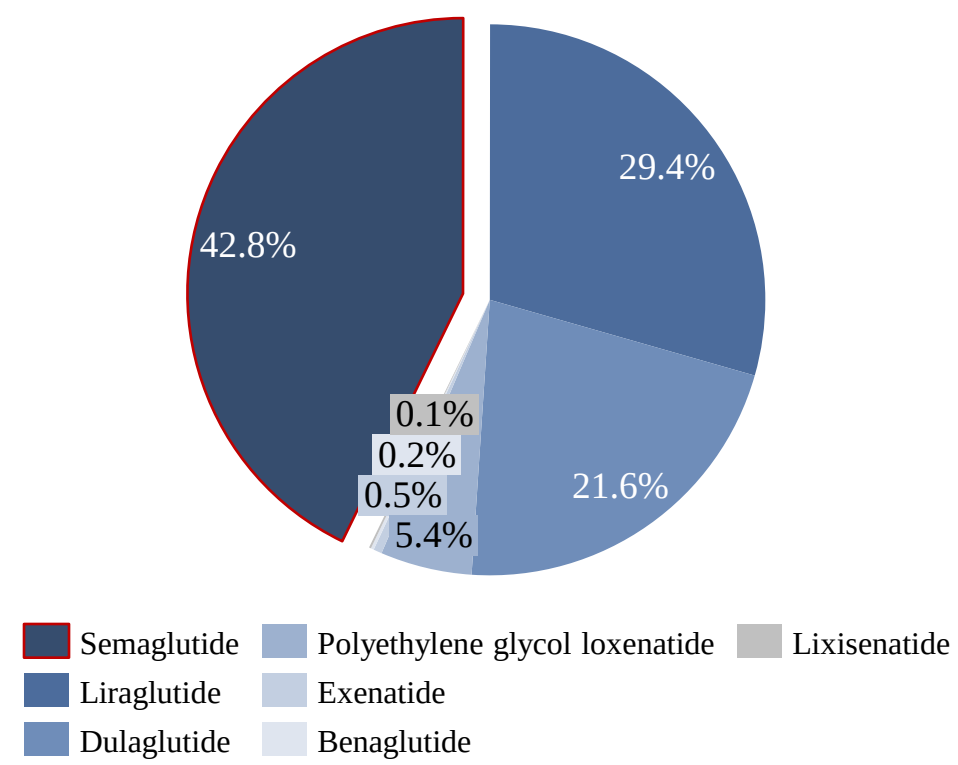
# Since its initial NMPA approval in April 2021, Semaglutide's market share increased from 3.5% in 2021 to 42.8% in 2022 in China T2DM GLP-1 Drug Market



**Competitive Landscape of the T2DM GLP-1 Drug Market in China, by generic drug name, 2021**




**Competitive Landscape of the T2DM GLP-1 Drug Market in China, by generic drug name, 2022**

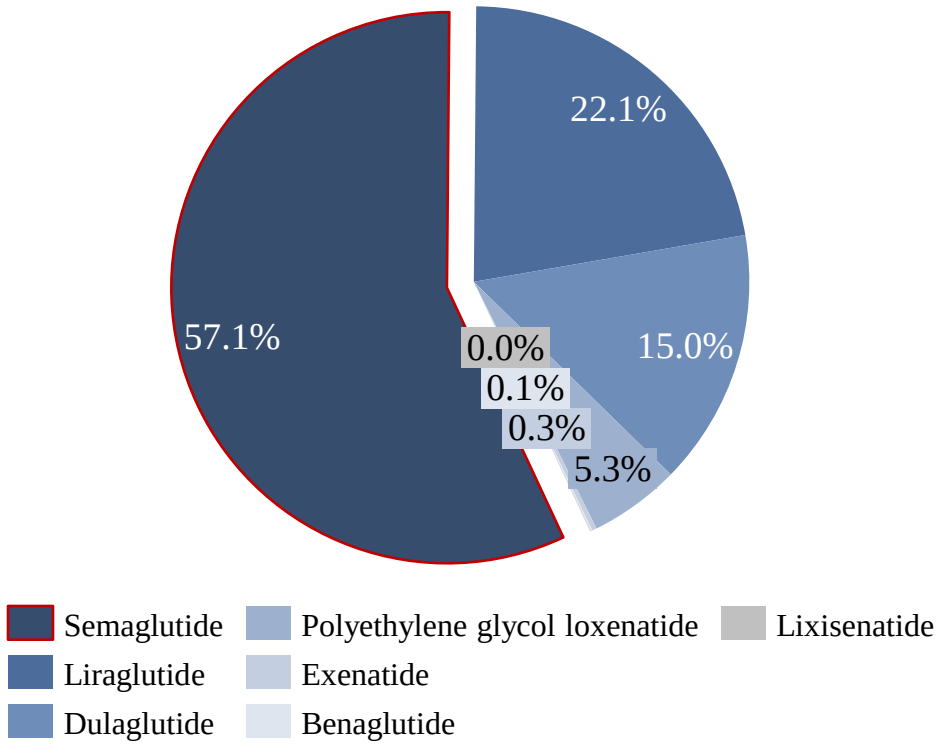



- In addition to domestic T2DM drug manufactures, we also compete with multinational pharmaceutical companies such as Novo Nordisk, Eli Lilly, Sanofi, and AstraZeneca, and the T2DM drugs market in China is currently undergoing significant consolidation.

# Competitive Landscape of the T2DM GLP-1 Drug Market in China, by generic drug name, 2023



**Competitive Landscape of the T2DM GLP-1 Drug Market in China, by generic drug name, 2023**



# As of the LPD, there are 240 clinical pipelines in China targeting GLP-1R for T2DM patients, of which 45 drugs are currently in phase III (1/4)



**Pipelines of GLP-1RA for T2DM, CDE-registered, phase III, as of the LPD**

| Drug Name | MoA | Company | Indications | Phase | First Posted Date | Trial Number |
|---|---|---|---|---|---|---|
| rExenatide-4 | GLP1R | CSPC Zhongqi<br>石药集团中奇制药技术（石家庄）有限公司 | T2DM | III | 2017-11-27 | CTR20170495 |
| Semaglutide | GLP1R | Novo Nordisk<br>诺和诺德 | T2DM with peripheral artery disease intermittent claudication | III | 2021-03-08 | CTR20210420 |
| | | | T2DM | III | 2019-12-31 | CTR20192079 |
| Tirzepatide | GLP1R; GIPR | Eli Lilly<br>礼来 | T2DM | III | 2023-07-05 | CTR20232036 |
| | | | T2DM; Glucose metabolism disorders; Endocrine system diseases | III | 2023-01-13 | CTR20230122 |
| | | | T2DM | III | 2022-12-05 | CTR20223054 |
| | | | T2DM; T2DM with MACE | III | 2020-09-09 | CTR20200498 |
| Liraglutide biosimilar | GLP1R | Beijing SL; Chongqing Punuowei<br>北京双鹭药业股份有限公司;<br>重庆浦诺维生物科技有限公司 | T2DM poorly controlled with Metformin | III | 2021-05-20 | CTR20211086 |
| Dulaglutide(LY05008) | GLP1R | Shandong Boan<br>山东博安生物技术股份有限公司 | T2DM | III | 2022-07-25 | CTR20221721 |

Imported products  Domestic products

*Note: GLP-1-Fc = glucagon like peptide-1/IgG-Fc fusion protein*

Source: CDE; China Insights Consultancy

# As of the LPD, there are 240 clinical pipelines in China targeting GLP-1R for T2DM patients, of which 45 drugs are currently in phase III (2/4)



**Pipelines of GLP-1RA for T2DM, CDE-registered, phase III, as of the LPD**

| Drug Name | MoA | Company | Indications | Phase | First Posted Date | Trial Number |
|---|---|---|---|---|---|---|
| Glutazumab(GMA102) | GLP1R; PRKAB1 | Hongyun Huaning 鸿运华宁（杭州）生物医药有限公司 | T2DM | III | 2022-10-11 | CTR20222558 |
| Glutazumab | GLP1R | | T2DM | III | 2021-07-30 | CTR20211661 |
| Long-acting Recombinant Glucagon-like Peptide-1 | GLP1R | Beijing SL 北京双鹭药业股份有限公司 | T2DM for adult | III | 2023-03-23 | CTR20230850 |
| Ecnoglutide(XW003) | GLP1R | Hangzhou Xianweida 杭州先为达生物科技有限公司 | T2DM | III | 2022-12-23 | CTR20223156 |
| | | | T2DM | III | 2022-12-12 | CTR20223157 |
| Dulaglutide biosimilar | GLP1R | Beijing Lepu 北京乐普医药科技有限公司 | T2DM | III | 2023-01-29 | CTR20230029 |
| Semaglutide | GLP1R | Qilu Pharmaceutical 齐鲁制药有限公司 | T2DM for adult | III | 2023-07-13 | CTR20230841 |
| Mazdutide(IBI362) | GLP1R; GCGR | Innovent Biologics（HK）Limited; Patheon Italia S.P.A.; 信达生物制药（苏州）有限公司 | T2DM; obesity | III | 2023-12-26 | CTR20234187 |
| | | | T2DM | III | 2022-11-10 | CTR20222740 |
| | | | T2DM | III | 2022-11-04 | CTR20222875 |
| Semaglutide | GLP1R | Chia Tai-Tianqing 正大天晴药业集团股份有限公司 | T2DM | III | 2024-01-12 | CTR20240069 |

Imported products  Domestic products

*Note: GLP-1-Fc = glucagon like peptide-1/IgG-Fc fusion protein*

Source: CDE; China Insights Consultancy

# As of the LPD, there are 240 clinical pipelines in China targeting GLP-1R for T2DM patients, of which 45 drugs are currently in phase III (3/4)



**Pipelines of GLP-1RA for T2DM, CDE-registered, phase III, as of the LPD**

| Drug Name | MoA | Company | Indications | Phase | First Posted Date | Trial Number |
|---|---|---|---|---|---|---|
| Semaglutide | GLP1R | Chongqing Paijin; Zhongmei Huadong<br>重庆派金; 中美华东 | T2DM for adult | III | 2023-08-02 | CTR20222558 |
| Orforglipron (LY3502970) | GLP1R | Eli Lilly<br>礼来 | T2DM | III | 2024-01-11 | CTR20240093 |
| | | | T2DM | III | 2023-12-29 | CTR20234303 |
| | | | T2DM | III | 2023-11-02 | CTR20233528 |
| | | | T2DM | III | 2023-10-10 | CTR20233100 |
| | | | T2DM and obesity | III | 2023-09-06 | CTR20232573 |
| Semaglutide | GLP1R | Livzon New North River<br>丽珠集团新北江制药股份有限公司 | T2DM for adult; T2DM with MACE | III | 2022-11-18 | CTR20222962 |
| Semaglutide | GLP1R | Federal Biotechnology<br>联邦生物 | T2DM for adult | III | 2023-02-15 | CTR20230379 |
| Semaglutide | GLP1R | Chongqing Chenan; Bovax<br>重庆宸安; 上海博唯 | T2DM | III | 2023-06-19 | CTR20231841 |
| Semaglutide | GLP1R | Qilu Pharmaceutical<br>齐鲁制药有限公司 | T2DM for adult | III | 2023-07-13 | CTR20230841 |
| Semaglutide | GLP1R | Huisheng<br>惠升生物制药股份有限公司 | T2DM | III | 2023-08-30 | CTR20232700 |
| Semaglutide | GLP1R | CSPC Zhongqi; Kangchuanglian<br>石药集团中奇制药技术（石家庄）有限公司; 北京抗创联生物制药技术研究有限公司 | T2DM | III | 2023-12-04 | CTR20233923 |

Imported products  Domestic products

*Note: GLP-1-Fc = glucagon like peptide-1/IgG-Fc fusion protein*

Source: CDE; China Insights Consultancy

# As of the LPD, there are 240 clinical pipelines in China targeting GLP-1R for T2DM patients, of which 45 drugs are currently in phase III (4/4)



**Pipelines of GLP-1RA for T2DM, CDE-registered, phase III, as of the LPD**

| Drug Name | MoA | Company | Indications | Phase | First Posted Date | Trial Number |
|---|---|---|---|---|---|---|
| Survodutide(BI 456906) | GLP1R; GCGR | Boehringer-Ingelheim 勃林格殷格翰(中国)投资有限公司 | Obesity with T2DM | III | 2023-12-15 | CTR20234043 |
| Cagrilintide | GLP1R; AMY3 | Novo Nordisk 诺和诺德 | T2DM | III | 2024-01-19 | CTR20240080 |
| | | | T2DM | III | 2024-05-23 | CTR20241583 |
| | | | T2DM | III | 2024-06-05 | CTR20241846 |
| Semaglutide | GLP1R | Chia Tai-Tianqing 正大天晴药业集团股份有限公司 | T2DM | III | 2024-01-12 | CTR20240069 |
| TG-103 | GLP1R | Chengdu Tianshizhen 成都天视珍生物技术有限公司 | T2DM | III | 2024-02-02 | CTR20240241 |
| | | | T2DM | III | 2024-02-26 | CTR20240429 |
| Semaglutide | GLP1R | Beijing Peptide Biomedical Technology 北京质肽生物医药科技有限公司 | T2DM | III | 2024-03-05 | CTR20240709 |
| Semaglutide | GLP1R | Brilliant Pharmaceuticals 成都倍特生物制药有限公司 | T2DM | III | 2024-03-11 | CTR20240787 |
| Exendin-4Fc fusion protein | GLP1R | Beijing Eastern Biotech 北京东方百泰生物科技 | T2DM | III | 2024-04-17 | CTR20240355 |
| | | | T2DM | III | 2024-04-25 | CTR20240359 |
| HR17031 | GLP1R | Jiangsu Hengrui 江苏恒瑞医药股份有限公司 | T2DM | III | 2024-04-28 | CTR20241529 |
| | | | T2DM | III | 2024-04-29 | CTR20241516 |

Imported products  Domestic products

*Note: GLP-1-Fc = glucagon like peptide-1/IgG-Fc fusion protein*

Source: CDE; China Insights Consultancy

# Barriers of China's T2DM drug industry mainly play emphasis on market competition and brand recognition, and high requirements in biotechnology techniques



## Industry Barriers

**Stringent regulatory requirements**

- Meeting regulatory standards for safety, efficacy, and quality is a technical challenge that requires rigorous testing and documentation throughout the T2DM drug development process.
- China **has specific clinical trial requirements**, and companies seeking to develop T2DM drugs must conduct trials to demonstrate the safety and efficacy of the products in the Chinese population.

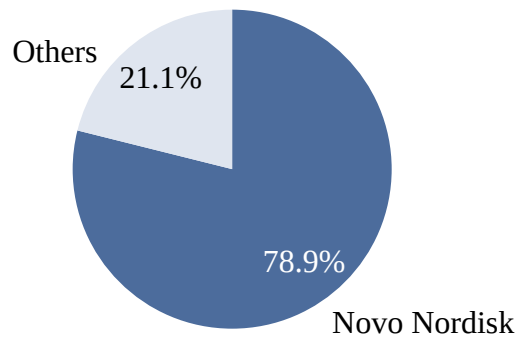
**The diversity of current T2DM drugs make the new entrants hard to stand out**

- The treatment pathway of T2DM in China follows the clinical guidelines, and the number of diabetic drugs under the Medical Insurance Catalog is increasing yearly. Some recommended existing medications may already have established market share, making it challenging for new products to gain traction.
- The competition in the generic drug market is extremely fierce. Under the policy of centralized procurement and evaluation of generic drugs, new entrants must differentiate their products and demonstrate superior efficacy or safety to compete effectively.

**Brand awareness is necessary for new entrants**

- The diabetes drug market in China is highly competitive, with numerous domestic and international pharmaceutical companies vying for market share. Entering this market requires companies to have **strong market positioning and brand promotion strategies** to differentiate themselves and attract the attention of patients and physicians.
- For instance, in the GLP-1 drug market, Novo Nordisk and Eli Lilly, with a strong presence, have taken the lead and most of the market. Currently, there are **more than 50** clinical trials targeting GLP-1R, and more than half of them are in Phase III.

**Market share of GLP-1 drugs in China, 2023**



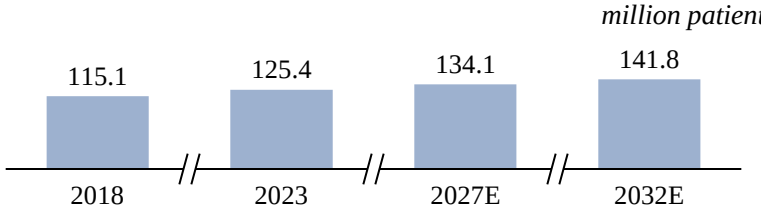

Source: NMPA; China Healthcare Security; China Insights Consultancy

# Growth drivers of China T2DM drug market include growing prevalence, favorable policies towards chronic disease management, improving affordability of T2DM medications and increasing availability of innovative T2DM medications

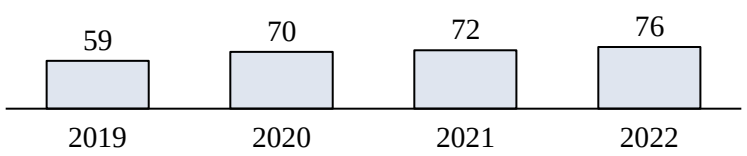


| Growth driver &future trends | |
|---|---|
| **Growing prevalence of T2DM in China** | • Rapid population aging, lifestyle changes, and increasing prevalence of overweight and obesity are all contributing to the rising prevalence of T2DM patients in China. The prevalence of T2DM in China is expected to grow from 123.2 million patients in 2022 to 141.8 million patients in 2032. |
| **Favorable policies towards chronic disease management** | • Numerous policies regarding disease awareness, disease management guidance and planning, payment and regulations has been issued to improve diabetes management in China. For example, the "14th Five-Year Plan" emphasized the implementation of comprehensive chronic disease prevention and control strategies and improve the capacity for comprehensive prevention and control of major chronic diseases including diabetes. Such high-level directional policy is expected to drive the screening and diagnosis of T2DM, thereby increasing the number of patients receiving regular T2DM treatment. |
| **Improving affordability of T2DM medications** | • The number of diabetes drugs under the National Medical Insurance Catalog has seen continuous increase in the past few years, from 59 diabetes drugs in 2019 to 76 diabetes drugs in 2022. It is expected that more diabetes drugs will be included in the catalog as more medications for T2DM treatment become available, leading to higher affordability of T2DM medications in China. |
| **Increasing number of targeted T2DM medications available in China** | • With research and development, targeted drugs such as GLP-1 receptor agonists, DPP-4 inhibitors and SGLT-2 inhibitors are addressing the unmet clinical needs in T2DM treatment.<br>• In addition, with core patents of these innovative medications reaching expiration date, more biosimilars are expected to be available in the China market in the coming years. It is expected that the T2DM drug market in China will continue to grow as more targeted drugs and biosimilars become available. |

**Prevalence of T2DM in China, 2018-2032E**




**Number of Diabetes Drugs under the Medical Insurance Catalog**






Source: NHC, IDF, NMPA; China Insights Consultancy

# Future trend of China T2DM drug market include “patient-centered” strategy and comprehensive benefits of T2DM management, and Pancreatic islet function restoration and alleviation of T2DM

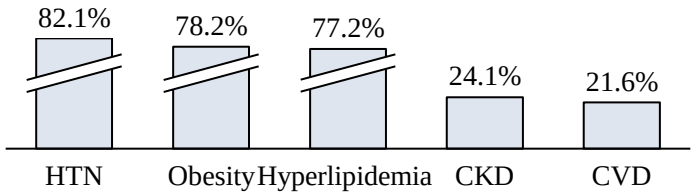


## Growth driver & Future trends

### “Patient-centered” strategy for the management of T2DM

- Unlike the past focus solely on the singular blood glucose indicator, HbA1c, there is now increased emphasis on complications and weight management.
- T2DM clinical guidelines highlight **comprehensive control objectives**, emphasizing the need for more **personalized treatment plans tailored to individual conditions** to enhance the overall therapeutic capacity for individual diseases.
- Therefore, **patient-centered diagnostic and therapeutic strategies** for T2DM are expected to become a future trend.

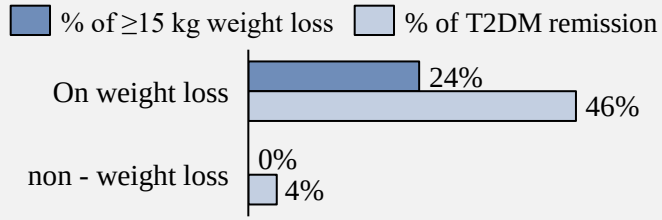
**Common co-prevalence of complications in T2DM patients**




### Comprehensive benefits of T2DM management paradigm

- Currently, diabetes treatment increasingly prioritizes comprehensive clinical benefits.
- Clinical guidelines stress the vital role of effectively managing diabetes-related risk factors in **reducing long-term complications**. Integrating **evidence-based pharmacotherapy and lifestyle interventions** are recommended to comprehensively address various risk factors such as cardiovascular health, kidney protection, obesity, hypertension, and high cholesterol.
- This approach **optimizes metabolic control and yields the exemplified clinical outcomes**. Therefore, evidence-based drug therapy and lifestyle interventions for enhancing comprehensive benefits are anticipated to be a future trend.

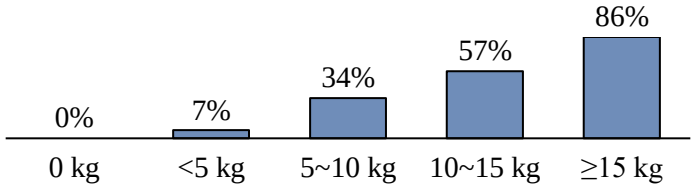
**Association between % of ≥15 kg weight loss and % of T2DM remission in 12 months**




### Pancreatic islet function restoration and alleviation of T2DM

- Clinical healthcare goals have shifted towards **improving the quality of life and achieving favorable prognoses for patients**, aiming to alleviate the societal burden and enhance socioeconomic benefits.
- GLP-1RAs have been shown to effectively reduce blood glucose levels without increasing the risk of hypoglycemia. Additionally, these medications demonstrate a protective effect on pancreatic β-cell function and have the ability to significantly reduce body weight.
- Hence, GLP-1RAs are anticipated to be the future trend of T2DM drug market for its premium long-term clinical efficacy.

**Association between kg of weight loss and % of T2DM remission in 12 months**






Source: Panminerva Medica; Current Medical Research and Opinion; Scientific Reports; Cardiovascular Diabetology; China Insights Consultancy

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# Obesity is an epidemic disease that threatens to inundate health care resources by increasing the incidence of cardiovascular diseases, diabetes, musculoskeletal disorders, and some cancers



## Introduction to obesity

- Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health. A body mass index (BMI) over 24 is considered overweight, and **over 28 is obese** in **China**.
- Obesity causes or exacerbates many health problems, both independently and in association with other diseases. In particular, it is associated with the development of **cardiovascular diseases, diabetes, musculoskeletal disorders, and some cancers.**

## Criteria for overweight/obesity diagnosis

| Category | Body Mass Index ($kg/m^2$) | | Waist Circumference | |
|---|---|---|---|---|
| | WHO | China | IDF | CDS |
| **Overweight** | 25.0~29.9 | 24.0~27.9 | - | - |
| **Obese** | ≥30.0 | ≥28.0 | - | - |
| **Concentric Obesity** | - | - | Male: ≥90.0 | Male: ≥90.0 |
| | | | Female: ≥80.0 | Female: ≥85.0 |

*Note: Concentric obesity refers to a type of obesity in which the fat deposits in the patient's body are centered on the heart and abdomen.*

## Risk factors

**Body weight is determined by an interaction between genetic, environmental and psychosocial factors acting through the physiological mediators of energy intake and expenditure.**

- **Genetics:** overweight and obesity can run in families.
- **Environmental factors:** social factors such as having a low socioeconomic status, built environment factors, exposure to chemicals known as osmogenes.
- **Lifestyle habits:** lack of physical activity, unhealthy eating patterns, not enough sleep, and high amounts of stress.
- **Age:** the risk of unhealthy weight gain increases as age.
- **Race or ethnicity:** overweight and obesity is highly prevalent in some racial and ethnic minority groups.

## Causes

**Obesity is a complex metabolic disorder with multiple causes. Globally, significant changes in dietary and physical activity patterns has led to the increasing prevalence of obesity.**

- Increasing intake of energy-dense foods that are high in fat and sugars
- Decreasing level of physical inactivity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization.

## Complications

**Raised BMI is associated with the development of certain noncommunicable, chronic diseases including cardiovascular diseases, diabetes, musculoskeletal disorders and some cancers.**

- Obesity is associated with an increased risk of developing cardiovascular disease(CVD), particularly heart failure and coronary heart disease.
- Obesity is a common risk factor that can lead to the development of prediabetes and T2DM.
- Obesity is highly associated with osteoarthritis, which is a disabling degenerative disease of the joints
- Obesity is a risk factor for developing endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon cancer.



Source: WHO, National Institutes of Health, IDF, China Diabetes Society; China Insights Consultancy

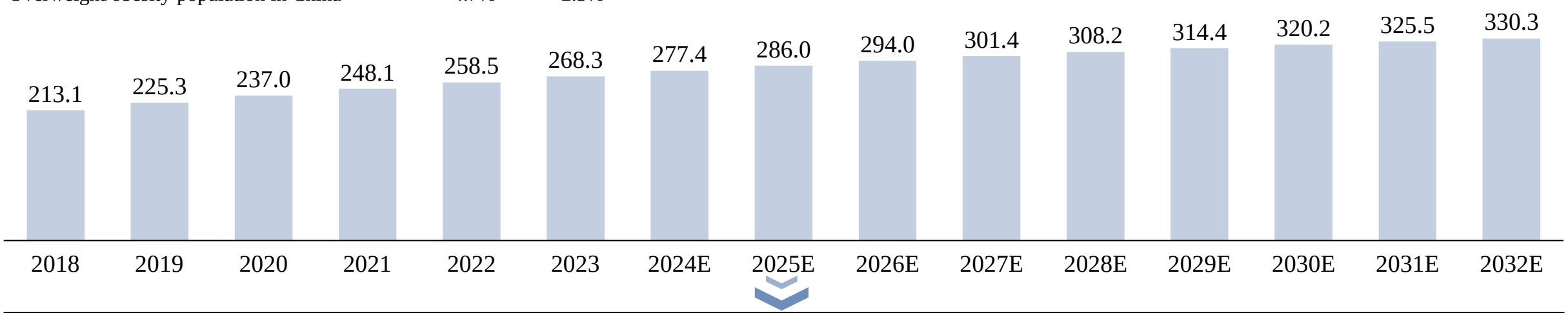
# The prevalence of obesity in China increased from 213.1 million patients in 2018 to 268.3 million patients in 2023 at the CAGR of 4.7%, and the overall prevalent population is expected to reach 330.3 million by 2032



**Overweight and obesity population in China, 2018-2032E**

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Overweight/obesity population in China | 4.7% | 2.3% |

*million patients*




**Key Analysis**

- Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health. A body mass index (BMI) over 24 is considered overweight, and over 28 is obese in China;
- The prevalence of obesity in China increased from 213.1 million patients in 2018 to 268.3 million patients in 2023 at the CAGR of 4.7%, and the overall prevalent population is expected to reach 330.3 million by 2032.
- Overweight/obesity is very harmful to the body, which is related to various chronic diseases, including diabetes, stroke, coronary artery disease, hypertension, respiratory diseases, obstructive sleep apnea, osteoarthritis and gallstones. For example, the prevalence rate of adult diabetes is as high as 11.2%, while overweight/obesity T2DM patients account for 58.3% of the total patients with diabetes. Among diabetes patients in China, overweight/obesity people account for 41.0% and 24.3%, respectively. Besides, the independent contribution (attributable risk percentage, PAR%) of overweight/obesity to the risk of hypertension in China is 19.4%. Therefore, increasing awareness of weight management is of great significance for a healthy lifestyle.



Source: Journal of Clinical Internal Medicine; Chinese Journal of Medical Frontiers; China Insights Consultancy

# Management of overweight and obesity primarily involves comprehensive lifestyle interventions, medication, and surgical treatments to mitigate associated health risks



## Treatment flow of obesity in China

**Overweight and obese patients**

- **Medical history investigation (disease history, family history, medication history)**
- **Dietary surveys, body composition analysis, lifestyle surveys**
- **Physical indicators, blood pressure, blood glucose, blood lipids, liver function, kidney function, etc.**
- **Energy consumption assessment (indirect energy measurement method, estimation method)**

Disease phase

| *Phase 0* | *Phase 1* | *Phase 2* | *Phase 3* |
|---|---|---|---|
| • Overweight, no related diseases or pre-related diseases | • Overweight or obese with one or more related preexisting diseases<br>• obese | Overweight or obese, with 1 or more related diseases | Overweight or obese with 1 or more severe related diseases/complications |
| • Comprehensive lifestyle interventions | • Comprehensive lifestyle interventions<br>• Medication | • Comprehensive lifestyle interventions<br>• Medication<br>• Surgery (BMI ≥ 35 kg/m2 or ≥ 32.5 kg/m2 with comorbidities) | |

**Continuous monitoring, monthly follow up, and health education for enhanced patient self-monitoring and management**

**Develop an individualized follow-up program for at least 3-6 months, if weight loss <5% within 3 months, reassess and adjust the program in a timely manner**

- Weight management aims for a **5% to 15% weight reduction or more**, improving metabolic health and reducing risks of obesity-related diseases, making medication use less necessary.
- **Lifestyle interventions**, including diet, exercise, and behavior changes, are the preferred treatment for overweight and obesity.
- If these interventions don't meet goals for patients with BMI≥24.0 kg/m2 and comorbidities or BMI≥28.0 kg/m2, **pharmacotherapy may be considered**.

*Note: 24 kg/m2 ≤ body mass index (BMI) <28 kg/m2 for overweight, BMI ≥28 kg/m2 for obesity;*

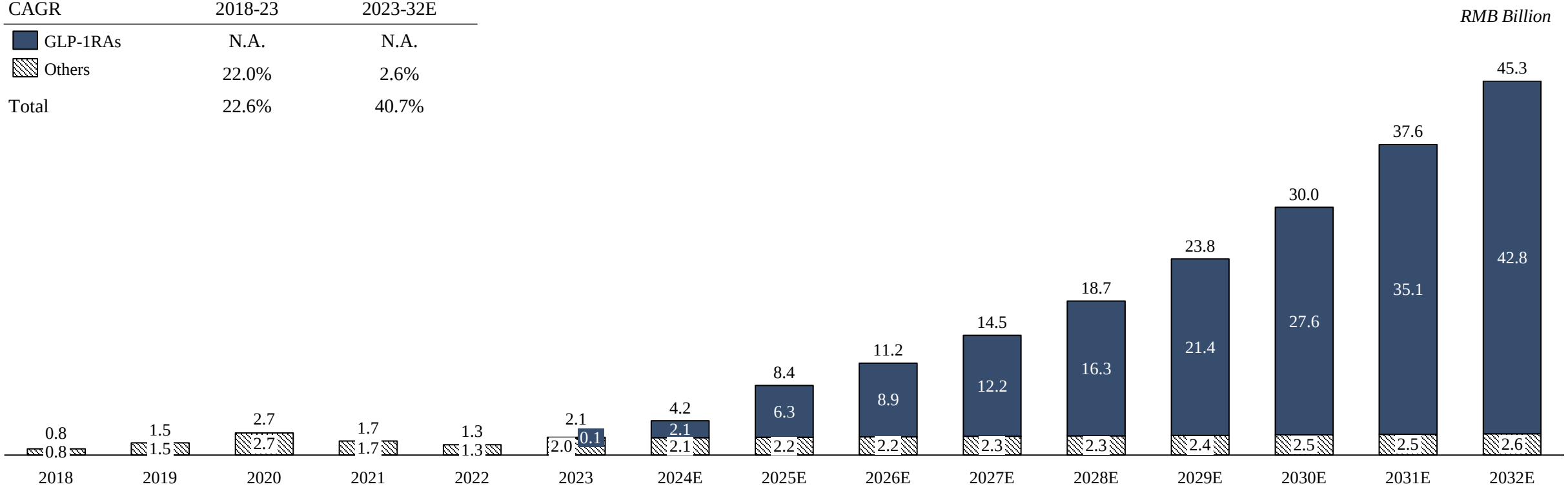
Source: Chinese Diabetes Society; China Insights Consultancy

# The market size of overweight/obesity drug in China is projected to increase from RMB[2.1] Billion in 2023 to RMB[45.3] Billion in 2032, with a CAGR of [40.7]%



## China overweight/obesity Drug Market Size, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| GLP-1RAs | N.A. | N.A. |
| Others | 22.0% | 2.6% |
| Total | 22.6% | 40.7% |




- There are primarily three currently used treatment methods for overweight and obesity: lifestyle interventions, medication, and surgery.
- Lifestyle interventions, encompassing diet, exercise, and behavioral adjustments, are the initial approach, focusing on diet control, exercise, and behavioral changes. This method is non-invasive and without side effects, promoting long-term metabolic health, but requires significant self-management and tends to show slow progress.
- The overweight and obesity drug market in China could potentially be limited by alternative prevention and treatment methods for such indications and medication treatment is used only for a portion of the total overweight and obesity population. See



Source: Menet; Expert interview

# There are 3 classes of drugs in terms of MoA approved for overweight/obesity management, with Liluping by Huadong Pharmaceutical being the first domestically approved GLP-1 product for weight loss management



**Approved overweight/obesity drugs by NMPA in China**

| Drug Name | Brand Name | MoA | Indication | Company | First Approval Date |
|---|---|---|---|---|---|
| Tirzepatide | Mounjaro | GLP-1R | Obesity/overweight | Eli Lilly | 2024/7/23 |
| Semaglutide | Wegovy | GLP-1R | Obesity/overweight | Novo Nordisk | 2024/06/18 |
| Beinaglutide | Feisumei | GLP-1R | Obesity/overweight | Shanghai Benemae Pharmaceutical | 2023/07/25 |
| Liraglutide | Liluping | GLP-1R | Obesity/overweight | Hangzhou Zhongmei Huadong Pharmaceutical/Our Company | 2023/06/30 |
| Mazindol | / | DAT; NET | Obesity/overweight | Jiangsu Disainuo Pharmaceutical | 2020/07/24 |
| Orlistat | / | LIPF | Obesity/overweight | 9 domestic manufacturers* | Since 2018 |
| Orlistat | Xenical | LIPF | Obesity/overweight | Cheplapharm Arzneimittel/ Roche | 2000/10/31 |

- *Note: include Shandong New Time Pharmaceutical, Zhongshan Wanhan Pharmaceuticals, Chongqing Pharscin Pharmaceutical, Zein Biotechnology, Zhejiang Hisun Pharmaceutical, Hangzhou Zhongmei Huadong Pharmaceutical, Argus(Hunan) Pharmaceutical, Hunan Dinuo Pharmaceutical, Hunan Zhengtai Jinhu Pharmaceutical.
- LIPF： Gastric lipase ; DAT: Dopamine transporter; NET: Norepinephrine transporter.

- As illustrated in the table, as of the Latest Practicable Date, there were 13 approved drugs under four drug names for the treatment of overweight and obesity in China. We compete with both domestic manufactures and multinational pharmaceutical companies such as Novo Nordisk, and Eli Lilly, and the overweight and obesity drugs market in China is currently undergoing significant consolidation.
- Medication is considered for patients who do not adequately respond to lifestyle interventions, typically recommended for those with a BMI of 24 or above with additional diseases, or a BMI of 28 or above.
- Surgical treatments are targeted at individuals with a BMI of 35 or above, or a BMI of 32.5 with severe complications. While surgery is effective in reducing weight, it carries certain risks and demands lifelong dietary management.
- We adjust the total overweight and obesity population in China by the drug treatment rate for overweight and obesity management and consider only the overweight and obesity population requiring medication intervention as the addressable patients for estimating the size of overweight and obesity drug market in China. See "— Metabolic Disease Drugs Market — Overweight and Obesity Drug Market — Size of overweight and obesity drug market in China."
- Specifically, the annual expenditures for Orlistat and Liraglutide, the two approved overweight and obesity drugs in China, are RBM1,000 to RMB1,500 and RMB4,000 to RMB5,000, respectively. And the average medication treatment duration for overweight and obesity is approximately three to four months.

Imported products  Domestic products



Source: NMPA; China Insights Consultancy

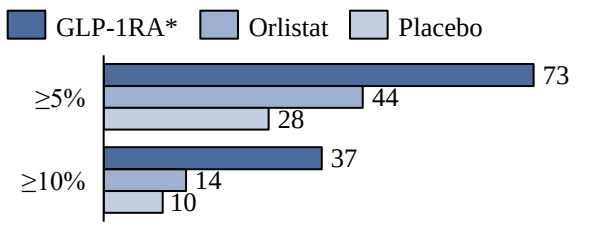
# There are only two classes of drugs approved for overweight/obesity management, with Liluping by Huadong Pharmaceutical being the first domestically approved GLP-1 product for weight loss management



**Approved overweight/obesity drug by NMPA in China, as of October 11th, 2023**

Refer to last page

**Percentage of patients achieving categorial weight loss at 1 year**




| Comparison of Clinical Efficacy | |
|---|---|
| Orlistat | GLP-1 RA |
| • Reversible inhibitor of gastrointestinal lipases | • Reduces appetite and food cravings |
| • Inhibits fat absorption | • Alters food preference and reward pathways |

| Comparison of clinical benefits of Liraglutide and Beinaglutide | | | | |
|---|---|---|---|---|
| Drug name | Weight loss | Renal benefit | Cardiovascular benefit | Metabolic benefit |
| Liraglutide | √ √ | √ | √ | √ |
| Beinaglutide | √ | N/A | N/A | Neutral |

**Key Analysis**

- In March 2023, Liluping received approval from the NMPA for the treatment of T2DM. In July 2023, Liluping received further approval for use in weight management among obese patients and is currently **the first and only liraglutide product approved for obesity treatment in China**.
- Liluping was also **the first GLP-1 product to be approved for obesity treatment in China**, followed by Feisumei, a Beinaglutide product approved later in the same month.

Note: * The observed group for GLP-1 RA was patients taken Liraglutide 3.0 mg.

Source: Advances in Therapy; Chinese Medical Frontier Journal; Chinese Journal of Health Management; China Insights Consultancy

# Numerous completed STEP trials investigating the effect of semaglutide in obese/overweight patients show preferable results in terms of bodyweight decrease



| Clinical Trial ID | Trial Name | Trial Population | Comparator Treatment | Results | | |
|---|---|---|---|---|---|---|
| | | | | Duration of Trial (Weeks) | Groups | Average Bodyweight Reduction % |
| NCT03548935 | STEP 1 | Obese or overweight people with related comorbidities, but not diabetes | Placebo | 68 | Semaglutide 2.4 mg | 14.9 |
| | | | | | Placebo | 2.4 |
| NCT03552757 | STEP 2 | Overweight or obese people with type 2 diabetes | Semaglutide 1.0 mg and placebo | 68 | Semaglutide 2.4 mg | 9.64 |
| | | | | | Semaglutide 1.0 mg | 6.99 |
| | | | | | Placebo | 3.42 |
| NCT03611582 | STEP 3 | Overweight or obese people with related comorbidities, but not diabetes | Placebo | 68 | Semaglutide 2.4 mg | 16.0 |
| | | | | | Placebo | 5.7 |
| NCT03548987 | STEP 4 | Overweight or obese people with related comorbidities, but not diabetes | Placebo | 68 | Semaglutide 2.4 mg | 17.4 |
| | | | | | Placebo | 5.0 |
| NCT03693430 | STEP 5 | Obese or overweight people with related comorbidities, but not diabetes | Placebo | 104 | Semaglutide 2.4 mg | 15.2 |
| | | | | | Placebo | 2.6 |
| NCT03811574 | STEP 6 | Obese or overweight East Asian people with related comorbidities | Placebo | 68 | Semaglutide 2.4 mg | 13.2 |
| | | | | | Semaglutide 1.7 mg | 9.6 |
| | | | | | Placebo | 2.1 |



Source：The Lancet Diabetes & Endocrinology; Cardiovasc Diabetol; China Insights Consultancy

# As of the LPD, there are 80 clinical pipelines in China targeting GLP-1R for overweight and obesity patients, of which 15 drugs are currently in phase III (1/2)



**Pipelines of GLP-1RA for overweight and obesity , CDE-registered, phase III, as of the LPD**

| Drug Name | MoA | Company | Indications | Phase | First Posted Date | Trial Number |
|---|---|---|---|---|---|---|
| Tirzepatide | GLP1R; GIPR | Eli Lilly 礼来 | Overweight/obesity | III | 2022-12-05 | CTR20223054 |
| | | | OSA; Obesity | III | 2022-07-04 | CTR20221560 |
| | | | Obesity with ejaculatory fraction preserving heart failure | III | 2023-08-30 | CTR20211863 |
| | | | Overweight/obesity | III | 2020-04-27 | CTR20200672 |
| Liraglutide | GLP1R | 江苏万邦生化医药集团有限责任公司 | Overweight/obesity | III | 2020-08-10 | CTR20201449 |
| Ecnoglutide(XW003) | GLP1R | Hangzhou Xianweida 杭州先为达生物科技有限公司 | Weight management for overweight/obesity patients | III | 2023-03-15 | CTR20230745 |
| Cagrilintide | GLP1R; AMY3 | Novo Nordisk 诺和诺德 | Overweight/obesity | III | 2023-07-05 | CTR20232030 |
| Orforglipron(LY3502970) | GLP1R | Eli Lilly 礼来 | Overweight/obesity with T2DM | III | 2023-09-06 | CTR20232573 |
| | | | Overweight/obesity with related comorbidities | III | 2023-08-11 | CTR20232459 |

Imported products  Domestic products

*Note: GLP-1-Fc = glucagon like peptide-1/IgG-Fc fusion protein*

Source: CDE; China Insights Consultancy

# As of the LPD, there are 80 clinical pipelines in China targeting GLP-1R for overweight and obesity patients, of which 15 drugs are currently in phase III (2/2)



**Pipelines of GLP-1RA for overweight and obesity , CDE-registered, phase III, as of the LPD**

| Drug Name | MoA | Company | Indications | Phase | First Posted Date | Trial Number |
|---|---|---|---|---|---|---|
| Mazdutide(IBI362) | GLP1R; GCGR | Innovent Biologics（HK）Limited; Patheon Italia S.P.A.; 信达生物制药（苏州）有限公司 | Overweight/obesity; T2DM | III | 2023-12-26 | CTR20234187 |
| | | | Overweight/obesity | III | 2023-12-01 | CTR20233902 |
| Survodutide(BI 456906) | GLP1R; GCGR | Boehringer-Ingelheim 勃林格殷格翰(中国)投资有限公司 | Overweight/obesity | III | 2024-01-11 | CTR20234328 |
| | | | Overweight/obesity with T2DM | III | 2023-12-15 | CTR20234043 |
| | | | Overweight/obesity | III | 2023-12-14 | CTR20234021 |
| | | | Overweight/obesity without T2DM | III | 2023-12-14 | CTR20234044 |

Imported products  Domestic products

*Note: GLP-1-Fc = glucagon like peptide-1/IgG-Fc fusion protein*

Source: CDE; China Insights Consultancy

# Major entry barriers of the obesity drug market in China include safety concerns about medications and intense competition in current market

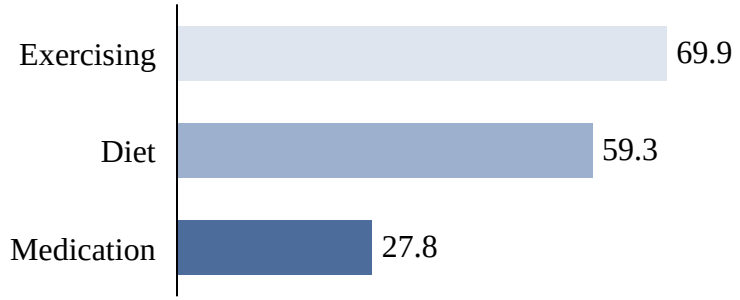


## Industry Barriers

**Safety concerns and side effects**

- The use of medication for weight loss is **not the mainstream** approach to losing weight. Based on a questionnaire survey conducted in 2022, 69.9% of the population chose exercising to lose weight because most people thought exercising was healthier than taking medications.
- Safety is one of the biggest concerns that people take into consideration. Over the past 40 years, 6 weight-loss drugs have been **withdrawn** from the market due to safety concerns. Studies indicate that people using GLP-1RA have a higher risk of pancreatitis, intestinal obstruction, and stomach paralysis. Negative perceptions and reports about the safety profile of obesity drugs can significantly impact market acceptance.

**Proportion of main weight loss methods among Chinese netizens in 2022, percentage (%)**




**Intense competition in obesity drug market**

- With the successful development of weight-loss drugs by international pharmaceutical companies such as Novo Nordisk, more and more domestic companies submitted clinical trail applications to start developing novel agents targeting obesity. By the end of October 2023, there are 26 GLP-1 agonists in clinical pipelines in China, and 7 of them are in clinical Phase III.
- New obesity drugs must compete with the new coming drugs or the current medications in the market, requiring the products to demonstrate superior efficacy, fewer side effects, or other unique selling points. However, establishing widespread brand recognition is challenging for new entrants in the short term, and gaining broad recognition from medical institutions such as hospitals is also not easy.



Source: NMPA; China Healthcare Security; China Insights Consultancy

# Drivers and future trends in China's obesity drug market include the increasing number of obesity patients, surging clinical needs due to improved social education, and GLP-1RA's widely recognized efficacy in weight management

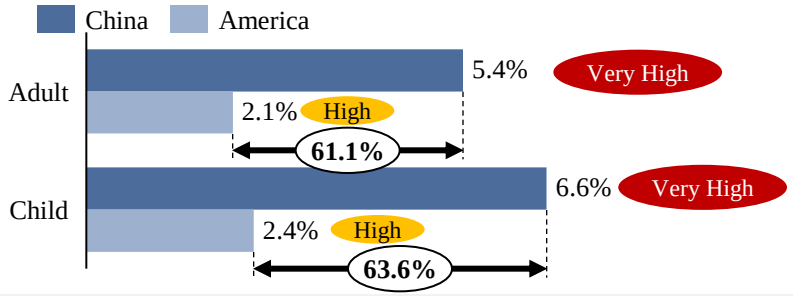


## Drivers & Future trends

### Increasing number of overweight/obesity patients

- Urbanization and economic growth in China have increased people's disposable income and food choices. However, the modern lifestyle characterized **by unhealthy dietary habits and reduced physical activity** has led to an **increasing prevalence of obesity** and may also result in earlier onset of obesity-related complications, placing a sustained burden on the Chinese healthcare system.
- As a result, the number of obese individuals in China continues to rise, accompanied by an **increasing demand for weight management,** which has led to the continuous expansion of the market for overweight and obesity medications.

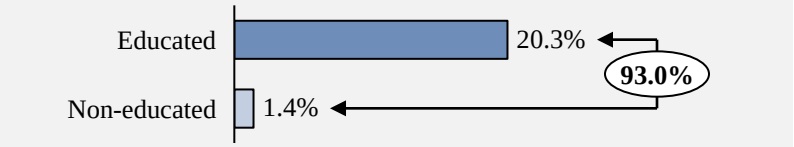
**Comparison of annual increase in obesity in China and the U.S.**




### Social education leads to surging clinical needs

- **Social education has heightened public health awareness**, shifting the focus on obesity from mere aesthetic considerations to issues closely linked to health. The widespread understanding of the comprehensive risks associated with overweight and obesity has **reinforced the inclination of residents to seek medical attention**, thereby further **increasing healthcare utilization and treatment rates**, driving the continuous expansion of the weight management and obesity medication market.

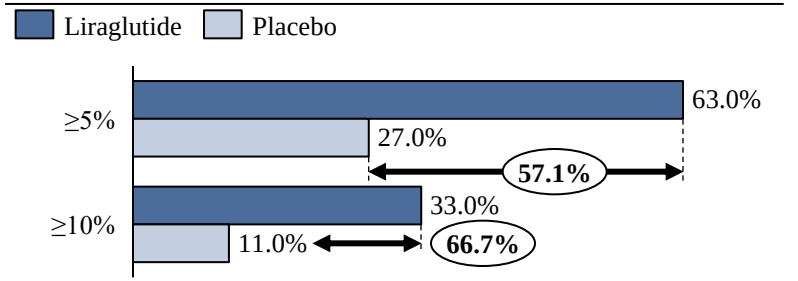
**Comparison of clinical visits between parents with and without education**




### Widely recognized weight loss efficacy and safety of GLP-1RA

- The first GLP-1 was approved for treating overweight and obesity in China in July 2023, demonstrating **significant weight reduction effects and safety**. The increasingly severe obesity issue in China has fostered the development of the GLP-1 drug market, offering a diverse range of GLP-1 medications for effective weight management and obesity treatment.
- Both **domestic and international pharmaceutical companies are actively R&D** GLP-1RA drugs, providing more treatment options for obese patients. The popularity of GLP-1RA among pharmaceutical companies further solidifies its position as the **preferred long-term treatment for overweight/obesity**.

**Percentage of patients achieving categorial weight loss at 1 year**






Source: Advances in Therapy; World Obesity Atlas; Chinese Journal of Child Health Care; Chinese Medical Information Guide; China Insights Consultancy

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# Semaglutide is a long-acting GLP-1RA demonstrating superior efficacy in effective blood glucose and body weight control, with lower risks of cardiovascular diseases



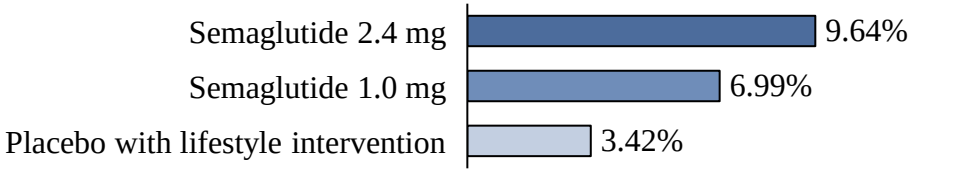
**Introduction of Semaglutide**

- Semaglutide is a long-acting GLP-1 receptor agonist drug originally developed by Novo Nordisk; it is sold under the brand name Ozempic and Rybelsus for T2DM indication and WEGOVY for obesity indication globally;
- Semaglutide demonstrated high efficacy in blood glucose control and body weight control in clinical trials across the world; with total sales of USD[10.9] billion, semaglutide is among the Top 10 best-selling drug by generic name globally in 2022;
- Due to the popularity and surge in prescription, semaglutide is facing a global shortage; as of August 2023, semaglutide (Ozempic) injection and semaglude (WEGOVY) injection are still on FDA's Drug Shortage List.
- On December 3, 2021, Semaglutide was included in the "National Basic Medical Insurance, Work Injury Insurance, and Maternity Insurance Drug Catalog (2021)." The price for a 1.5ml pen of Semaglutide is RMB478.8 yuan, and a 3ml pen is priced at RMB813.96.

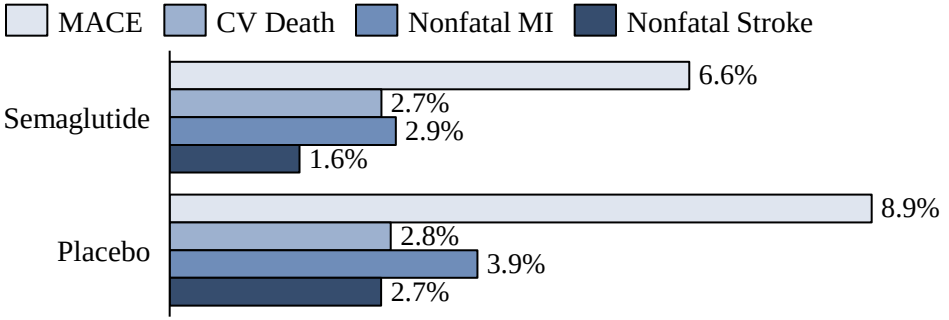

**Advantages of Semaglutide**

| | |
|---|---|
| Effective blood glucose control | Multiple trials show that semaglutide is superior to other T2DM drugs, such as sitagliptin, in improving patients' glycemic level (compared with patients' baseline HbA1c). |
| Effective body weight control | Trials also shows that semaglutide is effective in reducing bodyweight compared with other T2DM drugs (compared with patients' baseline body weight). |
| Low risks of cardiovascular diseases | Multiple trials show that subjects with T2DM at high CV risk treated with semaglutide had a relatively lower risk of the primary composite outcome of the first major cardiovascular events (MACE) compared to those only receiving placebos. This indicates that semaglutide can significantly lower the risk of MACE, especially in cardiovascular diseases. |

**Weight reduction at week 68 with semaglutide (2.4 mg and 1.0 mg) compared with that of the placebo**




**% of MACE events treated with semaglutide and placebo**






Source: FDA, The Lancet Diabetes & Endocrinology; Cardiovasc Diabetol; China Insights Consultancy

# As of November 2nd, 5 clinical trials of semaglutide for conditions other than T2DM or obesity reported exceptional efficacy. The FLOW trial was terminated in advance due to semaglutide's outstanding interim results



| Indication | Trial Number | Conditions | Study design | Results | |
|---|---|---|---|---|---|
| | | | | Efficacy | Safety |
| Metabolic | NCT02970942 | Hepatobiliary Disorders; NASH | Semaglutide 0.1mg (n=80), 0.2mg (n=78), 0.4mg (n=82) vs. Placebo (n=80) | • The percentage of patients achieved NASH resolution with no worsening of fibrosis was 40%, 36% and 59% respectively in the semaglutide groups, and 17% in placebo group | • The incidence of nausea, constipation, and vomiting was higher in semaglutide group versus placebo (42% vs. 11%; 22% vs. 12%; 15% vs. 12%) |
| | NCT03548935 | Metabolism and Nutriton disorder | Semaglutide 2.4mg (n=1306) vs. Placebo (n=655) | • 50.5% participants among semaglutide group achieved more than 15% weight loss versus 4.9% among placebo group<br>• 75.9% among semaglutide group versus 52.7% participants among placebo group had a change in Leptin (ng/ml) | • The serious adverse events happened about 9.8% in the semaglutide group and 6.45% among placebo group |
| Non-metabolic | NCT03819153 (FLOW) | T2DM with chronic kidney disease (CKD) | Start with 0.25mg, increased to 0.5mg after 4 weeks, and then increased to 1.0mg at 8 weeks | • Interim results of the study indicate that Semaglutide has significant clinical efficacy in kidney diseases.<br>• The study has been terminated in advance due to its outstanding interim outcomes.<br>• Detailed clinical results are still blind to the company, and was expected to be revealed to the public in the early 2024. | |
| | NCT04788511 | HFpEF; T2DM | Semaglutide (n=263) vs. Placebo (n=266) | • At week 52, body weight reduction <5% in 33 (13.4%), 5-10% in 51 (20.7%), 10-15% in 54 (22.0%), 15-20% in 50 (20.3%), and >20% in 58 (23.6%)<br>• The improvements in HF symptoms were associated with body weight reduction. Each 10% reduction in body weight with semaglutide was associated with a 6.4-point increase in KCCQ-CSS and a 14.4-m increase in 6MWD | • There were fewer serious adverse among semaglutide group versus placebo (32.2% vs. 53.7%) |
| | NCT01720446 | T2DM with MACE | Semaglutide 0.5mg (n=826), 1.0mg (n=822) vs. Placebo 0.5mg (n=824), 1.0mg (n=825) | • At week 109, the percentage of subjects experiencing first event of MACE was less in semaglutide group than in placebo group (6.6% vs. 8.9%) | • The serious adverse events are lower among semaglutide group (34.99% and 33.58%) versus among placebo group (39.93% and 36.12%) |



Note: HFpEF = Heart failure with preserved ejection fraction; KCCQ-CSS = Questionnaire-Clinical-Summary Score; 6WMD = 6-minute walk distance MACE = Major adverse cardiovascular events; NASH = Non-alcoholic steatohepatitis

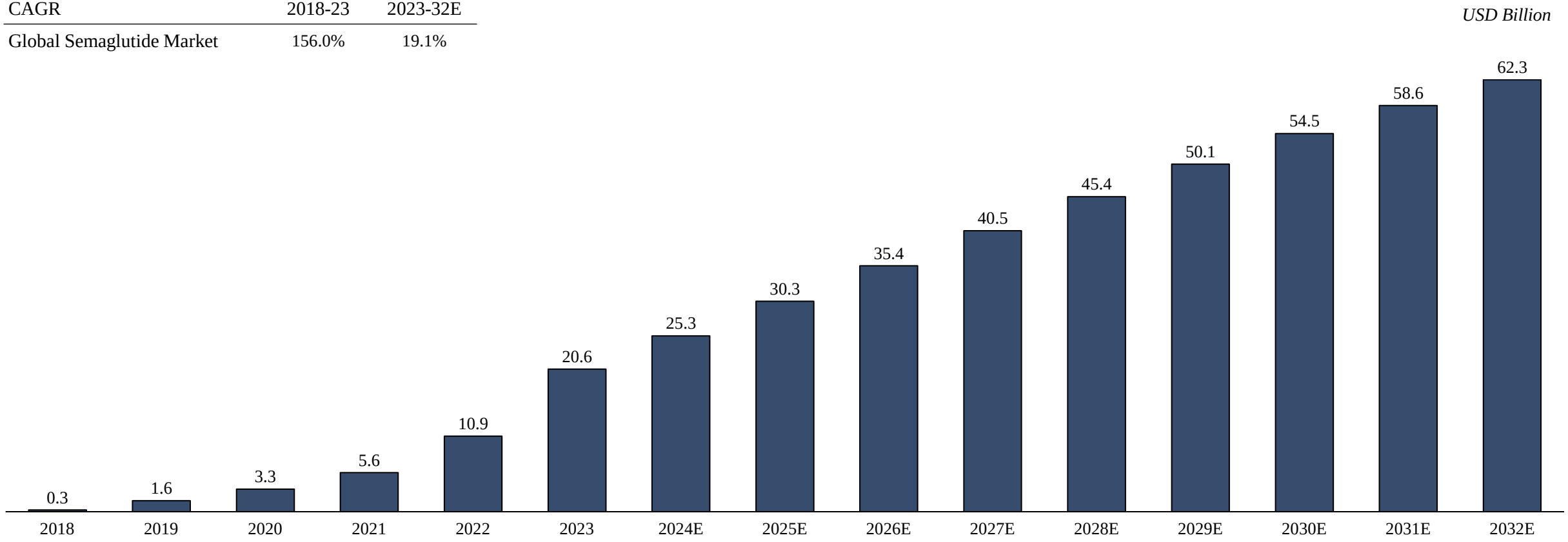
Source: ClinicalTrials.gov ; The New England Journal of Medicine; Nephrology Dialysis Transplantation; China Insights Consultancy

# The market size of global semaglutide market is expected to increase from USD[20.6] billion in 2023 to USD[62.3] billion in 2032 at the CAGR of [19.1]%



## Global Semaglutide Market Size, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Global Semaglutide Market | 156.0% | 19.1% |





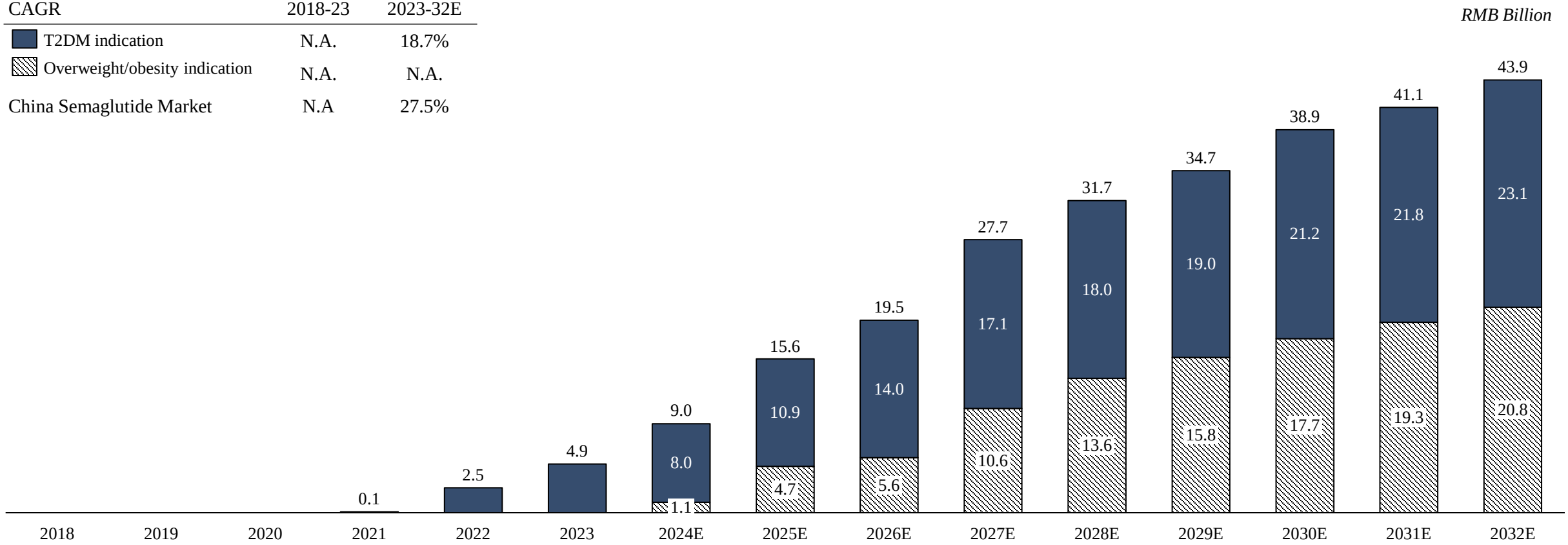

Source: China Insights Consultancy

# The market size of semaglutide in China is expected to increase from RMB[4.9] billion in 2023 to RMB[43.9] billion in 2032 at the CAGR of [27.5]%



## China Semaglutide Market Size, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| T2DM indication | N.A. | 18.7% |
| Overweight/obesity indication | N.A. | N.A. |
| China Semaglutide Market | N.A | 27.5% |





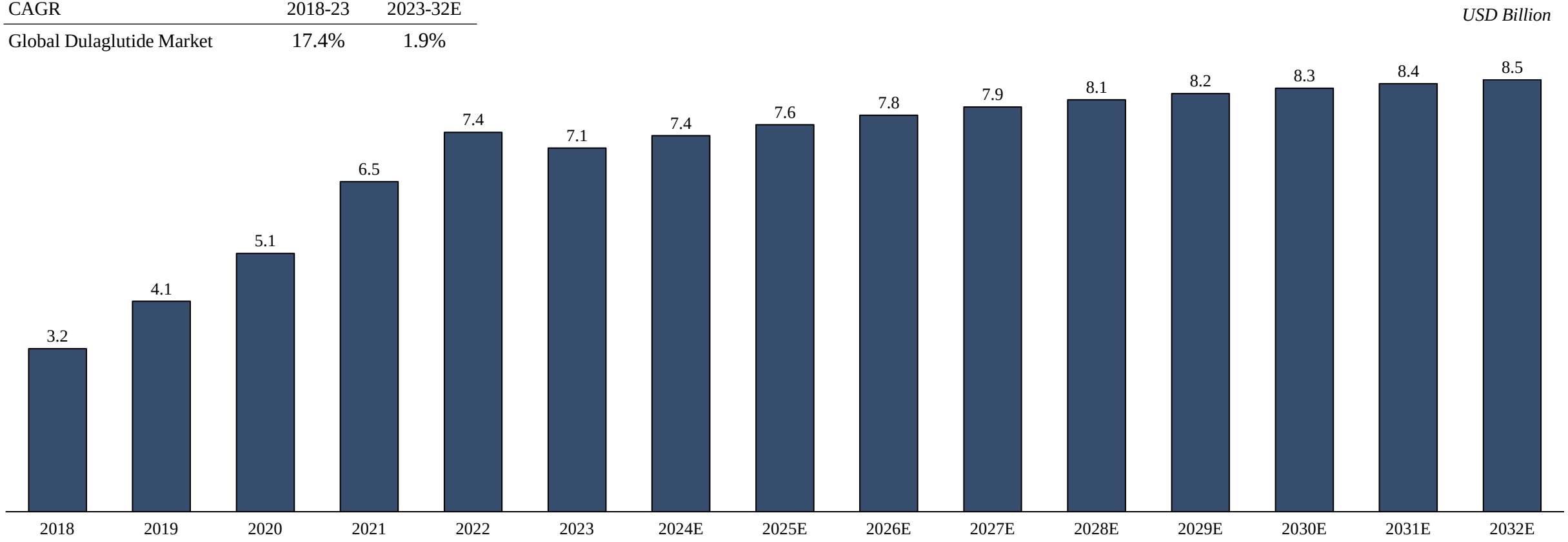

Source: Menet; Expert interview

# The market size of global dulaglutide market is expected to increase from USD[7.1] billion in 2023 to USD[8.5] billion in 2032 at the CAGR of [1.9]%



## Global Dulaglutide Market Size, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Global Dulaglutide Market | 17.4% | 1.9% |






Source: China Insights Consultancy

# As of LDP, there are 13 Semaglutide pipelines in ongoing phase III clinical trials for T2DM patients and 1 approved product.(1/2)



**Approved product/ pipelines of Semaglutide for T2DM, CDE-registered, as of LPD**

| Drug Name | MoA | Company | Manufacturing technique (生产工艺) | Indications | Phase | First Posted Date | Administration | Estimated Approval Year |
|---|---|---|---|---|---|---|---|---|
| Semaglutide | GLP-1R | Novo Nordisk | Fermentation | T2DM | Marketed | 2021/4/27 | p.o.<br>s.c. | / |
| Semaglutide | GLP-1R | Our Company | Fermentation | T2DM | III* | 2022/06/06 | s.c. | 2025 |
| Semaglutide | GLP-1R | Livzon Pharmaceutical Group | Fermentation | T2DM | III | 2022/11/18 | s.c. | 2025 |
| Semaglutide | GLP-1R | Zhuhai United Laboratories | Fermentation | T2DM | III | 2023/02/15 | s.c. | 2026 |
| Semaglutide | GLP-1R | Chongqing Chenan Biopharmaceutical/ Shanghai Bovax Biotechnology | Fermentation | T2DM | III | 2023/06/19 | s.c. | 2026 |
| Semaglutide | GLP-1R | QILU Pharmaceutical | Chemical synthesis | T2DM | III | 2023/07/13 | s.c. | 2026 |
| Semaglutide | GLP-1R | Chongqing Peg-Bio Biopharm /Hangzhou Zhongmei Huadong Pharmaceutical | Fermentation | T2DM | III | 2023/08/02 | s.c. | 2026 |
| Semaglutide | GLP-1R | Huisheng Biopharmaceutical | Fermentation | T2DM | III | 2023/08/30 | s.c. | 2026 |
| Semaglutide | GLP-1R | CSPC Pharmaceutical Group | Chemical synthesis | T2DM | III | 2023/12/04 | s.c. | 2027 |
| Semaglutide | GLP-1R | Chia Tai Tianqing Pharmaceutical Group | Fermentation | T2DM | III | 2024/1/12 | s.c. | 2027 |
| Semaglutide | GLP-1R | Beijing Peptide Biomedical Technology | Fermentation | T2DM | III | 2024/03/05 | s.c. | 2027 |
| Semaglutide | GLP-1R | Brilliant Pharmaceuticals | Fermentation | T2DM | III | 2024/03/11 | s.c. | 2027 |

Source: * our company has completed the phase III clinical trial.

Source: CDE; China Insights Consultancy

# As of LDP, there are 13 Semaglutide pipelines in ongoing phase III clinical trials for T2DM patients and 1 approved product.(2/2)



**Approved product/ pipelines of Semaglutide for T2DM, CDE-registered, as of LPD**

| Drug Name | MoA | Company | Manufacturing technique (生产工艺) | Indications | Phase | First Posted Date | Administration | Estimated Approval Year |
|---|---|---|---|---|---|---|---|---|
| Semaglutide | GLP-1R | CR Doubal-crane | Fermentation | T2DM | III | 2024/7/18 | s.c. | 2028 |
| Semaglutide | GLP-1R | Hybio Pharmaceutical | Fermentation | T2DM | III | 2024/9/5 | s.c. | 2028 |
| Semaglutide | GLP-1R | Wanbang Biopharmaceuticals | Fermentation | T2DM | III | 2024/9/12 | s.c. | 2028 |



Source: CDE; China Insights Consultancy

# As of LPD, there are 10 Semaglutide clinical pipelines in China for overweight/obesity patients



**Pipelines of Semaglutide for overweight/obesity , CDE-registered, as of LPD**

| Drug Name | MoA | Company | Indications | Phase | First Posted Date |
|---|---|---|---|---|---|
| Semaglutide | GLP-1R | Hangzhou Zhongmei Huadong Pharmaceutical | Overweight/obesity | IND approval | 2024/10/10 |
| Semaglutide | GLP-1R | Jilin Huisheng Biological Pharmaceutical | Overweight/obesity | IND approval | 2024/8/30 |
| Semaglutide | GLP-1R | Chia Tai Tianqing Pharmaceutical | Overweight/obesity | IND approval | 2024/6/24 |
| Semaglutide | GLP-1R | Thery Pharma | Overweight/obesity | IND approval | 2024/4/19 |
| Semaglutide | GLP-1R | Hybio Pharmaceutical | Overweight/obesity | IND approval | 2024/4/16 |
| Semaglutide | GLP-1R | CSPC Pharmaceutical | Overweight/obesity | IND approval | 2024/3/25 |
| Semaglutide | GLP-1R | Brilliant Pharmaceuticals | Overweight/obesity | IND approval | 2024/3/15 |
| Semaglutide | GLP-1R | Livzon Pharmaceutical Group | Overweight/obesity | IND approval | 2024/2/5 |
| Semaglutide | GLP-1R | Our Company | Overweight/obesity | IND approval | 2023/11/02 |
| Semaglutide | GLP-1R | Zhuhai United Laboratories | Overweight/obesity | IND approval | 2023/4/17 |

Imported products  Domestic products



Source: CDE; China Insights Consultancy

# The multi-targets collaboration and compound formulations based on GLP-1 will be one of the future research and development directions

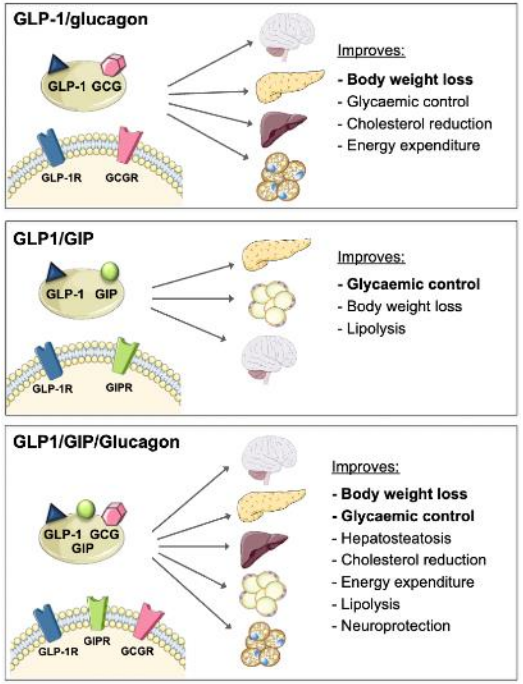


## Introduction of GLP-1 multi-targets

- The clinical **advantage of multi-targets** is that they can simultaneously activate multiple signaling pathways in the human body, producing superior hypoglycemic effects while reducing side effects. Because metabolic diseases such as diabetes have the characteristics of concurrency and heterogeneity, the therapeutic effect of single target and single molecule is limited, and the combined administration of multiple hypoglycemic drugs and clinical research are relatively complex, so single molecule multi receptor agonists become an important development direction in the field of diabetes.
- The commonly used receptors in clinical practice include **glucagon (GCG), glucose dependent insulinotropic peptide (GIP), fibroblast growth factor 21 (FGF21)**, etc.

## Mechanism of GLP-1 multi-targets

- Single **glucagon (GCG) receptor** drugs can effectively reduce blood sugar and glycosylated blood red eggs before and after meals in patients with T2DM, but they will also be accompanied by adverse reactions such as increased blood lipids and liver transaminase. When GLP-1R and GCGR are developed and used as co agonists, they can not only lower blood sugar but also effectively alleviate these adverse reactions.
- **GIP** is a peptide hormone containing 42 amino acids secreted by small intestinal epithelial K cells. After binding with GIPR, GIP activates adenylate cyclase, increases cAMP and Ca2+concentrations, activates cAMP dependent protein kinases, and has a proinsulin effect.
- **Fibroblast growth factor 21 (FGF21)** can promote glucose absorption by adipocytes, improve insulin resistance, and protect pancreatic islets β Cells can improve their function and survival, promote energy metabolism of sugars and lipids, consume excess glucose in the body, and have a certain effect on lipid-lowering.
- Most of the dual target agonists under research are concentrated in the fields of **GLP-1R/GIPR, GLP-1R/GCGR, and GLP-1R/FGF21R**. Among them, the **GLP-1R/GIPR field is led by Tirzepatide from Lilly** and has been approved by FDA, it has entered phase III in China. Based on the three target drugs derived from GLP-1, the combinations mainly include **GLP-1R/GIPR/GCGR and GLP-1R/GCGR/FGF21R**.
- Besides, **Cagrisem from Novo Nordisk is a compound of AMY3 agonist cagrelinide and GLP-1 receptor agonist semaglutide**. Amylin is another hormone related to hunger and satiety, in addition to the GLP-1 signaling pathway. The clinical trial of Cagrisem for weight control has entered phase III in China.





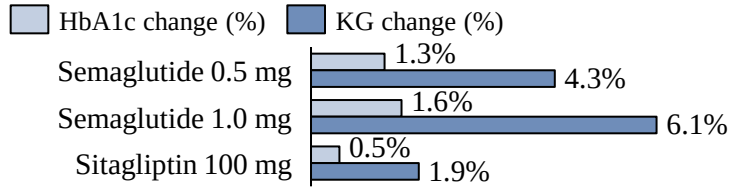

Source: Journal of Internal Medicine; China Insights Consultancy

# The growth drivers and future trends of the China Semaglutide market include its superior clinical efficacy, improved patient adherence, enhanced market availability, and greater market potential due to expanded indications

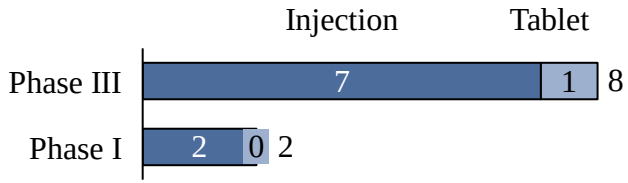


| Growth drivers & future trends | |
|---|---|
| **Superior clinical efficacy of Semaglutide compared with other T2DM drugs** | • Semaglutide has been shown to effectively reduce blood glucose levels without increasing the risk of hypoglycemia. Additionally, it is renowned for its significant weight loss efficacy. Clinical guidelines for T2DM highlight the importance of Semaglutide.<br>• Studies reveal that Semaglutide offers superior results in both glycemic control and weight loss compared to other T2DM drugs, such as Sitagliptin. This has led to a steadily increasing demand for Semaglutide in the clinical setting. |
| **Better patient adherence with lower dosing frequency** | • According to clinical research, Semaglutide undergoes enzymatic degradation prior to renal clearance. Its slow enzymatic breakdown and reduced renal clearance contribute to a prolonged half-life of 7 days, allowing for once-weekly dosing. Notably, the dosing frequency is reduced, and the initial dosage of Semaglutide, starting at 0.25 mg and titrated up to 1.0 mg, is lower than that of liraglutide, which initiates at 0.6 mg.<br>• This reduction in frequency and dosage not only enhances patients' adherence to the medication but also amplifies the advantages of clinical use. Consequently, an increasing number of patients are likely to opt for Semaglutide in the near future. |
| **Expected increase in availability as multiple biosimilars progressing into late clinical stage** | • Ten generic Semaglutide products are in clinical trials, indicating that a broader range of Semaglutide drugs will become available in the future. The global shortage of Semaglutide products, including APIs, results in significant market opportunities in the generic Semaglutide market.<br>• Notably, several biosimilars are advancing to late clinical stages, which may soon be marketed, increasing the accessibility of Semaglutide. |
| **Expanded indications for Semaglutide demonstrating greater market potentials** | • Besides its traditional approval for T2DM in adult patients (approved in China in April 2021 and by the FDA in December 2017), Semaglutide has expanded its indication to include weight loss (approved in China in June 2022).<br>• Research has also shown potential therapeutic effects of Semaglutide in new indications such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), further expanding the market potential of Semaglutide. |

**Mean HbA1c and kg change from baseline at week 56 with Semaglutide and Sitagliptin**




**Number of Semaglutide under clinical trials**





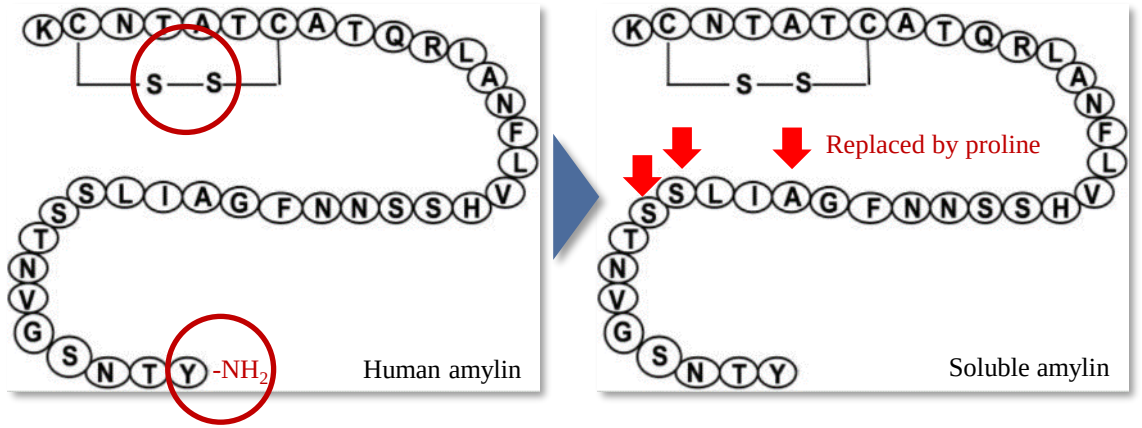

Source: Scientific Reports; Cardiovascular Diabetology; China Insights Consultancy

# Amylin and its analog have been found medicinally efficacious in the treatment of diabetes, obesity, etc. and also indicates potential in other therapeutic areas.



- Amylin, (islet amyloid polypeptide) or diabetes-associated peptide is co-secreted with insulin in the islet of Langerhans of diabetic patients in approximately 1:100, amylin-insulin ratio. **The soluble form of amylin, an analog of amylin, can be used as a supplement to insulin in the treatment of diabetes mellitus.** At the same time, recent research have studied its efficacy **for the treatment of obesity, able to in combination with the GLP-1 agonist to achieve sustained weight loss.**

## Medicinal chemistry of amylin




- Human amylin has a disulfide bond between cysteine residues 2 and 7. **The amidated C-terminal and the disulfide bond** must be intact in order for amylin or its analogs to be biologically active.
- But amylin is highly insoluble, and toxic to pancreatic beta cells because of deposition of fibrillary proteins, **an aqueous, non-aggregating form of amylin was established by replacing three amino acid residues.**

## Effects of amylin (analog)

| | |
|---|---|
| Food intake | • Peripherally administered amylin analog, induced anorectic effect through a direct action on the area postrema and/or nucleus tractus solitarius. Also it inhibits ghrelin release, an orexigenic peptide |
| Gastrointestinal tract | • Amylin analogs have been shown to slower gastric emptying, reduce the release of several digestive enzymes and bile acid, and inhibit the production of glucagon. |
| Skeletal muscle | • Amylin has been reported to oppose the metabolic actions of insulin in skeletal muscle cells. But the role of its skeletal muscle action on the maintenance of glycemic control is yet to be clarified. |



Source: The Open Medicinal Chemistry Journal; China Insights Consultancy

# So far there has been only one amylin analog product approved globally. Considering its significant clinical efficacy, an increasing number of pharmaceuticals are entering the market.



## Clinical efficacy of amylin analog in treatment of various indications

1

| Type 1 Diabetes | Amylin analog | Placebo |
|---|---|---|
| LSM Change in HbA1c Relative to Baseline (%) (SE) | -0.24 | +0.08 |
| Mean Change in Insulin Doses (U) at 6 Months (SE): | -2.00 | +0.30 |
| Mean weight reduction (kg) | -1.60 | +0.40 |

2

| Type 2 Diabetes | Amylin analog | Placebo |
|---|---|---|
| Change in HbA1c Relative to Baseline (%) (SE) | -0.66 | -0.32 |
| Mean Change in Insulin Doses (U) at 6 Months (SE): | -0.70 | -0.30 |
| Mean weight reduction (kg) | -1.40 | +0.30 |

3

| Obesity | Amylin analog | Metreleptin | Amylin + Metreleptin |
|---|---|---|---|
| LSM Unit of Measure: kg (SE) | -3.30 | -2.68 | -6.46 |

## Competitive landscape of amylin analog, as of Dec. 31th, 2023, worldwide

| Drug name | Manufacturer | Indication | Phase | First posted on |
|---|---|---|---|---|
| Symlin | AstraZeneca | Type 1/2 diabetes | Marketed | 2005 |
| Cagrilintide | Novo Nordisk | Type 2 diabetes | III | 2022-05-27 |
| | | Obesity or Overweight | III | 2022-10-05 |
| | | Chronic Kidney Disease | III | 2023-11-14 |
| | | CVD | III | 2023-01-03 |
| Symlin | AstraZeneca | Obesity | II | 2008-05-07 |
| NN9487 | Novo Nordisk | Obesity | II/I | 2023-10-03 |
| ZP8396 | Zealand Pharma | Obesity | I | 2022-11-14 |
| GUB014295 | Gubra A/S | Obesity | I | 2023-11-22 |

**Key takeaways**

- Worldwide there is only one marketed amylin analog product, **Symlin®. It was approved by FDA in 2005 for the adjuvant treatment in patients with type 1 or 2 diabetes who use insulin therapy.** 5 products have been found active clinical trials and applications for the treatment of various indications.



Note: LSM: least squares mean; SE: standard error; U: Units; CVD: cardiovascular disease;

Source: AstraZeneca; clinicaltrials; China Insights Consultancy

# Competitive landscape of amylin analog, as of Dec. 31th, 2023, in China



**Competitive landscape of amylin analog, as of Dec. 31th, 2023, in China**

| Drug name | Manufacturer | Indication | Phase | First posted on |
|---|---|---|---|---|
| CagriSema | Novo Nordisk | Obesity or Overweight | III | 2023-07-05 |
| Cagrilintide | Novo Nordisk | Obesity or Overweight | I | 2021-10-27 |

- On CDE, Novo Nordisk is the only player that has amylin analog product in clinical trial phase. And one of its clinical trials is to combine Cagrilintide with Semaglutide to treat obesity and overweight, currently in phase III.



Source: AstraZeneca; clinicaltrials; China Insights Consultancy

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# Overview of cancer diseases



## Overview of cancer diseases

***Definition of cancer :***

- Cancer is a disease that signifies the uncontrolled division of abnormal cells, potentially invading other tissues. Healthy, normal cells undergo a cycle of growth, division, and death. Conversely, abnormal cells persistently survive and continue to divide, forming a mass known as a tumor, which can be categorized as either benign or malignant. Currently, there are over a hundred types of cancer tumors, each requiring different methods of prevention, screening, and treatment/

### Causes and risk factors

- **Causes of cancer:** Cancer originates from a multi-stage process where normal cells transform into tumor cells, typically progressing from precancerous lesions to malignant tumors. These changes result from the interaction of an individual's genetic factors with three types of external factors. The external factors include:
  - **Physical carcinogens**, such as ultraviolet light and ionizing radiation;
  - **Chemical carcinogens**, such as asbestos, components of tobacco smoke, alcohol, aflatoxins (a food contaminant), and arsenic (a water contaminant);
  - **Biological carcinogens**, such as infections caused by certain viruses, bacteria, or parasites
- **Risk factors of cancer:** Tobacco use, alcohol consumption, unhealthy diet, lack of physical activity, and air pollution are risk factors for cancer (as well as other non-communicable diseases). In addition, HIV infection can increase the risk of cervical cancer sixfold and also significantly raise the risk of certain other cancers, such as Kaposi's sarcoma

### Cancer diseases

- According to American Society of Clinical Oncology (ASCO), **doctors divide cancer into types based on where it begins**. Four main types of cancer are:
  - **Carcinomas:** Carcinomas originate in skin or tissues covering organs, forming solid tumors— the most common cancer type (e.g., prostate, breast, lung, colorectal)
  - **Sarcomas:** Sarcomas originate in the supporting and connecting tissues of the body, which can include fat, muscles, nerves, tendons, joints, blood vessels, lymph vessels, cartilage, or bone
  - **Leukemias:** Leukemias, a blood cancer, result from uncontrolled blood cell growth—four main types: acute lymphocytic, chronic lymphocytic, acute myeloid, and chronic myeloid
  - **Lymphomas:** Lymphomas are cancers that start in the lymphatic system, a network of vessels and glands crucial for fighting infection. There are two main types of lymphomas: Hodgkin lymphoma and non-Hodgkin lymphoma

### Cancer management

***Cancer management = Early detection + cancer treatment***

- **Early detection:** According to WHO, early cancer detection is to detect the disease at an early stage when it has a high potential for cure. Two strategies for early cancer detection are:
  - Cancer screening is mainly targeted potential high-risk populations to identify whether there is cancer
  - Early diagnosis is to identify the cancer types when the patient's body has symptoms or when screening tests are positive
- **Treatment and prognosis monitoring:** The treatment of cancer involves employing surgery, chemotherapy, radiation therapy, medications, and various therapies with the aim of curing, reducing the size of, or halting the progression of the disease. Cancer treatments aim at removing cancer or curing patients with cancer, with prognosis monitoring which prevents the recurrence of cancer



*Source: American Society of Clinical Oncology (ASCO); WHO; China Insights Consultancy*

# Top 10 cancer and cancer incidence in China (2018-2023, 2024E-2032E)



| Top 10 cancer and cancer incidence in China (2018-2022, 2023E-2032E) | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Type** | **Unit** | **2018** | **2019** | **2020** | **2021** | **2022** | **2023** | **2024E** | **2025E** | **2026E** | **2027E** | **2028E** | **2029E** | **2030E** | **2031E** | **2032E** |
| **Lung** | K ppl | 886.3 | 916.4 | 946.8 | 977.7 | 1,008.8 | 1,040.2 | 1,071.8 | 1,103.8 | 1,136.0 | 1,168.5 | 1,201.2 | 1,234.1 | 1,267.1 | 1,298.8 | 1,330.6 |
| **Stomach** | K ppl | 482.5 | 500.3 | 514.1 | 525.0 | 533.6 | 542.1 | 550.5 | 558.9 | 567.2 | 575.4 | 583.6 | 591.7 | 599.8 | 607.8 | 615.8 |
| **Colon and rectum** | K ppl | 422.1 | 433.8 | 445.6 | 457.5 | 469.6 | 481.8 | 494.1 | 506.6 | 519.1 | 531.9 | 544.7 | 557.7 | 570.8 | 580.4 | 589.6 |
| **Liver** | K ppl | 421.5 | 434.4 | 447.5 | 460.6 | 473.8 | 487.1 | 500.4 | 513.8 | 527.2 | 540.7 | 554.2 | 567.8 | 581.3 | 591.0 | 600.2 |
| **Breast** | K ppl | 321.2 | 330.5 | 339.3 | 347.6 | 355.5 | 362.9 | 369.9 | 376.4 | 382.4 | 388.0 | 393.2 | 398.0 | 402.4 | 406.5 | 410.5 |
| **Esophagus** | K ppl | 315.6 | 332.8 | 347.4 | 359.6 | 370.9 | 381.3 | 390.9 | 399.6 | 407.5 | 414.7 | 421.2 | 427.0 | 432.2 | 436.6 | 441.0 |
| **Thyroid** | K ppl | 206.6 | 209.5 | 212.3 | 215.0 | 217.6 | 220.2 | 222.7 | 225.2 | 227.6 | 229.9 | 232.1 | 234.2 | 236.3 | 238.4 | 240.4 |
| **Brain, CNS** | K ppl | 115.7 | 118.3 | 120.8 | 123.1 | 125.2 | 127.2 | 129.0 | 130.6 | 132.2 | 133.5 | 134.8 | 135.9 | 136.9 | 137.9 | 138.8 |
| **Cervix** | K ppl | 114.6 | 115.7 | 116.7 | 117.8 | 118.8 | 119.7 | 120.6 | 121.5 | 122.3 | 123.1 | 123.9 | 124.7 | 125.4 | 126.0 | 126.7 |
| **Pancreas** | K ppl | 105.0 | 108.4 | 111.8 | 115.3 | 118.8 | 122.4 | 126.1 | 129.8 | 133.6 | 137.4 | 141.4 | 145.3 | 149.4 | 153.2 | 157.0 |



*Source: China Insights Consultancy*

# Analysis of the impact of Chinese medical policies on the oncology therapeutics market



| Date | Institution | Document | Main content |
|---|---|---|---|
| 2022/12 | National Health Commission | Clinical Guidelines for the Application of Novel Antitumor Drugs (2022 Edition) | The main goal is to further standardize the clinical application of novel antitumor drugs, enhance the rational use of oncology medications, ensure the quality and safety of medical care, and safeguard the health rights and interests of cancer patients |
| 2021/12 | NMPA | 14th Five-Year Plan for National Drug Safety and Promotion of High-Quality Development | Encourage the research and market launch of new drugs with clinical value and urgently needed generic drugs. Priority review and approval will be granted to innovative drugs with significant clinical value, clinically essential medications for malignant tumors, rare diseases, and pediatric use, provided they meet the specified criteria |
| 2021/11 | CDE | Guiding Principles for Clinically Oriented Clinical Research and Development of Antitumor Drugs | To implement a clinically oriented, patient-centric research and development approach, promoting the scientific and orderly development of antitumor drugs, and enhancing the quality of innovative cancer medications |
| 2020/12 | NMPA | Guidance Principles for the Preparation of Safety Summary Data in Antitumor Innovative Drug Marketing Applications (2020) | Primarily encourage the research and development of innovative antitumor drugs by providing direction on the sources of safety data, standardization of safety data, and specific writing recommendations. They play a role in regulating the safety data submission for marketing applications, thereby promoting the development of new antitumor drugs and ensuring their adherence to standardized safety documentation during the application process |
| 2020/12 | National Health Commission | Management Measures for the Clinical Application of Antitumor Drugs (Trial) | The main objective is to strengthen the management of the clinical application of antitumor drugs in healthcare institutions, enhance the level of clinical application of antitumor drugs, and ensure the quality and safety of medical care |
| 2020/12 | NMPA | Statistical Design Guidance Principles for Clinical Trials of Antitumor Drugs | The primary aim is to establish a standardized scale for statistical technical requirements in the design of clinical trials for antitumor drugs. The guidelines encourage and provide guidance for the industry to further optimize the statistical design of clinical trials for antitumor drugs, aiming to enhance the efficiency of clinical research and development |

## Key analysis

***Three primary influences :***

- **Standardize clinical application and enhance medication quality:** These policies focus on standardizing the use of anti-tumor drugs in medical settings, improving clinical practices, ensuring medical quality, and enhancing patient safety. China aims to streamline medication procedures, promote the rational use of drugs, and protect patient rights
- **Promote new drug research and market access:** These policies encourage the research and market entry of new drugs and generic medicines, particularly prioritizing the review and approval of innovative drugs with evident clinical value, those targeting malignant tumors, and drugs addressing rare diseases
- **Optimize clinical trial design and increase R&D efficiency:** These policies establish unified statistical standards and encouraging the industry to optimize clinical trial designs to enhance R&D efficiency. China aids in reducing the cost and duration of new drug development, facilitating the entry of more innovative drugs into the market, and promoting scientific advancements in the field of cancer treatment

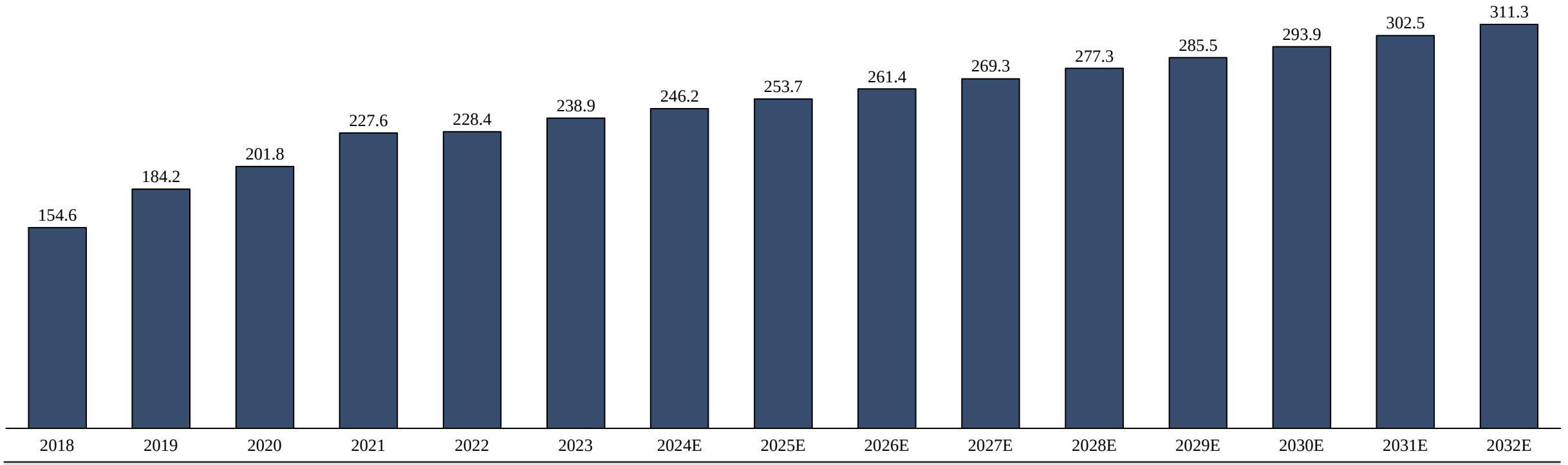
# The market size of China oncology drug market is expected to increase from RMB[238.9] billion in 2023 to RMB[311.3] billion in 2032 at the CAGR of [3.0]%



## China oncology drug market size, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Cancer treatment drug market | 9.1% | 3.0% |

*RMB Billion*




**Key Analysis**

- China oncology drug market consists of cancer drug market and chemotherapy/radiation therapy-induced adverse effect treatment market;
- The market size of China oncologydrug market is expected to increase from RMB[238.9] billion in 2023 to RMB[311.3] billion in 2032 at the CAGR of [3.0]%



Source: China Insights Consultancy

# Overview of common adverse effects of cancer chemotherapy/radiotherapy



## Introduction to adverse effects of cancer chemotherapy/ radiotherapy

- Chemotherapy/ radiotherapy involves using drugs or radiation to kill or slow down the growth of cancer cells. However, because those therapies act throughout the body (affecting all cells in specific stages of development), both cancer cells and healthy cells can be affected. Adverse effects can occur when healthy cells are damaged during the treatment.
- The specific adverse effects experienced can vary depending on the type of chemotherapy drugs a patient receives, the patient's overall health and the patient's tolerance to the treatment. Most adverse effects are temporary and can be managed or treated. Common adverse effects of cancer chemotherapy include nausea and vomiting, neutropenia, thrombocytopenia, oral ulcers or mouth sores, hair loss and diarrhea/enteritis.

### Nausea and vomiting

- For patients undergoing chemotherapy treatment, experiencing discomfort or nausea (emesis) and vomiting is a common adverse effect. After chemotherapy, some patients may develop symptoms of nausea and vomiting within minutes or hours, while others may not experience symptoms until 2 to 3 days later

### Neutropenia

- Chemotherapy-induced neutropenia (CIN) is a condition characterized by a decrease in the number of neutrophils, a type of white blood cell, in the body as a result of chemotherapy treatment

### Thrombocytopenia

- Chemotherapy-induced thrombocytopenia (CIT) is a condition in which antitumor chemotherapy drugs inhibit bone marrow megakaryocytes, resulting in a platelet count of less than $100 \times 10^9$/L in patient's peripheral blood

### Oral ulcers or mouth sores

- Oral ulcers can develop due to the damage to oral mucosa by chemotherapy or local radiation therapy. All chemotherapy drugs have the potential to cause oral ulcers
- Mouth sores, also called mucositis or stomatitis, can result from cancer treatment damaging the cells lining the mouth, throat, and gastrointestinal (GI) tract

### Hair loss

- Hair loss is one of the most common adverse reactions faced by cancer patients, especially those undergoing chemotherapy. Chemotherapy drugs, while killing cancer cells, can also induce apoptosis in hair follicle cells, leading to hair loss

### Diarrhea

- Gastrointestinal issues are a frequent side effect in immunotherapy patients. This is mainly due to immunotherapy drugs damaging the intestinal lining, causing excessive fluid secretion, gastrointestinal motility problems, and gut microbiota disruption, leading to diarrhea



Source: NMPA; China Insights Consultancy

# The Chinese market for drugs for adverse effects of chemotherapy/ radiotherapy is growing due to increased clinical demand, aging population, and rising cancer cases. Future trends: improved safety, competition, and lower prices



## Market drivers for drugs for adverse effects of chemotherapy/ radiotherapy

**1 Rising cancer incidence**

- The rising incidence of cancer has driven the development of anti-cancer drugs. In China, the number of cancer cases increased from 4,227.9 thousand people in 2017 to 4,873.9 thousand people in 2022, with a CAGR of 2.9%. Additionally, population aging is one of the factors contributing to the increase in cancer cases, as elderly individuals have weaker immune systems and poorer physical health, making them more susceptible to cancer

**2 Tremendous potential for extensive application**

- Cancer treatment regimens can lead to adverse effects such as bone marrow suppression, including leukopenia, severe neutropenia, and thrombocytopenia. Medications like G-CSF, rhIL-11, TPO, and erythropoietin (EPO) can be used to prevent and alleviate these adverse effects caused by bone marrow suppression. With the evolution of cancer treatment toward chronic disease management, these drugs will have a broader range of clinical applications

**3 Rising clinical demand**

- The incidence of adverse effects such as nausea and vomiting during treatment in certain cancer patient groups can reach over 70%, causing significant physiological and psychological burdens. The use of treatment methods to prevent or alleviate nausea and vomiting caused by anticancer drugs is crucial for improving patient treatment compliance. These treatment methods not only significantly enhance the quality of life for patients but also reduce the burden on the healthcare system by decreasing unnecessary emergency visits and hospitalizations. It is expected that in the future, with continuous advancements and innovations in medical technology and the growing demand from patients, the market for managing adverse effects in cancer treatment will continue to expand. This expansion will offer patients more choices to better cope with discomfort during treatment and improve the success rate of their treatments.

## Market trends for drugs for adverse effects of chemotherapy/ radiotherapy

**Enhanced safety and efficacy**

- In the field of chemotherapy/ radiotherapy adverse effects drugs, the future will prioritize safety and effectiveness, influenced by patient and healthcare provider demands. Pharmaceutical companies will invest in innovative technologies, personalized treatments, and stringent regulations to ensure the development of safer and more effective drugs. Competition will drive a focus on drug quality and performance, fostering scientific research and technological advancements to offer dependable treatment options and maximize patient safety and efficacy. Furthermore, the future of cancer adverse effects medications will trend towards the development of long-acting formulations to satisfy more clinical demand

**Growing accessibility of drugs for adverse effects**

- Many products in the field of cancer adverse effects drugs are gradually maturing, and the inclusion of these drugs in health insurance is making them more affordable, thus benefiting a greater number of patients. This trend suggests that more people will benefit from these drugs in the future, leading to a continued increase in the user base, offering a broader range of effective treatment options for patients

**More comprehensive regulation for drugs for adverse effects**

- The regulatory environment for adverse effects to cancer drugs will become more robust; currently, there is no very clear policy in this regard. This suggests that regulatory authorities may strengthen the monitoring and management of adverse effects to cancer treatment drugs to ensure patient safety and treatment efficacy. This may also involve more comprehensive assessments of drug safety and effectiveness to address potential risks and challenges in cancer treatment. This trend may help promote the development of more sustainable and efficient cancer treatment approaches



Source：NMPA; National Bureau of Statistics; China Insights Consultancy

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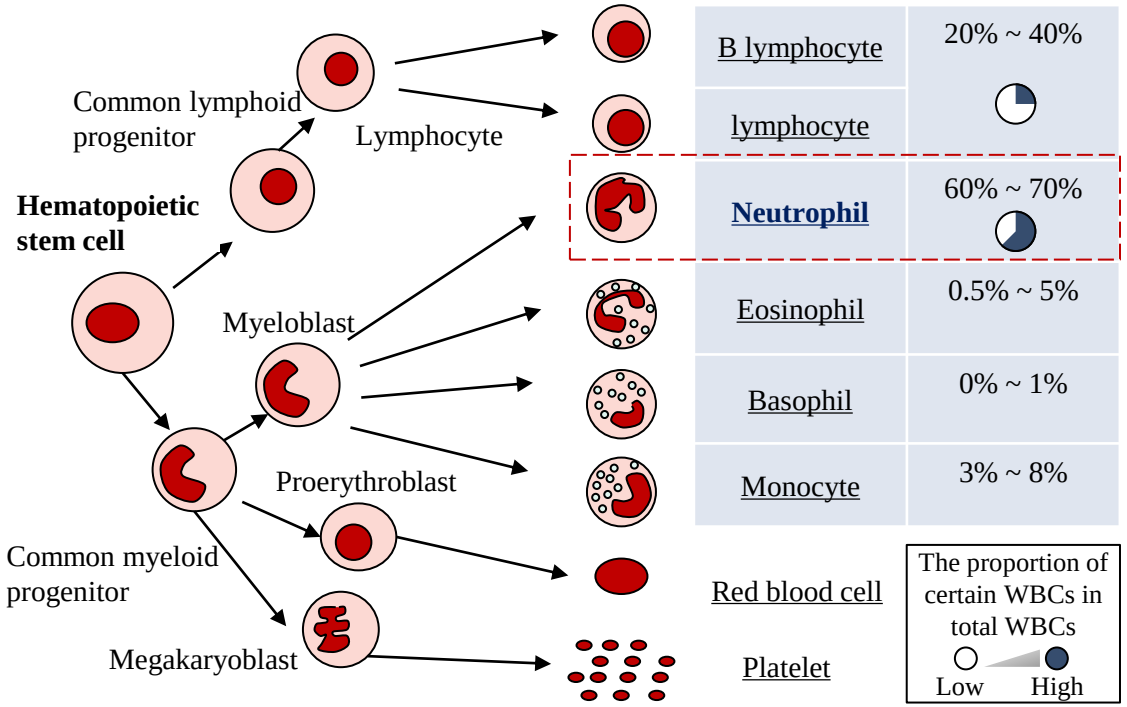
# Neutropenia is a common adverse effect of chemotherapy and radiotherapy and G-CSF is the major treatment regimen. In China, Jiuyuan Gene is the first company that received approval for short-acting G-CSF



## Introduction to Neutrophil




| | |
|---|---|
| B lymphocyte | 20% ~ 40% |
| lymphocyte | |
| **Neutrophil** | 60% ~ 70% |
| Eosinophil | 0.5% ~ 5% |
| Basophil | 0% ~ 1% |
| Monocyte | 3% ~ 8% |
| Red blood cell | |
| Platelet | |

The proportion of certain WBCs in total WBCs

Low High

- Neutrophils are the most important white blood cells (WBCs) in the human body, **accounting for about 60%-70% of all human WBCs.** WBCs are the second line of defense against invasion by microorganisms
- Neutropenia is defined as a neutrophil < 500/mm$^3$ or a neutrophil < 1000/mm$^3$ and is expected to be less than 500/mm$^3$, can be induced by chemotherapy treatment, bone marrow transplantation, and etc., **among which chemotherapy is the foremost**

## Cause-effect overview of Neutrophia

### Chemo/radiotherapy

- **Chemo/radiotherapy is one of the most effective ways to treat cancer and 50%-60% of cancer patients will undergo this treatment.** The key mechanism of action is utilizing chemotherapy drugs to kill cancer cells. However, some important cells such as red blood cells, granulocytes and platelets inside the patient's body are also destroyed at the same time

### Neutropenia

- **Neutropenia is the most common hematological adverse effect and dose-limiting toxicity associated with of chemotherapy and radiotherapy.** Granulocyte colony-stimulating factor (G-CSF) is the main treatment option and can also be used for prophylactic purposes. **The reduction of neutrophils can mitigate the body's capability of fighting infections**

### Treatment

- **G-CSF**, a recombinant protein biopharmaceutical, which can stimulates the growth, differentiation, and activation of neutrophils
  - There are **over 100 approved G-CSF** products in the China, including **8 long-acting products**
  - The first company in China to receive approval for short-acting G-CSF was **Hangzhou Jiuyuan Gene Engineering Co .,Ltd.**

### Results

- **Neutropenia** is prone to **cause infections and complications** such as fever, swallowing pain, skin abscess, and digestive tract infections. If **neutropenia** has not been promptly and effectively controlled, **it will be the main cause of delay in chemotherapy and radiotherapy treatment**



Source：Chinese Journal of Oncology; NMPA; China Insights Consultancy

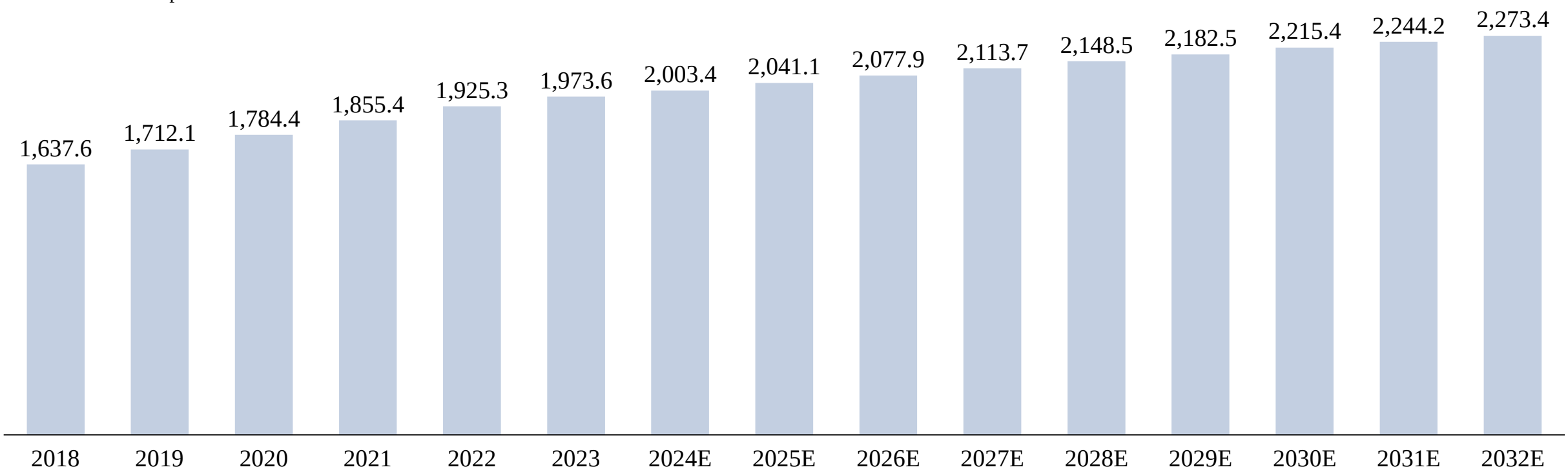
# Chinese historical number of neutropenia patients and future forecasts, 2018-2032E



**Incidence of neutropenia in China, 2018-2032E**

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Incidence of neutropenia in China | 3.7% | 1.6% |

*thousand patients*






Note: Both chemotherapy and radiotherapy are taken into considerations.

Source: China Insights Consultancy

# G-CSF is main medication for the treatment of neutropenia, and rhG-CSFs and PEG-rhG-CSF both play important roles in the treatment process



## Definition and categorization of G-CSFs

- **Definition:** G-CSF (granulocyte-colony stimulating factor) is a type of protein called a growth factor. G-CSF stimulates the bone marrow to make more blood cells, and increases the number of some types of white blood cells in the blood. It can be used with, or after, chemotherapy
- **Categorization**: G-CSFs can be classified into short-acting and long-acting types based on efficacy length

| | rhG-CSFs (short-acting type ) | PEG-rhG-CSF (long-acting type) |
|---|---|---|
| **Frequency** | The half-life is brief, requiring daily injections during each chemotherapy cycle. Patients typically receive 1 injection per day, depending on their physiological response and chemotherapy duration | Half-life is about 4 to 6 times longer than rhG-CSF, which allows it to be injected only once per chemotherapy cycle. The injection interval is about 10 to 21 days |
| **Efficacy** | The plasma concentration has a large difference between its top and bottom. It is unstable and also easily interacts with other drugs, thus affecting the treatment efficacy of chemotherapy | The plasma concentration is more stable, which lowers the risk of infection and adverse effects |
| **Use of safety** | Moderate safety: the drug is excreted mainly through glomerular filtration clearance and ANC-mediated clearance | High safety and with self-regulating mechanism: When neutrophil levels drop in a patient, the drug remains in the bloodstream, and it gets cleared on its own when neutrophil levels return to normal |
| **Adherence** | The frequency of medication is high and 24% of patients experienced bone pain and other adverse effects. Therefore, patient adherence was relatively poor | The frequency of medication is low. Although there is a tendency for patients to experience bone pain and other adverse effects, patient compliance is relatively good |

## Comparison of different generations of G-CSF

**1 The first-generation**

**rhG-CSF**

- **Short-acting,** it is a synthetic cytokine that promotes the proliferation, differentiation and activation of neutrophils
- In 1991, the FDA approved the new biologic Filgrastim**,** developed by Amgen to be used in FN treatment

**2 The second-generation**

**PEG-rhG-CSF**

- **Long-acting**, it is a new drug modified from rhG-CSF by PEG long-acting method
- In 2002, Neulasta® (pegfilgrastim) was introduced by Amega and approved to enter the market

| | | | |
|---|---|---|---|
| **Half-life** | Half life is around 3.5 hours | | Half life is around 15~80 hours |
| **Injection frequency** | Inject once a day 24 hours after chemotherapy | | Injected once per chemotherapy cycle and the interval is about 10~21 days |
| **Technical features** | Glycosylation modification | | PEG long-acting method: approximately double the molecules |
| **Treatment efficacy** | Alleviates mild to moderate Neutropenia | | Effectively alleviates moderate Neutropenia |
| **Use of safety** | High adverse effects rate | | Slightly increased risk of infection & decrease ADR 10~20% |



Source：China Insights Consultancy

# Overview of G-CSFs as preventive treatment in the clinical guideline

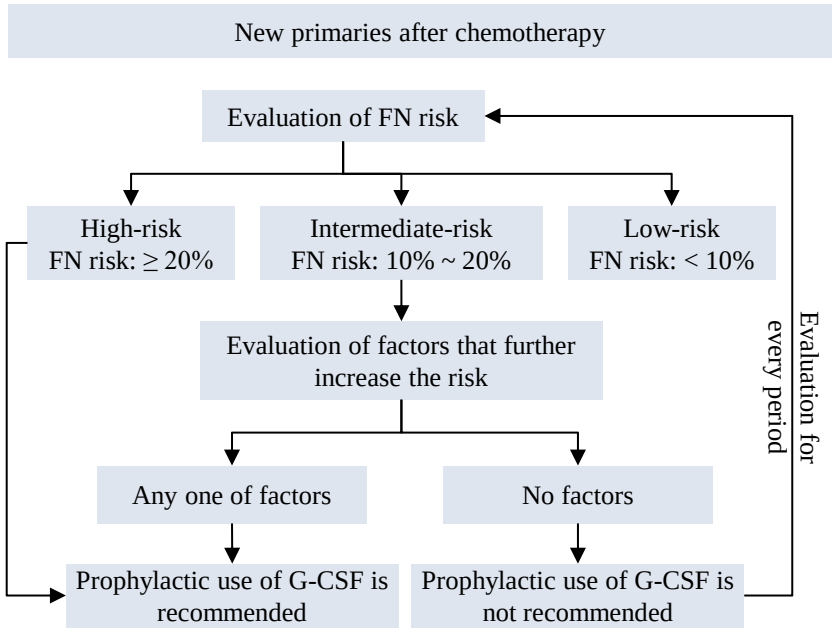


## Overview of G-CSFs as preventive treatment in the clinical guideline

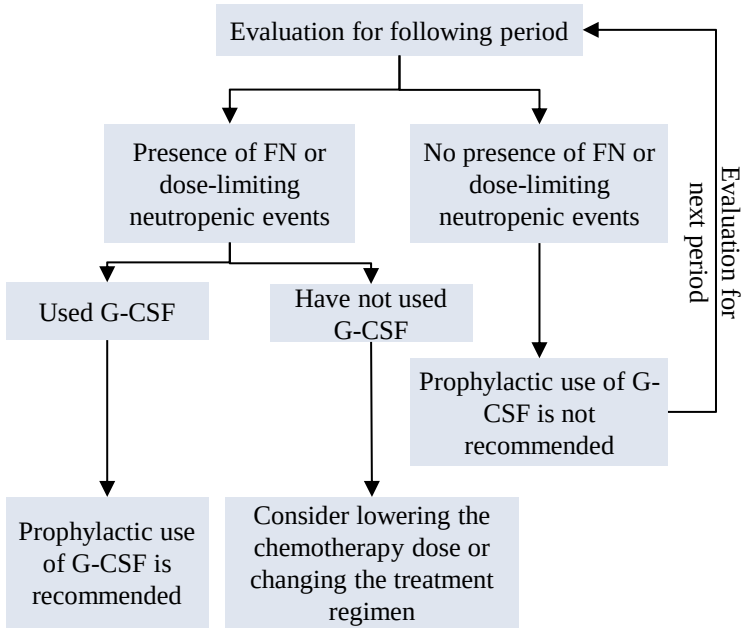
**Disease definition**

- **Neutropenia is a common chemotherapy/radiotherapy adverse effect** and is the presence of a neutrophil count (ANC) < 500 neutrophils/mcL or < 1,000 neutrophils/mcL which is predicted to decline to ≤ 500 neutrophils/mcL over the next 48 hours.
- **Febrile Neutropenia** (FN) is an oral temperature of >38.0℃ for 2 hours and a ANC < 500 neutrophils/mcL, or expected to fall below 500 neutrophils/mcL. The type of chemotherapy regimen and the patient's risk factors need to be considered before determining the febrile neutropenia (FN) risk level and the application of the suitable treatment regimen. When FN risk is < 10%, the patient's condition is classified as **low-risk**. When FN risk is 10-20%, it is classified as **intermediate-risk**. If FN risk is > 20%, it is classified as **high-risk.**

### Primary prevention pathway




### Secondary prevention pathway




### Dosing frequency

**1 rhG-CSF**

- Start the use of rhG-CSF the day after chemotherapy or up to 3-4 days after chemotherapy
- rhG-CSF 5 μg/kg (rounded to the nearest bottle size according to institutional weight limits), subcutaneous or intravenous injection, 1 time/d
- Until a ANC of over 2.0 × $10^9$ /L is reached

**2 PEG-rhG-CSF**

- PEG-rhG-CSF is used once 24 hours after the end of each chemotherapy
- The use of PEG-rhG-CSF requires an interval of at least 12 days between the next chemotherapy
- Subcutaneous injection at a fixed dose of 6 mg, or individualized treatment according to the patient's body weight (100 μg/kg)

**3 Antibacterial**

- Antibiotics are recommended for prophylaxis only in patients with hematologic malignancies not on rhG-CSF, or patients with other types of tumors who present with severe neutrophil deficiency (ANC < 0. 1 × $10^9$/ L)



Source： CSCO; China Insights Consultancy

# Overview of G-CSFs as treatment regimens in the clinical guideline

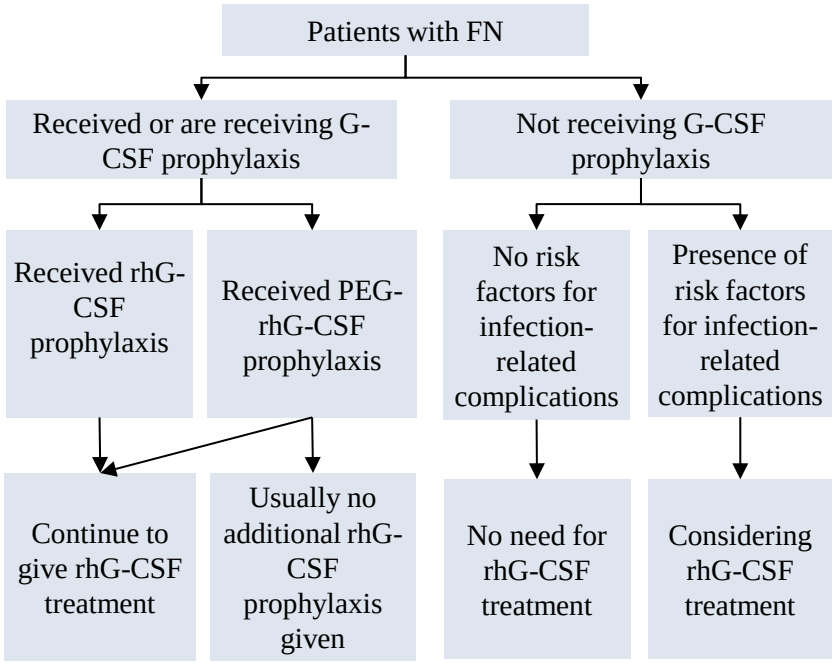


## Overview of G-CSFs as treatment regimens in the clinical guideline

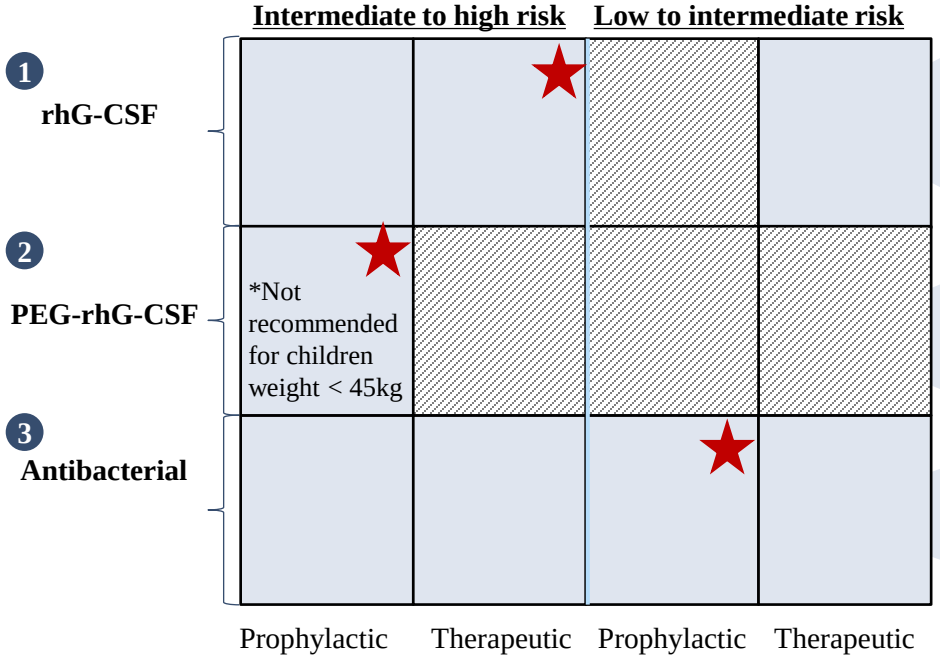
**Disease definition**

- **Neutropenia is a common chemotherapy/radiotherapy adverse effect** and is the presence of a neutrophil count (ANC) < 500 neutrophils/mcL or < 1,000 neutrophils/mcL which is predicted to decline to ≤ 500 neutrophils/mcL over the next 48 hours.
- **Febrile Neutropenia** (FN) is an oral temperature of >38.0℃ for 2 hours and a ANC < 500 neutrophils/mcL, or expected to fall below 500 neutrophils/mcL. The type of chemotherapy regimen and the patient's risk factors need to be considered before determining the febrile neutropenia (FN) risk level and the application of the suitable treatment regimen. When FN risk is < 10%, the patient's condition is classified as **low-risk**. When FN risk is 10-20%, it is classified as **intermediate-risk**. If FN risk is > 20%, it is classified as **high-risk.**

### Therapeutic pathways




### Drug choice among different groups of patients




### Dosing frequency

- rhG-CSF 5 μg/kg (rounded to the nearest vial size according to institutional weight limits), subcutaneous injection, 1 time/d;
- Continue to administer the drug until the ANC returns to normal or near-normal levels from the lowest point (ANC rebounded to more than $2.0\times10^9$/L)

- Subcutaneous injection at a fixed dose of 6 mg, or individualized treatment according to the patient's body weight (100 μg/kg)
- The use of PEG-rhG-CSF requires an interval of at least 12 d between the next chemotherapy

- Antibacterial therapy, which includes oral antibodies and intravenous antibodies, is determined by the specific pathogen



Source：NCCN; ESMO; CSCO; China Insights Consultancy

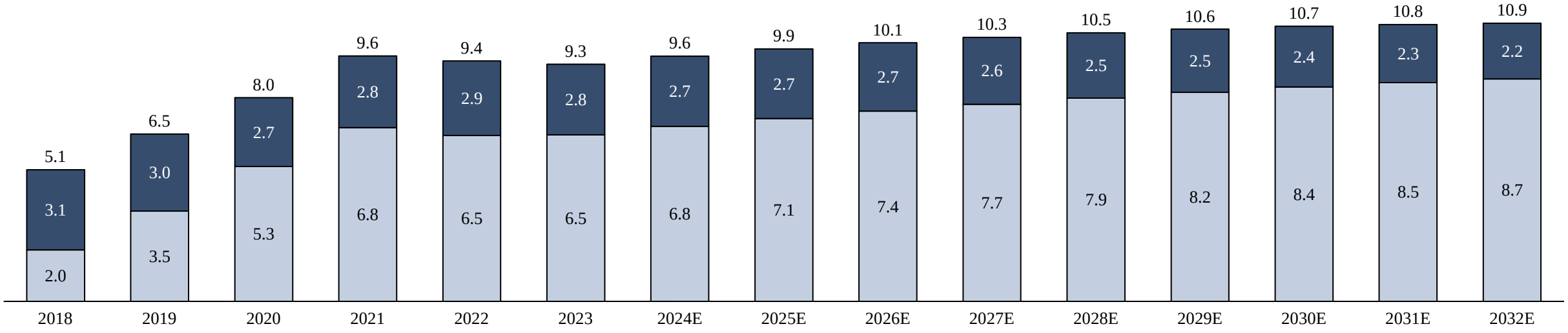
# China rhG-CSF market increased from RMB5.1 billion in 2018 to RMB9.3 billion in 2023 at the CAGR of 12.5%, and is expected to remain steady and reach RMB10.9 billion in 2032



## China rhG-CSF Market Size, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Short-Acting rhG-CSFs | -2.5% | -3.2% |
| Long-Acting rhG-CSFs | 26.4% | 3.3% |
| Overall China rhG-CSF Market | 12.5% | 1.6% |

*RMB Billion*




**Key Analysis**

- G-CSF is a commonly used drug in clinical practice for the treatment of CIN. In 2023, Anhui province announced the selection results from its 2022 provincial VBP, which includes the VBP results of G-CSF medication, including long-acting PEG-G-CSF medications. The selected manufacturers for VBP of G-CSG products include **Jiuyuan Gene** and Qilu Pharmaceuticals. Going forward, it is expected that more provinces will include G-CSF products in upcoming provincial VBPs as NHSA urges provincial VBPs to cover biologic products.
- China G-CSF market increased from RMB5.1 billion in 2018 to RMB9.3 billion in 2023 at the CAGR of 12.5%, and is expected to remain steady and reach RMB10.9 billion in 2032.



Source: China Insights Consultancy

# More than 30 G-CSF products have been approved by NMPA in China, including 5 PEG-G-CSFs, of which the latest four approved this year are from Amotop and the earliest approved is from Hengrui



**Top 5 earliest approved rhG-CSFs by NMPA**

| Initial Approval number | Product name | Generic name | Manufacturer | Indication | Initial approval date |
|---|---|---|---|---|---|
| S10980029 | Jilifen | Filgrastim | Hangzhou jiuyuan gene engineering Co., Ltd. | Neutropenia caused by various reasons; Mobilization of hematopoietic stem/progenitor cells in peripheral blood before bone marrow transplantation; Neutropenia associated with myelodysplastic syndromes (MDS); Severe infections of various types | 1996 |
| S19980009 | Lishengsu | Filgrastim | Beijing SL Pharmaceutical Co., Ltd. | Neutropenia caused by various reasons; Mobilization of hematopoietic stem/progenitor cells in peripheral blood before bone marrow transplantation; Neutropenia associated with myelodysplastic syndromes (MDS); Severe infections of various types | 1998 |
| S19980035 | Saigeli | Filgrastim | Shanghai Sunway Biotech | Neutropenia caused by various reasons; Mobilization of hematopoietic stem/progenitor cells in peripheral blood before bone marrow transplantation; Neutropenia associated with myelodysplastic syndromes (MDS); Severe infections of various types | 1998 |
| S10980098 | Jinleisaiqiang | Filgrastim | Changchun GeneScience Pharmaceutical Co., Ltd. | Neutropenia caused by various reasons; Mobilization of hematopoietic stem/progenitor cells in peripheral blood before bone marrow transplantation; Neutropenia associated with myelodysplastic syndromes (MDS); Severe infections of various types | 1998 |
| S19990040 | Topneuter | Filgrastim | Amotop | Neutropenia caused by various reasons; Mobilization of hematopoietic stem/progenitor cells in peripheral blood before bone marrow transplantation; Neutropenia associated with myelodysplastic syndromes (MDS); Severe infections of various types | 1999 |



Source：NMPA; China Insights Consultancy

# More than 30 G-CSF products have been approved by NMPA in China, including 5 PEG-G-CSFs, of which the latest four approved this year are from Amotop and the earliest approved is from Hengrui



**NMPA Approved PEG-G-CSFs, as of Auguest 2023**

| Approval number* | Product name | Generic name | Manufacturer | Indication | First approval date |
|---|---|---|---|---|---|
| S20110014 | Jinyouli | Pegfilgrastim | CSPC | Reduce the incidence of clinically significant febrile neutropenia-induced infections in non-myeloid malignant tumor patients receiving bone marrow-suppressing antineoplastic drug treatment; not used for the mobilization of peripheral blood progenitor cells in hematopoietic stem cell transplantation | 2011 |
| S20150013 | Xinruibai | Pegfilgrastim | Qilu Pharmaceutical | Reduce the incidence of clinically significant febrile neutropenia-induced infections in non-myeloid malignant tumor patients receiving bone marrow-suppressing antineoplastic drug treatment; not used for the mobilization of peripheral blood progenitor cells in hematopoietic stem cell transplantation | 2015 |
| S20180004 | Aiduo | Mecapegfilgrastim | Jiangsu Hengrui Pharmaceuticals Co., Ltd. | Reduce the incidence of clinically significant febrile neutropenia-induced infections in non-myeloid malignant tumor patients receiving bone marrow-suppressing antineoplastic drug treatment; not used for the mobilization of peripheral blood progenitor cells in hematopoietic stem cell transplantation | 2018 |
| S20210011 | / | Pegfilgrastim | Shandong Xinshidai Pharmaceutical Co., Ltd. | Reduce the incidence of clinically significant febrile neutropenia-induced infections in non-myeloid malignant tumor patients receiving bone marrow-suppressing antineoplastic drug treatment; not used for the mobilization of peripheral blood progenitor cells in hematopoietic stem cell transplantation | 2021 |
| S20230039；S20230036 S20230038；S20230037 | Peijin | Telpegfilgrastim | Amotop | Reduce the incidence of clinically significant febrile neutropenia-induced infections in non-myeloid malignant tumor patients receiving bone marrow-suppressing antineoplastic drug treatment; not used for the mobilization of peripheral blood progenitor cells in hematopoietic stem cell transplantation | 2023 |

- The PEG-rhG-CSFs product from Hangzhou Jiuyuan Gene Engineering Co., Ltd. submitted its NDA for market approval in May 2023



Note*: Multiple approval numbers indicate that the same drug has been approved in various dosages

Source：NMPA; China Insights Consultancy

# Competitive Landscape of the G-CSF Market in China, 2022



**Competitive landscape of G-CSF in China, 2022**

| Company | Generic Name | Brand Name | NMPA First Approval Year | NRDL Inclusion | Revenue (Ten thousand RMB) | Market Share | MoA | Indications | Route of Administration |
|---|---|---|---|---|---|---|---|---|---|
| QiLu Pharmaceutical Co., Ltd.<br>齐鲁制药 | Filgrastim | Ruibai | 1999 | Yes | 307,577.7 | 32.7% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |
| CSPC Baike(Shandong)Bio-Pharmaceutical Co., Ltd<br>石药百克(山东)生物制药 | Filgrastim | Jinxuli | 2000 | Yes | 258,627.8 | 27.5% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |
| Jiangsu Hengrui Pharmaceuticals Co., Ltd.<br>江苏恒瑞医药 | Mecapegfilgrastim | Aiduo | 2018 | Yes | 171,702.5 | 18.3% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |
| Kyowa Kirin Co Ltd<br>协和麒麟 | Filgrastim | Gran | 2017 | Yes | 42,613.7 | 4.5% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |
| Xiamen Amoytop Biotech Co., Ltd.<br>厦门特宝生物 | Filgrastim | Topneuter | 1999 | Yes | 28,997.7 | 3.1% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |
| Chugai Pharmaceutical Co., Ltd.<br>中外制药 | Filgrastim | Granocyte | 2014 | Yes | 17,118.6 | 1.8% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |
| Kexing Biopharm Co., Ltd.<br>科兴生物制药 | Filgrastim | Baitexi | 2001 | Yes | 16,977.4 | 1.8% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |
| Hangzhou jiuyuan gene engineering Co., Ltd.<br>杭州九源基因 | Filgrastim | Jilifen | 1996 | Yes | 16,596.64 | 1.8% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |



Note: This table lists the top 8 manufacturers of G-CSF in China, 2022

Source: NMPA; China National Intellectual Property Administration; China Insights Consultancy

# Competitive Landscape of the G-CSF Market in China, 2023



**Competitive landscape of G-CSF in China, 2023**

| Company | Generic Name | Brand Name | NMPA First Approval Year | NRDL Inclusion | Market Share | MoA | Indications | Route of Administration |
|---|---|---|---|---|---|---|---|---|
| QiLu Pharmaceutical Co., Ltd.<br>齐鲁制药 | Filgrastim | Ruibai | 1999 | Yes | 33.5% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |
| CSPC Baike(Shandong)Bio-Pharmaceutical Co., Ltd<br>石药百克(山东)生物制药 | Filgrastim | Jinxuli | 2000 | Yes | 25.2% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |
| Jiangsu Hengrui Pharmaceuticals Co., Ltd.<br>江苏恒瑞医药 | Mecapegfilgrastim | Aiduo | 2018 | Yes | 21.4% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |
| Kyowa Kirin Co Ltd<br>协和麒麟 | Filgrastim | Gran | 2017 | Yes | 4.2% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |
| Xiamen Amoytop Biotech Co., Ltd.<br>厦门特宝生物 | Filgrastim | Topneuter | 1999 | Yes | 2.5% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |
| Hangzhou jiuyuan gene engineering Co., Ltd.<br>杭州九源基因 | Filgrastim | Jilifen | 1996 | Yes | 2.2% | Stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream | Neutropenia | Injection |

Note: This table lists the top 8 manufacturers of G-CSF in China, 2022

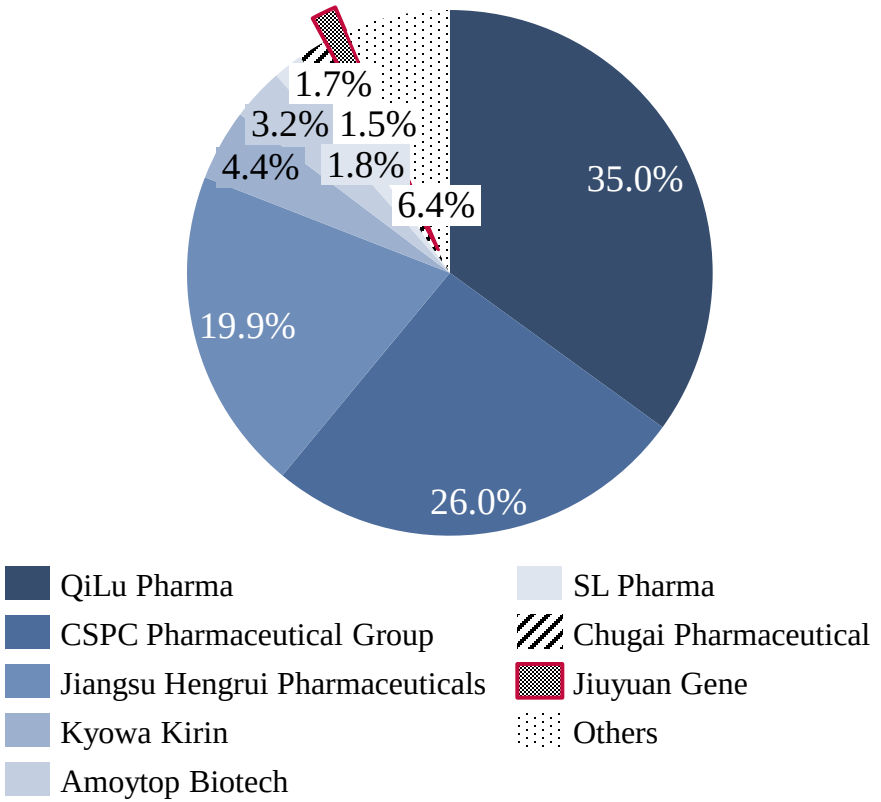
Source: NMPA; China National Intellectual Property Administration; China Insights Consultancy

# Competitive Landscape of the G-CSF Market in China, 2021 & 2022

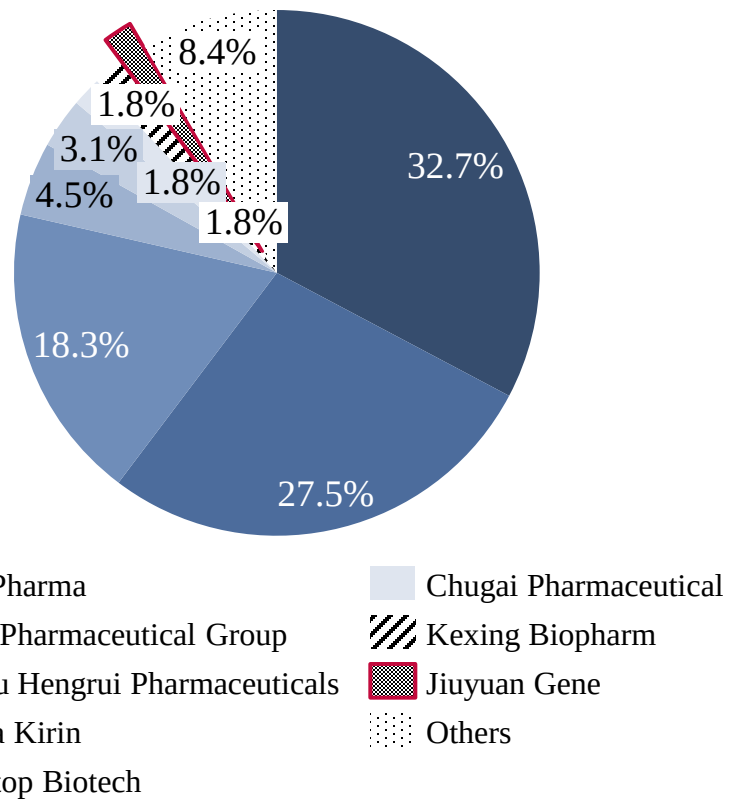


- The sales revenue of Jilifen is RMB[145.8 million] and RMB[165.9 million] in 2021 and 2022 with a market share of [1.5]% and [1.8]% of the rhG-CSF drug market in China, respectively, and ranked [8] and [8] nationally in the corresponding periods.

**Competitive Landscape of the G-CSF Market in China, 2021**




**Competitive Landscape of the G-CSF Market in China, 2022**





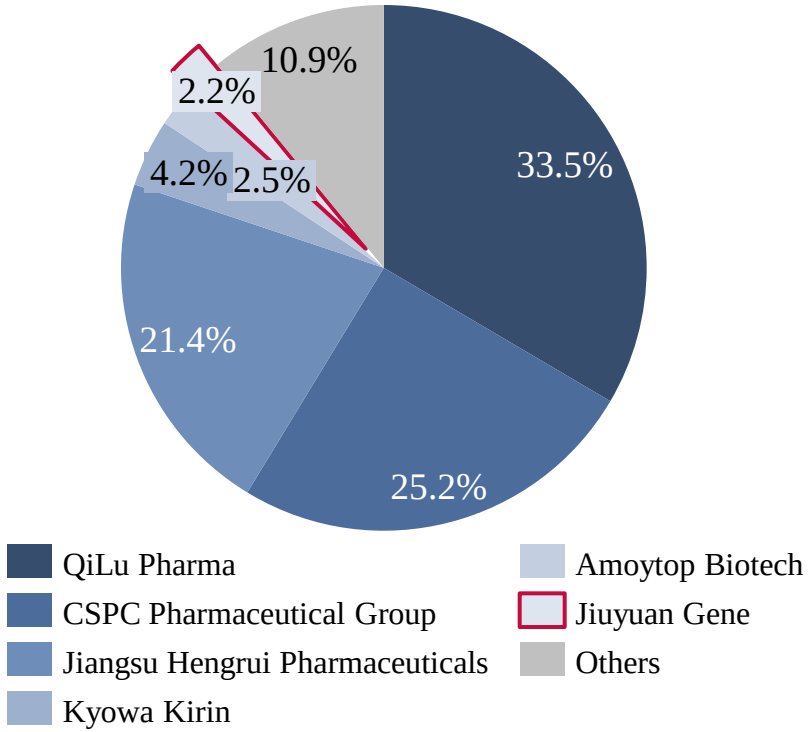

Source：; China Insights Consultancy

# Competitive Landscape of the G-CSF Market in China, 2023



- The market share of Jilifen is [2.2]% of the rhG-CSF drug market in China, and ranked [6] nationally in 2023.

**Competitive Landscape of the G-CSF Market in China, 2023**





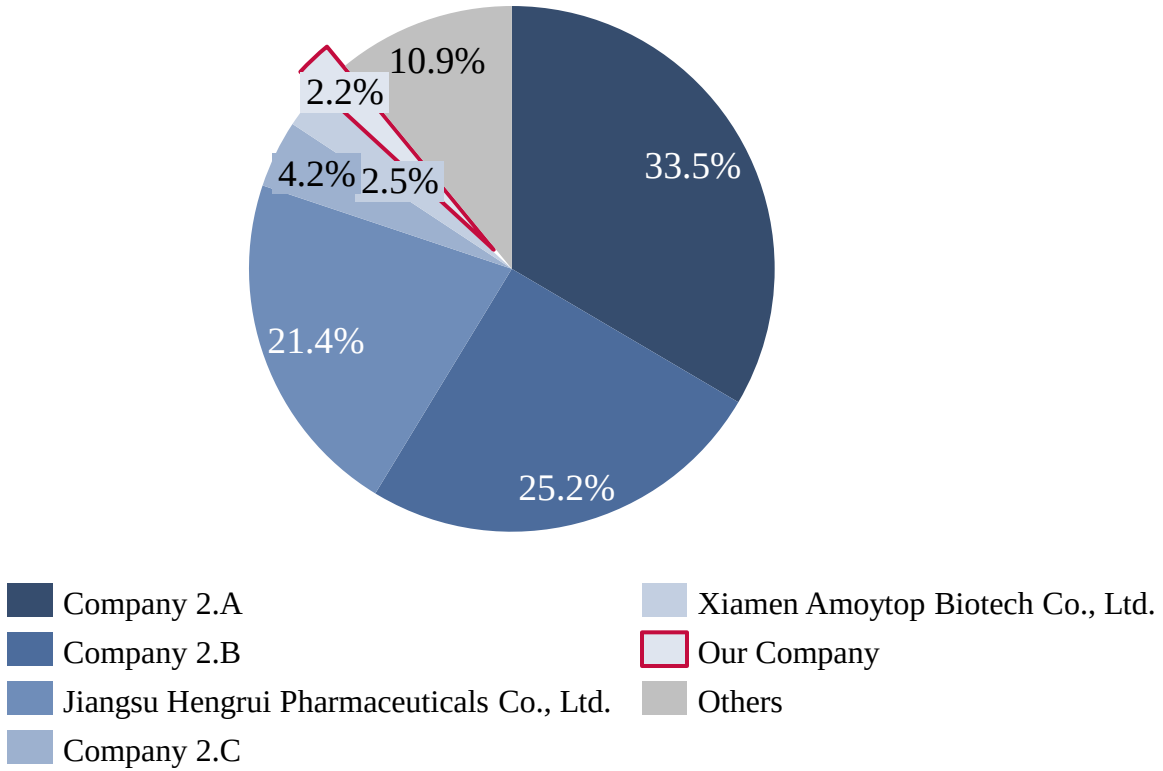

Source：; China Insights Consultancy

# Competitive Landscape of the G-CSF Market in China, 2023



- The market share of Jilifen is [2.2]% of the rhG-CSF drug market in China, and ranked [6] nationally in 2023.

**Competitive Landscape of the G-CSF Market in China, 2023**




- Company 2.A, headquartered in Shandong Province, was founded in 1992. It focuses on the R&D, production and sales of drugs used to treat common diseases and other diseases that seriously endanger human health. It entered the cancer treatment drug sector in 1999 and currently holds five approved drug candidates that are potentially competitive with the Company, including G-CSF, IL-11, palonosetron, fuvestrant, and fosaprepitant in China.
- Company 2.B, headquartered in Hebei, China, was founded in 1992. It is committed to the R&D, production, and sales of new drugs, mainly including monoclonal antibodies and fusion proteins. It entered the cancer treatment drug sector in 2000 and currently holds two approved G-CSF drug candidates in China.
- Jiangsu Hengrui Pharmaceuticals Co., Ltd. (江蘇恒瑞醫藥股份有限公司), headquartered in Jiangsu Province and listed in Shanghai Stock Exchange, was founded in 1997. It is dedicated to the R&D, production, and sales of drugs, mainly including oncology drugs, endocrine therapy drugs, cardiovascular drugs and so on.
- Company 2.C, headquartered in Tokyo, Japan, was founded in 1949. It is dedicated to the R&D, production, and sales of new drugs primarily for the treatment of cancer and kidney diseases. It entered the cancer treatment drug sector in 2017 and currently holds one approved G-CSF drug candidate in China.
- Xiamen Amoytop Biotech Co., Ltd. (廈門特寶生物工程股份有限公司), headquartered in Fujian Province and listed in Shanghai Stock Exchange, was founded in 1996. It is dedicated to the R&D, production, and sales of recombinant proteins and long-acting modified drugs.



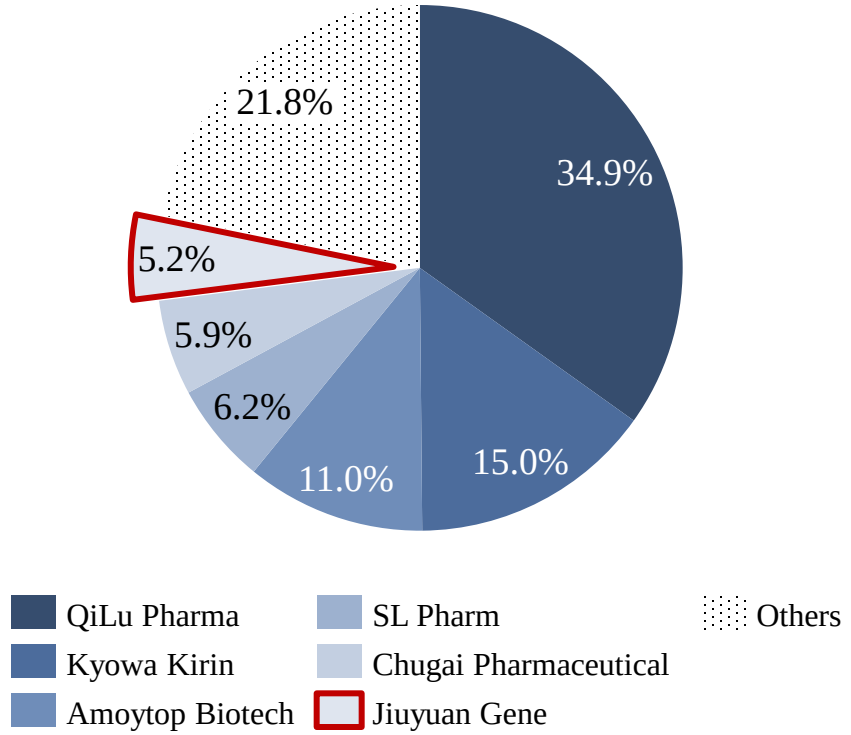
Source：; China Insights Consultancy

# Competitive Landscape of the short-acting G-CSF market in China, 2021 & 2022

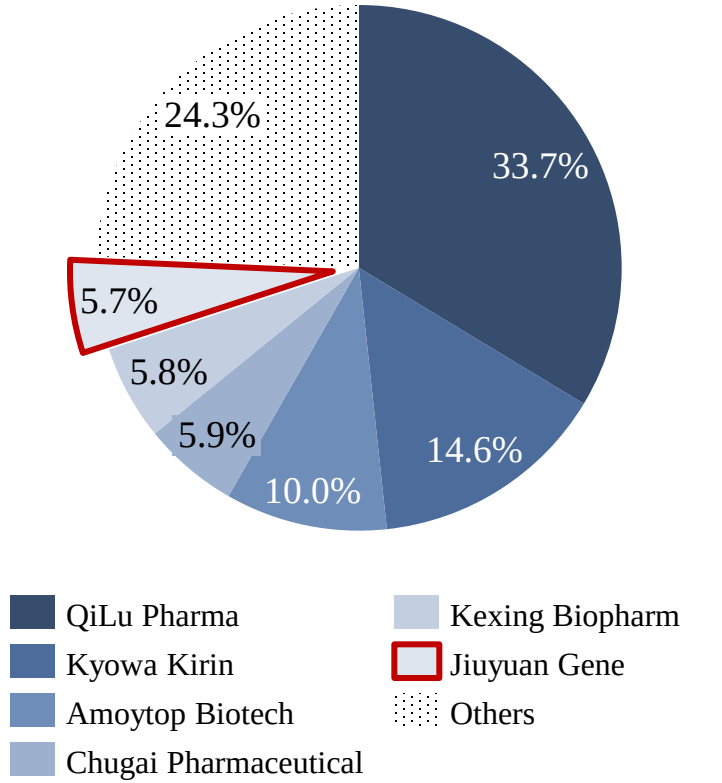


- The sales revenue of Jilifen is RMB[145.8 million] and RMB[165.9 million] in 2021 and 2022 with a market share of [5.2]% and [5.7]% of the short-acting rhG-CSF drug market in China, respectively, and ranked [6] and [6] nationally in the corresponding periods.

**Competitive Landscape of the short-acting G-CSF market in China, 2021**




**Competitive Landscape of the short-acting G-CSF market in China, 2022**





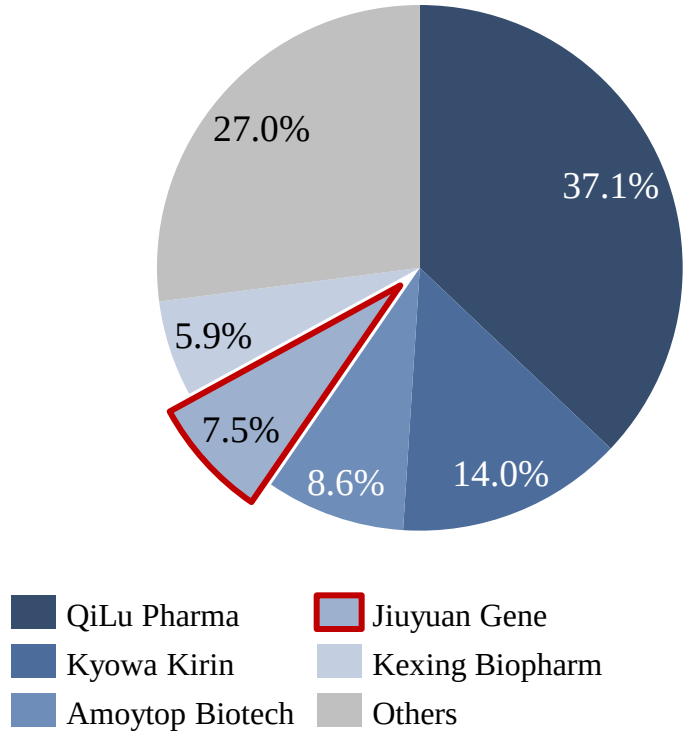

Source：; China Insights Consultancy

# Competitive Landscape of the short-acting G-CSF market in China, 2023



- The market share of Jilifen is [7.5]% of of the short-acting rhG-CSF drug market in China, and ranked [4] nationally in 2023.

**Competitive Landscape of the short-acting G-CSF market in China, 2023**





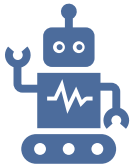

Source：; China Insights Consultancy

# Entry barriers of G-CSF drugs



**Entry barriers of G-CSF drugs**

## Technological barriers



- The successful development of long-acting G-CSF relies heavily on PEG modification, which offers advantages such as prolonging the drug's half-life in the body, reducing protein immunogenicity, and improving drug solubility. Currently, the main sites for PEG modification of rhG-CSF include the ε-amino group of lysine side chains, the α-amino group of N-terminus, the thiol group of cysteine, and the hydroxyl group of serine. However, these techniques demand highly specialized equipment and expertise, presenting certain technological barriers to new entrants.

## Talent barriers

- Whether it is long-acting G-CSF or short-acting G-CSF, a high level of expertise is required. However, for a company, recruiting or cultivating a highly skilled technical professional demands a significant investment of both funds and time. Therefore, the talent barrier is also a crucial factor that must be considered when entering the G-CSF market

# Demand for G-CSF is rising due to policy, aging population, and increased health awareness. Long-acting G-CSF will be developed, and more patients will have access to treatment with the improvement of medical insurance



## Market drivers for G-CSF

**1 Policy advocacy**

- MAH System
  - ➢ R&D enterprises without manufacturing licenses can entrust multiple other companies for production, allowing the R&D enterprise to transform its technology into stable and substantial revenue
- Priority Review and Approval System
  - ➢ By the conclusion of 2021, the annual time-bound completion rate reached an impressive **98.93%**, with both NDA and ANDA **exceeding 90%**
  - ➢ The reduced time-to-market costs have prompted enterprises to enhance their efforts in innovative R&D, such as long-acting G-CSFs

**2 Population aging and gradual rise in cancer incidences**

- Population aging is a key factor for the global G-CSFs market as it's commonly used to address neutropenia in post-chemotherapy patients, and cancer prevalence is higher in the elderly
  - ➢ The data from the seventh national population census shows that the elderly population aged 65 and above in China has exceeded 200 million, **accounting for approximately 14.2%** of the total population. This has significantly surpassed the **World Health Organization's threshold of 7% for an aging society**

**3 Increasing patient awareness and healthcare insurance coverage**

- Most developed countries like the U.S. have extensively employed 1st and 2nd G-CSF products for neutropenia therapy. In comparison, developing countries like China began adopting 2nd G-CSF products relatively recently
- With growing patient awareness and enhanced healthcare insurance systems, PEG-rhG-CSF treatment for neutropenia will gain standardization and improved patient affordability

## Market trends for G-CSF

**More innovations in long-acting modifications**

- The G-CSFs market is shifting towards long-acting drugs from short-acting ones, with ongoing R&D efforts for protein half-life extension through various modification approaches
- Polyethylene glycol (PEG) modification and Fc fusion technology upgrade short-acting G-CSF by extending half-life, enhancing treatment efficacy. Improved R&D capabilities drive innovation in drug delivery methods like transdermal therapeutic systems (TTS), enhancing safety, convenience, and comfort of G-CSF injections

**More market players and intense market competition**

- Amgen once led the global G-CSFs market, but with patents of long-acting G-CSF expiring (2015), companies from the U.S., Europe, Japan, and China have introduced biosimilars
- Many 2nd G-CSF products have already received approvals. However, numerous companies are entering this market to further develop G-CSFs that are not only more efficient but also possess a wider range of indications

**Incoming novel products and increasing patient affordability**

- China are expanding insurance coverage. Adding PEG-rhG-CSF to China's reimbursement list in 2017 lowered costs and improved patient affordability, and here are some achievements below:
  - ➢ In 2017, Jinyouli (CSPC) and Xinruibai (Qilu Pharmaceutical) were listed under National Medical Insurance Category B, with unit prices lowered to approximately 1,700 yuan (for 3mg). In subsequent years, prices have further decreased to around 1600 yuan (for 3mg)
  - ➢ Aiduo(Hengrui) was also added on the list, with the price around 3,000 yuan (for 6mg) in 2019 and around 1600 yuan (for 3mg) in 2023
  - ➢ In June 2023, Peijin (Amotop) was received regulatory approval for market launch and inclusion in medical insurance, priced below 3000 yuan( for 6mg)



Source：NMPA; NHSA; National Bureau of Statistics; China Insights Consultancy

# Table of contents



# Thrombocytopenia is one of the most common complications of tumor chemotherapy/radiotherapy; in China, rhIL-11 and rhTPO are two types of medications currently approved by the NMPA for treatment



## Definition and incidence of Thrombocytopenia

- **Definition**: Thrombocytopenia is a condition frequently resulted from antitumor chemotherapy drugs or radiotherapy **inhibiting bone marrow megakaryocytes, leading to a platelet count of less than 100×10⁹/L in the peripheral blood**

- The **incidence of CIT varies according to definition and inclusion criteria**, and is related to the type of chemotherapeutic agent, whether it is a combination therapy or not, and the type of tumor
  - When cisplatin or gemcitabine are used alone, the incidence of level III-IV CIT is 4.0% and 3.7%, respectively, whereas it is as high as 37% when both are used in combination
  - The incidence was as high as 79% in sarcoma patients receiving combination chemotherapy with ifosfamide, doxorubicin, and dacarbazine

| Level of CIT | Platelet count (×10⁹/L) |
|---|---|
| Level 1 | <LLN-75 |
| Level 2 | <75-50 |
| Level 3 | <50-25 |
| Level 4 | <25 |

LLN: Lower limit of normal value

- A clinical study[1] in the United States included patients with solid tumors and non-Hodgkin's lymphoma treated with multi-agent chemotherapy and investigated the relationship between the incidence of CIT and chemotherapeutic agents. **The results showed that the overall incidence of CIT was 9.7%, and the probability of CIT varied by chemotherapy regimen, with the highest incidence in the gemcitabine-containing regimen (13.5%), followed by carboplatin-containing regimens (13.2%), etc.**

## Cause-effect overview of Thrombocytopenia

### Chemotherapy/radiotherapy

- **Reduce platelets production**: Chemotherapeutic drugs can have an impact on various aspects of platelet production, including inhibition of hematopoietic stem cells and megakaryocyte progenitor cell proliferation, etc.
- **Increase platelets destruction**: Chemotherapeutic drugs can lead to drug-derived immune thrombocytopenia
- **Abnormal distribution of platelets**: Chemotherapeutic drugs lead to hepatic sinusoidal injury, platelet retention in the spleen and increased destruction, resulting in a decrease in peripheral blood platelet count

### Thrombocytopenia

- Thrombocytopenia is the most common complication of oncology treatment when antineoplastic chemotherapeutic agents/radiotherapy depress bone marrow function, resulting in a lower-than-normal Platelets (PLT) in the peripheral blood
- **Thrombocytopenia is one of the most common hematologic toxicities in cancer treatment**

### Treatment

- **Medicine：** Recombinant human interleukin 11(rhIL- 11) , rhIL-11(I) and recombinant human thrombopoietin(rhTPO)
- **Platelet transfusion:** Platelet transfusion is a fast and effective treatment method for severe thrombocytopenia to reduce the risk of hemorrhage and mortality

### Results

- Thrombocytopenia can lead to a **decrease in the intensity of the chemotherapy dose, a delay in the duration of hospitalization, an increase in health care costs and, in severe cases, death**, thus compromising antitumor efficacy and negatively affecting long-term survival of patients



1. Wu Y, Aravind S, Ranganathan G, et al. Anemia and thrombocytopenia in patients undergoing chemotherapy for solid tumors: a descriptive study of a large outpatient oncology practice database

Source：Chinese journal of clinical oncology; China Insights Consultancy

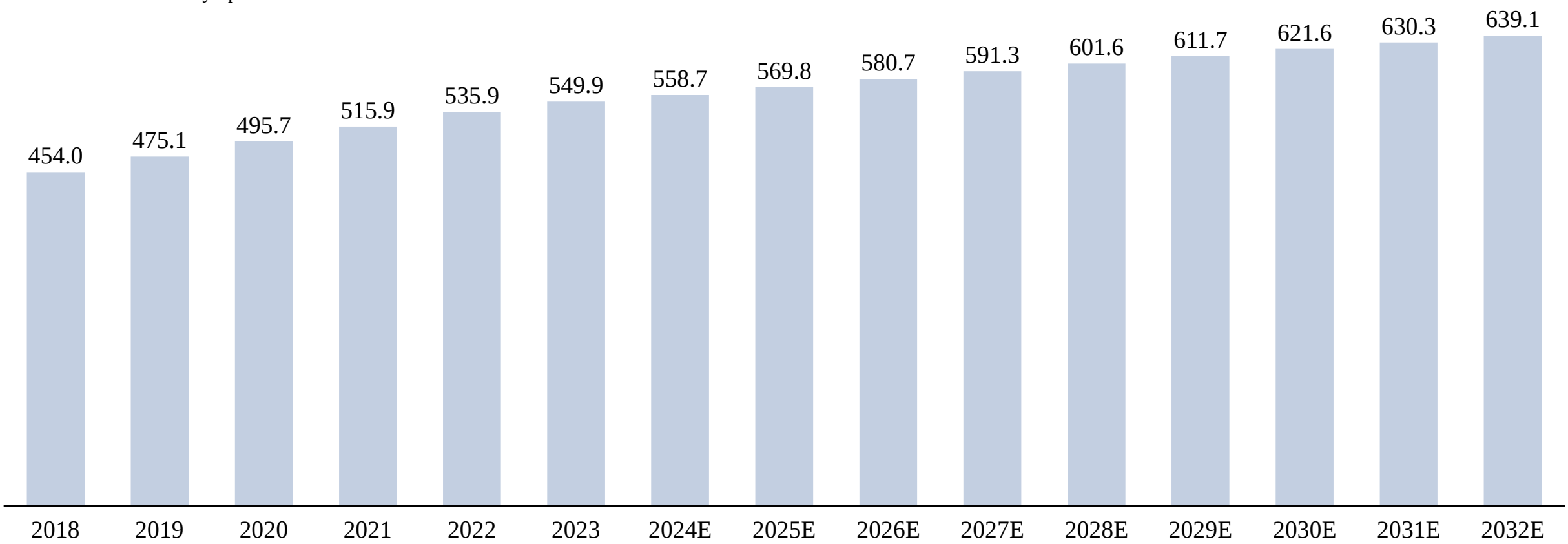
# Incidence of Thrombocytopenia in China, 2018-2032E



**Incidence of Thrombocytopenia in China, 2018-2032E**

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Incidence of Thrombocytopenia in China | 3.8% | 1.7% |

*thousand patients*






Note: Both chemotherapy and radiotherapy are taken into considerations.

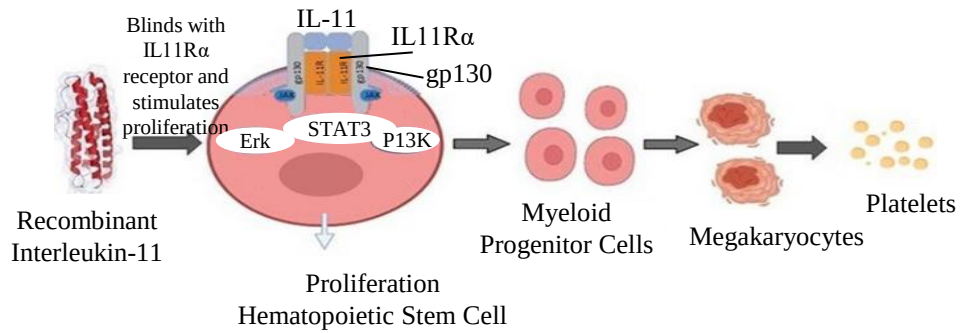
Source: China Insights Consultancy

# IL-11 is a pleiotropic cytokine present in the human body; recombinant human interleukin- 11 (rhIL-11) is a thrombopoietic growth factor and an effective therapeutic agent for the treatment of thrombocytopenia



## Definition and therapeutic pathway of rhIL-11

- **Definition:** Interleukin-11 (IL-11) is a pleiotropic cytokine derived from stromal cells and some mesenchymal cells in the hematopoietic microenvironment. **IL-11 was developed as a recombinant protein (Recombinant human interleukin-11, rhIL-11). RhIL-11 is a established thrombopoietic growth factor and an effective therapeutic agent for the treatment of thrombocytopenia that accelerates the recovery of platelet counts, facilitating the administration of the planned chemotherapy without dose modification**
- **Therapeutic pathway:** IL-11 plays its biological role by binding to the specific receptor-ligand binding chain, IL-11Rα, on the cell surface, and linking to the signal transduction chain soluble glycoprotein 130




- **The hematopoietic function of IL-11：** IL-11 promote the generation of platelet by stimulating the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells, inducing the differentiation and maturation of megakaryocytes, promoting the generation of hyperploid megakaryocytes, and increasing the production of single megakaryocyte platelets

## Development of rhIL-11

**1991**
- The IL-11 gene was cloned and successfully transferred to E. coli, and the study of rhIL-11 entered clinical trials

**1997**
- The U.S. Food and Drug Administration (FDA) has officially **approved rhIL-11 for the prevention of severe thrombocytopenia** caused by high-risk myelosuppressive chemotherapy regimens and to reduce the need for platelet transfusion in patients

**2003**
- China National Medical Products Administration (NMPA) approved the domestic **rhIL-11 in China for the secondary prevention and indicated treatment of level III/IV thrombocytopenia after chemotherapy in solid tumors and non-myeloid leukemia**

**2014**
- The U.S. Oncology Nursing Society (ONS) recommended **rhIL-11 as the drug for CIT**

**2018**
- The Chinese Expert Consensus on the Diagnosis and Treatment of chemotherapy-induced thrombocytopenia formulated by the Chinese Society of Clinical Oncology (CSCO) recommends **rhIL-11 for CIT as first line treatment with level 1b evidence and as secondary prevention with level 2b evidence**

**2021**
- Chinese Expert Consensus on rhIL-11 for the Prevention and Treatment of Thrombocytopenia **further elaborates on the dosage and considerations of rhIL-11**

- rhIL-11 can improve the hematopoietic microenvironment, delay the process of bone marrow adiposity, regulate inflammatory factors in the body, reduce the incidence of infection caused by chemotherapy, and improve the symptoms of mucosal inflammation caused by chemotherapy. rhIL-11 also aids in maintaining smooth anticancer chemotherapy by boosting PLT levels while reducing bleeding risk, thus lowering the chance of platelet transfusion dependency among patients



Source： Chinese journal of clinical oncology; China Insights Consultancy

# Overview of rhIL-11 as preventive treatment in the clinical guideline



## Overview of rhIL-11 as preventive regimens in the clinical guideline

**Mechanisms of prevention**

- **There's a negative feedback loop between platelet count and thrombopoietin (TPO) –** when peripheral platelet counts increase, circulating blood TPO decreases.
- Clinically, platelet counts usually begin to decline after 1 week of chemotherapy, with a slow rise in endogenous TPO levels, and it takes at least 5-7 days for endogenous TPO to elevate peripheral blood platelet counts, before which platelet count nadir may occur and may lead to the risk of hemorrhage and serious complications.
- **The theoretical basis for preventing thrombocytopenia is to increase the level and shorten the duration of platelet nadir counts in chemo- and radiation-treated patients by supplementing exogenous TPO when platelet counts have not yet declined and TPO levels are low.**

### Primary prevention pathway

- Multiple clinical trial results suggest that in patients who use adequate doses of chemotherapeutic agents that can cause thrombocytopenia and dose-limiting toxicity (e.g., high-dose cytarabine), and who are expected to have the potential to develop thrombocytopenia of level III or higher at the end of their first chemotherapy session, application of drugs such as **rhTPO prior to thrombocytopenia can reduce the extent of platelet decline and shorten the duration of platelets of level IV.**

- Primary prevention of CIT refers to prevention that targets the etiology of thrombocytopenia. **However, the target population, timing, and optimal administration of primary prevention of CIT have not yet been clarified**

### Secondary prevention pathway

Prophylactic use of thrombopoietic agents after the current cycle of chemotherapy

- Presence high risk factors → It is recommended to start prophylactic application of thrombopoietic drugs 6 to 24 hours after chemotherapy
- No high risk factors → It is recommended to start the use of thrombopoietic drugs at PLT<75×$10^9$/L, and stop the drugs when PLT≥100×$10^9$/L

### Dosing frequency for secondary prevention

1. **rhIL-11/rhIL-11（I）**
   *rhIL-11(I) is a biosimilar of rhIL-11
   - Subcutaneous injection, 25-50 μg/kg
   - Daily or every other day for 7-10 consecutive days, but rhIL-11 should not be used 2 days before the start of the next cycle of chemotherapy or during chemotherapy
2. **rhTPO**
   - Subcutaneous injection, 25-50 μg/kg
   - Daily or every other day for 7-10 consecutive days

### The target population for secondary prevention

- Patients with thrombocytopenia of level III or greater in the previous chemotherapy cycle and
- patients with thrombocytopenia of level II in the previous chemotherapy cycle who also have one of the following high-risk factors for bleeding



Source： CSCO; China Insights Consultancy

# Overview of rhIL-11 as treatment regimens in the clinical guideline

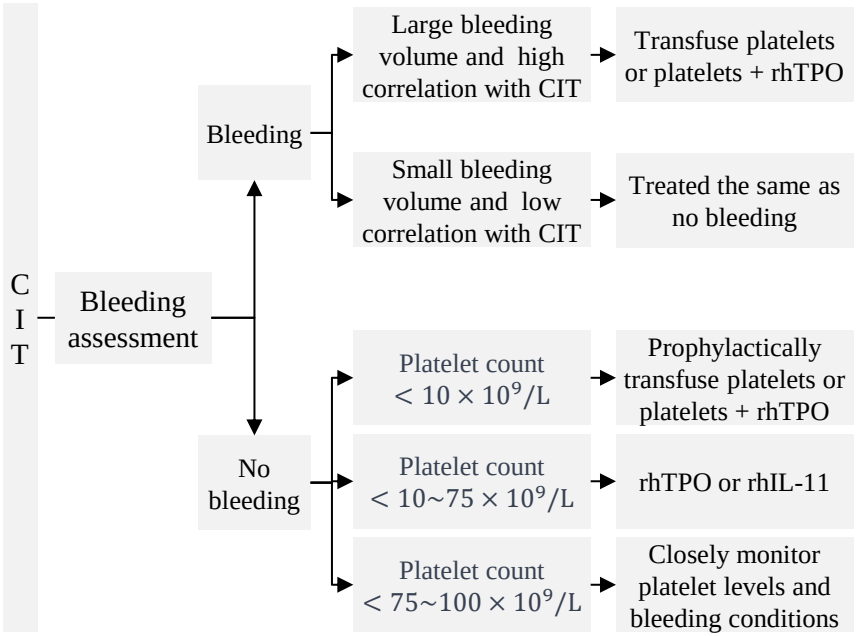


## Overview of rhIL-11 as treatment regimens in the clinical guideline

**Disease treatment**

- **Treatment goals:** (a) Increase the minimum platelet count; (b) Shorten the duration of platelet reduction; (c) Reduce the bleeding risk caused by platelet deficiency; (d) Decrease the reduction of chemotherapy dosage and the delay in chemotherapy duration due to platelet deficiency
- **Pre-treatment assessment**
  - **Etiological assessment:** There are many causes of platelet reduction, including decreased production, increased destruction, and abnormal distribution
  - **Bleeding risk assessment:** Assessing patient's bleeding risk and severity is crucial for selecting appropriate CIT treatment measures

### Therapeutic pathways




### Dosing frequency

**1 rhIL-11/ rhIL-11(I)**

Should not be used 2 days prior to the next chemotherapy cycle and during chemotherapy

- The dosage is 50 μg/kg, once daily via subcutaneous injection, for a duration of 7 to 14 days, until PLT≥ $100 \times 10^9$/L, or until the platelet count increases by $50 \times 10^9$/L from baseline
- The recommended dosage and usage of rhIL-11 (I) are the same as for rhIL-11

**2 rhTPO**

- It should be applied when the platelet count is $< 75 \times 10^9$/L The dosage is 300 U/kg/d, once daily, for continuous use. During usage, monitor the blood routine, generally 2 times per week
- For special patients, it can be adjusted to once every other day based on the situation

### Adverse effects analysis

- Fever: Antipyretic and analgesic drugs can be used after ruling out other factors
- Edema: During medication, closely monitor the patient's body weight and 24-hour fluid intake and output
- Cardiovascular system abnormalities: In cases of symptoms such as heart failure, arrhythmia, it is advisable to stop the medication

- Common adverse effects include: fever, chills, general discomfort, fatigue, knee joint pain, headache, dizziness, and elevated blood pressure
- Results from a large-scale case study indicate a favorable safety profile for rhTPO, with an overall adverse effects rate of 1.27%. Approximately 77.01% of adverse events occurred within 5 days after medication, primarily manifesting as systemic symptoms

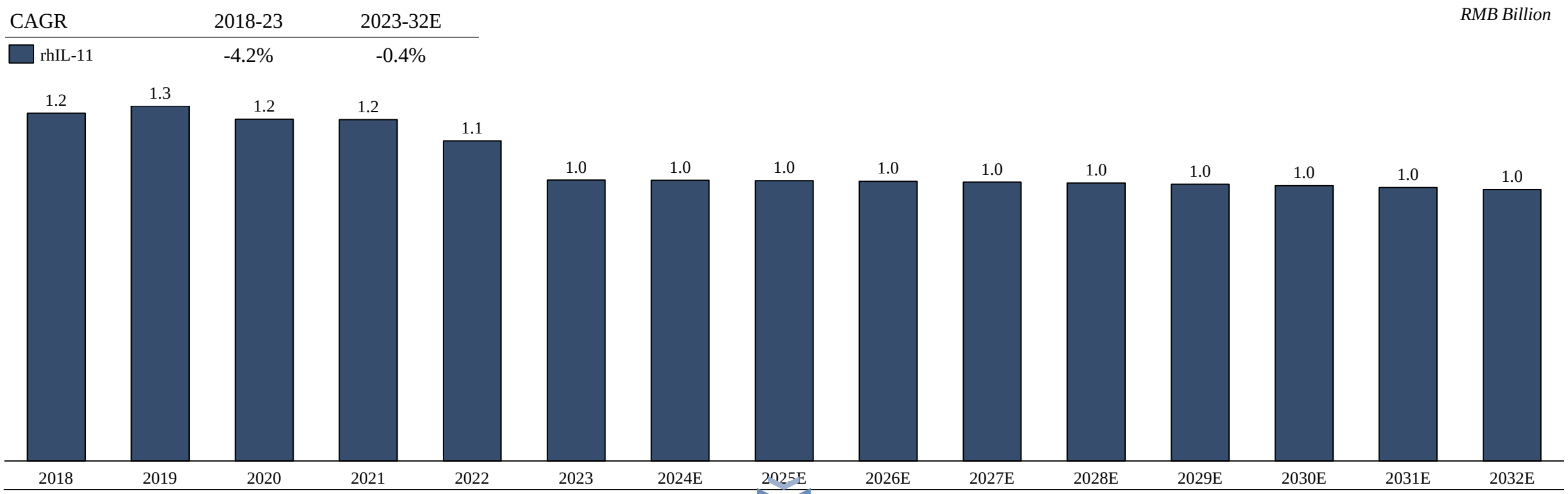


Source: Chinese journal of clinical oncology; CSCO; China Insights Consultancy

# China rhIL-11 market is expected to stabilize around RMB 1.0 Billion by 2032



## China rhIL-11 Market Size, 2018-2032E




**Key Analysis**

- RhIL-11 is a commonly used drug in clinical practice for the treatment of thrombocytopenia. In 2023, Anhui province announced the selection results from its 2022 provincial VBP, which includes the VBP results of rhIL-11 medication; the selected manufacturers for VBP of rhIL-11 products include CR Pharma and Qilu Pharmaceuticals. In 2023, Hebei led Beijing-Tianjin-Hebei (京津冀) VBP also includes rhIL-11 medications; the selected manufacturers include SL Pharm and Qilu Pharma. Going forward, it is expected that more provinces will include rhIL-11 products in upcoming provincial VBPs as NHSA urges provincial VBPs to cover biologic products.
- China rhIL-11 market is expected to stabilize around RMB 1.0 Billion by 2032



*Source: Chinese Medical Journal; China Insights Consultancy*

# As of LPD, there are 6 rhIL-11 drugs approved by the NMPA in China



**NMPA Approved rhIL-11 drugs, as of LPD**

| Approval number* | Product name | Generic name | Manufacturer | Indication | First approval date |
|---|---|---|---|---|---|
| S20030034 | Yixing | Oprelvekin (rhIL-11) | DIAO GROUP. | Used for the treatment of severe thrombocytopenia in patients with solid tumors, non-myeloid leukemia following chemotherapy. It is administered before the next cycle of chemotherapy to reduce the risk of bleeding and dependency on platelet transfusions due to thrombocytopenia | 2003.04 |
| S20030014; S20030015 | Maigeer | Oprelvekin (rhIL-11) | Beijing SL Pharmaceutical Co., Ltd. | Used for the treatment of severe thrombocytopenia in patients with solid tumors, non-myeloid leukemia following chemotherapy. It is administered before the next cycle of chemotherapy to reduce the risk of bleeding and dependency on platelet transfusions due to thrombocytopenia | 2003.03 |
| S20030077; S20060062; S20063110 | Jijufen | Oprelvekin (rhIL-11) | Hangzhou jiuyuan gene engineering Co., Ltd. | Used for the treatment of severe thrombocytopenia in patients with solid tumors, non-myeloid leukemia following chemotherapy. It is administered before the next cycle of chemotherapy to reduce the risk of bleeding and dependency on platelet transfusions due to thrombocytopenia | 2003.09 |
| S20030016; S20030017; S20053046 | Juheli | Oprelvekin (rhIL-11) | Qilu Pharmaceutical Co., Ltd. | Used for the treatment of severe thrombocytopenia in patients with solid tumors, non-myeloid leukemia following chemotherapy. It is administered before the next cycle of chemotherapy to reduce the risk of bleeding and dependency on platelet transfusions due to thrombocytopenia | 2003.03 |
| S20050036; S20050037; S20050038; S20050039; S20050040 | Topmega | Oprelvekin (rhIL-11) | Amoytop | Used for the treatment of severe thrombocytopenia in patients with solid tumors, non-myeloid leukemia following chemotherapy. It is administered before the next cycle of chemotherapy to reduce the risk of bleeding and dependency on platelet transfusions due to thrombocytopenia | 2005 |
| S20080009 | Baijieyi | rhIL-11(I) | China Resources Angde Biotech Pharma Co., Ltd. | Used for the treatment of severe thrombocytopenia in patients with solid tumors, non-myeloid leukemia following chemotherapy. It is administered before the next cycle of chemotherapy to reduce the risk of bleeding and dependency on platelet transfusions due to thrombocytopenia | 2008 |



Note*: Multiple approval numbers indicate that the same drug has been approved in various dosages

Source：NMPA; China Insights Consultancy

# Competitive Landscape of the rhIL-11 Market in China, 2022



**Competitive landscape of rhIL-11 in China, 2022**

| Company | Generic Name | Brand Name | NMPA First Approval Year | NRDL Inclusion | Revenue (Ten thousand RMB) | Market Share | MoA | Indications | Route of Administration |
|---|---|---|---|---|---|---|---|---|---|
| QiLu Pharmaceutical Co., Ltd.<br>齐鲁制药 | Oprelvekin (rhIL-11) | Juheli | 2003 | Yes | 62,871.9 | 55.0% | IL-11 plays its biological role by binding to the specific receptor-ligand binding chain, IL-11Rα, on the cell surface, and linking to the signal transduction chain soluble glycoprotein 130 | Chemotherapy-induced thrombocytopenia | Injection |
| Xiamen Amoytop Biotech Co., Ltd.<br>厦门特宝生物 | Oprelvekin (rhIL-11) | Topmega | 2005 | Yes | 16,011.7 | 14.0% | IL-11 plays its biological role by binding to the specific receptor-ligand binding chain, IL-11Rα, on the cell surface, and linking to the signal transduction chain soluble glycoprotein 130 | Chemotherapy-induced thrombocytopenia | Injection |
| China Resources Angde Biotech Pharma Co., Ltd.<br>华润昂德生物药业 | rhIL-11(I) | Baijieyi | 2008 | Yes | 15,320.3 | 13.4% | IL-11 plays its biological role by binding to the specific receptor-ligand binding chain, IL-11Rα, on the cell surface, and linking to the signal transduction chain soluble glycoprotein 130 | Chemotherapy-induced thrombocytopenia | Injection |
| Hangzhou jiuyuan gene engineering Co., Ltd.<br>杭州九源基因 | Oprelvekin (rhIL-11) | Jijufen | 2003 | Yes | 9,429.80 | 8.2% | IL-11 plays its biological role by binding to the specific receptor-ligand binding chain, IL-11Rα, on the cell surface, and linking to the signal transduction chain soluble glycoprotein 130 | Chemotherapy-induced thrombocytopenia | Injection |
| Beijing SL Pharmaceutical Co., Ltd.<br>北京双鹭药业 | Oprelvekin (rhIL-11) | Maigeer | 2003 | Yes | 7,860.6 | 6.9% | IL-11 plays its biological role by binding to the specific receptor-ligand binding chain, IL-11Rα, on the cell surface, and linking to the signal transduction chain soluble glycoprotein 130 | Chemotherapy-induced thrombocytopenia | Injection |

Note: This table lists the top 5 manufacturers of rhIL-11 in China, 2022

Source: NMPA; China National Intellectual Property Administration; China Insights Consultancy

# Competitive Landscape of the rhIL-11 Market in China, 2023



**Competitive landscape of rhIL-11 in China, 2023**

| Company | Generic Name | Brand Name | NMPA First Approval Year | NRDL Inclusion | Market Share | MoA | Indications | Route of Administration |
|---|---|---|---|---|---|---|---|---|
| QiLu Pharmaceutical Co., Ltd. 齐鲁制药 | Oprelvekin (rhIL-11) | Juheli | 2003 | Yes | 55.63% | IL-11 plays its biological role by binding to the specific receptor-ligand binding chain, IL-11Rα, on the cell surface, and linking to the signal transduction chain soluble glycoprotein 130 | Chemotherapy-induced thrombocytopenia | Injection |
| Xiamen Amoytop Biotech Co., Ltd. 厦门特宝生物 | Oprelvekin (rhIL-11) | Topmega | 2005 | Yes | 13.85% | IL-11 plays its biological role by binding to the specific receptor-ligand binding chain, IL-11Rα, on the cell surface, and linking to the signal transduction chain soluble glycoprotein 130 | Chemotherapy-induced thrombocytopenia | Injection |
| China Resources Angde Biotech Pharma Co., Ltd. 华润昂德生物药业 | rhIL-11(I) | Baijieyi | 2008 | Yes | 12.23% | IL-11 plays its biological role by binding to the specific receptor-ligand binding chain, IL-11Rα, on the cell surface, and linking to the signal transduction chain soluble glycoprotein 130 | Chemotherapy-induced thrombocytopenia | Injection |
| Hangzhou jiuyuan gene engineering Co., Ltd. 杭州九源基因 | Oprelvekin (rhIL-11) | Jijufen | 2003 | Yes | 11.84% | IL-11 plays its biological role by binding to the specific receptor-ligand binding chain, IL-11Rα, on the cell surface, and linking to the signal transduction chain soluble glycoprotein 130 | Chemotherapy-induced thrombocytopenia | Injection |
| Beijing SL Pharmaceutical Co., Ltd. 北京双鹭药业 | Oprelvekin (rhIL-11) | Maigeer | 2003 | Yes | 6.45% | IL-11 plays its biological role by binding to the specific receptor-ligand binding chain, IL-11Rα, on the cell surface, and linking to the signal transduction chain soluble glycoprotein 130 | Chemotherapy-induced thrombocytopenia | Injection |

Note: This table lists the top 5 manufacturers of rhIL-11 in China, 2022

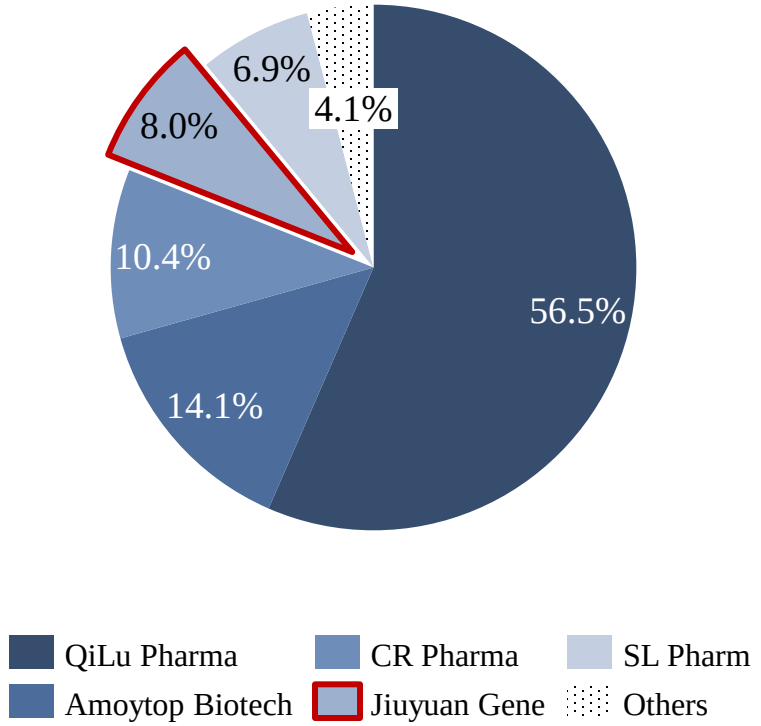
Source: NMPA; China National Intellectual Property Administration; China Insights Consultancy

# Competitive Landscape of the rhIL-11 Market in China, 2021 & 2022

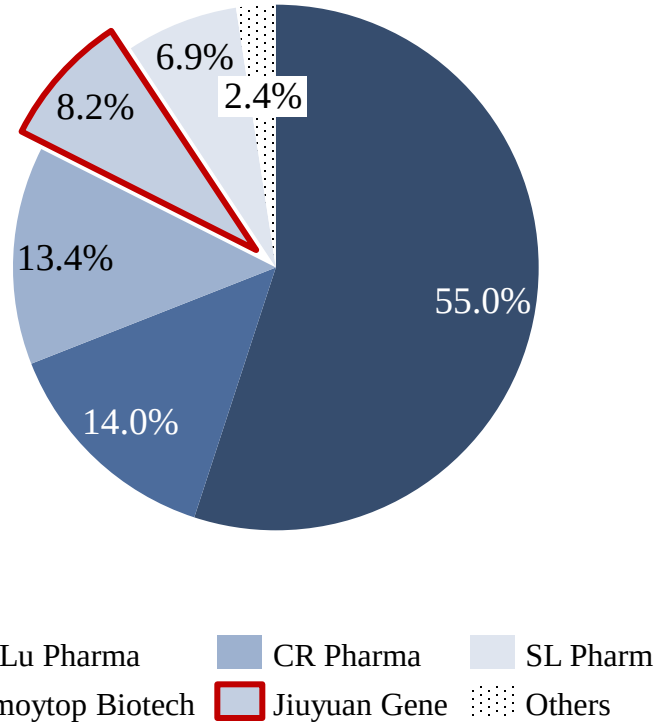


- The sales revenue of Jijufen is RMB[97.2 million]and RMB[94.3 million] in 2021 and 2022 with a market share of [8.0]% and [8.2]% of the interleukin-11 drug market in China, respectively, and ranked [4] and [4] nationally in the corresponding periods.

**Competitive Landscape of the rhIL-11 Market in China, 2021**




**Competitive Landscape of the rhIL-11 Market in China, 2022**





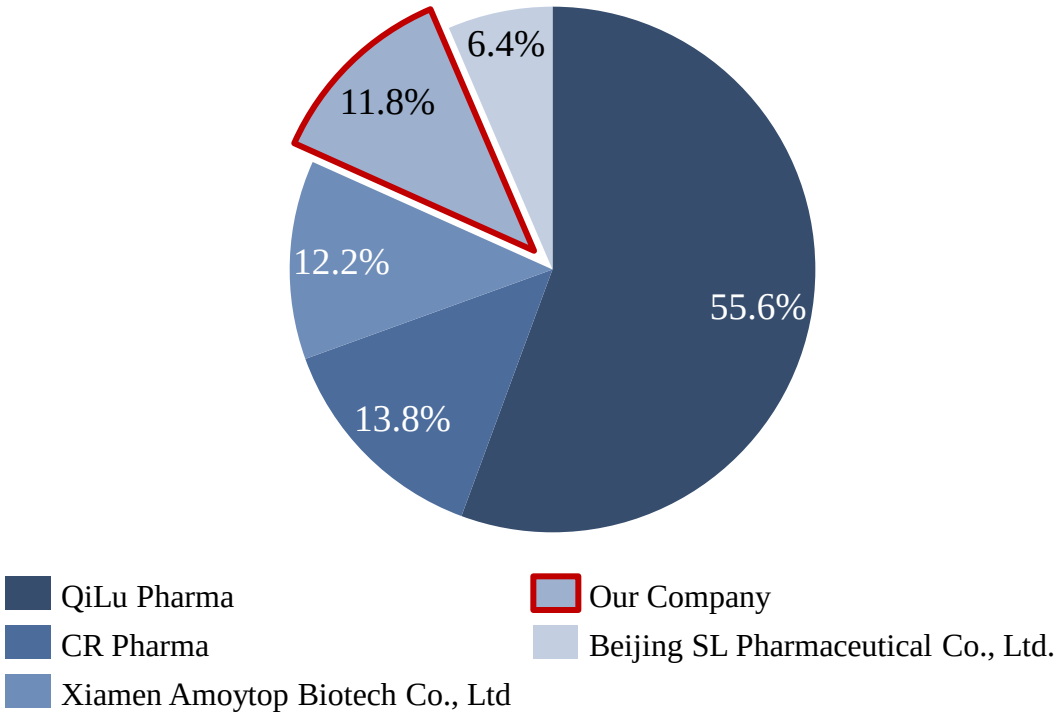

Source： China Insights Consultancy

# Competitive Landscape of the rhIL-11 Market in China, 2023



- The market share of Jijufen is [11.8]% of of the interleukin-11 drug market in China, and ranked [4] nationally in 2023.

**Competitive Landscape of the rhIL-11 Market in China, 2023**

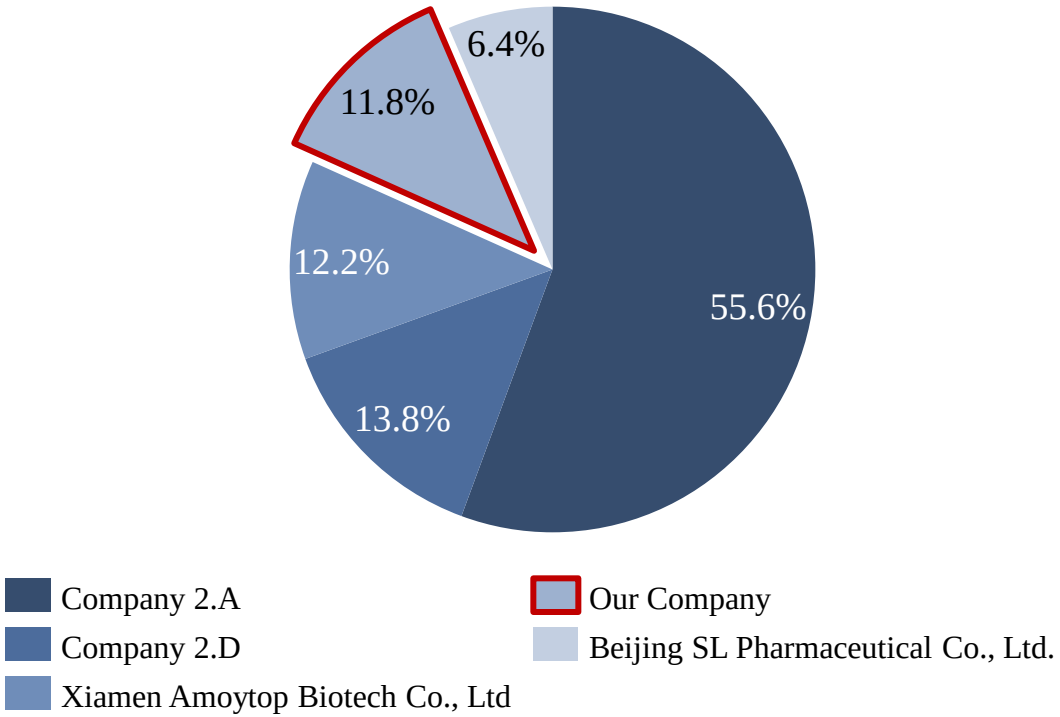


# Competitive Landscape of the rhIL-11 Market in China, 2023



- The market share of Jijufen is [11.8]% of of the interleukin-11 drug market in China, and ranked [4] nationally in 2023.

**Competitive Landscape of the rhIL-11 Market in China, 2023**




- Company 2.D, headquartered in Shandong, China, was founded in 1997. It is primarily dedicated to the R&D, production, and sales of recombinant protein drugs. It entered the cancer treatment drug sector in 2008 and currently holds one approved IL-11 drug candidate in China.
- Beijing SL Pharmaceutical Co., Ltd. (北京雙鷺藥業股份有限公司), headquartered in Beijing, China and listed on the Shenzhen Stock Exchange (stock code: 002038.SZ), was founded in 1994. It focuses on the R&D, production, and sales of genetically engineered drugs.



Source： China Insights Consultancy

# Entry barriers of rhIL-11 drugs

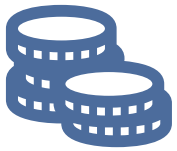


**Entry barriers of rhIL-11 drugs**

## Technological barriers

- rhIL-11 is a complex protein, and its accurate three-dimensional structure is crucial for its biological activity. Therefore, advanced techniques in biochemistry and structural biology are necessary to ensure the correct folding and functionality. Assessing the biological activity of rhIL-11 involves sensitive biological experiments and functional analysis techniques, posing a technical challenge. Hence, rhIL-11 presents a significant technical barrier, requiring enterprises entering this field to meet high technological demands

## Fund barriers



- The development of rhIL-11 requires a substantial amount of funding for laboratory equipment, researcher salaries, reagents, animal experiments, and more. These costs may need to be invested in the early stages of research and could increase as the development progresses. Transitioning rhIL-11 from the laboratory to clinical trials also demands significant financial investment, covering the manufacturing of drugs that meet quality standards, conducting clinical trials, obtaining regulatory approvals, and other related expenses. As such, Interleukin-11 presents a high financial barrier to entry

# Propelled by policy and guidelines, along with rising cancer cases, the rhIL-11 market has substantial growth potential. It aims for enhanced safety, efficacy diversity, and cost competitiveness



## Market drivers

### 1 Expert consensus guidelines

- According to the Expert Consensus on Prevention and Treatment of Thrombocytopenia Induced by Lymphoma Chemotherapy in China, issued by the Chinese Society of Clinical Oncology (CSCO), **rhIL-11 is identified as a key therapeutic agent for addressing thrombocytopenia induced by lymphoma chemotherapy**
- In Expert Consensus on Diagnosis and Treatment of Chemotherapy-Induced Thrombocytopenia in China, published by the Chinese Anti-Cancer Association, **rhIL-11 is recommended as a primary therapeutic approach for managing chemotherapy-related thrombocytopenia in cancer patients**

### 2 Increasing cancer patients

- China bears a substantial cancer burden, with the overall cancer incidence having consistently risen since 2000. In 2020, China reported 4.57 million new cancer cases, **accounting for 23.7% of global new cancer cases, thus positioning itself as the leading nation in terms of cancer patient numbers**
- The escalating number of cancer patients has led to a rise in recipients of chemotherapy, subsequently elevating the incidence of CIT. This phenomenon has propelled the expansion of the market for rhIL-11 class medications

### 3 Policy advocacy

- **Medical insurance**: **rhIL-11 has been incorporated into the national Category B medical insurance** list due to its unique pharmacological properties and clinical efficacy
- **Innovation drug policy**: The government introduced policies aimed at supporting research, registration, and market approval for innovative drugs, with the intention of incentivizing biopharmaceutical companies to develop novel pharmaceuticals, including rhIL-11

## Market trends

### Enhanced Safety and Efficacy

- At present, the prevailing approach for producing rhIL-11 in the domestic market involves isolation from fusion proteins expressed in Escherichia coli. However, opting for rhIL-11 expressed in eukaryotic cells, such as yeast cells, **not only ensures improved biological activity but also enhances pharmaceutical safety**

### Combined therapy extends across multiple indications

- **rhIL-11 with recovery solution during radiation therapy can significantly alleviate radiation-induced oral mucosal damage and mouth ulcers**. It also reduces pain intensity, shortens pain duration, alleviates oral dryness, and promotes ulcer healing. Notably effective, cost-efficient, and user-friendly, this approach is worthy of clinical promotion and application
- **rhIL-11 with low-dose rituximab demonstrates favorable efficacy in the treatment of primary immune thrombocytopenia (ITP) that is refractory or relapsed to hormones**, with minimal adverse reactions. However, the optimal treatment regimen, long-term effectiveness, and adverse reactions warrant further investigation

### Price reduction

- As the medication becomes part of the insurance coverage, its market share and utilization are poised to expand further. This scalability is expected to lead to **cost reduction through economies of scale and supply chain optimization, driving rational pricing and affordability of the drug in the future**, thereby benefiting a larger patient population. This virtuous cycle will also advance the sustainable development of the pharmaceutical industry, making a positive contribution to public health endeavors



Source：NMPA; NHSA; CSCO; China Insights Consultancy

# Table of contents



# Nausea and vomiting are common symptoms and signs that can result from various conditions, and chemotherapy-induced nausea and vomiting (CINV) is the one of the most serious type of nausea and vomiting



## Introduction to and different levels of nausea and vomiting

- **Nausea and vomiting:** Nausea is a condition characterized by a sensation of queasiness and/or an urgent need to vomit. Vomiting refers to the reflex action of expelling stomach contents through the mouth
- **CINV:** Vomiting and nausea caused by cancer treatment refer to the adverse effects that occur as a result of chemotherapy, radiation therapy, or other cancer treatments. Severe CINV can lead to anorexia, electrolyte imbalances, malnutrition, and impose a significant physiological and psychological burden on cancer patients

**Grades of nausea and vomiting**

| Grades | Nausea | Vomiting |
|---|---|---|
| Grade I | Decreased appetite without changes in eating habits | No intervention required |
| Grade II | Reduced oral food intake without significant weight loss, dehydration, or malnutrition | Outpatient intravenous rehydration, requiring medical intervention |
| Grade III | Inadequate oral intake of energy and fluids, requiring nasogastric feeding, total parenteral nutrition, or hospitalization | Requires nasogastric feeding, total parenteral nutrition, or hospitalization |
| Grade IV | / | Life-threatening, requiring urgent treatment |
| Grade V | / | Fatal |

## Classification of CINV

| | |
|---|---|
| **Acute** | • **Occur within 24 hours after chemotherapy**, typically peaking at 5-6 hours post-administration |
| **Delayed** | • **Occur more than 24 hours after chemotherapy**, typically peaking at 48-72 hours post-administration and can persist for 6-7 days |
| **Anticipatory** | • **Occur in patients who have previously undergone chemotherapy with inadequate antiemetic control**. Due to fear of chemotherapy and conditioned reflexes, they experience nausea and vomiting before the next cycle of chemotherapy |
| **Breakthrough** | • Refer to cases **where despite prophylactic antiemetic use before chemotherapy**, patients still experience nausea and vomiting, requiring rescue antiemetic treatment. **This can occur at any time after chemotherapy** |
| **Refractory** | • Occur **when previous preventive and/or rescue antiemetic treatments have failed during prior chemotherapy cycles**, and patients continue to experience nausea and vomiting during subsequent chemotherapy |

## Mechanisms of CINV

- **The exact mechanisms of nausea and vomiting are not fully understood**. Vomiting is considered a multi-step reflex process regulated by the vomiting center, **involving peripheral and central pathways**
- Peripheral pathways involve anticancer drugs stimulating the release of serotonin 5-$HT_3$ from gastrointestinal mucosal cells, typically leading to acute vomiting. Central pathways involve substance P binding to neurokinin-1 (NK-1) receptors in the vomiting center, often causing delayed vomiting. **Nausea and vomiting may share some mechanisms but could involve different neural pathways, with nausea being more common than vomiting**



Source: NCI-CTCAE v5.0; Chinese Medical Journal; China Insights Consultancy

# Introduction to and treatment pathways of CINV



## Introduction to and treatment pathways of CINV

**Overview**

- Definition: Chemotherapy-induced nausea and vomiting (CINV) is the most common adverse effect of chemotherapy. CINV can lead to metabolic disturbances, nutritional imbalances, and weight loss, significantly impacting patients' emotional, social, and physical functioning. It is also a major contributor to patients' fear of chemotherapy, decreased quality of life, and reduced treatment adherence
- High-risk factors for causing CINV include age (under 50 years), female gender, prior history of nausea and vomiting, anxiety, fatigue, motion sickness, and low quality of life

### Prophylactic drugs

- Antiemetic drugs should be administered **before each anticancer treatment session, covering the entire risk period**

| Drugs | Time to be administered |
|---|---|
| Intravenous injections | 30 minutes before the first dose |
| Oral formulations | 60 minutes before the first dose |
| Transdermal granisetron patches | 24-48 hours before the first dose |

### Selecting an antiemetic regimen

- Selecting an antiemetic regimen based on the risk grading of CINV caused by anticancer drugs: The incidence of nausea and vomiting is directly related to the emetogenicity of anticancer drugs. Therefore, the choice of antiemetic drugs should primarily be based on the risk grading of CINV associated with the specific anticancer drugs

| Emetogenic risk of anticancer drugs | Corresponding probabilities for acute vomiting[1] |
|---|---|
| Highly | >90% |
| Moderately | 30%-90% |
| Low | 10%-30% |
| Minimal | <10% |

### Personalized medication

- Conduct a comprehensive evaluation of high-risk factors and concurrent conditions for personalized medication. Alongside the inherent emetogenicity of anticancer drugs, doctors should consider various factors. Tailoring antiemetic therapy based on individual patient profiles and treatment contexts is crucial for effective management

**Factors**

- Drug dosage
- Infusion rate
- Patient characteristics (such as age, gender)
- Specific medical histories
- Treatment settings (whether inpatient or outpatient)

### Lifestyle management

- Adopting a healthy lifestyle can help alleviate nausea and vomiting reactions. This includes eating small, frequent meals, choosing easily digestible foods, controlling portion sizes, avoiding spicy, extremely hot or cold foods, and engaging in moderate exercise like walking or brisk walking under medical guidance

### Emphasize reevaluation

- Reassess post-treatment nausea and vomiting risk: Modify antiemetic strategies based on past effectiveness.

Dranitsaris scoring system + Online tool

**For personalized risk prediction**

- Patients scoring ≥16 have a >60% risk of moderate to severe nausea and vomiting in the next cycle. This system, with 87.4% sensitivity, despite 38.4% specificity2, can guide adjustments



Source: Chinese Medical Journal; China Insights Consultancy

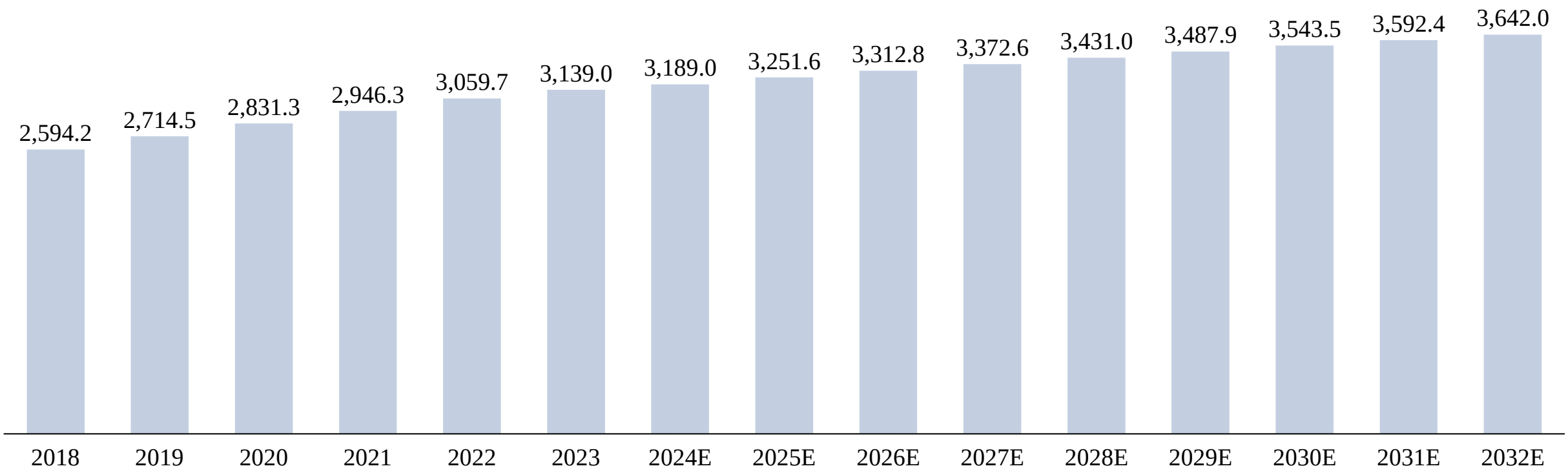
# Incidence of CINV in China and future forecasts, 2018-2032E



**Incidence of CINV in China, 2018-2032E**

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Incidence of CINV in China | 3.8% | 1.7% |

*thousand patients*






Note: Both chemotherapy and radiotherapy are taken into considerations.

*Source: Chinese Medical Journal; China Insights Consultancy*

# In Chinese clinical guidelines, 6 categories of drugs are recommended for the treatment of CINV, and the selection is based on the individual patient's condition



## Introduction to main CINV drugs

| • Categories | • Mechanism of drugs | • Key Drugs | • Note |
|---|---|---|---|
| **5-$HT_3$ receptor antagonists** | 5-$HT_3$ receptor antagonists work by blocking the interaction between 5-$HT_3$ receptors in the vagus nerve and the chemoreceptor trigger zone | There are two generations of 5-$HT_3$ receptor antagonists: the first generation includes ondansetron, granisetron, dolasetron, tropisetron, azasetron, and ramosetron, while **palonosetron** belongs to the second generation | / |
| **NK-1 receptor antagonists** | NK-1 receptor antagonists exert their antiemetic effects by competitively inhibiting the binding of substance P to NK-1 receptors. They are primarily used to prevent delayed-onset nausea and vomiting | Aprepitant, rolapitant, fosaprepitant and etc. | / |
| **Corticosteroids** | Dexamethasone can prevent nausea and vomiting by interacting with 5-$HT_3$, NK-1, and NK-2 receptor proteins, or by directly affecting the solitary nucleus within the medulla oblongata | Dexamethasone | For patients receiving highly emetogenic chemotherapy or regimens without cisplatin, especially those with minimal emetic risk factors, it may be considered to reduce the dose of dexamethasone or use dexamethasone only on the first day of treatment (Level 2A evidence, Grade II recommendation) |
| **Atypical antipsychotic drugs** | Atypical antipsychotic drugs can significantly prevent both acute and delayed nausea and vomiting by antagonizing various receptors such as 5-$HT_3$, 5-$HT_2$, dopamine, histamine, and acetylcholine | Olanzapine and mirtazapine | When using ondansetron for prophylactic antiemesis in the treatment of moderate-to-high emetic risk, the recommended dose of ondansetron is 5-10 mg (Level 1A evidence, Grade I recommendation) |
| **Glutamate derivatives** | The molecular mechanism for the prophylactic antiemetic effects of sarilumab in cancer drug treatment is not yet fully clear | Thalidomide | / |
| **Others** | Dopamine receptor antagonists (e.g., metoclopramide), benzodiazepines (e.g., lorazepam), phenothiazines (e.g., prochlorperazine and promethazine), and butyrophenones (e.g., droperidol) | | These types of medications are generally considered to have lower antiemetic efficacy and are not recommended for prophylactic antiemesis in moderate-to-high emetic risk regimens |

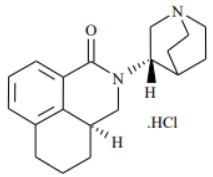


Source: Chinese Medical Journal; China Insights Consultancy

# Palonosetron is a second-generation 5-$HT_3$ receptor antagonist, and it is significantly superior to first-generation agents in both its therapeutic effects and adverse effects

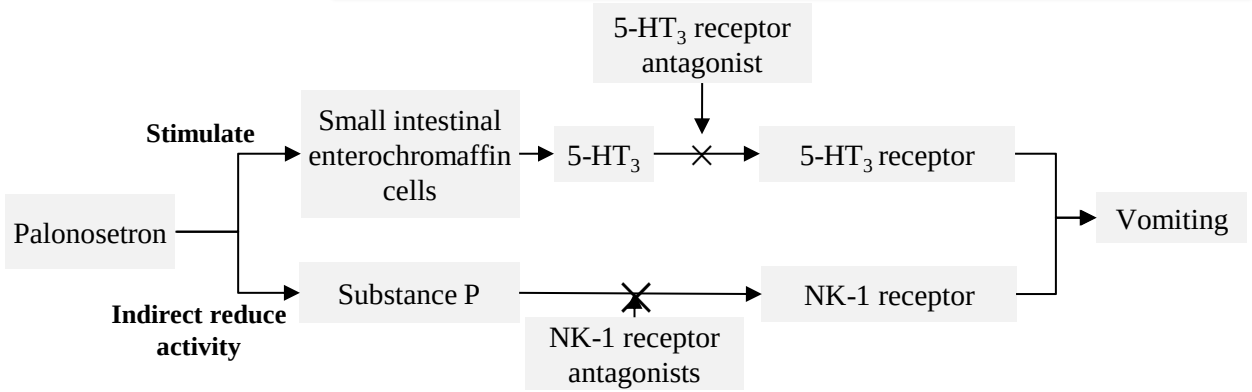


## Introduction to and mechanism of action of palonosetron



Chemical Formula: $C_{19}H_{24}N_2O \cdot HCl$

- Definition: Palonosetron is a **second-generation 5-$HT_3$ receptor antagonist**, highly potent with long-lasting antiemetic effects. It is also the **only 5-$HT_3$ receptor antagonist approved by the FDA for the prevention of delayed nausea and vomiting associated with chemotherapy.**
- Indications: Prevention of acute and delayed nausea and vomiting induced by chemotherapy, prevention of postoperative nausea and vomiting




- Mechanism of action : By **blocking the binding of 5-$HT_3$ to 5-$HT_3$ receptors in the gastrointestinal tract**, palonosetron inhibits the transmission to the emetic center, thereby suppressing acute nausea and vomiting. Another mechanism that contributes to palonosetron's high efficacy is its inhibition of cross talk between 5-$HT_3$ and NK-1 receptor signaling pathways, and **Palonosetron can reduce the activity of substance P**, which can bind to NK-1 receptors to lead vomiting

## Advantages of palonosetron

Palonosetron is significantly more effective than first-generation 5-$HT_3$ receptor antagonists in preventing delayed nausea and vomiting:

- Structural advantage: Compared to first-generation 5-$HT_3$ receptor antagonists, Palonosetron exhibits an approximately 100-fold increase in affinity for 5-$HT_3$ receptors and has a prolonged half-life of up to 40 hours[1]
- Mechanism advantage: Apart from inhibiting vomiting by blocking the binding of 5-$HT_3$ receptors, Palonosetron can reduce the activity of substance P by inhibiting the interaction between the 5-$HT_3$ and NK-1 signaling pathways. Palonosetron is significantly superior to 1st generation 5-$HT_3$ receptor antagonists in preventing delayed nausea and vomiting
- Adverse effects advantage: Palonosetron has a lesser impact on the cardiovascular system compared to first-generation drugs, but the incidence and severity of other adverse reactions with palonosetron are similar to that of the first-generation ondansetron

## Possible adverse effects of palonosetron

- Constipation: palonosetron is associated with the inhibition of gastrointestinal motility and secretory function
- Headache: The majority of patients experience mild symptoms that can self-resolve
- Cardiovascular system symptoms: Prolongation of the cardiovascular QT interval is relatively rare (incidence <0.1%)[2], but it should be closely monitored when using 5-$HT_3$ receptor antagonists

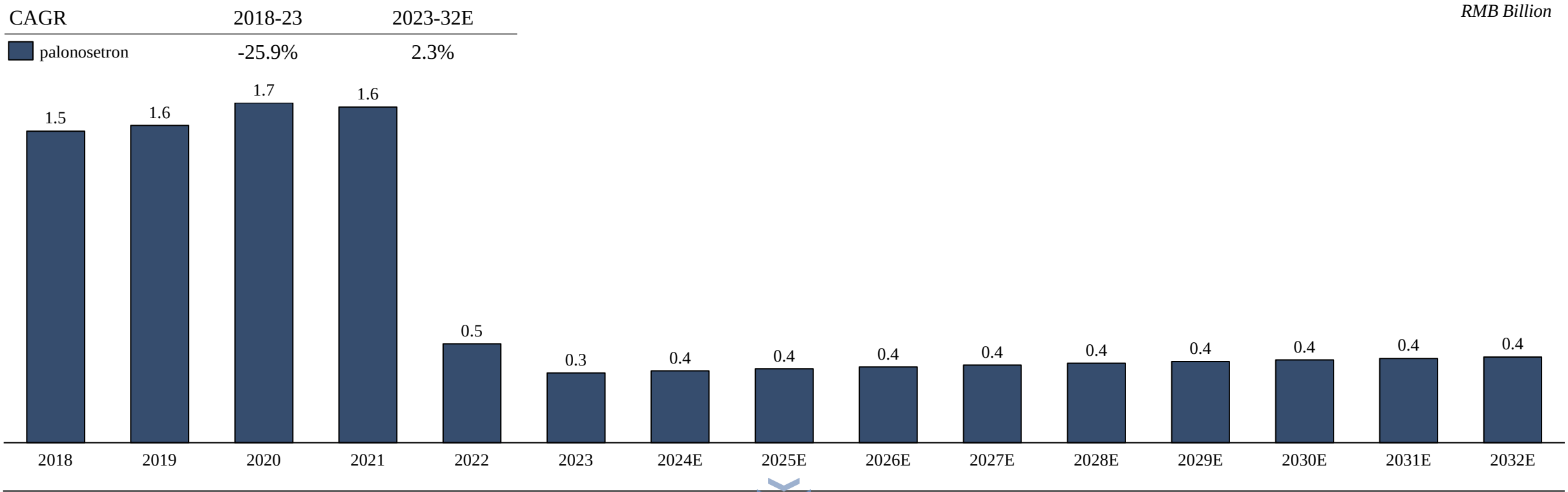


Source: Chinese Medical Journal; China Insights Consultancy

# China palonosetron market is expected to stabilize around RMB 0.4 Billion by 2032



## China palonosetron Market Size, 2018-2032E




**Key Analysis**

- Palonosetron injection 5ml:0.25mg was included in the fifth national VBP, and 1.5m1:0.075mg was included in the seventh national VBP. China palonosetron market experienced a sharp decline in 2022 due to the implementation of low VBP price. The average price reduction of palonosetron injection(1.5m1:0.075mg) post-VBP is over 80%. Six manufacturers, including **Jiuyuan Gene**, were selected manufacturers in the seventh national VBP.
- China palonosetron market is expected to stabilize around RMB 0.4 Billion by 2032



Source: Chinese Medical Journal; China Insights Consultancy

# As of August 2023, there are over 40 palonosetron drugs approved by the NMPA in China， and palonosetron has been included in the national category B medical insurance



**Top 5 earliest approved palonosetron by NMPA**

| Initial Approval number | Product name | Generic name | Manufacturer | Indication | Initial approval date |
|---|---|---|---|---|---|
| H20080226 | Ousai | Palonosetron | Qilu Pharmaceutical Co., Ltd. | To prevent acute nausea and vomiting caused by highly emetogenic chemotherapy. To prevent acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy. This product is suitable for pediatric patients aged 1 month to under 17 years for the prevention of acute CINV, including highly emetogenic chemotherapy | 2008 |
| H20080716 | Zhiruo | Palonosetron | ChiaTai Tianqing (CCTQ) | To prevent acute nausea and vomiting caused by highly emetogenic chemotherapy. To prevent acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy. This product is suitable for pediatric patients aged 1 month to under 17 years for the prevention of acute CINV, including highly emetogenic chemotherapy | 2008 |
| H20080747 | / | Palonosetron | Shanghai Huayuan Pharmacy | To prevent acute nausea and vomiting caused by highly emetogenic chemotherapy and to prevent nausea and vomiting caused by moderately emetogenic chemotherapy | 2008 |
| H20080811 | Jiouting | Palonosetron | Hangzhou jiuyuan gene engineering Co., Ltd. | To prevent acute nausea and vomiting caused by highly emetogenic chemotherapy. To prevent acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy. This product is suitable for pediatric patients aged 1 month to under 17 years for the prevention of acute CINV, including highly emetogenic chemotherapy | 2008 |
| H20100095 | Lowvo | Palonosetron | Simcere Pharmaceutical Group Limited | To prevent acute nausea and vomiting caused by highly emetogenic chemotherapy and to prevent nausea and vomiting caused by moderately emetogenic chemotherapy | 2010 |



Source：NMPA; China Insights Consultancy

# Competitive Landscape of the Palonosetron Market in China, 2022



**Competitive landscape of Palonosetron in China, 2022**

| Company | Generic Name | Brand Name | NMPA First Approval Year | NRDL Inclusion | Revenue (Ten thousand RMB) | Market Share | MoA | Indications | Route of Administration |
|---|---|---|---|---|---|---|---|---|---|
| ChiaTai Tianqing (CCTQ)<br>正大天晴药业集团 | Palonosetron | Zhiruo | 2008 | Yes | 22,482.5 | 46.5% | By blocking the binding of 5-$HT_3$ to 5-$HT_3$ receptors in the gastrointestinal tract, palonosetron inhibits the transmission to the emetic center, thereby suppressing acute nausea and vomiting | CINV | Injection |
| Hangzhou jiuyuan gene engineering Co., Ltd.<br>杭州九源基因 | Palonosetron | Jiouting | 2008 | Yes | 6,781.70 | 14.0% | By blocking the binding of 5-$HT_3$ to 5-$HT_3$ receptors in the gastrointestinal tract, palonosetron inhibits the transmission to the emetic center, thereby suppressing acute nausea and vomiting | CINV | Injection |
| Qilu Pharmaceutical Co., Ltd.<br>齐鲁制药(海南) | Palonosetron | Ousai | 2008 | Yes | 5,245.5 | 10.9% | By blocking the binding of 5-$HT_3$ to 5-$HT_3$ receptors in the gastrointestinal tract, palonosetron inhibits the transmission to the emetic center, thereby suppressing acute nausea and vomiting | CINV | Injection |
| Yangtze River Pharmaceutical Group Sichuan Hairong Pharmaceutical Co., Ltd.<br>扬子江四川海蓉药业 | Palonosetron | Payi | 2013 | Yes | 2,300.6 | 4.8% | By blocking the binding of 5-$HT_3$ to 5-$HT_3$ receptors in the gastrointestinal tract, palonosetron inhibits the transmission to the emetic center, thereby suppressing acute nausea and vomiting | CINV | Injection |
| Helsinn Healthcare S.A. | Palonosetron | Akynzeo | 2019 | Yes | 2,039.5 | 4.2% | By blocking the binding of 5-$HT_3$ to 5-$HT_3$ receptors in the gastrointestinal tract, palonosetron inhibits the transmission to the emetic center, thereby suppressing acute nausea and vomiting | CINV | Injection |



Note: This table lists the top 5 manufacturers of Palonosetron in China, 2022

Source: NMPA; China National Intellectual Property Administration; China Insights Consultancy

# Competitive Landscape of the Palonosetron Market in China, 2023



**Competitive landscape of Palonosetron in China, 2023**

| Company | Generic Name | Brand Name | NMPA First Approval Year | NRDL Inclusion | Market Share | MoA | Indications | Route of Administration |
|---|---|---|---|---|---|---|---|---|
| ChiaTai Tianqing (CCTQ)<br>正大天晴药业集团 | Palonosetron | Zhiruo | 2008 | Yes | 54.18% | By blocking the binding of 5-$HT_3$ to 5-$HT_3$ receptors in the gastrointestinal tract, palonosetron inhibits the transmission to the emetic center, thereby suppressing acute nausea and vomiting | CINV | Injection |
| Hangzhou jiuyuan gene engineering Co., Ltd.<br>杭州九源基因 | Palonosetron | Jiouting | 2008 | Yes | 12.51% | By blocking the binding of 5-$HT_3$ to 5-$HT_3$ receptors in the gastrointestinal tract, palonosetron inhibits the transmission to the emetic center, thereby suppressing acute nausea and vomiting | CINV | Injection |
| Qilu Pharmaceutical Co., Ltd.<br>齐鲁制药(海南) | Palonosetron | Ousai | 2008 | Yes | 10.94% | By blocking the binding of 5-$HT_3$ to 5-$HT_3$ receptors in the gastrointestinal tract, palonosetron inhibits the transmission to the emetic center, thereby suppressing acute nausea and vomiting | CINV | Injection |
| Yangtze River Pharmaceutical Group Sichuan Hairong Pharmaceutical Co., Ltd.<br>扬子江四川海蓉药业 | Palonosetron | Payi | 2013 | Yes | 8.38% | By blocking the binding of 5-$HT_3$ to 5-$HT_3$ receptors in the gastrointestinal tract, palonosetron inhibits the transmission to the emetic center, thereby suppressing acute nausea and vomiting | CINV | Injection |

Note: This table lists the top 5 manufacturers of Palonosetron in China, 2022

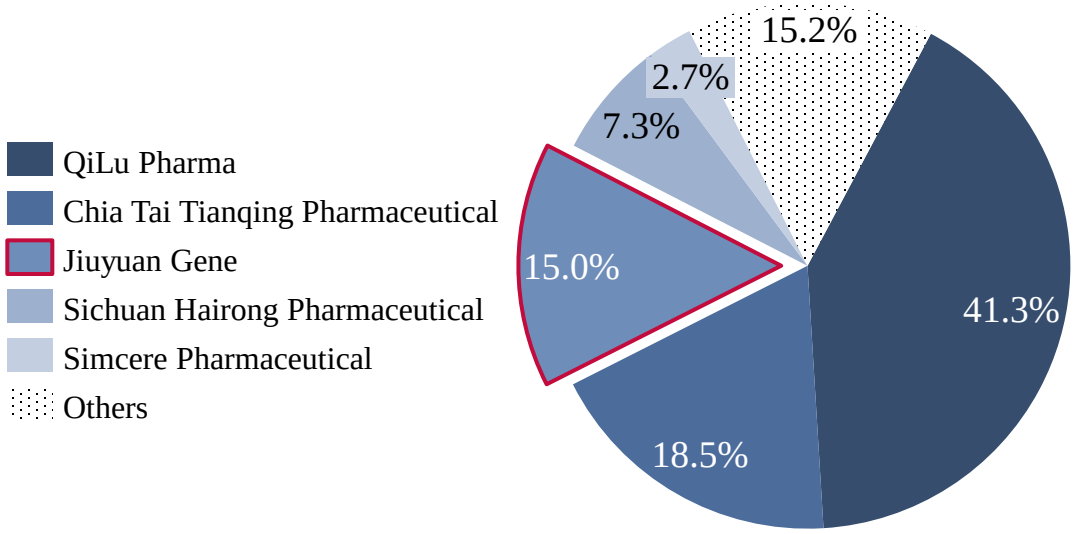
Source: NMPA; China National Intellectual Property Administration; China Insights Consultancy

# Competitive Landscape of the palonosetron Market in China, 2021 & 2022

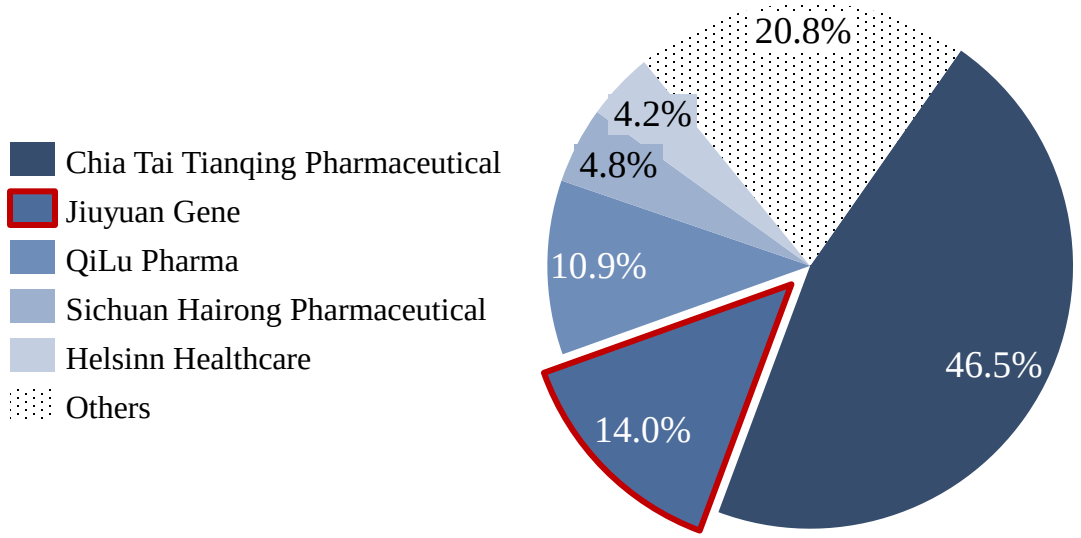


- The sales revenue of Jiouting is RMB[245.9 million] and RMB[67.8 million] in 2021 and 2022 with a market share of [15.0]% and [14.0]% of the palonosetron hydrochloride market in China, respectively, and ranked [3] and [2] nationally in the corresponding periods.

**Competitive Landscape of the palonosetron Market in China, 2021**




**Competitive Landscape of the palonosetron Market in China, 2022**





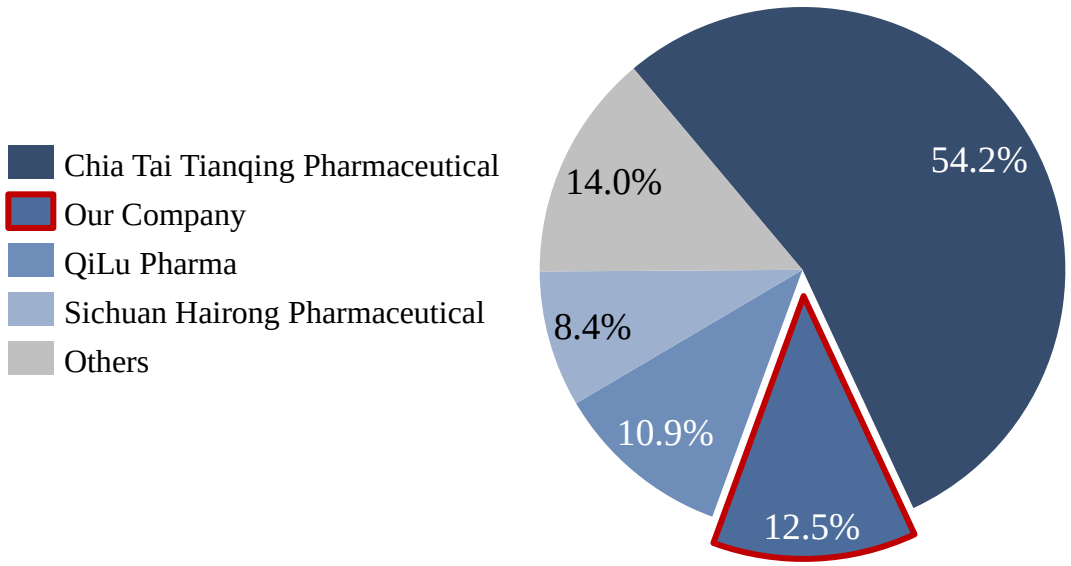

Source：Menet; China Insights Consultancy

# Competitive Landscape of the palonosetron Market in China, 2023



- The market share of Jiouting is [12.5]% of the palonosetron market in China, and ranked [2] nationally in 2023.

**Competitive Landscape of the palonosetron Market in China, 2023**





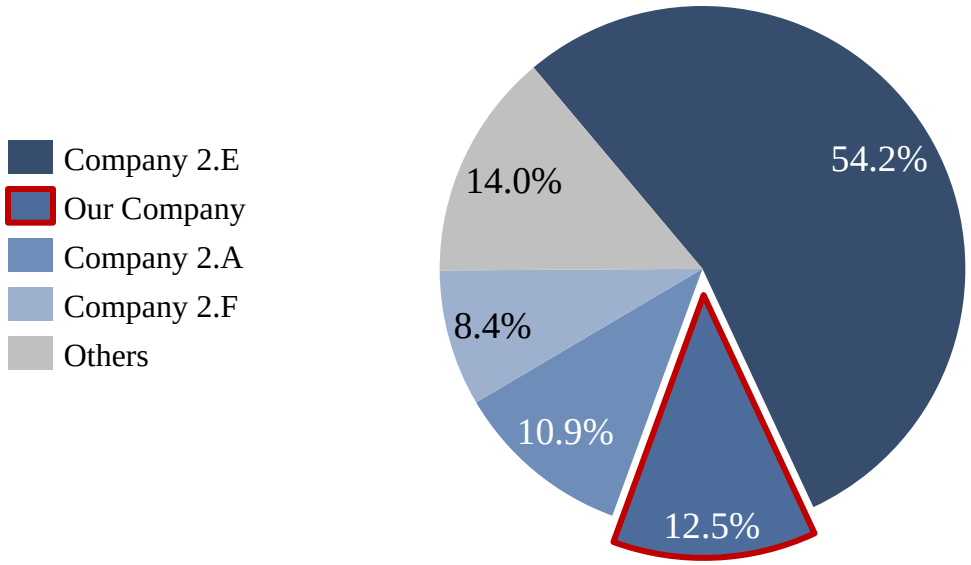

Source：Menet; China Insights Consultancy

# Competitive Landscape of the palonosetron Market in China, 2023



- The market share of Jiouting is [12.5]% of the palonosetron hydrochloride market in China, and ranked [2] nationally in 2023.

**Competitive Landscape of the palonosetron Market in China, 2023**




- Company 2.E, headquartered in Jiangsu, China, was founded in 1997. It focuses on the R&D, production and sales of innovative drugs. It entered the oncology drug sector in 2015 and currently holds three approved drug candidates that are potentially competitive with the Company, including palonosetron, fuvestrant, and fosaprepitant.
- Company 2.F, headquartered in Sichuan, China, was founded in 2001. It is dedicated to the R&D, production, and sales of chemical drugs, and traditional Chinese medicine. It entered the cancer treatment drug sector in 2013 and currently holds one approved palonosetron drug candidates in China.



Source：Menet; China Insights Consultancy

# Drivers and trends of palonosetron



**Drivers and trends of palonosetron**

## Increasing clinical demand

- With the increasing number of cancer patients and the widespread use of chemotherapy, there is a growing demand for effectively managing chemotherapy-induced nausea and vomiting (CINV). Patients aspire to alleviate treatment-related discomfort, especially with drugs like palonosetron, which, due to its longer half-life, can exert a sustained antiemetic effect. As a result, palonosetron is highly favored by patients, and this is expected to further drive the growth of the palonosetron market

## Novel treatment approaches

- Palonosetron, with its longer half-life and higher binding affinity compared to the first-generation 5-$HT_3$ receptor antagonists, demonstrates superior control over delayed chemotherapy-induced nausea and vomiting (CINV) when combined with dexamethasone, particularly in patients undergoing highly emetogenic chemotherapy. Palonosetron exhibits potential for combination therapy and qualifies as a candidate for novel combination treatments. This represents a promising avenue for future research and development in the field

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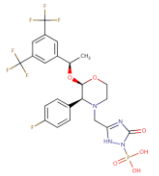
# Fosaprepitant is an NK-1 receptor antagonist and the prodrug of aprepitant. Its antiemetic effectiveness is comparable to that of aprepitant for both acute and delayed nausea and vomiting

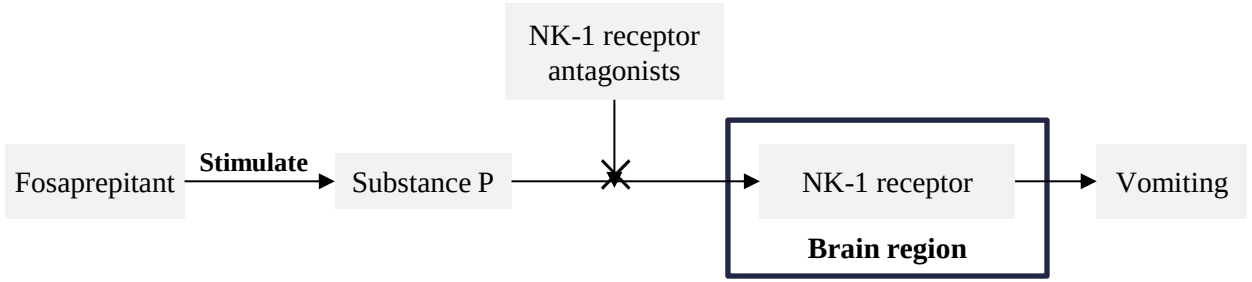


## Introduction to and mechanism of action of fosaprepitant



Chemical Formula: $C_{23}H_{22}F_7N_4O_6P$

- Definition: Fosaprepitant is an NK-1 receptor antagonist, as well as the intravenous prodrug of the orally administered anti-emetic aprepitant
- Indications: Fosaprepitant is indicated in adult and pediatric patients ≥6 months of age, in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin. It is also indicated for the treatment of delayed nausea and vomiting with initial and repeat courses of moderately emetogenic cancer chemotherapy




- Mechanism of action : Fosaprepitant is the prodrug of aprepitant, and its antiemetic effect is derived from aprepitant. Aprepitant is a highly selective, high-affinity antagonist for the human substance P/neurokinin 1 (NK1) receptor. Non-clinical and positron emission tomography (PET) studies in humans have demonstrated that aprepitant can penetrate the blood-brain barrier and **exert its antiemetic effect by competitively inhibiting the binding of NK-1 receptors with substance P**

## Advantages of fosaprepitant

- Fosaprepitant, as a non-oral alternative to aprepitant, can be used in patients who cannot take medications by mouth, have difficulty swallowing, or have impaired digestive function. It provides a safe and effective intravenous alternative for NK-1 receptor antagonist oral formulations
- Early studies of the clinical efficacy of fosaprepitant have shown improvement over treatment with ondansetron. Both aprepitant and fosaprepitant are well tolerated with most adverse events observed of mild or moderate intensity
- Numerous randomized, double-blind Phase III clinical trials conducted both domestically and internationally have shown that fosaprepitant's antiemetic efficacy is non-inferior to that of aprepitant for both acute and delayed nausea and vomiting
- Fosaprepitant (4.0 mg/kg) in addition to ondansetron, without application of dexamethasone, was well tolerated, safe, effective and superior to ondansetron only as CINV prophylaxis in pediatric patients during moderately and highly emetogenic chemotherapy

## Possible adverse effects of fosaprepitant

- Venous inflammation: Symptoms include redness, itching, swelling, pain, hardened veins, and discoloration at the injection site. Most cases occur within the first 1-3 fosaprepitant uses and may persist for over two weeks in some patients. Thrombotic and vasculitic inflammation occurs when fosaprepitant is used with vesicant chemotherapy drugs (e.g., anthracyclines). Avoid peripheral intravenous fosaprepitant administration when possible. For mild cases, use topical creams, magnesium sulfate, or antibiotics for infections. Severe cases may require surgical treatment



Source: Chinese Medical Journal; China Insights Consultancy

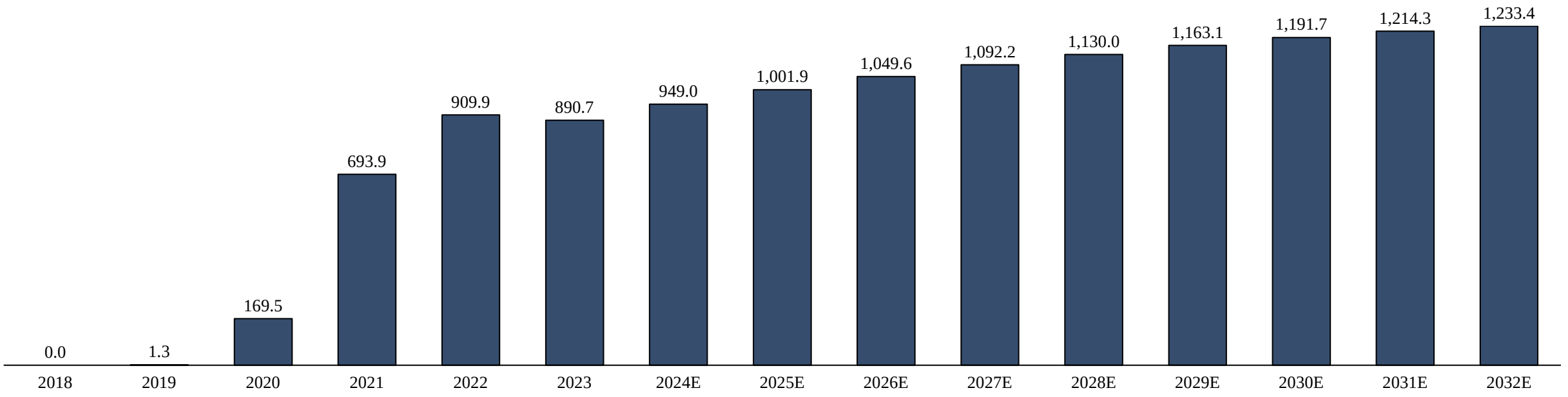
# China fosaprepitant market is expected to increase from RMB 890.7 million in 2023 to RMB 1,233.4 million in 2032 at the CAGR of 3.7%



## China fosaprepitant Market Size, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| China Fosaprepitant Market Size | N.A. | 3.7% |

*RMB Million*




**Key Analysis**

- **China fosaprepitant market grew from RMB1.3 million in 2019 to 890.7 million in 2023 at a CAGR of 407.8%. The market is expected to increase to RMB1,233.4 million in 2032 at the CAGR of 3.7%**



Source: Chinese Medical Journal; China Insights Consultancy

# Drivers and trends of China fosaprepitant market



**Drivers and trends of China fosaprepitant market**

## Rising patients' attention on treatment effectiveness

- Compared to the past, patients are increasingly focused on improving their quality of life and reducing treatment side effects. They also desire medications that take effect more quickly and have better efficacy. Fosaprepitant achieves antiemetic effects by blocking nausea and vomiting signals in the brain. When administered intravenously, the drug takes effect rapidly, typically within about half an hour, leading patients to prefer medications with faster onset for treatment. This trend has contributed to the growth of the fosaprepitant market

## Expansion of indications

- With the continuous advancement in the development of innovative drugs, the technology for expanding drug indications will become more sophisticated. Currently, fosaprepitant is primarily indicated for preventing acute and delayed nausea and vomiting in adult patients undergoing both initial and repeat highly emetogenic chemotherapy (HEC). In the future, it may also demonstrate efficacy in treating other types of nausea and vomiting, such as postoperative vomiting or nausea induced by radiation therapy, thereby expanding the potential market for fosaprepitant

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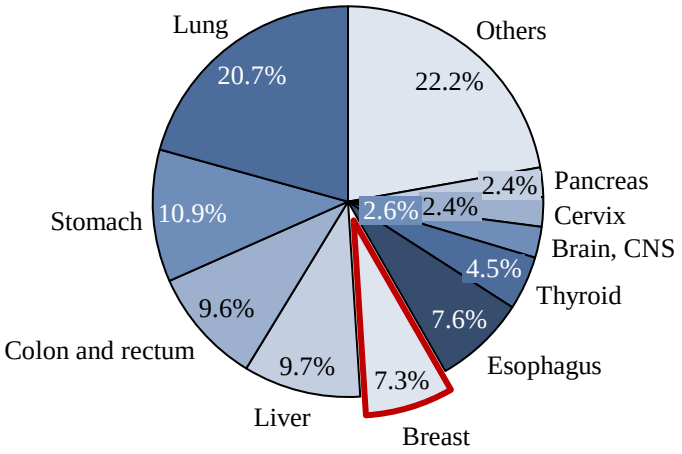
# Breast cancer is a commonly occurring cancer in China, exhibiting clinical manifestations both internally and externally, influenced by a combination of factors that can be modified or non-modifiable



## Introduction to breast cancer

- Breast cancer is a **malignant tumor that occurs in the breast tissue**.
- It typically originates in the lobules or ducts of the breast and can grow, spread, and invade surrounding tissues.
- Breast cancer is **one of the most common malignancies in women**, although **men can also develop breast cancer**, albeit at a lower rate.

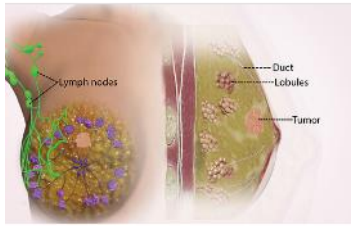
### Incidence by tumor location in China, Top 10, 2022




The incidence of breast cancer ranks fifth among the Chinese population, but first among Chinese women.

## Characteristics of breast cancer

- Treatable in its early stages
- Can last several months or years
- More common in females
- Common for ages 50 and older
- Requires lab test or imaging to diagnose
- Family history may increase likelihood




## Clinical manifestations

| | |
|---|---|
| Breast lump | Breast tissue feels thicker or different from the rest of the breast. |
| Nipple discharge | Nipple discharge consists of blood, milk, pus, and serous fluid. |
| Skin change | The skin surrounding the nipple becomes flaky or scaly. |
| Abnormalities around nipple | Common symptoms include nipple retraction, nipple skin itching, and erosion. |
| Enlarged lymph nodes | Enlarged axillary lymph nodes may feel firm, scattered, and movable when palpated. |

## Risk factors of breast cancer

The etiology of breast cancer is attributed to a complex interaction between various modifiable and non-modifiable factors.

**Non-modifiable factors:**

Generic mutations | Family history | Age | Hormone

**Modifiable factors:**

Environmental | Obesity | Nutritional

Alcohol | Postponed reproduction | Exercise



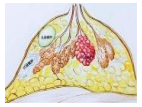
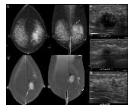
Source: Breast Cancer; Cancer Communications; UICC; CDC; Cell Biochemistry and Biophysics; China Insights Consultancy

# Breast nodules, commonly found in women in China, can be classified as benign or malignant, with malignant nodules indicating breast cancer; the clinical stage of breast cancer is based on disease progression

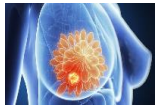
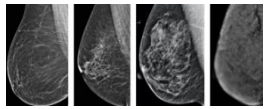
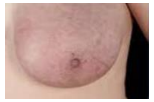


Breast nodules are a commonly observed issue among women in today's society. They are a common manifestation resulting from various breast abnormalities, such as breast hyperplasia, cysts, fat necrosis, and tumors.



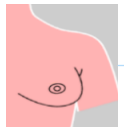
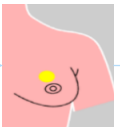
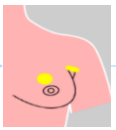
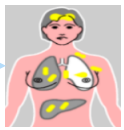
Breast nodules can be classified into benign and malignant nodules, with malignant nodules referring to breast cancer. Breast cancer is staged differently based on the tumor's morphology and the extent of lymph node involvement.

## BI-RADS grading[1] of breast nodules

| Grades | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| | Increasing risks of malignancy | | | | | |
| Clinical description | Negative | Consider positive changes | Possible benign lesion | Suspect malignancy | Highly suspect malignancy | Malignant lesions confirmed with biopsy results |
| Clinical measures | Suggest follow-up | Suggest follow-up regularly | Shorter follow-up period required (every 3 - 6 months) | Suggest biopsy, treated with caution | Surgical removal required | Surgical removal as soon as possible |

## Stages of breast cancer

| Stages | Stage 0 | Stage I (IA, IB) | Stage II (IIA, IIB) | Stage III (IIIA, IIIB, IIIC) | Stage IV |
|---|---|---|---|---|---|
| |  |  |  |  |  |
| Tumor morphology | Carcinoma in situ | Early invasive tumor Tumor < 2cm | Tumor 2cm - 5cm | Tumor > 5cm | Any size tumor |
| Lymph node metastasis | No metastasis | No metastasis yet or have only a small amount of cancer cells detected in the lymph nodes | Spread to 1-3 axillary lymph nodes or lymph nodes near the sternum | Spread to 4-10 lymph nodes in the chest wall or breast skin, causing swelling or ulceration. | Metastases to other organs |



Note: 1. Breast Imaging Reporting and Data System is a common clinical standard for the classification of breast nodules, which can be further used to evaluate the condition of breast lesions

Source: Current situation and trend of cancer in China; Research progress on epidemiological trends and risk factors of female breast cancer; China Insights Consultancy

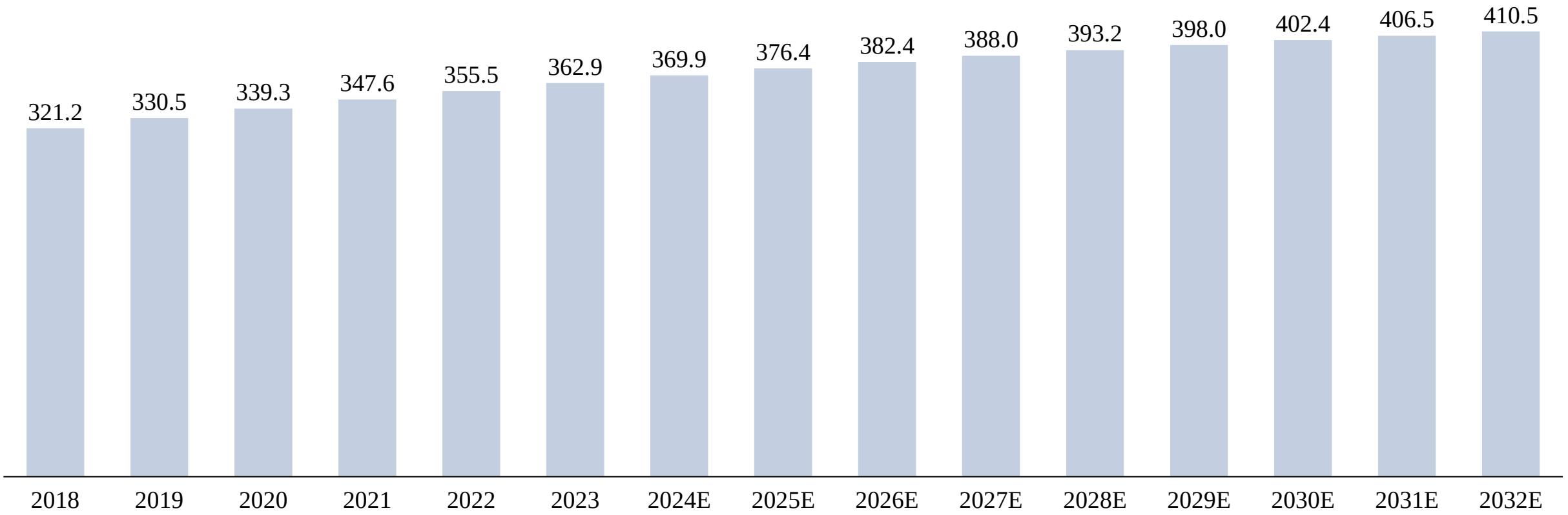
# Incidence of breast cancer in China and future forecasts, 2018-2032E



**Incidence of breast cancer in China, 2018-2032E**

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Incidence of breast cancer in China | 2.5% | 1.4% |

*thousand patients*



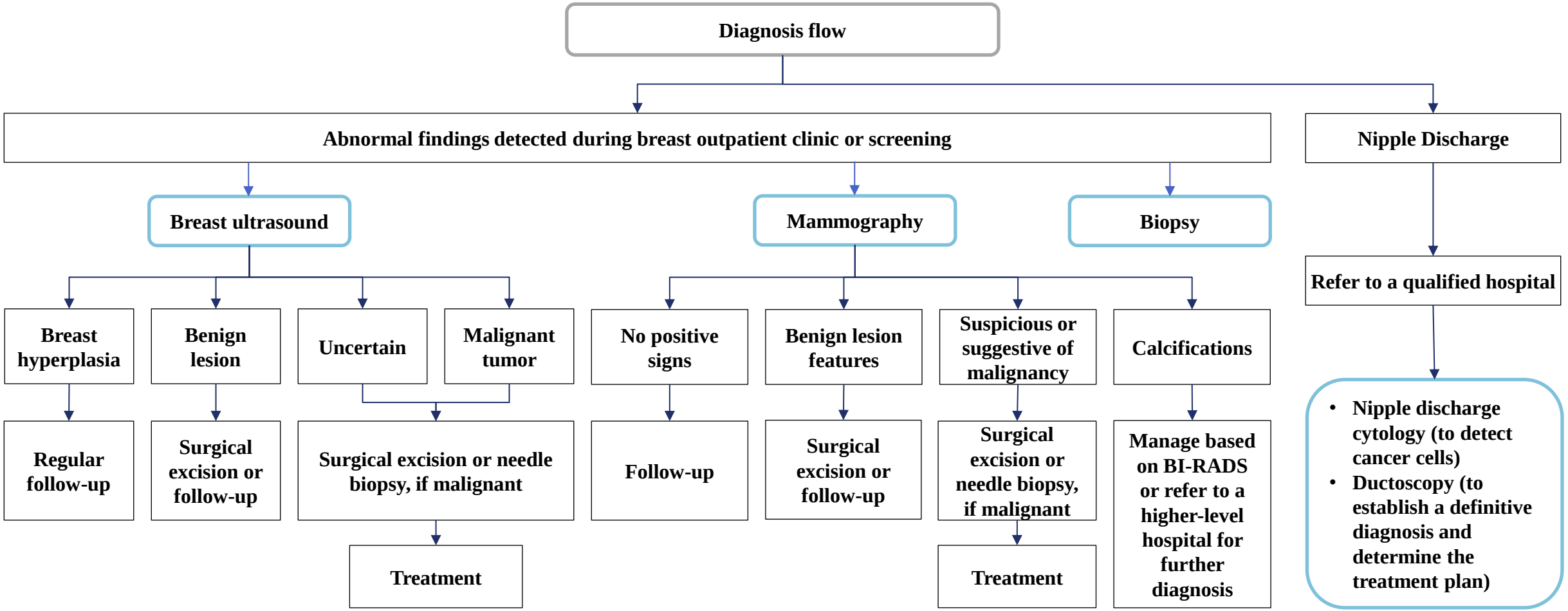



Source: China Insights Consultancy

# The diagnosis and differential diagnosis of breast cancer should be based on the patient's clinical presentation, physical examination, imaging studies, and histopathology



## Diagnosis flow of breast cancer in China



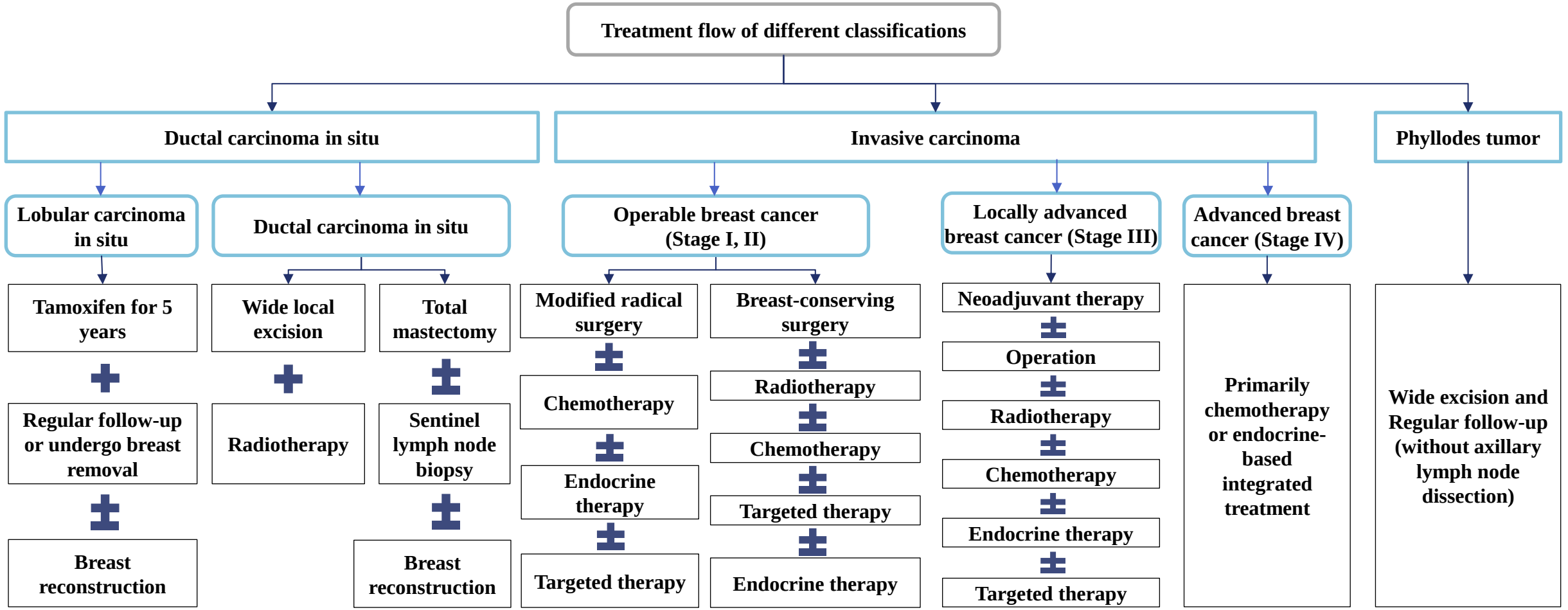



Source: Breast Cancer Diagnosis and Treatment Guidelines 2022; China Insights Consultancy

# Treatment of breast cancer uses a comprehensive approach which considers the tumor's biological status and the patient's physical condition, involving a combination of local and systemic therapies



## Treatment flow of different classifications of breast cancer in China






Source: Breast Cancer Diagnosis and Treatment Guidelines 2022; China Insights Consultancy

# Based on different molecular subtypes and progression stages of breast cancer, there are various treatment available; Fulvestrant was highly recognized for its clinical efficacy in the treatment of advaned HR+/HER2-



## Treatment flow of different molecular subtypes of breast cancer in China

Breast cancer can be classified into four most common types based on the status of hormone receptors (HR) and human epidermal growth factor receptor 2 (HER2) in breast tumor cells.

**Treatment flow of different molecular subtypes**

- **Early-stage breast cancer**
  - **Preoperative neoadjuvant therapy**
  - **Surgery**
  - **Postoperative neoadjuvant therapy**
- **Advanced breast cancer**
  - **First-line treatment**
  - **Second-line treatment**

| | Preoperative neoadjuvant therapy | Surgery | Postoperative neoadjuvant therapy | First-line treatment | Second-line treatment |
|---|---|---|---|---|---|
| **HR+/HER2-** ~ 62% | Chemotherapy | Corresponding surgical treatment | Intensive endocrine therapy | CDK4/6 inhibitors + Endocrine therapy (Fulvestrant; AI; SERM; OFS) | CDK4/6 inhibitors + Endocrine therapy (Fulvestrant; AI; SERM; OFS) |
| **HER2+/HR-; HER2+/HR+** ~ 11% each | Trastuzumab + Pertuzumab + Chemotherapy | | Trastuzumab + Pertuzumab; TDM-1 | Trastuzumab + Pertuzumab + Chemotherapy | TDM-1; Pyrrotinib + Chemotherapy |
| **Triple-negative breast cancer (TNBC)** ~ 62% | Chemotherapy | | Chemotherapy | Chemotherapy + Anti-PD-1; PARP inhibitors; Sacituzumab Govitecan | PARP inhibitors; Sacituzumab Govitecan |



Note: AI = Aromatase inhibitor; SERM = Selective estrogen-receptor modulator; OFS = Ovarian function suppression;

Source: Breast Cancer Diagnosis and Treatment Guidelines 2022; Chinese Journal of Rational Drug Use; China Insights Consultancy

# Hormone receptor-positive breast cancer, a common subtype, relies on endocrine therapy as a significant treatment method in the advanced stage, with Fulvestrant being highly recommended in clinical treatment guidelines



## Introduction to HR+ breast cancer

- Hormone receptor-positive (HR+) breast cancer is one of the common subtypes, accounting for approximately 60% of all breast cancer cases.
- Endocrine therapy serves as the cornerstone for advanced HR+ breast cancer, having evolved from tamoxifen (TAM) to aromatase inhibitors (AIs), and further into the era of selective estrogen receptor degraders (SERDs) such as Fulvestrant.
- Fulvestrant is highly recommended in clinical practice guidelines for the treatment of late-stage HR+ breast cancer.

## Unmet clinical treatment needs

1. **Drug resistance issues:** patients with breast cancer may develop drug resistance following treatment, leading to treatment failure.
2. **Disease progression concerns:** one of current clinical challenges in managing advanced breast cancer is controlling disease progression.
3. **Drug Efficacy Challenges:** despite the availability of some effective drugs and treatment regimens, not all patients respond uniformly to them.

Given the clinical efficacy of Fulvestrant in current HR+ advanced breast cancer, exploring combinations of Fulvestrant with novel targeted therapies holds great potential for addressing unmet needs.

**Endocrine therapy for advanced HR+ breast cancer**

| Indication | Level I recommendation | Level II recommendation | Level III recommendation |
|---|---|---|---|
| Patients without endocrine therapy | Aromatase inhibitor (AI) + CDK4/6 inhibitor (CDK4/6i) | 1. AI + Ribociclib<br>2. Fulvestrant + CDK4/6i<br>3. AI<br>4. **Fulvestrant** | Tamoxifen (TAM) |
| TAM treatment failure | AI + CDK4/6i | 1. AI + Chidamide<br>2. AI + Ribociclib<br>3. AI + Dalpiciclib<br>4. AI + Everolimus | 1. AI<br>2. **Fulvestrant** |
| Non-steroidal AI treatment failure | **Fulvestrant** + CDK4/6i | 1. Steroidal AI + Chidamide<br>2. **Fulvestrant** + Ribociclib<br>3. Steroidal AI + Everolimus | 1. **Fulvestrant**<br>2. Steroidal AI<br>3. TAM or Toremifene<br>4. Progestational hormone |
| Steroidal AI treatment failure | **Fulvestrant** + CDK4/6i | 1. **Fulvestrant** + Ribociclib<br>2. **Fulvestrant** + Everolimus<br>3. Non-steroidal AI + CDK4/6i | 1. **Fulvestrant**<br>2. Non-steroidal AI<br>3. TAM or Toremifene<br>4. Progestational hormone |
| CDK4/6i treatment failure | / | 1. Another CDK4/6i + endocrine therapy<br>2. Other targeted therapy (E.g., Everolimus, Chidamide, Alpelisib) + endocrine therapy<br>3. Participate in rigorously designed clinical trials | 1. Progestational hormone<br>2. Toremifene |



Source: CSCO; China Insights Consultancy

# Fulvestrant, a selective estrogen receptor antagonist, serves as an endocrine therapy for breast cancer, demonstrating superior clinical benefits when used either alone or in combination with CDK4/6 inhibitors

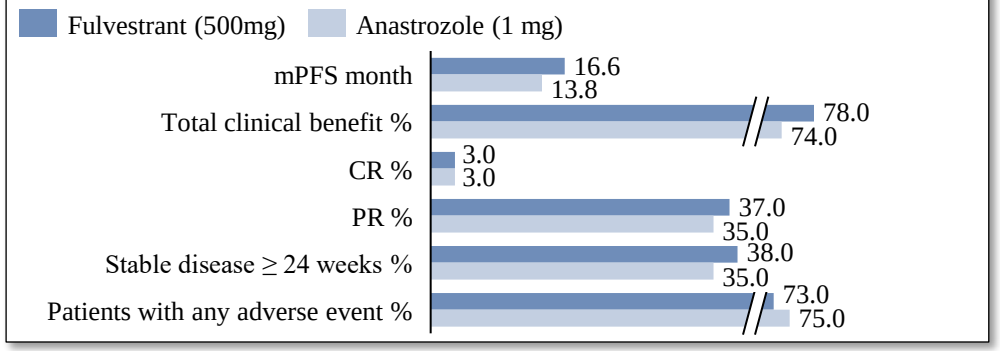


| | |
|---|---|
| Introduction of Fulvestrant | • Fulvestrant is a selective estrogen receptor antagonist and serves as a foundational medication for endocrine therapy in breast cancer.<br>• It is used in postmenopausal breast cancer patients with hormone receptor-positive locally advanced or metastatic disease who have not received prior endocrine therapy or have experienced relapse or disease progression during or after adjuvant antiestrogen therapy.<br>• Fulvestrant function by binding to estrogen receptors (ER) on the surface of cancer cells, reducing their stability, and inducing their degradation through the cell's normal protein degradation mechanisms. This results in decreased levels of estrogen receptors, thereby inhibiting the growth of cancer cells. |

## Fulvestrant as a monotherapy

- Aromatase inhibitors (AI) are a standard of care for hormone receptor-positive locally advanced or metastatic breast cancer.
- Research has demonstrated that the progression-free survival in the Fulvestrant monotherapy group was significantly longer than that in the AI (Anastrozole) group.
- Fulvestrant not only exhibits favorable safety but also demonstrates superior therapeutic efficacy, as evidenced by its clinical benefits.

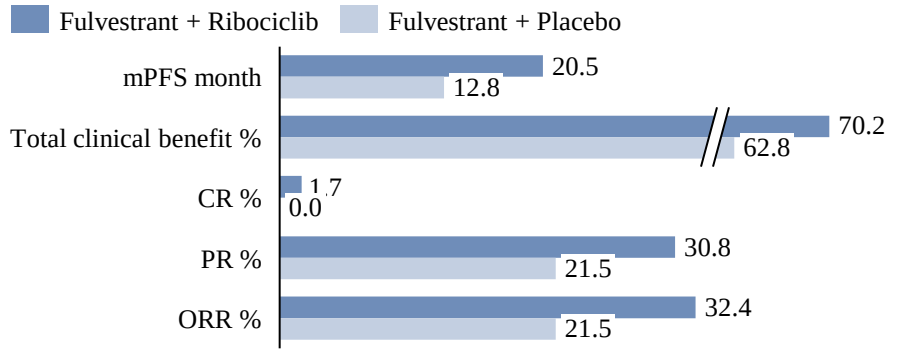
**Clinical efficacy of Fulvestrant (500mg) comparing with Anastrozole (1mg)[1]**




## Fulvestrant with CDK4/6i as a combination therapy

- A study on Ribociclib and Fulvestrant demonstrates that the combination of Ribociclib with CDK4/6 inhibitors, as opposed to monotherapy, yields superior clinical benefits.
- Fulvestrant, when used in combination therapy, has become a new first-line or second-line treatment option for patients with hormone receptor-positive, HER2-negative advanced breast cancer.

**Clinical efficacy of Fulvestrant combined with Ribociclib comparing with Fulvestrant as a monotherapy[2]**




## Others benefits

**Expediency**

Once monthly intramuscular injection can improve patient adherence

**Safe for use**

No dosage adjustment is needed for patients with mild to moderate renal impairment or kidney dysfunction

**Effectiveness**

Dual MoA, both blocking and degrading ER, remains effective in patients with TAM and AI resistance



Note: 1. FALCON study; 2. MONALEESA-3 study

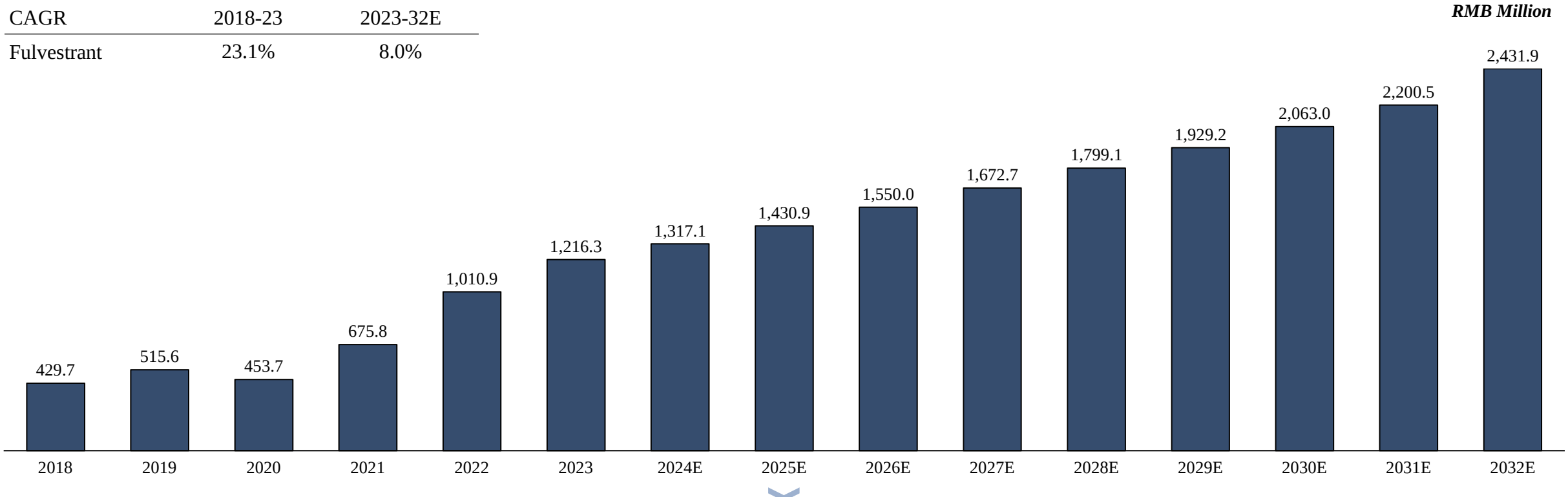
Source: CSCO; Journal of Clinical Oncology; China Insights Consultancy

# The market size of Fulvestrant in China is projected to increase from RMB[1,216.3] million in 2023 to RMB[2,431.9] million in 2032, with a CAGR of [8.0]%



## China Fulvestrant Market Size, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Fulvestrant | 23.1% | 8.0% |




**Key Analysis**

- China Fulvestrant market grew from RMB[429.7] billion in 2018 to RMB[1,216.3] billion in 2023 at the CAGR of [23.1]%, and is projected to increase to RMB[2,431.9] million in 2032, with a CAGR of [8.0]%



Source: British Journal of Cancer; Breast Cancer Research and Treatment; Chinese Medical Journal; Expert interview

# As of LPD, there are 9 approved Fulvestrant for the treatment of breast cancer in China



**Approved Fulvestrant for the treatment of breast cancer in China**

| Drug Name | Formulation | Target | Company | Approval Date | NRDL Inclusion | Revenue (Ten thousand RMB), 2022 | Market share, 2022 | Indications |
|---|---|---|---|---|---|---|---|---|
| Fulvestrant | Injection | ESR1 | Xuanzhu Biotechnology Co., Ltd.<br>轩竹生物 | 2024/02/06 | Yes | / | / | Breast cancer |
| Fulvestrant | Injection | ESR1 | QILU Pharmaceutical Co., Ltd.<br>齐鲁制药 | 2023/8/01 | Yes | / | / | Breast cancer |
| Fulvestrant | Injection | ESR1 | Dr. Reddy's Laboratories Limited | 2023/5/26 | Yes | / | / | Breast cancer |
| Fulvestrant | Injection | ESR1 | Sichuan Huiyu Pharmaceutical Co., Ltd.<br>四川汇宇制药 | 2023/4/17 | Yes | / | / | Breast cancer |
| Fulvestrant | Injection | ESR1 | Shandong New Time Pharmaceutical Co., Ltd.<br>山东新时代药业 | 2023/4/04 | Yes | / | / | Breast cancer |
| Fulvestrant | Injection | ESR1 | Hangzhou Jiuyuan Gene Engineering Co., Ltd.<br>杭州九源基因 | 2022/6/28 | Yes | / | / | Breast cancer |
| Fulvestrant | Injection | ESR1 | Jiangsu Hansoh Pharmaceutical Group Co., Ltd.<br>江苏豪森药业 | 2021/11/17 | Yes | 393.6 | 0.4% | Breast cancer |
| Fulvestrant | Injection | ESR1 | Jiangsu Chia Tai-Tianqing Pharmaceutical Co., Ltd.<br>正大天晴药业 | 2020/8/12 | Yes | 34,467.9 | 33.8% | Breast cancer |
| Fulvestrant | Injection | ESR1 | AstraZeneca AB | 2010/6/4 | Yes | 67,252.9 | 65.9% | Breast cancer |

- Compared to other current available treatments, fulvestrant is recommended for advanced HR+/HR2- breast cancer patients, which we consider as the addressable patients in estimating the fulvestrant market size in China. 2032.

Imported products  Domestic products



Source: NMPA; China Insights Consultancy

# As of LPD, there are 9 approved Fulvestrant for the treatment of breast cancer in China



**Approved Fulvestrant for the treatment of breast cancer in China**

| Drug Name | Formulation | Target | Company | Approval Date | NRDL Inclusion | Market share, 2023 | Indications |
|---|---|---|---|---|---|---|---|
| Fulvestrant | Injection | ESR1 | Xuanzhu Biotechnology Co., Ltd.<br>轩竹生物 | 2024/02/06 | Yes | / | Breast cancer |
| Fulvestrant | Injection | ESR1 | QILU Pharmaceutical Co., Ltd.<br>齐鲁制药 | 2023/8/01 | Yes | 0.2% | Breast cancer |
| Fulvestrant | Injection | ESR1 | Dr. Reddy's Laboratories Limited | 2023/5/26 | Yes | / | Breast cancer |
| Fulvestrant | Injection | ESR1 | Sichuan Huiyu Pharmaceutical Co., Ltd.<br>四川汇宇制药 | 2023/4/17 | Yes | / | Breast cancer |
| Fulvestrant | Injection | ESR1 | Shandong New Time Pharmaceutical Co., Ltd.<br>山东新时代药业 | 2023/4/04 | Yes | / | Breast cancer |
| Fulvestrant | Injection | ESR1 | Hangzhou Jiuyuan Gene Engineering Co., Ltd.<br>杭州九源基因 | 2022/6/28 | Yes | 0.1% | Breast cancer |
| Fulvestrant | Injection | ESR1 | Jiangsu Hansoh Pharmaceutical Group Co., Ltd.<br>江苏豪森药业 | 2021/11/17 | Yes | 1.1% | Breast cancer |
| Fulvestrant | Injection | ESR1 | Jiangsu Chia Tai-Tianqing Pharmaceutical Co., Ltd.<br>正大天晴药业 | 2020/8/12 | Yes | 34.7% | Breast cancer |
| Fulvestrant | Injection | ESR1 | AstraZeneca AB | 2010/6/4 | Yes | 64.0% | Breast cancer |

- Compared to other current available treatments, fulvestrant is recommended for advanced HR+/HR2- breast cancer patients, which we consider as the addressable patients in estimating the fulvestrant market size in China. 2032.

Imported products  Domestic products



Source: NMPA; China Insights Consultancy

# There are six companies have got the bid for VBP of Fulvestrant in China



**VBP of Fulvestrant in China**

| Drug Name | Formulation | Target | Company | Bid Price (RMB) |
|---|---|---|---|---|
| Fulvestrant | Injection | ESR1 | Jiangsu Chia Tai-Tianqing Pharmaceutical Co., Ltd.<br>正大天晴药业 | 302.60 |
| Fulvestrant | Injection | ESR1 | Jiangsu Hansoh Pharmaceutical Group Co., Ltd.<br>江苏豪森药业 | 306.00 |
| Fulvestrant | Injection | ESR1 | Shandong New Time Pharmaceutical Co., Ltd.<br>山东新时代药业 | 332.00 |
| Fulvestrant | Injection | ESR1 | QILU Pharmaceutical Co., Ltd.<br>齐鲁制药 | 511.00 |
| Fulvestrant | Injection | ESR1 | Hangzhou Jiuyuan Gene Engineering Co., Ltd.<br>杭州九源基因 | 533.72 |
| Fulvestrant | Injection | ESR1 | Sichuan Huiyu Pharmaceutical Co., Ltd.<br>四川汇宇制药 | 572.00 |

**Key Analysis**

- Currently, six companies have got the bid for VBP of Fulvestrant, with Jiuyuan Gene Engineering got the second highest price.



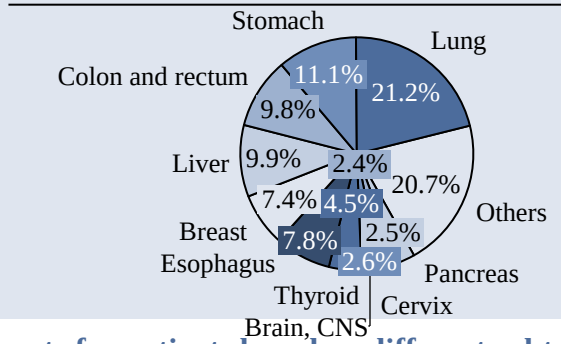
Source: NMPA; China Insights Consultancy

# Growth drivers of China's Fulvestrant drug market include favorable policies towards breast cancer management, the growing prevalence of breast cancer, and the promotion of the precision medicine initiative in the breast cancer treatment



| Growth drivers | |
|---|---|
| **Favorable policies towards breast cancer management** | • China has introduced several policies related to disease awareness, disease management guidance and programs, and payment methods and systems to enhance breast cancer management. For example, **the "14th Five-Year Plan" places a strong emphasis on promoting reproductive health services and preventing and controlling cervical and breast cancers among women**. This policy direction aims to increase both the rate and quality of screening, enabling the early detection of patients and, potentially, improving the chances that breast cancer patients will receive appropriate treatment. Additionally, the government, medical institutions, and non-governmental organizations are actively conducting breast cancer awareness and education activities in China.<br>• These initiatives have contributed **to raising public awareness of breast cancer** and encouraging more women to **undergo breast cancer screening and seek early treatment**. |
| **Growing incidence and mortality of breast cancer in China** | • With the **accelerated aging of the Chinese population, changing modern lifestyles, and the delayed average age of first childbirth among Chinese women**, the incidence of breast cancer in China has significantly risen.<br>• Breast cancer **has seen a continuous increase in its incidence**, becoming one of the significant health challenges affecting women in China. The incidence of breast cancer in China is expected to grow from 2.4 million patients in 2022 to 2.8 million patients in 2032.<br>• In this context, there is a **growing demand for breast cancer treatment**, driving a continuous **increase in the demand for breast cancer medications**. |
| **Precision medicine initiative promoting the demand for Fulvestrant** | • The precision medicine practices enables clinical physicians to **provide targeted treatments for patients based on different subtypes of breast cancer**. Fulvestrant is an example demonstrating outstanding clinical efficacy in the treatment of advanced HR+/HER2- breast cancer and highly recommended by the clinical practices and guidelines as the preferred endocrine therapy drug, especially suitable for patients who exhibit resistance to other endocrine therapy drugs.<br>• Precision medicine not only **improves patient survival rates but also enhances their quality of life**. Therefore, precision medicine such as Fulvestrant, has been widely promoted, driving the rapid development and clinical application of drugs targeting specific subtypes. |

**Incidence by tumor location in China, Top 10, 2022**





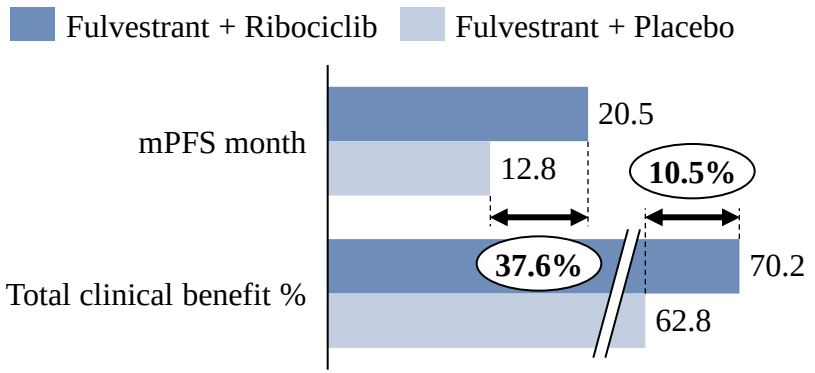

Source: NHC; NMPA; China Insights Consultancy

# Future trends of China's Fulvestrant drug market include increasing use of combined therapies, and domestic alternatives of breast cancer drugs

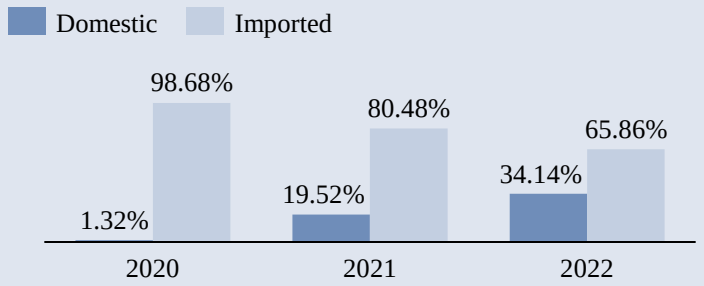


| Future trends | |
|---|---|
| **Increasing use of combined therapies** | • Single-agent endocrine therapy eventually leads to drug resistance, which is why combination therapy is widely adopted due to its **excellent clinical efficacy and effectiveness in some resistant patients**. For instance, in breast cancer treatment, the combination of CDK4/6 inhibitors with endocrine therapy, such as Fulvestrant, has significantly extended the progression-free survival of HR+/HER2- advanced breast cancer patients.<br>• The Chinese Society of Clinical Oncology (CSCO) guidelines recommend **the use of CDK4/6 inhibitors in combination with Fulvestrant** as the preferred treatment for advanced HR+/HER2- breast cancer. This underscores the tremendous **potential of Fulvestrant in breast cancer combination therapy** market, providing more effective treatment options for breast cancer patients. |
| **Domestic alternatives of breast cancer drugs** | • In the breast cancer pharmaceutical market, the trend of future **domestic drug substitution** is expected to become more pronounced.<br>• For instance, as the patent for Fulvestrant expires, **local companies have been introducing Fulvestrant injections**, increasing the accessibility of generic versions of Fulvestrant and **driving the continuous growth in sales of domestically produced Fulvestrant medications**.<br>• It is anticipated that in the future, there will be **more alternatives to Fulvestrant, and domestically produced Fulvestrant will gain a larger market share**. |

**Improved clinical efficacy with combined therapy**




**Market share comparison of imported and domestic Fulvestrant**






Source: NMPA; CSCO; Journal of Clinical Oncology; China Insights Consultancy

# Table of contents



# CD47/SIRPα inhibitors are agents that block the interaction between SIRPα on immune cells and CD47 on the cell surface, thereby disrupting the "do not eat me" signal and promoting the immune system's attack on cancer cells



## Introduction of SIRPα and CD47


SIRPα – Signal regulatory protein

- Ig-like protein; Single transmembrane domain; Long cytoplasmic region with 4 Y-sites; High in Mϕ, DC, neutrophils, neurons; Low in fibroblasts and endothelial cells
- SIRPα is an inhibitory receptor mainly expressed on the surface of macrophages cells and dendritic cells.
- Alternatively, SIRPα has a more restricted histological distribution vs. CD47, which could lead to less toxicity and greater blockade when therapeutically targeted.
- SIRPα combines with CD47, and it transmits inhibitory signals and inhibits the phagocytic activity of macrophages.


CD47 – integrin associated protein (IAP)

- Ig-like protein
- 5 membrane spanning segments
- Short cytoplasmic tail
- Ubiquitous expression including T, B, RBC, platelet, HSC

## Research direction of CD47/SIRPαi

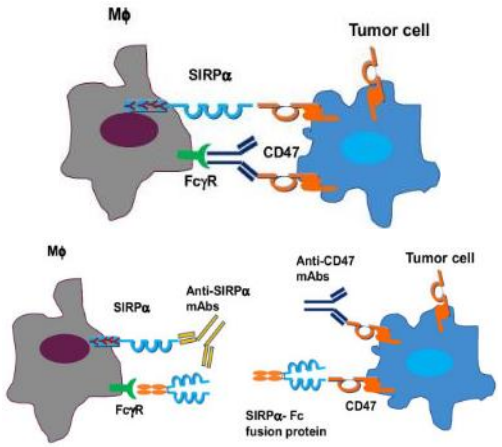
- The research direction of SIRPα inhibitors primarily focuses on anti-tumor therapy and immunotherapy, as it targets the CD47/SIRPα pathway.

**Solid Tumors**

**Autoimmune Diseases**

**Hematologic Malignancies**

## "Don't eat me" signal versus "eat me" signal




- The main function of SIRPα is to interact with another cell surface protein CD47, which is often expressed on the surface of healthy cells.
- **When CD47 on a cell binds to SIRPα** on a macrophage or phagocyte, it sends a **"don't eat me" signal** to the immune cell.
- This interaction **inhibits the immune cell's ability to phagocytose** the cell displaying CD47.
- SIRPα, therefore, is to serve as a checkpoint in the immune system, **preventing the unnecessary destruction of healthy, self-cells**. However, **tumor cells can overexpress CD47 as a way to evade the immune system**. By displaying CD47, they effectively trick immune cells into not attacking them.
- **CD47/SIRPα inhibitors (SIRPαi) disrupt the interaction between SIRPα and CD47**.In this manner, the macrophage does not receive the "do not eat me" signal, potentially allowing it to phagocytose cells that would otherwise be protected, such as cancer cells.

## Applications of CD47/SIRPαi

**Solid tumors:**

- SIRPα inhibitors might not only enhance macrophage-mediated phagocytosis but also impact other tumor-associated immune cells like T cells or natural killer cells.
- CD47 is highly expressed in many solid tumors, including ovarian cancer, breast cancer, colon cancer, bladder cancer, liver cancer and so on. Tumor cells interact with SIRPα on macrophages through high expression of CD47 to avoid being engulfed by macrophages to achieve immune escape

**Multiple myeloma:**

- Myeloma cells can potentially express high levels of CD47, preventing them from being destroyed by macrophages.
- Applying SIRPα inhibitors could enhance the phagocytosis by macrophages of myeloma cells.



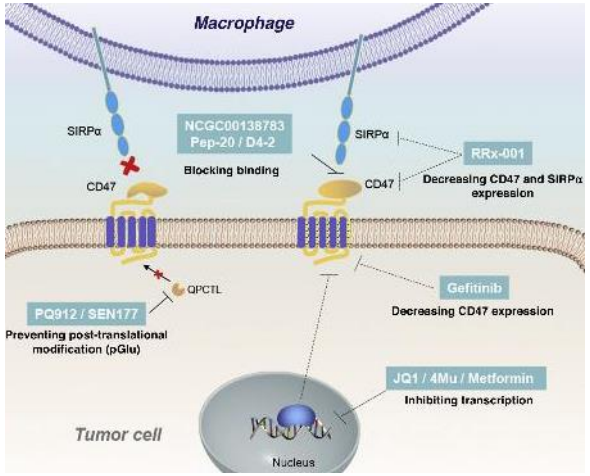
Source: Haematologica; Journals of Chinese Medical Association; Leukemia Research; Journal of Hematology & Oncology; China Insights Consultancy

# Current research on Small-molecule inhibitors targeting the CD47/SIRPα axis has shown promising outcomes and aims to improve the efficiency of eliminating tumor cells by blocking the CD47/SIRPα pathway



## The development of small-molecule inhibitors targeting CD47/SIRPα

### Small-molecule inhibitors targeting CD47/SIRPα

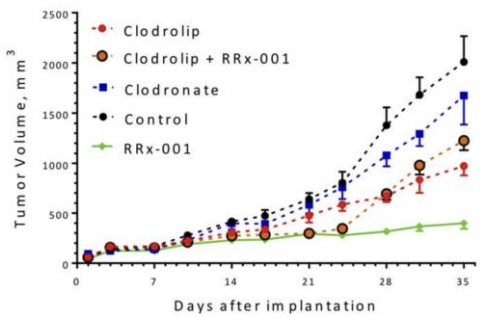



As the figure shows, current research focuses on small-molecule inhibitors targeting the CD47/SIRPα axis.

Most inhibitors action in the following directions:

- Block the binding of CD47 and SIRPα
- Prevent CD47 post-translational modification (pyroglutamate formation), thus interfering with the binding of CD47 and SIRPα
- Decrease CD47 expression at the transcriptional level
- Decreases both CD47 and SIRPα expression

### Advancing clinical trials and promising outcomes of inhibitors targeting CD47/SIRPα

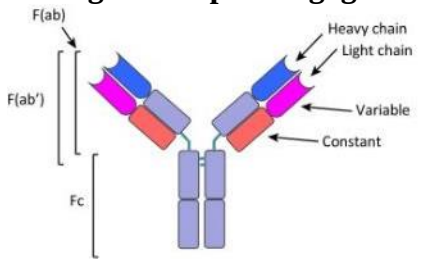



The small-molecule compound RRx-001 (targets at CD47, DNMT, EPGN, PD-L1) is in Phase III clinical trials as a cancer therapy. The deletion of macrophages in vivo showed diminished antitumor effects during RRx-001 treatment alone. Clinical studies of RRx-001 have shown encouraging results:

- Treatment with RRx-001 showed a **good response rate** (30%).
- RRx-001 **did not result in dosage-limiting toxicity**.
- RRx-001 **did not show any hematological toxicity**.
- RRx-001 shows **minor adverse effects**.

### Exploring enhanced CD47/SIRPα pathway blockade: Minimizing Fc receptor engagement

| Agent | Binds to | | |
|---|---|---|---|
| | CD47 | SIRPα | FcR |
| Anti-CD47 Antibody – intact | + | - | + |
| Anti-CD47 Antibody – F(ab')$_2$ | + | - | - |
| Anti-CD47 Antibody – F(ab') | + | - | - |
| Anti-SIRPα Antibody – intact | - | + | + |
| Anti-SIRPα Antibody – F(ab')$_2$ | - | + | - |
| Anti-SIRPα Antibody – F(ab) | - | + | - |
| Soluble SIRPα-Fc | + | - | + |
| Monomeric SIRPα | + | - | - |
| Anti-CD47 nanobody | + | - | - |
| Anti-CD47 single chain variable fragment | + | - | - |




Due to the involvement of **Fc receptors**, blocking the CD47/SIRPα alone may be insufficient to elimination tumor cells. Mechanism that **minimize the impact of FcR on the CD47/SIRPα pathway** are being studied.



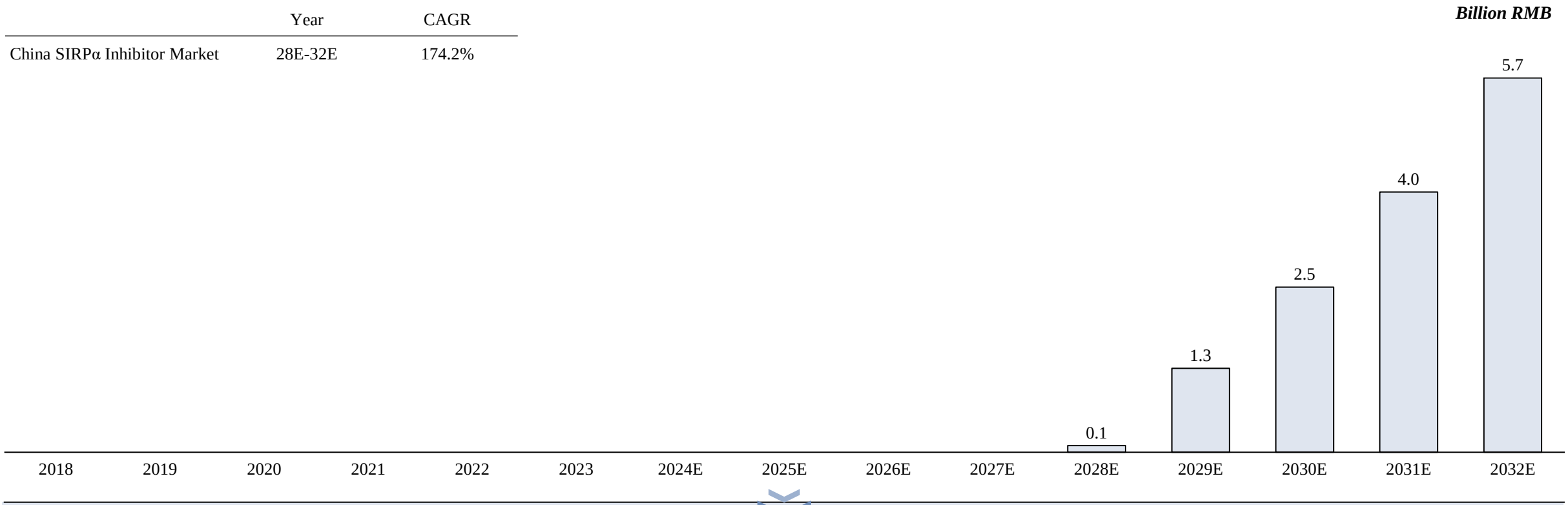
Source: Seminars in Oncology; Drug Discovery Today; Cancer Immunology, Immunotherapy; Trends in Immunology; Translational Oncology; China Insights Consultancy

# The market size of China SIRPα inhibitor market is projected to reach RMB5.7 billion with expected approval across solid and hematological malignancies



## China SIRPα inhibitor Market Size, 2018-2032E

| | Year | CAGR |
|---|---|---|
| China SIRPα Inhibitor Market | 28E-32E | 174.2% |




**Key Analysis**

- The market size of China SIRPα inhibitor market is projected to reach RMB5.7 billion by 2032 with expected approval across solid and hematological malignancies



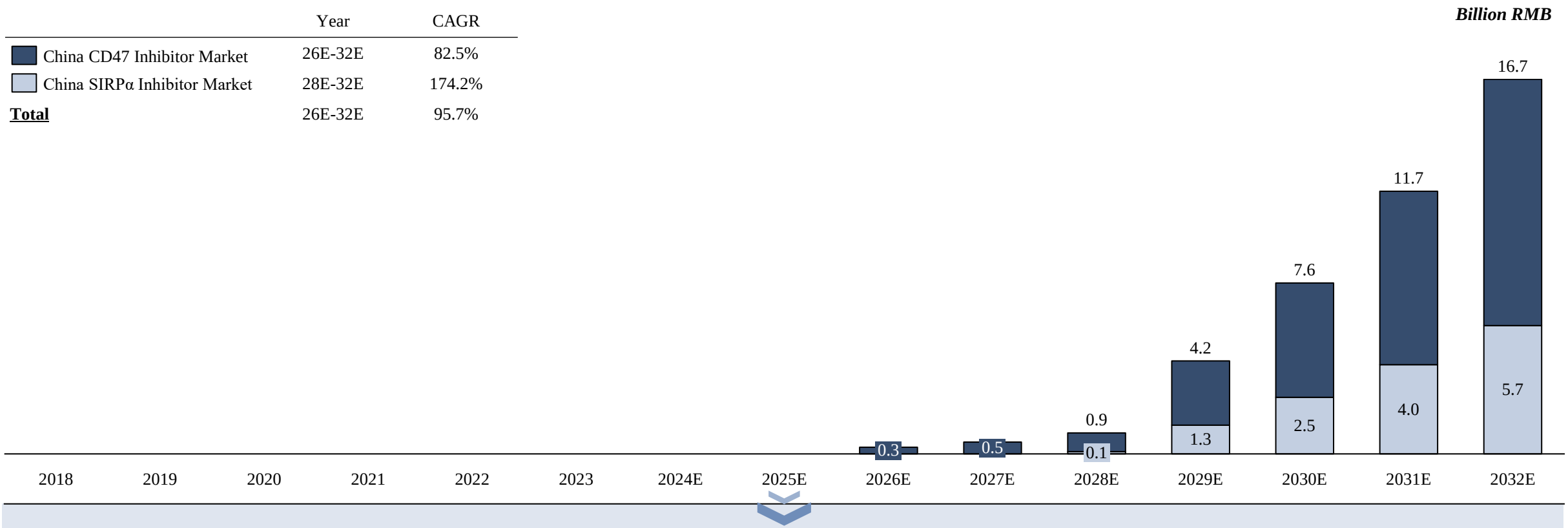
Source: China Insights Consultancy

# The market size of China CD47 and SIRPα market is projected to reach RMB16.7 billion with expected approval across solid and hematological malignancies



## China CD47 and SIRPα inhibitor Market Size, 2018-2032E

| | Year | CAGR |
|---|---|---|
| China CD47 Inhibitor Market | 26E-32E | 82.5% |
| China SIRPα Inhibitor Market | 28E-32E | 174.2% |
| **Total** | 26E-32E | 95.7% |




**Key Analysis**

- The market size of China CD47 and SIRPα inhibitor market is projected to reach RMB16.7 billion by 2032 with expected approval across solid and hematological malignancies



Source: China Insights Consultancy

# As of LPD, there are 4 IND-approval pipelines of SIRPα target in China



**Pipelines of Pipelines of SIRPα target in China , CDE-registered, as of 2/28/2024**

| Agent | Target | Company | Indications | Phase | First Posted Date | Latest Trial Number | Administration | Estimated Completion date |
|---|---|---|---|---|---|---|---|---|
| IBC-0966 | PD-L1; SIRPA | SunHo (China) Biopharmaceutical Co., Ltd. 盛禾（中国）生物制药有限公司 | Advanced tumor | I/II | 2021/7/08 | CTR20211609 | IV | 2024 |
| LM-101 | SIRPA | LaNova Medicines Ltd. 礼新医药科技（上海）有限公司 | Advanced malignant neoplasm | I/II | 2023/1/06 | CTR20223293 | IV | 2025 |
| BR105 | SIRPA | Zhejiang Hisun Pharmaceutical Co., Ltd. / BioRay Pharmaceutical Co., Ltd. 海正生物制药有限公司/ 浙江博锐生物制药有限公司 | Advanced Solid Tumor | I | 2022/3/14 | CTR20220467 | IV | 2024 |
| JY47 | SIRPA | Hangzhou Jiuyuan Gene Engineering Co .,Ltd. 杭州九源基因工程股份有限公司 | Advanced Solid Tumor | IND | 2022/12/9 | / | IV | 2025 |

Imported products  Domestic products



Source: CDE; China Insights Consultancy

# As of LPD, there are 4 IND-approval pipelines in China



**Pipelines of SIRPα target in China**

| Agent | Target | Phase | Company | Indications | First Posted Date | Latest Trial Number |
|---|---|---|---|---|---|---|
| IBC0966 | PD-1/ SIRPα | I/Iia | Sunho Biopharmaceutical | Advanced Tumor | 2021/7/8 | CTR20211609 |
| LM-101 | SIRPα | I/II | LaNova Medicines | Advanced malignant neoplasm | 2023/01/06 | CTR20223293 |
| BR105 | SIRPα | I | BioRay/Hisun | Advanced Solid Tumor | 2022/3/14 | CTR20220467 |
| JY47 | SIRPα | IND | Hangzhou Jiuyuan gene engineering | Advanced Solid Tumor | 2022/12/9 | / |

**Pipelines of SIRPα target in the rest of the world**

| Agent | Target | Phase | Company | Indications | First Posted Date | Latest Trial Number | Location[2] |
|---|---|---|---|---|---|---|---|
| ADU-1805 | SIRPα | I | Sairopa B.V | Solid Tumor; Metastatic Solid Tumor; Refractory Cancer | 2023/5/12 | NCT05856981 | AU; RoW |
| DS-1103a | SIRPα | I | Daiichi Sankyo, AstraZeneca | Advanced Solid Tumor; Breast cancer | 2023/3/13 | NCT05765851 | AU; RoW |
| BYON4228 | SIRPα | I | Byondis B.V. | Lymphoma | 2023/2/21 | NCT05737628 | RoW |
| ELA026 | SIRPα | I | Electra Therapeutics Inc. | Secondary Hemophagocytic Lymph Histiocytosis (sHLH) | 2022/6/13; 2022/9/27 | NCT05416307; NCT05556863 | AU; RoW |
| OSE-172 (BI 765063) | SIRPα | I | Boehringer Ingelheim; OSE | Colorectal cancer | 2022/7/6 | NCT05446129 | RoW |
| | | | | Head and Neck Squamous Cell Carcinoma (HNSCC) | 2022/2/21 | NCT05249426 | |
| | | | | Carcinoma; Melanoma; Squamous cell cancer; MSCLC (non-small cell cancer) | 2021/10/5 | NCT05068102 | |
| | | | | Solid tumours | 2019/6/18; 2020/12/4 | NCT03990233; NCT04653142 | |
| Anzurstobart (BMS-986351; CC-95251) | SIRPα | I | Bristol-Myers Squibb | Acute myeloid leukaemia; Myelodysplastic syndromes | 2021/12/23 | NCT05168202 | AU; RoW |
| | | | | Neoplasms | 2018/12/21 | NCT03783403 | |
| GS-0189 (FSI-189)[1] | SIRPα | I | Forty Seven | Non-hodgkin Lymphoma | 2020/8/6 | NCT04502706 | AU |



Note: 1. IBI397 and GS-0189 (FSI-189) have been ceased by the originators. 2. RoW = Rest of the World

Source: CDE; ClinicalTrials.gov; China Insights Consultancy

# As of 28th of September 2023, there are 23 pipelines targeting CD47/SIRPα in China



**Pipeline of CD47/SIRPα target in China (1/2)**

| Agent | Target | Phase | Company | Indications | First Posted Date | Latest Trial Number |
|---|---|---|---|---|---|---|
| RRx-001 | CD47; DNMT; EPGN; PD-L1 | Phase III | Saisheng Pharmaceutical | Small Cell Lung Cancer | 2022-07-15 | CTR20221527 |
| TJ011133 | CD47 | Phase III | Days of The Biotechnology | MDS; Advanced Solid Tumor; AML; MDS; CD20-Positive Lymphoma | 2021-03-18 | CTR20230090 |
| 6MW3211 | CD47; PD-L1 | Phase II | Mabwell (Shanghai) Bioscience | AML; MDS; Recurrent/Refractory Lymphoma; Advanced Lung Cancer; AMT | 2021-08-24 | CTR20230174 |
| AK117 | CD47 | Phase II | Zhongshan Kangfang Biology Medicine | AMT; Triple-Negative Breast Cancer; AML; MDS; Advanced Solid Tumor or Lymphoma | 2020-12-29 | CTR20220284 |
| HX009 | CD47; PD-L1 | Phase II | Hangzhou Hansi Biological Pharmaceutical; Wuhan Hanxiong Biotech | Recurrent/Refractory Lymphoma; Advanced Solid Tumor | 2019-11-12 | CTR20211292 |
| IMM0306 | CD20; CD47; FCGR | Phase Ib/IIa | ImmuneOnco Biopharmaceuticals | CD20-Positive B-NHL | 2020-03-23 | CTR20231000 |
| IMM01 | CD47 | Phase Ib/II | ImmuneOnco Biopharmaceuticals | Advanced Solid Tumor; Acute Myeloid Leukemia or Myelodysplastic Syndrome; Refractory or Recurrent Lymphoma | 2019-08-20 | CTR20220791 |
| TQB2928 | CD47 | Phase Ib | Nanjing Shunxin Pharmaceuticals Co., LTD. of Chiatai Tianqing Pharmaceutical Group | Hematologic Tumor; AMT | 2022-01-04 | CTR20232513 |
| TJ011133 | CD47 | Phase I/IIa | Days of The Biotechnology | Recurrent or Refractory AML; MDS | 2019-12-19 | CTR20192522 |
| IMM2520 | CD47; PD-L1 | Phase I | ImmuneOnco Biopharmaceuticals | Advanced Solid Tumor | 2023-02-07 | CTR20230255 |
| BC007 | CD47; CLDN18.2 | Phase I | Baochuan Biological Medicine Technology | Late-stage Solid Tumor with CLDN18.2 Expression | 2022-10-31 | CTR20222836 |
| SH009 | CD47; PD-L1 | Phase I | Nanjing Sanhome Pharmaceutical | AMT | 2022-07-01 | CTR20221585 |



Note: AML = Acute Myeloid Leukemia; MDS = Myelodysplastic Syndrome; AMT = Advanced Malignant Tumor; B-NHL = B-Cell Non-Hodgkin Lymphoma

Source: CDE; China Insights Consultancy

# As of 28th of September 2023, there are 23 pipelines targeting CD47/SIRPα in China



**Pipeline of CD47/SIRPα target in China (2/2)**

| Agent | Target | Phase | Company | Indications | First Posted Date | Latest Trial Number |
|---|---|---|---|---|---|---|
| HMPL-A83 | CD47 | Phase I | Hutchison MediPharma | AMT | 2022-05-26 | CTR20221224 |
| 3D-197 | CD47 | Phase I | Thinking Bio Pharmaceutical | Locally Advanced or Metastatic Solid Tumors and Recurrent or Refractory Hematologic Malignancies | 2022-03-09 | CTR20220544 |
| BAT7104 | CD47; PD-L1 | Phase I | Bio-Thera Solutions | AMT | 2022-02-22 | CTR20220098 |
| IMM2902 | CD47; HER2 | Phase I | ImmuneOnco Biopharmaceuticals | Advanced Solid Tumor with HER2 Expression | 2021-09-22 | CTR20212375 |
| JMT601 | CD47; CD20 | Phase I | Shanghai GeneMab Biological Technology | Recurrent/Refractory CD20-Positive B-Cell Non-Hodgkin Lymphoma | 2021-06-11 | CTR20211365 |
| SG12473 | CD47; PD-L1 | Phase I | Hangzhou Shangjian Biotechnology; China Gateway Biologics | AMT | 2021-05-13 | CTR20211029 |
| ZL-1201 | CD47 | Phase I | Zai Lab | Locally Advanced Solid Tumor or Malignant Hematologic Tumor | 2021-05-07 | CTR20210973 |
| Gentulizumab | CD47 | Phase I | Changchun GeneScience Pharmaceutical | Malignant Tumors of the Blood System; Late-stage Malignant Solid Tumors and Lymphomas | 2021-01-12 | CTR20210066 |
| SG404 | CD47 | Phase I | Zhongsheng Shangjian Biomedical | Malignant Tumor | 2020-12-10 | CTR20202489 |
| MIL95 | CD47 | Phase I | Beijing Mabworks Biotech; Beijing Huafang Tianshi Biopharmaceutical; Shanghai Lingyue Biomedical Technology | Lymphomas and Late-stage Malignant Solid Tumors | 2020-11-27 | CTR20201108 |
| IBI322 | CD47; PD-L1 | Phase I | Innovent Biologics | Myeloid Tumor; AMT; Malignant Hematologic Tumor | 2020-03-30 | CTR20211251 |



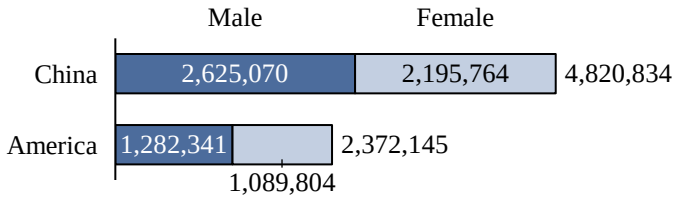
Source: CDE; China Insights Consultancy

# Growth drivers of China MM market include continuous increase of targeted patients, potential of immune therapies targeting intrinsic immune checkpoints, and emerging innate immune targets creating new immunotherapy pathways



| Drivers & Future Trends | |
|---|---|
| **Continuous increase of targeted patients** | • With improvements in medical accessibility and affordability, along with the increasing demand and penetration rate for effective cancer treatment in response to the rising number of new cases, the development of tumor immunotherapy and the continuous expansion of its market size will be fundamentally propelled.<br>• SIRPα inhibitors as a novel immunotherapy drug, have the potential to enhance the immune system's ability to target cancer cells.<br>• As a result, SIRPα inhibitors are expected to play a significant role in cancer treatment in China, driving the growth of the market for these drugs. |
| **Potential of immune therapies targeting intrinsic immune checkpoints** | • While immune-based immunotherapies, particularly immune checkpoint inhibitors, such as anti-PD-1/PD-L1, have shown remarkable success in some cancer types, they are not universally effective. This is partly due to the existence of other regulatory pathways like the intrinsic immune checkpoints that can hinder immune responses. Targeting intrinsic immune checkpoints in immunotherapy can address the limitations of currently approved adaptive immune-based immunotherapies and has demonstrated potential for wide clinical application.<br>• So far, several crucial intrinsic immune checkpoints, including CD47/SIRPα, have been identified. However, there are currently no approved global therapies targeting intrinsic immune checkpoints, indicating a vast and untapped global market. |
| **Emerging innate immune targets creating new immunotherapy pathways** | • In immunotherapeutic strategies, intrinsic immune checkpoints hold significant promise, with the CD47/SIRPα pathway as a key macrophage checkpoint garnering substantial attention in the industry. Emerging CD47/SIRPα-targeted therapies introduce a new strategy that, in addition to inhibiting the "don't eat me" signal to fully activate macrophages, can also induce the "eat me" signal, opening up additional avenues for immunotherapy.<br>• Therefore, the development and clinical application of immunotherapies targeting emerging intrinsic immune checkpoints will further enhance clinical benefits for patients and continue to drive growth in the tumor immunotherapy market. |

**New cancer cases by sex in China and US, 2022**





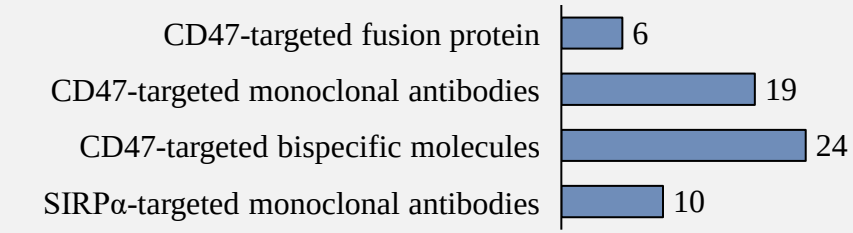

Source: Chinese Medical Journal; NMPA; OECD; China Insights Consultancy

# Future trends of China MM market includes rising focus on the efficacy of macrophages in cancer treatment, clinical benefits improved with drug combinations, and advancement of immunotherapy into first-line treatment



| Drivers & Future trends | |
|---|---|
| **MCN's focus on the efficacy of macrophages in cancer treatment** | • As a major component of the innate immune system, macrophages are widely distributed in various types of tumors, constituting 20% to 50% of the cellular composition in tumor tissues. Therefore, strategies to activate macrophages represent an effective approach to further improve the efficacy of cancer treatment.<br>• Considering the critical role of the CD47-SIRPα pathway in regulating macrophage activity, it has garnered attention from several multinational companies, indicating a trend toward the development of the next revolutionary immune checkpoint. |
| **Improved clinical benefits with bispecific molecules and drug combinations** | • Clinical evidence suggests that synergistic combinations and bispecific strategies can induce enhanced tumor cytotoxicity and improve clinical outcomes, presenting a significant market potential. SIRPα inhibitors have the potential for synergistic effects in the field of immunotherapy. By combining them with other immunotherapy medications such as PD-1/PD-L1 antibodies, the tumor immune response can be enhanced, leading to improved treatment outcomes.<br>• Combinations of drugs with synergistic effects, especially those that can simultaneously activate the dual immune systems and combine immunotherapy with targeted treatments, have shown tremendous potential in improving clinical outcomes for cancer patients, representing the future trend of tumor immunotherapy. |
| **Advancement of immunotherapy into first-line treatment** | • Developing immunotherapy for indications that were previously unexplored will benefit an ever-growing patient population. For instance, PD-1/PD-L1 inhibitors were initially approved for the treatment of melanoma in 2014 but have now been approved for various cancers. Moreover, tumor immunotherapies that were initially approved for second- or later-line treatments have gradually advanced into first-line treatment.<br>• The use of tumor immunotherapy, including drugs targeting the SIRPα pathway, in first-line clinical treatment can significantly expand the treatable patient population and treatment duration, further driving the market size of relevant drug treatments. |

**Number of pipelines targeting the CD47/SIRPα pathway, as of 28th of Sept 2023**






Source: CDE; China Insights Consultancy

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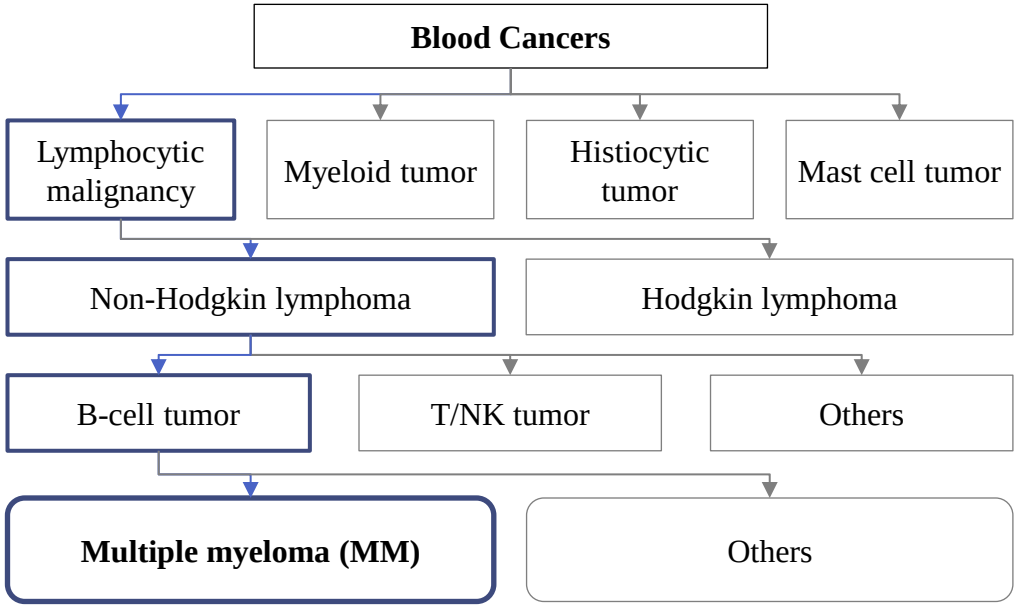
# Multiple myeloma is a neoplastic condition, predominantly affecting older individuals, and its pathogenesis is complex, often leading to complications related to organ dysfunction



## Introduction to multiple myeloma

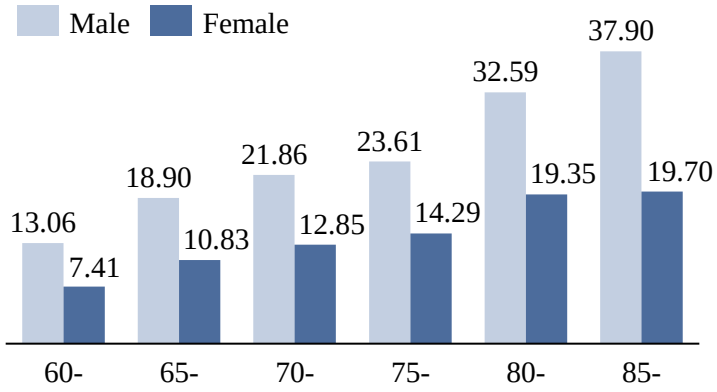
- Multiple myeloma (MM) is a neoplastic condition involving the abnormal proliferation of a single clone of plasma cells, resulting in an excessive production of monoclonal immunoglobulins.
- MM accounts for approximately **1% of neoplastic diseases** and **13% of hematologic cancers**.
- Since the tumor cells of MM **originate from plasma cells in the bone marrow**, which are the final stage of B lymphocyte development, multiple myeloma can be classified within the spectrum of **B-cell lymphomas**.




## Current condition of MM in China

- Multiple myeloma is **more common in the elderly population**, with higher incidence and mortality rates in males compared **to** females.
- According to an observational trial in China, the mortality rates of lymphomas and myelomas are influenced not only by **age and gender** but also by **regional environmental factors**.
- Higher mortality rates have been observed in **urban areas** compared to remote regions, and the mortality rates in **western China** are higher than the rates in other regions.

**Age-specific (over 60) mortality rates of lymphoma and myeloma, by gender, 2017 ($1/10^5$)**



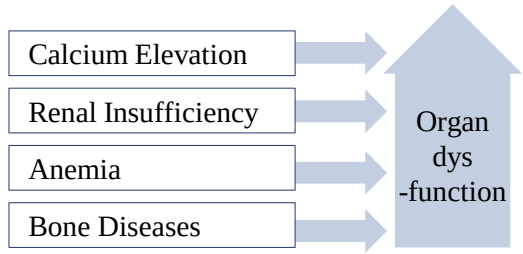

## Symptoms of MM

- Pain in bones
- Kidney damage
- Posture changes and loss of mobility
- Frequent infections
- Fatigue
- Blood clots and abnormal bleeding

## Causes and comorbidities

The etiology of multiple myeloma remains unclear, but is highly associated with **chromosomal abnormalities, genetic factors, radiation exposure, and exposure to certain chemicals**.

"CRAB" Comorbidities



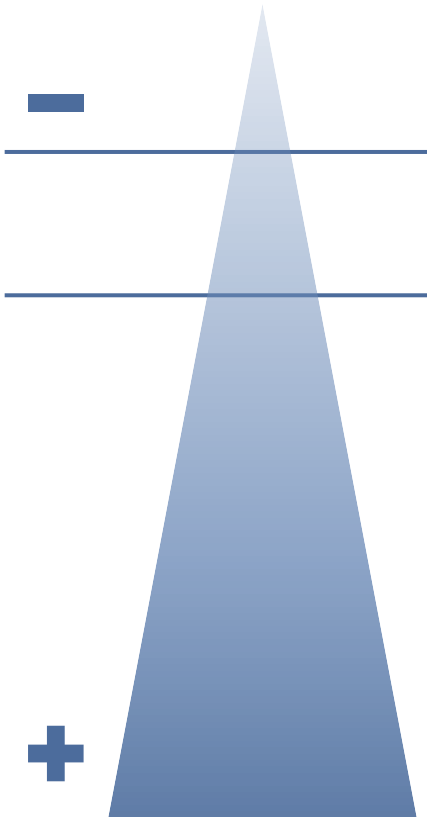



Source: Journal of Hematology & Oncology; Chinese Journal of Internal Medicine; China Insights Consultancy

# Diagnosis criteria indicates that monoclonal gammopathy of undetermined significance and smoldering multiple myeloma are precursor stages of MM, while MM has clinical symptoms and a higher tumor burden



**Diagnosis Criteria of MM in China**



| Tumor Burden | Monoclonal Gammopathies Diagnosis | Necessary Criteria | Additional Criteria: need to satisfy any one or more of the following criteria |
|---|---|---|---|
| − | Monoclonal Gammopathy of Undetermined Significance **(MGUS)** | No **SLiMCRAB** | • Clonal bone marrow plasma cells < 10%<br>• Serum monoclonal protein (MP) < 30 g/L<br>• 24-hour urine light chain < 0.5 g |
| | Smoldering Multiple Myeloma **(SMM)** | No **SLiMCRAB** | • Clonal bone marrow plasma cells ≥ 10%<br>• Serum monoclonal protein ≥ 30 g/L or 24-hour urine light chain ≥ 0.5 g |
| + | Active Multiple Myeloma **(MM/aMM)** | Clonal bone marrow plasma cells ≥ 10% or biopsy-confirmed plasma cell tumor | • Clonal bone marrow plasma cells ≥ 60% **(S)**<br>• Serum free light chain (FLC) ratio > 100 **(Li)** and involved FLC > 100 mg/L<br>• MRI showing more than one focal lesion **(M)**<br>• Hypercalcemia **(C)**: blood calcium exceeds the upper limit of normal value by 0.25 mmol/L or 10 mg/L; or blood calcium > 2.75 mmol/L or 110 mg/L<br>• Renal insufficiency **(R)**: Creatinine clearance < 40 ml/min; or blood creatinine > 177 mol/L or 20 mg/L<br>• Anemia **(A)**: hemoglobin below the normal line 20 g/L or < 100 g/L<br>• Bone Disease **(B)**: X-ray, CT, or PET/CT found one or more osteolytic bone damage |



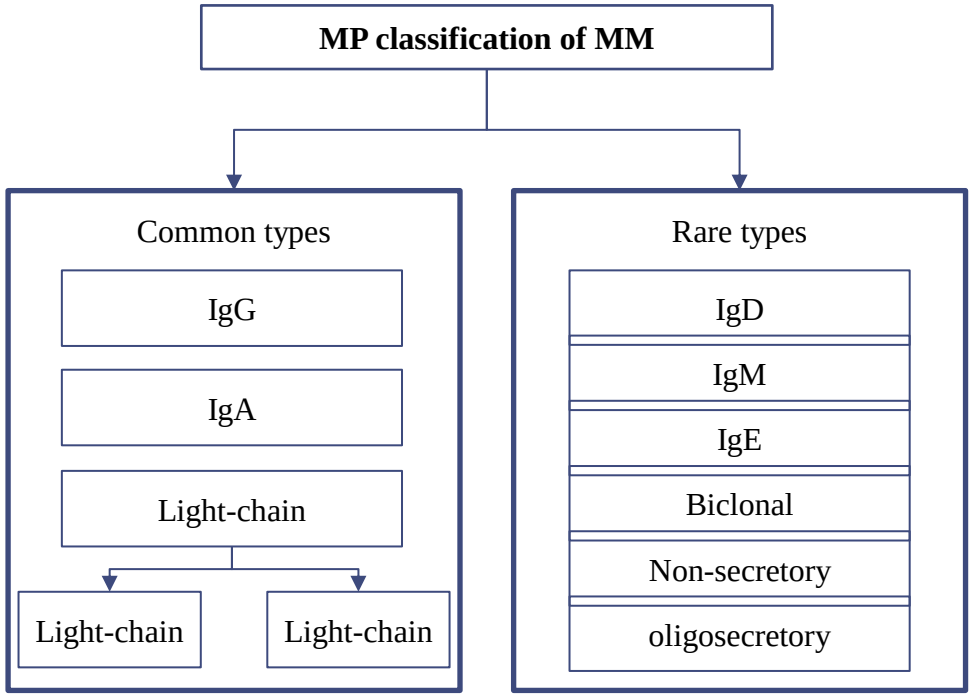
Source: CSCO; Chinese Journal of Internal Medicine; China Insights Consultancy

# MM has various subtypes based on M protein types; R-ISS staging system is currently preferred due to its simplicity and reliable prognostic assessment capability



## MM classification

- Multiple myeloma (MM) can be **classified according to the type of MP**, including IgG type, IgA type, IgD type, IgM type, IgE type, light chain type, biclonal type, and non-secretory type. Furthermore, based on the light chain type of M protein, it can be further classified into kappa (κ) type and lambda (λ) type. Rare types include biclonal myeloma, non-secretory myeloma, and oligosecretory MM.




## Stages of MM

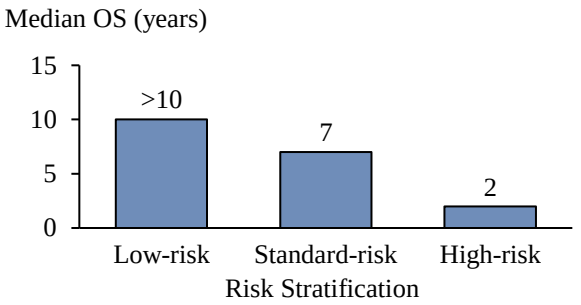
- The Durie-Salmon staging system was the standard for risk stratification for many years.
- It is based on the tumor cell mass, hemoglobin, calcium, IgA and IgG levels, urine monoclonal protein levels, and the extent of bone damage on X-rays. It divides patients into three stages (I, II, and III) and sub-classifies them further into groups A and B according to **serum creatinine level**.
- Given that there is some subjectivity, accuracy and reproducibility are difficult. Hence, the R-ISS is often used since it is simple and has robust prognostic information provided.

| Chromosomal abnormalities | |
|---|---|
| High-risk | Presence of t(4;14) or deletion 17p13 detected by fluorescence in situ hybridization |
| Standard-risk | t(11;14) detected by fluorescence in situ hybridization |
| Low-risk | No t(4;14) or deletion 17p13 or1q21+, patient is under 55 years old |

**Revised International Staging System (R-ISS)**

| | |
|---|---|
| Stage I | • Serum $\beta_2$-microglobulin < 3.5 mg/L<br>• Serum albumin ≥ 35 g/L<br>• Normal LDH<br>• Standard-risk cytogenetics |
| Stage II | • Neither stage 1 nor stage 3 |
| Stage III | • Serum $\beta_2$-microglobulin ≥ 5.5 mg/L<br>• High-risk cytogenetics |

Prognosis evaluation






Source: Chinese Journal of Internal Medicine; CSCO; China Insights Consultancy

# Induction therapy regimens for newly diagnosed multiple myeloma by transplantation eligibility



**Induction treatment regimen of MM in China**

MM patients should be assessed for their suitability for transplantation based on their age, physical condition, and comorbidities.

**Treatment regimen of newly diagnosed MM**

Transplant-eligible patients should preferably avoid regimens containing stem cell-toxic drugs.

| Transplantation eligibility | Level I recommendation | Level II recommendation | Level III recommendation |
|---|---|---|---|
| Eligible for transplantation | • Bortezomib + Lenalidomide + Dexamethasone (BRD)<br>• Bortezomib + Cyclophosphamide + Dexamethasone (BCD)<br>• Bortezomib + Doxorubicin + Dexamethasone (BAD)<br>• Bortezomib + Thalidomide + Dexamethasone (BTD)<br>• Carfilzomib + Lenalidomide + Dexamethasone (KRD)<br>• Carfilzomib + Cyclophosphamide + Dexamethasone (KCD)<br>• Ixazomib + Lenalidomide + Dexamethasone (IRD)<br>• Daratumumab + BRD<br>• Daratumumab + KRD<br>• Daratumumab + BTD | • Bortezomib + Dexamethasone (BD)<br>• Lenalidomide + Dexamethasone (RD)<br>• Lenalidomide + Thalidomide + Dexamethasone (CTD)<br>• Thalidomide + Doxorubicin + Dexamethasone (TAD)<br>• Cyclophosphamide + Lenalidomide + Dexamethasone (CRD) | VTD-PACE regimen: Bortezomib + Dexamethasone + Thalidomide + Cisplatin + Doxorubicin + Cyclophosphamide + Etoposide |
| Ineligible for transplantation | • BRD<br>• RD<br>• BCD<br>• BD<br>• Bortezomib + Melphalan + Dexamethasone<br>• Daratumumab + Lenalidomide + Dexamethasone<br>• Daratumumab + Bortezomib + Melphalan + Prednisone Acetate<br>• Thalidomide + Melphalan + Dexamethasone<br>• Bendamustine + Prednisone Acetate | • Carfilzomib + Lenalidomide + Dexamethasone<br>• Carfilzomib + Melphalan + Dexamethasone<br>• Carfilzomib + Cyclophosphamide + Dexamethasone<br>• Ixazomib + Lenalidomide + Dexamethasone<br>• Melphalan + Dexamethasone | Lenalidomide + Cyclophosphamide + Dexamethasone |

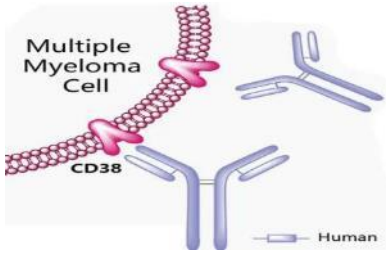


Source: CSCO; China Insights Consultancy

# Daratumumab is a monoclonal antibody targeting CD38, which is a membrane glycoprotein that is widely expressed on multiple myeloma and other tumor cells and plays a significant role in disease progression



## Introduction of Daratumumab and CD38




- **Daratumumab** (DARA) is a **monoclonal antibody** used in the treatment of **multiple myeloma** and specific types of **lymphocyte subset lymphoma, including cutaneous T-cell lymphoma.**
- It functions by targeting the **CD38 antigen** expressed on the surface of tumor cells.
- CD38 is a **membrane glycoprotein** that is widely expressed on multiple myeloma and other tumor cells and plays a significant role in disease progression.
- Daratumumab's mechanism of action includes **direct anti-tumor effects, antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and initiation of immune responses by the immune system**.

## Mechanism of Daratumumab monoclonal antibody

The first monoclonal antibody, CD38, acts directly on myeloma cells

**CDC**
Complement dependent cytotoxicity

**ADCC**
Antibody-dependent cell-mediated cytotoxicity

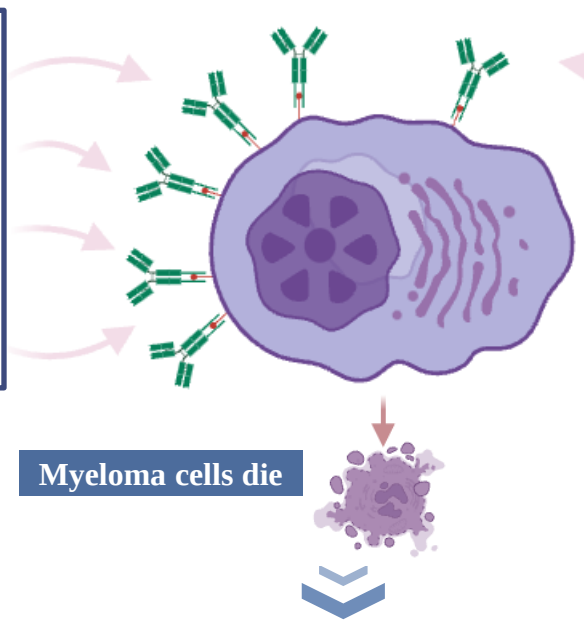
**ADCP**
Antibody-dependent phagocytosis

**Apoptosis**
Induced by crosslinking

**Daratumumab**

**CD38**

Activate immunity




Modulating the immune microenvironment

T cells

Activation of killer T cells CD8+ and helper T cells CD4+

Eliminate CD38+ immunosuppressive cells

**Specifically for MM**

- Daratumumab is approved for adult patients with relapsed and refractory multiple myeloma in China. It primarily exerts two major functions (as a cell membrane surface receptor and as an extracellular enzyme).
- It is significantly and persistently expressed on the surface of multiple myeloma cells, regardless of genetic and molecular heterogeneity, the stage of the patient's disease, or previous treatment history. Meanwhile, its expression levels in normal lymphocytes, myelocytes, and some non-hematopoietic tissues are relatively low.
- Therefore, CD38 can be considered an ideal target for multiple myeloma treatment.



Source: Immunology; China Insights Consultancy

# Daratumumab has received clinical approval for multiple myeloma (MM) and primary amyloidosis, showing significant therapeutic benefits, particularly in the case of relapsed or refractory MM



## Approval of DARA

- Daratumumab, developed by Johnson & Johnson in the United States, is the **first monoclonal antibody targeting the CD38 molecule**. The drug received FDA approval in 2015 (DARZALEX®) and has obtained multiple indications, **expanding from fourth-line therapy to first-line therapy**.
- In 2019, Daratumumab was approved for marketing in China: under the trade name DARZALEX® for intravenous formulation, indicated for **multiple myeloma**; under the trade name DARZALEX FASPRO® for subcutaneous formulation, indicated for **primary light chain amyloidosis (AL amyloidosis)**.

### AL amyloidosis

AL amyloidosis is a rare systemic disorder where abnormal misfolded proteins called amyloid fibrils are produced and deposited in organs and tissues throughout the body. The aim of daratumumab and other treatments for AL amyloidosis is to **alleviate the presence of abnormal light chains and prevent the advancement of the disease**.

**Comparison of Daratumumab with other treatments of MM**

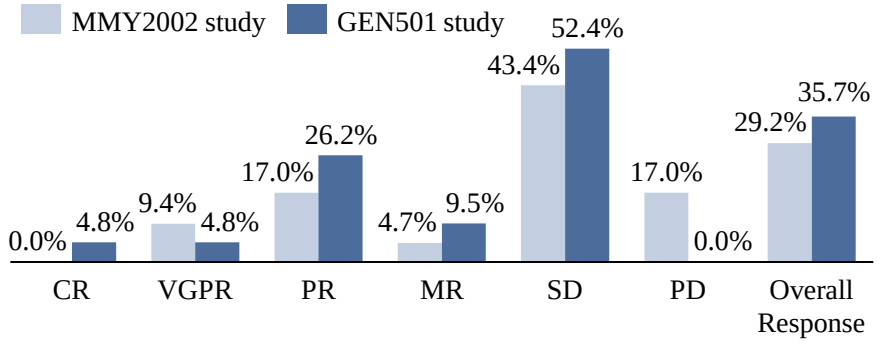
| Effects of MM | | Bortezomib | Lenalidomide | Daratumumab |
|---|---|---|---|---|
| Immune enhancement | | | √ | √ |
| Block cell cycle | | √ | √ | |
| Apoptosis of MM cells | | √ | √ | |
| Programmed cell death of MM cells induced by cell surface antibody cross-linking reaction | | | | √ |
| Immune-mediated mechanisms that directly kill tumor cells | ADCP | | | √ |
| | ADCC | | | √ |
| | CDC | | | √ |

## Clinical effectiveness

- Single-agent DARA (16 mg/kg) demonstrated remarkable clinical activity (**31% ORR**) in a combined analysis of two studies in heavily pretreated MM patients.
- The quality of the observed responses was **noteworthy in this highly refractory population**.

## Clinical efficacy of DARA as monotherapy for MM

**Clinical efficacy of DARA as a monotherapy in various groups**




- The GEN501 study focused on a population of **relapsed or refractory MM (RRMM) patients**. The DARA monotherapy group demonstrated a relatively **higher overall response rate and a longer progression-free survival**.
- The MMY2002 study targeted MM patients who were **ineligible for or intolerant to conventional treatments**. The DARA monotherapy group exhibited favorable **overall response rates and disease control efficacy**.
- These study findings suggest that daratumumab as a monotherapy **has significant therapeutic benefits for some patients with relapsed or refractory MM**.



Note: CR = Complete response; VGPR = Very good partial response; PR = Partial response; MR = Minimal response; SD = Stable disease; PD = Progressive disease

Source: Journal of Hematology & Oncology; Blood; China Insights Consultancy

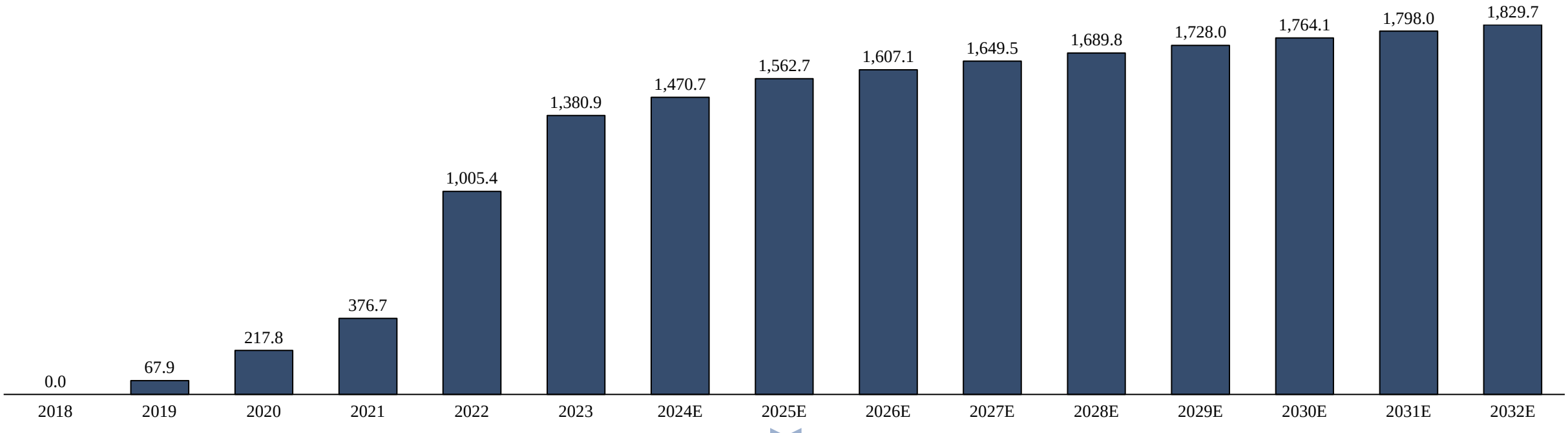
# The market size of China Daratumumab drug market is projected to increase from RMB[1,380.9] million in 2023 to RMB[1,829.7] million in 2032 at the CAGR of [3.2]%



## China Daratumumab Drug Market Size, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Daratumumab | N.A. | 3.2% |

*Million RMB*




**Key Analysis**

- Daratumumab is a effective targeted medication for the treatment of MM. Since 2022/1/1, Daratumumab is covered under NRDL Category B, which resulted in increased accessibility and lower out-of-pocket cost for MM patients in China.
- The market size of China Daratumumab drug market is projected to increase from RMB[1,380.9] million in 2022 to RMB[1,829.7] million in 2032 at the CAGR of [3.2]%



Source: Chinese Medical Journal; Menet

# As of LPD, there are 4 Daratumumab pipelines in China



**Summary of MM treatment path and Daratumumab alternatives**

- For newly diagnosed multiple myeloma (MM), excluding smoldering MM where treatment is not recommended, our approach is primarily driven by two main factors: eligibility for autologous stem cell transplantation (ASCT) and risk stratification. For patients aged ≤ 70 and in good physical condition, ASCT is recommended following antineoplastic therapy. For those over 70 or in poor physical condition, antineoplastic therapy is the next step in the treatment procedure.
- In the case of relapsed MM, patients are initially advised to consider enrollment in a suitable clinical trial. Subsequently, other treatment options such as CAR-T cell therapy, doublet or triplet chemotherapy regimens like dCEP±V or dT-PACE±V, hematopoietic stem cell transplantation, and emerging drugs can be explored. **Daratumumab stands out as a pivotal component in the treatment regimen, regardless of the patient's sensitivity or resistance to lenalidomide and bortezomib.** It is commonly used alongside other agents such as proteasome inhibitors (e.g., carfilzomib, bortezomib, ixazomib) and immunomodulators like selinexor.

**Pipeline of Daratumumab in China, as of LPD**

| Target | Phase | Company | Indications | First Posted Date | Latest Trial Number | Administration | Estimated Completion date |
|---|---|---|---|---|---|---|---|
| CD38 | II | Xian Janssen Pharmaceutical; Janssen Research & Development<br>西安杨森;强生 | Relapsed or refractory NK/ T-cell lymphoma | 2017-11-15 | CTR20171033 | IV | 2024 |
| CD38 | I | Shanghai Henlius Biopharmaceutical<br>复宏汉霖 | MM | 2023-01-03 | CTR20223275 | IV | 2025 |
| CD38 | I | Chiatai Tianqing Pharma<br>正大天晴 | MM | 2024-05-13 | CTR20241710 | IV | 2026 |
| CD38 | IND-approval | Our company | MM | 2023-04-14 | / | IV | 2026 |



Source: CDE; China Insights Consultancy

# As of August 2023, there are only 2 Daratumumab approved by the NMPA in China; subcutaneous daratumumab has several advantages over intravenous daratumumab



**NMPA Approved Daratumumab, as of August 2023**

| Approval number* | Product name | Generic name | Manufacturer | Indication | First approval date |
|---|---|---|---|---|---|
| 国药准字SJ20210025 | DARZALEX FASPRO | Daratumumab Injection | Janssen-Cilag International NV | AL amyloidosis; Multiple myeloma | 2021-09-30 |
| S20190030; S20190029 | DARZALEX | Daratumumab Injection（Subcutaneous Injection） | Janssen-Cilag AG | AL amyloidosis; Multiple myeloma | 2019-07-04 |

**Key Analysis**

- ✓ **Daratumumab has two types of injection which are intravenous and subcutaneous.** The research shows that intravenous (IV) daratumumab administration requires extended infusion times and is associated with higher rates of infusion related reactions (IRRs) when compared to the subcutaneous (SC) formulation. SC daratumumab may be given safely with a short initial observation period and without observation for subsequent doses, resulting in reduced infusion chair time as well as administration related cost and resources.
- ✓ Therefore, SC daratumumab has several advantages over the IV formulation **with significantly shorter administration time, lower rates of systemic reactions, and smaller volumes of administration, while preserving both efficacy and safety of the drug in its various combinations.** In the future, daratumumab will continue to develop towards subcutaneous injection.



Note*: Multiple approval numbers indicate that the same drug has been approved in various dosages

Source: CDE; Hematology; China Insights Consultancy

# Growth drivers and future trends of the China DARA market include the remarkable clinical efficacy of DARA as a monotherapy, and the enhanced clinical efficacy of DARA as a combined therapy when used with other drugs

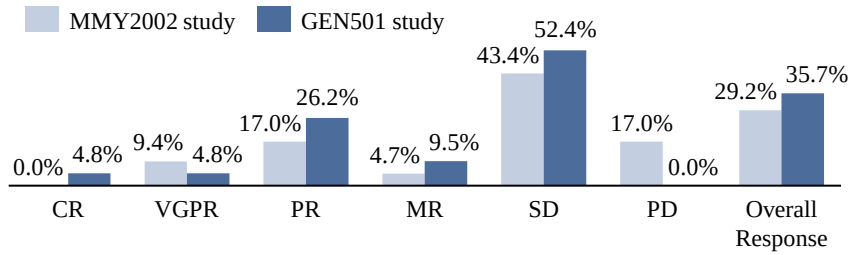


## Growth driver & Future trends

### Remarkable clinical efficacy of DARA as a monotherapy

- DARA has demonstrated a relatively **high level of clinical safety and significant efficacy** in multiple clinical trials, especially when **used as a monotherapy**. For instance, DARA monotherapy has shown a high overall response rate and prolonged progression-free survival, particularly in RRMM patients.
- These outstanding efficacy data provide robust scientific support for its promotion and application in clinical practice, indicating significant market potential.

**Clinical efficacy of DARA as a monotherapy for RRMM patients**




### Enhanced clinical efficacy of DARA as a combined therapy when used with other drugs

- An upregulation of CD38+/CD8+ T cells and proinflammatory cytokines was observed in DARA combination therapy, suggesting a **potential synergistic effect** of this regimen in patients previously exposed to anti-CD38 therapies. For instance, the TRIMM-2 study focused on RRMM patients who had not received anti-CD38 therapy within the past 90 days. At a median follow-up of 8.6 months, the study revealed **an ORR of 76.5%, with 70.6% of patients achieving VGPR**.
- Additionally, research has shown that when DARA is combined with traditional chemotherapy agents, immunomodulatory drugs, or other novel agents, it can **enhance cytotoxicity, promote apoptosis in tumor cells, and inhibit their proliferation**.
- Consequently, the emerging trend of utilizing combination therapy with DARA is aimed at **improving efficacy and expanding treatment options for drug-resistant patients**, indicating **significant potential for DARA in the treatment of MM**.

**Clinical efficacy of DARA used with Teclistamab as a combined therapy for RRMM patients**

| Best response, N (%) | Evaluable patients (n=51) | | |
|---|---|---|---|
| | Dara 1800 mg | | |
| | Tec 1.5 mg/kg Qw (n=20) | Tec 3 mg/kg Q2w (n=27) | Tec 3 mg/kg Qw (n=4) |
| ORR | 15 (75.0) | 20 (74.1) | 4 (100.0) |
| CR/SCR | 6 (30.0) | 3 (11.1) | 2 (50.0) |
| VGPR | 8 (40.0) | 15 (55.6) | 2 (50.0) |
| PR | 1 (5.0) | 2 (7.4) | 0 |
| SD | 3 (15.0) | 5 (18.5) | 0 |
| PD | 2 (10.0) | 2 (7.4) | 0 |



Note: CR = Complete response; VGPR = Very good partial response; PR = Partial response; MR = Minimal response; SD = Stable disease; PD = Progressive disease; QW = Weekly; Q2W = Every other week; sCR = Stringent complete response

Source: Journal of Hematology & Oncology; Blood; Janssen Science; Clinical Pharmacokinetics; China Insights Consultancy

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# Overview of hematologic diseases



- Hematologic diseases are conditions related to the blood and the hematopoietic system, marked by issues like anemia, bleeding, and fever. This system includes the blood, bone marrow, and lymphoid tissues. Any health problem primarily connected to the hematopoietic system falls under hematologic diseases. In 2022, the incidence of hematologic diseases in China reach approximately 33 million patients.
- Non-hodgkins lymphoma and leukemia are the two most common hematological malignancies in China.

## Introduction and classification of hematologic diseases

- Commonly encountered diseases in clinical practice include leukemia, aplastic anemia, myelodysplastic syndromes, thrombocytopenia, multiple myeloma, lymphoma, myelofibrosis, hemophilia, and thalassemia
- **Classification**

| | |
|---|---|
| **Based on whether it originates primarily within the hematopoietic system itself** | Primary hematologic diseases |
| | Secondary hematologic diseases |
| **Based on the benign or malignant nature** | Benign hematologic diseases |
| | Malignant hematologic diseases |
| **Based on cellular origin** | Red blood cell disorders |
| | White blood cell disorders |
| | Diseases caused by platelet abnormalities |
| **Based on the stage of maturation and the course of the disease where cell differentiation is obstructed** | Acute leukemia |
| | Chronic leukemia |

## Factors of hematologic diseases

**Internal factors**

- **Genetic factors:** It is one of the significant triggers in the blood. Hemophilia, for example, is a clearly hereditary disease. Some leukemias and myelodysplastic syndromes also have a certain genetic component.
- **Immunodeficiency**
- **Susceptibility to tumors**

**External factors**

- **History of exposure to radiation, chemical toxins/drugs:** This includes exposure to nuclear radiation, formaldehyde, pesticides or anticancer drugs, as well as factors like home renovations and new car materials

## The hazards and physical symptoms of hematologic diseases

- **Skin:** Pallor, bleeding points, and bruising on the skin. Low platelet count may lead to bleeding
- **Hepatosplenomegaly:** Enlargement of the liver, spleen, and lymph nodes. Painless masses should raise awareness of hematologic disorders or other conditions
- **Cardiovascular and Respiratory Systems:** Palpitations and chest tightness. Anemia or significant changes in blood cells can lead to palpitations and chest tightness
- **Urinary System:** Hematuria. Low platelet count may result in blood in the urine



Source: Chinese Medical Journal; China Insights Consultancy

# Thrombosis can be categorized as VTE, arterial thrombosis and microthrombi. Every year more than 100,000 people die due to blood clots



## Introduction to thrombosis

- Thrombosis refers to the pathological process in which, under certain conditions, blood components form clots within blood vessels, leading to partial or complete obstruction of blood vessels and corresponding disturbances in blood flow. Thromboembolism occurs when a thrombus formed at its site of origin dislodges and partially or completely obstructs certain blood vessels as it travels with the bloodstream, resulting in tissue or organ ischemia, hypoxia, necrosis, or congestion and edema
- Thrombosis can be categorized based on the type of blood vessel where it occurs into arterial thrombosis, venous thromboembolism (VTE), and microthrombi

| VTE | Arterial thrombosis | | Microthrombi | |
|---|---|---|---|---|
| Deep vein thrombosis (DVT) | Acute coronary syndrome (ACS) | Atrial fibrillation (AFib) | Disseminated intravascular coagulation (DIC) | Thrombotic thrombocytopenic purpura (TTP) |
| Pulmonary thromboembolism (PTE) | Ischemic arterial events | Cerebrovascular accidents (stroke) | | |

- VTE is a venous disorder caused by blood coagulation in deep veins, leading to impaired blood flow. PTE and DVT make up VTE. PTE primarily results from DVT in the lower limbs, representing the most common type of pulmonary embolism, over 90% of cases. Typically, "pulmonary embolism" refers to PTE
- Arterial thrombosis often results from atherosclerosis, where high blood flow velocity triggers clotting. Accumulation of clotting enzymes is insufficient until atherosclerotic plaques rupture or endothelial cells are damaged, causing platelet adhesion and aggregation. This narrows the lumen, enabling enzyme concentration to transform fibrinogen into fibrin, forming a thrombus
- Microthrombi occur in the microcirculation of small veins, as well as within capillaries, and can only be observed under a microscope

## Epidemiology of thrombosis

**11%**

The incidence of VTE is approximately 1 to 1.5 per thousand people, with an average individual risk of 11%

**100,000**

More than 100,000 people die of blood clots each year

- Furthermore, the recurrence rate of VTE within 5 years after its initial occurrence can be as high as 20%
- VTE affects as many as 900,000 Americans each year

## Risks of thrombosis

- Older age
- Overweight or obese
- Family history of VTE
- Recent or recurrent cancer
- During and just after pregnancy
- Estrogen-based medicine such as hormonal birth control or hormone replacement therapy
- Injury and trauma



Source：National Center on Birth Defects and Developmental Disabilities (NCBDDD); Centers for Disease Control and Prevention; Chinese Journal of Cardiology; China Insights Consultancy

# Overview of thrombosis diseases treatment modalities



**Overview of thrombosis diseases treatment modalities**

| | VTE | | Arterial thrombosis | | Microthrombi |
|---|---|---|---|---|---|
| | PTE | DVT | Coronary artery atherosclerotic heart disease | Ischemic stroke (IS) | DIC |
| Diagnosis | • Utilizing a strategy based on suspicion, confirmation, etiological investigation, and risk stratification | • Integrated assessment including Wells score for DVT, clinical presentation, D-dimer test results, and auxiliary examination findings | • Integrating clinical symptoms and electrocardiographic results | • CT, MRI | • No single test can establish or rule out the diagnosis of Disseminated Intravascular Coagulation (DIC). A comprehensive assessment of clinical signs and test results is necessary |
| Treatment | • Anticoagulant therapy in the acute phase: In cases highly suspicious for acute PTE, while awaiting diagnostic results, it is recommended to initiate parenteral anticoagulation therapy, such as unfractionated heparin (UFH), LMWH, fondaparinux, etc. with level 2C evidence. For the initial anticoagulant treatment of acute PTE, LMWH, UFH, fondaparinux, or a loading dose of rivaroxaban is recommended with 2B evidence<br>• Duration of Anticoagulation: Anticoagulant drugs for the extended phase are generally consistent with the initial regimen, and adjustments may be made based on clinical considerations | • Initial Anticoagulant Selection for Acute DVT: (1) For acute DVT without concomitant tumor, it is recommended to use rivaroxaban, apixaban, or LMWH with level 1C evidence. (2) For acute DVT with concomitant tumor, LMWH is recommended as the initial anticoagulant with level 1B evidence<br>• Long-term Anticoagulant Selection for Acute DVT:(1) For DVT without concomitant tumor, rivaroxaban or apixaban is recommended for long-term anticoagulation, superior to vitamin K antagonists (VKA). If unwilling or unable to use rivaroxaban or apixaban for long-term anticoagulation, VKA is suggested, superior to LMWH with level 2C evidence. (2) For DVT with concomitant tumor, long-term anticoagulation with LMWH is recommended, superior to VKA, rivaroxaban, or apixaban with level 2C evidence | • Anti-thrombotic therapy for stable coronary artery disease includes perioperative anti-thrombotic treatment for percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) following PCI<br>• Anti-thrombotic treatment for non-ST-segment elevation myocardial infarction (NSTEMI)<br>• Thrombolysis and anti-thrombotic treatment for ST-segment elevation myocardial infarction (STEMI) | • Acute phase antithrombotic therapy for IS: Intravenous thrombolysis, endovascular treatment, antiplatelet therapy, anticoagulation therapy, etc | • Drug recommendations: The doctor prescribes appropriate anticoagulant factor concentrates, anticoagulants, or antifibrinolytic drugs based on the patient's physical indicators |



Source: Chinese Medical Journal; China Insights Consultancy

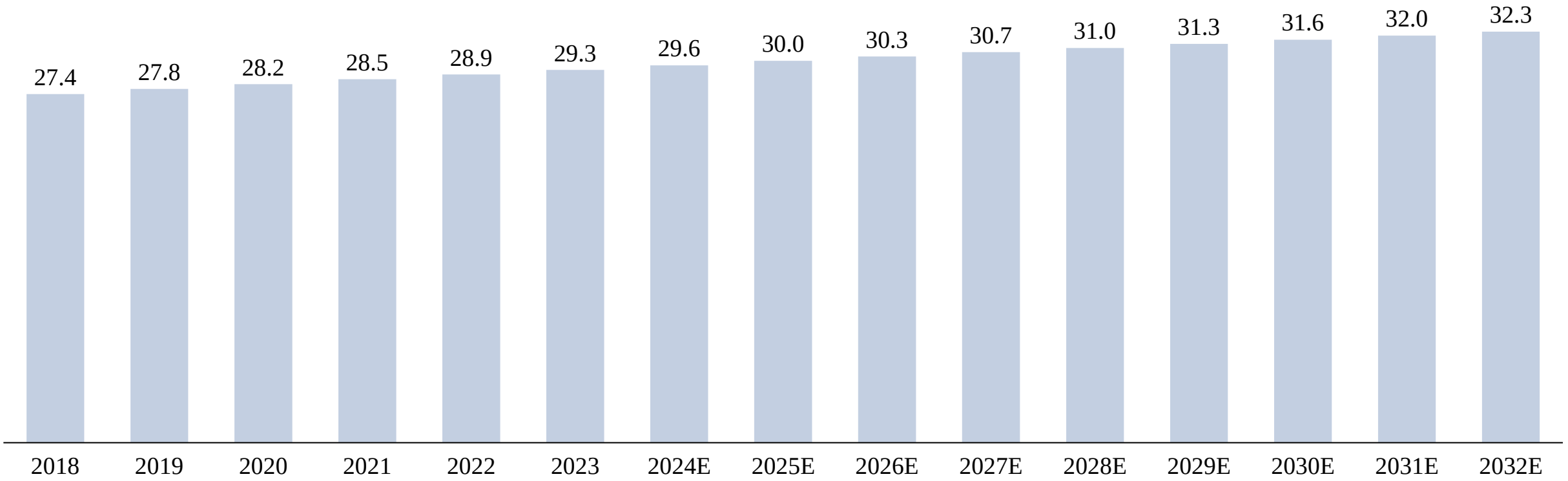
# Incidence of thrombosis in China, 2018-2032E



**Incidence of thrombosis[1] in China, 2018-2032E**

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Incidence of thrombosis in China | 1.3% | 1.1% |

*Million patients*






Source: AHA Journals, China Insights Consultancy

# Overview of anticoagulants (1/2)



## Introduction to anticoagulants

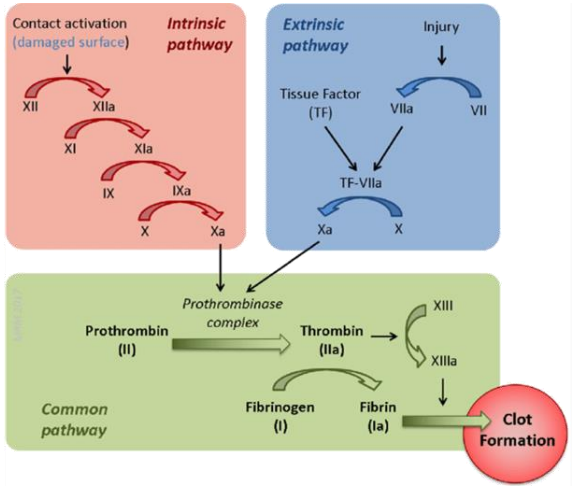
**Definition**

- Anticoagulants are medicines utilized to prevent the formation of blood clots. Their main purpose is to reduce the likelihood of serious diseases such as stroke and heart attack. These drugs act on the blood clotting process and are commonly used **to prevent or VTE, such as PTE and DVT, and arterial thrombosis, such as ACS and AFib. They are also used to prevent the formation of blood clots during surgery, dialysis, and cancer treatment, and are especially indicated for people who are highly sensitive to clotting**

### Mechanism of action of anticoagulant therapy

- Anticoagulants derive their effect by acting at different sites of the coagulation cascade. The coagulation cascade is a regulatory process that controls the clotting system, initiated through the extrinsic pathway and propagated via the intrinsic pathway. The extrinsic pathway begins with the activation of tissue factor, which occurs in response to vascular disruption or injury. When tissue factor is exposed, it binds to factor 7 and calcium, resulting in the conversion of factor 10 into its activated form

- The intrinsic pathway involves the activation of factor 11 by factor 12, HMW Kininogen, and prekallikrein. Once activated, factor 11 then triggers the activation of factor 9. Activated factor 9, in conjunction with its cofactor factor 8, leads to the activation of factor 10
- Both the intrinsic and extrinsic pathways converge on a common pathway that bridges the two. Activated factor 10, along with its cofactor factor 5, calcium, tissue, and platelet phospholipids, converts prothrombin into thrombin. Thrombin plays a crucial role in breaking down circulating fibrinogen into fibrin and activating factor 13, which facilitates the crosslinking of fibrin and the formation of a stable clot




- To achieve anticoagulation or prevent clot formation, interventions can target different points along the coagulation pathway, often overlapping at multiple stages. Direct thrombin inhibitors and direct factor 10a inhibitors are capable of inhibiting the formation of fibrin clots. Other mechanisms through which anticoagulation can be achieved include inhibiting the synthesis of vitamin K-dependent factors in the liver or modifying their calcium-binding properties



Picture source: Robertson, Sarah & Miller, Mark. (2018). Ambient air pollution and thrombosis. Particle and Fibre Toxicology. 15. 10.1186/s12989-017-0237-x.

Source：Chinese Journal of Cardiology; China Insights Consultancy

# Overview of anticoagulants (2/2)



## Overview of categories of anticoagulants

**Types**

- The available anticoagulants include vitamin K dependent antagonists, heparins, non-vitamin K antagonist oral anticoagulants (NOACs).Vitamin K antagonist anticoagulants (VKAs), such as warfarin, act as anticoagulants through inhibition of vitamin K-dependent blood coagulation proteins . The heparins are a group of anticoagulants that consist of unfractionated heparin and low molecular weight heparins. The heparins inhibits thrombin and factor Xa. NOACs are the non-vitamin K antagonist oral anticoagulants which are relatively newer in the market. NOACs act by two different mechanisms. Based on this, it is grouped as direct thrombin inhibitor and direct factor Xa inhibitor. The former category inhibits coagulation by directly binding to thrombin and prevents the formation of fibrin by restricting thrombin from breaking fibrinogen. The latter group inhibits factor Xa which is trypsin-like serine protease that plays a critical role in the blood coagulation cascade

**Types of anticoagulants**

| Types | Subtypes | Generic name | Mechanism of action |
|---|---|---|---|
| **VKAs** | Vitamin K Dependent Antagonists | • Warfarin | Works by limiting the availability of vitamin K a vitamin that is necessary for the blood coagulation pathway to produce clotting factors Il, VII, IX, and X. This decreases the blood's ability to clot |
| **Heparins** | Unfractionated Heparins (UFH） | • Heparin | Works by activating antithrombin, and then antithrombin keeps other parts of the clotting process from working normally |
| | Low Molecular Weight Heparin | • Low Molecular Weight Heparin Sodium<br>• Enoxaparin Sodium<br>• Dalteparin Sodium<br>• Nadroparin Sodium<br>• Bemiparin Sodium | Have a longer length of action, long half-life, and can be monitored using anti-factor Xa activity |
| **NOACs** | Factor Xa inhibitors | • Apixaban<br>• Edoxaban<br>• Betrixaban<br>• Rivaroxaban | Involves inhibition of the cleavage of prothrombin to thrombin by binding directly to factor Xa |
| | Direct thrombin inhibitors | • Dabigatram | Inhibits the cleavage of fibrinogen to fibrin by thrombin |

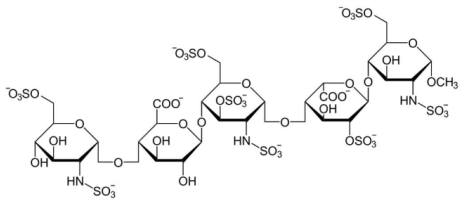


Source： Chinese Journal of Cardiology; Chinese Circulation Journal; China Insights Consultancy

# LMWH is a commonly used anticoagulant nowadays, and it offers better clinical outcomes compared to heparin



## Introduction to LMWH



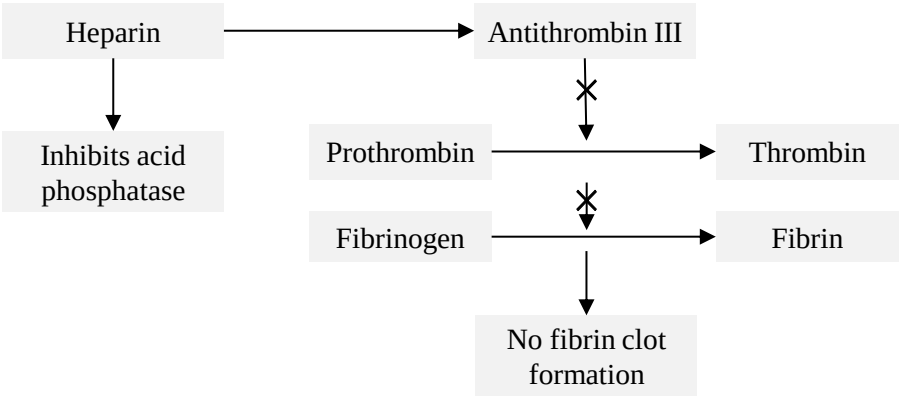
**Chemical formula of heparin**

- Heparin is a refined sulfated glycosaminoglycan extracted from the organs of mammals (such as pigs or cows). It is a mixture with an average molecular weight of approximately 15,000. **Low molecular weight heparin (LMWH) is derived from heparin through enzymatic or chemical depolymerization, resulting in sulfated glycosaminoglycan fragments with an average molecular weight ranging from 3,000 to 8,000**

## Comparison of clinical applications and effectiveness between LMWH and Heparin

| Items | LMWH | Heparin |
|---|---|---|
| Clinical applications | • Thromboembolic disorders and in preventing clot formation in hemodialysis machines<br>• Unstable angina and non-ST-segment elevation myocardial infarction | • Thromboembolic disorders and in preventing clot formation in hemodialysis machines<br>• Disseminated intravascular coagulation caused by various reasons and in anticoagulation of certain blood samples or devices |
| Whether need to monitor a patient's activated partial thromboplastin time (aPTT) | No | Yes |
| Side effects | The incidence of adverse reactions with LMWHs is lower, but LMWHs are primarily excreted through the kidneys, and individuals with renal impairment may experience drug accumulation, leading to a higher risk of bleeding | Bleeding, thrombocytopenia, and osteoporosis may occur with high-dose or long-term use of these medications |

## Mechanism of action of LMWH




- LMWHs exert their antithrombotic activity by binding to and accelerating the activity of antithrombin III. By activating antithrombin III, coagulation factor Xa and factor IIa (thrombin) are inhibited. The resultant thrombin inhibition prevents the formation of fibrin clots
- Compared to unfractionated heparin, LMWHs produce a more predictable anticoagulant response, reflecting their better bioavailability, longer half-life, and dose-independent clearance. LMWHs should be prescribed according to recommended dose regimens for each clinical indication to ensure optimal safety and efficacy



Source： Lifetimes; Labpedia.net；China Insights Consultancy

# In China, there are five categories of approved LMWH products including low molecular weight heparin, enoxaparin, nadroparin, dalteparin, and beminparin



## Overview of categories of LMWHs

- Currently, there are five approved original/reference LMWH formulations available in the domestic market, including bemiparin, dalteparin, enoxaparin, nadroparin, and low molecular weight heparin

**Comparison of LMWHs indications in China**

| Indications | Low Molecular Weight Heparin Sodium | Enoxaparin Sodium | Nadroparin Sodium | Dalteparin Sodium | Bemiparin Sodium |
|---|---|---|---|---|---|
| Extracorporeal circulation in blood dialysis to prevent thrombosis | √ | √ | √ | √ | √ |
| Prevention of thromboembolic disease in patients undergoing general and orthopedic surgery | √ | √ | | | √ |
| Treatment of unstable angina and non-Q-wave myocardial infarction, in combination with aspirin | | √ | √ | √ | |
| Treatment of acute ST-segment elevation myocardial infarction in combination with thrombolytic agents or concomitantly with percutaneous coronary intervention (PCI) | | √ | | | |

### Characteristics of Enoxaparin Sodium

- Since it was first approved in 1987, enoxaparin finished dose has been marketed in over 100 countries, with millions of patients worldwide and billions of doses consumed, which enables it to become the largest LMWH player in the world. Enoxaparin is the authorized generic that is identical to Lovenox, a top selling drug in Sanofi's established drug portfolio

### Advantages of Enoxaparin Sodium

- Enoxaparin sodium stands out among major LMWH finished doses due to its superior pharmacological and chemical attributes. These advantages include a longer elimination half-life, excellent bioavailability, and a higher anti Xa/IIa activity ratio
- Furthermore, enoxaparin sodium's manufacturing process via ß-elimination eliminates the risk of nitrite impurities, which can be carcinogenic and genetically toxic. In contrast, dalteparin sodium and nadroparin calcium are produced using nitrous acid degradation, which carries the potential for nitrite impurity. Enoxaparin sodium boasts a broader range of approved indications, diverse delivery routes, and superior clinical performance. Consequently, it is poised to replace other LMWH finished doses on a global scale



Source：Guangdong Pharmaceutical Association; China Insights Consultancy

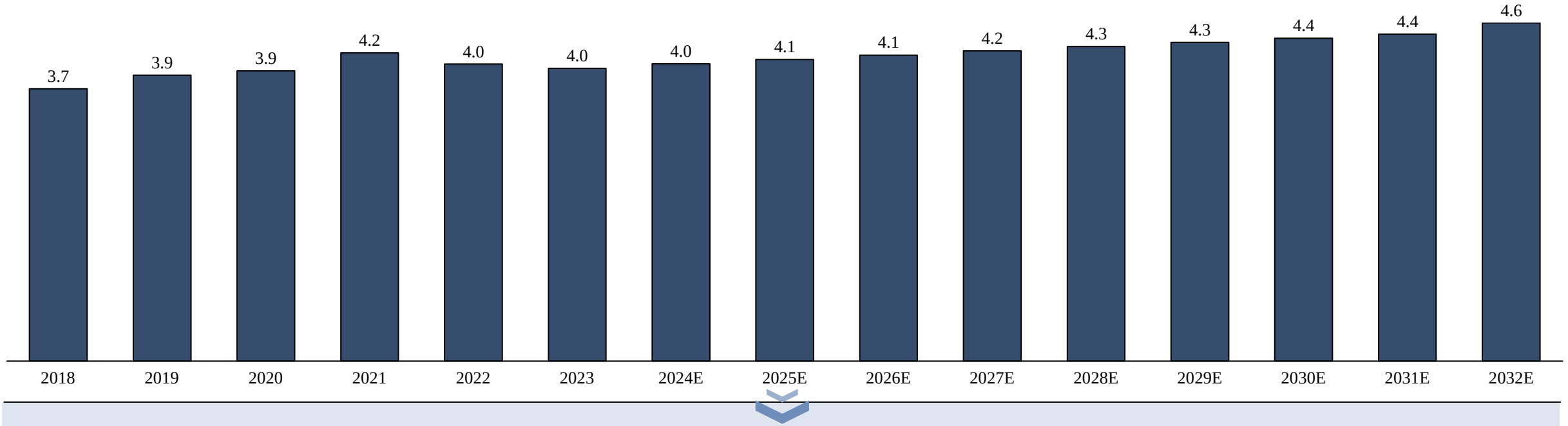
# Global LMWHs market grew from USD[3.7] billion in 2018 to USD[4.0] billion in 2023 at the CAGR of [1.5]%, and is projected to reach USD[4.6] billion by 2032



Global market size of LMWHs, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| Global LMWHs market | 1.5% | 1.6% |

***Billion USD***




**Key Analysis**

- Global LMWHs market grew from USD[3.7] billion in 2018 to USD[4.0] billion in 2023 at the CAGR of [1.5]%, and is projected to reach USD[4.6] billion by 2032



Source: China Insights Consultancy

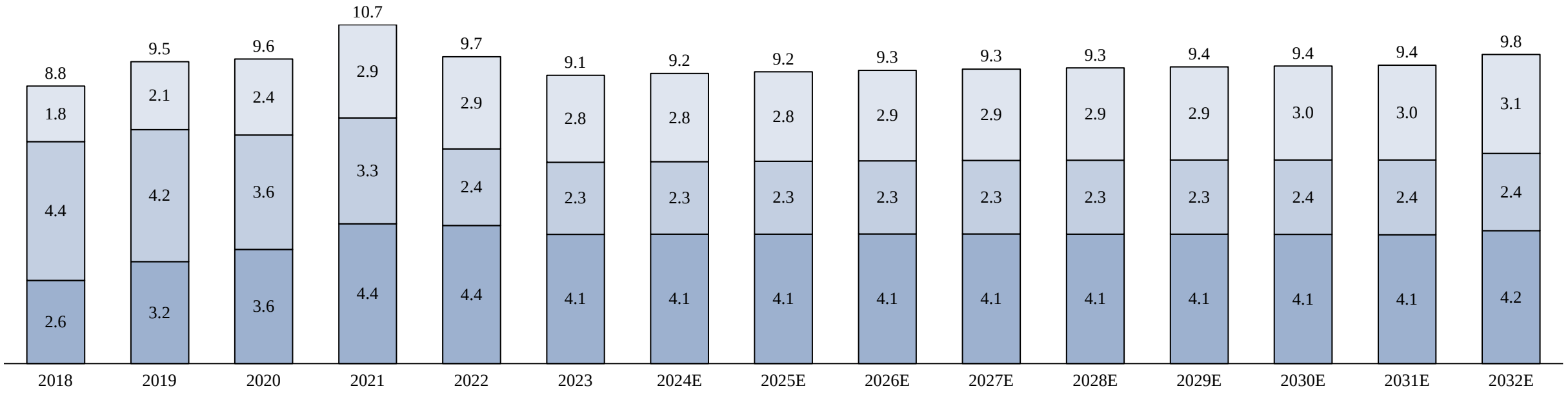
# China LMWHs market grew from RMB[8.8] billion in 2018 to RMB[9.1] billion in 2023 at the CAGR of [0.8]%, and is projected to reach RMB[9.8] billion by 2032



Market size of LMWHs in China, 2018-2032E

| CAGR | 2018-23 | 2023-32E |
|---|---|---|
| China Enoxaparin Market | 9.4% | 1.4% |
| China Uncategorized LMWH Market | -12.3% | 0.8% |
| Others | 9.2% | 0.3% |
| Total China LMWHs Market | 0.8% | 0.8% |

***Billion RMB***






Source: China Insights Consultancy

# Outstanding clinical advantages, rising PCI cases, and growing clinical demand are poised to enhance the clinical effectiveness of LMWHs, especially Enoxaparin. More patients have gained the ability to afford the treatment



## Market drivers

**1 Rising clinical demand**

- In 2019, stroke emerged as the leading cause of death in China, claiming the lives of a staggering 2,189,175 individuals. This represented a significant increase of 12.4% in mortality compared to the statistics from 2009. Furthermore, the crude mortality rate for cerebrovascular diseases among Chinese residents stood at 149.56 per 100,000 individuals, constituting a substantial 22.17% of the total number of deaths[1]. These alarming figures underscore a rising trend in cardiovascular and cerebrovascular diseases within China, which has, in turn, contributed to an increased prevalence of thrombotic conditions. Consequently, there is a growing demand for anticoagulant medications, particularly LMWHs, to address this emerging healthcare challenge

**2 Increasing PCI cases**

- As of 2021, China has conducted an impressive 1.26 million cases of percutaneous coronary intervention (PCI), and this number has been steadily rising with a CAGR of approximately 16% from 2012 to 2021[2]. This sustained increase in PCI procedures reflects the rapid growth in China's cardiovascular field and the ever-growing demand from patients. With the widespread application of PCI procedures, ensuring their successful execution is paramount. Anticoagulant medications, especially LMWHs, play a crucial role during these procedures to prevent clot formation and ensure postoperative safety for patients. Consequently, the rising demand for PCI procedures is accompanied by an increased need for LMWHs

**3 Clinical advantages**

- LMWH fragments, with their shorter molecular structure, excel in clinical use. They efficiently provide anticoagulant effects while minimizing the risk of bleeding. This popularity within healthcare drives market demand, meeting industry standards and ensuring patient safety. As a result, LMWH demand grows, spurring innovations in the field

## Market trends

**Broadening of indications and applications**

- Enoxaparin's clinical applications are expanding, effectively treating various conditions in cardiology, nephrology, and neurology. Unlike Novel Oral Anticoagulants (NOACs), enoxaparin has broader applications, being used in treatments where NOACs aren't approved. For instance, it manages acute ST-segment elevation myocardial infarction, prevents dialysis-associated thrombosis, and prophylaxes against ischemic complications

**Product enhancement**

- China has a significant number of unclassified LMWH finished doses with varying quality and limited clinical support. NMPA introduced Quality Control Evaluation (QCE) approval for injection doses in 2020 to enhance quality control. With NMPA and Chinese Pharmacopeia Commission (CPC) efforts, enoxaparin finished dose products are expected to replace low-quality LMWH products due to better clinical effects. In the EU, enoxaparin products are likely to surpass heparin due to superior efficacy and stable anticoagulation

**Improved patients' financial capability**

- China's pharmaceutical market, the world's second-largest, offers significant growth opportunities. With expanding clinical uses and potent therapeutic effects, enoxaparin finished dose is set to benefit from recent pharmaceutical policy reforms like Centralized Drug Procurement. This year, **enoxaparin has been included in the national centralized procurement, which started at the end of July. This national procurement will continue until the end of 2025, and during this period, there will be no changes in the price**. This mechanism is advantageous for a larger number of patients by enhancing their financial capacity, making it possible for them to afford enoxaparin



1. Annual report on cardiovascular health and diseases in China (2021)
2. National Interventional Cardiology Forum

Source：NMPA; ESC; Chinese Medical Journal Network; China Insights Consultancy

# As of August 2023, there are over 30 LMWHs approved by the NMPA in China; Sanofi is the original manufacturer of enoxaparin, and 9 companies were awarded contracts for enoxaparin in the 8th NVBP



**Companies Awarded Contracts for Enoxaparin in the 8th NVBP**

| Approval number* | Product name | Generic name | Manufacturer | Indication |
|---|---|---|---|---|
| H20223798; H20223799 | / | Enoxaparin sodium | Cisen Pharmaceutical | Anticoagulation and anti-thrombosis |
| H20140127; H20140126; H20223859; H20143370 | / | Enoxaparin sodium | Suzhou Erye Pharmaceutical Co., Ltd | Anticoagulation and anti-thrombosis |
| H20173386; H20143051; H20173385 | / | Enoxaparin sodium | Tiandong Pharma | Anticoagulation and anti-thrombosis |
| H20223252 | / | Enoxaparin sodium | Shandong New Era Pharmaceutical | Anticoagulation and anti-thrombosis |
| H20213972; H20213973 | Fupuai | Enoxaparin sodium | Chase Sun Pharmaceutical | Anticoagulation and anti-thrombosis |
| H20064066; H20064067; H20060347 | Yinuojia | Enoxaparin sodium | Hangzhou jiuyuan gene engineering Co., Ltd. | Anticoagulation and anti-thrombosis |
| H20056845; H20056850; H20056847; H20056848; H20056846; H20056849 | / | Enoxaparin sodium | Techdow Pharmaceutical | Anticoagulation and anti-thrombosis |
| H20194081; H20194082; H20194093; H20153098; H20153099 | / | Enoxaparin sodium | Qianhong Biopharma | Anticoagulation and anti-thrombosis |
| H20143002; H20163484; H20143003; H20143003 | / | Enoxaparin sodium | Kingfriend | Anticoagulation and anti-thrombosis |



Note*: Multiple approval numbers indicate that the same drug has been approved in various dosages

Source：NMPA; China Insights Consultancy

# As of August 2023, there are over 30 LMWHs approved by the NMPA in China; Sanofi is the original manufacturer of enoxaparin, and 9 companies were awarded contracts for enoxaparin in the 8th NVBP



- **Jiuyuan gene's Jipailin is the first low molecular weight heparin sodium approved by NMPA.**

**Top 5 earliest approved low molecular weight heparin sodium by NMPA**

| Initial Approval number | Product name | Generic name | Manufacturer | Indication | Initial approval date |
|---|---|---|---|---|---|
| H10980113 | Jipailin | Low molecular weight heparin sodium | Hangzhou jiuyuan gene engineering Co., Ltd. | Anticoagulant treatment for acute DVT. Prevention of clot formation during hemodialysis. Used in combination with aspirin to prevent ischemic complications of unstable angina and non-Q-wave myocardial infarction. Prevention of surgery-related DVT | 1998 |
| H19990215 | Low Molecular Weight Heparin Sodium | Low molecular weight heparin sodium | Nanjing Nanda Pharmaceutical Co., Ltd. | 1) Primarily used to prevent clot formation during hemodialysis and can also be used to prevent deep vein thrombosis. 2) Indicated for women with a history of thrombosis or existing venous thromboembolism during pregnancy | 1999 |
| H20000095 | Low Molecular Weight Heparin Sodium | Low molecular weight heparin sodium | Qilu Pharmaceutical Co., Ltd. | 1) Primarily used to prevent clot formation during hemodialysis and can also be used to prevent deep vein thrombosis. 2) Indicated for women with a history of thrombosis or existing venous thromboembolism during pregnancy | 2000 |
| H20184042 | Low Molecular Weight Heparin Sodium | Low molecular weight heparin sodium | Biozen Pharmaceutical Co., Ltd. | Anticoagulant treatment for acute DVT. Prevention of clot formation during hemodialysis. Used in combination with aspirin to prevent ischemic complications of unstable angina and non-Q-wave myocardial infarction. Prevention of surgery-related DVT | 2001 |
| H20020179 | Low Molecular Weight Heparin Sodium | Low molecular weight heparin sodium | Wanbang Biopharma | 1)Primarily used to prevent clot formation during hemodialysis and can also be used to prevent deep vein thrombosis. 2) Indicated for pregnant women with a history of thrombosis or existing venous thromboembolism | 2002 |



Source：NMPA; China Insights Consultancy

# As of August 2023, there are over 30 LMWHs approved by the NMPA in China; Sanofi is the original manufacturer of enoxaparin, and 9 companies were awarded contracts for enoxaparin in the 8th NVBP



- **Jiuyuan gene's Yinuojia is the second enoxaparin sodium approved by NMPA.**
- **The sales revenue of Yinuojia is RMB[243.3 million] and RMB[235.4 million] in 2021 and 2022 with a market share of [8.3]% and [8.1]% of the Enoxaparin market in China, respectively, and ranked [5] and [4] nationally in the corresponding periods.**

**Top 5 earliest approved enoxaparin sodium by NMPA**

| Initial Approval number | Product name | Manufacturer | Indication | Initial approval date |
|---|---|---|---|---|
| H20056845 | Prolongin | Techdow Pharmaceutical | Prevention and treatment of deep vein thrombosis or pulmonary embolism | 2005 |
| H20064066 | Yinuojia | Hangzhou jiuyuan gene engineering Co., Ltd. | 1) 2ml:20mg and 0.4ml:40mg injection: Prevention of venous thromboembolic disease (prevention of venous thrombosis), especially in relation to orthopedic or general surgical procedures. 2) 0.6ml:60mg, 0.8ml:80mg, and 1.0ml:100mg injection: Treatment of established deep vein thrombosis, with or without pulmonary embolism, when clinical symptoms are not severe and do not require surgical or thrombolytic treatment for pulmonary embolism. 3) Treatment of unstable angina and non-Q-wave myocardial infarction in combination with aspirin. Used during hemodialysis and extracorporeal circulation to prevent thrombosis formation. 4) Treatment of acute ST-segment elevation myocardial infarction in combination with a thrombolytic agent or simultaneously with percutaneous coronary intervention (PCI) | 2006 |
| H20143002 | Ledraxen | Nanjing Kingfriend | Prevention and treatment of deep vein thrombosis or pulmonary embolism | 2014 |
| H20143051 | / | Dongying Tiandong Pharmaceutical Co,.Ltd | Prevention and treatment of deep vein thrombosis or pulmonary embolism | 2014 |
| H20140126 | / | Suzhou Erye Pharmaceutical Co., Ltd | 1) Prevention of venous thromboembolic disease (prevention of venous thrombosis), especially in relation to orthopedic or general surgical procedures. 2) Treatment of established deep vein thrombosis, with or without pulmonary embolism, when clinical symptoms are not severe and do not require surgical or thrombolytic treatment for pulmonary embolism. 3) Treatment of unstable angina and non-Q-wave myocardial infarction in combination with aspirin. Used during hemodialysis and extracorporeal circulation to prevent thrombosis formation | 2014 |



Source：NMPA; China Insights Consultancy

# As of August 2023, there are over 30 LMWHs approved by the NMPA in China; Sanofi is the original manufacturer of enoxaparin, and 9 companies were awarded contracts for enoxaparin in the 8th NVBP



**Top 5 earliest approved low molecular weight heparin sodium by NMPA**

| Initial Approval number | Product name | Generic name | Manufacturer | Indication | Initial approval date |
|---|---|---|---|---|---|
| H10980113 | Jipailin | Low molecular weight heparin sodium | Hangzhou jiuyuan gene engineering Co., Ltd. | Anticoagulant treatment for acute DVT. Prevention of clot formation during hemodialysis. Used in combination with aspirin to prevent ischemic complications of unstable angina and non-Q-wave myocardial infarction. Prevention of surgery-related DVT | 1998 |
| H19990215 | Low Molecular Weight Heparin Sodium | Low molecular weight heparin sodium | Nanjing Nanda Pharmaceutical Co., Ltd. | 1) Primarily used to prevent clot formation during hemodialysis and can also be used to prevent deep vein thrombosis. 2) Indicated for women with a history of thrombosis or existing venous thromboembolism during pregnancy | 1999 |
| H20000095 | Low Molecular Weight Heparin Sodium | Low molecular weight heparin sodium | Qilu Pharmaceutical Co., Ltd. | 1) Primarily used to prevent clot formation during hemodialysis and can also be used to prevent deep vein thrombosis. 2) Indicated for women with a history of thrombosis or existing venous thromboembolism during pregnancy | 2000 |
| H20184042 | Low Molecular Weight Heparin Sodium | Low molecular weight heparin sodium | Biozen Pharmaceutical Co., Ltd. | Anticoagulant treatment for acute DVT. Prevention of clot formation during hemodialysis. Used in combination with aspirin to prevent ischemic complications of unstable angina and non-Q-wave myocardial infarction. Prevention of surgery-related DVT | 2001 |
| H20020179 | Low Molecular Weight Heparin Sodium | Low molecular weight heparin sodium | Wanbang Biopharma | 1)Primarily used to prevent clot formation during hemodialysis and can also be used to prevent deep vein thrombosis. 2) Indicated for pregnant women with a history of thrombosis or existing venous thromboembolism | 2002 |



Source：NMPA; China Insights Consultancy

# As of August 2023, there are over 30 LMWHs approved by the NMPA in China; Sanofi is the original manufacturer of enoxaparin, and 9 companies were awarded contracts for enoxaparin in the 8th NVBP



- **The sales revenue of Yinuojia is RMB[243.3 million] and RMB[235.4 million] in 2021 and 2022 with a market share of [8.3]% and [8.1]% of the Enoxaparin market in China, respectively, and ranked [5] and [4] nationally in the corresponding periods.**

**Top 5 earliest approved enoxaparin sodium by NMPA**

| Initial Approval number | Product name | Manufacturer | Indication | Initial approval date |
|---|---|---|---|---|
| H20056845 | Prolongin | Techdow Pharmaceutical | Prevention and treatment of deep vein thrombosis or pulmonary embolism | 2005 |
| H20064066 | Yinuojia | Hangzhou jiuyuan gene engineering Co., Ltd. | 1) 2ml:20mg and 0.4ml:40mg injection: Prevention of venous thromboembolic disease (prevention of venous thrombosis), especially in relation to orthopedic or general surgical procedures. 2) 0.6ml:60mg, 0.8ml:80mg, and 1.0ml:100mg injection: Treatment of established deep vein thrombosis, with or without pulmonary embolism, when clinical symptoms are not severe and do not require surgical or thrombolytic treatment for pulmonary embolism. 3) Treatment of unstable angina and non-Q-wave myocardial infarction in combination with aspirin. Used during hemodialysis and extracorporeal circulation to prevent thrombosis formation. 4) Treatment of acute ST-segment elevation myocardial infarction in combination with a thrombolytic agent or simultaneously with percutaneous coronary intervention (PCI) | 2006 |
| H20143002 | Ledraxen | Nanjing Kingfriend | Prevention and treatment of deep vein thrombosis or pulmonary embolism | 2014 |
| H20143051 | / | Dongying Tiandong Pharmaceutical Co,.Ltd | Prevention and treatment of deep vein thrombosis or pulmonary embolism | 2014 |
| H20140126 | / | Suzhou Erye Pharmaceutical Co., Ltd | 1) Prevention of venous thromboembolic disease (prevention of venous thrombosis), especially in relation to orthopedic or general surgical procedures. 2) Treatment of established deep vein thrombosis, with or without pulmonary embolism, when clinical symptoms are not severe and do not require surgical or thrombolytic treatment for pulmonary embolism. 3) Treatment of unstable angina and non-Q-wave myocardial infarction in combination with aspirin. Used during hemodialysis and extracorporeal circulation to prevent thrombosis formation | 2014 |



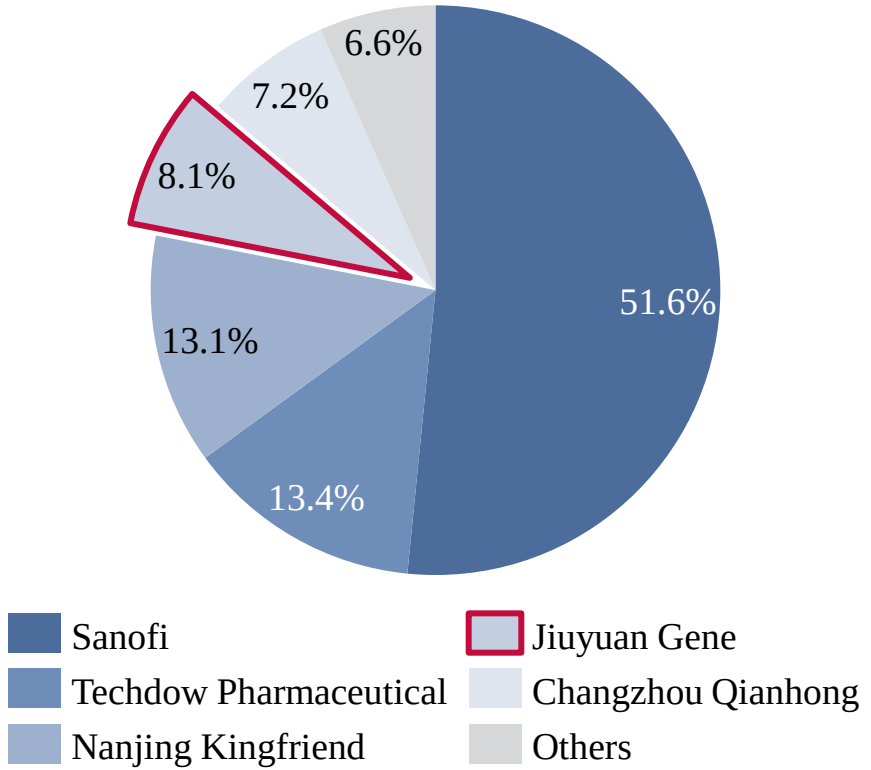
Source：NMPA; China Insights Consultancy

# Competitive Landscape of the enoxaparin Market in China, 2022&2023

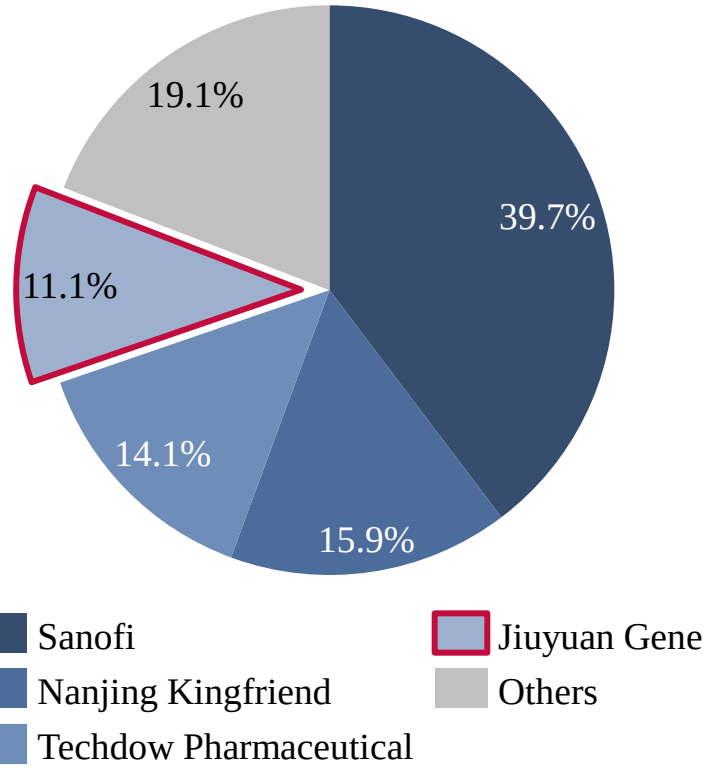


- The market share of Yinuojia is [11.1]% of the enoxaparin sodium market in China, and ranked [4] nationally in 2023.

**Competitive Landscape of the enoxaparin Market in China, 2022**




**Competitive Landscape of the enoxaparin Market in China, 2023**





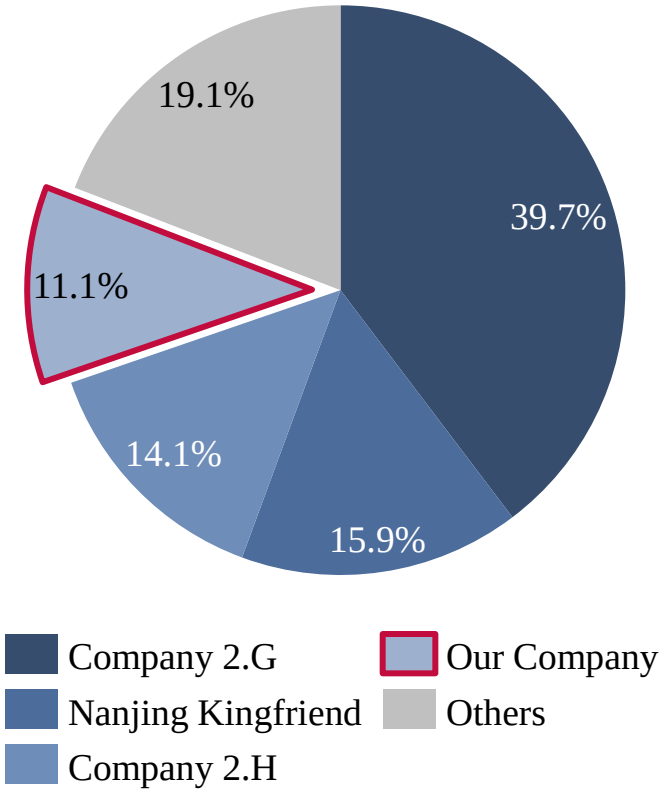

Source: Menet

# Competitive Landscape of the enoxaparin Market in China, 2023



- The market share of Yinuojia is [11.1]% of the enoxaparin sodium market in China, and ranked [4] nationally in 2023.

**Competitive Landscape of the enoxaparin Market in China, 2023**




- Company 2.G, headquartered in France, is a multinational pharmaceutical and healthcare company, focusing on cardiovascular disease, oncology, diabetes, and vaccines. It entered the hematology drug sector in 2017 and currently holds one approved enoxaparin drug candidates in China.
- Nanjing Kingfriend (南京健友生化製藥股份有限公司), headquartered in Jiangsu, China and listed on the Shanghai Stock Exchange (stock code: 603707.SH), was founded in 2000. It is a pharmaceutical group focusing on drug R&D, production and sales.
- Company 2.H, headquartered in Shenzhen, China, was founded in 2004. It is dedicated to the export of enoxaparin sodium API and low molecular weight heparin preparations. It entered the hematology drug sector in 2005 and currently holds one approved enoxaparin drug candidates in China.



Source: Menet

# Competitive landscape of enoxaparin sodium in China, 2022



**Competitive landscape of enoxaparin sodium in China, 2022**

| Company | Generic Name | Brand Name | NMPA First Approval Year | NRDL Inclusion | Revenue (Ten thousand RMB) | Market Share | MoA | Indications | Route of Administration |
|---|---|---|---|---|---|---|---|---|---|
| Sanofi<br>赛诺菲 | Enoxaparin Sodium | Clexane | 2019 | Yes | 150,000.0 | 51.5% | By binding to antithrombin III and its complex, it enhances the inhibitory effects on factor Xa and thrombin (factor IIa) in the coagulation cascade | VTE | Injection |
| Techdow Pharmaceutical<br>深圳天道 | Enoxaparin Sodium | Prolongin | 2005 | Yes | 39,000.0 | 13.4% | By binding to antithrombin III and its complex, it enhances the inhibitory effects on factor Xa and thrombin (factor IIa) in the coagulation cascade | VTE | Injection |
| Nanjing Kingfriend<br>南京健友生化制药股份有限公司 | Enoxaparin Sodium | Ledraxen | 2014 | Yes | 38,080.0 | 13.1% | By binding to antithrombin III and its complex, it enhances the inhibitory effects on factor Xa and thrombin (factor IIa) in the coagulation cascade | VTE | Injection |
| Hangzhou jiuyuan gene engineering Co., Ltd.<br>杭州九源基因工程有限公司 | Enoxaparin Sodium | Yinuojia | 2006 | Yes | 23,537.5 | 8.1% | By binding to antithrombin III and its complex, it enhances the inhibitory effects on factor Xa and thrombin (factor IIa) in the coagulation cascade | VTE | Injection |
| Changzhou Qianhong Biopharma Co., Ltd<br>常州千红生化制药股份有限公司 | Enoxaparin Sodium | Qianhongyinuo | 2015 | Yes | 20,995.0 | 7.2% | By binding to antithrombin III and its complex, it enhances the inhibitory effects on factor Xa and thrombin (factor IIa) in the coagulation cascade | VTE | Injection |



Note: This table lists the top 5 manufacturers of enoxaparin sodium in China, 2022

Source: NMPA; China National Intellectual Property Administration; China Insights Consultancy

# Competitive landscape of enoxaparin sodium in China, 2023



**Competitive landscape of enoxaparin sodium in China, 2023**

| Company | Generic Name | Brand Name | NMPA First Approval Year | NRDL Inclusion | Market Share | MoA | Indications | Route of Administration |
|---|---|---|---|---|---|---|---|---|
| Sanofi<br>赛诺菲 | Enoxaparin Sodium | Clexane | 2019 | Yes | 39.68% | By binding to antithrombin III and its complex, it enhances the inhibitory effects on factor Xa and thrombin (factor IIa) in the coagulation cascade | VTE | Injection |
| Techdow Pharmaceutical<br>深圳天道 | Enoxaparin Sodium | Prolongin | 2005 | Yes | 15.93% | By binding to antithrombin III and its complex, it enhances the inhibitory effects on factor Xa and thrombin (factor IIa) in the coagulation cascade | VTE | Injection |
| Nanjing Kingfriend<br>南京健友生化制药股份有限公司 | Enoxaparin Sodium | Ledraxen | 2014 | Yes | 14.11% | By binding to antithrombin III and its complex, it enhances the inhibitory effects on factor Xa and thrombin (factor IIa) in the coagulation cascade | VTE | Injection |
| Hangzhou jiuyuan gene engineering Co., Ltd.<br>杭州九源基因工程有限公司 | Enoxaparin Sodium | Yinuojia | 2006 | Yes | 11.13% | By binding to antithrombin III and its complex, it enhances the inhibitory effects on factor Xa and thrombin (factor IIa) in the coagulation cascade | VTE | Injection |

Note: This table lists the top 5 manufacturers of enoxaparin sodium in China, 2022

Source: NMPA; China National Intellectual Property Administration; China Insights Consultancy

# Development Trends of Artificial Bone Repair Materials

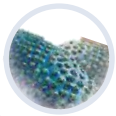
## Since 1960s

### Non-bioactive artificial materials

- Bioinert materials refer to materials that **has minimal interaction with surrounding tissue** when placed within the physical body.
- They have low efficacy in stimulating bone formation and can lead to the formation of fibrous tissue.

## Since 1990s

### Bioactive materials



- Bioactive bone repair materials includes synthetic or naturally derived biodegradable materials **adding osteogenesis-inducing components(e.g. BMP)**.
- This type can **promote the bone healing response** and be responsible for **inducing the formation of bone or cartilage**.

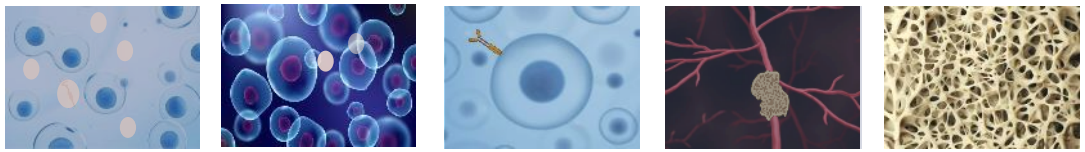
## Future Trends

### New generation bioactive materials

- **The sustained-release system** for delivery of bioactive agents through various biomaterials will promote bone regeneration **by long-term mechanical stability and osteogenic property.**
- **Injectable biomaterials** have indicated better **cellular interaction**, leading to faster resorption of the biomaterial and **promotion of new bone**, therefore driving the development of bone materials **.**



Source: Chinese Journal of Reparative and Reconstructive Surgery; Materials (Basel); Frontiers in Bioengineering and Biotechnology; China Insights Consultancy



植入rhBMP-2骨修复材料

MSCs趋化到植入处

rhBMP-2与MSCs表面受体结合，诱导向成骨细胞分化

成骨细胞在支架上沉淀钙质，血管长入

在局部力学刺激下塑性，形成骨小梁

含rhBMP-2的骨修复材料　rhBMP-2分子　骨小梁

间充质干细胞（MSCs）　钙质





Source: China Insights Consultancy

# GLOSSARY OF TECHNICAL TERMS

| | |
|---|---|
| **ADCC** | antibody-dependent cellular cytotoxicity, a mechanism of the immune system whereby immune cells can destroy target cells, such as virally infected cells or tumor cells, that are coated with antibodies |
| **ADCP** | antibody-dependent cellular phagocytosis, a process by which phagocytic cells, such as macrophages, neutrophils, and dendritic cells, engulf and digest target cells that have been opsonized (marked) by specific antibodies |
| **agonist** | a molecule that binds to a receptor on a cell and triggers a response by that cell which can be used therapeutically to activate receptors in order to treat certain conditions |
| **amylin** | a hormone that is co-secreted with insulin by the beta cells of the pancreas |
| **API** | active pharmaceutical ingredient, the substance in a pharmaceutical drug that is biologically active |
| **aplastic anemia** | a rare, noncancerous disorder in which the blood marrow is unable to adequately produce blood cells required for survival |
| **aprepitant** | a selective antagonist of the neurokinin-1 receptor, used as a medication to prevent nausea and vomiting |
| **avatrombopag** | a medication that increases platelet counts to reduce bleeding risks |
| **bioequivalence test** | a type of evaluation to determine whether a generic drug is equivalent to an original drug in terms of biochemical similarity |
| **biological drug or biologics** | a drug product derived from human, animal, or microorganisms using biotechnology |
| **biosimilar** | the generic version of a patented biological drug |
| **BMI** | body mass index, a numerical value calculated from height and weight, providing a standardized measure to classify underweight, healthy weight, overweight, and obesity |
| **BMP** | bone morphogenetic protein, a biologically active protein that stimulates bone growth and repair |
| **bone injury** | a disruption in the structural integrity of bones causing an array of symptoms including bone defects, bone nonunion, bone delayed union, spinal fusion, and joint fusion |

# GLOSSARY OF TECHNICAL TERMS

| | |
|---|---|
| **bone repair material** | a term used to refer materials used to facilitate the healing of bone injuries, including BMP bone repair materials, non-bioactive artificial bones and natural bones |
| **Category I innovative drug** | innovative chemical drugs that have not been marketed anywhere in the world according to the NMPA |
| **Category III biological products** | a biological product that is (i) manufactured outside China, having marketing authorization outside China, and applying for marketing authorization in China, (ii) has received marketing authorization outside China but not in China, and is applying for manufacturing and marketing authorization in China, or (iii) a biosimilar, (iv) other biological products |
| **CDC** | complement dependent cytotoxicity, a function of the complement system that kills pathogens by damaging their membranes without the involvement of antibodies or cells of the immune system |
| **CD4** | cluster of differentiation 4, a glycoprotein found on the surface of immune cells such as T helper cells |
| **CD38** | cluster of differentiation 38, a glycoprotein with ectoenzymatic functions, which is expressed on plasma cells and other lymphoid and myeloid cell populations |
| **CD47** | cluster of differentiation 47, a broadly expressed protein that co-stimulates T cells, facilitates leukocyte migration, and inhibits macrophage scavenger function |
| **centralized tender** | a procurement process in the form of public tender operated and organized by provincial or municipal government agencies for the procurement of drugs and medical devices by the public medical institutions, the bids of which will be assessed by a committee composed of pharmaceutical and medical experts based on a number of factors, including but not limited to, bid price, product quality, clinical effectiveness, product safety, qualifications and reputation of the manufacturer, after-sale services and innovation |
| **China Association of Medical Equipment** | 中國醫學裝備協會 |
| **chondrocyte** | a type of cell found in cartilage tissue that produces and maintains the cartilaginous matrix, essential for skeletal function and joint movement |
| **Class III medical device** | a category of medical devices characterized by higher risks, requiring rigorous evaluation and regulatory control to ensure safety and effectiveness, subject to specific oversight measures |
| **Class III hospital** | top-level hospital in China, typically having more than 500 beds, providing high-level specialist medical and healthcare services |
| **CMC** | chemistry, manufacturing, and controls |
| **CNIPA** | China National Intellectual Property Administration(國家知識產權局) |

# GLOSSARY OF TECHNICAL TERMS

| | |
|---|---|
| **CSD** | critical-size defect, bone or tissue wound or defect that will not heal by itself without intervention over a long period |
| **daratumumab** | an anti-CD38 drug for the treatment multiple myeloma |
| **delayed union** | when a fracture does not meet the standard for complete healing after a normal healing period (usually within 4 months) |
| **detemir** | a long-acting insulin analog used to control high blood sugar in diabetes by mimicking the body's natural insulin response |
| **diabetes** | a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces |
| **DPP-4 inhibitor** | dipeptidyl peptidase 4 inhibitor, a class of oral hypoglycemics that block the enzyme dipeptidyl peptidase-4 to prolong incretin hormone activity to regulate blood glucose levels for the treatment of T2DM |
| **drug-device combination** | therapeutical product that combines drugs and medical devices, capitalizing on the therapeutic and mechanistic advantages of each component |
| **drug master file** | a confidential document submitted to regulatory agencies containing detailed information about facilities, processes, or materials used in the manufacturing, processing, and packaging of a drug |
| **dulaglutide** | a GLP-1 receptor agonist used for the management of T2DM, enhancing insulin secretion and suppressing glucagon |
| **E. Coli expression system** | a widely used platform for producing recombinant proteins that utilizes engineered Escherichia coli bacteria for gene expression |
| **enoxaparin sodium** | a low molecular weight heparin used as an anticoagulant to prevent and treat thrombosis |
| **enterokinase** | an enzyme that catalyzes the conversion of trypsinogen to trypsin, playing a crucial role in the digestion of proteins in the small intestine |
| **excipient** | an inactive substance formulated alongside the active ingredient of a medication, used to bulk up formulations that contain potent active ingredients |
| **exenatide** | a GLP-1 receptor agonist used in T2DM treatment to enhance insulin secretion and lower blood glucose levels |
| **expert consensus** | a statement or guideline on a particular medical topic, formulated by a panel of experts reflecting the medical knowledge accumulated by those experts and provides information about professional medical care and advice |
| **factor IIa** | also known as thrombin, a key enzyme in the blood coagulation process that converts fibrinogen to fibrin, leading to clot formation |
| **factor Xa** | an enzyme in the coagulation cascade that plays a central role in converting prothrombin to thrombin, leading to blood clot formation |

# GLOSSARY OF TECHNICAL TERMS

| | |
|---|---|
| **first-to-market** | first to receive NDA approval |
| **FDA** | U.S. Food and Drug Administration |
| **FDA drug shortage list** | an official register maintained by the FDA detailing current shortages of pharmaceutical drugs in the U.S. |
| **fosaprepitant** | a medication used as an antiemetic to prevent nausea and vomiting caused by chemotherapy |
| **fulvestrant** | an estrogen receptor antagonist used for treating hormone-receptor-positive metastatic breast cancer in postmenopausal women |
| **G-CSF** | granulocyte colony-stimulating factor, a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream |
| **gastrointestinal peristalsis** | a series of wave-like muscle contractions that occur in the gastrointestinal tract that move food and liquid through the digestive system |
| **generic pharmaceutical or generic drug** | a pharmaceutical that contains the same active ingredients as an original formulation and is comparable in dosage form, strength, quality, performance and intended use |
| **genetic engineering** | a field of biotechnology involving the direct manipulation of the genome of an organism using biotechnology to alter its genetic makeup |
| **GFA** | gross floor area |
| **glass ampoules** | a small, sealed glass container that is used to hold a pharmaceutical compound, typically a liquid, in a sterile condition |
| **glioblastoma** | a fast-growing, aggressive type of central nervous system tumor that forms on the supportive tissue of the brain |
| **glucagon** | a hormone produced by the pancreas that raises blood glucose levels, acting as a counterbalance to insulin |
| **glucocorticoid osteoporosis** | a common form of secondary osteoporosis, resulting from chronic use of glucocorticoid medications, which can interfere with bone remodeling and calcium absorption, leading to increased bone fragility and risk of fractures |
| **GMP** | good manufacturing practice, the practices required in order to conform to the guidelines recommended by agencies that control the authorization and licensing of the manufacture and sale of products |
| **GSP** | good supply practice, guidelines and regulations from time to time issued pursuant to the Drug Administration Law of the PRC (《中华人民共和国药品管理法》) to provide quality assurance and ensure that pharmaceutical distribution enterprises distribute pharmaceutical products in compliance with the guidelines and regulations |

# GLOSSARY OF TECHNICAL TERMS

| | |
|---|---|
| **HbA1c** | glycated hemoglobin, a type of protein that is chemically linked to sugar, the level of which is indicative of the blood sugar level and can be used as a diagnostic test for diabetes |
| **helper T cell** | also known as CD+ cell or CD4-positive cell, a type of T cell that activate and direct other immune cells, orchestrating the response of body to infections and diseases by releasing signaling molecules called cytokines |
| **hematopoietic stem cell** | an undifferentiated cell found in the bone marrow that have the ability to give rise to all types of blood cells, including red blood cells, white blood cells, and platelets. |
| **hemodialysis** | a medical procedure used to remove waste products and excess fluid from the blood when the kidneys are not functioning properly |
| **hG-CSF** | human granulocyte colony-stimulating factor, a type of growth factor of human that stimulates the bone marrow to produce more white blood cells particularly neutrophils used clinically to reduce the risk of infection in patients with neutropenia. |
| **HR+ breast cancer** | hormone receptor-positive breast cancer, a subtype of breast cancer that has cells expressing receptors for hormones such as estrogen and/or progesterone |
| **hyaluronidase** | an enzyme that catalyzes the degradation of hyaluronic acid, breaking down its polysaccharide chains to facilitate the dispersion and absorption of fluids and drugs |
| **hypoglycemia** | a medical condition characterized by an abnormally low level of glucose (sugar) in the blood, often resulting in symptoms such as shakiness, sweating, confusion, and in severe cases, unconsciousness or seizures |
| **idiopathic** | a term used to describe a disease or condition that arises spontaneously or for which the cause is unknown |
| **IL** | interleukin, a type of cytokine that are expressed and secreted by white blood cells (leukocytes) and various other cells within the body |
| **IL-11 receptor or IL-11Ralpha** | a protein that binds interleukin-11 (IL-11), a cytokine involved in a variety of cellular processes such as inflammation, bone metabolism, and tissue regeneration |
| **IND** | investigational new drug, an application and approval process required before drug candidates may commence clinical trials |
| **intravenous administration** | a method of delivering medication or fluids directly into the bloodstream through a vein |

# GLOSSARY OF TECHNICAL TERMS

| | |
|---|---|
| **IP** | intellectual property |
| **KOLs** | Key Opinion Leaders, doctors that influence their peers' medical practice, including but not limited to prescribing behavior |
| **light-chain amyloidosis** | a rare and serious condition caused by the abnormal proliferation of plasma cells in the bone marrow, leading to the production of misfolded light chains that form amyloid deposits in tissues and organs, impairing their normal function |
| **liraglutide** | a GLP-1 receptor agonist with an extended half-life |
| **low molecular weight heparin sodium or LMWH** | a class of anticoagulant medications used to prevent and treat thrombosis |
| **lyophilized powder** | a medication or vaccine preparation that has been freeze-dried into a powder form |
| **lyophilized powder injection** | a medication or vaccine preparation that has been freeze-dried into a powder form for stability and is intended to be reconstituted with a solvent or diluent before use as an injectable therapy |
| **MASH** | metabolic dysfunction-associated steatohepatitis, also known as nonalcoholic steatohepatitis, severe form of nonalcoholic fatty liver disease characterized by inflammation of the liver and damage to liver cells, which can lead to fibrosis (scarring) or cirrhosis |
| **medical device** | instrument, apparatus, implement, machine, implant, in vitro reagent, or other similar or related article intended for the diagnosis, prevention, monitoring, treatment, or alleviation of disease |
| **megakaryocyte progenitor cell** | a precursor cell in the bone marrow that gives rise to megakaryocytes, which are the large bone marrow cells responsible for the production of platelets necessary for blood clotting |
| **metabolic disease** | a medical condition the occurs when the normal metabolism reactions of a patient are disrupted, affecting how the patient's body processes and distributes macronutrients like proteins, fats, and carbohydrates |
| **monoclonal antibody** | an antibody produced from a cell lineage made by cloning a unique white blood cell |
| **MSC** | mesenchymal stem cell, a type of cell that can differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells), and adipocytes (fat cells that give rise to marrow adipose tissue) |
| **multiple myeloma** | a type of blood cancer that affects plasma cells, which are a type of white blood cell made in the bone marrow |

# GLOSSARY OF TECHNICAL TERMS

| | |
|---|---|
| **myelodysplastic** | a group of diverse bone marrow disorders in which the bone marrow does not produce enough healthy blood cells |
| **NAFLD** | nonalcoholic fatty liver disease, a liver condition caused by a build-up of fat in the liver |
| **NASH** | nonalcoholic steatohepatitis, severe form of nonalcoholic fatty liver disease characterized by inflammation of the liver and damage to liver cells, which can lead to fibrosis (scarring) or cirrhosis |
| **NCCN** | National Comprehensive Cancer Network, an alliance of leading cancer centers dedicated to improving the quality, effectiveness, and efficiency of cancer care so that patients can live better lives who develops evidence-based clinical guidelines to provide high-quality, state-of-the-art care to cancer patients |
| **NDA** | New Drug Application, the formal proposal to apply for the approval a new pharmaceutical for sale and marketing |
| **NDRC** | National Development and Reform Commission (国家发展和改革委员会), a Chinese government agency that formulates and implements strategies for national economic and social development, guides overall economic restructuring, and oversees policies for environmental protection, pricing, and other economic regulations |
| **neutropenia** | a hematological disorder characterized by an abnormally low count of neutrophils, which are a type of white blood cell that serves as a primary defense against infections by destroying bacteria, fungi, and other pathogens in the blood |
| **NK-1** | neurokinin-1, a neurotransmitter that plays a role in the vomiting reflex |
| **NMPA** | National Medical Products Administration (国家药品监督管理局), the Chinese regulatory body responsible for the supervision and administration of pharmaceuticals, medical devices, and cosmetics in China |
| **non-Q-wave myocardial infarction** | a type of heart attack which does not produce the specific Q waves on an electrocardiogram that are typically associated with a classic heart attack |
| **non-ST myocardial infarction** | a type of heart attack that does not cause ST-segment elevation on an electrocardiogram |
| **nonunion** | when a broken bone fails to heal |

# GLOSSARY OF TECHNICAL TERMS

| | |
|---|---|
| **NRDL** | China's National Reimbursement Drug List |
| **obesity** | a medical condition characterized by an excess of body fat that presents a risk to health, typically defined by a body mass index (BMI) of 28 or higher in China |
| **ONFH** | osteonecrosis of the femoral head, a medical condition characterized by the death of bone tissue in the head of the femur (thigh bone) due to a lack of blood supply |
| **originator product** | the original pharmaceutical drug that has been authorized for market after having proven its safety, efficacy, and quality through extensive research, including preclinical and clinical studies |
| **orthopedic** | the branch of medicine dealing with the correction of deformities of bones or muscles |
| **osteoblast** | a type of cell that is responsible for bone formation. Osteoblasts synthesize and secrete the collagen matrix and calcium salts needed to build the hard structure of bone |
| **osteoconduction** | a property of a material acting as a scaffold that supports the attachment, growth, and proliferation of new bone cells |
| **osteoinductive** | the ability of drugs or medical devices to induce the differentiation of bone progenitor cells into osteoblasts |
| **osteoporosis** | a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture |
| **overweight** | a term used to refer an excess body weight relative to heigh, typically defined by a body mass index (BMI) of 25 to 29.9 |
| **palonosetron** | a 5-HT3 receptor antagonist used for the treatment of chemotherapy-induced nausea and vomiting |
| **Part A of the NRDL** | Part A of the National Reimbursement Drug List, a category of the NRDL that typically includes essential medicines that are covered at a higher reimbursement rate |
| **Part B of the NRDL** | Part B of the National Reimbursement Drug List, a category of the NRDL that typically includes considered non-essential but are still covered by the national insurance system, albeit at a lower reimbursement rate compared to Part A drugs |
| **PEG modification** | polyethylene glycol modification, also known as PEGylation, a process of covalent attachment of PEG polymer chains to another molecule, normally a drug or therapeutic protein |

# GLOSSARY OF TECHNICAL TERMS

| | |
|---|---|
| **peptide drug** | a type of pharmaceutical that is composed of peptides, which are short chains of amino acids, the building blocks of proteins |
| **Phase I trial** | an initial clinical study conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of a candidate drug or treatment in a small group of participants |
| **Phase II trial** | a clinical study designed to evaluate the efficacy, optimal dosing, and safety of a candidate drug or treatment in a targeted patient population |
| **Phase III trial** | a pivotal, large-scale study designed to evaluate the efficacy and monitor adverse reactions in diverse patient populations of a candidate drug or treatment to confirm its safety and effectiveness before regulatory approval |
| **Phase IV trial** | post-marketing surveillance study conducted to assess the long-term effects, optimal use, and additional safety parameters of a candidate drug or treatment in a broad patient population after regulatory approval |
| **protein expression system** | a method used in biotechnology to produce proteins by controlling the expression of genes in selected host cells |
| **R&D** | research and development |
| **receptor** | a protein molecule usually found on the surface of a cell that receives chemical signals from outside the cell |
| **recombinant DNA technology** | the technology used for producing artificial different genetic materials (DNA) through the combination of DNA from different sources |
| **recombinant protein** | a protein that has been produced in vitro using cells transfected with DNA engineered to carry the gene for a designed polypeptide |
| **rhBMP-2** | recombinant human bone morphogenetic protein 2, biologically engineered protein that is a synthetic version of a naturally occurring protein in the body known as bone morphogenetic protein 2 that stimulates bone growth and repair |
| **rhG-CSF** | recombinant human granulocyte colony-stimulating factor, a type of growth factor that stimulates the bone marrow to produce more white blood cells, particularly neutrophils used clinically to reduce the risk of infection in patients with neutropenia |
| **romosozumab** | a monoclonal antibody medication used for the treatment of osteoporosis |
| **sclerostin** | a negative regulator of bone growth |
| **semaglutide** | a peptide drug akin to the hormone GLP-1 developed for the treatment of diabetes, overweight and obesity and is being studied for 28 other indications, including non-alcoholic steatohepatitis, Alzheimer's disease, and cardiovascular diseases |

# GLOSSARY OF TECHNICAL TERMS

| | |
|---|---|
| **serotonin or 5-HT3** | a neurotransmitter that has a wide array of functions in the human body that is linked to the feeling of nausea |
| **SGLT-2 inhibitor** | sodium-glucose cotransporter-2 inhibitor, a class of medications used primarily in the treatment of type 2 diabetes that work by inhibiting the sodium-glucose cotransporter-2 protein in the kidneys, resulting in the reduction of blood glucose levels by promoting the excretion of excess glucose in the urine |
| **semaglutide** | a peptide drug akin to the hormone GLP-1 developed for the treatment of diabetes, overweight and obesity and is being studied for 28 other indications, including non-alcoholic steatohepatitis, Alzheimer's disease, and cardiovascular diseases |
| **serotonin or 5-HT3** | a neurotransmitter that has a wide array of functions in the human body that is linked to the feeling of nausea |
| **SGLT-2 inhibitor** | sodium-glucose cotransporter-2 inhibitor, a class of medications used primarily in the treatment of type 2 diabetes that work by inhibiting the sodium-glucose cotransporter-2 protein in the kidneys, resulting in the reduction of blood glucose levels by promoting the excretion of excess glucose in the urine |
| **SIRPα** | signal regulatory protein alpha, a transmembrane protein that is found on the surface of certain cells, including neurons, immune cells, and others |
| **subcutaneous drug administration** | a route of drug administration where medications are injected into the subcutaneous layer of tissue beneath the skin |
| **systemic lupus erythematosus** | an autoimmune disease in which the immune system mistakenly attacks healthy tissue in many parts of the body |
| **T1DM** | type 1 diabetes mellitus, a disorder characterized by the pancreas's failure to produce insulin, necessitating life-long insulin therapy |
| **T2DM** | type 2 diabetes mellitus, a metabolic disorder marked by insulin resistance and relative insulin deficiency, often associated with obesity and lifestyle factors |
| **thrombocytopenia** | a medical condition characterized by an abnormally low level of platelets in the blood |
| **thrombosis** | the formation of a blood clot, known as a thrombus, within a blood vessel |
| **trabecular bone** | a highly porous form of bone tissue that is organized into a network of interconnected rods and plates called trabeculae which surround pores that are filled with bone marrow |
| **unstable angina** | a medical condition characterized by sudden and unpredictable chest pain |

# Appendix - IO

- Globally, the market size for semaglutide had risen from RMB0.3 billion in 2018 to RMB10.9 billion in 2022, at a CAGR of 156.0% and is projected to reach RMB65.2 billion in 2032 at a CAGR of 19.6%, making it one of the top ten best-selling drugs by generic name worldwide in 2022 and potentially the top three best-selling drugs worldwide in 2023.
- In November 2023, Jifuwei won in the bidding processed under the seventh batch of national centralized volume-based procurement scheme.
- Entry barriers:

1) Market access barriers. The use of drugs and medical devices is directly related to people's lives and health. The state has formulated a series of laws and regulations in terms of market access, production and operation. From laboratory development to product launch, drugs and medical devices need to conduct comprehensive trials for registration and market approval. With increasingly stringent industry supervision, the difficulty of new product approval has increased.
2) Capital investment barriers. The cost of bringing a new drug/ medical device to market with post-approval research and development can be billions of dollars. Likewise, the investments on facilities and land for large-scale manufacturing is tremendous. When it comes to continuous technological innovation and product upgrading, pharmaceuticals and medical device companies need robust fund to sustain development.
3) Talent and technology barriers. The pharmaceutical and medical device industry has high requirements for talents and technical skills. Apart from clinical medicine, the industries involves biology, material sciences, electronics, computer sciences and other multiple subjects. The long-term experience, talent and technique accumulation are what new entrants cannot obtain in the short term.

- The National Healthcare Security Administration (國家醫保局) implemented the centralized volume-based procurement (VBP) scheme for high-value medical consumables since 2020, which focuses on medical devices and consumables with mature, high-volume clinical usage and sufficient market competition. In 2023, the Joint Office for the Procurement of High-Value Medical Consumables (國家組織高值醫用耗材聯合採購辦公室) published the 4th VBP List for High-Value Consumables (the "4th VBP List"), which covers, among other things, certain orthopedic medical devices. According to CIC, medical devices included in the 4th VBP List experience considerable price reductions. BMP bone repair materials, which are characterized by technology innovation and a combination of drug and device, are not included in this list. Instead, BMP bone repair materials are subject to certain price restrictions to be imposed by relevant regulatory authorities. Such price restrictions, when compared to the pricing policies applicable to the medical devices included in the 4th VBP List, are expected to exert less downward pressure on the price of the products. As of the Latest Practicable Date, the implementation details of such price restriction policies are to be published by the relevant regulatory authorities.
- According to CIC, China's pharmaceutical market is projected to grow significantly, from RMB1,680.0 billion in 2022 to RMB3,097.7 billion by 2032 at a CAGR of 6.3%. Within this market, the therapeutic areas of orthopedics, metabolic diseases, oncology, and hematology were particularly dominant, accounting for 52.0% of total market share in 2022, reflecting significant clinical demand in these key areas. The medical device sector, including medical instruments, equipment, appliances, in vitro diagnostic reagents and calibrators, materials, and other related medical items used directly or indirectly on the human body, is also expected to experience robust growth, driven by aging population and heightened health awareness. According to CIC, the size of China's medical device market is expected to grow from RMB1,050.3 billion in 2022 to approximately RMB2,901.1 billion by 2032, at a CAGR of 10.7%.





Source: China Insights Consultancy

# Appendix - IO

- The size of China's bone repair material market is estimated using a formula that multiplies orthopedic surgery volume (approximately 5.9 million in 2022) in China with the percentage of these surgeries using bone repair material, and the average costs of three kinds of bone repair materials. The orthopedic surgery volume includes spinal, joint, trauma, and sports medicine surgeries, and is derived from literature studies and interviews with healthcare professionals. The percentage of orthopedic surgeries using bone repair material is approximated at 20%, based on expert interviews. We consider such 20% of patients receiving orthopedic surgery using bone repair material as addressable patients for bone repair materials. The average costs of different kinds of bone repair materials are estimated with the average prices of allograft bone (around2,000RMB), bioactive artificial bone (around 5,000RMB), and non-bioactive artificial bone (around1,500RMB), multiplied by their respective usage percentages in bone repair surgeries. These price averages and usage percentages are gathered from interviews with manufacturers and sales representatives.
- Among the different types of bone repair materials, bioactive artificial bones (which mainly include bone repair materials containing bioactive agents such as BMP) is expected to grow most rapidly at a CAGR of 23.3% from RMB 544.4 million in 2022 to RMB 4,414.2 million in 2032. As shown in published clinical study results, bone repair materials containing rhBMP-2 demonstrate superior clinical efficacy and safety compared to allograft bones. Patients with sustained bone injuries treated with bone repair materials containing rhBMP-2 required further surgical revisions in 26.1% of the cases, whereas those receiving allograft bone transplants needed additional surgical revisions in 47.4% of the cases. The median time to bone union for patients treated with bone repair materials containing rhBMP-2 was 217 days, significantly shorter than the 416 days required for patients who underwent allograft bone transplants. Furthermore, the incidence of new-onset postoperative infections in patients treated with bone repair materials containing rhBMP-2 was 17.4%, which is lower compared to the 31.6% infection rate in patients receiving allograft bone transplants.
- Fractures are a critical concern in osteoporosis, frequently being the initial symptom and reason for seeking medical advice. The condition's severity is underscored by a high mortality rate, with 20-25% of patients dying within a year of a hip fracture due to complications, and over 50% suffering from varying degrees of disability post-recovery.
- Metabolism refers to the biochemical reactions occurring in human cells, crucial for maintaining cell and overall body health.
- According to CIC, the number of T2DM patients grew from 115.1 million in 2018 to 123.2 million in 2022 and is projected to reach 141.8 million by 2032 in China.
- GLP-1RAs have surpassed insulin to become the most widely used medication for T2DM globally in that year. The international embrace for GLP-1RA suggests a significant market potential for this medication in China.
- This surge in patient numbers along with heightened awareness and treatment rates of the disease necessitates an expanded demand for effective diabetes treatments.
- Such policy frameworks aid in better diagnosis and management of T2DM, consequently increasing the patient pool under regular treatment regimens. medications. The inclusion of a growing number of diabetes drugs, including multiple GLP-1RA medications such as liraglutide, semaglutide, exenatide, and dulaglutide, in the National Medical Insurance Catalog, rising from 59 in 2019 to 76 in 2022, leads to improved medication affordability. This trend is likely to continue, enhancing accessibility and treatment adherence among T2DM patients.

# Appendix - IO

- The expected influx of generic drugs, following the expiry of core patents, will further enrich the T2DM drug market in China, offering a wider range of treatment options for patients.
- GLP-1RAs are a class of drugs that have shown efficacy in reducing blood glucose levels without the risk of hypoglycemia, alongside protective effects on pancreatic β-cell function and significant weight reduction capabilities.
- GLP-1RAs with their significant weight reduction effects and safety profile meet the critical needs of a population grappling with escalating obesity rates. The active research and development of GLP-1RA drugs by both domestic and international pharmaceutical companies is leading to a broader spectrum of GLP-1RA options, further fueling their popularity and adoption. The increasing availability of various GLP-1RA formulations and brands is set to broaden treatment choices for patients, ensuring that GLP-1RAs remain at the forefront of long-term obesity and overweight management strategies. This trend is significantly contributing to the expansion of this market segment in China.
- According to the Chinese Journal of Diabetes, there are primarily three currently used treatments for T2DM: metabolic surgery, lifestyle interventions(such as healthy diet and exercise), and drug treatment. However, the effectiveness of lifestyle interventions in alleviatingT2DM is limited, and patient compliance is low. The Action for Health in Diabetes study demonstrates that lifestyle interventions have suboptimal effects in mitigating T2DM, with remission rates in the first, second, third, and fourth years being only 11.5%, 9.2%, 6.4%, and3.5%, respectively. Other studies, such as *Predictors of adherence to physical activity guidelines in patients with diabetes mellitus in the US in 2017: an exploratory analysis and Research on dietary behavior compliance and influencing factors in18-59-year-old patients with T2DM*, also indicate poor patient compliance with lifestyle intervention therapies. Most T2DM patients do not maintain regular physical activity and neglect daily diabetes management. Therefore, for long-term remission and medication adherence inT2DM, it is necessary for T2DM patients to seek drug treatment.
- According to CIC, the T2DM drugs market in China experienced a slight decrease from 2019 to 2020 and again from 2021 to 2022 primarily due to the strained medical resources, reduced patient willingness to seek medical care, and supply chain issues at the peak of the COVID-19 outbreak that resulted in some patients not continuously purchasing diabetes medications.
- The market size for T2DM drugs in China is estimated using a method that involves several key factors. It starts with calculating the prevalence of T2DM in China, based on the national population and prevalence rate. See“—Metabolic Disease Drugs Market—T2DM Drug Market—T2DM.”This figure is then adjusted for the diagnosis rate (around 49% in 2022), sourced from the International Diabetics Federation World Diabetes Atlas, and the drug treatment rate (around 68% in 2022), as reported in studies such as Prevalence and Treatment of Diabetes in China, 2013-2018.We then consider such adjusted number of T2DM patients receiving drug treatment as addressable patients for T2DM drugs. The estimation also takes into account the historical market shares of different types of T2DM drugs (GLP-1, insulin, and other types), determined by analyzing patient numbers and sales data from the Menet database. Finally, these shares are multiplied by the respective annual expenditures of these different types of T2DM drugs.

# Appendix - IO

- The market growth rate of GLP-1RAs in treating T2DM exceeds that of other T2DM medications due to several factors: (i) GLP-1RAs have a low risk of causing hypoglycemia because of their glucose-dependent blood sugar lowering mechanism, which leads to a favorable safety profile, (ii) the multi-faceted role of GLP-1 in regulating blood sugar results in effective glycemic control, (iii) the development and approval of oral formulations of GLP-1RAs are expected to improve patient compliance due to the convenience of oral dosing, and (iv) historical market data from 2018 to 2022 illustrates a rapid growth in GLP-1RAs, in stark contrast to the negative growth seen in insulin and other T2DM drugs.
- China is witnessing a significant rise in T2DM cases, driven by aging demographics, lifestyle changes, particularly increased sedentariness and dietary shifts, and an increase in obesity. This escalation inpatient numbers is paralleled by enhanced awareness and treatment rates, partly due to social education initiatives like the Healthy China Initiative (2019-2030), which aims to increase diabetes awareness among residents aged 18and over to at least 60%, and ensure standard management rates for diabetes patients of at least 70% by 2030. Community-based diabetes management care, including regular blood glucose tests, medication guidance, dietary control, and physical exercise, contributes to this awareness and the demand for effective diabetes treatments.
- The Chinese government has implemented several favorable policies for chronic disease management, particularly focusing on diabetes as part of their broader health strategy. Highlighted in the “14th Five-Year Plan”, these policies emphasize the implementation of comprehensive prevention and control strategies for major chronic diseases including diabetes. This high-level directional approach is designed to enhance the screening and diagnosis of Type 2 Diabetes Mellitus (T2DM), which is expected to increase the number of patients receiving regular treatment for the condition. These efforts are part of a larger policy framework, including the “Medium-to Long-Term Plan for the Prevention and Treatment of Chronic Diseases (2017-2025)”, the “Thirteenth Five-Year Plan on Health and Wellness(2016)”,andthe“HealthyChina2030”initiative.These policies collectively contribute to an increased demand for T2DM medication, driven by improved disease management, heightened screening and diagnosis rates, and enhanced public health services. This comprehensive approach reflects the government’s commitment to not only managing but also preventing chronic diseases like diabetes, thereby expanding the patient pool under regular treatment regimens.
- Initially approved for T2DM in adults, semaglutide’s indications now include obesity. Additionally, as of the Latest Practicable Date, there were over 200 clinical trials sponsored by the originator manufacturer or academic institutions evaluating semaglutide for 28 indications, including T2DM with chronic kidney disease, metabolism and nutrition disorder, and hepatobiliary disorders. Semaglutide has shown exceptional efficacy in all of these trials, demonstrating its significant therapeutic and market potential.
- The market size for overweight/obesity drugs in China is estimated by first assessing the prevalence of overweight and obesity in the country. See “— Overweight and Obesity Drug Market — Overweight and Obesity.” Then, the drug treatment rate for overweight/obesity management is considered. The market share of GLP-1 drugs versus other types of drugs used is calculated by dividing the actual sales data of the overweight/obesity drug market into sales of GLP-1 and other drugs, with sales data obtained from the Menet database. The annual expenditure on these drugs is then factored in, with unit prices sourced from NRDL files and Yaozhi Data.
- Social education leading to surging clinical needs. Social education has played a pivotal role in enhancing public health awareness for overweight and obesity, transforming these conditions from mere aesthetic concerns to recognized significant health issues. This shift in perception is largely attributable to various government initiatives and health and academic organizations undertaking extensive public education campaigns. Chinese government’s initiatives, such as the “Healthy China 2030” plan, and educational campaigns like the “National Nutrition Week,” have cultivated a greater public awareness of the health risks associated with obesity. Additionally, academic bodies, including the Chinese Nutrition Society and the Chinese Medical Association, have played a crucial role in disseminating authoritative information on healthy lifestyles and weight management. The increased awareness and understanding of the comprehensive health risks associated with obesity are motivating a growing number of individuals to seek medical intervention.
- To forecast the market size of GLP-1RAs for the treatment of overweight and obesity in China from 2023 onwards, we examine the global market penetration and growth of similar GLP-1RA drugs including Saxenda and Wegovy® developed by Novo Nordisk after they were approved for obesity treatment. Essentially, we look at how these drugs performed worldwide in terms of sales and penetration following their approval. We then assume that GLP-1RAs will follow a similar growth trend in China once they are approved for treating overweight and obesity.

# Appendix - IO

- To forecast the market size of semaglutide for the treatment of overweight and obesity in China from 2025 onwards, we examine the global market penetration and growth of Wegovy® developed by Novo Nordisk after it was approved for obesity treatment. We assumed that semaglutide will follow a similar growth trend in China once they are approved for treating overweight and obesity.
- As of the same date, there were five clinical-stage amylin analogs, including AM833 that is currently undergoing a Phase III clinical trial in the U.S. Based on the currently available clinical data in the public domain, the combination use of amylin analog and semaglutide demonstrates significant potential to yield promising clinical efficacy for the treatment of overweight and obesity.
- In Jan.2019, PMDA (Pharmaceuticals and Medical Devices Agency) approved Romosozumab for the treatment of osteoporosis with a high risk of fracture. And then in April and Dec. 2019, FDA and EMA respectively approved it for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture.
- As of the Latest Practicable Date, there were 45 clinical pipelines targeting the GLP-1RA receptor for the treatment of overweight and obesity in China. efficacy. This clinical superiority is recognized in various treatment guidelines, including “Management of Hyperglycaemia in Type 2 Diabetes (2022)” published by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) and “Clinical Guidelines for the Prevention and Treatment of Type 2 Diabetes in the Elderly in China (2022 Edition)” (《中國老年2型糖尿病防治臨床指南（2022年版）》) released by the Chinese Society of Endocrinology, a branch of the Chinese Medical Association, and is expected to lead to a surge in its clinical demand.
- The oncology drug market comprises two segments: the cancer treatment drug market, which includes drugs that are directly used to treat cancer itself.
- The market size for fulvestrant in China is calculated through a comprehensive method that starts by determining the incidence of breast cancer in China, as outlined in “Cancer incidence and mortality in China, 2022.” This figure is then refined by considering that around 62% of these cases are the luminal subtype (HR+/HER2–), a percentage slightly lower than the global average but consistent with findings from studies such as the Cancer MPact Survey 2019. From here, it’s estimated that 30-40% of early-stage patients, initially assumed to be 40% and decreasing annually, will progress to advanced breast cancer, as per the Chinese clinical consensus. Treatment rates, according to clinical key opinion leaders, were about 80% for advanced HR+/HER2–breast cancer in 2020, predicted to rise slightly by 2032. We then consider such number of advanced breast cancer patients receiving treatment as addressable patients for fulvestrant. The penetration rate of fulvestrant among addressable patients is then calculated based on actual market sales which is expected to rise in 2024 due to its inclusion in the ninth batch of the national VBP List with an over 90% price reduction. We assume the price of fulvestrant will stabilize after its price reduction of its inclusion into the VBP list.
- The incidence of breast cancer in China has increased from 321.2 thousand in 2018 to 355.5 thousand in 2022 and is expected to reach 410.5 thousand by 2032.
- CD38 serves dual functions as a cell membrane surface receptor and an extracellular enzyme. It is consistently and prominently present on multiple myeloma cells, regardless of the genetic diversity, disease stage, or prior treatments of the patient.
- Signal regulatory protein α (SIRPα) inhibitors are agents designed to block the interaction between the SIRPα on immune cells and CD47 on cell surfaces designed to treat various solid tumors including breast, lung, or colon cancers as well as multiple myeloma. Normally, CD47, often found on healthy cells, binds to SIRPα on macrophages or phagocytes, signaling the immune cells not to attack which is a vital mechanism for protecting healthy cells from unnecessary destruction. However, cancer cells can exploit this mechanism by overexpressing CD47, thereby tricking the immune system into leaving them unharmed.

# Appendix - IO

- The historical penetration of daratumumab is then calculated by dividing the actual market sales of daratumumab, sourced from the Menet database, by the annual expenditure on the drug obtained from NRDL files and commercial database. By comparing the number of patients using daratumumab to the total MM incidence in China, the historical penetration rate of daratumumab among MM patients is determined. This penetration rate is expected to have increased significantly following its inclusion in the NRDL at the end of 2021, with a steady rise anticipated until 2032. Finally, we multiply the results by the annual expenditure on the drug we estimate based on its historical annual expenditure.
- The market size of G-CSF in China is estimated by first considering the annual incidence of cancer, as reported in studies such as Cancer incidence and mortality in China. The next factor is the percentage of these cancer patients receiving chemotherapy and radiotherapy, where studies indicate an average neutropenia incidence rate of up to 80%. This establishes the potential addressable patient base. The market penetration of G-CSF is then determined by analyzing its actual market sales, sourced from the Menet database, in relation to the cancer incidence and the rate of chemotherapy and radiotherapy-induced neutropenia. Finally, the annual expenditure on G-CSF is accounted for, factoring in that G-CSF has been included in Part B of the NRDL, with unit prices derived from public information and databases.
- The market size of IL-11 in China is estimated by first considering the annual incidence of cancer, as reported in studies such as Cancer incidence and mortality in China. The percentage of these cancer patients undergoing chemotherapy and radiotherapy is then considered, based on a literature review. Next, the incidence rate of thrombocytopenia among these patients is factored in, set at an average of 10% and assumed to be stable, as indicated in related medical literature and expert consensus. This establishes the potential addressable patient base. The market penetration of IL-11 is then calculated by dividing its actual market sales sourced from the Menet database by the above potential addressable patient base. Lastly, the annual expenditure on IL-11, which has been included in Part B of the NRDL, is considered.
- The market size for palonosetron in China is estimated using a method that incorporates several factors, starting with the incidence of cancer in China as reported in Cancer incidence and mortality in China. Next, a literature review is used to determine the percentage of these cancer patients undergoing chemotherapy and radiotherapy. It is then assumed that all patients receiving chemotherapy and radiotherapy will undergo CINV preventive treatment, as per the expert consensus in China. This establishes the potential addressable patient base. The market penetration of palonosetron is calculated by dividing its actual market sales (information obtained from the Menet database) by the above potential addressable patient base. Finally, the annual expenditure on palonosetron, which has been included in Part B of the NRDL since 2017, is factored into the calculation.
- The market size for LMWHs in China is estimated using a multi-faceted approach. Firstly, the incidence of thrombosis in China is determined from various sources including the Global Burden of Thrombosis, the Chinese Center for Disease Control and Prevention, and the China Cardiovascular Health and Disease Report. Next, the treatment rate for thrombosis, found to be about 20% according to a single-center real-world clinical study, is considered. The market penetration of LMWHs is then calculated by dividing their actual market sales, sourced from the Menet database, by the product of the thrombosis incidence and treatment rate. Finally, the annual expenditure on LMWHs, considering their inclusion in Part B of the NRDL since 2004 and the impact of the inclusion of enoxaparin and nadroparin in the eighth national VBP list on average pricing, is taken into account.
- It is projected to decline to RMB8,224.8 million by 2032 due to the inclusion of two major types of LMWHs, enoxaparin and nadroparin, in the eighth national VBP List, leading to a 60-70% price drop. This will lower the average market price of LMWHs. Meanwhile, the sales volumes of the drugs are expected to grow only modestly, in line with a slight, stable increase in the number of patients using these medications.





Source: China Insights Consultancy

# Appendix - Financial Information

- While the inclusion of a pharmaceutical product in these national, provincial or other government-sponsored medical insurance programs can significantly increase its demand and potentially sales volume, pharmaceuticals so included were subject to relevant pricing regulation and face pricing pressure. In addition, innovative pharmaceuticals included in the national medical insurance negotiation list generally need to undergo pricing negotiation process with the PRC government.
- Our bidding strategy generally focuses on differentiating our products from those of our competitors instead of competing solely based on pricing. Therefore, our sales volumes and profitability depend on our ability to successfully differentiate our products from competing products and price our bids in a manner that enables us to succeed in the volume-based procurement at profitable levels.
- According to CIC, it is an industry norm that drug-device products have longer credit period than drug products.
- According to CIC, our trade receivables turnover days for the years ended December 31, 2021 and 2022, and nine months ended September 30, 2023 are in line with those of our market peers.

# Appendix - Connected Transaction

- The Royalty Arrangement was determined after arm's length negotiations between us and Zhongmei Huadong, taking into account that (i) it is common practice in the pharmaceutical industry to share future revenue from the sales of products developed under the transferred intellectual property; and (ii) according to China Insights Consultancy, the proportion of the net sales revenue to be enjoyed by us is in line with the industry average for similar arrangements.
- To advance the parties' collaborative plan regarding the commercialization of Liraglutide, Zhongmei Huadong and our Company may enter into separate agreements in relation to technology development and manufacturing, which is also in line with the industry practice.
- As the research and development of pharmaceutical products require significant capital investment, it is a common industry practice for the primary drug developer to mitigate risks and costs associated with the drug development process by collaborating with other business partners.
- China Insights Consultancy has confirmed that the Liraglutide Transfer Agreements are in line with the market practice in the industry practice.
- Therefore, taking into consideration of the above and that the Royalty Arrangement is arrived at after arm's length negotiation and is in line with the industry average for similar arrangements.
- Therefore, given our extensive experience in Liraglutide's technology development, coupled with our advanced R&D capabilities and mature manufacturing prowess, we stand as a competent partner to advance the commercialization process forward.
- We believe that such business arrangements are in line with the market practice that the technology transferer would assist in the establishment and refinement of the production line for the transferee.
- As the overseas market for Liraglutide's API is [widely dispersed], neither we nor Zhongmei Huadong has established a significant presence in the overseas market.
- (ii) as advised by China Insights Consultancy, it is a common practice in the pharmaceutical industry that [licensors] share with [licensees] a part of the profit generated from the sales of the relevant products; and (iii) taking into account the cost of the manufacturing and marketing of Liraglutide's API, the percentage of the net sales revenue to be enjoyed by us is in line with the industry average for an arrangement of similar nature, as advised by China Insights Consultancy.
- Huadong Medicine Connected Persons enjoys a better business reputation compared to other distributors, considering their ample experience and solid foundation in this field.



Source: China Insights Consultancy

# Appendix - Business

- Our marketed product portfolio includes one innovative drug-device combination, two biological products, and five chemical drugs in orthopedics, oncology and hematology. Among them, several of our products maintain a competitive position in their respective product category in terms of market share as measured by revenue in 2022.
- Notably, our drug-device combination, Guyoudao, is the first product containing bone repair material with rhBMP-2 approved for sale in China, according to CIC.
- According to CIC, Guyoudao is the first bone repair material with rhBMP-2 approved for sale in China, making us the second company in the world to have commercialized an rhBMP-2 product. Guyoudao ranked second by sales revenue in the bone repair materials market in China in 2022, with a market share of 17.2% nationally according to the same source.
- Bone regeneration naturally occurs in most cases, but in cases such as nonunions, malunions, tumors that cause bone defects, bones may not heal independently and there may be a need for surgery and a bone graft to induce bone regeneration. Bone grafting is also used in orthopedic, oncologic, and dental surgeries and procedures, making bone the second most transplanted tissue worldwide right behind blood transfusions.
- rhBMP-2 is an osteoinductive protein that plays a critical role in the differentiation of mesenchymal stem cells into osteoblasts, thus promoting bone and cartilage formation. By enhancing osteogenesis at implantation site and repairing bone defects, rhBMP-2 accelerates facture healing and reduces the necessity for subsequent intervention due to its biodegradable nature. Consequently, rhBMP-2 presents therapeutic potential for conditions like bone defects, bone non-union and delayed bone healing, and can be applied in spinal fusion, joint fusion, and various orthopedic implantation surgeries.
- Compared to BMP-2 [derived from animals], rhBMP-2 demonstrates better osteoinductive properties and can be manufactured on a large scale. The recombinant production also offers the advantage of tightly controlled manufacturing processes to ensure purity, consistency, and sterility. The rhBMP-2 was combined with carriers to achieve better compatibility with surrounding tissues and to promote rapid material degradation.
- Jilifen, commercialized in 1996, is the first domestically developed recombinant human granulocyte colony-stimulating factor (rhG-CSF) approved for sale in China according to CIC. In terms of sales revenue, Jilifen ranked [8th] in 2022 among all rhG-CSF drugs in China, taking up a market share of [1.8]% nationally, according to CIC.
- The rhG-CSF in Jilifen is produced by genetic engineering and the level of bioactivity of the recombinant protein is equivalent to [human CSF]. rhG-CSF stimulates the survival and proliferation of myeloid progenitor cells, as well as their differentiation towards neutrophilic granulocytes. In addition, G-CSF stimulates the release of mature neutrophils from bone marrow and brings about their activation. According to independent clinical studies, rhG-CSF has demonstrated that it is useful in treating patients suffering from neutropenia during or after chemotherapy and in mobilizing peripheral blood progenitor cells for harvesting and transplantation.
- Jipailin is the first domestically developed generic low molecular weight heparin sodium commercialized in China according to CIC, which was approved for sale in September 1997.
- JY29-2 is the first semaglutide biosimilar to have obtained IND approval and entered into a Phase III clinical trial in China as of the Latest Practicable Date.
- We have completed the patient enrolment of its Phase III clinical trial for the treatment of diabetes in November 2022 and expect to obtain the first NDA approval for this indication in 2025.
- Guyoudao aligns with, and significantly contributes to, the emerging trend of accelerated bone recovery in orthopedics sector in China.

# Appendix - Business

- Because of its clinical value, Guyoudao has been recommended by the "Expert Consensus on Clinical Diagnosis and Treatment Techniques for ONFH" (《股骨头坏死临床诊疗技术专家共识》) and the "Expert Consensus on Clinical Drug Prevention and Treatment of ONFH" (《股骨头坏死临床药物防治专家共识》), both issued by the Bone Microcirculation Professional Committee of Chinese Microcirculation Society in 2022, and the "Clinical Diagnosis and Treatment Standards for ONFH" (《股骨头坏死临床诊疗规范》) issued by the Chinese Medical Association in both 2015 and 2016.
- Commercialized in 1996, Jilifen is manufactured through genetic engineering and is the first domestically developed rhG-CSF product in China according to CIC.
- The sales revenue of Jilifen was RMB166.0 million in 2022, with a market share of [1.8]% of the rhG-CSF drug market in China and ranked [8th] nationally in the corresponding year according to CIC.
- Jilifen has been included in part B of the NRDL since 2004.
- The sales revenue of Jijufen was RMB94.9 million in 2022 with a market share of 8.2% of the interleukin-11 drug market in China, and ranked 4th nationally in the corresponding year according to CIC.
- Jijufen has been included in part B of the NRDL since 2009.
- [Interleukin (IL)-11 stimulates platelet production. The primary hematopoietic activity of interleukin-11 is stimulation of megakaryocytopoiesis and thrombopoiesis. At the molecular level, IL-11 binds to the IL-11 receptor (IL-11Ralpha) on megakaryocytes and megakaryocyte progenitor cells. Binding of IL-11 to IL-11Ralpha stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells and induces megakaryocyte maturation resulting in increased platelet production. Platelets produced in response to IL-11 are morphologically and functionally normal and possess a normal life span.
- With the approval for sale obtained in September 2003, Jijufen is the first  forth domestically developed biosimilar to oprelvekin, a human interleukin-11 injection.
- The sales revenue of Jiouting was RMB67.8 million in 2022, with a market share of 14.0% of the palonosetron hydrochloride market in China and ranked second nationally in the corresponding year according to CIC.
- With the approval for sale obtained in December 2008, Jiouting is the first  forth domestically developed generic of palonosetron hydrochloride injection.
- Chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine. The released serotonin then activates 5-HT3 receptors, which have been demonstrated to selectively participate in the emetic response, located on vagal afferents to initiate the vomiting reflex. Palonosetron is a 5-HT3 receptor antagonist with a strong binding affinity for the receptors and little or no affinity for other receptors, which enables it to inhibit vomiting reflux.





Source: China Insights Consultancy

# Appendix - Business

- Jiouting has been included in part B of the NRDL since 2017.
- Jifuwei obtained its marketing approval in June 2022 and became the 4th marketed fulvestrant product in China, according to CIC. It has been included in part B of the NRDL since it was commercialized in 2022.
- When fulvestrant binds to estrogen receptor monomers, it inhibits receptor dimerization, activation functions AF1 and AF2 are rendered inactive, translocation of receptor to the nucleus is reduced, and degradation of the estrogen receptor is accelerated. This results in antiestrogenic effects and inhibits the growth of estrogen-sensitive human breast cancer cell lines.
- The sales revenue of Yinuojia was RMB235.4 million in 2022 with a market share of 8.1% of the heparin product market in China and ranked 4th nationally in the corresponding year according to CIC.
- Yinuojia has been included in part B of the NRDL since 2009.
- Jipailin is the first domestically developed low molecular weight heparin sodium product commercialized in China according to CIC and was approved for sale in China in 1997.
- Jipailin has been included in Part B of the NRDL since 2004.
- Given its advanced clinical development status, we expect it to be the first-to-market semaglutide biosimilar in China. Under the "Prescription Management Measures" (处方管理办法) promulgated by the Ministry of Health, hospitals can procure no more than two brands for the same generic drug. Under this regulatory framework, the first-to-market biosimilar will have the first-mover advantage in acquiring market share.
- Semaglutide products have achieved significant commercial success in the global market.
- In addition, as of the Latest Practicable Date, there were five clinical trials of semaglutide for new indications including T2DM with chronic kidney disease, T2DM with cardiovascular conditions, metabolism and nutrition disorder, and hepatobiliary disorders.
- In addition to our current pipeline, we also independently developed a liraglutide product candidate in 2011, which is the first liraglutide biosimilar to have received an IND approval in China.
- We are led by a seasoned senior management team which guides and supports our transition into a leading biopharmaceutical company in China.
- Having established a diversified product pipeline and built expertise in R&D and commercialization, we will continue to implement our patient-oriented research and strengthen our market-leading position.
- We will expand the sales and marketing channels for such products to satisfy unmet clinical needs and solidify our leading market position in the respective market segments. Meanwhile, we will continue to invest in the marketing and promotion of our drug candidates in our focused therapeutic areas, such as orthopedics, where we have already achieved a leading position and metabolic diseases, where we are rapidly developing.
- According to CIC, the NRDL does not cover medical devices and there is no national level reimbursement list for medical devices, such as rhBMP-2 products. Nevertheless, rh-BMP-2 products have been expressly included in the provincial reimbursement lists for medical consumables published by ten provinces in China as of September 30, 2023.

# Appendix - Business

- rhBMP-2 is an osteoinductive protein that plays a critical role in the differentiation of mesenchymal stem cells into osteoblasts, thus promoting bone and cartilage formation. By enhancing osteogenesis at implantation site and repairing bone defects, rhBMP-2 accelerates facture healing and reduces the necessity for subsequent intervention due to its biodegradable nature. Consequently, rhBMP-2 presents therapeutic potential for conditions like bone defects, bone non-union and delayed bone healing, and can be applied in spinal fusion, joint fusion, and various orthopedic implantation surgeries.
- rhBMP-2 was coated with soy lecithin and gelatin to create sustained-release medical systems, so that rhMBP-2 can be gradually released and trigger or modulate new bone formation. In the meantime, the porous hydroxyapatite scaffold can induce the cells to migrate into the porous body and improve osteoconduction and remodeling at the implant site.
- Normal bone formation and healing involves the coordinated interaction between bone-forming cells and biologic signals, where the osteoblasts and their precursors, the mesenchymal stem cells, or MSCs, serve as the principal workforce in this process. When Guyoudao is implanted in the body, rhBMP-2 induces the migration of MSCs to the site of implantation. rhBMP-2 provides an environment where MSCs multiply prior to differentiation. rhBMP-2 binds to specific receptors on the surface of MSCs, inducing them to differentiate into osteoblasts. Osteoblasts produce new bone and initiate the release of biologic signals that direct the formation and remodeling of bone. These biologic signals further attract MSCs and other bone-forming cells to the site of bone formation as well as cause the differentiation of MSCs into osteoblasts. As the body continues to remodel bone in response to the local environmental and mechanical forces, normal trabecular bone will form.
- In the bone repair material market, bone morphogenetic proteins are recognized for their role in inducing bone tissue formation. Among these proteins, BMP-2 stands out as one of the factors with the strongest osteoinductive ability and has been recommended by a number of osteonecrosis of the femoral head (ONFH) clinical practice guidelines and expert consensus in China as a recommended therapy for ONFH patients. In particular, it has been recommended by the "2022 Expert Consensus on Clinical Diagnosis and Treatment Techniques for ONFH" (《股骨头坏死临床诊疗技术专家共识 (2022年)》), the "2022 Expert Consensus on Clinical Drug Prevention and Treatment of ONFH" (《股骨头坏死临床药物防治专家共识 (2022年)》), both issued by the Bone Microcirculation Professional Committee of Chinese Microcirculation Society, and the "Clinical Diagnosis and Treatment Standards for ONFH" (《股骨头坏死临床诊疗规范》) issued by the Chinese Medical Association in both 2015 and 2016.
- Surgeons are increasingly inclined to choose minimally invasive procedures instead of autograft owing to various benefits associated with such procedures including quick procedure, less recovery time, shorter hospital stays and less incisions. According to CIC, the number of minimally invasive orthopedic procedures performed in China has reached 1,448.6 thousand operations in 2022 and is expected to grow steadily [owing to growing aging population and universality of recognizing orthopedic procedures as standard treatment].
- In terms of sales revenue, the oncology pharmaceutical market grew at a CAGR of 10.3% from RMB143.3 billion in 2018 to RMB212.0 billion in 2022. The significant unmet clinical demands, increase in patients' affordability and willingness to pay for treatment, favorable government policies will continue to drive the rapid growth of the oncology pharmaceutical market in China, according to the same source.
- With the approval for sale obtained in October 1996, Jilifen is the first domestically developed biosimilar recombinant human granulocyte colony stimulating factor (rhG-CSF) in China, according to CIC.

# Appendix - Business

- We expect that the sales revenue of Guyoudao will continue to be a majority of our total revenue in the foreseeable future. According to CIC, the market size of rhBMP-2 bone repair materials increased from RMB102.8 million in 2018 to RMB544.4 million in 2022, with a CAGR of 51.7% and is expected to further increase to RMB4,414.2 million in 2032, with a CAGR of 23.3% from 2022 to 2032. Despite the growing demand, there is a limited supply of BMP-2 bone repair products. The gap between the supply and demand arises primarily because of the following:

1) Exclusive competitive landscape. The technical barriers in developing rhBMP-2 bone repair materials are relatively high, as it requires strong R&D and manufacturing capabilities in both pharmaceuticals and medical devices. The development cycles of drug-device combination products are generally longer when compared to those of chemical drugs. In addition, the production of biologics, which BMP-2 products belong to, involves higher technical difficulties and has higher standards with respect to production facilities. Furthermore, according to CIC, the complex and prolonged regulatory approval process for drug-device combination products, such as Guyoudao, also establishes a significant entry barrier for new market entrants. These heightened thresholds consequently shaped a more exclusive competitive landscape for rhBMP-2 products, with only four commercialized rhBMP-2 products in the Chinese market as of the Latest Practicable Date. Among them, Guyoudao is the earliest and the one with the largest market share, which was 81.6% in 2023.

2) Market leading position. Among the rhBMP-2 bone repair material products commercialized China as of the Latest Practicable Date, the approved indications of Guyoudao are the most extensive, covering the filling and repair of bone defects, bone nonunion, bone delayed union, and graft repair of spinal fusion, joint fusion, and orthopedic bone graft. In addition, Guyoudao is the first rhBMP-2 bone repair material commercialized in China. Over the past decade, Guyoudao has gradually built strong market recognition. The broad spectrum of cases where Guyoudao can be applied and its strong market recognition together distinguish it from other rhBMP-2 products available in China, and enables us to maintain a market leading position.

3) Growing market demand and large untapped market. Despite that Guyoudao was commercialized in 2010, it has significant market potential. According to CIC, the rhBMP-2 market in China increased from RMB102.8 million in 2018 to RMB544.4 million in 2022, with a CAGR of 51.7%. The growth momentum is expected to continue as a result of the aging population and the increasing number of cases of sports injuries, and the market is expected to increase to RMB4,414.2 milion in 2032 with a CAGR of 23.3% between 2022 and 2032. According to CIC, the market of rhBMP-2 products in China is still in a rapid development stage and there are relatively few industry players in this market. Therefore, the Chinese rhBMP-2 product market is still far from reaching market maturity or declining. Despite the growth of the potential market, the market penetration of rhBMP-2 products is relatively low. As of December 31, 2023, there were approximately 14,700 class II and class III hospitals in China which perform orthopedic surgeries. The large untapped market in China represents market potential to enable the long-term growth of Guyoudao. In addition, as the first entrant in China's rhBMP-2 market, we have accumulated deep expertise in the sales and marketing of rhBMP-2 products. We believe that we are able to maintain our competitive edge and capture the growth opportunities in the untapped market.

4) Continuous product upgrades. To maintain our competitiveness, we are actively researching on and developing more innovative rhBMP-2-based bone repair materials, which will help us maintain and strengthen our market leading position in the future.

- According to CIC, Guyoudao can continue to maintain a leading position in China in terms of market share and market recognition among products in China, and there is no material risk of Guyouda being replaced or rendered obsolete in the foreseeable future even though it was launched in 2010.

# Appendix - Business

- G-CSF and rhG-CSF have been recommended by a number of clinical practice guidelines and expert consensus as a recommended therapy for preventing and treating neutropenia caused by tumor radiotherapy and chemotherapy. In particular, G-CSF has been recommended by the "NCCN Guidelines: Hematopoietic Growth Factors Version 1 (2023)" issued by the National Comprehensive Cancer Network. rhG-CSF has been recommended by the "Guidelines for the Standardized Management of Neutropenia Associated with Tumor Radiotherapy and Chemotherapy" (《肿瘤放化疗相关中性粒细胞减少症规范化管理指南》) issued by the Chinese Society of Clinical Oncology in 2021.
- rhIL-11 has been recommended by a number of expert consensuses as a recommended therapy for preventing and treating low platelet count in patients who are undergoing chemotherapy. In particular, rhIL-11 has been recommended by the "Consensus on the clinical diagnosis, treatment and prevention of cancer treatment-induced thrombocytopenia in China (2023 edition)" (《中国肿瘤药物相关血小板减少诊疗专家共识(2023版)》) issued by the Society of Chemotherapy, China Anti-Cancer Association in 2023, and the "Expert Consensus on the Clinical Application of rhIL-11 in the Prevention and Treatment of Thrombocytopenia" (《重组人白介素-11防治血小板减少症临床应用中国专家共识》) issued by certain expert committees including the Anti-tumor Drug Safety Management Expert Committee of the Chinese Society of Clinical Oncology in 2021.
- China's first few developed palonosetron hydrochloride injection, included in the NRDL.
- Palonosetron has been recommended by a number of clinical practice guidelines and expert consensuses as a recommended therapy for antiemesis. In particular, palonosetron has been recommended by the "NCCN Guidelines: Antiemesis" issued by the National Comprehensive Cancer Network in 2023, and the "Expert Consensus on the Prevention and Treatment of Nausea and Vomiting Related to Cancer Drug Therapy" (《肿瘤药物治疗相关恶心呕吐防治专家共识》) issued by the China Anti-Cancer Association in 2022.
- Fulvestrant has been recommended by a number of clinical practice guidelines as a recommended therapy for breast cancer. In particular, fulvestrant has been recommended by the "NCCN Guidelines: Breast Cancer Version 5 (2023)" issued by the National Comprehensive Cancer Network, and the "Breast Cancer Diagnosis and Treatment Guidelines (2022)" (《乳腺癌诊疗指南(2022版)》) issued by the National Health Commission.
- Fosaprepitant is a phosphorylated analog of aprepitant with water-solubility, enabling it to convert to aprepitant after intravenous injection. Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK1) receptors present in both the central and peripheral nervous systems which play roles in the vomiting reflex. The binding of the aprepitant to NK-1 receptors may attenuate vagal afferent signals and contribute to the antiemetic effect.
- Fosaprepitant has been recommended by a number of clinical practice guidelines and expert consensuses as a recommended therapy for antiemesis. In particular, fosaprepitant has been recommended by the "NCCN Guidelines: Antiemesis Version 2 (2023)" issued by the National Comprehensive Cancer Network in 2023, and the "Expert Consensus on the Prevention and Treatment of Nausea and Vomiting Related to Cancer Drug Therapy (2022)" (《肿瘤药物治疗相关恶心呕吐防治专家共识(2022年版)》) issued by the China Anti-Cancer Association in 2022.
- The significant unmet clinical demands, increase in PCI cases and superior clinical advantages of hematology will continue to drive the rapid growth of the hematology pharmaceutical market in China, according to the same source.

# Appendix - Business

- A related condition, thromboembolism, occurs when a blood clot, known as a thrombus, breaks free from its original site and travels through the bloodstream to obstruct other vessels.
- Yinuojia is the second domestically developed biosimilar enoxaparin sodium commercialized in China.
- The significant unmet clinical demands, increase in PCI cases and superior clinical advantages of hematology will continue to drive the rapid growth of the hematology pharmaceutical market in China, according to the same source.
- Semaglutide boasts the following key advantages:

1) Superior efficacy in glycemic control. Novo Nordisk conducted extensive clinical studies on semaglutide, involving over 24,500 patients in its SUSTAIN and PIONEER series clinical studies for the treatment of diabetes. The trials revealed that semaglutide, either alone or combined with other medications, significantly controls blood sugar levels (superior to sitagliptin, insulin glargine, liraglutide, and other antidiabetic drugs) without increasing hypoglycemia risk. It also offers weight reduction, cardiovascular, and renal benefits. Specifically in Chinese populations, the SUSTAIN China study showed that semaglutide significantly lowers glycated hemoglobin (HbA1c) in type 2 diabetes patients, with a maximum reduction of 1.8% and a high achievement rate of HbA1c target at 86.1%. It also significantly reduces fasting blood sugar without increasing the risk of hypoglycemic events.

2) Superior efficacy in body weight control. Novo Nordisk's STEP and OASIS series clinical studies on the weight control effectiveness of semaglutide, which involve over 6,000 patients, have shown remarkable results. The STEP 1 study indicated a rapid and effective weight reduction effectiveness of semaglutide, with participants losing up to 16.9% of their body weight, over two-thirds losing more than 10%, and over a third losing more than 20%, compared to just a 2.4% reduction in the placebo group. In the STEP 7 study of the Asian population (80% Chinese), semaglutide significantly reduced the body weight of overweight/obese patients, with an average weight loss of 12.1% and over 34% of participants achieving more than 15% weight loss. Additional benefits in terms of changes in systolic blood pressure, fasting blood sugar, and lipid levels were also observed.

3) Significant cardiovascular benefits. Novo Nordisk conducted a series of clinical studies, including SELECT, SUSTAIN 6, and PIONEER 6, involving over 24,000 patients to investigate the cardiovascular benefits of semaglutide. The trials have shown that semaglutide reduces the risk of major adverse cardiovascular events in patients with diabetes, obesity, or overweight who have cardiovascular diseases or are at high cardiovascular risk. Additionally, semaglutide effectively alleviates symptoms of heart failure and enhances physical capability. Results from the SELECT study revealed that over five years, semaglutide significantly reduced the risk of major adverse cardiovascular events by 20% in patients with a history of cardiovascular disease who are obese or overweight. The risk of composite heart failure events, including cardiovascular death, urgent heart failure visits, and hospitalizations, was reduced by 18%, and the risk of death decreased by 19%. Semaglutide also showed significant effectiveness in reducing other cardiovascular risk factors such as blood pressure, cholesterol, and blood sugar.

- Semaglutide is a peptide akin to the hormone glucagon-like peptide-1 (GLP-1) but is modified with a fatty acid side chain. By emulating the actions of the hormone GLP-1, it augments the production of insulin, the hormone responsible for reducing blood sugar levels. Moreover, it curtails the production of glucagon, a hormone that facilitates the release of stored carbohydrates from the liver and prompts the creation of new glucose. Consequently, semaglutide employs these dual mechanisms to combat diabetes. Additionally, semaglutide diminishes food intake by suppressing appetite and decelerating digestion in the stomach, aiding in the reduction of hunger, food cravings, and body fat, thus ameliorating obesity and being overweight.
- However, the market size of semaglutide for the treatment of T2DM, overweight and obesity could potentially be limited by alternative prevention and treatment methods for such indications and medication treatment is used only for a portion of the total T2DM, overweight and obesity population.





Source: China Insights Consultancy

# Appendix - Business

- As diabetes and obesity are affecting global health, GLP-1 receptor agonists have been increasingly adopted by population with diabetes or weight management needs, demonstrating significant market potential.
- Amylin analog boosts promising market potential both as monotherapy and as combination therapy with GLP-1 drugs for the treatment of diabetes, obesity and overweight. As of the Latest Practicable Date, there was only one marketed amylin analog product, Symlin®, globally. It was approved by FDA in 2005 for the adjuvant treatment in patients with type 1 or 2 diabetes undergoing insulin therapy. As of the same date, there were 5 products of amylin analog in clinical phase globally and 1 in China, for the treatment of various diseases, including diabetes, obesity or overweight, chronic kidney disease, and cardiovascular disease.
- High market potential. Dulaglutide has been launched in many countries globally and has consistently held the top sales position among GLP-1 medications for several years attributed by its pharmaceutical advantages. Characterized by low renal clearance, dulaglutide ensures sustained therapeutic activity; following the administration of 0.75 or 1.5 mg doses, it exhibits a consistent elimination half-life of approximately five days, irrespective of the dosage. Its efficacy remains remarkably consistent across diverse demographic variables, including age, gender, race, and body weight. Moreover, the effectiveness does not substantially vary in patients with hepatic or renal impairments, obviating the need for dosage adjustments. The inclusion of dulaglutide in China's national medical insurance list at the end of 2020, further underscores its considerable market potential in China.
- The market of dulaglutide for T2DM in China has increased from RMB14.5 million in 2019 to RMB1,306.6 million in 2022 with a CAGR of 348.4%, according to CIC. The T2DM, overweight and obesity drug market in China could potentially be limited by alternative prevention and treatment methods for such indications and medication treatment is used only for a portion of the total T2DM, overweight and obesity population.
- In line with industry practice, we engage CROs to support our product development. Our CROs provide us with an array of services.
- We import most key equipment used in our production processes from developed countries, as we believe the use of such state-of-the-art equipment provides better quality control and assurance and increases our production efficiency.
- Consistent with industry practices, our distributors are not engaged to provide marketing and promotion services for our products.
- Our product return policy is in line with the market practice of the pharmaceutical industry in China, according to CIC.
- Patient-friendly dose schedule and high patient adherence. By optimizing the structure of the fatty acid side chain and peptide chain, the half-life of semaglutide in the body is prolonged, allowing for a dosing regimen of only one subcutaneous injection per week, enhancing the convenience and compliance of patients. Additionally, semaglutide is available in oral tablet form. This oral formulation reduces patients' fear associated with injections. The once-daily intake further ensures ease of access and high adherence to the medication regimen.
- Broad indications. In light of the clinical performance of semaglutide, Novo Nordisk and other organizations have expanded its indications globally to encompass 28 different conditions, including NASH (non-alcoholic steatohepatitis), Alzheimer's disease, and cardiovascular diseases, beyond its initial approvals for diabetes and obesity, with nearly 400 ongoing clinical trials. For NASH, Novo Nordisk conducted a phase II study named NN9931-4296, which showed that 66.7% of patients treated with 0.4mg of semaglutide experienced a reduction in NASH pathology without worsening liver fibrosis. Novo Nordisk is also currently conducting a phase III study named ESSENCE for NASH.

# Appendix - Business

- Dulaglutide boasts the following advantages:

1) Significant efficacy and safety. Dulaglutide's hypoglycemic effect surpasses that of other antidiabetic drugs like metformin, saxagliptin, exenatide, and insulin glargine. Moreover, it exhibits a good safety profile with gastrointestinal reactions being the most commonly reported side effects.

2) Renal-protective effects. Evidence suggests that dulaglutide demonstrates commendable renal protective properties, making it a suitable antidiabetic medication for Type 2 diabetes patients with renal impairment.

3) High market potential. Dulaglutide has been launched in many countries globally and has consistently held the top sales position among GLP-1 medications for several years. It was included in China's national medical insurance list at the end of 2020, indicating its considerable market potential in China.

- Compared to Guyoudao, JY23 has superior sustained release and osteoconduction properties, making it more suitable for use in minimally invasive orthopedic surgeries which have become increasingly prevalent.
- Besides its approved indications for postmenopausal female osteoporosis and male osteoporosis, Amgen is conducting clinical research on romosozumab for the treatment of glucocorticoid osteoporosis and premenopausal osteoporosis. [Romosozumab stands as the only anti-sclerostin antibody drug approved by the U.S. FDA. As of the Latest Practicable Date, there had been no approved anti-sclerostin antibody drugs in China] [Note: CIC to confirm], leaving the Chinese market for anti-sclerostin antibody drugs untapped, signaling immense market potential.
- Avatrombopag has no reported hepatotoxic adverse events or incidences of cataracts.
- Avatrombopag is included as a recommended drug in authoritative international and domestic guidelines, such as the "2019 Guidelines for Immune Thrombocytopenia" published by the American Society of Hematology (ASH).
- SIRPα is a typical inhibitory immune receptor within the SIRP family. Its binding to the ligand CD47 that produces a "don't eat me" signal, preventing macrophages from phagocytosing healthy cells. JY47 binds with high affinity and specificity to the SIRPα protein on the surface of cancer cells, obstructing the interaction between SIRPα and CD47. This inhibits the CD47-SIRPα signaling pathway, amplifying the phagocytic activity of macrophages towards cancer cells and potentially enhancing the cytotoxic activity of NK cells and T cells against cancer cells, thereby exerting an anti-tumor effect.
- The mechanism of action of CD47-SIRPα blockade differs from that of PD-1/PD-L1 blockade, positioning it as the next-generation immune checkpoint blockade strategy for various malignancies post PD-1/PD-L1 treatment.
- Given that CD47 is expressed in normal tissue cells throughout the body, therapies targeting CD47 might exhibit hematotoxicity, particularly attacking normal cells like red blood cells and platelets.
- JY47 binds with high affinity to SIRPα-V1, V2, and V8, covering over 90% of the population's genotypes. In clinical trials and subsequent clinical applications, there's no need to select patients based on genotype.





Source: China Insights Consultancy

# Appendix - Business

- According to CIC, in terms of injectable drug delivery, 90.6% of adverse events are associated with intravenous injections. Transitioning to subcutaneous drug administration can effectively reduce the risk of adverse events and enhance tolerability of a drug.
- Hyaluronidase can temporarily hydrolyze subcutaneous hyaluronic acid, thus improving the drugs' dispersion and permeability in tissue. Therefore, combining hyaluronidase with drug substance allows for large-volume subcutaneous delivery for drugs that originally require intravenous administration, and thereby offering enhanced safety and convenience for patients.
- According to CIC, oncology was the second largest therapeutic area in China in terms of sales revenue of pharmaceuticals in 2022, accounting for 17.4% of the overall pharmaceutical market in the same year.
- IL-11 stimulates platelet production. The primary hematopoietic activity of IL-11 is stimulation of megakaryocytopoiesis and thrombopoiesis. At the molecular level, IL-11 binds to the IL-11 receptor (IL-11Rα) on various cells involved in hematopoiesis, including hematopoietic stem cells, megakaryocys progenitor cells and megakaryocytes. Binding of IL-11 to IL-11Rα stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells and induces megakaryocyte maturation resulting in increased platelet production. Platelets produced in response to IL-11 are morphologically and functionally normal and possess a normal life span.
- Fulvestrant competitively and reversibly binds tonestrogen receptors present in cells. When fulvestrant binds to estrogen receptor monomers, it inhibits receptor dimerization, activation functions are rendered inactive, translocation of receptor to the nucleus is reduced, and degradation of the estrogen receptor is accelerated. This results in anti-estrogenic effects and inhibits the growth of estrogen-sensitive human breast cancer cell lines.
- Semaglutide: The mean change in body weight from baseline to week 68 was −14.9% in the semaglutide group with over two-thirds losing more than 10%, and over a third losing more than 20%, compared to just a 2.4% reduction in the placebo group. For the trial product estimand (showing the effect if the drug or placebo was taken as intended), the corresponding changes were –16.9% and –2.4%, respectively.
- The international embrace for GLP-1 receptor agonist suggests a significant market potential for this medication in China. According to CIC, the market for GLP-1 receptor agonists for obesity and overweight is projected to increase from RMB0.4 billion in 2023 to RMB45.5 billion in 2032.
- As of the same date, there were five clinical-stage amylin analogs globally, with the most advanced one in terms of clinical development stage currently in a Phase III clinical trial in combination with semaglutide for the treatment of overweight and obesity and T2DM in the U.S. Based on the currently available clinical data in the public domain, the combination use of amylin analog and semaglutide demonstrates significant potential to yield promising clinical efficacy for the treatment of overweight and obesity and T2DM.





Source: China Insights Consultancy

# Appendix - Business

- JY43

1) Remarkable clinical efficacy. Clinical trials conducted by Johnson & Johnson for Daratumumab demonstrated that using Daratumumab alone or in combination treatments for relapsed or refractory multiple myeloma patients significantly improved response rates, prolonged progression-free survival, and offered better outcomes than previous treatment regimens, enhancing the survival odds for these patients in subsequent treatment lines.
2) Favorable safety profile. Clinical trials for Daratumumab indicated a high tolerability among patients, with a low discontinuation rate due to adverse reactions Endorsed in clinical guidelines domestically and internationally. Daratumumab has been included in the 2020 “Chinese Multiple Myeloma Guidelines,” the 2021 National Comprehensive Cancer Network Guidelines, and the 2022 “Chinese Multiple Myeloma Guidelines.” It’s explicitly listed as a cornerstone therapy for clinical treatment of multiple myeloma, applicable in first-line, second-line, and post-second-line treatments.
3) Potential for expanded indications. Beyond its approval for treating multiple myeloma, Daratumumab has also been approved for treating primary light-chain amyloidosis. Clinical studies are underway for its application in conditions such as glioblastoma, systemic lupus erythematosus, and primary lymphoma-like hematopoietic malignancies, among others.

- Hyaluronic acid, acting as the “scaffold” of the skin interstitium, impedes the diffusion and absorption of the injected fluid. Typically, standard subcutaneous injections cannot administer large volumes (generally no more than 2ml). Hyaluronidase specifically hydrolyzes subcutaneous hyaluronic acid, altering the permeability of connective tissue, reducing its density and viscoelasticity, thereby increasing the space for subcutaneous infusion.
- The administration time for Daratumumab intravenous injection ranges from 3-7 hours, while the subcutaneous injection takes only 3-5 minutes. This significantly reduces the administration duration, minimizing discomfort for the patient associated with intravenous infusions.
- Ozempic®, given as a subcutaneous injection for T2DM, recorded sales revenue of US$8.5 billion worldwide in 2022. Rybelsus®, given as a tablet for T2DM, recorded sales revenue of US$1.6 billion worldwide in 2022. WEGOVY®, given as a subcutaneous injection for weight management, recorded sales revenue of US$877 million worldwide in 2022.
- Dulaglutide drugs recorded global sales of US$7.4 billion in 2022, ranking top 20 among all drugs worldwide in terms of sales revenue by generic name in 2022.
- Liraglutide products recorded an aggregate of global sales of US$1.7 billion in 2022, ranking among the top 100 best-selling drugs by generic name in the world in 2022.
- In terms of sales revenue, the hematology pharmaceutical market grew at a CAGR of 3.0% from RMB146.9 billion in 2018 to RMB165.2 billion in 2022.
- The market of PEG-G-CSF products in China is expected to increase from RMB6,485.7 million in 2022 to RMB8,694.3 million in 2032 with a CAGR of 3.0%, according to CIC, harboring significant market potential.
- Collectively, these four therapeutic areas accounted for 52.0% of the total pharmaceutical sales in China in 2022, and outpaced the broader Chinese pharmaceutical industry from 2018 to 2022, a trend which is expected to continue in the near future, according to CIC.

# Appendix - Business

**APIs and Excipients**

| Product | Generic Name | Product Type | Description |
|---|---|---|---|
| **JY16** | Fulvestrant | API | • [Fulvestrant/JY16] is an estrogen receptor antagonist that binds to estrogen receptors in breast cancer cells. The hormone estrogen encourages breast cancer cells to grow and fulvestrant works by binding, blocking and degrading the estrogen receptor and blocking the estrogen receptor signaling pathways, which slows the growth of cancer. |
| **JY07** | Enoxaparin sodium | API | • [Low molecular weight heparin], an anticoagulant drug, is mainly used for the prevention and treatment of thrombosis-related diseases, such as deep vein thrombosis, pulmonary embolism, myocardial infarction. It is effective in treating blood clots and has low risk of causing bleeding complications. |
| **JY05** | Dulaglutide | [Drug substance/API] | • [Dulaglutide] is a long-acting GLP-1 analog fused with an Fc antibody fragment used for the treatment of type 2 diabetes. It reduces insulin resistance and promotes insulin secretion and pancreatic islet cell proliferation. |
| **JY14** | rhG-CSF | [Drug substance/API] | • [rhG-CSF] stimulates the neutrophil development, production and release from the bone marrow by binding to its cognate cell surface receptor. rhG-CSF is commonly used in preventing and treating chemoradiotherapy-induced neutropenia. |
| **JY06** | PEG-G-CSF | [Drug substance/API] | • Compared to [ordinary G-CSF drugs], [PEG-G-CSF] has extended circulating half-life which allows for reduced dose frequency and improved patient compliance. |
| **JY29** | Liraglutide | [Lyophilized powder] | • [Liraglutide] is used as a treatment for patients with type 2 diabetes mellitus by stimulating insulin secretion and inhibiting glucagon secretion. It also delays gastric emptying and gastrointestinal peristalsis, and reduces food intake and increases satiety by suppressing the appetite. |
| **JY29-2** | Semaglutide | [Lyophilized powder] | • [Semaglutide] is used as a treatment for patients with type 2 diabetes mellitus by stimulating insulin secretion and inhibiting glucagon secretion. It also delays gastric emptying and gastrointestinal peristalsis, and reduces food intake and increases satiety by suppressing the appetite. |
| **JY23** | rhBMP-2 | [Lyophilized powder] | • [rhBMP-2] effectively induces the differentiation of mesenchymal stem cells and bone progenitor cells into osteoblasts |
| **JY53** | recombinant human hyaluronidase | Excipient | • By breaking down hyaluronic acid in skin tissue, hyaluronidase can increase membrane permeability and improve the absorption and dispersion of parenterally administered fluids and drugs into tissue. As an innovative excipient, hyaluronidase can be administered concurrently with antibodies and enables the shift from intravenous injection to subcutaneous injection and dose optimization. |
| / | Recombinant human enterokinase | Industrial enzyme | • Enterokinase is a specific protease that cleaves after lysine at its cleavage site Asp-Asp-Asp-Asp-Lys. Enterokinase is a commonly used enzyme for the cleavage of fusion proteins. |

# Appendix - Summary

- However, the market size of semaglutide for the treatment of T2DM, overweight and obesity could potentially be limited by alternative prevention and treatment methods for such indications and medication treatment is used only for a portion of the total T2DM, overweight and obesity population.
- According to CIC, the market size of rhBMP-2 bone repair materials increased from RMB102.8 million in 2018 to RMB544.4 million in 2022, with a CAGR of 51.7% and is expected to further increase to RMB4,414.2 million in 2032, with a CAGR of 23.3% from 2022 to 2032.
- According to CIC, it is common for pharmaceutical companies in China to have high supplier concentrations.

# Appendix – Risk Factors

- Considering the relatively lower risk in biosimilar and generic drug development as compared to innovative drugs and the visible market potential, the successful development and commercialization of biosimilars may be affected by multiple factors, including but not limited to the timing of product launch, the successful negotiation of new collaboration contracts, the potential patent extension of the originator products, the rapid development in the relevant therapeutic areas and the evolvement of the competitive landscapes.

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Cb =pH[H+] [OH-] Alpha(A-) Phi
7.403.98E-08 2.51E-07 0.201 0.201
7.602.51E-08 3.98E-07 0.285 0.285
8.001.00E-08 1.00E-06 0.500 0.500
8.403.98E-09 2.51E-06 0.715 0.715
8.801.58E-09 6.31E-06 0.863 0.864
9.001.00E-09 1.00E-05 0.909 0.910
9.403.98E-10 2.51E-05 0.962 0.963
9.801.58E-10 6.31E-05 0.984 0.988
10.001.00E-10 1.00E-04 0.990 0.996
10.206.31E-11 1.58E-04 0.994 1.003
10.403.98E-11 2.51E-04 0.996 1.011
10.602.51E-11 3.98E-04 0.997 1.021
10.801.58E-11 6.31E-04 0.998 1.037