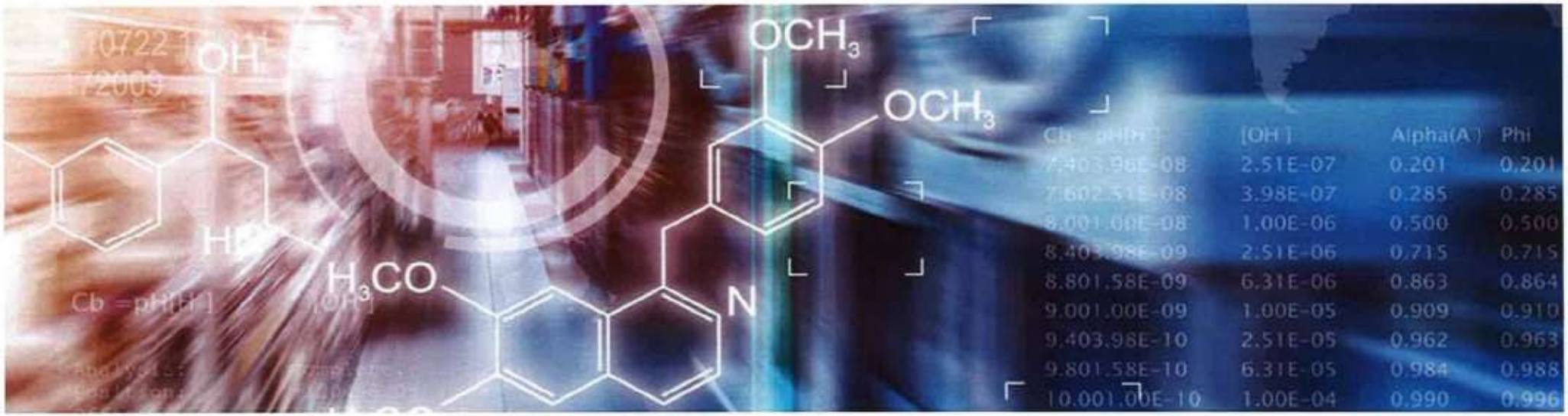

Industry report on global and China's metabolic and digestive disease drug market

China Insights Consultancy

19 May 2025

Glenn Yuchao Hou

Introduction, methodology and assumptions

China Insights Consultancy was commissioned to conduct research and analysis of, and to produce a report on China's drug market for metabolic disorders and digestive diseases. 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 cancer incidences mainly owing to aging population, strengthened public awareness of cancer 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.

Terms and abbreviations (1/3)

Terms and abbreviations

Abb	Terms	Abb	Terms
5-HT1A	5-Hydroxytryptamine	ANGPTL-3	Angiopoietin-Like 3
6-MP	6-mercaptopurine	AP	Acute Pancreatitis, a condition where the pancreas becomes inflamed over a short period of time
A1C	Hemoglobin A1C Test	API	active pharmaceutical ingredients
AASLD	American Association for the Study of Live· Disease	ApoC-III	Apolipoprotein C-III
AC	Alcohol-associated Cirrhosis	apoptosis	A type of programed cell death
ACEI	Angiotensin-Converting-Enzyme Inhibitors	APRI	Aspartate aminotransferase to platelet ratio index
AEs	Adverse Effects	ARB	Angiotensin Receptor Blockers
AH	Alcoholic Hepatitis	ASBT	Apical Sodium-dependent Bile Acid Transporter
AKR1C2	Aldo-Keto Reductase family 1, member C2	ASCVD	Atherosclerotic Cardiovascular Disease
ALD	Alcoholic Liver Disease	ASK1	Apoptosis Signal-Regulating Kinase 1
ALP	Alkaline Phosphatase,	AST	Aspartate aminotransferase
ALS	Amyotrophic Lateral Sclerosis,	ATP	Adenosine Triphosphate
ALT	Alanine transaminase	Aβ	Amyloid β
AMA	American Medical Association	AMPK	AMP-activated protein kinase
AMPK	AMP-activated protein kinase	ANGPTL-3	Angiopoietin-Like 3

Terms and abbreviations (2/3)

Terms and abbreviations

Abb	Terms	Abb	Terms
BID	Two times a day	EASL	European Association for the Study of the Liver
BIRC5	Baculoviral Inhibitor of Apoptosis Repeat-Containing 5	EBV	Epstein-Barr Virus
BP	Blood Pressure	ELF	Enhanced Liver Fibrosis
CAGR	Compound Annual Growth Rate	EMA	European Medicines Agency
CAR	Chimeric Antigen Receptor	IFG	Impaired Fasting Glycemia
CBP	CREB Binding Protein	IFN-γ	Interferon γ
CDE	Center for Drug Evaluation	IGF1R	Insulinlike Growth Factor1 Receptor
CMC	Chemistry, manufacturing, and controls	IGFBP9	Insulin-like Growth factor-Binding Protein 9
cT1	Corrected T1 value	IgG4	Immunoglobulin G4
CTCAE	Common Terminology Criteria for Adverse Events	IGT	Impaired Glucose Tolerance
CVDs	Cardiovascular Diseases, conditions affecting the heart or blood vessels	LDL-C	Low-Density Lipoprotein Cholesterol
CVM	Cardiovascular and Metabolic	LFC	liver fat content, fat accumulated in the liver
DN	diabetic neuropathy, nerve damages caused by diabetes	MASLD	Metabolic (dysfunction) Associated Fatty Liver Disease
DPP-4I	dipeptidyl peptidase 4 inhibitors	MAFL	Metabolic Associated Fatty Liver
DR	Diabetic Retinopathy	NAS	NAFLD activity score

Terms and abbreviations (3/3)

Terms and abbreviations

Abb	Terms	Abb	Terms
NASH	Nonalcoholic Steatohepatitis, an advanced form of NAFLD	p.o.	Peros
OGTT	Oral Glucose Tolerance Test	s.c.	Subcutaneous injection
PK	Pharmacokinetics	CHI	Congenital Hyperinsulinemia
Placebo	A medical treatment or preparation with no specific pharmacological activity	SPPS	solid-phase peptide synthesis
SAEs	Serious adverse events	LPPS	liquid-phase peptide synthesis
SGLT-2I	sodium-glucose cotransporter-2 inhibitors	NRDL	National Reimbursement Drug List
T1DM	Type 1 Diabetes	FGF21	Fibroblast growth factor 21
T2DM	Type 2 Diabetes	GIP	Gastric inhibitory polypeptide
TEAEs	Treatment-emergent adverse events	OSA	Obstructive sleep apnea
FXR	Farnesoid X receptor		
GLP-1	Glucagon-like peptide-1		
HbA1C	glycated hemoglobin		
HDL-C	High-density lipoprotein cholesterol		
OIC	Opioid-Induced Constipation		
PAMORA	Peripherally acting μ-opioid receptor antagonist		

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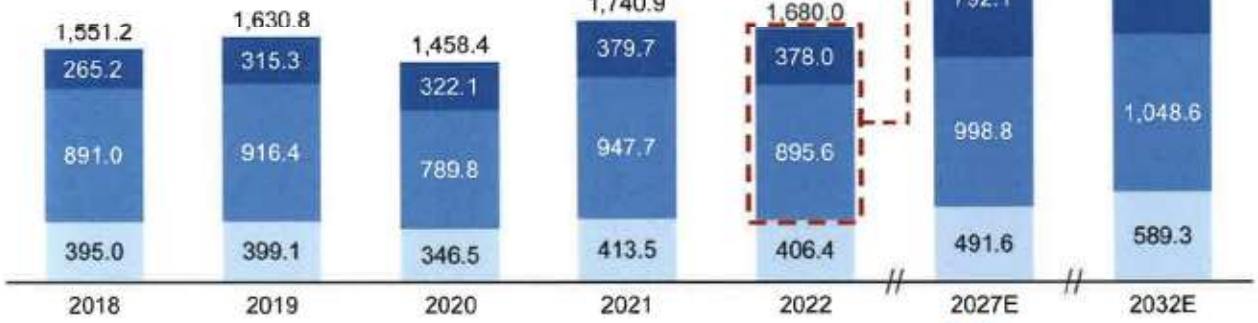
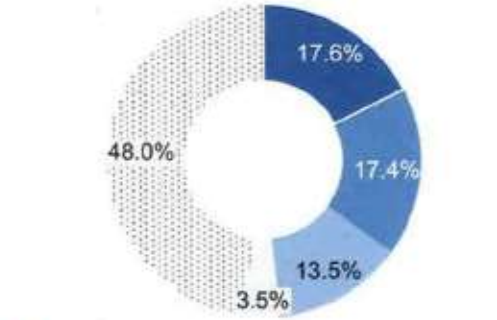
The market size of China pharmaceutical market is expected to increase from RMB1,680.0 billion in 2022 to RMB3,097.7 billion by 2032 at the CAGR of 6.3%

China pharmaceutical market size, 2018-2032E

CAGR	2018 2022	2022 2032E
Biological drugs	9.3%	14.5%
Small molecule drugs	0.1%	1.6%
Traditional Chinese Medicine(TCM)	0.7%	3.8%
Total	2.0%	6.3%



Breakdown by market segment, 2022(excl. TCM)



Key Analysis China pharmaceutical market s expected to increase from 1680.0 billion RMB in 2022 to 3,097.7 billion RMB in 2032. Orthopedics, metabolic diseases, oncology, and hematology. 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 [2017 and 2022], a trend which is expected to continue in the near future.

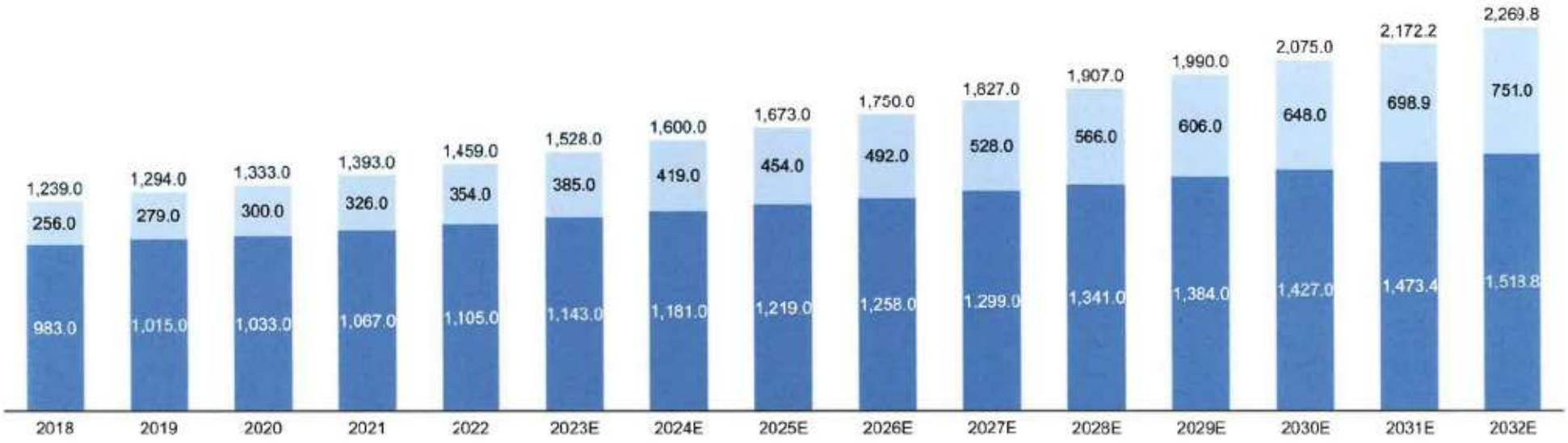
Source: China Statistical Yearbook; China Insights Consultancy

The market size of global pharmaceutical market is expected to increase from USD 1,459 billion in 2022 to USD 2,270 billion by 2032 at the CAGR of 4.5%

Global pharmaceutical market size, in terms of generic drugs and branded drugs, 2018-2032E

USD billion

CAGR	2018-22	2022-32E
Biologics	8.4%	7.8%
Small-molecule drugs	3.0%	3.2%
Total	4.2%	4.5%



Source: WHO, World Bank, China Insights Consultancy

The CDE of NMPA is responsible for evaluating drug clinical trial applications, drug marketing authorizations, supplementary applications, registration renewal applications of drugs manufactured overseas

Overview of NMPA and CDE new drug application process

Non-clinical research refers to various toxicity tests conducted in laboratory conditions using experimental systems to evaluate drug safety, including single-dose toxicity tests, repeated-dose toxicity tests, reproductive toxicity tests, mutagenicity tests, carcinogenicity tests, various irritancy tests, dependence tests and other toxicity tests related to drug safety evaluation.

Animal experiments are widely used in medical, biomedical and veterinary research, and are essential means of drug development and preclinical testing, including toxicology and safety studies. They help us advance our scientific understanding, serve as models to study disease, help us develop and test potential new medicines and therapies. Animal experiments eliminate some potential drugs as either ineffective or too dangerous to use on human beings.

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. The GCP guidelines detail the requirements for trial documentation, protocol amendments, requirements such as indemnity, reporting lines for adverse events and provision of medical care for trial participants. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected and that clinical-trial data are reliable.

Clinical trials of biomedical interventions typically proceed through four phases:

- Phase I evaluates the tolerability and pharmacokinetics of a drug in human body.
- Phase II conducts a preliminary assessment of the efficacy and safety of a drug in a specific population with defined indication.
- Phase III evaluates overall efficacy and safety profile with an adequate sample size and robust control measures, to provide confirmatory evidence.
- Phase IV is the post-marketing research conducted after the approval, to investigate the efficacy and AEs under widespread use conditions.

Source: NMPA; China Insights Consultancy

Following NDA, access to NRDL and bid for regional or centralized VBP are two major events that could potentially impose pressure of 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

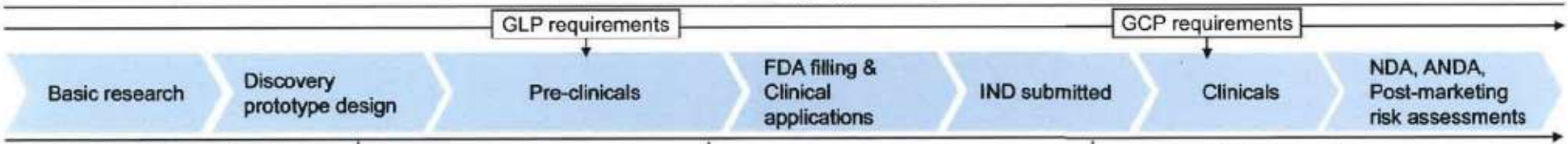
	2018.11 4+7 pilot	2019.9 4+7 expansion	2019.12 2nd round	2020.7 3rd round	2021.1 4th round	2021.6 5th round	2021.11 6th round	2022.7 7th round	2023.3 8th round
Scale	**11 pilot cities**	**25 provinces**	**nationwide**	**nationwide**	**nationwide**	**nationwide**	**Nationwide (for insulin)**	**nationwide**	**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: NHSA; frontiers; China Insights Consultancy

The FDA new drug application process is a formal submission wherein drug sponsors propose that the FDA grants approval for a new pharmaceutical to be sold and marketed in the United States

Overview of FDA new drug application process



- Mechanical parameters including In Vitro testing
- Histopathology,
- Nonclinical stability testing
- ...

- Materials selection
- Structure activity relationship
- Laboratory & Computer models
- ...

- Bench & Animal models
- Laboratory & Animal models
- ...

- Human & Animal studies
- Human effectiveness/efficacy
- Scale-up specifications
- Clinical quality assurance
- ...

The FDA approval process

- The FDA's Center for Drug Evaluation and Research (CDER) in charge of overseeing the drug approval process before a drug is marketed. CDER review each drug closely using an independent team of clinicians and scientists who evaluate safety, efficacy and labeling of the drug product. After approval, FDA follow-up continues to make sure new drugs continue to be safe and effective.
- Generally, there are four phases of a drug approval process: 1.Pre-clinical, IND; 2.Clinical; 3.NDA Review; 4.Post-marketing risk assessments. The full research, development and approval process can last from 12 to 15 years. However, In order to incentivize the development of therapies to fill unmet needs for serious conditions, the FDA has developed various programs to expedite drug development and review. These four programs are: **fast track**, breakthrough therapy, accelerated approval, and priority review.
- In addition, supporting the development and evaluation of new treatments for rare diseases is also a key priority for the FDA. The FDA has authority to grant **orphan drug designation** to a drug or biological product to prevent, diagnose or treat a rare disease or condition.

The FDA's Fast Track program is designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. The Fast Track program is intended to help patients with serious conditions receive new drugs more quickly.

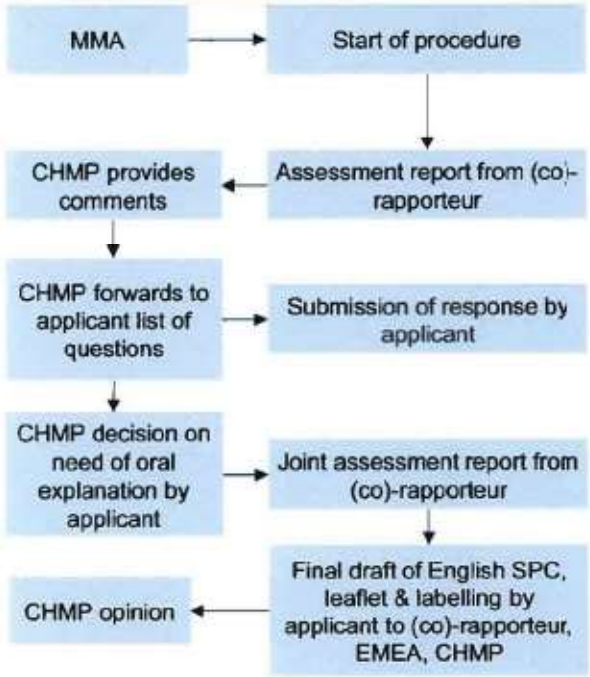
The Orphan Drug Act (ODA) was passed in 1983 to encourage the development of drugs for rare diseases. The FDA's Orphan Drug Designation program provides orphan status to drugs and biologics that are intended for the safe and effective treatment, diagnosis or prevention of rare diseases or disorders that affect fewer than 200,000 people in the US. The program provides incentives for sponsors to develop products for rare diseases.

Source: FDA, China Insights Consultancy

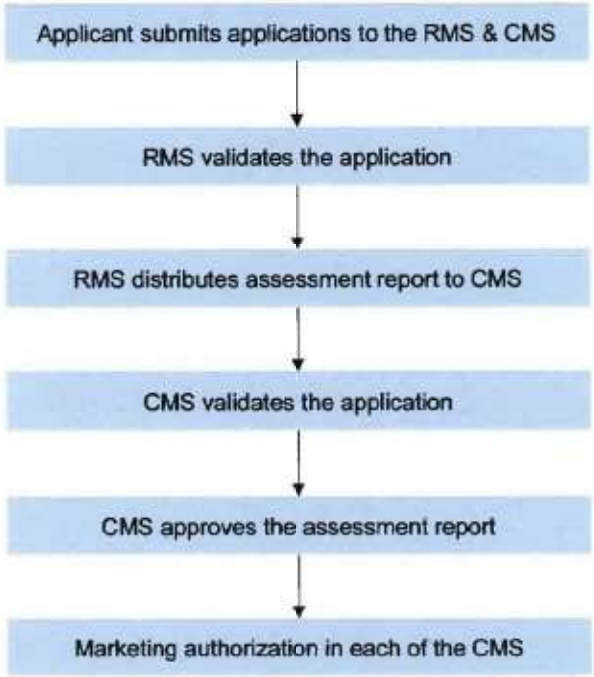
In Europe, clinical trial applications are approved at the member-state level, whereas marketing authorization applications are approved at both member-state and centralized levels

Overview of CE new drug application process

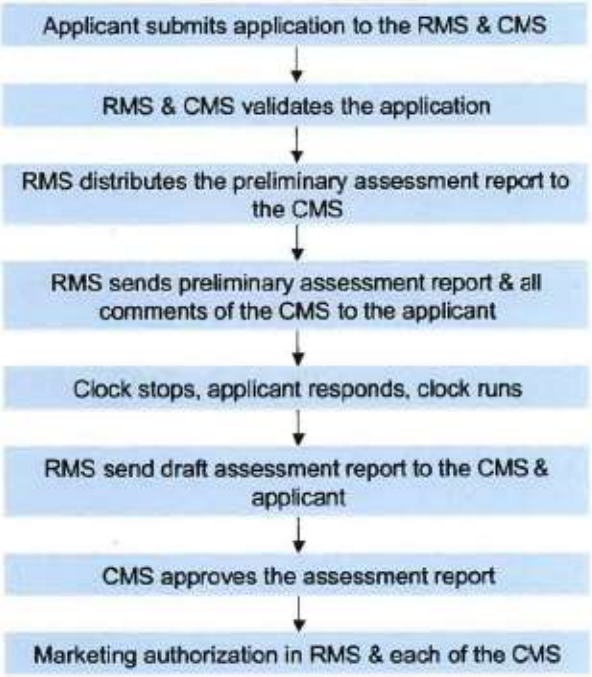
Flow chart of Centralized Procedure



Flow chart of Mutual Recognition Procedure



Flow chart of Decentralized Procedure



Source: International Journal of Drug Regulatory Affairs; China Insights Consultancy

Belt and Road Initiative is a large-scale infrastructure which has the potential to stimulate economic development, including drug importing and exporting, while ICH is a global organization brings pharmaceutical regulators together

Regulation of imported pharmaceuticals in Belt and Road Initiative countries

The Belt and Road Initiative established in 2023, is a missive China-led infrastructure project that amins to stretch around the globe. Over the past decade, the undertaking has expanded its scope to encompass Africa, Oceania, and Latin America, thereby substantially increasing China's economic and political sway on a global scale. As December. 2023, there are more than 150 Belt and Road Initiative countries.

Country	Food and heath related authorities	Drug registration process
Malaysia	National Pharmaceutical Regulatory Agency (NPRA)	The applicant submit the document to the NPRA to apply for inspection and registration of the products
Singapore	Health Science Authority (HAS)	The sponsor need to submit a Drug Master File(DMF) to the HAS, and provide the detailed information including clinical/non-clinical data, product info, etc.
Saudi Arabia	Saudi Food and Drug Authority (SFDA)	SFDA in collaboration with Ministry of Health (MoH) to regulates the medicine supply chain, registration, sale, pricing and licensing of any drug product
Russia	Ministry of Health of the Russian Federation	Companies are required to submit documents to meet the requirements for registering a drug, including the clinical data, safety information, etc.
Poland	Chief Pharmaceutical Inspectorate of Poland	For compliant market access manufactures must register their medicinal products with Chief Pharmaceutical Inspectorate of Poland
Brazil*	Brazilian Health Regulatory Agency (Anvisa)	Companies need to prepare and submit registration dossier to Anvisa, then Anvisa will conduct inspection of manufacturing sites

Introduction of ICH

- The International Council for harmonisation of Technical Requirements if Pharmaceuticals for Human Use (ICH) is a unique harmonization organization involving **regulators** and **the pharmaceutical industry**.
- ICH was launched in 1990s by the US, EU, and Japan. Currently, ICH includes 21 Members and 37 Observers.
- **NMPA joined ICH in 2017**. Becoming a member of the ICH signifies a significant milestone in advancing the global landscape of drug development and registration. It grants the privilege of actively contributing to and influencing decision-making processes within the realm of international drug development and registration technology.

Note: According to [illegible], Brazil has not been a member of Belt and Road Initiative countries yet as of December,2023

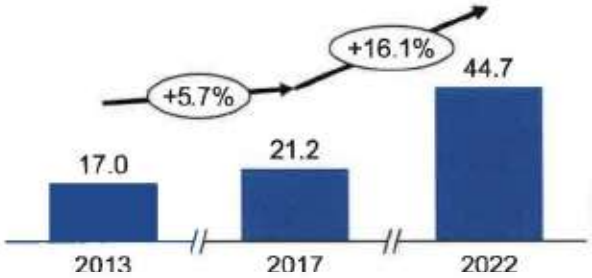
Source: yidaiyilu.gov.cn; ich.org; China Insights Consultancy

Driven by policy support and increased demand along the Belt and Road, China's pharmaceutical exports surged to $44.7 billion in 2022, with South Korea, Russia, and Vietnam comprising the largest share about 24.4%

Market size of Chinese pharmaceutical products in Belt and Road Initiative countries

- The export value of China's pharmaceutical products to countries and regions along the 'Belt and Road' initiative increased from $17.0 billion in 2013 to $44.7 billion in 2022, marking a 1.6-fold growth over the span of 10 years, with a CAGR of 10.15%. During the COVID-19 pandemic, China experienced rapid growth in pharmaceutical product exports, with a year-on-year increase of 82% in 2020 and 18% in 2021.
- Among these exports, Western medicine accounted for over half, medical devices exceeded 40%, and traditional Chinese medicine (TCM) comprised 5%.

Unit: Billion USD



Government's support drives Pharmaceutical Export Growth

- By the end of June 2023, China had signed an MoU with the WHO on health cooperation in BRI partner countries, inked health cooperation agreements with more than 160 countries and international organizations, and initiated or participated in 9 international and regional health cooperation mechanisms, including China-Africa Health Cooperation, China-Arab States Health Cooperation, and China-ASEAN Health Cooperation.

from January to September, 2023

Country	Export Value (Billion USD)	Share
South Korea	2.9	10.1%
Russia	2.3	8.1%
Vietnam	1.8	6.2%
Italy	1.7	5.8%
Thailand	1.5	5.3%
Indonesia	1.4	4.9%
Singapore	1.2	4.3%
Philippines	1.2	3.9%
Malaysia	1.1	3.9%
Turkey	1.1	3.8%
Others	125.4	44.9%

Source: China Chamber of Commerce for Import and Export of Medicines and Health Products (CCCMHPIE); 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

Overview of metabolic disorders

Introduction and symptoms of metabolic disorder

- A metabolic disorder (also named metabolic syndrome) 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.
- Common conditions of metabolic disorder include These conditions include increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels.

Causes of metabolic disorder

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.

Lifestyle risk factors: obesity, physical inactivity, smoking, and unhealthy diet are significantly associated to the risk of metabolic disorders

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

Different types of metabolic disorders

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

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

Mineral Disorders
- Wilson Disease
- Cystinosis
- Menkes Disease

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

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

Lysosomal Storage Disorders
- Hurler Syndrome
- Krabbe Disease

Glycolipid Disorders
- Gaucher's Disease

Vitamin Metabolism Disorders
- Biotinidase Deficiency

Peroxisomal Disorders
- Zellweger Syndrome
- Adrenoleukodystrophy

Diabetes is one of the most common metabolic disorder. In 2022, there are ~800 million T2DM patients globally , **accounting for over 30% of global metabolic disorder prevalence** with multiple comorbidities such as hypertension, obesity and dyslipidemia.

Source: Chapter1, Drug Delivery Systems for Metabolic Disorders, *Academic Press*; China Insights Consultancy

Metabolic disorders have been highlighted as a risk factor for digestive and other chronic diseases

Overview of Metabolic disorders and Digestive diseases

- **Digestive diseases (also called Gastrointestinal disorders)** are characterized by physiological and morphological abnormalities of the GI system. Key organs affected in the realm of digestive diseases are liver, stomach, pancreas and gallbladder, among others.
- **Metabolic disorders (metabolic syndrome) and digestive diseases occurs when a series of organs do not function normally due to a hormone or enzyme deficiency.** Multiple organs and factors are involved in the pathology of the two types of diseases, and the synergic effect between the organs or factors makes the diseases incline to deteriorate. Besides, a series of complications could be induced, and even in some cases, the management of the complications become the primary goal of the treatment currently.

	Indications	Analysis
Overall therapeutic areas	**Metabolic disorders** 	• Metabolic disorders is a complex, pathophysiological state composed of a cluster of clinically measured and typically unmeasured risk factor, is progressive in its course, and is associated with serious and extensive comorbidity, but tends to be clinically under-recognized.
Specific indication	**Adiposity**	• Sleep disordered breathing • Obesity
	Vascular	• ASCVD • Hypertension
	Insulin-related	• T2DM • Gestational diabetes • Congenital Hyperinsulinemia (CHI)
	Liver disease	• MASH/MASLD • Liver cirrhosis
	Others	• Hormonal dysfunction • Chronic kidney disease

Interrelated

- There is a well-established link between MS and inflammatory diseases of the gastrointestinal (GI) system
  - GI motility disorders caused by liver cirrhosis
  - Adiposity as a risk factor for inflammatory bowel disease

Indications	Analysis
Digestive diseases 	• The digestive system made up of gastrointestinal tract (GI), liver, pancreas, and gallbladder helps the body digest food. • Digestive diseases have become prevalent in a large part of the world population. Some digestive diseases and conditions are acute, lasting a short time, while others are chronic, or long-lasting.
Liver disease	• HBV, HCV
Pancreatitis	• Inflammation of the pancreas: including acute and chronic
Gastrointestinal disease	• Viral, bacterial or parasitic infections • GI motility disorders • Constipation
Inflammatory Bowel Disease	• Including Crohn's Disease and Ulcerative Colitis

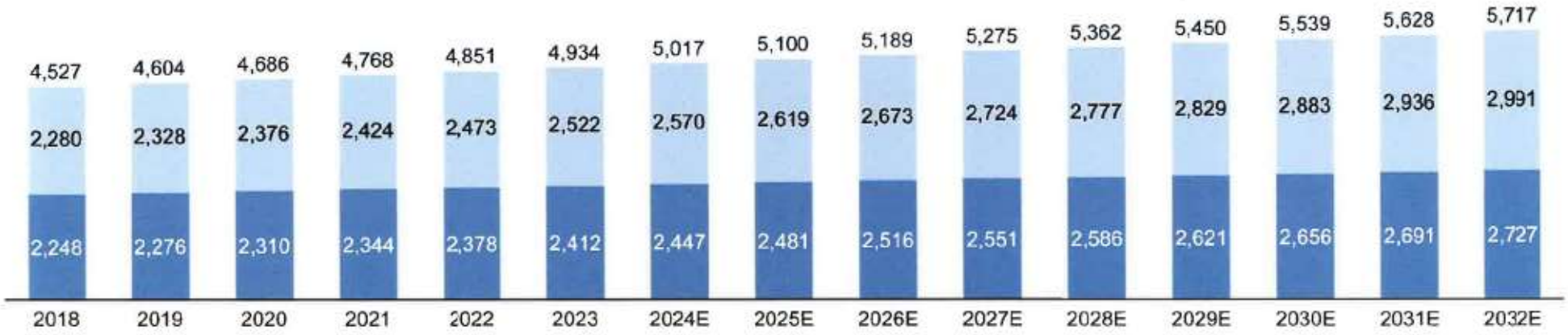
Source: Gastroenterol Res Pract., United European Gastroenterol J., China Insights Consultancy

Global prevalence of metabolic disorders and digestive diseases

Global prevalence of metabolic disorders and digestive diseases

CAGR	2018-23	2023-32E
Metabolic disorders	2.0%	1.9%
Digestive diseases	1.4%	1.4%
Total	1.7%	1.7%

Million cases



Note:

- *Major metabolic diseases include diabetes, hypertriglyceridemia, obesity, diabetic neuropathy, etc.*
- *Major digestive diseases include NAFLD and other chronic liver diseases, gallbladder and biliary diseases, inflammatory bowel disease, pancreatitis, upper digestive system diseases, etc.*

Source: China Insights Consultancy

China prevalence of metabolic disorders and digestive diseases

China prevalence of metabolic disorders and digestive diseases

CAGR	2018-23	2023-32E
Metabolic disorders	1.6%	1.9%
Digestive diseases	1.0%	1.4%
Total	1.3%	1.7%

Million cases

Note:

- *Major metabolic diseases include diabetes, hypertriglyceridemia, obesity, diabetic neuropathy, etc.*
- *Major digestive diseases include NAFLD and other chronic liver diseases, gallbladder and biliary diseases, inflammatory bowel disease, pancreatitis, upper digestive system diseases, etc.*

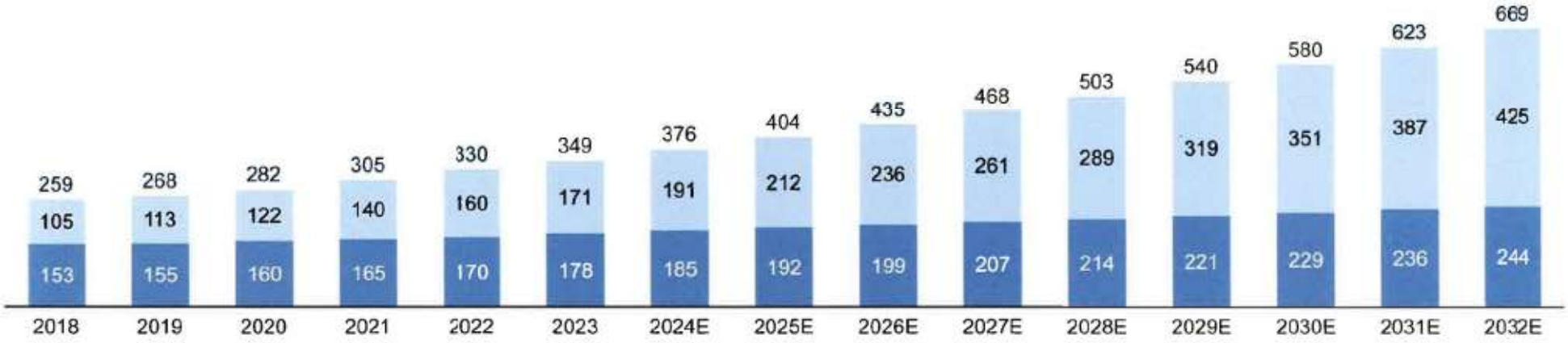
Source: China Insights Consultancy

Global market size of metabolic disorders and digestive diseases

Global market size of metabolic disorders and digestive diseases

CAGR	2018-23	2023-32E
Metabolic disorders	10.1%	10.6%
Digestive diseases	3.1%	3.5%
Total	6.2%	7.5%

Billion USD



Note:

- *Major metabolic diseases include diabetes, hypertriglyceridemia, obesity, diabetic neuropathy, etc.*
- *Major digestive diseases include NAFLD and other chronic liver diseases, gallbladder and biliary diseases, inflammatory bowel disease, pancreatitis, upper digestive system diseases, etc.*

Source: Annual reports published by market players, Expert interview, Literature research, China Insights Consultancy

China market size of metabolic disorders and digestive diseases

China market size of metabolic disorders and digestive diseases

CAGR	2018-23	2023-32E
Metabolic disorders	5.7%	8.5%
Digestive diseases	-2.6%	0.9%
Total	1.1%	5.3%

Billion RMB

Note:

- *Major metabolic diseases include diabetes, hypertriglyceridemia, obesity, diabetic neuropathy, etc.*
- *Major digestive diseases include NAFLD and other chronic liver diseases, gallbladder and biliary diseases, inflammatory bowel disease, pancreatitis, upper digestive system diseases, etc.*

Source: Annual reports published by market players, Expert interview, Literature research, China Insights Consultancy

Market drivers in metabolic and digestive diseases treatment include increased patient population, strengthened public awareness, improved affordability and novel technology with better disease understanding

Market drivers of metabolic disorders and digestive diseases treatment

Market drivers

1 Expansion of vulnerable population

- Metabolic disease and digestive disease may develop congenitally or from multiple factors such as stress, fatigue or diets. Abusing alcohol imposes the most significant risk for both diseases. Global aging results in more vulnerable population, due to the incidence of most digestive diseases and metabolic diseases increase with age. There were about 4,851 million diagnosed case of metabolic and digestive diseases around the world in 2022, and the patient population is expect to exceed 5,539 million in 2030.

2 Strengthened Public Awareness

- Along with the development of the economy and growth in the living standard, increasingly more attention is being paid to healthcare, with more and more resources and money therefore expected to be spent on healthcare in the future. Under such a condition, the improvement of government medical system and popularization of regular health examination are expected to result in decreasing in the ignorance of diseases that are easily overlooked before.

3 Improved affordability of patients

- Increased disposable income per capita and broader medical insurance coverage in China and the U.S. make it easier for patients to afforded relatively more expensive medical fees. Health expenditure per capita in China increased from 2981 RMB in 2015 to 5146 RMB in 2020 with compound annual growth rate of 11.5%. Health expenditure per capita in the U.S. increased from 9990 USD in 2015 to 12000 USD in 2020 with compound annual growth rate of 3.7%.

4 disease Understanding & novel technology

- Moreover, with the development of scientific research in the field of digestive diseases and metabolic diseases, a deep and comprehensive understanding of the diseases are surely expected. A better understanding of the diseases lays a solid foundation for new drug development. Databases for these diseases are being developed for further exploration.
- In addition to databases, novel technologies such as drug design platform and high-throughput drug screening platform help materialize these databases and extract insightful information that guides drug design and drug development, thus enabling a more efficient process of drug R&D, and ultimately drives the market growth.

Source: China Statistical Yearbook; China Insights Consultancy

Future trends of metabolic disorders and digestive diseases treatment

Future trends of metabolic disorders and digestive diseases treatment

Personalized treatment strategy:

- Technological advancements and clinical research breakthroughs have significantly revolutionized medicine and healthcare, leading to an enhanced capability for disease management. Personalized care will be the key to improve the treatment of chronic diseases for all individuals, which could benefits patients on aspects of physical health, mental health, and the ability to self-manage conditions.

Preferred treatments with long-term effects and better safety profile:

- Metabolic disorders and digestive diseases are chronic diseases that often carry the risks of complications. Long-term treatment strategies focus on better safety profiles, ease of using, and higher patients' compliance
- Preferred treatments aims to control symptoms and improve the patient's quality of life over the long term. Patient's compliance to prescribed medications and lifestyle recommendations are the key to success of long-term treatments

Widely recognition of treatment paradigms that could provide systematic metabolic and digestive benefits:

- Clinical guidelines stress the vital role of effectively managing risk factors in reducing long-term complications. The "Healthy China Action (2019-2030)" proposes to advance the co-management of the "three highs" *(三高共管)* and standardize the management of blood pressure, blood glucose, and blood lipids. The specific plan is to achieve a standardized management rate of ≥ 70% for hypertension and diabetes by 2030, and the annual blood lipid testing rate for residents aged 35 and over should be ≥ 35%.

Increasing market share of domestic products:

- Through ongoing research and development efforts, specialized medications like GLP-1 receptor agonists, FXR agonists, DPP-4 inhibitors, and SGLT-2 inhibitors are effectively meeting unmet clinical needs within the realm of metabolic disorders and digestive diseases.
- Numerous domestic pharmaceutical companies have initiated clinical studies focused on the treatment of metabolic diseases, and recent approvals for certain domestic GLP-1 products signify a growing trend. It is anticipated that an increasing number of domestic products will capture market share in China to replace the imported products.

Source: "三高"共管规范化诊疗中国专家共识(2023版); literature review; China Insights Consultancy

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GLP-1R agonists, as medications, replicate the effects of GLP-1, and used in the treatment of metabolic disorders such as T2DM and obesity

Introduction of GLP-1 peptide and GLP-1RAs

Glucagon-like peptide-1 (GLP-1) structure features	• GLP-1, an an endocrine hormone, originates from a proglucagon precursor and is secreted from **intestinal endocrine L cells** in response to nutrient intake. Primarily, it is found in the form of GLP-1(7–36) amide, hereafter referred to as GLP-1. • The cellular density of L-cells progressively increases along the length of the small intestine, being the lowest density in the duodenum and the highest in the distal ileum. 
GLP-1 signal transduction pathways	• GLP-1 stimulates **glucose-dependent insulin release** from the pancreatic islets. • This binding results in activation of adenylyl cyclase with consequent production of cAMP and subsequent activation of protein kinase A and the Epac family. • GLP-1 also **slows gastric emptying**, regulates postprandial glucagon, and reduces food intake.
GLP-1 receptors (GLP-1R)	• GLP-R is a member of GPCR family. Human GLP-1R comprises 463 amino acids, including **seven transmembrane domains** and an **N-terminal signal peptide** that is cleaved upon delivery to the plasma membrane. 
GLP-1R signaling	• Binding of GLP-1 to GLP-1R triggers a downstream signaling cascade that induces **a potent stimulation of glucose induced insulin secretion** (GIIS) in pancreatic beta-cells, as well **as inhibition of alpha cell glucagon release.** • GLP-1 also acts directly or indirectly in **different body organs.**
GLP-1R agonists (GLP-1RAs)	• Synthetic 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 MASH and ASCVD.

Note: GPCR, G protein-coupled receptors; ASCVD, atherosclerosis cardiovascular disease;

Source: Indian J Endocrinol Metab; China Insights Consultancy

Binding of GLP-1 and GLP-1R can regulate insulin secretion and glucagon release, and also has effects on various organs/tissues within the metabolic system

Metabolic actions of GLP-1/GLP-1RA in different body organs[1]

1. *Increase incretin secretion*
   - GLP-1RAs are modified to be less susceptible to rapid degradation by DPP-4 enzyme
2. *Improve insulin resistance and increase insulin secretion*
   - GLP-1RAs **helps with insulin resistance improvement by stimulating β-cell proliferation and neogenesis and increasing expression of glucose transporters in insulin-dependent tissues**
3. *Decrease glucagon secretion*
   - GLP-1RAs can inhibit glucagon secretion from pancreatic islet α-cells by stimulating insulin secretion
4. *Decrease glucose production*
   - GLP-1RAs can inhibit hepatic glucose production (HGP) and reduce liver lipid content

5. *Stimulate neuro protective ability*
   - GLP-1RAs can control glycemia via glucose-dependent mechanisms of action and promote weight loss
6. *Increase glucose uptake in skeletal muscle*
   - GLP-1RAs can significantly increase the uptake of glucose by muscle tissue, thus lowering blood glucose
7. *Prevent albuminuria and slow the decline of renal function*
8. *Increase lipolysis rate and free fatty acids*
9. *Reduce blood pressure; induction of heart rate and vasodilation*

Key Analysis

- The metabolic actions of GLP-1 across **diverse body organs** including the pancreas, kidney, gastrointestinal (GI) tract, liver, muscle, bone, liver as well as the cardiovascular systems
- L-cells produced by GLP-1 are predominantly located along the **ileum** and colon of the **GI**
- Glucose-stimulated insulin release from pancreatic β-cells is a tightly regulated process, which involves many **complementary pathways**

1. Müller TD, Finan B, Bloom SR, et al. Glucagon-like peptide 1 (GLP-1). Mol Metab. 2019;30:72-130. doi:10.1016/j.molmet.2019.09.010

Source: *Mol Metab. 2019;30:72-130. doi:10.1016/j.molmet.2019.09.010;* China Insights Consultancy

The comparison of different types of GLP-1RAs, including their molecular structures and clinical efficacy

GLP-1 and GLP-1RAs > Classifications

Drug name(generic)	Exenatide	Exenatide-LAR	Lixisenatide	Liraglutide	Semaglutide	Albiglutide	Dulaglutide
Molecular structure characteristics/Molecular modifications[1] ★ **A major factor to influence clinical efficacy, such as half-life**	The synthetic form of a naturally occurring parent compound exendin-4	Modified to an extended-release preparation	Based on exendin-4 with an addition of six lysines and a deletion of a proline at the C-terminus	An addition of a 16-carbon fatty-acid side-chain at Lys26 and an Arg34Lys substitution	A larger linker molecule comprising of increased length of fatty acid derivative	Developed as continuous-acting peptide by covalent binding of DPP-4 resistant-GLP-1 analog to human albumin	Consists of two DPP-4 resistant GLP-1 molecules covalently bound to a modified IgG4 Fc fragment
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

1. Sekar R, Singh K, Arokiaraj AW, Chow BK. Pharmacological Actions of Glucagon-Like Peptide-1, Gastric Inhibitory Polypeptide, and Glucagon. Int Rev Cell Mol Biol. 2016;326:279-341. doi:10.1016/bs.ircmb.2016.05.002

Note: LAR, long-acting release

Source: ClinicalTrial.gov; China Insights Consultancy

Long-acting GLP-1RAs have better effects in glycemic control and body weight loss

Main differences between short- and long-acting GLP-1RAs

Features[1]	Short-acting (Exenatide)				Long-acting (Exenatide-LAR, Semaglutide, PB-119)				
Fasting plasma glucose	++				+++				
Postprandial plasma glucose	+++				++				
Gastrointestinal effects	+++				++				
Adherence potential	+				++ / +++				
Injection burden	+++				+				
	DURATION-4 (NCT00676338)		**LEAD-3** (NCT00294723)		**SUSTAIN 1** (NCT02054897)			**PB-119301**	
	26 weeks		52weeks		30 weeks			24 weeks	
Effects	Metformin	Exenatide	Glimepiride	Liraglutide (1.8mg)	Placebo	Semaglutide (0.5mg)	Semaglutide (1.0mg)	Placebo	PB-119 (150μg group)
Reduction in HbA1c	-1.48%	-1.53%	-0.51%	-1.14%	0.0%	-1.47%	-1.56%	-0.63%	-1.37%
Reduction in fasting plasma glucose	98mmol/L	-2.25mmol/L	-5.29mg/dL	-25.57mg/dL	-0.55mmol/L	-2.41mmol/L	-2.39mmol/L	-0.522mmol/L	-1.263mmol/L
Change in body weight	-2.00kg	-2.04kg	1.12kg	-2.45kg	--0.89kg	-3.68kg	-4.67kg	-0.35kg	-0.52kg

+ = low ++ = median/moderate +++ = high

Note: HbA1c, glycated hemoglobin

1. Miñambres, I., Pérez, A. Is there a justification for classifying GLP-1 receptor agonists as basal and prandial?. *Diabetol Metab Syndr* **9**, 6 (2017). https://doi.org/10.1186/s13098-017-0204-6

Source: Diabetology & Metabolic Syndrome; China Insights Consultancy

Aside from GLP-1 RA mono-target product, there are currently multiple forms of combinations of adjacent targets under clinical development, of which most are dual agonists and triagonists

Comparison of different combinations of targets in the adjacent areas of GLP-1 RA

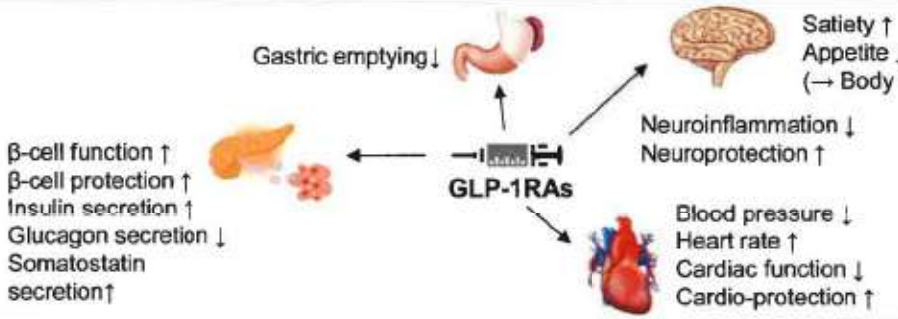
Drug type	GIPR/GLP-1R dual agonists	GLP-1R/GCGR dual agonists	GIPR/GLP-1R/GCGR triagonists[1]
Description	• Endocrine K cells in the intestine are responsible for producing gastric inhibitory polypeptide (GIP). Similar to GLP-1, **GIP promotes insulin secretion from pancreatic β cells** in a manner dependent on glucose levels. • Glucagon (GCG) is a 29-amino acid peptide released by pancreatic α cells **in response to low blood glucose levels**. • Dual agonists or tritagonists activate more than one receptor, and they usually can create a synergistic effect superior to the impact of any of individual receptor agonist acting alone.		
Drug Example	Tirzepatide	Mazdutide (IBI362)	Retatrutide (LY3437943)
FDA approval	2023.11.08	N/A (Currently in Phase III, started 2022.10)	N/A (Currently in Phase III, started in 2023.05)
Structure and activity	• $C_{225}H_{348}N_{48}O_{68}$ • Tirzepatide is a synthetic linear peptide molecule containing 39 amino acids • Largely **mediated by the GIP** component	• $C_{210}H_{322}N_{46}O_{67}$ • Mazdutide is a synthetic oxyntomodulin analog • Pathway: GPCR/G protein	• $C_{221}H_{342}N_{46}O_{68}$ • More potent at human GIP receptor, and less potent at glucagon and GLP-1R
Indication	• Obesity • Overweight associated comorbid conditions (e.g., T2DM)	• Under development for the treatment of: **T2DM** and **obesity**	• Under development for the treatment of: **T2DM**, **obesity** and **MASLD**
Modification for extended clearance time	Fatty-acid mocified peptide	A fatty-acyl moiety	N/A
Efficacy length	Long-acting	Long-acting	Long-acting
Administration frequency	Once a week	Once a week	Once a week
Half life	~116.7hrs	6.3-16.8days	~6days

1. Wang JY, Wang QW, Yang XY, et al. GLP-1 receptor agonists for the treatment of obesity: Role as a promising approach. Front Endocrinol (Lausanne). 2023;14:1085799. Published 2023 Feb.doi:10.3389/fendo.2023.1085799

Source: ClinialTrial.gov; China Insights Consultancy

Treatment mechanisms of GLP-1RAs on T2DM, MASLD/MASH, and obesity, and the common outcome measures in the clinical studies design (1/2)

T2DM, obesity, and MASLD/MASH are correlated: The initiation and progression of MASLD can be affected by organokines secreted from metabolic organs under metabolic disturbance. Clinically, T2DM coexists with MASLD, and it can aggravate MASLD to more serve forms of MASH.

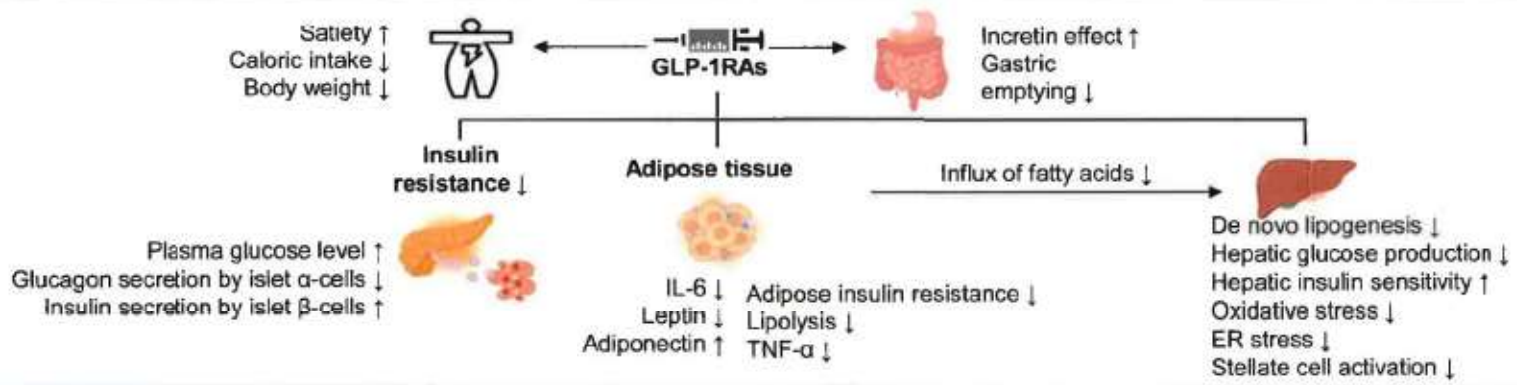
<table>
<tr><th>Indication</th><th colspan="2">T2DM</th><th>Obesity/Overweight</th></tr>
<tr><td>Therapeutic mechanisms of GLP-1RAs treatment</td><td colspan="3"> 

The mechanism for decrease in GLP-1 secretion is incompletely understood in obese people, some studies believe that the decrease of GLP-1 in obese subjects may be related to increase plasma non-esterified fatty acids (NEFA)</td></tr>
<tr><td rowspan="3">Common criteria in the phase III clinical studies design</td><td>Primary Outcome</td><td>• Change in glycated hemoglobin (HbA1c)</td><td>• Average body weight loss</td></tr>
<tr><td rowspan="2">Secondary Outcome</td><td>• Change in fasting plasma glucose (FPG) and postprandial glucose (PPG)
• Change in C-peptide and insulin levels
• Average weight loss/Percentage body weight change from baseline/Change in BMI
• Cardiovascular outcomes and others</td><td>• Waist circumference, or waist-hip ratio
• Change in free fatty acids, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL) and other indicators
• Hypertension and other indicators</td></tr>
<tr><td colspan="2">Half-life; Number of Treatment-emerging Adverse Events (TEAEs); Number of Serious Adverse events (SAEs)</td></tr>
</table>

Source: ClinicalTrial.gov; China Insights Consultancy

Treatment mechanisms of GLP-1RAs on T2DM, MASLD/MASH, and overweight, and the common outcome measures in the clinical studies design (2/2)

GLP-1 and GLP-1RAs > MASH/MASLD

Indication		MASLD/MASH
Therapeutic mechanisms of GLP-1RAs treatment		
Common criteria in the phase III clinical studies design	**Primary Outcome**	• Change in **liver fat** (absolute change in LFC as measured by MRI-PDFF from baseline) • Change in **intrahepatic triglycerides** (IHTG) quantified by proton magnetic resonance and spectroscopy (H-MRS)
	Secondary Outcome	• Average weight loss • Change in serum aspartate aminotransferase (AST) level • Change in **fibroscan parameters**: liver stiffness measurement(LSM), controlled attenuation parameter(CPA) • Change in **cardiometabolic markers**: IL-1, TNF-alpha, hs-CRP, leptin, adiponectin and homocysteine and fibrosis markers • Change in **biochemical markers**: serum alanine transaminase (ALT) levels, Gamma-glutamyl transpeptidase (GGT) levels
		Half-life; Number of Treatment-emerging Adverse Events (TEAEs); Number of Serious Adverse events (SAEs)

Note: LFC, liver fact content; MRI-PDFF, magnetic resonance imaging-derived proton density fat fraction

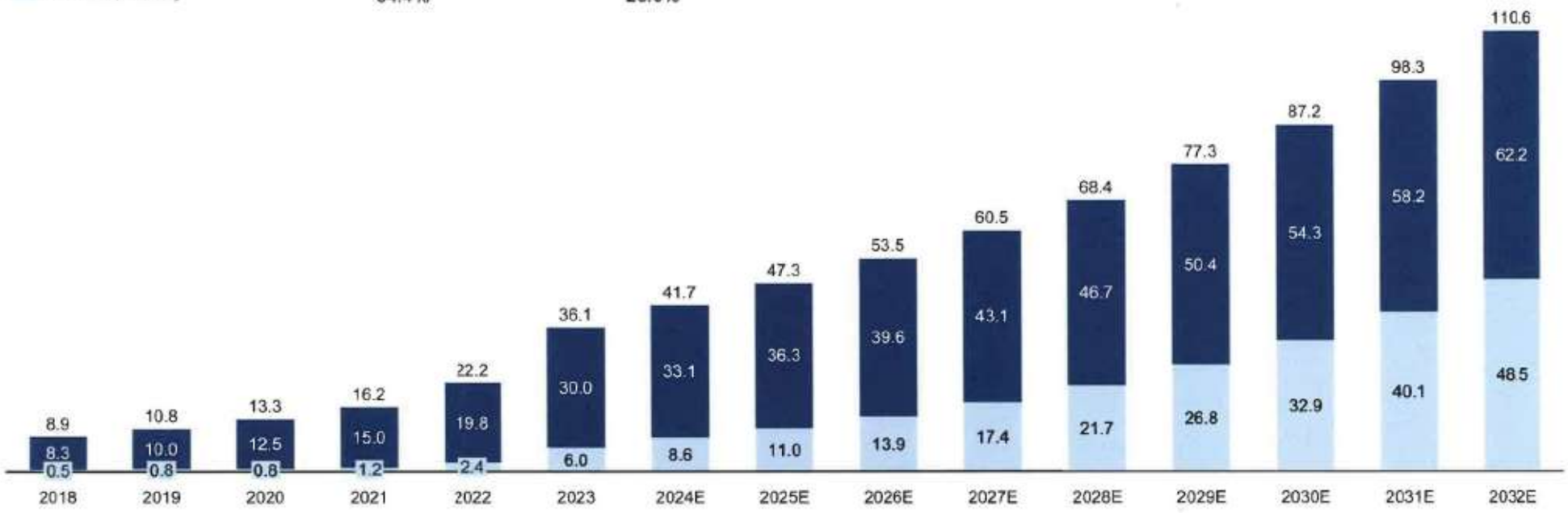
Source: ClinicalTrial.gov; China Insights Consultancy

Market size breakdown of global GLP-1RA market by indication*

Global GLP-1RA market size breakdown by indication, 2018-2032E

CAGR	2018-23	2023-32E
GLP-1RA, T2DM	29.3%	8.4%
GLP-1RA, Obesity	64.4%	26.0%

USD billion



Note: Only FDA/NMPA approved indications by 2023/12/31 included in the market size calibration

Source: China Insights Consultancy

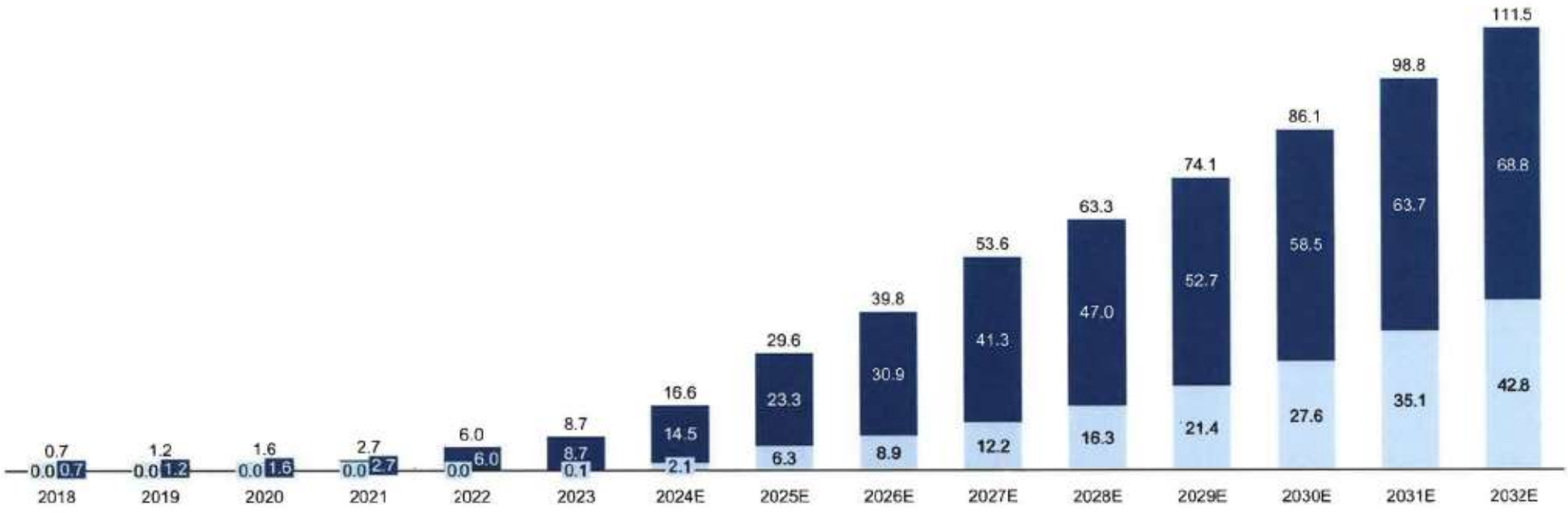
Market size breakdown of China GLP-1RA market by indication*

GLP-1 RA | Market size

China GLP-1RA market size breakdown by indication, 2018-2032E

RMB billion

CAGR	2018-23	2023-32E
GLP-1RA, T2DM	64.1%	25.9%
GLP-1RA, Obesity	NA	111.7%



Note: The First NMPA approved GLP-1RA indicated for obesity/overweight is in 2023 2H, this CAGR represents the expected average growth rate of GLP-1RA Indicated for obesity between 2023-2032

Source: China Insights Consultancy

The following table sets forth the pipeline of all approved GLP-1 receptor agonists in the United States as of the Latest Practicable Date

Pipeline of GLP-1 Receptor Agonists Approved in the United States

Drug Name	Brand Name	MoA	Efficacy Length	Indication		Administration	Company	Approval Date
				T2DM	Overweight/Obesity			
Exenatide	Byetta®	GLP-1R	Short-acting	✓		s.c.	AstraZeneca	2005/04/28
Liraglutide	Victoza®	GLP-1R	Short-acting	✓		s.c.	Novo Nordisk	2010/01/25
	Saxenda®	GLP-1R	Short-acting		✓	s.c.		2014/12/23
Exenatide ER	Bydureon®	GLP-1R	Long-acting	✓		s.c.	AstraZeneca	2012/01/27
Albiglutide	Tanzeum®	GLP-1R	Long-acting	✓		s.c.	GlaxoSmithKline	2014/04/15
Dulaglutide	Trulicity®	GLP-1R	Long-acting	✓		s.c.	Eli Lilly	2014/09/18
Lixisenatide	Adlyxin®	GLP-1R	Short-acting	✓		s.c.	Sanofi	2016/07/27
Semaglutide	Ozempic®	GLP-1R	Long-acting	✓		s.c.	Novo Nordisk	2017/12/05
	Rybelsus®	GLP-1R	Short-acting	✓		p.o.		2019/09/20
	Wegovy®	GLP-1R	Long-acting		✓	s.c.		2021/06/04

Notes:

- There is one GLP-1/GIP dual receptor agonist, Tirzepatide, that has been approved by the FDA for the treatment of T2DM or obesity indications in the United States, under the brand names Mounjaro and Zepbound, respectively

Source: FDA, China Insights Consultancy

Pipeline of GLP-1 Receptor Agonists Approved for the Treatment of T2DM and/or Overweight/Obesity in China

Pipeline of GLP-1 Receptor Agonists Approved for the Treatment of T2DM and/or Overweight/Obesity in China （1/2）

Drug Name	Brand Name	MoA	Efficacy Length	Indication	Administration	NRDL status	NRDL price (RMB/unit)	Monthly Spending (RMB) [4]	Company	Approval Date
Supaglutide	怡诺轻/Diabegone	GLP-1R	Long-acting	T2DM	s.c.	N/A	N/A	N/A	Innogen	2025/1/26
Exenatide	/	GLP-1R	Short-acting	T2DM	s.c.	N/A	N/A	N/A	Hybio Pharmaceutical	2024/9/10
Liraglutide[1]	贝乐林	GLP-1R	Short-acting	T2DM	s.c.	No	N/A[2]	N/A	Chia Tai Tianqing	2024/6/25
Semaglutide	诺和盈/Wegovy	GLP-1R	Long-acting	Overweight/Obesity	s.c.	No	N/A[2]	N/A	Novo Nordisk	2024/6/25
Semaglutide	诺和忻/Rybelsus	GLP-1R	Short-acting	T2DM	p.o.	No	N/A[2]	N/A	Novo Nordisk	2024/1/26
Liraglutide[1]	统博力	GLP-1R	Short-acting	T2DM	s.c.	Category B	268/(18mg:3ml)	~750	Tonghua Dongbao	2023/11/28
Beinaglutide	菲塑美	GLP-1R	Short-acting	Overweight/Obesity	s.c.	No	N/A[3]	N/A	Shanghai Benemae	2023/7/28
Liraglutide[1]	利善平	GLP-1R	Short-acting	Overweight/Obesity	s.c.	No	N/A[3]	N/A	Jiuyuan Gene	2023/7/4
Liraglutide[1]	利善平	GLP-1R	Short-acting	T2DM	s.c.	Category B	~300/(18mg:3ml)	~840	Jiuyuan Gene	2023/3/28
Exenatide[1]	/	GLP-1R	Short-acting	T2DM	s.c.	Category B	407.83/(0.25mg:2.4ml)	~815	Qinghai Chenfei	2022/7/29
Beinaglutide	诺生泰	GLP-1R	Short-acting	T2DM	s.c.	Category B	191/(4.2mg:2.1ml)	~764	Shanghai Benemae	2021/10/28
Semaglutide	诺和泰/Ozempic	GLP-1R	Long-acting	T2DM	s.c.	Category B	478.8/(2mg:1.5ml)	~957	Novo Nordisk	2021/4/27
Liraglutide	诺和力/Victoza	GLP-1R	Short-acting	T2DM	s.c.	Category B	339/(18mg:3ml)	~1,148	Novo Nordisk	2011/10/9
Polyethylene Glycol Loxenatide	孚来美	GLP-1R	Long-acting	T2DM	s.c.	Category B	187/(0.2mg:0.5ml)	~748	Hansoh	2019/5/5
Dulaglutide	度易达/Trulicity	GLP-1R	Long-acting	T2DM	s.c.	Category B	149/(1.5mg:0.5ml)	~596	Eli Lilly	2019/2/22
Exenatide Microspheres	百达扬/Bydureon	GLP-1R	Long-acting	T2DM	s.c.	Category B	496.25/(2 mg:0.65ml)	~1,985	AstraZeneca	2017/12/28
Lixisenatide	利时敏/Adlyxin	GLP-1R	Short-acting	T2DM	s.c.	Category B	157.65/(150μg)	~588	Sanofi	2017/9/29
Exenatide	百泌达/Byetta	GLP-1R	Short-acting	T2DM	s.c.	Category B	240/(5μg:1.2ml)	~815	AstraZeneca	2009/3/1

Source: NMPA; China Insights Consultancy

Pipeline of GLP-1 Receptor Agonists Approved for the Treatment of T2DM and/or Overweight/Obesity in China

Pipeline of GLP-1 Receptor Agonists Approved for the Treatment of T2DM and/or Overweight/Obesity in China （2/2）

Notes:

1. Generic or biosimilar product
2. Marketed price not yet available
3. Not yet included in NRDL
4. Monthly spending estimated on recommended dosage indicated on drug label for 4 weeks
5. GLP-1 receptor agonists target GLP-1 receptors in the brain, cerebral blood vessels, pancreas, heart, gastrointestinal tract, adipose tissue, kidney and muscles, and consequently affect a variety of organs and physiological processes
6. There is one GLP-1/GIP dual receptor agonist, Tirzepatide, that has been approved by the NMPA for the treatment of T2DM or obesity indications in China

Source: NMPA, Chinese Journal of Modern Applied Pharmacy, National Reimbursement Drug List, NHSA, drug labels, China Insights Consultancy

Pipeline of Insulin GLP-1 Receptor Agonist Combination Therapies Approved in China and the United States

Pipeline of Insulin GLP-1 Receptor Agonist Combination Therapies Approved in China and the United States

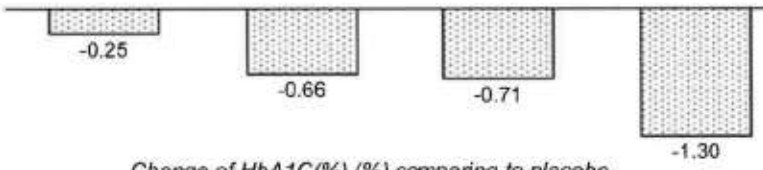
Drug Name	Brand Name	MoA	Efficacy Length	Administration	Company	Approval Date FDA	Approval Date NMPA	NRDL status
iDegLira	Xulophy/诺和盈	Insulin degludec/Liraglutide	Long-acting	s.c.	Novo Nordisk	2016/11/21	2021/10/28	Category B
iGlarLixi	Soliqua/赛益宁	Insulin degludec/Liraglutide	Short-acting	s.c.	Sanofi	2016/11/21	2023/1/13	Category B

Source: FDA, NMPA, China Insights Consultancy

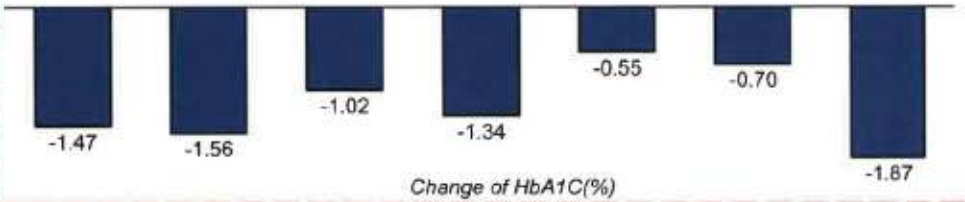
Clinical data comparisons of commercialized GLP-1RAs for the treatment of T2DM

GLP-1 and GLP-1RAs | Long-acting vs. shorting-acting

	Beinaglutide[1]*	Lixisenatide (NCT00688701)	Exenatide (NCT00765817)	Liraglutide (NCT00318442)	Semaglutide (NCT02054897)		Polyethylene Glycol Loxenatide[2]		Dulaglutide (NCT01126580)		Exenatide Microspheres (NCT00308139)
Treatment dosage	0.2mg as add-on to metformin	10 mcg for 2 weeks, then 12 mcg for 10 weeks	5mcg twice daily for 4 weeks, followed by 10mcg twice daily for 26 weeks	1.8mg daily	0.5mg once a week	1mg once a week	100μg once a week	200μg once a week	0.75mg once a week	1.5mg once a week	2mg once a week
Time of therapy	12 weeks	12 weeks	30 weeks	26 weeks	30 weeks		24 weeks		52 weeks		30 weeks
Baseline HbA1C (%)	N/A	8.07	N/A	8.5	8.09	8.12	N/A	N/A	7.58	7.63	8.3
Participants achieve HbA1C≤7%	21.4%	46.5%	58.8%	42.4%	74.2%	72.3%	34.7%	46.6%	53.2%	60%	70.9%



Change of HbA1C(%) (%) comparing to placebo



Change of HbA1C(%)

Compared with short-acting GLP-1RA, **long-acting GLP-1RAs generally has a better therapeutic effect and more significant reduction on HbA1c levels**

*Note: 1. Obesity Science & Practice, 5, 366–375. https://doi.org/10.1002/osp4.342.; *The control group of this study took placebo with metformin; 2.Diabetes Obes Metab. 2021; 23: :16–124. https://doi.org/10.1111/dom.14198*

Source: Diabetology & Metabolic Syndrome; China Insights Consultancy

GLP-1RAs drug market is developing towards long-acting efficacy, multi-target therapies, indication expansion and oral administration to address unmet needs in multiple therapeutic areas

Future trends of GLP-1RAs drug market

Long-acting formulations:

- Long-acting formulations of GLP-1RAs has become more prevalent in the past few years. This could **enhance patient adherence** by reducing the frequency of injections and potentially improving overall effectiveness
- PB-119 developed by PegBio is an once-weekly PEGylated exenatide injection, which is a long-acting GLP-1RA

Combination therapies and multi-targets agonists:

- The trend towards combining different classes of antidiabetic medications continues. Researchers may explore **combination therapies involving GLP-1RAs and other agents** to provide more comprehensive glycemic control and additional health benefits.
- There several dual agonists have been approved, such as Tirzepatide (FDA approval), and many novel clinical pipelines are under investigations

Expanded use and indications:

- GLP-1RAs have shown efficacy in managing type 2 diabetes and obesity, and their use may **expand to other conditions**. Ongoing research may explore their potential in obesity management, MASH/MASLD, cardiovascular disease, and other metabolic disorders.

Oral GLP-1RAs:

- While GLP-1RAs are currently administered via injection, there is ongoing research into developing oral formulations. Companies like Eli Lilly, Pfizer, vTv Therapeutics, and others are actively engaging. Orforglipron developed by Eli Lilly has started Phase III clinical trial in China from September 2023.
- However, in the beginning of Dec. 2023, Pfizer has **stopped the phase II trial of danuglipron**, a small molecule oral GLP-1RA cardidate. More than 50% of patients discontinued treatment across all dose compared about 40% with placebo. It is uncertain if oral GLP-1RAs could have the same clinical efficacy with the injections

Note: HbA1c, glycated hemoglobin

Source: FDA; literature review; China Insights Consultancy

Table of contents

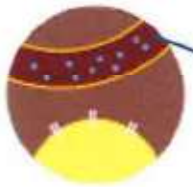
Type 2 diabetes mellitus is an impairment in the way the body regulates and uses glucose as a fuel. It is a chronic condition results in too much sugar circulating in the bloodstream

Introduction to Diabetes Mellitus

- **Diabetes** is a disease in which blood glucose level is too high. Glucose comes from the food, and insulin is a hormone produced by pancreas that helps the glucose get into cells to give them energy to maintain normal physiological function. With type 1 diabetes, body does not make insulin. With type 2 diabetes, body does not make or use insulin well.

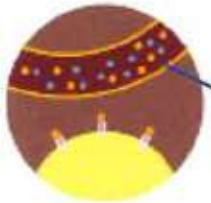
Types of diabetes

T1DM



No Insulin Produced

T2DM



Impaired Response to Insulin

Causes and diagnosis of diabetes

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

- Blood glucose increases, which increases the risk of diabetes
- Level of diabetes and diagnosis are measured by at least 3 key metrics

Metrics	A1C 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

There are several way to diagnose diabetes:

- **Hemoglobin A1C Test (A1C)** 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.

Source: Medscape, American Diabetes Association, China Insights Consultancy

The prevalence of T2DM in China is estimated to be 123.2 million in 2022 and expected to exceed 140 million in 2032

Prevalence of T2DM in China, US and globally, 2018-2032E

CAGR	2018-23	2023-32E
China	1.7%	1.4%
the U.S.	1.2%	0.7%
ROW	2.0%	1.6%
Total	1.9%	1.5%

Million patients

Data estimated based on:
1. T2DM accounts for over 96% of diabetes prevalence globally
2. Countries and territories adopt their individual diagnostic criteria to report epidemiology for prevalence calibration globally

Source: WHO, IDF, World Bank, the Lancet, ADA, China Insights Consultancy

A range of therapies is available for the management of T2DM, and each class has advantages and disadvantages based on their mechanism of action and clinical evidence

Glucose-lowering medications in the treatment of T2DM recommended by the ADA

Goal: achievement and maintenance of glycemic and weight management

Glycemic management			Achievement and maintenance of weight management goals	
Metformin	**or**	**Combination therapy**	General **lifestyle advice**: Medical nutrition therapy/eating patterns/physical activity	Intensive evidence-based structured weight management program
			Medication for weight loss	Metabolic surgery

Efficacy	Glycemic management	Achievement and maintenance of weight management goals
Very high	• Dulaglutide (high dose), Semaglutide, Trizepatide • Insulin • Combination oral, combination injectable (GLP-1RAs/Insulin)	• Semaglutide, Trizepatide
high	• GLP-1RA (not used previous), Metformin	• Dulaglutide, Liraglutide
Intermediate	• DDP-4i	• GLP-1RAs (not used previous), SGLT2i
Neutral		• DDP-4i, Metformin

If HbA1c above target:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

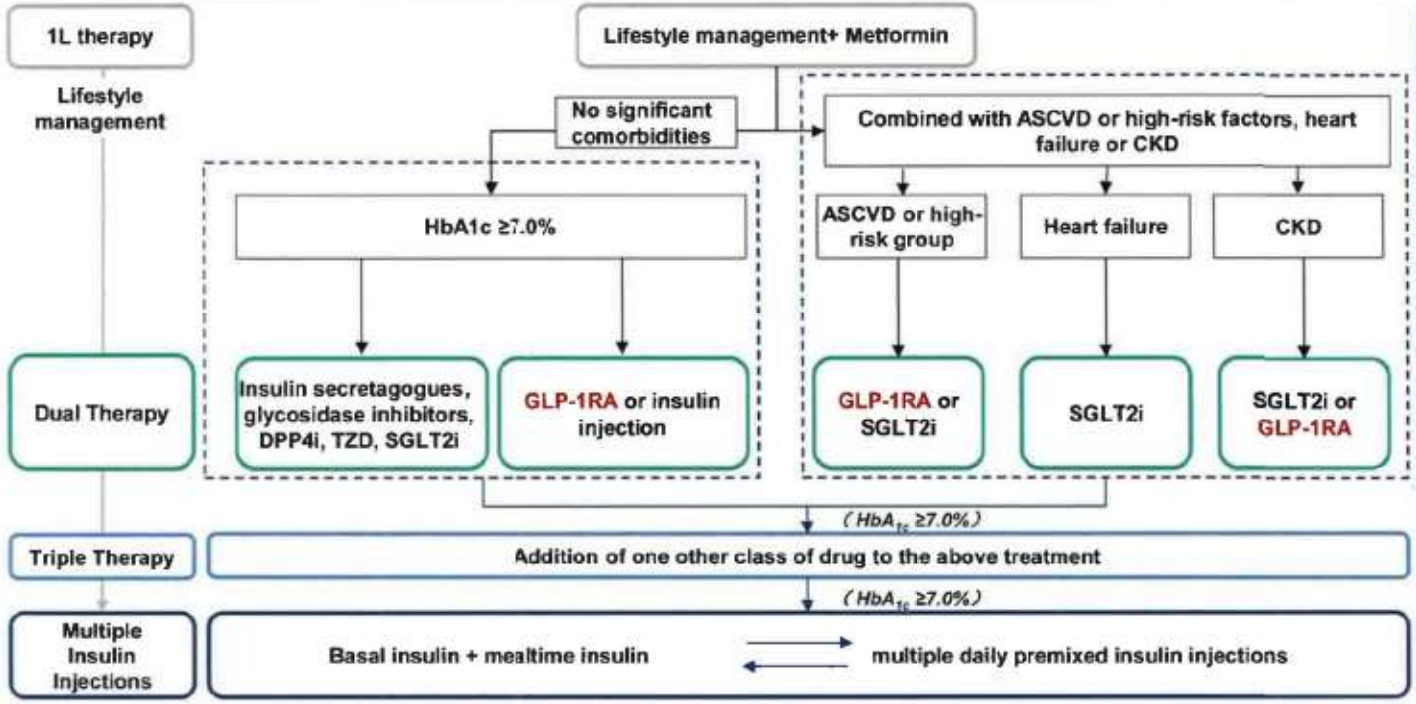
Note: CGM=continuous glucose monitoring, SDOH, social determinants of health

1. In January 2023, the FDA approved label update for Semaglutide, allowing its use as first-line option for adults with T2DM. This label update removes a previous limitation that stated the medication should not be used as initial therapy for treating patients with T2DM.

Source: American Diabetes Association; 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 comorbidties including ASVCD(or high-risk group), heart failure or CKD regardless HbA1c level in China;
- Some medications in the treatment of T2DM exhibit poor or sustainable therapeutic effects, significant fluctuations in blood sugar control, low achievement rates in meeting standards, and inadequate control of complications and comorbidities;
- 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 Guidelines for the Prevention and Treatment of Type 2 Diabetes (2020 edition); 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 (1/2)

T2DM drug market | Drug class

Drug Class	Mechanism of Action	Blood glucose control	Hypoglycemia risk	Weight loss	CV effects		Renal effects	Common adverse reaction
					MACE	HF	DKD	
GLP-1RA	• Activate GLP-1 receptor, increase insulin secretion, decrease glucagon secretion • Sometimes combined with agonists targeting GCGR and/or GIPR	• High to very high	• ×	• High	• Benefit	• Neutral	• Benefit on CVOT measured by Albuminuria	• GI effects
Metformin	• Decrease in hepatic glucose production; increase in muscle insulin sensitivity by activating AMPK	• High	• ×	• Neutral	• Potential benefit	• Neutral	• Neutral	• GI effects
TZDs	• Bind PPAR-γ, decrease insulin resistance and increase glucose utilization	• High	• ×	• Gain	• Potential benefit: • pioglitazone	• Increased risk	• Neutral	• Edema
Sulfonylureas	• Stimulates beta cell insulin secretion	• High	•	• Gain	• Neutral	• Neutral	• Neutral	• Hypoglycemia

Note: CV=cardiovascular, MACE=major adverse cardiovascular events, HF= heart failure

Source: American Diabetes Association; 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 (2/2)

Drug Class	Mechanism of Action	Blood glucose control	Hypoglycemia risk	Weight loss	CV effects		Renal effects	Common adverse reaction
					MACE	HF	DKD	
DPP-4i	• Prevent degradation of GLP-1	• Intermediate	• ×	• Neutral	• Neutral	• Neutral(potential risk: saxagliptin)	• Neutral	• N/A
SGLT2i	• Prevent glucose reabsorption and facilitate its excretion in urine by inhibiting SGLT-2	• Intermediate to high	• ×	• Interme diate	• Benefits shown by selected SGLT2is	• Benefits shown by selected SGLT2is	• Benefits shown by selected SGLT2is	• urinary tract infection
Insulin	• Stimulate glycogen synthesis, increase glycolysis and glucose transport, inhibit glycogenolysis, gluconeogenesis, and glucagon secretion	• High to very high		• Gain	• Neutral	• Neutral	• Neutral	• Hypoglycemia
GKA	• Acts as a glucose sensor, triggering counter regulatory responses following a change in glucose levels to aid restoration of normoglycemia.	• High	• ×	• Neutral	• N/A	• N/A	• Neutral	• N/A

Note: CV=cardiovascular, MACE=major adverse cardiovascular events, HF= heart failure, DKD=diabetic kidney disease

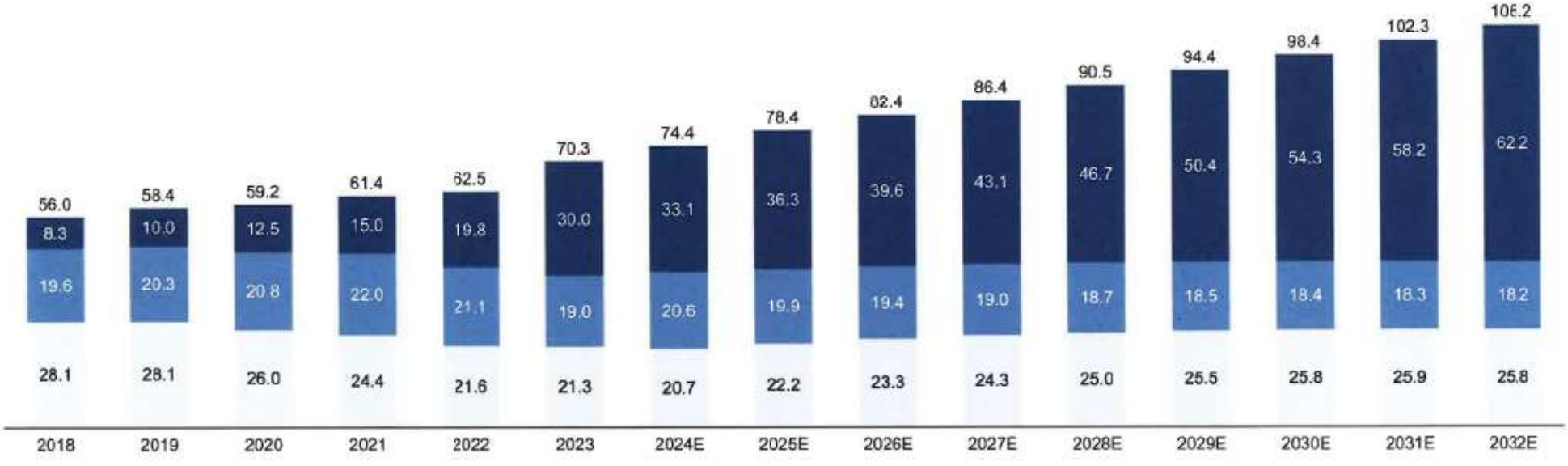
Source: American Diabetes Association; China Insights Consultancy

Global T2DM Drug Market Size, 2018-2032E

Global T2DM Drug Market Size, 2018-2032E

CAGR	2018-23	2023-32E
GLP-1 RA	29.3%	8.4%
Insulin	-0.6%	-0.5%
Others	-5.4%	2.2%
Total	4.7%	4.7%

USD billion



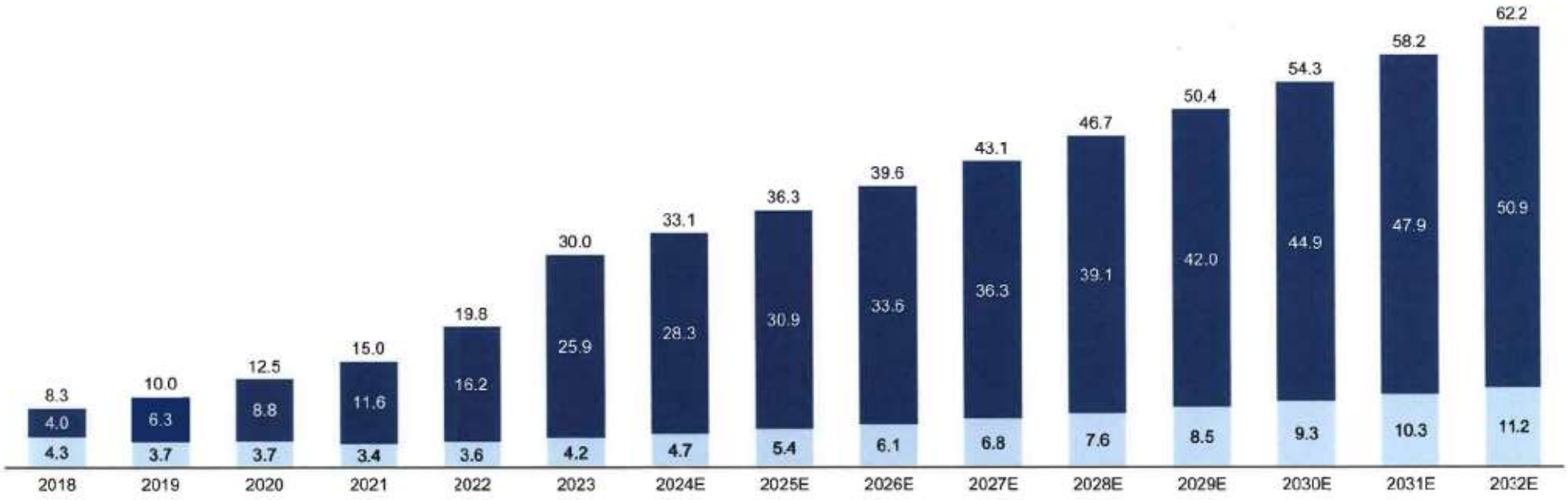
Source: China Insights Consultancy

Market size breakdown of long-acting vs. short-acting GLP-1RAs in the global T2DM GLP-1RA market

Global GLP-1RA T2DM market size breakdown, 2018-2032E

CAGR	2018-23	2023-32E
Long-acting GLP-1RA, T2DM	45.1%	7.8%
Short-acting GLP-1RA, T2DM	-0.7%	11.7%

USD billion



Source: China Insights Consultancy

China T2DM Drug Market Size, 2018-2032E

China T2DM Drug Market Size*, 2018-2032E

CAGR	2018-23	2023-32E
GLP-1 RA	64.1%	25.9%
Insulin	-5.8%	0.4%
Others	3.0%	-1.8%
Total	2.1%	7.5%

RMB billion

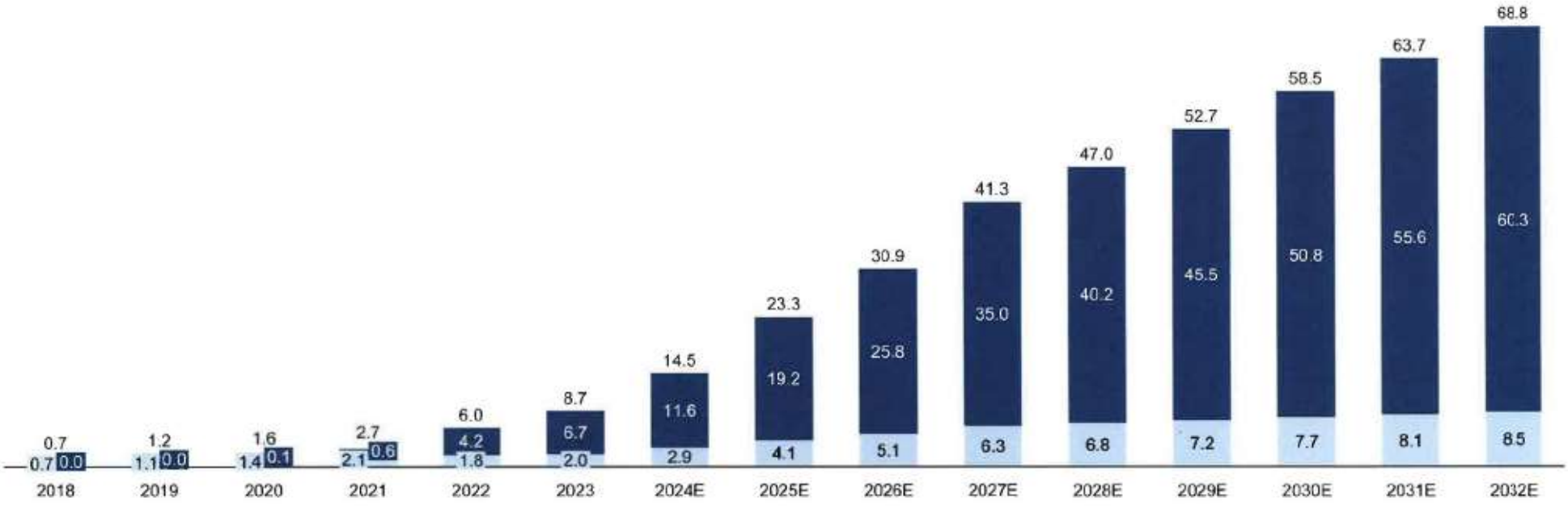
Source: China Insights Consultancy

Market size breakdown of long-acting vs. short-acting GLP-1RAs in the China T2DM GLP-1RA market

China GLP-1RA T2DM market size breakdown, 2018-2032E

CAGR	2018-23	2023-32E
Long-acting GLP-1RA, T2DM	292.1%*	27.6%
Short-acting GLP-1RA, T2DM	21.8%	17.7%

RMB billion



Note: The CAGR shown for long-acting GLP-1RA in treating T2DM in China represents CAGR in the period of 2019-2022E

Source: China Insights Consultancy

Key clinical comparisons of long-acting GLP1-RAs in treating T2DM patients, PB-119 shows comparable advantages in clinical efficacy and safety

Long-acting GLP-RAs | Comparison

	PB-119	Semaglutide	Polyethylene Glycol Loxenatide[2]	Exenatide-ER[3]	Dulaglutide[4]
Company	Opegbio	诺和诺德 NOVO NORDISK	豪森药业 HANSOH PHARMA	AstraZeneca 阿斯利康	Lilly
Dose Titration	×	✓	✓	×	✓
Production	• Chemosynthesis	• Biosynthesis+ Chemosynthesis	• Chemosynthesis	• Chemosynthesis	• Chemosynthesis
Cardiovascular benefit	✓	✓	×	×	✓
Trial	NCT03520972	NCT02054897	CTR20140233	NCT00308139	AWARD-11
Weight loss	• Among diabetic patients with BMI>32 kg/m^2, average weight reduction of [4.77kg][1]	• Average of [4.53kg] reduction for high dose group with BMI>32 kg/m^2	• Only effective in obese patients, **no proved evidence** in T2DM patients	• [2.6kg] of weight reduction after 26 weeks treatment duration	• [3.0kg] weight reduction for low dose group at 36 weeks
Gastrointestinal disorders (GI disorders)	• In clinical phase III study, GI AEs among PB119 group was [8.0%]	• In SUSTAIN 1 study, [20.3%] among low dose group, and [23.9%] among high dose group	• In the Shuai et al, 2021, [19.6%] GI disorders among PEG-Loxe group	• In the study of DURATION-2, the reported GI disorders was [26.4%]	• [13.4%] among low dose group, and [16.4%] for high dose group
Discontinuation due to AEs	• [2.2%] withdrawal rate due to AEs for all PB-119 groups in phase III	• [20%]	• [2.5%]	• [4.1%]	• [6.0%] for low dose, [8.5%] for high dose

PB-119 shows advantages in demonstrating rapid onset, significance and sustained efficacy, high achievement rates, and lipid reduction. And the product is characterized by excellent safety profile and an optimal benefit-risk ratio

1. Diabetologia. https://doi.org/10.1007/s00125-021-05392-9; 2. Sci Rep 13, 19041 (2023). https://doi.org/10.1038/s41598-023-46274-x. 3. Diabetes Metab Syndr Obes. 2014;7:229-239. Published 2014 Jun 24. doi:10.2147/DMSO.S35331, 4. Diabetes Care 2021;44:765–773 | https://doi.org/10.2337/dc20-1473

Source: ClinicalTrials.gov, China Insights Consultancy

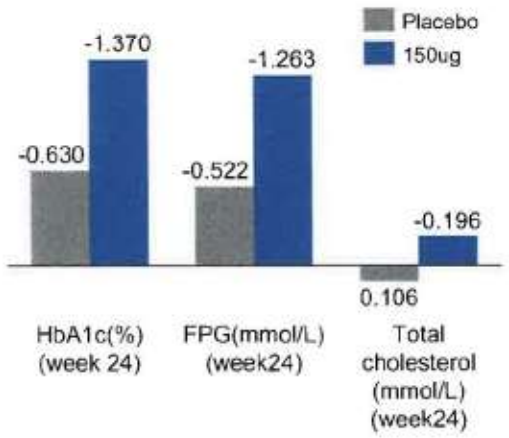
PB-119 shows significant and sustained clinical efficacy in blood glucose control, lipid reduction, weight loss, and blood pressure control

Introduction of PB119

- PB-119 is long-acting GLP-1RA developed by PegBio, which has completed multiple phase III clinical trials in China, and **got NDA approval** in 2023.09.
- The clinical trials of PB-119 for the treatment of T2DM were designed alone, and in combination with metformin, basal insulin, or SGLT-2 inhibitor, respectively.
- PB-119 is designed for a one-time dosage **without the need for dose adjustment**. Coupled with the utilization of an automated disposable pen injector, PB-119 offers the convenience of administration, presenting a substantial improvement in the quality of life for millions of diabetic patients.

Premium efficacy and systematic benefits for metabolic profile of PB119

Phase III clinical efficacy of PB-119 vs. placebo[1]



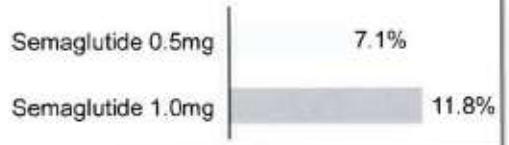
- During phase III of PB-119, the reduction in HbA1c from baseline was significantly better in the PB-119 group (-1.37%) than in placebo group (-0.63%)
- Following the extension period when all patients received PB-119, it was observed that the efficacy of the PB-119 group **remained consistently stable**. At week 52, the HbA1C showed further decrease compared to the baseline(-1.39%)
- The results also show **comprehensive benefits of PB-119** in blood pressure, lipid profile and body weight.

Comparison of PB-119 vs. Semaglutide in HbA1c reduction at week 4 in clinical phase III

- The phase III clinical results indicate that PB-119 exhibits **rapid efficacy**, with a reduction of 0.83% in HbA1c after 4 weeks of treatment, while semaglutide and dulaglutide showed a HbA1c decrease of around 0.5%

- The PB-119 group demonstrated a continued decrease in HbA1c levels from week 24 to week 52 in the Phase II study, while semaglutide group was observed HbA1c regained after week 24

Percentage of HbA1c regained after 24 weeks in SUSTAIN study[2]



1. *PB119301CSR, chart11-14*
2. *Lancet Diabetes Endocrinol.* 2017;5(4):251-260. doi:10.1016/S2213-8587(17)30013-X

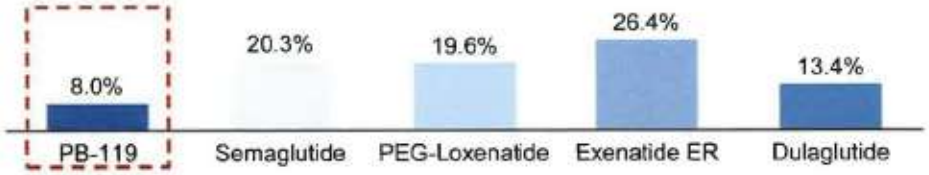
Source: Diabetologia, PegBio, NIH, China Insights Consultancy

Advantages of PB119: superior safety profile with mild adverse events, easy administration, and competitive advantage in costs

GLP-1 and GLP-1RAs | PB-119

Superior safety profile

Incidence of GI disorders among clinical studies



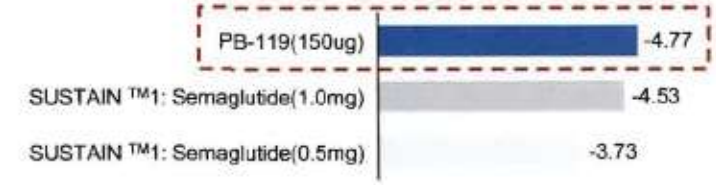
- PB-119 presents favorable safety profile after 24 weeks of treatments with only **mild GI effects**, and no incidence of drug-related SAEs.
- Phase II clinical study of PB119 was registered and conducted in the U.S., and there was **no racial differentiation** among the enrolled patients.
- The **treatment compliance** of 150ug PB-119 group was **90.5%** in the phase II.

Easy administration

- PB-119 utilizes a pre-filled, disposable device, which is easy to use. With a simple and convenient **one-step injection process** involving the removal of the protective cap, it proves especially significant for trial participants who are elderly and with disability.
- Additionally, it **eliminates the need for titration**, making it convenient for both doctor education and patient self-administration. Semaglutide treatment requires dose titration, starting from 0.25mg and increasing the dose every 4 weeks. To achieve a stable dose of 1.0mg, it takes a minimum of 12 weeks.

Excellent weight loss effect

PB-119 (Phase II: NCT03520972) has better effect in weight loss for T2DM patients with BMI≥32kg/m², kg



- For diabetic individuals who are overweight or obese, PB119 treatment can selectively reduce body weight, **with a more pronounced effect as the BMI baseline increases**.
- In diabetic patients with a BMI greater than 32 kg/m2, PB-119 treatment for 52 weeks resulted in **an average weight loss of 4.77kg**, this numerically greater to the absolute weight reduction observed in 30 weeks, in individuals with similar weight in studies of semaglutide in the SUSTAIN™1 study[1].

Comparative advantages in the production

Bio-fermentation	Chemosynthesis (PB-119)
• High initial investment • Relatively low purity of the products • Hard to achieve structural modifications	• Convenient modification with non-natural amino acids • **Competitive advantage in production cost**

1. *Lancet Diabetes Endocrinol.* 2017;5(4):251-260. doi:10.1016/S2213-8587(17)30013-X

Source: PegBio, NIH, literature review, China Insights Consultancy

Pipeline of GLP-1 Receptor Agonists for T2DM with Accepted NDA or Undergoing Phase III Clinical Trial in China

Pipeline of GLP-1 Receptor Agonists for T2DM with Accepted NDA or Undergoing Phase III Clinical Trial in China (1/2)

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
PB-119	GLP-1R	PegBio	T2DM	s.c.	NDA	2023/9/26	CTR20201492	NMPA
Liraglutide biosimilar	GLP-1R	Chenan; Paijin	T2DM	s.c.	NDA	2024/12/3	CTR20210173	NMPA
Ecnoglutide	GLP-1R	Hangzhou Sciwind	T2DM	s.c.	NDA	2024/11/23	CTR20223156	NMPA
Semaglutide	GLP-1R	Qilu Pharmaceutical	T2DM	s.c.	NDA	2024/9/15	CTR20230841	NMPA
Semaglutide biosimilar	GLP-1R	Lvzon Group	T2DM	s.c.	NDA	2024/6/16	CTR20222962	NMPA
CJC-1134-PC	GLP-1R	Hebei Changshan; Hbcsbio	T2DM	s.c.	NDA	2024/4/24	CTR20222496	NMPA
HDG1901	GLP-1R	Hangzhou Jiuyuan Gene Engineering	T2DM	s.c.	NDA	2024/4/3	CTR20232286	NMPA
Liraglutide biosimilar	GLP-1R	Zhuhai United	T2DM	s.c.	NDA	2023/8/22	CTR20200348	NMPA
GZR-18	GLP-1R	Ganlee	T2DM	s.c.	III	2024/12/26	CTR20244787	NMPA
Semaglutide	GLP-1R	Sinopep Allsino	T2DM	s.c.	III	2024/11/28	CTR20244501	NMPA
Noiiglutide	GLP-1R	Jiangsu Hengrui	T2DM	s.c.	III	2024/10/15	CTR20243773	NMPA
HRS-7535	GLP-1R	Shandong Suncadia	T2DM	p.o.	III	2024/9/13	CTR20243398	NMPA
Semaglutide biosimilar	GLP-1R	Zhuhai United	T2DM	s.c.	III	2024/9/10	CTR20243310	NMPA

Pipeline of GLP-1 Receptor Agonists for T2DM with Accepted NDA or Undergoing Phase III Clinical Trial in China

Pipeline of GLP-1 Receptor Agonists for T2DM with Accepted NDA or Undergoing Phase III Clinical Trial in China (2/2)

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
Semaglutide	GLP-1R	China Resources Double-Crane	T2DM	s.c.	III	2024/7/18	CTR20242569	NMPA
JY09	GLP-1R	Beijing Dongfang Biotech; Beijing Jingyitaixiang	T2DM	s.c.	III	2024/4/17	CTR20240355	NMPA
TG103	GLP-1R	CSPC Baike (Shandong) Biopharmaceutical	T2DM	s.c.	III	2024/2/26	CTR20240429	NMPA
Orforglipron	GLP-1R	Eli Lilly	T2DM	p.o.	III	2023/11/2	CTR20233528	NMPA
Recombinant GLP-1RA	GLP-1R	Beijing Lepu	T2DM	s.c.	III	2023/1/29	CTR20230029	NMPA
GMA102	GLP-1R	Hongyun Huaning	T2DM	s.c.	III	2022/10/11	CTR20222558	NMPA
rExenatide-4	GLP-1R	CSPC Zhongqi	T2DM	s.c.	III	2017/11/27	CTR20170495	NMPA

Note:
1. denotes the date when CDE announces it receives the NDA for applicable pipelines
2. denotes the Phase III trial number

Source: CDE, China Insights Consultancy

Pipeline of Candidates for T2DM Undergoing Phase III Clinical Trial in United States

Pipeline of Candidates for T2DM Undergoing Phase III Clinical Trial in United Sates

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
CagriSema	AMY3; GLP-1R	Novo Nordisk	T2DM	s.c.	III	2024/3/21	NCT06323174	FDA
CMG190303	SGLT2; HMGCR	Cmg Pharma	T2DM	N/A	III	2025/1/13	NCT06772168	FDA
GZR-18	GLP-1R	Ganlee	T2DM	s.c.	III	2025/1/15	NCT06777238	FDA
HGD1901	GLP-1R	Hangzhou Zhongmei Huadong	T2DM	s.c.	III	2024/12/10	NCT06739044	FDA
BGM-0504	GIPR; GLP-1R	BrightGene	T2DM	s.c.	III	2024/12/4	NCT06716203	FDA
HRS-7535	GLP-1R	Shandong Suncadia	T2DM	p.o.	III	2024/11/4	NCT06672172	FDA
HRS-9531	GIPR; GLP-1R	Shandong Suncadia	T2DM	s.c.	III	2024/10/18	NCT06649344	FDA
Noiiglutide	GLP-1R	Jiangsu Hengrui	T2DM	s.c.	III	2024/10/21	NCT06649773	FDA
Insulin Degludec/Liraglutide	INSR; GLP-1R	Tonghua Dongbao	T2DM	s.c.	III	2024/8/19	NCT06559722	FDA
IcoSema	INSR; GLP1R	Novo Nordisk	T2DM	s.c.	III	2024/2/21	NCT06269107	FDA
Retatrutide	GIPR; GLP-1R; GCGR	Eli Lilly	T2DM	s.c.	III	2024/2/15	NCT06260722	FDA
TG103	GLP-1R	CSPC Baike (Shandong) Biopharmaceutical	T2DM	s.c.	III	2024/2/14	NCT06258148	FDA
Survodutide	GLP-1R; GCGR	Boehringer Ingelheim	T2DM	s.c.	III	2023/10/4	NCT06066528	FDA
Orforglipron	GLP-1R	Eli Lilly	T2DM	p.o.	III	2023/8/24	NCT06010004	FDA
MSDC-0602K	MPC	Cirius Therapeutics Inc	T2DM	p.o.	III	2019/5/31	NCT03970031	FDA

Source: ClinicalTrials.gov, China Insights Consultancy

Pipeline of Candidates for T2DM with Accepted NDA in China

Pipeline of Candidates for T2DM with Accepted NDA in China

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date[2]	Competent authurity
PB-119	GLP-1R	PegBio	T2DM	s.c.	NDA	2023/9/26	NMPA
IcoSema	INSR; GLP-1R	Novo Nordisk	T2DM	s.c.	NDA	2024/12/7	NMPA
Liraglutide biosimilar	GLP-1R	Chenan; Paijin	T2DM	s.c.	NDA	2024/12/3	NMPA
Ecnoglutide	GLP-1R	Hangzhou Sciwind	T2DM	s.c.	NDA	2024/11/23	NMPA
Semaglutide	GLP-1R	Qilu Pharmaceutical	T2DM	s.c.	NDA	2024/9/15	NMPA
IBI362	GCGR; GLP-1R	Innovent	T2DM	s.c.	NDA	2024/8/1	NMPA
Semaglutide[1]	GLP-1R	Livzon Group	T2DM	s.c.	NDA	2024/6/16	NMPA
CJC-1134-PC	GLP-1R	Hebei Changshan; Hbcsbio	T2DM	s.c.	NDA	2024/4/24	NMPA
HDG1901[1]	GLP-1R	Hangzhou Jiuyuan Gene Engineering	T2DM	s.c.	NDA	2024/4/3	NMPA
HEC-44616	SGLT2	HEC Pharm	T2DM	p.o.	NDA	2024/1/11	NMPA
Brenzavvy	SGLT2	Newsoara Biopharma; Piramal Healthcare; TheracosBio	T2DM	p.o.	NDA	2024/1/4	NMPA
HR20031[4]	DPP-4; PRKAB-1; SGLT-2	Shengdi Medical	T2DM	p.o.	NDA	2023/11/11	NMPA
Liraglutide[1]	GLP-1R	Zhuhai United	T2DM	s.c.	NDA	2023/8/22	NMPA
ORMD-0801	INSR[3]	Oramed Ltd	T2DM	p.o.	NDA	2023/4/25	NMPA

Notes:

1. *Biosimilar or generic candidates*
2. *denotes the date when CDE announces it receives the NDA*
3. *INSR = insulin receptor*
4. *compound formulation of SGLT-2i, DPP-4i and metformin*

Source: CDE, China Insights Consultancy

Growth drivers and future trends (1/3)

- T2DM drug market drives by growing prevalence, favorable policies towards chronic disease management, and increasing availability of innovative medications

Growth drivers & Future trends

Growing prevalence of T2DM in China & Unmet clinical needs in rural regions

- Patients from rural regions in China face more challenges in terms of access to healthcare facilities, limited preventive healthcare services such as routine screenings and early detection programs, which lead to a lower control rate of blood glucose and **increased burden of T2DM**.
- Compared to urban residents, it is expected that the potential reduction in mortality and the improvement in quality-adjusted life years **for rural residents, especially females, will be greater**.
- If 70% of diabetes patients achieve optimal control, the number of deaths before the age of 70 is expected to **decrease by 7.1%** over the next 10 years, leading to a direct **reduction of 14.9% in healthcare costs**.

Optimal control rate of blood glucose and blood pressure in China, rural vs. city[1]

Favorable policies towards chronic disease management

- **The Healthy China Initiative (2019–2030)** serves as a strategic blueprint for fostering a healthier China and represents an innovative public policy initiative. Within this comprehensive framework, the Diabetes Prevention and Control Action stands out as one of the key measures among the four actions targeting the prevention and control of chronic and noncommunicable diseases outlined in the Healthy China Initiative (2019–2030).
- The **"Medium-to-Long Term Plan of China for the Prevention and Treatment of Chronic Diseases (2017–2025)"** emphasizing the promotion of health education to boost national healthy quality, enforcing early diagnosis and cooperation between medical treatment and prevention to achieve comprehensive healthcare management.

1. Quan, Jianchao et al. The Lancet Regional Health -Western Pacific2023;33: 100690

Source: Literature review; China Insights Consultancy

Growth drivers and future trends (2/3)

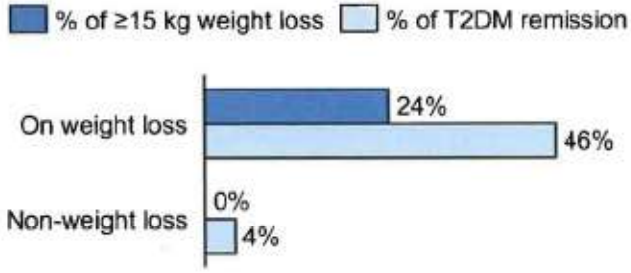
- T2DM drug market drives by growing prevalence, favorable policies towards chronic disease management, and increasing availability of innovative medications

Growth drivers & Future trends

Comprehensive benefits of T2DM management paradigm

- 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



Improved patient compliance and efficacy resilience

- T2DM is a major chronic disease that requires consistent medical attention and long-term or even lifetime disease management. Current drugs in T2DM treatment paradigm faces challenges such as **loss of efficacy over time that leads to lower disease control rate** and **suboptimal long-term patient adherence due to adverse effects**. T2DM management paradigm awaits a new modality that could address these unmet clinical needs and help achieve better clinical outcome.
- As innovative drugs are being developed, drugs that could simultaneously provide superior safety profile and long-lasting blood sugar control would improve patient compliance and efficacy resilience and drive substantial growth of the T2DM drug market.

Source: Literature review; China Insights Consultancy

Growth drivers and future trends (3/3)

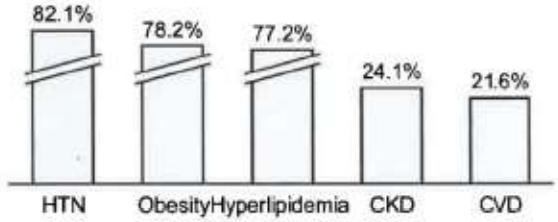
- T2DM drugs market can drive by personalized treatment strategy, benefits of T2DM management paradigm, and restoration of pancreatic islet function

Growth drivers & 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.

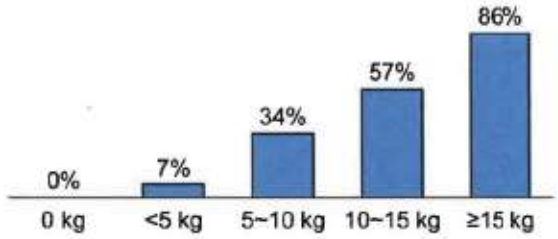
Common co-prevalence of complications in T2DM patients



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: Literature review; China Insights Consultancy

Table of contents

Introduction to obesity and its pathogenesis

- 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/m²)		Waist Circumference (cm)	
	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
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			Female: ≥80.0	Female: ≥85.0

Risk factors

Body weight is determined by energy intake and expenditure and is influenced by genetic, environmental and psychosocial factors, etc.

- **Genetics:** overweight and obesity can run in families
- **Environmental factors:** social factors such as having a low socioeconomic status, lack of physical exercise facilities, 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 has multiple causes. Significant changes in dietary and 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

Serious chronic disease are associated with overweight and obesity, such as CVDs, diabetes, musculoskeletal disorders, etc.

- **Increased risk of developing CVD, particularly Hyperlipidemia** and heart failure
- Lead to the development of **prediabetes and T2DM**
- Obesity is the major risk factor for **obstructive sleep apnoea**
- **Cancer**, like endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, etc.
- **Osteoarthritis**, which is a disabling degenerative disease of the joints

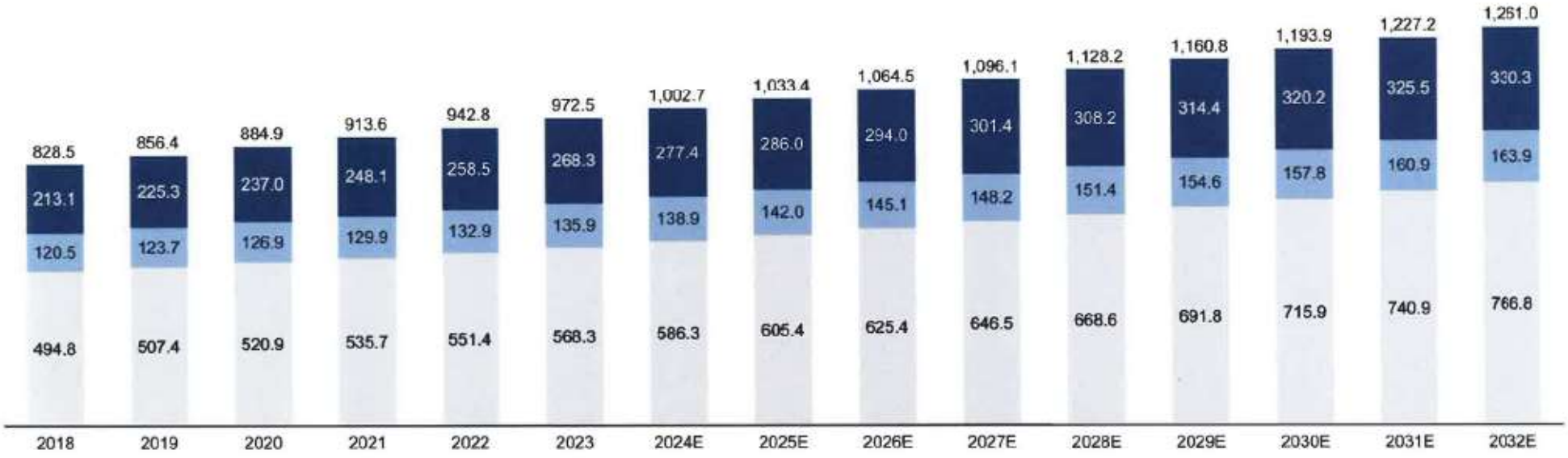
Source: WHO, National Institutes of Health, IDF, China Diabetes Society, China Insights Consultancy

Global prevalence of obesity with breakdown of key geographies, 2018-2032E

Global prevalence of obesity, 2018-2032E

million patients

CAGR	2018-23	2023-32E
China	4.7%	2.3%
the US	2.4%	2.1%
ROW	2.8%	3.4%
Total	3.3%	2.9%



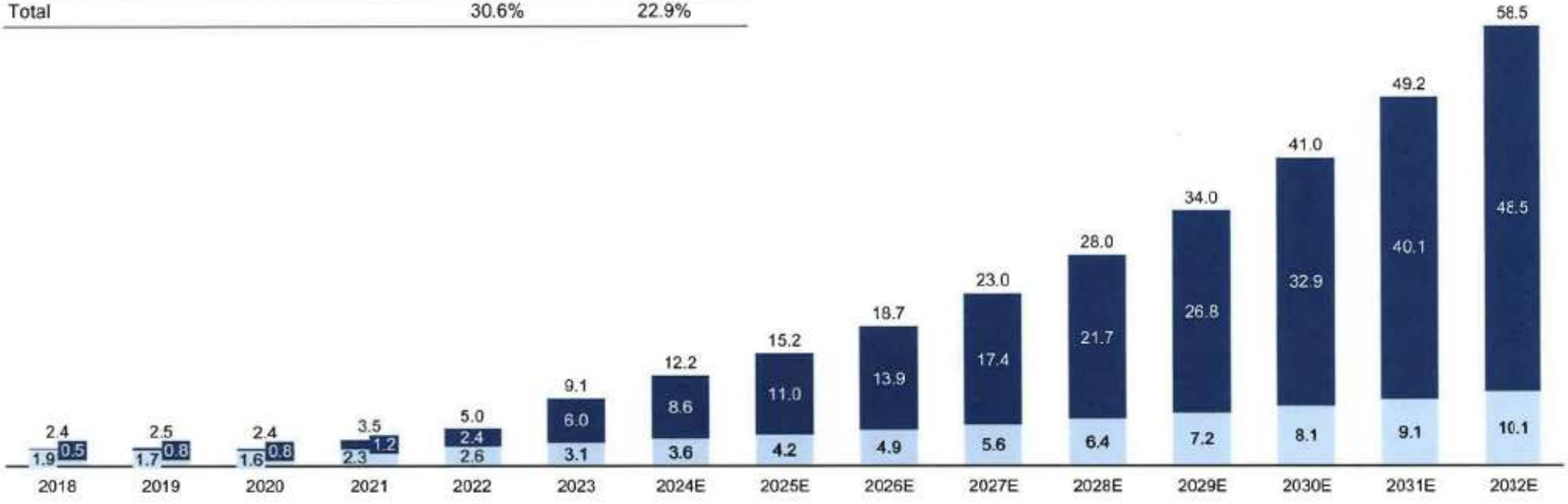
Source: World Obesity Atlas, WHO, China Insights Consultancy

Global obesity drug market size, 2018-2032E

Global Obesity Drug Market Size, 2018-2032E

CAGR	2018-23	2023-32E
Global GLP-1RA, Obesity	64.4%	26.0%
Global non-GLP-1RA, Obesity	10.8%	14.0%
Total	30.6%	22.9%

USD billion



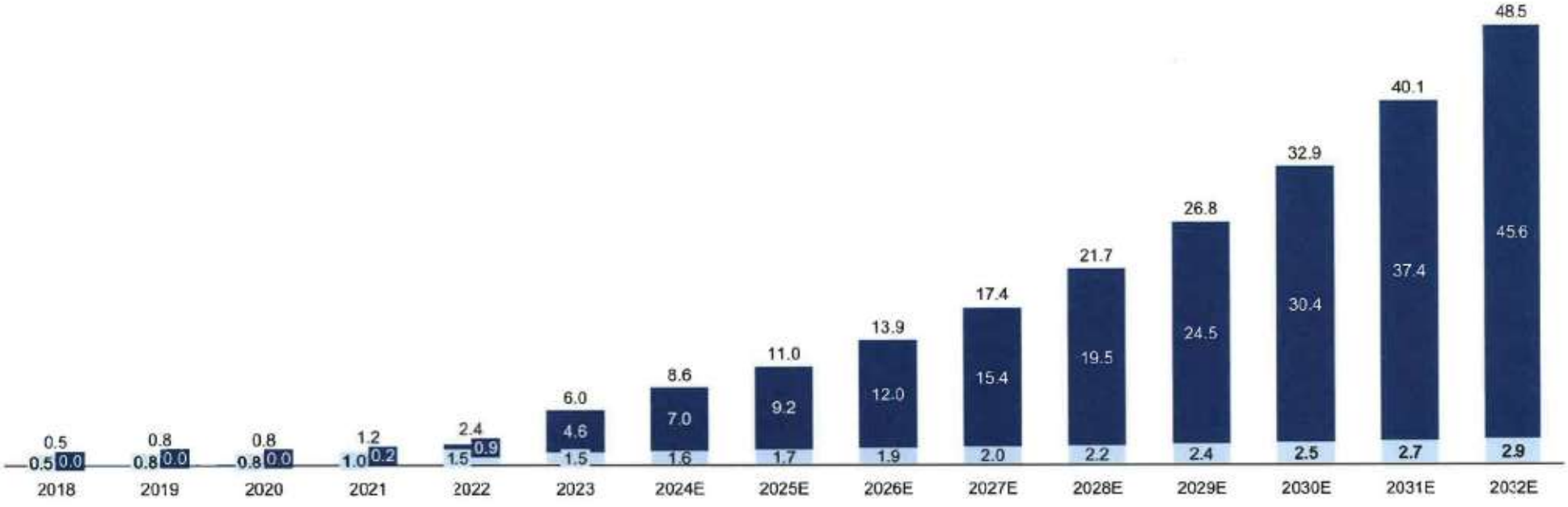
Source: FDA, periodic reports released by public companies, China Insights Consultanc

Market size breakdown of long-acting vs. short-acting GLP-1RAs in the global obesity GLP-1RA market

Global GLP-1RA obesity market size breakdown, 2018-2032E

CAGR	2018-23	2023-32E
Long-acting GLP-1RA, obesity	N/A	29.0%
Short-acting GLP-1RA, obesity	21.6%	7.8%

USD billion



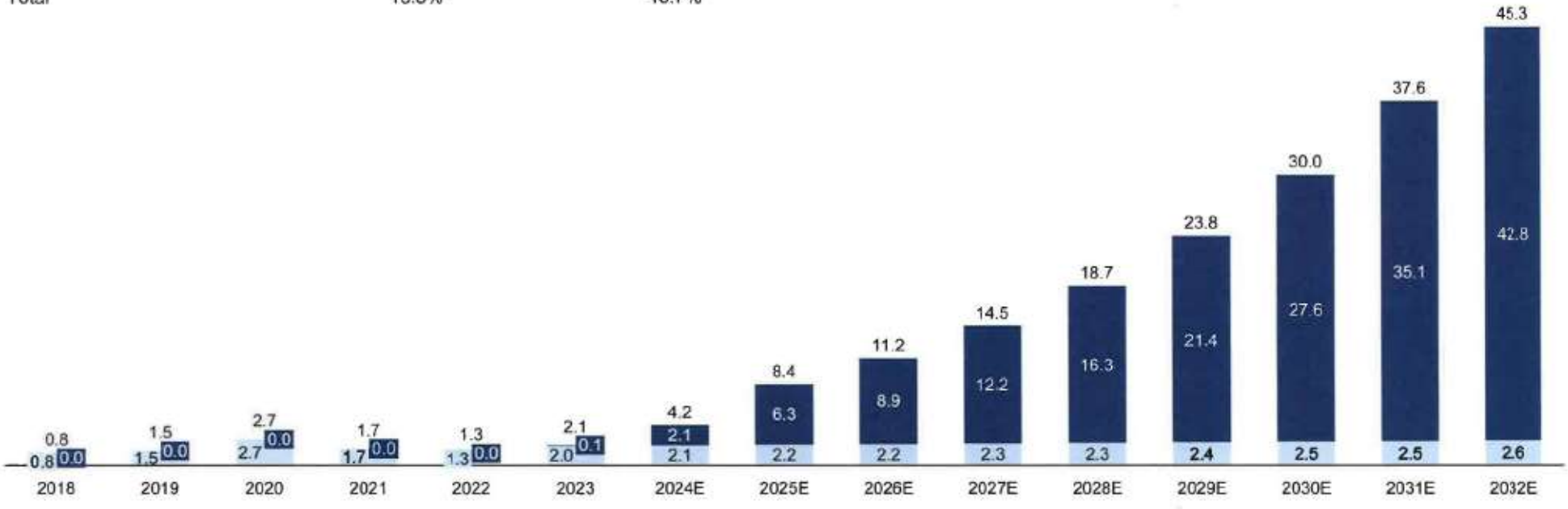
Source: FDA, ClinicalTrials.gov, periodic reports released by public companies, China Insights Consultanc

China obesity drug market size, 2018-2032E

China Obesity Drug Market Size, 2018-2032E

CAGR	2018-23	2023-32E
China Obesity GLP-1RA market size	NA	111.7%
China Obesity non GLP-1RA market size	13.5%	2.6%
Total	13.5%	43.7%

RMB billion



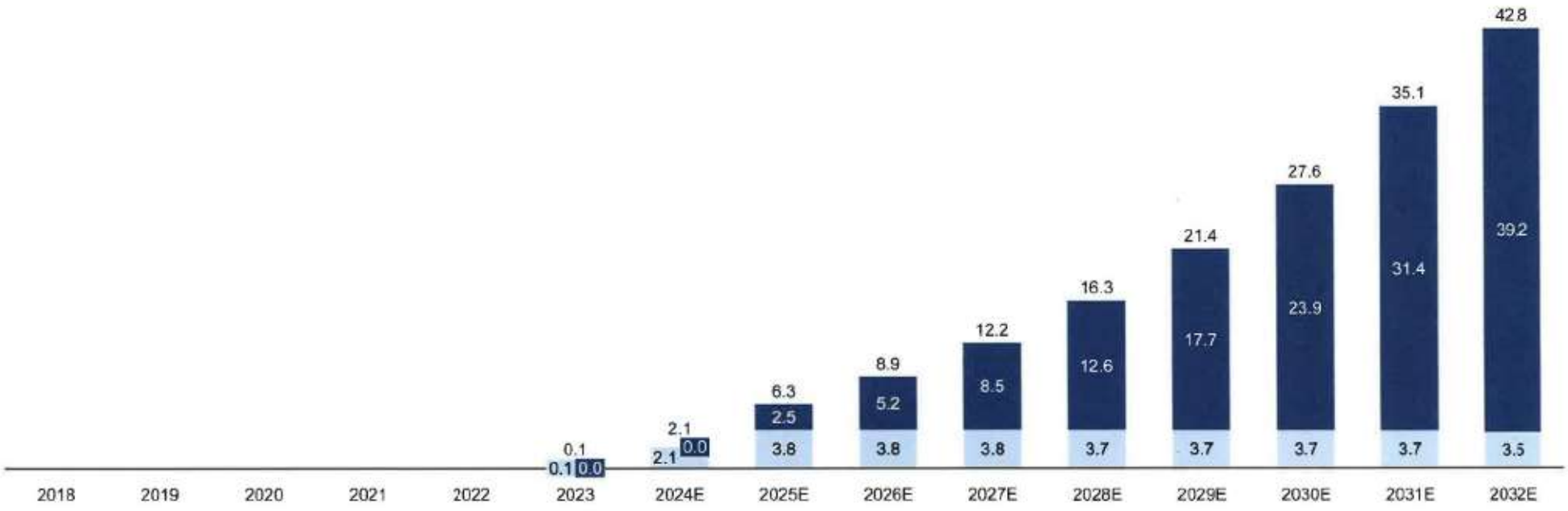
Source: NMPA, periodic reports released by public companies, China Insights Consultanc

Market size breakdown of long-acting vs. short-acting GLP-1RAs in China obesity GLP-1RA market

Market size of obesity treatment with GLP-1 receptor agonists in China, 2018-2032E

CAGR	2023-32E
Long-acting GLP-1RA, obesity	4[illegible].0%*
Short-acting GLP-1RA, obesity	60.4%

RMB billion



Note: The CAGR shown for long-acting GLP-1RA in treating Obesity in China represents CAGR in the period of 2024-2032E

Source: NMPA, CDE, periodic reports released by public companies, China Insights Consultanc

Treatment flow of obesity in recommended by AACE and ACE

Treatment flow of obesity in recommended by AACE and ACE

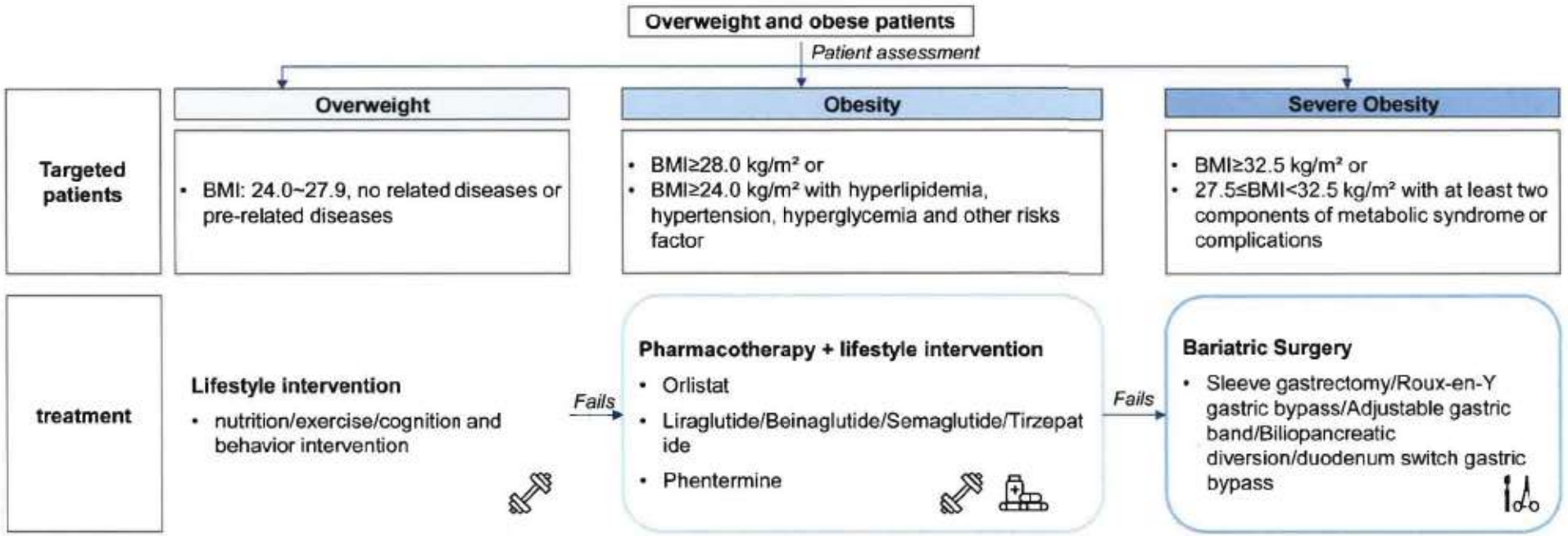
Diagnosis		Staging and treatment	
BMI, kg/m2 Anthropometric component	**Clinical component**	**Disease stage**	**Suggested therapy (based on clinical judgement)**
<25 <23 in patients of certain ethnicities; waist circumference below regional/ethic cutoffs	Evaluate for presence or absence of adiposity-related complications and severity of complication • Metabolic syndrome • Prediabetes • Type 2 diabetes • Dyslipidemia • Hypertension • Cardiovascular disease • Nonalcoholic fatty liver disease • Polycystic ovary syndrome • Infertility (women) • Hypogonadism (men) • Obstructive sleep apnea • Asthma/reactive airway disease • Osteoarthritis • Urinary stress incontinence • Gastroesophageal reflux disease • Mental depression	Normal weight (no obesity)	• **Healthy lifestyle:** Healthy meal plan/physical activity
25-29.9 23-24.9 in patients of certain ethnicities		Overweight stage 0 (no complications)	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/ physical activity/behavioral interventions
≥30 ≥25 in patients of certain ethnicities		Obesity stage 0 (no complications)	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/ physical activity/behavioral interventions • **Anti-obesity medications:** Consider if lifestyle therapy fails to prevent progressive weight gain(BMI≥27)
≥25 ≥23 in patients of certain ethnicities		Obesity stage 1 (1 or more mild to moderate complications)	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/ physical activity/behavioral interventions • **Anti-obesity medications:** Consider if lifestyle therapy fails to achieve therapeutic target or initiate concurrently with lifestyle therapy(BMI≥27)
≥25 ≥23 in patients of certain ethnicities		Obesity stage 2 (at least 2 severe complications)	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/ physical activity/behavioral interventions • **Anti-obesity medications:** Initiate concurrently with lifestyle therapy(BMI≥27); consider bariatric surgery(BMI≥35)

Globally, the treatment regimen for obesity is generally consistent across international guidelines. The American Association of Clinical Endocrinology ("AACE") and American College of Endocrinology ("ACE") separately recommend a treatment framework that mainly consist of lifestyle intervention, maintenance medication, and surgical intervention, depending on the disease stage. Before the commercialization of GLP-1 receptor agonists, there were several traditional medications approved for the treatment of obesity. However, such medications are often limited in efficacy with potential severe adverse effects. The development of GLP-1 receptor agonists and the increasing number of such approved drugs has been shifting the standard of care for obesity patients globally and in China. The above table sets forth the treatment regimen according to AACE/ACE treatment framework.

Source: AACE, ACE; China Insights Consultancy

Treatment pathway for obesity in China

Treatment flow of obesity in China



Source: Chinese Diabetes Society; Chinese Journal of Epidemiology; China Insights Consultancy

Commonly used anti-obesity medications

GLP-1 receptor agonists have demonstrated significant efficacy in reducing body weight. Also importantly, approved GLP-1 receptor agonists are generally well tolerated and do not generally do not result in potentially severe side effects observed for other types of obesity treatment, such as dizziness, raised blood pressure or insomnia. Certain traditional treatment options for obesity also lead to complications such as unstable hormone levels and other metabolic disorders. The weight-controlling effect is often unsustainable as well and is prone to relapses. The following table summarizes the effects and limitations of traditional treatment options for obesity.

Drug	Mechanism	Effects on weight	Adverse effects	Status	Comments
Medications for short-term weight management or selected medications used off-label to promote weight loss					
Phentermine[a]	Sympathomimetic amine (appetite suppressant)	3.6 kg placebo-subtracted weight loss in studies ranging from 2-24 weeks	Insomnia, tremor, ↑ blood pressure and pulse rate, headache, palpitation, constipation	Currently approved drug for short-term weight management (≤ 12 weeks) in U.S., Korea and some countries, withdrawn 2000 in U.K.	Diffusion controlled release preparation is available
Diethylpropion[a]	As above	3.0 kg placebo-subtracted weight loss in studies ranging from 6-52 weeks	As above	Currently approved drug for short-term weight management	
Zonisamide[a]	Anti-convulsant agent	5.0% placebo-subtracted weight loss at 12 weeks	↑ Nervousness, sweating, tremors, gastrointestinal adverse effects, hypersomnia, fatigue, and insomnia	Used off-label	No enough clinical trials; should not exceed 400 mg/day
Topiramate[a]	As above	6.5% placebo-subtracted weight loss at 24 weeks	Paresthesia, dizziness, altered taste, fatigue, memory impairment, somnolence, anorexia, and abdominal pain	Used off-label	Associated with teratogenicity; should not exceed 400 mg/day
Medication for long-term weight management					
Orlistat[a]	Pancreatic lipase inhibitor	2.9 kg placebo-subtracted weight loss at 1 year	Abdominal pain, bloating, flatulence, oily stools, diarrhea, ↓ absorption of fat soluble vitamins	Only approved drug for long-term weight management	Available over the counter in several countries

Overweight/obesity Approved drugs in U.S.

- Currently, six overweight/obesity drugs have been approved by FDA

Approved overweight/obesity drug by FDA in U.S., As of LPD

Drug Name	MoA	Company	Approval	Indication	Administration	Dosage Frequency	Annual Cost	Pros	Cons
Orlistat	Lipase Inhibitor	Roche	04/1999	Obesity	p.o.	TID.	$1,095	• Oral formulation can increase compliance • Effective weight loss	• Has side-effects that affect quality of life, such as faecal incontinence • Lack of fat-soluble vitamins
Phentermine/ Topiramate	NE/GABA	Vivus	07/2012	Overweight/ obesity	p.o.	QD.	$1,615	• Good patient compliance • Effective weight loss	• Bothersome side effect, such as dry mouth and a tingling sensation in hands
Naltrexone/ Bupropion	Opioid antagonist	Orexigen	09/2014	Overweight/ obesity	p.o.	BID.	$3,234	• Good patient compliance • Moderate weight loss	• Carry FDA black box warning about suicidal thinking
Liraglutide	GLP-1	Novo Nordisk	12/2014	Overweight/ obesity	s.c.	QD.	$3,276	• Simultaneously controls blood glucose • Effective weight loss	• Short-acting • Higher injection frequency • Increase the risk of GI adverse effect
Semaglutide	GLP-1	Novo Nordisk	06/2021	T2DM; Overweight/ obesity	s.c.	QW.	$3,527	• Long acting • Simultaneously controls blood glucose • Marked weight loss	• Increase the risk of GI adverse effect
Tirzepatide	GIP/GLP-1	Eli Lilly	11/2023	T2DM; Overweight/ obesity	s.c.	QW.	$12,276	• Long acting • Simultaneously controls blood glucose • Significant weight loss	• Increase the risk of GI adverse effect • Withdraw drug lead to weight rebound
Setmelanotide	MC4R	Rhythm Pharmaceuticals	11/2020	Rare genetic diseases of obesity	s.c.	QD.	$390,559	• Applicable to patients with specific types of rare obesity disorders	• Skin hyperpigmentation • Increase the risk of GI adverse effect • Depression and suicidal ideation

Notes: Approval refers to the time when the weight loss indication was granted; GABA = gamma-aminobutyric acid; GIP = Gastric inhibitory polypeptide; NE = norepinephrine; Rare genetic diseases of obesity refers to POMC, PCSK1, or LEPR deficiency

Source: The Lancet; FDA; China Insights Consultancy

Overweight/obesity Approved drugs in China

- Currently, only three overweight/obesity drugs have been approved in the domestic market

Approved overweight/obesity drug by NMPA in China, As of LPD (1/2)

Drug Name	MoA	Company	Approval	Indication	Administration	Dosage Frequency	Unit Price	Annual Cost	NRDL	Pros	Cons
Orlistat[1]	Lipase Inhibitor	Roche	03/2001	Obesity/ overweight	p.o.	TID.	¥ 598 (0.12g*42)	¥ 15,548[2]	Not covered[5]	• Oral intake is more convenient	• Has socially inconvenient side-effects, such as faecal incontinence
Liraglutide[8]	GLP-1	Hangzhou Zhongmei Huadong	07/2023	T2DM; Obesity/ Overweight[6]	s.c.	QD.	¥ 300 (18mg:3ml)	¥ 18,200[3]	Not covered[5]	• Effective weight loss	• Short-acting • Higher injection frequency • expensive • Increase the risk of GI adverse effect
Beinaglutide	GLP-1	Shanghai Benemae	07/2023	Obesity/ Overweight[7]	s.c.	TID.	¥ 216 (4.2mg:2.1ml)	¥ 11,232[4]	Not covered[5]	• Modest weight loss	• Short-acting • Higher injection frequency • expensive
Mazindol	blocks dopamine & norepinephrine reuptake	Desano	07/2020	Simple obesity	p.o.	QD.	N/A	N/A	Not covered[5]	• Direct suppression of appetite	• Rebound weight gain discontinuation of mazindol • significant side effects
Semaglutide	GLP-1	Novo Nordisk	06/2024	Obesity/ Overweight	s.c.	QW.	N/A	N/A	Not covered[5]	• Long acting • Simultaneously controls blood glucose • Marked weight loss	• Increase the risk of GI adverse effect
Tirzepatide	GLP-1R; GIPR	Eli Lily	07/2024	Obesity/ Overweight	s.c.	QW.	N/A	N/A	Not covered[5]	• Long acting • Effective weight • loss	• Expensive

Overweight/obesity Approved drugs in China

- Currently, only three overweight/obesity drugs have been approved in the domestic market

Approved overweight/obesity drug by NMPA in China, As of LPD (2/2)

Notes:

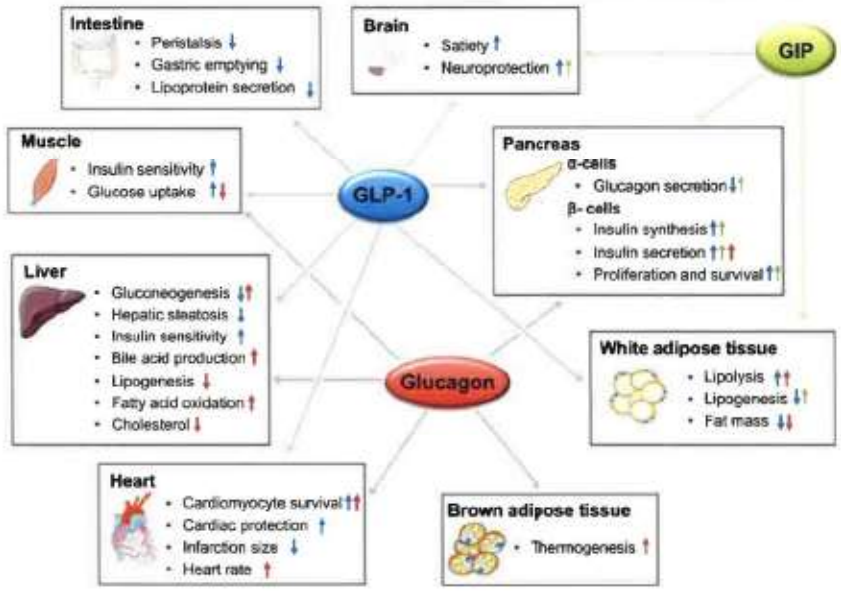
1. The originator, Orlistat, was developed by Roche and named Xenical. However, due to a business adjustment by Roche, Xenical began to gradually exit the Chinese market in 2008. In 2010, Zein Biotechnology launched a generic version of the Orlistat capsule, and several branded generic products have been approved in the Chinese market since then. As of LPD, 2023, there are 21 generic Orlistat products approved in China
2. 120mg TID. dosage based on the Summary Review of Orlistat (NDA 020766), expected treatment duration is 52 weeks
3. 3.0mg daily dosage based on clinical data (NCT01272219), expected treatment duration is 52 weeks
4. 0.2mg TID. dosage based on clinical data (CTR20190403), expected treatment duration is 52 weeks
5. Only T2DM indications are covered by medical insurance. obesity/overweight indications are not covered by medical insurance
6. Indications and usage on labeling: adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m2 or greater (obesity), or 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)
7. Indications and usage on labeling: Indicated for weight management in adult patients with a BMI ≥ 28kg/m2, or BMI ≥ 24kg/m2 and at least one weight associated metabolic disorders (eg, hypertension, hypertension, dyslipidemia, fatty liver, obstructive sleep apnea syndrome)
8. Generic or biosimilar product.
9. There is one GLP-1/GIP dual receptor agonist, Tirzepatide, that has been approved by the NMPA for the treatment of T2DM or obesity indications in China.

Sources: Advances in Therapy, Chinese Medical Frontier Journal, Chinese Journal of Health Management, NMPA, China Insights Consultancy

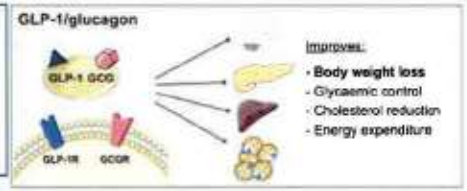
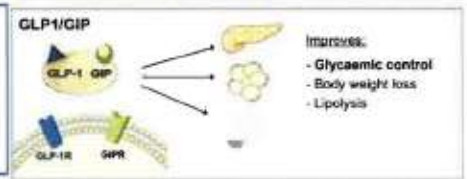
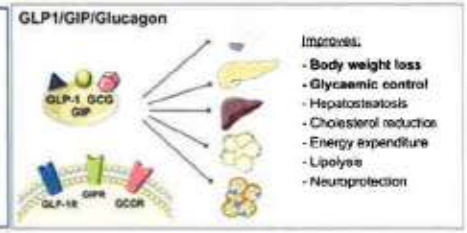
Introduction to GLP-1 class MoA

- **GLP-1 is produced from the proglucagon gene in L cells** of the small intestine and exerts its main effect by **stimulating glucose-dependent insulin** release from the pancreatic islets
- GIP is another member of the glucagon peptide family and **stimulates the release of glucagon under conditions of hypoglycaemia**
- **GCG is secreted by pancreatic α cells when blood glucose levels are low and has ability to increase energy expenditure**

Effects of GLP-1, GCG & GIP in key metabolic tissues



Effects, working principles and target tissues of dual agonists & triple agonist

Dual agonist	• Concurrent activation of GLP-1 and GCG receptors • Combine the anorectic and energy expenditure effect of GLP-1 and GCG	
	• Concurrent activation of GLP-1 and GIP • Combine anorectic and insulinotropic activities of GLP-1 and GIP	
Triple agonist	• Concurrent activation of GLP-1, GIP and GCG receptor • Combine anorectic and insulinotropic activities of GLP-1 and GIP with engery expenditure effect of GCG	

Source: Journal of Internal Medicine, China Insights Consultancy

Clinical results of GLP-1 target drugs

- Although GLP-1 RAs have reshaped the treatment of overweight/obesity, there is an unmet need to improve efficacy and reduce adverse effect of current GLP-1 therapy

Indirect comparison of current overweight/obesity medications

- GLP-1 RAs showed **strong efficacy** compared with conventional overweight/obesity treatment, especially in long-acting GLP-1 RAs

GLP-1 RAs

- **Higher discontinuation rate** in GLP-1 RAs were observed and were driven by GI tract events

Trial	European Multicenter Study		ChiCTR1900023428[1]		SCALE		STEP 1		SURMOUNT-3	
										
	Orlistat (120mg)		**Beinaglutide (0.2mg)**		**Liraglutide (3mg)**		**Semaglutide (2.4mg)**		**Tirzepatide (10/15 mg)**	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Trial duration (weeks)	52		16		56		68		72	
Dose	TID.		TID.		QD.		QW.		QW.	
Mean BMI (kg/m²)	28-47		28/24-27.9		≥30/≥27		≥30/≥27		≥30/≥27	
sAE (%)	7.4%	7.0%	2.8%	0.0%	6.2%	5.0%	9.8%	6.4%	5.9%	4.8%
Discontinuation rates due to AE (%)	3.5%	0.6%	5.9%	0.7%	9.9%	3.8%	7.0%	3.1%	10.5%	2.1%
Weight loss (%)	-10.2%	-6.1%	-6.0%	-2.4%	-8.0%	-2.6%	-14.9%	-2.4%	-21.1%	-3.3%

Safety concerns

GLP-1 RA showed strong efficacy, especially long-acting GLP-1 RAs

Notes: 1. Chen K, Chen L, Shan Z, et al. Beinaglutide for weight management in Chinese individuals with overweight or obesity: A phase 3 randomized controlled clinical study. Diabetes Obes Metab. 2024;26(2):690-698. doi:10.1111/dom.15360

Source: The Lancet; NIH; JAMA; Clinical trials; China Insights Consultancy

Pipeline of Clinical-stage GLP-1 Receptor Agonists for Obesity in the United States

Pipeline of Clinical-stage GLP-1 Receptor Agonists for Obesity in the United States

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
Orforglipron	GLP-1R	Eli Lily	T2DM/Obesity/Overweight/CVDs/CKDs	p.o.	III	2023/4/7	NCT05803421	FDA
			Obesity/Overweight/T2DM	p.o.	III	2023/3/24	NCT05872620	FDA
			Overweight/Obesity	p.o.	III	2023/3/22	NCT05869903	FDA
AZD5004	GLP-1R	AstraZeneca	Overweight/Obesity	p.o.	II	2024/10/8	NCT06579092	FDA
ROSE-010	GLP-1R	Rose Pharma	Overweight/Obesity	s.c.	II	2024/10/1	NCT06621017	FDA
RGT-075	GLP-1R	Regor	Obesity	p.o.	II	2024/2/26	NCT06277934	FDA
K-757	GLP-1R	Kallyope	Obesity	p.o.	II	2023/8/31	NCT06019559	FDA
S-309309	GLP-1R	Shionogi	Obesity	p.o.	II	2023/6/29	NCT05925114	FDA
Danuglipron	GLP-1R	Pfizer	Obesity/Overweight/T2DM	p.o.	II	2021/1/13	NCT04707313	FDA
GSBR-1290	GLP-1R	Gasherbrum Bio	Obesity/Overweight/T2DM	p.o.	I/II	2023/1/25	NCT05762471	FDA
CT-996	GLP-1R	Carrot	Obesity/Type 2 Diabetes	p.o.	I	2023/5/9	NCT05814107	FDA
XW014	GLP-1R	Sciwind	Obesity/Type 2 Diabetes/MASH	p.o.	I	2022/10/13	NCT05579314	FDA

Source: ClinicalTrials.gov, China Insights Consultancy

Pipeline of Clinical-stage GLP-1 Receptor Agonists for Obesity in China

Pipeline of Clinical-stage GLP-1 Receptor Agonists for Obesity in China

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
PB-119	GLP-1R	PegBio	Overweight/obesity	s.c.	I	2024/4/17	CTR20241107	NMPA
Semaglutide	GLP-1R	Jiangsu Thery	Obesity	s.c.	III	2024/12/23	CTR20244777	NMPA
GZR-18	GLP-1R	Ganlee	Overweight/obesity	s.c.	III	2024/12/18	CTR20244647	NMPA
Semaglutide	GLP-1R	Jiangsu Sinopep	Obesity	s.c.	III	2024/12/12	CTR20244492	NMPA
VCT220	GLP-1R	Vincentage	Overweight/obesity	p.o.	III	2024/11/20	CTR20244365	NMPA
Semaglutide	GLP-1R	Chengdu Beite	Obesity	s.c.	III	2024/9/30	CTR20243408	NMPA
ZT006	GLP-1R	QL Biopharm	Overweight	p.o.	I	2024/11/15	CTR20244313	NMPA
Semaglutide	GLP-1R	CSPC	Obesity	s.c.	III	2024/9/14	CTR20243491	NMPA
Orforglipron	GLP-1R	Eli Lilly	Overweight/obesity	p.o.	III	2023/8/11	CTR20232459	NMPA
Ecnoglutide	GLP-1R	Sciwind	Overweight/obesity	s.c.	III	2023/3/15	CTR20230745	NMPA
Semaglutide	GLP-1R	Novo Nordisk	Weight management	s.c.	III	2023/9/8	CTR20232812	NMPA
BPYT01	GLP-1R	Baiji Youtang	Overweight/obesity	s.c.	II	2024/8/13	CTR20242957	NMPA
ZT002	GLP-1R	QL Biopharm	Overweight/obesity	s.c.	II	2024/7/12	CTR20242527	NMPA
HDM1002	GLP-1R	Hangzhou Zhongmei Huadong	Overweight/obesity	p.o.	II	2024/4/11	CTR20241151	NMPA
Supaglutide	GLP-1R	Innogen	Overweight/obesity	s.c.	II	2024/3/11	CTR20240801	NMPA
HRS-7535	GLP-1R	Shandong Shengdi	Obesity	p.o.	II	2024/2/18	CTR20240369	NMPA
GMA-105	GLP-1R	Hongyun Huaning	Overweight/obesity	s.c.	Ib/II	2022/6/27	CTR20221601	NMPA
MDR-001	GLP-1R	MirdRank	Overweight/obesity	s.c.	II	2024/8/23	CTR20243057	NMPA
SAL-0112	GLP-1R	Salubris	Overweight/obesity	p.o.	I	2023/12/18	CTR20233948	NMPA

Notes: Biosimilars registered at CDE not included
Source: CDE, China Insights Consultancy

Pipeline of Clinical-stage GLP-1/GCG Dual Receptor Agonists for Obesity in the United States

Pipeline of Clinical-stage GLP-1/GCG Dual Receptor Agonists for Obesity in the United States

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
IBI362 (Mazdutide)	GLP-1R/GCGR	Eli Lilly/Irnovent	Diabetes Mellitus/T2DM/Obesity	s.c.	III	2023/12/28	NCT06184568	FDA
			Diabetes Mellitus/T2DM	s.c.	III	2022/11/7	NCT05606913	FDA
Survodutide	GLP-1R/GCGR	Boehringer Ingelheim	Obesity/NASH	s.c.	III	2024/3/13	NCT06309992	FDA
			Obesity	s.c.	III	2023/10/11	NCT06077864	FDA
			Obesity/T2DM	s.c.	III	2023/10/4	NCT06066528	FDA
			Obesity	s.c.	III	2023/10/4	NCT06066515	FDA
Pemvidutide	GLP-1R/GCGR	Altimmune	Obesity/Overweight	s.c.	II	2022/3/25	NCT05295875	FDA
Efinopegdutide	GLP-1R/GCGR	Merck Sharp & Dohme LLC	Obesity/T2DM	s.c.	II	2018/7/16	NCT03586830	FDA
			Obesity	s.c.	II	2018/4/3	NCT03486392	FDA
DA-1726	GLP-1R/GCGR	Neurobo	Obesity	s.c.	I	2024/2/9	NCT06252220	FDA
DD01	GLP-1R/GCGR	Neuraly	Overweight/Obesity/T2DM/MASLD	s.c.	I	2021/3/23	NCT04812262	FDA
NNC9204-1177	GLP-1R/GCGR	Novo Nordisk	Overweight/Obesity	s.c.	I	2019/8/16	NCT04059367	FDA
			Metabolism and Nutrition Disorder/Obesity	s.c.	I	2016/10/21	NCT02941042	FDA

Source: ClinicalTrials.gov, China Insights Consultancy

Pipeline of Clinical-stage GLP-1/GCG Dual Receptor Agonists for Obesity in China

Pipeline of Clinical-stage GLP-1/GCG Dual Receptor Agonists for Obesity in China

Candidate	MoA	Company	Phase	Indication	Administration	Firrst Posted Date	Trial Number
PB-718	GLP-1/ GCG	PegBio	I	Overweight/obesity	s.c.	2023/05/31	CTR20231655
Mazdutide	GLP-1/ GCG	Innovent	NDA	Overweight/obesity	s.c.	2023/12/26[1]	CTR20231655
Survodutide	GLP-1/ GCG	Boehringer Ingelheim	III	Overweight/obesity	s.c.	2023/12/14	CTR20231655

Notes:
1. Mazdutide's NDA was accepted by the CDE in February 2024, its First Post Date and Trial Number denote its earliest Phase III clinical trial registered at the CDE.

Source: CDE, China Insights Consultancy

Clinical results of GLP-1 dual agonists

- GLP-1 dual-target agonists has shown superior efficacy to mono target drugs

Indirect comparison of current GLP-1 class clinical results

	GLP-1 mono agonists	GLP-1 dual agonists		
Trial	SURPASS-II	SURPASS-II	SURPASS-II	NCT04904913
	Semaglutide (1 mg)	**Tirzepatide (10mg)**	**Tirzepatide (15mg)**	**Mazdutide(9mg)**
Trial duration(weeks)	40	40		48
MoA	GLP-1	GLP-1/GIP		**GLP-1/GCG**
Dose	QW.	QW.		QW.
Mean BMI (kg/m²)	34.2	34.3	34.5	31.8
Baseline weight (kg)	93.7	94.8	93.8	89.3
SAE (%)	2.8%	5.3%	5.7%	**0%**
Discontinuation rate%	4.1%	8.5%	8.5%	**0%**
Weight loss (%)	-6.7%	-11.0%	-13.1%	***Superior weight loss efficacy*** **-18.6%***

Notes:*: Placebo adjusted

Source: NEJM; nature communications; Innovent; China Insights Consultancy

Drivers and future trends in domestic obesity drug market

- Drivers and future trends in domestic 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

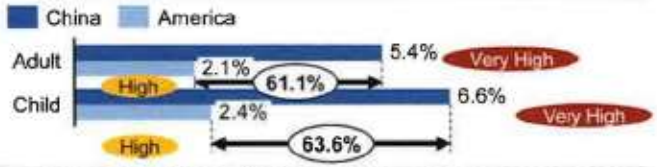
Obesity market → Trends

Drivers & Future trends

Increasing number of overweight/obesity patients

- Urbanization and economic growth have changed people's food choices. However, the modern lifestyle characterized **by unhealthy dietary habits and reduced physical activity** has led to an **increasing prevalence of obesity**, placing a sustained burden on the Chinese healthcare system
- As a result, the prevalence of obesity 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

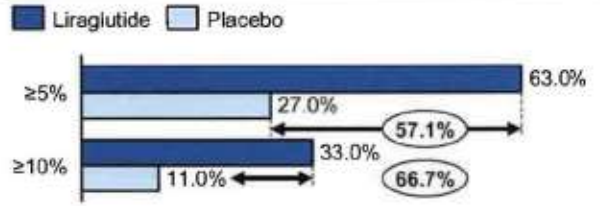
- **Social education has heightened public health awareness**, shifting the focus on obesity from mere aesthetic to issues closely linked to health, which has **reinforced the inclination of residents to seek medical attention**, further **increasing healthcare utilization and treatment rates**, driving 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
- Since the first **dual-target obesity drug** Tirzepatide (GIP/GLP-1) was approved and demonstrated **unprecedented weight loss effects**, more dual-target obesity drugs have entered clinical trials and have great development potential
- The evidence from numerous clinical studies clearly demonstrates **that weight loss can significantly lower the risk of obesity-related complications and chronic diseases**. Losing weight provides individuals with numerous overall benefits, leading to improved physical and mental health.

Percentage of patients achieving 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

Table of contents

MASLD is a condition in which excess fat is stored in liver. Two types of MASLD are MAFL and NASH. People with NAFLD may develop liver complications or other health problems

Introduction of metabolic associated fatty liver disease (MASLD)

Metabolic associated fatty liver disease (MASLD) also known as **non-alcoholic fatty liver disease (NAFLD)** is excessive fat build-up in the liver that is not a result of excess alcohol consumption or other secondary causes. Two types of NAFLD are metabolic associated fatty liver (**MAFL**) and metabolic dysfunction-associated steatohepatitis **(NASH).** Some individuals with non-alcoholic fatty liver disease (NAFLD) will face mortality due to either liver failure, hepatocellular carcinoma (HCC).

Development and Classification of MASLD

Reversible → Hardly Reversible

Stage	Image	Biopsy	Pathogenicity
Healthy Liver			Healthy liver controls the levels of glucose, fat and protein in the blood.
MAFL			Hepatocytes accumulate excess fat, a process called steatosis.
NASH			Accumulated fat causes stress and injury to hepatocytes which leads to fibrosis
Cirrhosis			Dead hepatocytes are broken down and scar tissue accumulates, which stiffens the liver.
HCC			Cancer and liver failure might be caused as complications by long-standing cirrhosis.

Symptoms of MASLD

MAFL

Most MAFL patients are asymptomatic.

- Fatigue
- Pain or discomfort in the upper right abdomen

NASH/Cirrhosis

- Abdominal swelling Enlarged blood vessels just beneath the skins' surface
- Enlarged spleen
- Red palms
- Yellowing of the skin and eyes

Risk Factors of MASLD

- Type 2 diabetes
- High cholesterol
- High triglycerides level
- Metabolic syndrome
- Polycystic ovary syndrome
- Hypothyroidism
- Hypopituitarism
- Obesity
- Obesity, particularly when fat is concentrated in the abdomen

Source: Nature, China Insights Consultancy

NASH is an advanced form of MASLD, and risk of cirrhosis and hepatocellular carcinoma increases with NASH

Introduction of metabolic dysfunction-associated steatohepatitis (NASH)

Metabolic dysfunction-associated steatohepatitis (NASH) is an advanced form of metabolic associated fatty liver disease (MASLD). MASLD is caused by buildup of fat in the liver. When this buildup causes inflammation and damage, it is known as NASH. T2DM and insulin resistance increases the risk of NASH, besides, obesity, high blood cholesterol and triglycerides, and metabolic syndrome increases the risk too.

Diagnosis for NASH

No single test can diagnose NASH

Blood Tests

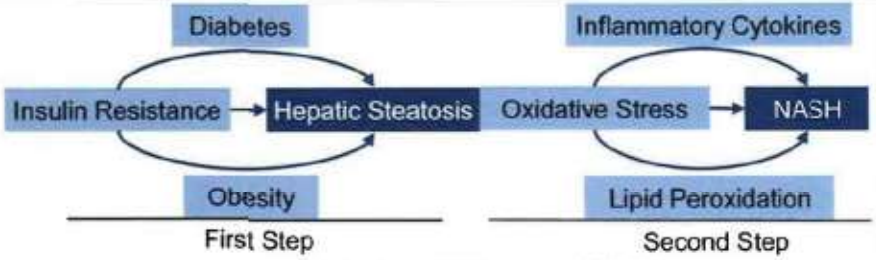
Biopsy

The only test can prove a diagnosis of NASH

Imaging Test

CT scan | MRI scan | Ultrasound

Liver fat triggers harmful inflammation that creates scar tissue in liver. About 3 of 4 T2DM or prediabetes patients have too much fat in liver, and about half of them have harmful inflammation and scaring.



The two-hit theory of NASH

Complications of MASH

MASH can be silent diseases with no symptoms at all or very mild symptoms such as tiredness and fatigue in early stages of the disease. Often the first sign occurs when cirrhosis has developed typically after many years.

- **Fibrosis and cirrhosis**

The inflammation and liver cell damage will start to fibrosis. If left untreated, scar tissue will continue to replace healthy liver tissue leading to cirrhosis, which is advanced, late-stage scarring. About 20% of people with MASH will progress to cirrhosis over several years.

- **Liver failure**

If cirrhosis is not treated, the liver will not be able to work well or work at all. A liver transplant may be need at this stage.

- **Liver Cancer**

One of the complications of cirrhosis is liver cancer. Risk of hepatocellular carcinoma(HCC) increases.

- **Cardiovascular disease/ Type 2 Diabetes**

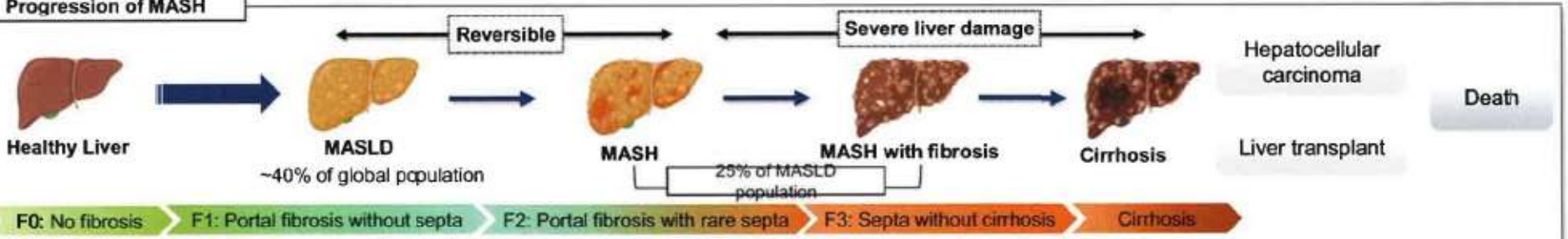
People with MASLD or MASH are more likely to have cardiovascular disease/T2DM and cardiovascular disease is the most common cause of death in people who have MASLD/MASH.

Source: ALF, NIHR, NIDDK, Stanfordhealthcare, China Insights Consultancy

MASH is chronic and progressive disease without approved treatment options

Introduction of metabolic dysfunction-associated steatohepatitis (MASH)

Progression of MASH



MASH classification

Fibrosis Stage

F0 | F1 | F2 | F3 | F4

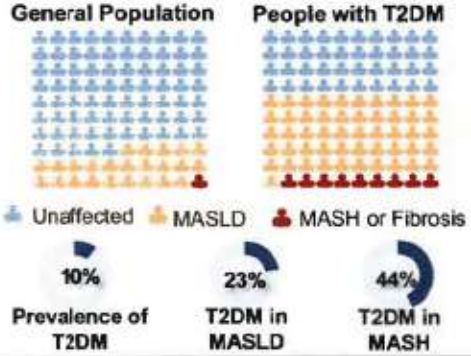
NAS Score

Reflects disease activity; composite of three features (steatosis, inflammation and ballooning)

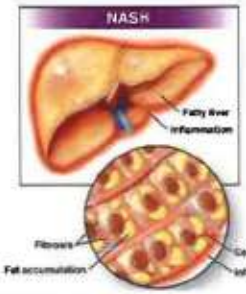
SAF Score

Semi-quantitative score of steatosis, activity and fibrosis

MASH is associated with T2DM



MASH is mainly diagnosed through liver biopsy



Liver biopsy is currently the method of reference; broader adoption of non-invasive tests and launch of disease-modifying therapies may make diagnosis easier

MASH has high unmet needs

Key unmet needs F2 F3

Lack of treatment targeting both MASH and resolution and fibrosis

Key unmet needs F4

Lack of treatment for cirrhosis

Source: ALF, NIHR, NIDDK, Stanfordhealthcare, China Insights Consultancy

Global prevalence of NASH with breakdown of key geographies, 2018-2032E

Global prevalence of NASH, 2018-2032E

million patients

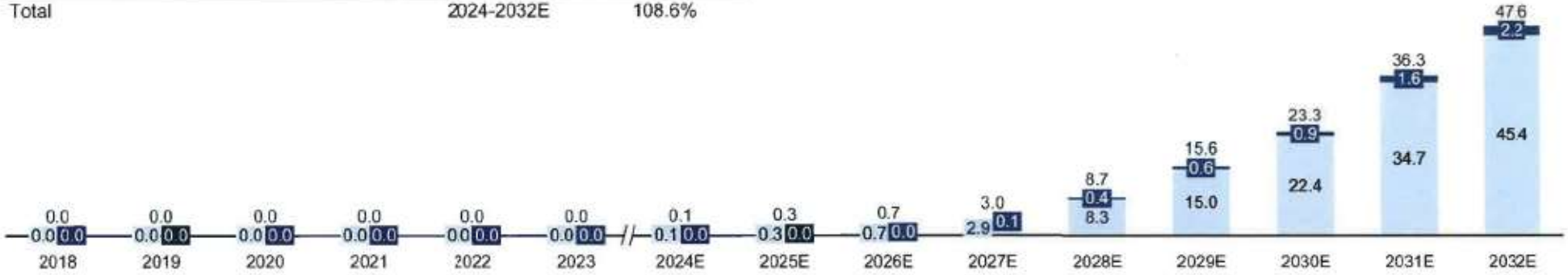
CAGR	2018-23	2023-32E
China	2.9%	2.3%
the US	3.2%	2.8%
ROW	2.1%	2.0%
Total	2.3%	2.1%

Source: World Obesity Atlas, WHO, China Insights Consultancy

Global NASH drug market size, 2018-2032E

Global NASH Drug Market Size, 2018-2032E

CAGR	Period	CAGR
China	2027-2032E	83.4%
ROW	2024-2032E	107.4%
Total	2024-2032E	108.6%



Notes and Assumptions::

- Notes: The market size of NASH is estimated as the average annual treatment expenditure of NASH drug multiplied by the number of treated patients. For the global market, the annual treatment price assumption is based on the first approved NASH drug Resmetirom, with an expected wholesale price of approximately US$4.0 thousand for a pack of 30 tablets and an initial expected price of US$47.4 thousand per year in 2024, and the price between 2024 and 2032 globally is expected to be within the range of US$15.0 thousand to US$30.0 thousand. The number of addressable patients is estimated as the number of NASH patients globally multiplied by the percentage of patients with advance stage (F2~F3) of fibrosis, which is expected to be within 35%~40% globally. The number of patients who adopt approved NASH-indicated drug is expected to be within 1,500~2,000 in 2024 globally, and the treatment rate at 2032 is expected to be around 1% out of the total addressable patients.
- For the China market, the annual treatment price is expected to be US$2,000~US$2,400, the number of addressable patients is estimated as the number of NASH patients in China multiplied by the percentage of patients with advance stage (F2~F3) of fibrosis, which is expected to be within 25%~35% in China between 2027 and 2032. The first drug indicated for NASH is expected to be approved in 2027, when the patient treatment rate is expected to be 0.3% out of the total addressable patients, and is expected to be within 5%~6% in 2032.

Source: Journal of Hepatology, FDA, ClinicalTrials.gov, China Insights Consultancy

AGA recommends that management for NASLD/NASH patients varies depending on their risk of clinically liver fibrosis. Due to its complex pathogenesis, medication for MASH is underdeveloped currently

Recommendation for NASLD/NASH patient management

MASLD/MASH Clinical Care Pathway multidisciplinary task force - Recommended management of patients with MASLD/MASH			
Risk level	**Low risk**	**Intermediate risk**	**High risk**
Patient stratification	FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	FIB-4 1.3 – 2.67 and /or LSM 8 – 12 kPa and liver biopsy not available	FIB-4 > 2.67 or LSM >12 kPa or liver biopsy F2-F4
Lifestyle intervention	All patients require regular physical activity, healthy diet, and avoid excess alcohol intake		
Weight loss recommended if overweight or obese	May benefit	Greater need	Strong need
	• Structured weight loss programs • Anti-obesity medications • Bariatric surgery		
Pharmacotherapy for MASH	Not recommended	No pharmacological agent is FDA-approved so far for MASH treatment, patients with T2DM may benefit from some diabetes medications such as pioglitazone and some GLP-1 RAs; Vitamin E improves steatohepatitis in patients with MASH without diabetes, with less evidence in patients with T2DM	
		Not applicable	Pharmacotherapy for MASH cirrhosis is very limited and should be avoided
CVD risk reduction	Statins can be used safely in patients with steatohepatitis and liver fibrosis, but is to be avoided in decompensated cirrhosis		
Diabetes care	Standard of Care of diabetes	Medications with efficacy in MASH (pioglitazone, GLP-1 RAs) preferred	

Notes: FIB-4: fibrosis-4; LSM: liver stiffness measurement; CVD: cardiovascular disease; GLP-1 RA: glucagon-like peptide 1 receptor agonis

- GLP-1RAs can improve insulin sensitivity, reduce hepatic glucose production, and promote weight loss. These metabolic effects may contribute to better management of MASH, as insulin resistance and obesity are common factors associated with the condition.
- GLP-1RAs have demonstrated anti-inflammatory effects which can be beneficial in reducing liver inflammation, a key component of MASH pathology.
- Some studies suggest that GLP-1RAs may have anti-fibrotic effects, potentially helping to prevent or reduce liver fibrosis, a serious consequence of MASH.

Source : Gastroenterology, China Insights Consultancy

Pipeline of Clinical-stage GLP-1 Receptor-Targeted NASH Drug Candidates in the United States

Pipeline of Clinical-stage GLP-1 Receptor-Targeted NASH Drug Candidates in the United States

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
PB-718	GLP-1R/GCGR	PegBio	NASH	s.c.	I	2021/8/25	NCT05021666[1]	FDA
Survodutide	GLP-1R/GCGR	Boehringer Ingelheim	NASH	s.c.	III	2024/3/13	NCT06309992	FDA
Semaglutide	GLP-1R	Novo Nordisk	NASH	s.c.	III	2021/3/30	NCT04822181	FDA
DD-01	GLP-1R/GCGR	Neuraly Inc	NAFLD	s.c.	II	2024/5/13	NCT06410924	FDA
Pemvidutide	GLP-1R/GCGR	Altimmune	NASH	s.c.	II	2023/8/14	NCT05989711	FDA
Efinopegdutide	GLP-1R/GCGR	Merck Sharp & Dohme LLC	MASH, NASLD	s.c.	II	2023/5/26	NCT05877547	FDA
Efocipegtrutide (HM15211)	GLP-1R/GCGR/GIPR	Hanmi Pharmaceutical	NASH	s.c.	II	2020/8/7	NCT04505436	FDA
AZD9550	GLP-1R/GCGR	AstraZeneca	NASLD	s.c.	I/II	2023/11/30	NCT06151964	FDA
VK2735	GLP-1R/GCGR	Viking Therapeutics	NASLD	p.o.	I	2022/1/24	NCT05203237	FDA

Notes:
1. *Trial NCT05021666 is conducted on healthy participants*

Source: ClinicalTrials.gov, China Insights Consultancy

Pipeline of Clinical-stage GLP-1 Receptor-Targeted NASH Drug Candidates in China

Pipeline of Clinical-stage GLP-1 Receptor-Targeted NASH Drug Candidates in China

Candidate	MoA	Company	Indication	Administration	Phase	First Posted Date	Trial Number	Competent authurity
Survodutide	GLP-1R/GCGR	Boehringer Ingelheim	NASH	s.c.	III	2024/11/26	CTR20244843	NMPA
Semaglutide	GLP-1R	Novo Nordisk	NASH	s.c.	III	2021/07/27	CTR20211818	NMPA
Efinopegdutide	GLP-1R/GCGR	Merck & Co.	NASH	s.c.	II	2023/10/19	CTR20233311	NMPA
HEC88473	GLP-1R/FGF21	GUANGDONG HEC TECHNOLOGY	NASH, T2DM, Obesity	s.c.	II	2023/08/17	CTR20232481	NMPA
UBT251	GLP-1R/GCGR/GIPR	Federal Biotechnology	T2DM, Overweight/Obesity, NASH	s.c.	Ia	2023/09/20	CTR20232997	NMPA

Source: CDE, China Insights Consultancy

Growth drives of MASH/MASLD drug market include the growing patient population, unmet clinical needs of MASH/MASLD and the positive achievement in current R&D

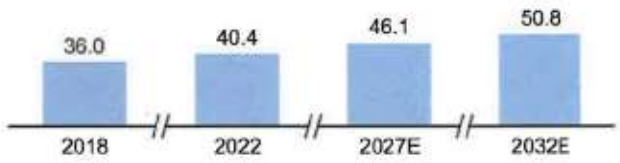
Growth drivers & Future trends

Expansion of vulnerable population and increasing prevalence

- As a metabolic disease, MASH is associated with risk factors such as obesity, T2DM, abnormal fat levels in the blood, age, and obstructive sleep apnea, among others. As the world obesity and T2DM population grow, so will the MASH population grow steadily.
- The rising prevalence of metabolic disorders, including fatty liver disease, is a significant driver. Factors such as sedentary lifestyles, poor dietary habits, and obesity contribute to the increasing incidence of MASLD.

Prevalence of MASH in China, 2018-2032E

Million patients



Novel treatments to fulfil the unmet medical needs of MASH and MASLD

- As of December 2023, there are no FDA, EMA, or PMDA-approved drug for treatment of MASH and MASLD. The absence of approved drugs presents an opportunity for companies to pioneer novel therapies for MASH. The initial company to successfully introduce an FDA-approved MASH drug stands to attain a substantial competitive edge, given the considerable and expanding patient population seeking effective treatments.
- With the increasing prevalence of MASH, the economic burden of the disease is on the rise, leading to a growing demand for new treatments capable of mitigating healthcare costs linked to the condition.

Ongoing positive achievement in R&D

- The existing pipeline for MASH encompasses a wide array of medications, notably including FXR agonists, FGF21 stimulants, FGF19 analogs, GLP-1 agonists, PPAR regulators, THR-β agonists, and other prominent classes. Ongoing research and ongoing clinical trials possess the capability to reshape the MASH market landscape.

Note: EMA, European Medicines Agency; PMDA, Pharmaceutical and Medical Devices Agency

Source: Literature review; China Insights Consultancy

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Congenital Hyperinsulinemia

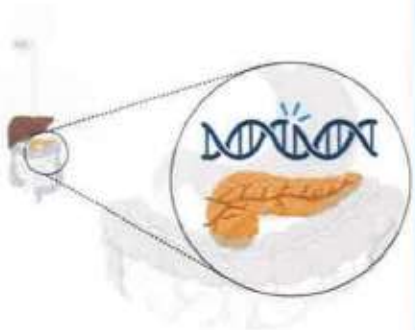
- Congenital Hyperinsulinism is a rare disorder associated with dysregulated insulin secretion

Introduction to Congenital Hyperinsulinemia

- **Congenital Hyperinsulinemia (CHI)** is an endocrine disorder characterized by dysfunction of pancreatic β cells, leading to sustained insulin release and inappropriate elevation of blood insulin levels, resulting in hypoglycemia
- CHI is a common cause of persistent hypoglycemia in newborns/children, with severe implications for the central nervous system and even mortality
- CHI was included in the "first batch of the Rare Disease Catalog" (《第一批罕见病目录》) in 2018

Pathophysiology of CHI

- Deficiency in the key regulatory pathways for synthesis and secretion of insulin in congenital pancreatic β cells
- **K_{ATP} ion channels in pancreatic β cells gene (ABCC8/ KCNJ11)** mutations are common genetic variations in patients with CHI (approximately 40-45% of total)
- For nearly half of the CHI patients, the cause remains unidentified



Clinical manifestations

Primarily characterized by **hypoglycemic symptoms**, manifesting as sympathetic nervous system activation symptoms such as sweating, tremors, palpitations, anxiety, hunger, and increased heart rate. In severe cases, there may be consciousness alterations, including seizures, drowsiness, and coma, posing a potential life-threatening risk

Diagnosis of CHI

Typical symptoms are present, **venous blood glucose is <2.8 mmol/L**, and the following three criteria are simultaneously met:

- ✓ Serum insulin >1 mU/L, or blood C-peptide ≥0.5 μg/L, along with blood β-hydroxybutyrate <2 mmol/L and free fatty acids <1500 μmol/L
- ✓ Positive glucagon stimulation test: Glucagon 30-100 μg/kg (maximum 1 mg) is administered subcutaneously or intravenously over 15-45 minutes, and blood glucose increases by >1.5 mmol/L
- ✓ Intravenous glucose infusion rate >8 mg/(kg·min) is required to maintain normal blood glucose levels

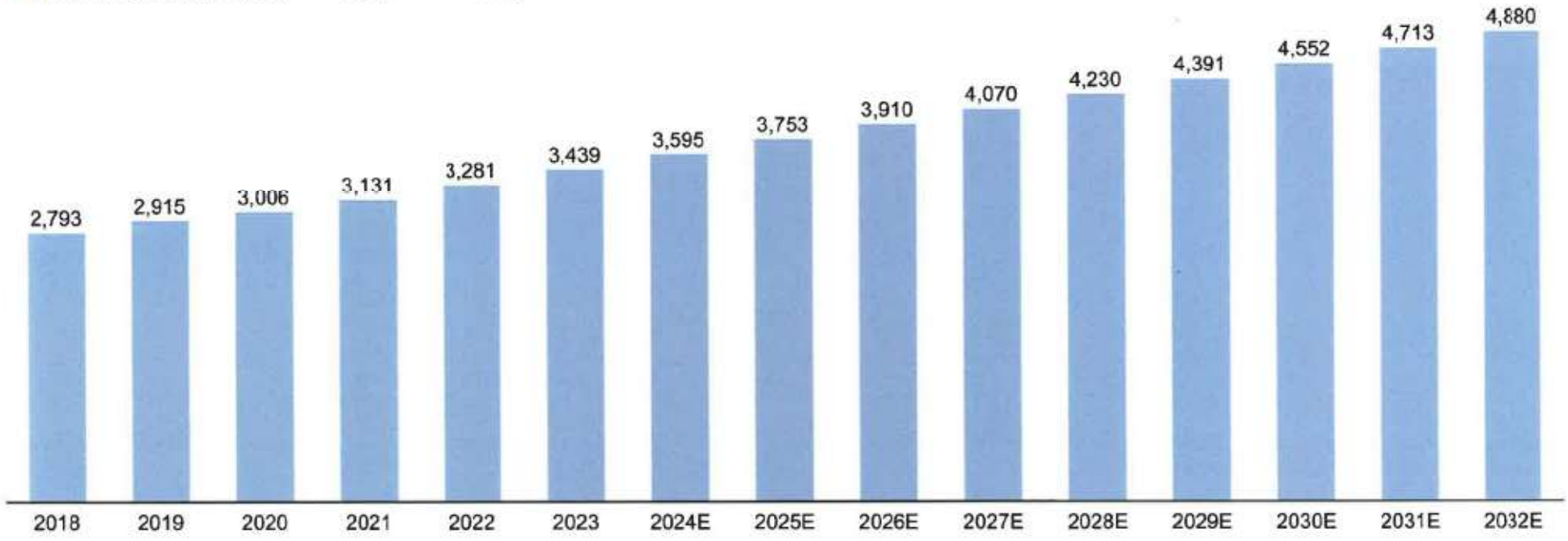
Source: Expert consensus (2022); China Insights Consultancy

CHI patients 2018-2023, 2023-2032E

Incidence of CHI in Global, 2018-2032E

CAGR	2018-23	2023-32E
Incidence of CHI in Global	4.2%	4.0%

Patients



Source: China Insights Consultancy

CHI patients 2018-2023, 2023-2032E

Incidence of CHI in China, 2018-2032E

CAGR	2018-23	2023-32E
Incidence of CHI in China	-1.7%	3.0%

Patients

Source: China Insights Consultancy

Treatment pathway for CHI

- Diazoxide is a first-line therapeutic medication for CHI, exhibits suboptimal efficacy in certain cases with specific mutations

Treatment pathway for CHI

	First-line	Second-line		Other therapies	
Classification	• Non-diuretic benzothiadiazine derivative	• Somatostatin analog	• Glucoregulatory peptide hormone	• Surgical treatment	• Nutritional auxiliary therapy
Representative Drugs	• Diazoxide	• Octreotide • Lanreotide	• Glucagon		
Efficacy	• Suboptimal for patients with CHI caused by the most common K_{ATP} ion channal mutations (ABCC8/ KCNJ11)	• Employed where the efficacy of diazoxide is suboptimal • Prone to developing drug resistance	• Rapidly elevates blood glucose, • Used for emergency rather than long-term use	• Surgery is recommended for patients with ineffective single-drug and multi-drug combination therapy and for patients with focal lesions or insulinoma	• For children with pathogenic variants in GLUD1 and HADH genes, dietary intervention is recommended
AE	• Fluid retention • Electrolyte disturbances • Gastrointestinal discomfort	• More severe hypoglycemia	• High blood glucose and low blood potassium levels • Nausea • Vomiting • Polymorphic erythema	• Risk of reoperation	
Guideline recommendation status	• AAP • Chinese guideline[1]	• Chinese guideline		• Chinese guideline	

Abbreviations: CHI = congenital hyperinsulinemia; AE = adverse event

1. Chinese guideline refers to中华医学会儿科学分会内分泌遗传代谢学组, 中华儿科杂志编辑委员会. 先天性高胰岛素血症性低血糖诊治专家共识（2022）[J]. 中华儿科杂志, 2023, 61(5) : 412-417. DOI: 10.3760/cma.j.cn112140-20221031-00924.

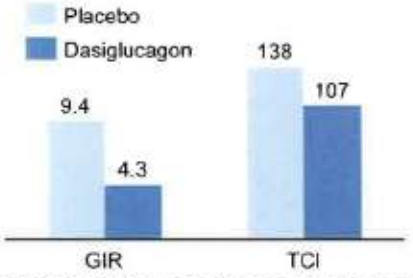
Source:Expert consensus (2022), China Insights Consultancy

Competitive landscape of CHI drugs

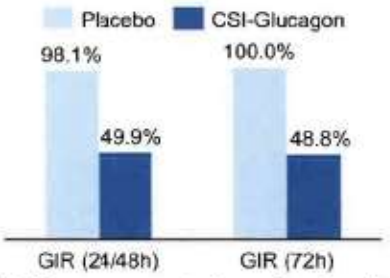
Pipelines of CHI drug candidates, CDE/FDA-registered, as of LPD

MoA	Drug Name	Company	Indication	Phase	First Posted Date	Trial Number	Approval Authority
GCGR	**PB-722 (PEGylated)**	**PegBio**	**CHI**	**IND approval**	**2023/02/27**	-	**CDE**
	Dasiglucagon	Zealand Pharma	CHI	NDA	2018/12/17	NCT04172441	FDA
	HM15136 (PEGylated)	Hanmi Pharm	CHI	II	2021/02/01	NCT04732416	FDA
	CSI-glucagon	Xeris Pharmaceuticals	CHI	II	2016/10/18	NCT02937558	FDA
INSR	RZ358	Rezolute; XOMA	CHI	III	2015/11/13	NCT04538989	FDA
GLP-1R	Exendin-(9-39)	Diva De Leon	CHI	I/II	2007/12/12	NCT00571324	FDA

Positive clinical results of GCGR candidates



GIR(mg/kg/min): mean glucose infusion rate
TCI(g/day): total carbohydrate intake



GIR(%): mean percent change from baseline

Key takeaways

- There are no commercialized CHI- targeted drugs worldwide
- Currently, several CHI drug candidates have entered into Phase II clinical trials or more advanced stages globally, but none in clinical develpoment in China
- **PB-722 is the first domestically CHI-targeted drug candidate with IND approval**
- GCGR targeted therapy for CHI has shown potential in several successful Clinical trials

Source: CDE; Zealand Pharma; ClinicalTrials; China Insights Consultancy

Growth Drivers and Market Trends of CHI

Highly specific targeted drugs is a key future trend of China CHI market

Unmet Clinical Demand

- Current SOC therapies often fall short in achieving optimal glycemic control, highlighting the necessity for more effective treatment modalities. The scarcity of targeted medications for CHI empahsizing the need for novel therapeutic interventions. A few targeted CHI medications are currently undergoing intensive development, with the prospect of being introduced in the near future

Medical Advancements

- Improved diagnostic tools, such as genetic testing and advanced imaging techniques, enable early and accurate identification of patients with CHI. Ongoing progress in medical research may lead to an improved understanding of CHI pathophysiology, driving the development of new therapeutic methods and drugs

Favorable policy environment

- NMPA emphasizes expediting the review and approval process for drugs treating rare diseases, fully committed to safeguarding the health rights and interests of patients with rare diseases. There are currently no targeted drugs for CHI that have been approved for marketing, encouraging the research and development of drugs for rare diseases

Personalized treatment strategy

- Personalized treatment strategies, considering factors such as diverse causative genetic mutations, represent the future trend in CHI therapy. Tailoring interventions based on individual patient profiles is poised to enhance the effectiveness and precision of CHI treatment

Promising Market Outlook

- CHI is a rare disease with a substantial patient population globally. Despite its rarity, there is a high demand for CHI drug treatments
- The establishment of diagnostic standards is anticipated to drive rapid growth in the domestic CHI drug market. Globally, existing CHI drugs fall short of meeting patient needs, highlighting significant potential for the development of new CHI medications in the future

Source: Literature review; China Insights Consultancy

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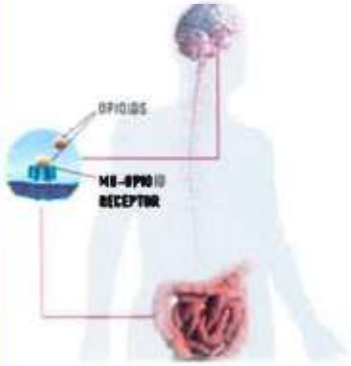
Opioid-Induced Constipation

- Opioid-Induced Constipation is a common consequence of opioid use for cancer-related and non-cancer-related chronic pain

Introduction to Opioid-Induced Constipation

- Opioids represent a mainstay for treatment **chronic cancer- and noncancer-related pain**
- **Opioid-Induced Constipation(OIC)** is the most common gastrointestinal adverse associated with opioid pharmacotherapy and negatively affects pain management, quality of life and daily functioning
- The development of OIC is quite common even at low dosages of opioids and does not spontaneously decrease over time due to opioids tolerance

Pathophysiology of OIC



- Opioids exert analgesic effects via activation of central μ-opioid receptors
- **μ-opioid receptors also ubiquitously distributed in the GI tract**
- **Activation of μ-opioid receptors located in GI tract** results in decrease bowel tone and contractility and increase colonic fluid absorption and anal sphincter tone while reducing rectal sensation
- **Leads to harder stools, which can be difficult to pass**

Diagnosis of OIC

- ***Diagnosis made according to the Rome criteria***
  - New or worsening symptoms must include 2+ of the following
  - Loose stools rarely present without the use of laxatives

More than 1/4 of defecations	✓ Straining ✓ Lumpy or hard stools ✓ Sensation of incomplete evacuation ✓ Sensation of anorectal obstruction/blockage ✓ Manual maneuvers to facilitate
Less than 3 times/week	✓ Spontaneous bowel movements

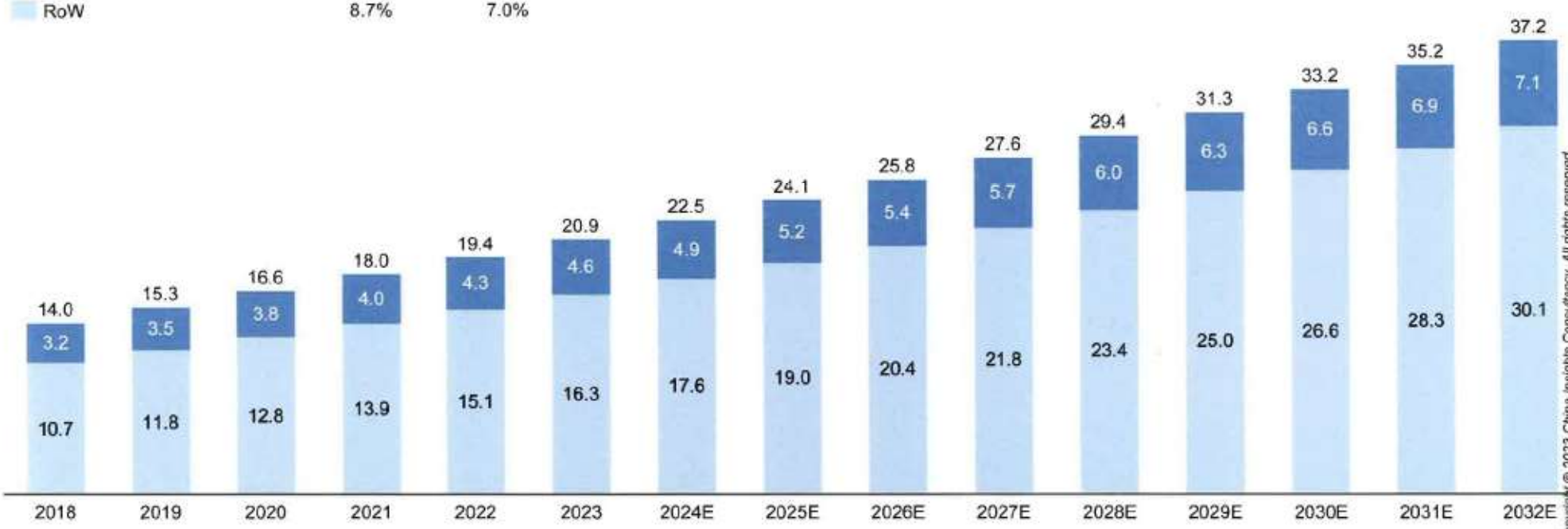
Source: Alkermes; uptodate; China Insights Consultancy

Global incidence of OIC

China and Global incidence of OIC, 2018-2032E

CAGR	2018-23	2023-32E
China	7.5%	5.0%
RoW	8.7%	7.0%

Million patients



Source:WHO, Pain Manag., J Anaesthesiol Clin Pharmacol., China Insights Consultancy

Treatment pathway for OIC

- Starting with laxatives as first line agents, opioid receptor antagonists are recommended for refractory OIC

Treatment pathway for OIC

	First-line		Second-line		Other therapies	
Classification	• conventional laxatives	• Peripherally acting μ-opioid receptor antagonists(PAMORAs)	• CLCN2	• 5-HT	• Lifestyle therapy	• Traditional Chinese Medicine
Representative Drugs	• lactulose • PEG	• Naloxegol • Naldemedine, • Methylnaltrexone	• Lubiprostone	• Prucalopride		
Efficacy	• Effectiveness is often limited • Time to action is unpredictable	• Proven efficacy superior to placebo • Alleviates constipation without compromising the analgesic effects	• Proven efficacy superior to placebo	• Leading to increased colonic motility and accelerated transit	• Increase fiber intake/increase fluid intake/increase physical activity • Efficacy is limited esp for cancer pts	• Effective in treating OIC, but lack of double-blinded multi-center clinical studies with large sample size
AE	• GI side effects such as nausea, vomiting, diarrhea and abdominal pain	• flatulence and diarrhea	• nausea and diarrhea	• abdominal pain and nausea		
Guideline recommendation status	• AGA • Chinese guideline[1]	• AGA • Chinese guideline	• Chinese guideline		• AGA • Chinese guideline	• Chinese guideline

1. Chinese guideline refers to中华医学会消化病学分会胃肠动力学组, 功能性胃肠病协作组. 中国慢性便秘专家共识意见(2019，广州)[J]. 中华消化杂志,2019,39(9): 577-598. DOI: 10.3760/cma.j.issn.0254-1432.2019.09.001.

Source: 中华消化杂志, American Gastroenterological Association, China Insights Consultancy

OIC Approved products in US

- PAMORAs drugs such as methyltrexone, naldemedine and naloxegol are the mainstream of OIC in US

Mainstay drugs for 2L OIC therapy in US, as of LPD

MoA	Generic Name	Brand Name	Company	Administration	Approved Indication	First Approval Date	2022 global sales (Mn USD)
PAMORA	Naloxegol	Movantik	RedHill Biopharma	p.o.	chronic non-cancer pain OIC	2014/09/16	~180
	Methylnaltrexone	Relistor	Salix Pharmaceuticals	p.o.	OIC in adult patients with chronic non-cancer pain	2016/07/19	~250
				s.c.	OIC in adult patients with chronic non-cancer pain, OIC in adults with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient	2008/04/25	
	Naldemedine	Symproic	Shionogi	p.o.	chronic non-cancer pain OIC	2017/03	~60
CLCN2	Lubiprostone	Amitiza	Mallinckrodt Pharmaceuticals	p.o.	Chronic idiopathic constipation OIC in people with chronic, noncancer pain, or in patients with long-lasting pain caused by a previous cancer or its treatment, irritable bowel syndrome with constipation in women	2006/01/31	~190

Abbreviations: PAMORA = peripherally acting μ-opioid receptor antagonist

As of the Latest Practicable Date, there were four drug products approved by the FDA for the treatment of OIC, being three peripherally acting μ-opioid receptor antagonists ("PAMORAs") and one CLCN2 activator, respectively.

OIC Approved products in China

Mainstay drugs for 2L OIC therapy in China, as of LPD

MoA	Genric Name	Brand Name	Company	Administration	Approved Indication	Approval Date
Opioid antagonist & opioid analgesic	Prolonged-release oxycodone/naloxone	米美欣	Luye Pharma	p.o.	For adults with severe pain that requires opioid analgesics to adequately control. The addition of the opioid receptor antagonist naloxone alleviates the symptoms of opioid-induced constipation by blocking the effect of oxycodone on the intestinal opioid receptors	2024/6/28
Opioid antagonist& opioid analgesic	Prolonged-release oxycodone/naloxone	奥施瑞定	Mundipharma	p.o.	For adults with severe pain that requires opioid analgesics to adequately control. The addition of the opioid receptor antagonist naloxone alleviates the symptoms of opioid-induced constipation by blocking the effect of oxycodone on the intestinal opioid receptors	2022/11/22

As of the Latest Practicable Date, there were two drugs approved by the NMPA for the treatment of OIC in China, which are both opioid receptor antagonists.

Source: NMPA; China Insights Consultancy

Comparison of PAMORA approved drugs

- Approved PAMORAs are derivatives of naloxone, of which naloxegol demonstrated superior safety profile

Summary of clinical results in PAMORA drugs(*indirect comparison*)

		Naloxegol		Methylnaltrexone		Naldemedine	
Modification Type		**PEGylated** derivatives of naloxone		**Methylated** form of naltrexone		**Amide** derivative of naltrexone	
Trial Name		KODIAC-04	KODIAC-05	NCT01186770 (Oral)	NCT00804141(Injection)	COMPOSE-I	COMPOSE-II
Patient Baseline		50% or more of patients with an inadequate response to laxatives		Currently taking laxative therapy for ≥30 days	≥1L	≥1L	≥1L
Number of Patients		652	700	804	1040	547	553
Trial Protocol		12.5/25 mg of naloxegol vs. placebo		150/300/450 mg MNTX vs. placebo	MOA-728 12 mg	0.2 mg Naldemedine vs. placebo	
Efficacy	12-week Response Rate	44.4% (25mg) 29.4% (placebo)	39.7% (25mg) 29.3% (placebo)	49.3% (300mg) 51.5% (400mg) 38.3% (placebo)		47.6% (0.2 mg) 34.6% (placebo)	52.8% (0.2 mg) 33.8% (placebo)
	Median Time to First SBM	5.9h	12h	/	/	/	/
	No. of SBM/Week (Change from Baseline)	25 mg: 3.02 vs 2.02	25 mg: 3.14 vs 2.10	2.4 vs. 1.9	1.5	3.42 vs. 2.12	2.58 vs. 1.57
AE	Abdominal Pain	1.9%	3.9%	10.5%	24.0%	5.0%	6.0%
	Diarrhea	2.8%	3.4%	8.0%	16.4%	7.0%	9.0%
	Nausea	1.7%	1.7%	6.0%	15.1%	5.0%	5.0%

Source: FDA; Pubmed; China Insights Consultancy

Competitive landscape of OIC drugs

Pipelines of OIC drug candidates, CDE-registered, as of LPD

Drug Name	MoA	Company	Administration	Indication	Phase	First Posted Date	Trial Number
PB-1902 (PEGylated)	**PAMORA**	**PegBio**	**Oral**	OIC	**I**	**2021/10/21**	**CTR20212557**
					I	**2021/04/02**	**CTR20210655**
Methylnaltrexone Bromide	PAMORA	Ychang Renfu Pharmaceutical	Oral	OIC	BE	2024/5/6	CTR20241542
	PAMORA	Shenyang Eliving Pharmaceutical Technology	Injection	OIC	I	2018/07/02	CTR20180953
	PAMORA	Beijing Collab Pharma	Injection	OIC	III	2015/06/18	CTR20150393
	PAMORA	Furuikangzheng	Injection	OIC	II	2015/07/06	CTR20150290
	PAMORA	Institute of Toxicology, Academy of Military Medical Sciences, PLA. Beijing Molike Technology	Injection	OIC	III	2018/10/18	CTR20181837
Naldemedine	PAMORA	Shionogi	Oral	OIC	III	2022/03/22	CTR20220673
Prolonged-release oxycodone/naloxone	Opioid antagonist & opioid analgesic	Luye Pharma	Oral	OIC	NDA	2021/07/23	CTR20211699
Lubiprostone	CLCN2	Langxite	Oral	OIC in adult patients with chronic non cancer pain	BE	2018/12/20	CTR20182238
Naloxone Hydrochloride/ Oxycodone Hydrochloride Hydrate	Opioid receptors antagonist & opioid receptors agonist	Jiangsu Nhwa	Oral	OIC	BE	2024/7/18	CTR20242606

Source: CDE, China Insights Consultancy

Competitive landscape of OIC drugs in the US

Pipelines of OIC drug candidates, FDA-registered, as of LPD

MoA	Drug Name	Company	Administration	Indication	Phase	First posted date	Trial Number
PAMORA	Naloxegol	Trihealth	Oral	Constipation Constipation Drug Induced	II/III	2017/10/20	NCT03316859
	Naldemedine	Shionogi	Oral	Paediatric Participants Receiving Opioids	I/II	2022/10/20	NCT05588323
N/A	BGP345A	BioGaia Pharma	Oral	Opioid-Induced Constipation	II	2021/11/24	NCT05133076

As of the Latest Practicable Date, there were three clinical-stage drug candidates for the treatment of OIC in the United States.

Growth Drivers and Market Trends of OIC

Using oral innovative PAMORAs is a key future trend of China OIC market

Increased Clinical Demand

- As the global trend of aging intensifies, the need for cancer and chronic non-cancer pain is continuously escalating, leading to a higher usage of opioids among patients. These patients, however, are confronted with a challenging dilemma: managing pain while grappling with severe constipation caused by opioid analgesics. This situation has resulted in a growing market demand for medications treating OIC

China Opioid analgesics market size

Inadequate Traditional Treatments

- The 1L treatment of OIC in China primarily involves lifestyle modifications and taking conventional laxatives. Despite the available methods, many patients still do not experience an improvement in constipation symptoms. There is an urgent need to develop new drugs to alleviate the situation of weak effectiveness and high adverse reactions of existing treatments

Upgrading OIC Medications

- The domestic market for OIC medications is still dominated by traditional drugs (such as lactulose, PEG, etc.). The market share of newer OIC medications (e.g., PAMORAs) remains significantly lower compared to international markets. By now, no specialized drugs have been approved by NMPA, but several OIC oral drugs are in late stages of clinical development

PAMORAs as the Research Focus

- Non-selective opioid receptor antagonists (e.g., naloxone), can relieve OIC, but they may concurrently diminish the analgesic effects of opoids, thereby restricting their clinical application. As a result, PAMORAs, which can alleviate intestinal dysfunction induced by opoids without impacting their analgesic effect, have become a hot topic in the research and development of OIC medications

Increased Purchasing Power

- With the improvement in the level of economic development, people's income level increases along with the ability to bear medical insurance burdens, enhancing patients' ability to pay. The penetration rate of innovative OIC drugs such as PAMORAs is expected to further increase

Source: Literature review; China Insights Consultancy

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Confirmation

#	Content
1	According to the World Health Organization, chronic diseases tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioral factors. Metabolic disorders (such as diabetes) and some digestive diseases are among the major types of chronic diseases
2	China has a vast population base, with the highest number of T2DM patients globally andconsiderable market potential. However, the treatment of T2DM in China faces a range of challenges. The traditional treatment options often provide limit patient benefits due to their adverse effects. Considering the chronic nature of T2DM, there are higher requirements for medication accessibility, compliance, safety, and comprehensive benefits. The affordability, long-term treatment experience and overall effectiveness is crucial in T2DM management in China. Additionally, there is a more urgent need for clinical solutions in remote areas, with a higher emphasis on the affordability oftreatments.GLP-1 receptor agonists have shown considerable potentials to combat such challenges, including favorable safety and efficacy profiles with fewer adverse effects and prolonged clinical benefits demonstrated in various clinical studies. Additional advantages of certain GLP-1 receptor agonist candidates such as PB-119 also include easy administration, increased patient compliance and better accessibility.
3	According to the ADA guidelines, the glucose-lowering agents for T2DM include GLP-1receptor agonists, metformin, DPP-4 inhibitors, $GLT-2 inhibitors, TZDs, insulintropic agents, insulin and others. The following table sets forth the pipeline of all approved GLP-1receptor agonists in the United States as of the Latest Practicable Date.
4	In China, it is expected that more than 80% of the market share of GLP-1 receptor agonists for the treatment of T2DM will be occupiedby long-acting GLP-I receptor agonists as of 2032, and more than 80% of the global market share of GLP-1 receptor agonists for the treatment of T2DM will be occupiedby long-acting GLP-I receptor agonists as of 2032
5	Increasing patient accessibilily of T2DM medicatons. Considering the chronic nature of T2DM, medication accessibility is crucial for patients to receive stable treatments. The affordability, long-term treatment experience and overall effectiveness is especially vital in T2DM management in China. Going forward, treatment options available to the vast majority of T2DM patients are likely to occupy more market share and benefit from the huge market potential.
6	Obesity has been a rising public health concern globally with relevant patient group expected to exceed one billion in size by the end of 2024. China has the largest obesity patient population in the world, and the number of obesity patients in China is expected to grow at a higher rate than that of more developed countries, such as the United States.
7	As of the Latest Practicable Date, there were five drug products approved by the FDA forthe treatment of OIC, being three peripherally acting μ-opioid receptor antagonists ("PAMORAs"), one opioid receptor antagonist and one CLCN2 activator, respectively. The following table sets forth the approved drugs for OIC in the United States.

Confirmation

#	Content
8	The NASH patients represent a large group globally, resulted from a combination of genetic and environmental causes and various risk factors. NASH has also been a rising public health concern in China with the country's rapid development in recent years and changes in people's lifestyles
9	The global and China markets follow the same treatment regimen for NASH. The international and national guidelines recommend that management for NAFLD and NASH patients varies depending on their risk of clinical liver fibrosis. Due to its complex pathogenesis, medication for NASH is still currently underdeveloped. In both the United States and China, no evidence-based pharmacological therapy is approved, and currently treatment of NASH is primarily limited to lifestyle changes, such as body mass management, controlling diabetes, avoiding alcohol, exercising regularly, reducing the total cholesterol level, and taking supplement with vitamin E. In addition, while there is no specific medication that directly treats NASH, taking metformin and statins treats the related metabolic disorders such as insulin resistance and high cholesterol. In addition, the American Association for the Study of Liver Diseases confirms that vitamin E and pioglitazone (a drug used to treat diabetes) are the two best drug choices for biopsy-confirmed NASH, but the safety and efficacy of such methods remain unclear.
10	GLP-1 receptor agonists exhibit promising treatment potential in the context of NAFLD. Research suggests that GLP-1 agonists may play a beneficial role in addressing the intricate interplay between insulin resistance, inflammation, and hepatic lipid accumulation associated with NAFLD. By targeting GLP-1 receptors, these agents not only contribute to glycemic control but also demonstrate potential in improving liver health. The anti-inflammatory and anti-fibrotic properties of GLP-1 receptor agonists are being investigated for their impact on reducing hepatic steatosis and preventing disease progression. As NAFLD is closely linked to metabolic dysfunction, the multifaceted effects of GLP-1 agonists make them a subject of interest in exploring comprehensive therapeutic strategies for this prevalent liver condtion
11	As of the Latest Practicable Date, there was no drug approved specifically for the treatment of NASH globally. There were a number of product candidates under clinical development in the United States, 11 of which were GLP-1 targeted, as of the same date.
12	In China, management of overweight and obesity primarily involves comprehensive lifestyle interventions, medications, and in severe cases, surgical treatments. However, there are only limited medications currently approved for the treatment of obesity, often with significant safety concerns for long-term usage and limited overall clinical benefits. Consequently, there are considerable unmet medical needs for the treatment of obesity in China. The following chart demonstrates the current treatment options for obesity patients with different severities in China.
13	Non-alcoholic steatohepatitis is liver inflammation and damage caused by excessive fat accumulation. It is the more severe form of non-alcoholic fatty liver disease ("NAFLD"), a term for a broad spectrum of liver conditions affecting people who consume little to no alcohol. NAFLD is characterized by fat deposition in the liver, and NASH is a necro-inflammatory process in which the liver cells are injured by fat accumulation. NASH can lead to liver scarring, which results in irreversible scarring (cirrhosis) and liver cancer if untreated. The risk factors of NASH include, among others, T2DM, insulin resistance, obesity, high blood choesterol and triglycerides, with a combination of which often simultaneously present in NASH patients.

Confirmation

#	Content
14	The NASH patients represent a large group globally, resulted from a combination of genetic and environmental causes and various risk factors. NASH has also been a rising public health concern in China with the country's rapid development in recent years and changes in people's lifestyles
15	At EASL Congress 2023, the multinational liver societies leaders from La Asociación Latinoamericana para el Estudio del Hígado (ALEH), American Association for the Study of Liver Diseases (AASLD), and European Association for the Study of the Liver (EASL) as well as the cochairs of the NAFLD Nomenclature Initiative announced that steatotic liver disease (SLD) was chosen as an overarching term to encompass the various aetiologies of steatosis. Nonalcoholic fatty liver disease (NAFLD) will now be metabolic dysfunction-associated steatotic liver disease (MASLD). Metabolic dysfunction-associated steatohepatitis (MASH) is the replacement term for nonalcoholic steatohepatitis (NASH).
16	Strengthened public awareness. The surge in metabolic diseases prevalence including NASH has garnered heightened attention from the public, governments, medical institutions and social media, contributing to an enhanced awareness of NASH. Diverse channels are employed to educate physicians and NASH patients about disease diagnosis and pharmaceutical interventions. For instance, the National Health Commission of China initiated a specialized training program for metabolism physicians from regional medical and health services in 2022. This program aims to ensure accurate diagnoses of metabolic diseases, including NASH. Additionally, the establishment of more NASH care clinics in China enables physicians to offer comprehensive treatment, emphasizing rational medication use and lifestyle interventions.
17	As of the Latest Practicable Date, there was no drug approved specifically for the treatment of congenital hyperinsulinemia globally. The current treatment options of congenital hyperinsulinemia include diazoxide, octreotide, glucagon and sirolimus. While diazoxide treatment tends to exhibit efficacy initially, rapidly occurred tolerance issues and adverse reactions include elevated liver enzymes and asymptomatic gallbladder disorders often limit its long-term use. Therefore, as the treatment duration extends, the need for continuous alternation of new drugs or alternative treatment approaches persists.
18	Obesity is also a non-neglectable public health issue in China and globally, which is sometimes associated with other metabolic diseases such as NASH as well. As of February 19, 2024, there were six GLP-1/GCG dual receptor agonist candidates under clinical development for the treatment of obesity in the United States.
19	While no head-to-head studies were conducted, PB-119 distinguished itself as the only GLP-1 drug amongst the agents tested in the clinical trial with a sustained glucose-lowering effect till 52 weeks and no rebound, based on the published clinical trial results of the GLP-1 receptor agonists approved for commercialization.
20	For patients with ◎IC, laxatives are usually given as first-line treatment option. However, laxatives could only partially alleviate the symptoms for some of the OIC patients with limited clinical benefits, As a result, opioid receptor antagonists are being developed as potentially more effective treatment options. The following table demonstrates the current treatment options for OIC patients globally and in China as well as their corresponding features.

The following table sets forth the pipeline of all approved GLP-1 receptor agonists in the United States as of the Latest Practicable Date

Pipeline of GLP-1 Receptor Agonists Approved in the United States

Drug Name	Brand Name	MoA	Efficacy Length	Indication		Administration	Company	Approval Date
				T2DM	Overweight/Obesity			
Exenatide	Byetta®	GLP-1R	Short-acting	✓		s.c.	AstraZeneca	2005/04/28
Liraglutide	Victoza®	GLP-1R	Short-acting	✓		s.c.	Novo Nordisk	2010/01/25
	Saxenda®	GLP-1R	Short-acting		✓	s.c.		2014/12/23
Exenatide ER	Bydureon®	GLP-1R	Long-acting	✓		s.c.	AstraZeneca	2012/01/27
Albiglutide	Tanzeum®	GLP-1R	Long-acting	✓		s.c.	GlaxoSmithKline	2014/04/15
Dulaglutide	Trulicity®	GLP-1R	Long-acting	✓		s.c.	Eli Lilly	2014/09/18
Lixisenatide	Adlyxin®	GLP-1R	Short-acting	✓		s.c.	Sanofi	2016/07/27
Semaglutide	Ozempic®	GLP-1R	Long-acting	✓		s.c.	Novo Nordisk	2017/12/05
	Rybelsus®	GLP-1R	Short-acting	✓		p.o.		2019/09/20
	Wegovy®	GLP-1R	Long-acting		✓	s.c.		2021/06/04

Notes:

- There is one GLP-1/GIP dual receptor agonist, Tirzepatide, that has been approved by the FDA for the treatment of T2DM or obesity indications in the United States, under the brand names Mounjaro and Zepbound, respectively

Source: FDA, China Insights Consultancy

Pipeline of GLP-1 Receptor Agonists Approved for the Treatment of T2DM and/or Overweight/Obesity in China

Pipeline of GLP-1 Receptor Agonists Approved for the Treatment of T2DM and/or Overweight/Obesity in China (1/2)

Drug Name	Brand Name	MoA	Efficacy Length	Indication	Administration	NRDL status	NRDL price (RMB/unit)	Monthly Spending (RMB) [4]	Company	Approval Date
Exenatide	/	GLP-1R	Short-acting	T2DM	s.c.	N/A	N/A	N/A	Hybio Pharmaceutical	2024/9/10
Liraglutide[1]	贝乐林	GLP-1R	Short-acting	T2DM	s.c.	No	N/A[2]	N/A	Chia Tai Tianqing	2024/6/25
Semaglutide	诺和盈/Wegovy	GLP-1R	Long-acting	Overweight/Obesity	s.c.	No	N/A[2]	N/A	Novo Nordisk	2024/6/25
Semaglutide	诺和泊/Rybelsus	GLP-1R	Short-acting	T2DM	p.o.	No	N/A[2]	N/A	Novo Nordisk	2024/1/26
Liraglutide[1]	纯博力	GLP-1R	Short-acting	T2DM	s.c.	Category B	268/(18mg:3ml)	~750	Tonghua Dongbao	2023/11/28
Beinaglutide	菲塑美	GLP-1R	Short-acting	Overweight/Obesity	s.c.	No	N/A[3]	N/A	Shanghai Benemae	2023/7/28
Liraglutide[1]	利善平	GLP-1R	Short-acting	Overweight/Obesity	s.c.	No	N/A[3]	N/A	Jiuyuan Gene	2023/7/4
Liraglutide[1]	利善平	GLP-1R	Short-acting	T2DM	s.c.	Category B	~300/(18mg:3ml)	~840	Jiuyuan Gene	2023/3/28
Exenatide[1]	/	GLP-1R	Short-acting	T2DM	s.c.	Category B	407.83/(0.25mg:2.4ml)	~815	Qinghai Chenfei	2022/7/29
Beinaglutide	谊生泰	GLP-1R	Short-acting	T2DM	s.c.	Category B	191/(4.2mg:2.1ml)	~764	Shanghai Benemae	2021/10/28
Semaglutide	诺和泰/Ozempic	GLP-1R	Long-acting	T2DM	s.c.	Category B	478.8/(2mg:1.5ml)	~957	Novo Nordisk	2021/4/27
Liraglutide	诺和力/Victoza	GLP-1R	Short-acting	T2DM	s.c.	Category B	339/(18mg:3ml)	~1,148	Novo Nordisk	2011/10/9
Polyethylene Glycol Loxenatide	孚来美	GLP-1R	Long-acting	T2DM	s.c.	Category B	187/(0.2mg:0.5ml)	~748	Hansoh	2019/5/5
Dulaglutide	度易达/Trulicity	GLP-1R	Long-acting	T2DM	s.c.	Category B	149/(1.5mg:0.5ml)	~596	Eli Lilly	2019/2/22
Exenatide Microspheres	百达扬/Bydureon	GLP-1R	Long-acting	T2DM	s.c.	Category B	496.25/(2 mg:0.65ml)	~1,985	AstraZeneca	2017/12/28
Lixisenatide	利时敏/Adlyxin	GLP-1R	Short-acting	T2DM	s.c.	Category B	157.65/(150μg)	~588	Sanofi	2017/9/29
Exenatide	百达达/Byetta	GLP-1R	Short-acting	T2DM	s.c.	Category B	240/(5μg:1.2ml)	~815	AstraZeneca	2005/8/1

Source: NMPA; China Insights Consultancy

Pipeline of GLP-1 Receptor Agonists Approved for the Treatment of T2DM and/or Overweight/Obesity in China

Pipeline of GLP-1 Receptor Agonists Approved for the Treatment of T2DM and/or Overweight/Obesity in China （2/2）

Notes:

1. Generic or biosimilar product
2. Marketed price not yet available
3. Not yet included in NRDL
4. Monthly spending estimated on recommended dosage indicated on drug label for 4 weeks
5. GLP-1 receptor agonists target GLP-1 receptors in the brain, cerebral blood vessels, pancreas, heart, gastrointestinal tract, adipose tissue, kidney and muscles, and consequently affect a variety of organs and physiological processes
6. There is one GLP-1/GIP dual receptor agonist, Tirzepatide, that has been approved by the NMPA for the treatment of T2DM or obesity indications in China

Source: NMPA, Chinese Journal of Modern Applied Pharmacy, National Reimbursement Drug List, NHSA, drug labels, China Insights Consultancy

Pipeline of Insulin GLP-1 Receptor Agonist Combination Therapies Approved in China and the United States

Pipeline of Insulin GLP-1 Receptor Agonist Combination Therapies Approved in China and the United States

Drug Name	Brand Name	MoA	Efficacy Length	Administration	Company	Approval Date FDA	Approval Date NMPA	NRDL status
iDegLira	Xulophy/诺和达	Insulin degludec/Liraglutide	Long-acting	s.c.	Novo Nordisk	2016/11/21	2021/10/28	Category B
iGlarLixi	Soliqua/赛达宁	Insulin degludec/Liraglutide	Short-acting	s.c.	Sanofi	2016/11/21	2023/1/13	Category B

Source: FDA, NMPA, China Insights Consultancy

Pipeline of GLP-1 Receptor Agonists for T2DM with Accepted NDA or Undergoing Phase III Clinical Trial in China

Pipeline of GLP-1 Receptor Agonists for T2DM with Accepted NDA or Undergoing Phase III Clinical Trial in China (1/2)

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
PB-119	GLP-1R	PegBio	T2DM	s.c.	NDA	2023/9/26	CTR20201492	NMPA
Liraglutide biosimilar	GLP-1R	Chenan; Paijin	T2DM	s.c.	NDA	2024/12/3	CTR20210173	NMPA
Ecnoglutide	GLP-1R	Hangzhou Sciwind	T2DM	s.c.	NDA	2024/11/23	CTR20223156	NMPA
Semaglutide	GLP-1R	Qilu Pharmaceutical	T2DM	s.c.	NDA	2024/9/15	CTR20230841	NMPA
Semaglutide biosimilar	GLP-1R	Livzon Group	T2DM	s.c.	NDA	2024/6/16	CTR20222962	NMPA
CJC-1134-PC	GLP-1R	Hebei Changshan; Hbcsbio	T2DM	s.c.	NDA	2024/4/24	CTR20222496	NMPA
HDG1901	GLP-1R	Hangzhou Jiuyuan Gene Engineering	T2DM	s.c.	NDA	2024/4/3	CTR20232286	NMPA
Liraglutide biosimilar	GLP-1R	Zhuhai United	T2DM	s.c.	NDA	2023/8/22	CTR20200348	NMPA
GZR-18	GLP-1R	Ganlee	T2DM	s.c.	III	2024/12/26	CTR20244787	NMPA
Semaglutide	GLP-1R	Sinopep Allsino	T2DM	s.c.	III	2024/11/28	CTR20244501	NMPA
Noiiglutide	GLP-1R	Jiangsu Hengrui	T2DM	s.c.	III	2024/10/15	CTR20243773	NMPA
HRS-7535	GLP-1R	Shandong Suncadia	T2DM	p.o.	III	2024/9/13	CTR20243398	NMPA
Semaglutide biosimilar	GLP-1R	Zhuhai United	T2DM	s.c.	III	2024/9/10	CTR20243310	NMPA

Pipeline of GLP-1 Receptor Agonists for T2DM with Accepted NDA or Undergoing Phase III Clinical Trial in China

Pipeline of GLP-1 Receptor Agonists for T2DM with Accepted NDA or Undergoing Phase III Clinical Trial in China (2/2)

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
Semaglutide	GLP-1R	China Resources Double-Crane	T2DM	s.c.	III	2024/7/18	CTR20242569	NMPA
JY09	GLP-1R	Beijing Dongfang Eiotech; Beijing Jingyitaixiang	T2DM	s.c.	III	2024/4/17	CTR20240355	NMPA
TG103	GLP-1R	CSPC Baike (Shandong) Biopharmaceutical	T2DM	s.c.	III	2024/2/26	CTR20240429	NMPA
Orforglipron	GLP-1R	Eli Lilly	T2DM	p.o.	III	2023/11/2	CTR20233528	NMPA
Recombinant GLP-1RA	GLP-1R	Beijing Lepu	T2DM	s.c.	III	2023/1/29	CTR20230029	NMPA
GMA102	GLP-1R	Hongyun Huaning	T2DM	s.c.	III	2022/10/11	CTR20222558	NMPA
rExenatide-4	GLP-1R	CSPC Zhongqi	T2DM	s.c.	III	2017/11/27	CTR20170495	NMPA

Note:
1. denotes the date when CDE announces it receives the NDA for applicable pipelines
2. denotes the Phase III trial number

Source: FDA, NMPA, China Insights Consultancy

Pipeline of Candidates for T2DM Undergoing Phase III Clinical Trial in United States

Pipeline of Candidates for T2DM Undergoing Phase III Clinical Trial in United Sates

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
CagriSema	AMY3; GLP-1R	Novo Nordisk	T2DM	s.c.	III	2024/3/21	NCT06323174	FDA
CMG190303	SGLT2; HMGCR	Cmg Pharma	T2DM	N/A	III	2025/1/13	NCT06772168	FDA
GZR-18	GLP-1R	Ganlee	T2DM	s.c.	III	2025/1/15	NCT06777238	FDA
HGD1901	GLP-1R	Hangzhou Zhongmei Huadong	T2DM	s.c.	III	2024/12/10	NCT06739044	FDA
BGM-0504	GIPR; GLP-1R	BrightGene	T2DM	s.c.	III	2024/12/4	NCT06716203	FDA
HRS-7535	GLP-1R	Shandong Suncadia	T2DM	p.o.	III	2024/11/4	NCT06672172	FDA
HRS-9531	GIPR; GLP-1R	Shandong Suncadia	T2DM	s.c.	III	2024/10/18	NCT06649344	FDA
Noiiglutide	GLP-1R	Jiangsu Hengrui	T2DM	s.c.	III	2024/10/21	NCT06649773	FDA
Insulin Degludec/Liraglutide	INSR; GLP-1R	Tonghua Dongbao	T2DM	s.c.	III	2024/8/19	NCT06559722	FDA
IcoSema	INSR; GLP1R	Novo Nordisk	T2DM	s.c.	III	2024/2/21	NCT06269107	FDA
Retatrutide	GIPR; GLP-1R; GCGR	Eli Lilly	T2DM	s.c.	III	2024/2/15	NCT06260722	FDA
TG103	GLP-1R	CSPC Baike (Shandong) Biopharmaceutical	T2DM	s.c.	III	2024/2/14	NCT06258148	FDA
Survodutide	GLP-1R; GCGR	Boehringer Ingelheim	T2DM	s.c.	III	2023/10/4	NCT06066528	FDA
Orforglipron	GLP-1R	Eli Lilly	T2DM	p.o.	III	2023/8/24	NCT06010004	FDA
MSDC-0602K	MPC	Cirius Therapeutics Inc	T2DM	p.o.	III	2019/5/31	NCT03970031	FDA

Source: FDA, NMPA, China Insights Consultancy

Pipeline of Candidates for T2DM with Accepted NDA in China

Pipeline of Candidates for T2DM with Accepted NDA in China

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date[2]	Competent authurity
PB-119	GLP-1R	PegBio	T2DM	s.c.	NDA	2023/9/26	NMPA
IcoSema	INSR; GLP-1R	Novo Nordisk	T2DM	s.c.	NDA	2024/12/7	NMPA
Liraglutide biosimilar	GLP-1R	Chenan; Paijin	T2DM	s.c.	NDA	2024/12/3	NMPA
Ecnoglutide	GLP-1R	Hangzhou Sciwind	T2DM	s.c.	NDA	2024/11/23	NMPA
Semaglutide	GLP-1R	Qilu Pharmaceutical	T2DM	s.c.	NDA	2024/9/15	NMPA
IBI362	GCGR; GLP-1R	Innovent	T2DM	s.c.	NDA	2024/8/1	NMPA
Semaglutide[1]	GLP-1R	Livzon Group	T2DM	s.c.	NDA	2024/6/16	NMPA
CJC-1134-PC	GLP-1R	Hebei Changshan: Hbcsbio	T2DM	s.c.	NDA	2024/4/24	NMPA
HDG1901[1]	GLP-1R	Hangzhou Jiuyuan Gene Engineering	T2DM	s.c.	NDA	2024/4/3	NMPA
HEC-44616	SGLT2	HEC Pharm	T2DM	p.o.	NDA	2024/1/11	NMPA
Brenzavvy	SGLT2	Newsoara Biopharma; Piramal Healthcare; TheracosBio	T2DM	p.o.	NDA	2024/1/4	NMPA
HR20031[4]	DPP-4; PRKAB-1; SGLT-2	Shengdi Medical	T2DM	p.o.	NDA	2023/11/11	NMPA
Liraglutide[1]	GLP-1R	Zhuhai United	T2DM	s.c.	NDA	2023/8/22	NMPA
ORMD-0801	INSR[3]	Oramed Ltd	T2DM	p.o.	NDA	2023/4/25	NMPA

Notes:

1. *Biosimilar or generic candidates*
2. *denotes the date when CDE announces it receives the NDA*
3. *INSR = insulin receptor*
4. *compound formulation of SGLT-2i, DPP-4i and metformin*

Source: CDE, China Insights Consultancy

Overweight/obesity Approved drugs in U.S.

- Currently, six overweight/obesity drugs have been approved by FDA

Approved overweight/obesity drug by FDA in U.S., As of LPD

Drug Name	MoA	Company	Approval	Indication	Administration	Dosage Frequency	Annual Cost	Pros	Cons
Orlistat	Lipase Inhibitor	Roche	04/1999	Obesity	p.o.	TID.	$1,095	• Oral formulation can increase compliance • Effective weight loss	• Has side-effects that affect quality of life, such as faecal incontinence • Lack of fat-soluble vitamins
Phentermine/ Topiramate	NE/GABA	Vivus	07/2012	Overweight/ obesity	p.o.	QD.	$1,615	• Good patient compliance • Effective weight loss	• Bothersome side effect, such as dry mouth and a tingling sensation in hands
Naltrexone/ Bupropion	Opioid antagonist	Orexigen	09/2014	Overweight/ obesity	p.o.	BID.	$3,234	• Good patient compliance • Moderate weight loss	• Carry FDA black box warning about suicidal thinking
Liraglutide	GLP-1	Novo Nordisk	12/2014	Overweight/ obesity	s.c.	QD.	$3,276	• Simultaneously controls blood glucose • Effective weight loss	• Short-acting • Higher injection frequency • Increase the risk of GI adverse effect
Semaglutide	GLP-1	Novo Nordisk	06/2021	T2DM; Overweight/ obesity	s.c.	QW.	$3,527	• Long acting • Simultaneously controls blood glucose • Marked weight loss	• Increase the risk of GI adverse effect
Tirzepatide	GIP/GLP-1	Eli Lilly	11/2023	T2DM; Overweight/ obesity	s.c.	QW.	$12,276	• Long acting • Simultaneously controls blood glucose • Significant weight loss	• Increase the risk of GI adverse effect • Withdraw drug lead to weight rebound
Setmelanotide	MC4R	Rhythm Pharmaceuticals	11/2020	Rare genetic diseases of obesity	s.c.	QD.	$390,559	• Applicable to patients with specific types of rare obesity disorders	• Skin hyperpigmentation • Increase the risk of GI adverse effect • Depression and suicidal ideation

Notes: Approval refers to the time when the weight loss indication was granted; GABA = gamma-aminobutyric acid; GIP = Gastric inhibitory polypeptide; NE = norepinephrine; Rare genetic diseases of obesity refers to POMC, PCSK1, or LEPR deficiency

Source: The Lancet; FDA; China Insights Consultancy

Overweight/obesity Approved drugs in China

- Currently, only three overweight/obesity crugs have been approved in the domestic market

Approved overweight/obesity drug by NMPA in China, As of LPD (1/2)

Drug Name	MoA	Company	Approval	Indication	Administration	Dosage Frequency	Unit Price	Annual Cost	NRDL	Pros	Cons
Orlistat[1]	Lipase Inhibitor	Roche	03/2001	Obesity/ overweight	p.o.	TID.	¥ 598 (0.12g*42)	¥ 15,548[2]	Not covered[5]	• Oral intake is more convenient	• Has socially inconvenient side-effects, such as faecal incontinence
Liraglutide[3]	GLP-1	Hangzhou Zhongmei Huadong	07/2023	T2DM; Obesity/ Overweight[6]	s.c.	QD.	¥ 300 (18mg:3ml)	¥ 18,200[3]	Not covered[5]	• Effective weight loss	• Short-acting • Higher injection frequency • expensive • Increase the risk of GI adverse effect
Beinaglutide	GLP-1	Shanghai Benemae	07/2023	Obesity/ Overweight[7]	s.c.	TID.	¥ 216 (4.2mg:2.1ml)	¥ 11,232[4]	Not covered[5]	• Modest weight loss	• Short-acting • Higher injection frequency • expensive
Mazindol	blocks dopamine & norepinephrine reuptake	Desano	07/2020	Simple obesity	p.o.	QD.	N/A	N/A	Not covered[5]	• Direct suppression of appetite	• Rebound weight gain discontinuation of mazindol • significant side effects
Semaglutide	GLP-1	Novo Nordisk	06/2024	Obesity/ Overweight	s.c.	QW.	N/A	N/A	Not covered[5]	• Long acting • Simultaneously controls blood glucose • Marked weight loss	• Increase the risk of GI adverse effect
Tirzepatide	GLP-1R; GIPR	Eli Lily	07/2024	Obesity/ Overweight	s.c.	QW.	N/A	N/A	Not covered[5]	• Long acting • Effective weight • loss	• Expensive

Overweight/obesity Approved drugs in China

- Currently, only three overweight/obesity drugs have been approved in the domestic market

Approved overweight/obesity drug by NMPA in China, As of LPD (2/2)

Notes:

1. The originator, Orlistat, was developed by Roche and named Xenical. However, due to a business adjustment by Roche, Xenical began to gradually exit the Chinese market in 2008. In 2010, Zein Biotechnology launched a generic version of the Orlistat capsule, and several branded generic products have been approved in the Chinese market since then. As of LPD, 2023, there are 21 generic Orlistat products approved in China
2. 120mg TID. dosage based on the Summary Review of Orlistat (NDA 020766), expected treatment duration is 52 weeks
3. 3.0mg daily dosage based on clinical data (NCT01272219), expected treatment duration is 52 weeks
4. 0.2mg TID. dosage based on clinical data (CTR20190408), expected treatment duration is 52 weeks
5. Only T2DM indications are covered by medical insurance. obesity/overweight indications are not covered by medical insurance
6. Indications and usage on labeling: adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m2 or greater (obesity), or 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)
7. Indications and usage on labeling: Indicated for weight management in adult patients with a BMI ≥ 28kg/m2, or BMI ≥ 24kg/m2 and at least one weight associated metabolic disorders (eg, hypertension, hypertension, dyslipidemia, fatty liver, obstructive sleep apnea syndrome)
8. Generic or biosimilar product.
9. There is one GLP-1/GIP dual receptor agonist, Tirzepatide, that has been approved by the NMPA for the treatment of T2DM or obesity indications in China.

Sources: Advances in Therapy, Chinese Medical Frontier Journal, Chinese Journal of Health Management, NMPA, China Insights Consultancy

Pipeline of Clinical-stage GLP-1 Receptor Agonists for Obesity in the United States

Pipeline of Clinical-stage GLP-1 Receptor Agonists for Obesity in the United States

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
Orforglipron	GLP-1R	Eli Lilly	T2DM/Obesity/Overweight/CVDs/CKDs	p.o.	III	2023/4/7	NCT05803421	FDA
			Obesity/Overweight/T2DM	p.o.	III	2023/3/24	NCT05872620	FDA
			Overweight/Obesity	p.o.	III	2023/3/22	NCT05869903	FDA
AZD5004	GLP-1R	AstraZeneca	Overweight/Obesity	p.o.	II	2024/10/8	NCT06579092	FDA
ROSE-010	GLP-1R	Rose Pharma	Overweight/Obesity	s.c.	II	2024/10/1	NCT06621017	FDA
RGT-075	GLP-1R	Regor	Obesity	p.o.	II	2024/2/26	NCT06277934	FDA
K-757	GLP-1R	Kallyope	Obesity	p.o.	II	2023/8/31	NCT06019559	FDA
S-309309	GLP-1R	Shionogi	Obesity	p.o.	II	2023/6/29	NCT05925114	FDA
Danuglipron	GLP-1R	Pfizer	Obesity/Overweight/T2DM	p.o.	II	2021/1/13	NCT04707313	FDA
GSBR-1290	GLP-1R	Gasherbrun Bio	Obesity/Overweight/T2DM	p.o.	I/II	2023/1/25	NCT05762471	FDA
CT-996	GLP-1R	Carmo	Obesity/Type 2 Diabetes	p.o.	I	2023/5/9	NCT05814107	FDA
XW014	GLP-1R	Sciwind	Obesity/Type 2 Diabetes/MASH	p.o.	I	2022/10/13	NCT05579314	FDA

Source: ClinicalTrials.gov, China Insights Consultancy

Pipeline of Clinical-stage GLP-1 Receptor Agonists for Obesity in China

Pipeline of Clinical-stage GLP-1 Receptor Agonists for Obesity in China

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
PB-119	GLP-1R	PegBio	Overweight/obesity	s.c.	I	2024/4/17	CTR20241107	NMPA
Semaglutide	GLP-1R	Jiangsu Thery	Obesity	s.c.	III	2024/12/23	CTR20244777	NMPA
GZR-18	GLP-1R	Ganlee	Overweight/obesity	s.c.	III	2024/12/18	CTR20244647	NMPA
Semaglutide	GLP-1R	Jiangsu Sinopep	Obesity	s.c.	III	2024/12/12	CTR20244492	NMPA
VCT220	GLP-1R	Vincentage	Overweight/obesity	p.o.	III	2024/11/20	CTR20244365	NMPA
Semaglutide	GLP-1R	Chengdu Beite	Obesity	s.c.	III	2024/9/30	CTR20243408	NMPA
ZT006	GLP-1R	QL Biopharm	Overweight	p.o.	I	2024/11/15	CTR20244313	NMPA
Semaglutide	GLP-1R	CSPC	Obesity	s.c.	III	2024/9/14	CTR20243491	NMPA
Orforglipron	GLP-1R	Eli Lilly	Overweight/obesity	p.o.	III	2023/8/11	CTR20232459	NMPA
Ecnoglutide	GLP-1R	Sciwind	Overweight/obesity	s.c.	III	2023/3/15	CTR20230745	NMPA
Semaglutide	GLP-1R	Novo Nordisk	Weight management	s.c.	III	2023/9/8	CTR20232812	NMPA
BPYT01	GLP-1R	Baiji Youtang	Overweight/obesity	s.c.	II	2024/8/13	CTR20242957	NMPA
ZT002	GLP-1R	QL Biopharm	Overweight/obesity	s.c.	II	2024/7/12	CTR20242527	NMPA
HDM1002	GLP-1R	Hangzhou Zhongmei Huadong	Overweight/obesity	p.o.	II	2024/4/11	CTR20241151	NMPA
Supaglutide	GLP-1R	Inrogen	Overweight/obesity	s.c.	II	2024/3/11	CTR20240801	NMPA
HRS-7535	GLP-1R	Shandong Shengdi	Obesity	p.o.	II	2024/2/18	CTR20240369	NMPA
GMA-105	GLP-1R	Hongyun Huaning	Overweight/obesity	s.c.	Ib/II	2022/6/27	CTR20221601	NMPA
MDR-001	GLP-1R	MindRank	Overweight/obesity	s.c.	II	2024/8/23	CTR20243057	NMPA
SAL-0112	GLP-1R	Saubris	Overweight/obesity	p.o.	I	2023/12/18	CTR20233948	NMPA

Notes: Biosimilars registered at CDE not included
Source: CDE, China Insights Consultancy

Pipeline of Clinical-stage GLP-1/GCG Dual Receptor Agonists for Obesity in the United States

Pipeline of Clinical-stage GLP-1/GCG Dual Receptor Agonists for Obesity in the United States

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
IBI362 (Mazdutide)	GLP-1R/GCGR	Eli Lilly/Innovent	Diabetes Mellitus/T2DM/Obesity	s.c.	III	2023/12/28	NCT06184568	FDA
			Diabetes Mellitus/T2DM	s.c.	III	2022/11/7	NCT05606913	FDA
Survodutide	GLP-1R/GCGR	Boehringer Irgelheim	Obesity/NASH	s.c.	III	2024/3/13	NCT06309992	FDA
			Obesity	s.c.	III	2023/10/11	NCT06077864	FDA
			Obesity/T2DM	s.c.	III	2023/10/4	NCT06066528	FDA
			Obesity	s.c.	III	2023/10/4	NCT06066515	FDA
Pemvidutide	GLP-1R/GCGR	Altimmune	Obesity/Overweight	s.c.	II	2022/3/25	NCT05295875	FDA
Efinopegdutide	GLP-1R/GCGR	Merck Sharp & Dohme LLC	Obesity/T2DM	s.c.	II	2018/7/16	NCT03586830	FDA
			Obesity	s.c.	II	2018/4/3	NCT03486392	FDA
DA-1726	GLP-1R/GCGR	Neurobo	Obesity	s.c.	I	2024/2/9	NCT06252220	FDA
DD01	GLP-1R/GCGR	Neuraly	Overweight/Obesity/T2DM/MASLD	s.c.	I	2021/3/23	NCT04812262	FDA
NNC9204-1177	GLP-1R/GCGR	Novo Nordisk	Overweight/Obesity	s.c.	I	2019/8/16	NCT04059367	FDA
			Metabolism and Nutrition Disorder/Obesity	s.c.	I	2016/10/21	NCT02941042	FDA

Source: ClinicalTrials.gov, China Insights Consultancy

Pipeline of Clinical-stage GLP-1/GCG Dual Receptor Agonists for Obesity in China

Pipeline of Clinical-stage GLP-1/GCG Dual Receptor Agonists for Obesity in China

Candidate	MoA	Company	Phase	Indication	Administration	Firrst Posted Date	Trial Number
PB-718	GLP-1/ GCG	PegBio	I	Overweight/obesity	s.c.	2023/05/31	CTR20231655
Mazdutide	GLP-1/ GCG	Innovent	NDA	Overweight/obesity	s.c.	2023/12/26[1]	CTR20231655
Survodutide	GLP-1/ GCG	Boehringer Ingelheim	III	Overweight/obesity	s.c.	2023/12/14	CTR20231655

Notes:
1. Mazdutide's NDA was accepted by the CDE in February 2024, its First Post Date and Trial Number denote its earliest Phase III clinical trial registered at the CDE.

Source: CDE, China Insights Consultancy

Pipeline of Clinical-stage GLP-1 Receptor-Targeted NASH Drug Candidates in the United States

Pipeline of Clinical-stage GLP-1 Receptor-Targeted NASH Drug Candidates in the United States

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
PB-718	GLP-1R/GCGR	PegBio	NASH	s.c.	I	2021/8/25	NCT05021666[1]	FDA
Survodutide	GLP-1R/GCGR	Boehringer Ingelheim	NASH	s.c.	III	2024/3/13	NCT06309992	FDA
Semaglutide	GLP-1R	Novo Nordisk	NASH	s.c.	III	2021/3/30	NCT04822181	FDA
DD-01	GLP-1R/GCGR	Neuraly Inc	NAFLD	s.c.	II	2024/5/13	NCT06410924	FDA
Pemvidutide	GLP-1R/GCGR	Altimmune	NASH	s.c.	II	2023/8/14	NCT05989711	FDA
Efinopegdutide	GLP-1R/GCGR	Merck Sharp & Dohme LLC	MASH, NASLD	s.c.	II	2023/5/26	NCT05877547	FDA
Efocipegtrutide (HM15211)	GLP-1R/GCGR/GIPR	Hanmi Pharmaceutical	NASH	s.c.	II	2020/8/7	NCT04505436	FDA
AZD9550	GLP-1R/GCGR	AstraZeneca	NASLD	s.c.	I/II	2023/11/30	NCT06151964	FDA
VK2735	GLP-1R/GCGR	Viking Therapeutics	NASLD	p.o.	I	2022/1/24	NCT05203237	FDA

Notes:

1. *Trial NCT05021666 is conducted on healthy participants*

Source: ClinicalTrials.gov, China Insights Consultancy

Pipeline of Clinical-stage GLP-1 Receptor-Targeted NASH Drug Candidates in China

Pipeline of Clinical-stage GLP-1 Receptor-Targeted NASH Drug Candidates in China

Candidate	MoA	Company	Indication	Administration	Phase	Firrst Posted Date	Trial Number	Competent authurity
Survodutide	GLP-1R/GCGR	Boehringer Ingelheim	NASH	s.c.	III	2024/11/26	CTR20244843	NMPA
Semaglutide	GLP-1R	Novo Nordisk	NASH	s.c.	III	2021/07/27	CTR20211818	NMPA
Efinopegdutide	GLP-1R/GCGR	Merck & Co.	NASH	s.c.	II	2023/10/19	CTR20233311	NMPA
HEC88473	GLP-1R/FGF21	GUANGDONG HEC TECHNOLOGY	NASH, T2DM, Obesity	s.c.	II	2023/08/17	CTR20232481	NMPA
UBT251	GLP-1R/GCGR/GIPR	Federal Biotechnology	T2DM, Overweight/Obesity, NASH	s.c.	Ia	2023/09/20	CTR20232997	NMPA

Source: CDE, China Insights Consultancy

Competitive landscape of CHI drugs

Pipelines of CHI drug candidates, CDE/FDA-registered, as of LPD

MoA	Drug Name	Company	Indication	Phase	First Posted Date	Trial Number	Approval Authority
GCGR	**PB-722 (PEGylated)**	**PegBio**	**CHI**	**IND approval**	**2023/02/27**	-	**CDE**
	Dasiglucagon	Zealand Pharma	CHI	NDA[1]	2018/12/17[2]	NCT04172441	FDA
	HM15136 (PEGylated)	Hanmi Pharm	CHI	II	2021/02/01	NCT04732416	FDA
	CSI-glucagon	Xeris Pharmaceuticals	CHI	II	2016/10/18	NCT02937558	FDA
INSR	RZ358	Rezolute; XOMA	CHI	III	2015/11/13	NCT04538989	FDA
GLP-1R	Exendin-(9-39)	Diva De Leon	CHI	I/II	2007/12/12	NCT00571324	FDA

Notes:
1. Zealand Pharma has submitted NDA to FDA regarding Dasiglucagon in June 2023. In January 2024, the FDA issued a complete response letter related to deficiencies identified at a third-party manufacturing facility. In October 2024, the FDA issued a complete response letter regarding the timing of a re-inspection.
2. The first posted date and trial number represents the Phase II/III trial of Dasiglucagon registered at ClinicalTrials.gov.

Source: CDE; Zealand Pharma; ClinicalTrials; China Insights Consultancy

OIC Approved products in US

- PAMORAs drugs such as methyltrexone, naldemedine and naloxegol are the mainstream of OIC in US

Mainstay drugs for 2L OIC therapy in US, as of LPD

MoA	Generic Name	Brand Name	Company	Administration	Approved Indication	First Approval Date	2022 global sales (Mn USD)
PAMORA	Naloxegol	Movantik	RedHill Biopharma	p.o.	chronic non-cancer pain OIC	2014/09/16	~180
	Methylnaltrexone	Relistor	Salix Pharmaceuticals	p.o.	OIC in adult patients with chronic non-cancer pain	2016/07/19	~250
				s.c.	OIC in adult patients with chronic non-cancer pain, OIC in adults with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient	2008/04/25	
	Naldemedine	Symproic	Shionogi	p.o.	chronic non-cancer pain OIC	2017/03	~60
CLCN2	Lubiprostone	Amitiza	Mallinckrodt Pharmaceuticals	p.o.	Chronic idiopathic constipation OIC in people with chronic, noncancer pain, or in patients with long-lasting pain caused by a previous cancer or its treatment, irritable bowel syndrome with constipation in women	2006/01/31	~190

Abbreviations: PAMORA = peripherally acting μ-opioid receptor antagonist

Source: FDA; China Insights Consultancy

OIC Approved products in China

Mainstay drugs for 2L OIC therapy in China, as of LPD

MoA	Genric Name	Brand Name	Company	Administration	Approved Indication	Approval Date
Opioid antagonist & opioid analgesic	Prolonged-release oxycodone/naloxone	来美欣	Luye Pharma	p.o.	For adults with severe pain that requires opioid analgesics to adequately control. The addition of the opioid receptor antagonist naloxone alleviates the symptoms of opioid-induced constipation by blocking the effect of oxycodone on the intestinal opioid receptors	2024/6/28
Opioid antagonist& opioid analgesic	Prolonged-release oxycodone/naloxone	奥施玛定	Mundipharma	p.o.	For adults with severe pain that requires opioid analgesics to adequately control. The addition of the opioid receptor antagonist naloxone alleviates the symptoms of opioid-induced constipation by blocking the effect of oxycodone on the intestinal opioid receptors	2022/11/22

Source: NMPA; China Insights Consultancy

Competitive landscape of OIC drugs in the US

Pipelines of OIC drug candidates, FDA-registered, as of LPD

MoA	Drug Name	Company	Administration	Indication	Phase	First posted date	Trial Number
PAMORA	Naloxegol	Trihealth	Oral	Constipation Constipation Drug Induced	II/III	2017/10/20	NCT03316859
	Naldemedine	Shionogi	Oral	Paediatric Participants Receiving Opioids	I/II	2022/10/20	NCT05588323
N/A	BGP345A	BioGaia Pharma	Oral	Opioid-Induced Constipation	II	2021/11/24	NCT05133076

Source: clinicaltrials.gov; China Insights Consultancy

Competitive landscape of OIC drugs

Pipelines of OIC drug candidates, CDE-registered, as of LPD

Drug Name	MoA	Company	Administration	Indication	Phase	First Posted Date	Trial Number
PB-1902 (PEGylated)	**PAMORA**	**PegBio**	**Oral**	OIC	**I**	**2021/10/21**	**CTR20212557**
					I	**2021/04/02**	**CTR20210655**
Methylnaltrexone Bromide	PAMORA	Yichang Renfu Pharmaceutical	Oral	OIC	BE	2024/5/6	CTR20241542
	PAMORA	Shenyang Eliving Pharmaceutical Technology	Injection	OIC	I	2018/07/02	CTR20180953
	PAMORA	Beijing Collab Pharma	Injection	OIC	III	2015/06/18	CTR20150393
	PAMORA	Furuikangzheng	Injection	OIC	II	2015/07/06	CTR20150290
	PAMORA	Institute of Toxicology, Academy of Military Medical Sciences, PLA. Beijing Molike Technology	Injection	OIC	III	2018/10/18	CTR20181837
Naldemedine	PAMORA	Shionogi	Oral	OIC	III	2022/03/22	CTR20220673
Prolonged-release oxycodone/naloxone	Opioid antagonist & opioid analgesic	Luye Pharma	Oral	OIC	NDA	2021/07/23	CTR20211699
Lubiprostone	CLCN2	Langxite	Oral	OIC in adult patients with chronic non cancer pain	BE	2018/12/20	CTR20182238
Naloxone Hydrochloride/ Oxycodone Hydrochloride Hydrate	Opioid receptors antagonist & opioid receptors agonist	Jiangsu Nhwa	Oral	OIC	BE	2024/7/18	CTR20242606

Notes:
1. Registered by Shanghai Hanmai, a subsidiary of PegBio
2. Bioequivalence trial

Source: CDE, China Insights Consultancy

Prospectus Confirmation

Confirmation

#	Content
1	According to CIC, long-acting GLP-1 receptor agonists referred to products that require an once-weekly dosing schedule such as that of PB-119, as compared to the frequent once- or multiple-daily dosing schedule required by short-acting GLP-1 receptor agonists
2	The clinical results regarding both monotherapy and combination therapy for T2DM have underpinned our NDA for PB-119 in China, which was accepted by the NMPA in September 2023, making it one of the earliest clinical-stage long-actng GLP-1 receptor agonists in China, according to CIC.
3	In addition, while we believe in the potential of PB-119 for the treatment of T2DM, obesity, overweight and even NASH, for instance, it has potential to be included in the standard treatment recommendations for these disease which help to change the treatment paradigms, according to CIC, however, it is premature at this stage to accurately predict the knock-on impact of PB-119 in the relevant markets
4	PB-1902 is the first and one of the only two domestically developed clinical-stage oral μ-opioid receptor antagonist drug candidates for the treatment of opioid-induced constipation ("OIC") under clinical trials in China as of the Latest Practicable Date, according to CIC.
5	During the Track Record Period and as of the Latest Practicable Date, we did not have any commercialized product. Our near-commercialized Core Product is one of the earliest domestically developed long-acting GLP-1 receptor agonists in China, according to CIC.
6	As of the Latest Practicable Date, the NMPA had accepted the NDAs of seven GLP-1 receptor agonists for the treatment of T2DM, and PB-119 was the second earliest to receive NDA acceptance from the NMPA among such candidates, according to CIC.
7	With the development of PB-119 and PB-718, we were among the few companies with multiple clinical-stage GLP-1-based product candidates for the treatment of overweight/obesity in China as of the Latest Practicable Date, according to CIC.
8	As of the Latest Practicable Date, there had been no new GLP-1-based product being approved in the markets that PB-119 and PB-718 intend to address, according to CIC.
9	According to CIC, our insurance policy is in line with the industry practice
10	Our Core Product PB-119 is one of the earliest domestically developed long-acting GLP-1 receptor agonists in China, according to CIC
11	According to CIC, metabolic diseases are among the fastest growing diseases worldwide with a global prevalence of 2,522 million in 2023, which is expected to increase to 2,991 million by 2032, representing a CAGR of 1.9%

Source: FDA, China Insights Consultancy

Confirmation

#	Content
12	While no head-to-head studies were conducted, PB-119 distinguished itself as the only GLP-1 drug with a sustained glucose-lowering effect till 52 weeks and no rebound demonstrated in clincal trial, based on the published clinical trial results of the GLP-1 receptor agonists approved for commercialization, according to CIC
13	PB-119 demonstrated rapid, significant and sustained efficacy with a differentiated broad range of benefits in the clinical trials, according to CIC.
14	We believe that multiple features of PB-119 can facilitate its administration and enhance patient compliance, according to CIC, which is critical for the long-term management of chronic and metabolic diseases.
15	The potency of PB-119 at relatively low dosage levels also allows us to pursue competitive pricing as another potential advantage, especially for patients who are more cost-sensitive in China and other emerging markets, according to CIC.
16	These effects are mutually beneficial and may lead to a more robust physiological response compared to those of GLP-1 receptor agonists alone, and provide improved glycemic control and substantial weight reduction. GLP-1/GCG dual receptor agonists have furthermore been shown to ameliorate liver fat content and fibrosis, as well as promoting liver regeneration, according to CIC.
17	Our near-commercialized Core Product is one of the earliest domestically developed long-acting GLP-1 receptor agonists in China, according to CIC.
18	PB-119 is one of the earliest domestically developed long-acting GLP-1 receptor agonists in China, according to CIC, and has demonstrated good safety and efficacy across 11 clinical trials in China and the United States.
19	Overall, PB-119 achieved significant glycemic control. While no head-to-head studies were conducted, PB-119 distinguished itself as the only GLP-1 drug with a sustained glucose-lowering effect till 52 weeks and no rebound demonstrated in clincal trial, based on the published clinical trial results of the GLP-1 receptor agonists approved for commercialization, according to CIC.
20	NASH is a chronic and progressive disease with Rezdiffra as the only FDA-approved treatment option as of the Latest Practicable Date, according to CIC.
21	According to CIC, as of the Latest Practicable Date, there was no GLP-1 receptor-targeted drug approved specifically for the treatment of NASH globally
22	According to CIC, as of the Latest Practicable Date, there were seven GLP-1/GCG dual receptor agonist candidates under clinical development for the treatment of obesity in the United States.

Prospectus Confirmation

Confirmation

#	Content
23	The clinical results regarding both monotherapy and combination therapy for T2DM have underpinned our NDA for PB-119 in China, which was accepted by the NMPA in September 2023, making it one of the earliest clinical-stage long-acting GLP-1 receptor agonists in China, according to CIC.
24	According to CIC, the global market size of T2DM and obesity treatment was US$70.3 billion and US$9.1 billion in 2023, respectively, and is anticipated to reach US$106.2 billion and US$58.5 billion in 2032, with CAGRs of 4.9% and 22.9%, respectively.
25	According to CIC, the global market size of GLP-1 receptor agonists is expected to reach US$110.6 billion by 2032. In 2022, GLP-1 receptor agonists accounted for more than 44% of the T2DM drug market in the United States, while they only accounted for approximately 10% in China's T2DM drug market, underscoring the market potential in China.
26	PB-1902 is the first and one of the only two domestically developed clinical-stage oral μ-opioid receptor antagonist drug candidates for the treatment of OIC in China as of the Latest Practicable Date, according to CIC.
27	As of the Latest Practicable Date, PB-1902 was the first and one of the only two domestically developed clinical-stage oral μ-opioid receptor antagonist drug candidates for the treatment of OIC in China, according to CIC.
28	As of the Latest Practicable Date, PB-722 was the first and only drug candidate with IND approval for the treatment of congenital hyperinsulinemia in China, according to CIC.
29	According to CIC, it is industry norm to engage CDMOs and utilize their equipment and resources required for mass production of drug substances, which could be costly in particular for biotech companies in the early stage of commercialization that are ramping up their production capacities.
30	During the Track Record Period and as of the Latest Practicable Date, we did not have any commercialized product. Our Core Product is one of the earliest domestically developed long-acting GLP-1 receptor agonists in China, according to CIC, upon obtaining the regulatory approvals from the NMPA.
31	Our Core Product PB-119 is one of the earliest domestically developed long-acting GLP-1 receptor agonists in China, according to CIC
32	According to CIC, metabolic diseases are among the fastest growing diseases worldwide, and they are also among the most common diseases in China.

The comparison of different types of GLP-1RAs

Drug name (generic)[1]		PB-119	Semaglutide	Polyethylene Glycol Loxenatide	Dulaglutide	Exenatide-ER
Efficacy length		Long-acting	Long-acting	Long-acting	Long-acting	Long-acting
Dose frequency		Once a week	Once a week	Once a week	Once a week	Once a week
Half life		2~3 days	~7 days	4~5 days	~5 days	One-week sustained release
Dose titration		No	Yes	No	Yes	No
T2DM	***Pricing in China***	N/A	478.8 RMB (2mg:1.5ml)	187 RMB (0.2mg:0.5ml)	149 RMB (1.5mg:0.5ml)	496.25 RMB (2mg:0.65ml)
	Monthly spending[2]	N/A	~957 RMB	~748 RMB	~596 RMB	~1,985 RMB
	NMPA approval date	N/A	诺和泰/Ozempic 2021/4/27	孚来美 2019/5/5	度易达/Trulicity 2019/2/22	百达扬/Bydureon 2017/12/28
Overweight/Obesity	***Expected Pricing in China***	N/A	N/A[4]	NM[3]	NM[3]	NM[3]
	NMPA approval date	N/A	诺和盈/Wegovy 2024/6/25	NM[3]	NM[3]	NM[3]

1. *Other long-acting GLP-1 receptor agonists include albiglutide. Albiglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist used for the treatment of type 2 diabetes. It was originally developed by GlaxoSmithKline (GSK) and was approved by FDA for marketing in 2014. By the end of 2017, GlaxoSmithKline announced that it would cease all further research, development, manufacturing, and sales activities for albiglutide, effectively withdrawing it from the market.*
2. *Monthly spending estimated on recommended dosage indicated on drug labels for 4 weeks*
3. *NM = Not Meaningful, no trials of overweight/obesity of underlying products registered at CDE*
4. *Not yet available*

Source: ClinicalTrial.gov; China Insights Consultancy

Representative drugs in T2DM treatment, FDA, NMPA, other than GLP-1 class

Representative drugs in T2DM treatment, FDA, NMPA, other than GLP-1 class

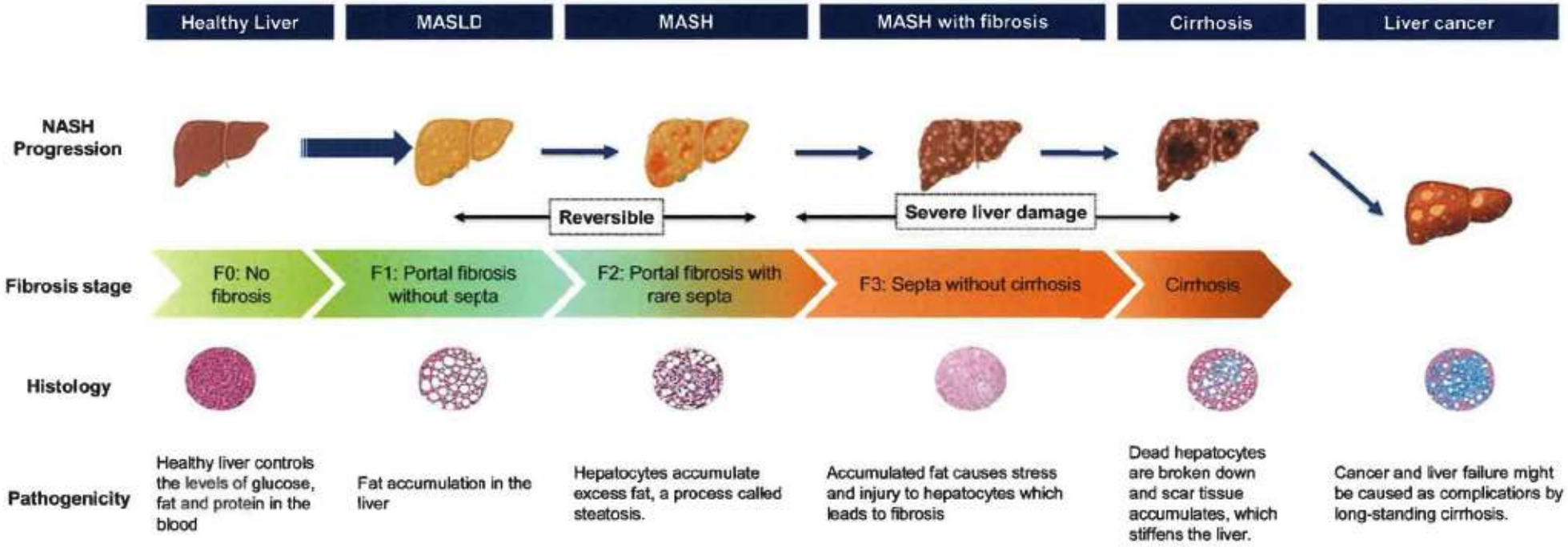
Medication	Brand name	Drug class	Company	Dosage	Global pricing[1]	NRDL pricing in China
Metformin[5]	Glucophage/格华止	Metformin	Merck	• Initial dose: 500 to 1000 mg orally once a day; increase in 500 mg weekly increments as tolerated	• ~$40 per 30 500mg oral tablet	• ~￥20 per 20 500mg oral tablets[3]
Insulin Glargine[5]	Lantus/兰格仕	Insulin	Sanofi	• 100 units/mL once daily	• ~$80 per 10 milliliters[2]	• ￥65.32 per 300 units[4]
Empagliflozin[5]	Jardiance/欧唯净	SGLT2	Boehringer Ingelheim/Eli Lilly	• Initial dose: 10 mg orally daily, dose may be increased to 25 mg	• ~$650 per 30 10mg oral tablet	• ~￥40 per 10 10mg tablets
Sitagliptin	Januva/捷诺维	DPP-4	MSD	• 100mg once daily	• ~$600 per 30 100mg oral tablet	• ~￥50 per 7 100mg tablets

Notes:

1. *Price in the US in US dollars, extracted from drugs.com*
2. *Sanofi announced that starting January 2024, the company will establish a cap on out-of-pockets prices of $35 on Lantus*
3. *Glucophage included in the NRDL but is not included for centralized procurement for metformin, the price level of metformin included in the centralized procurement costs ~ ￥0.4 per day*
4. *Lantus included in the insulin centralized procurement in 2024*
5. *Centralized procurement executed in China*

Source : AASLD, China Insights Consultancy

Progression of NASH



Source: ALF, NIHR, NIDDK, China Insights Consultancy

AASLD practice guideline recommends several available medications on patients with NAFLD; none of the below medications have been approved to treat NASH by the FDA

Recommendation for MASLD/MASH medication, AASLD

Medication[1]	Patient population	Liver clinical benefits	Non-liver related clinical benefits	Potential side effect
Vitamin E	NASH without T2DM or cirrhosis	• Improves steatosis • No proven benefit on fibrosis	/	• Hemorrhagic stroke • Potential risk of prostate cancer
Pioglitazone	NASH with or without T2DM	• Improves steatosis • Potential benefit on fibrosis	• Improves insulin sensitivity • Prevention of diabetes • CV risk reduction • Stroke prevention	• Weight gain • Risk of heart failure exacerbation • Bone loss
Liraglutide[2]	NASH without cirrhosis	• Improves steatosis • Non proven impact on fibrosis	• Improves insulin sensitivity • Weight loss • CV risk reduction • May slow progression of renal disease	• Gastrointestinal • Gallstones (related to weight loss), Pancreatitis
Semaglutide[3]	NASH without cirrhosis	• Improves steatosis • NASH resolution • May slow fibrosis progression	• Improves insulin sensitivity • Weight loss • Improves CV and renal outcomes • Stroke prevention	• Gastrointestinal • Gallstones (related to weight loss), Pancreatitis
Tirzepatide	T2DM or obesity with NAFLD	• Reduces steatosis on imaging	• Improves in insulin sensitivity • Significant weight loss	• Gastrointestinal • Gallstones related to weight loss Pancreatitis
SGLT2i	T2DM and NAFLD	• Reduces steatosis on imaging	• May improve insulin sensitivity • Improves CV and renal outcomes • Benefit in heart failure • Modest weight loss	• Risk of genitourinary yeast infection • Volume depletion • Bone loss

Notes:

1. *Available data on semaglutide, pioglitazone, and vitamin E do not demonstrate an antifibrotic benefit, and none has been carefully studied in patients with cirrhosis; Metformin, ursodeoxycholic acid, dipeptidyl peptidase-4, statins, and silymarin are well studied in NASH and should not be used as a treatment for NASH as they do not offer a meaningful histological benefit.*
2. *Study with small sample size and underpowered to determine key histological outcomes (fibrosis)*
3. *Phase 3 trial to determine efficacy currently ongoing*

Abbreviations: CV, cardiovascular; SGLT-2i, sodium glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus.

Source : American Association for the Study of Liver Disease, China Insights Consultancy

Comparison of clinical trials and endpoints of approved GLP-1 based medication on treating obesity

Comparison of clinical trials and endpoints of approved GLP-1 based medication on treating obesity

Products	MOA	Trial identity	Summary of clinical trials				Other safety profile
			Baseline profile[1]	*Intervention*	*Treatment difference*[2] *(%)*	*Adverse effects*[3]	
Liraglutide	GLP-1	SCALE	• Mean weight 106.2 kg • Mean BMI 38.3 kg/m^2	• 3.0mg daily plus counseling on lifestyle modification for 56 weeks	• 5.4%	• Discontinuation rates[4] 9.8% (4.3%) • Nausea 40.2% (14.7%) • Diarrhea 20.9% (9.3%) • Vomiting 16.3% (4.1%)	• Black box warning of thyroid C-cell tumors
Semaglutide	GLP-1	STEP1	• Mean weight 105.4 kg • Mean BMI 37.8 kg/m^2	• 2.4mg weekly plus lifestyle intervention for 68 weeks	• 12.4%	• Discontinuation rates 7.0% (3.1%) • Nausea 44.2% (17.4%) • Diarrhea 31.5%(15.9%) • Vomiting 24.8% (6.6%)	• Black box warning of thyroid C-cell tumors
Tizerpatide	GLP-1/GIP	SURMOUNT-3[5]	• Mean weight 105.8 kg • Mean BMI 38.2 kg/m^2	• 10mg weekly plus lifestyle intervention for 72 weeks	• 16.4%	• Discontinuation rates 7.1% (2.6%) • Nausea 33.3% (9.5%) • Diarrhea 21.2% (7.3%) • Vomiting 10.7% (1.7%)	• Black box warning of thyroid C-cell tumors

Notes
1. Trial subject profile in treatment group
2. Treatment difference = mean percentage of weight loss in treatment group subtracted by mean percentage of weight loss in placebo group
3. Adverse effect shown as percentage of adverse events in treatment group (percentage of adverse events in placebo group)
4. Data from Saxenda drug label, a cumulative parameter based on multiple clinical trials
5. Trial with 3 treatment groups, 10mg group results shown in table

Source: New England Journal of Medicine, China Insights Consultancy

Confirmation

#	Content
1	We have self-developed one Core Product and other five product candidates to capture the market potential in prevalent chronic and metabolic diseases.
2	GLP-1 receptor agonist is an agent that activates the GLP-1 receptor to simulate the receptor activation functions of GLP-1, which primarily include insulin secretion promotion, glucagon secretion inhibition, suppressing gastric motility and appetite, glucose uptake and fat degradation.
3	It has demonstrated multiple benefits in glycemic control, cardiovascular health, and a good efficacy profile in weight management across several clinical trials. According to CIC, long-acting GLP-1 receptor agonists referred to products that require an once-weekly dosing schedule such as that of PB-119, as compared to the frequent once- or multiple-daily dosing schedule required by short-acting GLP-1 receptor agonists.
4	These trials have revealed its broad-ranging benefits, good safety profile, rapid and sustained effectiveness, and potentially a high level of patient compliance.
5	The clinical results regarding both monotherapy and combination therapy for T2DM have underpinned our NDA for PB-119 in China, which was accepted by the NMPA in September 2023, making it one of the earliest clinical-stage long-acting GLP-1 receptor agonists in China, according to CIC.
6	We face fierce competition from existing products and product candidates under development in the T2DM and obesity market. Such fierce competition may limit the anticipated market size for PB-119 and therefore negatively affect our anticipated growth. In addition to alternative treatment methods and prevention methods, such as adopting a healthier lifestyle that facilitates weight management, there are various marketed drugs with new modalities available to patients with T2DM or obesity. In China and the United States, GLP-1-based therapeutic options for T2DM and/or obesity mainly include exenatide, liraglutide, exenatide ER, albiglutide, dulaglutide, lixisenatide, semaglutide, tirzepatide, insulin degludec/liraglutide and insulin glargine/lixisenatide.
7	In addition, the market competition may be fierce with the potential development of generic medications once the relevant patents of brand name drugs have expired. While we believe PB-119 is adequately protected by our intellectual property rights, the patent expiration of certain other GLP-1 receptor agonists may lead to the entry of generic drug products, subject to market conditions, regulatory trends and the strategic focus of market players. In addition to GLP-1-based therapeutics, prevalent treatment options for T2DM in China and the United States mainly include metformin, SGLT-2i, DPP-4i, GKA, among others, and prevalent treatment options for obesity in China and the United States mainly include orlistat, phentermine and naltrexone. In China, traditional Chinese medicines are also used for the treatment of T2DM and/or obesity, among which Mulberry Twig Alkaloids Tablet was approved by the NMPA for the treatment of T2DM. In addition to approved treatment options for T2DM and obesity, there are a large number of competing drug candidates currently under different clinical stages. For additional information, see "Industry Overview."
8	It has potential to be included in the standard treatmert recommendations for these disease which help to change the treatment paradigms, according to CIC
9	PB-1902 is the first and one of the only two domestically developed clinical-stage oral μ-opioid receptor antagonist drug candidates for the treatment of opioid-induced constipation ("OIC") under clinical trials in China as of the Latest Practicable Date, according to CIC.

Confirmation

#	Content
10	The PEGylation technology enables reduced renal clearance and enhanced water solubility of the PEGylated molecules, thereby extending their half-lives. In addition, the steady release of PEGylated molecules enables less titration frequency and minimizes fluctuations of drug levels. There are other technologies to achieve similar effects, for instance, lipidation also extends the half-lives of molecules by enhancing their stability.
11	Our near-commercialized Core Product is one of the earliest domestically developed long-acting GLP-1 receptor agonists in China, according to CIC.
12	With such commercialization arrangement, we expect to benefit from its decades of market experience and know-how in navigating through the rapidly evolving China healthcare landscape, market access ability to provide umbrella coverage for a portfolio of products and sales network covering both higher- and lower-tier markets to enable broad market penetration across China.
13	As of the Latest Practicable Date, the NMPA had accepted the NDAs of seven GLP-1 receptor agonists for the treatment of T2DM, and PB-119 was the second earliest to receive NDA acceptance from the NMPA among such candidates, according to CIC.
14	With the development of PB-119 and PB-718, we were among the few companies with multiple clinical-stage GLP-1-based product candidates for the treatment of overweight/obesity in China as of the Latest Practicable Date, according to CIC.
15	On June 18, 2024, Wegovy (semaglutide), a GLP-1 receptor agonist developed by Novo Nordisk A/S, received marketing approval from the NMPA for the treatment of obesity or overweight patients in China with a BMI over 30 kg/m2 or with a BMI between 27 to 30 kg/m2 and least one weight-related comorbidity.
16	As of the Latest Practicable Date, there had been no new GLP-1-based product being approved in the markets that PB-119 and PB-718 intend to address, according to CIC.
17	The pharmaceutical industry is subject to intense competition.
18	As of the Latest Practicable Date, there were 16 GLP-1 receptor agonists approved in China and more than 20 GLP-1 receptor agonist candidates undergoing clinical trials for the treatment of T2DM in China.
19	The currently marketed GLP-1-based products and pipelines undergoing clinical trials have exhibited certain common adverse effects such as mild-to-moderate gastrointestinal disturbances.
20	Additionally, the recent shortage of GLP-1-based products has led to an increased consumption of compounded GLP-1-based medications — custom formulations that may contain the same active ingredients as the original drug but are not regulated for safety and efficacy. Compounded medications present a higher risk to patients compared to FDA-approved drugs. According to the FDA's adverse event database, there have been reports of fatalities associated with compounded GLP-1-based products, although the specific cause of death has not been determined and may not be linked to the GLP-1-based products. While these reports are not directly related to and are not indicative of the safety profile of our drug candidates, any negative publicity surrounding the potential risks of compounded GLP-1 products could adversely affect our reputation, clinical trials, and overall business operations.

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21	However, given the presence of various prevention methods, such as adopting a healthier lifestyle that facilitates weight management, as well as existing and potential alternative treatment options (i.e. thiazolidinediones ("TZDs"), oral sulfonylureas, dipeptidyl peptidase-4 ("DPP-4") inhibitors for T2DM and Wegovy or Ozempic for the treatment of obesity), for our targeted indications, the market potential of the Core Product may be limited
22	Additionally, the growth of the NASH market in China might potentially be less pronounced than the global trend given the relatively lower level of obesity in China as compared to other countries, which could affect the number of addressable patients of our other drug candidates being developed for the NASH indication.
23	Type 1 diabetes is a lifelong condition where the body's immune system attacks and destroys the cells that produce insulin. In type 2 diabetes, also referred to as T2DM, the body does not produce enough insulin, or the body's cells do not react to insulin properly. Consequently, T2DM causes excess sugar to circulate in the bloodstream.
24	According to the International Diabetes Federation, approximately 50% of the adults with T2DM are aware of their condition, being the addressable patient group for this indication.
25	The treatment regimen of T2DM is mainly based on insulin therapy and diabetes medications. If adequate glycemia control cannot be achieved by insulin therapy, metformin is also often used. Other therapeutic options include glucagon-like peptide-1 ("GLP-1") receptor agonists, thiazolidinediones ("TZDs"), oral sulfonylureas, dipeptidyl peptidase-4 ("DPP-4") inhibitors, sodium-glucose co-transporter-2 ("SGLT-2") inhibitors, as well as glucokinase activators ("GKAs"). Traditional Chinese medicines are also used for the treatment of T2DM and its related syndromes clinically. Weight-loss surgeries are sometimes adopted for more severe cases.
26	In recent years, GLP-1 receptor agonists have been increasingly recommended for the treatment of T2DM as a result of their favored treatment outcomes demonstrated in various clinical studies and real-world applications.
27	T2DM implications: 1. Existing drug modalities such as metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and insulin offer various options for glycemic control. 2. These drugs help in managing blood glucose levels, reducing the risk of diabetic complications, and improving quality of life for patients with T2DM. (Source: FDA, China Insights Consultancy)
28	T2DM challenges: 1. Adherence: Complex dosing regimens and potential side effects may affect patient adherence to treatment. 2. Hypoglycemia: Certain medications, such as sulfonylureas and insulin, can increase the risk of hypoglycemia, which poses a safety concern. 3. Cost: Some newer medications, such as GLP-1 receptor agonists and SGLT2 inhibitors, may be expensive, limiting access for certain patient populations. 4. Weight Gain: Certain medications, such as sulfonylureas and insulin, are associated with weight gain, which can exacerbate obesity in patients with T2DM. (Source: FDA, China Insights Consultancy)

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29	T2DM is often influenced by both lifestyle factors and genetic factors. Certain ethnic groups and population with related family history are shown to exhibit elevated risk of developing T2DM. Specific genes including CALPN10 and TCF7L2 have also been identified to be associated with T2DM. Lifestyle factors including unbalanced diet may cause insulin resistance, and sedentary lifestyle also potentially increases the risk of developing T2DM. Lifestyle interventions for T2DM include both dietary control and regular exercise. Lifestyle interventions are beneficial in multiple manners, and may potentially decrease the risk of developing T2DM or delay the disease progression. However, they also require long-term adherence and higher self-management ability of patients, and it is usually difficult to achieve ideal glycemic control with lifestyle interventions alone.
30	In recent years, the development of GLP-1 receptor agonists has revolutionized the treatment of metabolic disorders and particularly T2DM, and such modality has been increasingly taking over the market share for the treatment of T2DM.
31	Penetration of GLP-1 receptor agonists lags behind in China due to its late entry and significant costs. However, given the comprehensive advantages demonstrated by GLP-1 receptor agonists in clinical trials, the Chinese market for GLP-1 receptor agonists is expected to experience an accelerated growth.
32	The drop in market size of T2DM drugs in China in 2022 was mainly due to the allocation of medical resources, patients' decreased willingness to seek medical treatment, supply chain obstacles and economic impact at the peak of the COVID-19 outbreak in China, resulting in some patients unable to continue diabetes treatment. The growth in market size of GLP-1 receptor agonists for the treatment of T2DM in China during 2022 and 2032 are stimulated by three factors: (1) the diagnosis rate for T2DM in China is expected to rise from approximately 50% to 54%, (2) the treatment rate for T2DM in China is expected to rise from approximately 68% to 71%, and (3) the percentage of T2DM patients being treated with GLP-1 receptor agonists is estimated to rise from approximately 1% to 10%, from 2022 to 2032.
33	The in vivo half-lives of the first synthetic GLP-1 receptor agonists were relatively short and therefore require dosing as frequent as one or twice daily. Subsequent modifications have been made to produce long-acting GLP-1 receptor agonists with longer in vivo half-lives, less frequent dosing and consequently higher compliance for chronic and metabolic disease patients where long-term treatments are often necessary, although subcutaneous short-acting GLP-1 receptor agonists tend to be more affordable. Recent development of short-acting GLP-1 receptor agonists shows potentially higher patient compliance compared to subcutaneous dosage if they are administered orally.
34	As of the Latest Practicable Date, there were over 300 products of metformin, over 50 products of insulin, over 30 products of SGLT-2 inhibitors, and over 40 products of DPP-4 inhibitors approved by the FDA for the treatment of T2DM in the United States.
35	The companies with approved GLP-1 receptor agonist products listed above are mostly multinational pharmaceutical companies with ample financial resources, robust R&D capabilities and well-established in-house commercialization teams. The Company currently has relatively limited resources and operations in the United States. However, it plans to seek collaboration with a reputable local partner in the United States for the Phase III clinical development of PB-119.

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36	As of the Latest Practicable Date, there were over 250 products of metformin, over 50 products of insulin, over 35 products of SGLT-2 inhibitors, and over 40 products of DPP-4 inhibitors approved by the NMPA for the treatment of T2DM in China
37	The NRDL was updated in 2024 to include nine new drugs for the treatment of diabetes. Among these newly added diabetes drugs, there are no new GLP-1 drug products. Therefore, the implementation of the updated NRDL does not have a significant impact on the competitive landscape of the GLP-1-based drug products.
38	As of the Latest Practicable Date, there were two combination therapies of insulin and GLP-1 receptor agonist approved in China and the United States, both were approved for the treatment of T2DM.
39	According to CIC, a network meta-analysis published on the British Medical Journal (volume 384, January 2024) studied the results of over 30 thousand participants with T2DM in more than 70 eligible clinical trials, and all 15 GLP-1 receptor agonists covered by the analysis effectively lowered HbA1c and fasting plasma glucose concentrations. Such GLP-1 receptor agonists were also shown with benefits for weight management for patients with T2DM. Another network meta-analysis published on Medicine (volume 102, July 2023) which studied the results of over six thousand participants with T2DM showed that GLP-1 receptor agonists were generally well-tolerated in the trials examined, with common adverse events (such as gastrointestinal disturbances) mostly of mild to moderate in severity, and were generally self-manageable.
40	The following tables set forth the comparisons of PB-119 with major approved GLP-1 receptor agonists as of the Latest Practicable Date. Such conclusions are based on parallel comparisons of PB-119 clinical trial results with results from the published clinical trials of these products rather than head-to-head comparisons.
41	HbA1c measures the average blood sugar level over the past few months, and its level is adopted commonly as primary efficacy endpoint by clinical trials for T2DM medications including GLP-1 receptor agonists. For instance, the aforementioned clinical trial results illustrated that the marketed long-acting GLP-1 receptor agonists that are widely adopted by physicians and patients decreased the HbA1c level by 0.71% to 1.55% during the treatment period ranging from 24 to 30 weeks, while the low dose of PB-119 was shown to decrease the HbA1c level by 1.37% during the 24-week treatment period, which falls closer to the upper boundary within the comparative range. On the other hand, GI disorders, including nausea, vomit and diarrhea occurrences are the major adverse event metrics when evaluating the safety profile of GLP-1 receptor agonists in clinical trials. For instance, comparing the aforementioned clinical trial results, PB-119 also showed a favorable safety profile in terms of GI effects.

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42	As of the Latest Practicable Date, there were more than 25 GLP-1 receptor agonist candidates undergoing clinical trials for the treatment of T2DM in the United States. In September 2023, the NMPA accepted the NDA of PB-119 for the treatment of T2DM in China, making it one of the earliest clinical-stage long-acting GLP-1 receptor agonists in China. As of the Latest Practicable Date, there were more than 25 GLP-1 receptor agonist candidates undergoing clinical trials for the treatment of T2DM in China, including 20 GLP-1 receptor agonist candidates with accepted NDAs or undergoing Phase III clinical trials, as of the same date. The following table sets forth the pipeline of such advanced-stage product candidates in China. GLP-1 receptor agonists could also be divided intc peptide-based and small molecule GLP-1 receptor agonists. As compared to peptide-based GLP-1 receptor agonists, small molecule GLP-1 receptor agonists are generally short-acting products that are administered orally. Among the pipelines set forth below, Orforglipron, Noiiglutide, HRS-7535 and rExenatide-4 are short-acting candidates while the other pipelines are long-acting candidates.
43	As of the Latest Practicable Date, there were 15 candidates undergoing Phase III clinical trials for the treatment of T2DM in the United States
44	As of the Latest Practicable Date, there were 14 candidates for the treatment of T2DM with accepted NDAs by the NMPA, and there were more than 35 candidates undergoing Phase III clinical trials in China, as of the same date
45	Development of long-acting GLP-1 receptor agonists. In recent years, long-acting GLP-1 receptor agonists with longer in vivo half-lives and less frequent dosing requirements are being increasingly developed. Such favorable properties are expected to bring enhanced overall clinical benefits for T2DM patients that usually require long-term treatments. Both globally and in China, it is expected that more than 80% of the market share of GLP-1 receptor agonists for the treatment of T2DM will be occupied by long-acting GLP-1 receptor agonists as of 2032.
46	The prevalence of patients with T2DM in China is growing due to various factors including unhealthy diet, sedentary lifestyle, lack of exercise, genetics and other disease complications such as obesity.
47	Outside China, the prevalence of T2DM also demonstrates a continued rise across all regions of the world. According to CIC, the prevalence of T2DM in the United States is expected to increase from 32.4 million in 2023 to 34.7 million in 2032. There are also concerning trends of rising prevalence and medical needs in lower-income countries according to the International Diabetes Federation, which are expected to be the major demographic drivers of the global T2DM market in the future.
48	Increasing market share of GLP-1 receptor agonists. In recent years, the development of GLP-1 receptor agonists has revolutionized the treatment of metabolic disorders and particularly T2DM, and such modality has been increasingly taking over the market share for the treatment of T2DM. It is expected that more than 60% of the market share for T2DM both in China and globally will be occupied by GLP-1 receptor agonists as of 2032, respectively.
49	Medications that alone could bring a wide range of benefits would also be much favored by physicians and patients going forward.

Confirmation

#	Content
50	The T2DM drug market has the following entry barriers: 1. Stringent regulatory requirements. Meeting regulatory standards for safety, efficacy and quality presents a technical challenge necessitating thorough testing and documentation at every stage of T2DM drug development. China imposes specific clinical trial requirements, mandating companies intending to develop T2DM drugs to conduct trials demonstrating product safety and efficacy within the Chinese population. 2. Diversity of current T2DM drugs. There are a number of drugs being used for the management of T2DM. Certain recommended medications may have already secured significant market share, posing challenges for new products attempting to establish themselves. Competition within the generic drug market is also intense. Newcomers must distinguish their products and demonstrate superior efficacy or safety to effectively compete. 3. Brand awareness. The diabetes drug market in China is characterized by intense competition, with numerous competing domestic and international pharmaceutical companies. Successfully entering this market requires strong market positioning and effective brand promotion strategies to differentiate products and attract both patients and physicians.
51	Obesity is a chronic health condition characterized by abnormal or excessive fat accumulation that poses comprehensive health concerns, such as cardiovascular diseases, T2DM, musculoskeletal disorders, and carcinogenesis. Body mass index ("BMI") serves as a common measure of body fat based on height and weight. According to standards recommended by World Health Organization ("WHO"), BMI values exceeding 25 kg/m2 indicate overweight, and those exceeding 30 kg/m2 indicate obesity. In China, it is recommended that overweight is indicated by BMI values over 24 kg/m2 and obesity is indicated by BMI values over 28 kg/m2. Individuals exceeding the corresponding BMI levels are considered among the addressable patient group for this indication.
52	Obesity can lead to or exacerbate various health complications, either independently or in conjunction with other diseases. Specifically, obesity heightens the risk of CVDs, particularly heart failure and coronary heart disease, as well as osteoarthritis, a debilitating joint condition. Additionally, it is associated with prediabetes, T2DM and certain cancers.
53	Obesity/Overweight Implications: 1. Pharmacotherapy: Drugs such as orlistat, phentermine/topiramate, liraglutide, and bupropion/naltrexone can aid weight loss and improve metabolic parameters in obese individuals. 2. Multimodal Approaches: Combined with lifestyle modifications, pharmacotherapy can enhance weight loss outcomes and improve overall health. (Source: FDA, China Insights Consultancy)
54	Obesity/Overweight Challenges: 1. Limited Efficacy: Weight loss medications may have modest efficacy, and long-term sustainability of weight loss is challenging. 2. Side Effects: Common side effects of weight loss drugs include gastrointestinal disturbances, insomnia, and increased heart rate, which may limit their tolerability. 3. Safety Concerns: Some weight loss medications have been associated with adverse effects such as cardiovascular events and psychiatric disorders. 4. Cost: Cost-effectiveness and insurance coverage for weight loss medications may be barriers to access for some patients. (Source: FDA, China Insights Consultancy)
55	With the continuous development of novel drugs and the increasing clinical demands, the global obesity drug market has witnessed significant expansion in the past years and is expected to grow at an expedited pace

Confirmation

#	Content
56	The development of obesity drug market in China occurred relatively recent with significant potential in the coming years. The following chart sets forth the historical and projected China market size of obesity drugs from 2018 to 2032, with breakdowns of GLP-1 receptor agonists and other modalities, respectively. The market size is calculated by the number of eligible patients (estimated based on epidemiology of obesity) times percentage of obesity patients being treated with GLP-1 receptor agonists times the annual patient expenditure of such medications. The percentage of obesity patients being treated with GLP-1 receptor agonists is estimated to be 0.01% in China in 2023 as two GLP-1 receptor agonists were approved for the treatment of obesity in 2022, and is expected to rise to 0.57% as more GLP-1-based treatment options are expected to be approved by the NMPA over the next 10 years. The annual patient expenditure is expected to be approximately RMB15.0 thousand in 2023, and is expected to reach approximately RMB24.0 thousand in 2032.
57	In recent years, in addition to the significant efficacy observed in the treatment of metabolic disorders such as T2DM, GLP-1 receptor agonists have demonstrated encouraging weight reduction effects in overweight/obese patients. An increasing number of research endeavors have also been dedicating to the development of long-acting GLP-1 receptor agonists, whose longer half-lives in vivo reduce the need of frequent dosing, alleviate patient burdens, increase overall compliance and clinical benefits compared to those of short-acting GLP-1 receptor agonists, although subcutaneous short-acting GLP-1 receptor agonists may be more affordable. The following chart sets forth the historical and projected global market size of GLP-1 receptor agonists for the treatment of obesity from 2018 to 2032, with breakdowns of long-acting and short-acting GLP-1 receptor agonists, respectively.
58	It is also expected that long-acting GLP-1 receptor agonists will gradually dominate the overall GLP-1 receptor agonist market in China with considerable market potential. The following chart sets forth the historical and projected China market size of GLP-1 receptor agonists for the treatment of obesity from 2018 to 2032, with breakdowns of long-acting and short-acting GLP-1 receptor agonists, respectively.
59	As of the Latest Practicable Date, there were sever drugs approved for the treatment of obesity in the United States, three of which were GLP-1 receptor agonists
60	As of the Latest Practicable Date, there were six drugs approved for the treatment of obesity in China, three of which were GLP-1 receptor agonists and two of these GLP-1 receptor agonists were in short-acting form.
61	As of the Latest Practicable Date, there were over 150 clinical-stage pipeline candidates with various modalities for the treatment of obesity in the United States. As of the Latest Practicable Date, there were 10 GLP-1 receptor agonist candidates under clinical development for the treatment of obesity in the United States.
62	Additionally, there were other GLP-1-based pipeline candidates under clinical development for the treatment of obesity in the United States, such as maridebart cafraglutide, a novel antibody-peptide conjugate which functions as a GLP-1 receptor agonist and GIP receptor antagonist, undergoing Phase II clinical trial.
63	As of the Latest Practicable Date, there were over 30 clinical-stage pipeline candidates with various modalities for the treatment of obesity in China. As of the Latest Practicable Date, there were approximately 20 GLP-1 receptor agonist candidates under clinical development for the treatment of obesity in China.

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#	Content
64	As of the Latest Practicable Date, there were seven GLP-1/GCG dual receptor agonist candidates under clinical development for the treatment of obesity in the United States
65	As of the Latest Practicable Date, there were three GLP-1/GCG dual receptor agonist candidates under clinical development for the treatment of obesity in China
66	The obesity drug market has the following entry barriers: 1. Safety concerns and side effects. The utilization of medication for weight loss remains a non-dominant approach. Safety considerations represent a paramount concern for individuals contemplating weight-loss interventions. Adverse perceptions and reports regarding the safety profiles of traditional obesity drugs can potentially hinder market acceptance. 2. Intense competition. New obesity drugs face competition from both upcoming candidates and established products already present in the market. To succeed, the new products must demonstrate superior efficacy, reduced side effects, or other unique benefits, and establishing widespread brand recognition poses a challenge for new entrants.
67	The following charts set forth the historical and projected prevalence of NASH globally and in China, respectively, from 2018 to 2032. The growth of the NASH market in China might potentially be less pronounced than the global trend given the relatively lower level of obesity in China as compared to other countries. Given the first drug approved by the FDA for the treatment of NASH is indicated for NASH patients with F2–F3 Fibrosis without the need of liver biopsy, and liver fibrosis stage F2–F3/F1–F3 is often the key patient inclusion criteria for the majority of Phase II and Phase III clinical trials for the treatment of NASH, therefore patient stratification of fibrosis stage is the major parameter to estimate the addressable market of NASH treatment.
68	Despite the number of NASH patients reaching approximately 300 million globally, the first drug for the treatment of NASH was recently approved by the FDA in March 2024, and the global market size of NASH drug is expected to grow at an expedited pace in the following years. The following chart sets forth the projected global and China market size of NASH drug.
69	On March 14, 2024, resmetirom, a thyroid hormone receptor -selective agonist developed by Madrigal Pharmaceuticals Inc. with brand name Rezdiffra, became the first drug receiving marketing approval from the FDA for the treatment of NASH patients with moderate to advanced liver fibrosis, with mechanism of action designed by stimulating thyroid hormone receptor in the liver to reduce intrahepatic triglycerides and decrease liver fat content. There were a number of product candidates under clinical development in the United States, nine of which were GLP-1 receptor-targeted, as of the Latest Practicable Date. The following table shows the details of GLP-1 receptor-targeted drug candidates under clinical development for the treatment of NASH in the United States
70	Opioid-induced constipation ("OIC") is a common and challenging side effect associated with the use of opioid medications for pain management. Opioid drugs, while effective in alleviating pain, can lead to a range of gastrointestinal issues, and constipation is one of the most prevalent complications. OIC occurs due to the interaction of opioid drugs with opioid receptors in the gastrointestinal tract, resulting in slowed bowel movement. This condition significantly impacts the quality of life for individuals using opioid drugs for pain relief, and often leads to discomfort, abdominal pain and adverse effects in overall well-being. It is crucial to recognize the unique mechanism that leads to OIC, as traditional laxatives may not effectively address the underlying complications.

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71	The development of OIC is common among patients using even low dosages of opioid drugs. The symptoms of OIC do not spontaneously decrease over time. Consequently, the OIC patient group is growing steadily with the rapid increase of cancer incidents and other severe pain indications.
72	As of the Latest Practicable Date, there were two drugs approved by the NMPA for the treatment of OIC in China, which are both opioid receptor antagonists.
73	As of the Latest Practicable Date, there were three clinical-stage drug candidates for the treatment of OIC in the United States, as shown in the following table.
74	As of the Latest Practicable Date, there were 10 clinical-stage drug candidates for the treatment of OIC in China, being seven PAMORAs, two opioid receptor antagonists and one CLCN2 activator, respectively. PB-1902 was the first and one of the only two domestically developed clinical-stage oral μ-opioid receptor antagonist drug candidates for the treatment of OIC in China, as of the same date.
75	As a rare disease, the patient group of congenital hyperinsulinemia is relatively small. The incidence of congenital hyperinsulinemia globally grew from 2.8 thousand in 2018 to 3.4 thousand in 2023 with a CAGR of 4.2%. The incidence of congenital hyperinsulinemia globally is expected to further grow to 4.9 thousand in 2032 with a CAGR of 4.0% from 2023 to 2032
76	As of the Latest Practicable Date, there was no drug approved specifically for the treatment of congenital hyperinsulinemia globally. There were six clinical-stage drug candidates for the treatment of congenital hyperinsulinemia globally, as of the same date. The following table sets forth the pipeline of congenital hyperinsulinemia drug candidates under clinical development.
77	Our Core Product PB-119 is one of the earliest domestically developed long-acting GLP-1 receptor agonists in China, according to CIC.
78	According to CIC, metabolic diseases are among the fastest growing diseases worldwide with a global prevalence of 2,522 million in 2023, which is expected to increase to 2,991 million by 2032, representing a CAGR of 1.9%. Metabolic diseases are also among the most common diseases in China with a prevalence of 545 million in 2023, which is expected to increase to 646 million by 2032, representing a CAGR of 1.9%

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#	Content
79	Despite the increased prevalence of chronic and metabolic diseases and efforts to address them, there remains significant medical needs. Patients with chronic and metabolic diseases typically require prolonged medical interventions that provide comprehensive benefits across various disease complications. Successful treatments for these conditions lie in delivering all-encompassing benefits, robust clinical effectiveness and safety, unparalleled affordability, and significant patient compliance. Despite the availability of various treatments for T2DM and obesity, there lacks available treatment options that offer promising long-term outcomes, minimize side effects, with satisfying affordability and patient compliance. NASH, a less recognized but increasingly concerning condition, often correlates with obesity and T2DM, yet it still lacks specific, targeted treatments. Current treatment paradigms for these chronic and metabolic diseases often involve complex treatment regimens consisting of either multiple interventions administered simultaneously that are costly and inconvenient, or therapies providing more comprehensive benefits but are expensive and demand significant medical resources. This treatment landscape underscores the need for not only more effective and holistic treatment options that bring comprehensive benefits at the same time, but also improved accessibility and patient compliance.
80	PB-119 is primarily designed for the first-line treatment of T2DM and obesity. In recent years, GLP-1 receptor agonists have been increasingly recommended for the treatment of T2DM and obesity as a result of their favored treatment outcomes demonstrated in various clinical studies and real-world applications.
81	The clinical results regarding both monotherapy and combination therapy for T2DM have underpinned our NDA for PB-119 in China, which was accepted by the NMPA in September 2023, making it one of the earliest clinical-stage long-acting GLP-1 receptor agonists in China, according to CIC.
82	According to CIC, the global market size of T2DM and obesity treatment was US$70.3 billion and US$9.1 billion in 2023, respectively, and is anticipated to reach US$106.2 billion and US$58.5 billion in 2032, with CAGRs of 4.9% and 22.9%, respectively. The NASH treatment market is also witnessing growth in line with the rising occurrence of T2DM and obesity, yet there are still limited treatment options available.
83	GLP-1 receptor agonists are based on validated mechanism of action and represent the trend of metabolic disorders treatment, demonstrating significant potential in treating diabetes and obesity. According to CIC, the global market size of GLP-1 receptor agonists is expected to reach US$110.6 billion by 2032. In 2022, GLP-1 receptor agonists accounted for more than 44% of the T2DM drug market in the United States while they only accounted for approximately 10% in China's T2DM drug market, underscoring the market potential in China.
84	We anticipate to receive the NDA approval and commercially launch PB-119 for the treatment of T2DM in China in 2025, making it one of the earliest domestically developed long-acting GLP-1 receptor agonists which potentially brings a substantial impact on the landscape of diabetes treatment in the China market.
85	PB-1902 is the first and one of the only two domestically developed clinical-stage oral μ-opioid receptor antagonist drug candidates for the treatment of OIC in China as of the Latest Practicable Date, according to CIC
86	A key component of our drug molecular design platform is the PEG technology, a versatile and proven modification that can be applied to a wide array of drugs, including peptide, protein, and small molecule drugs, to optimize their physio-chemical properties

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#	Content
87	By adjusting the parameters of PEGylation, such as the length of the PEG molecules and the amount of PEGylation, we are able to increase the total molecular weight and the hydrodynamic radius of the PEGylated drug, thereby significantly slowing its clearance from the body and prolonging its half-life to achieve long-acting efficacy.
88	For example, PEG technology allows for PB-119 to be administered once a week, in contrast to certain other GLP-1 receptor agonists on the market, which require dosing as frequent as twice-daily.
89	The PEG technology also contributes to improved compound stability, arising from improved overall solubility and protection by the attached PEG molecules against degradation or enzymatic breakdown. As an example, PEGylation of PB-119 considerably increases the stability and half-life compared with the native GLP-1. Similarly, more stable drug molecules in the body can result in long-acting efficacy and less frequent dosing, which can potentially improve the overall treatment outcome and patients' compliance.
90	As PEG molecules can shield drugs from recognition by the immune system, PEG technology is able to diminish the likelihood of generating antibodies against the therapeutic agent and may contribute to safer and more tolerable therapeutics.
91	The PEG technology allows us to alter the ability of small molecules to traverse the blood-brain barrier by enlarging its molecular size.
92	This targeted approach holds promise for designing medications that can exert their therapeutic effects within the digestive tract, potentially offering solutions for conditions such as gastrointestinal pain or motility disorders. PEG technology's precision in modulating drug properties signifies a groundbreaking strategy in drug development, providing a platform for the creation of highly targeted and efficacious treatments.
93	While no head-to-head studies were conducted, PB-119 distinguished itself as the only GLP-1 drug with a sustained glucose-lowering effect till 52 weeks and no rebound demonstrated in clinical trial, based on the published clinical trial results of the GLP-1 receptor agonists approved for commercialization, according to CIC.
94	PB-119 demonstrated rapid, significant and sustained efficacy with a differentiated broad range of benefits in the clinical trials, according to CIC. While GLP-1 receptor agonists generally bring more benefits as compared to many other traditional types of T2DM treatment options, only a few long-acting GLP-1 receptor agonists are on par with PB-119 in terms of the breadth and degree of clinical benefits.
95	We believe that multiple features of PB-119 can facilitate its administration and enhance patient compliance, according to CIC, which is critical for the long-term management of chronic and metabolic diseases.
96	The potency of PB-119 at relatively low dosage levels also allows us to pursue competitive pricing as another potential advantage, especially for patients who are more cost-sensitive in China and other emerging markets, according to CIC.
97	Our near-commercialized Core Product is one of the earliest domestically developed long-acting GLP-1 receptor agonists in China, according to CIC.
98	We expect to benefit from its decades of market experience and know-how in navigating through the rapidly evolving China healthcare landscape, market access ability to provide umbrella coverage for a portfolio of products and sales network covering both higher-and lower-tier markets to enable broad market penetration across China.

Confirmation

#	Content
99	PB-119 is one of the earliest domestically developed long-acting GLP-1 receptor agonists in China, according to CIC, and has demonstrated good safety and efficacy across 11 clinical trials in China and the United States.
100	In September 2023, the NMPA accepted our NDA of PB-119 for the treatment of T2DM in China, marking a key milestone for its upcoming commercialization.
101	PB-119 led to relatively low gastrointestinal AEs, taking into account the published results of other GLP-1 receptor agonists, although no head-to-head comparisons were conductec in the clinical trials of PB-119
102	PB-119 led to relatively low gastrointestinal TEAEs, taking into account published results of other GLP-1 receptor agonists, although no head-to-head comparisons were conducted in the clinical trials of PB-119.
103	NASH is an advanced form of non-alcoholic fatty liver disease, which is caused by abnormal accumulation of fat in the liver. Such excessive fat causes inflammation and damage that leads to NASH. The risk factors of NASH include, among others, T2DM, insulin resistance, obesity, high blood cholesterol and triglycerides, with a combination of which often simultaneously present in NASH patients. The prevalence of NASH in China is 41.5 million in 2023 and is expected to reach 50.8 million in 2032, with CAGR of 2.3%.
104	NASH is a chronic and progressive disease with Rezdiffra as the only FDA-approved treatment option as of the Latest Practicable Date, according to CIC.
105	According to CIC, as of the Latest Practicable Date there was no GLP-1 receptor-targeted drug approved specifically for the treatment of NASH globally.
106	As of the Latest Practicable Date, there were a number of product candidates under clinical development in the United States, 10 of which were GLP-1 receptor-targeted. There were five GLP-1 receptor-targeted drug candidates under cinical development for the treatment of NASH in China, as of the same date.
107	According to CIC, as of the Latest Practicable Date there were seven GLP-1/GCG dual receptor agonist candidates under clinical development for the treatment of obesity in the United States. As of the Latest Practicable Date, there were three GLP-1/GCG dual receptor agonist candidates under clinical development for the treatment of obesity in China.
108	As of the Latest Practicable Date, there had not been a GLP-1/GCG dual receptor agonist approved for the treatment of NASH or obesity in China or the United States
109	Opioid analgesics alleviate moderate to severe pain of patients by binding to the μ receptors in the central nervous system. Simultaneously, opioid drugs also bind to μ receptors in the gastrointestinal tract, inhibiting gastrointestinal motility, reducing bile and pancreatic secretion, and causing constipation. Naltrexone and naloxone are both non-selective antagonists of opioid receptors. While both compounds can alleviate the symptoms of OIC, they can also cross the blood-brain barrier and antagonize the analgesic effects of opioid drugs in the central nervous system.
110	Such mechanism renders PB-1902 as a potential ideal treatment for OIC that can antagonize the peripheral gastrointestinal effects of opioid receptor activation while avoiding interference with the central analgesic effects of opioid drugs.

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#	Content
111	OIC is the most common gastrointestinal adverse effects associated with opioid pharmacotherapy which negatively affects pain management and life quality of patients. The occurrence of OIC is common among patients using even low dosages of opioid drugs. Usually, the symptoms of OIC does not spontaneously decrease over time. Consequently, the OIC patient group is growing steadily along with the rapid increase of cancer incidents and other severe pain indications. The incidence of OIC in China grew from 3.2 million in 2018 to 4.6 million in 2023 with a CAGR of 7.5%. The incidence of OIC in China is expected to further grow to 7.1 million in 2032 with a CAGR of 5.0% from 2023 to 2032.
112	The majority of the commercially available opioid receptor antagonists are not selectively targeting intestinal opioid receptors, whereas the binding of opioid receptors in the central nervous system could partially hinder the central pain-relieving effect of opioid drugs. Therefore, a selective μ receptor antagonist represents the optimal combination of treating OIC while simultaneously maintain the functions of opioid drugs.
113	As of the Latest Practicable Date, there were two drugs approved by the NMPA for the treatment of OIC in China, which are both non-selective opioid receptor antagonists. There were 10 clinical-stage drug candidates for the treatment of OIC in China, being seven μ-opioid receptor antagonists, two non-selective opioid receptor antagonists and one CLCN2 activator, respectively. As of the Latest Practicable Date, PB-1902 was the first and one of the only two domestically developed clinical-stage oral μ-opioid receptor antagonist drug candidates for the treatment of OIC in China, according to CIC.
114	As of the Latest Practicable Date, there were only two approved opioid receptor antagonists in oral formulations in China. The peripheral opioid receptor antagonists available for the treatment of OIC are primarily in the form of naloxone injections which requires daily subcutaneous administration. PB-190 is one of the only two domestically developed clinical-stage oral PAMORA drug candidates for the treatment of OIC in China.
115	As of the Latest Practicable Date, there was no approved drug for the treatment of congenital hyperinsulinemia
116	Glucagon is an important hormone secreted by pancreatic cells, which triggers a series of downstream metabolic reactions by activating the GCG receptors. Glucagon stimulates the hydrolysis of fats and glycogen in the liver, leading to increased blood glucose and lipid concentrations. Glucagon also promotes glycogenolysis and gluconeogenesis in the liver, leading to a significant increase in blood glucose levels.
117	For patients with congenital hyperinsulinemia, glucagon is initially used in clinical practice for rapid blood glucose elevation in cases of severely low blood glucose when the patient could not consume food. However, the short half-life (5-10 minutes) of glucagon limits its long-term application and it is generally reserved for emergency treatment of severe hypoglycemia.
118	PB-722 is created by a single amino acid modification of human glucagon and PEGylation on the modification site. The amino acid sequence of the active site of the glucagon derivative is identical to natural glucagon. By binding to the GCG receptors in vivo, PB-722 exhibits pharmacological effects similar to glucagon. PB-722 is able to retain its activity with extended half-life. PB-722 acts as a long-acting GCG receptor agonist that increases blood glucose levels persistently, thereby treating hypoglycemic symptoms in patients with congenital hyperinsulinism. The following diagram illustrates the design of PB-722 and benefits of such design.

Confirmation

#	Content
119	As a rare disease, the patient group of congenital hyperinsulinemia is relatively small. The incidence of congenital hyperinsulinemia globally grew from 2.8 thousand in 2018 to 3.4 thousand in 2023 with a CAGR of 4.3%. The incidence of congenital hyperinsulinemia globally is expected to further grow to 4.9 thousand in 2032 with a CAGR of 4.0% from 2023 to 2032. However, since there is currently no approved drug for the treatment of congenital hyperinsulinemia globally, there remains significant medical needs for such patients and the successful development of drugs for congenital hyperinsulinemia will bring considerable socio-economic benefits.
120	As of the Latest Practicable Date, there was no drug product being approved for the treatment of congenital hyperinsulinemia globally. There were six clinical-stage drug candidates for the treatment of congenital hyperinsulinemia globally. As of the Latest Practicable Date, PB-722 was the first and only drug candidate with IND approval for the treatment of congenital hyperinsulinemia in China, according to CIC.
121	Certain other GLP-1 receptor agonists on the market that require dosing as frequent as twice-daily.
122	According to CIC, it is industry norm to engage CDMOs and utilize their equipment and resources required for mass production of drug substances, which could be costly in particular for biotech companies in the early stage of commercialization that are ramping up their production capacities.
123	Our Core Product is one of the earliest domestically developed long-acting GLP-1 receptor agonists in China, according to CIC, upon obtaining the regulatory approvals from the NMPA.
124	For instance, PB-119 distinguished itself as the only GLP-1 receptor agonist with a sustained glucose-lowering effect till 52 weeks and no rebound demonstrated in clinical trial, and led to relatively low gastrointestinal AEs, based on the published results of other GLP-1 receptor agonists while no head-to-head studies were conducted.
125	Taking into account the payments we are entitled to receive as specified in the Collaboration Agreement, the expected timetable of PB-119's NRDL inclusion and the overall arrangement for the Promotion Service Fee payment, we believe the commercial arrangement is in line with industry practice for newly approved drugs, as confirmed by CIC.
126	Our Core Product PB-119 is one of the earliest domestically developed long-acting GLP-1 receptor agonists in China, according to CIC.
127	According to CIC, metabolic diseases are among the fastest growing diseases worldwide, and they are also among the most common diseases in China.

Confirmation

#	Content
128	At EASL Congress 2023, the multinational liver societies leaders from La Asociación Latinoamericana para el Estudio del Hígado (ALEH), American Association for the Study of Liver Diseases (AASLD), and European Association for the Study of the Liver (EASL) as well as the co-chairs of the NAFLD Nomenclature Initiative announced that steatotic liver disease (SLD) was chosen as an overarching term to encompass the various aetiologies of steatosis. Nonalcoholic fatty liver disease (NAFLD) will now be metabolic dysfunction-associated steatotic liver disease (MASLD). Metabolic dysfunction-associated steatohepatitis (MASH) is the replacement term for nonalcoholic steatohepatitis (NASH). The following diagram illustrates the progression of NASH in different stages.
129	In this industry report, MASH is equal to MASH.
130	Research has shown that certain genetic factors are associated with NASH, such as a certain variation in the PNPLA3 gene which determines inter-individual and ethnicity-related differences in hepatic fat content independent of insulin resistance and serum lipid concentration. Non-genetic risk factors of NASH include obesity, insulin resistance, high levels of blood lipids, and other metabolic abnormalities. Lifestyle interventions and preventive methods may potentially alleviate the symptoms of NASH and/or delay the disease progression.
131	On March 14, 2024, resmetirom, a thyroid hormone receptor selective agonist developed by Madrigal Pharmaceuticals Inc. with brand name Rezdiffra, became the first drug receiving marketing approval from the FDA for the treatmert of NASH patients with moderate to advanced liver fibrosis, with mechanism of action designed by stimulating thyroid hormone receptor in the liver to reduce intrahepatic triglycerides and decrease liver fat content. There were a number of product candidates under clinical development in the United States, nine of which were GLP-1 receptor-targeted, as of the Latest Practicable Date. The following table shows the details of GLP-1 receptor-targeted drug candidates under clinical development for the treatment of NASH in the United States.
132	The OIC drug market growth has primarily been driven by the following key factors: 1. Increased clinical demand. The escalating global trend of aging has resulted in an increasing demand for pain management in conditions such as cancer and other chronic pain. Consequently, there has been a rise in the use of opioid drugs among such patients. However, these patients face a significant challenge of managing pain while dealing with severe constipation induced by opioid analgesics. This dilemma has led to a growing market demand for medications that specifically address OIC. 3. Inadequate traditional treatments and development of targeted drugs. In China, the primary first-line treatment for OIC involves lifestyle modifications and the use of conventional laxatives such as lactulose and PEG. Despite the available methods, many patients do not experience improvement in constipation symptoms. Emerging OIC medications including PAMORAs have significant market potential for their efficacy in the overall management of OIC patients. 3. PAMORAs as the research focus. Non-selective opioid receptor antagonists, such as naloxone, have demonstrated efficacy in alleviating the symptoms of OIC. However, their clinical application is constrained by the concurrent attenuation of opioid analgesic effects. Consequently, there is a heightened focus on the research and development of medications for OIC that fall under the category of PAMORAs These agents aim to mitigate intestinal dysfunction caused by opioids without compromising their analgesic efficacy.

Confirmation

#	Content
133	Congenital hyperinsulinemia is a rare hereditary erdocrine disease whose patients experience constant hypoglycemia induced by hyperinsulinemia. Congenital hyperinsulinemia is caused by dysfunction of pancreatic cells, leading to sustained insulin release and inappropriate reduction of blood sugar levels, resulting in hypoglycemia. Congenital hyperinsulinemia is the most common cause of severe and persistent hypoglycemia in newborns and infants, with severe implications for the central nervous system and even mortality. It requires prompt and aggressive treatment to prevent neurological sequelae. If remain untreated, congenital hyperinsulinemia can lead to permanent brain damage, resulting in conditions such as epilepsy and cerebral palsy. In China, congenital hyperinsulinemia was included in the "Rare Disease Catalog of China First Edition" in 2018.
134	The congenital hyperinsulinemia drug market growth has primarily been driven by the following key factors: 1. Medical advancements. Enhanced diagnostic tools, including genetic testing and advanced imaging techniques, facilitate early and precise identification of patients with congenital hyperinsulinemia. Continued advancements in medical research hold the potential to deepen our understanding of its pathophysiology, paving the way for the development of novel therapeutic approaches and medications for more effective treatment of congenital hyperinsulinemia. 2. Favorable policy environment. Regulatory authorities such as the NMPA in China emphasize the acceleration of the review and approval process for drugs targeting rare diseases, demonstrating a full commitment to safeguarding the health rights and interests of patients with rare diseases. Currently, there are no approved targeted drugs for congenital hyperinsulinemia, and there are relevant policies to encourage and support the research and development of pharmaceuticals dedicated to addressing rare diseases such as congenital hyperinsulinemia.

Prospectus Confirmation

Confirmation

Core Product	Target Indication	Addressable Patients (million)				Number of Competitors[1]	
		China		Global		China	United States[2]
		2023	2032E	2023	2032E		
PB-119	T2DM	125.4	141.8	533.8	609.6	13[3]	Over 15[4]
PB-119	Obesity	268.3	330.3	972.5	1261.0	Over 15	Over 10

Notes:

1. "Competitors" refer only to pipelines with the same target for the same indication registered at CDE or ClinicalTrials.gov as our Core Product.
2. With active clinical trials in the United States.
3. Number of pipelines with NDA submitted to the NMPA and pipelines in Phase III clinical-stage in China.
4. Number of pipelines undergoing Phase II or Phase III clinical trials in the United States

Source: China Insights Consultancy

Confirmation

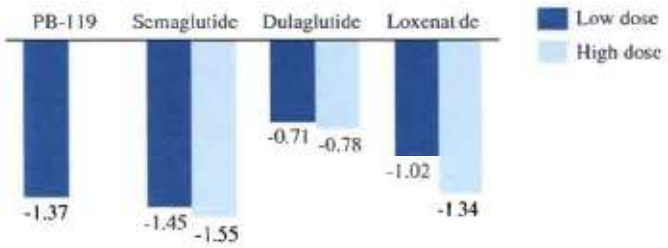
The following table sets forth the features of major prevention and maintenance methods for the treatment of T2DM.

	Healthy diet	Regular exercise	Weight loss	Blood sugar monitoring
T2DM	A balanced diet rich in fruits, vegetables, whole grains, lean proteins, and healthy fats can help prevent and manage T2DM. Emphasizing low glycemic index foods and controlling portion sizes can aid in blood sugar regulation.	Engaging in regular physical activity helps improve insulin sensitivity, regulate blood glucose levels, and manage weight. Both aerobic exercise (e.g., brisk walking, swimming) and resistance training are recommended.	Achieving and maintaining a healthy weight is critical for preventing and managing T2DM. Even modest weight loss (5-10% of body weight) can lead to significant improvements in insulin sensitivity and glycemic control.	Regular monitoring of blood glucose levels, either through self-monitoring or continuous glucose monitoring (CGM), allows individuals with T2DM to track their response to treatment, make informed decisions about diet and exercise, and prevent complications.

Source: FDA, China Insights Consultancy

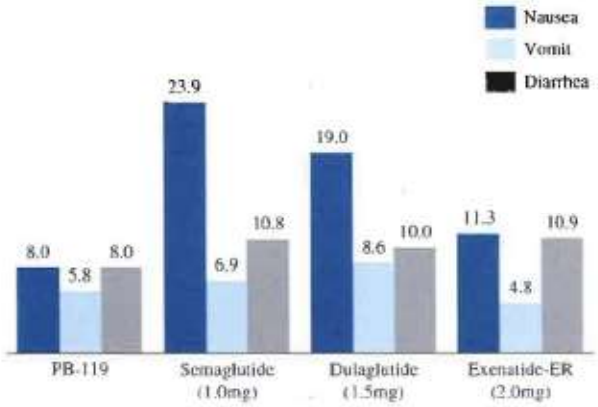
Confirmation

Decrease in HbA1c as primary clinical endpoint (%)



Note: The time period of primary clinical endpoints of PB-119, Semaglutide, Dulaglutide and Loxenatide was24 weeks, 30 weeks, 26 weeks and 24 weeks, respectively. The primary efficacy endpoirts of placebo-controlled clinical trials for T2DM medications are usually evaluated at the end of a treatment period of approximately 24 to 30 weeks, and sometimes an extension period until 52 weeks is also included to gather additional information from the clinical trials.

Major GI disorders occurrence (%)



Note: This conclusion is based on parallel comparisons of PB-119 clinical trial results with results from these published clinical trials rather than head-to-head comparisons. Cross clinical trial comparison based on published clinical trials rather than head-to-head comparisons may involve risks and may not be representative of all the relevant clinical data.

Confirmation

The following table sets forth the features of major prevention and maintenance methods for the treatment of obesity.

	Healthy diet	Regular exercise	Weight loss	Blood sugar monitoring
Obesity/ Overweight	Adopting a calorie-controlled diet that prioritizes nutrient-dense foods while limiting processed and high-calorie items can support weight loss. Strategies such as mindful eating, meal planning, and avoiding sugary beverages are also beneficial.	Exercise plays a key role in weight management by increasing energy expenditure, preserving lean muscle mass, and promoting fat loss. Consistent physical activity, including cardio workouts, strength training, and flexibility exercises, is essential.	Weight loss is a cornerstone of obesity management and can be achieved through a combination of dietary changes, physical activity, behavior modification, and, in some cases, pharmacotherapy or bariatric surgery.	While not directly related to weight management, blood sugar monitoring may be important for individuals with obesity or overweight who are at risk of developing T2DM. Monitoring fasting blood glucose or hemoglobin A1c levels can help identify early signs of impaired glucose metabolism.

Source: FDA, China Insights Consultancy

Confirmation

The following table sets forth the features of major prevention and maintenance methods for the treatment of NASH.

	Healthy diet	Regular exercise	Weight loss	Blood sugar monitoring
NASH	Dietary modifications targeting weight loss and improved liver health are crucial for managing NASH. This may include reducing intake of refined carbohydrates, saturated fats, and added sugars while increasing consumption of fiber-rich foods and healthy fats.	Regular exercise can reduce liver fat accumulation, inflammation, and fibrosis associated with NASH. Incorporating both aerobic and resistance exercises into the routine can improve liver health and metabolic parameters.	Weight loss is the primary therapeutic target for NASH as it can improve liver histology and reduce the risk of disease progression. Lifestyle interventions aimed at sustained weight reduction are recommended as the first-line approach.	Monitoring blood glucose levels may indirectly benefit individuals with NASH by helping to control insulin resistance and prevent further liver damage. Tight glycemic control is important, especially in individuals with comorbid T2DM or insulin resistance.

Source: FDA, China Insights Consultancy