Hua Medicine
华领医药

全控血糖 稳而有道

Jefferies 4th Annual Asia Forum
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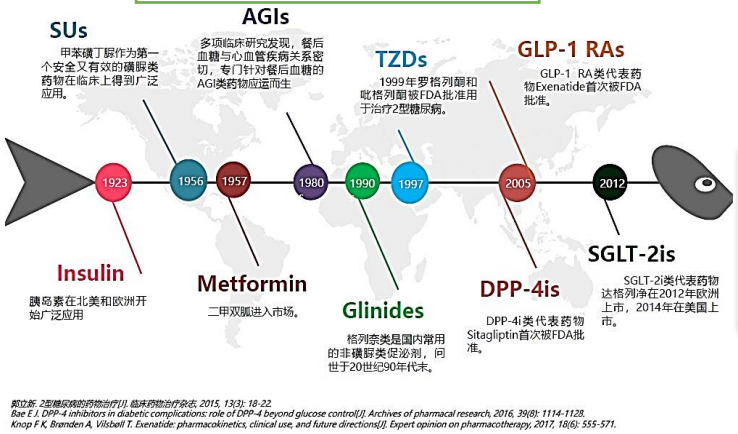
Diabetes Remains a Global Epidemic

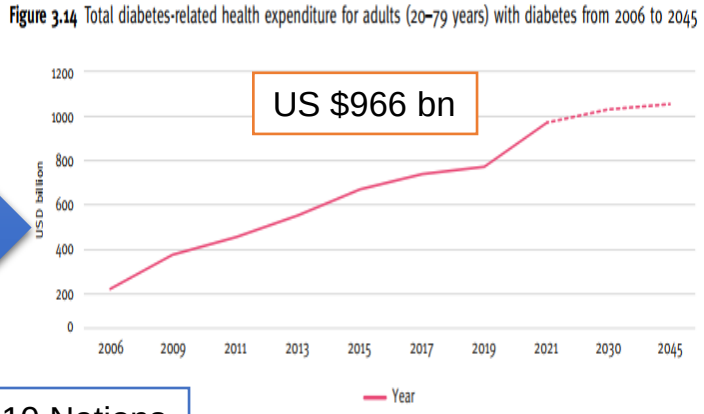
9 Classes of Drugs



Global Unmet Medical Needs in Glycemic Control

IDF 2021

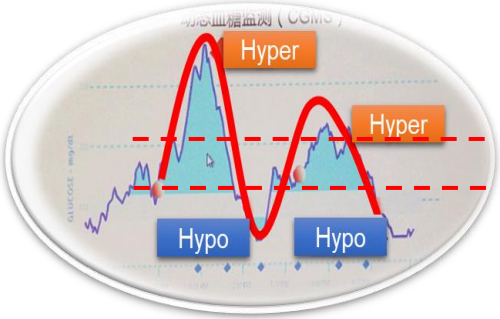
537 Mn Diabetes Many Complications



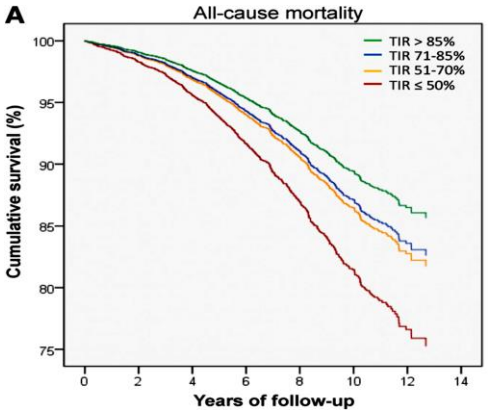
Top 10 Nations

Rank	Country or territory	Total diabetes-related health expenditure in 2021 (USD billion) in adults (20–79 years)
1	United States of America	379.5
2	China	165.3
3	Brazil	42.9
4	Germany	41.3
5	Japan	35.6
6	United Kingdom	23.4
7	France	22.7
8	Mexico	19.9
9	Spain	15.5
10	Italy	14.7

Economic Burden



Lost Glucose Homeostasis

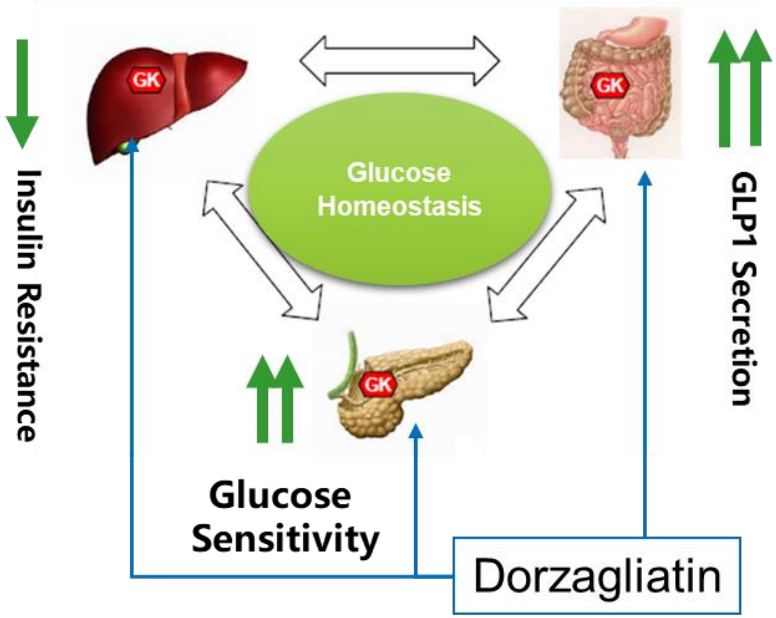


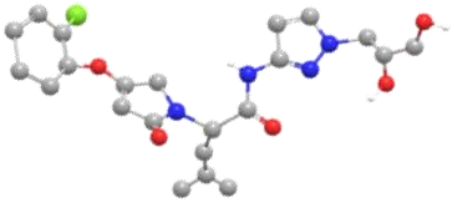
TIR in Diabetes Survival

Source: Cheng YY, Chen L. Global J Obesity, Diabetes and Metabolic Syndrome 2020, 7：018-023
Source: IDF DIABETES ATLAS Tenth edition 2021

Dorzagliatin –First-In-Class Drug to Restore Glucose Homeostasis

Glucokinase (GK) as glucose sensor plays central role in glucose homeostasis
Loss of GK sensor function leads to impaired glucose sensitivity and diabetes





- **Dorzagliatin improves glucose sensitivity** and **glucose stimulated early phase insulin secretion** to repair **glucose homeostasis**.
- Clinical Trials:
  - DREAM study demonstrated **65% of T2D patients achieved diabetes remission** without antidiabetic agent for 52 weeks
  - **Elevated Time-in-Range (TIR)** of T2D patients and effectively improved the islet function represented by early phase insulin secretion. Dorzagliatin is expected to help people with IGT to improve islet function and **prevent diabetes**.
  - **Improves glucose stimulated GLP-1 secretion** in obese T2D patients
- Animal Studies
  - Validated DREAM study results - sustained improvement in pancreatic islet function in mice after drug discontinuation was observed.
  - **Stabilizes the expression of glucose transporter protein in hippocampus**, and **improves cognitive impairment**

Source: Chen L, Zhang JY et al. Nature Communications , A phase I open-label clinical trial to study drug-drug interactions of Dorzagliatin and Sitagliptin in patients with type 2 diabetes and obesity 2023, 3： 1405.

华堂宁® (HuaTangNing) Approved by NMPA in China

Approved in Sep 2022, and Launched in Oct 2022

1. One Breakthrough: restores the impaired glucose homeostasis in T2D patients
2. Two Indications: with dietary and exercise to treat
    1. Drug naïve T2D
    2. Metformin tolerated T2D
3. Three Allowances
    1. No dose adjustment for DKD
    2. No dose adjustment when combined with sitagliptin
    3. No dose adjustment when combined with empagliflozin

Retail Launch Price: 420 RMB / 28 Tablet Pack

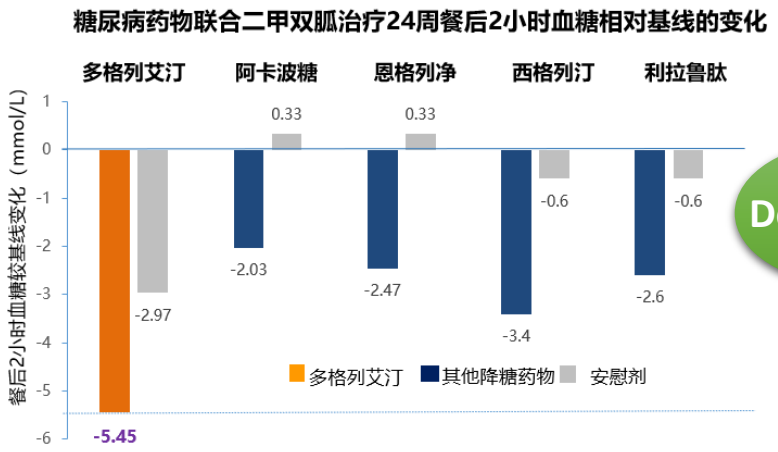
Two Key Takeaways on Label:
1) Improves ß-cell function
2) Restores impaired glucose homeostasis

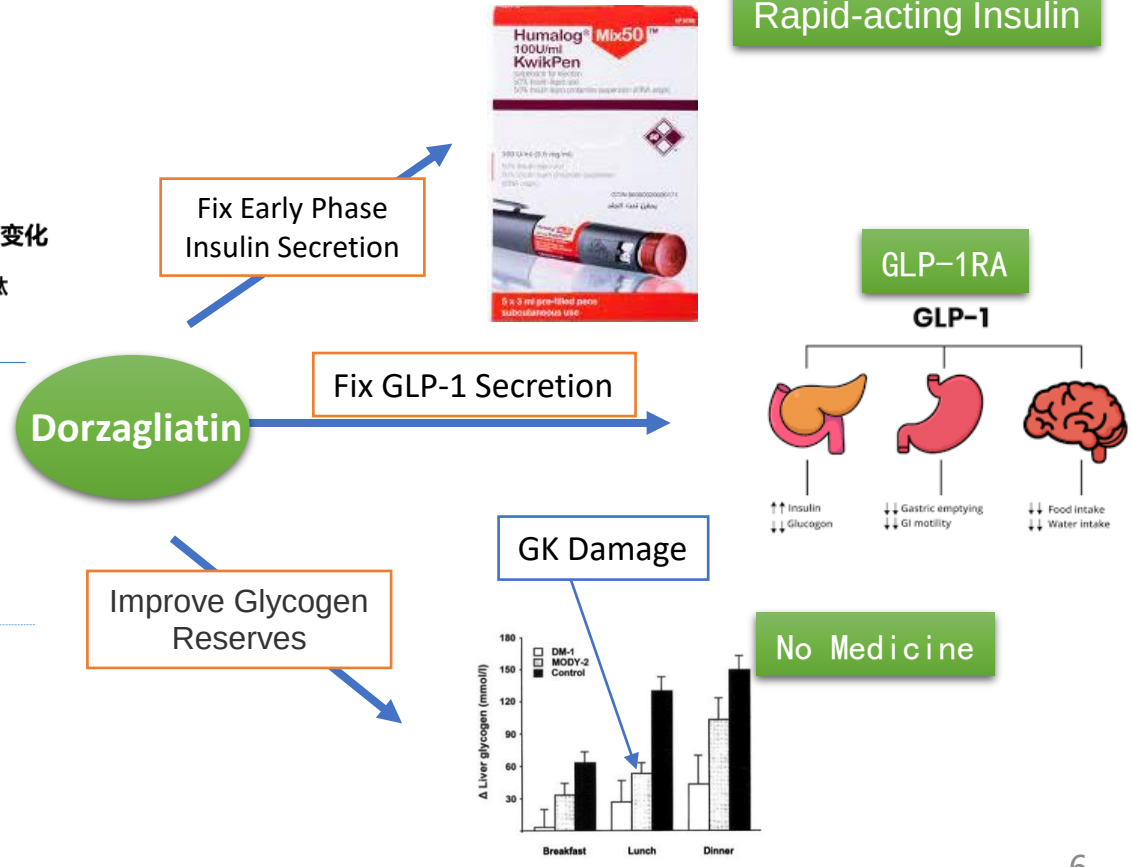
Bayer Healthcare is Exclusive Commercial Partner in China (shares ~ 50% sales)
- RMB 300m upfront payment
- RMB 400m commercial milestone payment
- RMB 800m development milestone payment

Dorzagliatin - Fix Three Core Issues of Type 2 Diabetes Simultaneously

- Early phase insulin secretion function impairment is the core cause of diabetes, resulting in insufficient insulin secretion and insulin resistance.
- Impairment of GLP-1 secretion function leads to decreased insulin secretion ability and abnormal diet control.
- Impairment of liver glucokinase function causes insulin resistance and blood glucose fluctuation

Significant Postprandial Blood Sugar Reduction Compared to Other Top-Selling Anti-Diabetes Drugs





Technology-led, Innovation-driven, Evidence-based Medicine, High-quality Development

Dorzagliatin monotherapy in Chinese patients with type 2 diabetes: a dose-ranging, randomised, double-blind, placebo-controlled, phase 2 study

Improve Insulin Secretion And Reduce Insulin Resistance

nature medicine ARTICLES

Dorzagliatin in drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 3 trial

Phase 3 SEED

news & views

DIABETES

A new class of drug in the diabetes toolbox

The DAWN and SEED trials demonstrate the potential of glucokinase activators for the treatment of type 2 diabetes, but how they fit in the overall treatment algorithm remains to be determined.

Klara R. Klein and John B. Buse

First-In-Class Antidiabetic Drug

nature medicine ARTICLES

Dorzagliatin add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 3 trial

Phase 3 DAWN

nature communications

Article

A phase I open-label clinical trial to study drug-drug interactions of Dorzagliatin and Sitagliptin in patients with type 2 diabetes and obesity

Improve GLP-1 Secretion

ORIGINAL ARTICLE

WILEY

Diabetes remission in drug-naïve patients with type 2 diabetes after dorzagliatin treatment: A prospective cohort study

DREAM Study Remission of Diabetes

7

TIR Algorithm Thesis

Clinical Expert Consensus

Pharmaceutical Expert Consensus

DoRzagliatin Effect in DiAbetes ReMission

DREAM study: a diabetes remission in drug naïve patients who completed SEED study

- Total 69 subjects with average A1c of 6.61%, 2.2 year disease history
- Blood glucose are on target without any glucose lower drug
- 65.2% diabetes remission achieved at 52 week
- IIT study at 5 clinical centers in China

Drug Naïve T2D

40 center → SEED n = 310

Dorzagliatin treatment
24+28 week

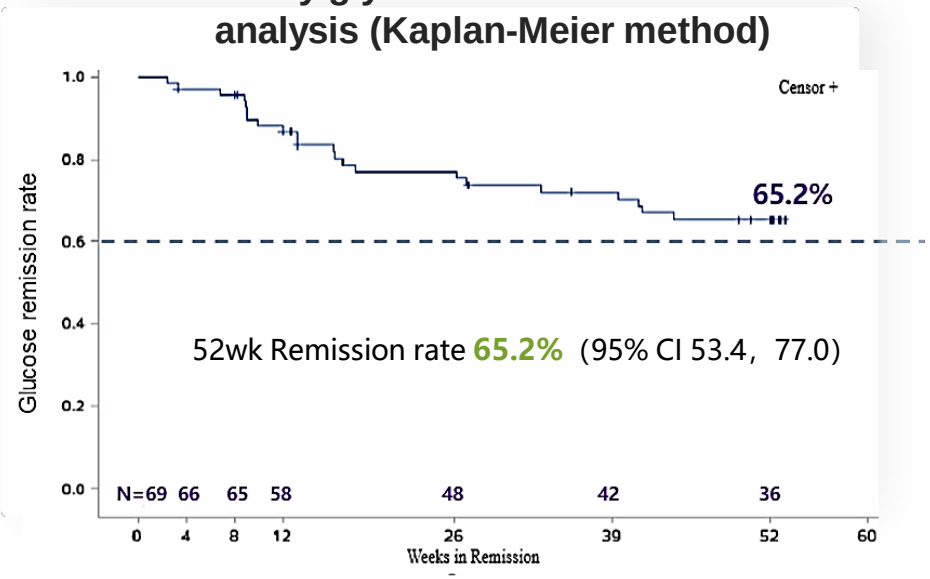
40 center → Control rate 45%*

Glucose Controlled

5 center → Remission 65.2%

52 week
Diabetes Remission**

DREAM study glycemic remission time survival analysis (Kaplan-Meier method)

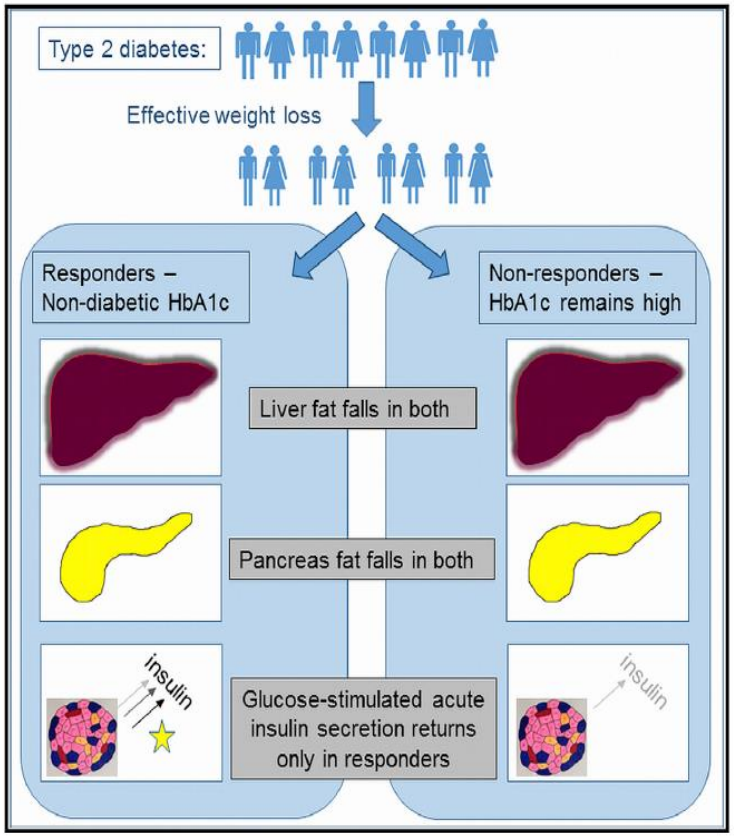


* Control rate at 24 week of SEED study: HbA1c < 7%

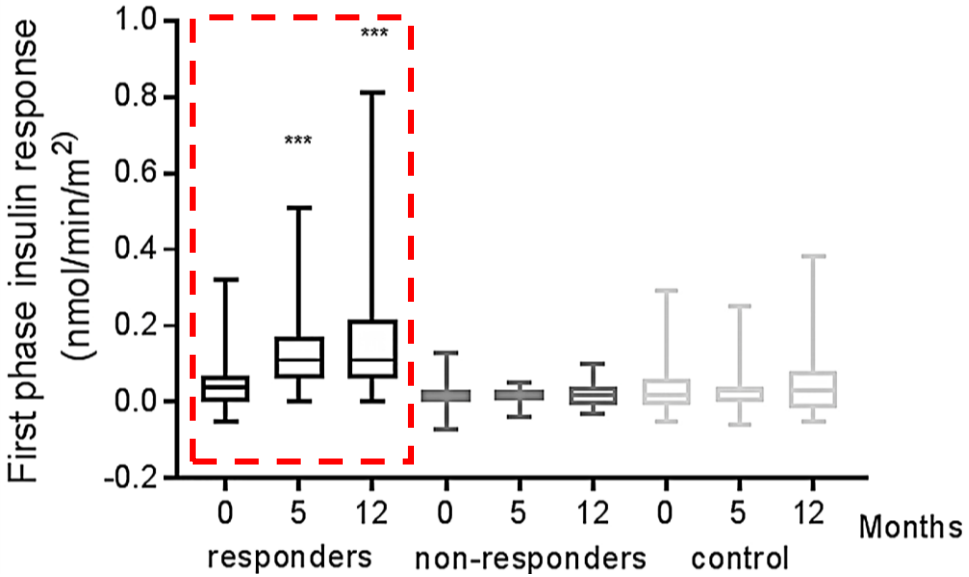
** Based on the 2021 "Expert Consensus on Diabetes Remission" (HbA1c lasting less than 6.5% within 3 months without medication), survival analysis showed that the remission rate at 12 weeks was **52.0%** (95% CI 31.2%, 69.2%)

Improving early-phase insulin secretion is a key factor in glycemic remission in T2D

DiRECT Study: For patients with diabetes remission driven by weight loss, weight loss of 15 kg to reduce liver and islet organ fat can contribute to a certain proportion of diabetes remission, but glucose-stimulated early insulin secretion have to be improved.



Patients who achieved blood sugar target in the trial
Glucose-stimulated early-phase insulin secretion was significantly improved



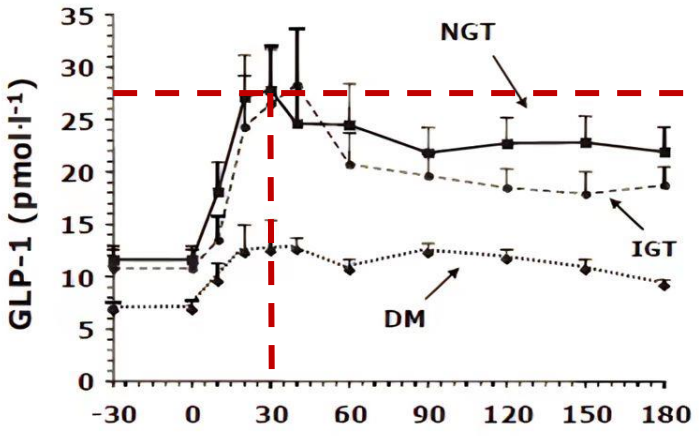
1.DiRECT Cell Metabolism 2018;28:547-556

Dorzagliatin Improve GLP-1 Secretion in T2D Patients with Obesity

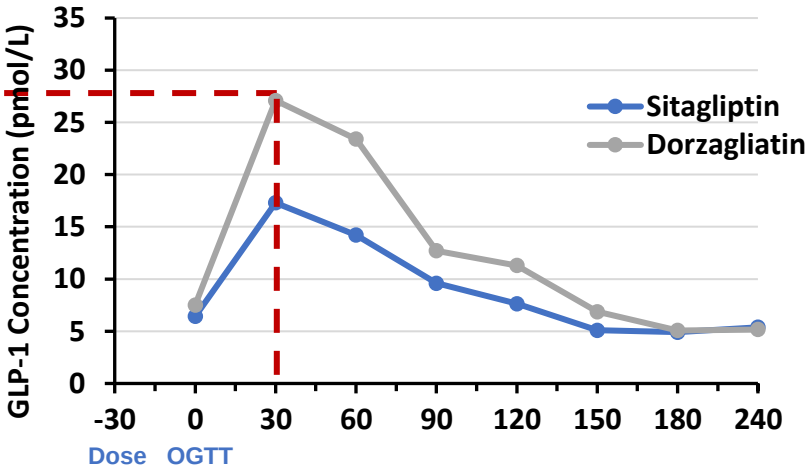
Ferrannini et al. reported that glucose-stimulated GLP-1 secretion was significantly decreased in T2D patients with obesity.

The result of OGTT showed that **dorzagliatin regulated GLP-1 secretion**. At 30 minutes after OGTT, the **GLP-1 level of T2D patients with obesity was close to that of people with normal glucose tolerance**.

GLP-1 Levels of IGT and NGT



GLP-1 levels in T2D Patients with Obesity Treated with Dorzagliatin or Sitagliptin



It was proven for the first time in a clinical trial that dorzagliatin improves GLP-1 secretion in both islets and intestines, thereby increasing glucose-stimulated insulin secretion.

GK: Trigger for Insulin Secretion

As a glucose receptor, it is the first step in intracellular glucose utilization.

GK senses increased glucose concentration, rapidly responds to the release of insulin stored in the vesicles, and increases insulin secretion.**(Phase I is dominant, Phase II is complementary)**

GLP-1: Amplifier of insulin secretion

GLP-1 binds to GLP-1 receptor, activates cAMP pathway and vesicular insulin releases after β-cells perceive the increase of glucose concentration.

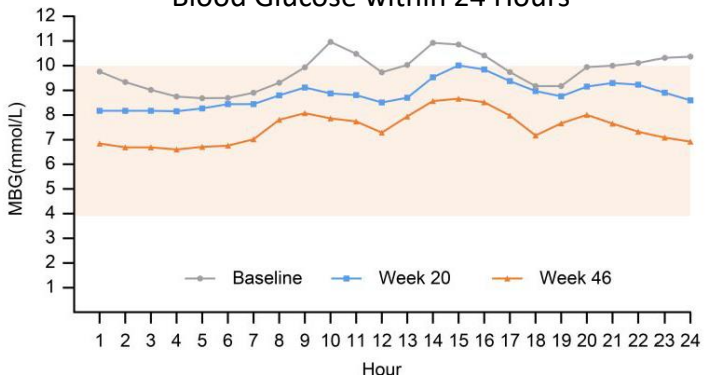
It also promotes insulin transcription and replenishes vesicular insulin refilling (Phase II) to improve insulin secretion. **(Phase II is dominant, Phase I is complementary)**

Cooperative Improvement Insulin Secretion

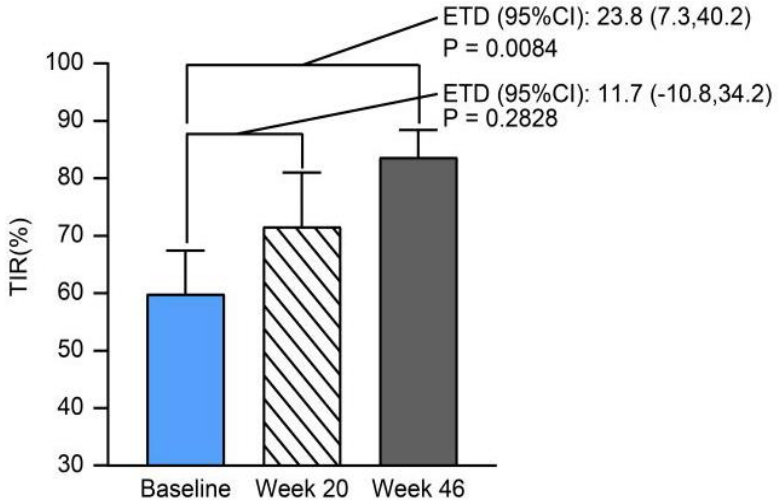
Ferrannini, E. et al, Diabetes, 2008, 57(5), 1340-1348

Dorzagliatin Improved TIR and Repaired Islet Function

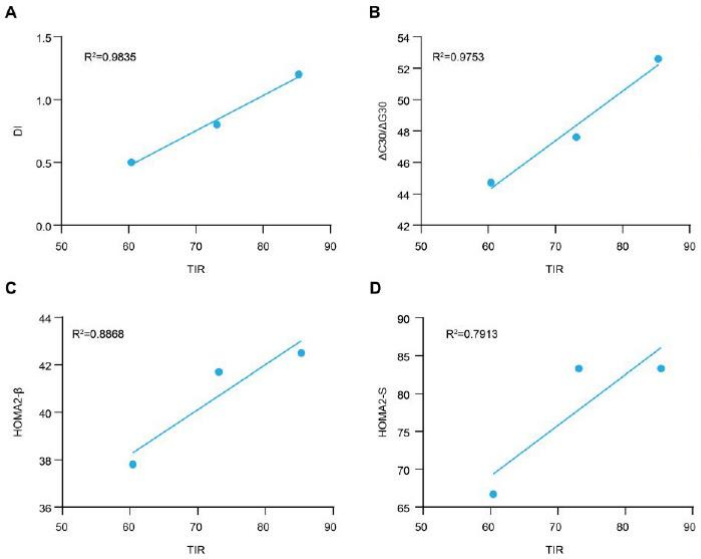
Dorzagliatin Significantly Improved Patients' Blood Glucose within 24 Hours



TIR Increased with the Duration of Treatment, Reaching 83.7% at 46 Weeks



The Islet Function was Improved Synchronously by TIR



- Dorzagliatin significantly improved daily glucose homeostasis in diabetic patients.
- Long-term use of dorzagliatin brings a steady improvement in TIR.
- The patients' damaged islet function was gradually restored.

Diabetes Obes Metab.2023 Jun 29. doi: 10.1111/dom.15179

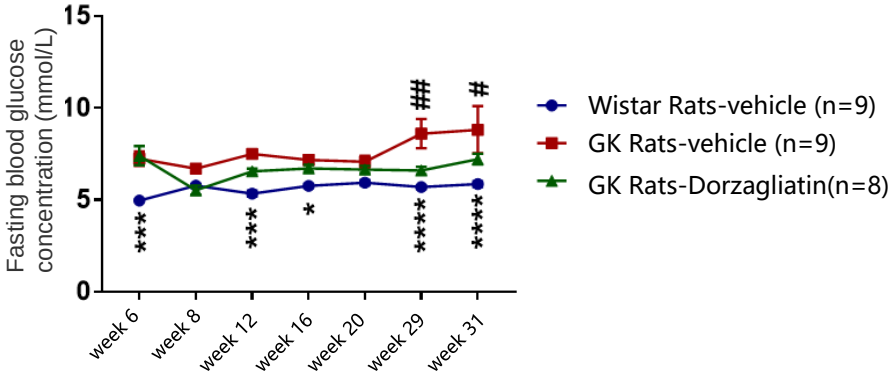
Dorzagliatin Improves Cognitive Impairment in Rats

- Non-obese diabetic Goto-Kakizaki rats (GK rats) exhibit increase in blood glucose and decreased memory function with age.
- With 26 weeks treatment of low-dose dorzagliatin, **the trend of elevated fasting blood glucose in GK rats was significantly lower than that in the vehicle group, and it had a protective effect against the decline of memory function.**

Long-term administration of dorzagliatin prevents the reduction of insulin receptor protein expression and stabilizes the protein expression level of glucose transporters in hippocampus of GK rats.

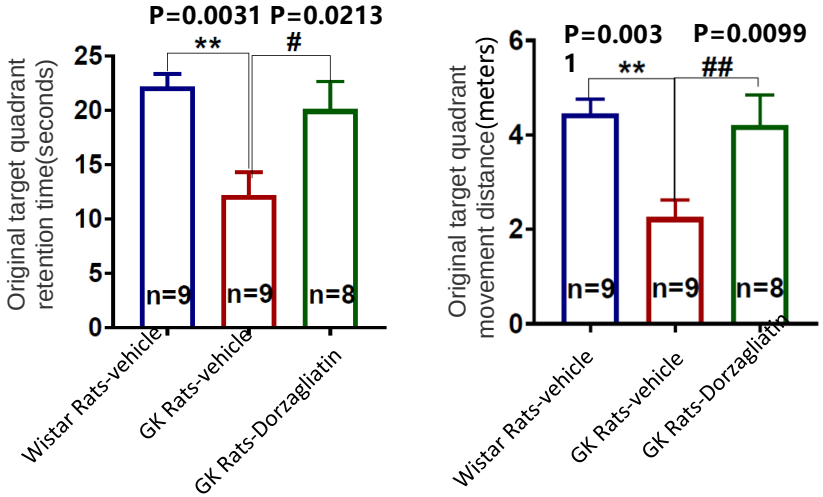
Dorzagliatin exerts a protective effect on memory function by protecting the glucose metabolism function in body and inhibiting the decline of glucose metabolism function in the brain of GK rats.

Changes of Fasting Blood Glucose in Rats with Age



GK-vehicle compared with Wistar group, *P < 0.05, ***P < 0.001, ****P < 0.0001.
GK-vehicle compared with GK-dorzagliatin group, #P < 0.05, ##P < 0.01.

Morris Water Maze Spatial Memory Test at 33 Weeks of Age

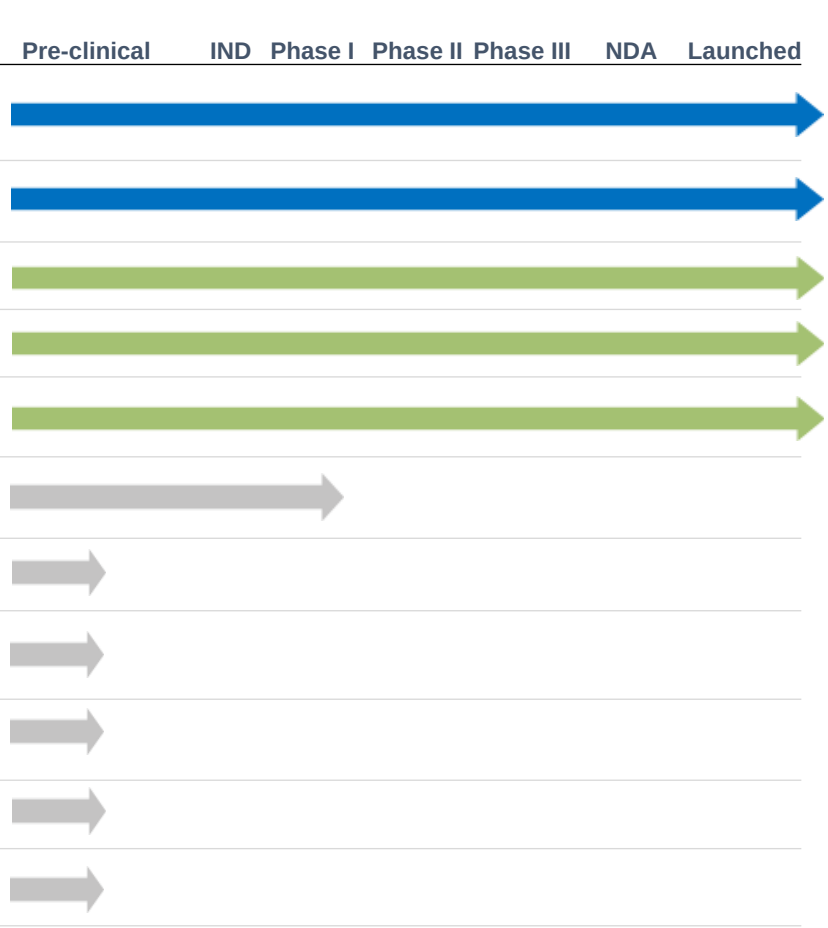


2023 ADA Poster, 247-LB

Outlook

Hua Medicine R&D Pipeline

Product Name	Indication	Development phase
HuaTangNing (华堂宁®)	T2D –Drug Naïve	Launched (China)
	T2D –Metformin Tolerated	Launched (China)
HuaTangNing (华堂宁®) No dose adjustment in	DKD	Launched (China) - Allowances
	Combination therapy with DPP4i	Launched (China) - Allowances
	Combination therapy with SGLT2i	Launched (China) - Allowances
Fixed dose combinations - dorzagliatin and OADs	T2D	Phase I ready
2nd Generation GKA	Metabolic Diseases	Pre-clinical
Glucokinase regulator	Congenital Hyperinsulinism	Pre-clinical
Fructose Kinase Inhibitor	Metabolic Disease	Pre-clinical
mGLUR5 NAM- CNS	PD-LID	Pre-clinical
Clinical Fructose detection	IVD	Pre-clinical



2nd Generation GKA Ready to IND in US

1st Generation GKA

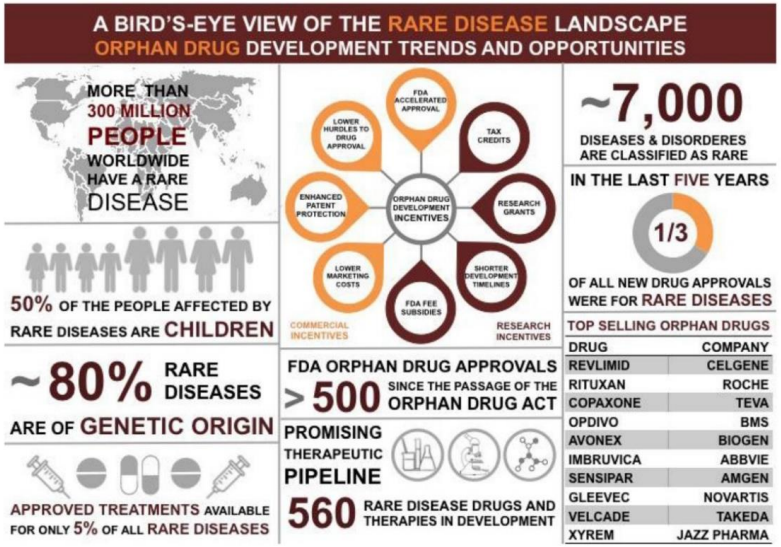
- Chinese market, Chinese patients
- One tablet twice daily
- Restore impaired glucose homeostasis, improve β-cell function
- Cooperate with major pharmaceutical companies in the Chinese market

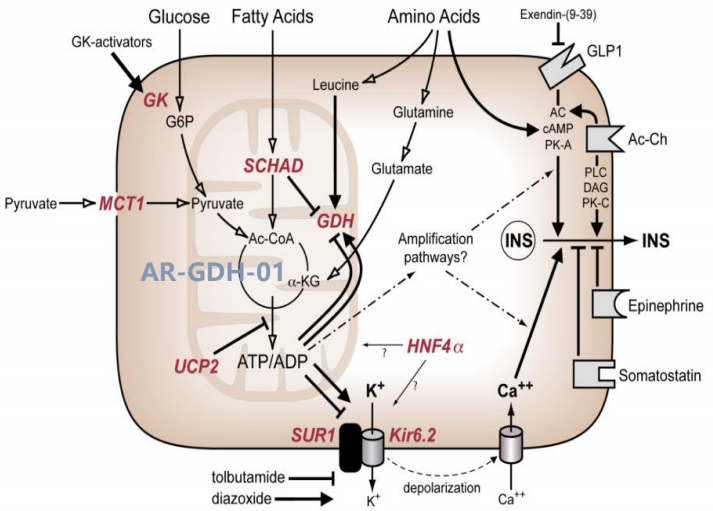
2nd Generation GKA

- Western markets, the majority of patients with obesity
- Rare diseases treatment
- Consistent with western patients' drug usage habits
- Restore impaired glucose homeostasis, improve β-cell function, seek diabetes prevention and remission
- Explore the possibility of breakthrough therapy designation in the field of rare disease

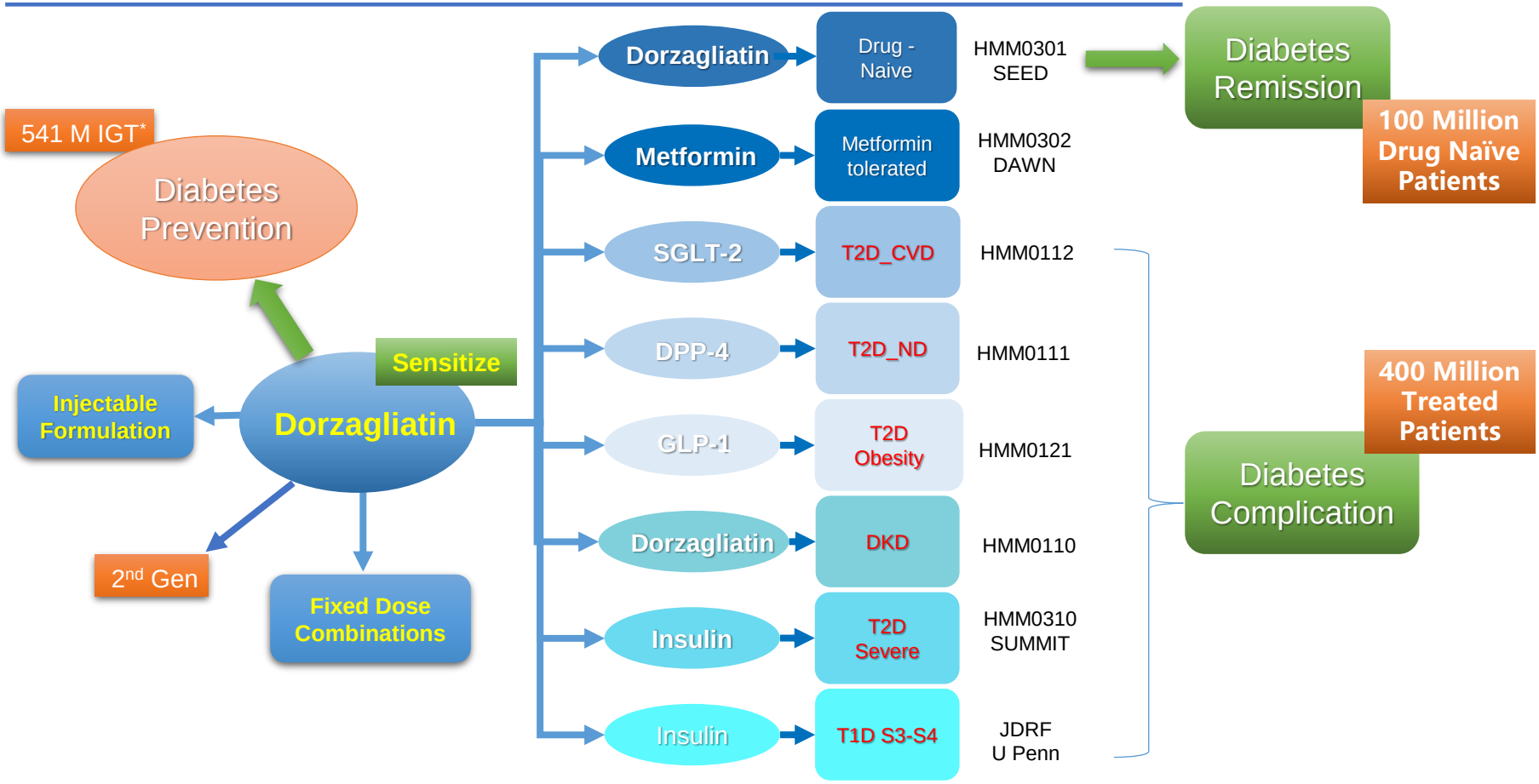
Drug Development of Congenital Hyperinsulinemia

- Congenital hyperinsulinemia is a serious disease threatening the health of newborns, which will cause permanent brain damage and life-long disability, or even life threatening in half of the patients without proper treatment.
- Congenital hyperinsulinemia is a rare disease, which has been listed in the list of rare diseases in China. Effective medical intervention is urgently needed, and the patients also need effective new drugs.
- The number of people with hypoglycemia due to genetic mutations is estimated to be 47,000 in China and nearly 150,000 globally.





Restore Glucose Homeostasis: New Chance of Diabetes Remission and Ultimately Prevention



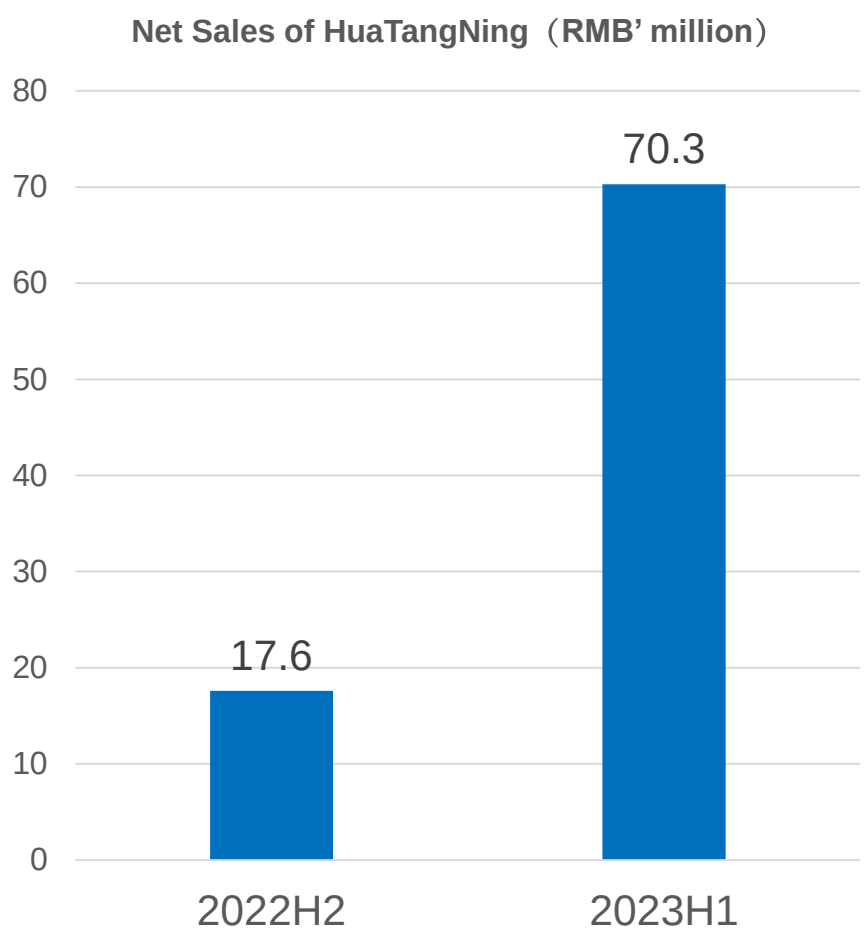
- **Diabetes remission** by early intervention of Dorzagliatin: impact about 100 M diabetes patients
- **Diabetes prevention** by Dorzagliatin for IGT subjects: about 541 M IGT patients worldwide
- **Diabetes complication prevention** by early combination of Dorzagliatin: about 440 M T2D patients have one or more comorbidities

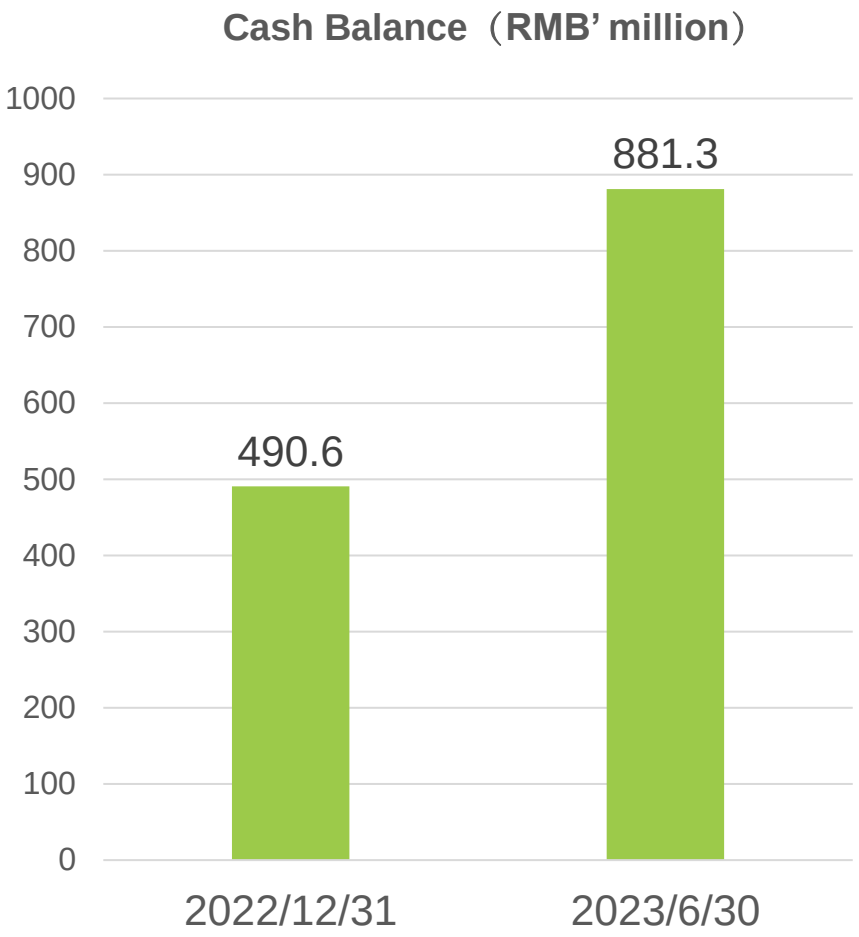
*IDF Diabetes Atlas 10th Edit; Leon Litwak *Diabetology & Metabolic Syndrome* 2013, 5: 57; Yuanyuan Cheng, Li Chen *Global J Obesity, Diabetes and Metabolic Syndrome* 2020, 7: 18

Future Action

- **Prepare for NRDL Negotiation**
  - We have submitted materials to the National Healthcare Security Administration.
  - Dorzagliatin has officially passed the formal examination NRDL, according to the NHSA public website.
  - Hua will participate in the NRDL price negotiation in the fourth quarter of 2023.
- **Expand Production Capacity**
  - We have initiated investment into dorzagliatin manufacturing capability at Changzhou SynTheAll, Zhejiang Raybow and Shanghai Desano.
  - The expanded capacity will better fulfill the enlarged demand expected in the future.
- **More Milestone Payment**
  - We will receive an 800 million milestone payment from Bayer related to product development in the fourth quarter of 2023
  - Hua is expected to receive milestone payments up to RMB 2.94 billion from Bayer in the future; RMB 1.5 billion of upfront & milestone payments already achieved.
  - We have strong cash balance to accelerate our R&D pipeline.

Strong Financial Results





Approximately 212,000 packs of HuaTangNing have been sold, generating net sales of approximately RMB70.3 million, an increase of 299.6% compared to the second half of 2022.

RMB400 million was received as milestone payment of commercialization in Q1. Achievement of a Bayer milestone of RMB800 million has been confirmed and will be received in Q4 2023.

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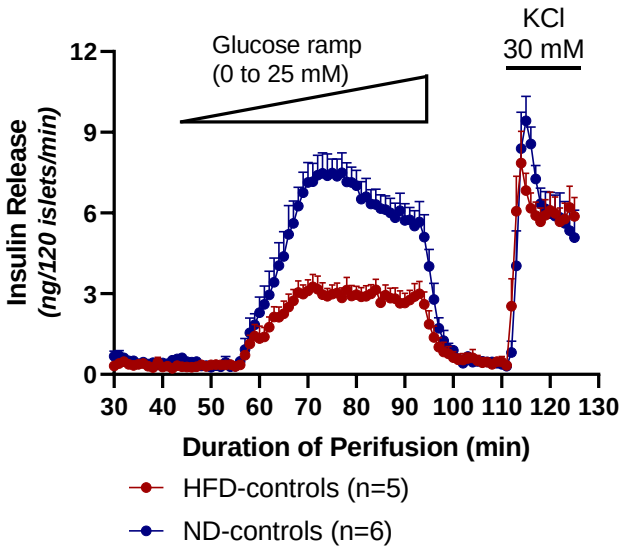
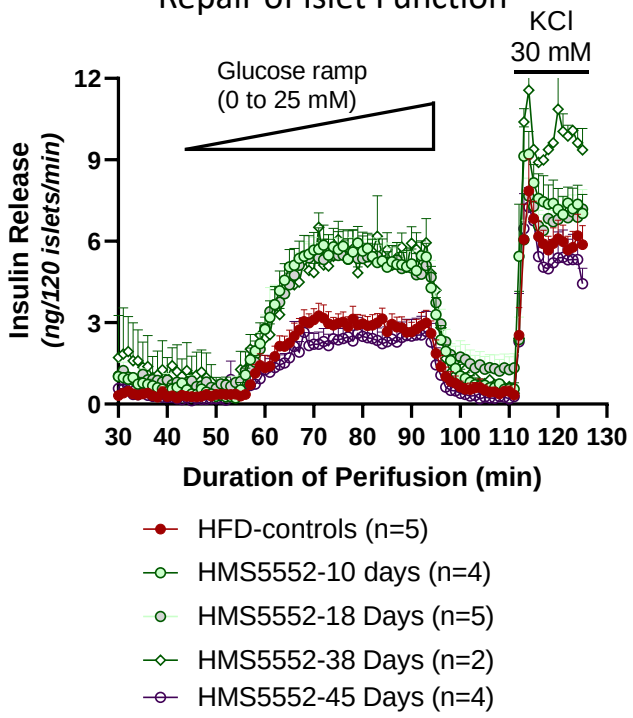
Dorzagliatin Continued to Repair Impaired Islet Function of Diabetic Rats

Impaired Islet Function in Obese/Diabetic Rats Induced by HFD



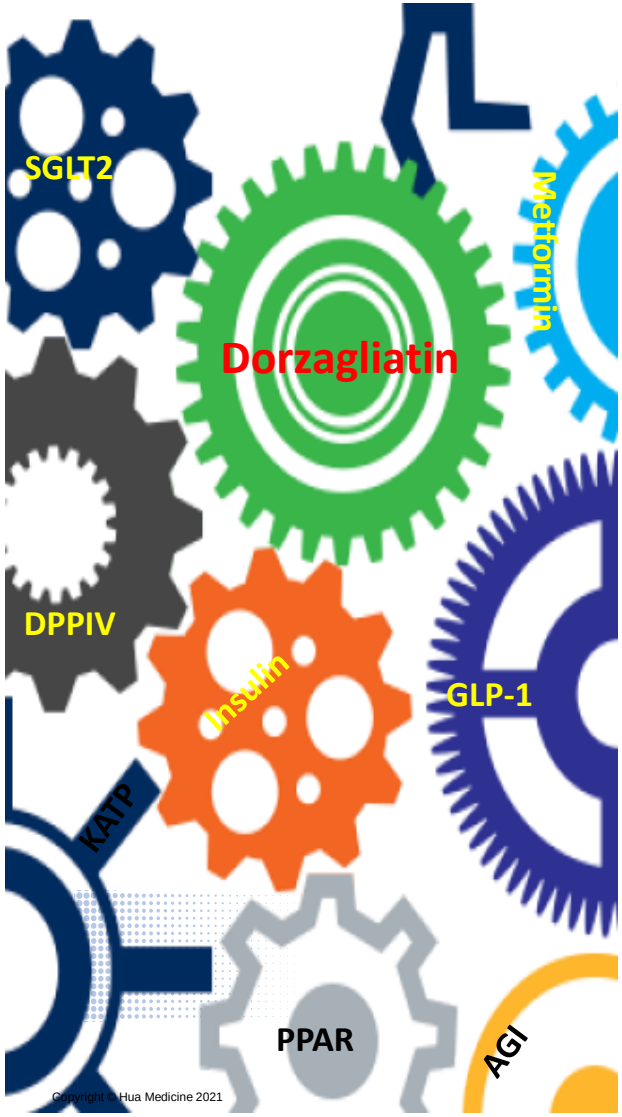
Dorzagliatin Achieves Long-term Repair of Islet Function



- Dorzagliatin **significantly improved impaired islet function in diabetic rats** during 19 days of administration.
- Islet function **continued to improve on day 10, day 18 , and day 38 in the absence of antidiabetic agents,** until the impairment of islet function reappeared on day 45.

2023 ADA Poster, 247-LB

Goal 2030—Integrated Interventional Diabetes Management



In the medical community environment, explore the potential benefits, broaden the indication, promote a new model of diabetes treatment, and contribute to Healthy China 2030

- Dorzagliatin in combination with metformin, sitagliptin and empagliflozin in the early stage improves the glucose control rate and remission rate in untreated patients and patients treated with oral hypoglycemic agents
- Dorzagliatin combined with insulin or GLP-1RA leads to disease remission and control of diabetic complications.
- Dorzagliatin prevents diabetes in patients with IGT.

Enhancing the comprehensive value of hospital care: Bayer-Hua Medicine DKD joint team

- Management of diabetic kidney disease patients in chronic kidney disease
- Glucose management in the treatment of cardiovascular disease
- Fixed compound formulations provide better medical value

New era of personalized diabetes care

- Artificial intelligence can help to better define disease and enable the precision treatment of diabetes
- Glucose management in neurodegenerative diseases