GLUCOKINASE: Advancing Diabetes Care

Hua Medicine
华 领 医 药

BIO International San Diego
June 2024

Disclaimer

This document may contain statements that constitute “forward-looking statements”, including, but not limited to, statements relating to the implementation of strategic initiatives, and other statements relating to our future business development and economic performance.

While these forward-looking statements represent our judgments and future expectations concerning the development of our business, a number of risks, uncertainties and other statutory requirements may render actual developments and results to differ materially from our expectations.

These factors include, but are not limited to, (1) general market, macro-economy, governmental and regulatory trends, (2) movements in local and international securities markets, currency exchange rates and interest rates, (3) competitive pressures, (4) technological developments, (5) changes in the financial position or creditworthiness of our customers, partners, vendors obligors and counterparts, and changes in the developments in the markets in which they operate, (6) legislative or regulatory developments, (7) management changes and changes to our business group structure and (8) other key factors that may adversely affect our business and financial model.

We are not under any obligation to (and expressly disclaim any such obligations to update or alter forward-looking statements whether as a result of new information, future events, or otherwise.

This material may not be reproduced, distributed or transmitted to any other person or incorporated in any way into another document or other material without the prior written consent of us.

This document is not:

(a) an offer of securities for sale in Hong Kong or elsewhere; or

(b) an invitation to enter into an agreement to acquire, dispose of, subscribe for or underwrite securities; or related to the issue of any securities.

All documents and conference contents are for institutional investors, no unauthorized audio and video recordings and may not be directly or indirectly reproduced even modified, redistributed or forwarded to any other person and may not be published in whole or in part for any purpose.

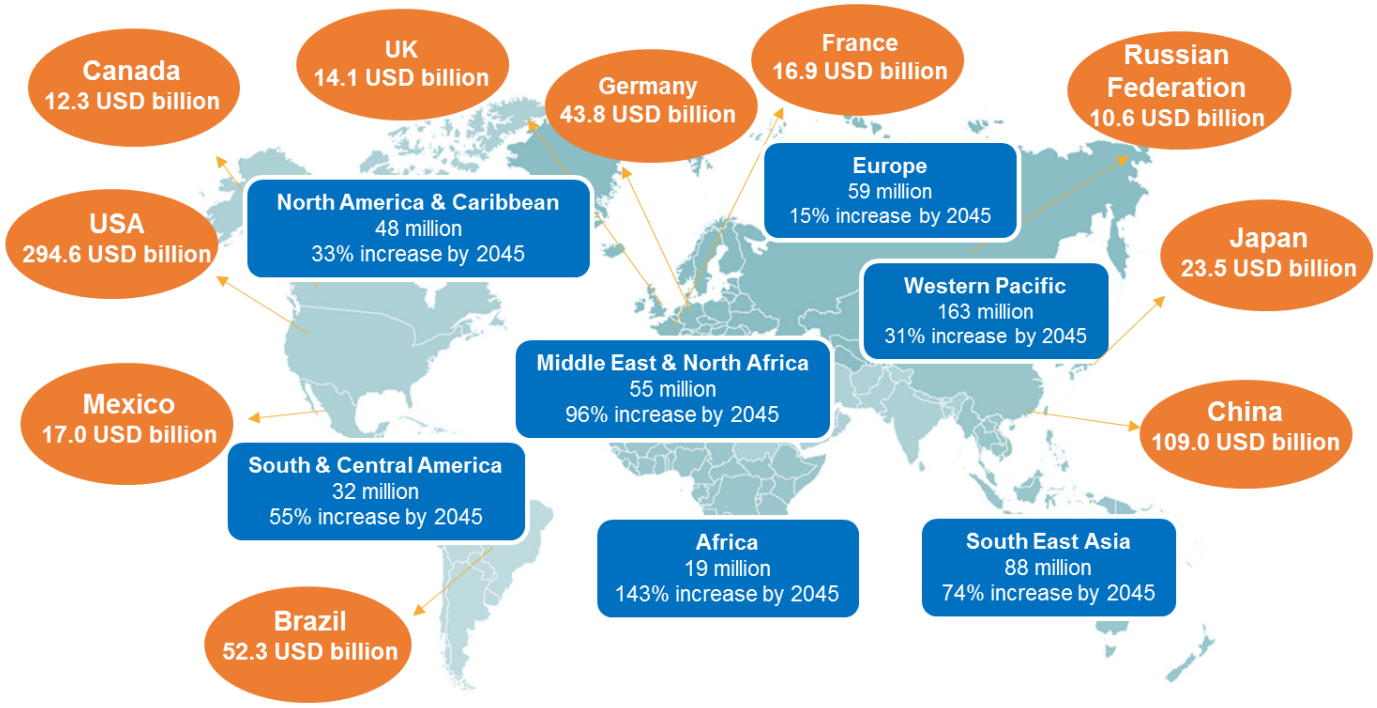
For the accuracy and completeness of the context, references to information related to products launched in China, especially label or requirements, should follow the relevant documents approved by the Chinese regulatory authorities.

The abovementioned information should not be interpreted as a recommendation or promotion of any drug or treatment regimen, nor should it substitute for the medical advice of any healthcare professional. Please consult a healthcare professional for any matters related to medical treatment.

Type 2 Diabetes: A Global Epidemic

No drug modifies diabetes… until now

- **~537 million** adults live with diabetes globally; **>120+ million in China and >38 million** in the U.S. (IDF, 2021; CDC, 2021)
- No currently approved therapeutics to deal with **the underlying cause of T2D**. Existing drugs on the market are **not disease modifying**.
- Total diabetes-related health expenditure will reach **USD 825 billion** by 2030. (IDF, 2019)

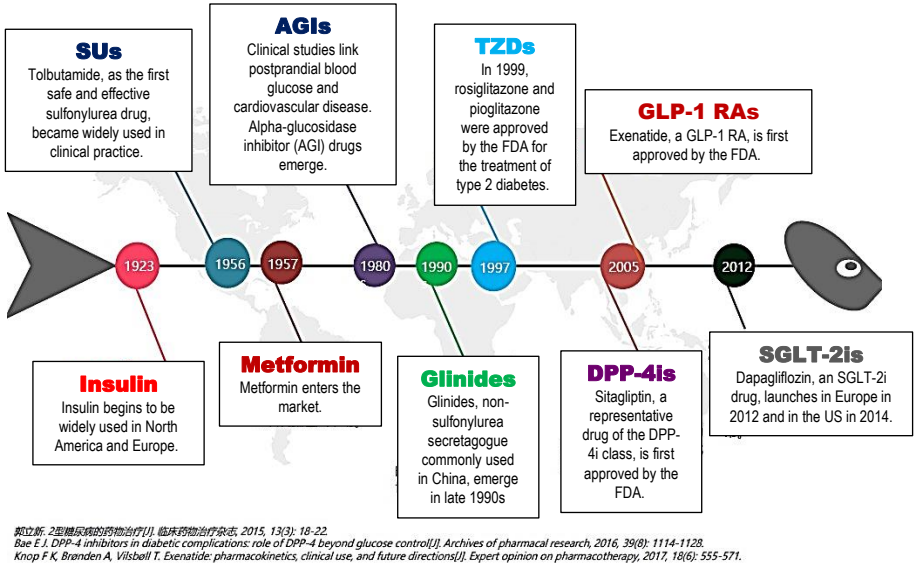


Number of people (20-79 years) with diabetes

Top 10 countries or territories for total health expenditure due to diabetes

Source: IDF DIABETES ATLAS Ninth edition 2019.
Note: Diabetes-related health expenditure refers to the direct costs. Direct costs are the health expenditures due to diabetes – regardless of whether this expenditure is born by patients themselves or by private or public payers or by government.

Global unmet need in glycemic control

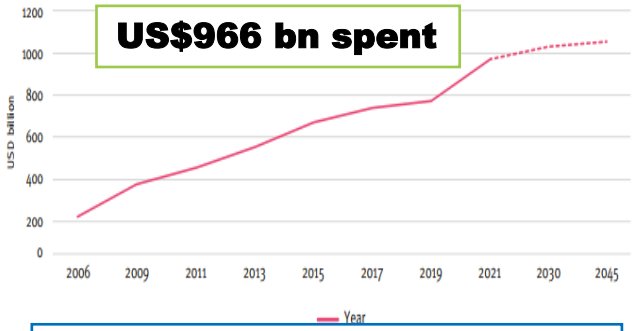


郭立新. 2型糖尿病的药物治疗[J]. 临床药物治疗杂志, 2015, 13(3): 18-22.
Bae E J. DPP-4 inhibitors in diabetic complications: role of DPP-4 beyond glucose control[J]. Archives of pharmacal research, 2016, 39(8): 1114-1128.
Knop F K, Brønden A, Vilsbøll T. Exenatide: pharmacokinetics, clinical use, and future directions[J]. Expert opinion on pharmacotherapy, 2017, 18(6): 555-571.

9 Classes of Drugs

- 9 classes of diabetes drugs on the market treat symptoms, **not underlying causes**.
- Activating the glucokinase can lead to glucose homeostasis, modification of diabetes and remission.
- **Published data** on remission for 52 weeks.
- China making strides in “treating” diabetes.
- **What’s next?**

Figure 3.14 Total diabetes-related health expenditure for adults (20–79 years) with diabetes from 2006 to 2045



Diabetes Expenditure: Top 10

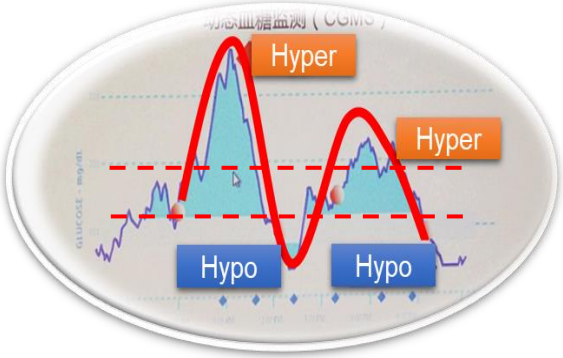
Rank	Country or territory	Total diabetes-related health expenditure in 2021 (USD billion) in adults (20–79 years)
1	United States of America	379.5
2	China	165.3
3	Brazil	42.9
4	Germany	41.3
5	Japan	35.6
6	United Kingdom	23.4
7	France	22.7
8	Mexico	19.9
9	Spain	15.5
10	Italy	14.7

Source: IDF DIABETES ATLAS Tenth edition 2021

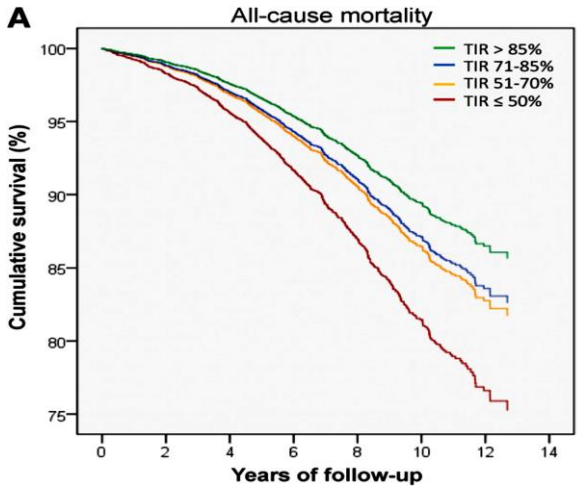
Managing T2D symptoms is not enough

How do we stop Type 2 Diabetes?

- Lowering blood glucose levels alone does not stop the progressive degenerative nature of diabetes, leading to complications.
- **Glucose Time In Range (TIR)** is a key metric to track and treat diabetes.



Lost Glucose Homeostasis



TIR in Diabetes Survival

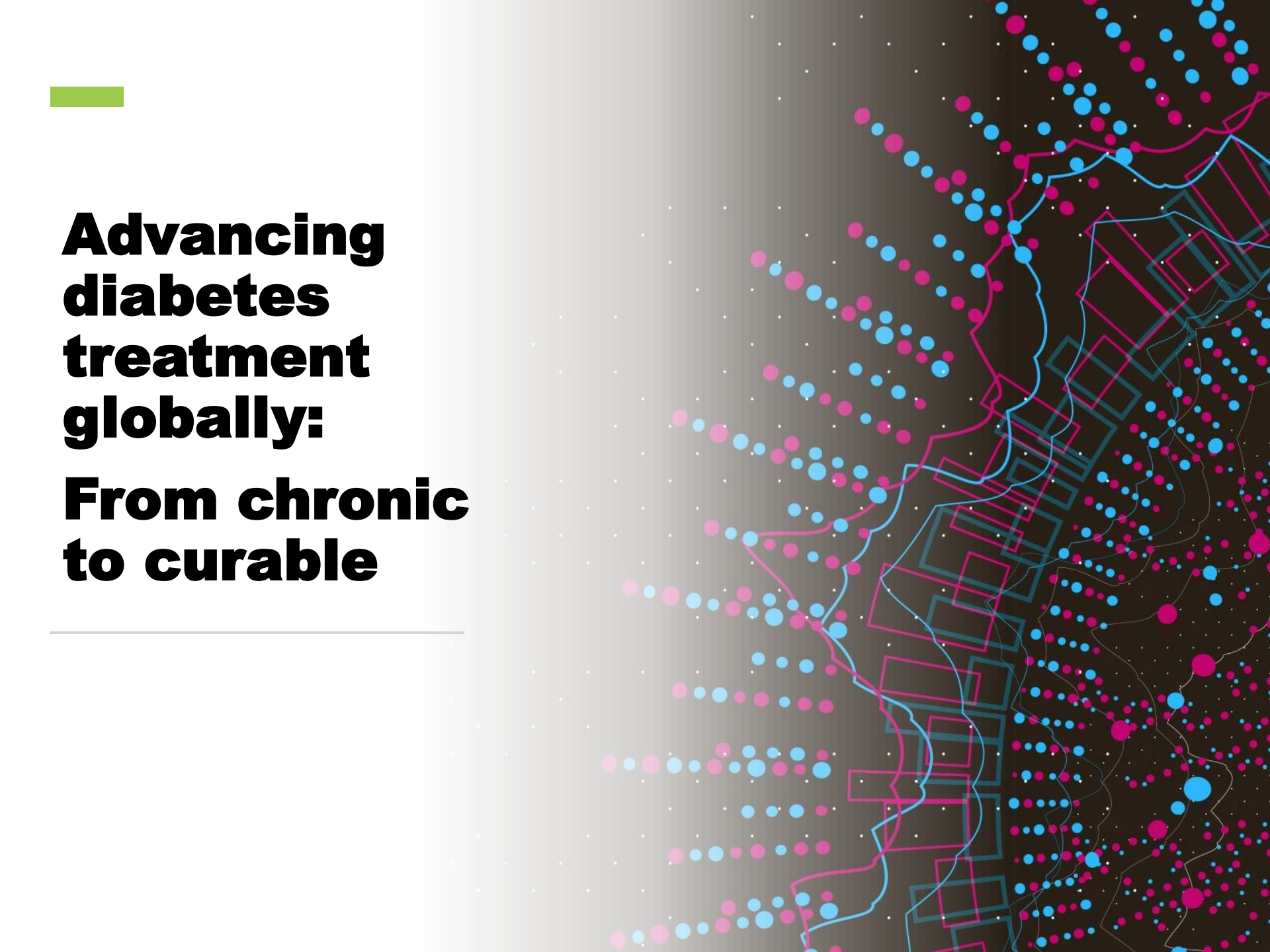
Goal in treating T2D:

Maintain blood glucose levels within a healthy range **autonomously**, achieving **glucose homeostasis** (4-6.5mM).

Source: Cheng YY, Chen L. Global J Obesity, Diabetes and Metabolic Syndrome 2020, 7：018-023

Advancing diabetes treatment globally:

From chronic to curable



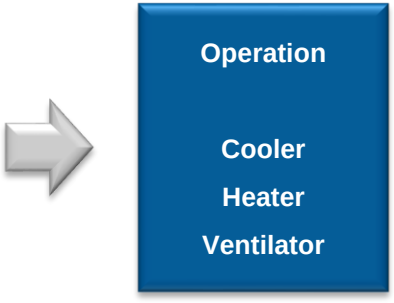
Glucokinase is the sensor in glucose homeostasis

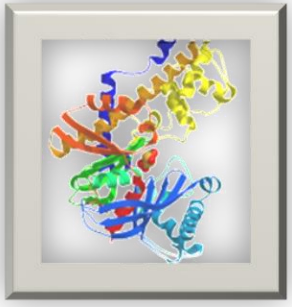
Thermostat in a Building

- Primary Messenger: air temperature
- Set Point: 22º Celsius
- Threshold: 21-23º Celsius
- Controller: Thermo Sensor (thermostat)
- 2nd Messenger: Electronic signal
- Operator: Heater, Cooler, Ventilator

Glucose Homeostasis in Human Body

- Primary Messenger: Glucose level
- Set Point: 5 mmol/liter[1]
- Threshold: 4-6 mmol/liter[1]
- Controller: Glucokinase in the pancreas and small intestine-Glucose Sensor
- 2nd Messenger: insulin, glucagon, GLP-1
- Operator: Glucose uptake, utilization, storage and production organs





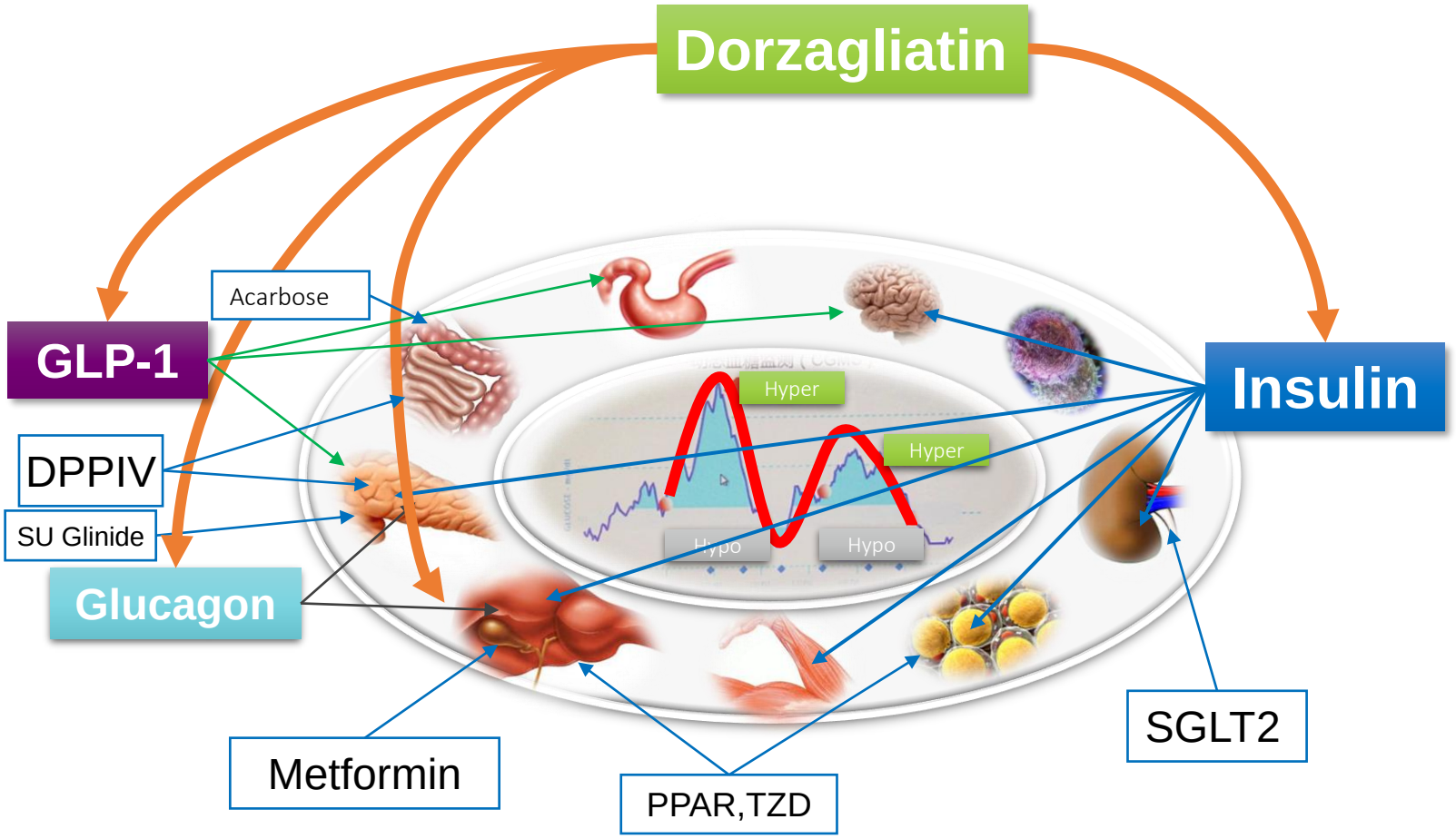
When the **sensor GK malfunctions** or is impaired, automatic control is lost.
This causes insulin resistance and a reduction of beta cell function and **leads to T2D**.

Source: Franz Matschinsky, Mol. and Cell Biology of Type 2 Diabetes and Its Complications, 1998, vol 4, pp 14-29

[1] A common measure of blood glucose levels is hemoglobin A1c, or HbA1c, which measures average glycated blood glucose levels for the 3 months prior to testing. HbA1c levels for people without diabetes is between 4% and 5.6% (equivalent to 4-5.6 mmol/liter), for people with impaired glucose tolerance (IGT), or pre-diabetics, is between 5.74% and 6.4% (equivalent to 5.74 -6.4 mmol/liter) and for people with diabetes is 6.5% or higher (equivalent to 6.5 mmol/liter or higher).

[2] In addition to GK (also referred to as hexokinase type 4), Hexokinase types 1-3 play a role in the glucose homeostasis process. Unlike a properly functioning GK, which is only active at blood glucose levels over 5.5 mmol/liter, hexokinase types 1-3 are active in the presence of even small amounts of glucose in the bloodstream – providing as a bodily survival mechanism needed energy to the brain, muscles and other core bodily functions.

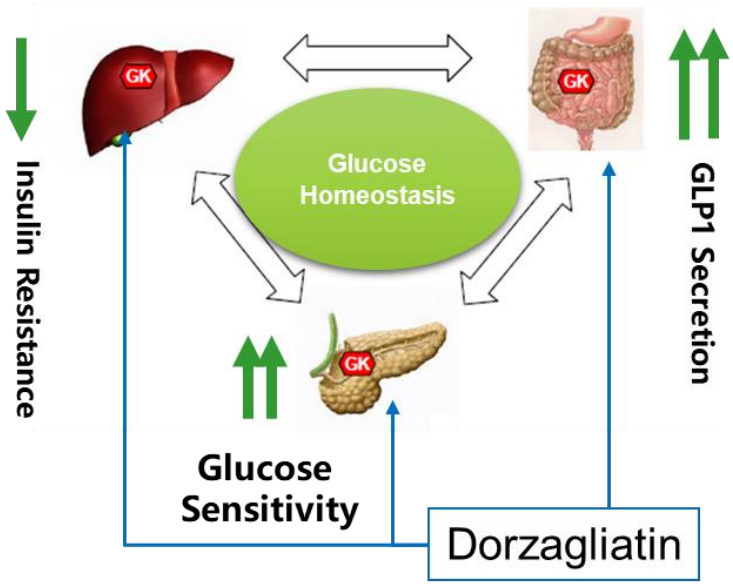
Dorzagliatin: Central role in diabetes control

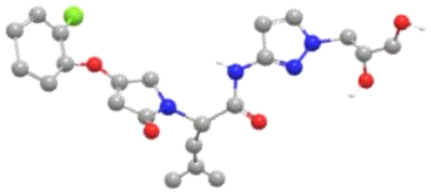


Dorzagliatin as **cornerstone therapy** for diabetes management and control.

Combination of dorzagliatin with other T2D therapies creates **synergy to restore glucose homeostasis** and better health.

Dorzagliatin: First-in-class drug to restore glucose homeostasis





Repair early-phase insulin secretion:
Diabetes remission

Repair GLP-1 secretion:
Control obesity

Improvement of TIR:
PPG reduction

Reduce insulin resistance:
Diabetes remission

Restore glucose homeostasis:
Prevention, remission, rejuvenation

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.

DREAM: DoRzagliatin's Effect in DiAbetes ReMission

DREAM study: **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 levels remained on target** without glucose-lowering drugs.
- 65.2% diabetes remission achieved at week 52.
- IIT study at 5 clinical centers in China.

Drug Naïve T2D

40 centers → SEED n = 310

Dorzagliatin treatment 24+28 week

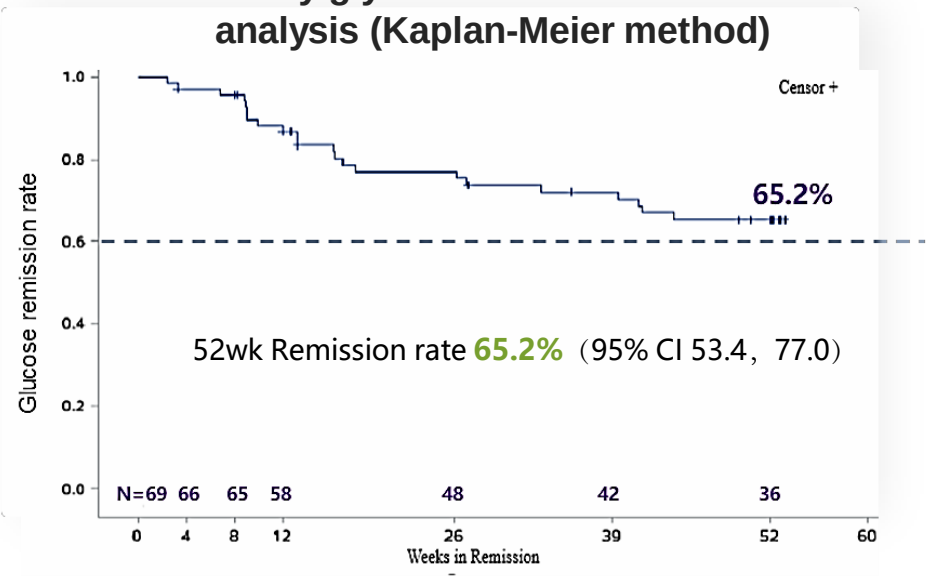
40 centers → Control rate 45%*

Glucose Controlled

5 centers → Remission 65.2%

52 week Diabetes Remission**

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



Fix the system instead of playing 'whack-a-mole' with symptoms.

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

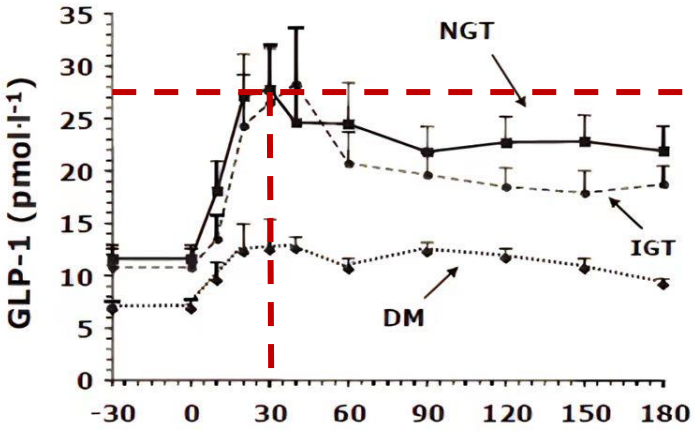
** Based on the 2021 "Expert Consensus on Diabetes Remission" (HbA1c lasting less than 6.5% within 3 months without medication), survival analysis showed that the remission rate at 12 weeks was **52.0%** (95% CI 31.2%, 69.2%).

Improved GLP-1 secretion in patients with obesity

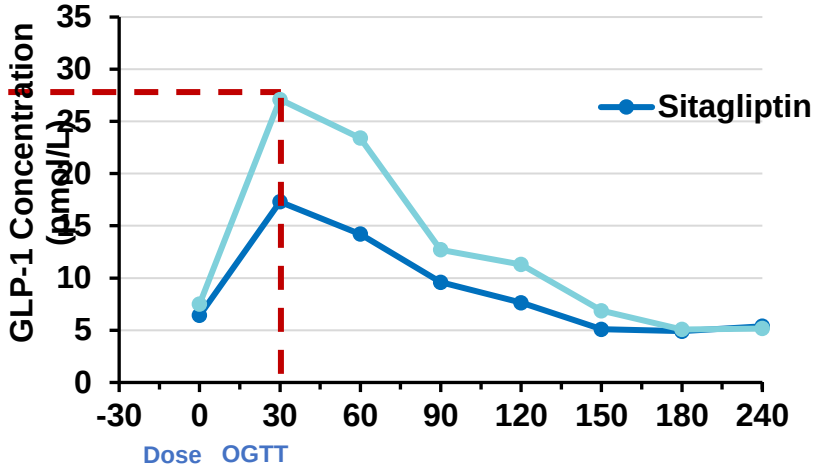
Ferrannini et al. reported that glucose-stimulated **GLP-1 secretion was significantly decreased** in T2D patients with obesity.

Dorzagliatin regulates GLP-1 secretion. 30 minutes after OGTT, GLP-1 levels of T2D patients with obesity were **close to those 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.)

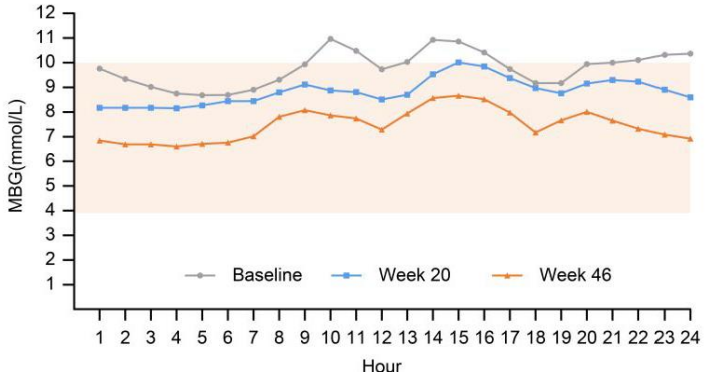
GLP-1: Amplifier of insulin secretion
GLP-1 binds to GLP-1 receptor, activates cAMP pathway and vesicular insulin releases after β-cells perceive the increase of glucose concentration. It also promotes insulin transcription and replenishes vesicular insulin refilling (Phase II) to improve insulin secretion. (Phase II is dominant, Phase I is complementary.)

Cooperative improvement insulin secretion

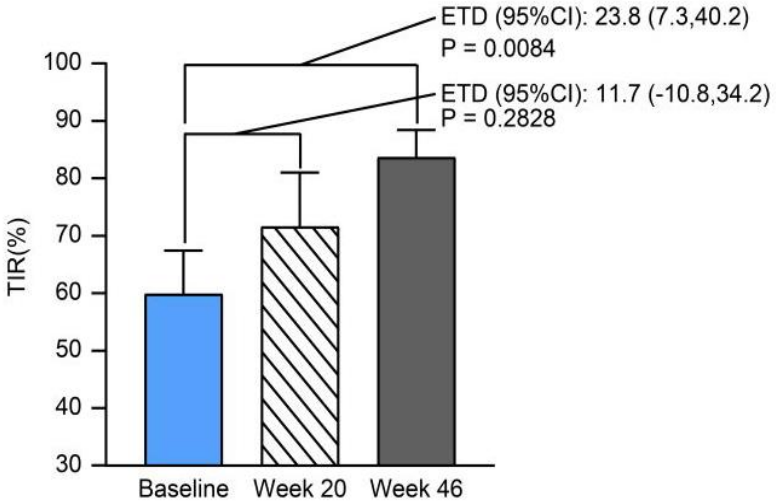
Ferrannini, E. et al, Diabetes, 2008, 57(5), 1340-1348

Dorzagliatin improved TIR, repaired islet function

Dorzagliatin significantly Improved blood glucose within 24 hours

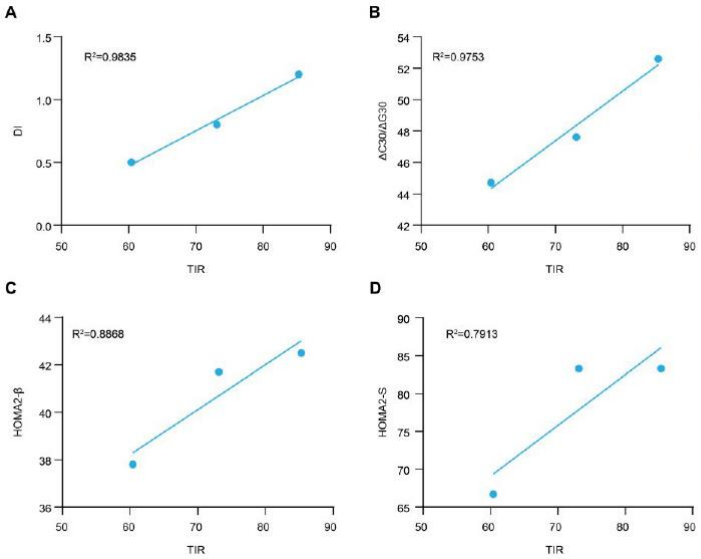


TIR increased with the duration of treatment, reaching 83.7% at 46 Weeks



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

Islet function was improved synchronously by TIR



- Dorzagliatin **improves daily glucose homeostasis** in T2D patients.
- Long-term use of dorzagliatin brings a **steady improvement in TIR**.
- Damaged islet function is gradually restored.
- Potential to be **only T2D therapeutic for more severe stages of diabetic kidney disease patients**, which make up 20 - 40%.

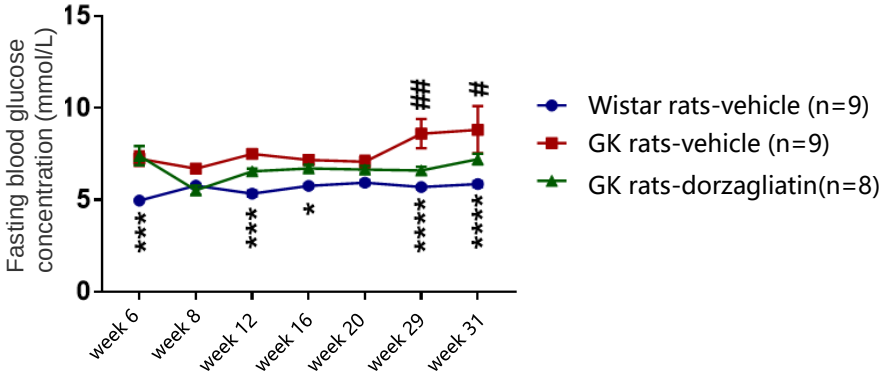
Dorzagliatin improves cognitive impairment in rats

- 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 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.

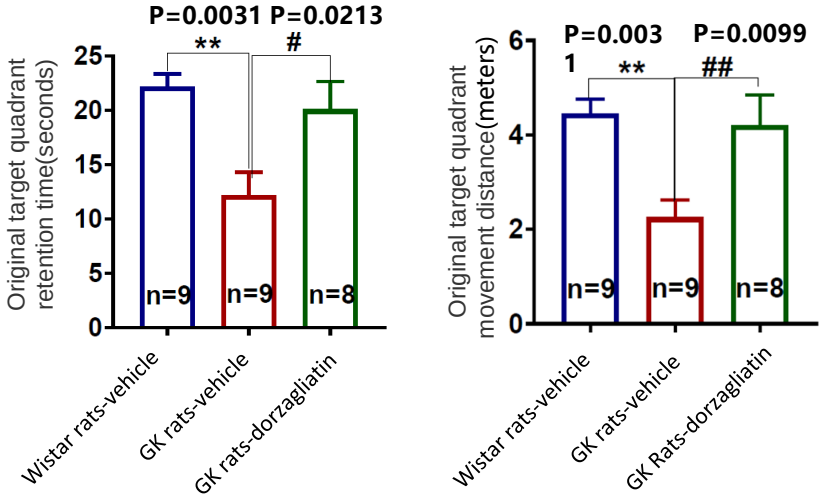
Dorzagliatin exerts a protective effect on memory function by protecting the glucose metabolism function in body and inhibiting the decline of glucose metabolism function in the brain of GK rats.

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



2023 ADA Poster, 247-LB

Dorzagliatin: Int'l peer-reviewed publications

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 obes

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

16

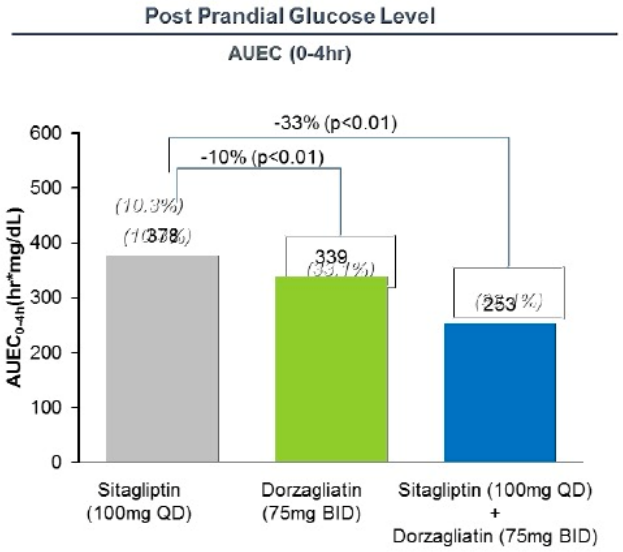
TIR Algorithm Thesis

Clinical Expert Consensus

Pharmaceutical Expert Consensus

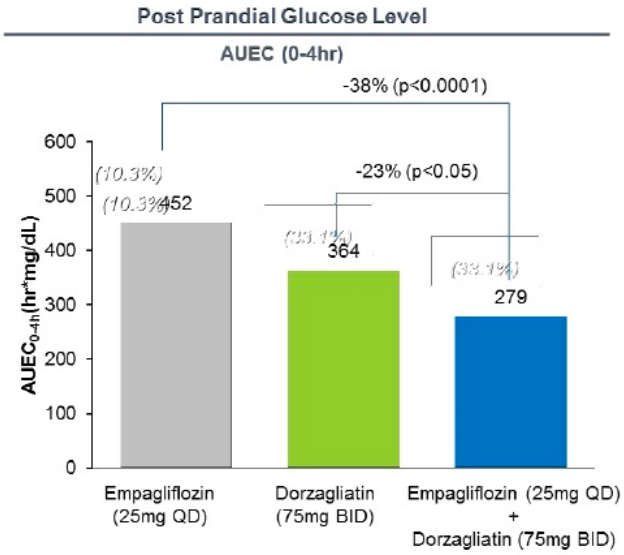
Successful combination potential with oral anti-diabetes drugs

- No drug interaction observed in Phase I trials in US with sitagliptin (DPP-4 inhibitor) and empagliflozin (SGLT-2 inhibitor).
- **Significant synergies demonstrated in glycemic control and improvement of beta cell function**
  - Data demonstrating dorzagliatin stimulates GLP-1 release in T2D patients, increasing circulating active GLP-1 when used in combination with sitaglipin.
  - In both trials, the combined use of sitaglipin or empagliflozin in combination with dorzagliatin increases insulin secretion as measured by C-peptide and reduces glucose over using each of the drugs alone.



DPP-4 inhibitor:

✓ US$ 4B global sales in 2019



SGLT-2 inhibitor:

✓ Fastest growing among OAD with US$ 6B global sales in 2019 and ~24% yoy growth

Note: AUC represents area under the curve, while AUEC represents area under the effect curve.

Dorzagliatin:

Making an impact and going global

Dorzagliatin approved and reimbursed in China

Approved and Launched Year-End 2022.

China Reimbursement - Dec 2023.

1. Differentiated MOA on Label: Improves β-cell function and restores impaired glucose homeostasis.
2. Two Indications. With diet 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.

China National Reimbursement Since Dec 2023

RMB 5.39 / tablet = RMB 10.78 daily
(~USD $1.54 daily = USD $46.20 monthly)

80-90% reimbursed by govt. Net monthly patient cost ~USD $9.24 – USD$ 4.62.

Bayer Healthcare is the exclusive commercial partner in China.

RMB 1.5B (~USD $214m) cash collected in payments from Bayer.

HuaTangNing (dorzagliatin) sold in hospitals, pharmacies and online with prescription.

Dorzagliatin: Second Generation

Acceleration in technology to advance medicine:

- 4 generations of insulin required ~100 years.
- 4 generations of GLP-1 required less than 20 years.

Advanced 2nd generation of GKA in Phase I in U.S.

- Once a day oral formulation for better homeostasis control.
- New molecular entity with substance patent.
- New formulation with increase MRT of API.
- Broaden the therapeutic indication in diabetes, obesity, NASH, DKD.
- FDA accepted IND application in Dec. 2023.
- Safety trial to support IND underway.

Hua Medicine: Global First-in-Class Diabetes Care

Hua Medicine

Li Chen
CEO & CSO

Bob Nelsen
Chairman

Arch Ventures

Roche

JUNO THERAPEUTICS
DENALI THERAPEUTICS
GRAIL
VIR
gossamerbio

Arch Ventures
Fidelity INVESTMENTS
venrock
SAIL
WuXi AppTec
J Baldwin

Founding Investors

China-Based First-In-Class

- **International Collaboration**
  - Roche (Switzerland) – in-licensed dorzagliatin & founding scientific team
  - US VC Series A funding
  - China clinical research & POC
  - Commercial partnership in China with Bayer (German)
- **Advancing Meaningful Diabetes Treatment** from targeting symptoms of Type 2 diabetes (leading to improved treatment of chronic disease) to addressing root cause of Type 2 diabetes (leading to a potential cure)
- **First Novel Concept** addressing impaired glucose sensor function - the underlying cause of T2D
- Scientific POC validated in China; Commercial POC and RWE in China expected in next 3-5 years
- Publicly listed on Stock Exchange of Hong Kong under ticker: 2552
- Cash balance as of Dec 31, 2023, of RMB 1.4 billion (USD $200m)

Hua Medicine
华领医药

A China-Based First-in-Class Biotechnology Company Focused on Unmet Medical Needs