Hua Medicine
华领医药

# Hua Medicine Company Presentation

*2021 Q4*

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# Hua Medicine – A Global First-in-Class Biotech Diabetes Care Innovation

## Hua Medicine

***Li Chen***
*CEO & CSO*

***Bob Nelsen***
*Chairman*

Roche

Arch Ventures

JUNO THERAPEUTICS
DENALI THERAPEUTICS
GRAIL
VIR
gossamerbio

Arch Ventures | Fidelity INVESTMENTS | venrock | SAIL | WuXi AppTec | J Baldwin

**Founding Investors**

## China-Based First-In-Class

- **Global rights** to dorzagliatin composition of matter, chemical process, formulation and multiple products in FDC with OADs
- **China strategic partner selected – Bayer AG**
- **Met Primary Endpoint** in both pivotal Phase III monotherapy and combination with metformin trials for China regulatory approval purposes
- **First-in-Class (GKA) drug** to significantly and sustainably reduce HbA1c safely over 52 week as a glucose sensitizer
- **First Novel Concept** addressing impaired glucose sensor function - the underlying cause of T2D
- **First Diabetes Remission** demonstrated for 52-weeks with oral anti-diabetes drug in drug-naïve T2D patients – 65% diabetes remission rate (applying Kaplan-Maier method)
- Broad indications diabetes care
  - Demonstrated viability in combination with DPP-4 inhibitor & SGLT-2 inhibitor
  - Suitable for DKD patients
- Publicly listed on HKEX (ticker: 2552)

# Type 2 Diabetes is a Worldwide Epidemic!

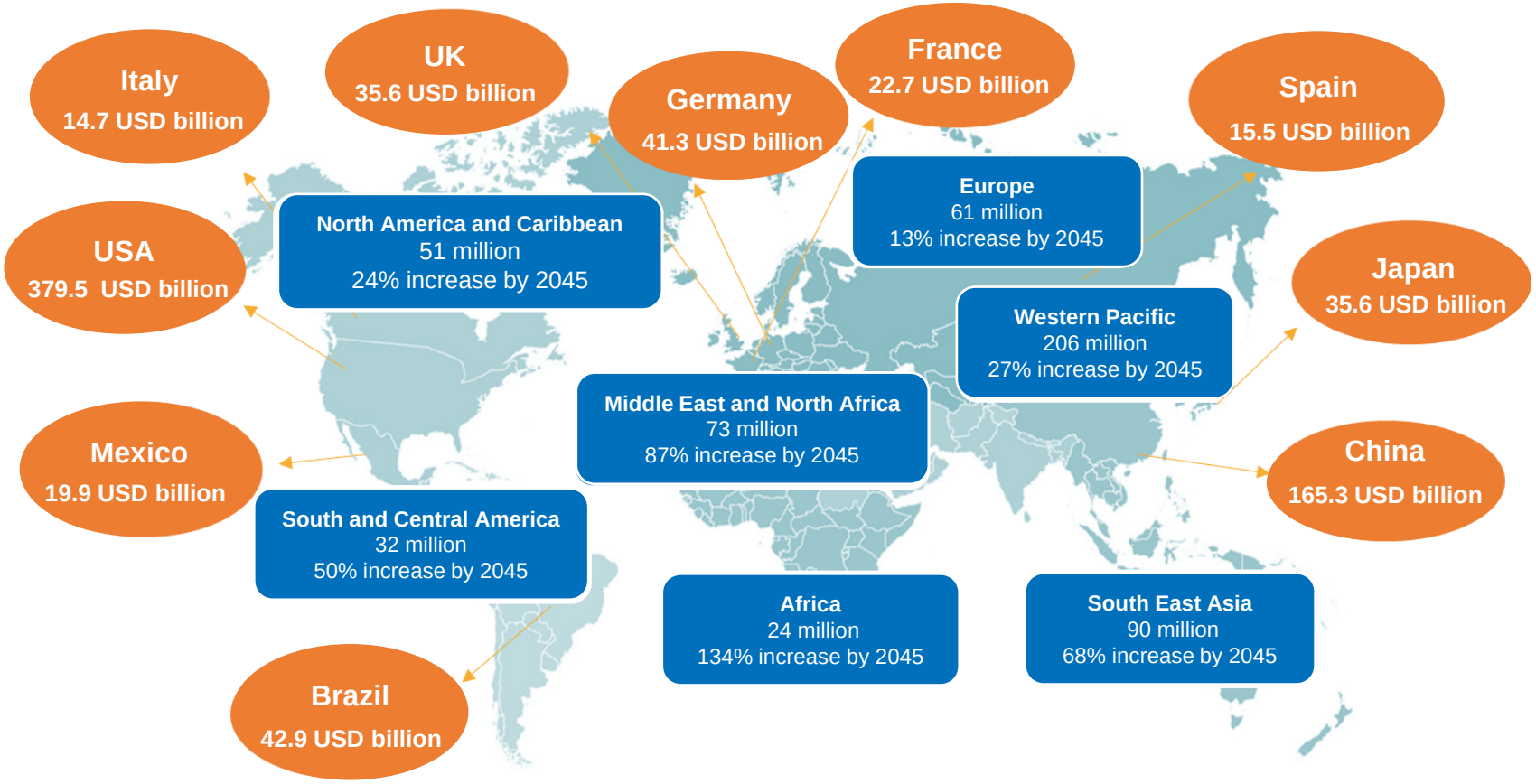
Type 2 diabetes is a worldwide epidemic fueled by the increasing prevalence of obesity, sedentary lifestyles and poor nutrition. Diabetes is characterized by hyperglycemia, which chronic sustained exposure to is associated with long-term damage, dysfunction, and failure of various organs leading to microvascular complications (e.g., retinopathy, nephropathy and neuropathy), as well as macrovascular complications (e.g., stroke, myocardial infarction and peripheral arterial disease). As a result, diabetes is an expensive disease leading to progressively higher medical costs.

*"Confounding the diabetes epidemic and high costs,* ***therapeutic targets are not being met.*** *There is a lack of improvement in reaching clinical targets since 2005 despite advancements in medication and technology treatment modalities.* ***Indeed, between 2010 and 2016 improved outcomes stalled or reversed."***[1]

*Source 1: Consensus Report, Diabetes Self-management Education and Support in Adults with Type 2 Diabetes, published in Diabetes Care in July 2020, the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association.*

# Despite multi-billion global spending on diabetes treatment, diabetes is still not being treated properly

- **~537 million** people live with diabetes across the world. It is projected the total number of diabetes patients worldwide will increase to 643 million (11.3%) by 2023 and 783 million (12.2%) by 2045
- **~ 541 million** adults have Impaired Glucose Tolerance (IGT)
- In 2021, IDF estimates that total diabetes-related health expenditure will reach USD 966 billion




**Number of people (20-79 years) with diabetes**

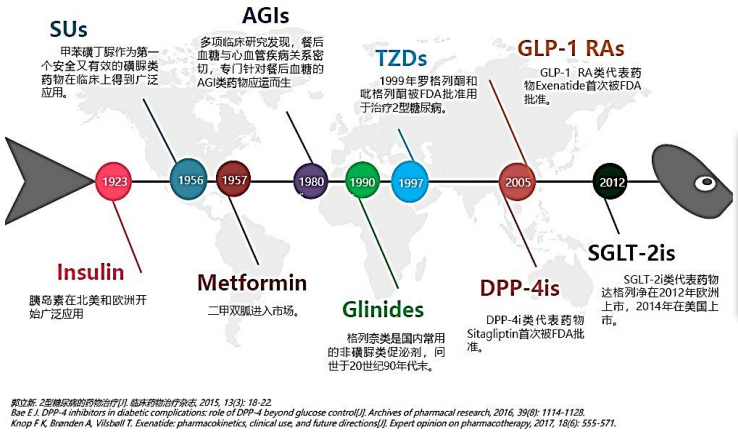
**Top 10 countries or territories for total health expenditure due to diabetes**

*Source: IDF DIABETES ATLAS Tenth edition 2021*

*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 Medical Needs in Glycemic Control

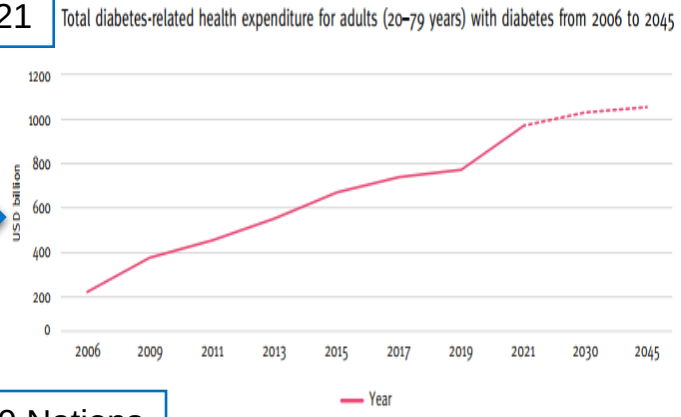
9 Classes of Drugs




US $966 bn

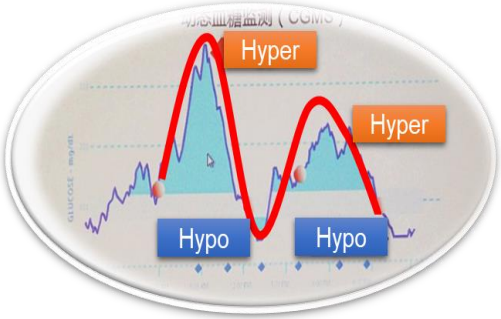
**450 Mn Diabetes Many Complications**

IDF 2021

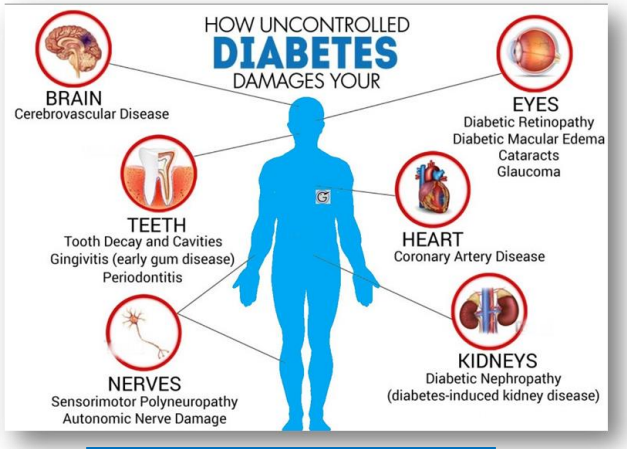



Top 10 Nations

| 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 |




Blood glucose fluctuation




Diabetes Complications

Economic Burden

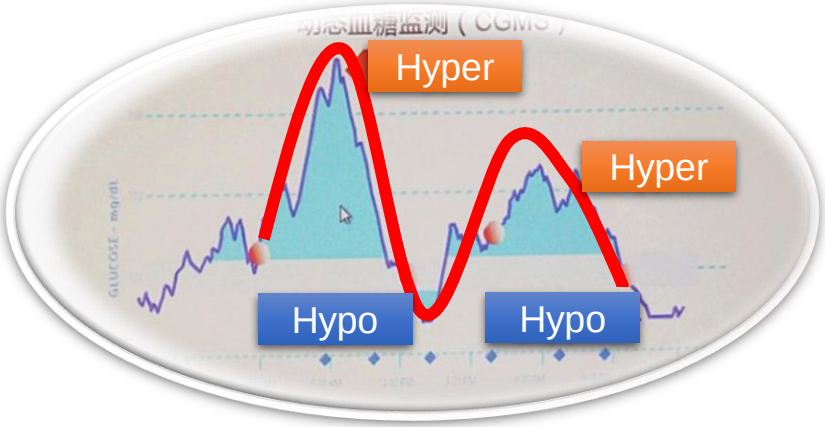
*Source: Cheng YY, Chen L. Global J Obesity, Diabetes and Metabolic Syndrome 2020, 7：018-023*
*Source: IDF DIABETES ATLAS Tenth edition 2021*

# How Do We Stop Type 2 Diabetes?

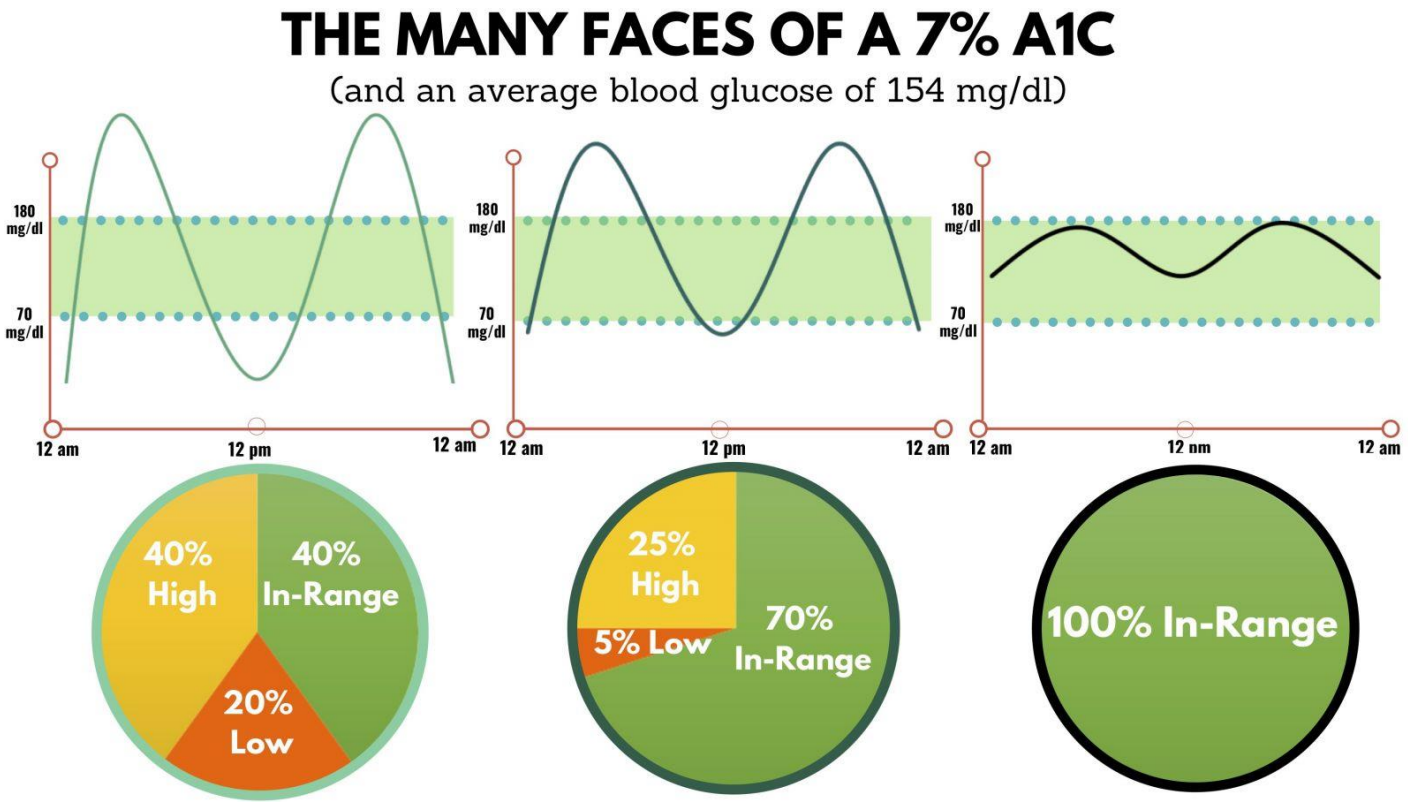
## Goal in treating diabetes:

To maintain blood glucose levels within a healthy range, achieving ***glucose homeostasis*** (4-6.5mM)

*Lowering blood glucose levels alone will not stop the progressive degenerative nature of diabetes, leading to complications*




# The current treatment paradigm for Type 2 diabetes is beginning to shift



# The current treatment paradigm for Type 2 diabetes is unsatisfactory... and have to focus on diabetes complications

*"Confounding the diabetes epidemic and high costs,* ***therapeutic targets are not being met.*** *There is a lack of improvement in reaching clinical targets since 2005 despite advancements in medication and technology treatment modalities.* ***Indeed, between 2010 and 2016 improved outcomes stalled or reversed."***[1]

## ADA Guideline 2020

- New recommendations are added on use of the ambulatory glucose profile (AGP) report and **time in range (TIR)** for assessment of glycemic management.
- New evidence and a recommendation were added on early combination therapy for Type 2 Diabetes
- SGLT-2 inhibitors or GLP-1 receptor agonists are introduced in strategy in patients with cardiovascular disease meeting A1C goals for cardiovascular benefit.

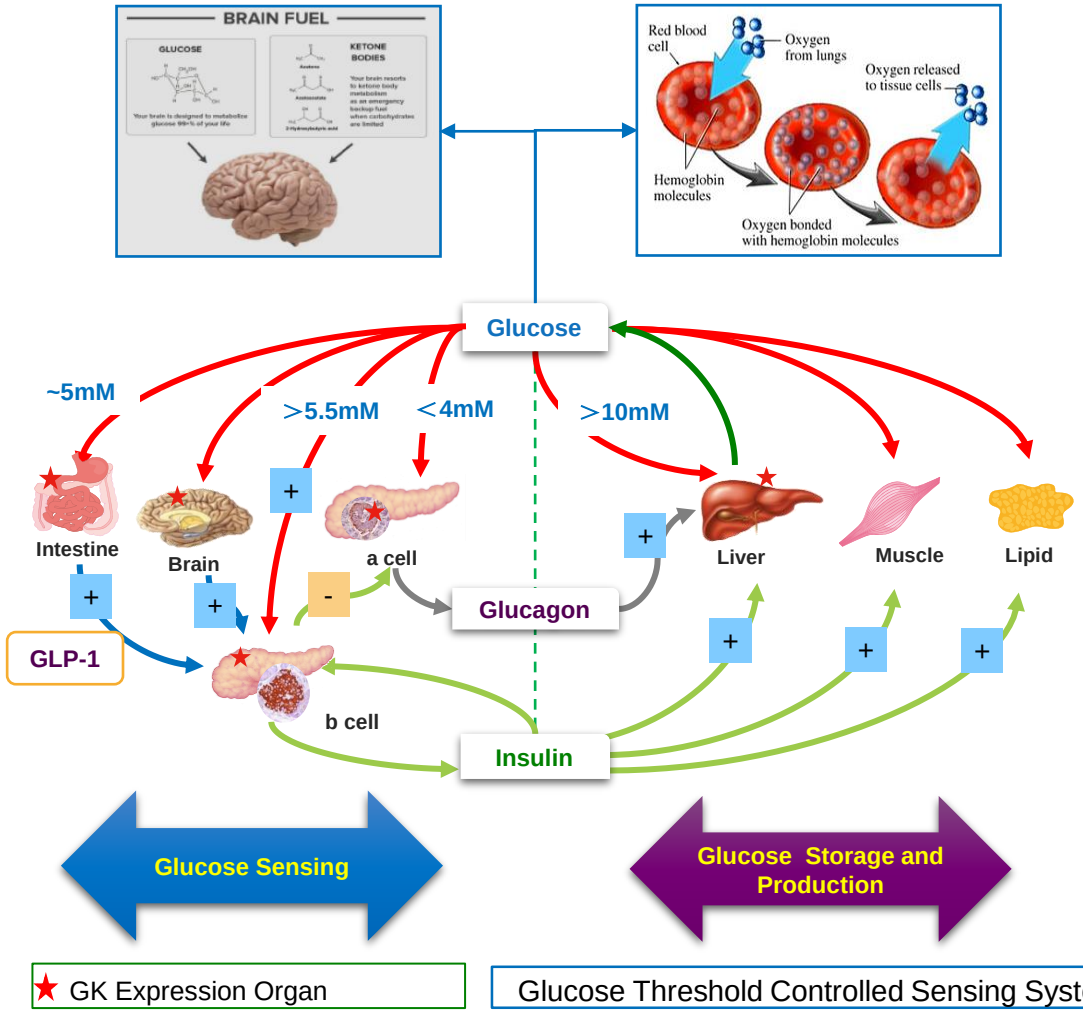
## CDS Guideline 2020

- **HbA1c** is incorporated into the diagnostic criteria for diabetes
- **Time in Range (TIR)** added to blood sugar control goals
- The guideline clarifies that lifestyle intervention and metformin are the first-line treatments for hyperglycemia in patients with T2D.
- For patients with T2D with ASCVD or high risk of cardiovascular risk, GLP-1RA or SGLT2i with evidence of ASCVD benefit should be added to metformin treatment.

*Source 1: Consensus Report, Diabetes Self-management Education and Support in Adults with Type 2 Diabetes, published in Diabetes Care in July 2020, the American Diabetes Association, et. al.*

# How is dorzagliatin different?

# Glucose Regulates whole Body Glucose Homeostasis via glucokinase GK a Glucose Sensor Protein




Bioenergy Demand ATP

**Glucose Homeostasis**

Glucose Controls Blood Glucose in a Narrow Range:
***4- 6.5 mM***

Set Point:
***5 mM***

Glucokinase GK expression and function are impaired in T2D patients

*Source: Li Chen，2016 《药物进展》 modified based on Franz Matschinsky publication*

# Glucokinase is a Glucose Sensor in Glucose Homeostasis

## Thermostat in a Building

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

## Glucostat in Human Body

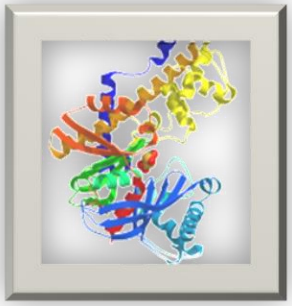
- Primary Messenger: glucose level
- Set Point: 5 mmol/liter[1]
- Threshold: 4-6 mmol/liter[1]
- Controller: Glucokinase in the pancreas and small intestine-Glucose Sensor
- 2$^{nd}$ Messenger: insulin, glucagon, GLP-1
- Operator: Glucose uptake, utilization, storage and production organs


**Operation**

**Cooler**

**Heater**

**Ventilator**



**Operation**

**Insulin / GLP-1**

**Glucagon**

**Liver GK**

When the sensor GK malfunctions or is impaired, automatic control is lost
This will cause insulin resistance and reduction of beta cell function that lead to T2D

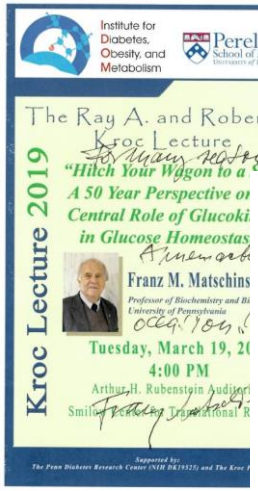
*Source: Franz Matschinsky, Mol. and Cell Biology of Type 2 Diabetes and Its Complications, 1998, vol 4, pp 14-29*

*[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.*

# Key Recognitions of Glucokinase

- ✓ Discovered in the 1960s by Dr. Franz Matschinsky, "Godfather of Glucokinase"
- ✓ The 1st GKA Published in Science Magazine in 2003, Roche
- ✓ Dorzagliatin completed POC in 2016, Lancet DE 2018
- ✓ Winner of Rolf Luft Award 2020

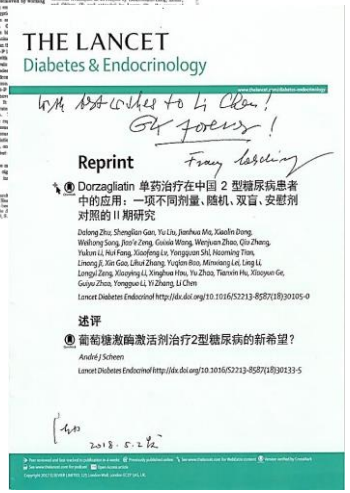





**Science 2003:**

**Allosteric Activators of Glucokinase: Potential Role in Diabetes Therapy**

*"In several rodent models of type 2 diabetes mellitus, GKAs lowered blood glucose levels, improved the results of glucose tolerance tests, and increased hepatic glucose uptake.* ***These findings may lead to the development of new drug therapies for diabetes****."*





**Lancet 2018: Dalong Zhu and Li Chen**

*Dorzagliatin Ph II results*

*A New Hope for Glucokinase Activator for T2D*


**Rolf Luft Award 2020 awarded to Dr. Franz Matschinsky by Karolinska Institutet**

*For the discovery that* ***glucokinase (GK) is the sensor controlling glucose-stimulated insulin secretion*** *in the pancreatic β-cell. And culminating in the discovery of novel* ***allosteric GK activators*** *currently being assessed in* ***phase III clinical trials****. Speech at the Nobel Forum (Stockholm, Sweden) awards ceremony in the spring of 2021*

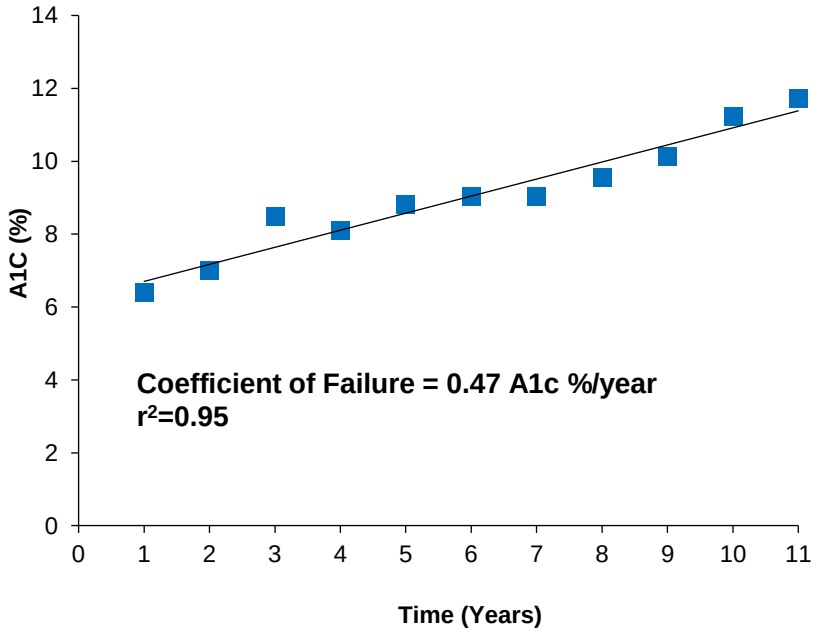
*Source: Franz Matschinsky et al . Science: Vol 301, Issue 5631, 18 July 2003*

# DREAM Results – Presented Sep 2021

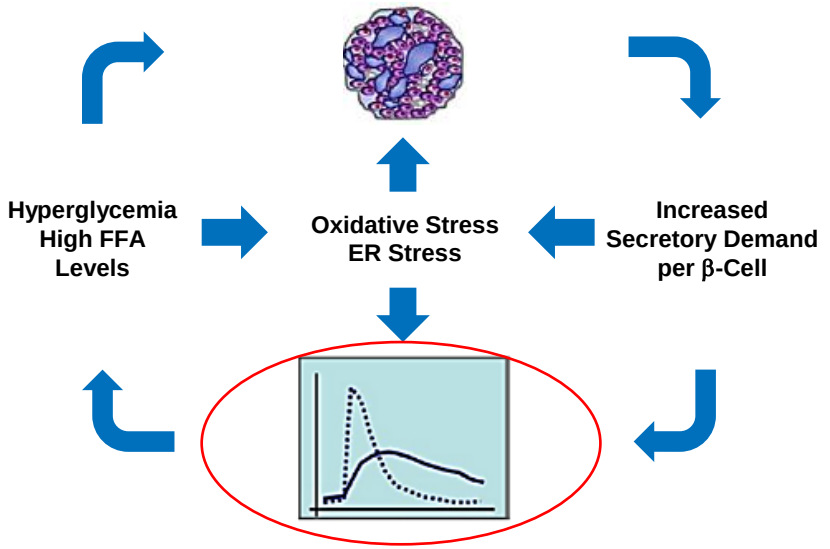
# T2D is a Progressive Disease with Degeneration of β Cell Function and Increasing Insulin Resistance

- Type 2 diabetes is a progressive disease with deterioration of β cells function
- Loss of glucose sensitivity in Type 2 diabetes patients is the first step in the progressive destruction of β cells
- Impaired β cells function results in hyperglycemia stress which causes progressive damage of β cells
- Deterioration of the 1st phase insulin secretion is the leading cause of impaired glucose homeostasis

**Patients with Monotherapy: HbA1c Increased by 1% Every 2 Years, β-Cell Function Decreased Accordingly[1]**




**Impaired β-Cell Function Results in Hyperglycemia Stress which Causes Progressive Damage of β Cells**



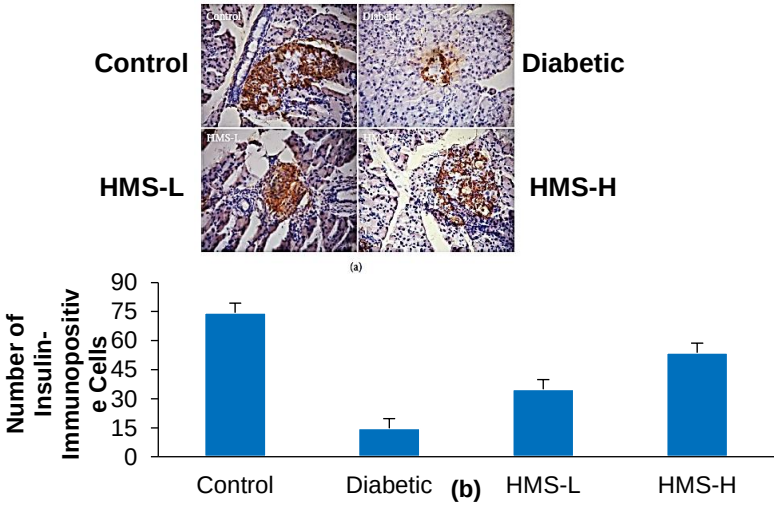

- Deficiency in the ability of glucose to trigger insulin release
- Cells have **lost glucose sensitivity** and early phase insulin release is reduced
- Reduction in glucose sensitivity is the key culprit behind Type 2 Diabetes

*Source: Vivian Fonseca, Diabetes Care, 2009, Vol 32, S2; Source: J Merier, R Bonadonna Diabetes Care (2013) 36, S113*
*[1] Retrospective survey.*

# Dorzagliatin Has the Potential to Repair the Glucokinase Glucose Sensor

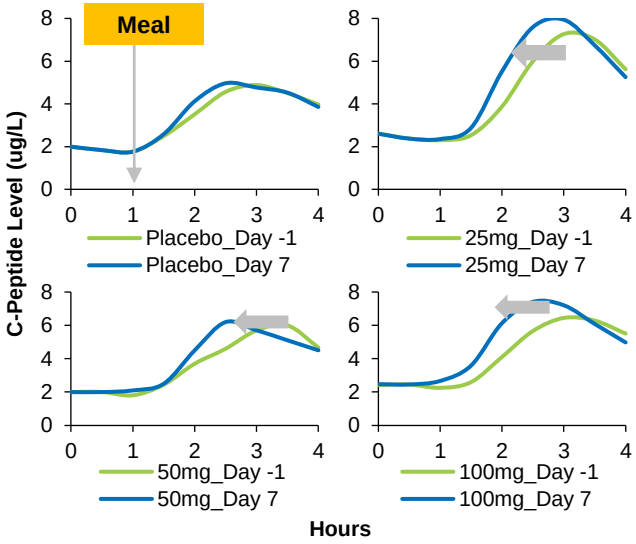
## Type 2 Diabetes Rat Pancreas

Pre-clinical



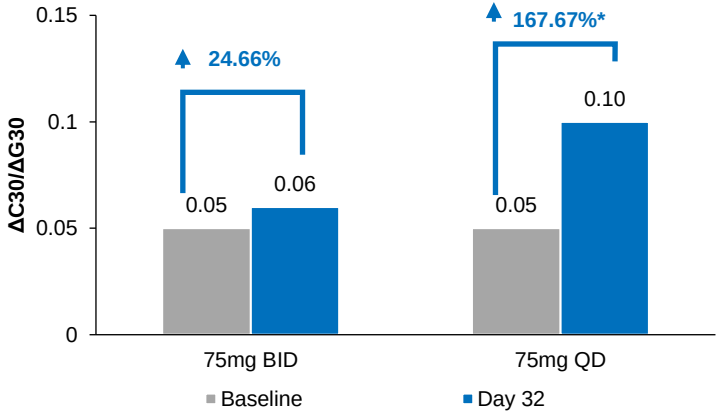

## T2D Patient Early-stage insulin release

Phase Ib



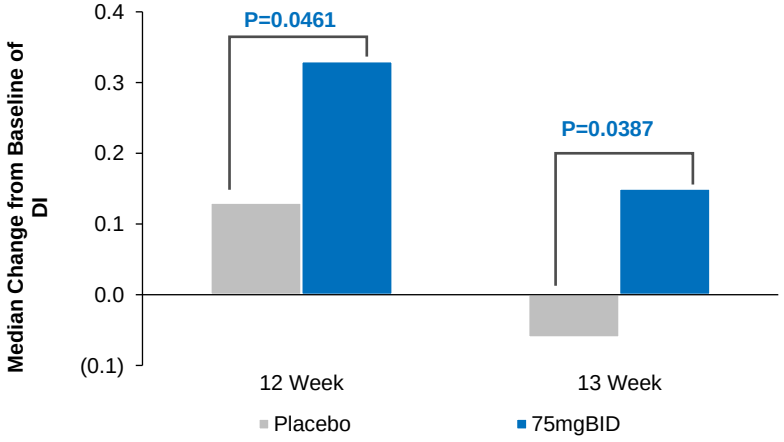

## T2D Patient Early Insulinogenic index

Phase Ic



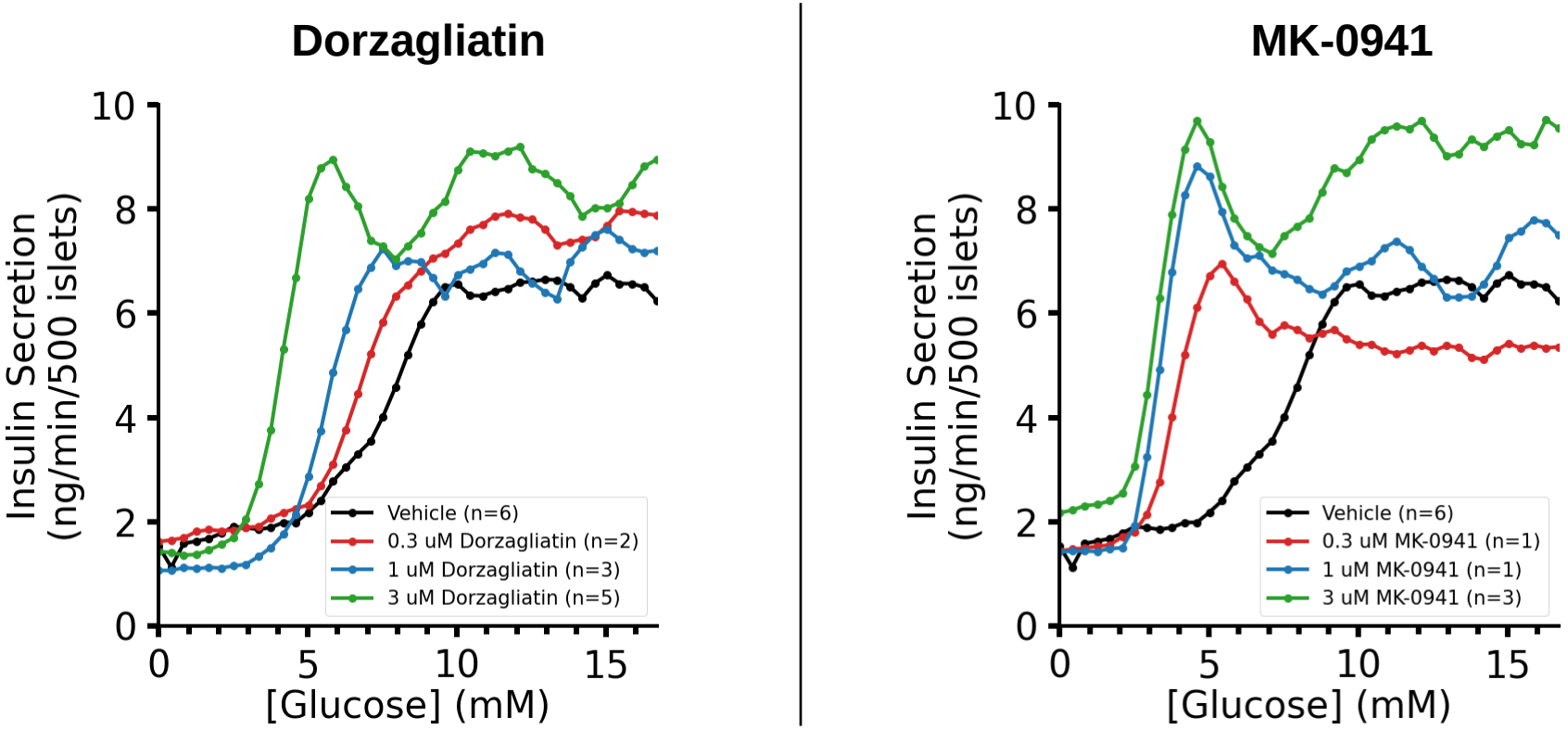

## T2D Patients Disposition Index

Phase II



# Glucokinase Activators Potentiate Glucose-Stimulated Insulin Secretion in T2D Islets in a Dose-Dependent Fashion

Glucose Dependence

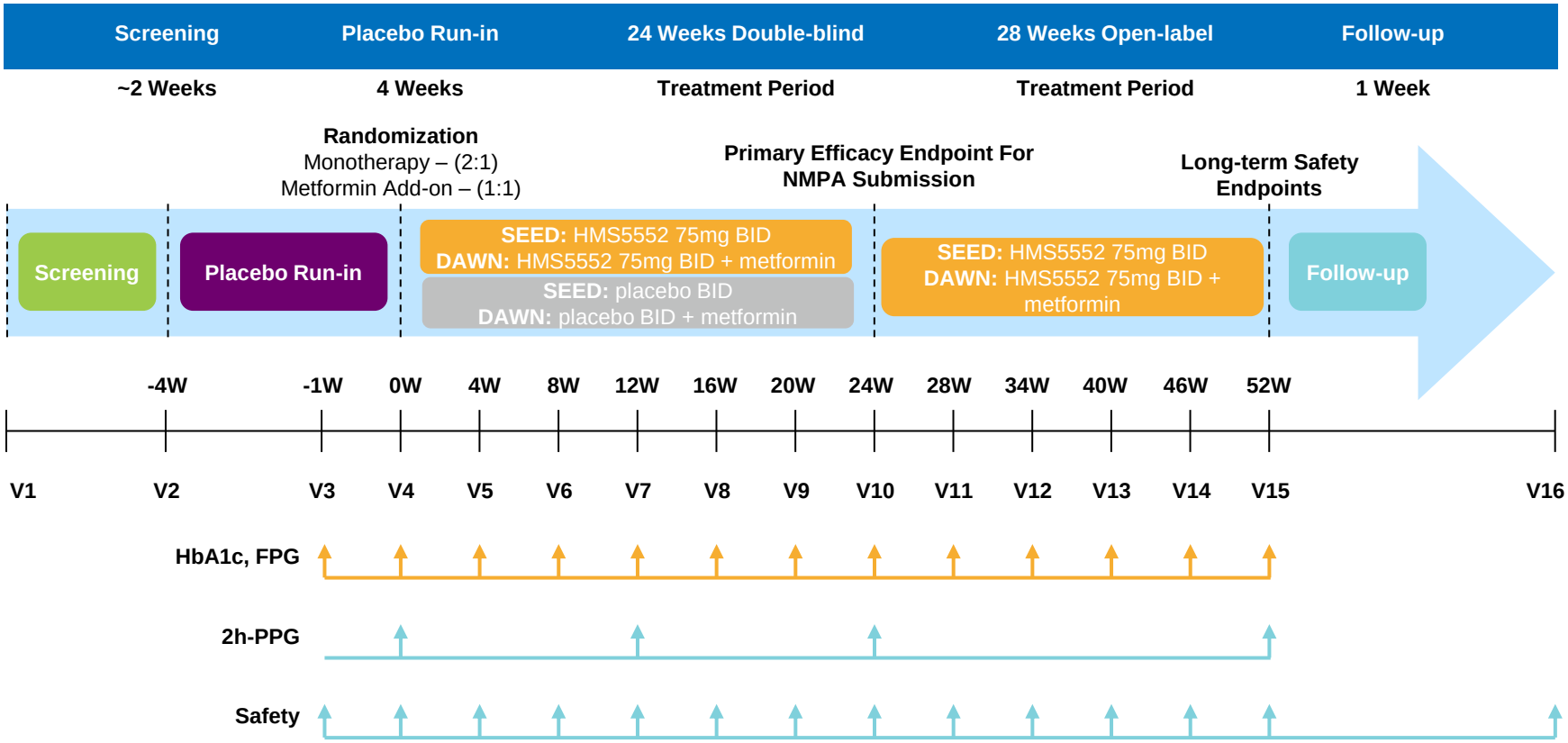



Franz Matschinsky 20211201

# Prelude to DREAM: Phase III Trials: SEED/ DAWN Study Design

## Study Design for:

- SEED: 52-week completed ✓
  Dorzagliatin Mono-therapy Trial for Drug Naïve T2D Patients (463 Patients)
- DAWN: 52-week completed ✓
  Dorzagliatin Metformin Add-on Therapy Trial for Metformin Users (767 Patients)

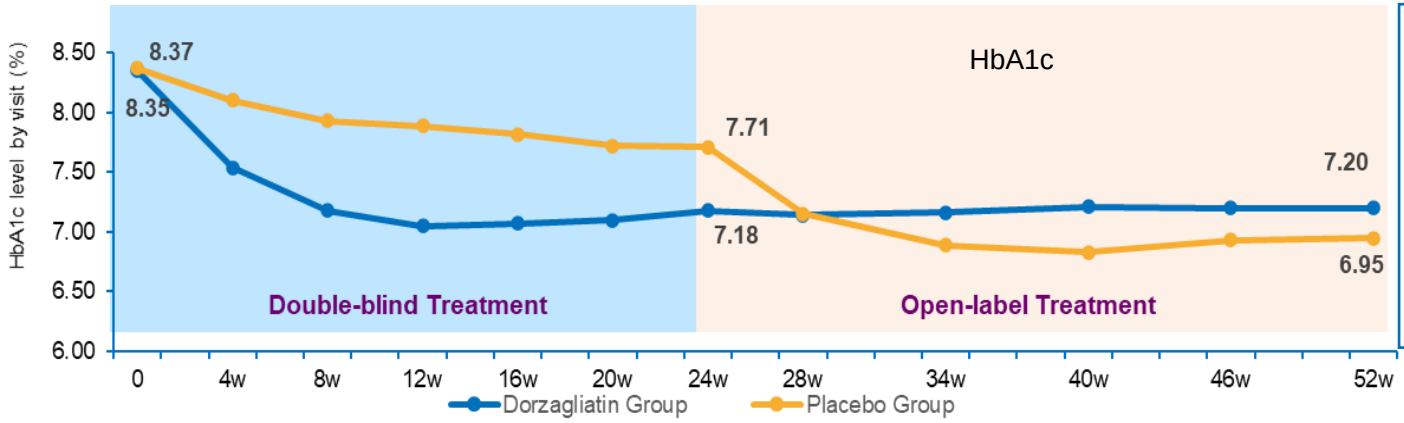



**Primary endpoint of HbA1c reduction of 0.4% over placebo, p-value < 0.05**

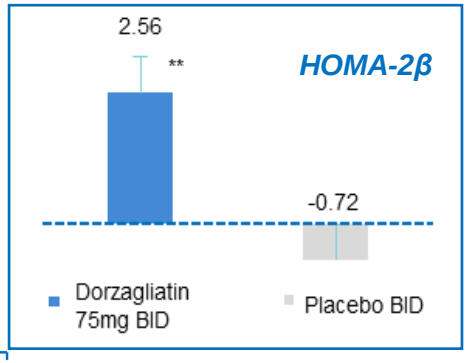
**ACHIEVED FOR BOTH SEED AND DAWN STUDIES AT 24-WEEK**

# Dorzagliatin Phase III Results: SEED and DAWN
# Significantly improve β-cell function and reduce insulin resistance

## SEED HMM0301

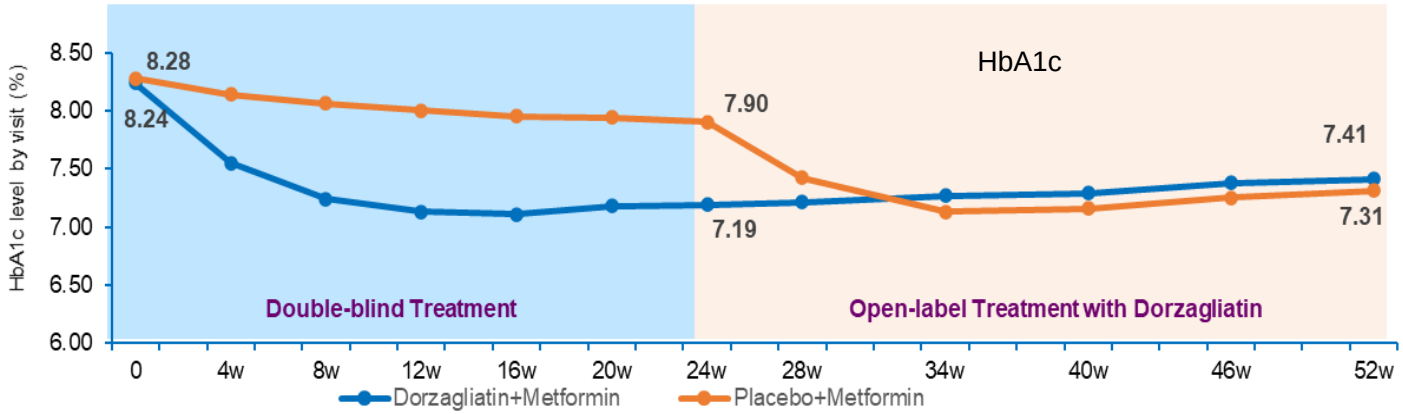



Significantly improve β-cell function at week 24

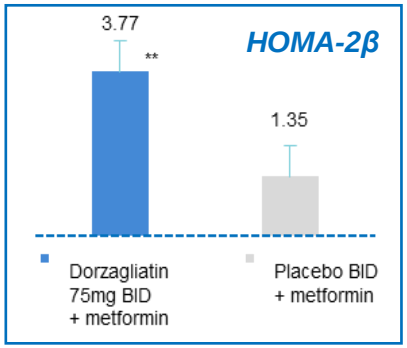



Change from Baseline to Week 24

## DAWN HMM0302




Significantly improve β-cell function at week 24




Change from Baseline to Week 24

# DoRzagliatin Effect in DiAbetes ReMission

## DREAM Study

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

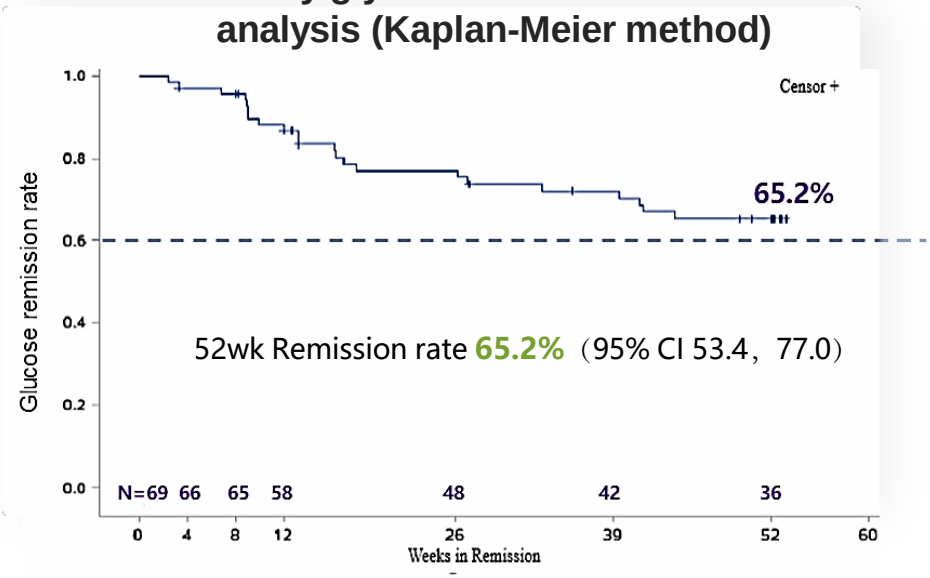
40 center → Control rate 45%*

Glucose Controlled

5 center → Remission 65.2%

52 week
Diabetes Remission**

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



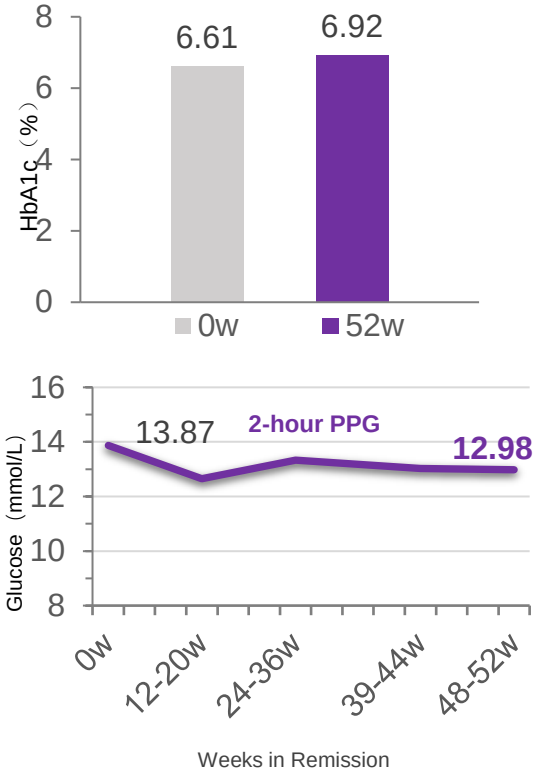

* Control rate at 24 week of SEED study: HbA1c < 7%

** 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%)

# Other Type 2 Diabetes drugs have failed in demonstrating remission

Dorzagliatin (over 52-weeks) substantially outperformed other anti-diabetes drugs (over 3 months) as measured by glucose control biomarkers for remission purposes

**DREAM: Sustained HbA1c and glucose level after the drug discontinuation for 12 months**



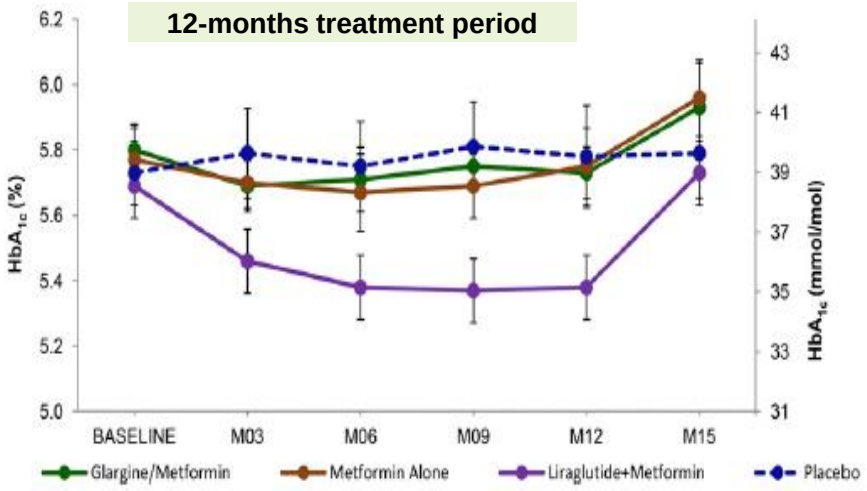

Lack of Durable Improvements in β-Cell Function Following Withdrawal of Pharmacological Interventions in Adults With Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes

The RISE Consortium*

Diabetes Care 2019 Jun; dc190556.
https://doi.org/10.2337/dc19-0556

Check for updates

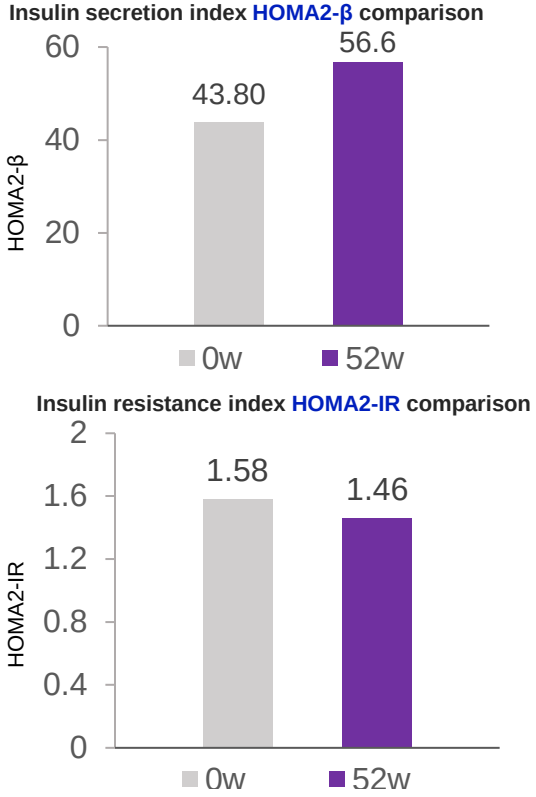
**RISE: Elevated HbA1c after the drug discontinuation for 3 months**



# Other Type 2 Diabetes drugs have failed in demonstrating remission (cont'd)

Unlike dorzagliatin which demonstrated sustained beta cell function and reduced insulin resistance over a 52-week period, other anti-diabetes drugs in RISE failed to show sustained effect after 3 months

**DREAM: Improved β-cell function and insulin resistance index was maintained after drug discontinuation for 12 months**

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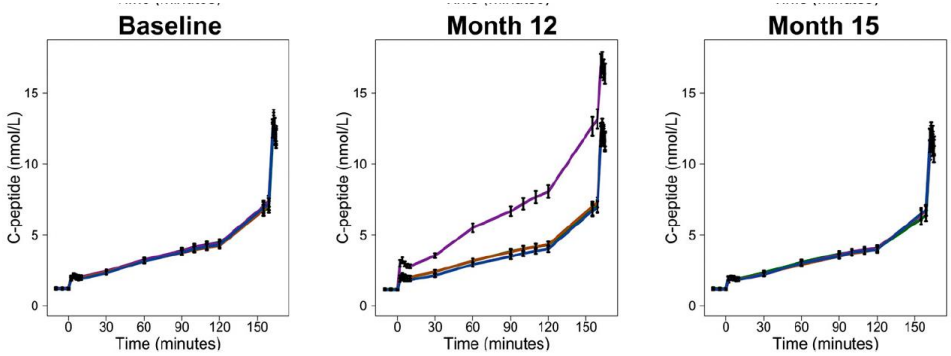
The RISE Consortium*

Diabetes Care 2019 Jun; dc190556.
https://doi.org/10.2337/dc19-0556

Check for updates

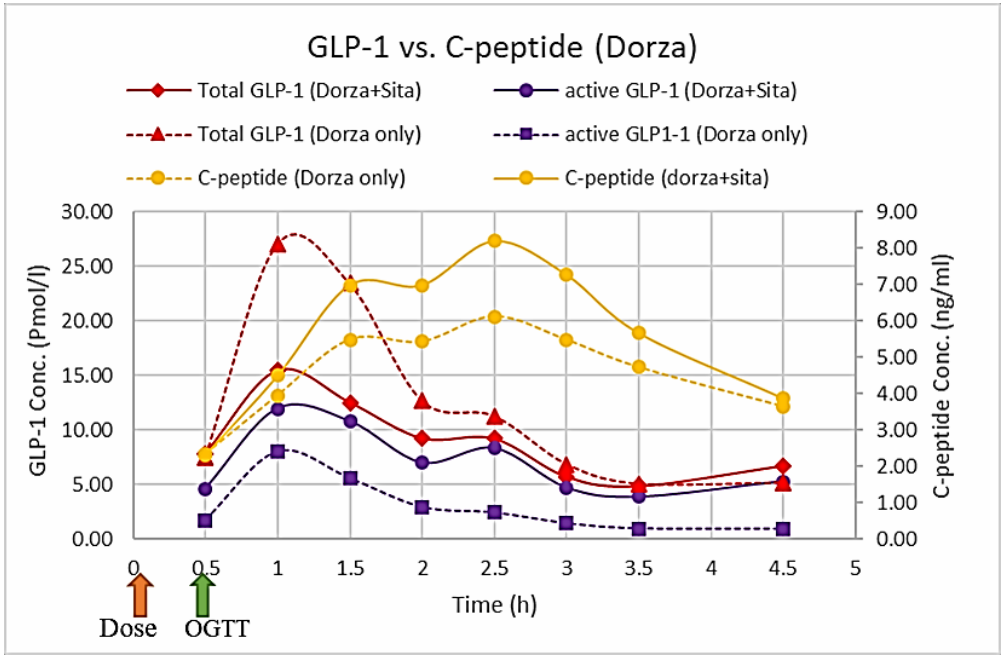
**RISE: no sustained improvements in b-cell function in any treatment group after drug discontinuation for 3 months**

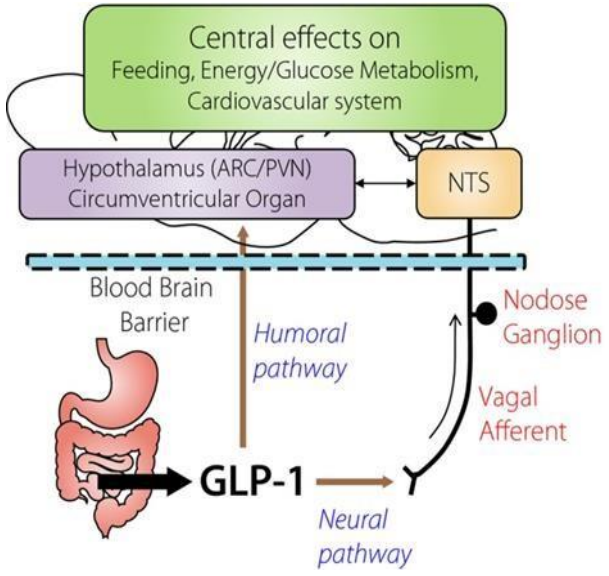


# Dorzagliatin up-regulate GLP-1 secretion in T2D

Dorzagliatin stimulate GLP-1 secretion in T2D patients in USA

- Stimulate total GLP1 secretion reaches Cmax at 30 minute post oral glucose
- Augment C-peptide peak left shift




**Neuroendocrine Regulation**

- Dorzagliatin acts on intestinal L cells and improve glucose sensitivity
- Both GK and SGLT1 regulate intestinal GLP-1 release
- Effects on neuroendocrine regulation is under investigation

*Source: Li Chen, JY Zhang et al ADA 2021 117-LB*

# Diabetic remission has been achieved only in 2 other situations tailored to different patient profile

Remission after dorzagliatin treatment reaches the target, and patients who have remission with intensive lifestyle intervention and intensive insulin therapy have different baseline characteristics (compared from SEED study data with other studies)

**DiRECT （UK）**

Strengthen lifestyle intervention study

01

Obese and overweight patients

- Average course of illness 3 years, 53 years old
- 75% have been treated with anti-diabetic drugs
- BMI 35kg/$m^2$
- SBP/DBP 133/85mmHg
- HbA1c 7.7%、FPG 9.2mmol/L

**SEED-DREAM（China）**

Glucose sensitizer therapy study

**Before treatment of Dorzagliatin characteristics**

03

Newly diagnosed untreated patients*

- Newly diagnosed untreated patients*
- BMI 25kg/$m^2$、126/78mmHg
- HbA1c 8.1%、FPG 8.9mmol/L、2hPPG 16.8mmol/L
- HOMA-β 19.9、HOMA-IR 2.2

**Intensive insulin therapy study（China）**

02

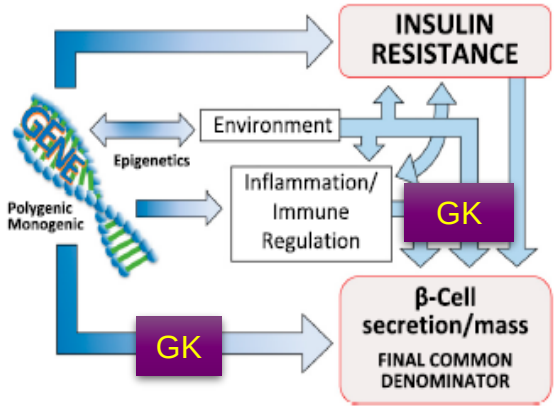
Newly diagnosed untreated patients*

- Newly diagnosed untreated patients*
- BMI 25.5kg/$m^2$
- HbA1c 9.7%、FPG 9.5mmol/L、2hPPG 17.5mmol/L
- HOMA-β 33.6、HOMA-IR 6.0

*Note: * The results of BMI, HbA1c, FPG, 2hPPG, SBP, DBP are average; the results of HOMA-β and HOAM-IR are median*

*Lean MEJ, et al. Lancet 2018; 391:541-51. Lean MEJ, et al. Lancet Diabetes Endocrinal. 2019; 7: 344-55. Weng JP, et al. Lancet. 2008; 371: 1753-60*

# Loss of GSIS function in beta cells is the root cause of T2D Glucokinase GK plays central rule in diabetes remission

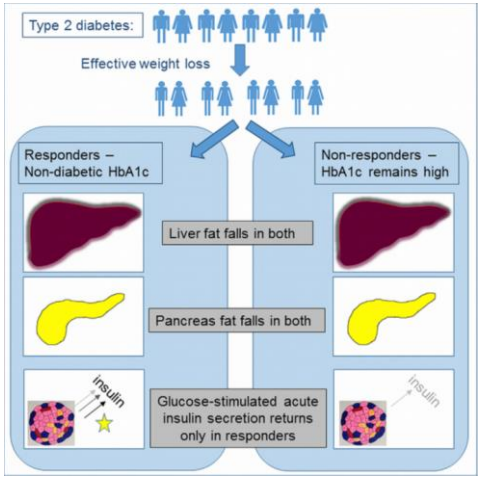



- The root cause of diabetes is the loss of beta cell Glucose Stimulated Insulin Secretion (GSIS) function that is regulated by Glucokinase GK
- Genetic, epigenetic, autoimmunity and insulin resistance with obesity have impact on GK expression and function

Stanley Schwartz. Diabetes Care 2016, 39(2): 179-186

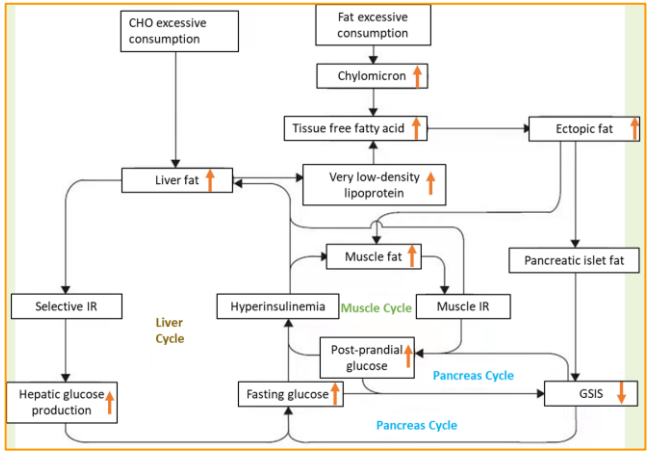
Franz Matschinsky Frontiers in Physiology 2019, 10:148

## Dual cycle hypothesis by UK KOL in T2D remission




- Return to non-diabetic glucose control depends upon β cell ability recover

## Triple cycle hypothesis by Chinese KOL from China Diabetes Society

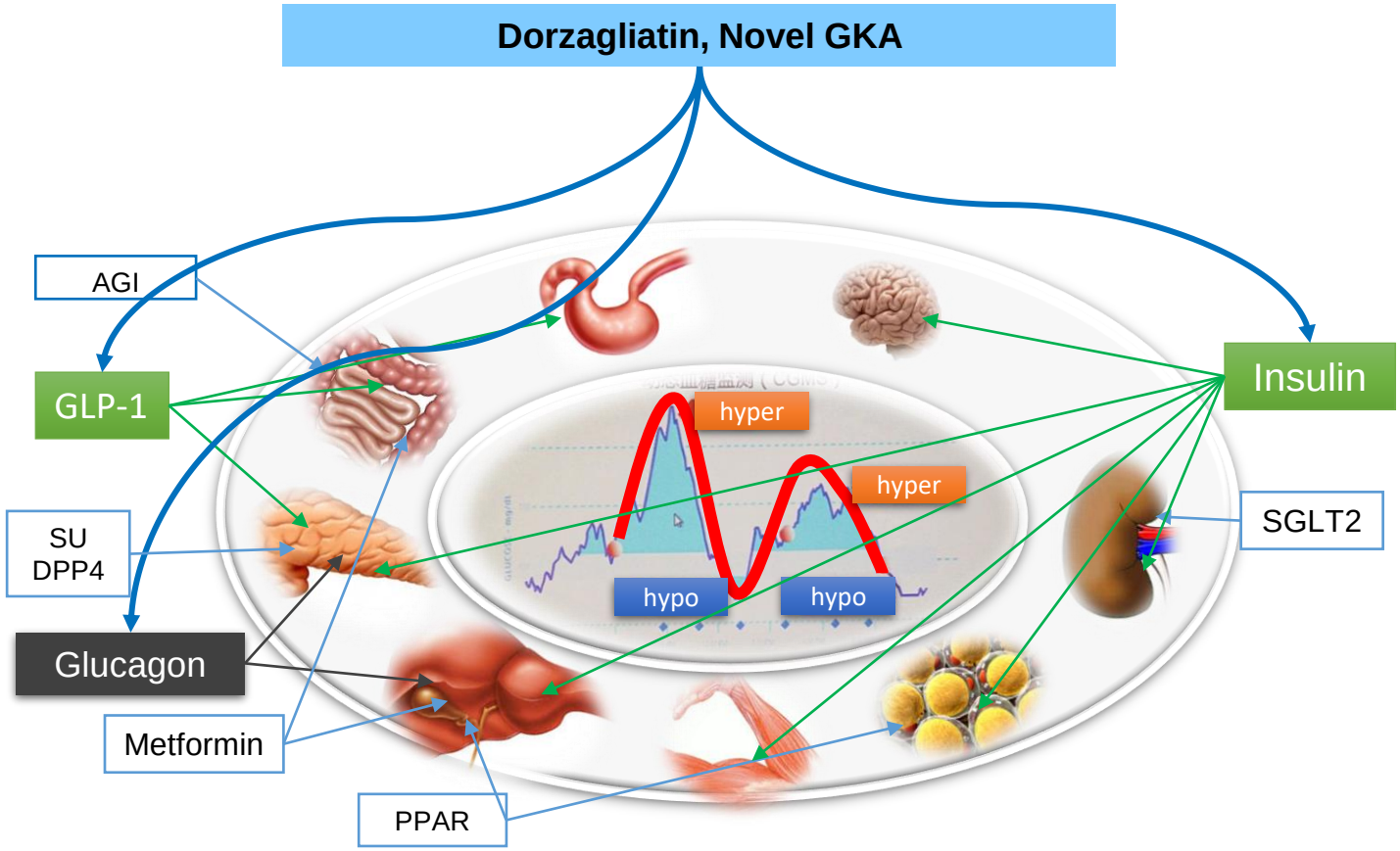



- Triple cycle including hepatic circle, pancreatic islet circle and muscle circle may be the mechanism of the occurrence, development and remission of T2D.
- According to view of Chinese KOL, GSIS also plays central role in T2D occurrence, development and remission, in consistence with the point of view from UK KOL .

Dalong ZHU et al. Chin J Diabetes Mellitus 2021; 13(10): 930-935

*Note: Taylor et al. Cell Metabolism 2018,28:547-556*

# Diabetes Remission: a new frontier in diabetes care




- Insulin, Glucagon and GLP-1 secretion
- Synergy with existing 9 classes
- Prevention, Remission and Resolution of complication

# Commercializing Dorzagliatin

# Bayer is the Best Partner for Hua Medicine in China

- ✓ **Established Leadership in Diabetes Care** in China for **20+ years**
  - Leading oral anti-diabetic drug in China 1995-2019: Glucobay® cumulative treated > 30 million patients
  - Industry leading market coverage: Glucobay® listed in 13k+ hospitals / CHCs and 10k+ retail pharmacies
  - RMB 40 billion Glucobay® cumulative net sales reported from 2009 - 2019
- ✓ **Full commitment and dedication of Bayer China** to achieve top-selling results for dorzagliatin's launch - no conflicts
  - Potential synergies in the future with Bayer's WaveForm CGM device for studies relating to optimizing time-in-range (TIR)

- Novel first-in-class drug
- Aspiration to cure diabetes

- Leader in diabetes treatment in China
- Integrated diabetes solutions

***Collaborate to Cure***

- Hua Medicine: Clinical development, registration, product supply, and distribution
- Bayer: marketing, promotion and medical education activities
- Upfront payment: RMB 300 million
- Milestone payments: Up to RMB 4.18 billion
- Bayer: exclusive rights to commercialize product in China, tiered service fee based on net sales

# GLP-1RA Price Comparison (2021)

| No. | Generic Name | Brand Name | Year of negotiations | product Information | Usage and Dosage | | Price（2021） | Standard Dosage | Daily Cost (RMB) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Benaglutide | 谊生泰® | 2020 | 2.1ml:4.2mg(42000U)×1/piece | TID | The starting dose is 0.1 mg each time, three times a day. After 2 weeks of treatment, the dose should be increased to 0.2 mg each time. | 191.00 | 0.2mg/ time *3 times /day | 27.29 |
| 2 | Dulaglutide | Trulicity® | 2020 | 1.5mg:0.5ml×1/piece | Weekly | The recommended starting dose of this product is 0.75 mg once a week. To further improve glucose control, the dose can be increased to 1.5 mg once a week. | 149.00 | 1.5mg/7day | 21.29 |
| 3 | Polyethylene Glycol Loxenatide | 孚来美® | 2020 | 0.5ml:0.1mg×1/piece | Weekly | For patients with poor glucose control based on diet control and exercise, the recommended starting dose of this product is 0.1mg, subcutaneously injected into the abdomen once a week (7 days). If the glucose control effect is not satisfactory, it can be increased to 0.2mg per week. | 110.00 | - | - |
| | | | | 0.5ml:0.2mg×1/piece | | | 187.00 | 0.2mg/7day | 26.71 |
| 4 | Liraglutide | Victoza® | 2017 (First negotiation) 2019 (Renewal negotiation) | 3ml:18mg×1/piece | QD | The starting dose is 0.6 mg/day. After at least 1 week, the dose should be increased to 1.2 mg. It is expected that some patients will benefit when the dose is increased from 1.2 mg to 1.8 mg. According to the clinical response, in order to further improve the hypoglycemic effect, the dose can be increased to 1.8 mg after at least one week, and the recommended daily dose does not exceed 1.8 mg. | 339.00 | 1.2mg/day | 22.60 |
| 5 | Exenatide | Byetta® | 2019 | 5 μg dose scale injection pen: 0.25 mg/ml, 1.2 ml/piece, a single injection dose of 5 μg, containing the dose of 60 injections | BID | The starting dose of this product is 5μg each time, twice a day. According to the clinical response, the dose can be increased to 10 μg twice a day after 1 month of treatment. | 240.00 | - | - |
| | | | | 10 μg dose scale injection pen: 0.25 mg/ml, 2.4 ml/piece, a single injection dose of 10 μg, containing the dose of 60 injections | | | 408.00 | 10 μg/ time, 2 times /day | 13.60 |
| 6 | Lixisenatide | Lyxumia® | 2019 | 10μg dose injection pen (green): 0.05mg/ml, 3ml/piece, a single injection of 10μg (0.2ml) | QD | Starting dose: 10 μg, once a day for 14 days. Maintenance dose: On the 15th day, 20μg is a fixed maintenance dose, once a day. | 157.65 | - | - |
| | | | | 20μg dose injection pen (dark purple): 0.10mg/ml, 3ml/piece, single injection dose 20μg (0.2ml) | | | 268.00 | 20 μg (0.2ml) /day | 17.87 |
| 7 | Semaglutide | Ozempic® | Not included (Already applied for 2021NRDL) | 1.34mg/ml,1.5ml/piece *(Net specifications，2mg/piece)* | Weekly | The starting dose is 0.25 mg once a week. After 4 weeks, should be increased to 0.5 mg weekly. After treatment with 0.5 mg weekly for at least 4 weeks can be increased to 1 mg weekly to further improve glucose control. 0.25mg is not a maintenance dose. It is not recommended to exceed 1 mg weekly. | 1,120.00 (Non-medical insurance price) | 0.5mg/7day | 40.00 |

*Source: 医药魔方数据库、医保局*

# Bayer / Hua Medicine *Collaboration to Cure* has launched in China — October 2020





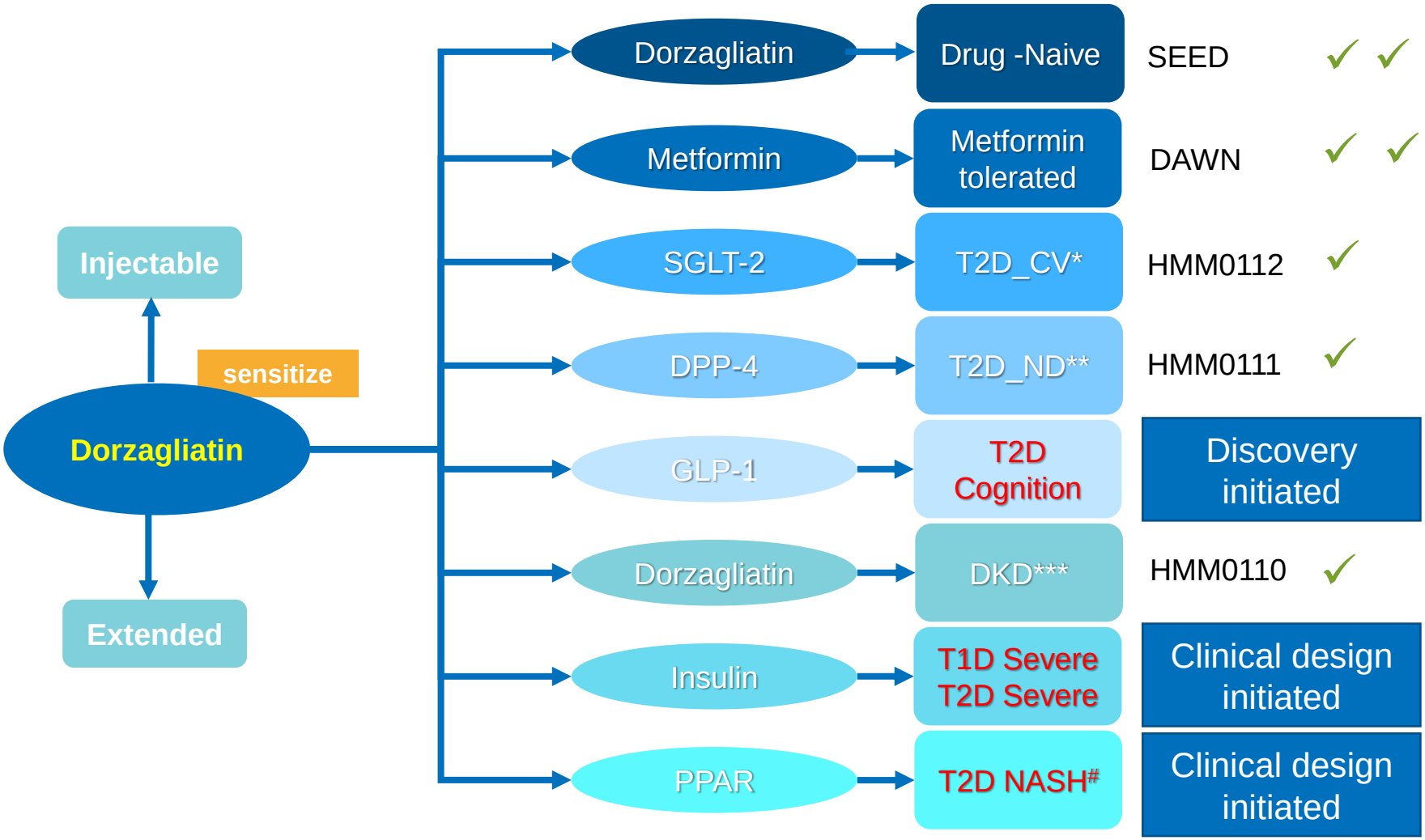
Hua Medicine and Bayer team build strategic consensus to global diabetes care between 21 and 22 October, 2020

# Hua Medicine is Receiving Nationwide Recognition


Hua Medicine selected as only Healthcare Company representative to Pudong Celebration hosted by President Xi Jinping in 12 November, 2020

# Hua Medicine – Future Developments

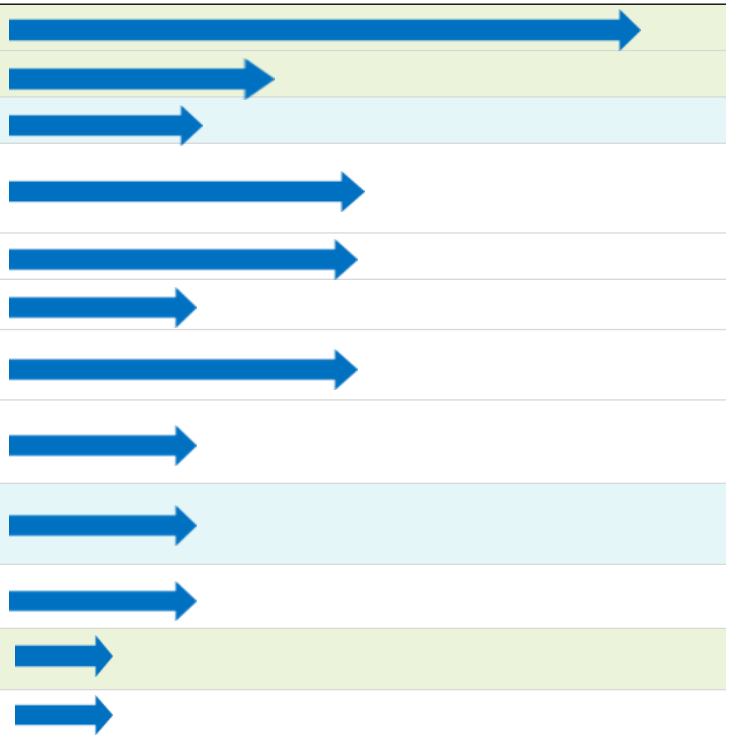
# New Cornerstone Medication, New Opportunity




*CV cardiovascular disease; **ND neurodegeneration disease; ***DKD diabetes kidney disease
#NASH non-alcoholic steatohepatitis

# Hua Medicine R&D Pipeline

| Product Name | Indication | Development phase |
|---|---|---|
| Dorzagliatin HMS5552 | T2D | NDA Filed (China) |
| | DKD | Phase I enabling |
| | T1D | IND-enabling |
| HMSFDC 6857<br>Dorzagliatin + Metformin | T2D | Phase I ready |
| HMSFDC 6868<br>Dorzagliatin +Sitagliptin | T2D | Phase I ready |
| | Insulin Sparing | IND-enabling |
| HMSFDC 5868<br>Dorzagliatin +Empagliflozin | T2D CVR | Phase I ready |
| HMSFDC 5688<br>Dorzagliatin +pioglitazone | NASH | IND-enabling |
| HMS 5678<br>Dorzagliatin + GLP-1 | Alzheimer Disease | IND-enabling |
| HMS 6789<br>Dorzagliatin + Insulin | Late Stage T2D<br>Insulin sparing | Ph III Design |
| mGLUR5 NAM | PD-LID | Pre-clinical |
| Fructose Kinase Inhibitor | Metabolic Disease | Pre-clinical |

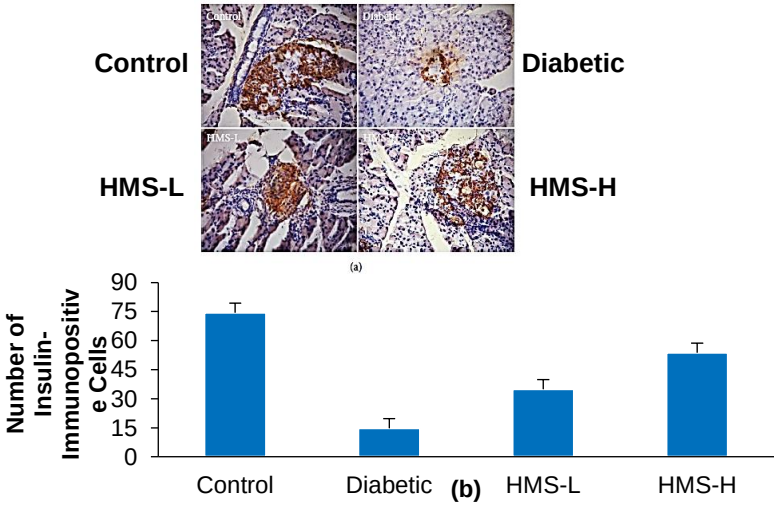


# Extensive Supporting Data for Dorzagliatin

# Dorzagliatin Has the Potential to Repair the Glucokinase Glucose Sensor

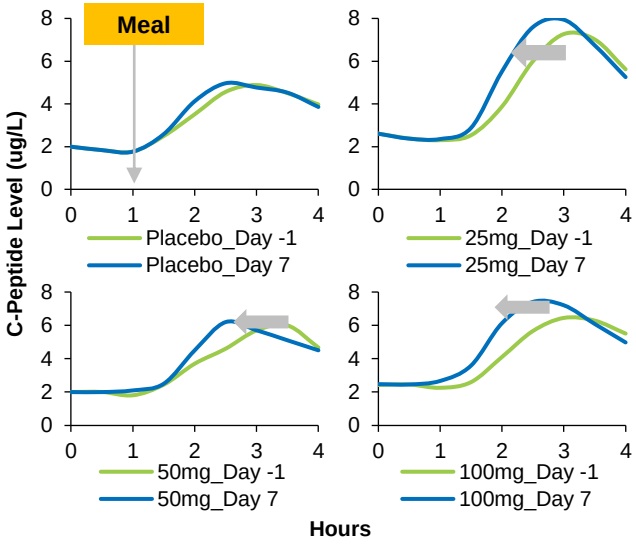
## Type 2 Diabetes Rat Pancreas

Pre-clinical



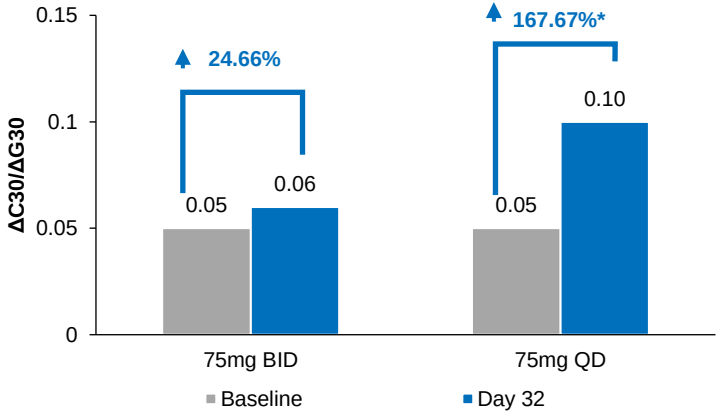

## T2D Patient Early-stage insulin release

Phase Ib



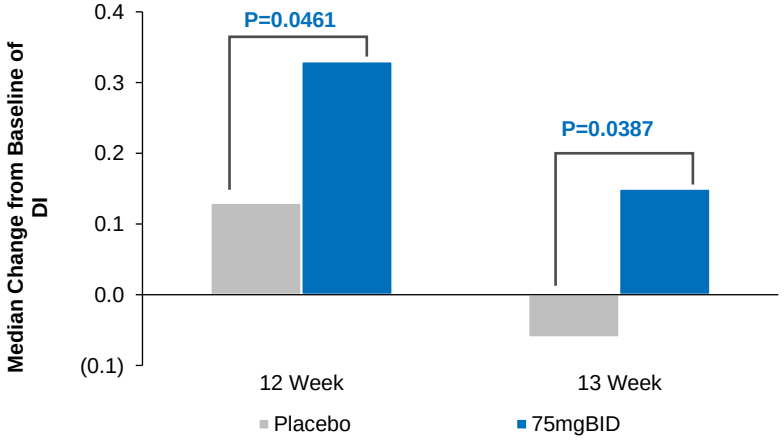

## T2D Patient Early Insulinogenic index

Phase Ic




## T2D Patients Disposition Index

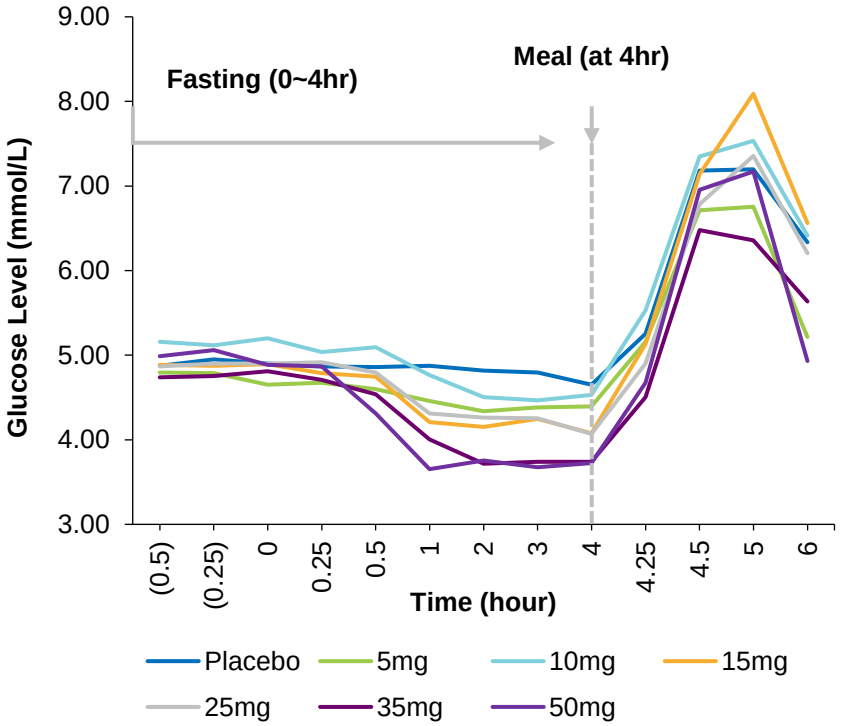
Phase II

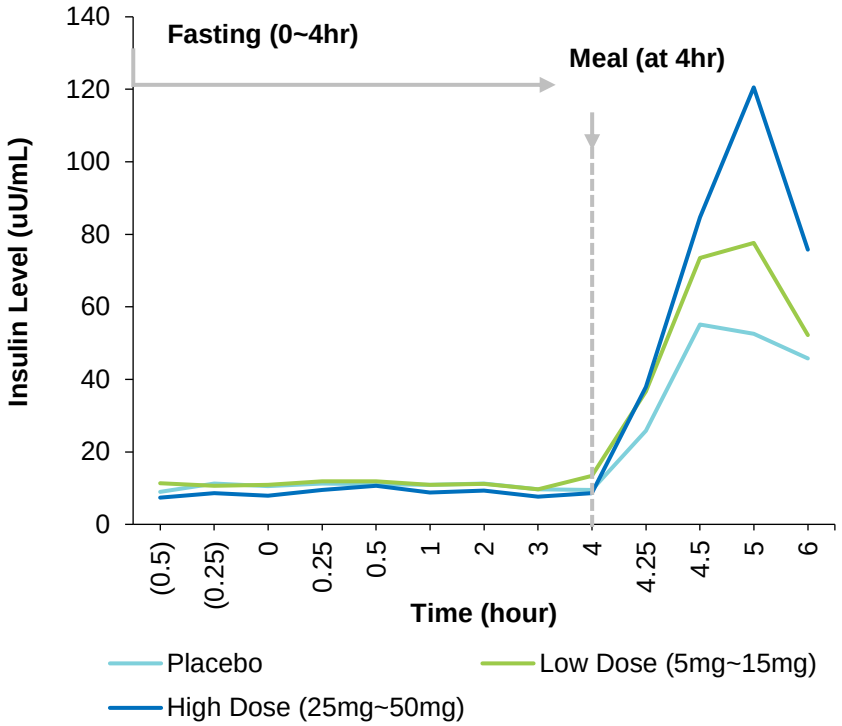


# Dorzagliatin Modulates GK Glucose Sensor Function as a Glucose Sensitizer

HMM0101

- Phase Ia trial targeted healthy adults in China with a single ascending dose (SAD)
- Patients were fasted over night and having HMS5552 next morning at time hr 0, continued fasting till hr 4 when meal is given

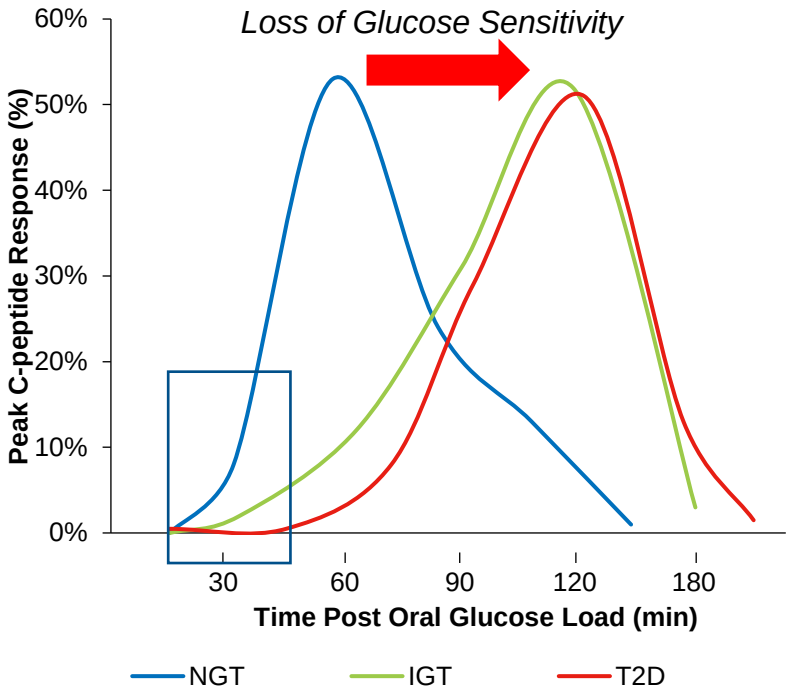



- **Dose dependent reductions in fasting plasma glucose without increases in insulin secretion**
- **Reduce hepatic glucose output by Dorzagliatin**
- **Glucose stimulated Insulin release (GSIR) is enhanced by Dorzagliatin**

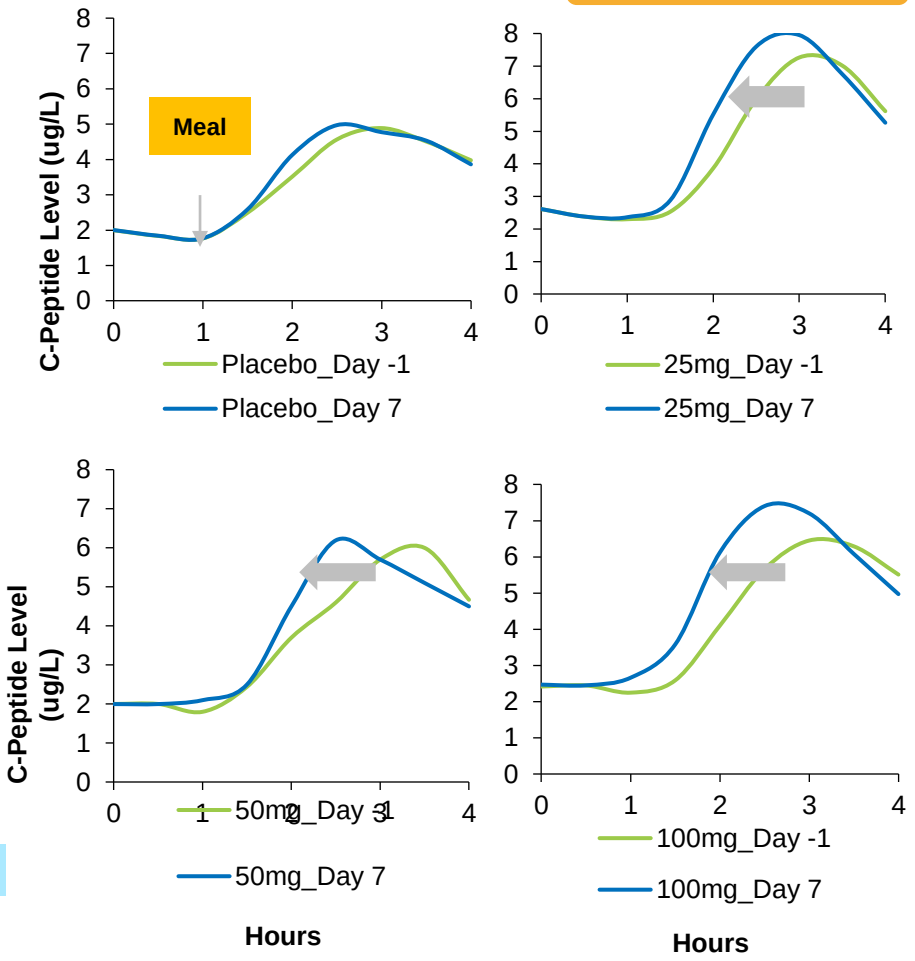
*Source: H Xu, X Li, Y Zhang, L Chen etal Drug Design, Development and Therapy 2016, 10, 1-8*

# Dorzagliatin Resets the Thresholds in T2D Patients with Improved Glucose Sensitivity




- **Impaired threshold of GSIR in IGT and T2D patients**

***HMM0102***



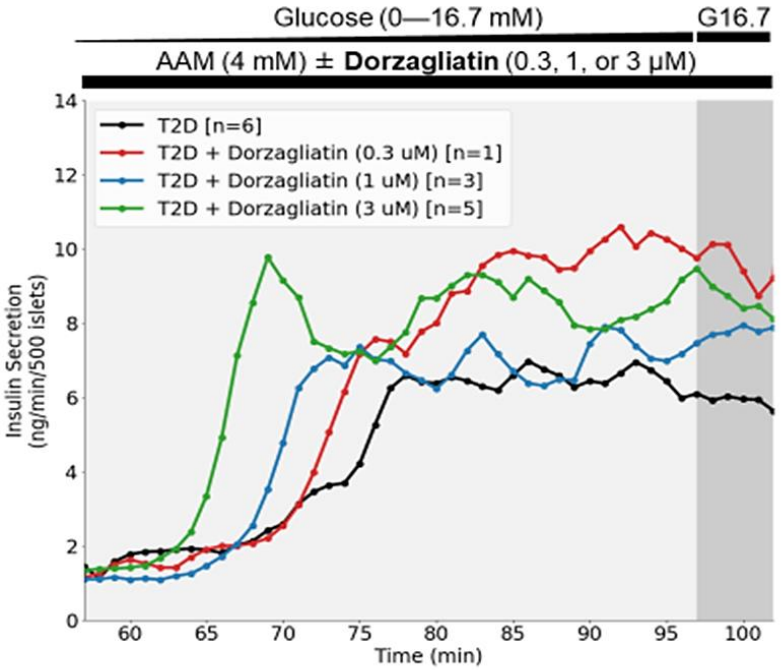

- **Dorzagliatin improves glucose sensitivity in T2D patients**

*Source: R.W.Bergstrom J. Clin. Endocrinol. Metab. (1990), 71(6):1447-53*
*Source: DL Zhu, Y. Zhang, L Chen et al ADA 75th Scientific Session, June 5-9, 2015, Boston*

# Dorzagliatin treats the root cause of diabetes

- Dorzagliatin is a novel dual acting full glucokinase allosteric activator that re-models the glucose set point and improves glucose sensitivity in type 2 diabetes patients
- Acts on: glucose sensor GK in pancreas, liver and intestine organs
- Improve glucose dependent insulin, glucagon and GLP-1 secretion in T2D patients
- Improve early insulin secretion and beta cell function to enhance 24hr glycemic range control
- Rescue the beta cell mass and hepatic GK function in animal model
- Completed 17 clinical trials including 2 pivotal Phase III trials in China and USA with excellent glycemic control with minimum hypoglycemia risk, accompanied with improve beta cell function and insulin sensitivity

## Dorzagliatin Improves beta Cell Secretion Function in T2D




## AI application for Systematic Diabetes Care

- **Dorzagliatin + Antidiabetics offers**
- **Remission + Prevention of Diabetes Complication**

## Dorzagliatin glucose dose dependently improves GSIR

- **A study in islets from T2D patients**

Franz Matschinsky 2021

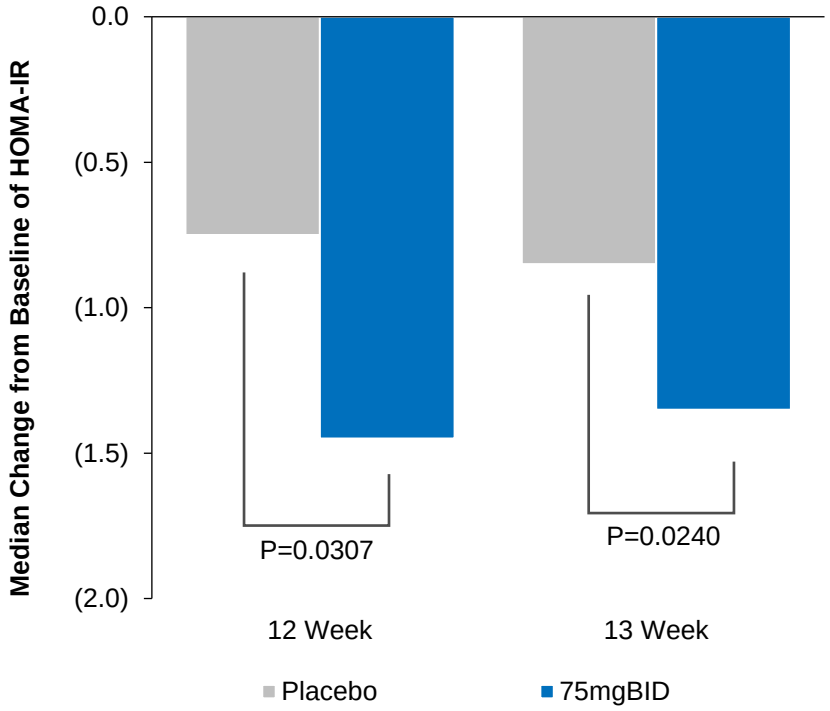
# Dorzagliatin Improved β-cell Function and Reduced Insulin Resistance – Phase II Trial

HMM0201

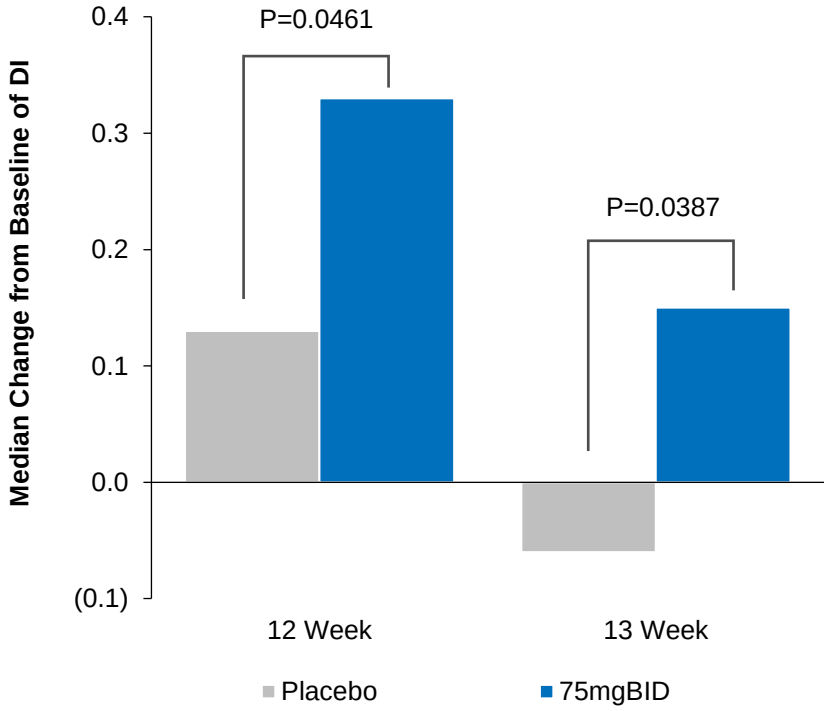
Chinese drug naive Type 2 diabetes patients 3 month treatment

Improves pancreatic β-cell function
Reduces insulin resistance

## Reduced Insulin Resistance




## Improved β-cell Function

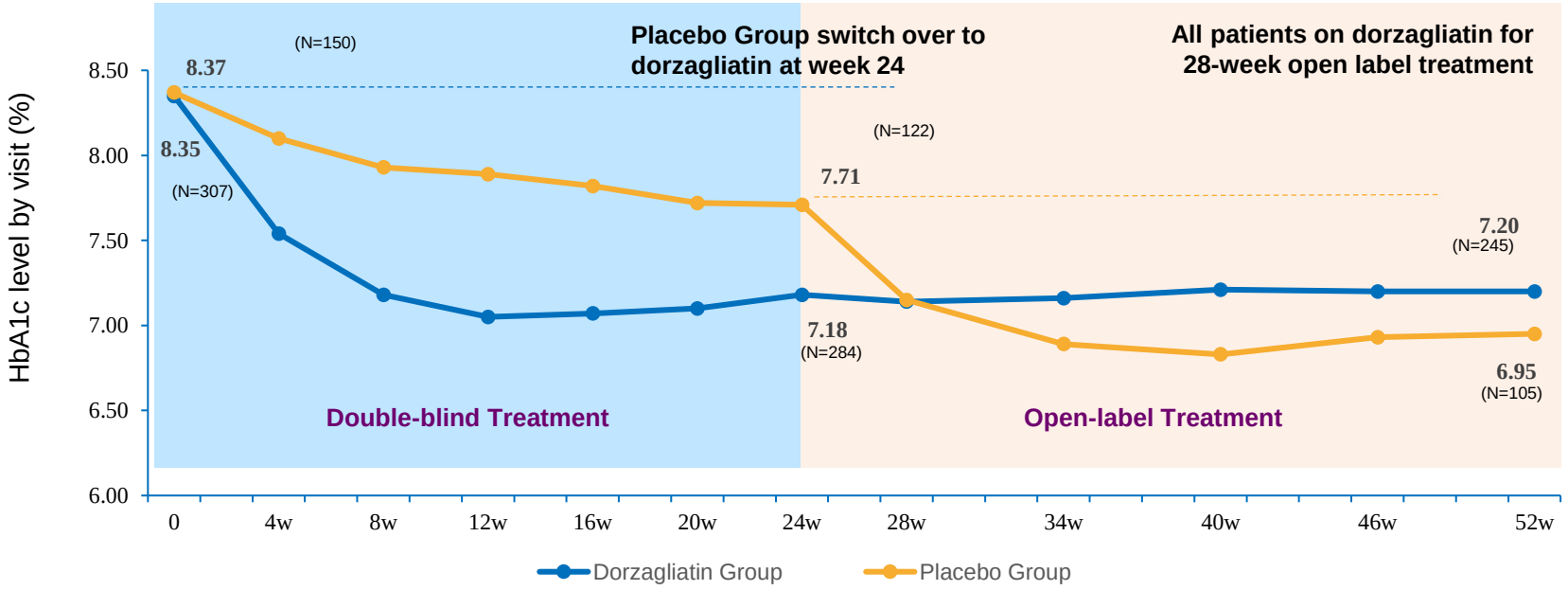



**One week after the conclusion of the trial, patients continue to see sustained effect in the HOMA-IR and Disposition Index**

*Source: Dalong Zhu Lancet Diabetes and Endocrinology 2018 May 4*
*Note: HOMA-IR represents homeostatic model assessment – insulin resistance, while DI measures β-cell function*

# SEED Phase III: Effective & Sustained HbA1c Reduction with monotherapy in drug naïve T2D patients

Change of HbA1c during the 52-week treatment period




## Efficacy Endpoints:

- Met primary efficacy endpoint at 24 weeks
- 45.4% of patients in treatment group achieved target HbA1c below 7% at 24 weeks vs. 21.5% of placebo
- Sustained efficacy at 52 weeks

## Safety endpoints:

- Dorzagliatin is well tolerated and safe during the 52 week study
- No drug related SAE and severe hypoglycemia
- Hypoglycemia incidence rate (glucose <3.0 mmol/L) is less than 1 percent

*Note: Numbers presented in the Figure were computed from descriptive statistical analysis.*
**p<0.001 compared with baseline at 52 week.*

# SEED Benchmark 52-Week Data

| Study | Drug | MOA | Baseline HbA1c | HbA1c reduction at | | HbA1c rebound from 24/26 weeks |
|---|---|---|---|---|---|---|
| | | | | 24/26 weeks | 52 weeks | |
| SEED | Dorzagliatin 75mg BID | GKA | 8.4 | -1.15 | -1.11 | 0.04 |
| Pioneer-4 | Oral semaglutide 14mg QD | GLP-1 | 8.0 | -1.3 | -1.2 | 0.1 |
| | Liraglutide 1.8mg QD | GLP-1 | 8.0 | -1.1 | -0.9 | 0.2 |
| Pioneer-2 | Empaglifozin 25mg QD | SGLT-2 | 8.1 | -0.9 | -0.8 | 0.1 |
| Award-3 | Dulaglutide 1.5mg QD | GLP-1 | 7.6 | -0.78 | -0.7 | 0.08 |
| | Dulaglutide 0.75mg QD | GLP-1 | 7.6 | -0.71 | -0.55 | 0.16 |
| | Metformin | Biguanide | 7.6 | -0.56 | -0.51 | 0.05 |
| Pioneer-3 | Sitagliptin 100mg QD | DPP-4 | 8.3 | -0.8 | -0.5 | 0.3 |

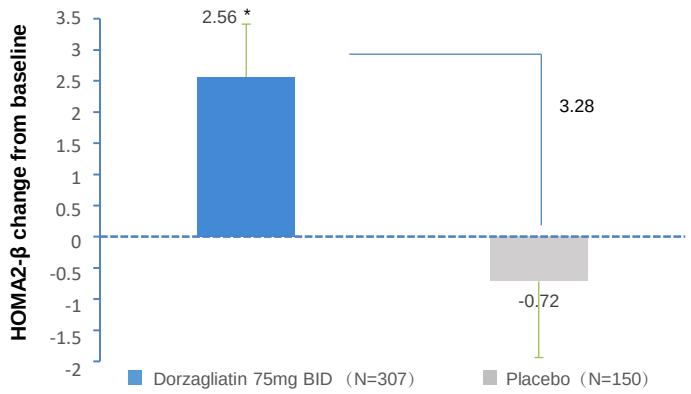
**Figure : Summary of selected anti-diabetes therapy HbA1c reductions from baseline at week 24/26 and week 52**

# SEED Phase III 24-WEEK Secondary Results + Safety Results — Presented at ADA

## Secondary Results

- Reduction of ***2hPPG*** was observed in Dorzagliatin 75mg BID than placebo (-2.83 vs -0.50mmol/L, p<0.001)
- Significant ***Beta-cell Function Improvement*** (HOMA2-β)

### *HOMA2-β* Change from Baseline to week 24 (FAS)




Data are least squares means. *p<0.05 vs placebo.

## Safety Results

**During the period of 24 weeks double blinded treatment, dorzagliatin (75 mg, BID) was well tolerated and had a good safety profile**

- The incidence of AE was similar between the treatment and placebo groups
- Majority of the AEs were mild in severity
- No death, no drug-related SAE
- No clinically significant abnormal trends or findings in safety lab tests, ECG, physical examination,and vital signs
- Hypoglycemia occurred in one of 310 patients (0.3%) in dorzagliatin group. No severe hypoglycemia was reported

## Supports first-line treatment of new-onset Type 2 Diabetes（ADA）

- Quick response, 4 weeks hypoglycemic, 12 weeks β function
- Sustained efficacy
- Address both symptoms and root causes
- Good safety
- Low hypoglycemia risk
- Keep blood glucose in range

# Dorzagliatin has potential to be the ONLY oral anti-T2D therapeutic for select DKD patients

| Drug use guidelines for T2D patients with diabetic kidney disease | | |
|---|---|---|
| Dorzagliatin |  | *Oral* |
| Metformin |  | |
| DPP-4 |  | |
| SGLT-2 |  | |
| GLP-1 |  | *Injectibles* |
| Insulin |  | |

 No dose adjustment required

 Dose adjustment required

 Contraindicated

- Patients with diabetic kidney disease make **up 20-40% of the total** T2D patient population globally
- In China, **patients with moderate, severe, and end-stage chronic kidney disease comprise 21.9%** of the T2D patients

**Study:**

HMM0110 was conducted in China to evaluate whether dorzagliatin can be readily used in Type 2 diabetes (T2D) patients with impaired renal function.

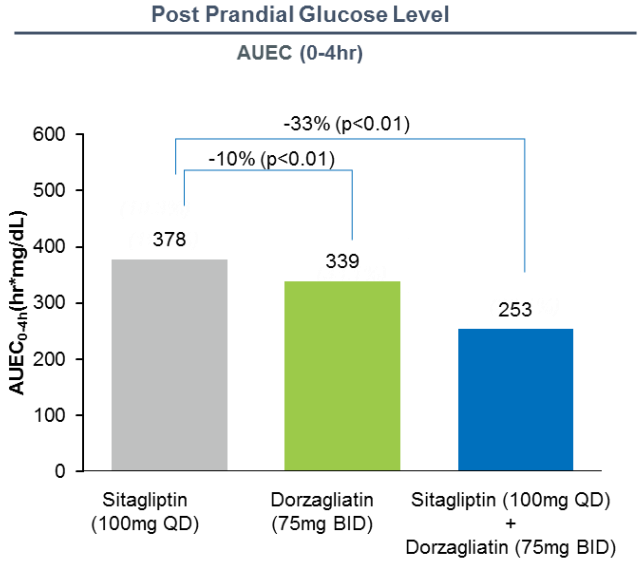
**Conclusion:**

- In subjects with end stage renal disease and are not on dialysis, **the study indicated no significant impact on PK properties in subjects treated with dorzagliatin.**
- This result **supports dorzagliatin as a promising solution and potential supplementary option for T2D patients with moderate, severe and end stage chronic kidney disease** (i.e., stages 3-5 of CKD) which can **provide satisfactory blood glucose control safely and without dose adjustment**.

# Dorzagliatin Has Demonstrated Successful Combination Potential with other Global Top Oral Anti-Diabetic Drugs

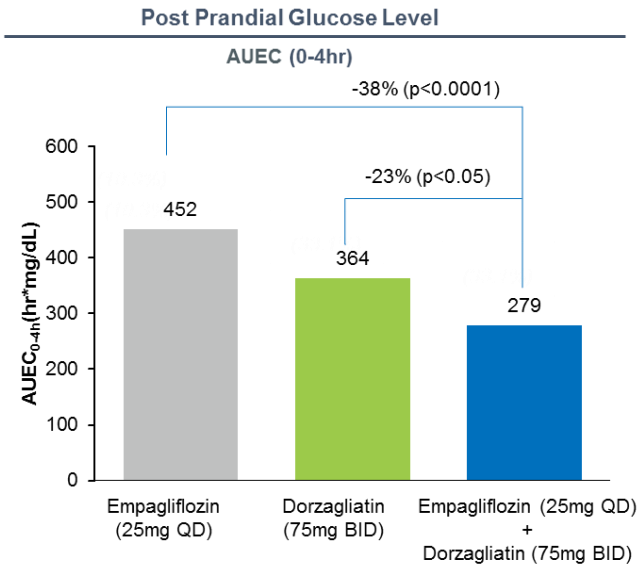
- No drug-drug interaction observed in Phase I trials in USA with sitagliptin (DPP-4 inhibitor) and empagliflozin (SGLT-2 inhibitor)

- **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 sitagliptin
  - In both trials, the combined use of sitagliptin 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:**

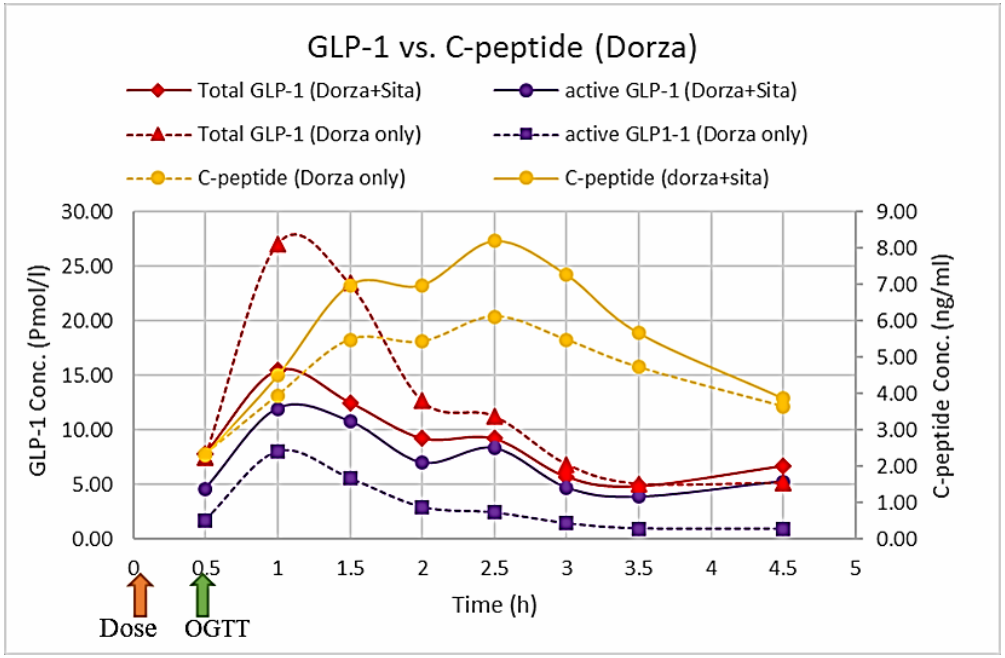
✓ Fastest growing among OAD with US$ 6B global sales in 2019 and ~24% yoy growth

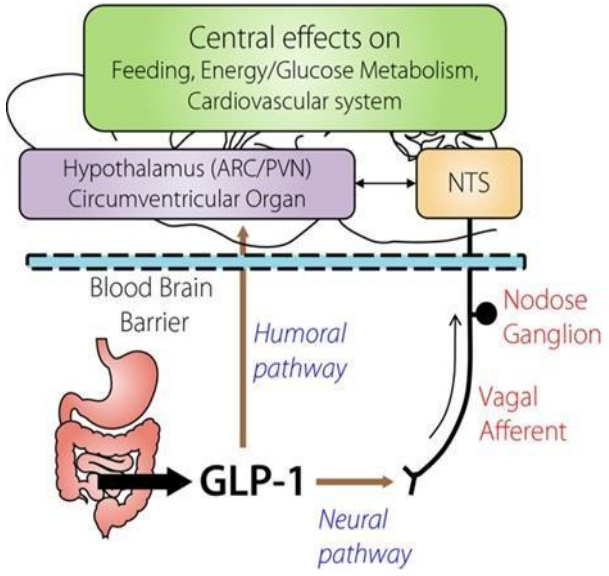
*Note: AUC represents area under the curve, while AUEC represents area under the effect curve.*

# Dorzagliatin up-regulate GLP-1 secretion in T2D

Dorzagliatin stimulate GLP-1 secretion in T2D patients in USA

- Stimulate total GLP1 secretion reaches Cmax at 30 minute post oral glucose
- Augment C-peptide peak left shift




**Neuroendocrine Regulation**

- Dorzagliatin acts on intestinal L cells and improve glucose sensitivity
- Both GK and SGLT1 regulate intestinal GLP-1 release
- Effects on neuroendocrine regulation is under investigation

*Source: Li Chen, JY Zhang et al ADA 2021 117-LB*

# Hua Management Team

# Highly Experienced R&D Team with Extensive China and Global Pharmaceutical Experience

## Founder & CEO

**Li Chen, Ph.D.,** *Founder & Board Director*

- CSO and Founding Director of Roche R&D Center (China), responsible for development of China's drug discovery strategy, creation of discovery portfolio and management of operations
- Former head of HTC technology at Roche
- Adjunct professor at Tongji University, Ph D advisor
- Over 90 publications and patents in basic research and medical sciences

**George Lin**
*EVP, CFO*
Bank of America Merrill Lynch · Credit Suisse

**Yi Zhang, Ph.D., MD**
*SVP, Clinical R&D, CMO-China*
Roche

**Jin She, Ph.D.**
*VP, Chemistry CMC*
Roche · MSD

**FuxingTang, Ph.D.**
*VP, CTO, Chemistry CMC*
Forest Laboratories, Inc. · Allergan

**Yilei Fu, BS, MBA**
*VP, Quality Assurance*

**Wenjie Xu, BS, MBA**
*VP, Commercial Strategy and Marketing*
AstraZeneca · Lilly

**Di Hong, DBA**
*VP, Operations*
Roche · Lilly · AMGEN

# A Blue Chip Board

## Chairman
## Robert Nelsen

## Li Chen

## Lian Yong Chen

FIL Capital Management (Hong Kong)

## George Lin

## Walter Kwauk

## William Keller

## Junling Liu


## Alec Tsui

# World-renowned Advisors and Influential Key Opinion Leaders

## Advisors

**Franz Matschinsky, M.D.**

- Professor of biochemistry and biophysics at the University of Pennsylvania, Perelman School of Medicine
- Founded Penn Diabetes Research Center of the University of Pennsylvania
- Founder of the Islet Cell Biology Core in the University of Pennsylvania
- Received Banting Award (1995), Rolf Luft Award (2020)
- Formulated the glucokinase glucose sensor concept
- *"Glucokinase is a glucose sensor, diabetes gene and drug target"*

**Ralph A. DeFronzo, M.D.**

- Professor and Division Chief of Diabetes Division at the University of Texas Health Science Center
- Deputy Director of Texas Diabetes Institute
- Led the U.S. development of metformin, and FDA approval in 1995
- Discovered a new approach to diabetes treatment that targets glucose reabsorption in the kidneys, which led to the development and approval of SGLT-2
- Received several prestigious awards, including the Lilly Award (1987) by the American Diabetes Association, Banting Lectureship Award (1988) by the Canadian Diabetes Association, Novartis Award (2003), ADA's Albert Renold Award (2002), the ADA's Banting Award (2008), and the Harold Hamm International Prize (2018)
- Published over 800 articles in peer-reviewed medical journals

## Chinese KOLs

**Wenying Yang, M.D.**

- Director of Endocrinology, Director of Department of Internal Medicine, Vice Chairman of Ethics Committee at China-Japan Friendship Hospital
- Ex President, Chinese Diabetes Society
- Published articles in numerous prestigious journals such as New England Journal of Medicine, Lancet Diabetes and Endocrinology

**Dalong Zhu, M.D.**

- Director of Endocrinology, Nanjing Drum Tower Hospital
- Current President, Chinese Diabetes Society
- Published articles in numerous prestigious journals such as the Lancet Diabetes and Endocrinology , Diabetes

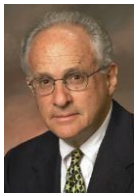
**Xiaoying Li, MD, Ph.D.**

- Director of Endocrinology, Zhongshan Hospital
- Vice President, Chinese Diabetes Society
- Published articles in numerous prestigious journals such as the Lancet Diabetes and Endocrinology , Cell Metabolism

# World-renowned Portfolio Advisory Board

**John J. Baldwin, Ph.D.**

- Former EVP at Merck – 30+ years, with several drugs to his credit including Trusopt®, Cosopt®, Aggrastat®, and Pepcid®, etc
- Hall of Fame Medicinal Chemist
- American Chemical Society, Philadelphia Section Award for Ingenious Contributions to Chemistry
- Published 125+ scientific articles
- Holds over 240 issued US patents



**Bennett Shapiro, M.D.**

- Ex-EVP Merck
- Well known Pharmacologist
- Former Professor and Chairman, Department of Biochemistry, University of Washington
- 120+ papers on the molecular regulation of cellular behavior and the biochemical events that integrate the cascade of cellular activations at fertilization
- Former Guggenheim Fellow

**Christopher Walsh, Ph.D.**

- Ex-professor, Harvard Medical School
- Consulting professor and advisor to Stanford ChEM-H institute
- Advisor to Global Pharma
- Former President and CEO of the Dana Farber Cancer Institute
- 2010 Welch Prize in Chemistry

**Catherine Strader, Ph.D.**

- COO, Synergy Partners
- Held executive positions at Schering-Plough and Merck
- Formerly EVP of Discovery Research and Chief Scientific Officer for Schering-Plough
- Formerly Site Head for Merck's large NJ discovery research sites
- 30 years of pharmaceutical R&D experience

**James MacDonald, Ph.D.**

- CEO, Synergy Partners
- Former EVP, Preclinical Development, at Schering-Plough Research Institute
- 17+ years at Merck, ending as Executive Director of Toxicology in the Department of Safety Assessment

# Hua Medicine

# 华领医药