



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

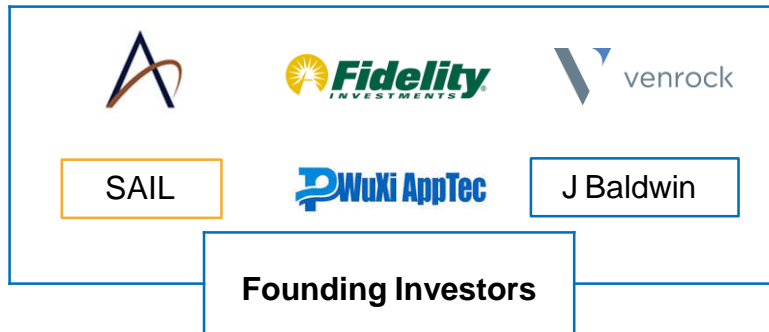


Bob Nelsen
Chairman



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.

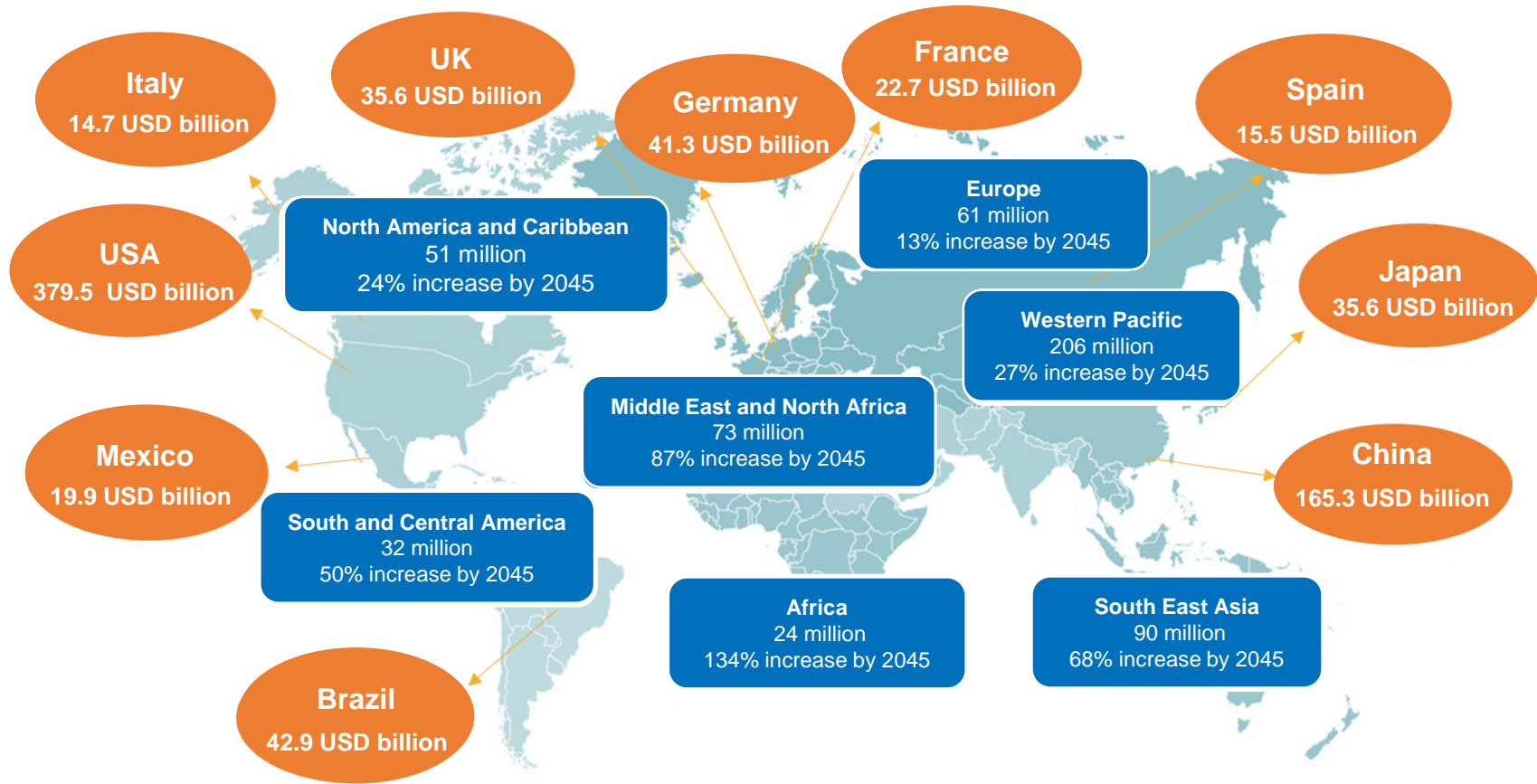
*“Confounding the diabetes epidemic and high costs, **therapeutic targets are not being met.** There is a lack of improvement in reaching clinical targets since 2005 despite advancements in medication and technology treatment modalities. **Indeed, between 2010 and 2016 improved outcomes stalled or reversed.**”¹*

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

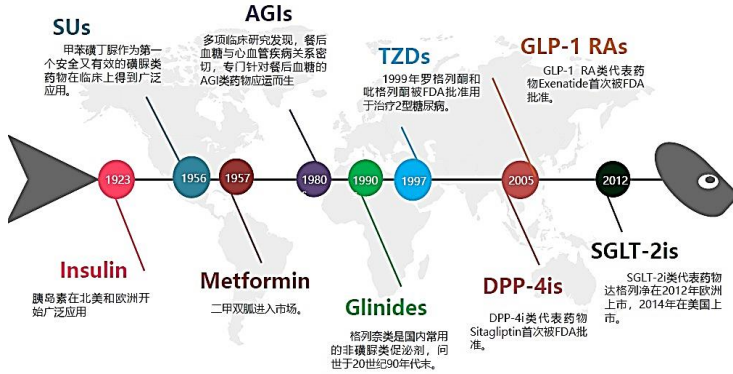
● Top 10 countries or territories for total health expenditure due to diabetes

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

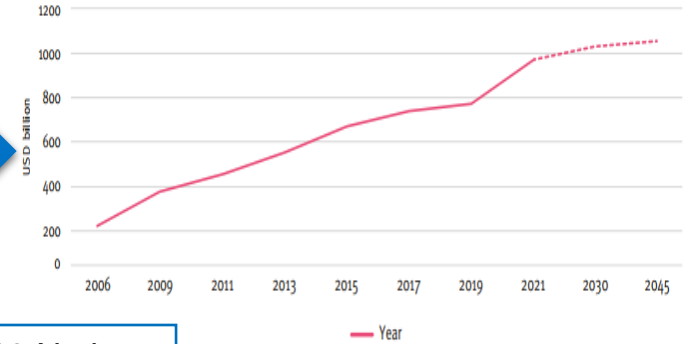


US \$966 bn

IDF 2021

450 Mn Diabetes
Many Complications

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

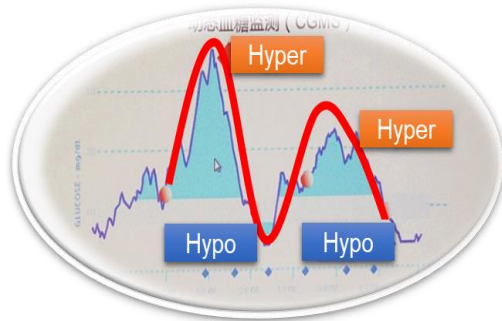


新近: 2型糖尿病的药物治疗(1). 临床药物治疗杂志, 2015, 13(3): 18-22.
Bae E J. DPP-4 inhibitors in diabetic complications: role of DPP-4 beyond glucose control[J]. Archives of pharmaceutical research, 2016, 33(8): 1114-1128.
Knop FK, Branden A, Vilsbøll T. Exenatide: pharmacokinetics, clinical use, and future directions[J]. Expert opinion on pharmacotherapy, 2012, 13(6): 555-571.

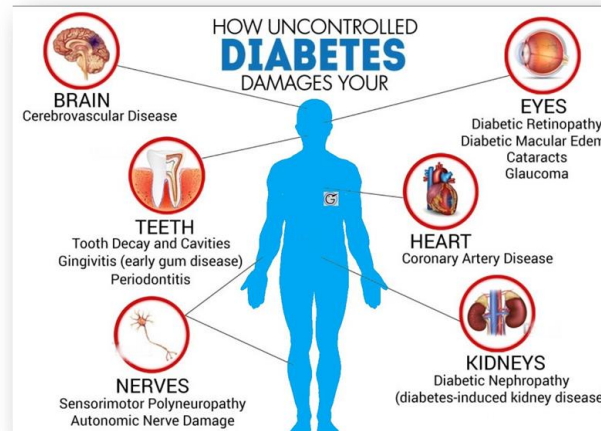
Top 10 Nations

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



Blood glucose fluctuation



Diabetes Complications

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

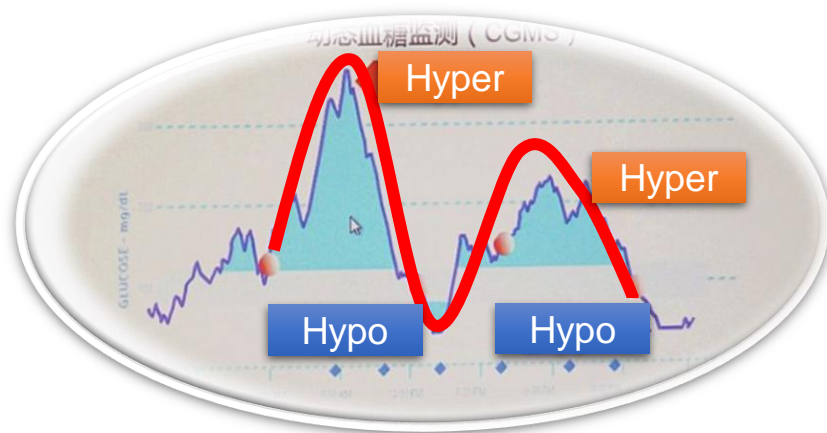
How Do We Stop Type 2 Diabetes?



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

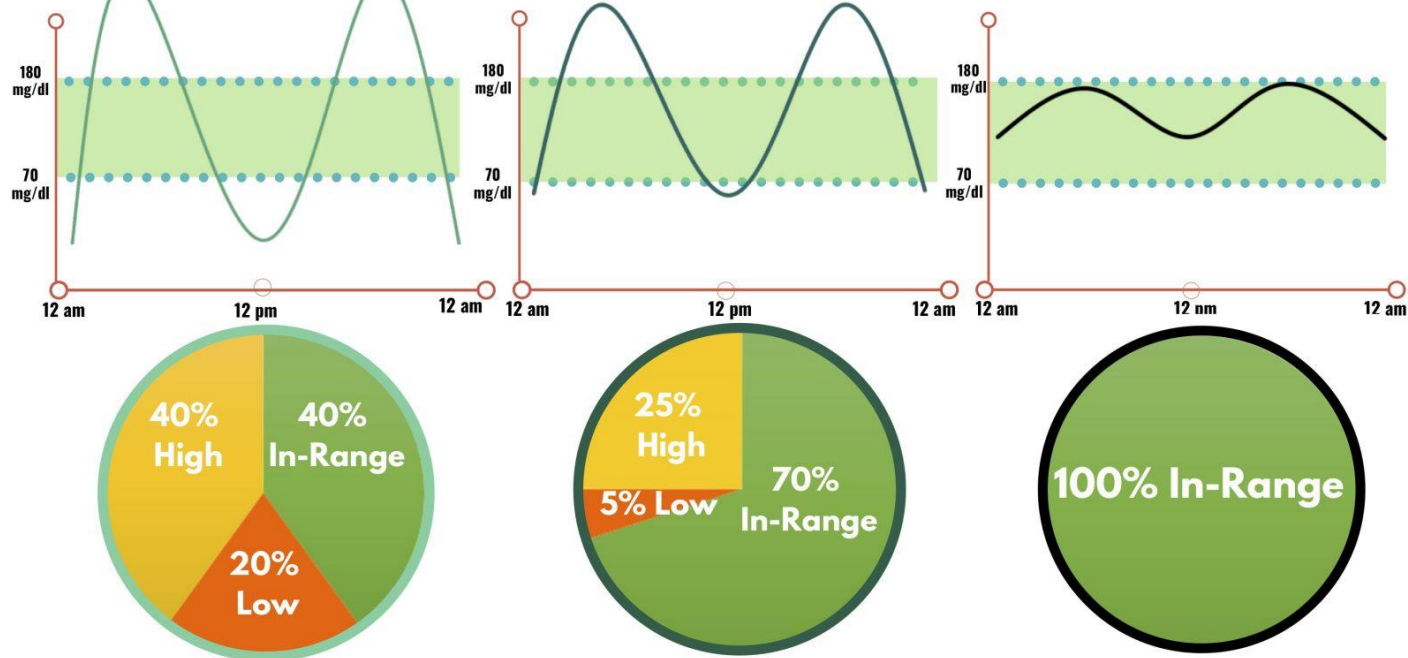


The current treatment paradigm for Type 2 diabetes is beginning to shift



THE MANY FACES OF A 7% A1C

(and an average blood glucose of 154 mg/dl)



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

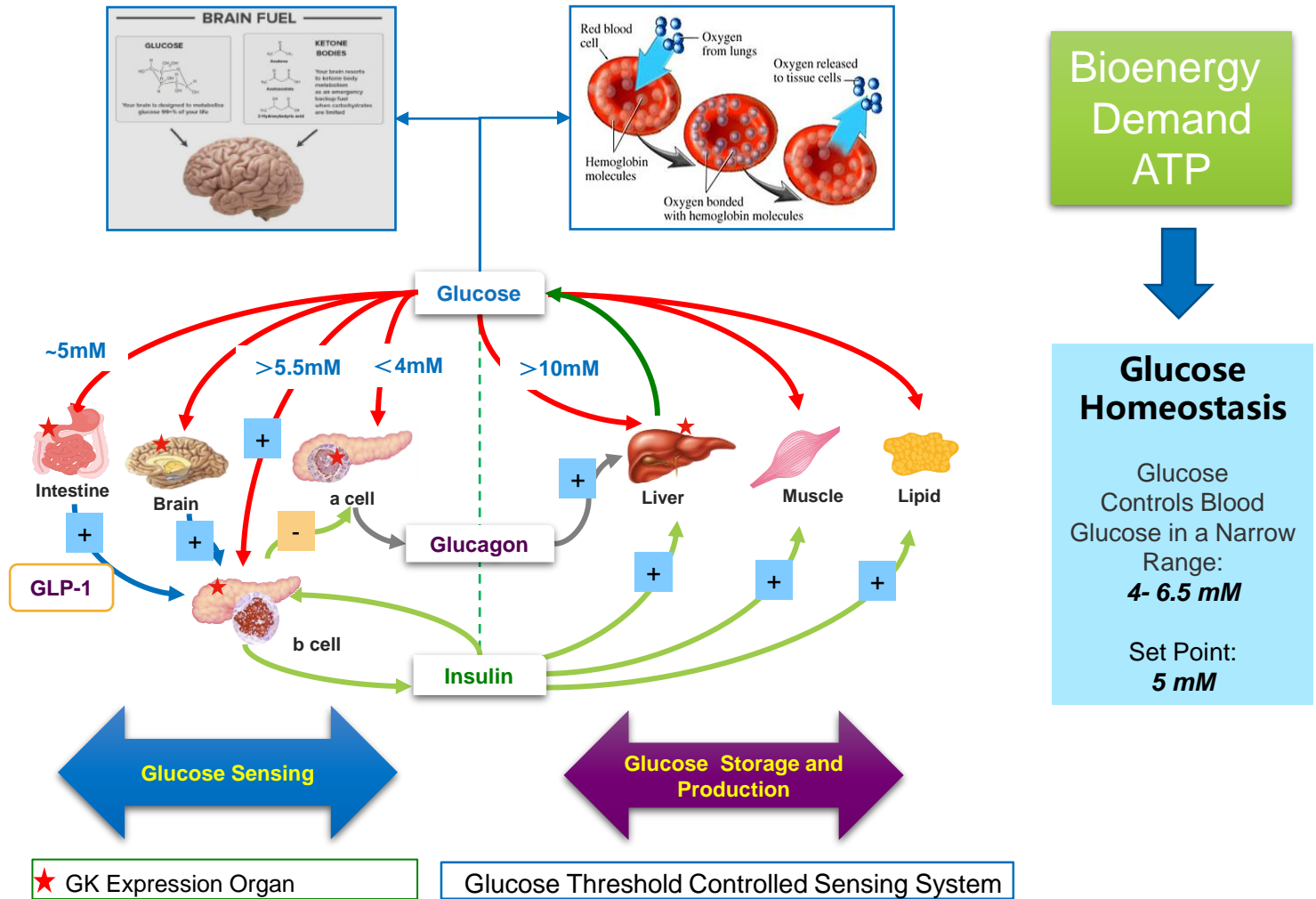
- **HbA1c** is incorporated into the diagnostic criteria for diabetes
- **Time in Range (TIR)** added to blood sugar control goals
- The guideline clarifies that lifestyle intervention and metformin are the first-line treatments for hyperglycemia in patients with T2D.
- For patients with T2D with ASCVD 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

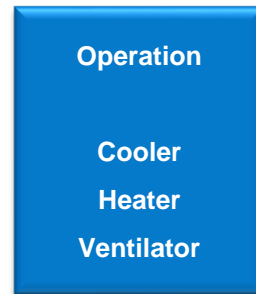


Glucokinase GK expression and function are impaired in T2D patients

Glucokinase is a Glucose Sensor in Glucose Homeostasis

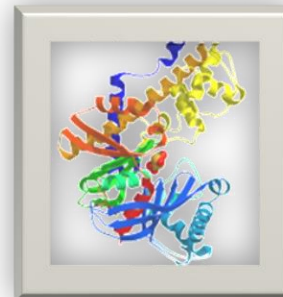
Thermostat in a Building

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



Glucostat in Human Body

- Primary Messenger: glucose level
- Set Point: 5 mmol/liter¹
- Threshold: 4-6 mmol/liter¹
- 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 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.”



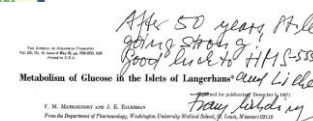
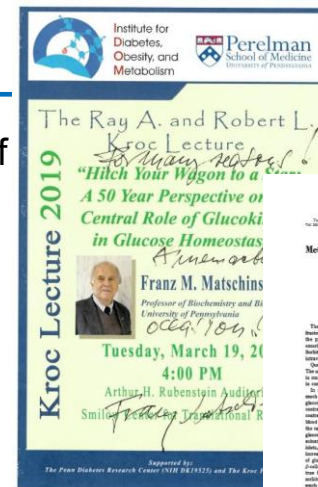
Lancet 2018: Dalong Zhu and Li Chen

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***



THE LANCET Diabetes & Endocrinology





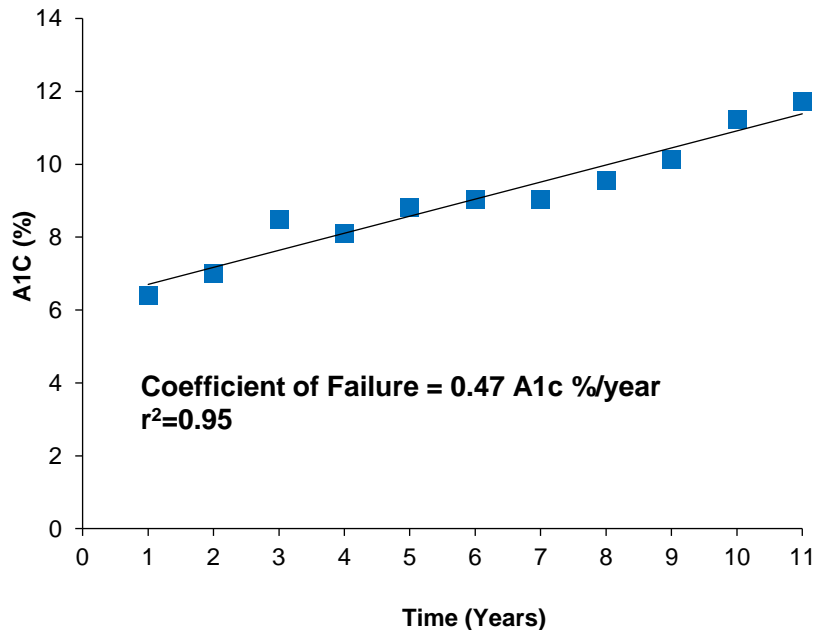
DREAM Results – Presented Sep 2021

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

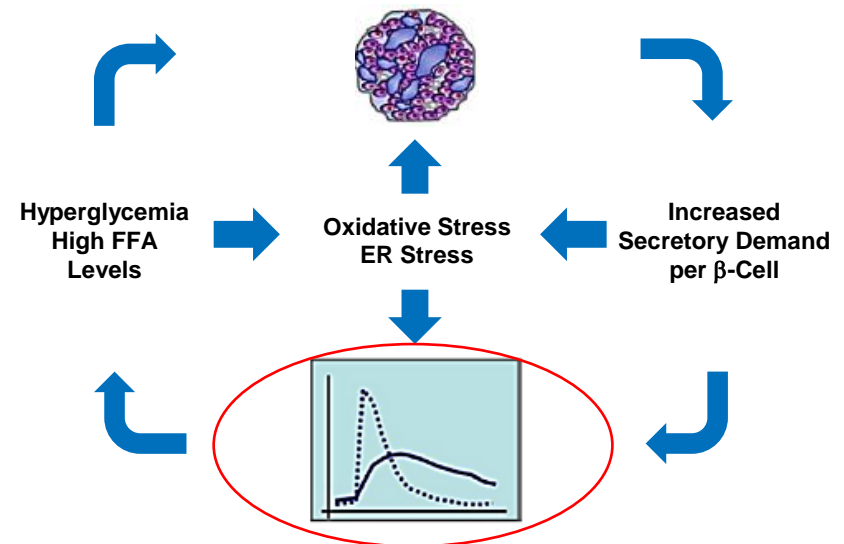


- Type 2 diabetes is a progressive disease with deterioration of β cells function
- Loss of glucose sensitivity in Type 2 diabetes patients is the first step in the progressive destruction of β cells
- Impaired β cells function results in hyperglycemia stress which causes progressive damage of β cells
- 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 Accordingly¹



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

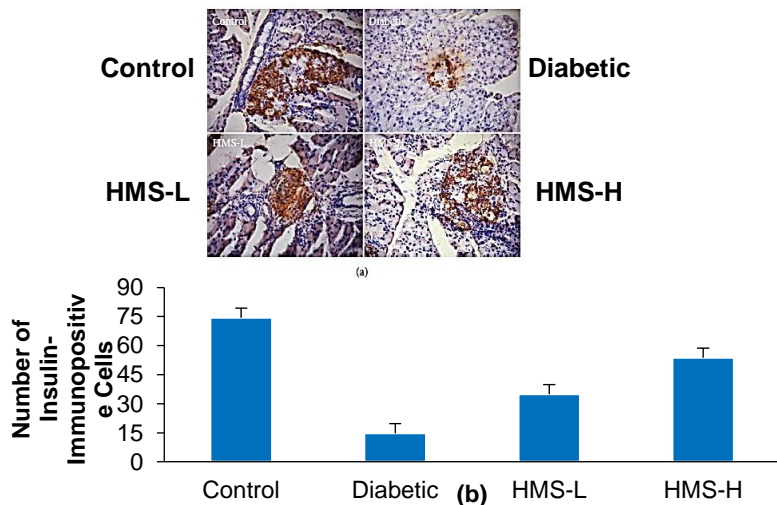
Source: Vivian Fonseca, *Diabetes Care*, 2009, Vol 32, S2; Source: J Merier, R Bonadonna *Diabetes Care* (2013) 36, S113
¹ Retrospective survey.

Dorzagliatin Has the Potential to Repair the Glucokinase Glucose Sensor



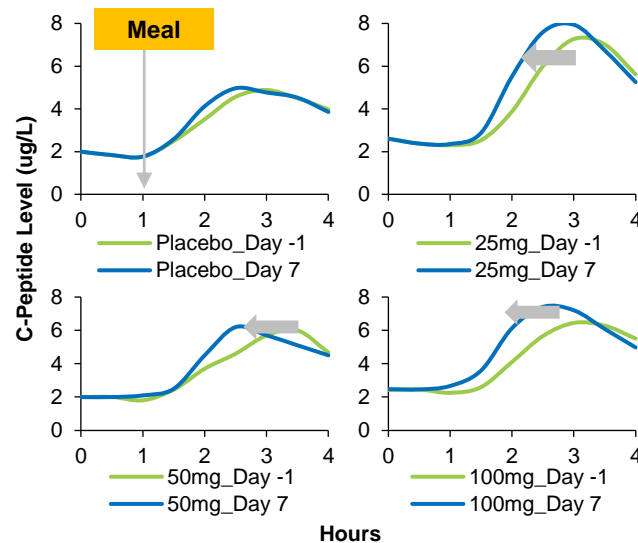
Type 2 Diabetes Rat Pancreas

Pre-clinical



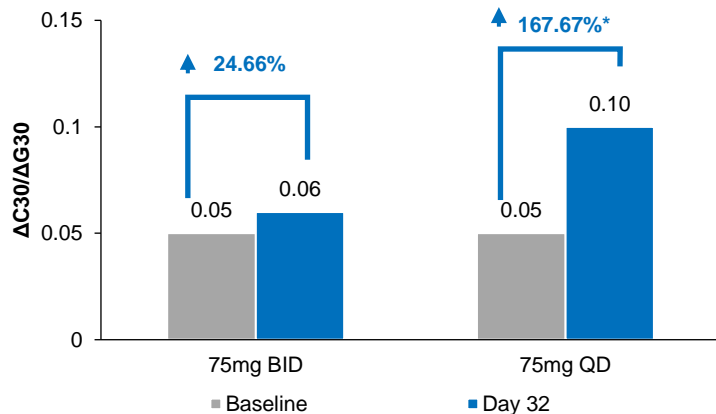
T2D Patient Early-stage insulin release

Phase Ib



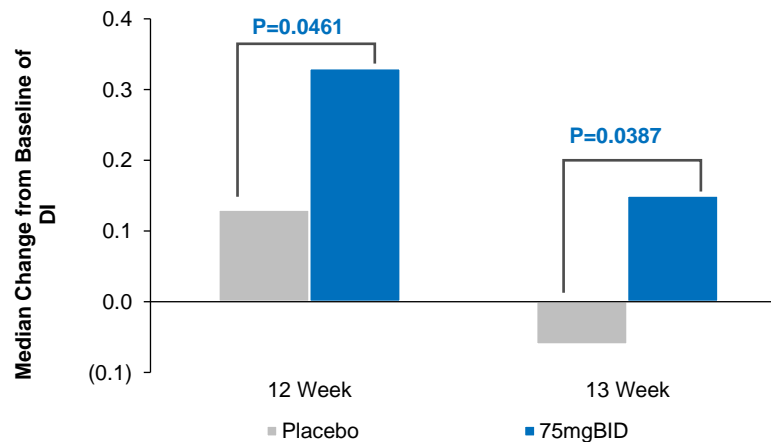
T2D Patient Early Insulinogenic index

Phase Ic



T2D Patients Disposition Index

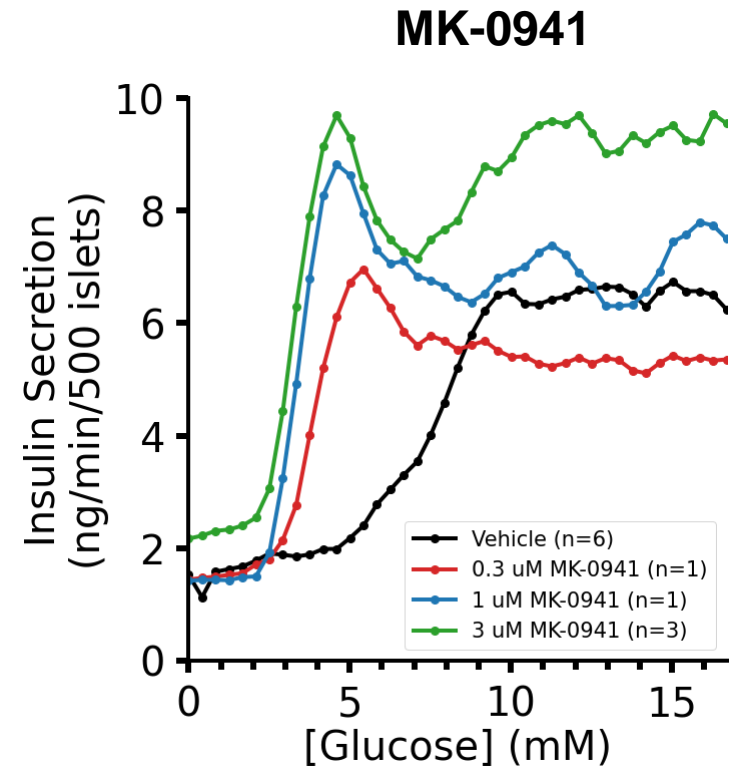
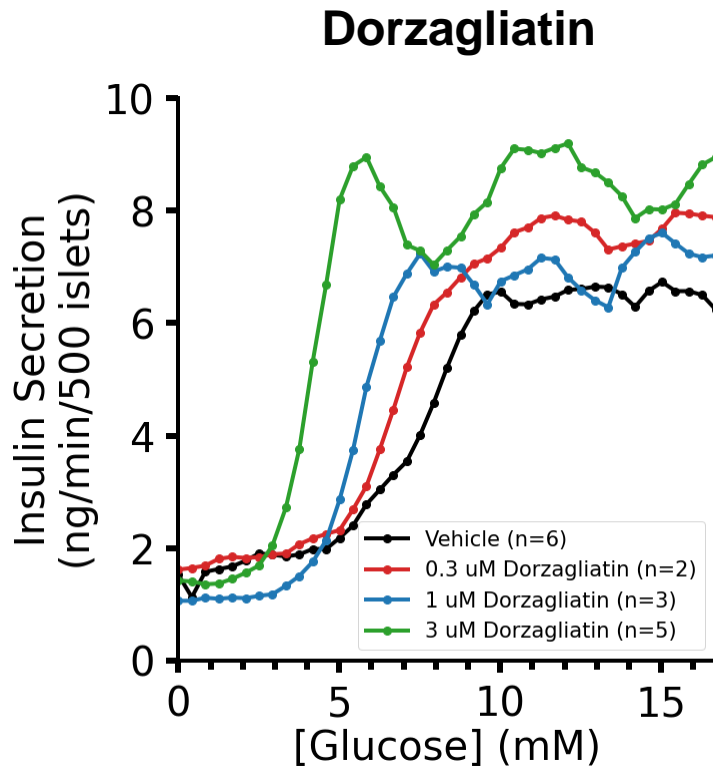
Phase II



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



Glucose Dependence



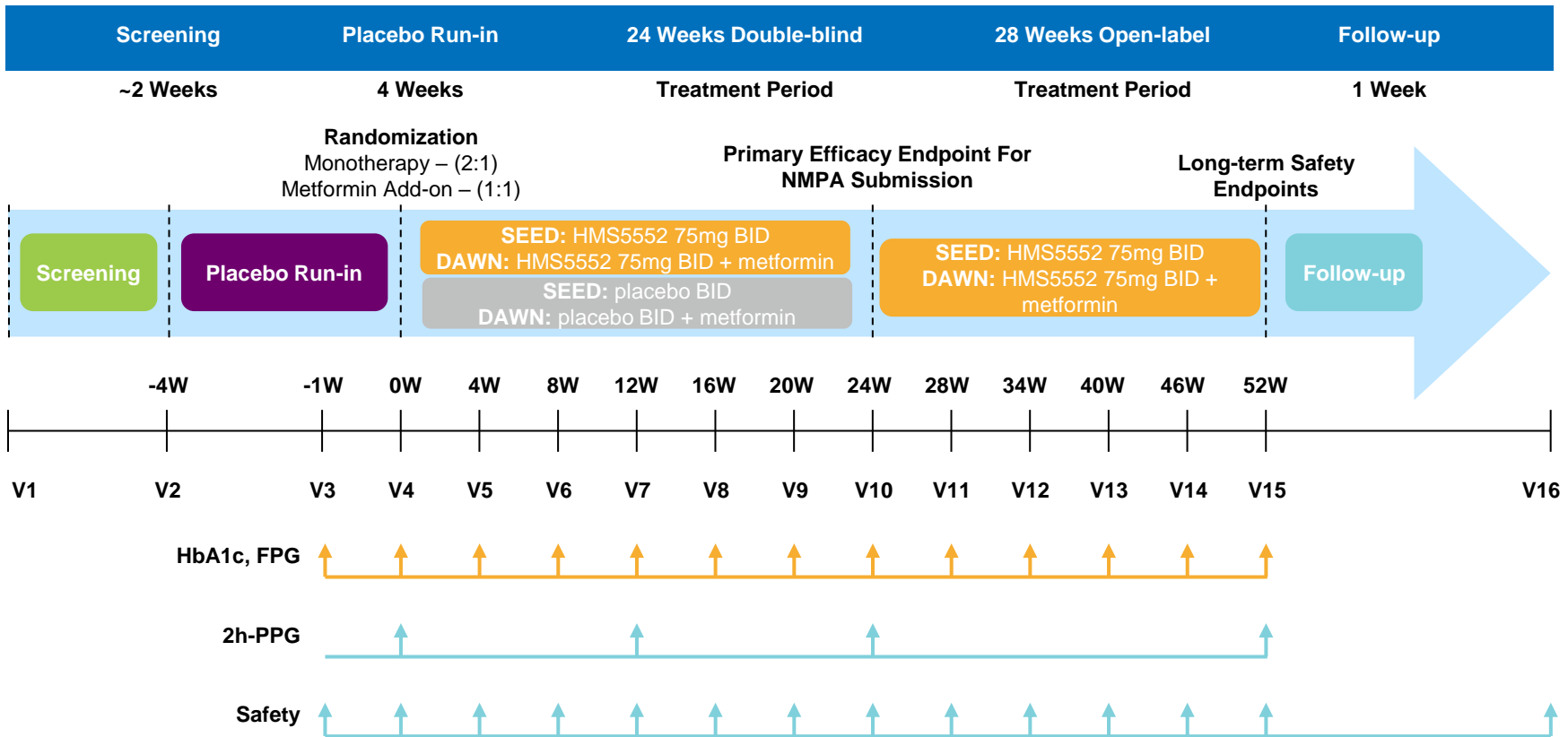
Franz Matschinsky 20211201

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)



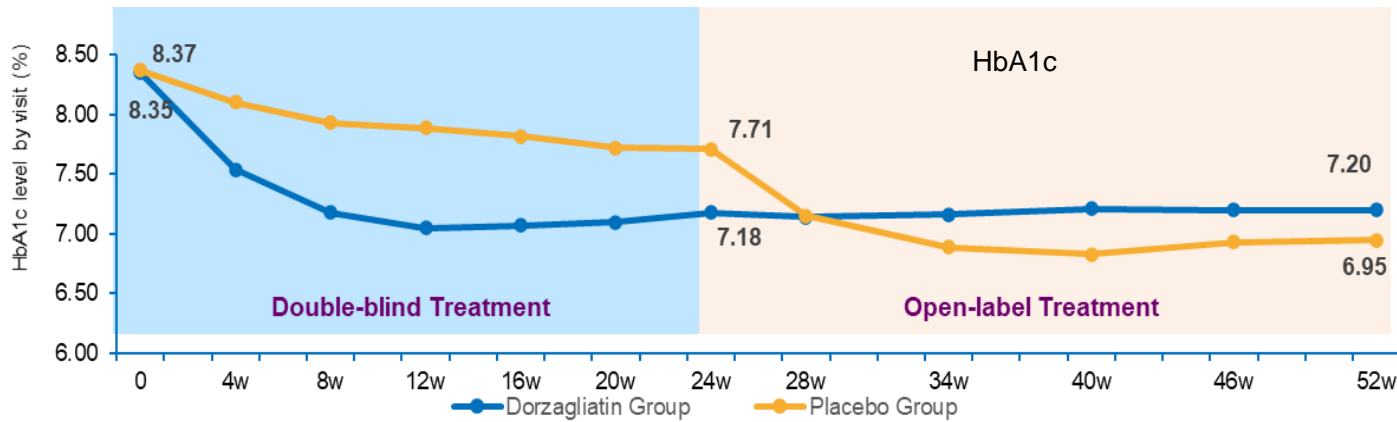
Primary endpoint of HbA1c reduction of 0.4% over placebo, p-value < 0.05

ACHIEVED FOR BOTH SEED AND DAWN STUDIES AT 24-WEEK

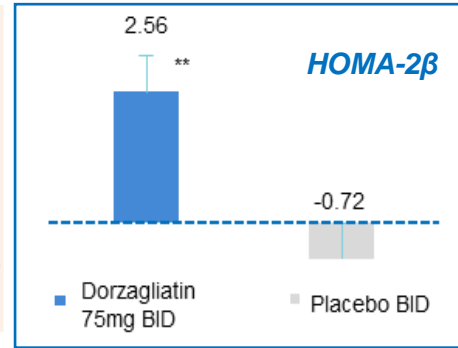
Dorzagliatin Phase III Results: SEED and DAWN Significantly improve β -cell function and reduce insulin resistance



SEED HMM0301

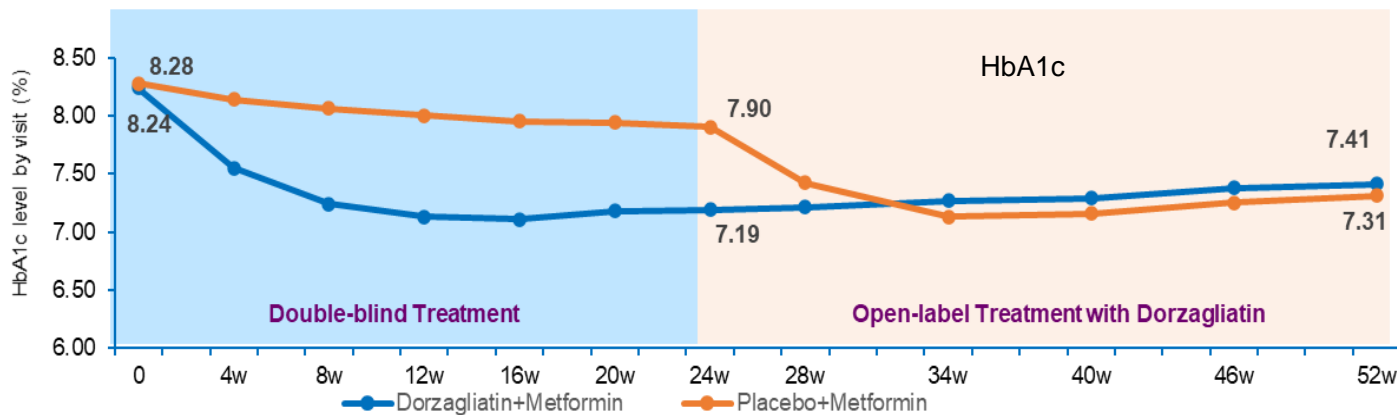


Significantly improve β -cell function at week 24

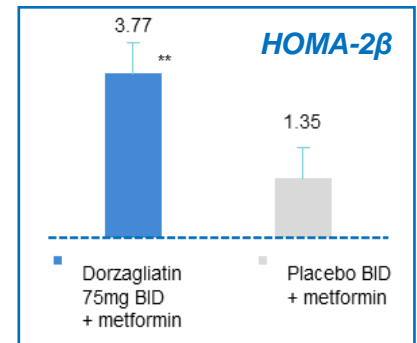


Change from Baseline to Week 24

DAWN HMM0302



Significantly improve β -cell function at week 24



Change from Baseline to Week 24

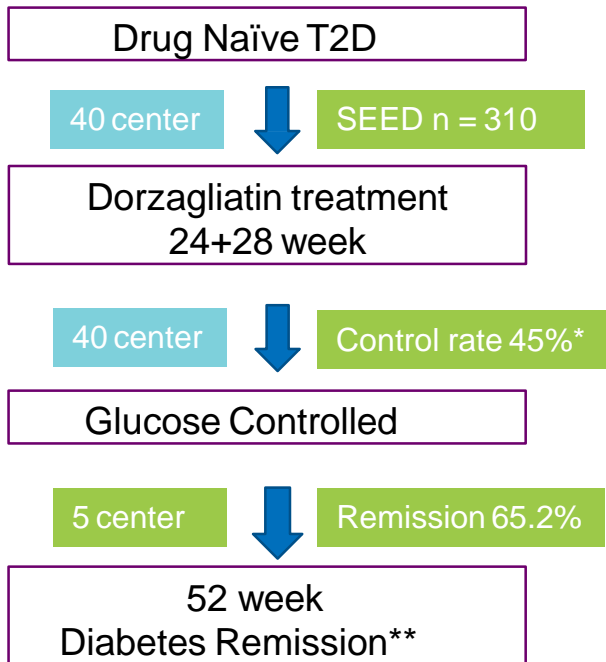
DoRzagliatin Effect in DiAbetes ReMission



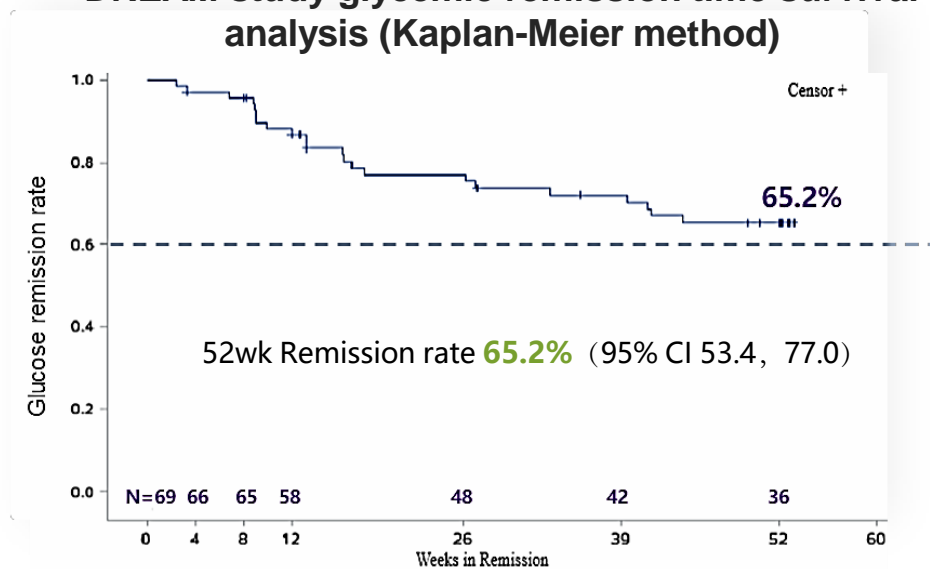
DREAM Study

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



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



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

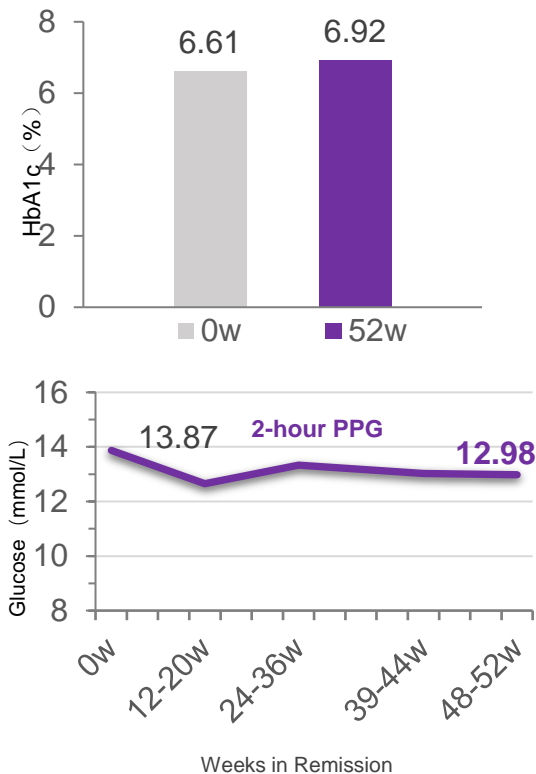
** Based on the 2021 "Expert Consensus on Diabetes Remission" (HbA1c lasting less than 6.5% within 3 months without medication), survival analysis showed that the remission rate at 12 weeks was **52.0%** (95% CI 31.2%, 69.2%)

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

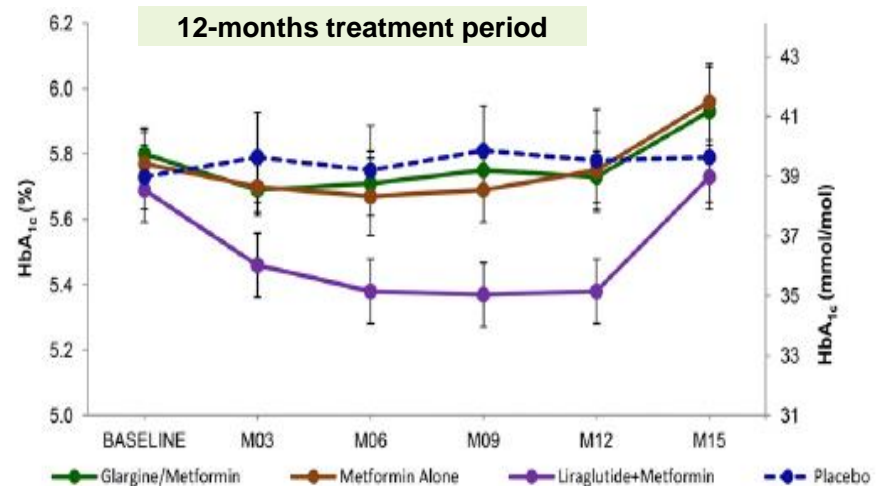


Lack of Durable Improvements in β -Cell Function Following Withdrawal of Pharmacological Interventions in Adults With Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes

The RISE Consortium*
Diabetes Care 2019 Jun; dc190556.
<https://doi.org/10.2337/dc19-0556>



RISE: Elevated HbA1c after the drug discontinuation for 3 months



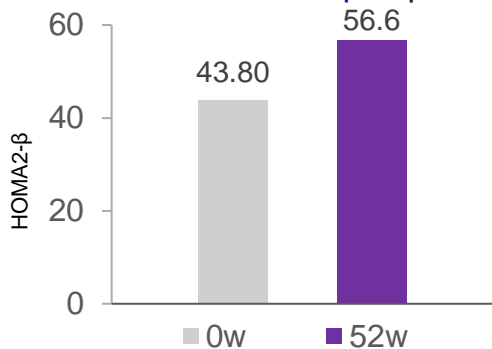
Other Type 2 Diabetes drugs have failed in demonstrating remission (cont'd)



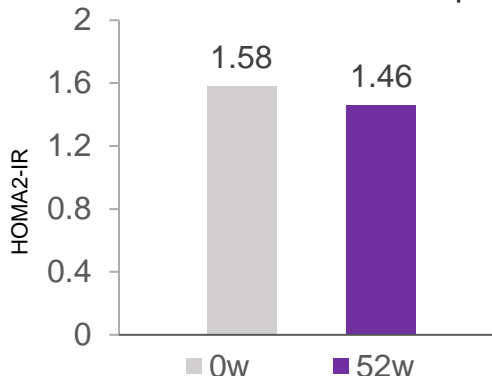
Unlike dorzagliatin which demonstrated sustained beta cell function and reduced insulin resistance over a 52-week period, other anti-diabetes drugs in RISE failed to show sustained effect after 3 months

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

Insulin secretion index **HOMA2- β** comparison



Insulin resistance index **HOMA2-IR** comparison

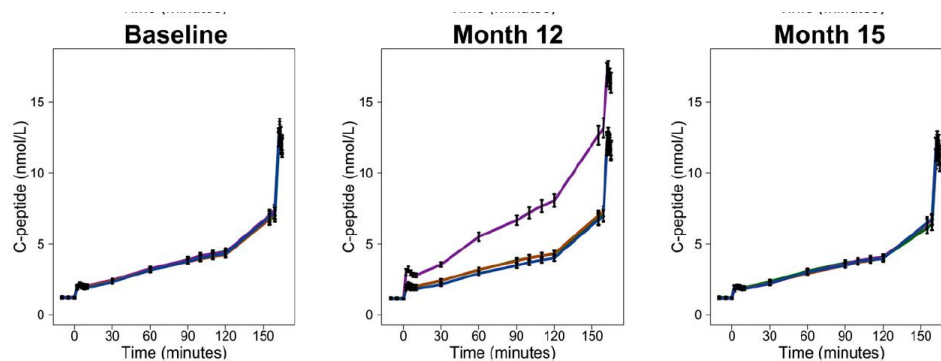


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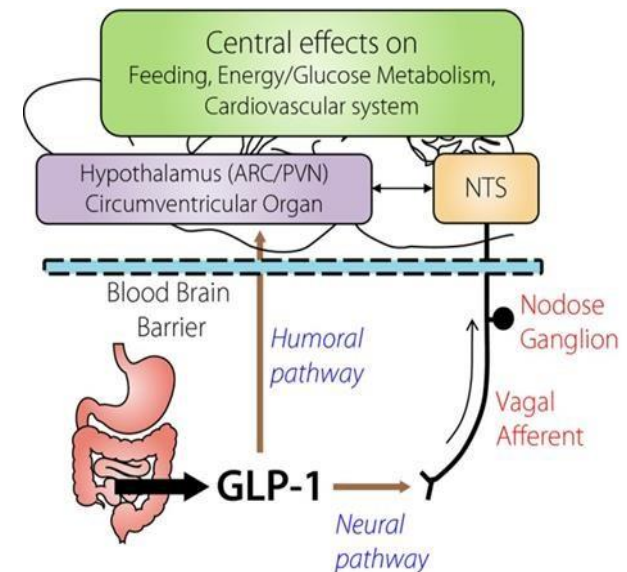
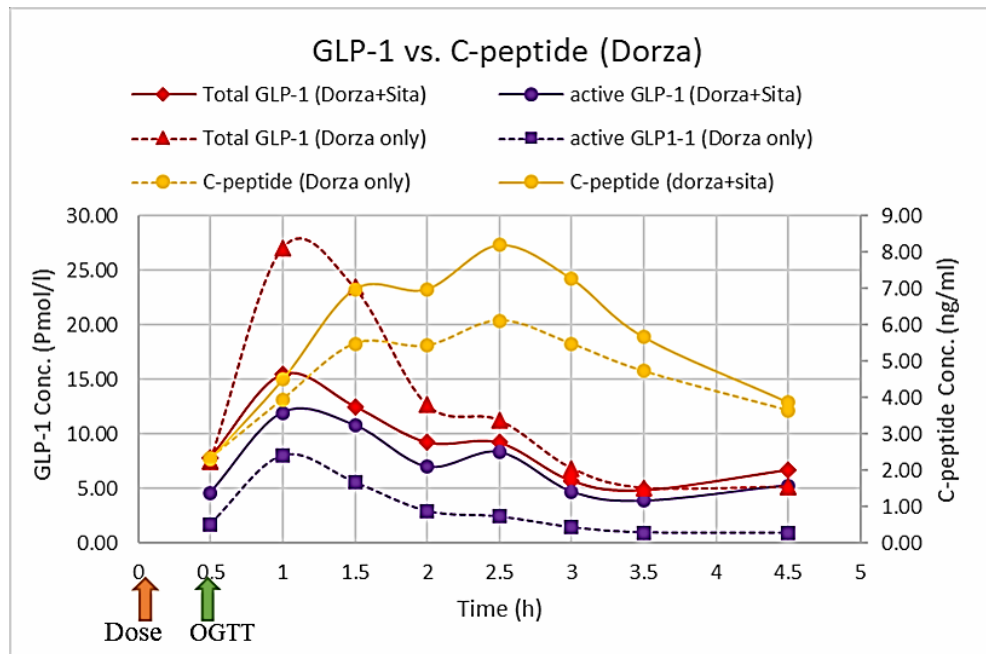
RISE: no sustained improvements in b-cell function in any treatment group after drug discontinuation for 3 months



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)

SEED-DREAM (China)

Glucose sensitizer therapy study



Before treatment of Dorzagliatin characteristics

03

Newly diagnosed untreated patients*

- Newly diagnosed untreated patients*
- BMI 25kg/m²、126/78mmHg
- HbA1c 8.1%、FPG 8.9mmol/L、2hPPG 16.8mmol/L
- **HOMA-β 19.9**、HOMA-IR 2.2

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/m²**
- SBP/DBP 133/85mmHg
- HbA1c 7.7%、FPG 9.2mmol/L

Intensive insulin therapy study (China)



02

Newly diagnosed untreated patients*

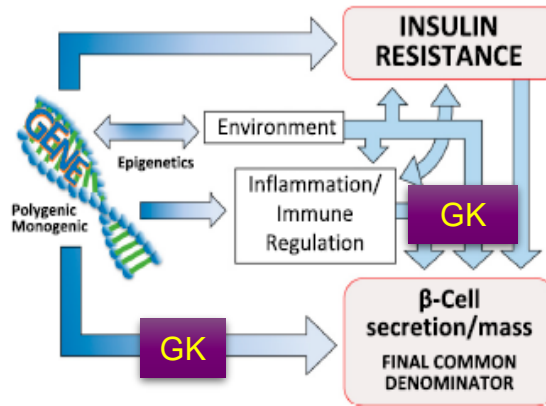
- Newly diagnosed untreated patients*
- BMI 25.5kg/m²
- **HbA1c 9.7%**、FPG 9.5mmol/L、2hPPG 17.5mmol/L
- HOMA-β 33.6、**HOMA-IR 6.0**

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

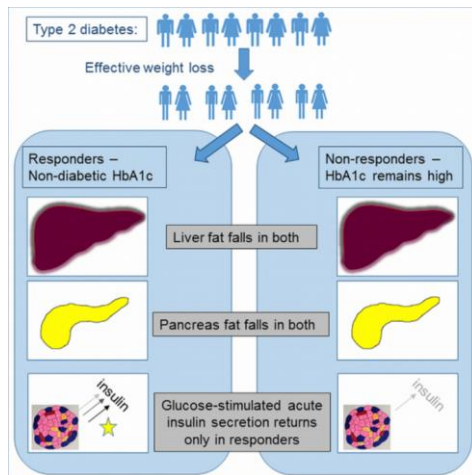
Loss of GSIS function in beta cells is the root cause of T2D

Glucokinase GK plays central rule in diabetes remission



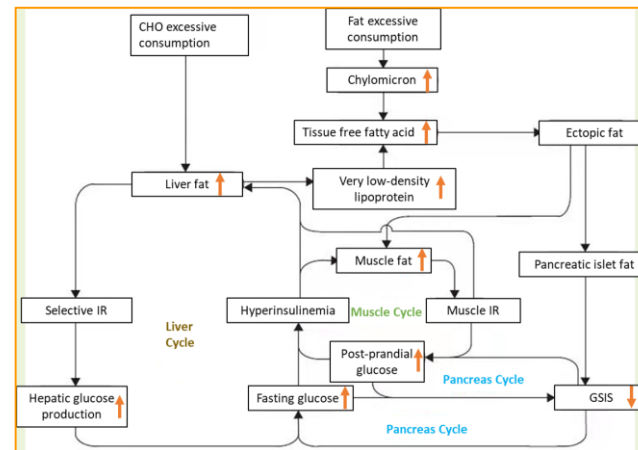
- The root cause of diabetes is the loss of beta cell Glucose Stimulated Insulin Secretion (GSIS) function that is regulated by Glucokinase GK
- Genetic, epigenetic, autoimmunity and insulin resistance with obesity have impact on GK expression and function
Stanley Schwartz. Diabetes Care 2016, 39(2): 179-186
Franz Matschinsky Frontiers in Physiology 2019, 10:148

Dual cycle hypothesis by UK KOL in T2D remission



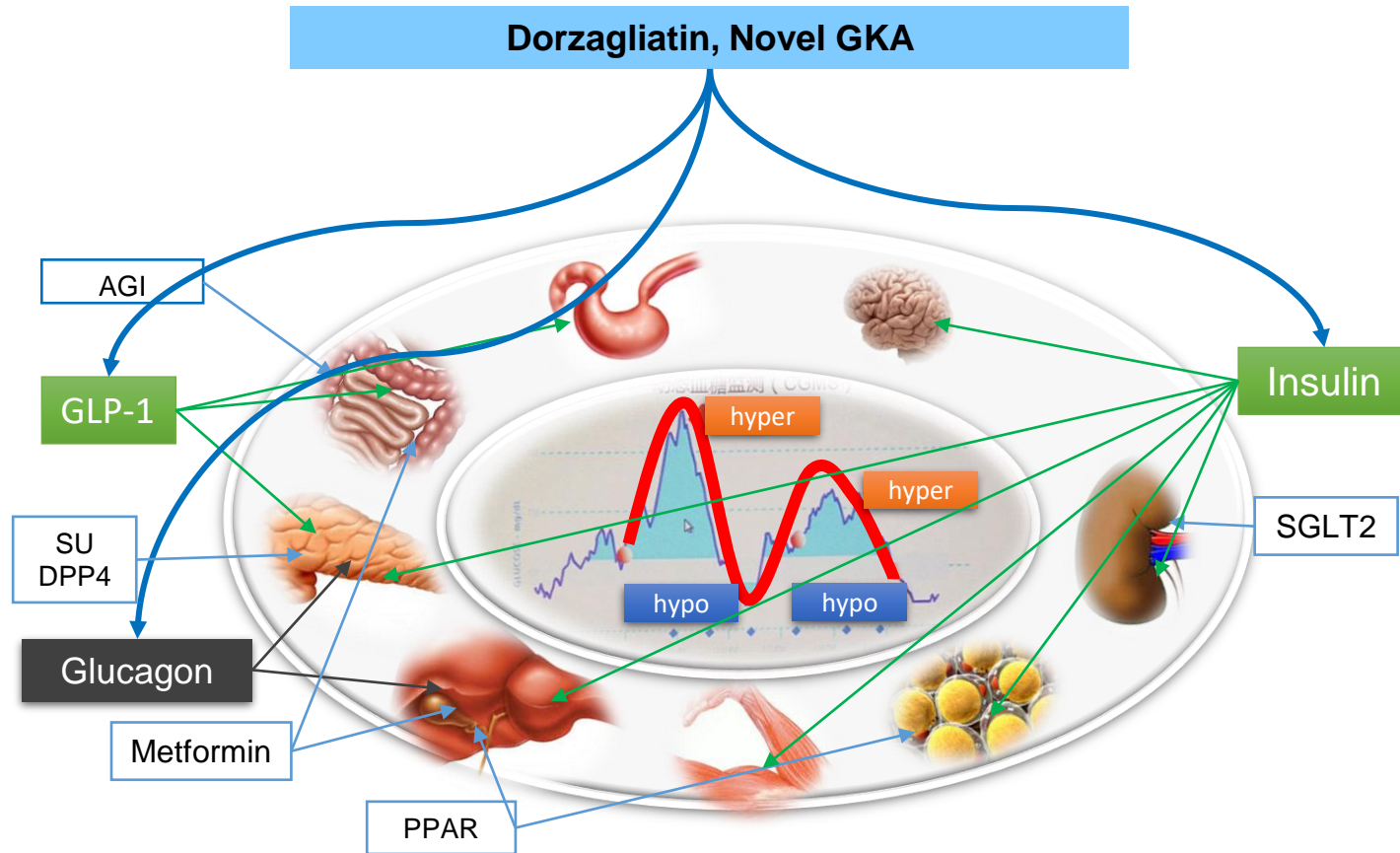
- Return to non-diabetic glucose control depends upon β cell ability recover

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

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

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

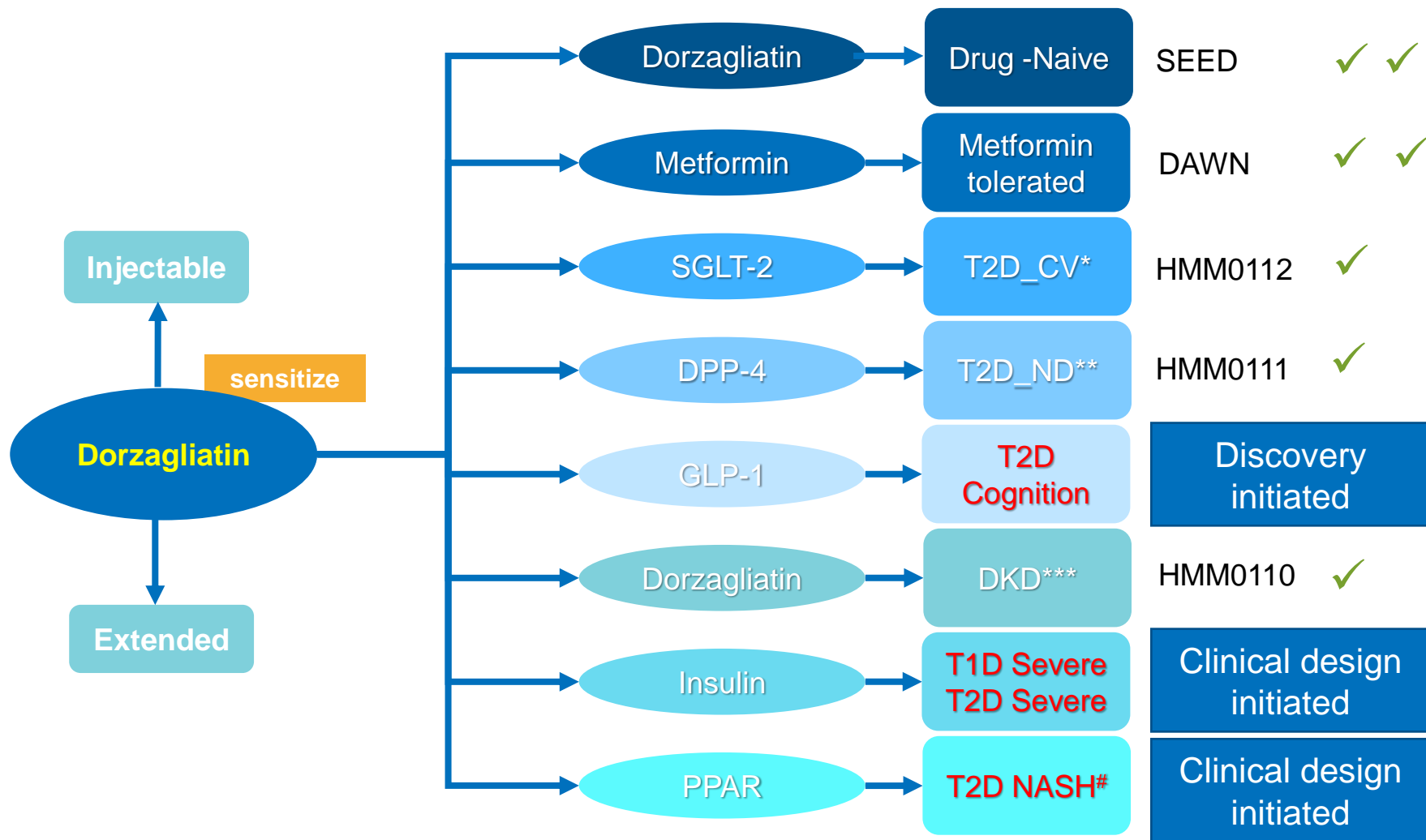


Hua Medicine selected as only Healthcare Company representative to Pudong Celebration hosted by President Xi Jinping in 12 November, 2020



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	Pre-clinical	IND	Phase I	Phase II	Phase III	NDA
Dorzagliatin HMS5552	T2D	NDA Filed (China)						
	DKD	Phase I enabling						
	T1D	IND-enabling						
HMSFDC 6857 Dorzagliatin + Metformin	T2D	Phase I ready						
HMSFDC 6868 Dorzagliatin +Sitagliptin	T2D	Phase I ready						
	Insulin Sparing	IND-enabling						
HMSFDC 5868 Dorzagliatin +Empagliflozin	T2D CVR	Phase I ready						
HMSFDC 5688 Dorzagliatin +pioglitazone	NASH	IND-enabling						
HMS 5678 Dorzagliatin + GLP-1	Alzheimer Disease	IND-enabling						
HMS 6789 Dorzagliatin + Insulin	Late Stage T2D Insulin sparing	Ph III Design						
mGLUR5 NAM	PD-L1D	Pre-clinical						
Fructose Kinase Inhibitor	Metabolic Disease	Pre-clinical						



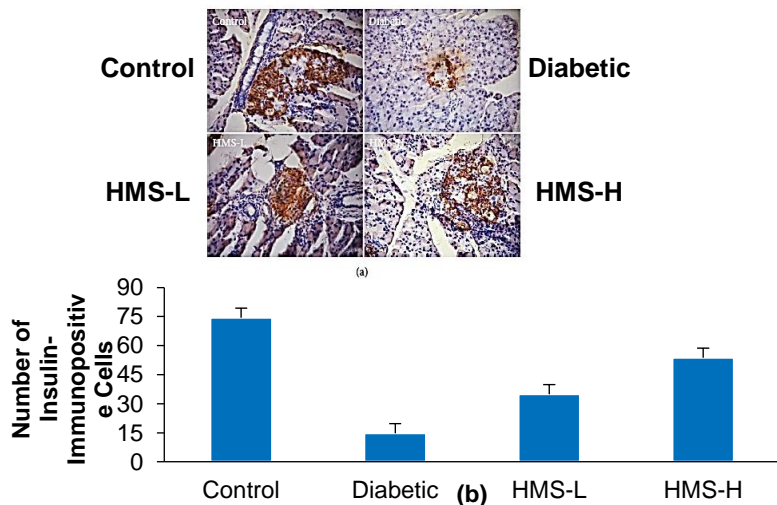
Extensive Supporting Data for Dorzagliatin

Dorzagliatin Has the Potential to Repair the Glucokinase Glucose Sensor



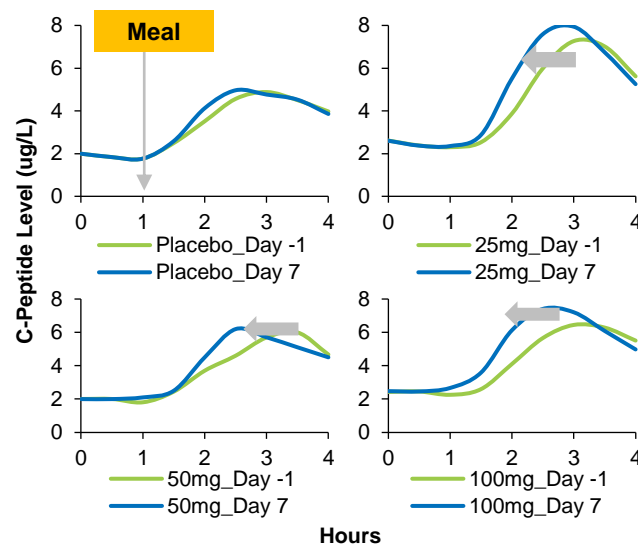
Type 2 Diabetes Rat Pancreas

Pre-clinical



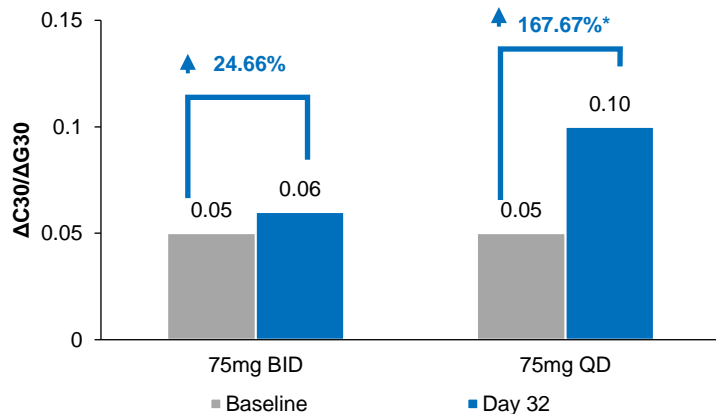
T2D Patient Early-stage insulin release

Phase Ib



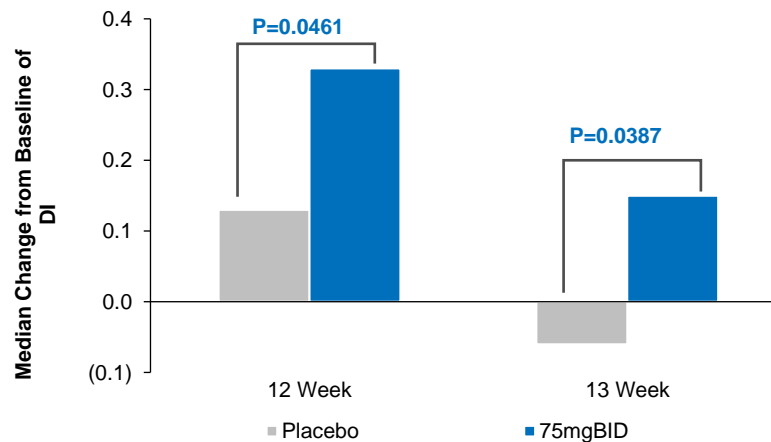
T2D Patient Early Insulinogenic index

Phase Ic



T2D Patients Disposition Index

Phase II

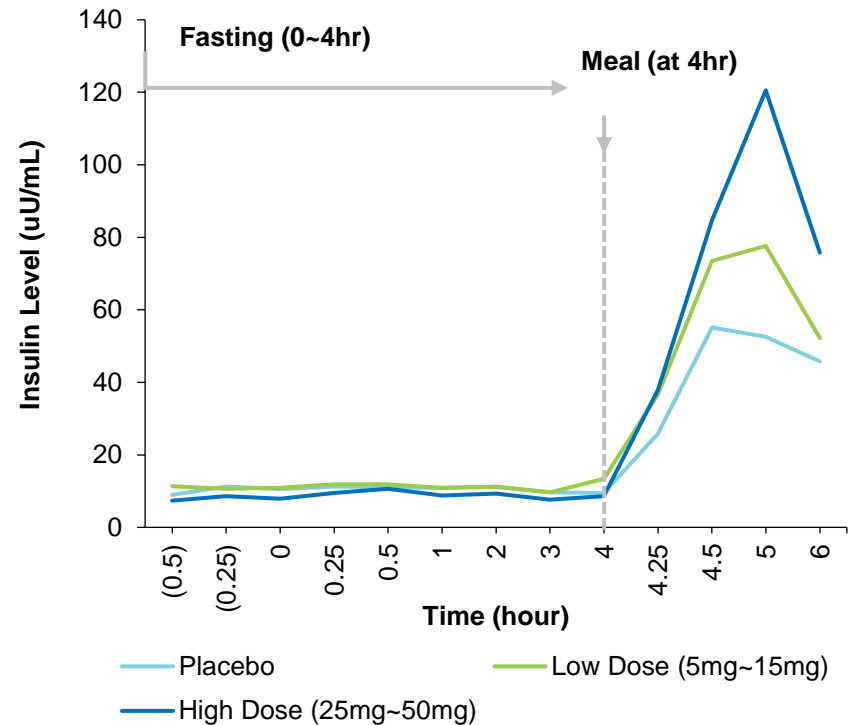
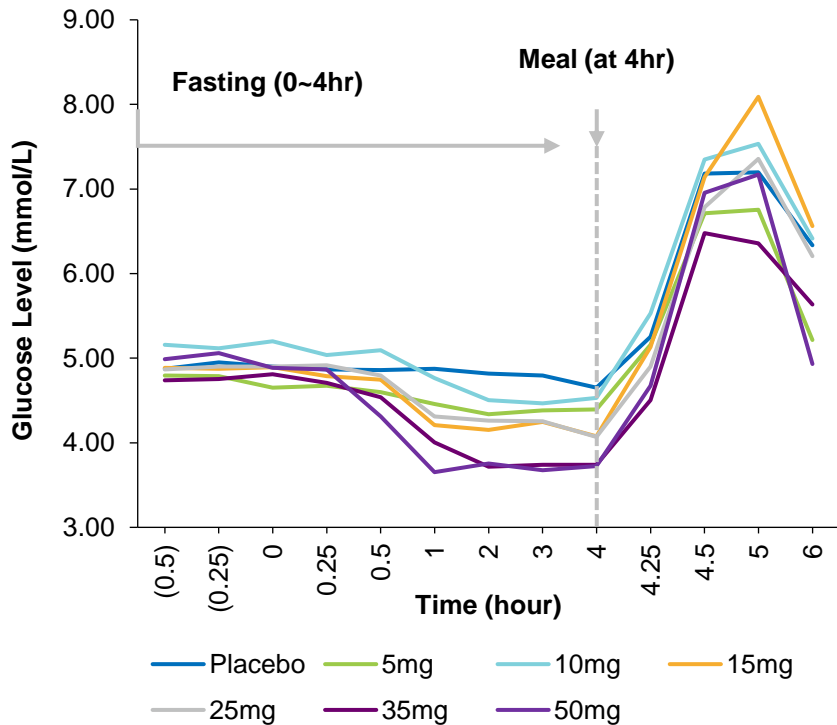


Dorzagliatin Modulates GK Glucose Sensor Function as a Glucose Sensitizer



HMM0101

- Phase Ia trial targeted healthy adults in China with a single ascending dose (SAD)
- Patients were fasted over night and having HMS552 next morning at time hr 0, continued fasting till hr 4 when meal is given



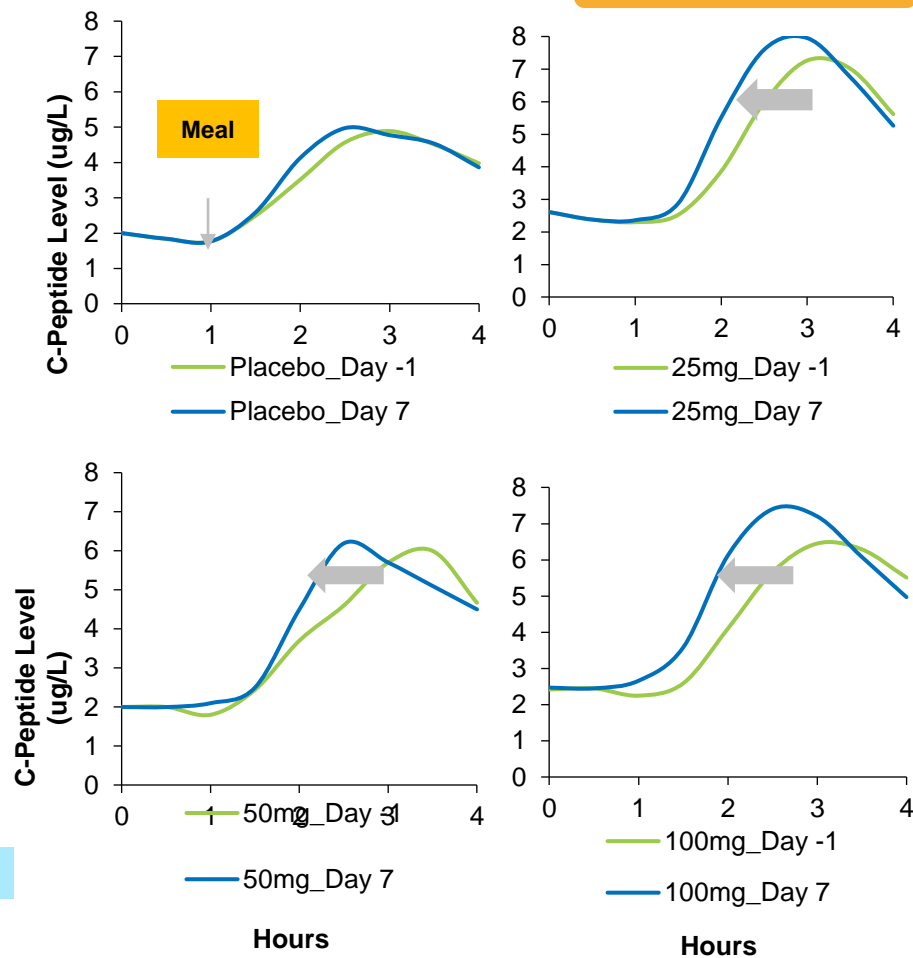
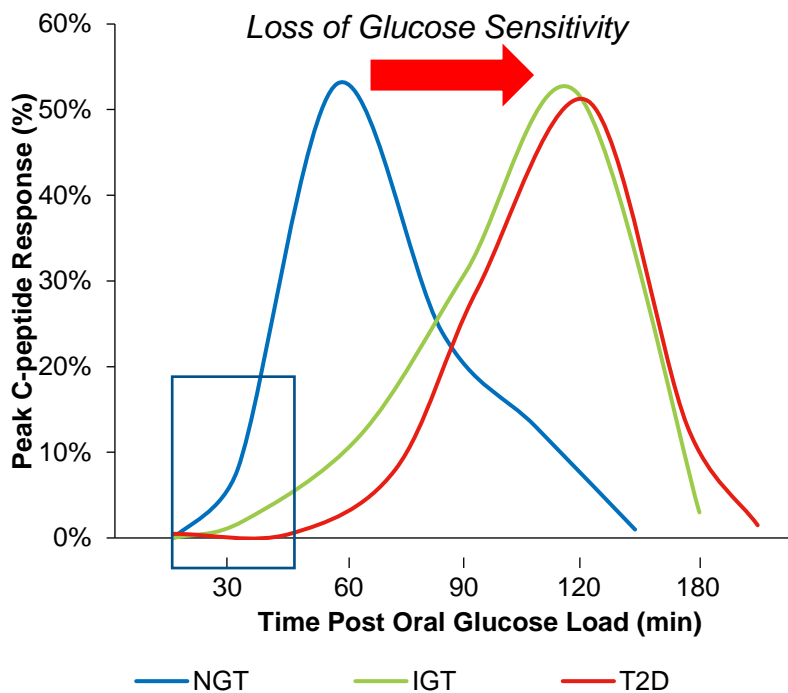
- Dose dependent reductions in fasting plasma glucose without increases in insulin secretion**
- Reduce hepatic glucose output by Dorzagliatin**
- Glucose stimulated Insulin release (GSIR) is enhanced by Dorzagliatin**

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

Dorzagliatin Resets the Thresholds in T2D Patients with Improved Glucose Sensitivity



HMM0102



■ Impaired threshold of GSIR in IGT and T2D patients

■ 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

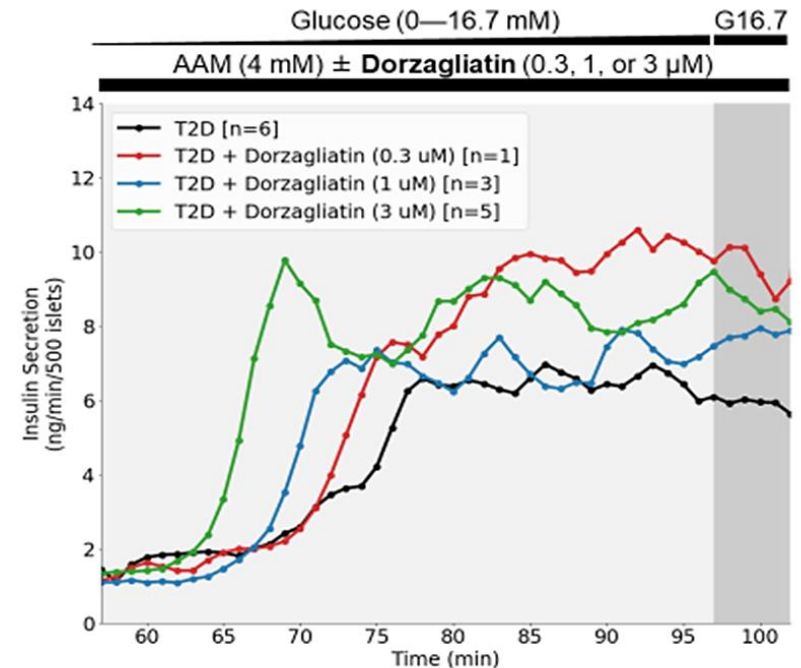


- Dorzagliatin is a novel dual acting full glucokinase allosteric activator that re-models the glucose set point and improves glucose sensitivity in type 2 diabetes patients
- Acts on: glucose sensor GK in pancreas, liver and intestine organs
- Improve glucose dependent insulin, glucagon and GLP-1 secretion 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

AI application for Systematic Diabetes Care

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

Dorzagliatin Improves beta Cell Secretion Function in T2D



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

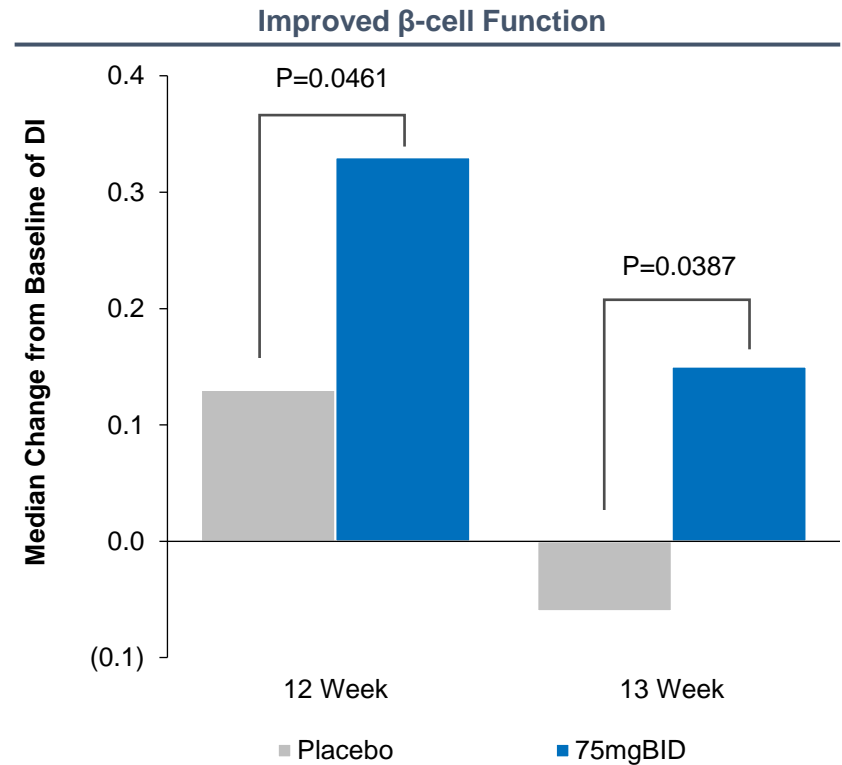
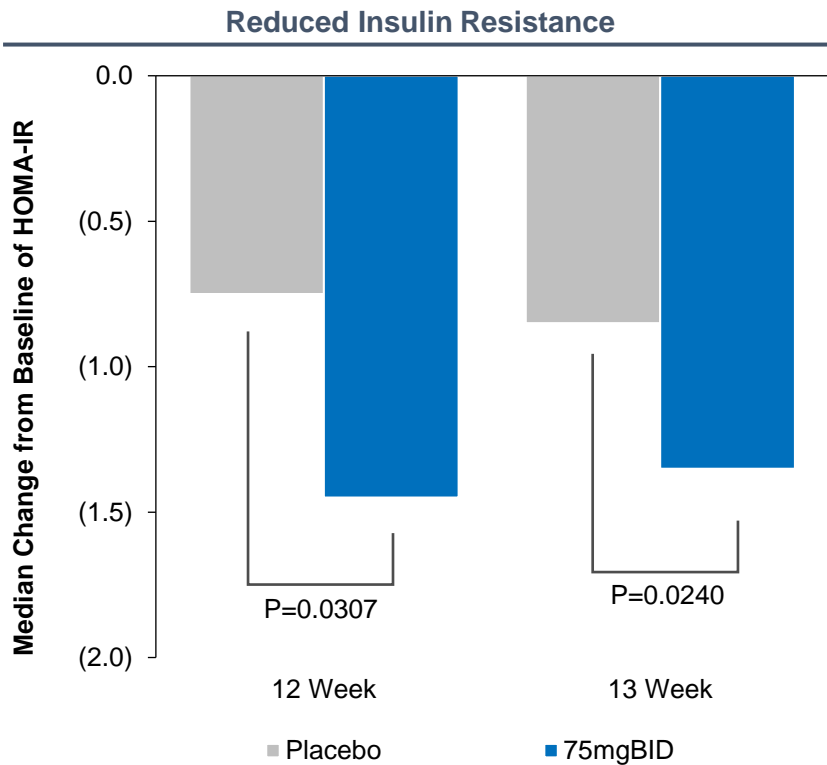


HMM0201

Chinese drug naive Type 2 diabetes patients 3 month treatment



Improves pancreatic β -cell function
Reduces insulin resistance



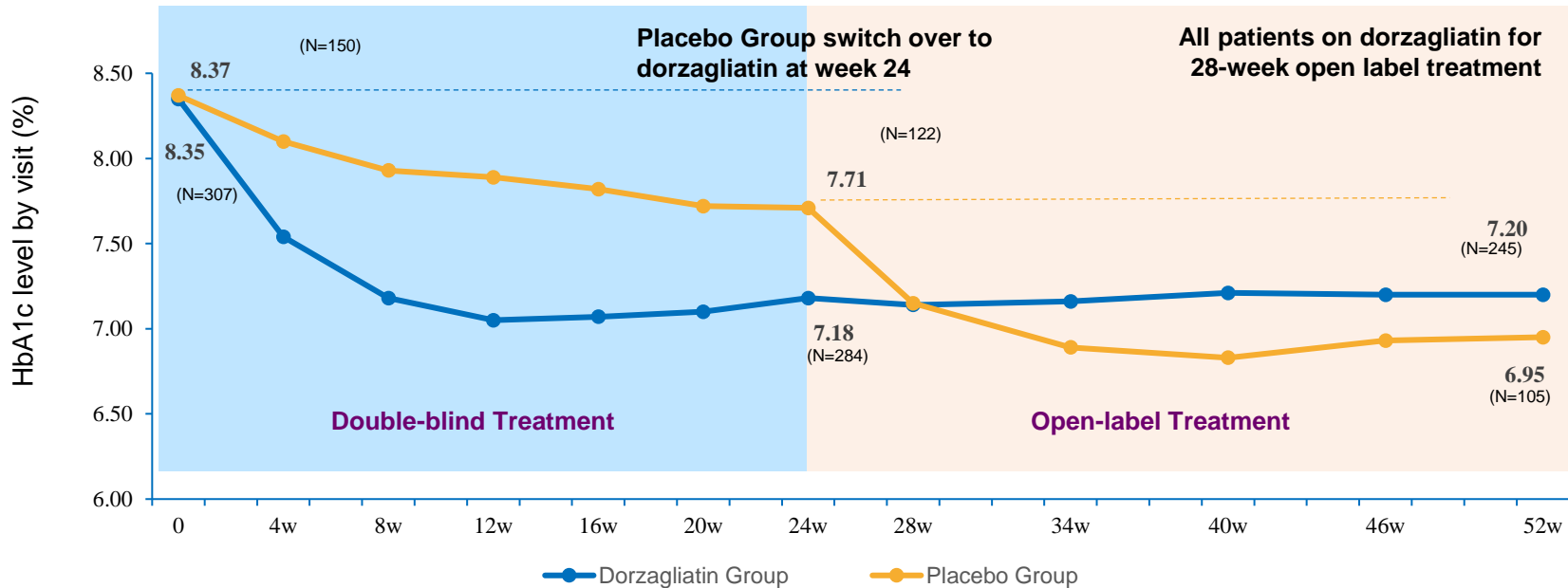
One week after the conclusion of the trial, patients continue to see sustained effect in the HOMA-IR and Disposition Index

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

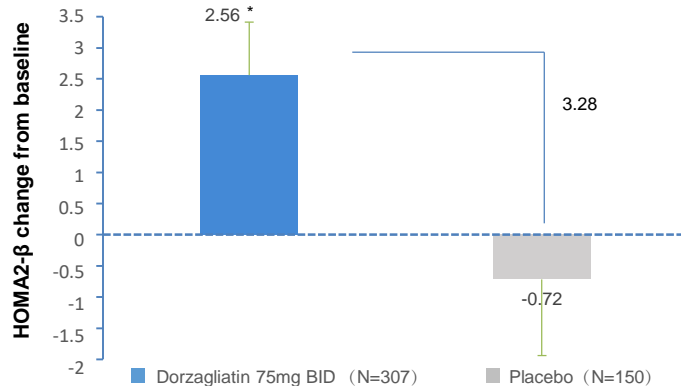
SEED Phase III 24-WEEK Secondary Results + Safety Results — Presented at ADA



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.

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

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

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.

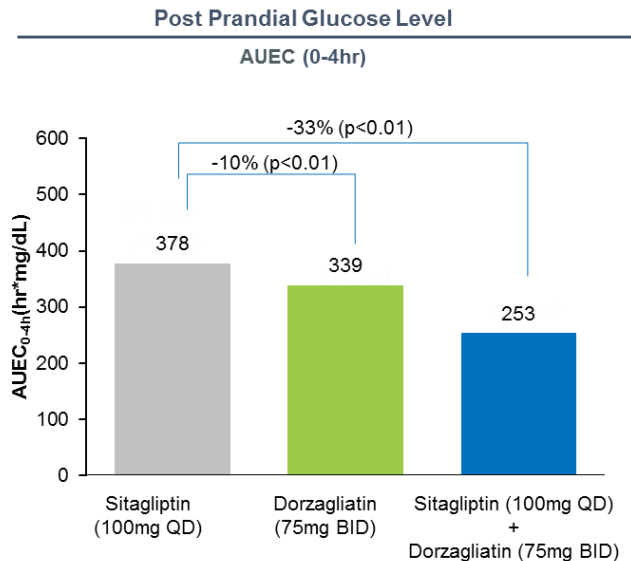
Conclusion:

- 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

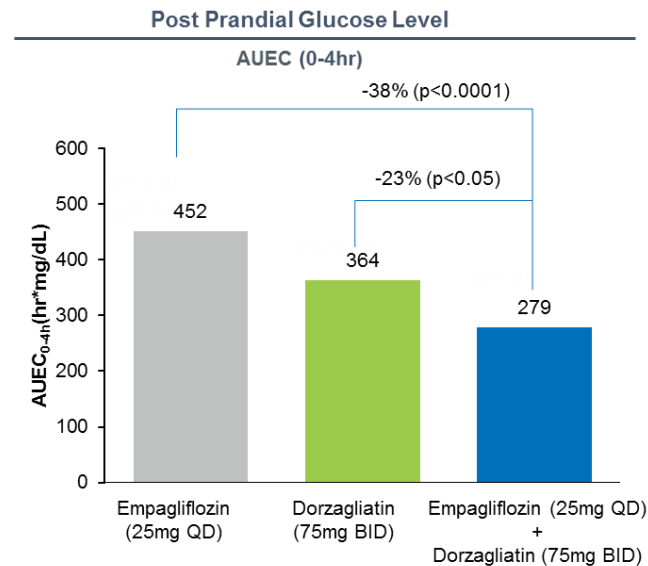


- No drug-drug interaction observed in Phase I trials in USA with sitagliptin (DPP-4 inhibitor) and empagliflozin (SGLT-2 inhibitor)
- **Significant synergies demonstrated in glycemic control and improvement of beta cell function**
 - Data demonstrating dorzagliatin stimulates GLP-1 release in T2D patients, 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:

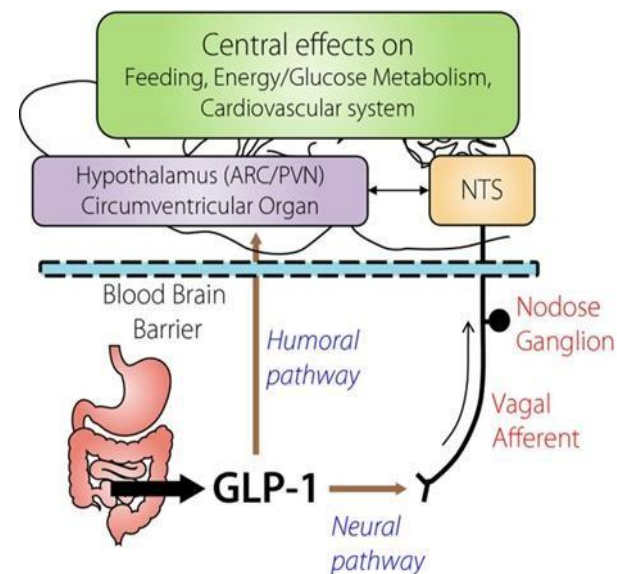
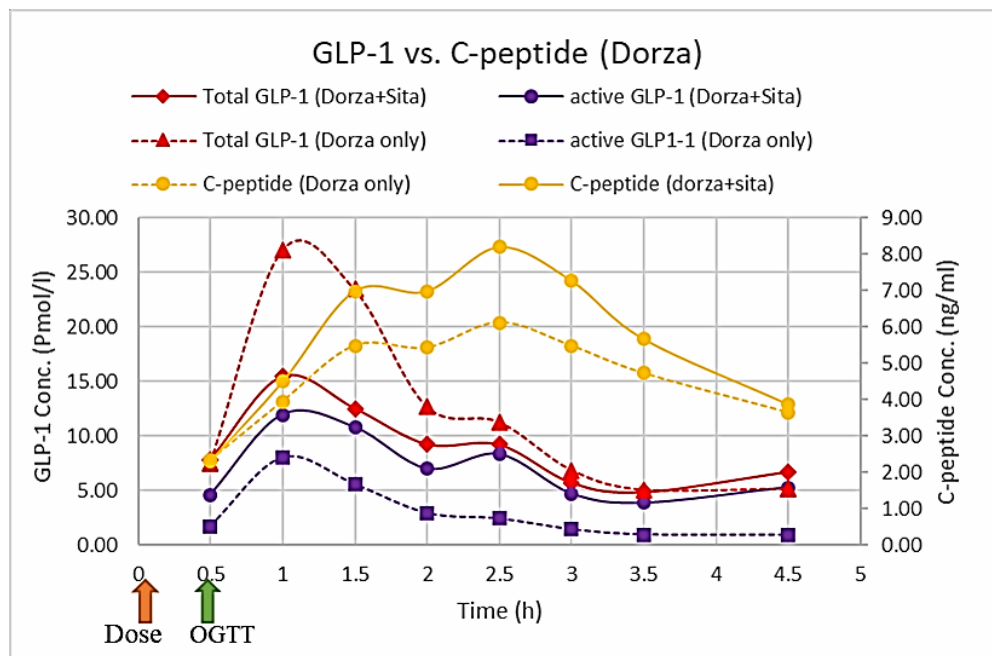
- ✓ Fastest growing among OAD with US\$ 6B global sales in 2019 and ~24% yoy growth

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



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



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



Jin She, Ph.D.
VP, Chemistry CMC



FuxingTang, Ph.D.
VP, CTO, Chemistry CMC



Yilei Fu, BS, MBA
VP, Quality Assurance



Wenjie Xu, BS, MBA
VP, Commercial Strategy and Marketing



Di Hong, DBA
VP, Operations



A Blue Chip Board



Chairman
Robert Nelsen



Walter Kwauk



Li Chen



William Keller



Lian Yong Chen



FIL Capital
Management (Hong Kong)

Junling Liu



George Lin



O'Melveny

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

