Hua Medicine
华领医药

2022 Interim Results Presentation

August 2022

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Company Overview

Hua Medicine: A Roadmap to Global First-In-Class

- **June 2010:** Dr. Li Chen served as CEO
- **June 2011:** Hua Medicine (Shanghai) Ltd. established, initiates R&D operations
- **Feb. 2012:** Initiated glucokinase activator (GKA) program
- **Sep. 2012:** Submitted IND, initiated Phase I clinical study in China in September 2013
- **Sep. 2016:** Successfully completed Phase II clinical trial; validates the scientific concept of dorzagliatin in the treatment of T2D
- **Sep. 2018:** IPO on HKEX
- **Aug. 2020:** Signed commercialization agreement and strategic partnership with Bayer for investigational first-in-class novel diabetes treatment dorzagliatin in China
- **Sep. 2020:** Successfully completed Phase III trials: SEED and DAWN
- **Apr. 2021:** NDA for dorzagliatin for the treatment of T2D was accepted by the China NMPA
- **Feb. 2021:** Shanghai Hua Medicine Biotechnology Ltd. established
- **June 2021:** Presentation at 2021 ADA: dorzagliatin can regulate GLP-1 release in T2D patients
- **Sep. 2021:** Signed a supply chain strategic cooperation agreement with Sinopharm
- **Sep. 2021:** Announced positive results for DREAM study: remission rate reached 65.2% within 1 year after drug withdrawal
- **Feb. 2022:** Announced supply agreement with WuXi STA for commercial manufacturing of dorzagliatin
- **May 2022:** Published two peer-reviewed papers in *Nature Medicine* on the results of the Phase III trials of dorzagliatin
- **June 2022**: 2022 ADA conference 3 presentations on DREAM, SENSITIZE, and IGI of Dorzagliatin

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

George Lin J.D
EVP, CFO

Bank of America Merrill Lynch · Credit Suisse

Yi Zhang, Ph.D., MD
SVP, Pharma Development, Chief Medical Officer

Roche

Jin She, Ph.D.
SVP, CMC Chief Manufacture Officer,

Roche · MSD

FuxingTang, Ph.D.
President Hua USA, CTO

Forest Laboratories, Inc. · Allergan

Yilei Fu, BS, MBA
SVP, Quality Assurance Chief Quality Officer

Di Hong, DBA
VP, Corp Alliance and Operation

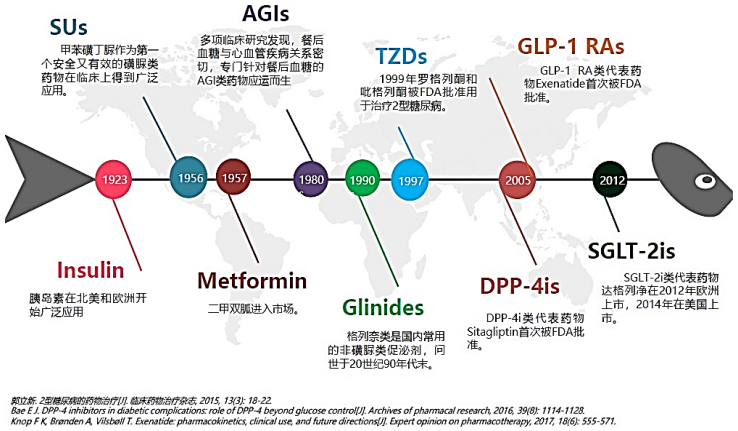
Roche · Lilly · AMGEN

Qing Dong, BP
VP, Pharmaceutical Commercialization

Bayer · Gilead

Global Unmet Medical Needs in Glycemic Control

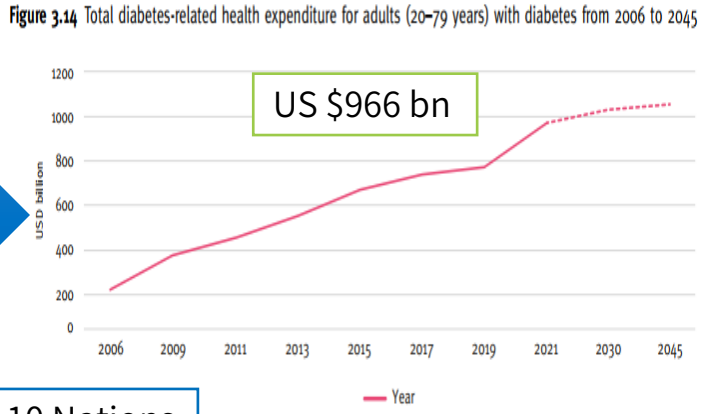
9 Classes of Drugs



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

IDF 2021

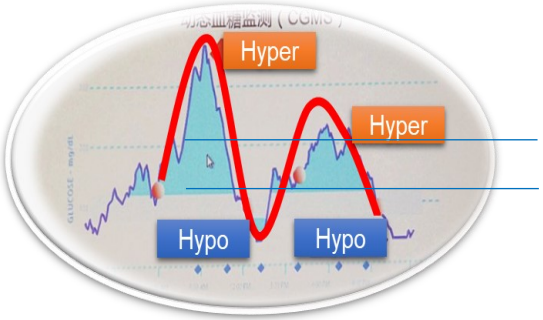
537 Mn Diabetes
Many
Complications



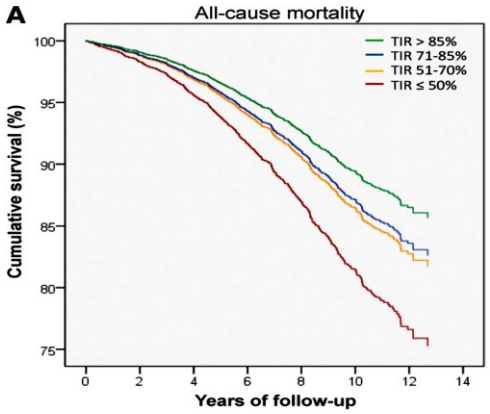
Top 10 Nations

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

Economic Burden



Lost Glucose Homeostasis

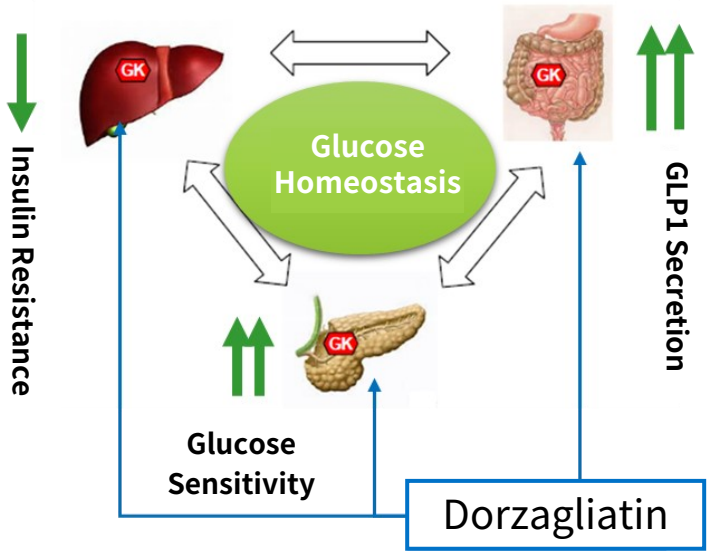


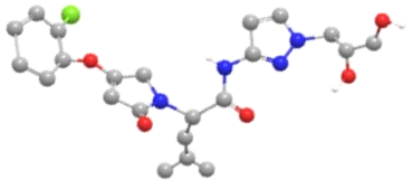
TIR in Diabetes Survival

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

Dorzagliatin – A Differentiated First-In-Class Antidiabetic Drug Advance Diabetes Care Globally

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





Dorzagliatin improves glucose sensitivity and beta cell function as novel mechanism to treat diabetes

- In clinical trials - Dorzagliatin improves β-cell function in T2D in China, and repairs GLP-1 secretion in obese T2D patients in US
- Phase 3 SEED, DAWN studies demonstrated the potential for best homeostasis control for drug naïve and metformin-tolerant T2D patients in China
- Diabetes remission achieved in Dorzagliatin treated drug naïveT2D patients in the DREAM study

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

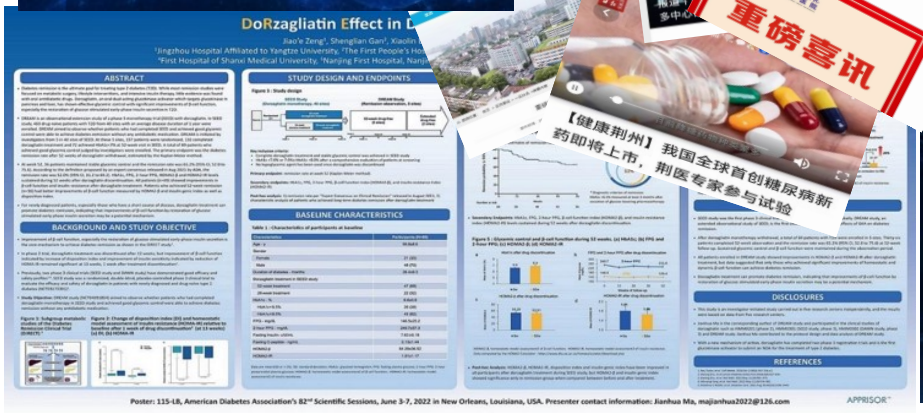
SEED and DAWN Results on Nature Medicine

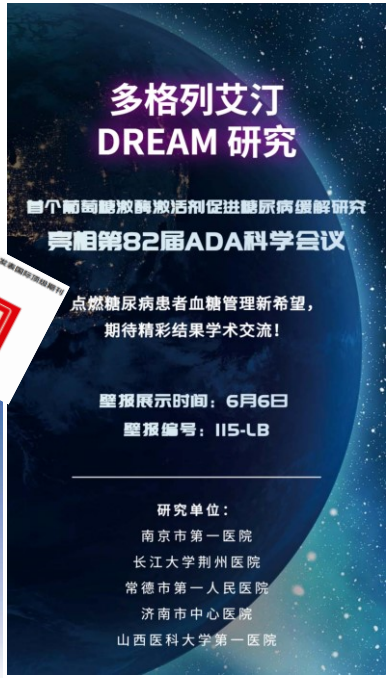
- President Dalong Zhu, Ex-President Wenying Yang of Chinese Diabetes Society led SEED and DAWN studies and as 1st authors in back-to-back Nature Medicine (2021 IF: 87.24) on 12th May 2022
- Dr John Buse, former ADA president: A New Class of Drug in Diabetes Toolbox (NMED)
- The news of SEED and DAWN publication in NM were reported or forwarded by multiple media. In particular, it was reported 6 times in 3 days by relevant platforms of the mainstream media People ‘s Daily (人民日报).

序号	人民日报平台	标题
1	人民日报 健康客户端	荣登顶刊！中国原研全球首创降糖药新成果来了
2		人民端学术频道首页推荐位 历时10年！我国原研全球首创糖尿病新药登上顶刊
3		中国原创糖尿病新药研究成果登上《自然-医学》
4		人民端首页推荐位第一条 多格列艾汀III期结果发布：为2型糖尿病治疗提供新靶点
5	今日头条 人民康养	朱大龙教授学术论文登上国际顶级医学期刊《自然-医学》
6	微博人民康养	喜讯！南京鼓楼医院朱大龙教授学术论文登上国际顶级医学期刊《自然-医学》

Connect with Medical and Academic Community

- Dorzagliatin Nature Medicine Symposium was held on 13th May. In particular, Prof. Kaixian Chen, Prof. Zhiyi He and Prof. Xiaoming Zhu as the industry leader recognized Dorzagliatin as a break through in GKA drug development and a major achievement in China drug discovery.
- Leading KOLs in Dorzagliatin, Prof Dalong Zhu, Wenying Yang and Xiaoying Li presented discovery stories
- SEED and DAWN Publication Sharing meeting with 80 Co-Authors on 28th May
- DREAM Presentation shared with investigators at 5 clinical sites on 5th June.





Dorzagliatin Improves Beta-Cell Function
Clinical Expert Opinions

- Dorzagliatin has been included into a new Expert Opinions on <Evaluation and Protection of beta cell Function in T2D Patients> published on 20th June. The latest SEED and DAWN results and publications were sited in the Opinions.
- Dorzagliatin rescues insulin secretion in rat beta cell, and improves HOMA2-b in type 2 diabetes patients either drug naïve or metformin tolerated.

中华糖尿病杂志 2022 年 6 月第 14 卷第 6 期 Chin J Diabetes Mellitus, June 2022, Vol. 14, No. 6 · 533 ·

·规范与指南·

2型糖尿病胰岛β细胞功能评估与保护临床专家共识

中华医学会糖尿病学分会胰岛β细胞学组 江苏省医学会内分泌学分会
通信作者：马建华，南京医科大学附属南京医院 南京市第一医院内分泌科，南京 210012，Email：majianhua@china.com；朱大龙，南京大学医学院附属鼓楼医院内分泌科，南京 210008，Email：zhudalong@nju.edu.cn；母义明，解放军总医院第一医学中心内分泌科，北京 100853，Email：muyiming@301hospital.com.cn

【摘要】 胰岛β细胞功能缺陷是2型糖尿病的基本病理生理学特征之一，正确评估胰岛β细胞功能对于糖尿病的诊断分型和治疗具有重要价值，保护胰岛β细胞功能对于延缓2型糖尿病进展具有重要的临床意义。因此，中华医学会糖尿病学分会胰岛β细胞学组、江苏省医学会内分泌学分会组织专家撰写了《2型糖尿病胰岛β细胞功能评估与保护临床专家共识》。本共识提出临床上可以通过基于血糖的方法简单评估，或结合血糖、内源性胰岛素、C肽检测的方法评估胰岛β细胞功能；强调通过减轻体重、及早干预并持久平稳控制血糖等代谢指标均可有效保护胰岛β细胞功能，部分药物还可能具有降糖之外的改善胰岛β细胞功能的作用。

【关键词】 胰岛； β细胞； 功能评估； 减轻体重； 胰岛素强化治疗； 专家共识

4. 葡萄糖激酶激活剂（glucokinase activator，GKA）：GKA多格列艾汀可通过葡萄糖浓度依赖性地促进胰岛素分泌、抑制胰高糖素释放、促进GLP-1分泌和肝糖原合成，维持人体血糖稳态。除了降糖作用外，动物实验还显示多格列艾汀可以显著提升胰岛素阳性细胞数量，修复胰岛β细胞功能[75]。小样本的探索性研究显示，T2DM患者接受多格列艾汀治疗28 d后，HOMA-β较基线提高36.31%~40.59%，C肽30 min分泌功能动态参数提升24.66%~167.67%[76]。随机对照试验显示，多格列艾汀可显著改善患者的葡萄糖处置指数和稳态模型评估胰岛素抵抗指数（homeostasis model assessment insulin resistance，HOMA-IR）[77]。2项注册3期试验显示，对于初治T2DM患者或二甲双胍足量稳定治疗仍血糖控制不佳的T2DM患者，多格列艾汀可显著改善新的稳态模型评估胰岛β细胞功能指数（HOMA2-β）[78-79]。

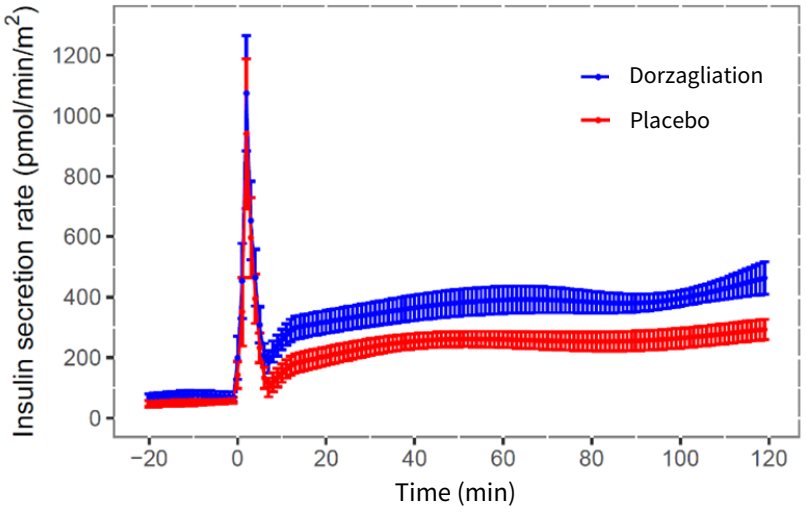
[75] Wang P, Liu H, Chen L, et al. Effects of a novel glucokinase activator, HMS5552, on glucose metabolism in a rat model of type 2 diabetes mellitus[J]. J Diabetes Res, 2017, 2017: 5812607. DOI: 10.1155/2017/5812607.
[76] Zhu XX, Zhu DL, Li XY, et al. Dorzagliatin (HMS5552), a novel dual-acting glucokinase activator, improves glycaemic control and pancreatic β-cell function in patients with type 2 diabetes: a 28-day treatment study using biomarker-guided patient selection[J]. Diabetes Obes Metab, 2018, 20(9): 2113-2120. DOI: 10.1111/dom.13338.
[77] Zhu D, Gan S, Liu Y, et al. Dorzagliatin monotherapy in Chinese patients with type 2 diabetes: a dose-ranging, randomised, double-blind, placebo-controlled, phase 2 study[J]. Lancet Diabetes Endocrinol, 2018, 6(8):627-636. DOI: 10.1016/S2213-8587(18)30105-0.
[78] Zhu D, Li X, Ma J, et al. Dorzagliatin in drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 3 trial[J]. Nat Med, 2022,28(5): 965-973. DOI: 10.1038/s41591-022-01802-6.
[79] Yang W, Zhu D, Gan S, et al. Dorzagliatin add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 3 trial[J]. Nat Med, 2022, 28(5): 974-981. DOI: 10.1038/s41591-022-01803-5.

Improve Glucose Sensitivity in MODY-2 Patients

- Heterozygous GCK mutation leads MODY-2 disease condition:
  - elevated blood glucose
  - reduced 2nd Phase insulin secretion
- A single dose of Dorzagliatin improves 2nd phase insulin secretion and improves the beta cell glucose sensitivity
- Proof of mechanism of action (MOA) of Dorzagliatin in hyperglycemic clamp study

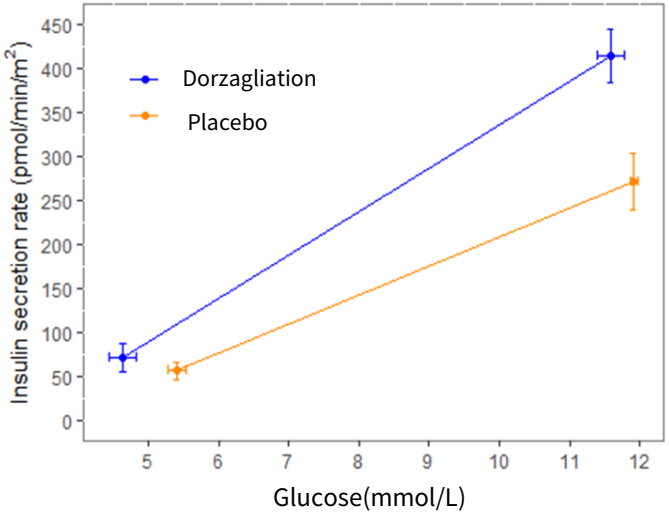
Significant Improves 2nd P Insulin Secretion

GK-MODY



Significant Improves Glucose Sensitivity

GCK-MODY

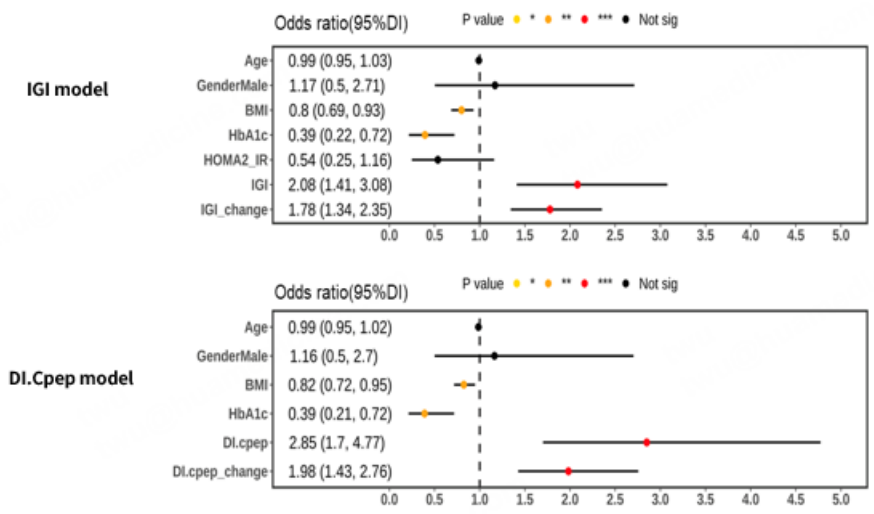


Source: E Chow, E Ferrannini, J Chan, 2022 ADA 261-OR

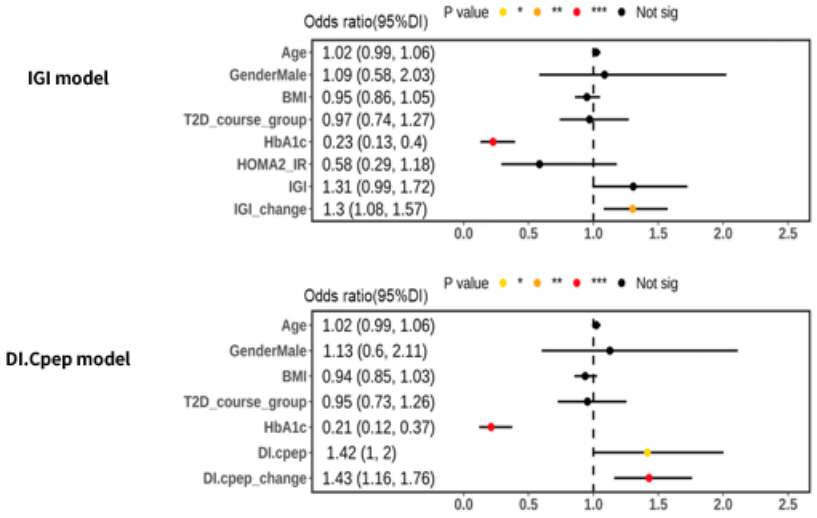
Improvement of GSIS by Dorzagliatin Drives Glycemic Control

- Patients in SEED and DAWN achieved effective glycemic control in 43-45%
- Glycemic control (HbA1c < 7%) in SEED and DAWN is dependent on the early phase insulin secretion (IGI & DI) baseline status and improvement from baseline by Dorzagliatin treatment
- Improvement of disposition index (DI) and IGI are validated in large Ph III registration trials

SEED: Drug Naïve T2D

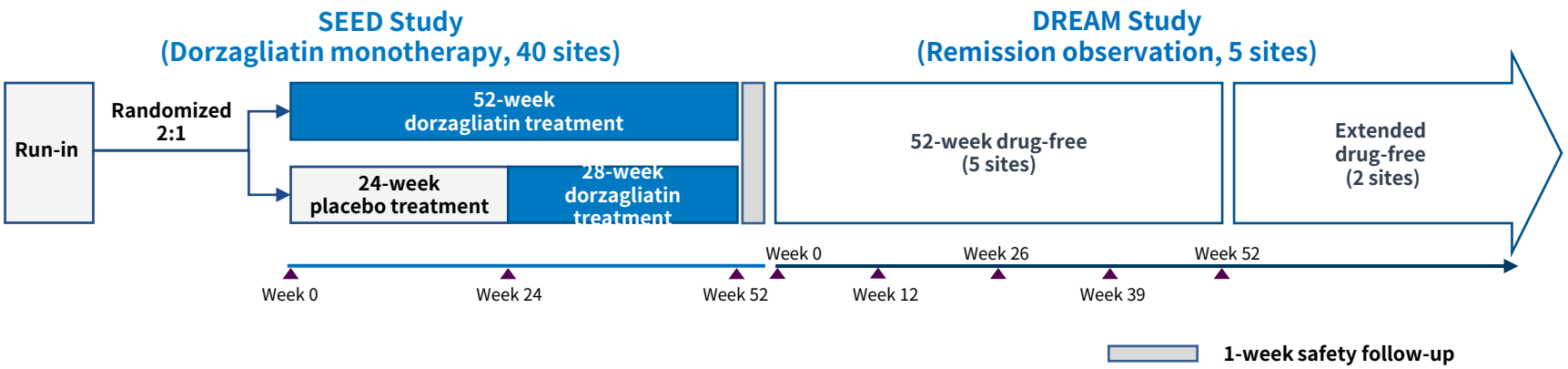


DAWN: Metformin Failed T2D



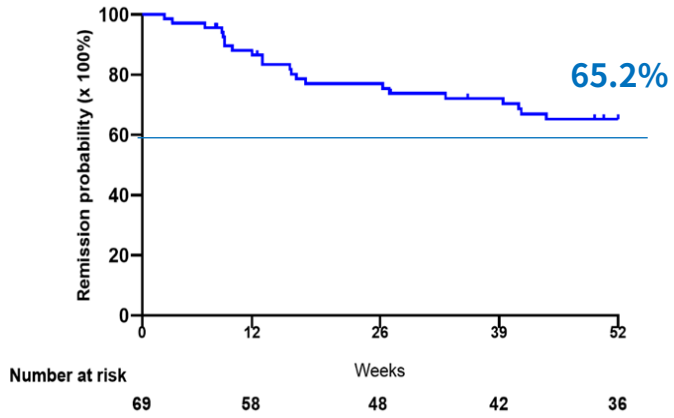
Source: LG Feng, L Chen, WY Yang, 2022 ADA 117-LB; ; Diabetes 2022;71(Supplement_1):117-LB

Dorzagliatin Treatment Leads to Diabetes Remission



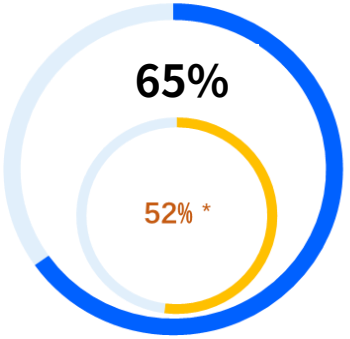
a

Kaplan-Meier estimate of remission rate
During 52-week observation period



b

Remission rate calculated by Kaplan-Meier method using two definitions



* Diagnostic criterion of remission:
HbA1c <6.5% measured at least 3 months after cessation of glucose-lowering pharmacotherapy

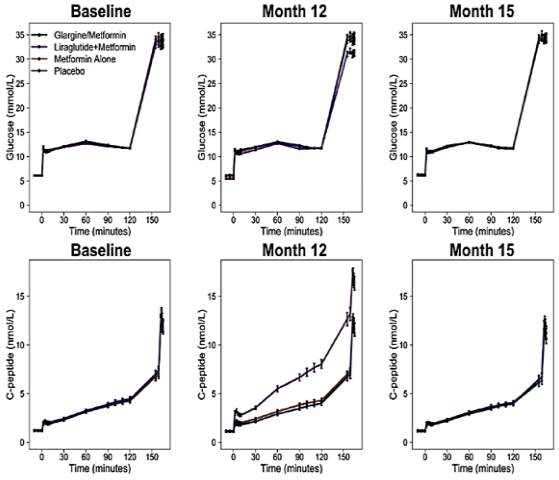
Source: JH Ma, et al 2022 ADA 115-LB; Diabetes 2022;71(Supplement_1):115-LB

Source; Matthew C Riddle, et al. Diabetes Care. 2021 Aug 30;44(10):2438-2444.

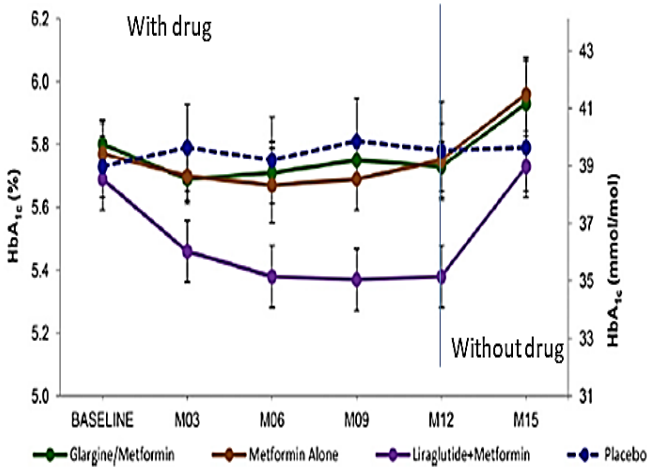
Loss of GSIS function in β-cells
The root cause of T2D

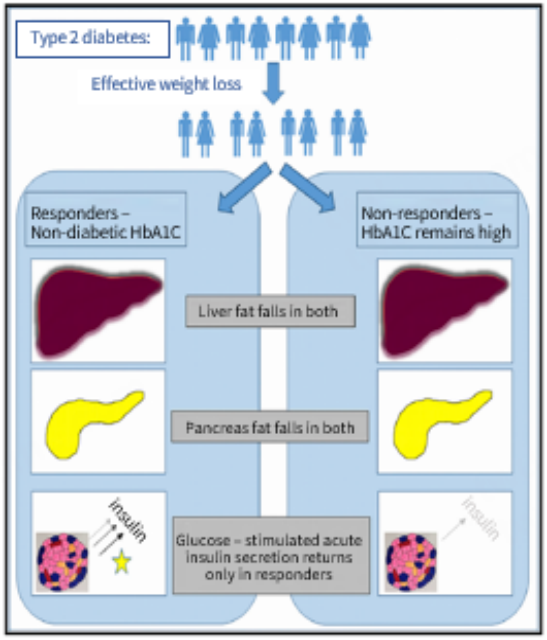
- RISE Study: Drug naive T2D and IGT subjects were treated for 12 month with Metformin (Red), GLP-1 + Metformin (Purple) and Glargine + Metformin (Green) did not show sustained improvement of beta cell function in 15 Month, 3 months after drug withdraw
- DiRECT Study: Weight loss driven diabetes remission is dependent on restoring glucose stimulated acute-insulin secretion. That is, through external factors (weight loss) affecting the root of the disease (glucose-stimulated early-phase insulin secretion) to promote remission (Hb1Ac <6.5%) for 2 months (8 weeks)

Lack of **insulin secretion** enhancement by leading T2D drugs



Blood glucose well controlled by drugs (A1c < 6.0) but not when drug withdrawn



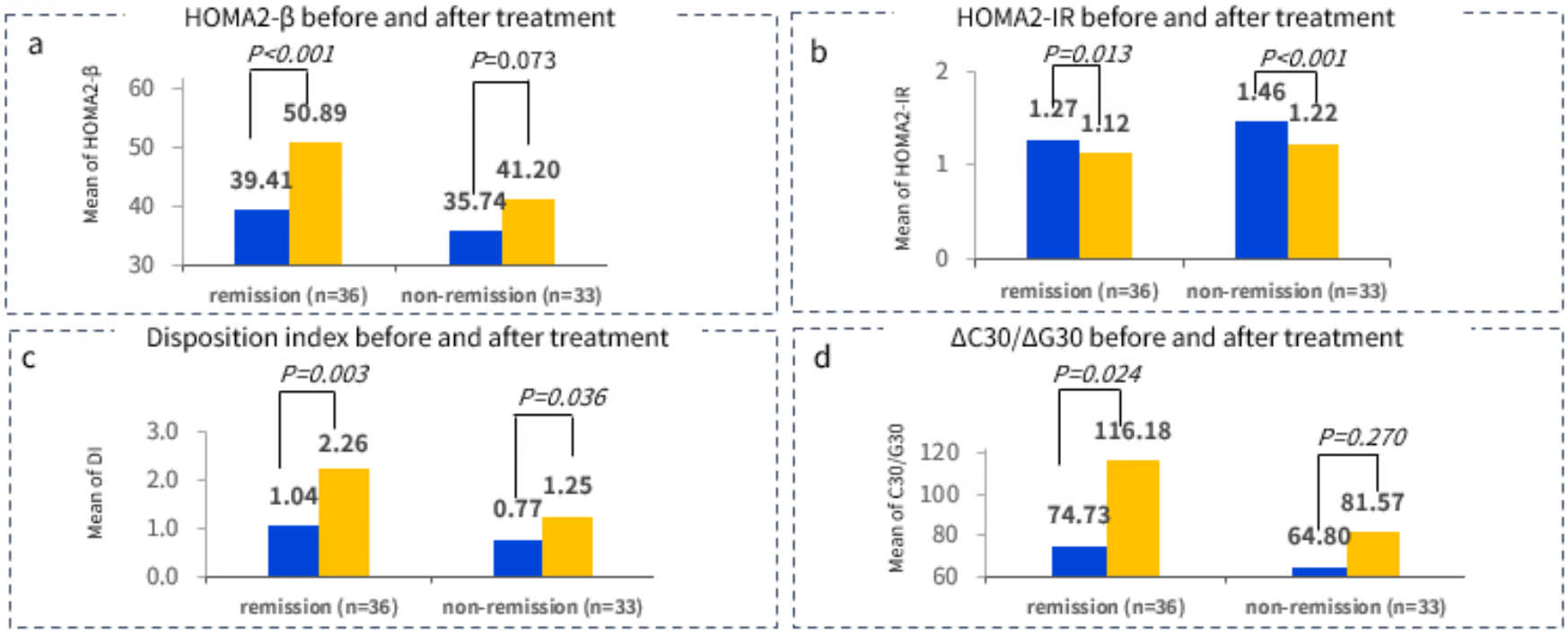


source: RISE Consortium. Diabetes Care. 2019 Sep;42(9):1742-1751.

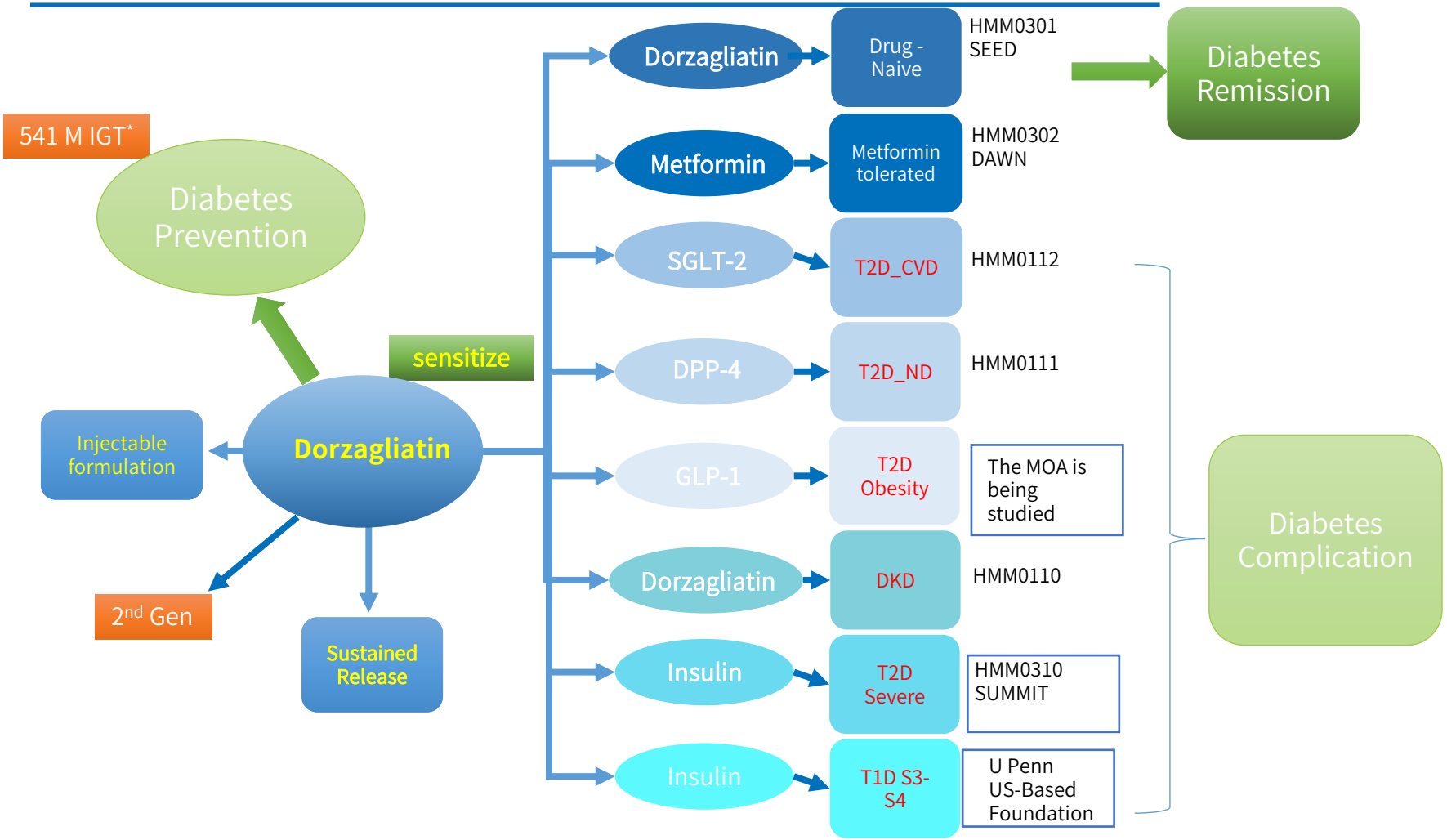
DiRECT Cell Metabolism 2018;28:547-556

Improved beta cell Function Drives Diabetes Remission

- HOMA2-β, HOMA2-IR, disposition index (DI) and IGI (ΔC30/ΔG30) have been improved in all participants after Dorzagliatin treatment during SEED study, which leads to 44% patients achieved glycemic control
- Improvement of HOMA2-β, disposition index (DI) and IGI (ΔC30/ΔG30) is statistically significant and in intensity in the remission group when compared between before and after treatment.



Restore glucose homeostasis and advance diabetes care diabetes remission and ultimately prevention



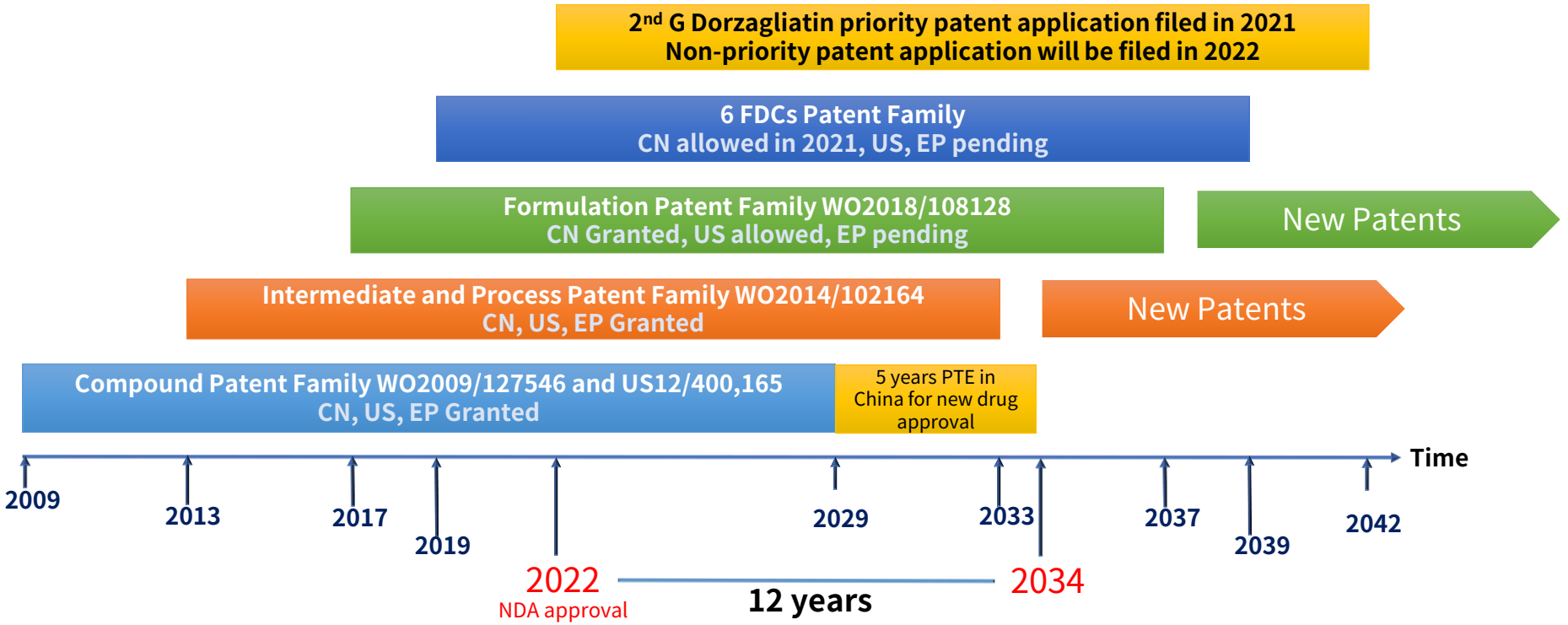
- Diabetes remission by early intervention of Dorzagliatin: impact about 100 M diabetes patients
- Diabetes prevention by Dorzagliatin for IGT subjects: about 541 M IGT patients worldwide
- Diabetes complication prevention by early combination of Dorzagliatin: about 440 M T2D patients have one or more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

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

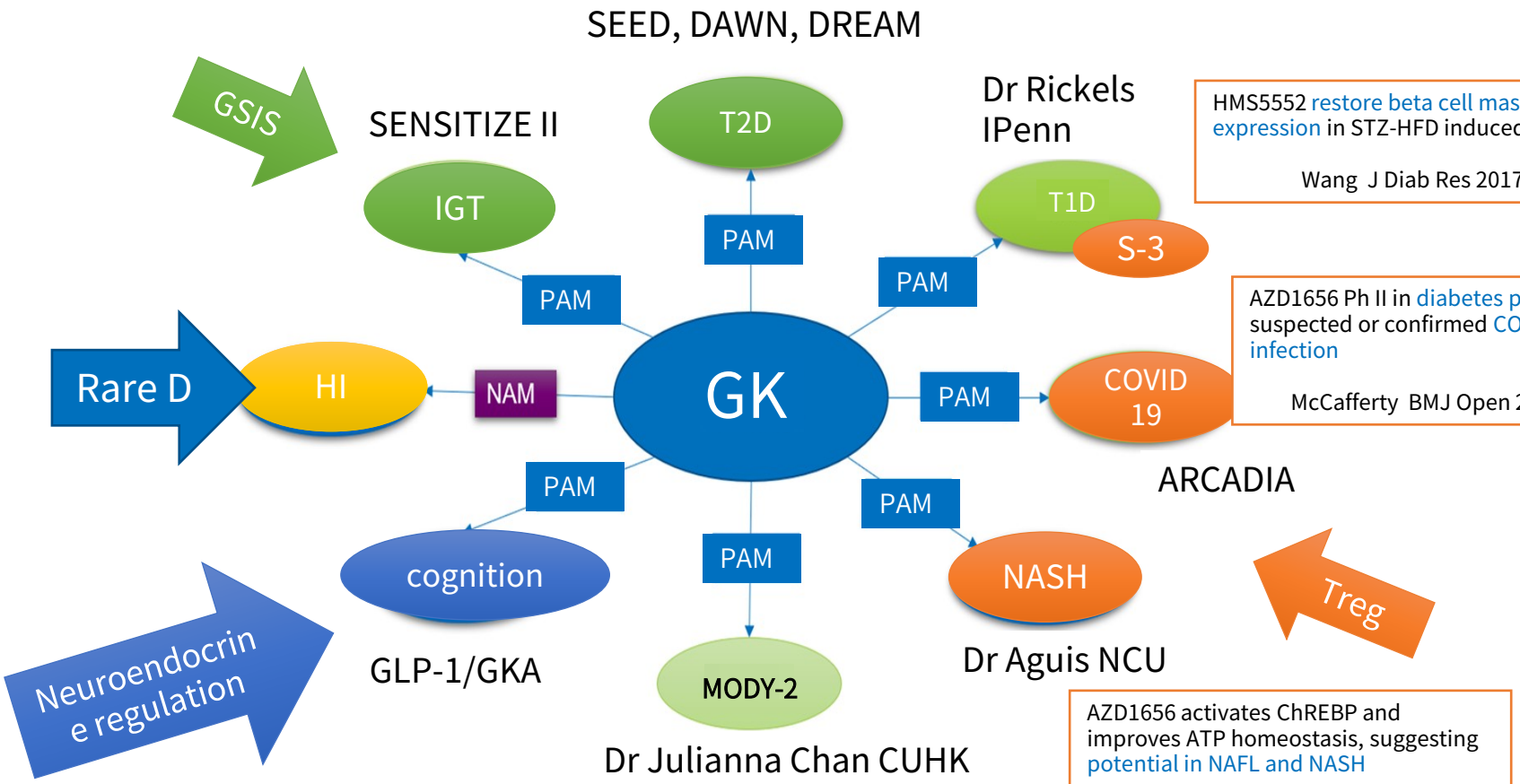
Outlook

Dorzagliatin Patent Portfolio

The Chinese patent for dorzagliatin is expected to be extended to 2034, and various global patents including the 2nd generation GKA are in urgent application and prosecution



Glucokinase with a broader indication in homeostatic control of endocrine, immunity and neurology



HMS5552 restore beta cell mass and GK expression in STZ-HFD induced diabetic rats

Wang J Diab Res 2017, AID 5812607

AZD1656 Ph II in diabetes patients with suspected or confirmed COVID19 infection

McCafferty BMJ Open 2021, e049650

AZD1656 activates ChREBP and improves ATP homeostasis, suggesting potential in NAFL and NASH

Ford DOM 2020;22:1985

Dorzagliatin business development strategy

Seek opportunities to continue to expand the development opportunities of dorzagliatin in the European, American and Japanese markets, Southeast Asian market and the "Belt and Road" market to realize the value of innovation.

- Partner with Bayer China and achieve commercial excellence in Diabetes Care
  - An innovative model to shape the Chinese diabetes market and management
  - Raising the standard of care and management of diabetes and related diseases

- Partner with local leader in China for drug development clinical opportunities for diabetes prevention, mitigation and elimination of complications
  - Opportunity in diabetes prevention in China and SE Asia (IGT population)

- Partner with local leader in US and EU for drug development and market entry with FDC (once a day tablet) and 2nd generation of dorzagliatin
  - Opportunity in T1D and T2D care in US
  - Opportunity in DKD care in US and EU
  - Opportunity in T2D partners in the Middle East and North Africa

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, NDA under active review in China**
- **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 oral antidiabetes drug to demonstrate potential for diabetes remission –** in DREAM Study, 65% diabetes remission rate at week 52 without any antidiabetes medication
- Broad indications diabetes care
  - Diabetes remission
  - Demonstrated viability in combination with DPP-4 inhibitor & SGLT-2 inhibitor
  - Suitable for DKD patients

Financial Section

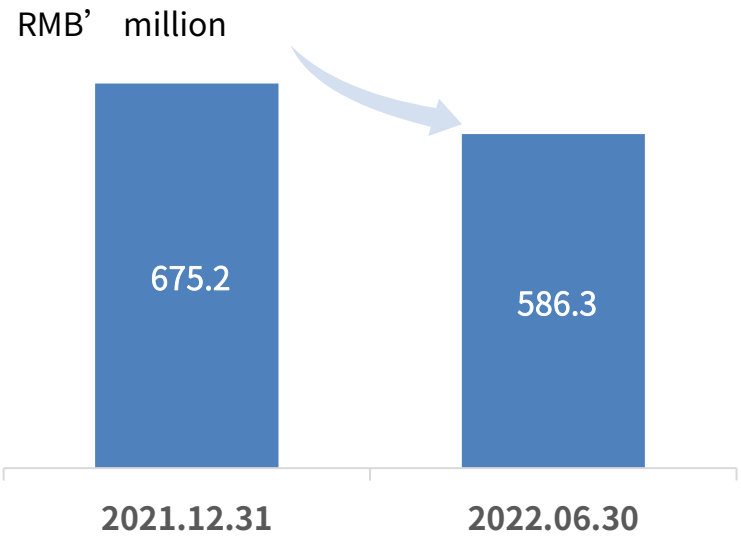
Financial Summary

Cash Balance: RMB586.3 million of cash at 06/30/2022 vs. 675.2 million at 12/31/2021.

Total cash decrease of RMB88.9 million, consisted of:

- Net cash used in operating activities was RMB116.6 million
- Net cash from investing activities was RMB17.0 million
- Net cash used in financing activities was RMB4.3 million
- Net effect of exchange rate changes was RMB15.0 million

Net cash used in operation activities of RMB116.6 million, mainly includes cash payment of RMB70.6 million for the research and development activities and of RMB91.6 million for the administrative activities, adjusted for cash received of RMB45.6 million for government grants and VAT refund.



Financial Summary- continued

Loss before tax of RMB104.6 million in the first half of 2022 vs. RMB165.3 million in the first half of 2021.

Research and development expenses of RMB72.3 million in the first half of 2022 vs. RMB98.0 million in the first half of 2021.

- A decrease of RMB15.6 million for dorzagliatin clinical trials, which was primarily attributable to the data analysis and TMF report preparation of SEED/HMM0301 and DAWN/HMM0302 were conducted in the first half of 2021. In the first half of 2022, we primarily focused on our NDA approval and conducted several additional clinical research to support the review of NMPA;
- A decrease of RMB2.4 million for dorzagliatin non-clinical studies, which was primarily attributable to the ISS data and analysis expense for NDA filing, FDC efficacy study of dorzagliatin with insulin/acarbose and efficacy study of dorzagliatin in animal model of T2D complicating cognitive disorder conducted in the first half of 2021 and no such studies happened in the first half of 2022;
- A decrease of RMB7.0 million for labor costs, which was primarily attributable to decreased annual bonus and the decrease of share-based payment under the accelerated amortization method;
- A decrease of RMB3.0 million for other expenses, which was primarily attributable to the less travelling cost, meeting cost and utility cost due to the impact of COVID-19 in the first half of 2022;
- Adjusted for an increase of RMB1.6 million in chemical, manufacturing, and control expenses, which was primarily attributable to the process validation, drug substance and production for clinical trail for the review of our NDA approval conducted in the first half of 2022.

Financial Summary- continued

Administrative expenses of RMB68.5 million in the first half of 2022 vs. RMB63.5 million in the first half of 2021.

- An increase of RMB6.9 million in consultant fee, which was mainly due to our NDA application related consulting, pricing strategy consulting and economic evaluation consulting of dorzagliatin conducted during the six months ended June 30, 2022 and no such consulting activities conducted during the six months ended June 30, 2021;
- Adjusted for a decrease of RMB1.2 million in recruitment expense due to our recruitment strategy;
- Adjusted for a decrease of RMB0.4 million in meeting fee and RMB0.5 million in travelling expense due to less meeting and travelling activities compared to the six months ended June 30, 2021, which was impacted by COVID-19 in the first half of 2022.

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