ATTD
Advanced Technologies & Treatments for Diabetes
19-22 MARCH 2025, AMSTERDAM & ONLINE

Harnessing Menin Inhibition

Exploring Icovamenib as a Potential First-in-Class Medicine for Precision Diabetes Care

Juan Pablo Frías, MD
Chief Medical Officer
Biomea Fusion, Inc.

Steven V. Edelman, MD
Professor of Medicine
University of California, San Diego

Rohit N. Kulkarni, MD, PhD
Professor of Medicine
Joslin Clinic, Harvard Medical School

ATTD Breakfast Symposium – 21 March 2025

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Steven V. Edelman, MD

- Founder and Director of Taking Control of Your Diabetes (TCOYD)
- Professor of Medicine in the Division of Endocrinology and Metabolism at the University of California, San Diego
- Director of the Diabetes Care Clinic at the Veterans Affairs Medical Center in San Diego
- Awards and Honors:
  - Distinguished Alumnus Award from the University of California Davis, School of Medicine
  - Lifetime Achievement Award, Association of Diabetes Care Specialists
  - AACE Distinction in Clinical Endocrinology award
  - UC Davis School of Medicine Transformational Leadership award
  - Outstanding Educator in Diabetes Award from the ADA

My only important disclosures are that…

- I have been living with type 1 diabetes since the age of 15
- I am a consultant for Biomea Fusion

Rohit N. Kulkarni, MD, PhD

- Physician scientist and diabetes researcher
- Professor of Medicine at Harvard Medical School; Diabetes Research and Wellness Foundation Chair
- Co-Head of the Section on Islet and Regenerative Biology at the Joslin Diabetes Center, Principle Faculty of the Harvard Stem Cell Institute and Associate Member of the Broad Institute
- Received numerous accolades, including the Ernst Oppenheimer Award (Endocrine Society), the Albert Renold Prize (European Association for Study of Diabetes) and Paul E. Lacy Medal (Midwest Islet Consortium)
- Elected Fellow of the American Society for Clinical Investigation, the Association of American Physicians, and the American Association for the Advancement of Science

Disclosures

- Scientific Advisory Boards: Biomea Fusion, Novo Nordisk, REDD Pharmaceuticals

Harnessing Menin Inhibition

Exploring Icovamenib as a Potential First-in-Class Medicine for Precision Diabetes Care

Icovamenib: A Novel Approach to Diabetes Management	**Juan P. Frías, MD**
Precision Care in Diabetes: Understanding Patient Heterogeneity	**Steven V. Edelman, MD**
Beta-Cell Biology and Menin Inhibition	**Rohit Kulkarni, MD, PhD**
COVALENT-111: Topline Results at 26 Weeks	**Juan P. Frías, MD**
Q&A	

Introduction to Biomea Fusion and Icovamenib

A Novel Approach to Diabetes Management

Juan Pablo Frías, MD
Chief Medical Officer and Head of Diabetes
Biomea Fusion

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A long history of developing successful drugs - together

Thomas Butler
Chairman & CEO

biomea FUSION™
Co-Founder

The FUSION™ SYSTEM
icovamenib*
Co-Inventor

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Veklury® remdesivir 100 MG FOR INJECTION
Co-Inventor

Ramses Erdtmann
President & COO

biomea FUSION™
Co-Founder

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Juan Frías, M.D.
Chief Medical Officer

once weekly mounjaro® (tirzepatide) injection 0.5 mL
2.5 mg | 5 mg | 7.5 mg | 10 mg | 12.5 mg | 15 mg

once weekly trulicity® (dulaglutide) injection 0.5 mL
0.75 mg | 1.5 mg | 3.0 mg | 4.5 mg

OZEMPIC® semaglutide injection 0.5 mg, 1 mg, 2 mg

Byetta® (exenatide) injection

ONCE-WEEKLY wegovy® semaglutide injection 2.4 mg

Januvia® sitagliptin

Invokana® (canagliflozin) tablets

Jardiance® (empagliflozin) tablets 10 mg/25 mg

farxiga® (dapagliflozin) 5 mg & 10 mg tablets

Naomi Cretcher
Chief of People

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Heow Tan
Chief Technical & Quality Officer

ZADAXIN

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES

PLENAXIS

HylatopicPlus® Cream

Steve Morris, M.D.
Chief Development Officer

XALKORI® 250 MG CAPSULES CRIZOTINIB

ZYKADIA® ceritinib 150 mg tablets

LORBRENA® LORLATINIB 100 mg tablets

ALECENSA® alectinib 150 mg capsules

ALUNBRIG™ BRIGATINIB 30mg TABLETS

*Note: icovamenib is an investigational new drug

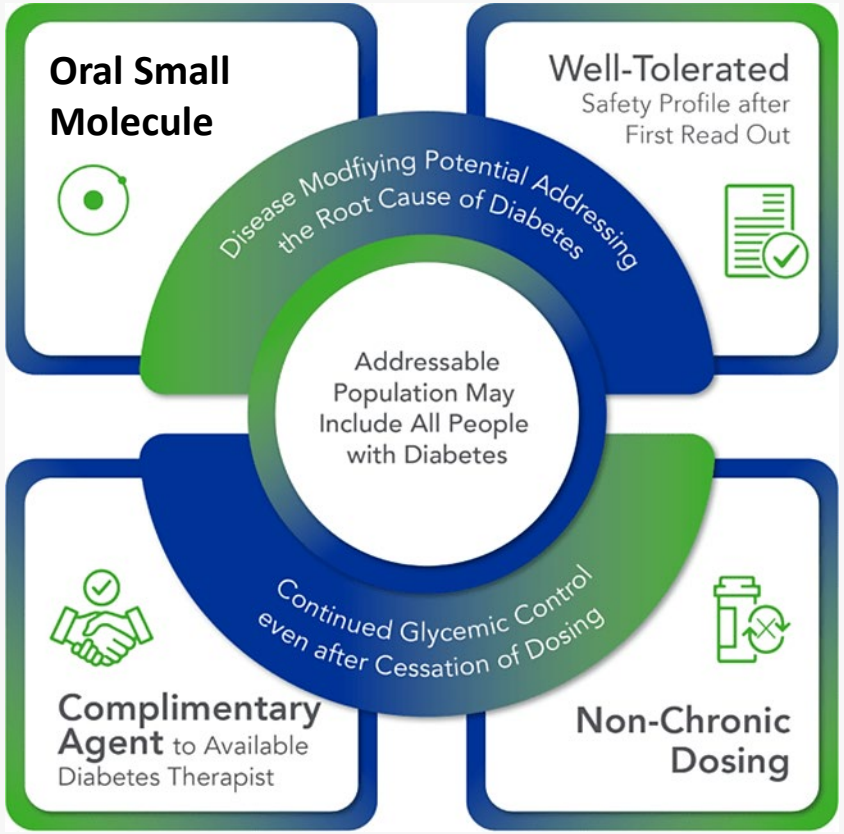
Icovamenib: An Oral Covalent Menin Inhibitor

Targeting Beta Cells to Advance Diabetes Management

What is menin?

Menin is a scaffold protein that regulates glucose homeostasis

Inhibiting menin enhances insulin secretion through beta-cell proliferation and increased GLP-1 receptor expression



Dual Effect

Beta Cell Mass & Function

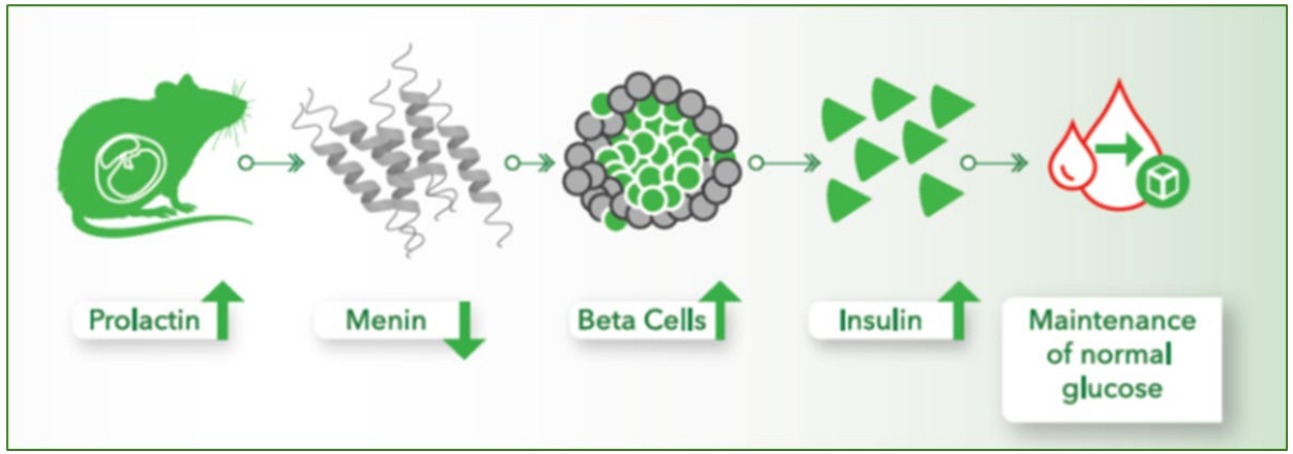
- **Increased beta cell mass and function**
- **Increased Insulin Synthesis and Secretion**

GLP-1 Receptor Expression

- **Increased GLP-1 Receptor Expression & Incretin Effect**
- **Enhanced Weight Loss with Preservation of Lean Mass**

Menin is downregulated by prolactin during pregnancy allowing for beta cell replication and preventing gestational diabetes

- In 2007, Stanford University researchers found that menin regulated adaptive islet growth in pregnant mice
- Prolactin, a hormonal regulator of pregnancy, repressed beta cell menin levels and stimulated beta cell proliferation



Science
AAAS

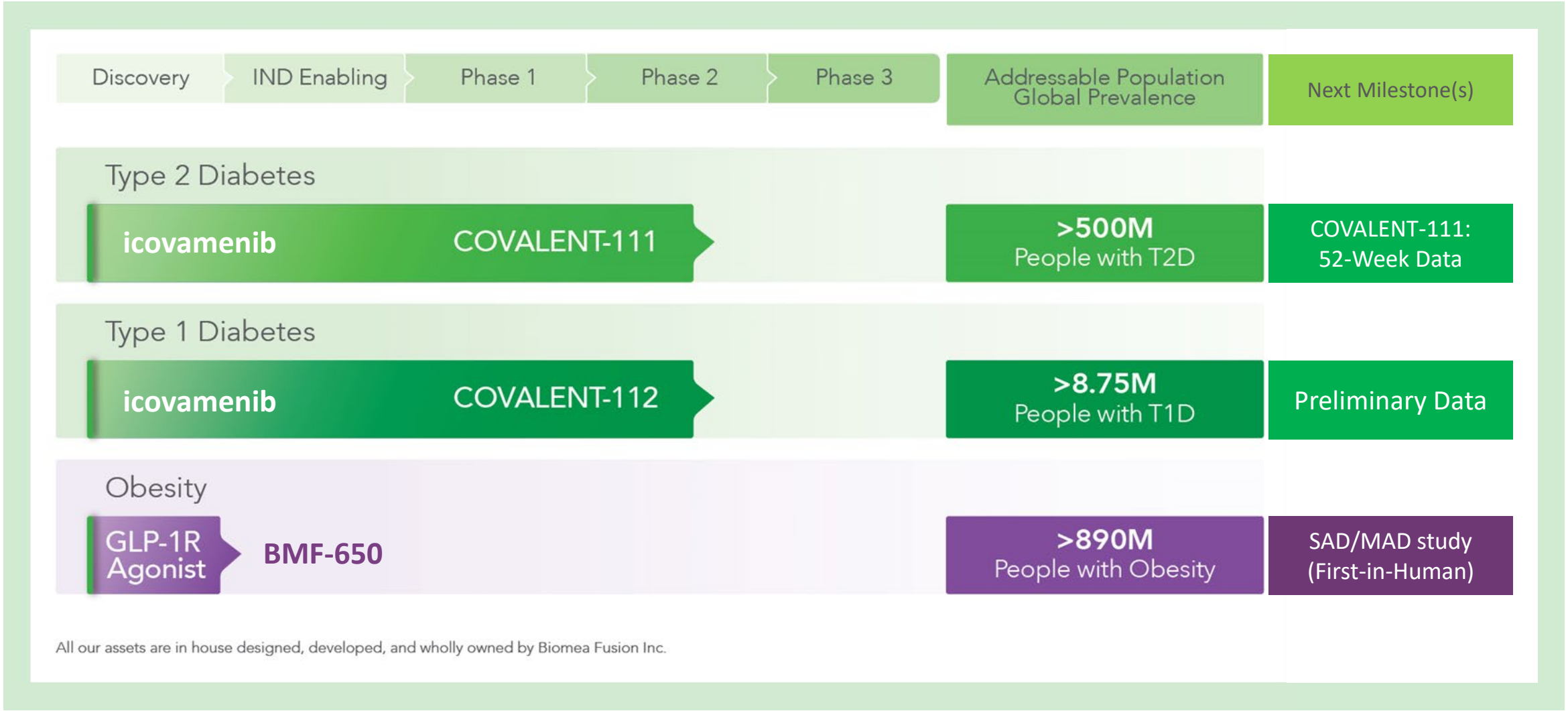
Menin Controls Growth of Pancreatic β-Cells in Pregnant Mice and Promotes Gestational Diabetes Mellitus

Satyajit K. Karnik,[1] Hainan Chen,[1*] Graeme W. McLean,[1*] Jeremy J. Heit,[1*] Xueying Gu,[1] Andrew Y. Zhang,[1] Magali Fontaine,[2] Michael H. Yen,[1,3] Seung K. Kim[1,3]†

During pregnancy, maternal pancreatic islets grow to match dynamic physiological demands, but the mechanisms regulating adaptive islet growth in this setting are poorly understood. Here we show that menin, a protein previously characterized as an endocrine tumor suppressor and transcriptional regulator, controls islet growth in pregnant mice. Pregnancy stimulated proliferation of maternal pancreatic islet β-cells that was accompanied by reduced islet levels of menin and its targets. Transgenic expression of menin in maternal β-cells prevented islet expansion and led to hyperglycemia and impaired glucose tolerance, hallmark features of gestational diabetes. Prolactin, a hormonal regulator of pregnancy, repressed islet menin levels and stimulated β-cell proliferation. These results expand our understanding of mechanisms underlying diabetes pathogenesis and reveal potential targets for therapy in diabetes.

Karnik SK, et al. Science. 2007;318:806-809

Our product pipeline includes diabetes and obesity



Precision Care in Diabetes:

Understanding Patient Heterogeneity

Steven V. Edelman, MD
Professor of Medicine
University of California, San Diego

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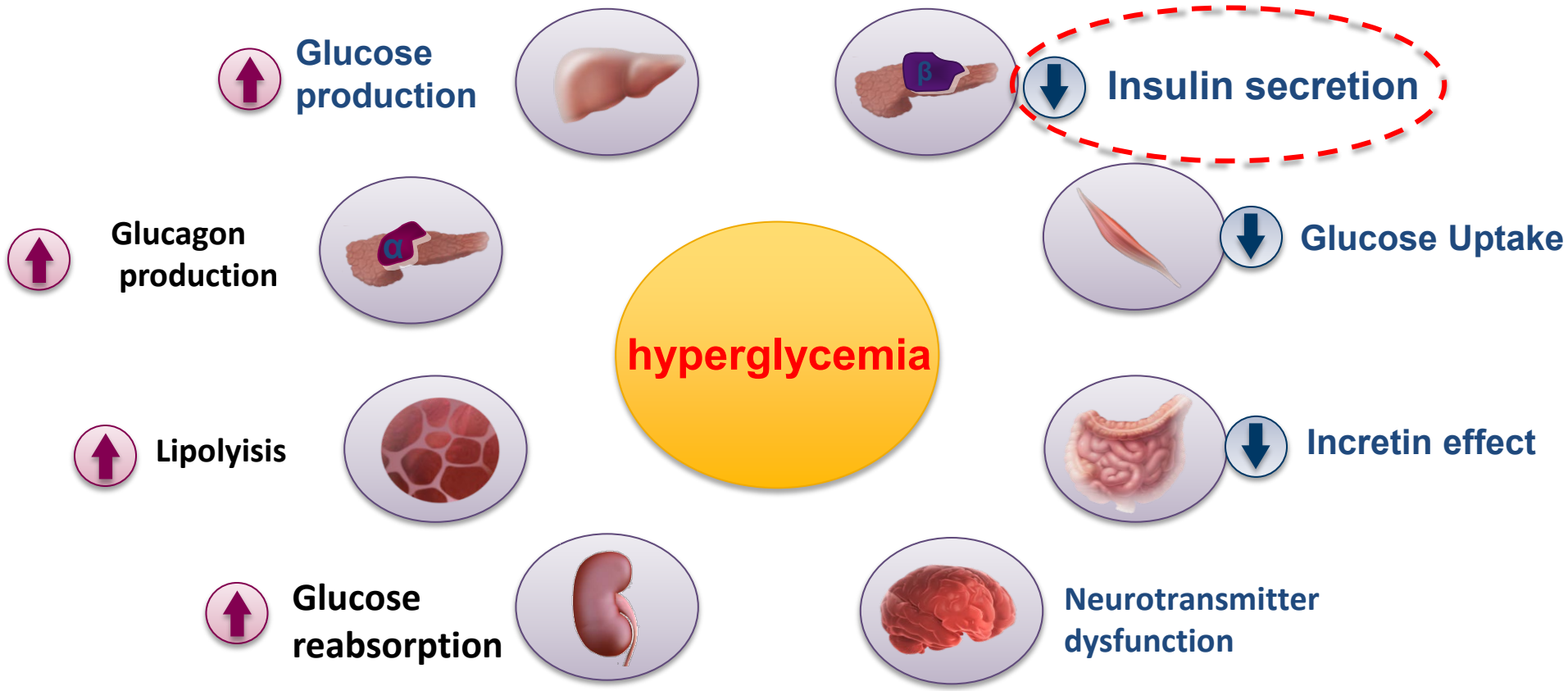
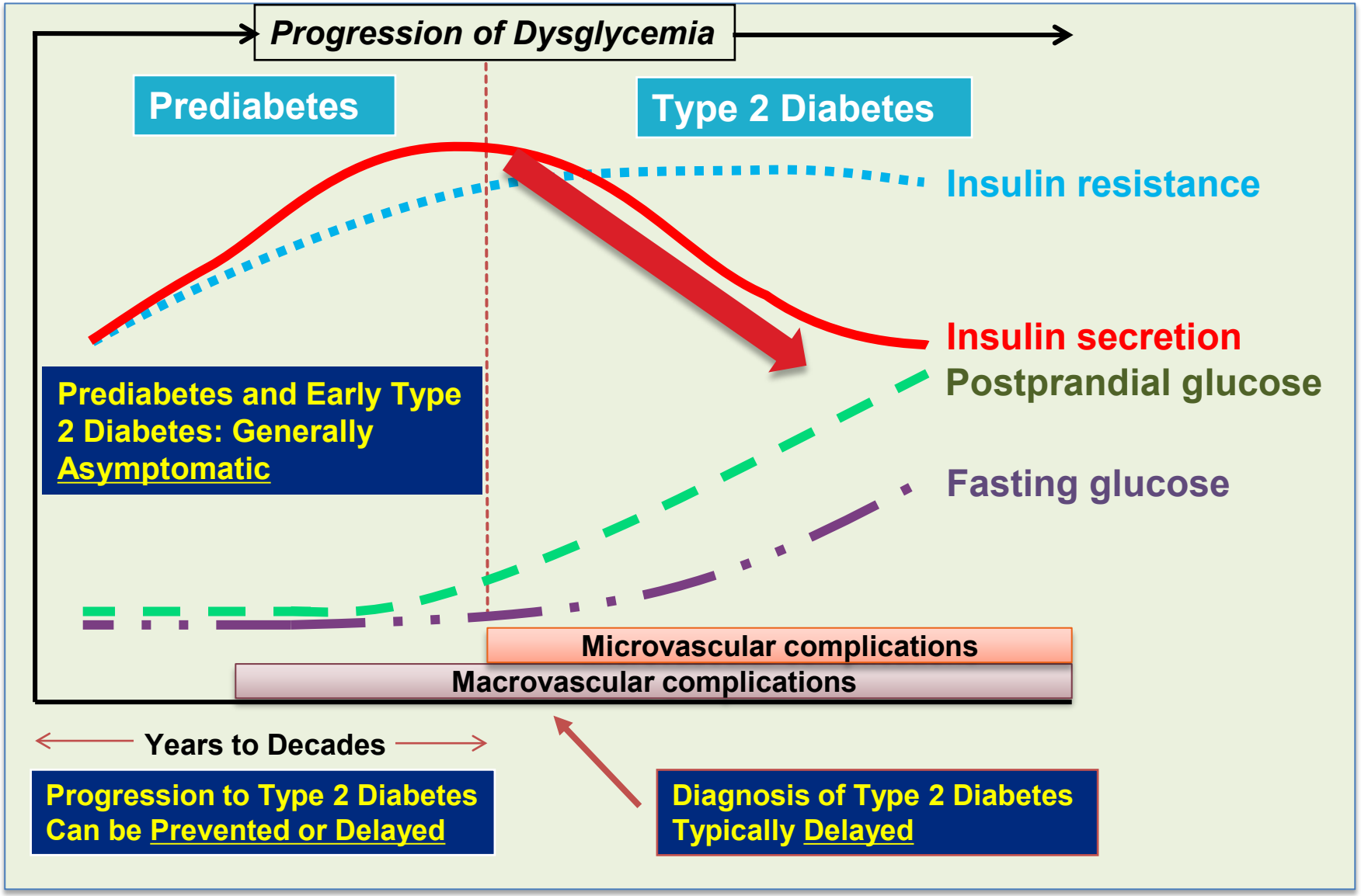
Multiple Defects Contribute to the Pathophysiology of Type 2 Diabetes Necessitating Targeted Therapy



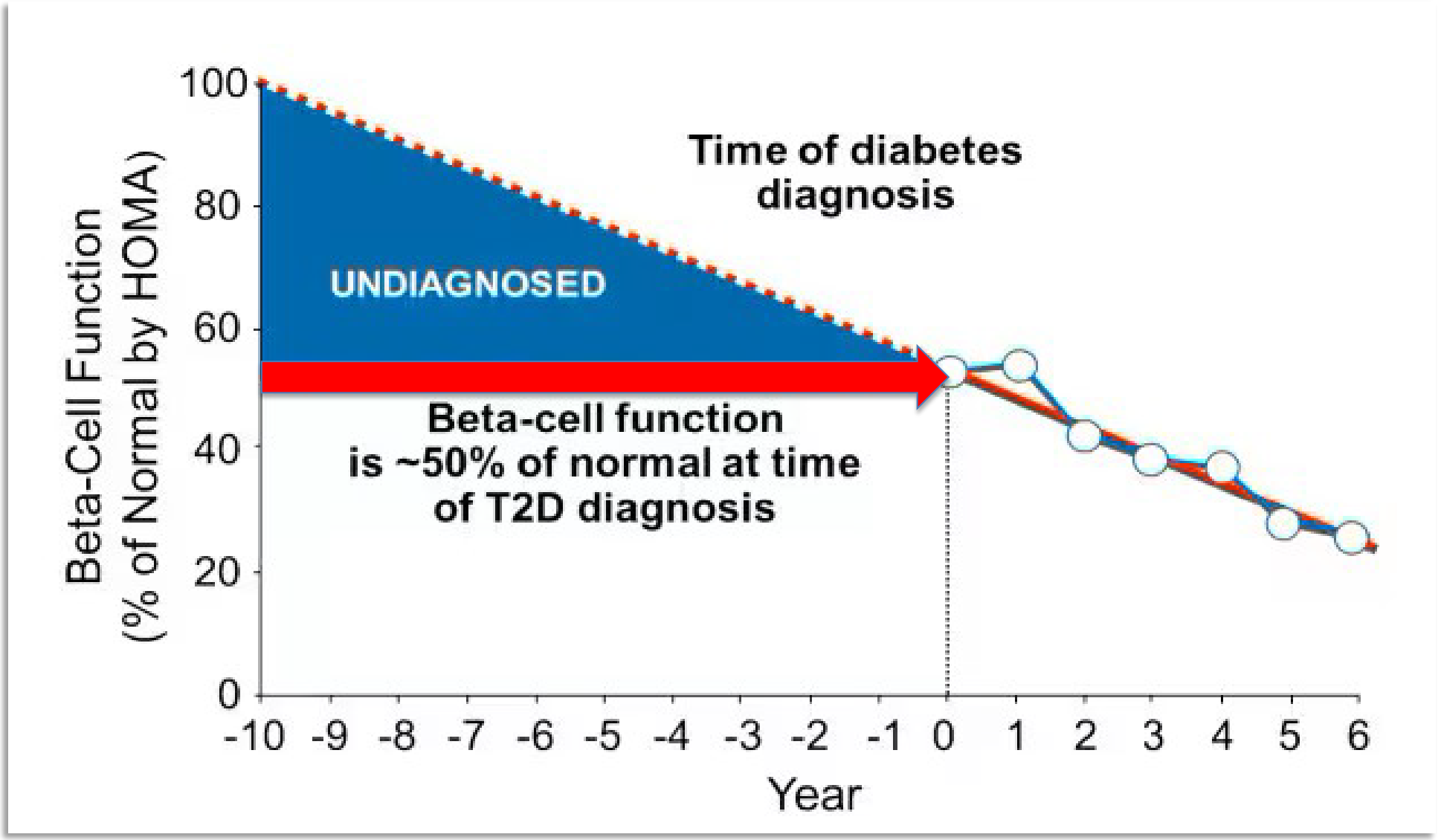
DeFronzo RA. *Diabetes*. 2009;58(4):773-795

Natural History of Type 2 Diabetes Is Characterized by Progressive Loss Of Beta Cell Function



Adapted from Ramlo-Halsted BA, Edelman SV. *Prim Care.* 1999;26:771-789.

Natural History | Loss of Beta Cells

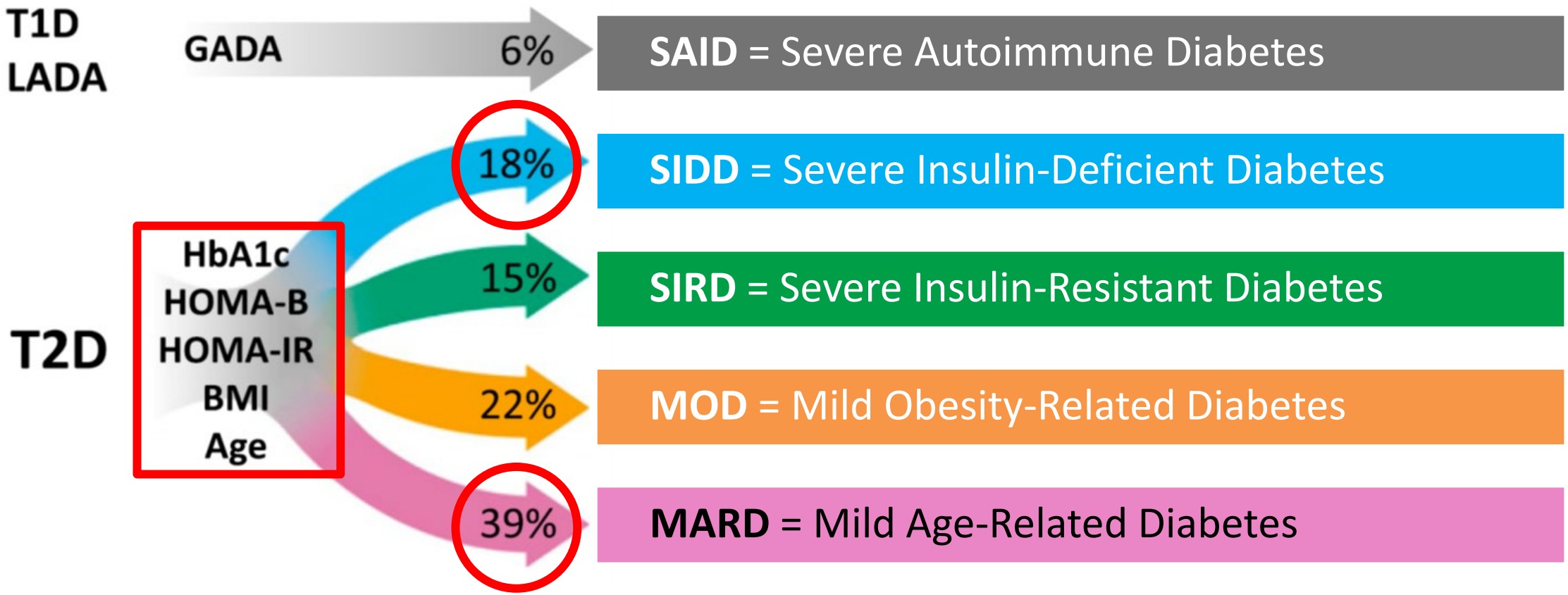


Adapted from Lebovitz H. Diabetes Rev. 1999;7:139-153.

T2D is a heterogeneous disease

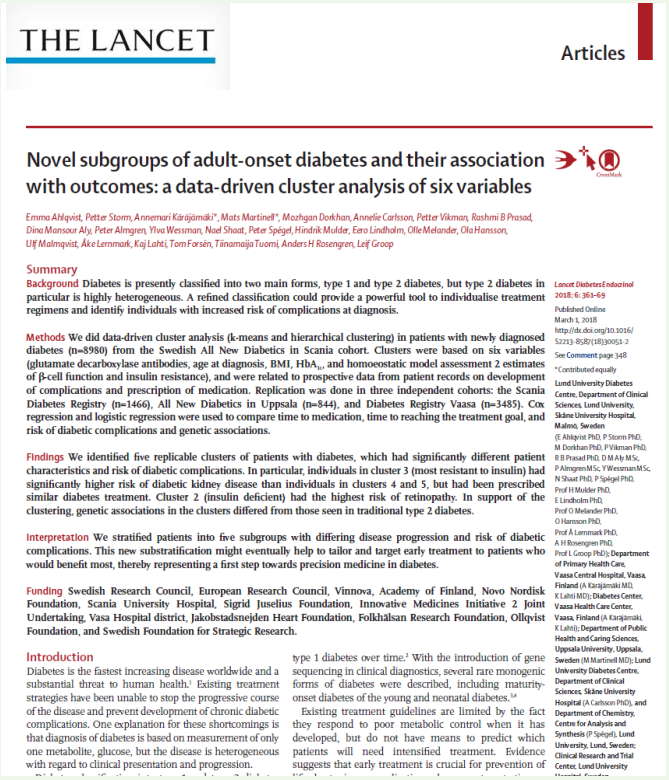
T2D is a heterogeneous disease

“While diabetes is diagnosed on the basis of a single metabolite, glucose, hyperglycemia can arise due to multiple complex etiological processes that can vary between individuals.”[1,2]



1. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2019. Diabetes Care 2019;42(Suppl. 1):S13–S28
2. Ahlqvist E, et al. Diabetes 2020;69:2086–2093
3. Ahlqvist E, et al. Lancet Diabetes Endocrinol. 2018;6:361-369

T2D Subtyping



THE LANCET

Articles

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki*, Mats Martinell*, Mozhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Naif Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop

Summary

Background Diabetes is presently classified into two main forms, type 1 and type 2 diabetes, but type 2 diabetes in particular is highly heterogeneous. A refined classification could provide a powerful tool to individualise treatment regimens and identify individuals with increased risk of complications at diagnosis.

Methods We did data-driven cluster analysis (k-means and hierarchical clustering) in patients with newly diagnosed diabetes (n=8980) from the Swedish All New Diabetics in Scania cohort. Clusters were based on six variables (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA_{1c}, and homoeostatic model assessment 2 estimates of β-cell function and insulin resistance), and were related to prospective data from patient records on development of complications and prescription of medication. Replication was done in three independent cohorts: the Scania Diabetes Registry (n=1466), All New Diabetics in Uppsala (n=844), and Diabetes Registry Vaasa (n=3485). Cox regression and logistic regression were used to compare time to medication, time to reaching the treatment goal, and risk of diabetic complications and genetic associations.

Findings We identified five replicable clusters of patients with diabetes, which had significantly different patient characteristics and risk of diabetic complications. In particular, individuals in cluster 3 (most resistant to insulin) had significantly higher risk of diabetic kidney disease than individuals in clusters 4 and 5, but had been prescribed similar diabetes treatment. Cluster 2 (insulin deficient) had the highest risk of retinopathy. In support of the clustering, genetic associations in the clusters differed from those seen in traditional type 2 diabetes.

Interpretation We stratified patients into five subgroups with differing disease progression and risk of diabetic complications. This new substratification might eventually help to tailor and target early treatment to patients who would benefit most, thereby representing a first step towards precision medicine in diabetes.

Funding Swedish Research Council, European Research Council, Vinnova, Academy of Finland, Novo Nordisk Foundation, Scania University Hospital, Sigrid Juselius Foundation, Innovative Medicines Initiative 2 Joint Undertaking, Vasa Hospital district, Jakobstadsnejden Heart Foundation, Folkhälsan Research Foundation, Ollqvist Foundation, and Swedish Foundation for Strategic Research.

Introduction

Diabetes is the fastest increasing disease worldwide and a substantial threat to human health.[1] Existing treatment strategies have been unable to stop the progressive course of the disease and prevent development of chronic diabetic complications. One explanation for these shortcomings is that diagnosis of diabetes is based on measurement of only one metabolite, glucose, but the disease is heterogeneous with regard to clinical presentation and progression.

type 1 diabetes over time.[2] With the introduction of gene sequencing in clinical diagnostics, several rare monogenic forms of diabetes were described, including maturity-onset diabetes of the young and neonatal diabetes.[3,4]

Existing treatment guidelines are limited by the fact they respond to poor metabolic control when it has developed, but do not have means to predict which patients will need intensified treatment. Evidence suggests that early treatment is crucial for prevention of

Lancet Diabetes Endocrinol 2018; 6: 361–69
Published Online March 1, 2018 http://dx.doi.org/10.1016/S2213-8587(18)30051-2
See Comment page 348

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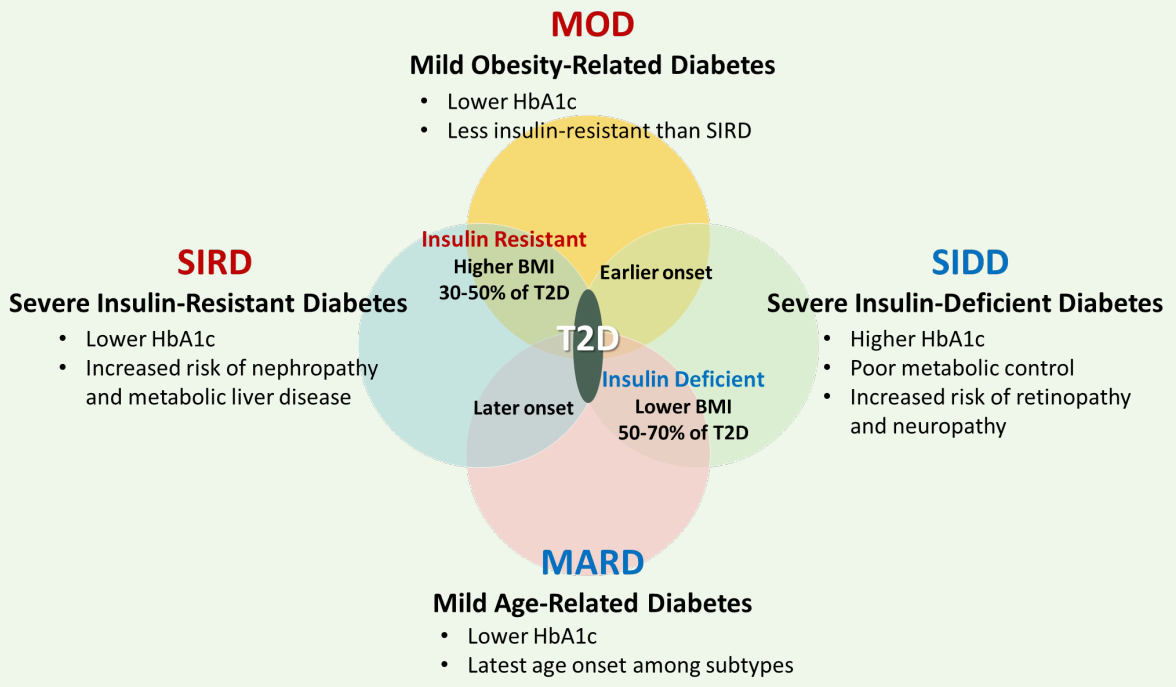
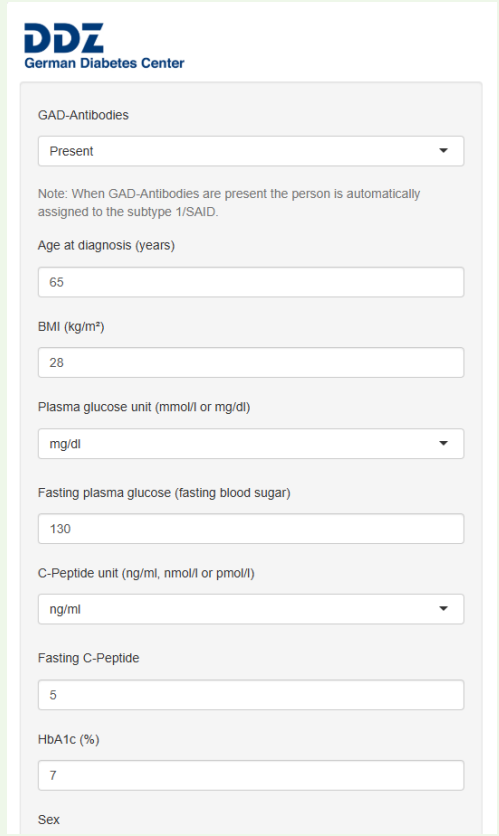




Ahlqvist et al. Lancet Diabetes Endocrinol 2018; 6: 361–69

DDZ Diabetes-Cluster-Tool

https://diabetescalculator.ddz.de/

T2D is a Heterogeneous Disease – Two Core Drivers

Analysis from two independent 4,000 patient studies (ADOPT and RECORD)

INSULIN-DEFICIENT DIABETES

Severe insulin-deficient diabetes

low BMI, severe beta-cell dysfunction, low insulin resistance, and high HbA1c, often with early onset and a high risk of complications.

18%

Median HOMA-B	49%
Median HbA1c	8.3%
Median BMI	29 kg/m^2

Mild age-related diabetes

older age at onset, normal to slightly elevated BMI, mild beta-cell dysfunction, low insulin resistance, and slow disease progression

39%

Median HOMA-B	64%
Median HbA1c	7.0%
Median BMI	29 kg/m^2

INSULIN-RESISTANT DIABETES

Mild obesity-related diabetes

high BMI, insulin resistance, preserved beta-cell function, and a strong link to obesity with moderate HbA1c levels.

22%

Median HOMA-B	74%
Median HbA1c	7.2%
Median BMI	36 kg/m^2

Severe insulin-resistant diabetes

high BMI, severe insulin resistance, normal or elevated insulin production, and a high risk of cardiovascular disease and metabolic complications.

15%

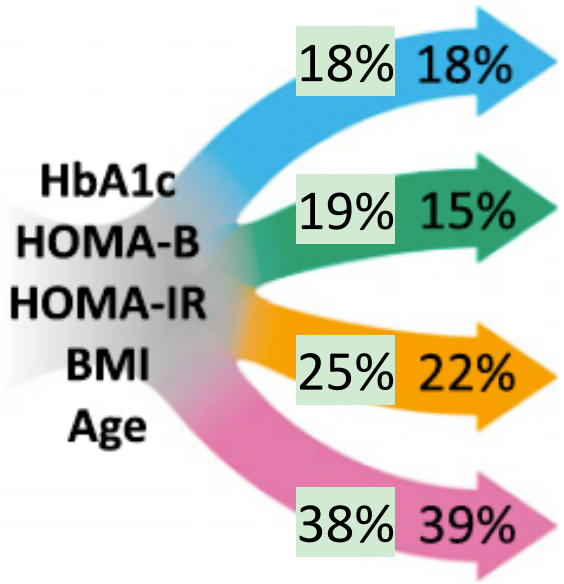
Median HOMA-B	101%
Median HbA1c	7.0%
Median BMI	34 kg/m^2

Adjusted from: https://www.thelancet.com/journals/landia/article/PIIS2213-8587(18)30051-2/abstract
"Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables"

1. Ahlqvist et al. Lancet Diabetes Endocrinol 2018; 6: 361–69

Identifying subtypes of type 2 diabetes mellitus based on real-world electronic medical record data in China

EMR data from tertiary hospital in Beijing, China (2000-2022)
n= 2652 people with T2D

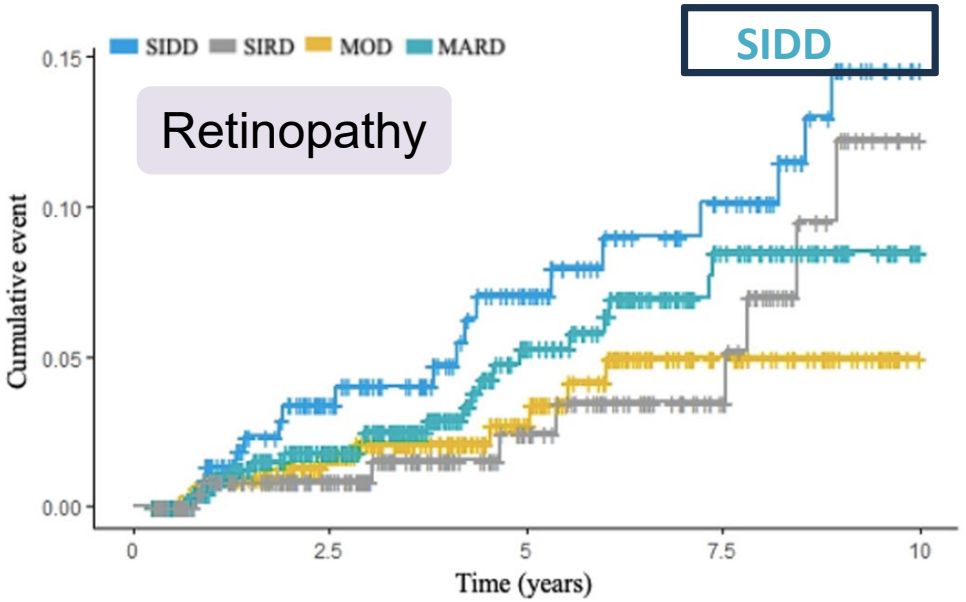


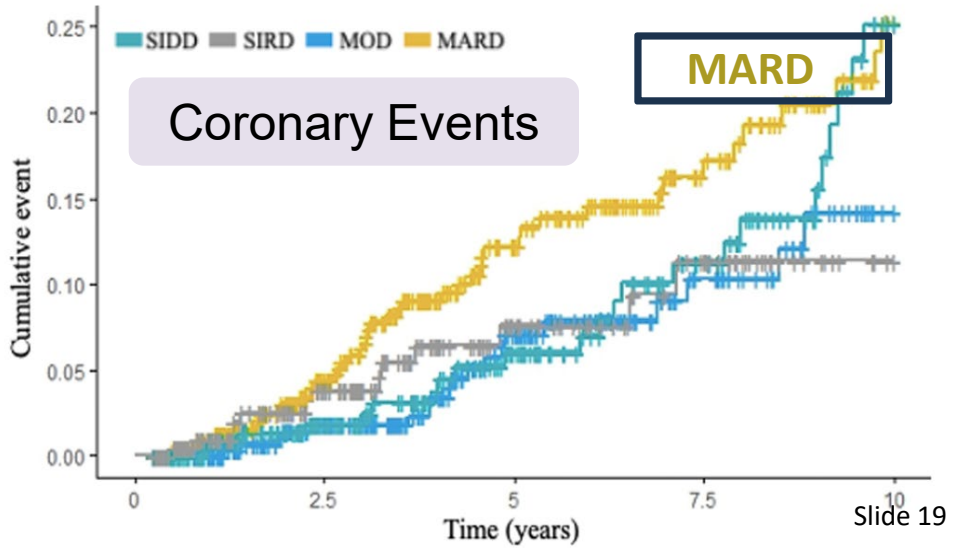
SIDD = Severe Insulin Deficient Diabetes
Low insulin secretion, poor metabolic control, increased risk of retinopathy and neuropathy

SIRD = Severe Insulin Resistant Diabetes
Insulin resistance, obesity, late onset, increased risk of nephropathy and fatty liver

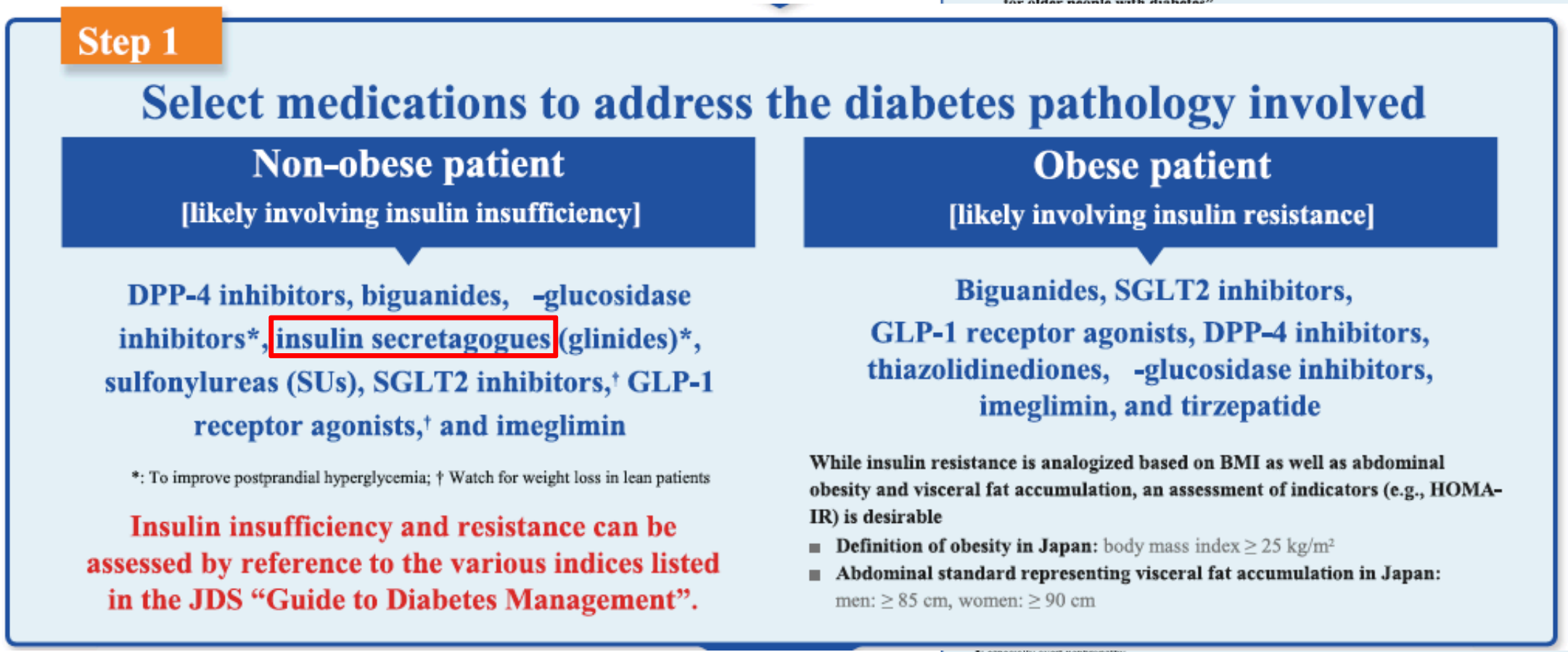
MOD = Mild Obesity-Related Diabetes
Obesity, early onset

MARD = Mild Age-Related Diabetes
Late onset, low risk of complications





Wang JY et al. Diab Res Clin Pract 2024 Nov;217:111872.



Determine if the patient has a relative/absolute indication for insulin

No

Yes → Insulin therapy

Determine the patient's HbA1c target value

In reference to the "Kumamoto Declaration 2013" and "Glycemic targets (HbA1c values)

*: especially overt nephropathy
†: some medications

Step 4

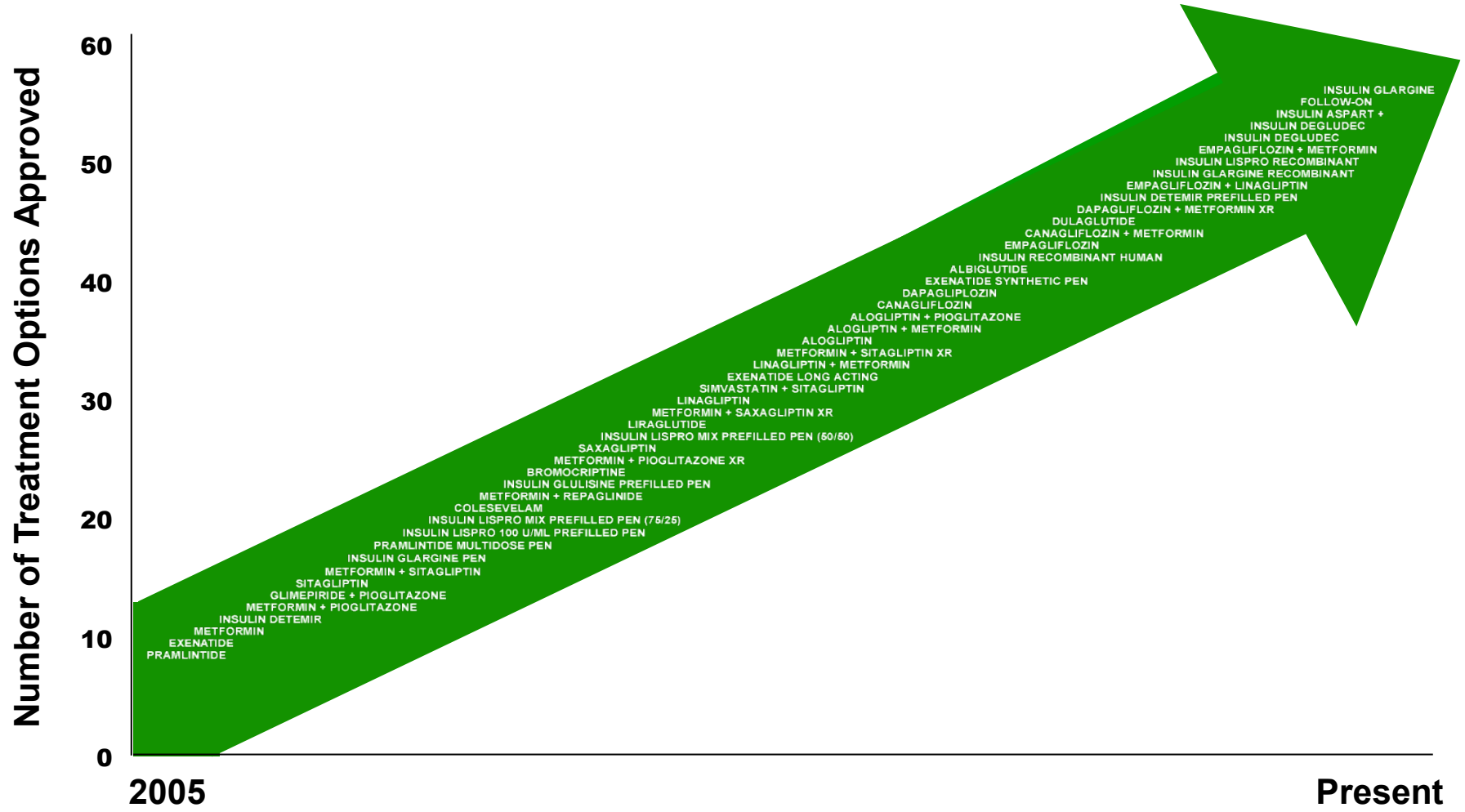
Select medication options with relevant patient characteristics in mind

in reference to adherence rates and medication costs listed in the separate table

Review the current medication regimen for possible revision every 3 months

Bouchi R, et al. J Diabetes Investig. 2024;15(9):1326-1342

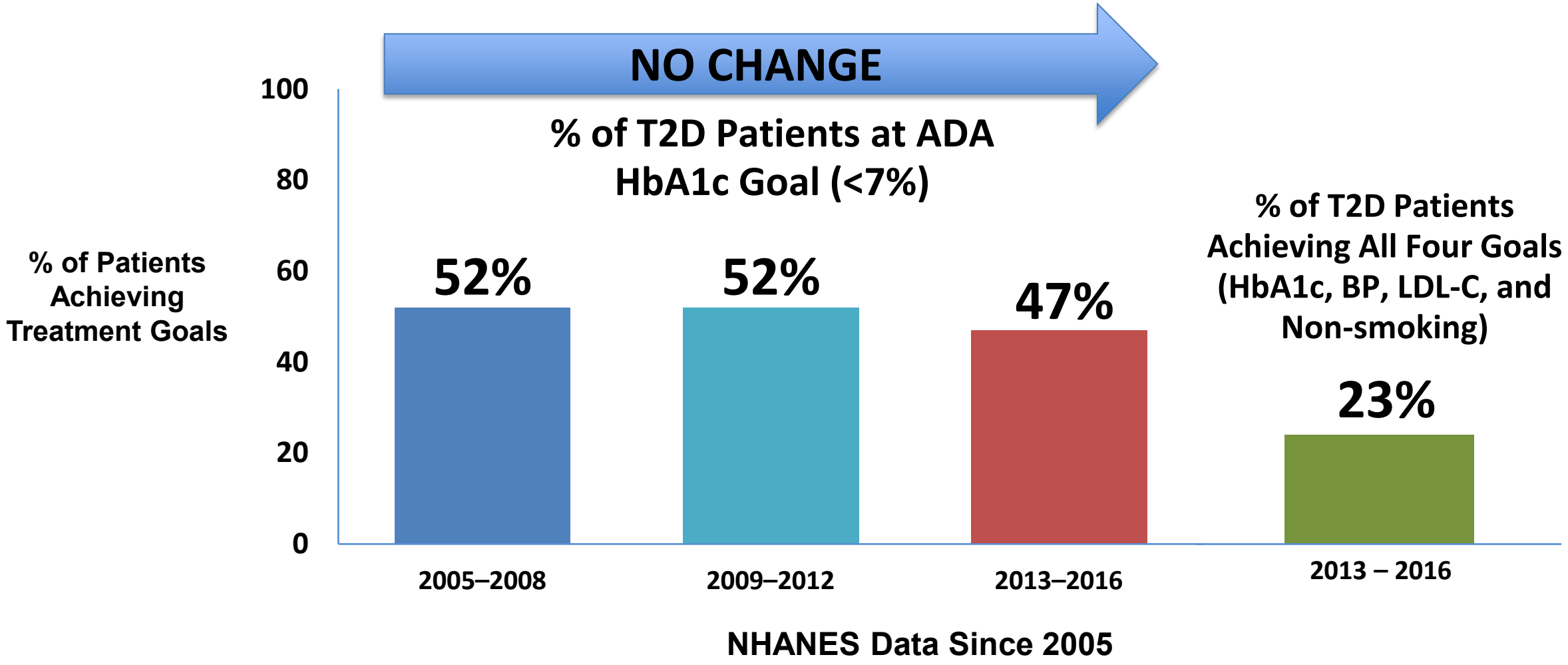
More Than 55 Type 2 Treatment Options Have Been Approved in the US Since 2005



Food and Drug Administration website.
https://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

T2D Glycemic Control is not Improving & Even Worsening

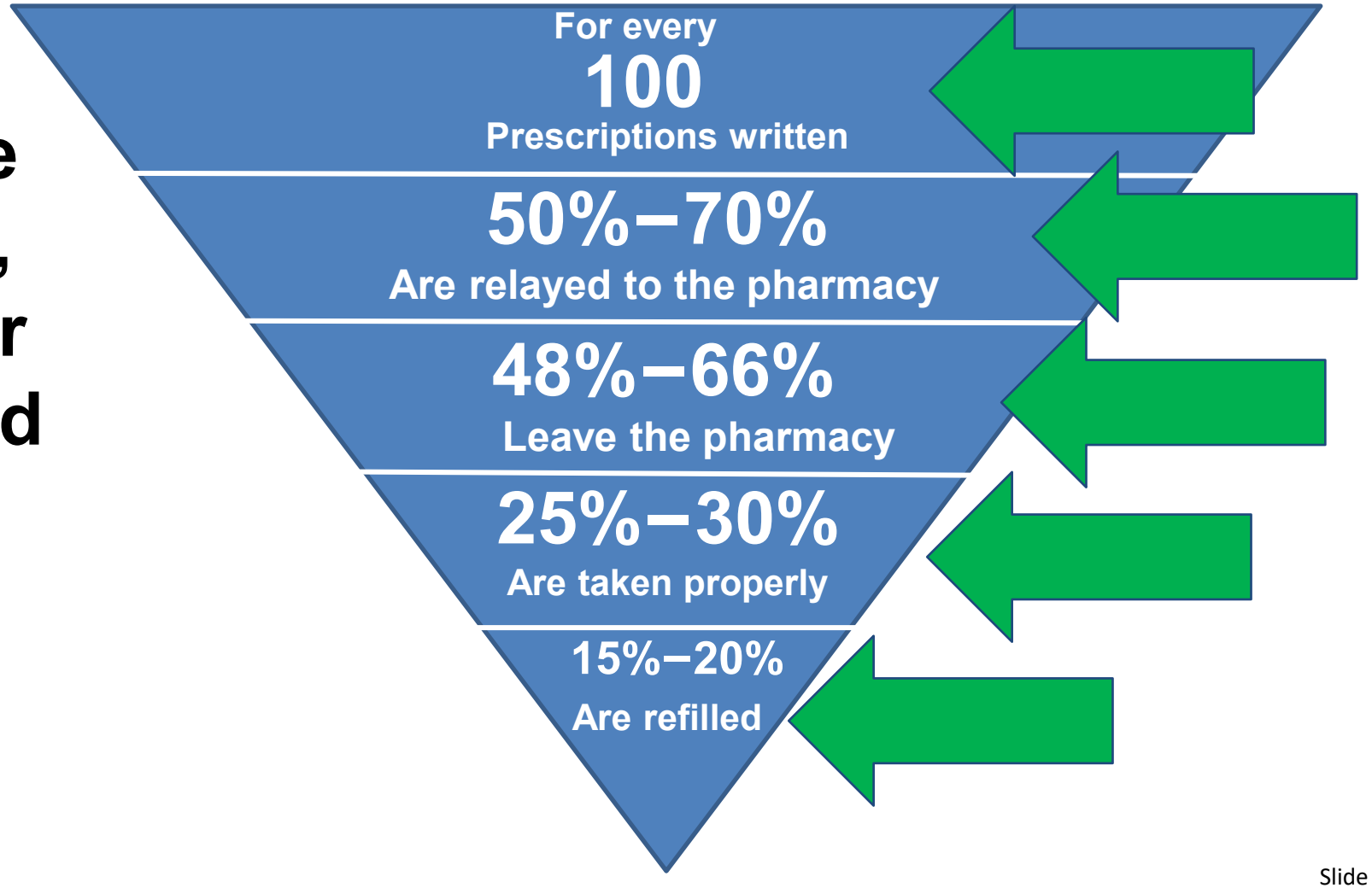
NHANES Data Analysis by Massachusetts General Hospital



P. Kazemian, D. Wexler; *JAMA Intern Med*. doi:10.1001/jamainternmed.2019.2396.

“Poor Adherence” with Type 2 Medications in the Real World

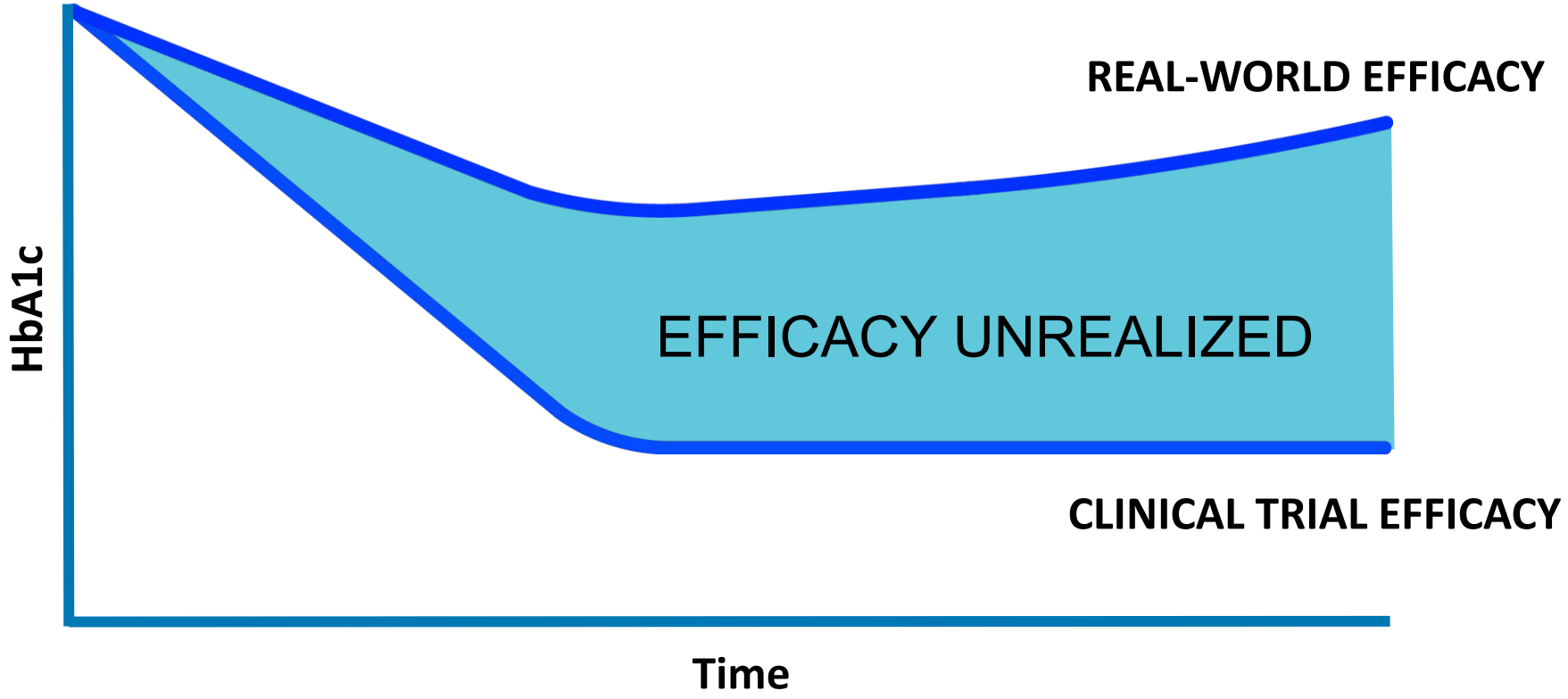
Prescriptions are not always <u>filled</u>, <u>taken properly</u>, or <u>refilled</u> as directed



Type 2 Diabetes in the Real World: The Elusive Nature of Glycemic Control

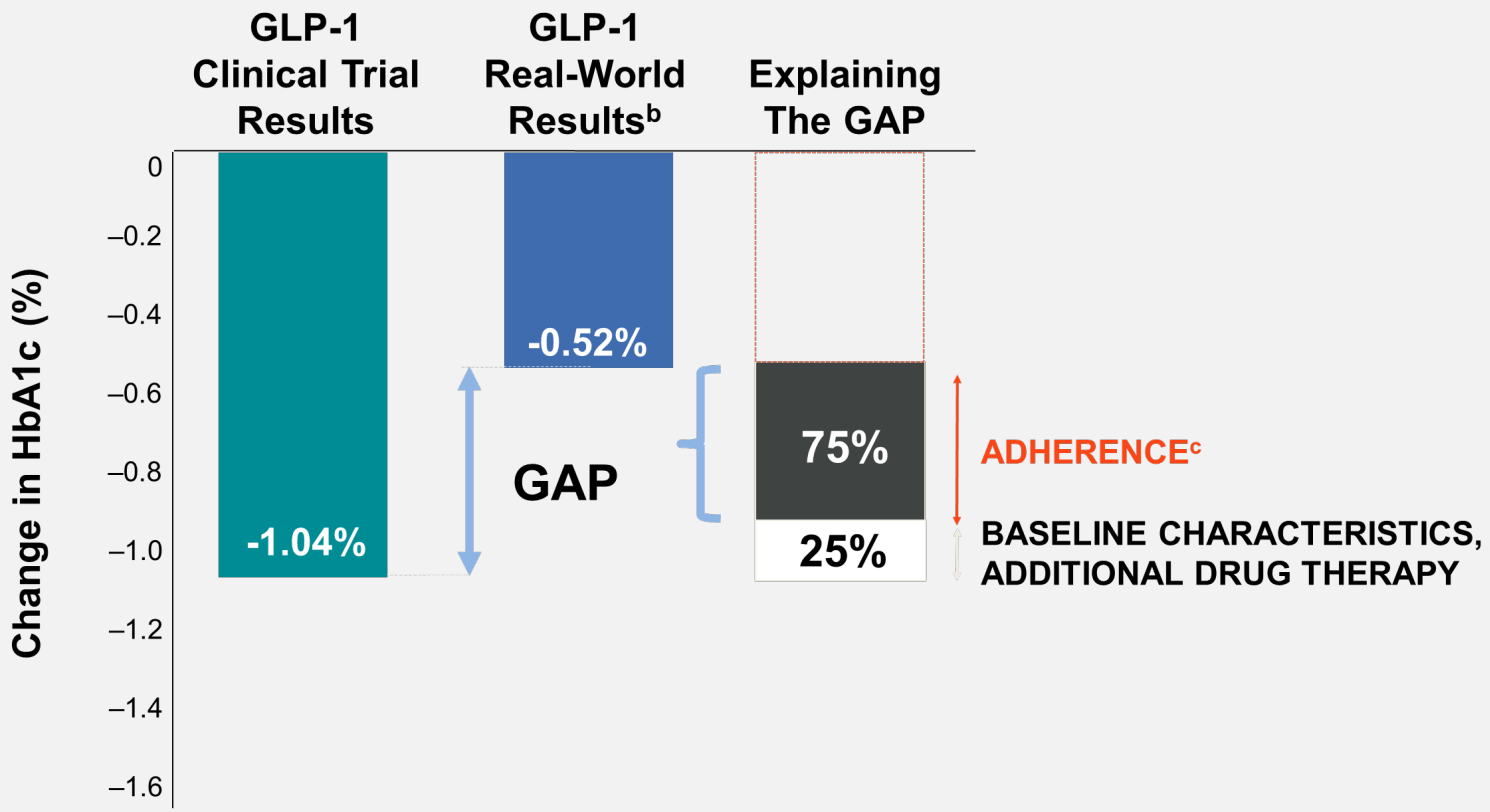
Steven V. Edelman[1,2,3] and William H. Polonsky[4,5]

Diabetes Care 2017;40:1425–1432 | https://doi.org/10.2337/dc16-1974



Efficacy in Clinical Trials is Not Translating to the Real World

Poor Adherence is a Key Contributor to the Efficacy Gap Between Clinical Trial Results & Real-World Results



RCT, randomized clinical trial.

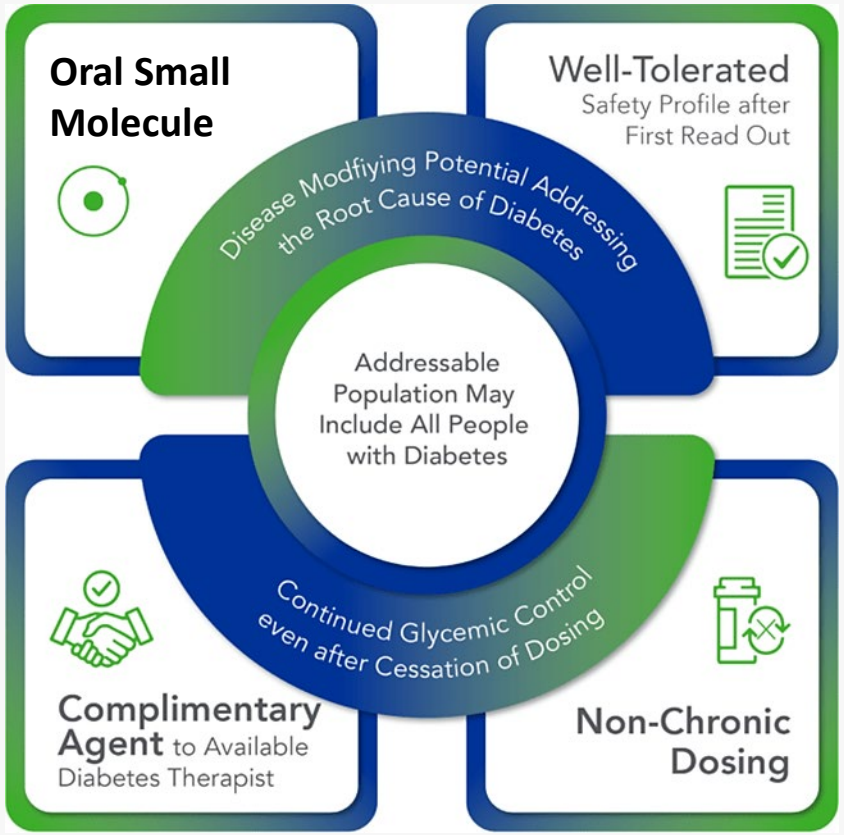
*A Linear regression model fitted to estimate the change in HbA1c 1 year after initiating GLP-1 RA or DPP-4i based on baseline and treatment characteristics.

[b]Optum/Humedica SmartFile database (2007–2014) was used [GLP-1 RA (221 patients); DPP-4i (652 patients)]. Change in HbA1c measured from drug initiation to 365±90 days later.

[c]Medical adherence classified as poorly adherent if percentage of days covered (PDC) <80%.

Carls GS et al. 76th ADA Scientific Sessions. June 10–14, 2016; Poster 117-LB.

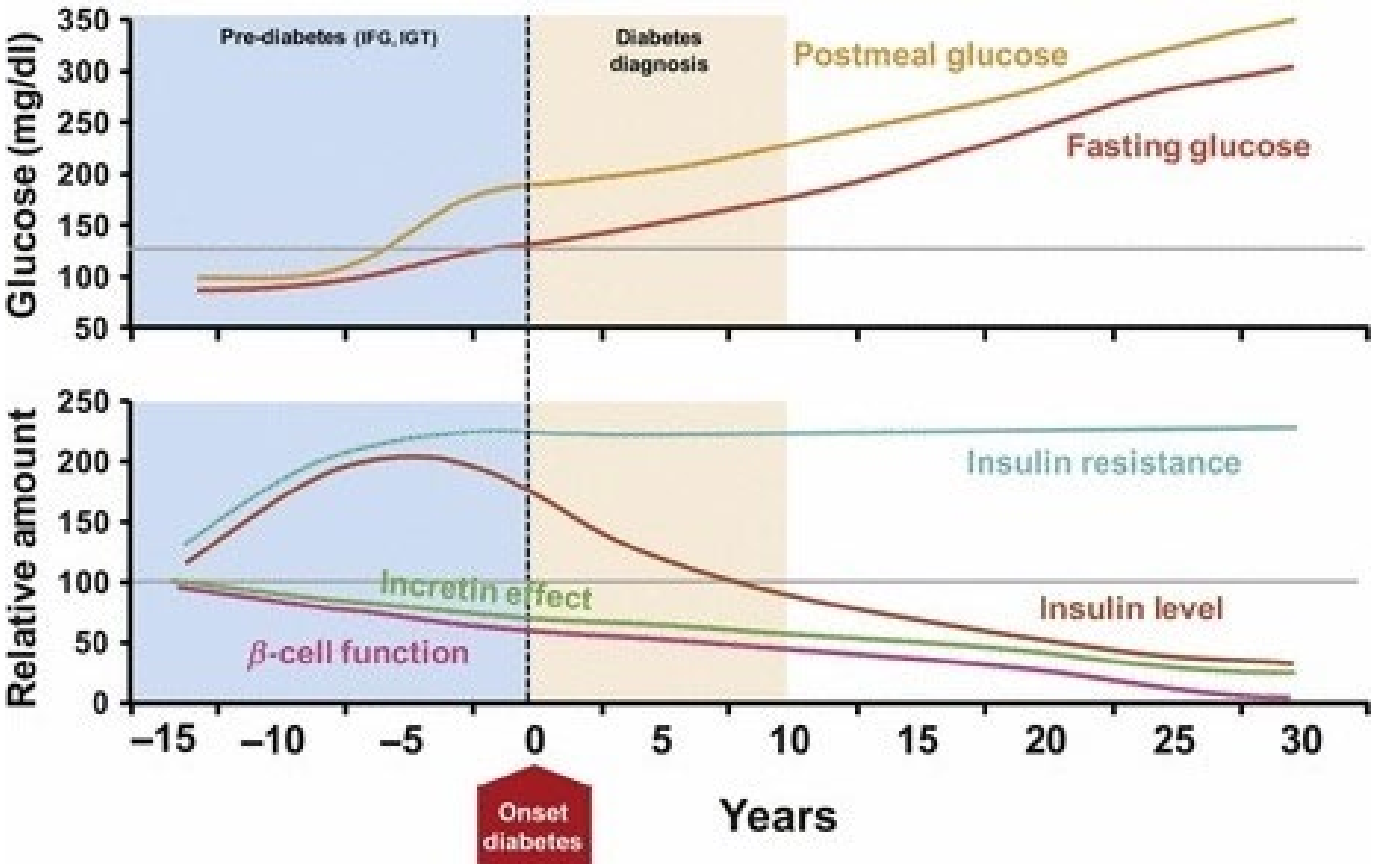
Icovamenib: First-in-Class Covalent Menin Inhibitor for the Treatment of Diabetes

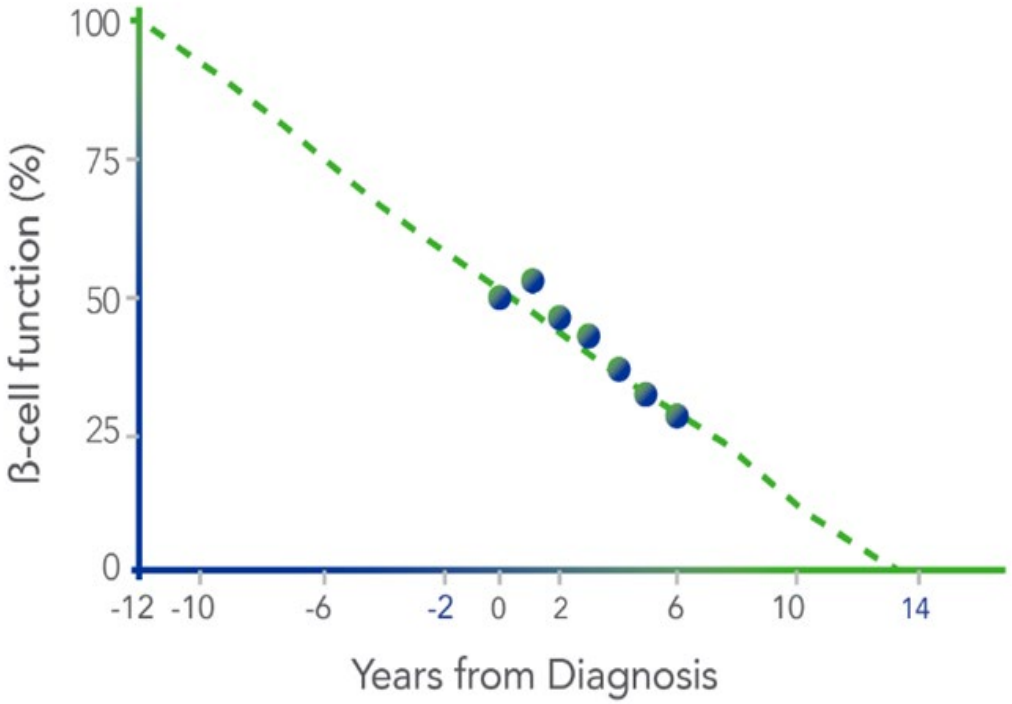


Key MOA: Beta Cell Mass & Function

- **Increased beta cell mass and function**
- **Increased Insulin Synthesis and Secretion**

Natural history of type 2 diabetes





DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

Menin Inhibition and Beta cell Function

Rohit N. Kulkarni, MD, PhD
Joslin Diabetes Center

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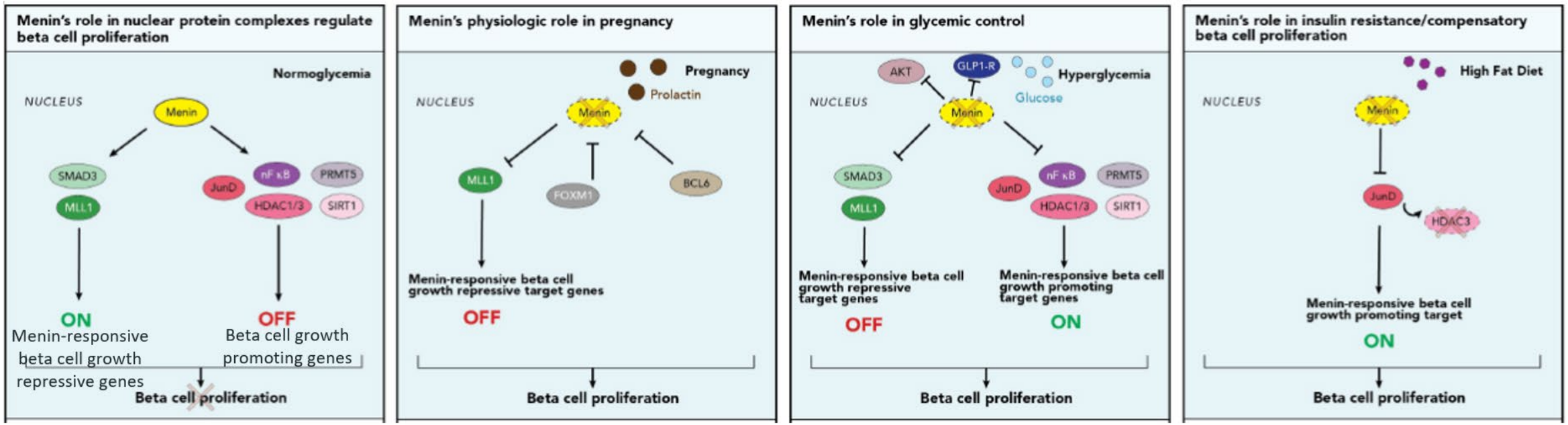
Role of Menin in Beta Cell Physiology

Pregnancy

Hyperglycemia

High fat diet



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Icovamenib

Preclinical Human Islet Data

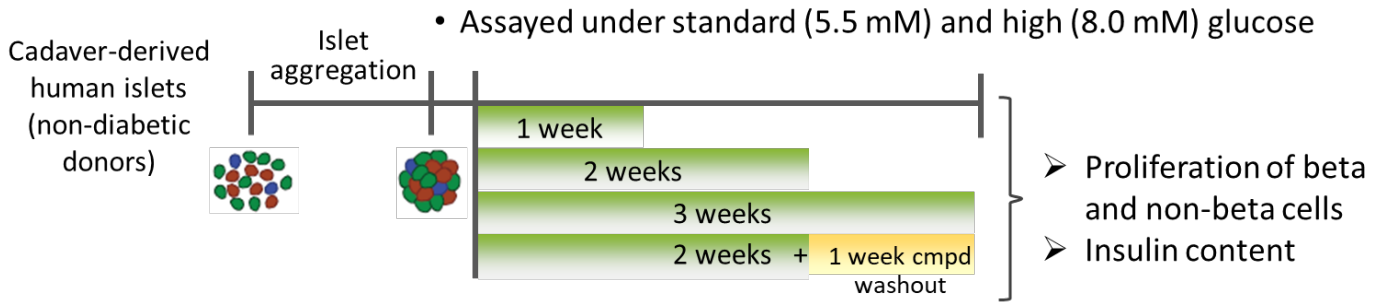
in vitro

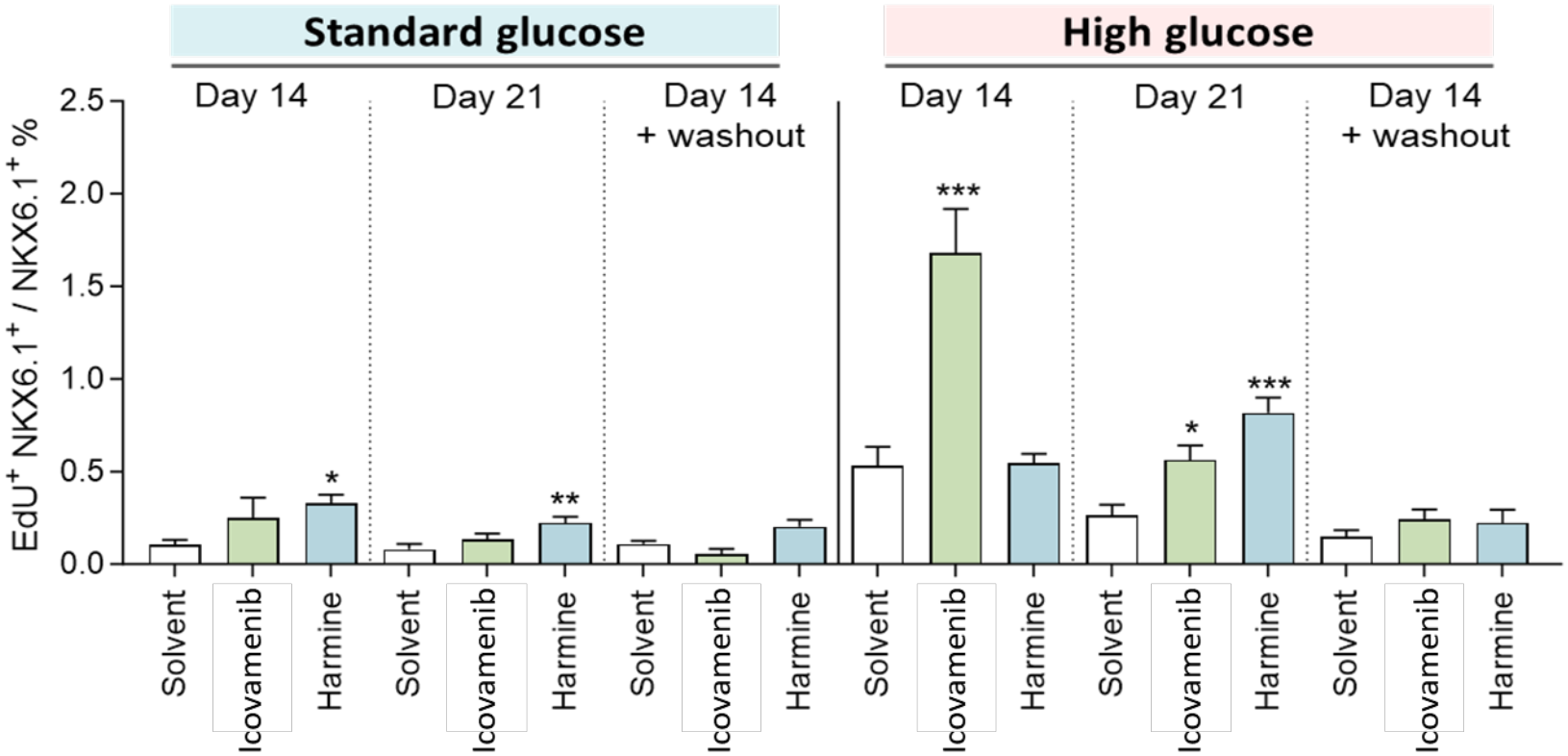
Icovamenib promotes selective proliferation of islet beta cells

Donor characteristics:

	Age	BMI	HbA1c
Donor 1	19	23.2	5.8

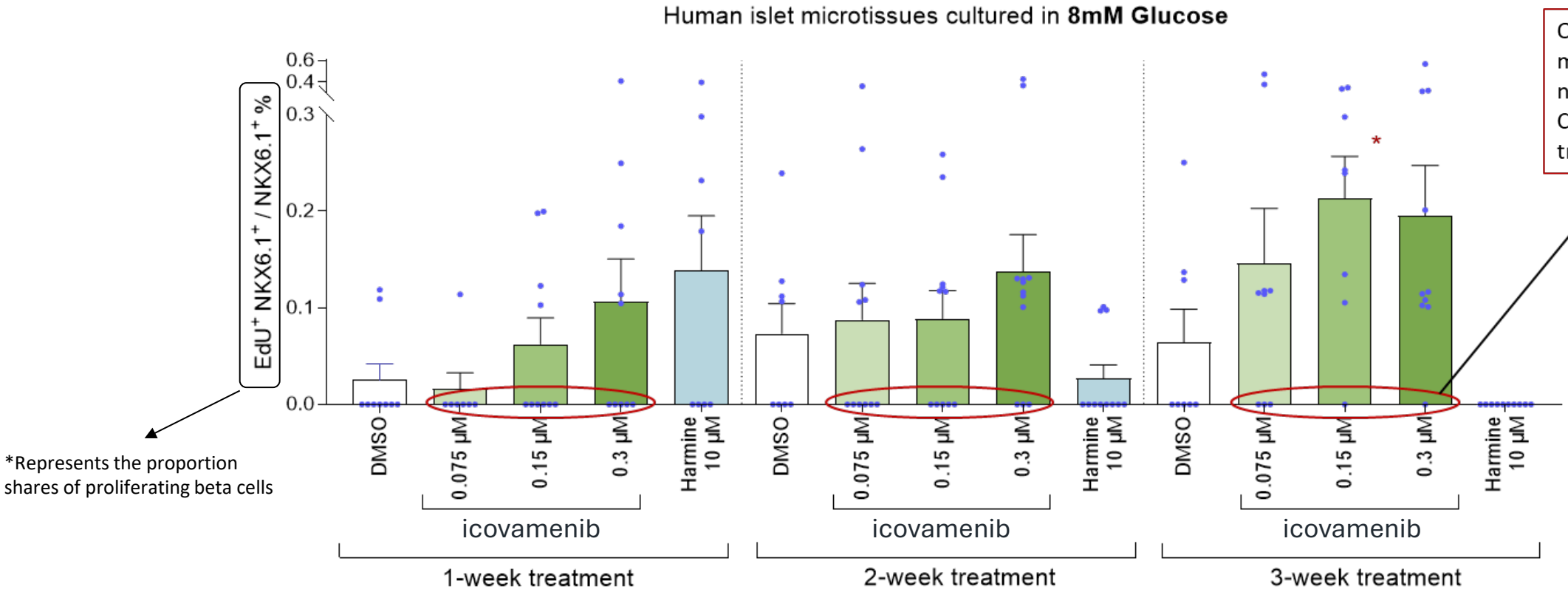
Icovamenib: 0.3 µM
Harmine: 10 µM





Longer dosing is predicted to generate an increase in responder rates based on human donor islet experiments

Proliferating beta cells plotted as fraction of total beta cells



Data represent mean ±SEM of 1 donor with n = 9-12 technical replicates.
One-way ANOVA with Dunnett's post hoc test rel. to DMSO control. *p < 0.05, **p < 0.01, ***p < 0.001

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Icovamenib

Combination with GLP-1-based therapies *in vitro*

Menin suppresses GLP-1 receptor signaling*

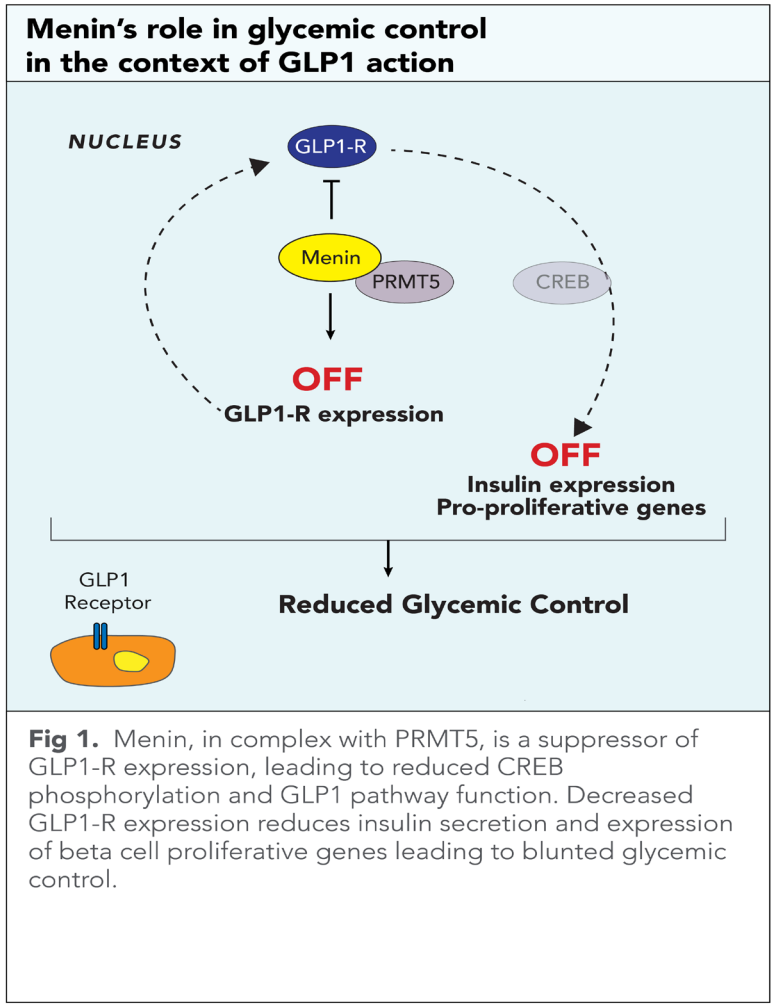


Fig 1. Menin, in complex with PRMT5, is a suppressor of GLP1-R expression, leading to reduced CREB phosphorylation and GLP1 pathway function. Decreased GLP1-R expression reduces insulin secretion and expression of beta cell proliferative genes leading to blunted glycemic control.

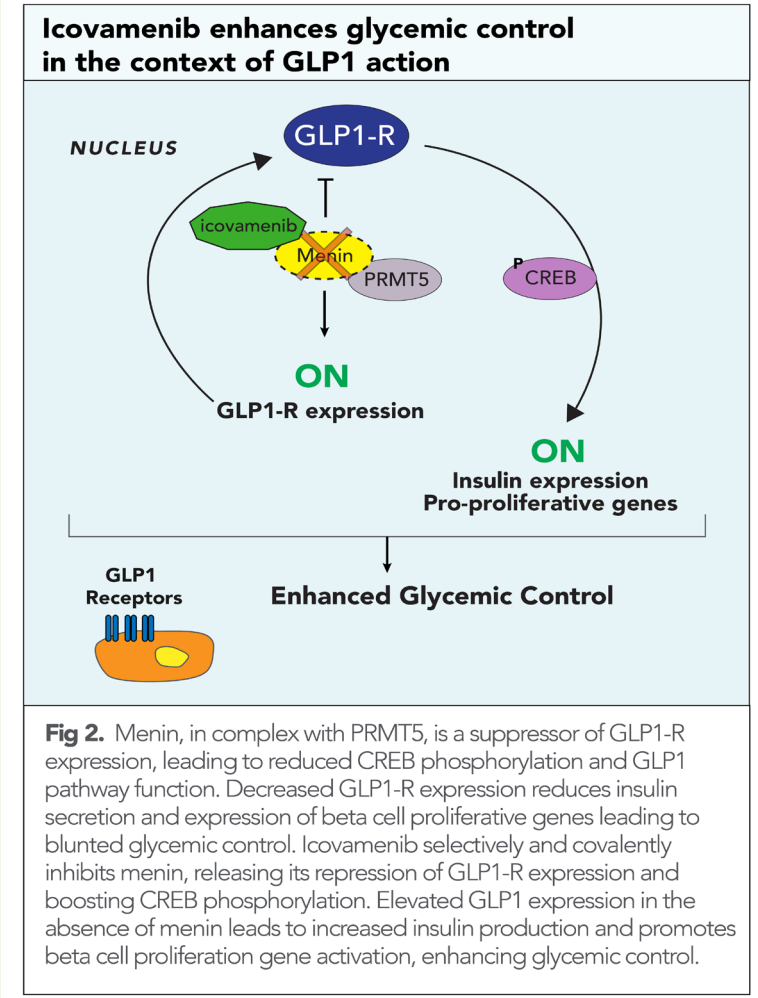
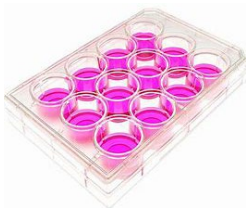


Fig 2. Menin, in complex with PRMT5, is a suppressor of GLP1-R expression, leading to reduced CREB phosphorylation and GLP1 pathway function. Decreased GLP1-R expression reduces insulin secretion and expression of beta cell proliferative genes leading to blunted glycemic control. Icovamenib selectively and covalently inhibits menin, releasing its repression of GLP1-R expression and boosting CREB phosphorylation. Elevated GLP1 expression in the absence of menin leads to increased insulin production and promotes beta cell proliferation gene activation, enhancing glycemic control.

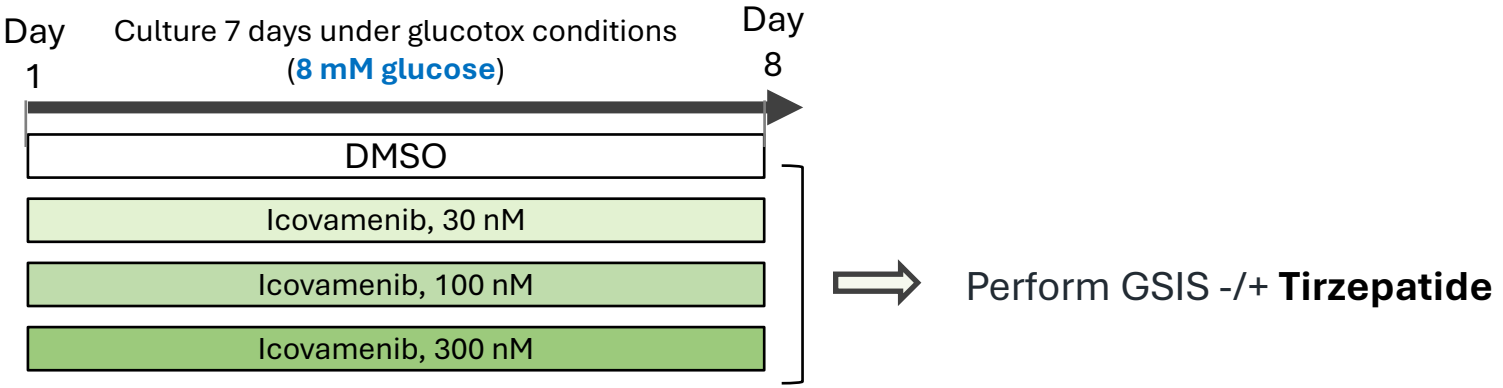
*AJP-Endocrinol Metab • doi:10.1152/ajpendo.00241.2016 • www.ajpendo.org; J. Cell Biol. 2019 Vol. 218 No. 3 855–870; The FASEB Journal. 2025;39:e70370.

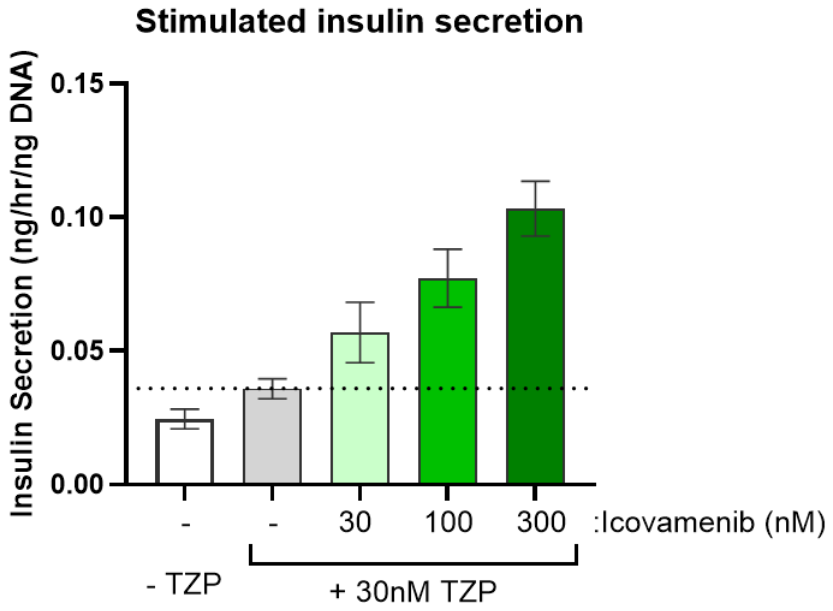
Combination Treatment: Icovamenib enhanced responsiveness of islets to GLP-1/GIP dual receptor agonist Tirzepatide

Cadaver derived human islets



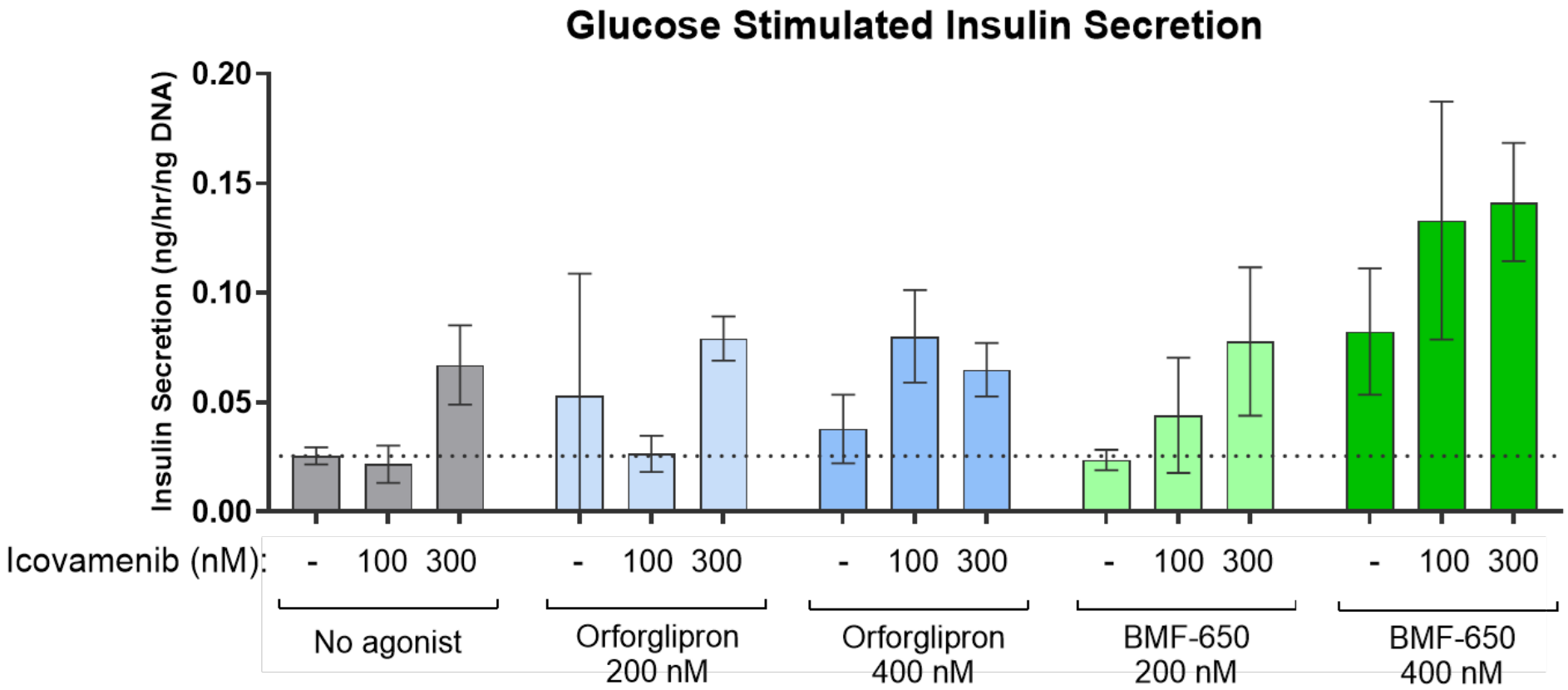
Non-diabetic donor:
38-year old white male, BMI: 29.2, HbA1C 5.2%



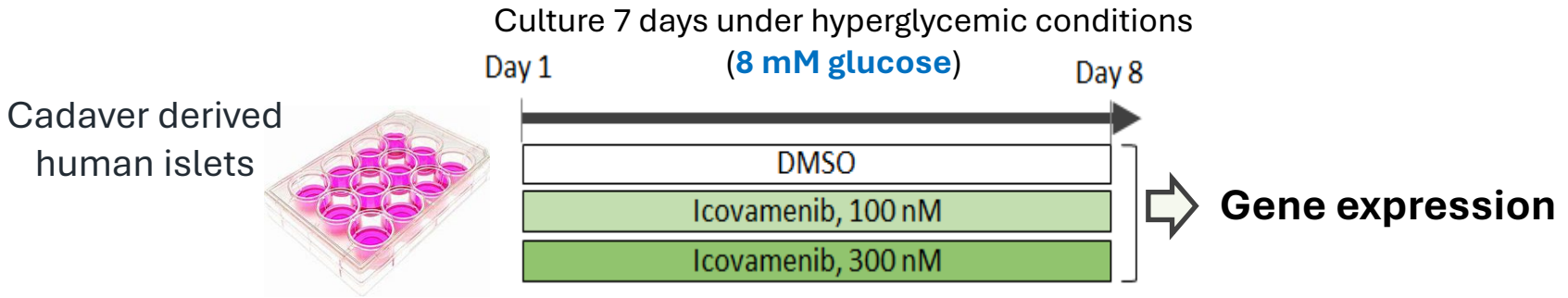


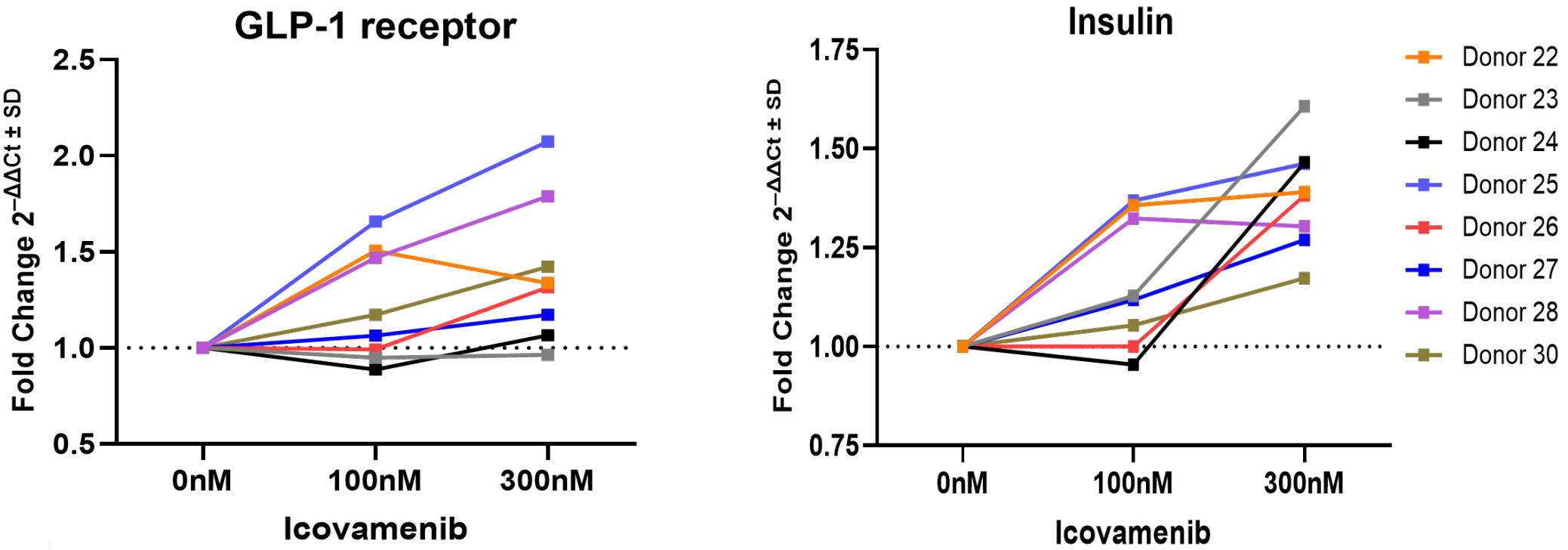
GSIS increased by 58 to 186% with combination of icovamenib + tirzepatide vs tirzepatide alone

Combination Treatment: Icovamenib enhanced responsiveness of islets to the small molecule GLP-1 receptor agonists - Orforglipron and BMF-650

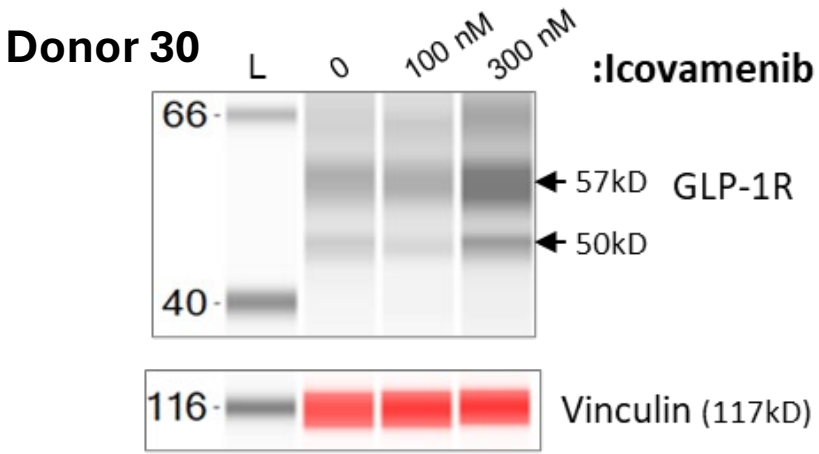


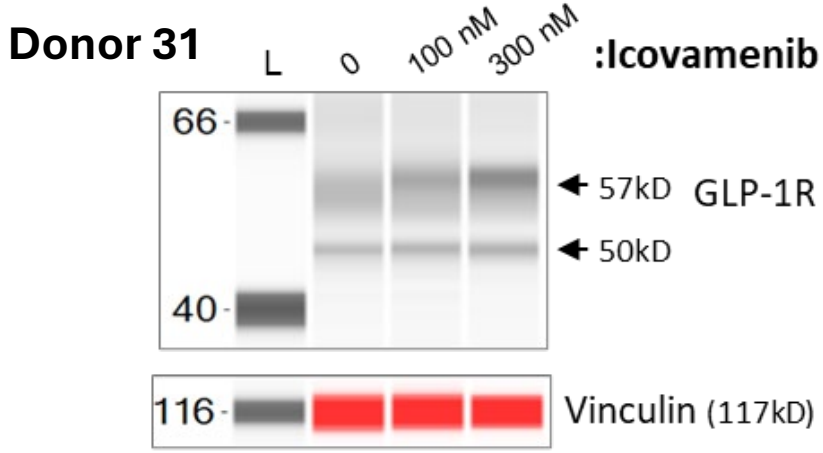
Icovamenib enhances GLP-1 receptor and insulin transcript levels

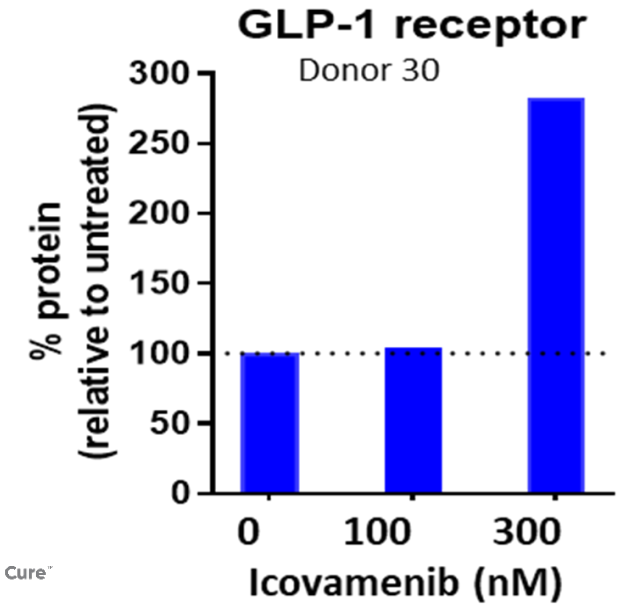


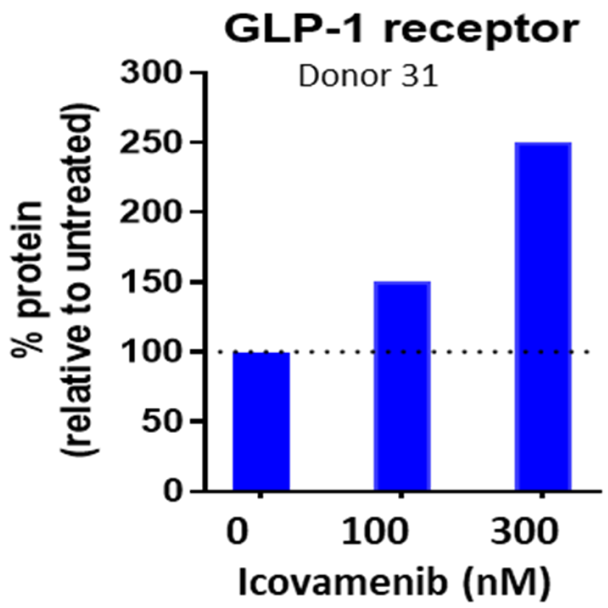


Icovamenib treatment increases GLP-1 receptor protein expression

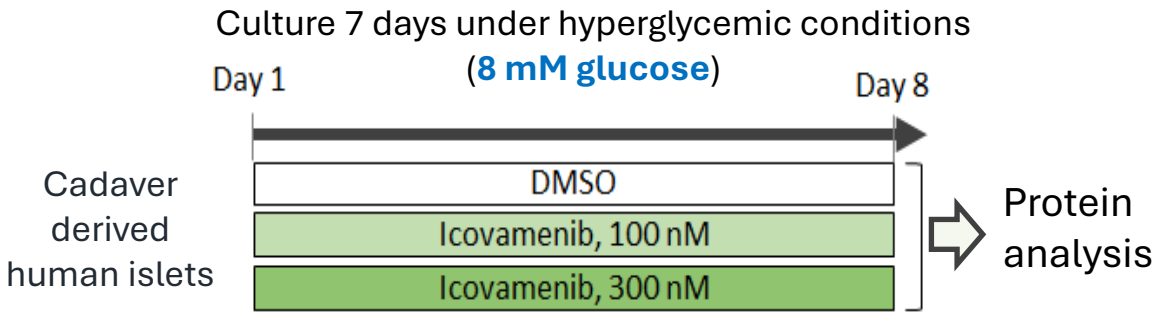


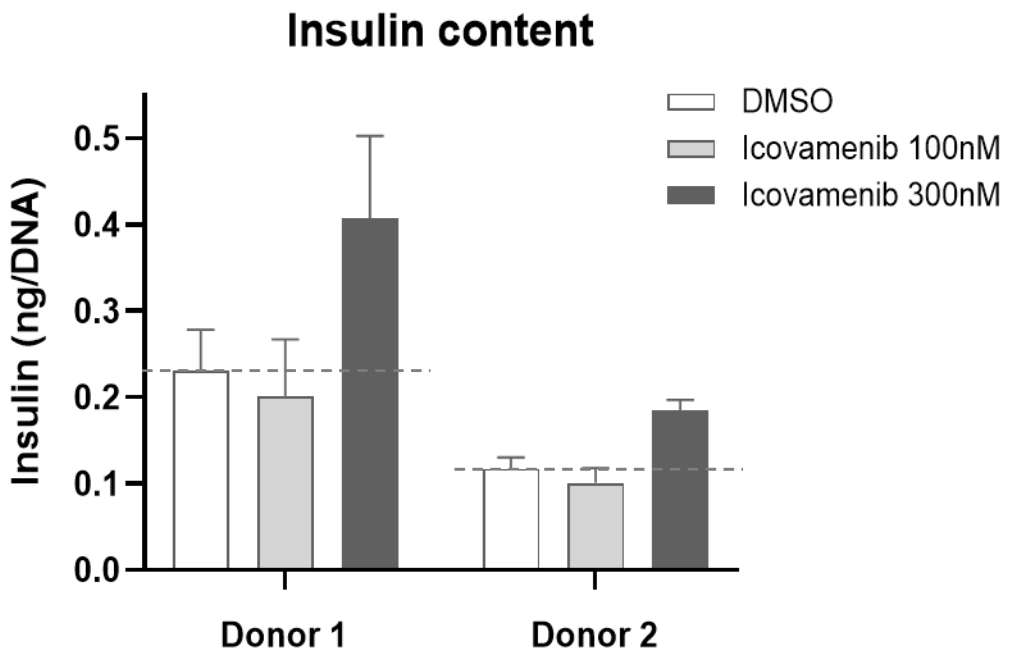


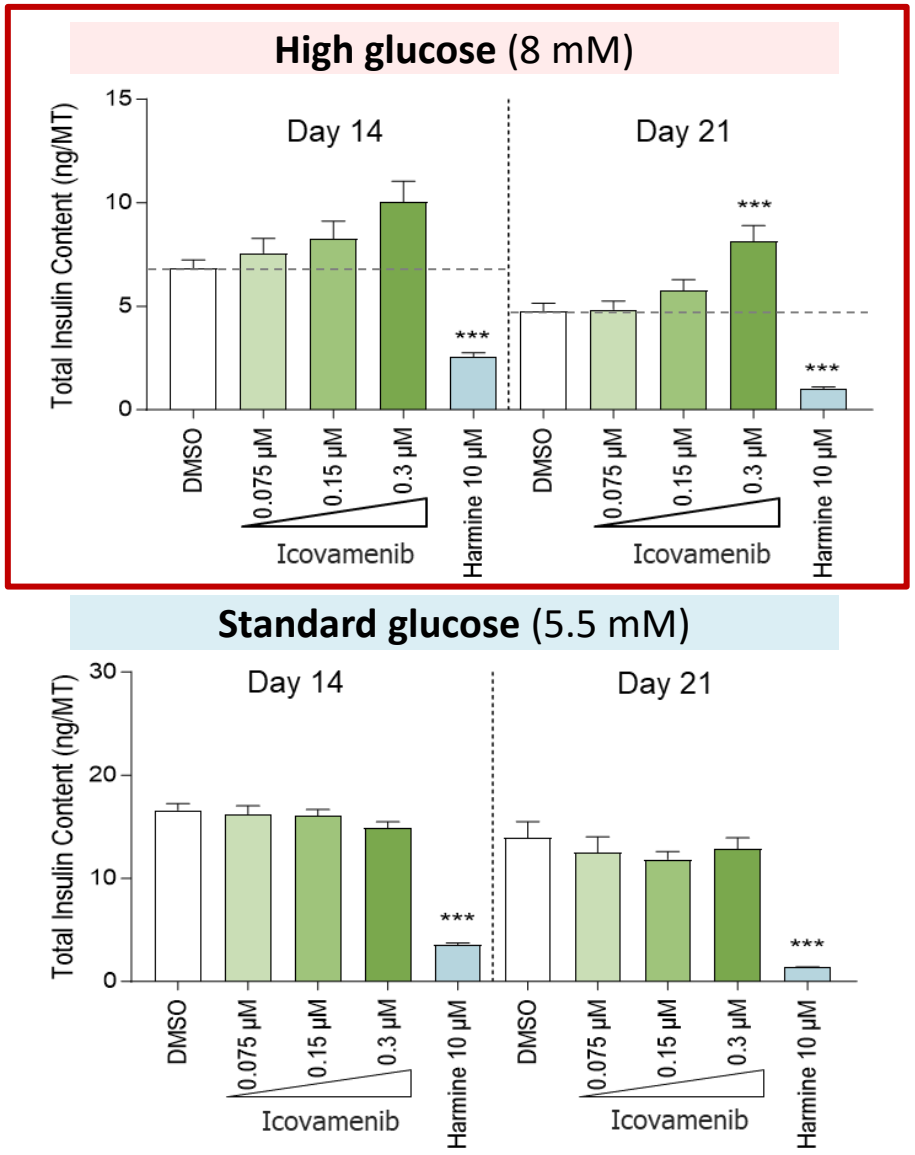




Icovamenib treatment increases cellular insulin expression







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Icovamenib

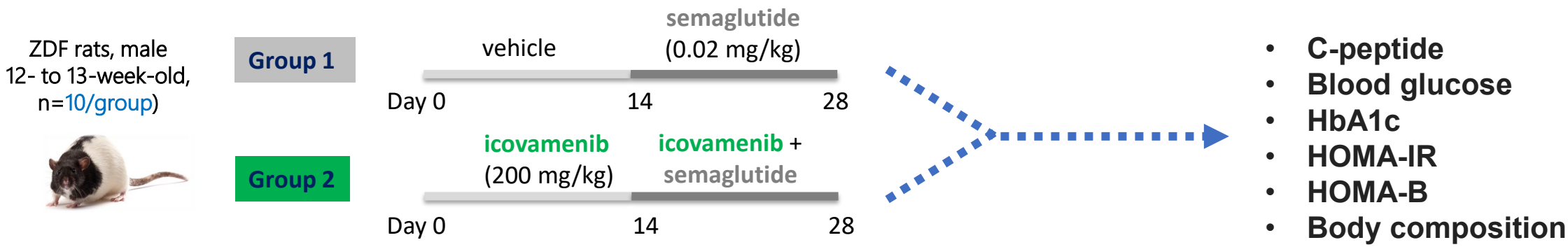
Combination with GLP-1 based therapies *in vivo*

Icovamenib + Low-dose Semaglutide Study in ZDF Rat Model of T2D

- Efficacy of icovamenib in combination with a GLP-1 receptor agonist (i.e., semaglutide) was evaluated in the Zucker Diabetic Fatty rats, a T2D animal model of insulin resistance

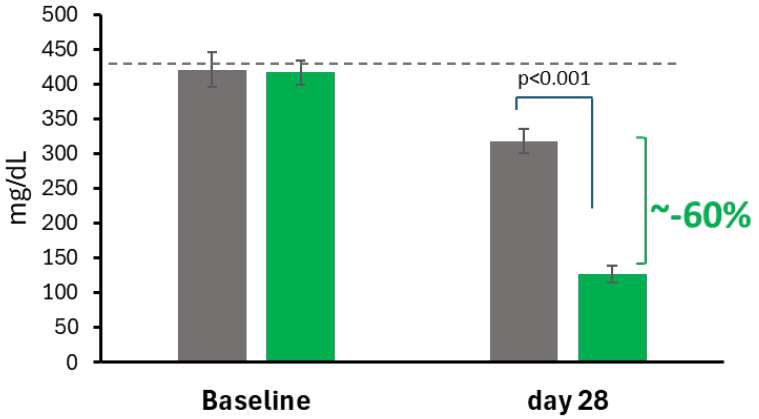
- Two groups of 10 ZDF rats each

  Group 1: Icovamenib (day 1 through day 28) + low dose semaglutide (day 14 through day 28)
  Group 2: Semaglutide alone (day 14 through day 28)

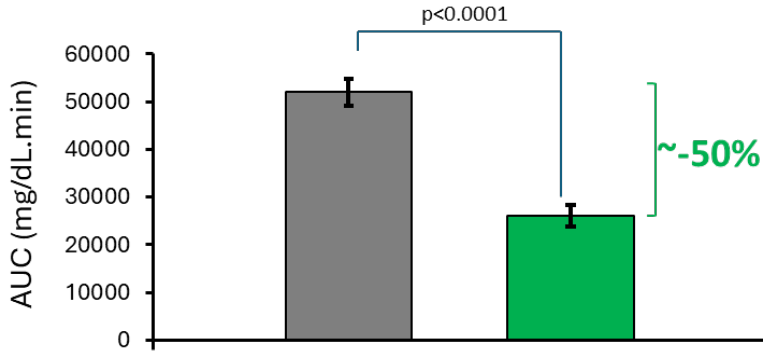


Icovamenib + Low-dose Semaglutide Study in ZDF Rat Model of T2D

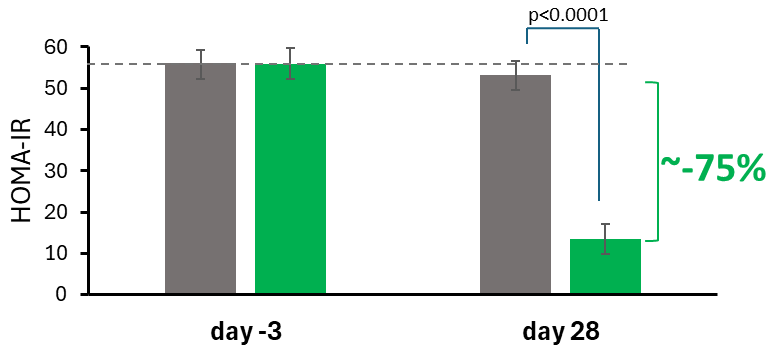
Fasting Blood Glucose



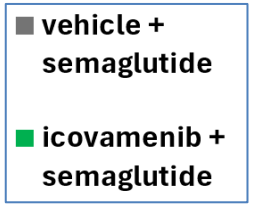
OGTT – Day 28



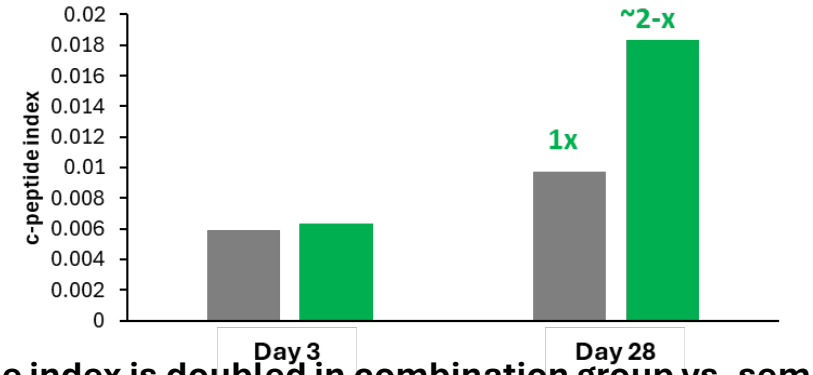
HOMA-IR



Significant reduction in combination group vs. semaglutide alone



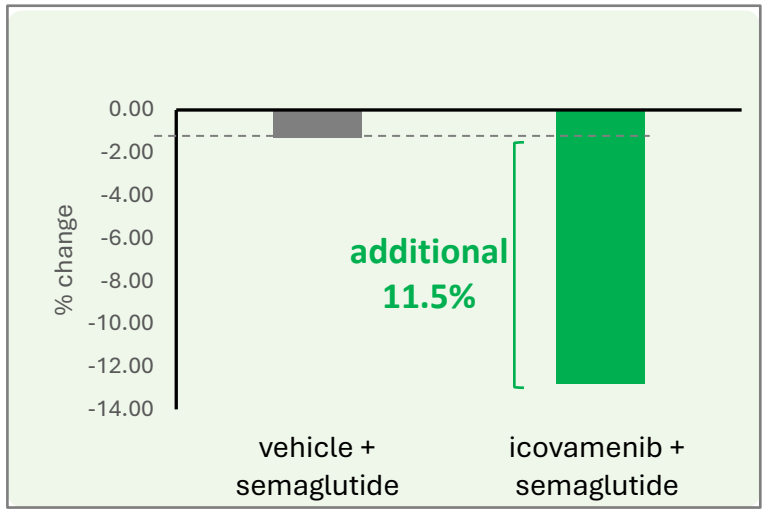
C-peptide Index



C-peptide index is doubled in combination group vs. semaglutide alone

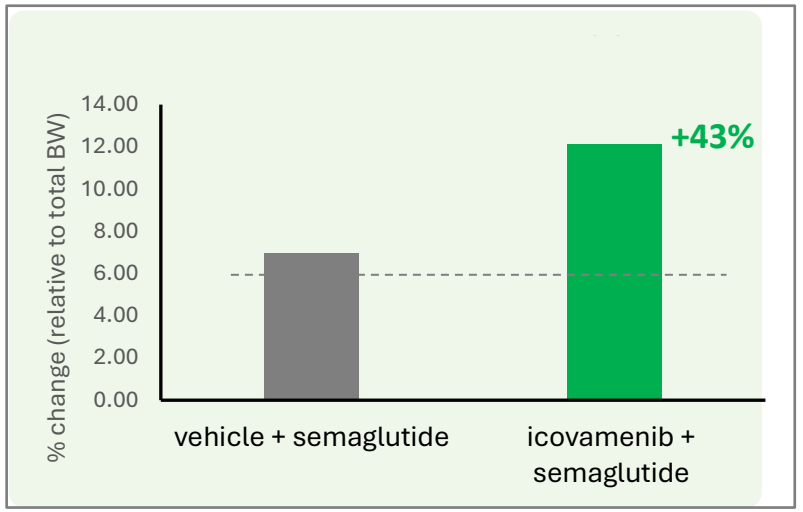
Combination treatment of icovamenib and low-dose semaglutide reduces body weight and boosts lean mass

Body Weight



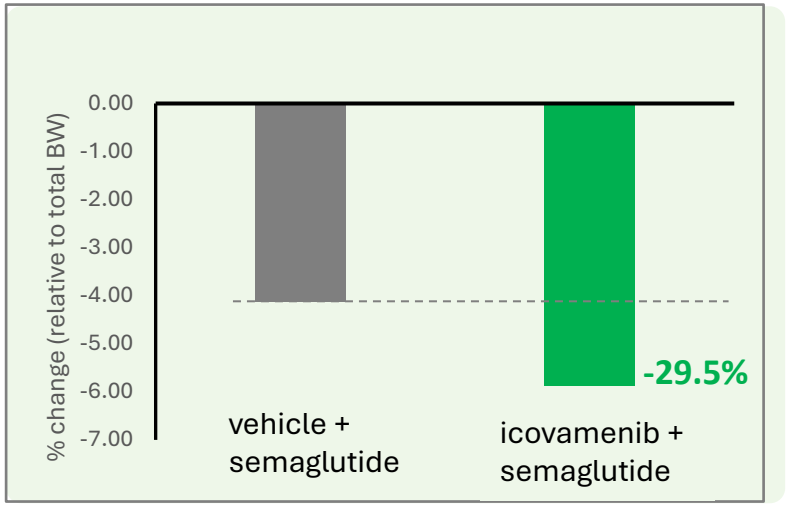
Greater body weight loss in combination group vs. low dose semaglutide at Day 25

Lean Mass Composition



Higher gain in lean mass in combination group vs. low dose semaglutide at Day 25

Fat Mass Composition



Greater reduction in fat mass in combination group vs. low dose semaglutide at Day 25

Icovamenib | Preclinical Summary

Icovamenib promotes controlled proliferation of beta cells in human islet microtissues ex vivo, in a glucose- and dose- dependent manner

In combination studies with GLP-1 receptor agonists, icovamenib enhanced the responsiveness of human islets to semaglutide and tirzepatide.

In vivo data indicates potential for combination therapy with GLP-1 receptor agonists with improvements in glycemic control and body composition

Next, we will explore how this mechanism of action translates to real-world patients with T2D

COVALENT-111: Topline Results at 26 Weeks

Juan Pablo Frías, MD
Chief Medical Officer and Head of Diabetes
Biomea Fusion

ATTD Breakfast Symposium – 21 March 2025

biomea FUSION™ | We Aim to Cure™

Trial Design

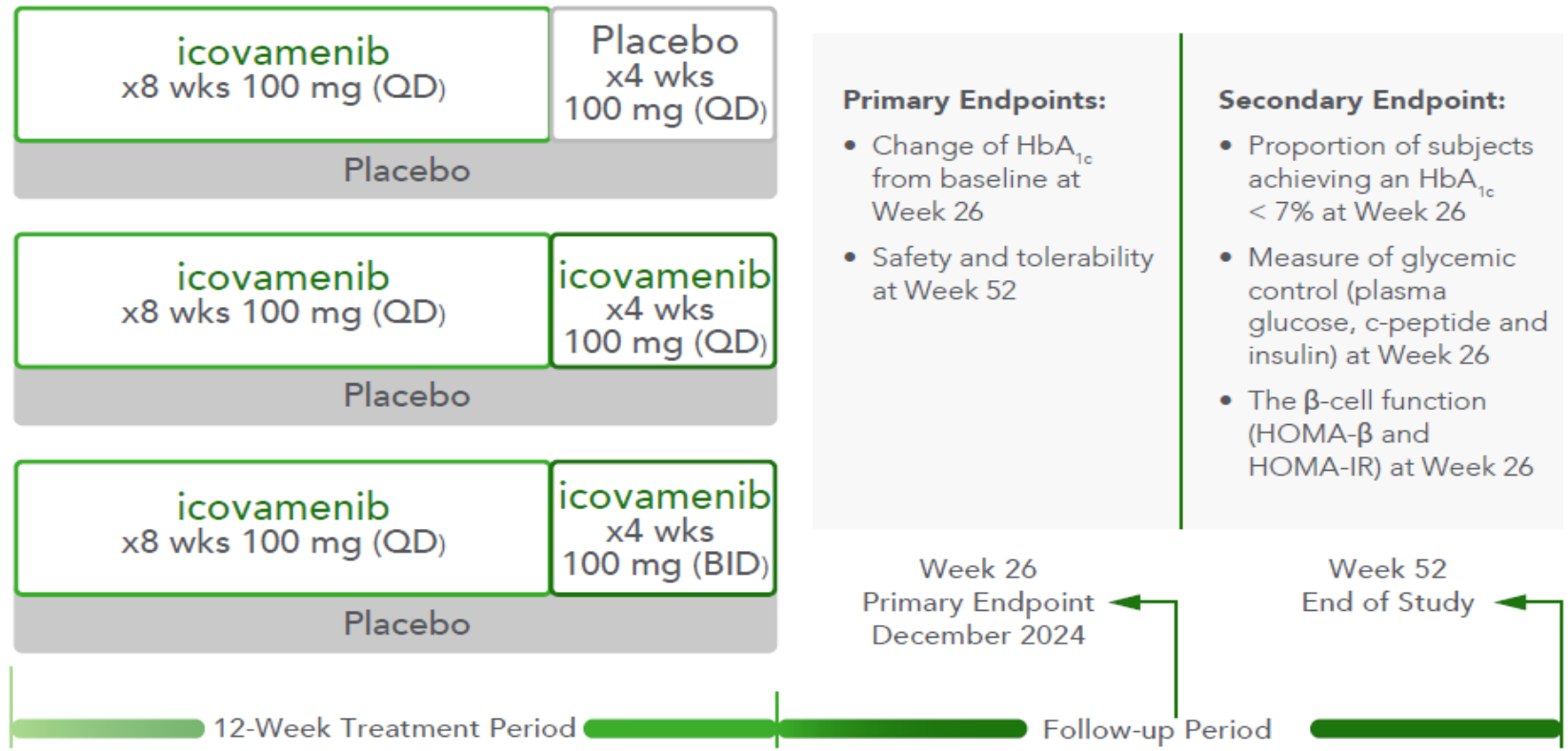
Phase 2a Randomized, Double-Blind, Placebo-controlled Study in Participants with T2D

N=216 Planned Participants

3:1

Eligibility Criteria

- Adults (18-65 yo) with T2D (<7 yrs)
- HbA1c 7.0-10.5%
- BMI 25-40 kg/m2
- Treated with up to 3 antidiabetic agents (excluding insulin and SFUs)
- N=72 participants per arm (3:1 ratio, icovamenib:PBO)



Primary Endpoints:

- Change of HbA_{1c} from baseline at Week 26
- Safety and tolerability at Week 52

Secondary Endpoint:

- Proportion of subjects achieving an HbA_{1c} < 7% at Week 26
- Measure of glycemic control (plasma glucose, c-peptide and insulin) at Week 26
- The β-cell function (HOMA-β and HOMA-IR) at Week 26

Baseline Demographics and Characteristics

Per Protocol Population on 1+ antihyperglycemic agents at baseline (N=165)

Parameter Mean (SD) or %	Arm A icovamenib (N=45)	Arm B icovamenib (N=37)	Arm C icovamenib (N=33)	Combined Arms icovamenib (N=115)	Combined Arms Placebo (N=50)
Age (yr)	55 (7)	56 (6)	51 (10)	54 (8)	55 (7)
Duration of T2D Diagnosis (yr)	4.3 (1.8)	4.7 (1.8)	4.2 (2.2)	4.4 (1.9)	4.3 (2.0)
Sex (% Female)	31	54	36	40	42
HbA1c (%)	8.3 (1.1)	8.3 (1.0)	8.0 (0.8)	8.2 (1.0)	8.3 (1.0)
Fasting C-peptide (ng/mL)	3.4 (1.2)	3.9 (1.7)	3.7 (1.8)	3.7 (1.5)	3.5 (1.4)
BMI (kg/m^2)	30.9 (4.7)	32.6 (4.5)	32.4 (4.9)	31.9 (4.7)	32.6 (4.1)
BMI <30 kg/m^2 (%)	49	24	30	36	26
BMI ≥30 kg/m^2 (%)	51	73	70	63	74

Demographics and baseline characteristics well matched between icovamenib- and placebo-treated participants

Antihyperglycemic Agents at Baseline

Per Protocol Population on 1+ antihyperglycemic agents at baseline (N=165)

Parameter	Arm A icovamenib (N=45)	Arm B icovamenib (N=37)	Arm C icovamenib (N=33)	Combined Arms icovamenib (N=115)	Combined Arms Placebo (N=50)
Number of T2D Medications, n (%)					
0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1	39 (87)	23 (62)	23 (70)	85 (74)	41 (82)
2	4 (9)	11 (30)	7 (21)	22 (19)	7 (14)
3	2 (4)	3 (8)	3 (9)	8 (7)	2 (4)
Metformin Monotherapy, n (%)	36 (80)	18 (49)	22 (67)	76 (66)	38 (76)
SGLT2i, n (%)	6 (13)	13 (35)	8 (24)	27 (23)	8 (16)
DPP4i, n (%)	3 (7)	5 (14)	3 (9)	11 (10)	2 (4)
GLP-1 based agent, n (%)	3 (7)	3 (8)	5 (15)	11 (10)	4 (8)

Most participants treated with metformin monotherapy with approximately 20% treated with SGLT2i, 10% with DPP4i, and 10% with GLP-based medicines

T2D Subtype at Baseline

Per Protocol Population on 1+ antihyperglycemic agents at baseline (N=165)

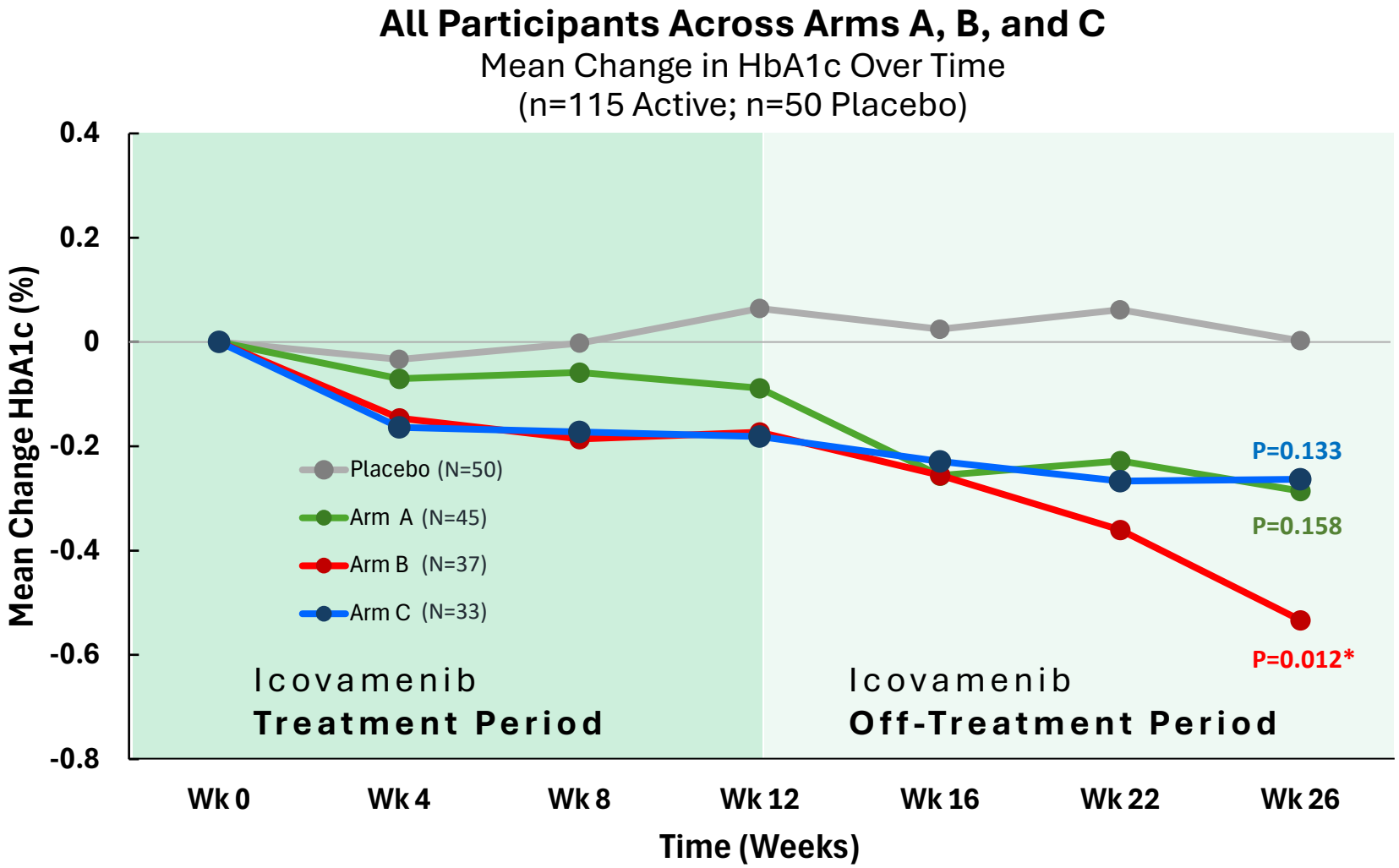
Parameter	Arm A icovamenib (N=45)	Arm B icovamenib (N=37)	Arm C icovamenib (N=33)	Combined Arms icovamenib (N=115)	Combined Arms Placebo (N=50)
SIDD, n (%)	12 (27)	7 (19)	4 (12)	23 (20)	11 (22)
MARD, n (%)	11 (24)	6 (16)	5 (15)	22 (19)	8 (16)
MOD, n (%)	20 (44)	21 (57)	23 (70)	64 (56)	27 (54)
SIRD, n (%)	2 (4)	3 (8)	1 (3)	6 (5)	4 (8)

SIDD, Severe Insulin-Deficient Diabetes
MARD, Mild Age-Related Diabetes
MOD, Mild Obesity-Related Diabetes
SIRD, Severe Insulin-Resistant Diabetes

Despite all participants being overweight or obese, approximately 40% were in the insulin-deficient subgroups (SIDD and MARD)

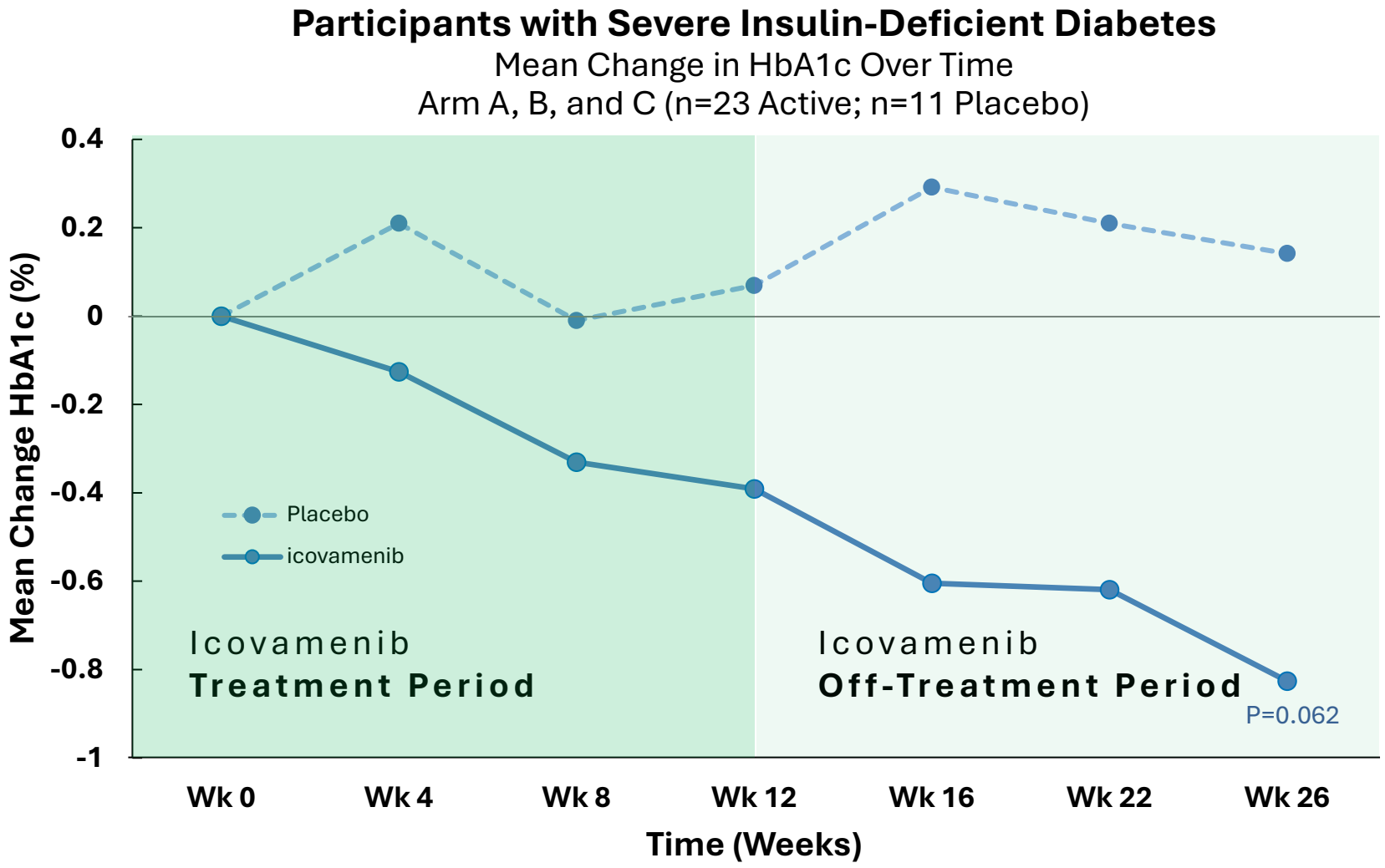
Change in HbA1c from Baseline at Week 26 by Study Arm

Per Protocol Population taking 1+ antihyperglycemic medications at Baseline, by study arm (A, B, C, and Placebo)

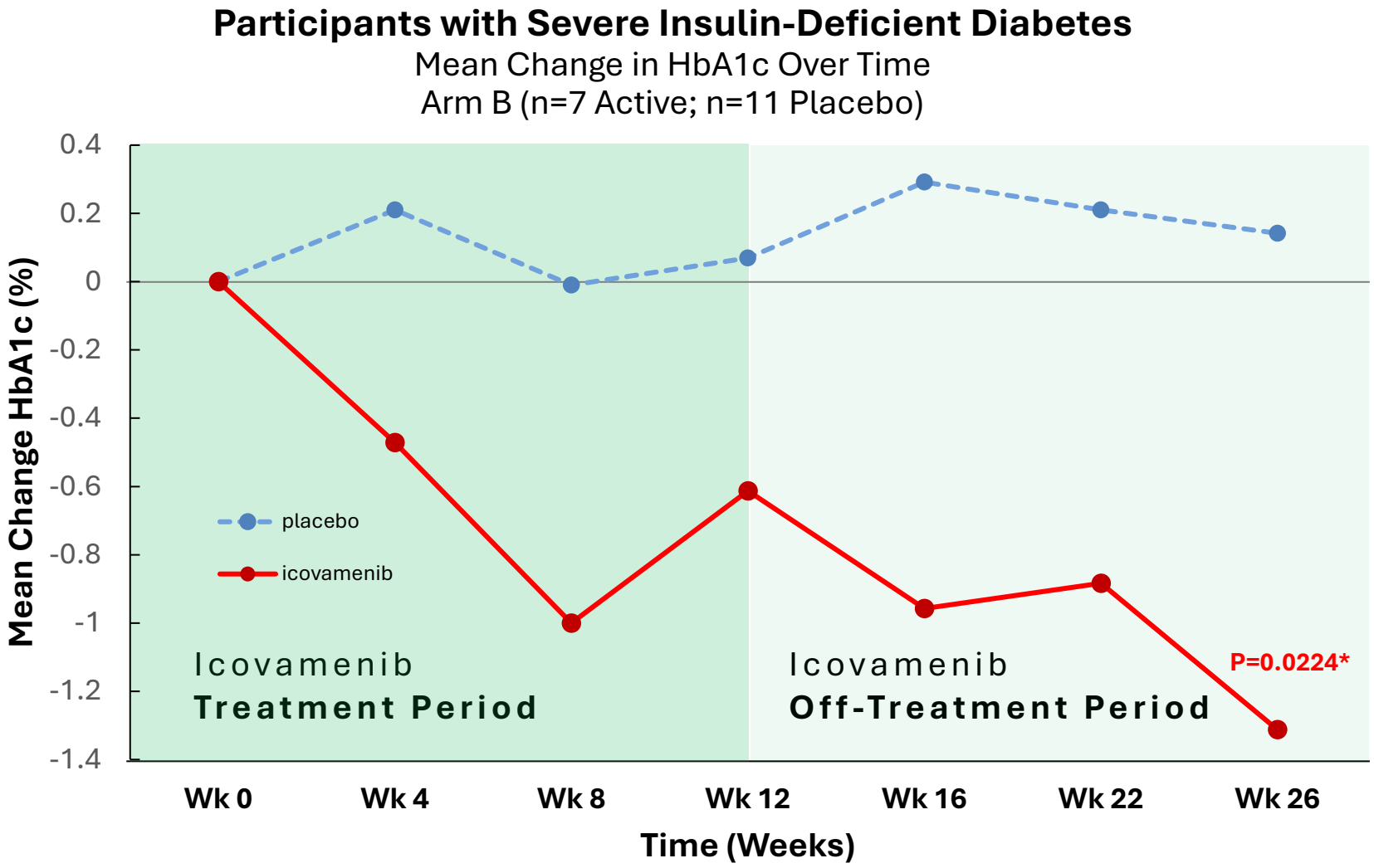


Change in HbA1c from Baseline at Week 26, SIDD Participants

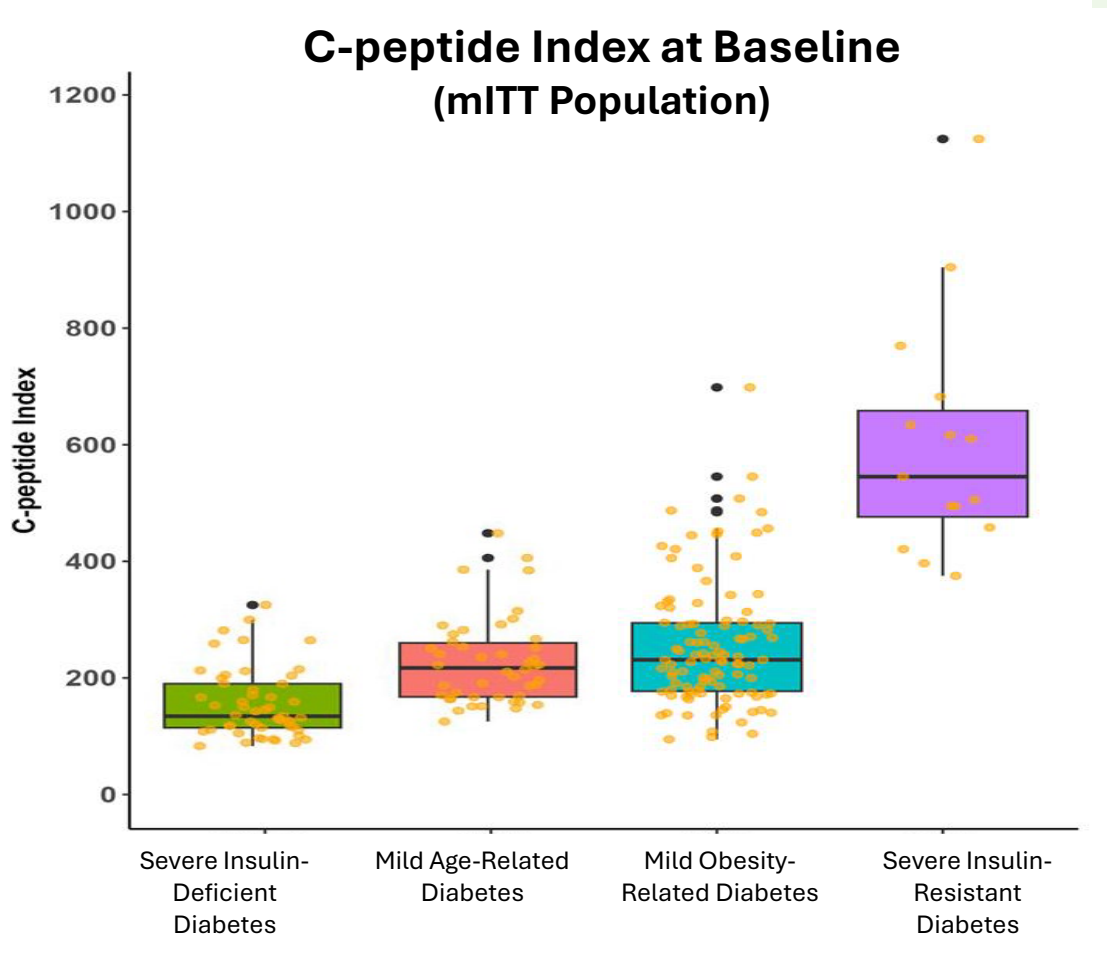
Per Protocol Population taking 1+ antihyperglycemic medications at Baseline (study arms combined and placebo)



Mean Change in HbA1c from Baseline to Week 26 in Participants with SIDD

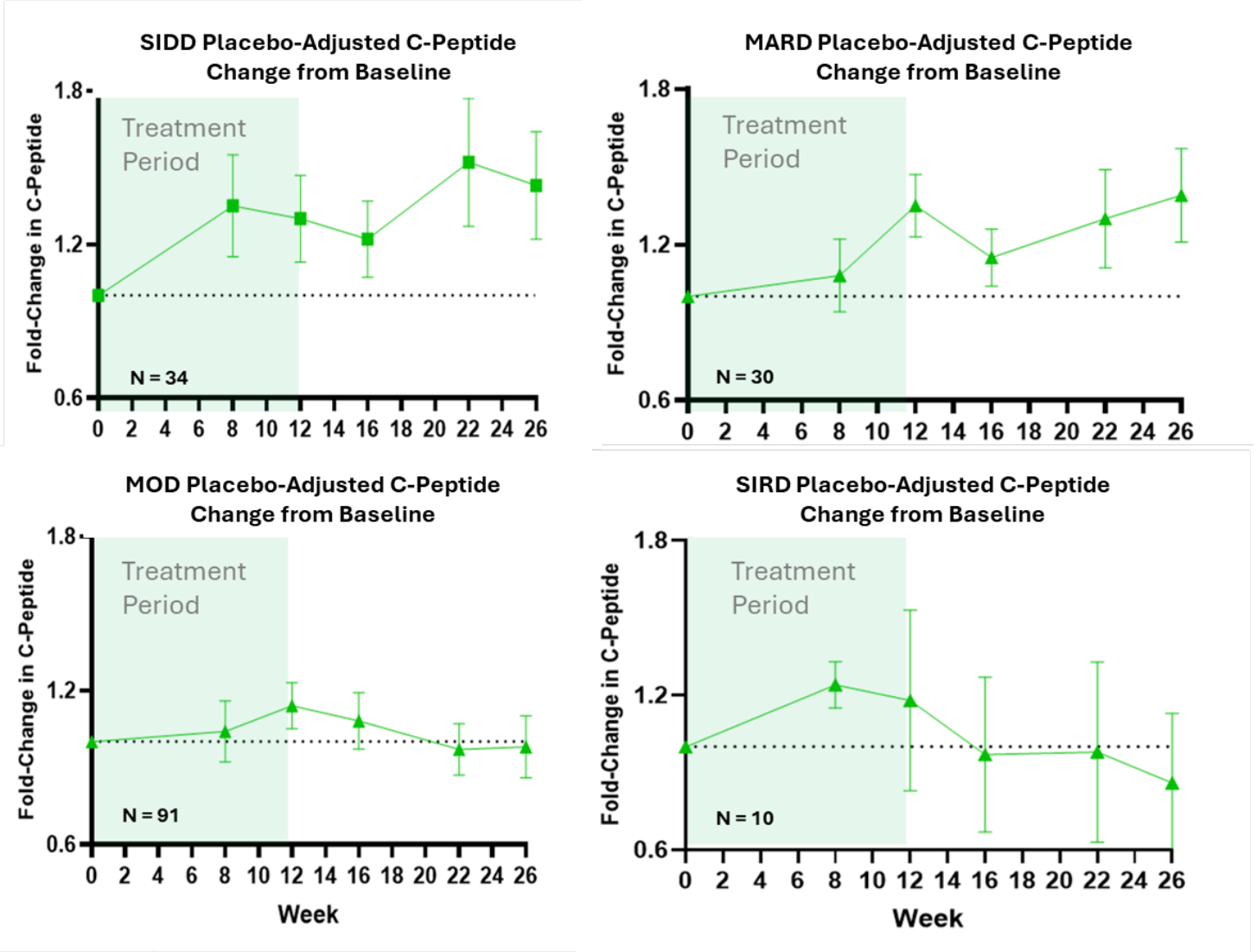


Patients with Severe Insulin-Deficient Diabetes (SIDD) had the Lowest Baseline Insulin Production as Measured by the C-peptide Index During a 2-hr OGTT



- The **C-peptide Index** is a well-validated measure of beta-cell function
- As expected, the lowest insulin production occurred in participants with **Severe Insulin-Deficient Diabetes** (SIDD)
- By contract, the highest insulin production occurred in participants with **Severe Insulin-Resistant Diabetes** (SIRD)

Icovamenib Increased Insulin Secretion (measured by C-peptide) in Insulin-Deficient but Not in Insulin-Resistant T2D



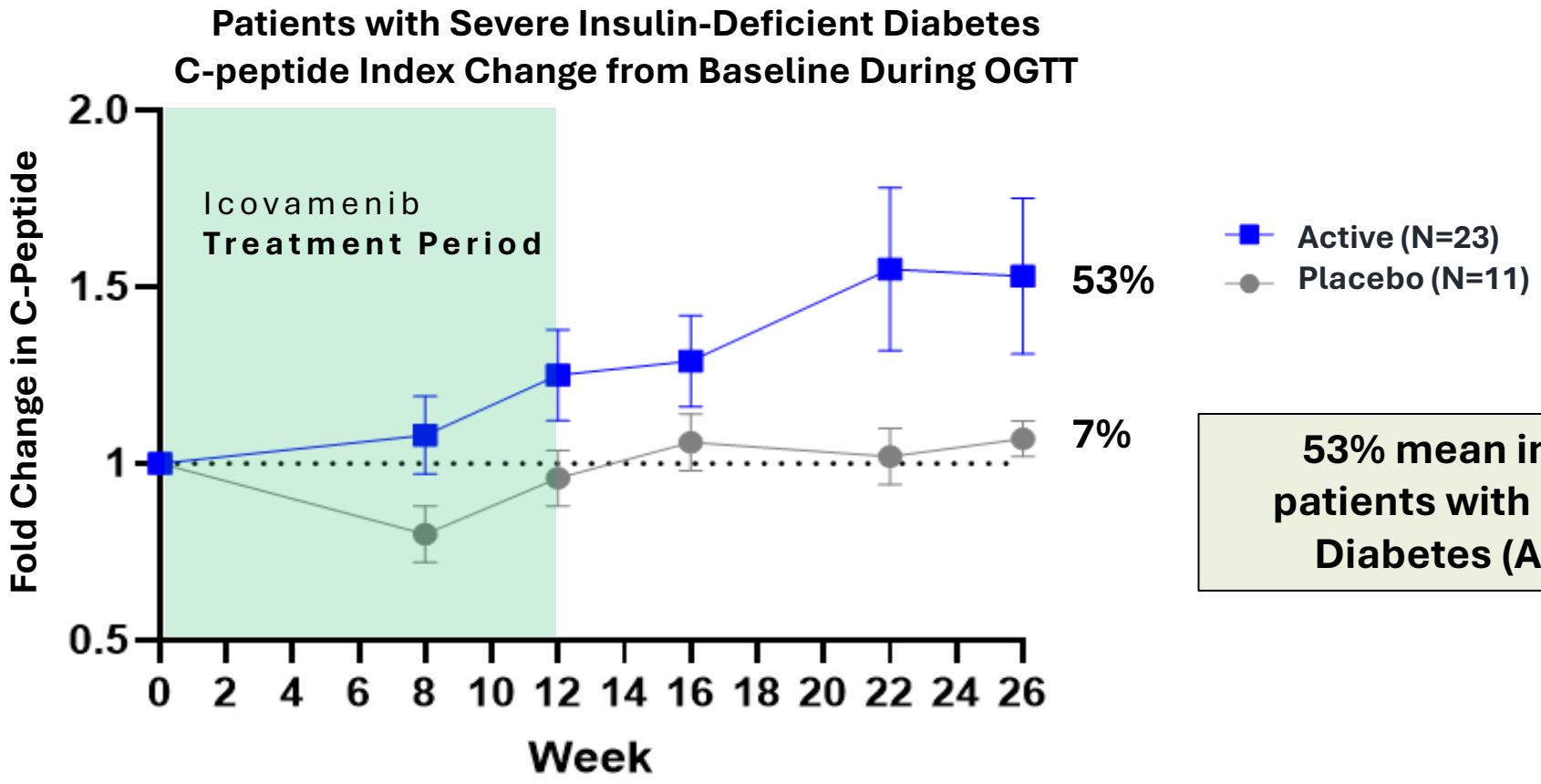
Insulin-Deficient participants demonstrated an **increase** in C-peptide over time

Insulin-Resistant participants did **not** demonstrate an **increase** in C-peptide over time

SIDD, Severe Insulin-Deficient Diabetes
MARD, Mild Age-Related Diabetes
MOD, Mild Obesity-Related Diabetes
SIRD, Severe Insulin-Resistant Diabetes

Icovamenib Increased Insulin Secretion as Measured by C-peptide

At Week 26, 53% increase in insulin secretion, with over half the increase occurring while off icovamenib

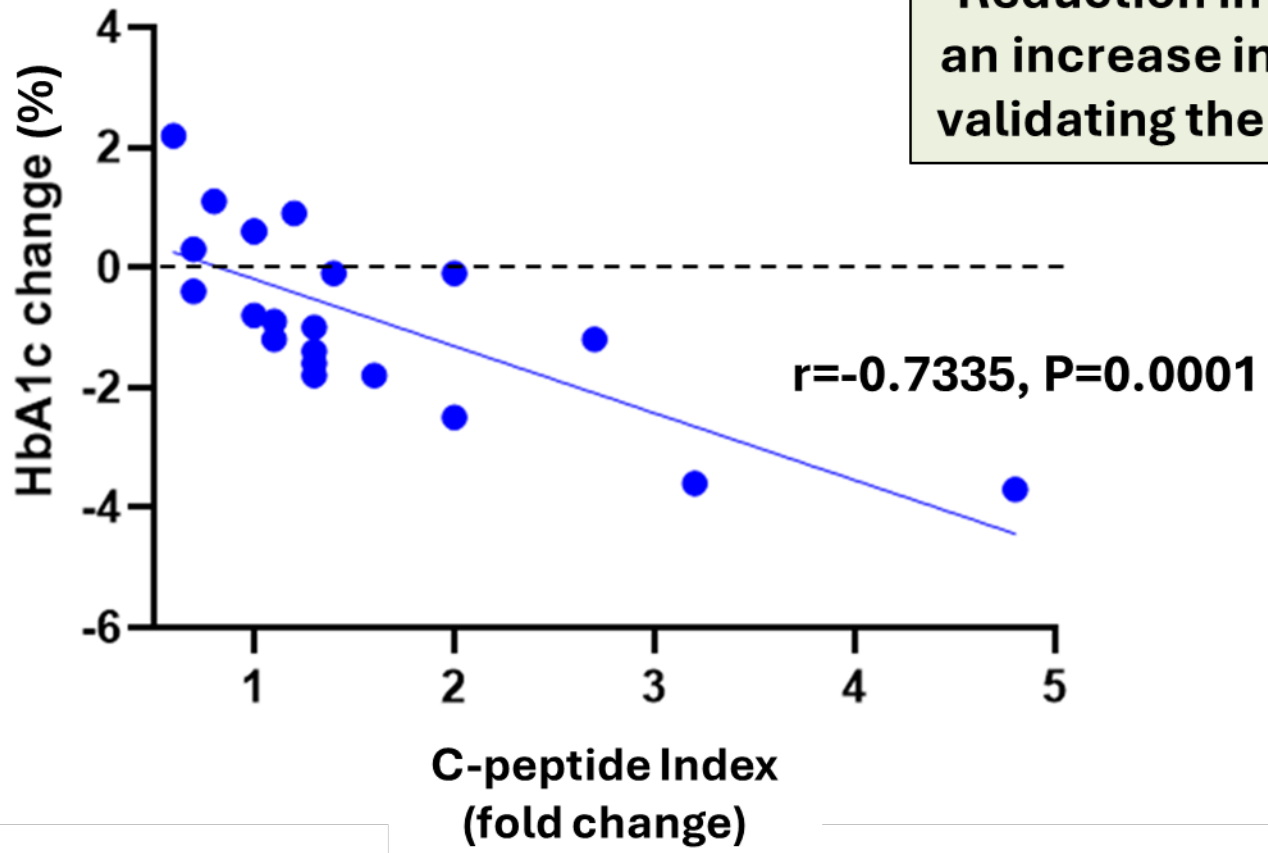


53% mean increase in C-peptide in patients with Severe Insulin-Deficient Diabetes (Arms A, B, and C, N=23)

Change from Baseline at Week 26 in C-peptide Index versus HbA1c

Severe Insulin-Deficient Diabetes (SIDD) Participants (Arms A, B and C; N=23)

Reduction in HbA1c correlated significantly with an increase in insulin secretion (C-peptide Index), validating the mechanism of action of icovamenib



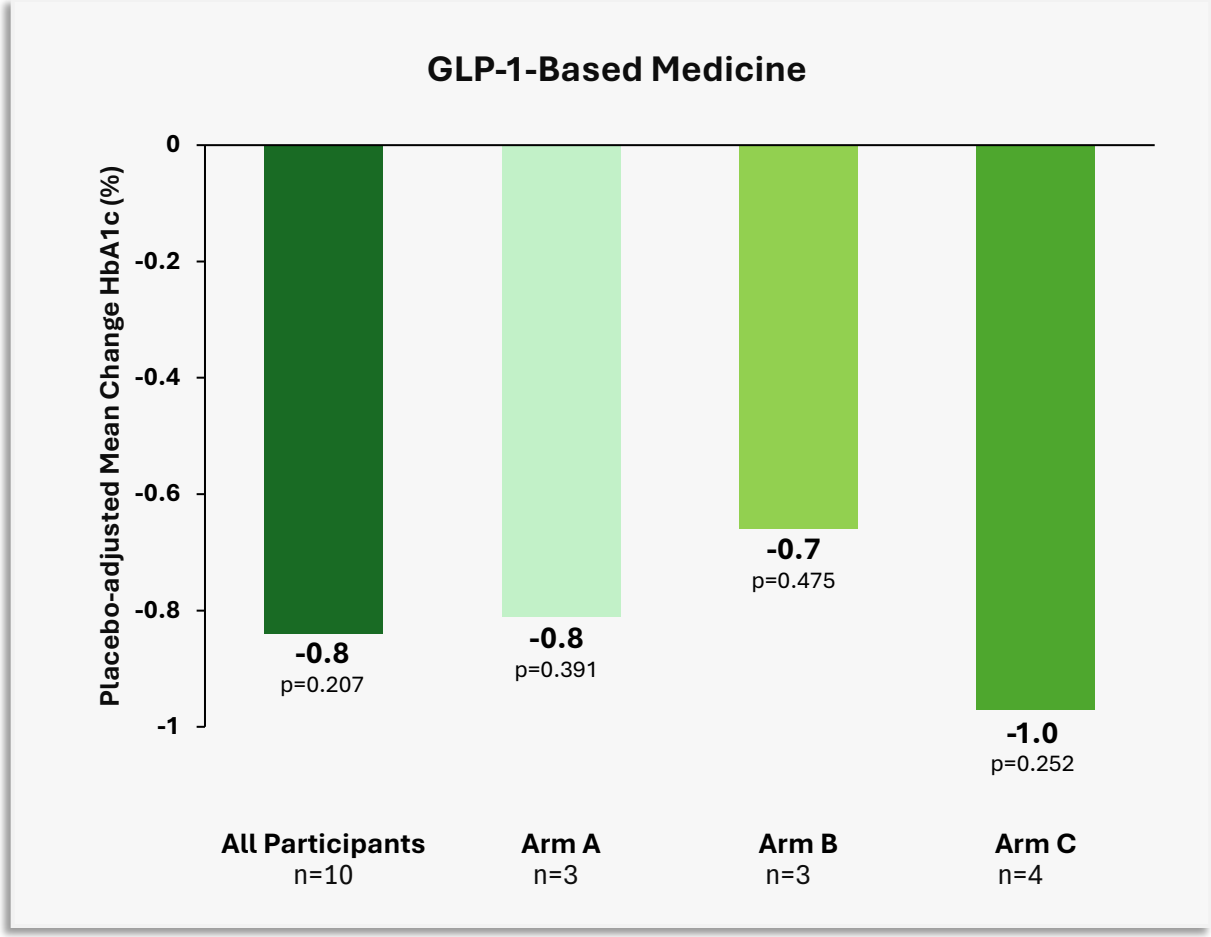
C-peptide Index (CPI) = 10^4 x Mean AUC C-peptide/Mean AUC glucose

Change in HbA1c from Baseline to Week 26 in patients taking GLP1-RA at Baseline

Patients taking GLP1-RA at baseline across all active arms (N=10)

Icovamenib displayed **clinically meaningful 1.0% reduction in HbA1c** in participants **uncontrolled** on GLP-1-based therapies at Baseline

- ~1.0% reduction in HbA1c with icovamenib as add-on to “failing” GLP-1 RA-based therapy
- 5/5 pts on 0.25mg to 1mg semaglutide lost additional weight when initiating icovamenib
- Up to 14% of additional weight loss observed at Week 26
- COV-111 did not have protocol-mandated dietary requirements/restrictions



Arm A: 8 weeks of dosing 100mg QD;
Arm B: 12 weeks of dosing 100 mg QD;
Arm C: 8 weeks of 100 mg QD + 4 weeks of 100 BID

Overview of Treatment Emergent Adverse Events Through 26 Weeks

(Safety Population, N=267)

Parameter	Arm A icovamenib (N=67)	Arm B icovamenib (N=66)	Arm C icovamenib (N=67)	Combined Arms icovamenib (N=200)	Combined Arms placebo (N=67)
Patients with ≥1 TEAE	18 (27)	20 (30)	14 (21)	52 (26)	19 (28)
SAEs*	1 (1)	0 (0)	1 (1)	2 (1)	1 (1)
Treatment Discontinuation due to TEAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Study Discontinuation due to TEAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Data are n (%)
TEAE, Treatment Emergent Adverse event
SAE, Serious adverse event
*Arm A had an SAE of atrial fibrillation. Unrelated to study treatment and occurred during the treatment period. Subject required hospitalization and was discharged in 3 days. Subject continued in the study.
*Arm C had an SAE of COVID-19. Unrelated to study treatment and occurred during the treatment period. Subject required hospitalization and was discharged in 3 days. Subject continued in the study.
*Placebo Arm had an SAE of nephrolithiasis. Unrelated to study treatment and occurred during the treatment period. Subject required hospitalization and was discharged in 3 days. Subject continued in the study.

Treatment Emergent Adverse Events Occurring in ≥5% in any Study Arm and TEAEs reported for ALT and/or AST Elevations

(Safety Population, N=267)

Parameter	Arm A icovamenib (N=67)	Arm B icovamenib (N=66)	Arm C icovamenib (N=67)	Combined Arms icovamenib (N=200)	Combined Arms placebo (N=67)
Diarrhea	4 (6)	2 (3)	1 (1)	7 (4)	0 (0)
Nausea	2 (3)	3 (5)	2 (3)	7 (4)	1 (1)
Hyperglycemia	1 (1)	4 (6)	1 (1)	6 (3)	3 (4)
Headache	0 (0)	3 (5)	1 (1)	4 (2)	3 (4)
ALT increase	2 (3)	0 (0)	2 (3)	4 (2)	0 (0)
AST increase	2 (3)	0 (0)	1 (1)	3 (2)	0 (0)

Data are n (%) of TEAE with ≥5% frequency in any arm and ALT or AST increase irrespective of incidence; Safety population
TEAE, treatment-emergent adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase
Diarrhea: In the icovamenib arms, all 7 events were Grade 1.
Nausea: In the icovamenib arms, 6 of 7 events were Grade 1 and 1 event was Grade 2 (Arm B). In the placebo arm, the 1 event was Grade 1.
Hyperglycemia: In the icovamenib arms, 5 of 6 events were Grade 2 and 1 event was Grade 1 (Arm C). In the placebo arm, all 3 events were Grade 2.
Headache: In the icovamenib arms, 3 of the 4 events were Grade 1 and 1 event was Grade 2 (Arm B). In the placebo arm, 2 of the 3 events were Grade 1 and 1 event was Grade 2.
ALT increase: In the icovamenib arms, 3 of the 4 events were Grade 1 and 1 event was Grade 2 (Arm A).
AST increase: In the icovamenib arms, all 3 events were Grade 1.

Summary and Conclusions

- 12 weeks of icovamenib therapy resulted in clinically and statistically significant improvements in HbA1c at Week 26 (14 weeks after final dose)
- Improvements in glycemic control were greatest in participants with severe insulin-deficient diabetes (SIDD)
- Participants with SIDD in Arm B (100 mg QD X 12 weeks) demonstrated an ~1.5% placebo-adjusted reduction in HbA1c at Week 26; this dosing regimen will be assessed further in future trials in insulin-deficient T2D
- Change in HbA1c significantly correlated with change in stimulated C-peptide, validating the mechanism of action
- Icovamenib was safe and well-tolerated, without clinically significant elevations in aminotransferases and with no treatment emergent hypoglycemia

Icovamenib: Late-Stage Clinical Development in Type 2 Diabetes

Development of icovamenib to focus on two key patient segments
- People with Severe Insulin Deficient T2D
- In Combination with a GLP-1 RA in people with T2D, irrespective of T2D subgroup

1. Severe Insulin Deficient Diabetes (SIDD)
We aim to improve glycemic control in the patient population with the highest unmet medical need in T2D

2. GLP-1 Combination
We aim to maximize the incretin effect and increase body weight loss with lean mass preservation

A. Patients initiating a GLP-1 RA based therapy
B. Patients uncontrolled on a GLP-1 RA based therapy

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Thank you

Q & A Session

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