COVALENT-111: 26-Week Efficacy and Safety after 8 and 12 Weeks of Daily Oral Icovamenib in Patients with Poorly Controlled Type 2 Diabetes

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	No, Nothing to disclose
X	Yes, please specify disclosures

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
Biomea Fusion							**X**	

PHOTOGRAPHY ALLOWED

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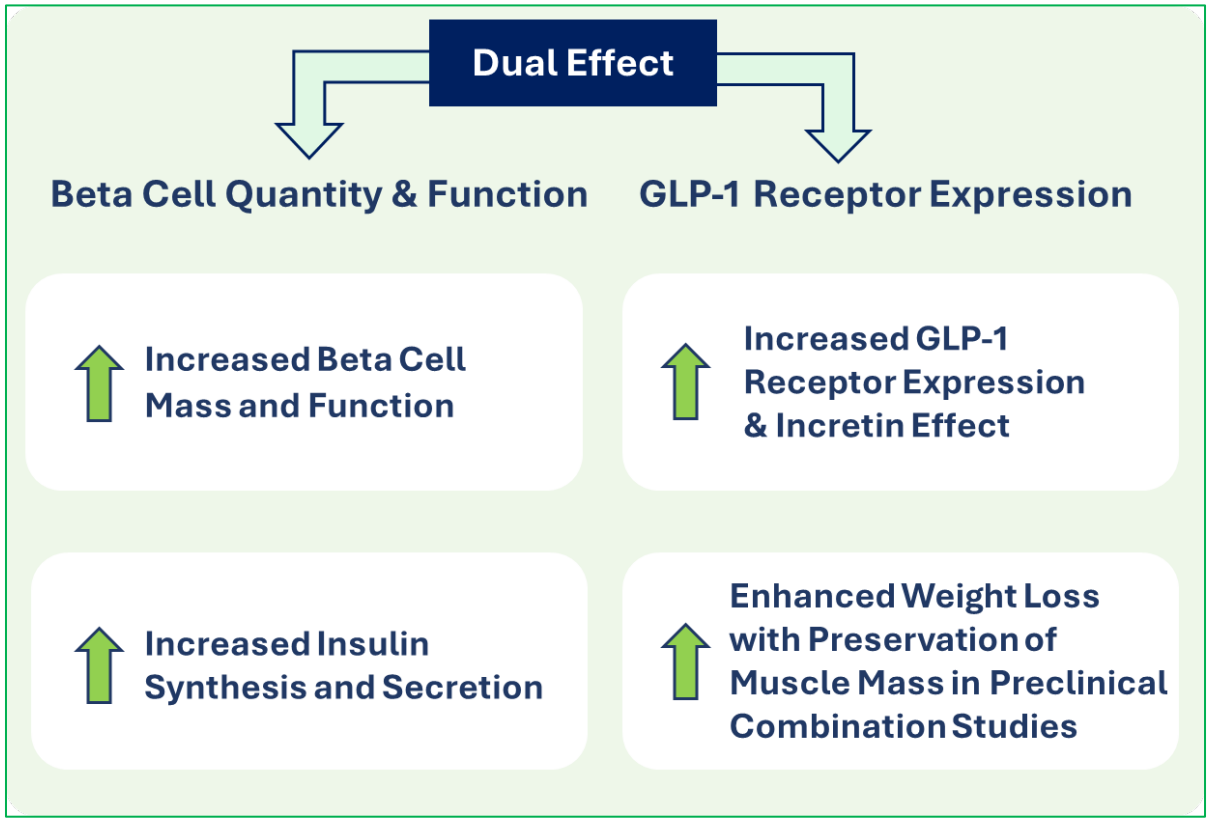
Background

The scaffold protein **menin** and **icovamenib**, an oral covalent menin inhibitor

Menin

- Nuclear scaffold protein that plays a physiological role in glucose homeostasis[1]
- Inhibition of menin enhances beta-cell proliferation and increased GLP-1 receptor expression[2]

Icovamenib



Icovamenib Key Characteristics

- Oral – Convenient, once-daily oral therapy
- Non-Chronic – Limited duration dosing with sustained effect
- Well-Tolerated – Favorable safety profile observed to date
- MOA complementary to other agents used

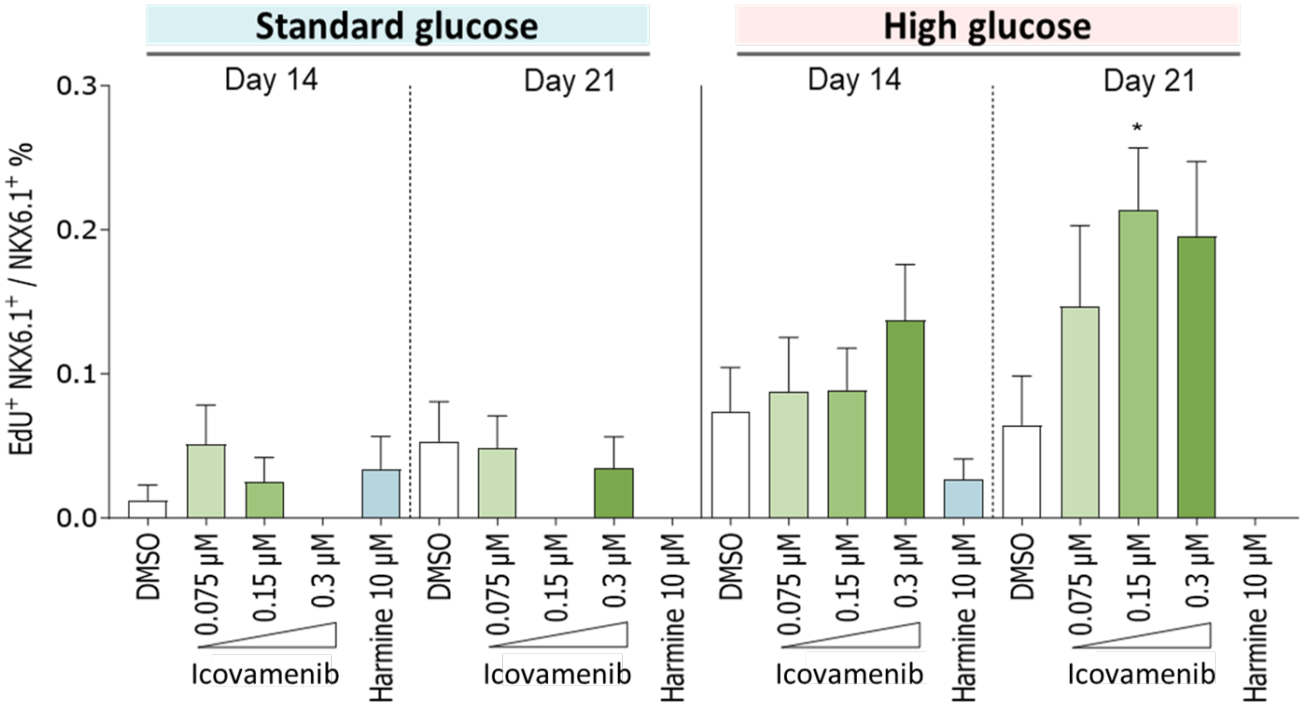
[1]Matkar et al. Trends in biochemical sciences 2013; 38(8):394-402;
[2]Muhammad et al. Am J Physiol Endcrinol Metab 2017; 313(2):E148-E166

Background

Icovamenib's dual mechanism of action assessed in human islets

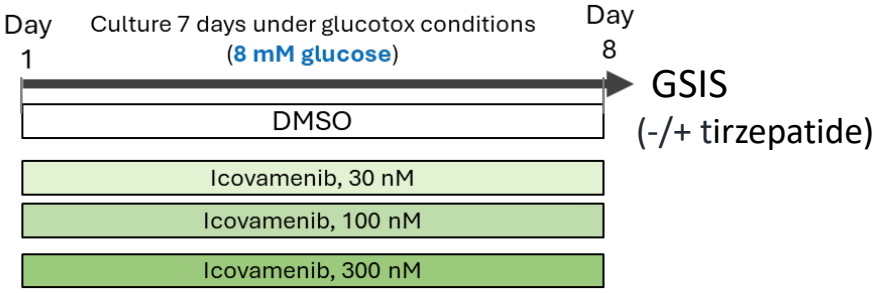
Glucose-dependent increase in beta-cell proliferation

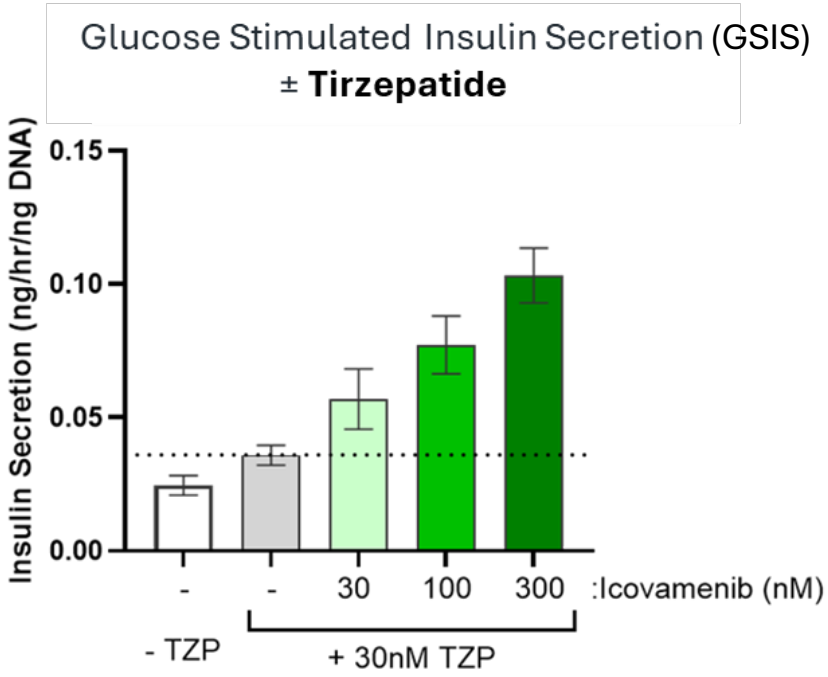
Proliferating beta cells as a fraction of total beta cells



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

Dose-dependent increase in GSIS with icovamenib + tirzepatide *vs* tirzepatide alone





Balakrishnan et al. Metabolism 2025; 168:156226

Background

T2D is a heterogeneous disease – two core pathophysiologic drivers

INSULIN-DEFICIENT DIABETES

Severe insulin-deficient diabetes (SIDD)

18%

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

Mild age-related diabetes (MARD)

39%

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

INSULIN RESISTANT DIABETES

Mild obesity-related diabetes (MOD)

22%

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

Severe insulin resistant diabetes (SIRD)

15%

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

Adapted from Gómez-Peralta et al. J Clin Med 2024; 13(16): 4839
Ahlqvist et al. Diabetes 2020; 69(10): 2086-2093

COVALENT 111 | Study Objective and Definitions

Primary Objective	Primary Endpoint
To assess the effect on glycemic control	Change in HbA1c from baseline at Week 26

Study Population

Per protocol (PP) population includes placebo and active participants who received at least 80% of their total dose[1]

Statistics

The change from baseline in HbA1c at the valid last HbA1c measurement at or prior to Week 26 (Last Observation Carried Forward) calculated using an ANCOVA model

[1]excludes redosing for Arm A participants

Trial Design

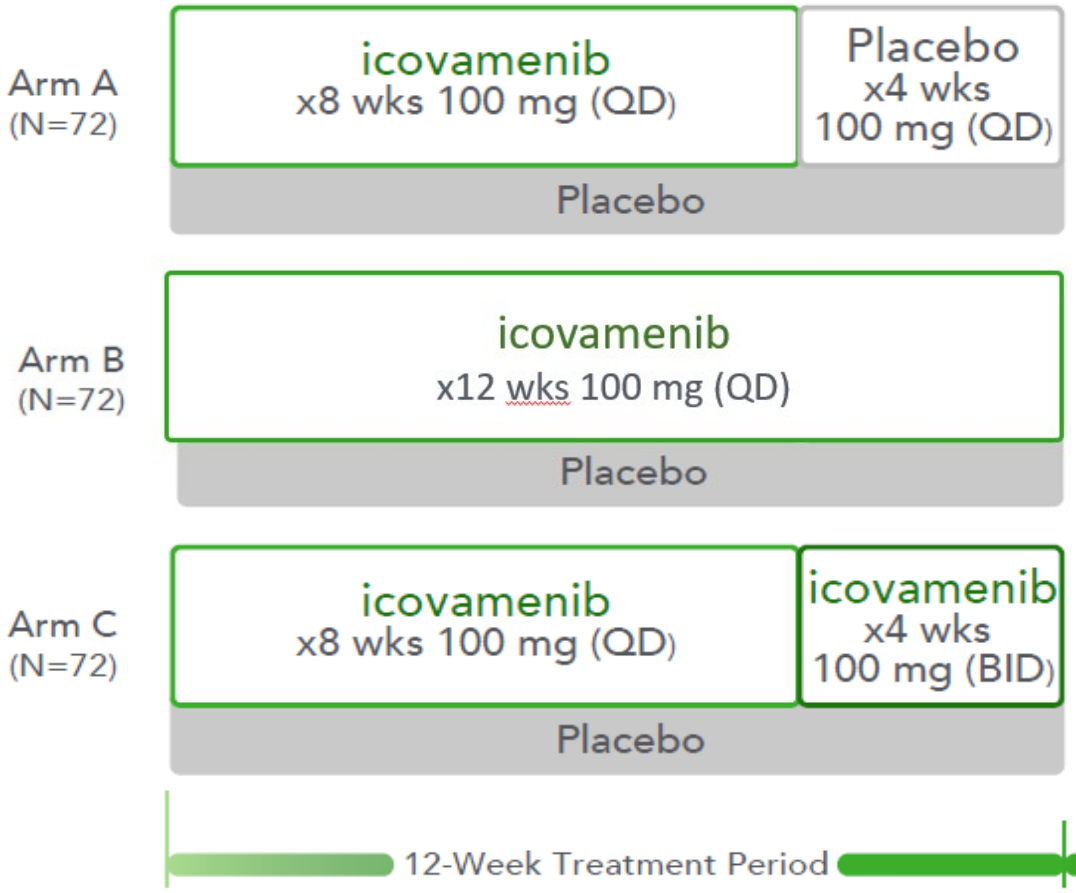
Phase 2a randomized, double-blind, placebo-controlled study in participants with T2D

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)

N=216 Planned Participants

3:1



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

Week 26
Primary Endpoint
December 2024

Week 52
End of Study

Baseline Demographics and Characteristics

Parameter Mean (SD) or %	Arm A icovamenib (N=51)	Arm B icovamenib (N=41)	Arm C icovamenib (N=36)	Combined Arms icovamenib (N=128)	Combined Arms Placebo (N=57)
Age (yr)	55 (7)	56 (6)	52 (10)	54 (8)	54 (8)
Duration of T2D Diagnosis (yr)	4.1 (1.9)	4.6 (1.9)	4.1 (2.2)	4.2 (2.0)	4.1 (2.1)
Sex (% Female)	31	56	33	40	42
Ethnicity (%)					
Hispanic	59	39	42	48	67
Non-Hispanic	41	61	58	52	33
Race (%)					
Asian	12	12	11	12	7
Black	22	15	25	20	16
White	67	68	64	66	77
Other	0	5	0	2	0
HbA1c (%)	8.3 (1.1)	8.3 (1.0)	8.1 (0.9)	8.2 (1.0)	8.3 (0.9)
BMI (kg/m^2)	31.1 (4. 7)	32.1 (4.5)	32.2 (4.8)	31.7 (4.7)	32.2 (4.3)
BMI <30 kg/m^2 (%)	47	29	33	38	30
BMI ≥30 kg/m^2 (%)	53	68	67	62	70

Per protocol population, N=185

Baseline Antihyperglycemic Agents

Parameter n (%)	Arm A icovamenib (N=51)	Arm B icovamenib (N=41)	Arm C icovamenib (N=36)	Combined Arms icovamenib (N=128)	Combined Arms Placebo (N=57)
Number of T2D Medications					
0	6 (12)	4 (10)	3 (8)	13 (10)	7 (12)
1	39 (76)	23 (56)	23 (64)	85 (66)	41 (72)
2	4 (8)	11 (27)	7 (19)	22 (17)	7 (12)
3	2 (4)	3 (7)	3 (8)	8 (6)	2 (4)
Metformin Monotherapy	36 (71)	18 (44)	22 (61)	76 (59)	38 (67)
SGLT2i	6 (12)	13 (32)	8 (22)	27 (21)	8 (14)
DPP4i	3 (6)	5 (12)	3 (8)	11 (9)	2 (4)
GLP-1 based agent	3 (6)	3 (7)	5 (14)	11 (9)	4 (7)

Per protocol population, N=185

T2D Subtype at Baseline

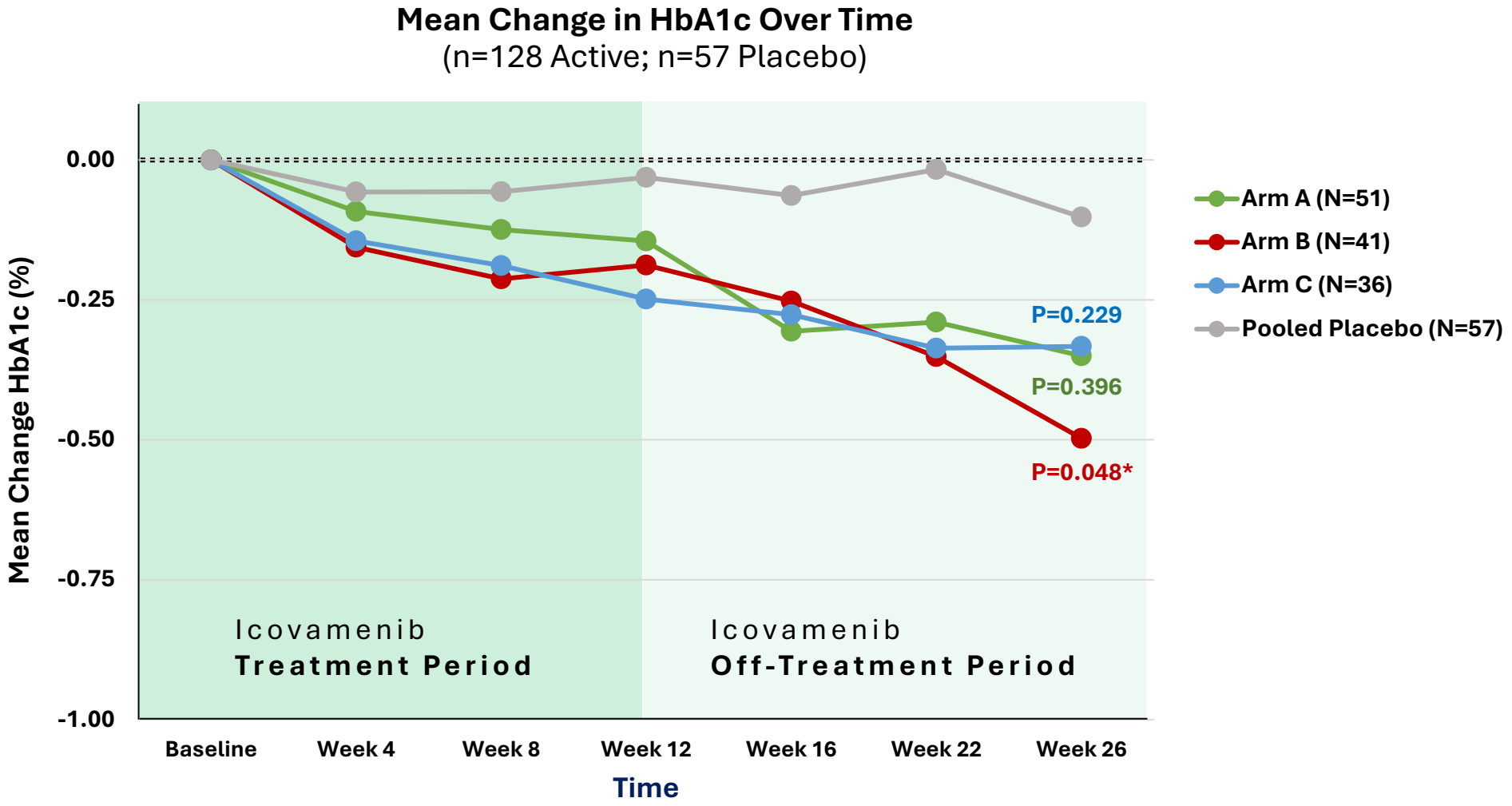
Parameter n (%)	Arm A icovamenib (N=51)	Arm B icovamenib (N=41)	Arm C icovamenib (N=36)	Combined Arms icovamenib (N=128)	Combined Arms Placebo (N=57)
SIDD	14 (27)	9 (22)	6 (17)	29 (23)	14 (25)
MARD	13 (25)	7 (17)	6 (17)	26 (20)	10 (18)
MOD	21 (41)	21 (51)	23 (64)	65 (51)	29 (51)
SIRD	3 (6)	4 (10)	1 (3)	8 (6)	4 (7)

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

Per protocol population, N=185

Mean Change in HbA1c from Baseline at Week 26

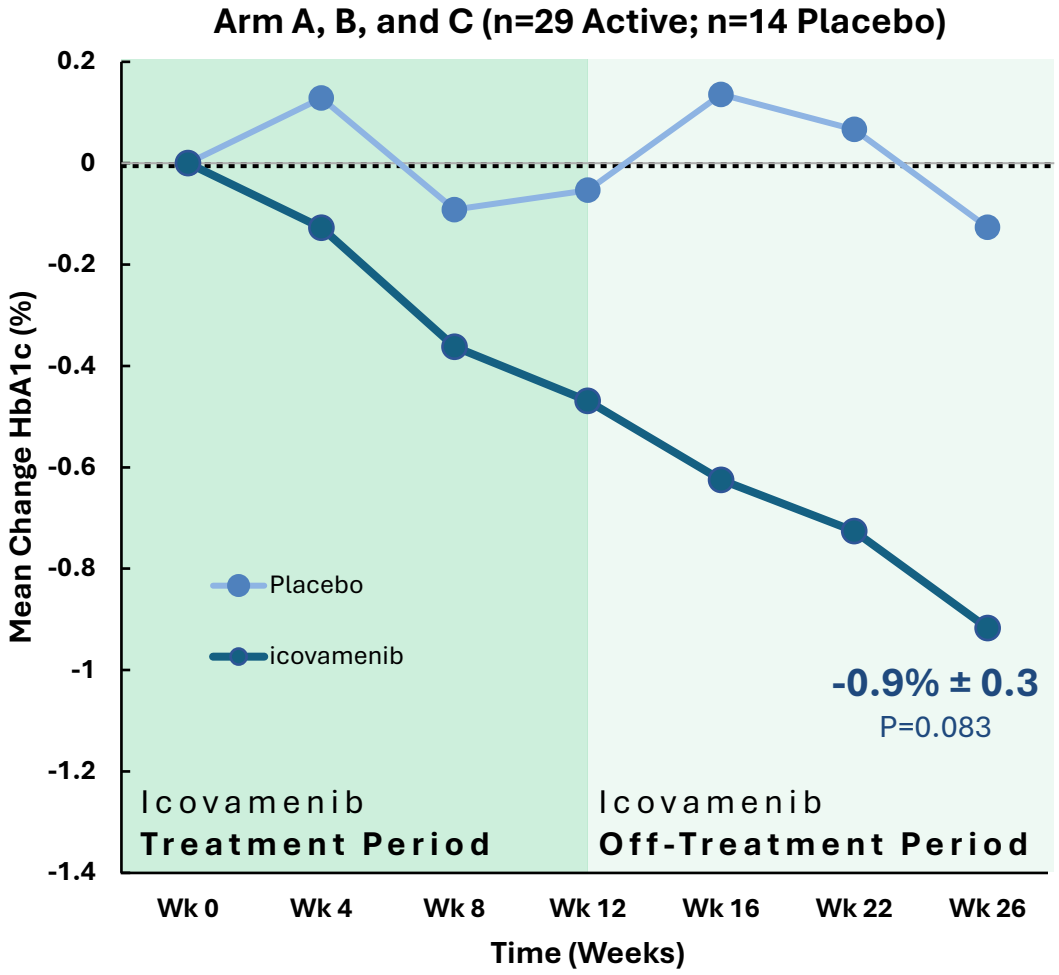
Per Protocol Population, by study arm

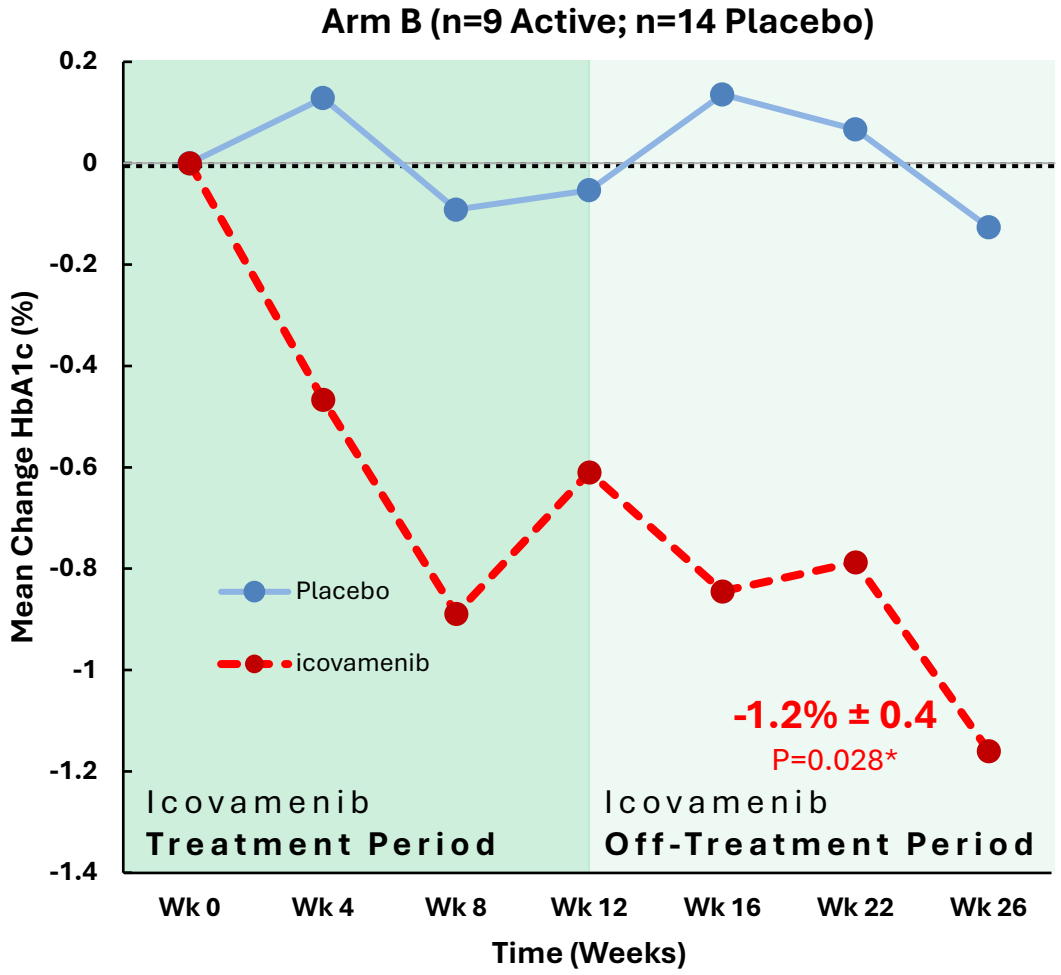


Per protocol population, N=185

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

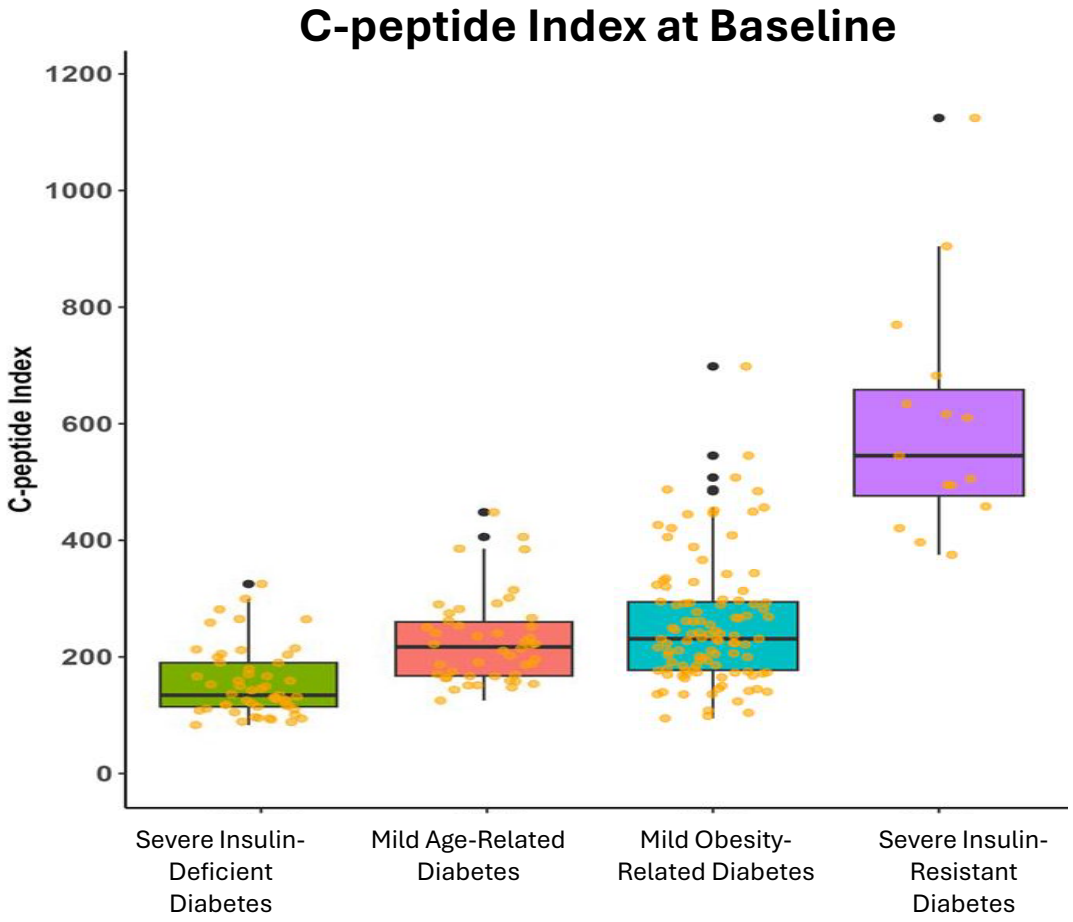
Per Protocol Population – SIDD by study arm





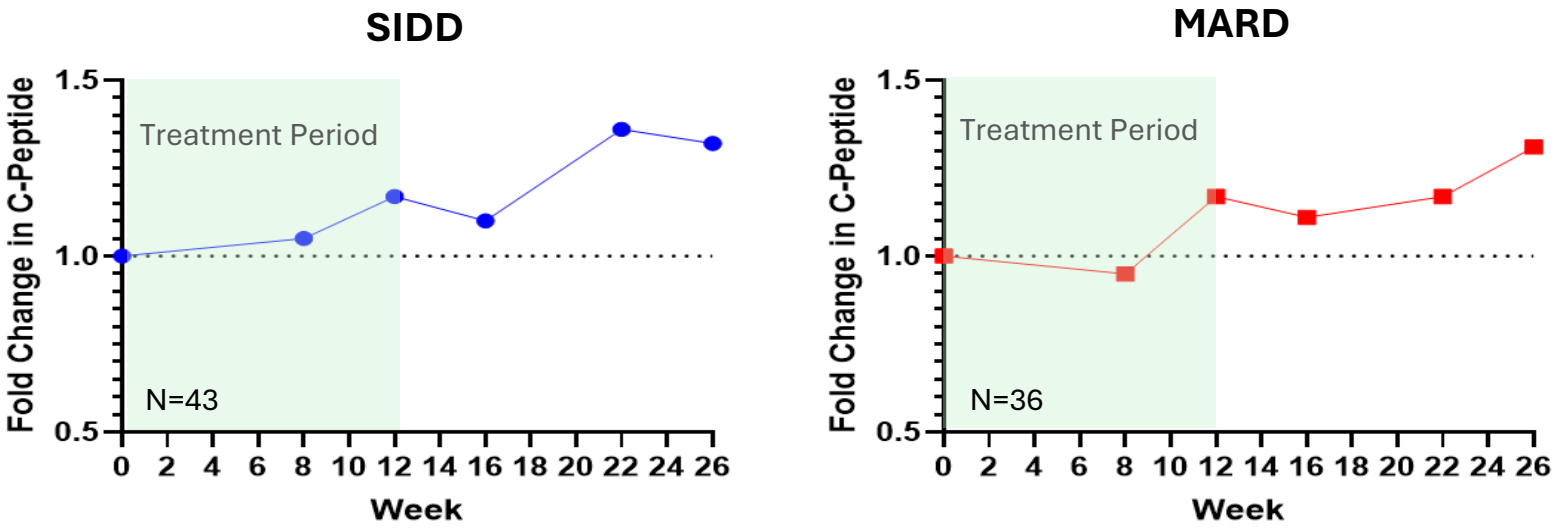
SIDD, severe insulin-deficient diabetes

Participants with SIDD had the Lowest Baseline Insulin Production as Measured by the C-peptide Index During a 2-hr OGTT

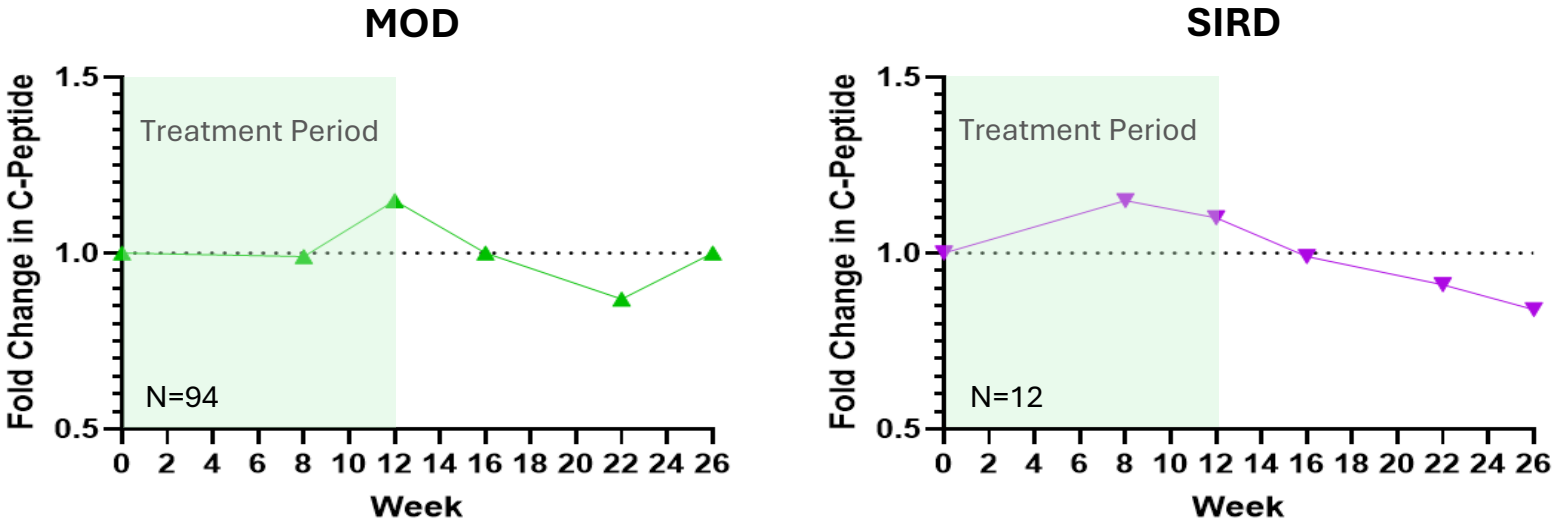


- The **C-peptide Index** is a well-validated measure of beta-cell function
- As expected, the lowest insulin production occurred in participants with **Severe Insulin-Deficient Diabetes** (SIDD)
- By contract, the highest insulin production occurred in participants with **Severe Insulin-Resistant Diabetes**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

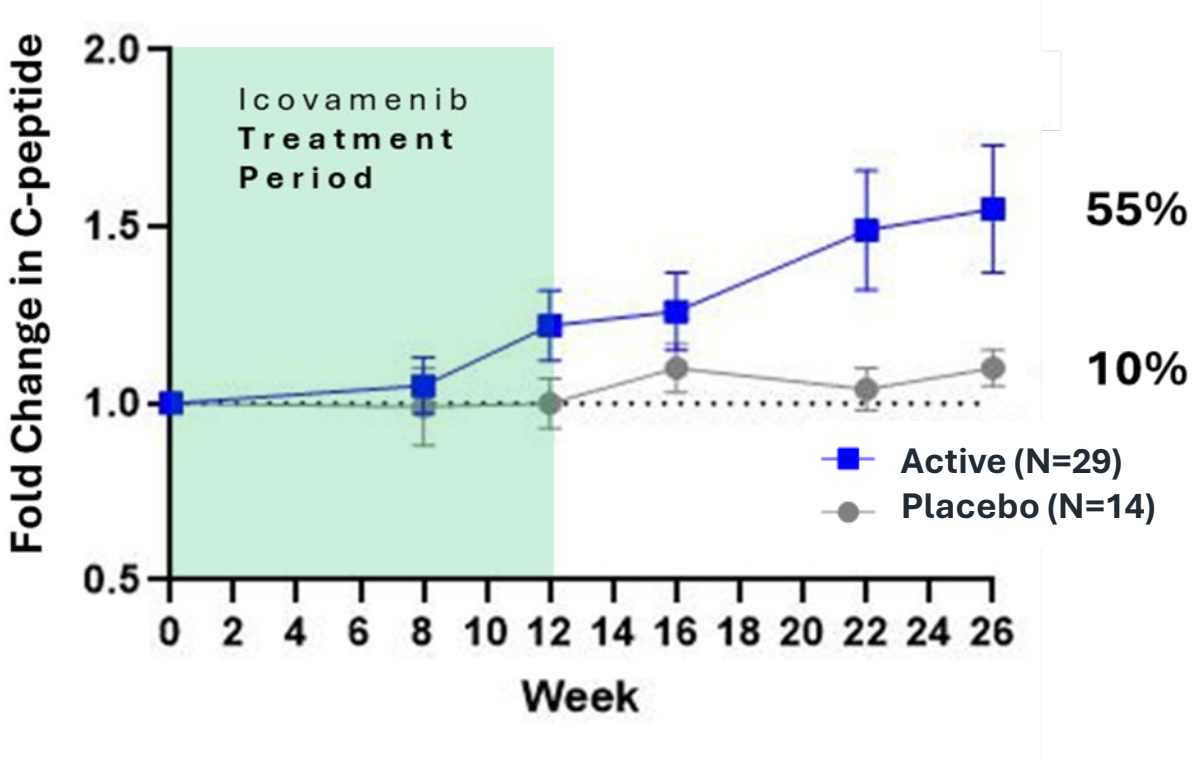
Placebo-adjusted C-peptide change from baseline

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, 55% increase in insulin secretion, with over half the increase occurring while off icovamenib

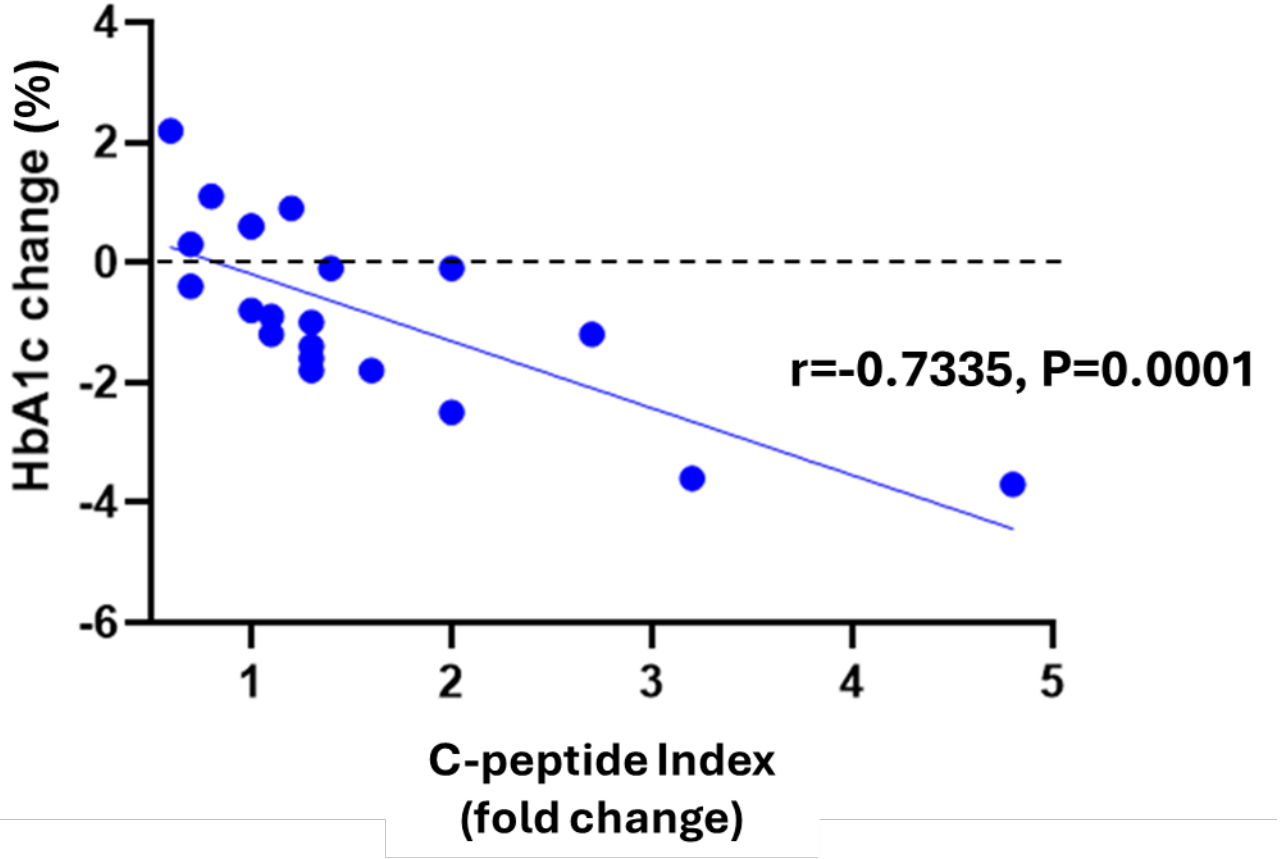
Participants with Severe Insulin-Deficient Diabetes
C-peptide Index Change from Baseline During OGTT



55% mean increase in C-peptide in participants with Severe Insulin-Deficient Diabetes

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

Icovamenib-treated participants with SIDD



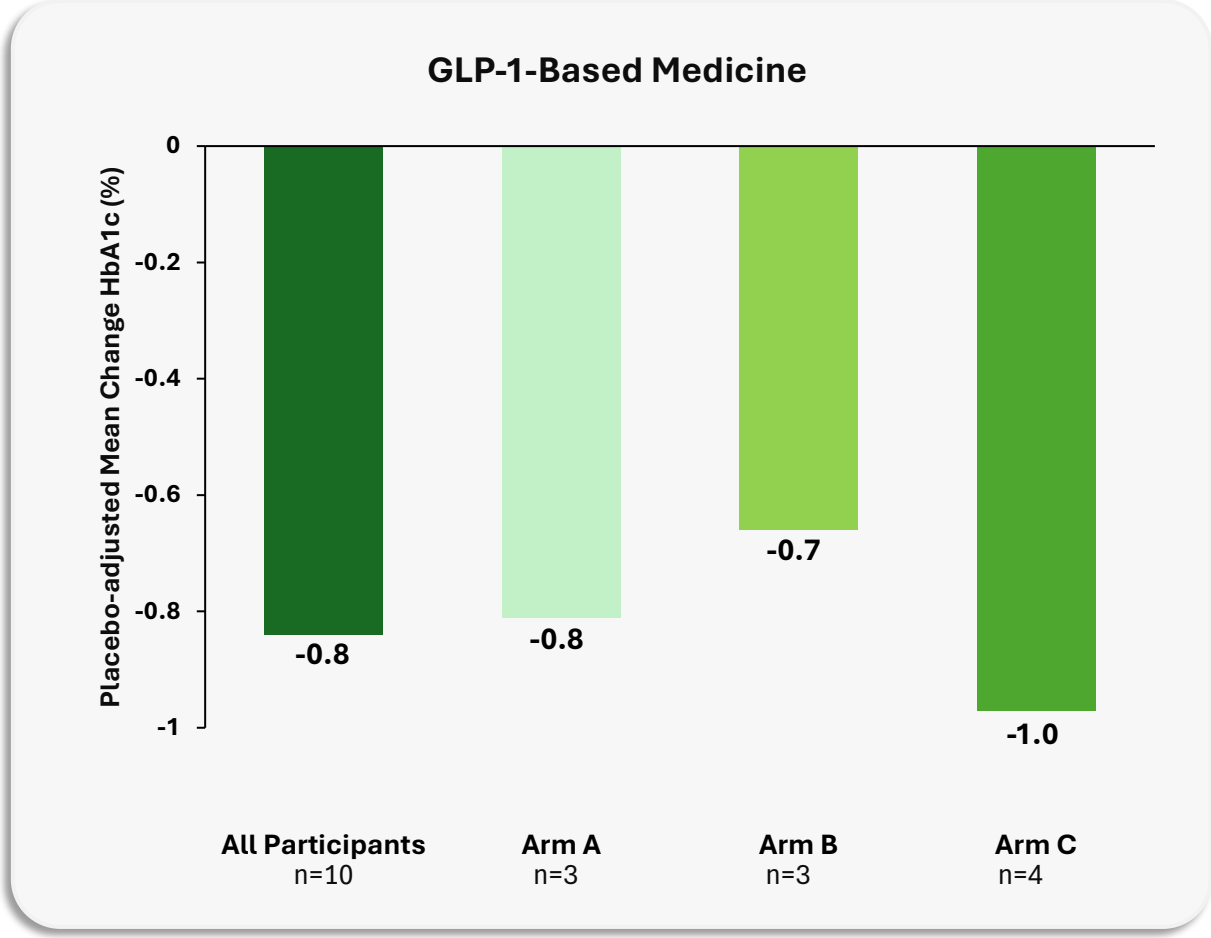
Reduction in HbA1c correlated significantly with an increase in insulin secretion (C-peptide index), validating the mechanism of action of icovamenib

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

SIDD, severe insulin-deficient diabetes

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

Participants treated with GLP1-RA at baseline across all arms (N=10)



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

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)
Participants 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.

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 a 1.2% 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, helping to validate the mechanism of action
- Icovamenib was safe and well-tolerated, without clinically significant elevations in aminotransferases and with no treatment emergent hypoglycemia

Future Directions for Clinical Development of Icovamenib:

- Evaluate further in people with insulin-deficient T2D
- Investigate people with T2D who are not achieving glycemic targets despite treatment with GLP-1-based medicines

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Thank you