biomea FUSION™

COVALENT-111 Phase II Study Icovamenib in Type 2 Diabetes

52-Week Results

October 7, 2025

We Aim to Cure™

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COVALENT-111 – A Phase II Study of Icovamenib in Type 2 Diabetes
52-Week Follow Up - Conference Call October 3, 2025

Agenda

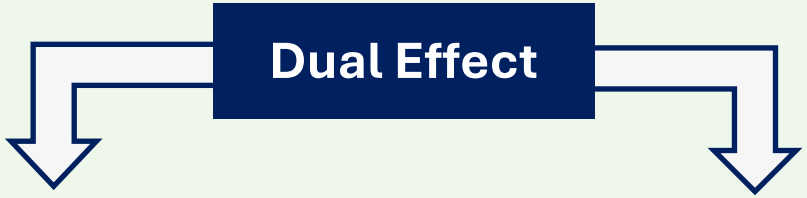
Introduction	**Ramses Erdtmann** *Founder and Chief Operating Officer & President, Biomea Fusion*
COVALENT-111 52-Week Follow-up Results	**Juan Pablo Frias, MD** *Co-Chair of the Scientific Advisory Board, Biomea Fusion*
Key Opinion Leader Insights	**Ralph DeFronzo, MD** *Professor of Medicine, Chief of Diabetes Division at the University of Texas Health Science Center at San Antonio and Deputy Director of the Texas Diabetes Institute*
Executive Summary	**Mick Hitchcock, PhD** *Interim Chief Executive Officer & Board Member, Biomea Fusion*
Question & Answer Session	

COVALENT-111, A Phase II Study of Icovamenib in Type 2 Diabetes 52-Week Follow Up Data

Juan Pablo Frias, MD
Co-Chair of the Scientific Advisory Board, Biomea Fusion

Icovamenib: Potential Disease-Modifying Candidate for Diabetes

Mechanism of Action: Selective & Partial Menin Inhibition



Beta Cell Quantity & 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 Muscle Mass in Preclinical Combination Studies**

Icovamenib Differentiating Features

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

Trial Design

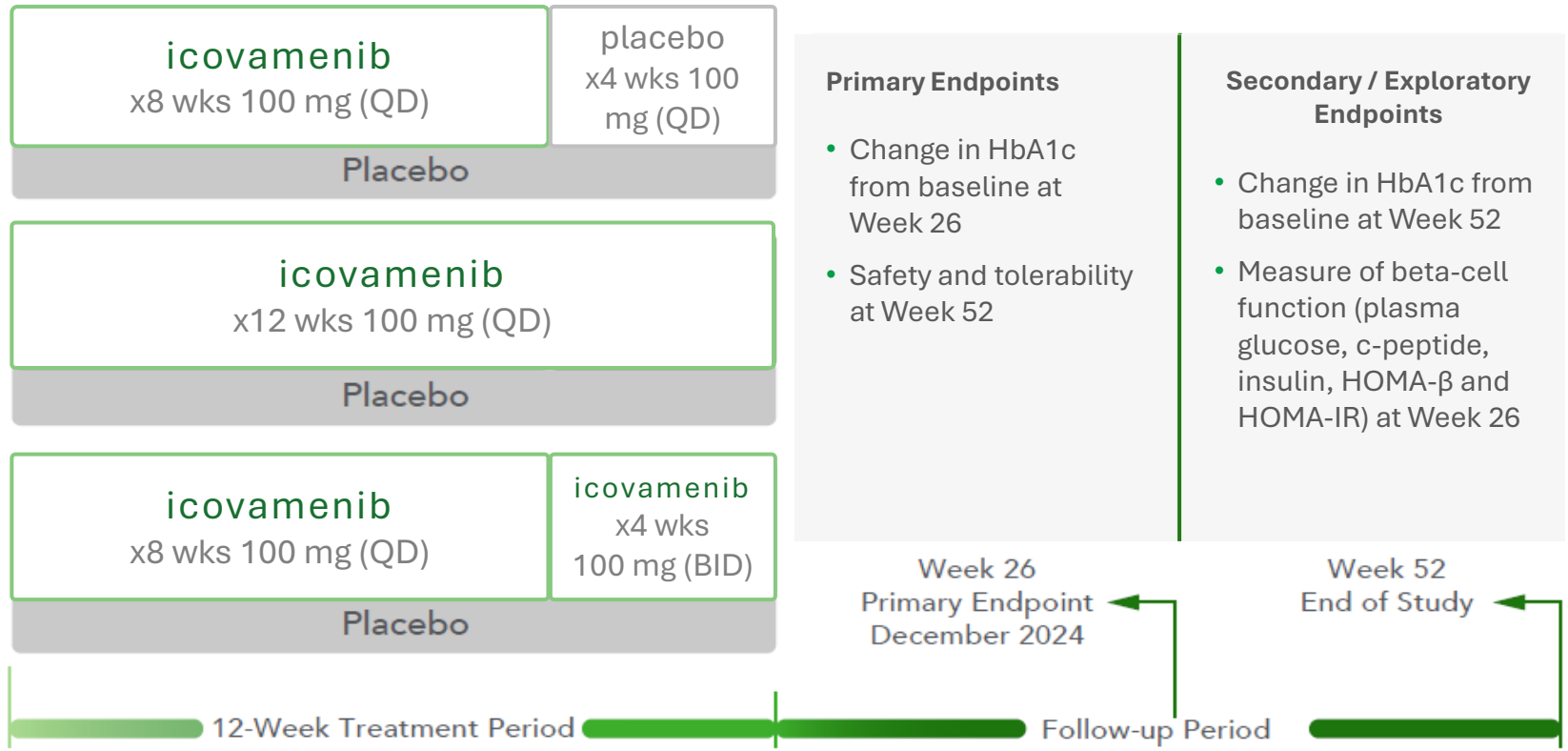
Phase 2 Randomized, Double-Blind, Placebo-controlled Study in Participants – ALL SUBTYPES - with T2D

N=216 Planned Participants

3:1

Eligibility Criteria

- Adults (18-65 years) with T2D (<7 years)
- HbA1c 7.0-10.5%
- BMI 25-40 kg/m^2
- Treated with up to 3 antidiabetic agents (excluding insulin and SFUs)
- N=72 participants per arm (3:1 ratio, icovamenib: PBO)



Primary Endpoints

- Change in HbA1c from baseline at Week 26
- Safety and tolerability at Week 52

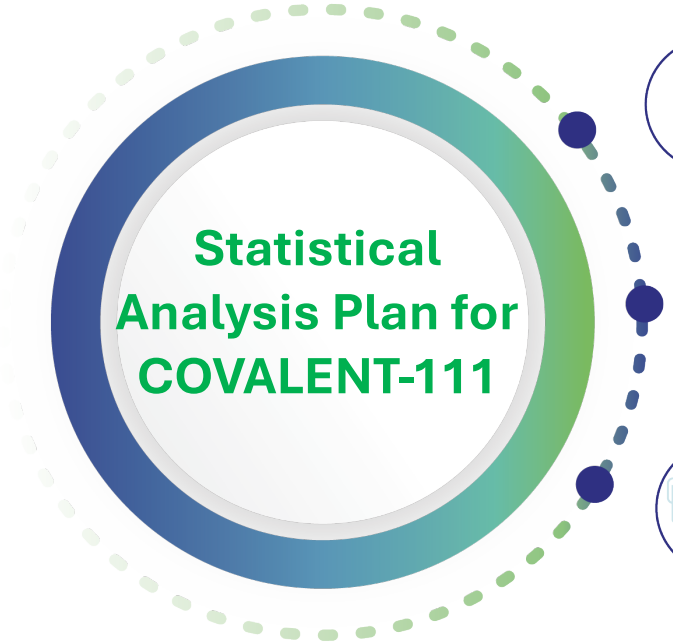
Secondary / Exploratory Endpoints

- Change in HbA1c from baseline at Week 52
- Measure of beta-cell function (plasma glucose, c-peptide, insulin, HOMA-β and HOMA-IR) at Week 26

BID: twice daily **BMI**: Body Mass Index **HbA1c**: glycated hemoglobin **PBO**: Placebo **QD**: daily **SFUs**: sulfonylureas **T2D:** Type 2 Diabetes

COVALENT-111 Statistical Analysis Plan

Read Out of Insulin-Deficient and Insulin Resistant Subgroups at Weeks 26 and 52



Arm A, B, and C primary analysis: change in HbA1c

Prespecified subgroup analysis to include assessment of HbA1c change within each T2D subgroup (SIDD, MARD, MOD, and SIRD)

Subgroup analysis based on algorithm established per Ahlqvist et al. (Lancet Diabetes Endocrinol. 2018;6:361-369)

Baseline Demographics and Characteristics

Per Protocol Population on 1 or More Antihyperglycemic Agents at Baseline (N=163)*

Parameter Mean (SD) or %	Arm A icovamenib (8 wks 100mg QD) (N=45)	Arm B icovamenib (12 wks 100 mg QD) (N=36)	Arm C icovamenib (8 wks 100 mg QD then 4 wks of 100mg BID) (N=33)	Combined Arms icovamenib (N=114)	Combined Arms placebo (N=49)
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)	(56)	(36)	(40)	(43)
HbA1c % (SD)	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)	3.8 (1.5)	3.7 (1.8)	3.6 (1.5)	3.5 (1.4)
BMI (kg/m^2)	30.9 (4.7)	32.7 (4.5)	32.4 (4.9)	31.9 (4.7)	32.6 (4.2)
BMI <30 kg/m^2 (%)	(49)	(22)	(30)	(35)	(27)
BMI ≥30 kg/m^2 (%)	(51)	(75)	(70)	(64)	(73)

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

*Per the Covalent 111 Protocol the population analyzed includes only subjects who received ≥80% of their planned dosing. A clinical hold interrupted the dosing. Patients were also excluded if they had significant protocol deviation

Antihyperglycemic Agents at Baseline

Per Protocol Population on 1 or More Antihyperglycemic Agents at Baseline (N=163)*

Parameter		Arm A icovamenib (8 wks 100mg QD) (N=45)	Arm B icovamenib (12 wks 100 mg QD) (N=36)	Arm C icovamenib (8 wks 100 mg QD then 4 wks of 100mg BID) (N=33)	Combined Arms icovamenib (N=114)	Combined Arms placebo (N=49)
Number of T2D Medications, n (%)						
	1	39 (87)	23 (64)	23 (70)	85 (75)	41 (84)
	2	4 (9)	11 (31)	7 (21)	22 (19)	6 (12)
	3	2 (4)	2 (6)	3 (9)	7 (6)	2 (4)
Metformin Monotherapy, n (%)		36 (80)	18 (50)	22 (67)	76 (67)	38 (78)
SGLT2i, n (%)		6 (13)	12 (33)	8 (24)	26 (23)	7 (14)
DPP4i, n (%)		3 (7)	4 (11)	3 (9)	10(9)	2 (4)
GLP-1 based medicines, 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-1 based medicines

T2D Subtype at Baseline

Per Protocol Population on 1 or More Antihyperglycemic Agents at Baseline (N=163)*

Parameter	Arm A icovamenib (8 wks 100mg QD) (N=45)	Arm B icovamenib (12 wks 100 mg QD) (N=36)	Arm C icovamenib (8 wks 100 mg QD then 4 wks of 100mg BID) (N=33)	Combined Arms icovamenib (N=114)	Combined Arms placebo (N=49)
SIDD, n (%)	11 (24)	6 (17)	4 (12)	21 (18)	12 (24)
MARD, n (%)	11 (24)	6 (17)	5 (15)	22 (19)	8 (16)
MOD, n (%)	21 (47)	22 (61)	22 (67)	65 (57)	24 (49)
SIRD, n (%)	2 (4)	2 (6)	2 (6)	6 (5)	5 (10)

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

Type 2 Diabetes is a Heterogeneous Disease – Two Core Drivers

INSULIN-DEFICIENT DIABETES

Severe insulin-deficient diabetes (SIDD)

Initial target group for icovamenib

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

Ahlqvist et al. Lancet Diabetes Endocrinol 2018; 6: 361–69 Analysis from two independent 4,000 patient studies, (ADOPT and RECORD)

Icovamenib in Type 2 Diabetes - Learnings through Week 26

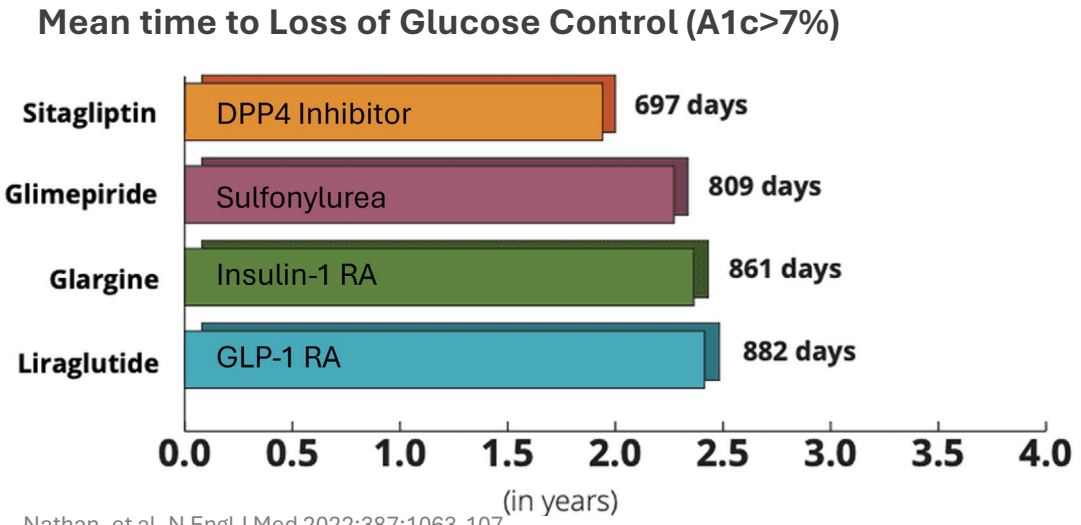
- **Icovamenib is being assessed as a short-duration treatment (12 weeks)** while all approved type 2 diabetes agents are chronic therapies
- **Primary endpoint is 26-Week HbA1c reduction (3 months post dosing) and tolerability at Week 52** with the secondary endpoint being 52-Week HbA1c reduction (9 months post dosing)
- **26-Week Data:**
  - Prespecified subgroup of severe insulin-deficient diabetes patients performed the best
  - Patients not achieving target HbA1c with a GLP-1-based therapy at study entry also achieved a clinically meaningful reduction in HbA1c

Question after 26-week analysis?

Will these results be maintained at Week 52 in Severe Insulin-Deficient Diabetes patients and those who are failing on a GLP-1-based therapy?

High Unmet Need in Diabetes

- Diabetes is a progressive disease
- Approved agents are all chronic, none address the root cause – the failing beta cell
- Average time to loss of glucose control with a SOC T2D therapy ranges from 2 - 2.5 years
- 47.1% of T2D are uncontrolled with HbA1c > 7%[1]



Nathan, et al. N Engl J Med 2022;387:1063-107

Severe Insulin-Deficient Diabetes

18-44%

Worldwide depending on ethnicity[2-4]

~165M

Severe Insulin-Deficient T2D worldwide cases[5]

- Highest treatment failure rates among all T2D subtypes[6]
- Lowest insulin production of all adults with T2D[6]
- Represents a very high unmet medical need, with the highest risk of retinopathy, neuropathy[6]
- Severe Insulin-Deficient Diabetes patients progress the fastest to insulin therapies[6]

1. Centers for Disease Control and Prevention (CDC). 2. Ahlqvist et al Diabetes 2020;69:2086–2093. 3. Mohan V. Diabetes Care 2025;48:153–163. 4. Song A. et al. Front Endocrinol. 2022;13:978612. 5. International Diabetes Federation. IDF Diabetes Atlas www.diabetesatlas.org (Based on company calculations): 6. Ahlqvist et al. Lancet Diabetes Endocrinol 2018;

Icovamenib in Type 2 Diabetes: 52-Week Highlights

in Patients on 1 or more Antihyperglycemic Agent - 9 Months After Last Dose

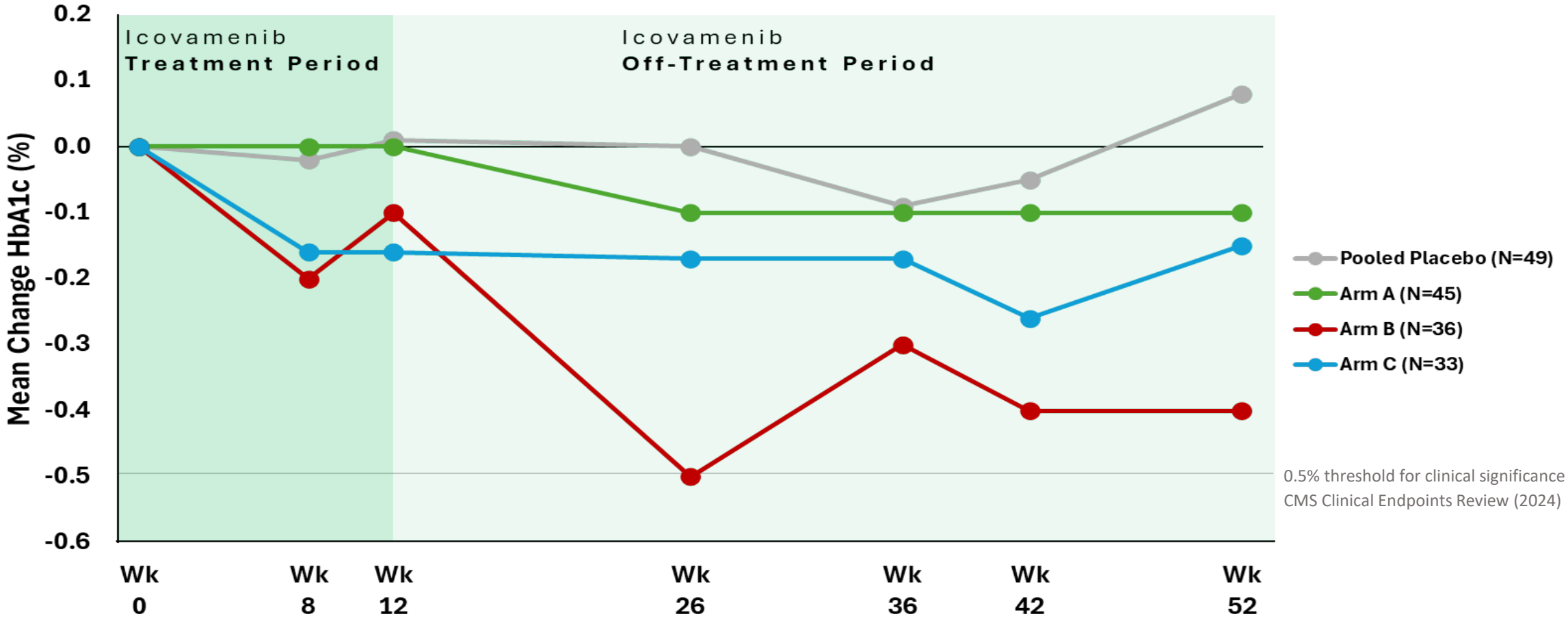
- **Icovamenib achieved clinically meaningful HbA1c reduction in multiple subgroups**
- **Sustained treatment effect in pre-defined severe insulin-deficient patient population**
  - Continued benefit observed in severe insulin-deficient diabetes patients
- **Treatment effect in GLP-1 failures also improved and continued**
  - Demonstrated marked levels of activity in patients not achieving HbA1c target on GLP-1 therapy at study entry
- **Higher icovamenib exposure led to improved responses**
  - PK analysis shows that better HbA1c reductions occurred in patients with better exposure to the drug
- **Favorable safety profile continued**
  - Icovamenib was generally well-tolerated, with no adverse-event related discontinuations and no related serious adverse events

All Dosing Arms A, B and C

52-Week Data

Change in HbA1c from Baseline through Week 52 – <u>All Subtypes</u>

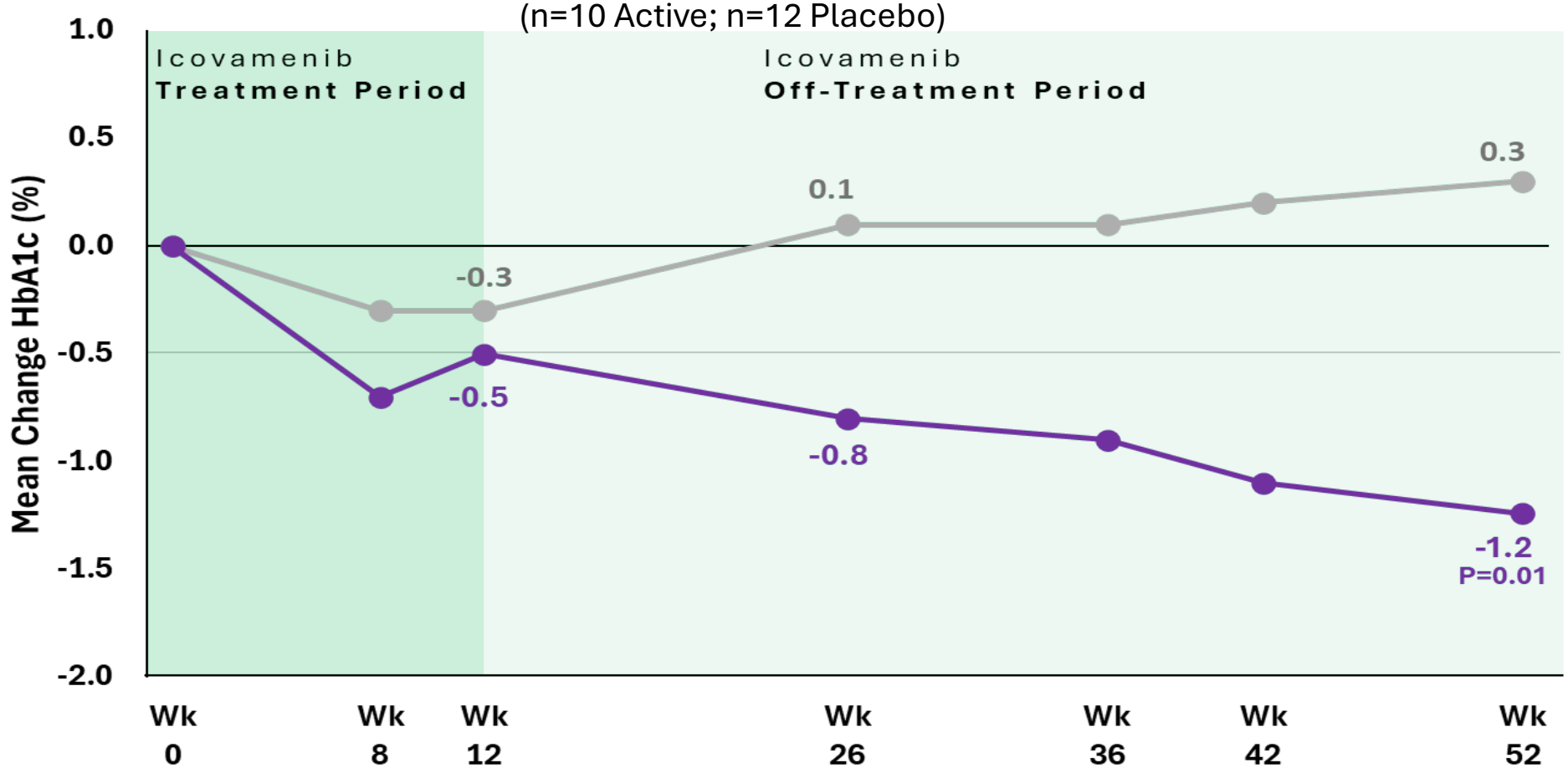
Across Treatment Durations (Arm A = 8 weeks 100 mg, Arm B = 12 weeks 100 mg, Arm C = 8 weeks 100 mg 4 weeks at 200 mg)
Per Protocol participants taking one or more antihyperglycemic medications at baseline



All presented data utilized a while-on-treatment estimand with mixed model repeated measures (MMRM) analysis and was censored for use of rescue medication, defined as any modification in anti-diabetic therapy

12 Weeks of Dosing (Arms B & C) Delivered Lasting Benefit Through 52 Weeks for Severe Insulin-Deficient Diabetes Patients *(9 Months After Last Dose)*

Severe Insulin-Deficient Diabetes Patients Arms B & C w/12 Weeks of Treatment
(n=10 Active; n=12 Placebo)



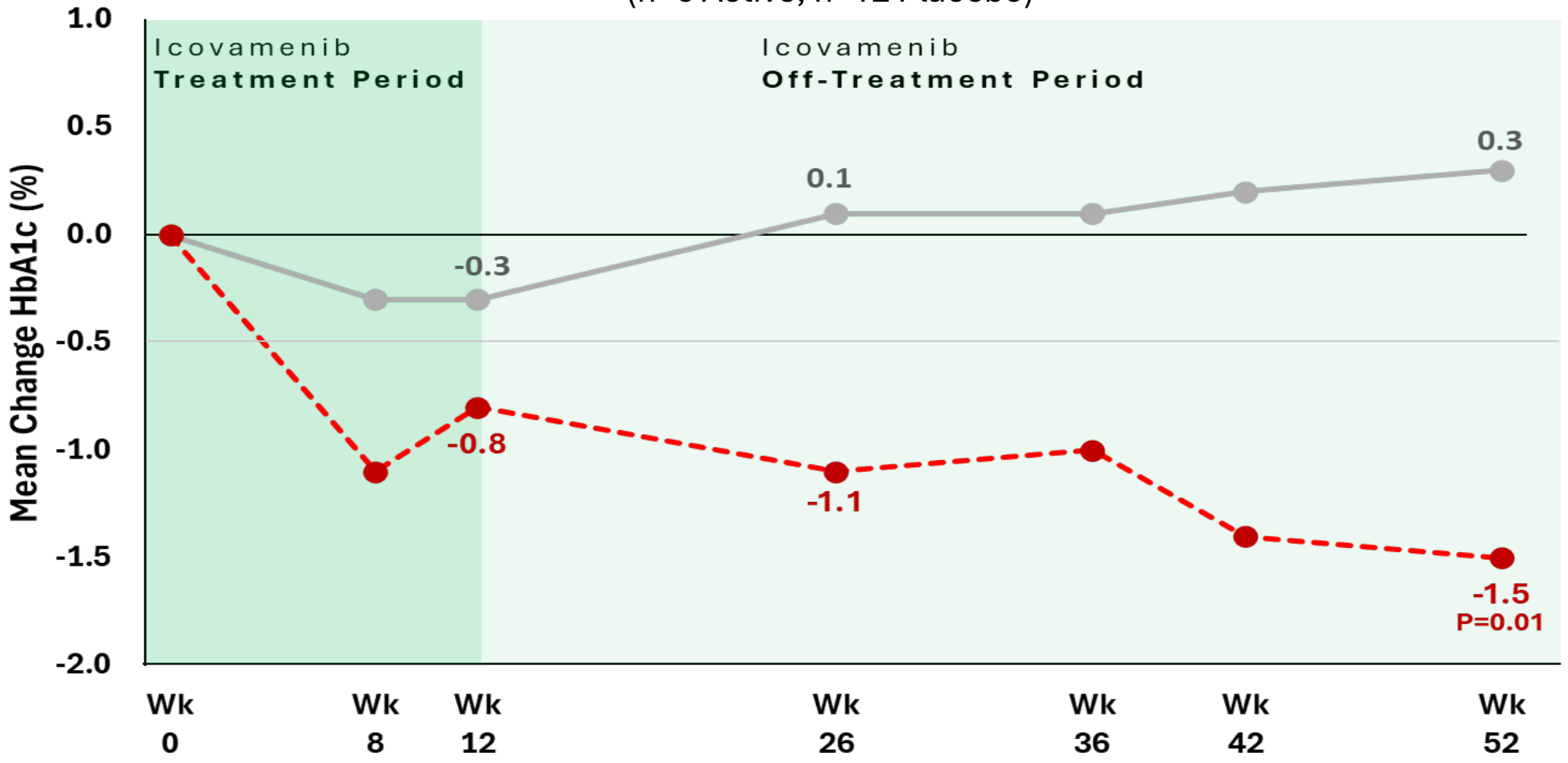
-0.5% threshold for clinical significance
CMS Clinical Endpoints Review (2024)

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

Arm A was excluded from this analysis because it included only 8 weeks of dosing which the company is not planning to pursue.

12 Weeks of Dosing (Arm B) Delivered Most Improved Results Through 52 Weeks for Severe Insulin-Deficient Diabetes Patients *(9 Months Post Dosing)*

Severe Insulin-Deficient Diabetes Patients only Arm B w/12 Weeks of Treatment at 100 mg QD
(n=6 Active; n=12 Placebo)

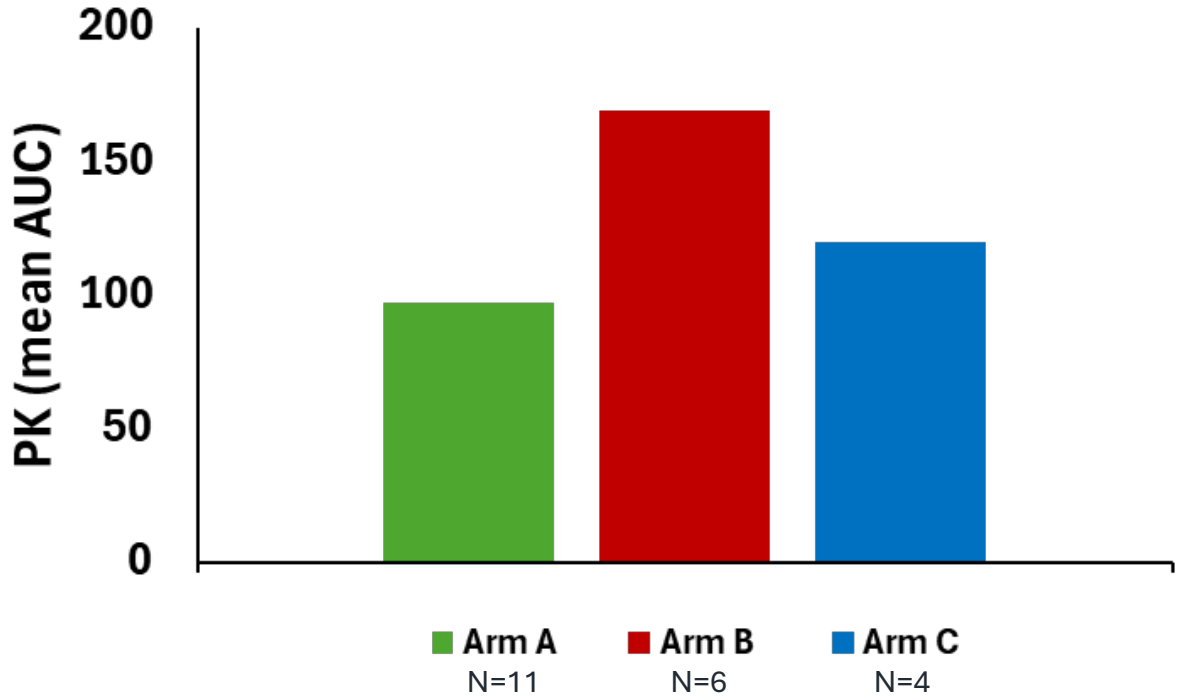


-0.5% threshold for clinical significance
CMS Clinical Endpoints Review (2024)

Arm B: 12 weeks of dosing 100 mg QD

Why did Arm B perform better than Arm C in Severe Insulin-Deficient Patients?

Patients in Arm B had greater icovamenib exposure which may have led to greater HbA1c reduction than Arms A and C

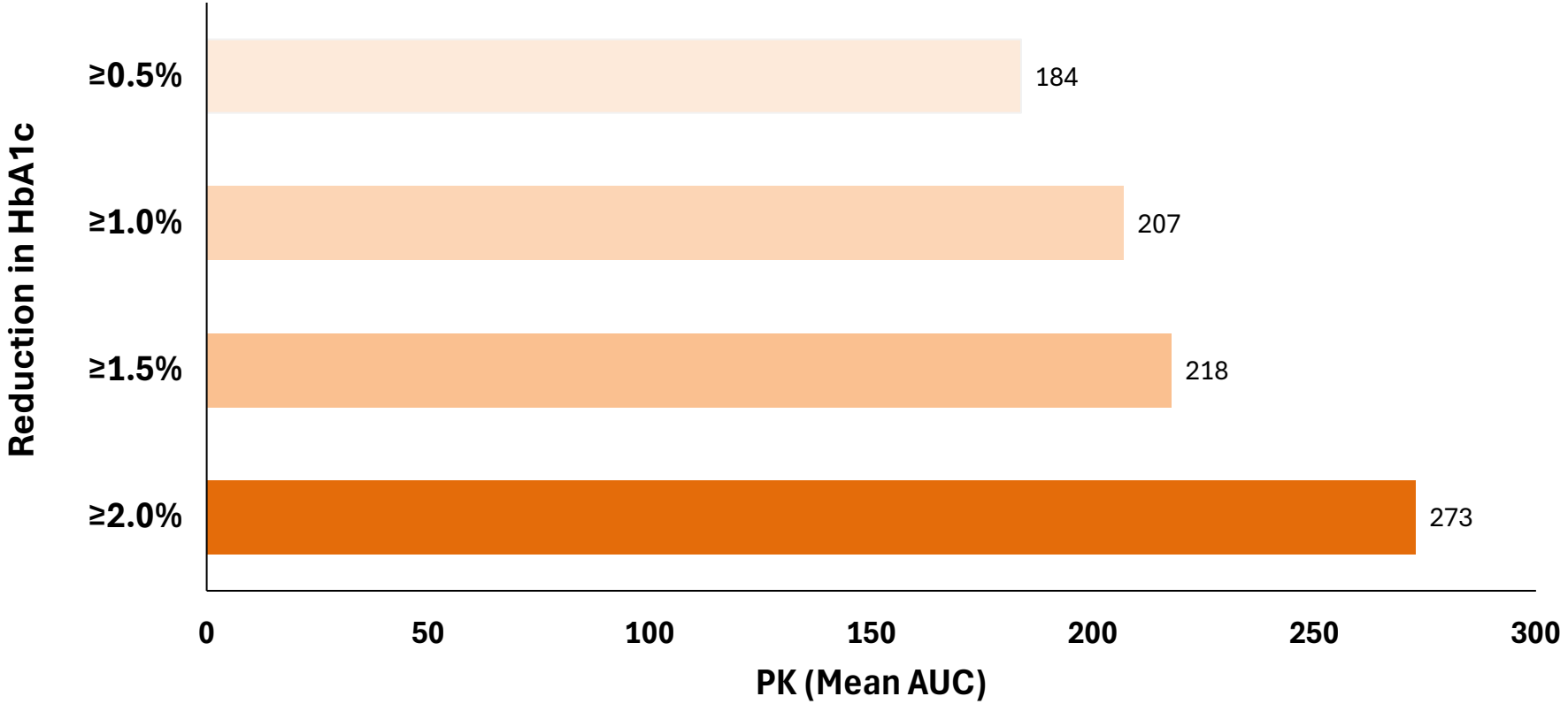


PK Mean AUC (Pharmacokinetic Mean Area Under the Curve) is a summary metric to evaluate drug exposure during dosing using PK concentration data collected at multiple time points across different visits. PK values of 0 (zero) are also included.

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

Higher HbA1c Reduction was Associated with Higher Icovamenib Exposure

Week 52, All Dosing Arms (N=114), HbA1c Reduction vs. Icovamenib Exposure (Mean AUC)



Food type and timing of dosing impact icovamenib's pharmacokinetics. Food-effect study under way to optimize dosing instructions, which we expect will further improve exposure and improve consistency of outcome across patients.

KEY FINDINGS through 52 Weeks

Per Protocol participants taking one or more antihyperglycemic medications at baseline

- **Continued HbA1c reduction achieved at Week 52 in predefined subset of patients**
  Severe insulin-deficient T2D patients (Arm B) showed the greatest clinically meaningful response (mean HbA1c reduction of 1.5%, p=0.01) through Week 52.
- **Exposure-response correlation**
  Patients with the greatest exposure achieved the highest reduction in HbA1c. We believe data suggest that a readily achievable exposure level could provide ≥1.5% HbA1c reductions in T2D patients.

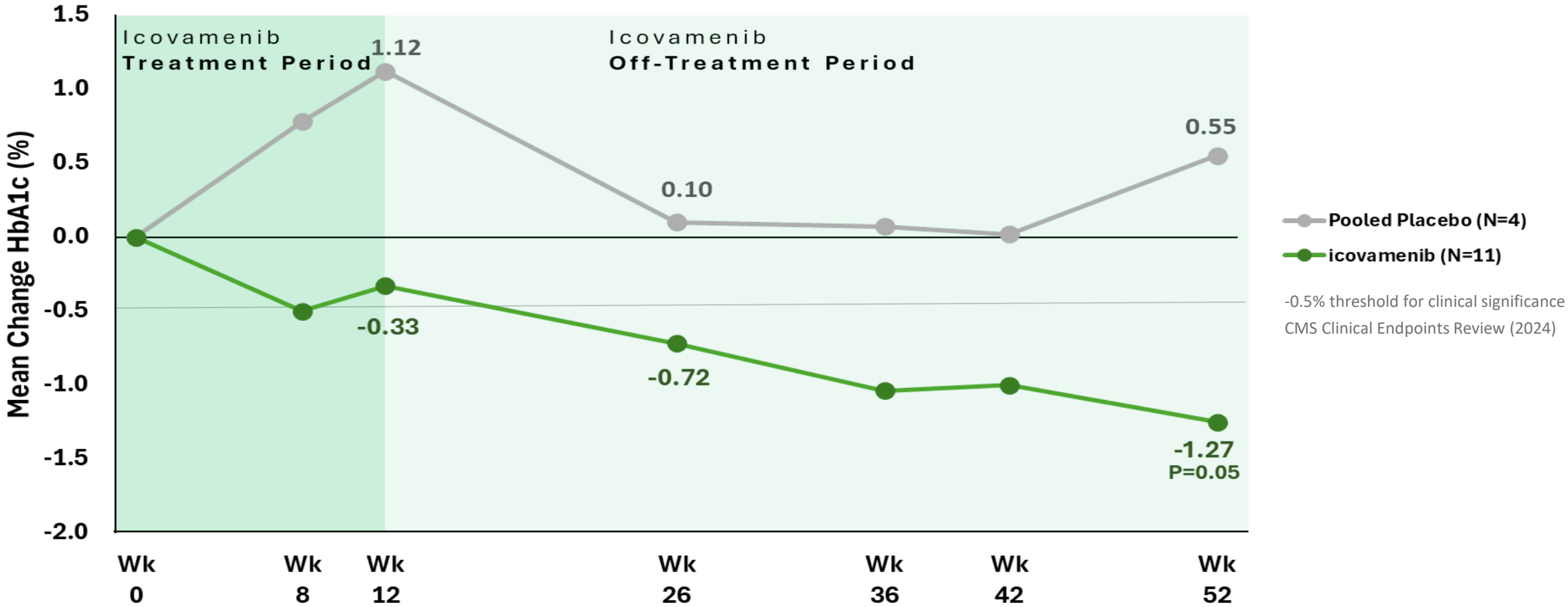
Efficacy of Icovamenib in Patients on GLP-1-Based Therapy

52-Week Data

Patients on a GLP-1 Based Therapy at Enrollment (n=11, All Obese Patients) Showed Durable and Clinically Meaningful Response

9 Months After Last Dose

Post-hoc Analysis of Enrolled Patients on GLP-1 Therapy Not Achieving Target HbA1c <7.0%
(n=11 Active; n=4 Placebo)



-0.5% threshold for clinical significance
CMS Clinical Endpoints Review (2024)

Icovamenib Prespecified Subgroup Performed with its Early Results in-line with Top-performing Chronically-Dosed Diabetes Agents

Currently Approved Type 2 Diabetes Agents w/Chronic Dosing				
Therapy	**Dosing Regimen**	**Administration Route**	**Observation Period**	**Mean HbA1c Reduction (placebo adj. %)**
Ozempic (GLP 1 Agonist)	Chronic Dosing	Injectable	Week 30	-1.2 (0.5mg) -1.4 (1mg)
Mounjaro (GLP-1/GIP Agonist)	Chronic Dosing	Injectable	Week 40	-1.8 (5mg) -1.7 (15mg)
Jardiance (SGLT2 Inhibitor)	Chronic Dosing	Oral	Week 24	-0.7 (10mg) -0.9 (25mg)
Januvia (DPP4 Inhibitor)	Chronic Dosing	Oral	Week 24	-0.8 (100mg)

Ozempic FDA Label; Mounjaro FDA Label; Jardiance FDA Label; Januvia FDA Label

ICOVAMENIB (Menin Inhibitor)	**12 Weeks**	**Oral**	**Week 52**	**-1.5% to -1.8% (100mg)**

Disclaimer: The data presented above are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities and differences. The values shown in the cross-study comparisons are directional and may not be directly comparable.

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- **Exposure-response correlation**
  Patients with the greatest exposure achieved the highest reduction in HbA1c. We believe data suggest that a readily achievable exposure level could provide ≥1.5% HbA1c reductions in T2D patients.
- **GLP-1 failing patients benefited markedly from 12 weeks of icovamenib**
  Patients not achieving HbA1c targets with GLP-1 based therapy showed clinically meaningful responses (HbA1c reduction of 1.3%, p=0.05) through Week 52.

Safety Summary

52-Week Data

Overview of Treatment Emergent Adverse Events (TEAEs) Through 52 Weeks

(Safety Population, N=267)

Parameter	Arm A icovamenib (N=67)	Arm B icovamenib (N=67)	Arm C icovamenib (N=67)	Combined Arms icovamenib (N=201)	Combined Arms placebo (N=66)
Patients with ≥1 TEAE, N (%)	19 (28)	22 (33)	14 (21)	55 (27)	18 (27)
Treatment-Related SAEs, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs*, N (%)	1 (1)	0 (0)	1 (1)	2 (1)	1 (1)
Treatment Discontinuation due to TEAE, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Study Discontinuation due to TEAE, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Deaths, N (%)	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 (TEAEs) 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=67)	Arm C icovamenib (N=67)	Combined Arms icovamenib (N=201)	Combined Arms placebo (N=66)
Diarrhea, N (%)	4 (6)	2 (3)	1 (1)	7 (3)	0
Urinary tract infection, N (%)	0	1 (2)	0	1 (.5)	3 (5)
Hyperglycemia, N (%)	2 (3)	5 (7)	1 (1)	8 (4)	3 (5)
Headache, N (%)	0	4 (6)	1 (1)	5 (2)	2 (3)
ALT increase, N (%)	3 (4)	0	2 (3)	5 (2)	0
AST increase, N (%)	3 (4)	0	1 (1)	4 (2)	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.

Subjects with Treatment Emergent Adverse Events of Hypoglycemia

(Safety Population, N=267)

	Arm A icovamenib (N=67)	Arm B icovamenib (N=67)	Arm C icovamenib (N=67)	Combined Arms icovamenib (N=201)	Combined Arms placebo (N=66)
Grade 1, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 2, N (%)	0 (0)	1 (1)*	0 (0)	1 (0.5)*	0 (0)
Grade 3, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*Hypoglycemic adverse event occurred outside of the 12-week treatment window

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  Patients with the greatest exposure achieved the highest reduction in HbA1c. We believe data suggest that a readily achievable exposure level could provide ≥1.5% HbA1c reductions in T2D patients.
- **GLP-1 failing patients benefited markedly from 12 weeks of icovamenib**
  Patients not achieving HbA1c targets with GLP-1 based therapy showed clinically meaningful responses (HbA1c reduction of 1.3%, p=0.05) through Week 52.
- **Favorable safety profile**
  Icovamenib was generally well-tolerated, with no adverse-event related discontinuations and no related serious adverse events.

Key Opinion Leader - Insights

Ralph DeFronzo, MD
Professor of Medicine, Chief of Diabetes Division at the University of Texas Health Science Center at San Antonio and Deputy Director of the Texas Diabetes Institute

Executive Summary

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Icovamenib in Type 2 Diabetes: 52-Week Highlights

in Patients on 1 or more Antihyperglycemic Agent - 9 Months After Last Dose

- **Icovamenib achieved clinically meaningful HbA1c reduction in multiple subgroups**
- **Sustained treatment effect in pre-defined severe insulin-deficient patient population**
  - Continued benefit observed in severe insulin-deficient diabetes patients
- **Treatment effect in GLP-1 failures also improved and continued**
  - Demonstrated marked levels of activity in patients not achieving HbA1c target on GLP-1 therapy at study entry
- **Higher icovamenib exposure led to improved responses**
  - PK analysis shows that better HbA1c reductions occurred in patients with better exposure to the drug
- **Favorable safety profile continued**
  - Icovamenib was generally well-tolerated, with no adverse-event related discontinuations and no related serious adverse events

NEXT STEPS

1. **Optimize icovamenib exposure and define dosing criteria with a Food Effect Study**
   (Food Effect Study COVALENT-121 – started 9/11/25; expected completion 12/25)
2. **Investigate icovamenib in severe insulin deficient diabetes patients in a Phase IIb Type 2 Diabetes Study**
   (T2D Study COVALENT-211 – initiation expected 4Q 25)
3. **Investigate icovamenib in combination with a GLP-1 based therapy in a Phase II Type 2 Diabetes Study**
   (T2D Study COVALENT-212 – initiation expected 4Q 25)
4. **Initiate a Phase I with Biomea Fusion's oral GLP-1 RA BMF-650 in obese, otherwise healthy volunteers**
   (Obesity Study GLP-131 – initiation ongoing, expected completion 1H 26)

Question & Answer Session

Thank you