

Glycemic Improvements with Icovamenib in Adults with T2D Receiving Background GLP-1 Therapy: Subgroup Analysis from the COVALENT-111 Study

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Juan Pablo Frías, MD; Jeffrey Kim, PhD
Biomea Fusion, 1599 Industrial Road, San Carlos, CA 94070 USA

Background

Type 2 Diabetes (T2D) and Beta-Cell Dysfunction

- T2D is characterized by hyperglycemia driven by a progressive loss of beta-cell mass and insulin secretory capacity
- At diagnosis, beta-cell function is often reduced by >50%, with further decline over the disease course¹
- Most standard therapies improve glycemia but do not address the underlying loss of insulin-producing beta cells
- As beta-cell function worsens, many patients ultimately require lifelong insulin therapy, which can be associated with hypoglycemia risk, weight gain, and patient burden related to injections and monitoring
- Although GLP-1 receptor agonists (RA) improve glycemia and provide important metabolic benefits, many individuals with T2D remain above glycemic targets despite GLP-1 RA-based therapy

Menin: A Negative Regulator of Beta-Cell Regeneration

- Menin is a scaffold protein that regulates gene expression through multiple protein complexes
- In beta cells, menin acts as a key repressor of proliferation and adaptive expansion, maintaining them in a quiescent state
- Hyperglycemia and metabolic stress strengthen this menin-driven repression, creating a biological brake on beta-cell recovery

Icovamenib: A Selective Oral Menin Inhibitor

- Icovamenib is an orally administered investigational small molecule currently in Phase 2 clinical development for the treatment of T2D and T1D
- Icovamenib targets menin and has been shown preclinically in both animal and ex vivo human islet studies to induce transient reductions in menin protein levels, thereby modulating pathways associated with insulin secretion and glycemic control
- In diabetic rodent models, short-course icovamenib led to sustained, treatment-free glycemic improvements^{2,3}
- In human islet microtissues, icovamenib induced dose- and duration-dependent beta-cell proliferation under hyperglycemic conditions⁴

Clinical Rationale

- COVALENT-111 results showed short-term icovamenib dosing (4–12 weeks) to lead to continued HbA1c improvements for months after treatment cessation, together with increases in C-peptide, consistent with enhanced beta-cell function⁵
- This subgroup analysis evaluated whether icovamenib provided additional glycemic benefit in adults with T2D who were receiving stable background GLP-1 RA-based therapy at baseline

Safety | Treatment Emergent Adverse Events

Parameter	Pooled Placebo (N=4)	Icovamenib Combined arms (N=12)	Arm A icovamenib (N=3)	Arm B icovamenib (N=3)	Arm C icovamenib (N=6)
Patients with ≥1 TEAE, N (%)	3 (75)	3 (25)	1 (33)	1 (33)	1 (17)
Treatment-Related SAEs, N (%)	1 (25)	1 (8)	1 (33)	0	0
SAEs*, N (%)	0	0	0	0	0
Treatment Discontinuation due to TEAE, N (%)	0	0	0	0	0
Study Discontinuation due to TEAE, N (%)	0	0	0	0	0
Deaths, N (%)	0	0	0	0	0
Diarrhea, N (%)	1 (25)	1 (8)	1 (33)	0 (0)	0 (0)
Nausea, N (%)	1 (25)	0	0	0	0
Hyperglycemia, N (%)	0	0	0	0	0
Headache, N (%)	0	0	0	0	0
AST/ALT increase, N (%)	2 (50)	5 (42)	1 (33)	1 (33)	3 (50)
Resolution of ALT/AST w/o interruption in study treatment, %	100	100	100	100	100

Data are n (%) of TEAE with ≥5% frequency in any arm and ALT or AST increase irrespective of incidence; ALT, alanine aminotransferase; AST, aspartate aminotransferase
AST/ALT increase: In the icovamenib arms, 4 of the 5 events were Grade 1 and 1 event was Grade 2 (Arm C)

- Icovamenib was generally well tolerated in participants receiving background GLP-1 RA-based therapy
- No serious adverse events or discontinuations due to adverse events were reported in this subgroup
- No new safety signals were identified. The safety profile was consistent with the overall COVALENT-111 study population

COVALENT-111 (Expansion Phase): Study Overview & Design

Study Design

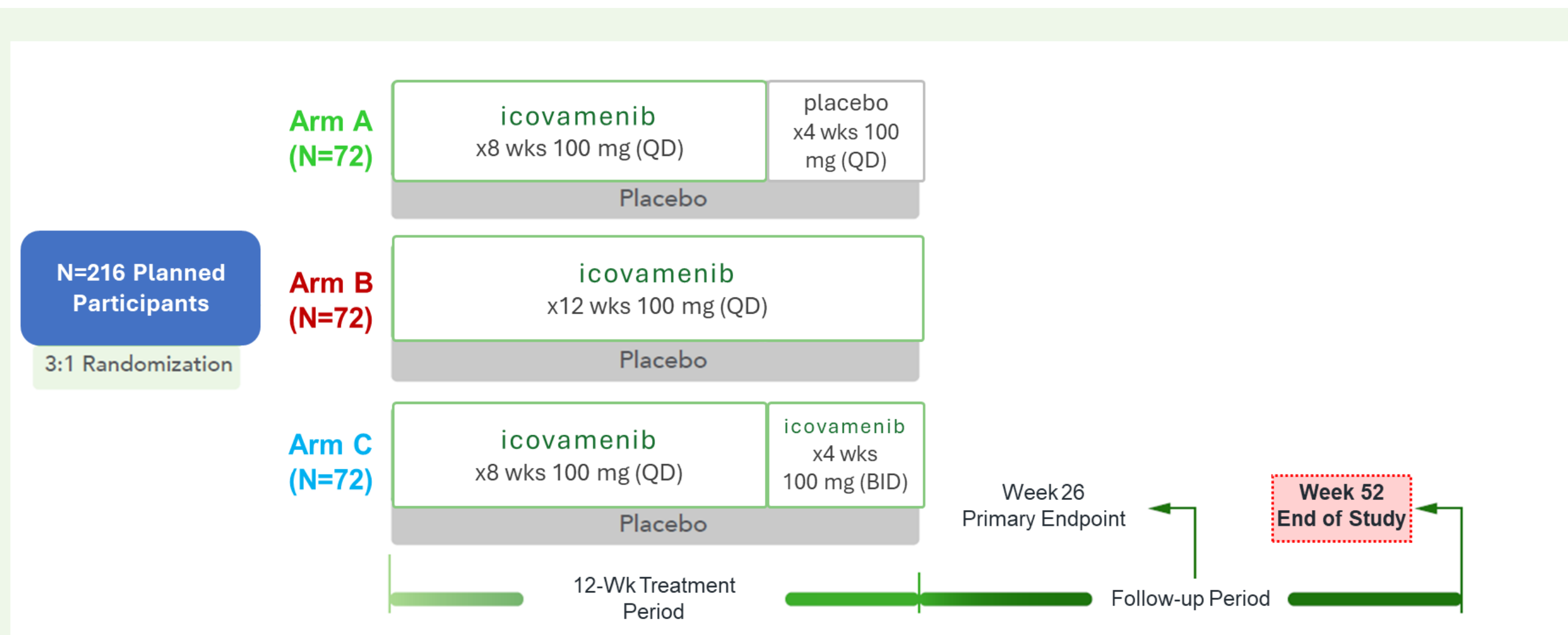
- 52-week, randomized, double-blind, placebo-controlled

Primary Endpoints

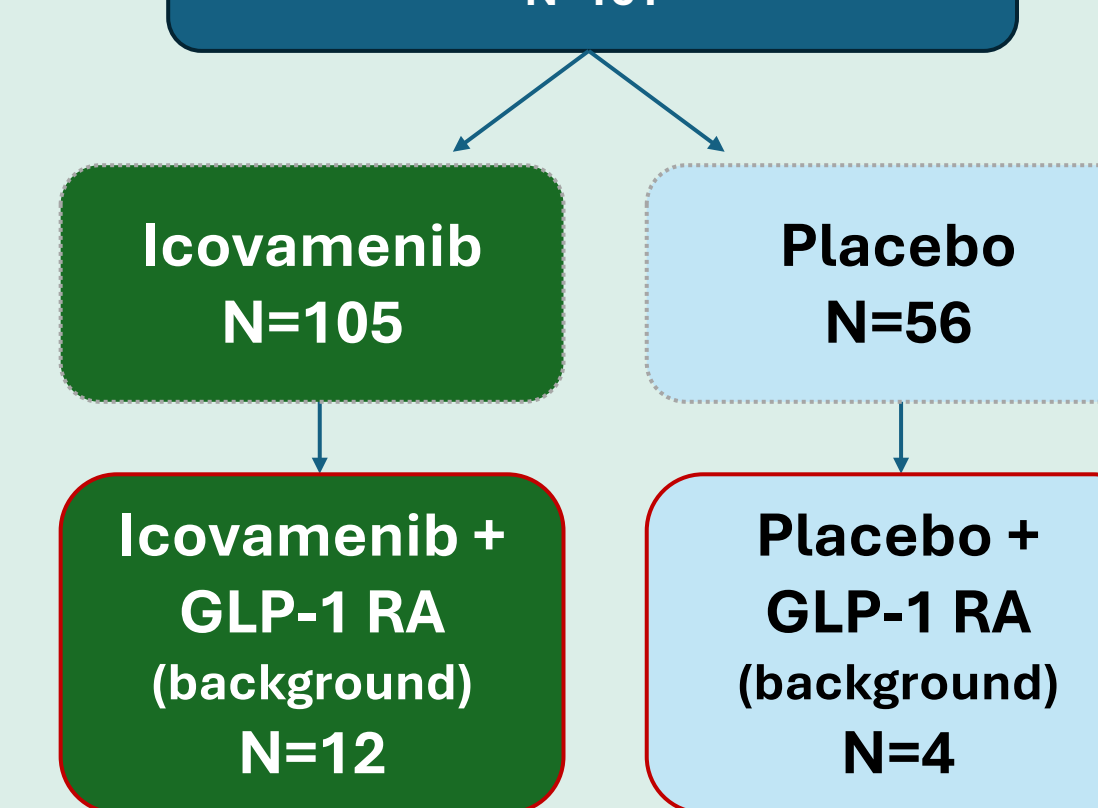
- Change in HbA1c from baseline at Week 26
- Safety and tolerability at Week 52

Key Eligibility Criteria

- Adults (18-65 years) with T2D (<7 years)
- HbA1c 7.0-10.5%
- BMI 25-40 kg/m²
- Treated with up to 3 antihyperglycemic agents (excluding insulin and SFUs)



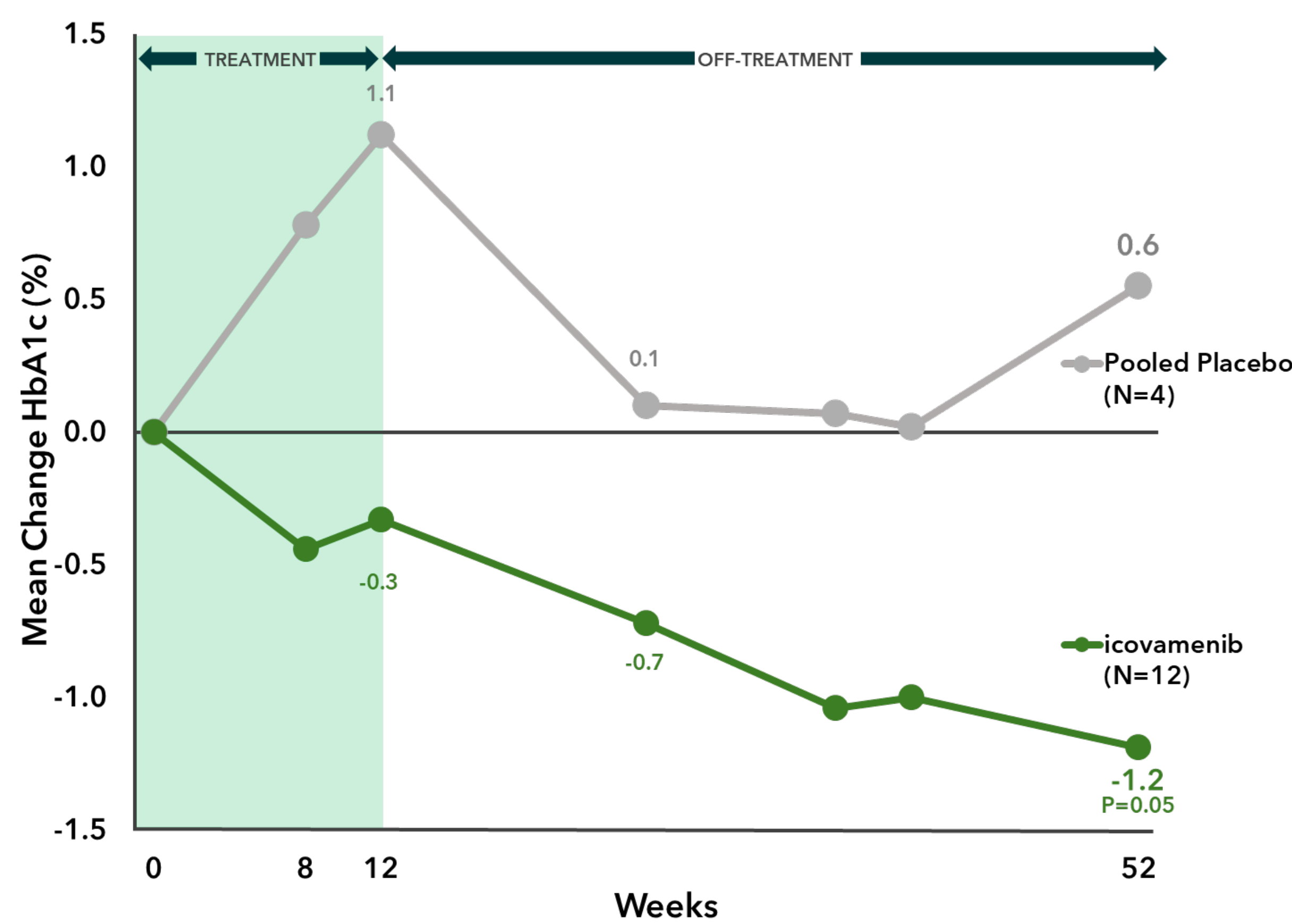
Per Protocol Population* N=161



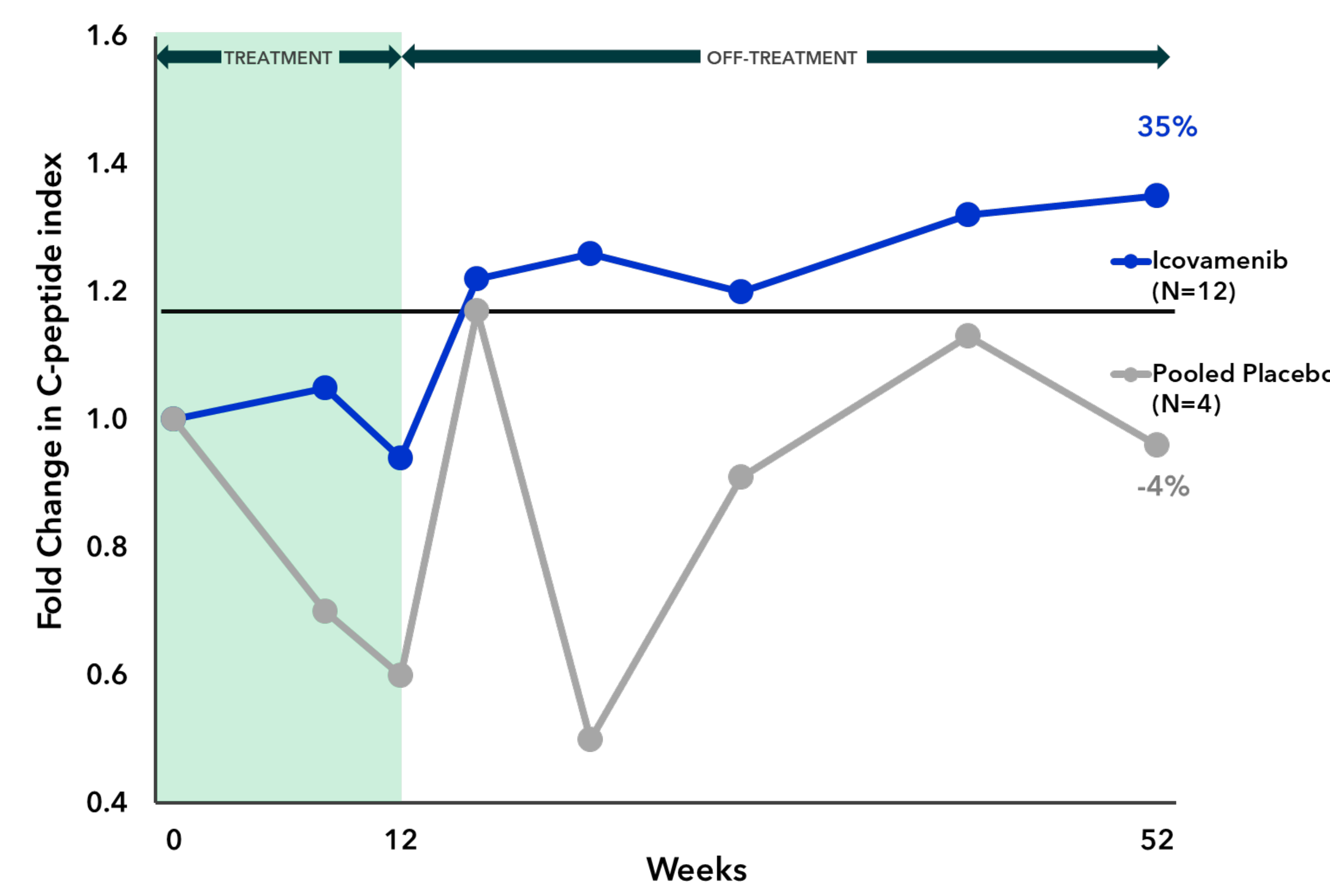
Characteristic	Icovamenib (n=12)	Placebo (n=4)
Age, years	53 ± 9	58 ± 9
T2D duration, years	5.4 ± 0.8	4.8 ± 2.6
HbA1c, %	8.4 ± 0.9	7.9 ± 0.3
BMI, kg/m ²	35.1 ± 3.3	32.5 ± 3.5

*Reduction in study population impacted by FDA hold and major protocol deviations related to quality and study conduct at certain clinical trial sites

Short-Term Dosing Resulted in Lasting Benefit Through 52 Weeks



Patients on GLP-1 RA-based therapy not achieving HbA1c target at baseline demonstrated durable and clinically meaningful persistent decline in HbA1c through Week 52 (9 months after last dose)



Icovamenib increased insulin secretion (C-peptide index) in GLP-1 RA-based therapy treated patients (9 months after last dose)

Conclusions

- In adults with T2D receiving background GLP-1 RA based-therapy, icovamenib demonstrated durable HbA1c improvement through Week 52, 40 weeks after treatment discontinuation
- At Week 52, HbA1c decreased by 1.2% with icovamenib versus an increase of 0.6% with placebo, corresponding to a clinically meaningful 1.8% placebo-adjusted reduction, comparable to leading therapies
- An increase in C-peptide index compared to placebo points to the mechanism driving the improved glycemia
- Icovamenib was generally well tolerated, with no serious AEs, no AE-related discontinuations, and no new safety signals, supporting further evaluation as a beta-cell-directed therapeutic approach for T2D
- These findings suggest icovamenib may provide additional glycemic benefit when used alongside GLP-1 RA-based therapy
- The results support further evaluation of icovamenib as a directed therapeutic approach for patients with T2D not achieving glycemic targets

References

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