THE 19TH INTERNATIONAL CONFERENCE ON ATTD Advanced Technologies & Treatments for Diabetes

COVALENT-111: 52-Week Efficacy and Safety of Icovamenib in Insulin-Deficient Type 2 Diabetes

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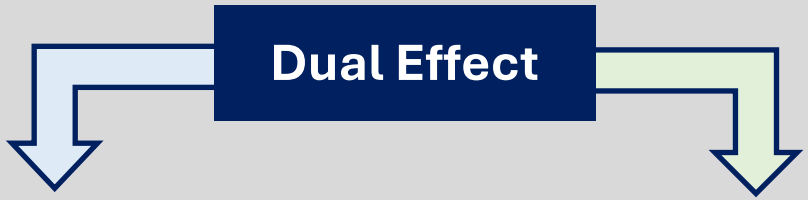
Disclosures

- **Research Support:** Eli Lilly, Novo Nordisk, Sparrow Pharmaceuticals
- **Advisory Boards and Consulting:** Abbvie, Biomea Fusion, Sparrow Pharmaceuticals, Zealand Pharmaceuticals
- **Speakers Bureau:** Eli Lilly
- **Board of Directors:** T1D Exchange
- **Stockholder:** Biomea Fusion, Inc.

Icovamenib: A Novel Approach Targeting Beta-Cell Function in 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 GLP-1 Combination Studies**

Icovamenib Differentiating Features

- ✓ Oral, once daily
- ✓ Non-chronic
- ✓ Well tolerated
- ✓ MOA complementary to other agents used

COVALENT-111 Trial Design

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

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
- Measures of beta-cell function (plasma glucose, c-peptide, insulin, and HOMA-β) at Week 26

Key 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 antihyperglycemic agents (excluding insulin and SFUs)

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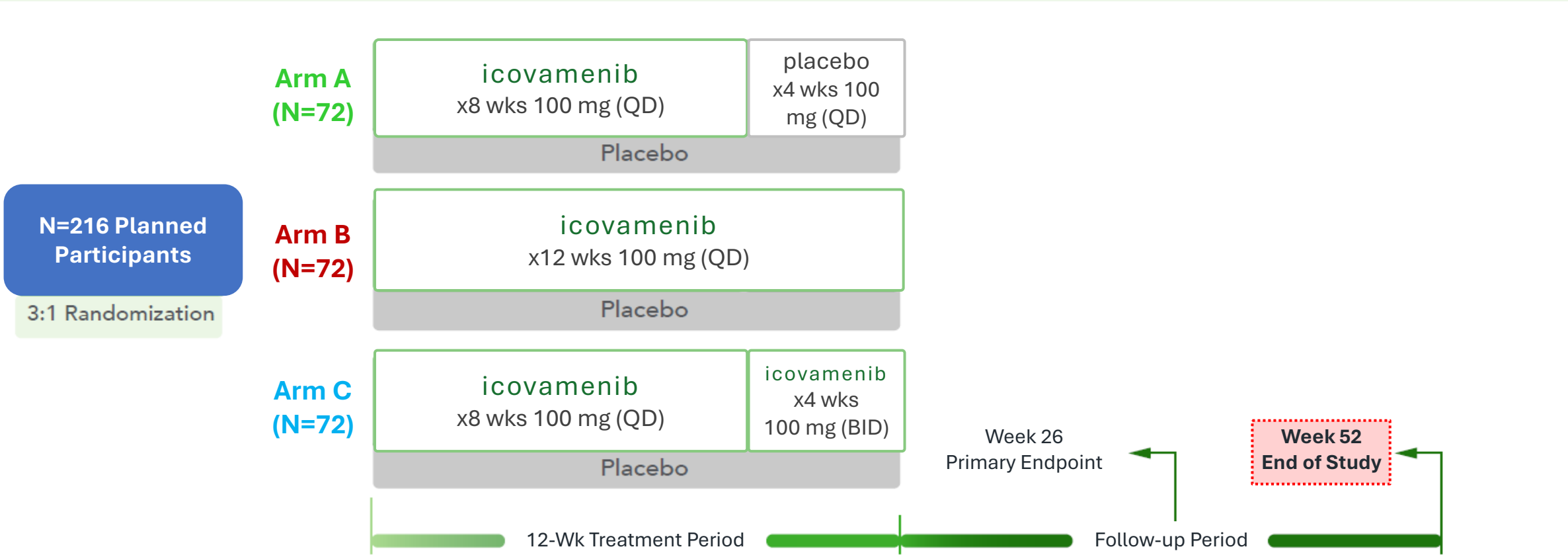
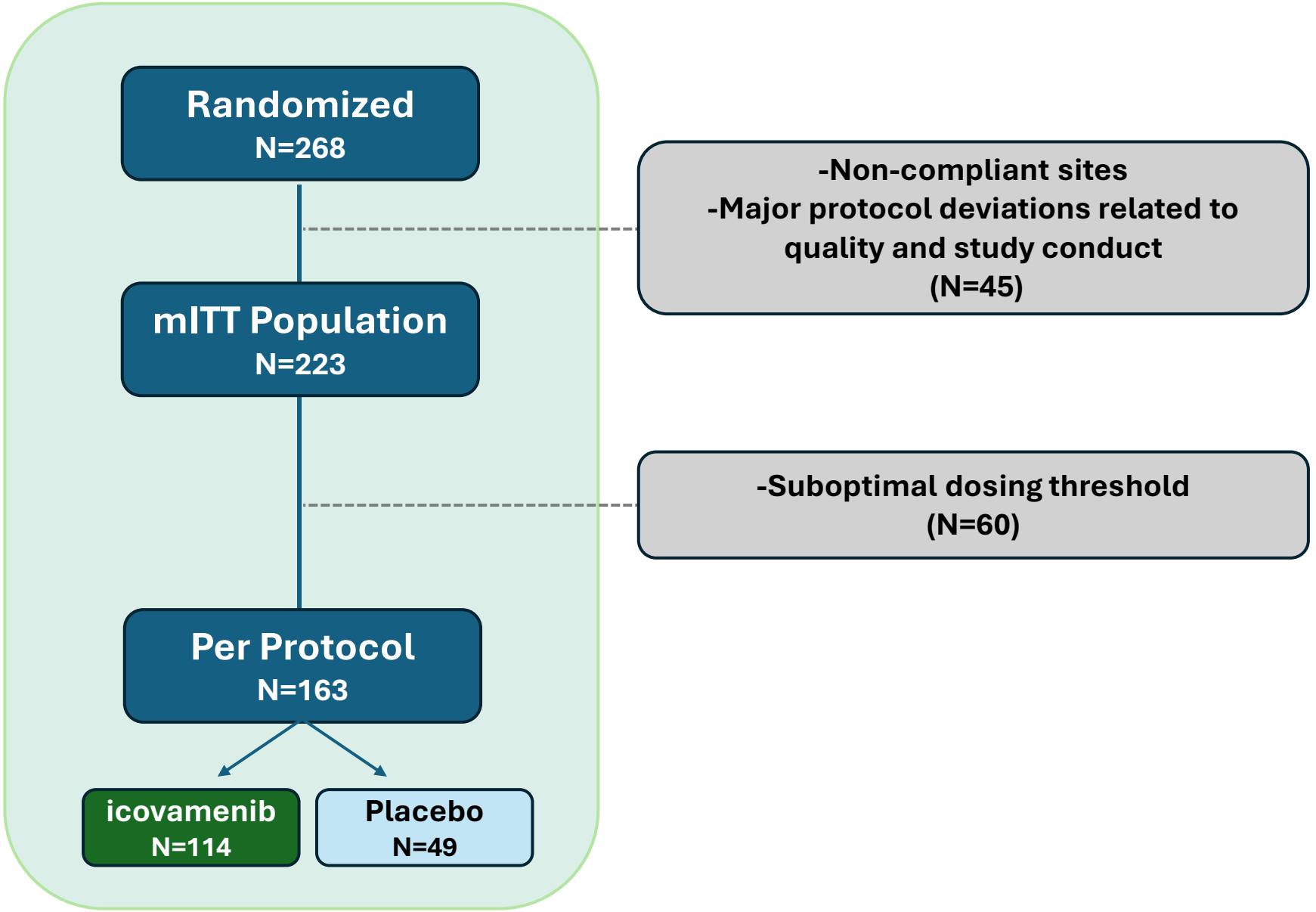
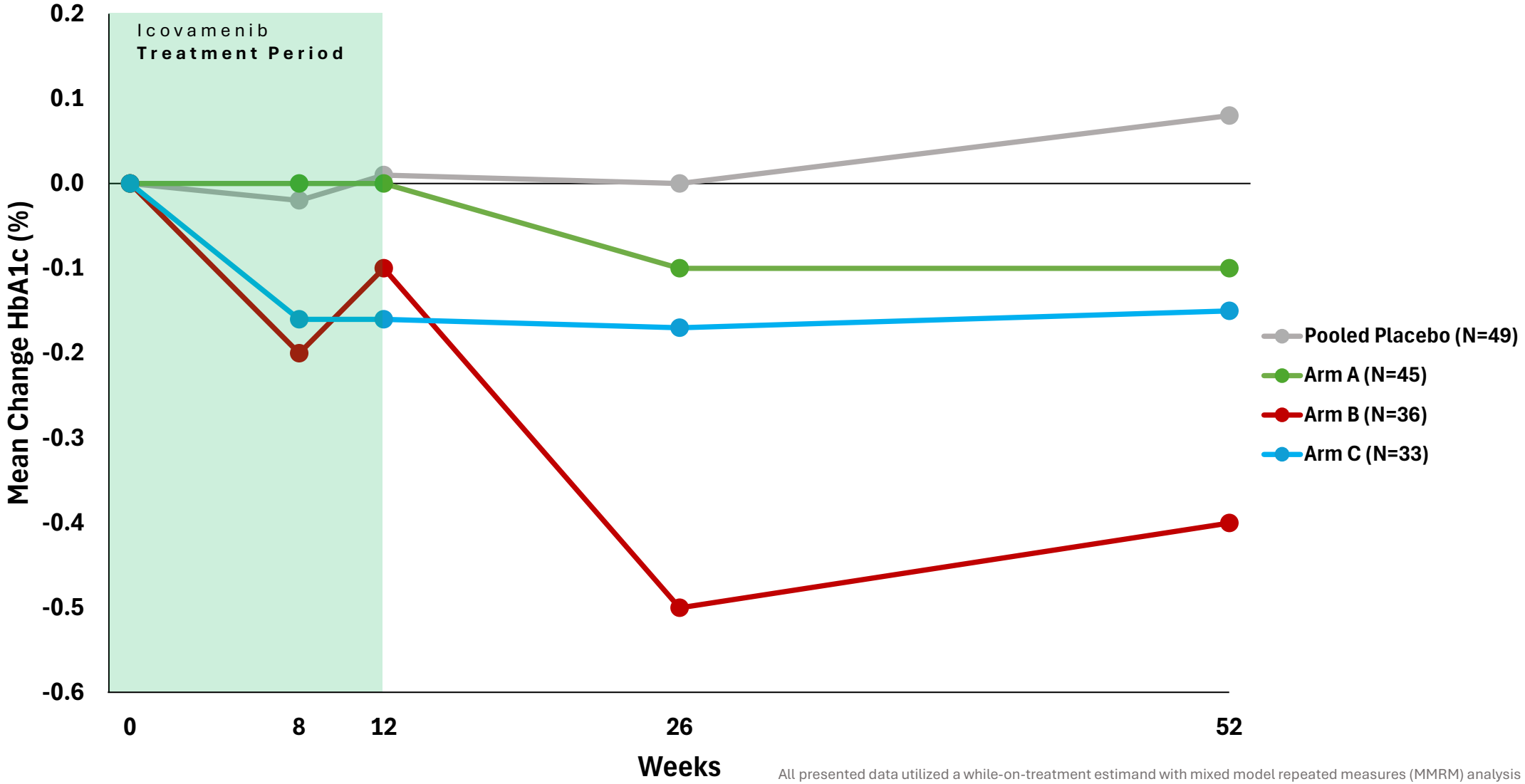


Study Disposition



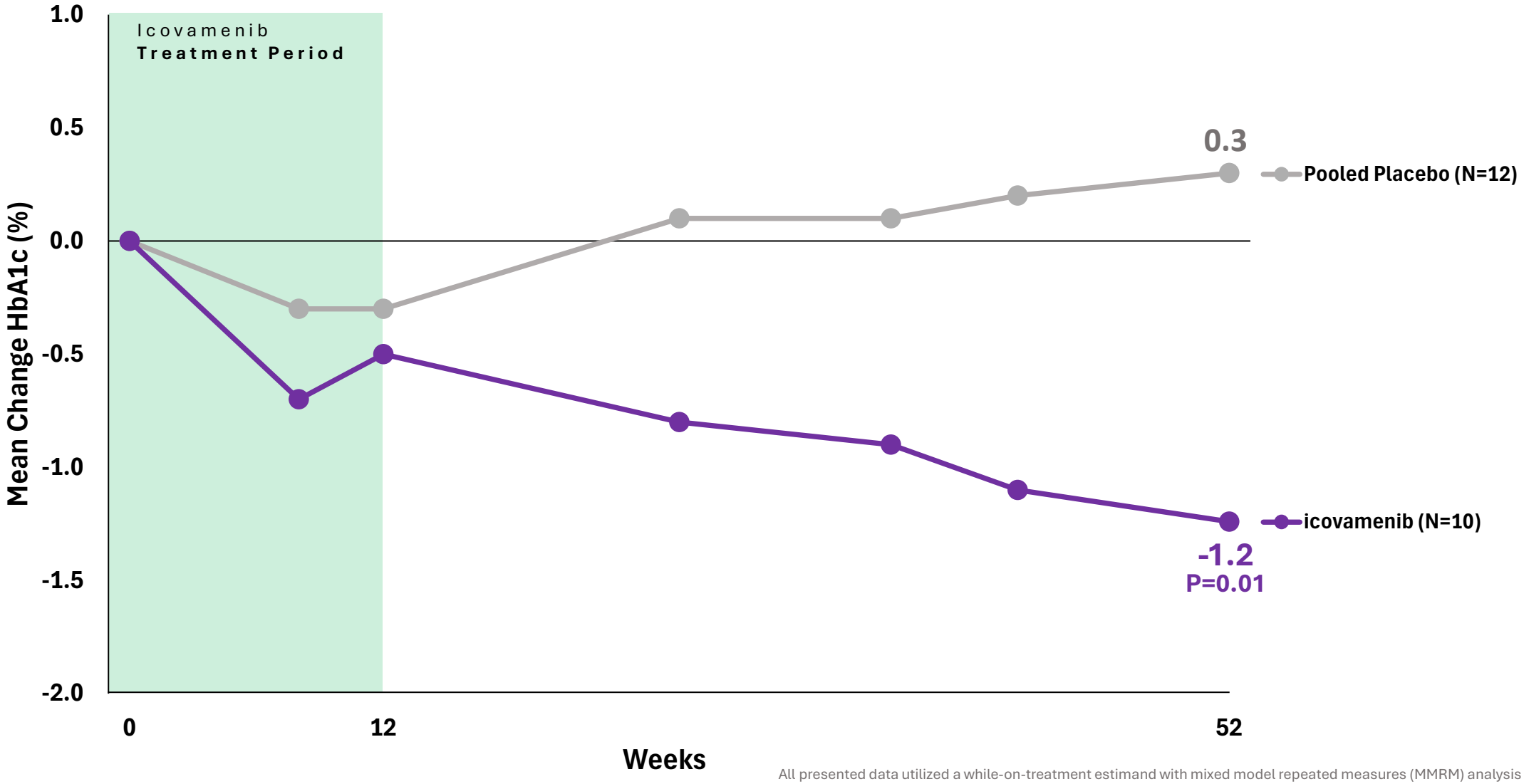
Change in HbA1c from Baseline through Week 52 – All Subtypes

Across Treatment Durations (Arm A = 8 weeks 100 mg, Arm B = 12 weeks 100 mg, Arm C = 8 weeks 100 mg / 4 weeks 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 antihyperglycemic therapy

12-Week Treatment (Arms B & C) Resulted in Continued HbA1c Improvement Through Week 52 (9 Months After Last Dose) in Participants with Severe Insulin-Deficient T2D



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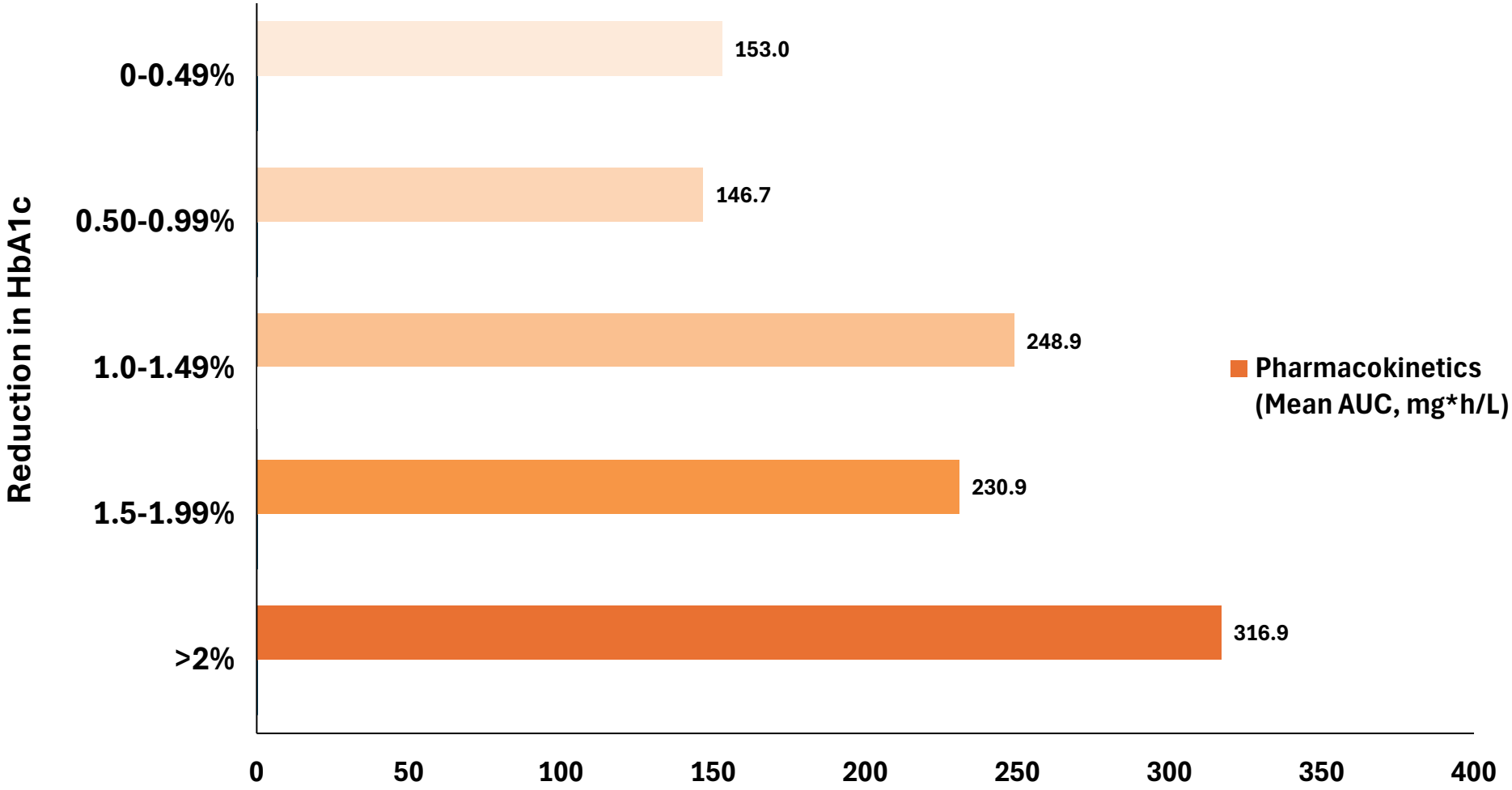
Higher HbA1c Reduction and C-peptide Index at Week 52 was Associated with Higher Icovamenib Exposure

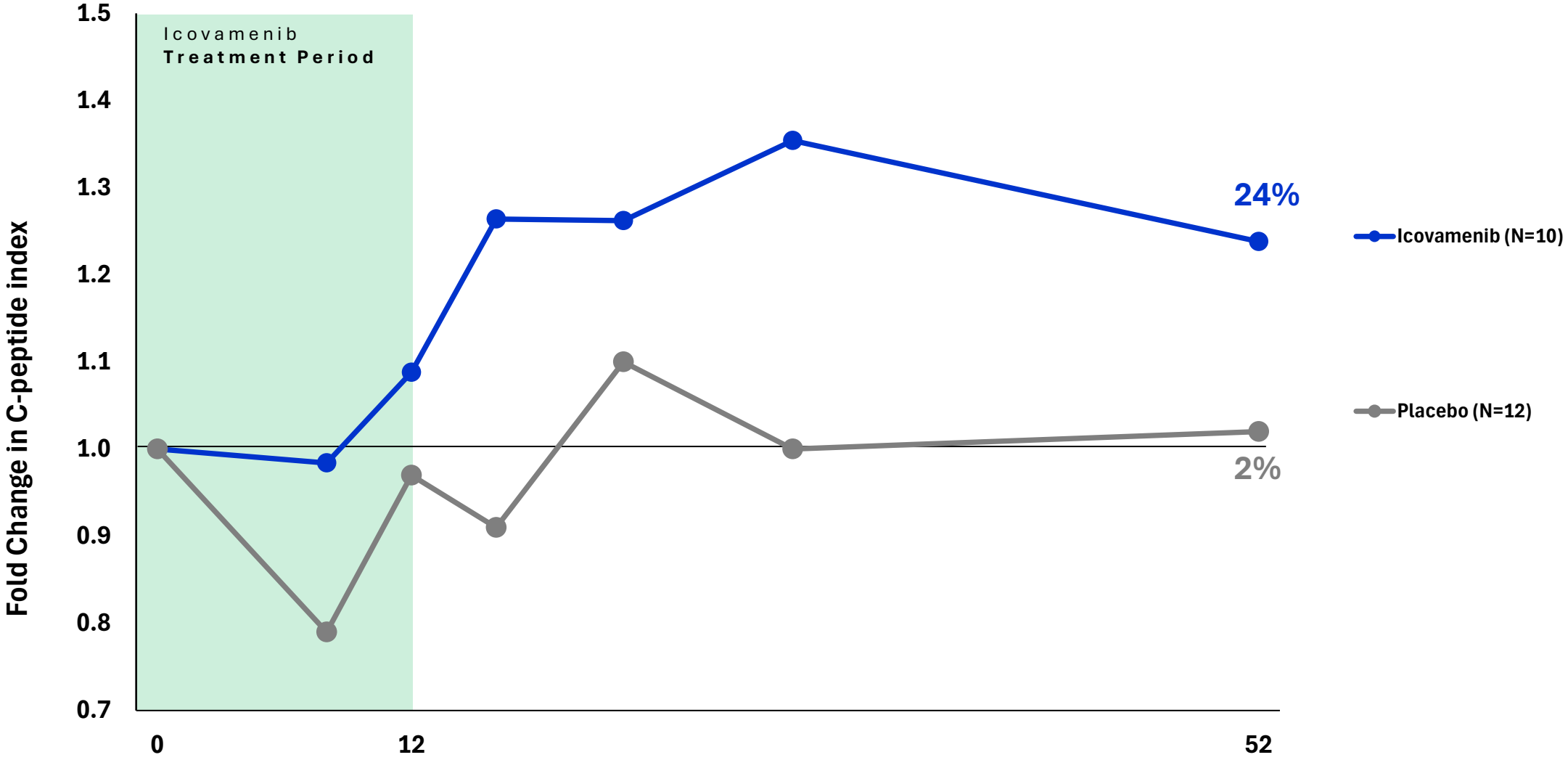
12 Weeks of Dosing (Arms B & C, N=69)



Data censored at onset of rescue medication, defined as any modification in antihyperglycemic therapy

Icovamenib Increased Insulin Secretion as Measured by C-peptide Index

Severe insulin-deficient patients (12-Week Treatment, arms B+C)



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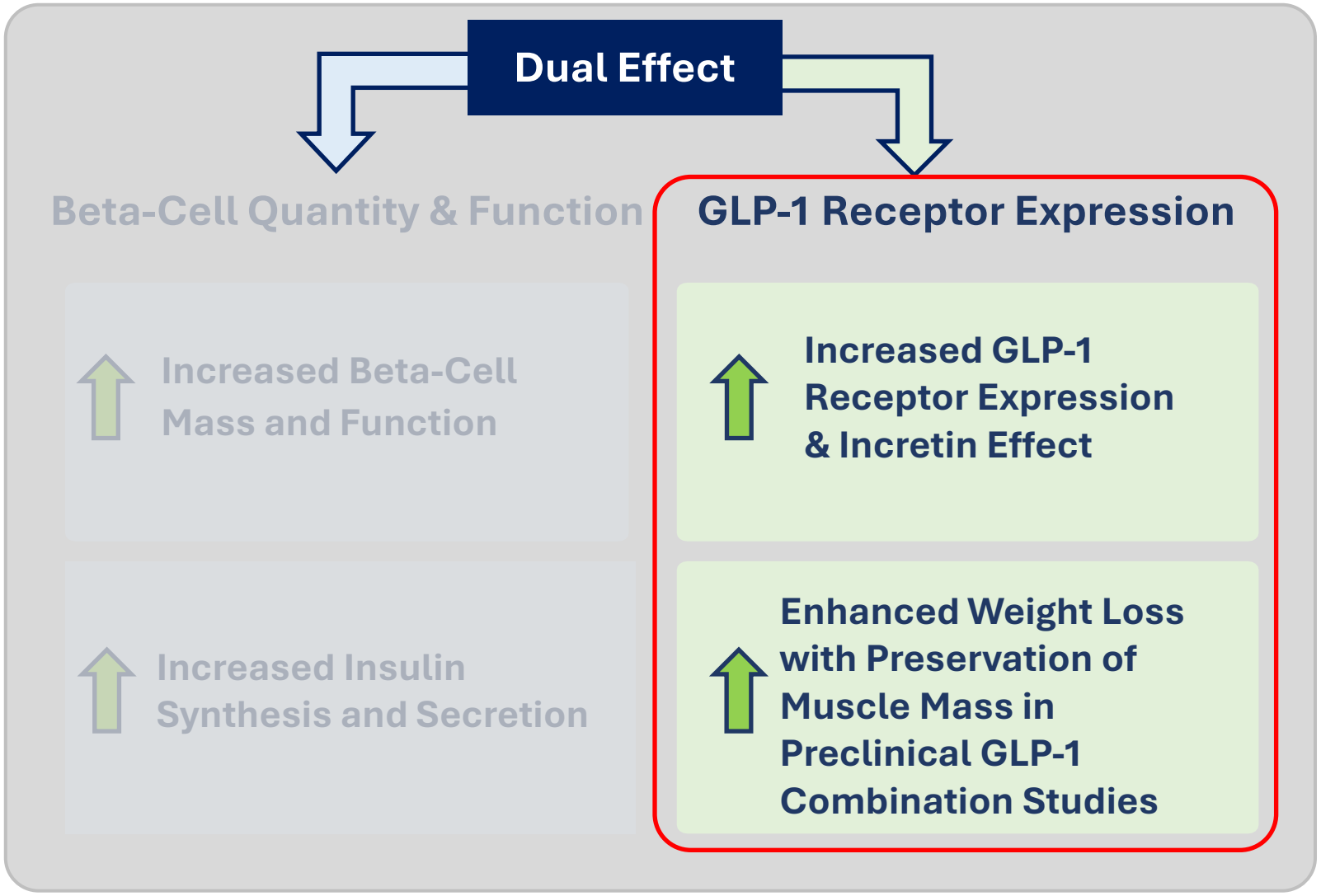
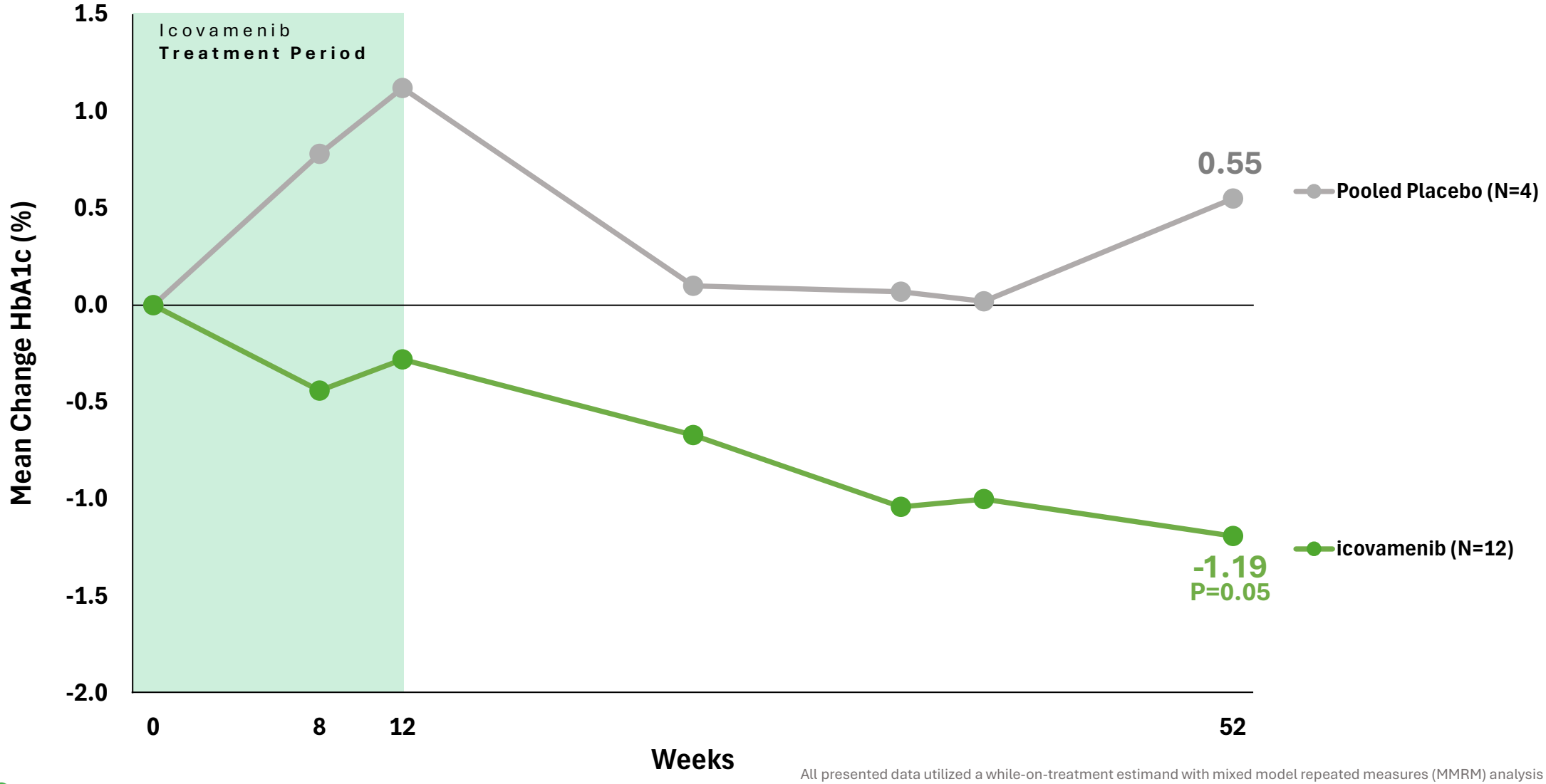


Icovamenib Differentiating Features

- ✓ Oral, once daily
- ✓ Non-chronic
- ✓ Well tolerated
- ✓ MOA complementary to other agents used

Patients on a GLP-1 Based Therapy at Baseline Demonstrated Durable and Clinically Meaningful Persistent Decline in HbA1c Through Week 52 (9 Months After Last Dose)



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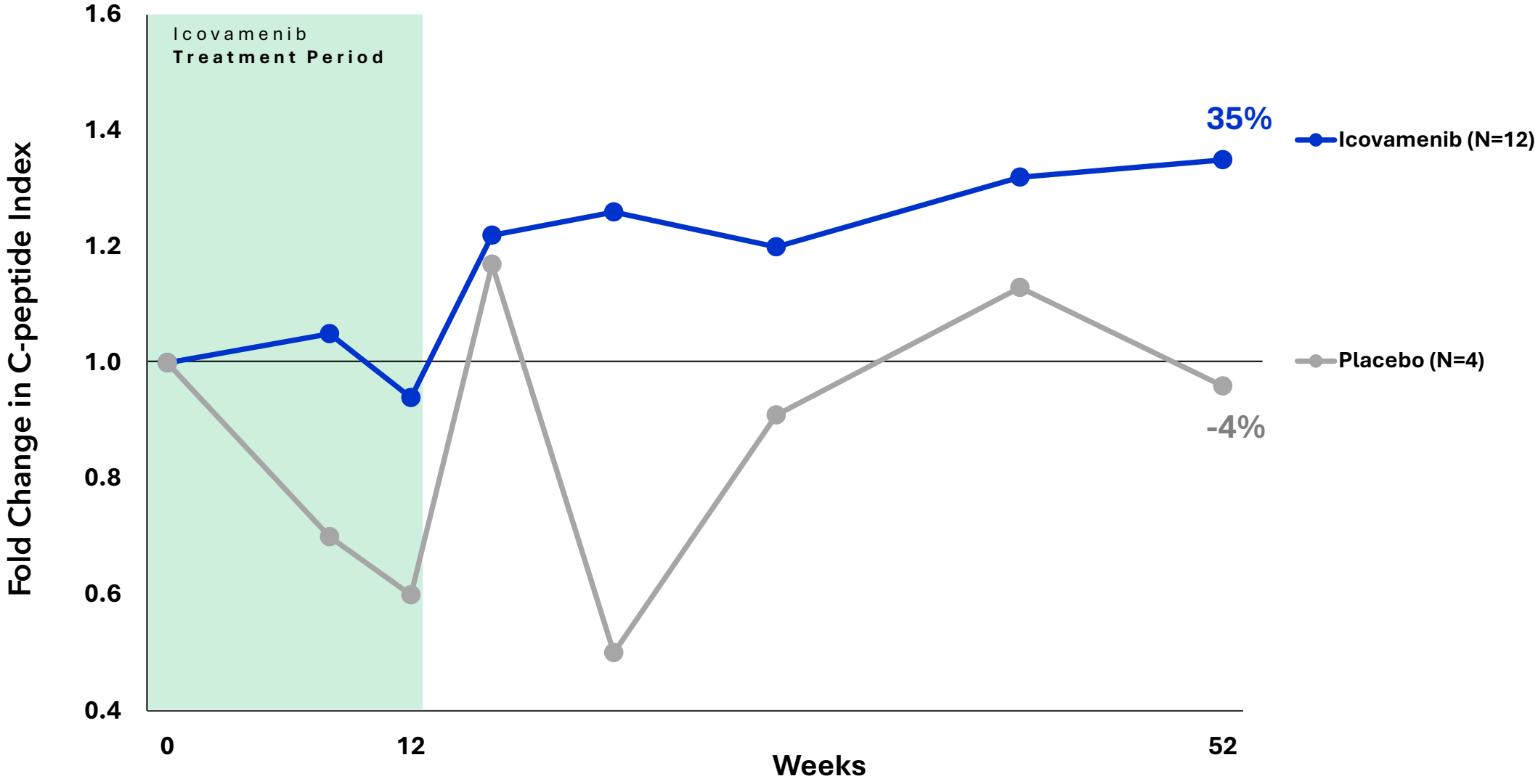
Icovamenib Increased Insulin Secretion as Measured by C-peptide Index

GLP-1 RA – Treated Patients



Data censored at onset of rescue medication, defined as any modification in antihyperglycemic therapy

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

(Safety Population, N=267)

Parameter	Placebo Combined arms (N=66)	Icovamenib Combined arms (N=201)	Arm A icovamenib (N=67)	Arm B icovamenib (N=67)	Arm C icovamenib (N=67)
Patients with ≥1 TEAE, N (%)	18 (27)	55 (27)	19 (28)	22 (33)	14 (21)
Treatment-Related SAEs, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs*, N (%)	1 (1)	2 (1)	1 (1)	0 (0)	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.

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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	Placebo Combined arms (N=66)	icovamenib Combined arms (N=201)	Arm A icovamenib (N=67)	Arm B icovamenib (N=67)	Arm C icovamenib (N=67)
Diarrhea, N (%)	0	7 (3)	4 (6)	2 (3)	1 (1)
Urinary tract infection, N (%)	3 (5)	1 (0)	0	1 (2)	0
Hyperglycemia, N (%)	3 (5)	8 (4)	2 (3)	5 (7)	1 (1)
Headache, N (%)	2 (3)	5 (2)	0	4 (6)	1 (1)
ALT increase, N (%)	0	5 (2)	3 (4)	0	2 (3)
AST increase, N (%)	0	4 (2)	3 (4)	0	1 (1)
Resolution of ALT/AST w/o interruption in study treatment, %	N/A	100	100	100	100

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)

	Placebo Combined arms (N=66)	Icovamenib Combined arms (N=201)	Arm A icovamenib (N=67)	Arm B icovamenib (N=67)	Arm C icovamenib (N=67)
Level 1, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Level 2, N (%)	0 (0)	1 (0)*	0 (0)	1 (1)*	0 (0)
Level 3, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Icovamenib in Type 2 Diabetes: 52-Week Highlights

- **Durable treatment effect in severe insulin-deficient T2D**

  Continued benefit observed in severe insulin-deficient diabetes patients

- **Higher icovamenib exposure (PK) led to improved responses**

  PK analysis shows that greater HbA1c reductions occurred in patients with higher drug exposure

- **Icovamenib increased endogenous insulin secretion**

  Improvement in C-peptide index suggests restoration of beta cell function

- **Treatment effect in GLP-1 “failures” continued to improve**

  Durable and clinically significant improvements in HbA1c in participants on GLP-1 therapy at baseline

- **Favorable safety profile through Week 52**

  Icovamenib was generally well-tolerated, with no adverse-event related discontinuations and no related serious adverse events

Clinical Implications

- Icovamenib represents a novel oral menin inhibitor designed to restore beta-cell function in insulin-deficient T2D
- Short-course oral therapy (3 months) may provide durable glycemic benefit, with HbA1c reductions continuing months after treatment cessation
- Potential to delay progression to lifelong insulin therapy in patients with advanced beta-cell dysfunction

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Thank you