

COVALENT-111: Durable Glycemic and C-Peptide Improvements Through Week 52 with Icovamenib, a Menin Inhibitor Targeting Beta-Cell Restoration in Insulin-Deficient Type 2 Diabetes

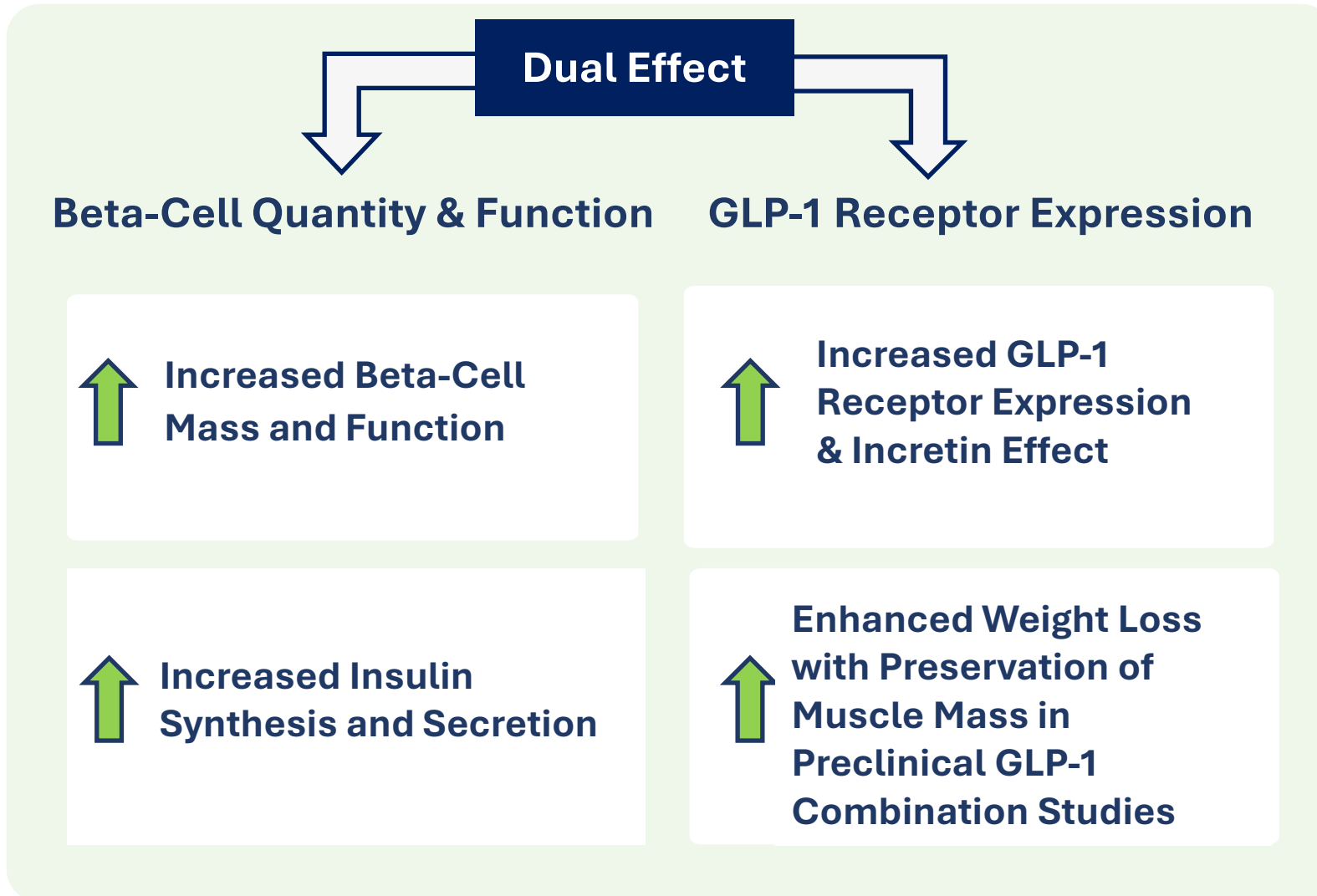
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Icovamenib: A Novel Approach Targeting Beta-Cell Function in Diabetes

Mechanism of Action: Selective & Partial Menin Inhibition



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

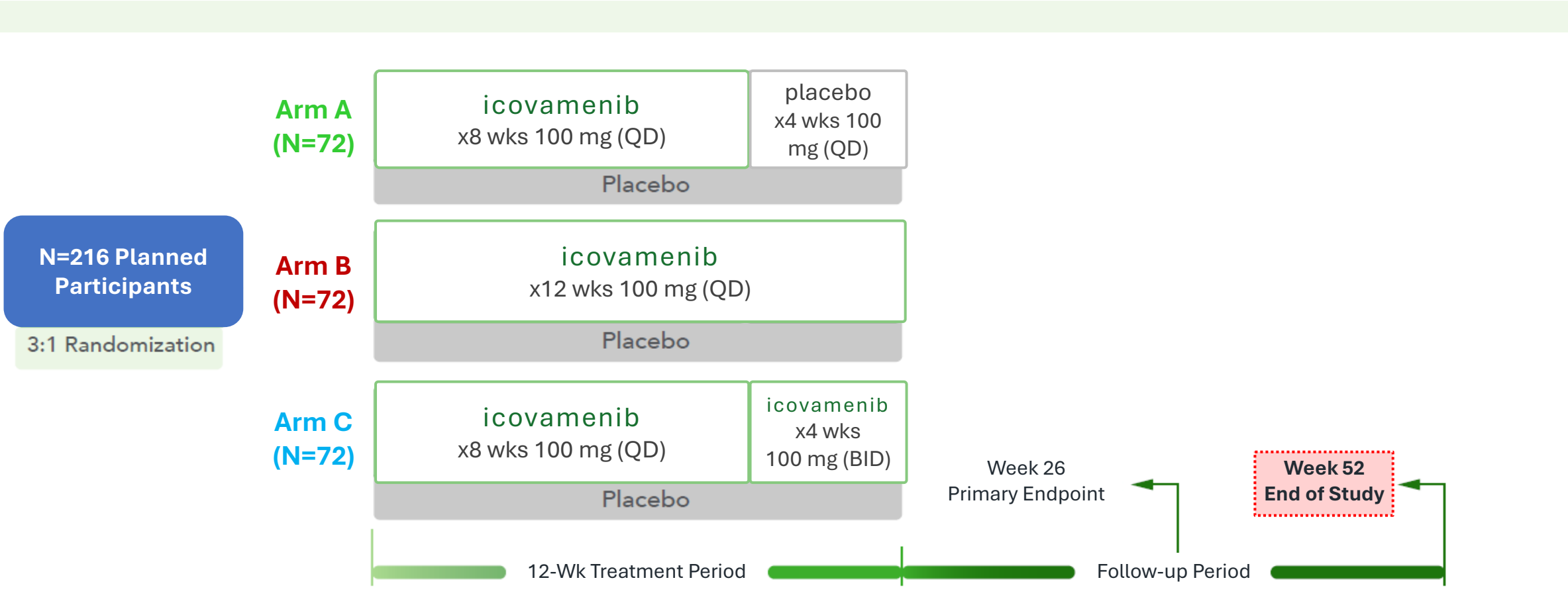
- Change in HbA1c from baseline at Week 52
- Measure of beta-cell function (plasma glucose, c-peptide, insulin, HOMA- β and HOMA-IR) at Week 26

Key Eligibility Criteria

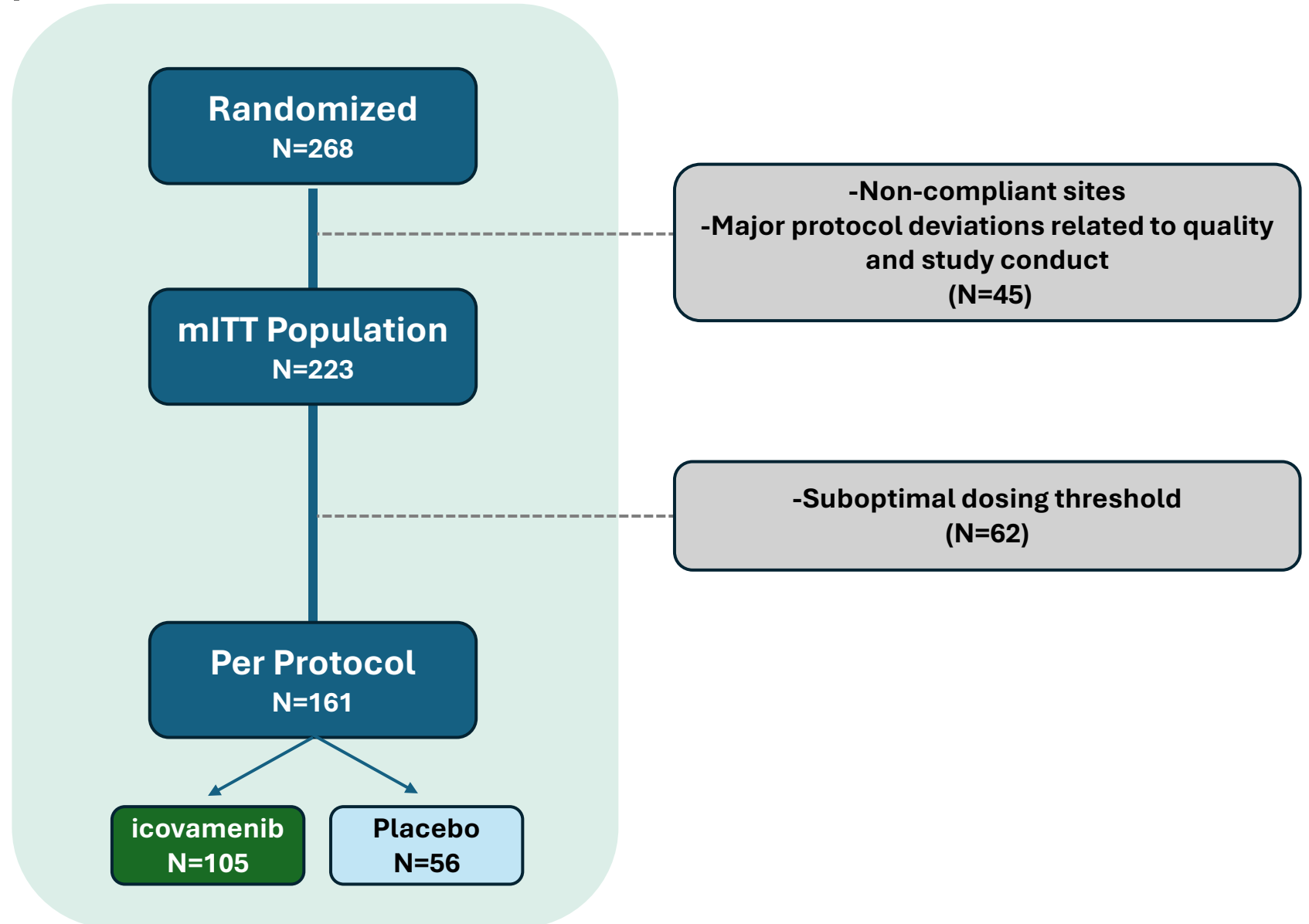
- Adults (18-65 years) with T2D (<7 years)
- HbA1c 7.0-10.5%
- BMI 25-40 kg/m²
- Treated with up to 3 antihyperglycemic agents (excluding insulin and SFUs)

COVALENT-111 Trial Design

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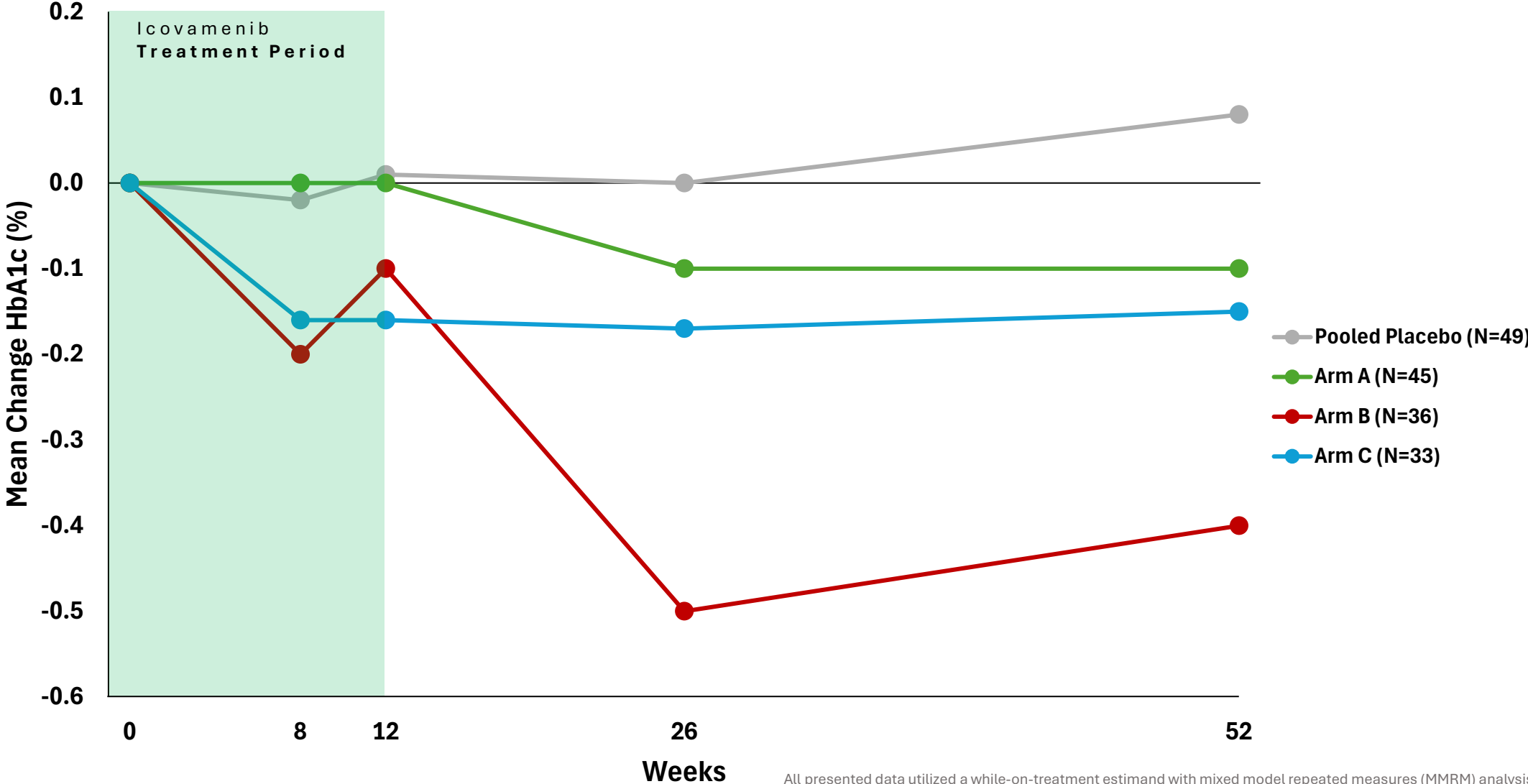


Study Disposition

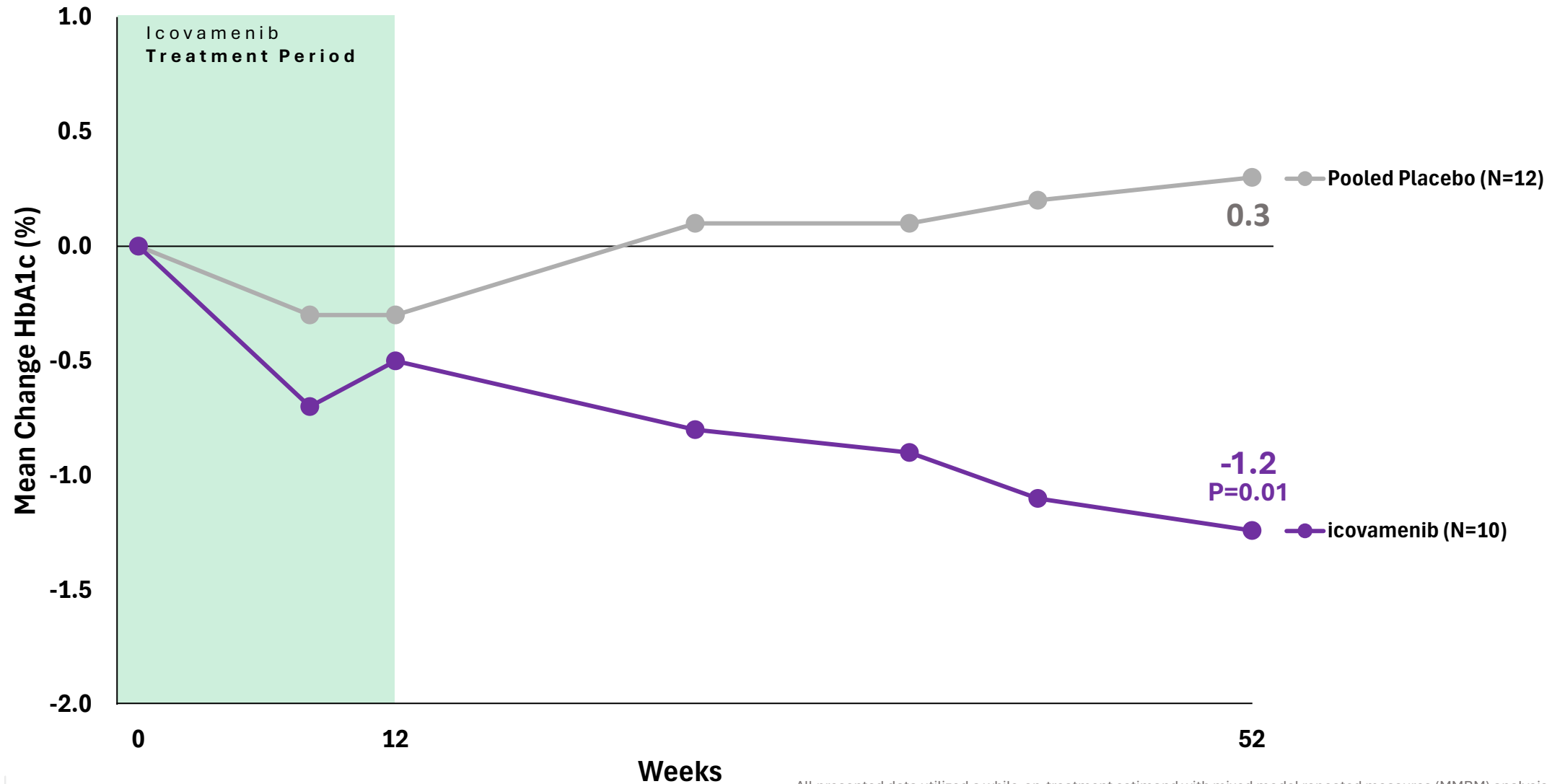


Change in HbA1c from Baseline through Week 52 – All Subtypes

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



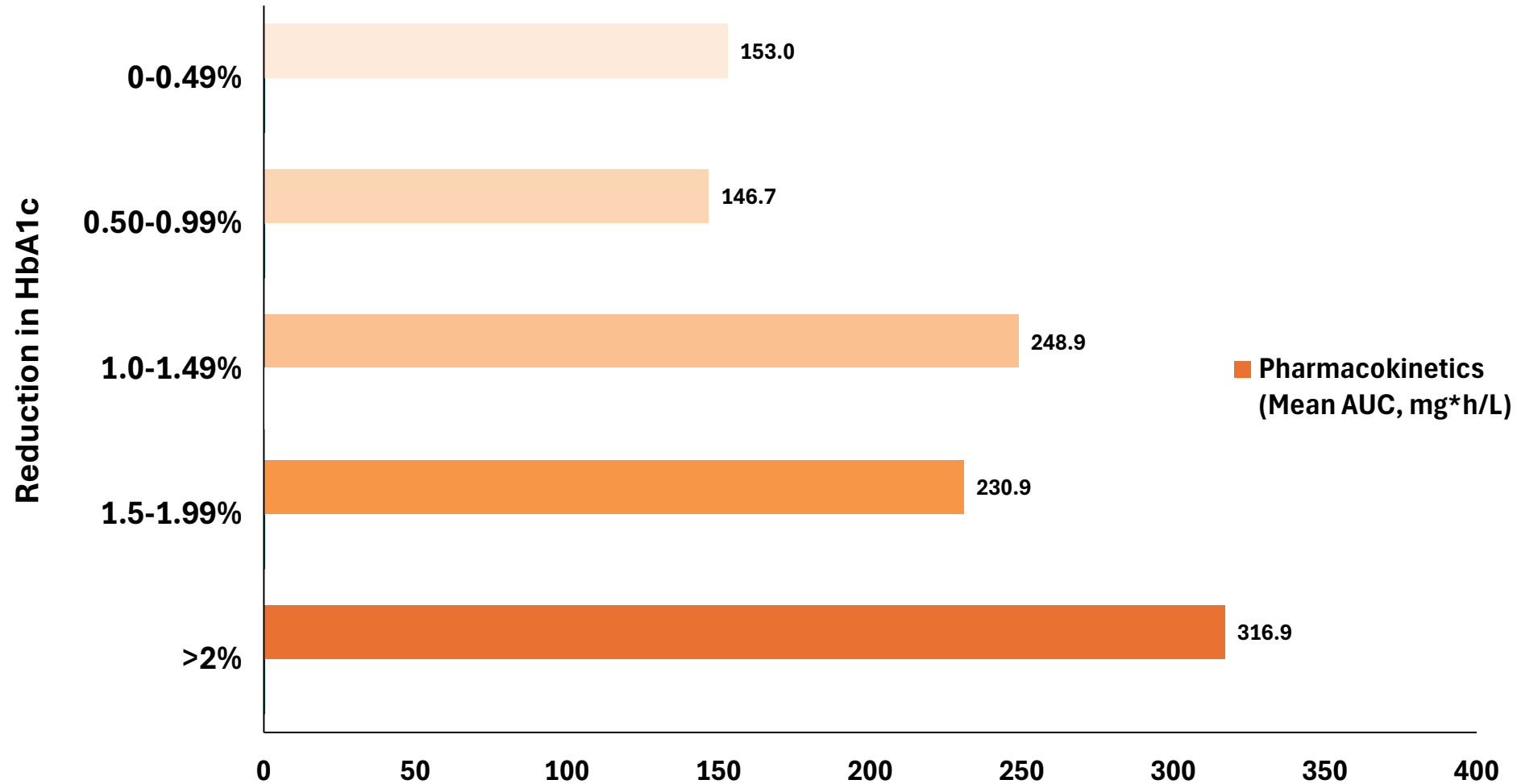
12-Week Treatment (Arms B & C) Resulted in Continued HbA1c Improvement Through Week 52 (9 Months After Last Dose) in Participants with Severe Insulin-Deficient T2D



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

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

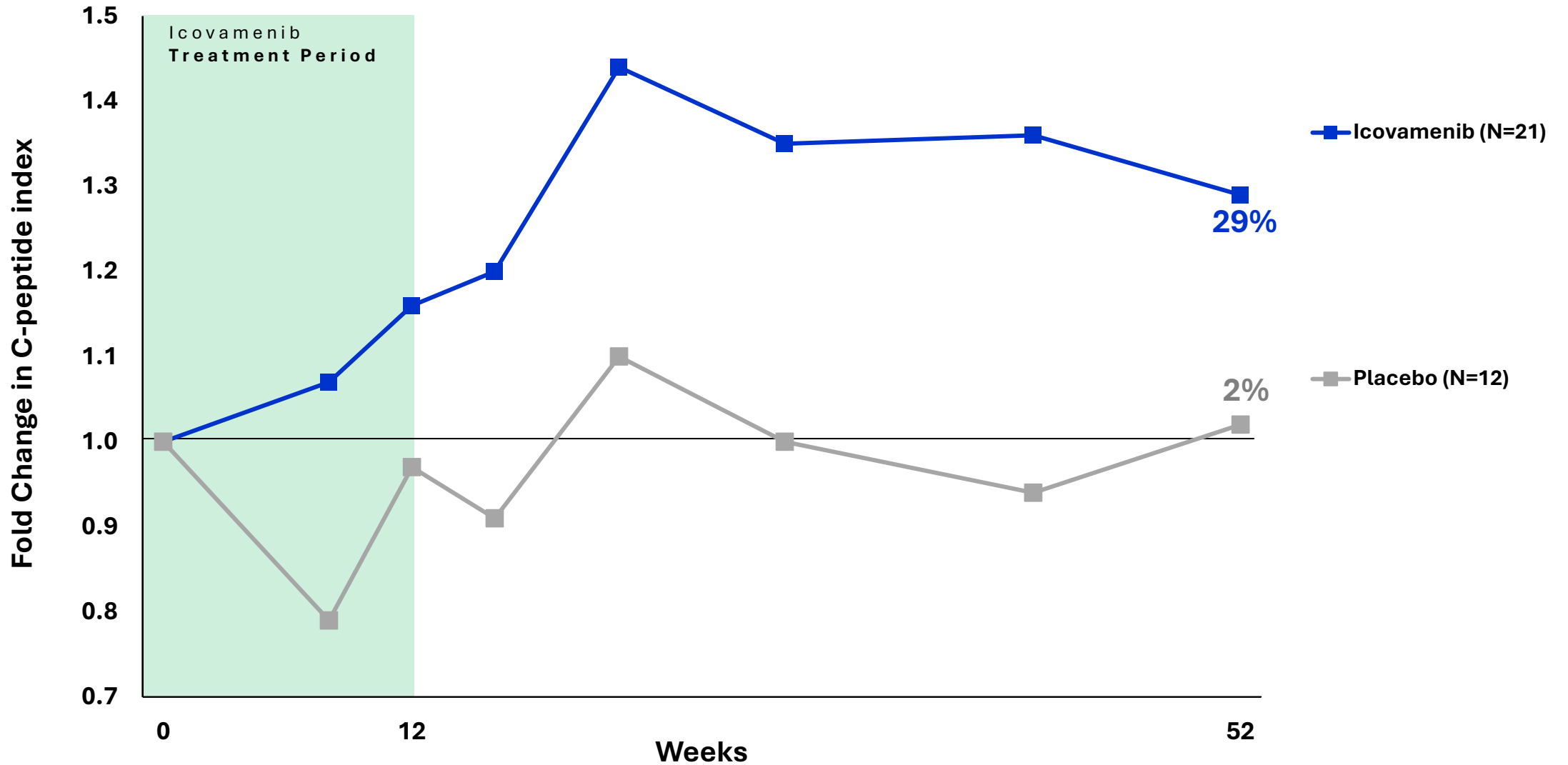
12 Weeks of Dosing (Arms B & C, N=69)



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

Icovamenib Increased Insulin Secretion as Measured by C-peptide Index

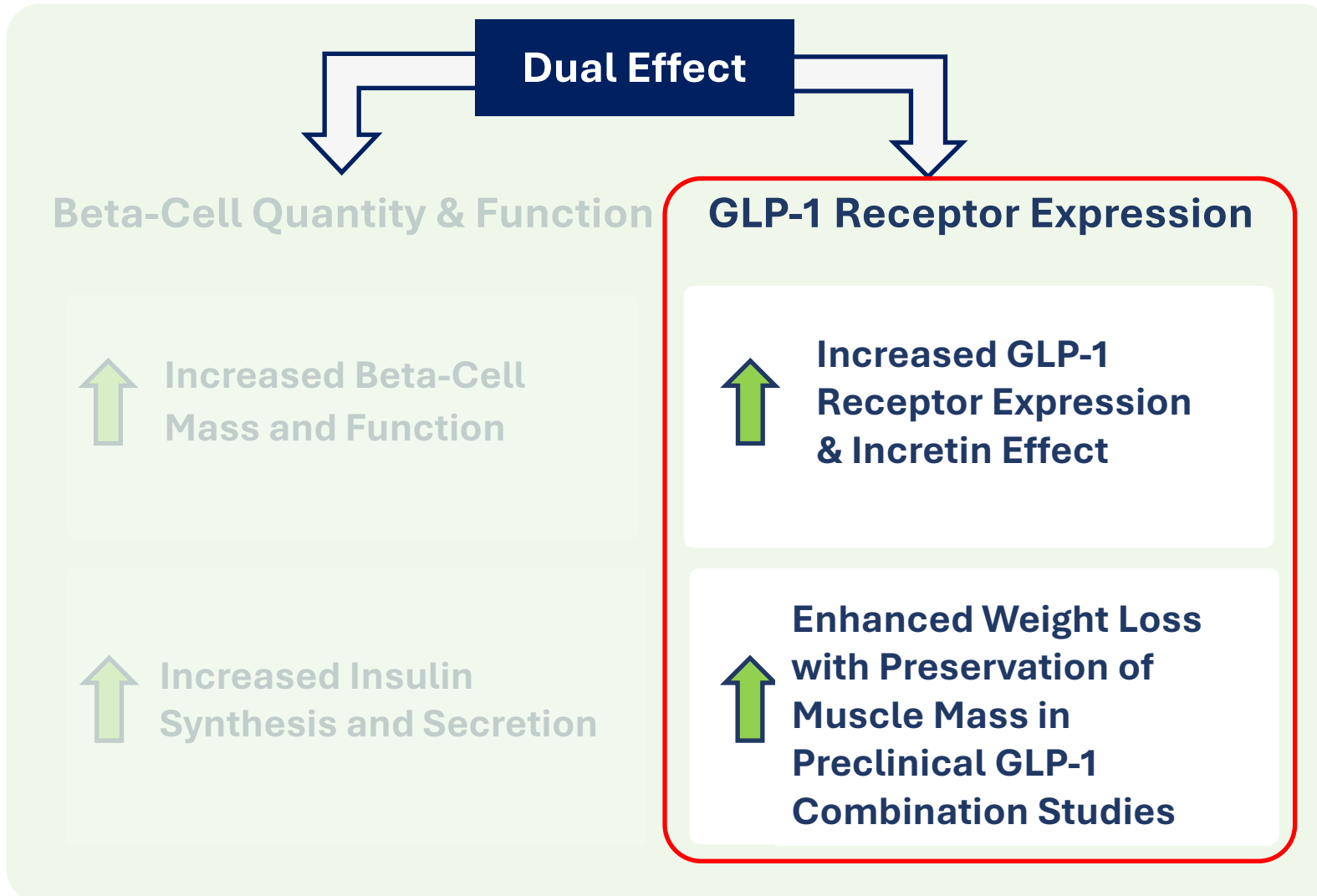
All severe insulin-deficient patients (All Arms)



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

Icovamenib: A Novel Approach Targeting Beta-Cell Function in Diabetes

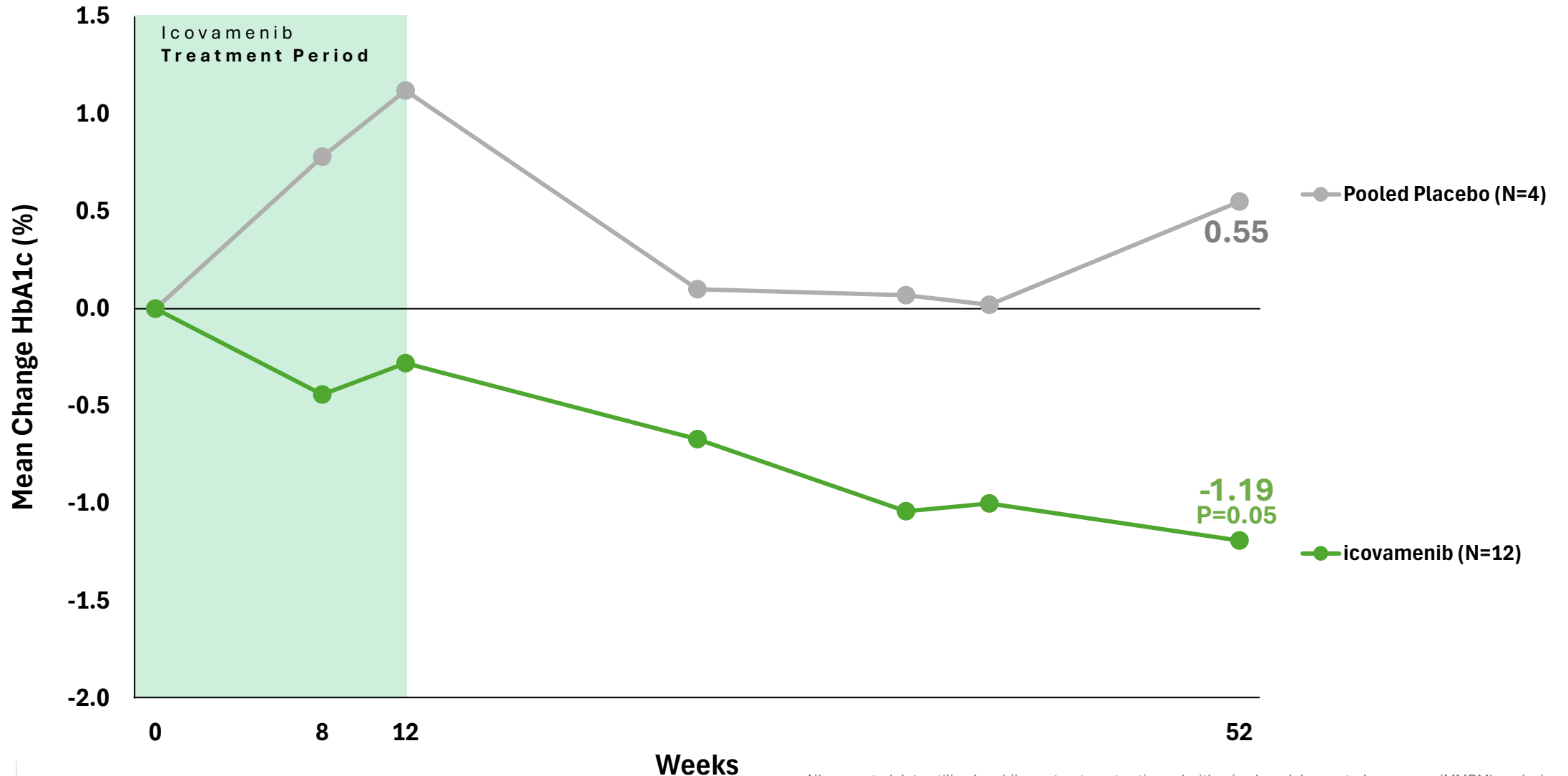
Mechanism of Action: Selective & Partial Menin Inhibition



Icovamenib Differentiating Features

- ✓ Oral, once daily
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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)



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.

Treatment Emergent Adverse Events (TEAEs) Occurring in $\geq 5\%$ 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 $\geq 5\%$ 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 insulin secretion (C-peptide Index) in severe insulin-deficient T2D**
- **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



Thank you



We Aim to Cure™

