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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Abstract #0062

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Background

Type 2 Diabetes (T2D) and β-Cell Dysfunction

- T2D is characterized by hyperglycemia driven by a progressive loss of β-cell mass and insulin secretory capacity
- At diagnosis, β-cell function is often reduced by >50%, with further decline over the disease course[1]
- Most standard therapies improve glycemia but do not address the underlying loss of insulin-producing β-cells
- As β-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

Menin: A Negative Regulator of β-Cell Regeneration

- Menin is a scaffold protein that regulates gene expression through multiple protein complexes
- In β-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 β-cell recovery

Icovamenib: A Selective Oral Menin Inhibitor

- Icovamenib is an oral, menin inhibitor in clinical development for T2D and T1D
- 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 β-cell proliferation under hyperglycemic conditions[4]

Clinical Rationale

- Early COVALENT-111 results showed short-term icovamenib dosing (4–12 weeks) lead to continued HbA1c improvements for months after treatment stops, along with increases in C-peptide, consistent with enhanced β-cell function[5]
- Because icovamenib targets the underlying β-cell deficit, it may be particularly relevant for insulin-deficient T2D, a population that otherwise faces progression toward insulin therapy
- Therapies that enhance endogenous insulin production may help patients maintain glucose control without transitioning prematurely to exogenous insulin, which carries treatment complexity

Safety | Treatment Emergent Adverse Events

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)
Diarrhea, N (%)	0	7 (4)	4 (6)	2 (3)	1 (1)
Nausea, N (%)	1 (2)	7 (4)	2 (3)	3 (4)	2 (3)
Hyperglycemia, N (%)	3 (5)	8 (4)	2 (3)	5 (7)	1 (1)
Headache, N (%)	2 (3)	5 (3)	0	4 (6)	1 (1)
ALT increase, N (%)	0	5 (3)	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 (%) 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.

Data are n (%) of TEAE with ≥5% frequency in any arm and ALT or AST increase irrespective of incidence; Safety population
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.

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

Study Design

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

Primary Endpoints

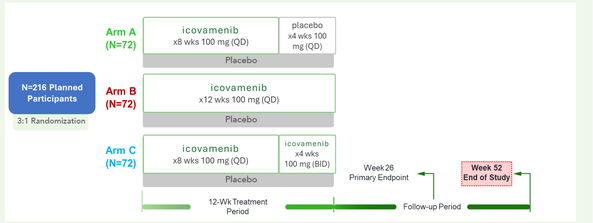
- Change in HbA1c from baseline at Week 26
- Safety and tolerability at Week 52

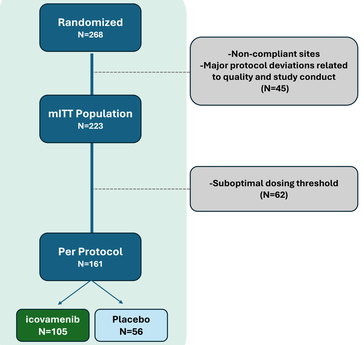
Secondary / Exploratory Endpoints

- 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

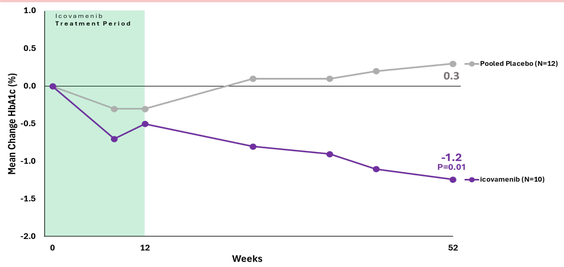
- Adults (18-65 years) with T2D (<7 years)
- HbA1c 7.0-10.5%
- BMI 25-40 kg/m^2
- Treated with up to 3 antihyperglycemic agents (excluding insulin and SFUs)



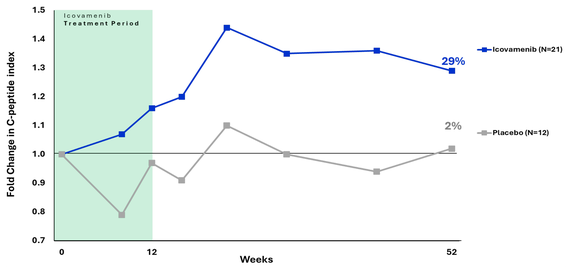


Short-term Dosing Resulted in Lasting Benefit Through 52 Weeks

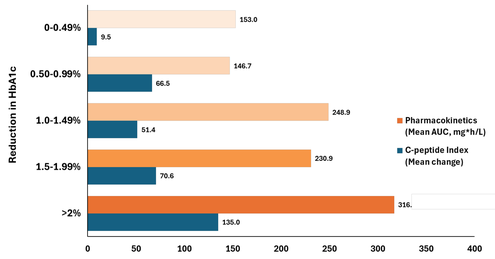
12-Week Treatment (Arms B+C) Resulted in Continued HbA1c Improvement Through Week 52 (9 Months After Last Dose) in Severe Insulin-Deficient T2D



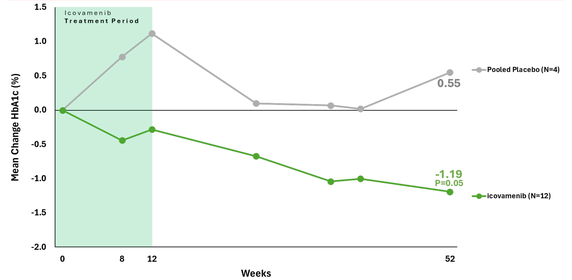
Icovamenib Increased Insulin Secretion (C-peptide Index) in Severe Insulin-Deficient T2D (All Arms)



Higher HbA1c Reduction and C-peptide Index at Week 52 was Associated with Higher Icovamenib Exposure in 12-Week Dosed Patients

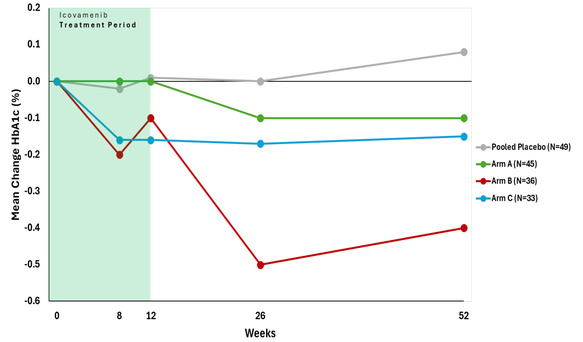


Patients on GLP-1 Based Therapy Not Achieving HbA1c Target at Baseline Demonstrated Durable and Clinically Meaningful Persistent Decline in HbA1c Through Week 52 (9 Months After Last Dose)



Change in HbA1c from Baseline through Week 52

Glycemic Response Was Not Uniform, Reflecting Biological Heterogeneity in T2D



Conclusions

- Icovamenib is an investigational menin inhibitor in development to address the root cause of diabetes: the progressive decline in beta-cell mass and function
- **Icovamenib demonstrated 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 improved 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

References

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