

# COVALENT-112: A Phase 2 Trial of the Oral Covalent Menin Inhibitor Icovamenib (BMF-219) In Type 1 Diabetes

FUSION™

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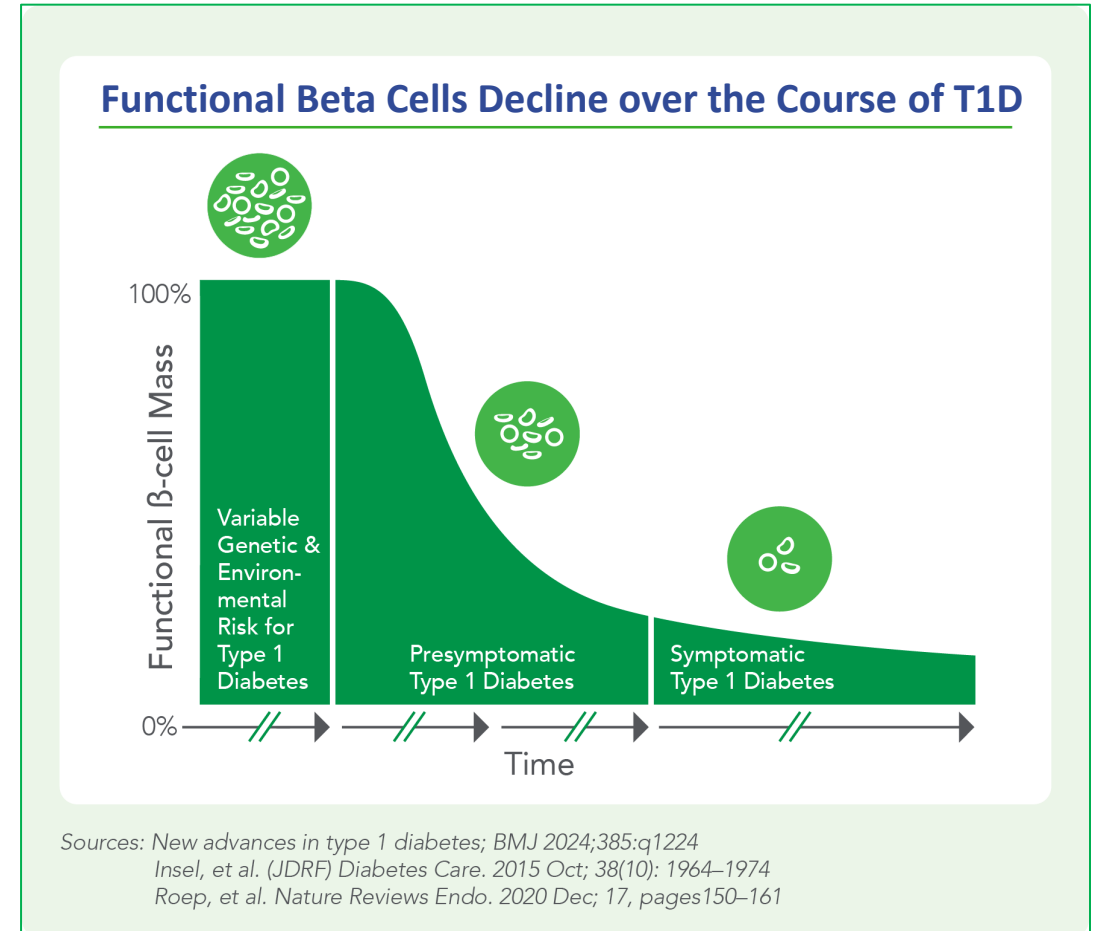
Redwood City, CA, USA



# Type 1 Diabetes – Addressing the root cause

## Type 1 Diabetes (T1D)

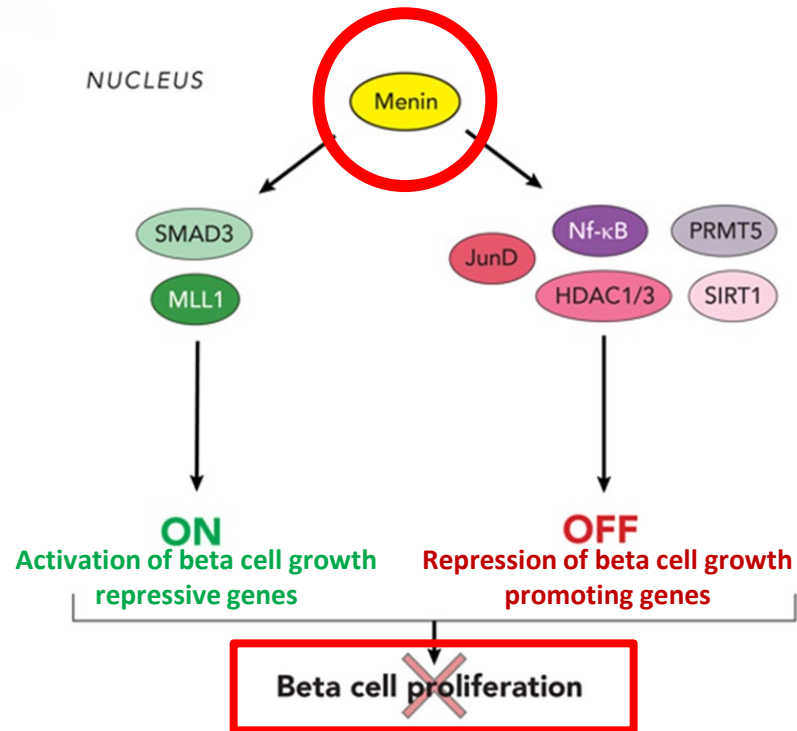
- T1D is a metabolic condition characterized by hyperglycemia due to autoimmune destruction of pancreatic beta-cells.
- Current treatment of patients with Stage 3 (clinical) T1D is almost exclusively limited to exogenous insulin administration, often resulting in:
  - significant glycemic variability
  - risk of hypoglycemia
  - weight gain
- There is an important unmet need to develop T1D treatments that address the root cause of the disease: **the loss of insulin-secreting beta-cells.**



# Menin's role in beta cell proliferation and glucose homeostasis

- **Menin is a scaffold protein** with multiple functions, including the **regulation of gene transcription and cellular signaling**
- Through interacting with its binding partners, menin acts as an important regulator of glycemic control, whereby **inhibition of menin activity enhances beta cell proliferation and function**

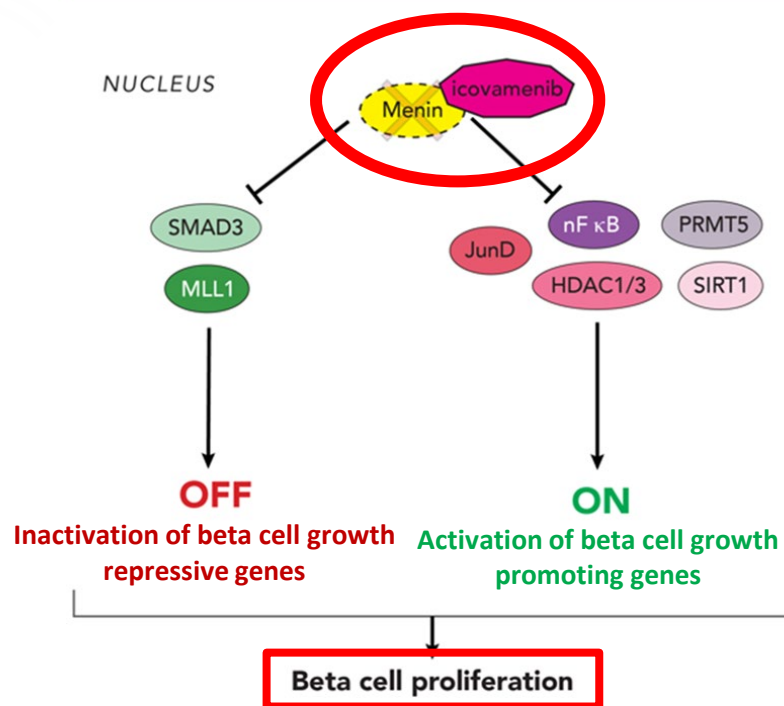
Menin's Role in Nuclear Protein Complexes  
Regulate Beta Cell Proliferation



# Icovamenib: A potent and selective covalent menin inhibitor

- **Icovamenib is an oral covalent menin inhibitor** in clinical development for the management of T2D and T1D
- In **preclinical models of diabetes**, icovamenib showed durable glycemic control following short-term treatment in ZDF and STZ rat models<sup>1,2</sup>
- In a **multiple ascending dose (MAD) cohorts in patients with T2D**, 4 weeks of daily icovamenib improved glycemic control at Week 26 (22 weeks after the final dose) and was generally safe and well tolerated<sup>3</sup>

## icovamenib-Mediated Inhibition of Menin Nuclear Complexes Permits Beta Cell Proliferation



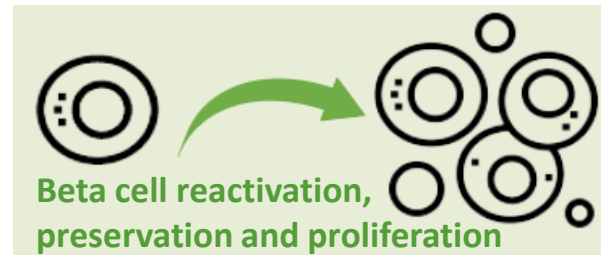
1. Butler T. et al. Diabetes. 2022; 71 (Supplement\_1): 851–P

2. Somanath P. et al. Diabetes. 2022; 71 (Supplement\_1): 113–LB

3. Abitbol A, et al. (ATTD 2024, March 6, 2024)

# Icovamenib: Menin Inhibition to Stimulate Beta Cell Proliferation

Icovamenib: Menin Inhibition  
a Potential New Class of  
Diabetes Agents



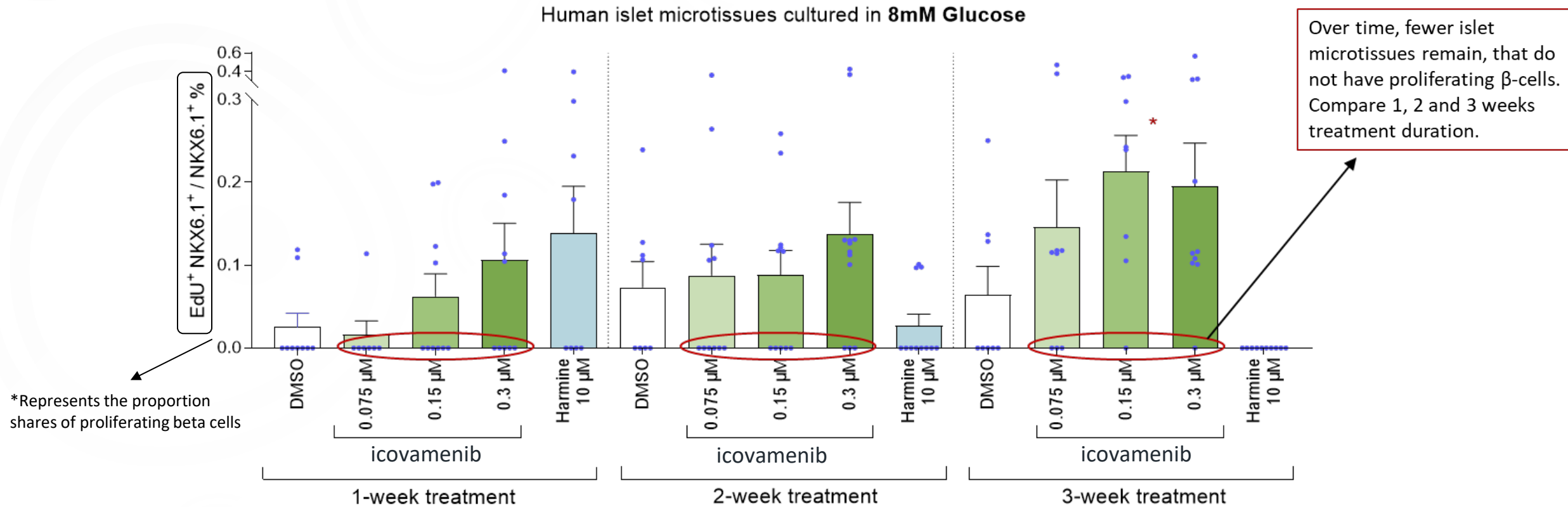
Beta Cell Mass ↑ Beta Cell Health ↑

Control of glycemia even after cessation of dosing

Icovamenib represents a potential new class of diabetes agents addressing the **root cause of diabetes - loss of beta cell mass and function**

# Longer dosing is predicted to generate an increase in responder rates based on human donor islet experiments

## Proliferating beta cells plotted as fraction of total beta cells

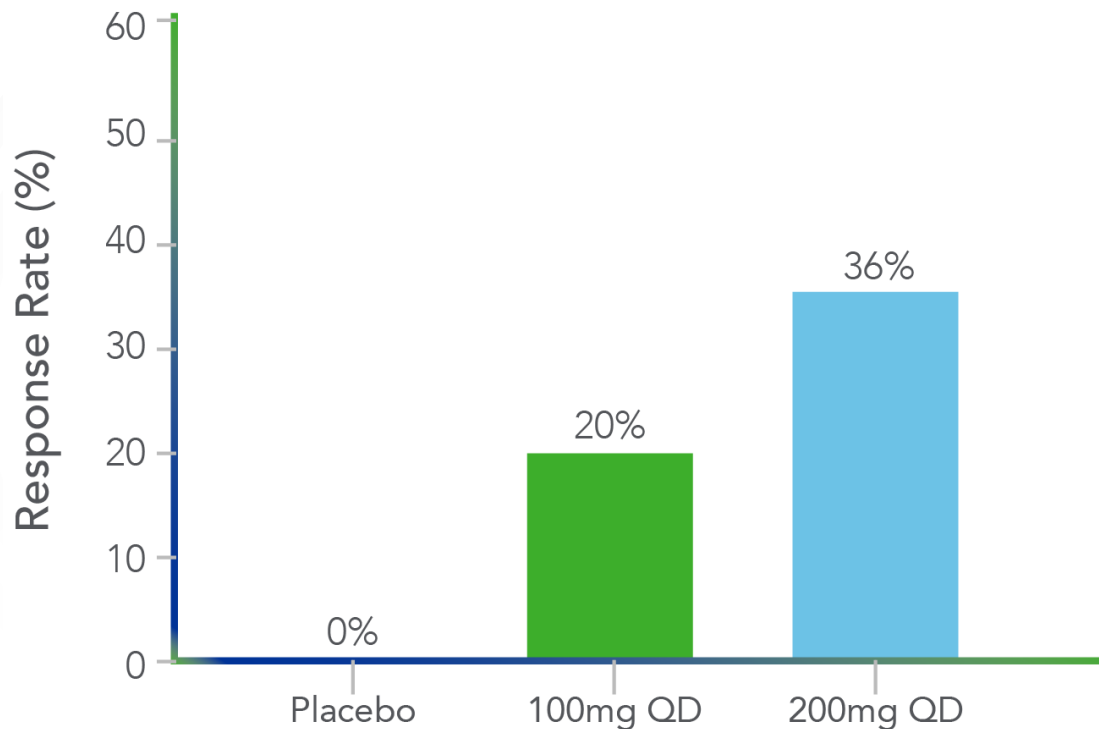


Data represent mean  $\pm$ SEM of 1 donor with n = 9-12 technical replicates.  
One-way ANOVA with Dunnett's post hoc test rel. to DMSO control. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001

## Proportion of patients with $\geq 1.0\%$ HbA<sub>1c</sub> reduction at Week 26

Icovamenib demonstrated dose-dependent response

Response Rate, 100mg and 200mg



**At Week 26** (22 weeks after 4 weeks icovamenib),  $\geq 1.0\%$  HbA<sub>1c</sub> reduction in:

- **20%** of patients across **100 mg** cohorts
- **36%** of patients across **200 mg** cohorts
- Across **100 and 200 mg** cohorts (**N=31**)
  - **39%** (12/31) had  $\geq 0.5\%$  HbA<sub>1c</sub> reduction at Week 26 (mean HbA<sub>1c</sub> reduction 1.3%)
  - **26%** (8/31) had  $\geq 1.0\%$  HbA<sub>1c</sub> reduction at Week 26 (mean HbA<sub>1c</sub> reduction 1.5%)



# Key Eligibility Criteria + Study Design

- COVALENT-112 is being conducted in the US and Canada.
- First patient enrolled: December 28, 2023

## Inclusions

1. Adults with stage 3 T1D with HbA1c  $\geq 6.5\%$  and  $\leq 10.0\%$
2. Diagnosed within the following timeframes + fasting c-peptide levels at screening:

### Part 1

Cohort 1: T1D duration  $\leq 3$  years (c-peptide  $\geq 0.2$  nmol/L)

Cohort 2: T1D diagnosed between  $\geq 3$  and  $\leq 15$  years (c-peptide  $\geq 0.08$  nmol/L)

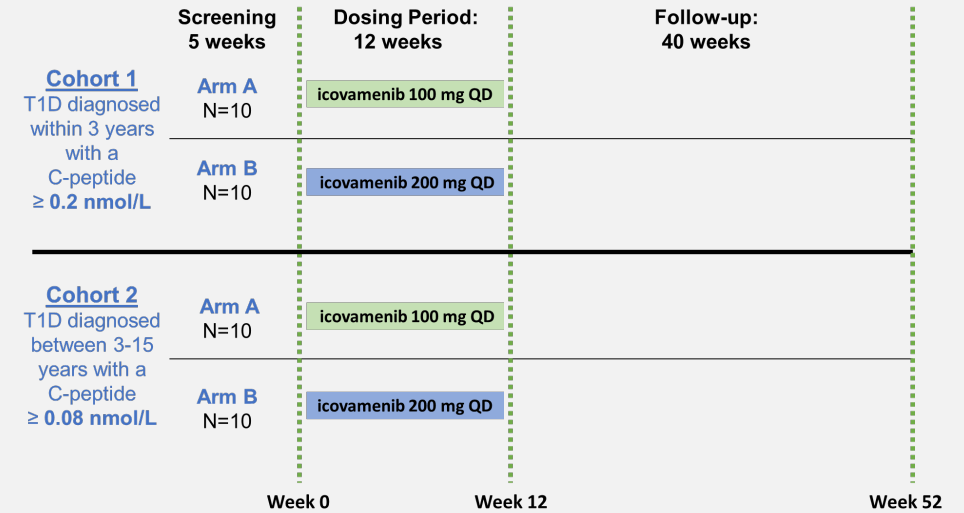
### Part 2

Participants diagnosed within 15 years prior to screening

## Exclusions

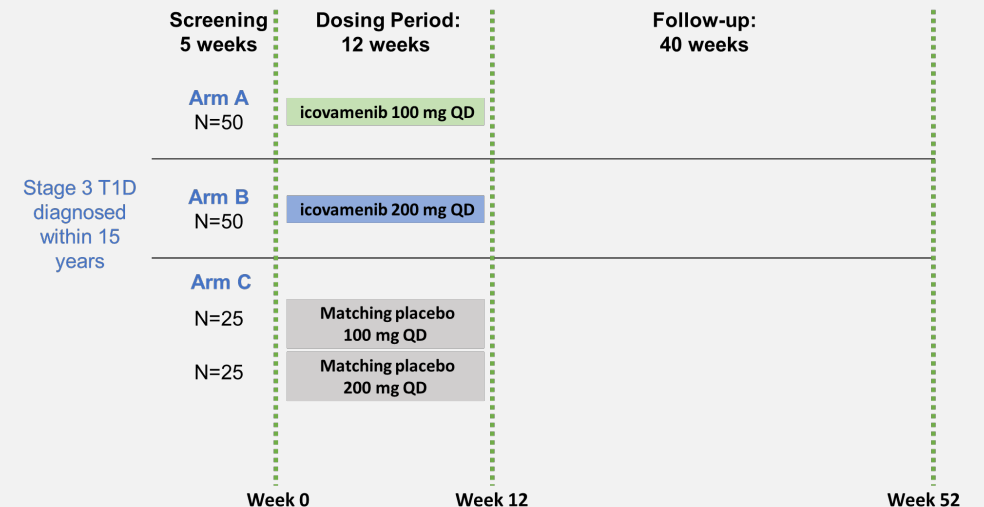
1. Diagnosis of MODY, T2D or any other subtype of diabetes mellitus other than T1D
2. Known self or family history (first-degree relative) of multiple endocrine neoplasia type 1

**Part 1:** Randomized, open-label design with parallel assignment between two treatment arms in each cohort



**Part 2:** Randomized, double-blinded, placebo-controlled design with parallel assignment among 3 treatment arms

Design of Part 2 will be finalized contingent of Part 1 data



# COVALENT 112 | Objectives and Endpoints

Primary Objective	Primary Endpoint
To assess the effect on endogenous insulin secretion	Mean change from baseline in stimulated C-peptide AUC at Week 26
Secondary Objectives	Secondary Endpoints
To assess safety and tolerability	TEAEs and SAEs, safety laboratory tests, results of physical examinations, including vital signs, and 12-lead ECGs
To assess the effect on endogenous insulin secretion	Maximum stimulated C-peptide: the highest value at any time point during the 4-hour MMTT at Week 26
To assess effect on insulin doses	Change from baseline in mean daily insulin dose at Week 26
To assess the effect on additional glycemic parameters	Change from baseline in HbA1c, FPG, and CGM parameters at Week 26
To assess hypoglycemia events	Percentage of participants with hypoglycemic episodes including Level 2 hypoglycemic events (<54 mg/dL regardless of symptoms) and Level 3 (severe) hypoglycemia through Week 26

# Conclusion

## Role of menin in glucose homeostasis

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Menin is a scaffold protein that regulates glucose homeostasis

Inhibiting menin promotes beta-cell proliferation thereby enhancing insulin secretion

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## Icovamenib: an oral covalent small molecule menin inhibitor

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Currently in clinical development for T2D and T1D to address the root cause of diabetes: the progressive decline in beta-cell mass and function.

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## COVALENT-112 (T1D)

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Efficacy and safety of 12-week once daily administration of icovamenib in T1D is being evaluated, to address an important unmet need in this patient population.

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Topline data of the open-label portion of COVALENT-112 will be disclosed in Dec 2024

# THANK YOU



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