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

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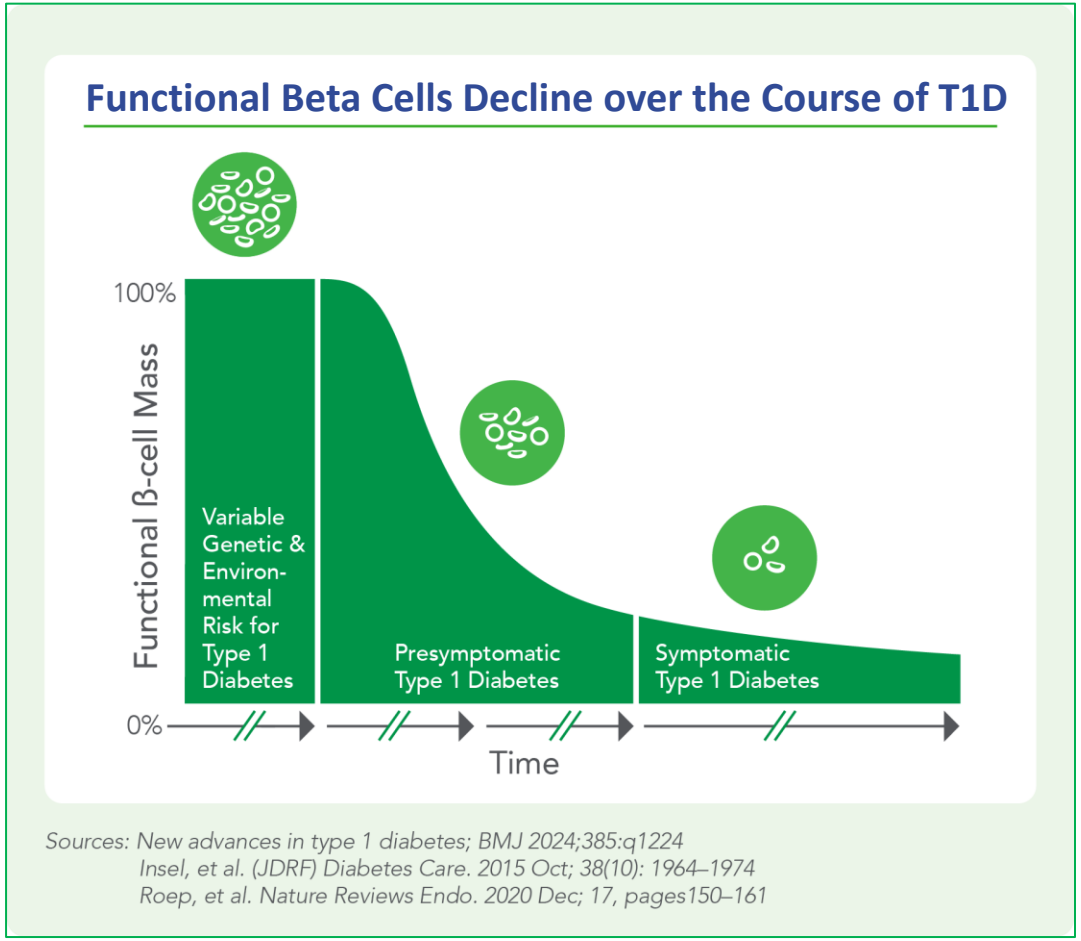
	No, Nothing to disclose
X	Yes, please specify disclosures

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
Biomea Fusion					X		X	

Type 1 Diabetes – Addressing the root cause

Type 1 Diabetes (T1D)

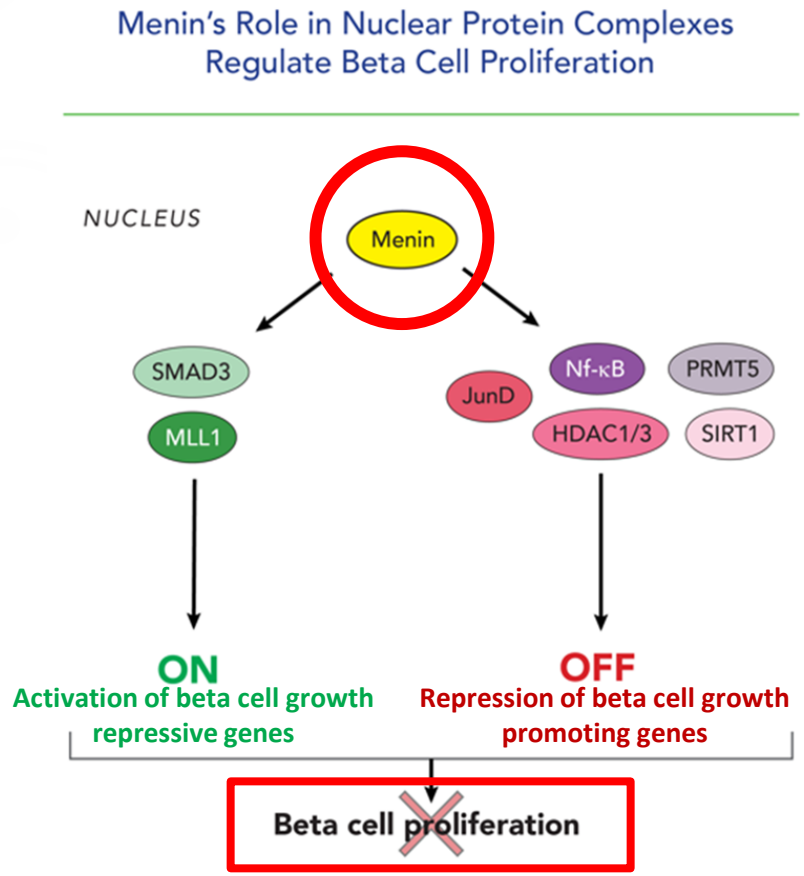
- T1D is a metabolic condition characterized by hyperglycemia due to autoimmune destruction of pancreatic beta-cells.
- Current treatment of patients with Stage 3 (clinical) T1D is almost exclusively limited to exogenous insulin administration, often resulting in:
  - significant glycemic variability
  - 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**.



Sources: New advances in type 1 diabetes; BMJ 2024;385:q1224
Insel, et al. (JDRF) Diabetes Care. 2015 Oct; 38(10): 1964–1974
Roep, et al. Nature Reviews Endo. 2020 Dec; 17, pages150–161

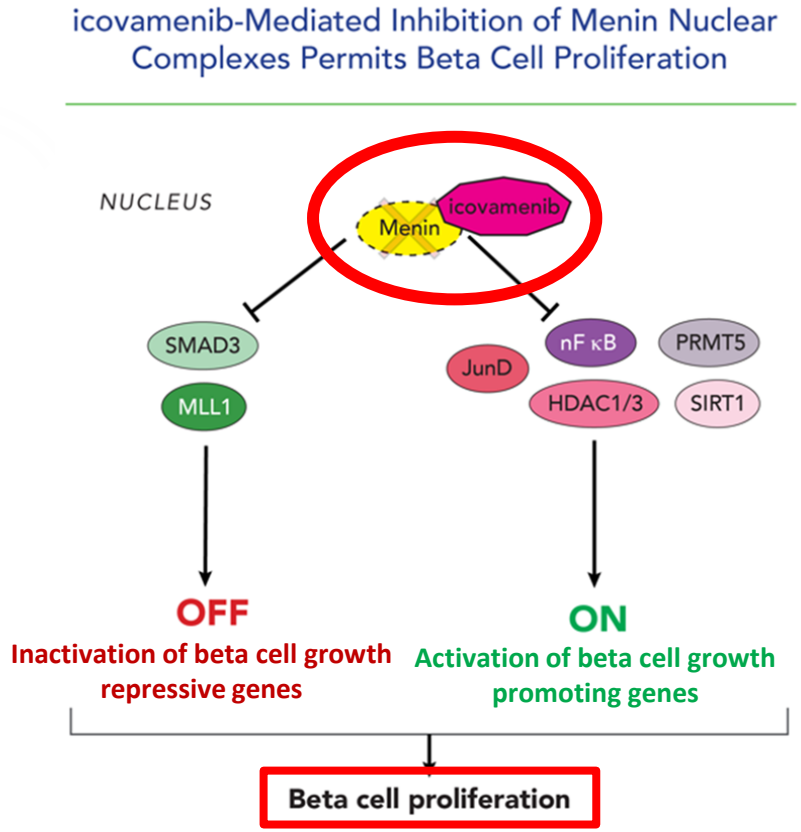
Menin's role in beta cell proliferation and glucose homeostasis

- **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**



Icovamenib: A potent and selective covalent menin inhibitor

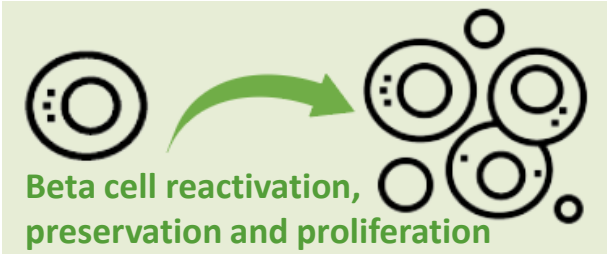
- **Icovamenib is an oral covalent menin inhibitor** in clinical development for the management of T2D and T1D
- In **preclinical models of diabetes**, icovamenib showed durable glycemic control following short-term treatment in ZDF and STZ rat models[1,2]
- In a **multiple ascending dose (MAD) cohorts 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[3]



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



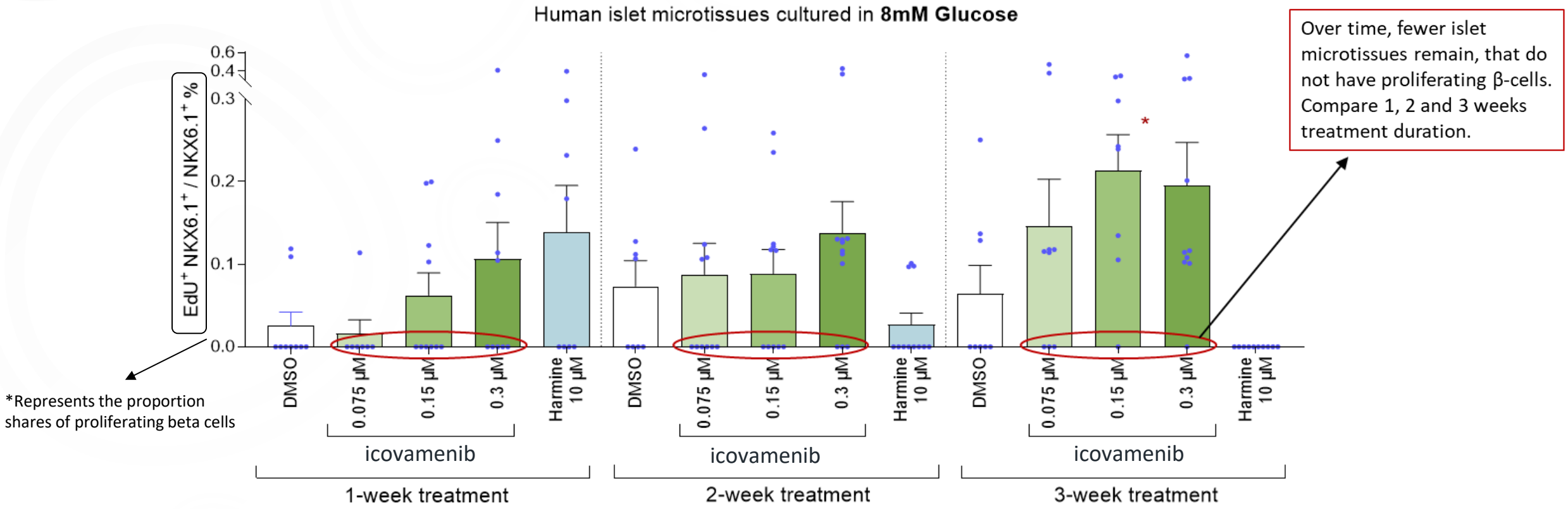
Beta Cell Mass ↑ Beta Cell Health ↑

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

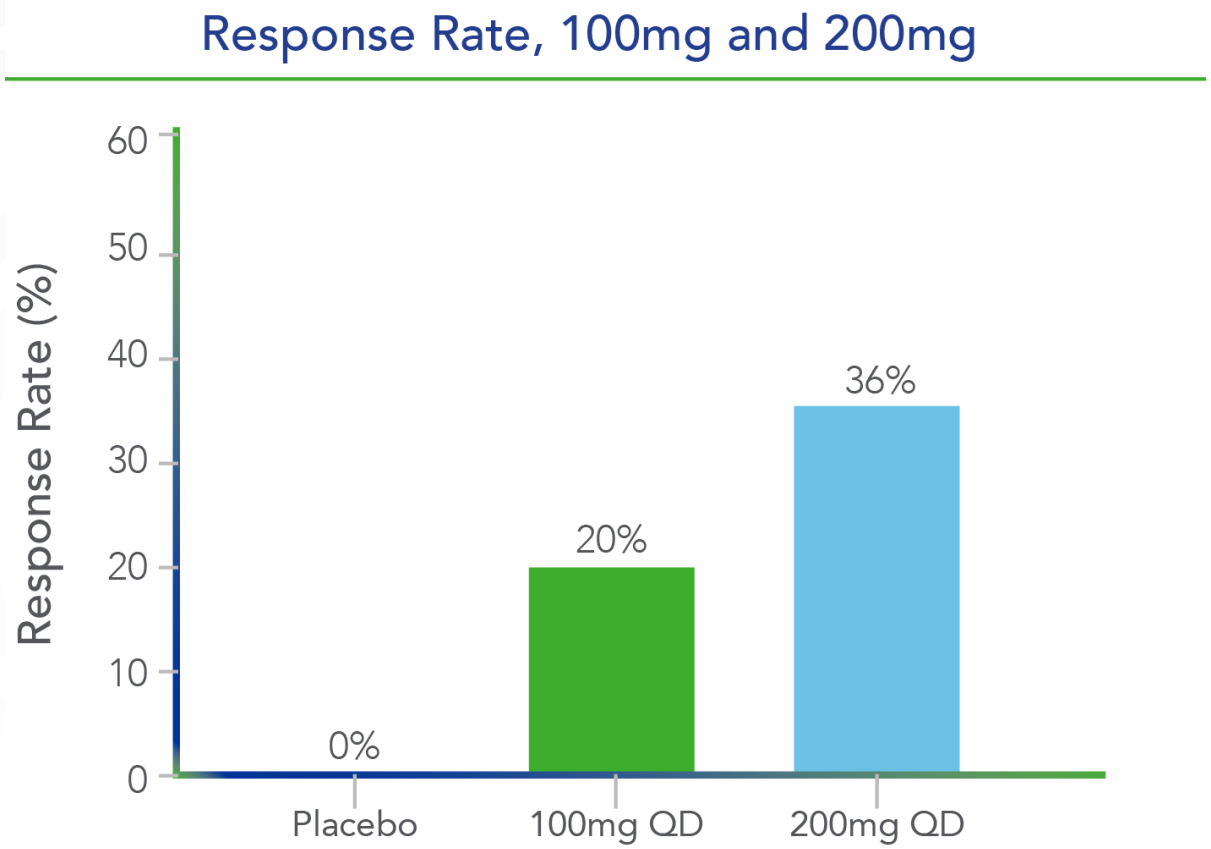
Proliferating beta cells plotted as fraction of total beta cells



Data represent mean ±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 ≥1.0% HbA_{1c} reduction at Week 26

Icovamenib demonstrated dose-dependent response



At Week 26 (22 weeks after 4 weeks icovamenib), **≥1.0% HbA_{1c}** 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 **≥0.5%** HbA_{1c} reduction at Week 26 (mean HbA_{1c} reduction 1.3%)
  - **26%** (8/31) had **≥1.0%** HbA_{1c} reduction at Week 26 (mean HbA_{1c} reduction 1.5%)

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

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 ≥6.5% and ≤10.0%
2. Diagnosed within the following timeframes + fasting c-peptide levels at screening:

   Part 1

   Cohort 1: T1D duration ≤ 3 years (c-peptide ≥0.2 nmol/L

   Cohort 2: T1D diagnosed between ≥ 3 and ≤ 15 years (c-peptide ≥0.08 nmol/L)

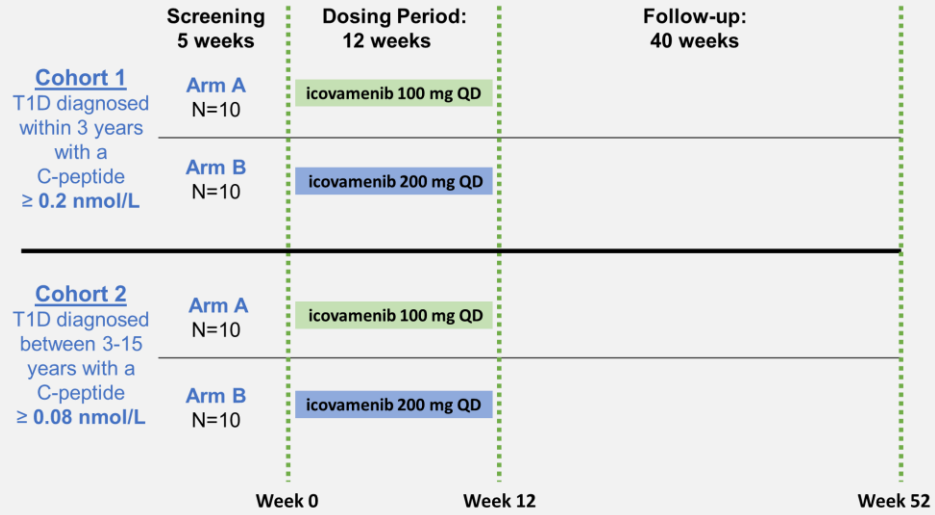
   Part 2

   Participants diagnosed within 15 years prior to screening

Exclusions

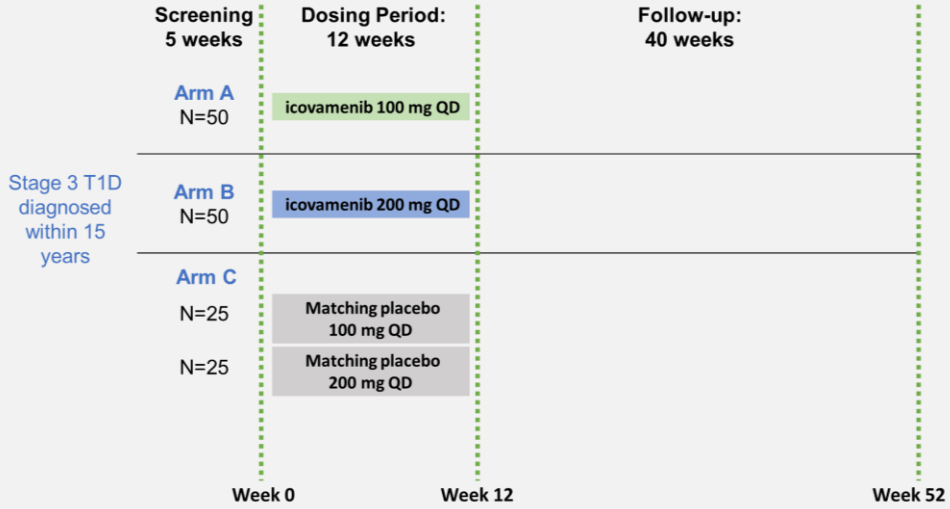
1. Diagnosis of MODY, T2D or any other subtype of diabetes mellitus other than T1D
2. Known self or family history (first-degree relative) of multiple endocrine neoplasia type 1

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



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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	Menin is a scaffold protein that regulates glucose homeostasis
	Inhibiting menin promotes beta-cell proliferation thereby enhancing insulin secretion
Icovamenib: an oral covalent small molecule menin inhibitor	Currently in clinical development for T2D and T1D to address the root cause of diabetes: the progressive decline in beta-cell mass and function.
COVALENT-112 (T1D)	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.
	Topline data of the open-label portion of COVALENT-112 will be disclosed in Dec 2024

THANK YOU

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