# Icovamenib, a Menin Inhibitor, Improves Endogenous Insulin Secretion in T1D: Results from the COVALENT-112 Study

Juan Pablo Frías, MD; Jeffrey Kim, PhD
Biomea Fusion, 1599 Industrial Road, San Carlos, CA 94070 USA

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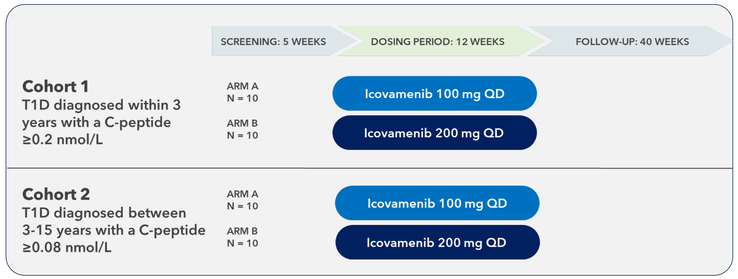
## Background

- **Type 1 diabetes (T1D)** is characterized by progressive autoimmune loss of functional pancreatic beta-cell mass, leading to declining endogenous insulin secretion and chronic hyperglycemia
  - Current Stage 3 T1D management remains centered on insulin replacement and diabetes technologies, which improve glycemic control but do not address beta-cell loss
  - Disease-modifying approaches in Stage 3 T1D have primarily focused on preserving residual beta-cell function; while some have slowed C-peptide decline, they have not consistently demonstrated durable restoration or improvement of endogenous insulin secretion
  - Therapies capable of restoring or sustainably improving beta-cell function remain a major unmet need
- **Menin** is a scaffold protein that regulates gene expression and cell signaling in a tissue-specific manner. In pancreatic beta-cells, menin negatively regulates beta-cell proliferation and mass, supporting menin inhibition as a potential approach to enhance residual beta-cell function
- **Icovamenib**, formerly BMF-219, is an orally administered investigational small molecule currently in Phase 2 clinical development for the treatment of T2D and T1D. Icovamenib targets menin and has been shown preclinically in both animal and ex vivo human islet studies to induce transient reductions in menin protein levels, thereby modulating pathways associated with insulin secretion and glycemic control
- **COVALENT-112** evaluated icovamenib in adults with T1D to assess effects on endogenous insulin secretion

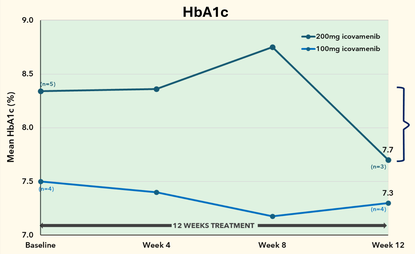
## COVALENT-112: Study Overview

- COVALENT-112 (NCT06152042) is a phase 2 trial that was designed to examine beta-cell function (as measured by C-peptide change) and glucose and lipid metabolism in participants with T1D treated with icovamenib
- COVALENT-112 was conducted in the US and Canada
- Enrollment, dosing exposure, and the final evaluable population in COVALENT-112 were affected by a temporary FDA clinical hold related to liver enzyme elevations, which was subsequently resolved

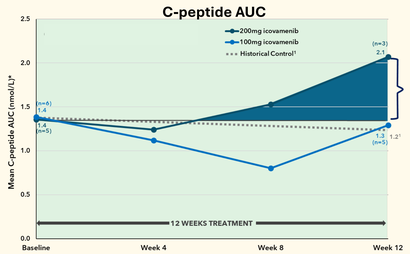



## Results | HbA1c & C-peptide

### Cohort 1 (<3 years since diagnosis)

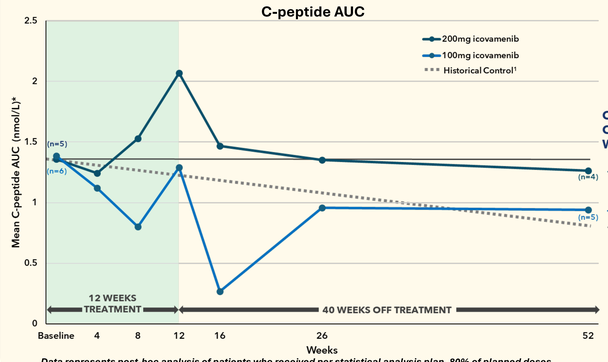



0.6% reduction in mean HbA1c from baseline




52% mean increase from baseline

+0.7 P<0.001




Change in mean C-peptide AUC at Week 52 vs baseline

-7%

-32%

-47%†

*Data represents post-hoc analysis of patients who received per statistical analysis plan, 80% of planned doses*

† *Historical control in T1D patients (n=1549) C-peptide declining over first 7 years at 47% yearly. Diabetes Care. 2018 Jun 7;41(7):1486–1492*

* *4-hour Mixed Meal Tolerance Test (MMTT)*

#### Demographic + Baseline Data

**200 mg Group (means) | n=5**
Age: 31 years
Sex: 40% female
BMI: 24 kg/m²
Disease course: 2.1 years
HbA1c: 8.3%
Fasting Plasma Glucose: 155 mg/dL
Fasting C-Peptide: 0.8 ng/mL

**100 mg Group (means) | n=6**
Age: 28 years
Sex: 67% female
BMI: 25 kg/m²
Disease course: 2.4 years
HbA1c: 7.5%
Fasting Plasma Glucose: 178 mg/dL
Fasting C-Peptide: 0.7 ng/mL

### Cohort 2 (3-15 years since diagnosis)

#### Demographic + Baseline Data

**200 mg Group (means) | n=4**
Age: 38 years
Sex: 25% female
BMI: 26 kg/m²
Disease course: 7 years
HbA1c: 7.3%
Fasting Plasma Glucose: 120 mg/dL
Fasting C-Peptide: 0.3 ng/mL

**100 mg Group (means) | n=5**
Age: 37 years
Sex: 60% female
BMI: 25 kg/m²
Disease course: 10 years
HbA1c: 6.8%
Fasting Plasma Glucose: 117 mg/dL
Fasting C-Peptide: 0.4 ng/mL

#### Key Findings

- Cohort 2 included participants with 3–15 years since T1D diagnosis, a population with potentially lower residual beta-cell reserve than those earlier in disease course
- C-peptide AUC was relatively stable during the dosing period in both icovamenib dose groups
- At Week 52, C-peptide AUC changed by –3.2% with 200 mg and –29.4% with 100 mg versus baseline
- These findings suggest that longer-standing T1D may require additional dose and/or duration optimization to support durable preservation of endogenous insulin secretion

## Results | Cohort 1 Cytokine Profile

| | Week 12 | | | Week 26 | | | Week 52 | | |
|---|---|---|---|---|---|---|---|---|---|
| | pg/mL | change | status | pg/mL | change | status | pg/mL | change | status |
| IL-1β | 1.07 | 0.40 | Non-Inflammatory | 1.00 | 0.27 | Non-Inflammatory | 0.70 | -0.27 | Non-Inflammatory |
| IL-2 | 3.43 | -0.83 | Non-Inflammatory | 3.57 | -1.20 | Non-Inflammatory | 1.20 | -3.23 | Non-Inflammatory |
| IL-6 | 3.27 | 0.70 | Non-Inflammatory | 0.53 | -1.70 | Non-Inflammatory | 0.53 | -1.70 | Non-Inflammatory |
| IL-8 | 6.57 | 0.77 | Non-Inflammatory | 7.17 | -0.07 | Non-Inflammatory | 5.37 | -1.18 | Non-Inflammatory |
| IL-10 | 1.30 | -0.03 | Non-Inflammatory | 1.33 | 0.00 | Non-Inflammatory | 1.30 | -0.03 | Non-Inflammatory |
| IFN-γ | - | - | Non-Inflammatory | - | - | Non-Inflammatory | - | - | Non-Inflammatory |
| TNF-α | 7.53 | -0.17 | Non-Inflammatory | 7.73 | -1.35 | Non-Inflammatory | 4.07 | -5.33 | Non-Inflammatory |

- Mean values were assessed for all patients for each cytokine. Cytokine profiling showed no evidence of systemic immune activation in Cohort 1 participants receiving 200 mg icovamenib
- All cytokines remained classified as 'Non-Inflammatory' through Week 52
- Small increases in IL-1β, IL-6, and IL-8 observed at Week 12 were transient and not associated with increases in IL-2 or TNF-α
- By Week 52, most pro-inflammatory cytokines remained stable or decreased relative to baseline
- These findings suggest that increased C-peptide was not accompanied by a measurable systemic inflammatory cytokine response but rather led to stabilization and mild reductions of inflammatory markers over time

## Safety

| | Cohort 1 | | | Cohort 2 | | |
|---|---|---|---|---|---|---|
| | Arm A 100 mg QD (N = 8) | Arm B 200 mg QD (N = 9) | Cohort 1 Total (N = 17) | Arm A 100 mg QD (N = 9) | Arm B 200 mg QD (N = 10) | Cohort 2 Total (N = 19) |
| **Patients with ≥1 TEAE, N (%)** | 3 (38) | 0 (0) | 3 (18) | 1 (11) | 3 (30) | 4 (21) |
| **Treatment-Related SAEs, N (%)** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **SAEs*, N (%)** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Treatment Discontinuation due to TEAE, N (%)** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Study Discontinuation due to TEAE, N (%)** | 0 | 0 | 0 | 0 | 0 | 0 |
| **Deaths, N (%)** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Diarrhea, N (%)** | 1 (13) | 0 | 1 ( 6) | 1 (11) | 0 | 1 ( 5) |
| **Nausea, N (%)** | 1 (13) | 1 (11) | 2 (12) | 1 (11) | 1 (10) | 2 (11) |
| **Hyperglycemia, N (%)** | 0 | 0 | 0 | 0 | 1 (10) | 1 ( 5) |
| **Headache, N (%)** | 1 (13) | 0 | 1 ( 6) | 0 | 1 (10) | 1 ( 5) |
| **AST/ALT increase, N (%)** | 3 (38 | 2 (22) | 5 (29) | 1 (11) | 7 (70) | 8 (42) |
| **Resolution of ALT/AST w/o interruption in study treatment, %** | 100 | 100 | 100 | 100 | 80 | 90 |

## Summary

- Icovamenib was associated with preservation of endogenous insulin secretion among evaluable participants, with a directional response favoring 200 mg over 100 mg
- In Cohort 1 participants diagnosed with T1D <3 years, 200 mg icovamenib increased C-peptide AUC by ~52% at Week 12 versus baseline
- At Week 52, C-peptide AUC was ~7% below baseline, compared with a ~47% decline in historical placebo
- Cytokine profiling showed no evidence of systemic immune activation, with inflammatory markers stable or reduced through Week 52
- Overall, these findings suggest that menin inhibition may enhance or preserve residual beta-cell function in T1D without a measurable systemic inflammatory cytokine response

## References

1. Butler T. et al. Oral Long-Acting Menin Inhibitor Normalizes Type 2 Diabetes Mellitus (T2DM) in Two Rat Models. *Diabetes,* 2022 Jun 1; 71 (Supplement_1): 851–P.
2. Somanath P. et al. Oral Menin Inhibitor, BMF-219, Displays a Significant and Durable Reduction in HbA1c in a Type 2 Diabetes Mellitus Rat Model. *Diabetes,* 2022 Jun 1; 71 (Supplement_1): 113–LB.
3. Frias J. et al. BMF-219: A Novel Therapeutic Agent to Re-Establish Functional Beta Cells and Provide Long-Term Glycemic Control. *Metabolism-Clinical and Experimental,* 2024: 0088.
4. Rodriquez J. et al. Durable Glycemic Control With BMF-219 During Off-treatment Period At Week 26: A Phase 1/2 Trial Of BMF-219 In Patients With Type 2 Diabetes. *Diabetes Technol Ther,* 2024; 26:S2: PD064.



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