Icovamenib, a Menin Inhibitor, Improves Endogenous Insulin Secretion in Type 1 Diabetes: Results from the COVALENT-112 Study

Steve Morris, MD (Chief Development Officer, Biomea Fusion, Inc.)

Breakthrough T1D™ Clinical & Research Congress

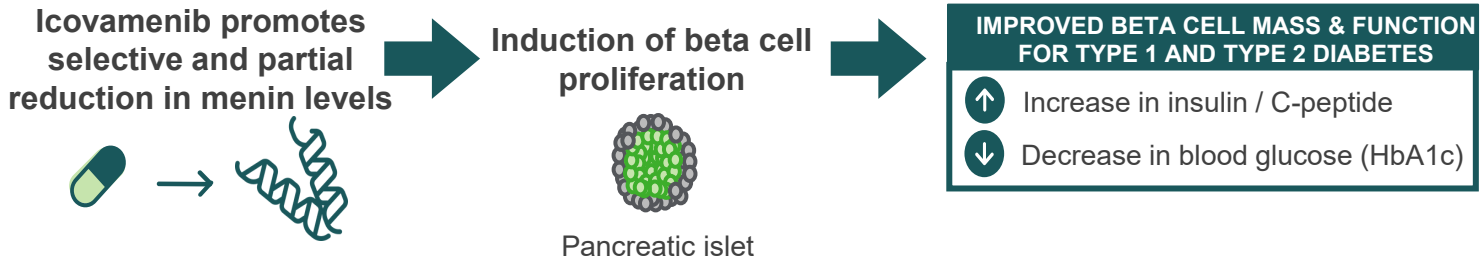
Limitations of current approaches in stage 3 T1D

- Most investigational agents in T1D focus on immune modulation to slow autoimmune destruction or on preserving residual beta cell function[1]
- C-peptide area under the curve (AUC) has become the accepted endpoint, driving enrollment early after diagnosis (<90 days, new-onset T1D) to preserve residual beta-cell function[2]
- To date, investigational therapies have not demonstrated durable restoration of beta cell function or sustained increases in C-peptide, outside of cell-based transplantation approaches[3]

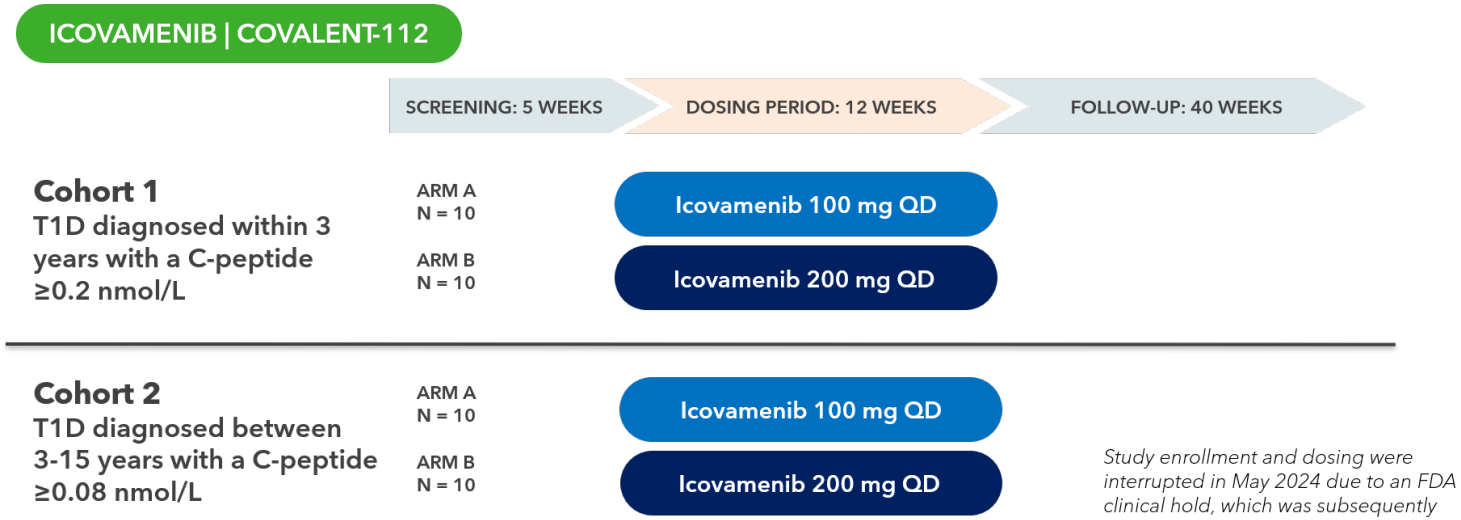
1. *Zarei M et al. Diabetes Epidemiology and Management 2025;17*
2. *Diabetes Care 2025*
3. *NIDDK. Diabetes in America, 2024*

What's Needed

- Restoring beta cell function and mass, beyond only slowing the decline of C-peptide
- Expanding the treatment window beyond early, new onset T1D populations
- Enabling persistence of newly generated beta cells despite autoimmune pressure



Lowering menin levels releases the brake on beta cell proliferation



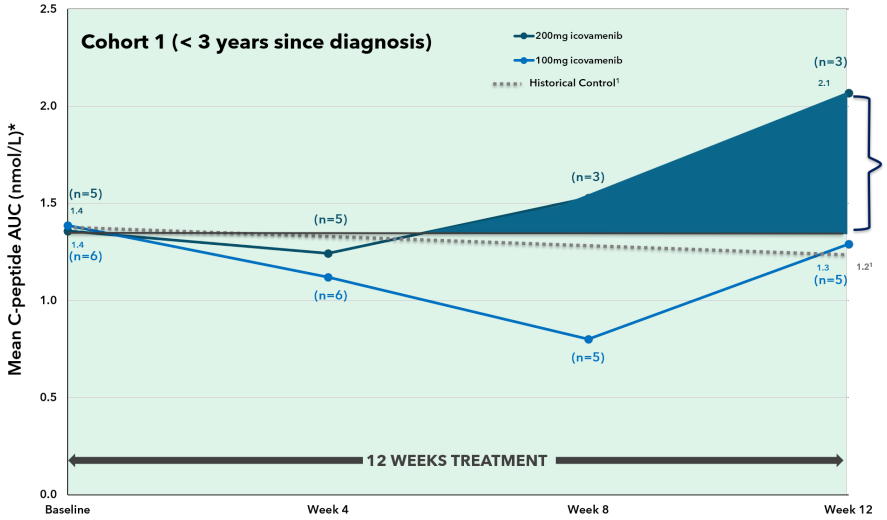
Study enrollment and dosing were interrupted in May 2024 due to an FDA clinical hold, which was subsequently resolved, but reduced the number of patients enrolled and followed through to the 52-week readout.

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Increase in C-peptide during 12 weeks of icovamenib treatment



52% mean increase from baseline

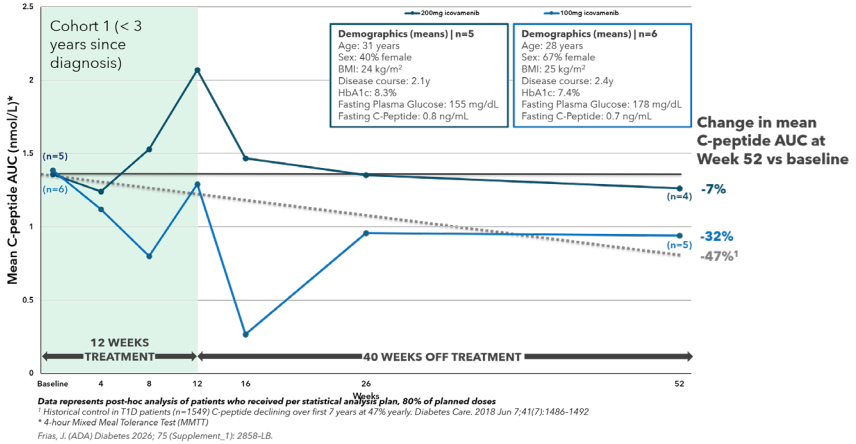
+0.7
P<0.001

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

¹ 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)*

Frias, J. (ADA) Diabetes 2026; 75 (Supplement_1): 2858-LB.

C-peptide levels were sustained through Week 52 following 12 weeks of icovamenib 200 mg QD



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Cytokine Profiling of Cohort 1 (< 3-year diagnosis) participants receiving 200 mg icovamenib

	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 (n=3) relative to baseline.

- All cytokines remained classified as Non-Inflammatory from baseline through Week 52, indicating no evidence of systemic immune activation in participants
- Minor Week 12 increases in IL-1β, IL-6, and IL-8 were transient and not associated with increases in IL-2 or TNF-α
- By Week 52, pro-inflammatory cytokines were stable or decreased from baseline
- **The increase in C-peptide was not accompanied by a measurable systemic inflammatory cytokine response but rather led to a stabilization or reduction of inflammatory markers**

C-peptide increase was not observed in Cohort 2 (3-15 years since diagnosis)

- Cohort 2 included participants (3–15 years since T1D diagnosis) a population with potentially lower residual beta-cell reserve than those earlier in their disease
- 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

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

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Favorable 52-week safety profile

	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)
Hypoglycemia, N(%)	4 (50)	5 (56)	9 (53)	4 (44)	6 (60)	10 (53)
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, HbA1c improved by 0.6% while C-peptide AUC was ~7% below baseline, compared with a ~47% decline in historical placebo control
- 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**

Future Plans

Study plans for a Phase 2 trial in patients with T1D diagnosed within the past 3 years are underway

- The study will evaluate whether extended dosing (up to 6 or 12 months) at 200 mg further improves C-peptide and whether the addition of an immunosuppressive agent enhances clinical outcomes