Investigating the Effects of Icovamenib in Poorly Managed Severe Insulin-Deficient Diabetes (SIDD): Insights from COVALENT-111 Case Studies

Alexander Abitbol, MDCM, FRCPC[1]; Douglas Denham, DO[2]; Apinya B. Vutikullird, DO[3]; Adolfo Cueli, MD[4]; Alexander Osowa, MD[5]; Sanchita Mourya, MD[6]; Brian Munneke, PhD[6]; Jeffrey Kim, PhD[6]; Thomas Butler, MS, MBA[6]; Juan Pablo Frías, MD[6]

[1]Centricity Research/LMC, 1929 Bayview Avenue, Suite 125 & 107 Toronto, Ontario M4G 3E8 Canada; [2] Flourish Research, 5430 Fredericksburg Rd. Ste 200 San Antonio, TX 78229 USA; [3]Ark Clinical Research, LLC, 2220 Clark Ave. Unit A Long Beach, CA 90815 USA;

[4]Entrust Clinical Research, 10621 North Kendall drive suite 218, Miami Fl, 33176 USA; [5]Omera Health, 757 60th Street, BROOKLYN, NY 11220 USA; [6]Biomea Fusion, 900 Middlefield Rd, 4th Floor, Redwood City, CA 94063 USA

Abstract #0063

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Background

Type 2 Diabetes (T2D)

- T2D is characterized by hyperglycemia due to a progressive decline in beta-cell mass and function
- At diagnosis, beta-cell function is typically reduced by over 50%, with further decline as the disease progresses[1]
- Current treatments do not specifically address this underlying beta-cell dysfunction
- There is an important unmet need to develop T2D treatments that address the core defect of the disease: the loss of insulin-secreting beta cells

Menin

- Menin is a ubiquitous scaffold protein that displays tissue-specific roles through regulating gene expression and cell signaling pathways, dependent on various menin-bound protein complexes
- Menin is a key negative regulator of both beta-cell proliferation and mass

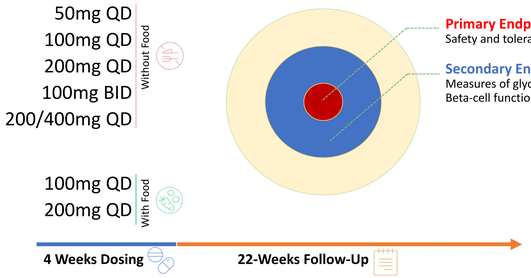
Icovamenib

- Icovamenib is an oral, selective, covalent menin inhibitor that is currently in clinical development for the treatment of T2D (NCT05731544) and type 1 diabetes (T1D) (NCT06152042)
- In Zucker Diabetic Fatty and streptozotocin-induced T2D rat models, a short-course of icovamenib resulted in durable glycemic control[2,3]
- In human islet microtissues, icovamenib exposure resulted in beta-cell proliferation in the presence of hyperglycemia that was dependent on icovamenib dose and duration of exposure[4]
- In poorly controlled patients with T2D, 4-weeks of icovamenib (100mg or 200mg daily) resulted in durable improvements in glycemic control. At Week 26, 22 weeks after completion of the 4-week course of icovamenib[5]:
  - ≥1.0% HbA1c reduction in 20% and 36% of patients treated with 100mg (n=20) and 200mg (n=11) daily, respectively
  - Across 100 and 200-mg cohorts (n=31): 26% of patients had ≥1.0% HbA1c reduction (mean HbA1c reduction 1.5%)
- In patients with poorly controlled diabetes, efficacy and safety of up to 12 weeks of icovamenib, with subsequent follow-up until week 52, is being assessed to test the hypothesis that a longer duration of therapy will result in greater improvements in durable glycemic control

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

Study Design: 26-week, randomized, double-blind, placebo-controlled

Subjects: Adults with T2D (duration ≤15 years, HbA1c 7-10.5%, BMI 25-40 kg/m^2) and treated with up to 3 antidiabetic agents



T2D Heterogeneity and Subtyping

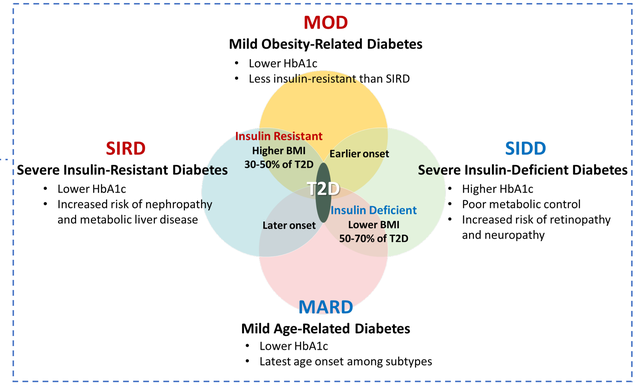
- T2D is highly heterogeneous in clinical characteristics, progression, drug response, and complication risks
- Ahlqvist et al.[6] identified five adult-onset diabetes subtypes using: GAD autoantibodies, age at onset, HbA1c, BMI, insulin resistance (HOMA2-IR), and insulin secretion (HOMA2-B):

1. Severe Autoimmune Diabetes (SAID)
2. Severe Insulin-Deficient Diabetes (**SIDD**)
3. Severe Insulin-Resistant Diabetes (**SIRD**)
4. Mild Obesity-Related Diabetes (**MOD**)
5. Mild Age-Related Diabetes (**MARD**)

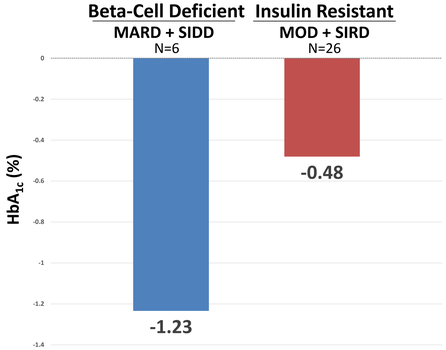
T2D Subtypes

- Key subtype differences:
  - Complication risks
  - Disease progression
  - Genetic factors
  - Treatment responses
  - **Insulin Resistance**
  - **Insulin Deficient**
- Benefits of subtyping:
  - Framework for personalized and precision medicine
  - Improved resource allocation and research focus

Subtype Clustering: Subtype assignment performed post-hoc using diabetes clusters proposed by Alqvist et al.[6]



Reduction of HbA1c in Beta-Cell Deficient vs Insulin Resistant Patients

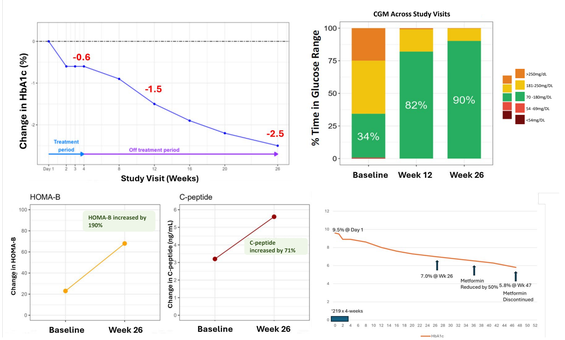


Placebo-adjusted change in HbA1c by T2D subtype at Week 26*

*includes Cohorts 2,3,4 & 7 (100mg QD/BID and 200mg QD, cohorts representative of exposure expected in expansion phase, Arms A-C)

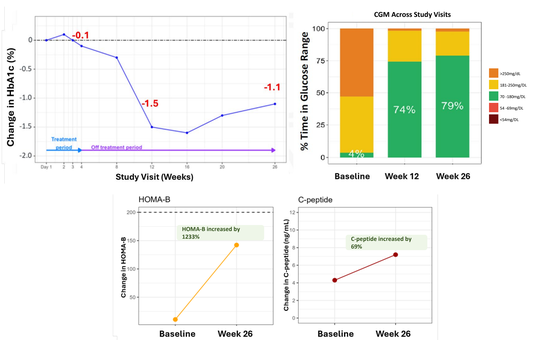
Severe Insulin-Deficient Diabetes Case #1

- 29-year-old man with 4-year history of T2D, SIDD classification
- Metformin 1000 mg BID and empagliflozin 25 mg BID
- At baseline, HbA1c 9.5%; FPG 134 mg/dL; CGM with 34% TIR$_{70\text{-}180\ mg/dL}$; BMI 25.6 kg/m^2
- Icovamenib 200 mg once daily for 4 weeks
- At Week 26, HbA1c 7.0% (-2.5%), FPG 105 mg/dL (-29 mg/dL), HOMA-B increased by 190%, and C-peptide increased by 71%
- CGM at Week 26 with 90% TIR$_{70\text{-}180\ mg/dL}$ (+56%)
- No adverse events
- The patient's endocrinologist observed additional HbA1c reduction at Week 36, adjusting metformin to 500 mg BID. By Week 47, HbA1c dropped to 5.8% and metformin discontinued



Severe Insulin-Deficient Diabetes Case #2

- 45-year-old man with 10-year history of T2D, SIDD classification
- Metformin 500 mg BID
- At baseline, HbA1c 8.6%; FPG 235 mg/dL; CGM with 4% TIR$_{70\text{-}180\ mg/dL}$; BMI 29.6 kg/m^2
- Icovamenib 100 mg once daily with food for 4 weeks
- At Week 26, HbA1c 7.5% (-1.1%), FPG 144 mg/dL (-91 mg/dL), HOMA B increased by 1233%, and C-peptide increased by 59%
- CGM at Week 26 with 79% TIR$_{70\text{-}180\ mg/dL}$ (+73%)
- No adverse events reported



Conclusions

- Icovamenib is an investigational covalent menin inhibitor in development to address the root cause of diabetes: the progressive decline in beta-cell mass and function
  - COVALENT-111 (Escalation Phase) assesses the efficacy and safety of 4-week once daily administration of icovamenib in T2D to address this important unmet need in this patient population
- T2D subtyping reveals distinct risk profiles and provides a framework for precision medicine
  - Enhancing the power of experimental and clinical studies through more homogeneous patient populations
- Case studies demonstrate the potential of short-term icovamenib treatment to modify disease progression and provide lasting effects in patients with uncontrolled T2D
  - Many patients showed continued improvement in HbA1c levels and time in range on CGM until Week 26 after completing 4 weeks of treatment; the first patient presented here showed continued improvement beyond Week 26 of study follow-up
  - The observed increases in HOMA-B and C-peptide, which correlate with improved glycemic control, align with icovamenib's primary mechanism of action: enhancing beta-cell mass and function
- COVALENT-111 is ongoing, and results of the Expansion Phase, consisting of data from over 200 patients dosed with icovamenib, are currently being analyzed and prepared for dissemination

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