A. Abitbol, D. Denham, A. Vutikullird, A. Cueli, A. Osowa, S. Mourya, B. Munneke, J. Kim, T. Butler, J.P. Frias

Icovamenib in COVALENT-111: Targeting Beta-Cell Dysfunction

Heterogeneous Nature of T2D: T2D is a heterogeneous disease with varying degrees of insulin deficiency and peripheral insulin resistance

Subtyping T2D Patients: Subtyping T2D patients helps identify specific subgroups for targeted treatment approaches

SIDD and MARD Subgroups: The Severe Insulin-Deficient Diabetes (SIDD) and Mild Age-Related Diabetes (MARD) subgroups, described by Ahlqvist et al., comprise approximately 50-70%[1,2] of patients with T2D, depending on the population, are characterized by significant insulin deficiency due to beta-cell dysfunction

Mechanism of icovamenib: Icovamenib leads to beta-cell proliferation and enhanced insulin secretion in T2D

COVALENT-111 Trial: The COVALENT-111 Phase I/II trial (NCT05731544) is investigating icovamenib, an oral covalent small molecule menin inhibitor in participants with T2D

[1]Ahlqvist E, et al. *Lancet Diabetes Endocrinol*. 2018;6:361-369 | [2]Zaghlool SB, et al. *Nat Commun. 2022;*13(1):7121

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Assessment of Icovamenib (BMF-219) in Persons with Poorly Controlled Severe Insulin-Deficient (SIDD) Type 2 Diabetes (T2D): COVALENT-111 Case Studies

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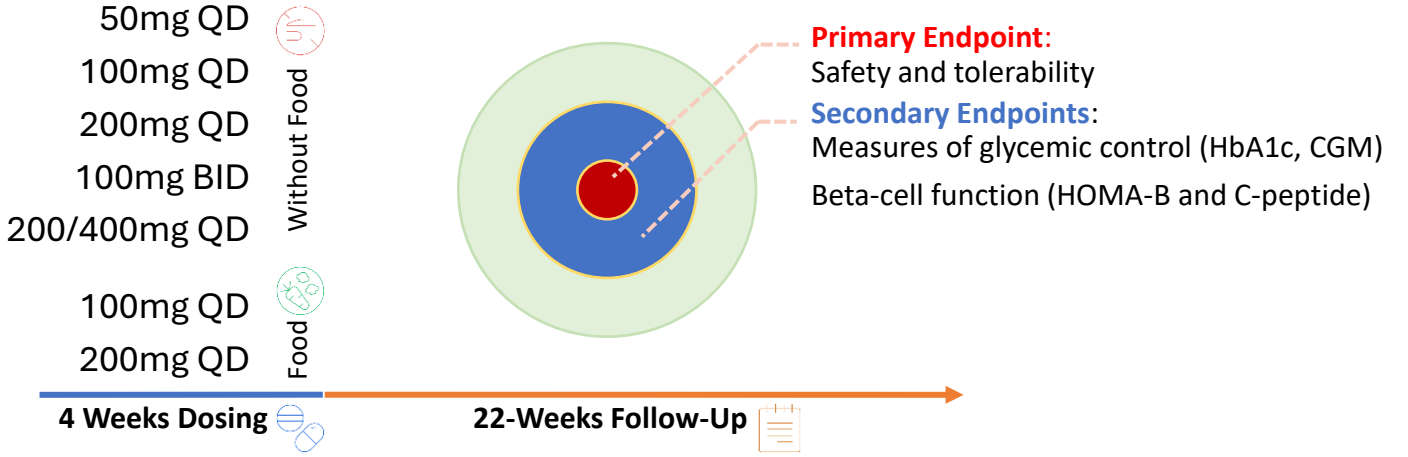
COVALENT-111 MAD: Overview of Study Design and HbA1c Change by T2D Subtype

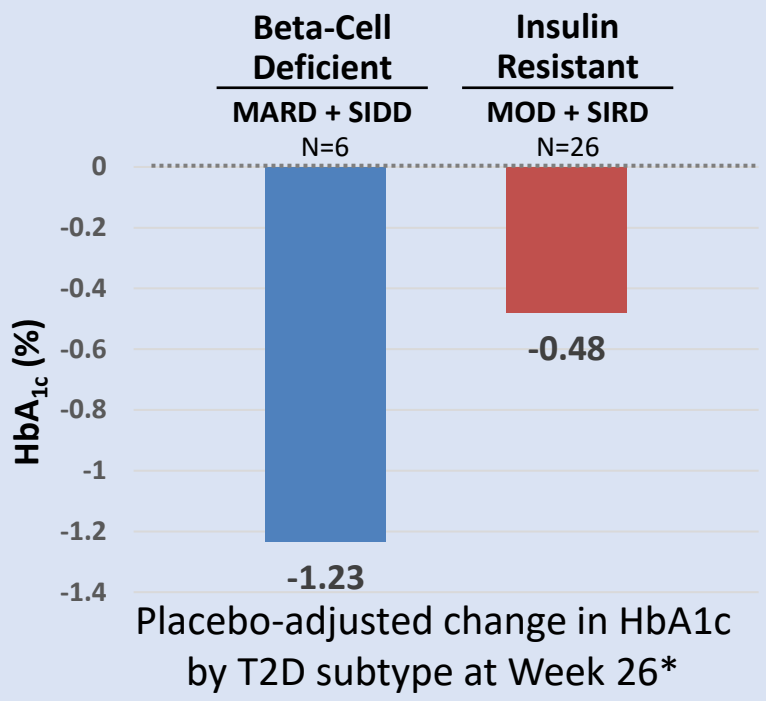
Study Design: 26-week, randomized, double-blind, placebo-controlled

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

MAD Cohort 2-8: Participants with T2D (4 weeks dosing with follow-up until Week 26)



Subtype Clustering: Subtype assignment performed post-hoc using diabetes clusters proposed by Ahlqvist et al 2018[1]



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)

MARD, mild age-related diabetes
SIDD, severe insulin-deficient diabetes
MOD, mild obesity-related diabetes
SIRD, severe insulin-resistant diabetes

[1]Ahlqvist E, et al. *Lancet Diabetes Endocrinol*. 2018;6:361-369

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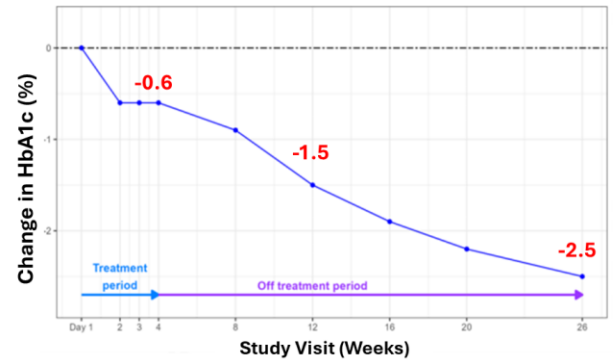
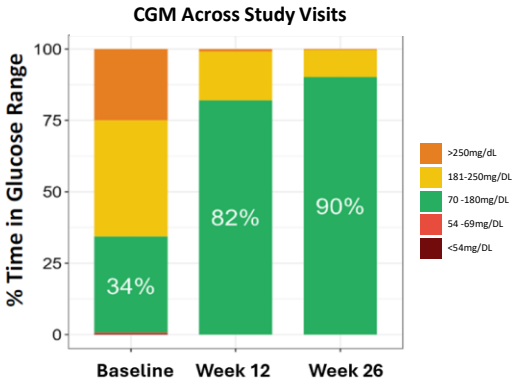
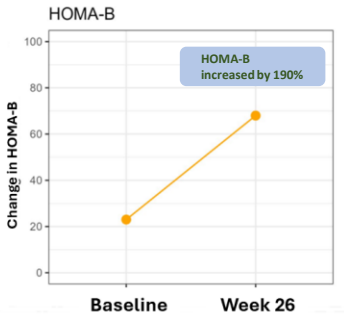
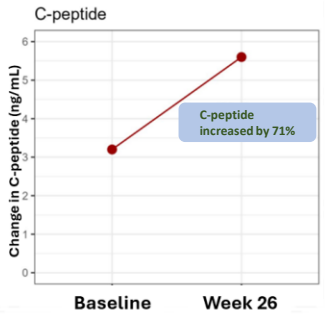
Exploratory investigation suggests increased efficacy of menin-inhibition by icovamenib in insulin deficient patients

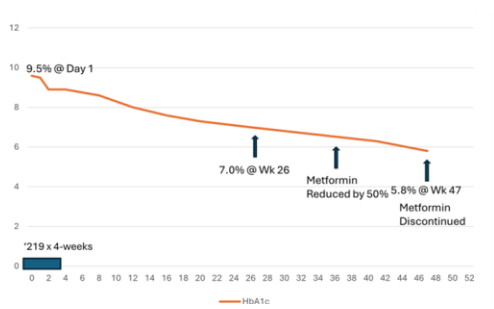
- 29-year-old man with 4-year history of T2D, SIDD classification
- Metformin 1000 mg BID and empagliflozin 25 mg BID
- At baseline, HbA1c 9.5%; FPG 134 mg/dL; CGM with 34% $TIR_{70\text{-}180\ mg/dL}$; BMI 25.6 kg/$m^2$
- Icovamenib 200 mg once daily without food for 4 weeks
- At Week 26, HbA1c 7.0% [change from baseline (CFB), -2.5%], FPG 105 mg/dL (CFB, -29 mg/dL), HOMA-B increased by 190%, and C-peptide increased by 71%
- CGM at Week 26 with 90% $TIR_{70\text{-}180\ mg/dL}$ (CFB, +65%)
- 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%, leading to discontinuation of metformin



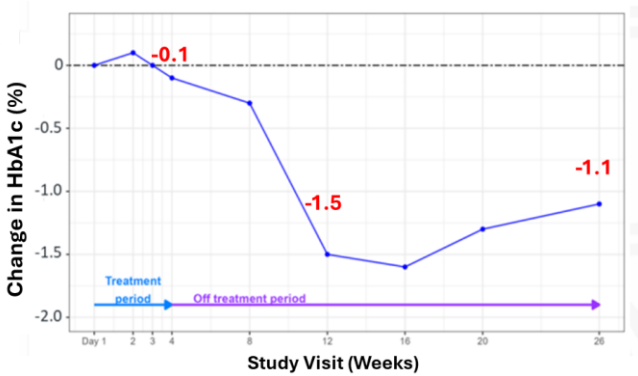


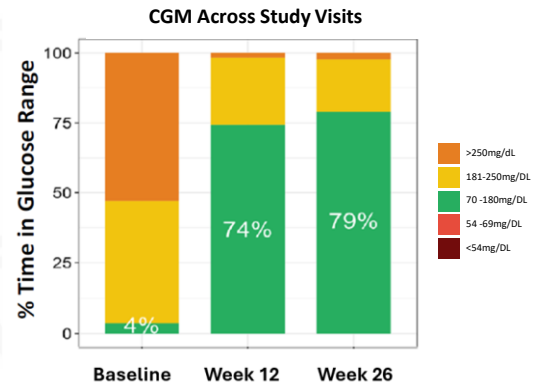


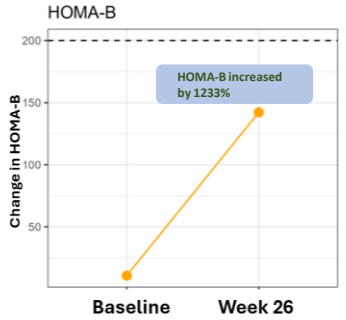


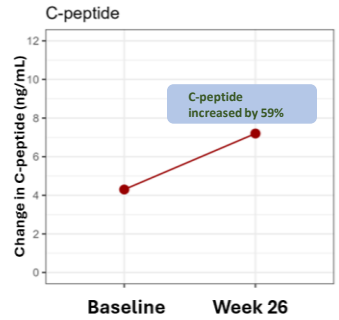


- 45-year-old man with 10-year history of T2D, SIDD classification
- Metformin 500 mg BID
- At baseline, HbA1c 8.6%; FPG 235 mg/dL; CGM with 4% $TIR_{70\text{-}180\ mg/dL}$ BMI 29.6 kg/m^2
- Icovamenib 100 mg once daily with food for 4 weeks
- At Week 26, HbA1c 7.5% (CFB, -1.1%), FPG 144 mg/dL (CFB,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









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