Combination Therapy of Icovamenib and Semaglutide Enhances Body Weight Loss and Glycemic Control While Preserving Lean Mass in a Type 2 Diabetes Animal Model

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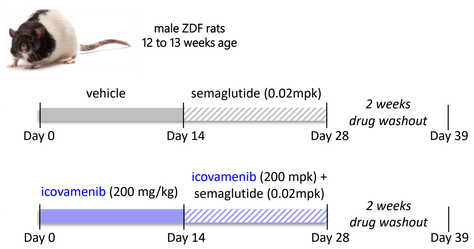
Background

- Icovamenib is an oral, selective, menin inhibitor that has demonstrated durable glycemic control following short course treatments in both the Zucker Diabetic Fatty (ZDF) rat and the Streptozotocin-induced (STZ) T2D rat models.[1,2]
- In a randomized, placebo-controlled multiple ascending dose study in participants with type 2 diabetes (T2D), 12 weeks of daily icovamenib resulted in improved glycemic control at week 26 (14 weeks after cessation of treatment with icovamenib).[3]
- In ex-vivo human islet studies, icovamenib has reproducibly demonstrated:
  - i) Dose and glucose-dependent, selective proliferation of β cells.[4]
  - ii) Enhancement in the responsiveness of islets to peptide and small molecule GLP-1 receptor agonists.[5]
  - iii) Increased insulin and GLP-1 receptor expression, consistent with the reported role of menin in regulating expression of these targets. [5,6]
- Given their complementary mechanisms of action, we sought to explore if icovamenib can enhance the therapeutic effects of semaglutide in an in vivo setting, e.g. an animal model of T2D.

1. Butler T. et al. Oral Long-Acting Menin Inhibitor Normalizes Type 2 Diabetes Mellitus (T2DM) in Two Rat Models. Diabetes 1 June 2022; 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 1 June 2022; 71 (Supplement_1): 113–LB.
3. Abitbol A et al. COVALENT-111: A phase 2 trial of the oral menin inhibitor BMF-219 in patients with Type 2 diabetes, Diabetes Technol Ther, 2025; 27:S2: EPD056
4. Frias, Juan P. et al. BMF-219: A Novel Therapeutic Agent to Reestablish Functional Beta Cells and Provide Long-Term Glycemic Control, Metabolism - Clinical and Experimental, 153, 155884.
5. Balakrishnan et al. Combination of icovamenib and GLP-1-based therapeutic agents improves beta cell function and insulin secretion. 2025 Metabolism - Clinical and Experimental, Vol 168, 156226
6. 2025Muhammad AB et al. Menin and PRMT5 suppress GLP1 receptor transcript and PKA-mediated phosphorylation of FOXO1 and CREB. Am J Physiol Endocrinol Metab. 2017

Figure 1: Study Design in the ZDF Rat Model of T2D

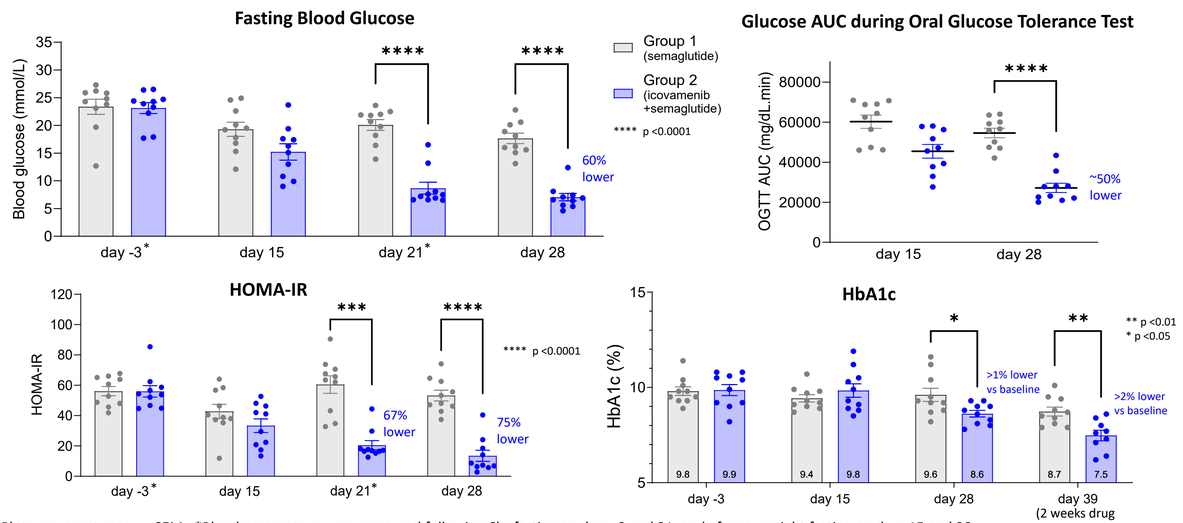


Icovamenib administered p.o, QD and semaglutide s.c, QD

Readouts at multiple time points throughout the study period.

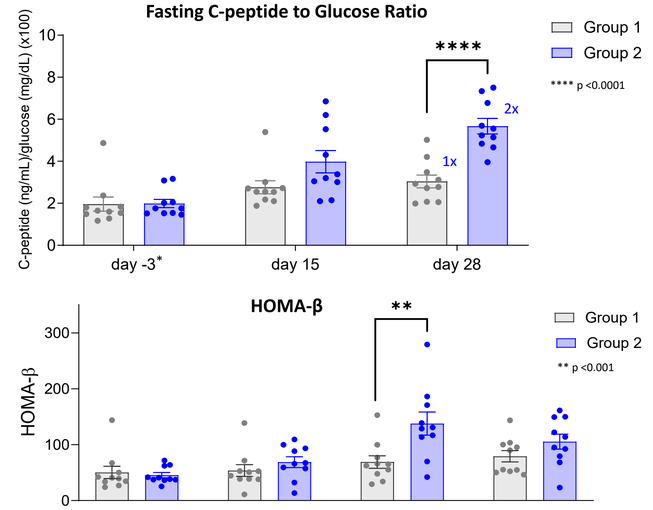
- Glycemic control: Fasting blood glucose, serum insulin and C-peptide, HbA1c, oral glucose tolerance test OGTT, insulin resistance (HOMA-IR), beta cell function (HOMA-B).
- Food and water consumption and body weight measured regularly. Body composition by Minispec analysis (days -3, 25 and 38).

Figure 2: Combination Therapy with Icovamenib and Low Dose Semaglutide Improves Glycemic Parameters



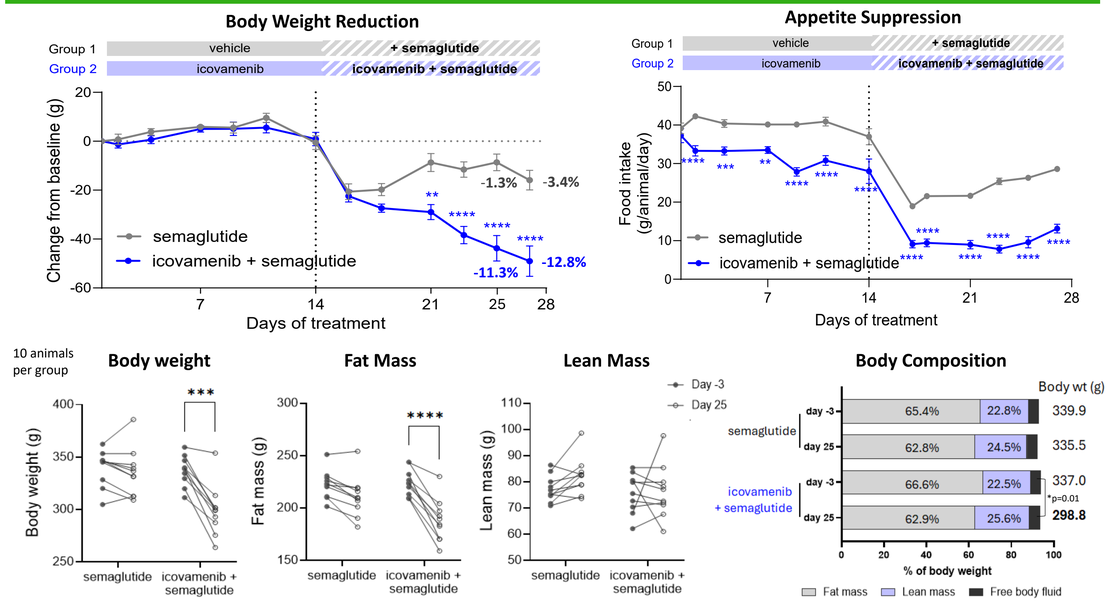
Plots represent mean ± SEM. *Blood parameters were measured following 6hr fasting on days -3 and 21, and after overnight fasting on days 15 and 28

Figure 3: Combination Therapy Improves Beta Cell Function



Plots represent mean ± SEM. C-peptide to glucose ratio = C-peptide (ng/mL)/glucose (mg/dL) (x100).
* Blood parameters were measured following 6hr fasting on days -3 and 21, and after overnight fasting on days 15 and 28.

Figure 4: Combination Therapy Enhances Appetite Suppression and Weight Loss While Preserving Lean Mass



Conclusions

Efficacy of combination therapy with icovamenib and low dose semaglutide was evaluated in the ZDF rat model of T2D and compared against semaglutide alone.

- ❑ Combination treatment had superior glycemic control vs semaglutide alone
  - ➢ 60% lower fasting blood glucose and 50% lower glucose OGTT AUC
  - ➢ Greater reduction in HbA1c; >1% by Day 28, >2% by Day 39
  - ➢ Greater improvement in insulin sensitivity; 75% lower HOMA-IR
  - ➢ Significant increase in C-peptide to glucose ratio
- ❑ Combination treatment had superior appetite suppression and body weight reduction while fully preserving lean mass
  - ➢ 10% greater reduction in body weight (Day 25)
  - ➢ Body weight reduction almost exclusively due to fat mass loss with complete preservation of lean mass
- ❑ The overall results demonstrate the enhanced efficacy of the combination of icovamenib and semaglutide (vs semaglutide alone), potentially allowing lower doses of GLP-1-based therapies to achieve glycemic and weight loss targets and improve tolerability of these agents.

Acknowledgements

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