Icovamenib and Semaglutide Combination Enhances Weight Loss While Preserving Lean Mass in ZDF Rats

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Background

- Icovamenib is an oral, selective, menin inhibitor that has demonstrated durable glycemic control following short course treatments in type 2 diabetes patients as well as in preclinical models of type 2 diabetes.[1,2]
- In a double-blind, randomized, placebo-controlled phase 2 trail in participants with type 2 diabetes, 12 weeks of icovamenib treatment resulted in sustained treatment benefit through Week 52 (9 months after cessation of treatment).[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 GLP-1 receptor and insulin expression in islets, 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 using the Zucker Diabetic Fatty (ZDF) rat 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. 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
3. Biomea Fusion Inc. (Oct 6, 2025) *Biomea Fusion Announces Positive 52-Week Results from Phase II COVALENT-111 Study in Type 2 Diabetes Demonstrating Non-Chronic Treatment with Icovamenib Benefits Two Distinct Patient Populations* [Press Release].
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: Icovamenib Enhances Insulin & GLP-1 Receptor Expression

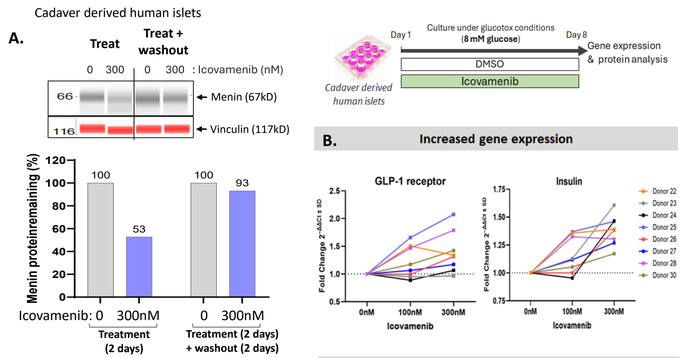
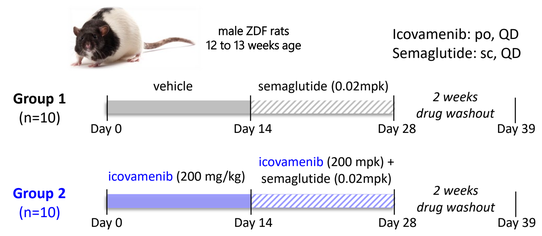


Figure 1. Effects of icovamenib on menin GLP-1 receptor and insulin expression were evaluated in human islet cultures from healthy donors. Islets were cultured ex vivo under 8mM glucose conditions for the indicated duration in the presence of icovamenib or vehicle (DMSO). Islets were harvested and analyzed for menin (A) and GLP-1 receptor (C) protein levels by automated Western Blot (JESS system), intracellular insulin levels by ELISA (C) and gene expression by qRT-PCR (B).

Figure 2: Study Design in the ZDF Rat Model of T2D



Readouts at multiple time points throughout the study period.

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

Figure 2. Study design. Male ZDF rats, 12 -13 weeks of age, randomized into two groups were dosed daily (PO) with vehicle or icovamenib for 28 days and low dose semaglutide (5nmol/kg) was dosed daily (SC) from Day 15 -28. Effects on body weight, food and water intake, body composition and glycemic parameters were monitored through the study.

Figure 3. Mean daily food intake (A) and mean change in body weight from baseline (B) are plotted for the 4 weeks of treatment. Plots represent mean ± SEM. Body weight and composition were measured on Day 25 (C). Lines represent individual animal data and denote change on Day 25 from baseline. Lean mass and fat mass fraction were calculated as percentage of body weight (D). Bar charts represent mean± SD for each group at baseline (Day -3) and Day 25 of treatment.

Figure 3: Combination Therapy Enhances Appetite Suppression and Weight Loss While Preserving Lean Mass

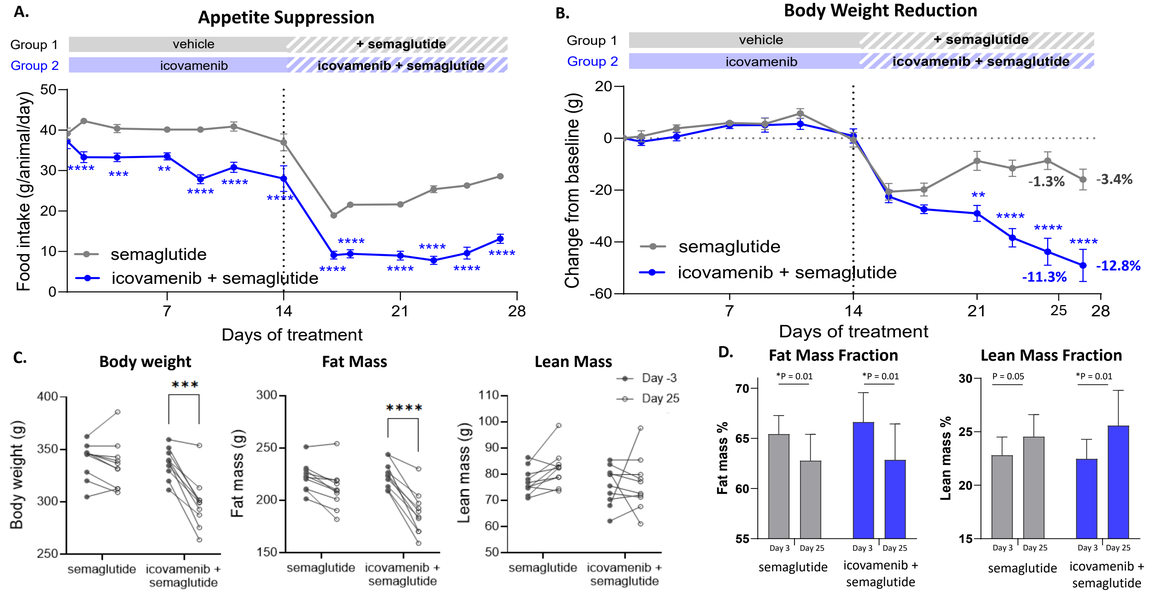
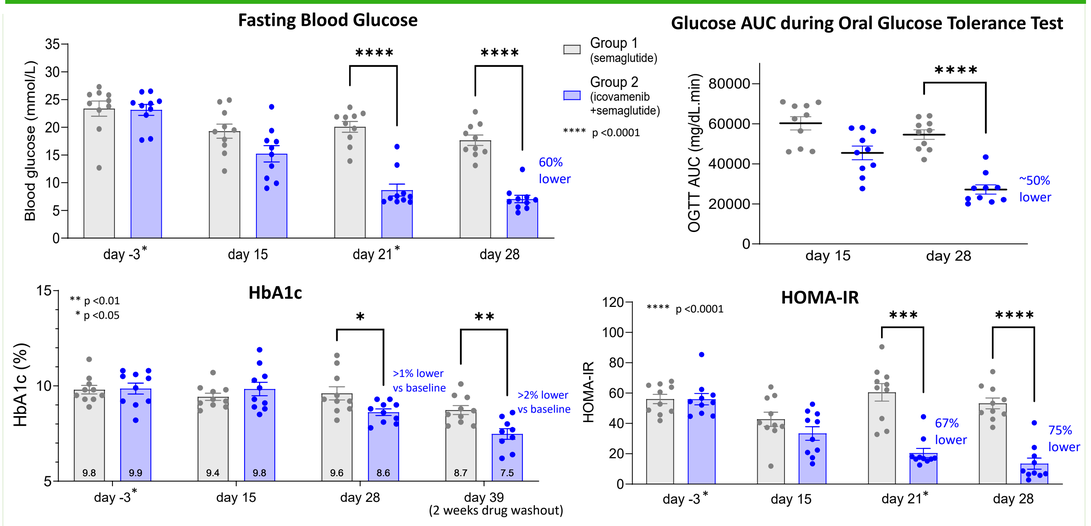


Figure 4: Combination Therapy with Icovamenib and Low Dose Semaglutide Improves Glycemic Parameters



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

Conclusions

Efficacy of combination therapy of 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% more reduction in body weight
  - ➢ 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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