Combination of Icovamenib and GLP-1-Based Therapeutic Agents Improves Beta Cell Function and Insulin Secretion

*Mini Balakrishnan, PhD, Tracy Zhang, PhD, Kung-Hsien Ho, PhD, Dina Mousavi, MS, Juan Pablo Frias, MD, Thomas Butler, MS, MBA
Biomea Fusion, Inc., Redwood City, CA

Abstract PV363

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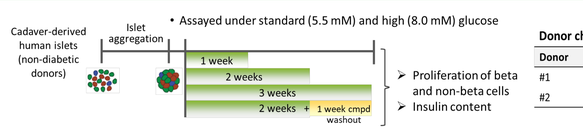
Background

- Icovamenib is an oral, selective, covalent menin inhibitor that has demonstrated durable glycemic control following short course treatments in both Zucker Diabetic Fatty (ZDF) rat and Streptozotocin-induced (STZ) Type 2 diabetic rat models.[1,2]
- In a randomized, placebo-controlled multiple ascending dose study in participants with T2D, 4 weeks of daily icovamenib resulted in improved glycemic control at Week 26 (22 weeks after cessation of treatment with icovamenib).[3]
- Human islets treated ex-vivo with icovamenib has reproducibly demonstrated selective proliferation of beta cells.[4]
- Menin has been shown to regulate GLP-1 receptor (GLP-1R) expression and consequently, the GLP-1 receptor pathway.[5] We therefore sought to explore the effects of icovamenib in this context, and the potential for combining icovamenib with current GLP-1-based therapies in the clinic, namely semaglutide and tirzepatide.

Figure 1: Icovamenib Promotes Selective Proliferation of Islet Beta Cells



Donor characteristics:

Donor	Age	BMI	HbA1c
#1	19	23.2	5.8
#2	32	25.0	5.2

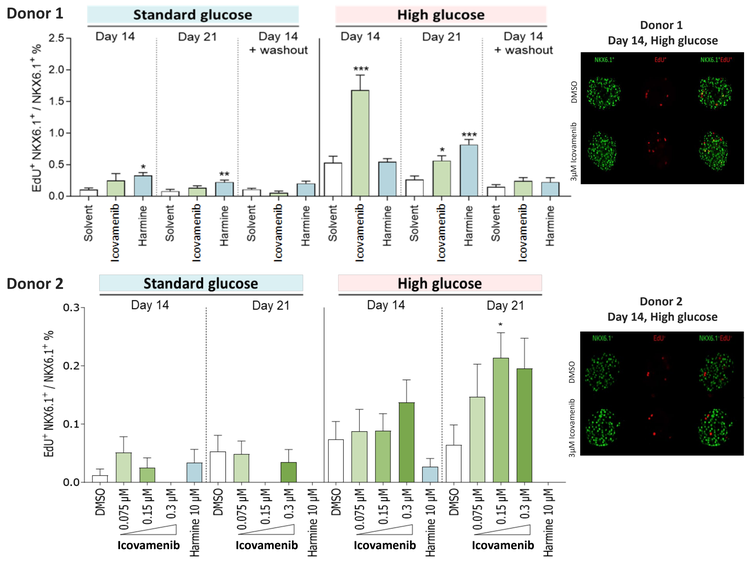


Figure 1. Effects of icovamenib (BMF-219) on beta cell proliferation were evaluated using human islet microtissues (MTs) generated from cadaver-derived islet from non-diabetic donors. Experimental set up and Donor characteristics are shown. Assays were performed under 5.5 mM (standard glucose) or 8 mM (high glucose) culture conditions. Islet MTs (9 to 12 replicates per condition) were cultured in the presence of icovamenib, harmine (10 µM) or vehicle (DMSO) for 2 or 3 weeks, or 2 weeks followed by 1 week no treatment (washout). EdU incorporation was used to detect proliferating cells. At the end of treatment islets were fixed, stained and imaged to quantify proliferating beta and non-beta cells. Y-axis represents proliferating beta cell fraction (proliferating beta cells as a fraction of total beta cells).

Figure 2: Icovamenib Increases Expression of GLP-1 Receptor in Human Islets

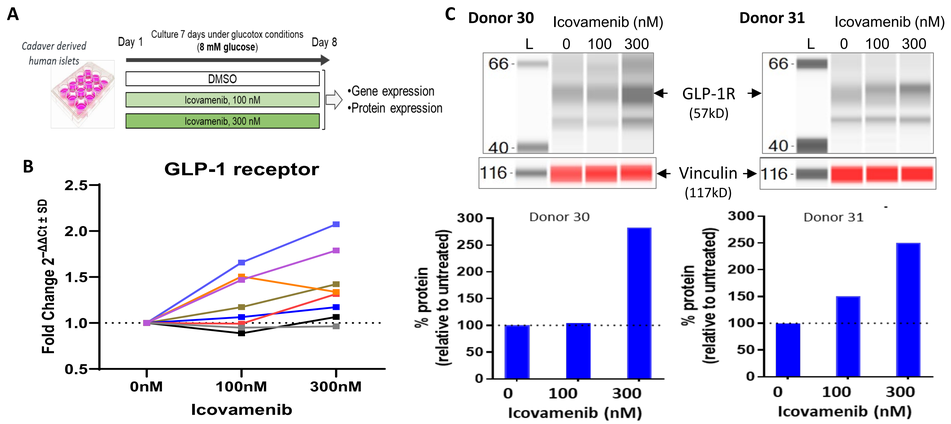
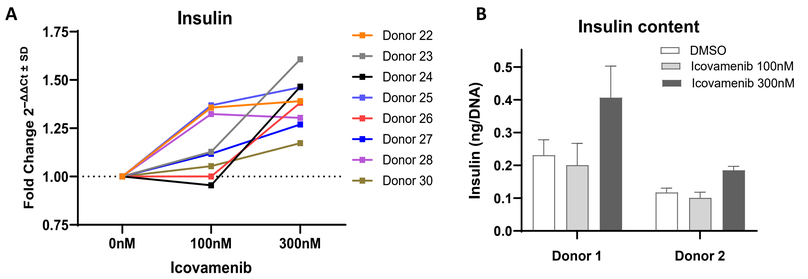
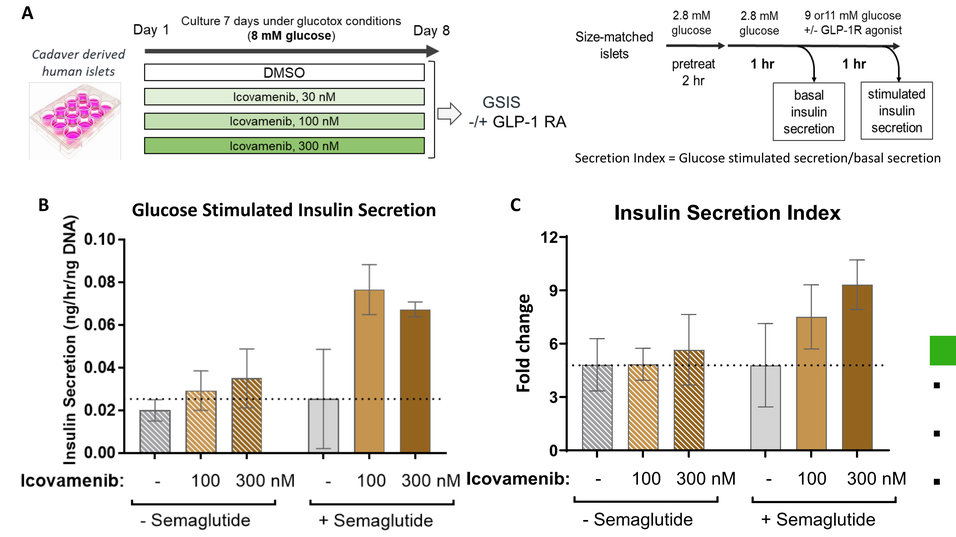


Figure 3: Icovamenib Increases Expression of Insulin in Human Islets



Figures 2 and 3. (2A) Schematic of the experimental setup. Human islets were cultured ex vivo under high glucose (8mM) conditions for 7 days in the presence of icovamenib (100nM or 300nM) or vehicle (DMSO). On Day 8, islets were harvested and analyzed for GLP-1R (Fig 2) and insulin (Fig 3) expression. RNA was extracted from size-matched islets, and gene expression for GLP-1R (2B), insulin (3A), and RPL30 measured by quantitative RT-PCR. Expression levels of the target genes were normalized to RPL30 and relative fold change in transcript levels following icovamenib treatment calculated as $2^{-\Delta\Delta Ct}$. Effects on GLP-1 receptor and insulin gene expression were evaluated using islets from 8 independent non-diabetic donors. GLP-1 receptor protein expression was measured using Jess (automated Western Blot system) (2C). Intracellular insulin levels in the islets were measured by ELISA and normalized by islet DNA content (3B). Effects of icovamenib on GLP-1 R and insulin protein levels were evaluated using islets from 2 independent non-diabetic donors.

Figure 4: Icovamenib Enhances Insulin Secretion Potentiated by GLP-1 Receptor Agonists



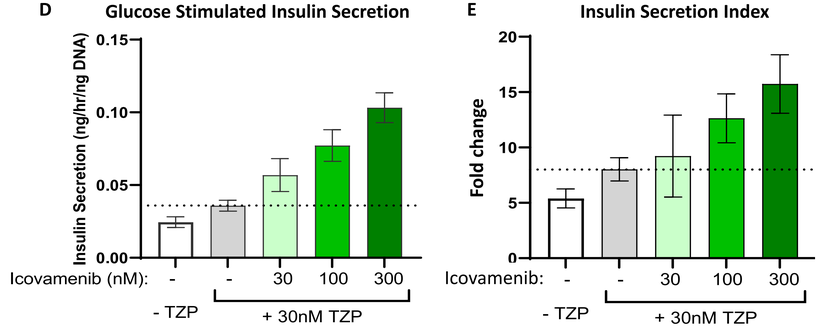


Figure 4. The effects of combination treatment with icovamenib and a GLP-1 peptide agonist on beta cell function were evaluated using human islet from non-diabetic donors. Islets were cultured ex vivo under 8mM glucose conditions for 7 days in the presence of icovamenib (30nM, 100nM or 300nM) or vehicle (DMSO). On Day 8, size-matched islets were harvested and evaluated for function using GSIS assay in the presence or absence of GLP-1 receptor agonist (GLP-1 RA). (A) Schematic of the overall experimental setup is shown. Human islets pretreated with icovamenib or vehicle (DMSO) were tested for glucose-stimulated insulin secretions in the absence (-) or presence of 200nM semaglutide (B and C), or 30 nM tirzepatide (TZP) (D and E). Data are expressed as stimulated insulin secretion normalized by total DNA (B and D) or secretion Index (stimulated insulin secretion/basal insulin secretion) (C and E). Icovamenib was not included during testing of GSIS.

Conclusions

- Icovamenib promotes controlled proliferation and enhances insulin content in beta cells in human islet microtissues ex vivo, in a glucose- and dose- dependent manner.
- Icovamenib enhanced the responsiveness of human islets to the GLP-1-based therapeutic agents, semaglutide and tirzepatide.
- Icovamenib-induced enhancement in beta cell function correlated with an increase in the expression levels of both the GLP-1 receptor as well as intracellular insulin. Both transcript and protein levels were increased.
- The overall results demonstrate synergy of the combination therapy. Additionally, the increase in beta cell mass and improved beta cell function induced by icovamenib may allow lower doses of GLP-1-based therapies to achieve glycemic targets, potentially improving tolerability of these agents.

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3. Rodriquez J. et al. Durable Glycemic Control With BMF-219 During Off-treatment Period At Week 26: A Phase 1/2 Trial Of BMF-219 In Patients With Type 2 Diabetes. Diabetes Technol Ther, 2024; 26:S2: P0064.
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, Volume 153, 155884
5. Muhammad AB et al. Menin and PRMT5 suppress GLP1 receptor transcript and PKA-mediated phosphorylation of FOXO1 and CREB. Am J Physiol Endocrinol Metab. 2017