BIOMEA CONFERENCE CALL

Preclinical Data Combining icovamenib with a GLP-1-Based Therapy & Biomea's Oral GLP-1 RA Candidate BMF-650

October 30, 2024

biomea FUSION

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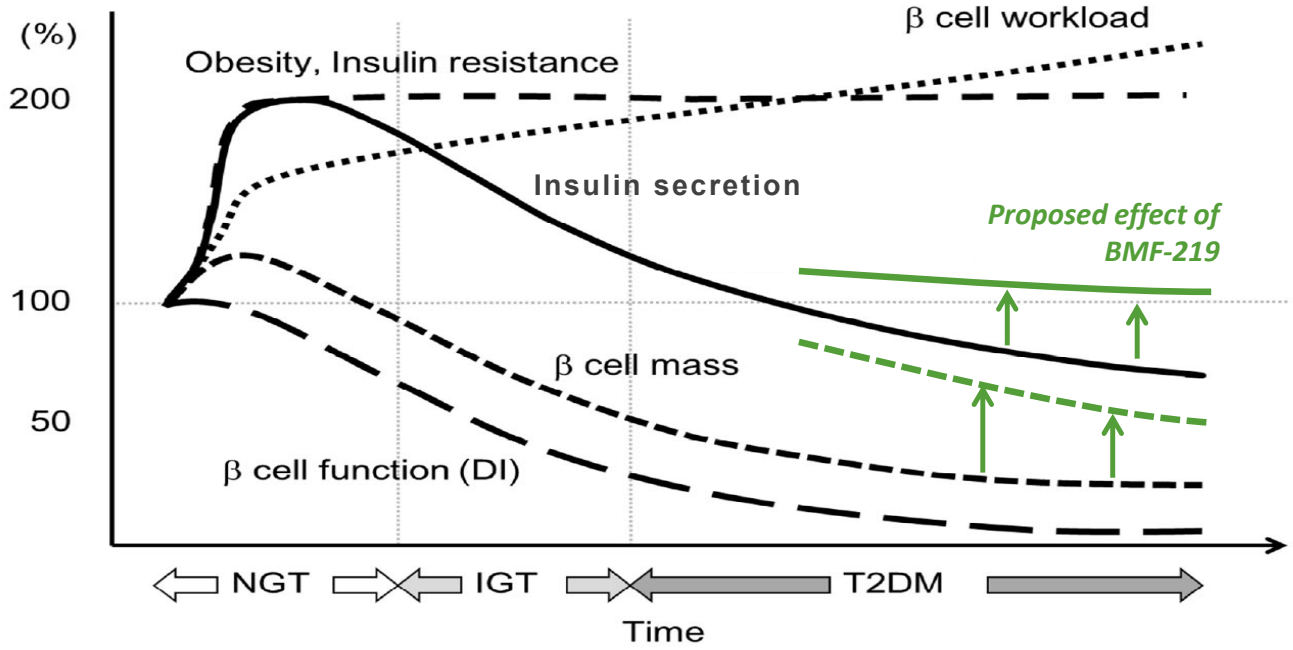
Agenda

Introduction	Ramses Erdtmann *Chief Operating Officer & Co-Founder of Biomea*
Executive Summary	Thomas Butler *Chief Executive Officer, Chairman of the Board & Co-Founder of Biomea*
GLP-1 Based Therapy Background & Overview	Juan Frias, M.D. *Chief Medical Director of Biomea*
Icovamenib in combination with GLP-1 Based Therapy	Mini Balakrishnan, Ph.D. *Executive Director of Biology, Biomea*
BMF-650 Preclinical Summary	Thorsten Kirschberg, Ph.D. *Executive Vice President of Chemistry, Biomea*
Closing Remarks	Thomas Butler *Chief Executive Officer, Chairman of the Board & Co-Founder of Biomea*

Type 2 Diabetes Progression is Driven by Loss of Beta Cell Mass



Type 1 and type 2 diabetes both result in beta cell loss and reduction in beta cell mass.

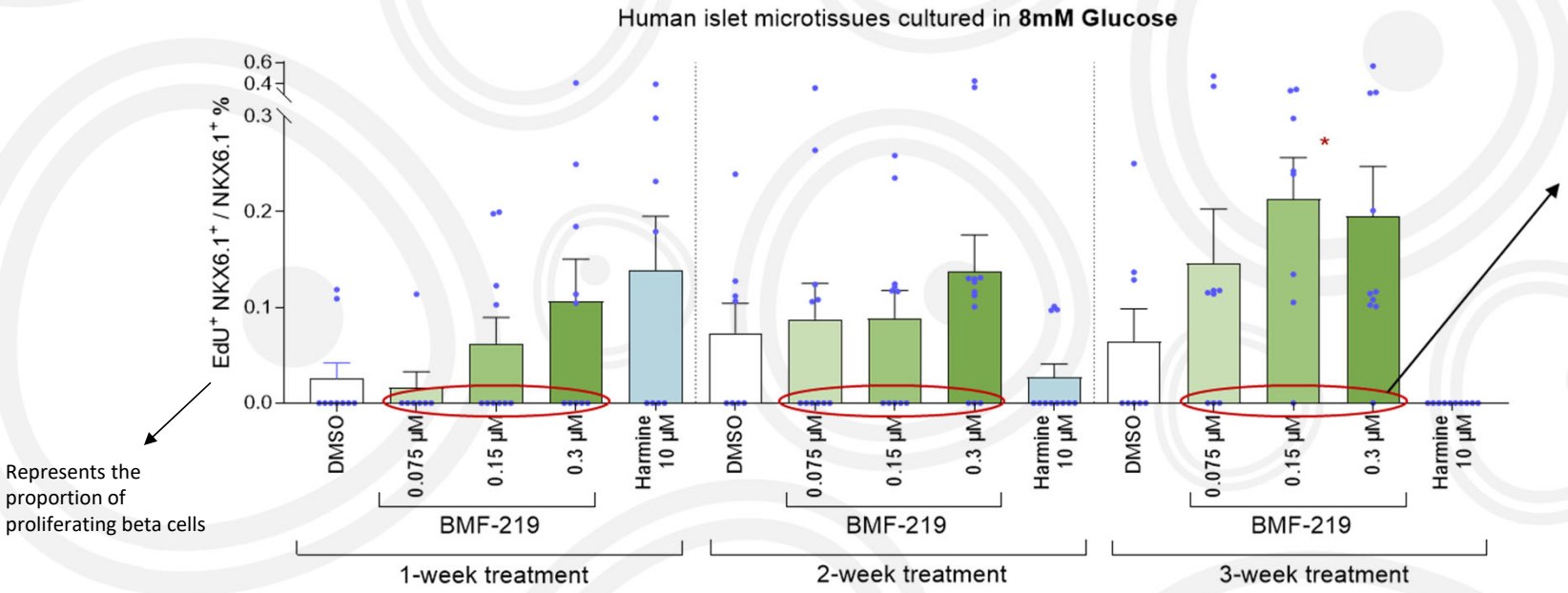
Current diabetes therapies are generally **not** observed to address the decrease in beta cell mass and beta cell health.

Normal glucose tolerance (NGT) followed by impaired glucose tolerance (IGT) followed by type 2 diabetes mellitus (T2DM) insulin resistance has been observed to lead to an increase in beta cell workload which may ultimately lead to beta cell failure and death, and the progression of type 2 diabetes.

*Int. J. Mol. Sci. 2016, 17, 744; doi:10.3390/ijms17050744

Longer Dosing and Higher Dose Concentration Resulted in Greater Proportion of Proliferating Human Islet Beta Cells

Proliferating beta cells plotted as fraction of total beta cells



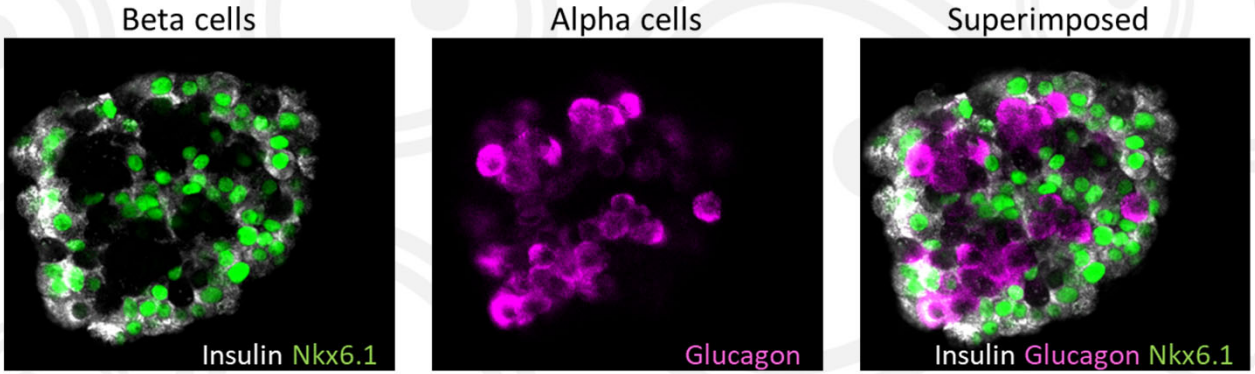
Over time, fewer islet microtissues remain, that do not have proliferating β-cells. Compare 1, 2 and 3 weeks treatment duration.

Represents the proportion of proliferating beta cells

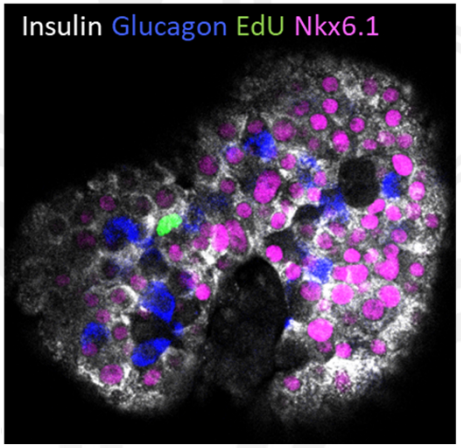
Data represent mean ±SEM of 1 donor with n = 9-12 technical replicates.
One-way ANOVA with Dunnett's post hoc test rel. to DMSO control. *p < 0.05, **p < 0.01, ***p < 0.001

Application of Advanced Confocal Microscopy to Study the Impact of Therapeutics on Human Beta Cell Health and Function

- An optical cross-section through an intact human islet, showing distribution of alpha and beta cells.



- Imaging tools aid in studying physiological events within the islet cells and the effects of drug treatment, e.g. quantifying compound treatment induced effects on beta cell proliferation in whole human islets.



EdU positive = Proliferating cell

Icovamenib (BMF-219) in Combination with a GLP-1 Based Therapy – An Overview of Pre-Clinical Findings

Menin Suppresses GLP-1 Receptor Transcript Levels

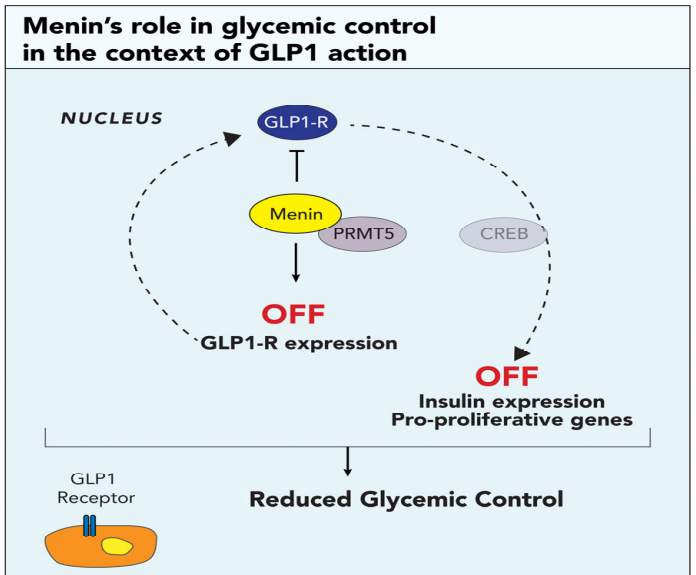


Fig 1. Menin, in complex with PRMT5, is a suppressor of GLP1-R expression, leading to reduced CREB phosphorylation and GLP1 pathway function. Decreased GLP1-R expression reduces insulin secretion and expression of beta cell proliferative genes leading to blunted glycemic control.

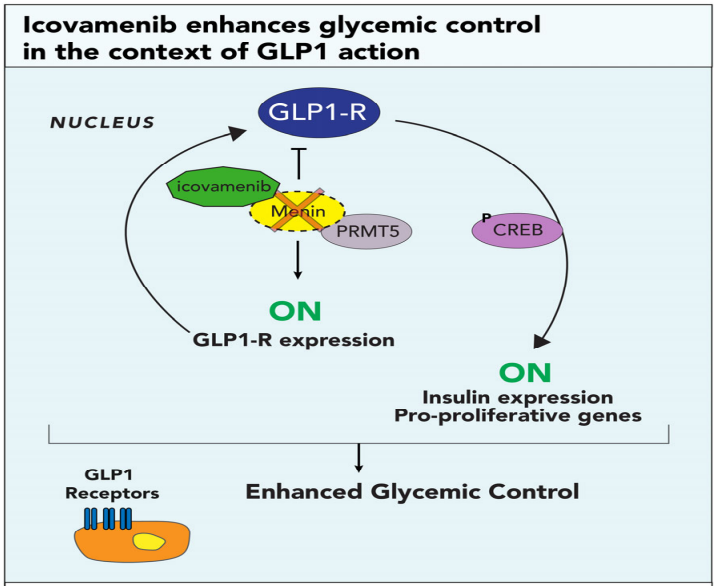
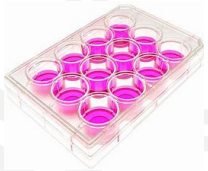


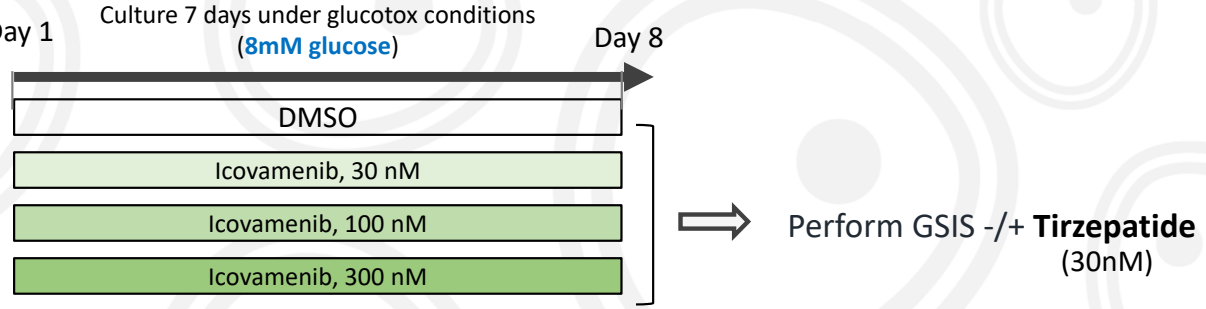
Fig 2. Menin, in complex with PRMT5, is a suppressor of GLP1-R expression, leading to reduced CREB phosphorylation and GLP1 pathway function. Decreased GLP1-R expression reduces insulin secretion and expression of beta cell proliferative genes leading to blunted glycemic control. Icovamenib selectively and covalently inhibits menin, releasing its repression of GLP1-R expression and boosting CREB phosphorylation. Elevated GLP1 expression in the absence of menin leads to increased insulin production and promotes beta cell proliferation gene activation, enhancing glycemic control.

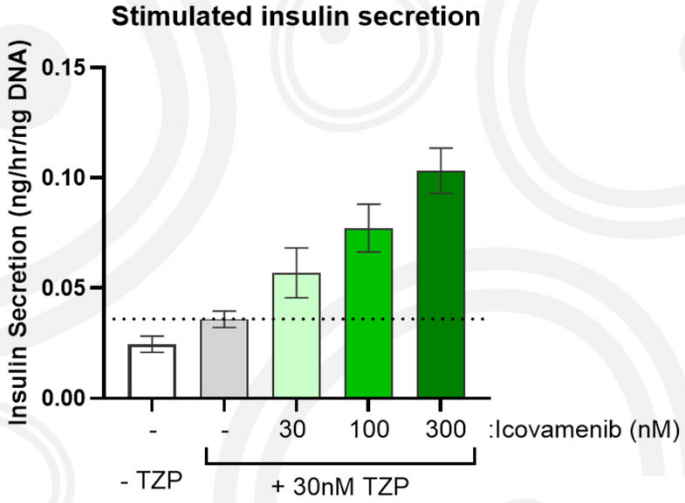
Combination Treatment: icovamenib Enhanced Responsiveness of Islets to GLP-1/GIP Dual Receptor Agonist - Tirzepatide

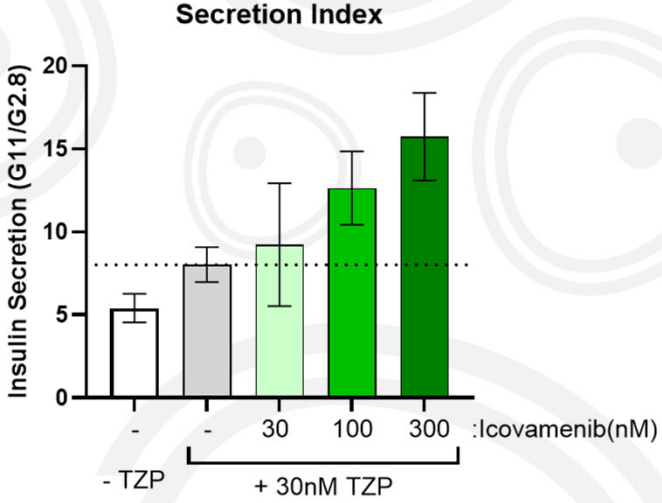
Cadaver derived human islets



Non-diabetic donor:
38-year white male, BMI: 29.2, HbA1C 5.2%

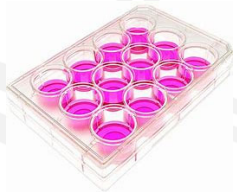






Combination Treatment: icovamenib Enhanced Responsiveness of Islets to GLP-1 Receptor Agonist - Semaglutide

Cadaver derived human islets

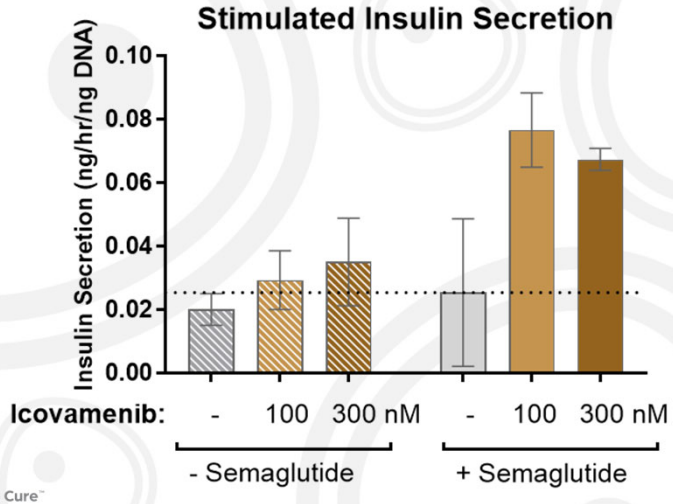


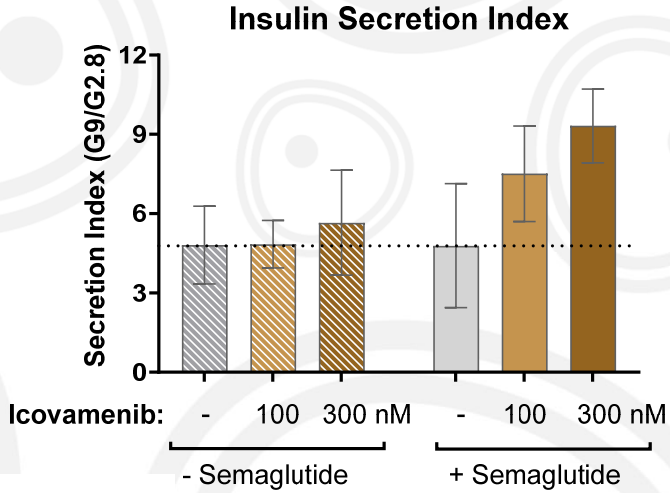
Non-diabetic donor:
41-year Hispanic male, BMI: 27.8, HbA1c 5.3%

Day 1 — Culture 7 days under glucotox conditions (**8mM glucose**) — Day 8

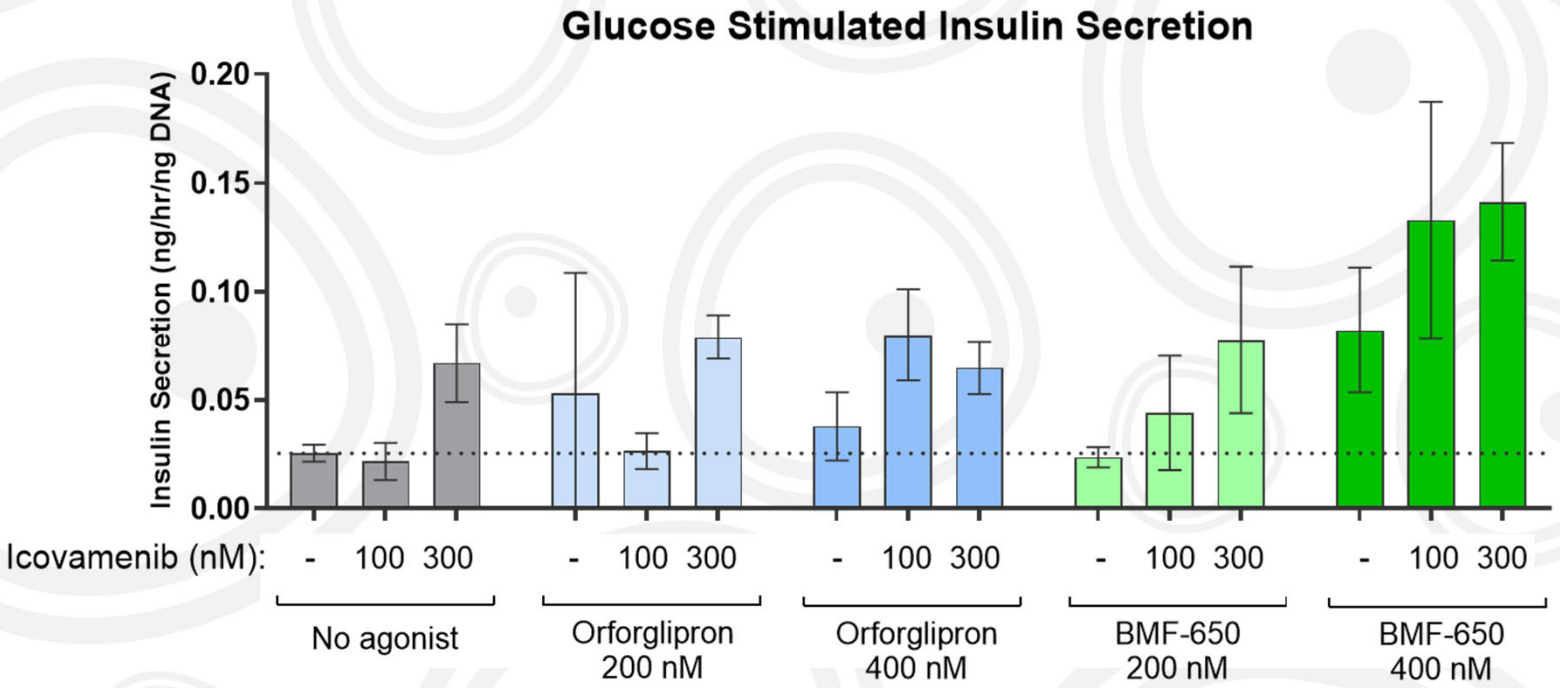
- DMSO
- Icovamenib, 100 nM
- Icovamenib, 300 nM

⇨ Perform GSIS -/+ **Semaglutide** (200nM)





Combination Treatment: icovamenib Enhanced Responsiveness of Islets to Small Molecule GLP-1 Receptor Agonists - Orforglipron and BMF-650



New Treatment Potential in Diabetes and for Obesity

Combining Covalent Binding Menin Inhibitor icovamenib with GLP-1 Based Therapy

Potential benefits of using *icovamenib together with approved GLP-1 based therapeutics:*

- Lower dosing requirements of existing GLP-1 based therapy
- Improved tolerability
- Improved adherence
- Improved therapeutic window
- Improved initial responsiveness
- Greater patient persistence and treatment results with GLP-1 based therapeutics

Next steps in Biomea's clinical development:

- COVALENT-211 (icovamenib in combination with GLP-1 based therapeutics)

BMF-650 – An Investigational, Next-Generation, Oral Small Molecule GLP-1 Receptor Agonist

Drive for a Greater "Therapeutic Window" with our Next-Generation GLP-1 Receptor Agonist – BMF-650

Attributes of Biomea's GLP-1 Receptor Agonist Development Candidate:

- Less PK variability
- Greater bioavailability
- Greater protein binding
- Less side effects

Why a greater "Therapeutic Window"?

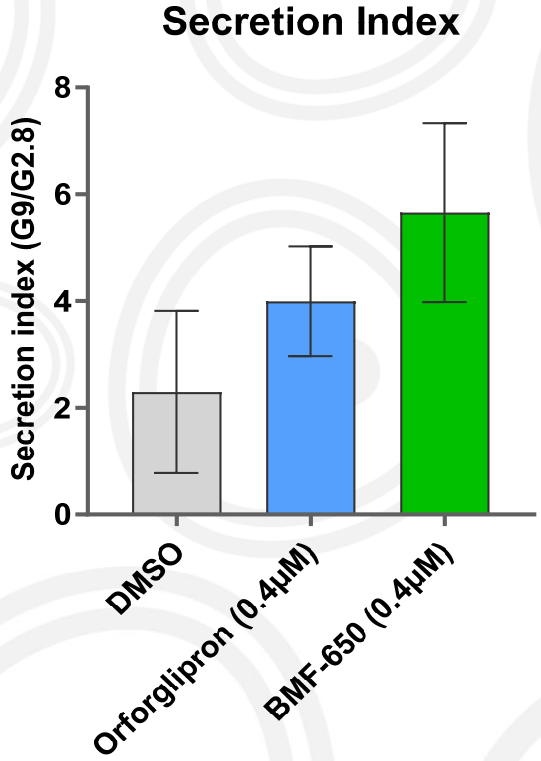
Only 3 of 10 patients in the real-world setting are staying on a GLP-1 based therapy after 12 months

BMF-650 Showed Favorable In Vitro On-Target Activity and Off-Target Selectivity

	GLP-1 human EC_{50}	β-arrestin1 EC_{50}	β-arrestin2 EC_{50}
BMF-650	< 5 nM	> 10 μM	> 10 μM
orforglipron	< 5 nM	> 10 μM	> 10 μM

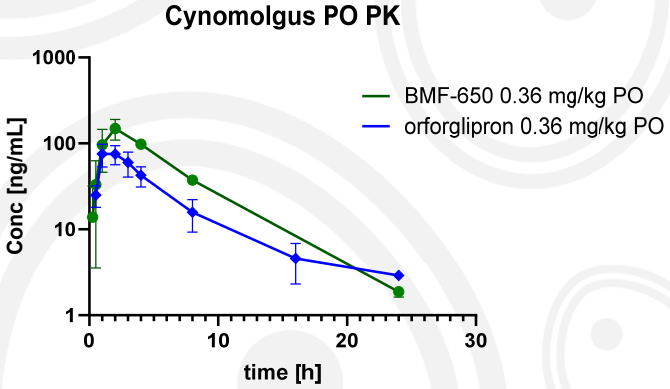
- Good potency on-target
- No off-target concerns from counter-screening assays

BMF-650 Showed Improved Glucose-Stimulated Insulin Secretion in Ex Vivo Cultured Healthy Human Islet Experiment

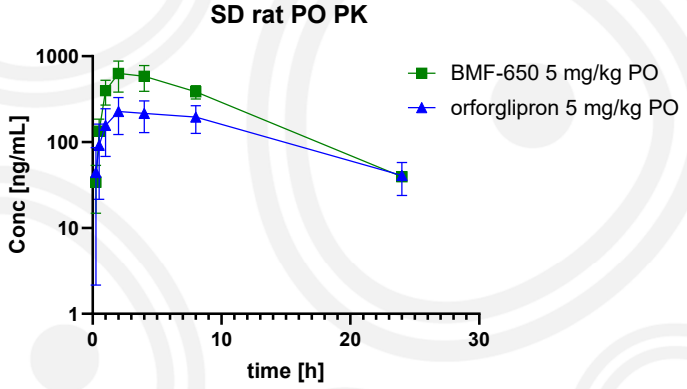


BMF-650 demonstrated improved insulin secretion vs orforglipron

Pharmacokinetics of BMF-650 Showed Very Good Non-Human Primate and Rodent Bioavailability with Low Inter-Individual Variability



Compound	cynomolgus PO	$T_{1/2}$ (h)	%F
BMF-650	**0.36 mg/kg**	**3.66**	**54.0**
orforglipron	**0.36 mg/kg**	**3.70**	**29.4**



Compound	rat PO	$T_{1/2}$ (h)	%F
BMF-650	**5 mg/kg**	**5.14**	**32.6**
orforglipron	**5 mg/kg**	**7.44**	**11.2**

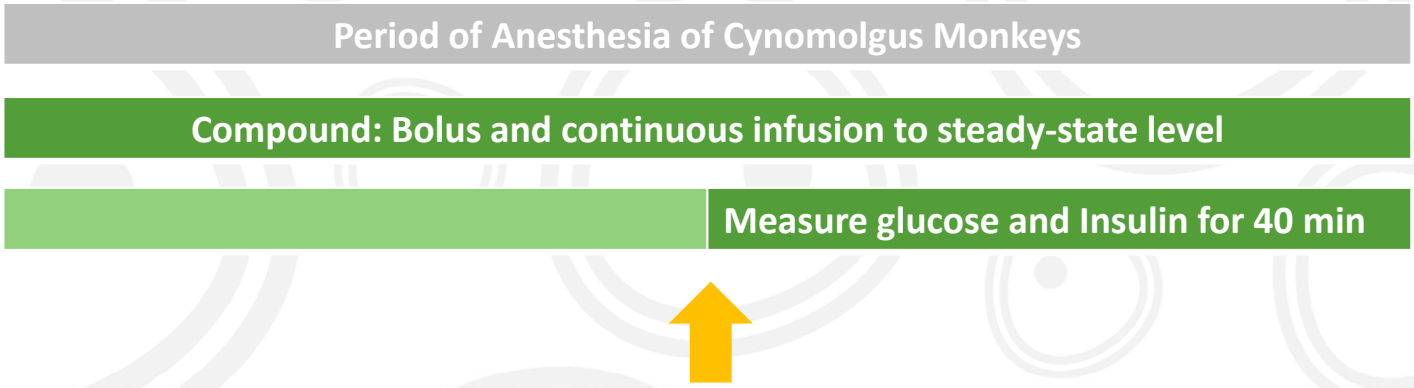
Projected Human Dose for BMF-650 Similar Among the Oral Agents

Dosages Used in Cynomolgus Monkeys are Species Dependent and Specific to Properties of Compounds

	Orforglipron Eli Lilly	BMF-650 Biomea	GSBR-1290 Structure Therapeutics	CT-996 Roche (Carmot)
Doses tested in cynomolgus monkeys to address food intake	HD LD: 0.1 & 0.05 mg/kg	2 and 10 mg/kg	2 to 10 mg/kg	3 to 30 mg/kg
Clinical titration target	45 mg	100 mg (projected)	120 mg	120 mg

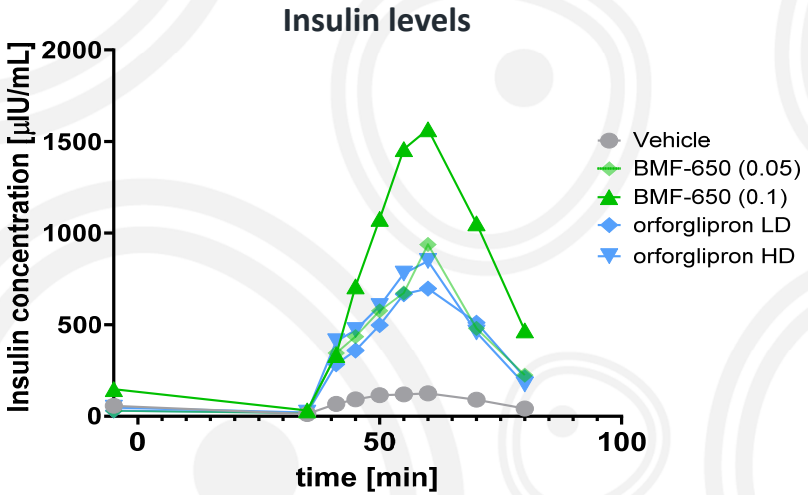
Primary Evaluation of Preclinical Activity
Set up of Intravenous Glucose Tolerance Test in Cynomolgus Monkeys

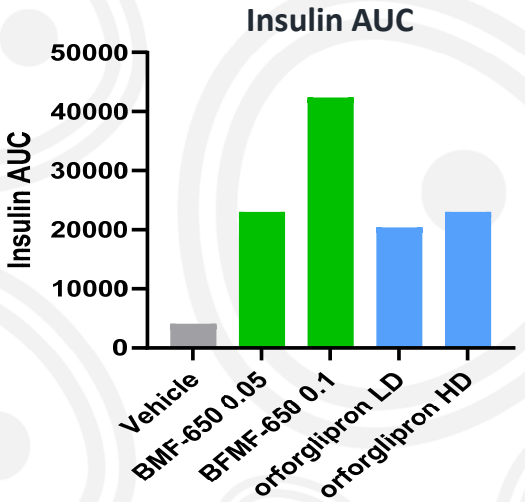
Cynomolgus monkeys (n=4) were anesthetized. Compounds were administered via IV route. Glucose was infused. Blood Glucose and Insulin levels were measured during the following 40 minutes window.



Study designed to capture both glucose lowering and insulin release properties

BMF-650 Potentiated Glucose-Stimulated Insulin Secretion in Cynomolgus Monkeys





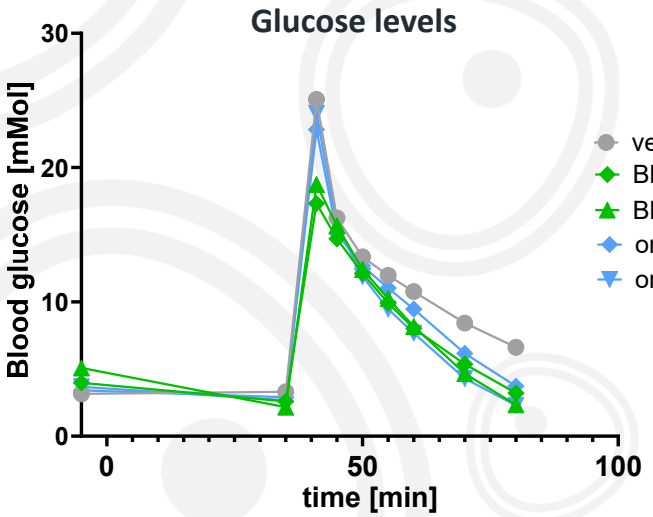
	Vehicle	BMF-650 0.05mg/kg	BMF-650 0.1 mg/kg	orforglipron Low dose (lit)*	orforglipron High dose (lit)*
AUC Mean (N=4)	4021	22930	42262	20304	22922
Insulin improvement	0	470%	951%	405%	470%

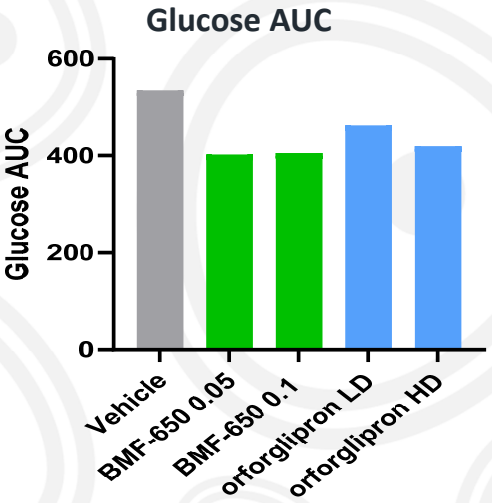
*PNAS November 24, 2020. vol. 117 no. 47 29959-29967

High and low dosing levels for orforglipron based on publications: 0.0018 and 0.0054 mg/kg

High levels of insulin release observed with small molecule GLP-1 R agonists

BMF-650 Potentiated Blood Glucose Reduction in Cynomolgus Monkeys





	Vehicle	BMF-650 0.05mg/kg	BMF-650 0.1mg/kg	orforglipron Low dose (lit)*	orforglipron high dose (lit)*
AUC Mean (N=4)	533	401	404	461	418
Glucose lowering	0	-25%	-24%	-14%	-22%

*PNAS November 24, 2020. vol. 117 no. 47 29959-29967

High and low dosing levels for orforglipron based on publications: 0.0018 and 0.0054 mg/kg

Good glucose control observed with small molecule GLP-1 R agonists

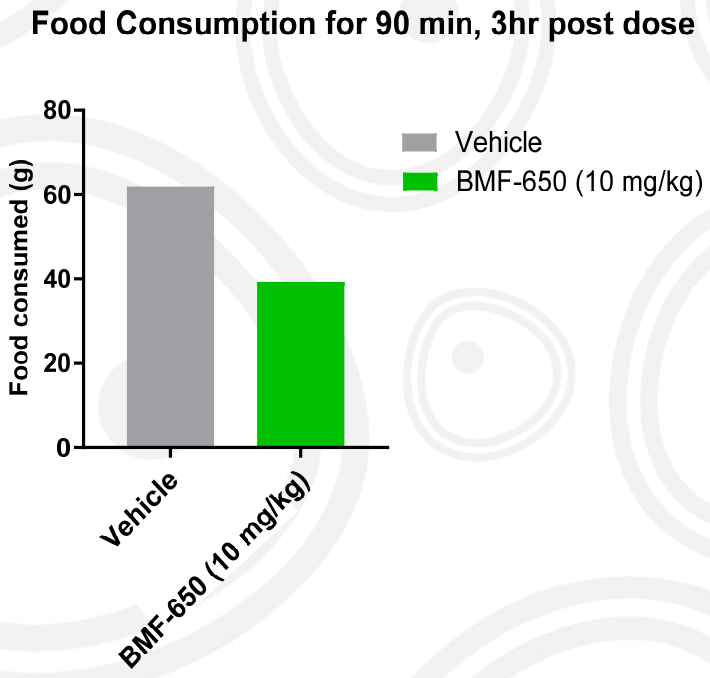
Primary Evaluation of Preclinical Activity
Set up of Appetite Suppression Test in Cynomolgus Monkeys

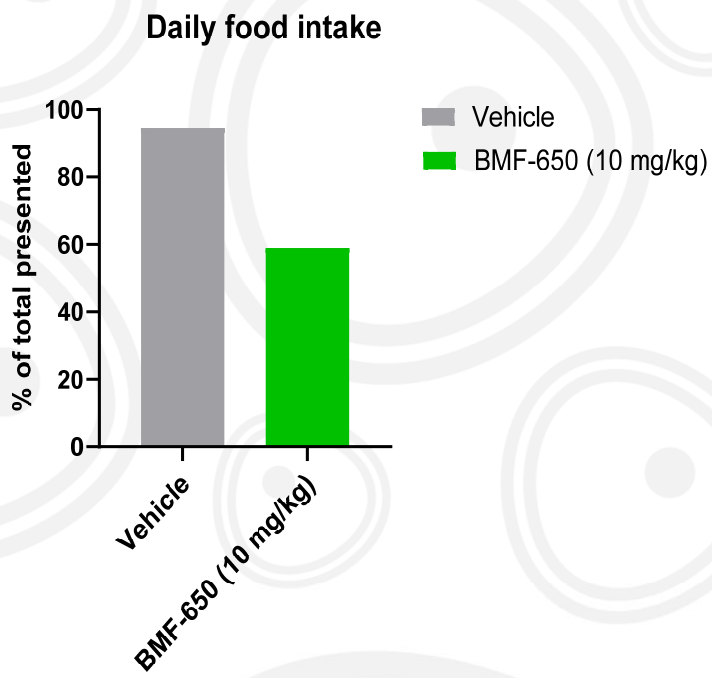
- Fasted monkeys (n=4) were dosed orally (PO) with compound. Food was presented starting at 3 hours post dose. Recorded food intake for time window 3 hours to 4.5 hours and the whole day.
- Design of study as multiday of active drug and multiday of washout

Study designed to capture both peak and daily food intake reduction.

BMF-650 Appetite Suppression in Cynomolgus Monkeys

Average of First 90 Minute Window and Average for All Six Days of the Experiment





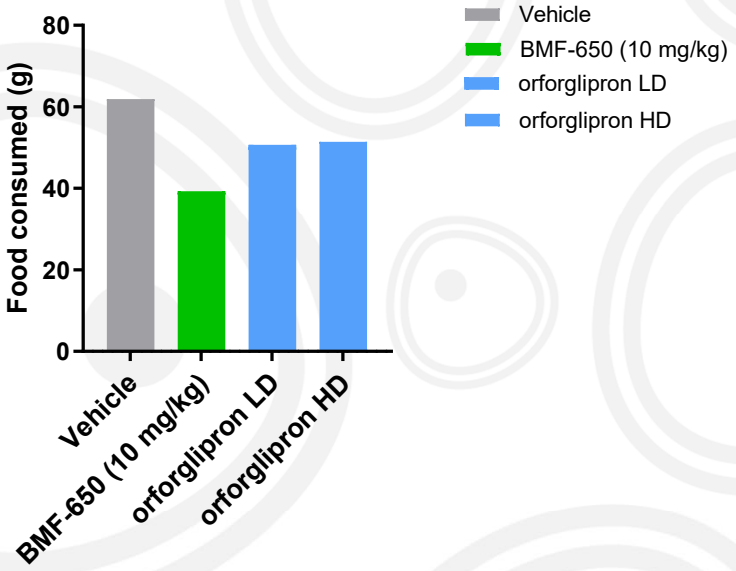
Food consumption tested daily in cynomolgus monkeys (n=4)

BMF-650 demonstrated good appetite suppression over 6 days

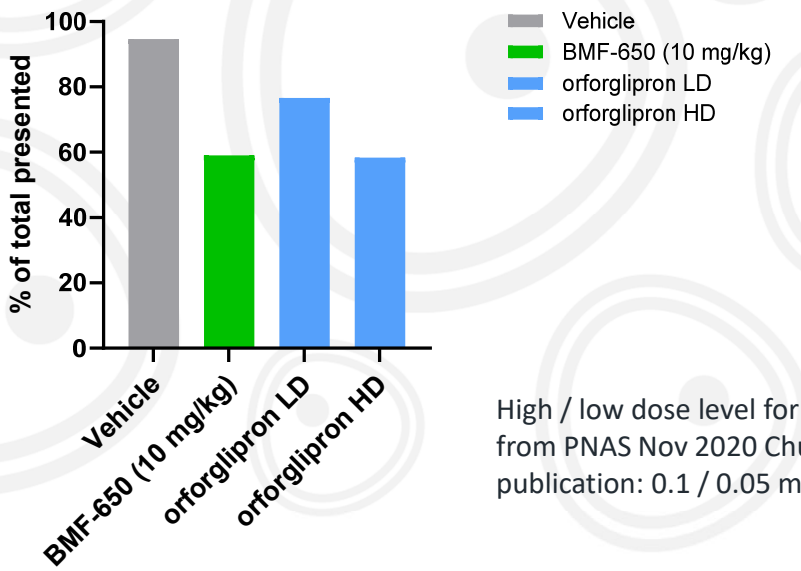
BMF-650 Appetite Suppression in Cynomolgus Monkeys Compares Well to Orforglipron

Average of First 90 Minute Window and Average for All Six Days of the Experiment

Food Consumption for 90 min, 3hr post dose



Daily food intake



High / low dose level for orforglipron from PNAS Nov 2020 Chugai/Lilly publication: 0.1 / 0.05 mg/kg

Food consumption tested daily in cynomolgus monkeys (n=4)

BMF-650 demonstrated good appetite suppression over 6 days and compares well to orforglipron

Projected Timeline for BMF-650 with IND Filing Anticipated in 2H 2025

Program was placed on a timeline targeting IND submission in 2H 2025
Development plan for obesity and type 2 diabetes

THANK YOU

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