

Biomea Fusion Corporate Presentation

Q4 2026

biomea FUSION™

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Transforming diabetes and obesity with novel oral medicines

Biomea Fusion founded in 2017 (public in 2021; NASDAQ: BMEA)
Clinical-stage company advancing two differentiated metabolic investigative programs

ICOVAMENIB

First-in-class oral small molecule for the treatment of diabetes targeting menin - the natural control switch to beta cell restoration in Type 1 and Type 2 Diabetes

Restores functional beta-cell mass and improve endogenous insulin production

BMF-650

Next-generation oral GLP-1 receptor agonist

Designed for consistent exposure, higher bioavailability and improved tolerability with scalable weight reduction

1. www.breakthrought1d.org Scherer et al., Scientific Reports, 2020; 2. Nichols et al., Diabetes Care, 2015; 3.UKPDS Group. Lancet, 1998; 4. Prime Therapeutics & Magellan Rx Management, 2023

Investment Thesis

Biomea is building a leading metabolic disease company with two differentiated programs and multiple near-term catalysts

- First-in-class beta-cell restorative therapy targeting menin in development for diabetes
- Potential best-in-class Type 1 & 2 diabetes agent
- Next-generation oral GLP-1 receptor agonist (BMF-650) with positive Phase I weight loss results and favorable GI tolerability
- Multiple Phase II readouts over the next 12 months
- Experienced leadership team with a clear vision and execution plan
- Cash runway through key upcoming value inflection read outs

The Opportunity

Growing market with large unmet need

Diabetes

>38M

People living with diabetes in U.S.[1]

>35M

People with T2D in U.S.[2]

1:3

People in U.S. with T2D using Insulin[3]

25%

Of U.S. healthcare dollars go to treat those diabetes[4]



Obesity

>190M

People in U.S. are obese or overweight[5]

100M +

People in U.S. are obese[5]

5M+

People in U.S. discontinue GLP-1[6]

Large unmet need

for durable, well-tolerated therapies

Addressing root biology has the potential to address patient outcomes

1. CDC, Natl. Diabetes Stat. Rep., 2022
2. ADA, Standards of Care in Diabetes, Diabetes Care, 2024
3. Li J Diabetes Complications 2012;26(1):17-22
4. CDC Health and Economic Benefits of Diabetes Interventions
5. CDC National Health and Nutrition Examination Survey
6. IQVIA prescription data

Icovamenib milestones – overview next 18 months

Icovamenib in Type 1 Diabetes

PLANNED T1D Investigator Sponsored Study | Phase 2 Study | n=40 | Enrollment anticipated to start 1Q 27

PLANNED T1D Biomea Sponsored Study | Phase 2 Study | n=36 | Enrollment anticipated to start 1Q 27

T1D
FDA End of Phase 2 Meeting and Phase 3 Initiation

Icovamenib in Obesity

LEICESTER DIABETES CENTER in Obesity | Phase 2 Study | n=64 | Topline data anticipated: End of 27

Icovamenib in Type 2 Diabetes

COVALENT-211 in insulin deficient T2D | Phase 2 Study | n=64 | Fully enrolled | Topline data anticipated: 1Q 27

Secondary Endpoint: HbA1c change at Week 52

COVALENT-212 in GLP-1 uncontrolled T2D | Phase 2 Study | n=60 | Start: 2Q 26 | Enrollment ongoing | Topline data anticipated: 2Q 27

Secondary Endpoint: HbA1c change at Week 52

T2D
FDA End of Phase 2 Meeting and Phase 3 Initiation

4Q 2026 | 1Q 2027 | 2Q 2027 | 3Q 2027 | 4Q 2027 | 2028

Current Cash Position
Runway into 2Q 2027



ICOVAMENIB

First-in-class menin targeting agent in development for the treatment of diabetes - TYPE 1 DIABETES

biomea FUSION™

Opportunity - Type 1 Diabetes

Biomea is aiming to advance icovamenib to be the first fully approved therapy for Type 1 Diabetes patients
New Phase II Study planned for initiation in 4Q 2026

- Icovamenib is the first-in-class beta cell restorative therapy targeting menin in development in diabetes
- Icovamenib is potentially the best-in-class oral agent addressing diabetes at the root cause level – the depleted pool of beta cells
- Preclinical on target evidence of direct impact on beta cells, their proliferation and insulin productivity
- Over 500 patients dosed to date with icovamenib, demonstrating with the effective dosing scheme a safety profile comparable to placebo
- Two Phase II Type 1 diabetes study designed with world-renown Type 1 Investigator Team, initiation planned for 1Q 27 with first 6 month data expected before year-end 27

Type 1 Diabetes – Opportunity

Established market with large unmet need. Patients suffer from loss of beta cells and require the use of exogenous insulin - Type 1 diabetes untreated is deadly.

Type 1 Diabetes in the US and WW

US>2M WW>10M

People living with Type 1 diabetes [1]

of approved Agents

one

Teplizumab is approved in Stage 2 of T1D and has an accelerated approval in Stage 3 for children 8-17 years old, contingent on confirmatory evidence of clinical benefit.

Investigational Therapies in Development

Focus primarily on immune modulation and preservation

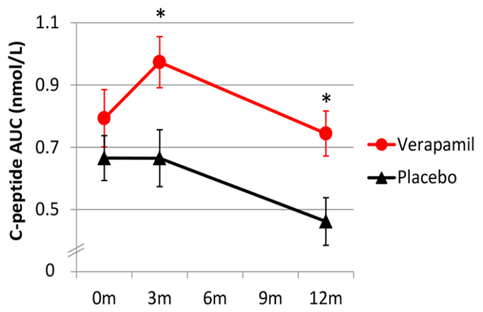
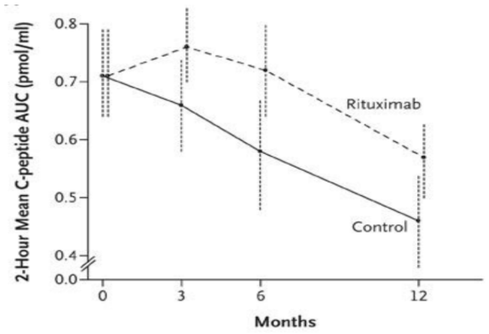


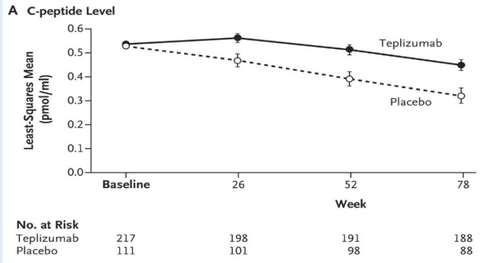
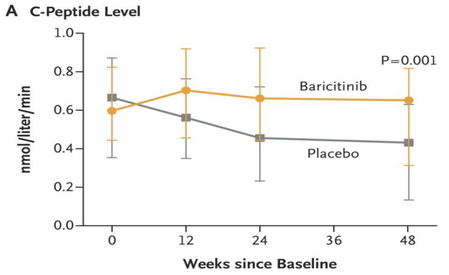
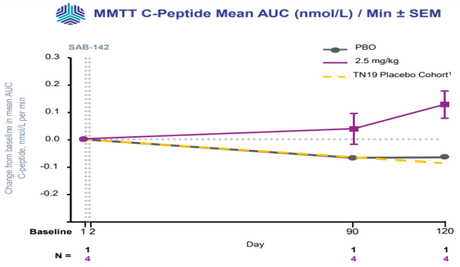
- Immune modulation to slow autoimmune destruction[1]
- Preserve remaining beta-cell function
- Mose effective when started shortly after diagnosis[2] *(<90 days, new onset T1D)*
- Slows decline in C-peptide over time[3]

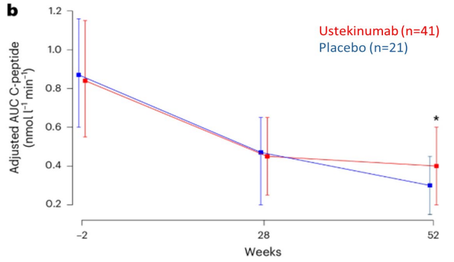
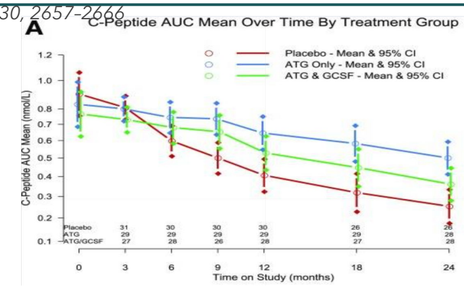
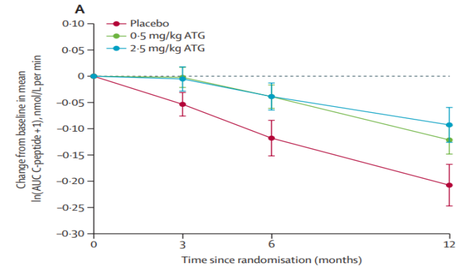
GOAL: Slow disease progression

1. CDC, Natl. Diabetes Stat. Rep., 2022
2. ADA, Standards of Care in Diabetes, Diabetes Care, 2024
3. Li J Diabetes Complications 2012;26(1):17-22

Therapies in development for Type 1 Diabetes aim to slow the disease progression - decline of C-peptide

DRUG	Mean C-PEPTIDE AUC VS PLACEBO
Verapamil	 *Nature. 2018 Aug;24(8):1108-1112*
Rituximab	 *NEJM. 2009 361:2143–2152*

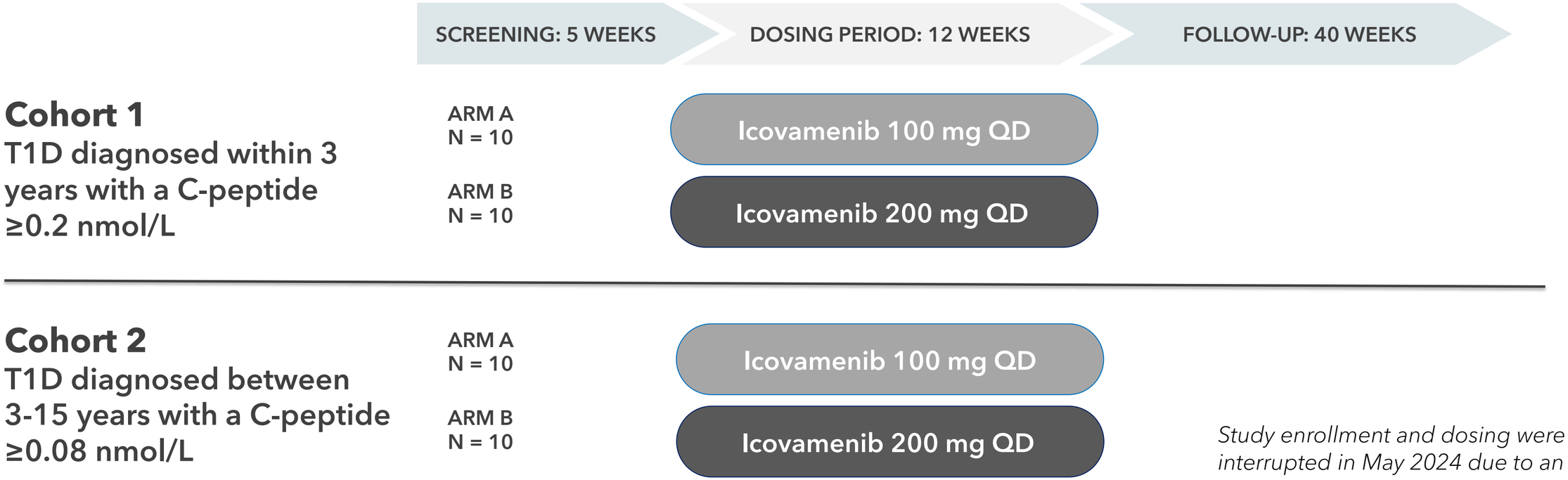
DRUG	Mean C-PEPTIDE AUC VS PLACEBO
Teplizumab (Tzield)	 *ESPE Yearbook of Paediatric Endocrinology (2024) 21 10.2*
Baricitinib	 *N Engl J Med 2023;389:2140-2150*
SAB-142	 *SAB Bio website corporate presentation (March 10, 2026) https://www.sab.bio/*

DRUG	Mean C-PEPTIDE AUC VS PLACEBO
Ustekinumab	 *Nature Medicine 2024 vol 30, 2657–2666*
ATG (TrialNet)	 *Diabetes Care 2018 Jul 16;41(9):1917–1925*
MELD-ATG	 *Lancet 2025 Sep 27;406(10510):1375-1388*

**Ladarixin and Diamyd,* *both Immune modulating, not mentioned here as they demonstrated no meaningful difference compared to placebo*

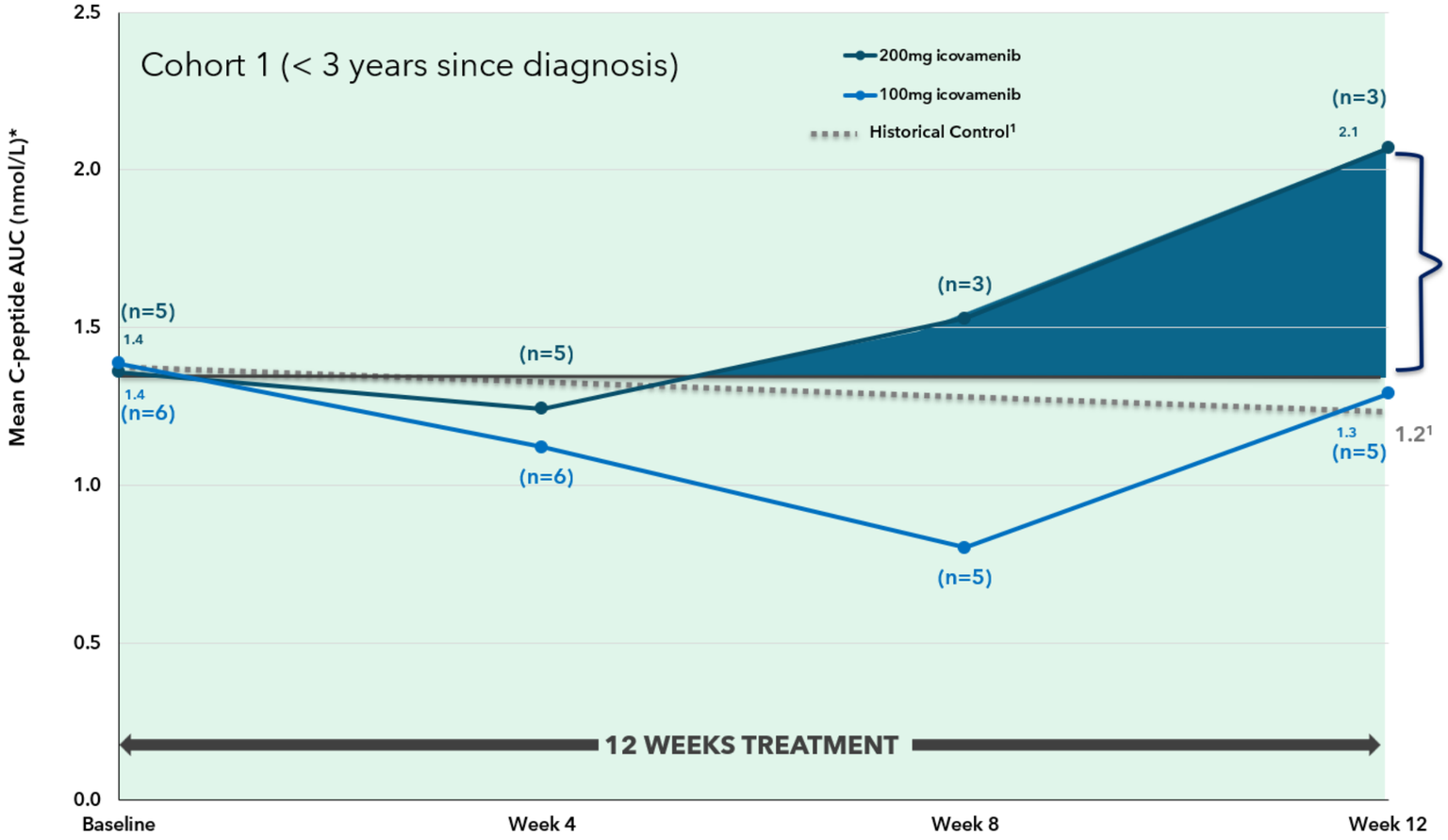
All-comers Study COVALENT-112 - completed

COVALENT-112 (NCT06152042) was a Phase 2 trial designed to examine beta cell function (as measured by C-peptide change and the change of exogenous insulin usage) and glucose and lipid metabolism in participants with T1D treated with standard of care insulin and icovamenib.



Study enrollment and dosing were interrupted in May 2024 due to an FDA clinical hold, which was subsequently resolved, but reduced the number of patients enrolled and followed through to the 52-week readout.

Compelling Signal of Beta Cell Restoration in T1D with Icovamenib



- 52% Mean increase in C-Peptide AUC* at Week 12
- Durable effect through Week 52 after only 12 weeks of dosing
- Greatest response in patients ≤3 years since diagnosis
- No Systemic immune activation
- Favorable safety profile through 52 weeks

Data represents post-hoc analysis of patients who received per statistical analysis plan, 80% of planned doses

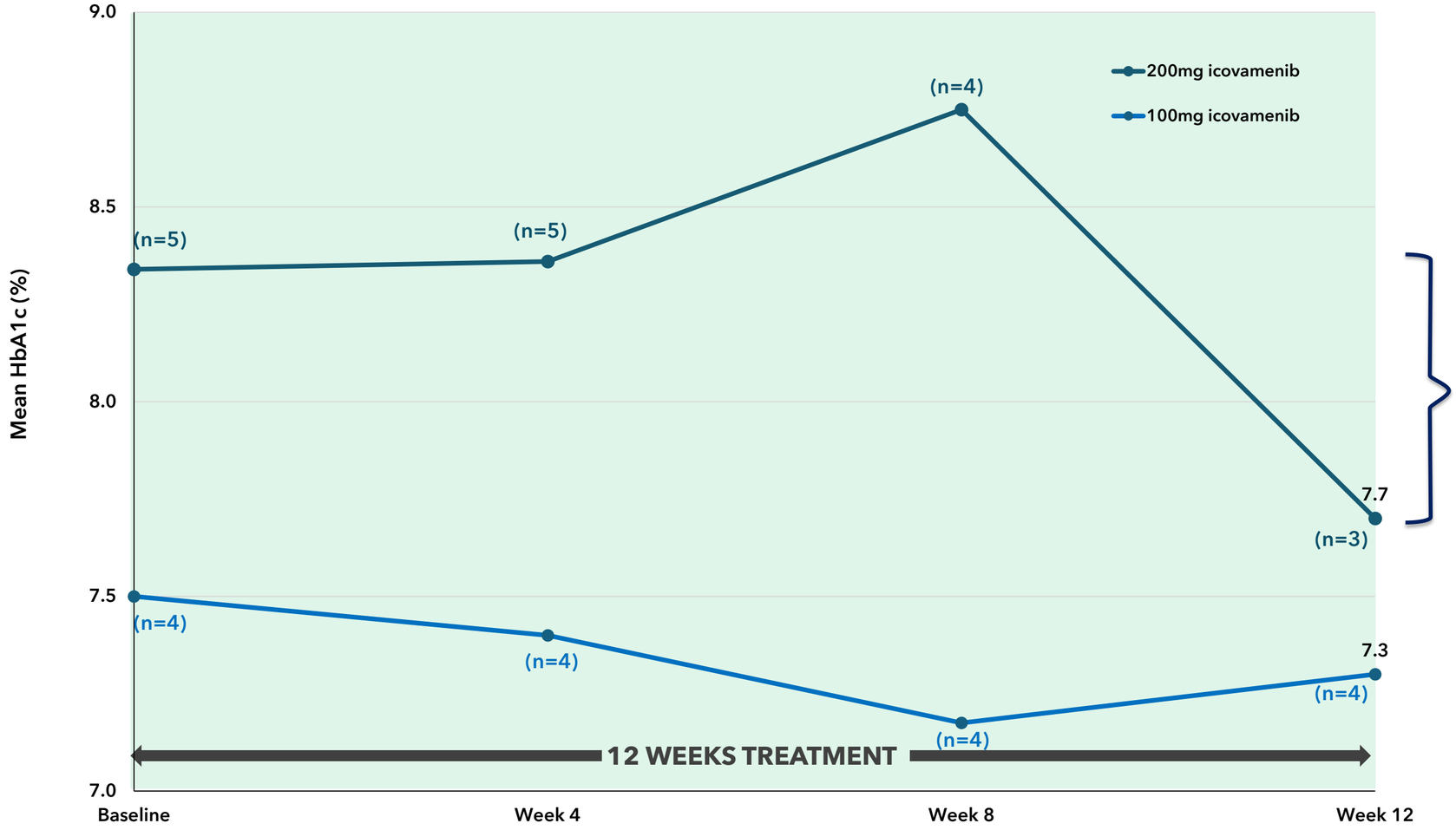
[1] Historical control in T1D patients (n=1549) C-peptide declining over first 7 years at 47% yearly. Diabetes Care. 2018 Jun 7;41(7):1486–1492

** 4-hour Mixed Meal Tolerance Test (MMTT)*

Frias, J. (ADA) Diabetes 2026; 75 (Supplement_1): 2858–LB.

ICOVAMENIB in TYPE 1 DIABETES

0.6% mean reduction in HbA1c during the 12 weeks treatment period of icovamenib



0.6% reduction in mean HbA1c from baseline

Frias, J. (ADA) Diabetes 2026; 75 (Supplement_1): 2858–LB.

ICOVAMENIB in TYPE 1 DIABETES

Cytokine profiling of cohort 1 (<3 years since T1D diagnosis) participants receiving 200mg icovamenib

	Week 12			Week 26			Week 52		
	pg/mL	change	status	pg/mL	change	status	pg/mL	change	status
Il-1β	1.07	0.40	Non-Inflammatory	1.00	0.27	Non-Inflammatory	0.70	-0.27	Non-Inflammatory
IL-2	3.43	-0.83	Non-Inflammatory	3.57	-1.20	Non-Inflammatory	1.20	-3.23	Non-Inflammatory
IL-6	3.27	0.70	Non-Inflammatory	0.53	-1.70	Non-Inflammatory	0.53	-1.70	Non-Inflammatory
IL-8	6.57	0.77	Non-Inflammatory	7.17	-0.07	Non-Inflammatory	5.37	-1.18	Non-Inflammatory
IL-10	1.30	-0.03	Non-Inflammatory	1.33	0.00	Non-Inflammatory	1.30	-0.03	Non-Inflammatory
IFN-γ	-	-	Non-Inflammatory	-	-	Non-Inflammatory	-	-	Non-Inflammatory
TNF-α	7.53	-0.17	Non-Inflammatory	7.73	-1.35	Non-Inflammatory	4.07	-5.33	Non-Inflammatory

Mean values were assessed for all patients for each cytokine (n=3) relative to baseline.

- All cytokines remained classified as Non-Inflammatory from baseline through Week 52, indicating no evidence of systemic immune activation in participants receiving 200 mg icovamenib
- Small Week 12 increases in IL-1β, IL-6, and IL-8 were transient and not associated with increases in IL-2 or TNF-α
- By Week 52, most pro-inflammatory cytokines were stable or decreased from baseline
- **The increase in C-peptide was not accompanied by a measurable systemic inflammatory cytokine response but rather led to a stabilization and mild reduction of inflammatory markers over time**

Frias, J. (ADA) Diabetes 2026; 75 (Supplement_1): 2858-LB.

Favorable 52-week safety profile

	Cohort 1			Cohort 2		
	Arm A 100 mg QD (N = 8)	Arm B 200 mg QD (N = 9)	Cohort 1 Total (N = 17)	Arm A 100 mg QD (N = 9)	Arm B 200 mg QD (N = 10)	Cohort 2 Total (N = 19)
Patients with ≥1 TEAE, N (%)	3 (38)	0 (0)	3 (18)	1 (11)	3 (30)	4 (21)
Treatment-Related SAEs, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs*, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Treatment Discontinuation due to TEAE, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Study Discontinuation due to TEAE, N (%)	0	0	0	0	0	0
Deaths, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea, N (%)	1 (13)	0	1 (6)	1 (11)	0	1 (5)
Nausea, N (%)	1 (13)	1 (11)	2 (12)	1 (11)	1 (10)	2 (11)
Hyperglycemia, N (%)	0	0	0	0	1 (10)	1 (5)
Headache, N (%)	1 (13)	0	1 (6)	0	1 (10)	1 (5)
AST/ALT increase, N (%)	3 (38	2 (22)	5 (29)	1 (11)	7 (70)	8 (42)
Resolution of ALT/AST w/o interruption in study treatment, %	100	100	100	100	80	90

Frias, J. (ADA) Diabetes 2026; 75 (Supplement_1): 2858-LB.

Potential to Expand the Treatable Population in Type 1 Diabetes

Approved Therapy in T1D TEPLIZUMAB (Tzield®)	Key Characterization	ICOVAMENIB
Newly diagnosed Stage 3 T1D	Eligible Population	Newly diagnosed and established T1D with residual beta cell function
0-90 days from diagnosis	Time From Diagnosis	0-3+ years demonstrated clinically
Pediatric only (8 to 17 years)	Age	Adult T1D patients at first with pediatric to follow in development
Immune modulation	Mechanism of Action	Beta cell restoration / preservation
Two 12-day infusion 26 weeks apart	Treatment	Oral, once daily
Delay insulin dependence	Goal	Restore endogenous insulin secretion and preserve beta cell function

A SUBSTANTIALLY LARGER TREATABLE PATIENT POPULATION

Icovamenib potentially expands the treatment window and the patient population by more than 10-fold

CLINICAL DEVELOPMENT TIMELINE

2026
- New Type 1 Diabetes Study Initiation

2027
- Enrollment completion (n=36)
- Phase 2 data readout

2028
- End of Phase II FDA meeting
- Fast Track/ Break-through potential
- Potential to initiate registrational study in broader T1D

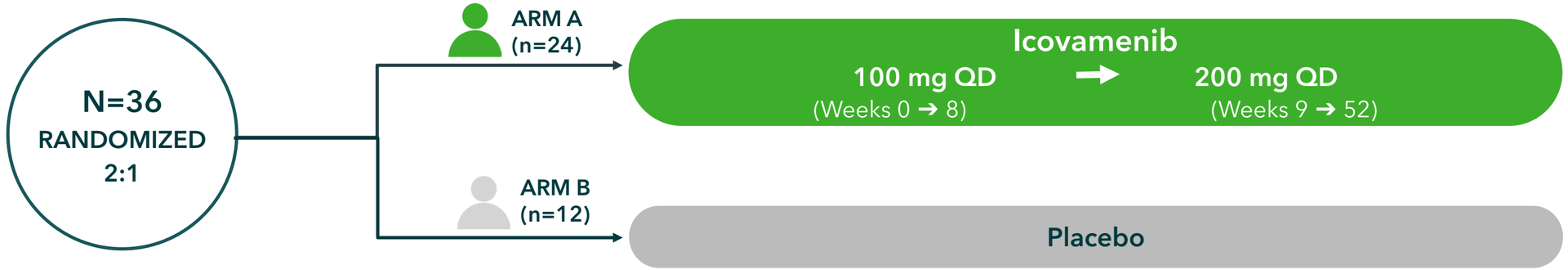
ICOVAMENIB in TYPE 1 DIABETES

Planned Biomea sponsored T1D study*

Inclusion Criteria

- Adult participants with T1D with a C-peptide ≥0.2 nmol/L





Icovamenib

Placebo

MMTT + Proteomics
+ Biobanking

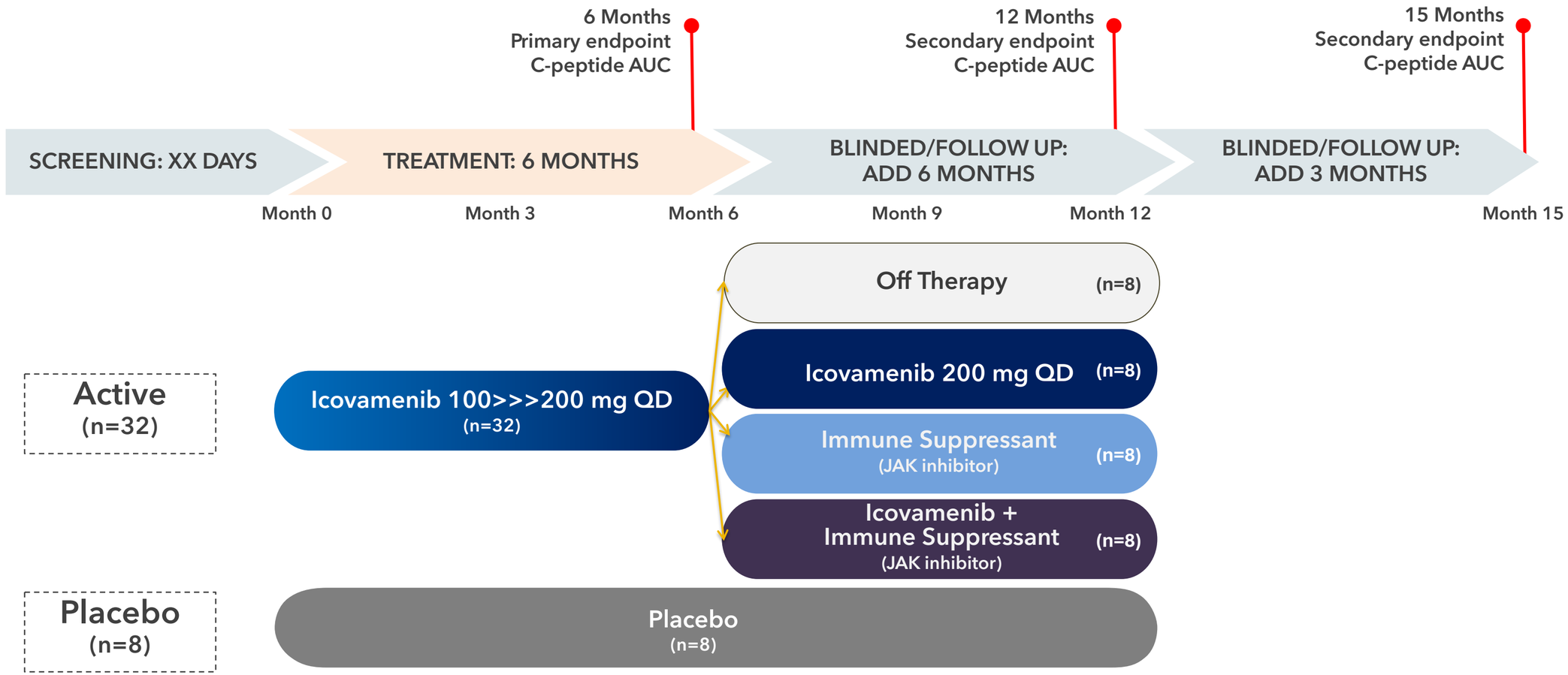
Subject to regulatory and investigator alignment, and feedback from applicable health authorities.

ICOVAMENIB in TYPE 1 DIABETES

Planned investigator sponsored phase II trial*

Inclusion Criteria

- Adult participants with T1D diagnosed within 3 years with a C-peptide ≥0.2 nmol/L



**Subject to regulatory and investigator alignment, and feedback from applicable health authorities.*

Planned study investigators *

Primary Investigator

Peter Gottlieb, MD

Professor of Pediatrics and Medicine | Barbara Davis Center, University of Colorado

- Professor of Pediatrics and Medicine and holds the Orr Family Endowed Chair in Adult Diabetes at the Barbara Davis Center, one of the world's leading centers for Type 1 diabetes research and clinical care.
- Long-standing member of Type 1 Diabetes TrialNet and chairs its Collaborative Mechanistic Studies Panel, helping drive pivotal immunotherapy trials across all stages of T1D.
- With 190+ publications, his work focuses on T- and B-cell–driven autoimmunity.

Anschutz | Barbara Davis Center for Diabetes

Sub-Investigators

Jason Gaglia, MD, MMSc

Ass. Professor | Joslin Diabetes Center, Harvard Medical School

Worlds leading diabetes center (36,000 patients annually, 150 MDs/PhDs)

Joslin Diabetes

David Baidal, MD

Ass. Professor | Diabetes Research Institute, University of Miami Miller School of Medicine

DRI Diabetes Research Institute FOUNDATION

Ralph A. DeFronzo, MD

Professor and Chief of the Diabetes Division | UT Health of San Antonio

UT Health San Antonio Long School of Medicine

**Subject to regulatory and investigator alignment, and feedback from applicable health authorities.*

KOL perspectives across clinical significance, biology, and future development in T1D

Efforts to intervene against type 1 diabetes (T1D) have historically focused on preserving remaining insulin secretion in people just diagnosed with T1D. These icovamenib data are unique in showing increased C-peptide-reflected insulin secretion in patients with established T1D during dosing and persistence of this effect after treatment was stopped. In people with established T1D, endogenous insulin secretion progressively declines to very low levels. Any evidence of improvement in endogenous insulin secretion—even among a few T1D individuals—is unprecedented and of immense biologic and clinical significance. These findings warrant rigorous and longer-term evaluation.



G. Alexander "Zan" Fleming, MD

FOUNDER & EXECUTIVE CHAIRMAN, KINEXUM
FORMER FDA SENIOR MEDICAL OFFICER AND DIVISION LEADER FOR METABOLIC & ENDOCRINE DRUGS, INVOLVED IN THE REVIEW OF LANDMARK DIABETES AND METABOLIC THERAPIES INCLUDING METFORMIN, THE FIRST RAPID-ACTING INSULIN ANALOGS, EARLY STATINS, AND PPAR AGONISTS

The new data presented today with icovamenib in patients with type 1 diabetes suggest a potential new therapeutic avenue in a disease where fundamental unmet need has long persisted. To date, approved therapies have not directly addressed the progressive loss of functional beta cells that underlies diabetes. Biomea has made critical progress in identifying and characterizing this molecule, which has demonstrated the ability to reduce menin protein levels and activate pathways associated with beta cell function. Today's icovamenib type 1 data further validates and deepens our understanding of icovamenib's mechanism of action. Congratulations to the Biomea team on reaching this important therapeutic milestone.



Rohit Kulkarni, MD, PhD

PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL | SENIOR INVESTIGATOR & SECTION CO-HEAD (ISLET CELL & REGENERATIVE BIOLOGY), JOSLIN DIABETES CENTER

What stands out to me in the icovamenib diabetes data is not only the emerging signal of biological activity, but also the safety profile observed to date with using icovamenib in diabetes studies. That combination is important, because safety ultimately determines whether rational combination strategies can be explored as the program moves forward. Looking ahead, future studies will be critical in determining whether the improvements observed in beta cell function of these Type 1 diabetes patients can be maintained over time, particularly in the presence of ongoing immune activity. It will also be important to understand whether combination approaches—including immunomodulatory therapies— are needed and can further enhance or stabilize the observed effects. These are key questions that will inform the long-term clinical potential of this approach.



David Baidal, MD

ASSISTANT PROFESSOR DIABETES RESEARCH INSTITUTE, UNIVERSITY OF MIAMI MILLER SCHOOL OF MEDICINE

KOL perspectives across clinical significance, biology, and future development in T1D

"The icovamenib data in Type 1 diabetes naturally makes us pause and reflect on what it could ultimately mean for people living with Type 1 diabetes. While these early findings require confirmation, they suggest a different way of thinking about treatment, one that extends beyond glucose management and begins to engage underlying disease biology. For younger individuals in particular, the possibility of preserving or improving endogenous beta cell function over time could have meaningful implications for lifelong disease burden.
Results like these invite consideration of how the treatment landscape in Type 1 diabetes may evolve if such approaches prove durable and safe.



Alice Cheng, MD

ENDOCRINOLOGIST, ASSOCIATE PROFESSOR OF MEDICINE UNIVERSITY OF TORONTO

"The icovamenib data in type 1 diabetes are encouraging, this is particularly interesting as icovamenib targets a pathway that has not been meaningfully explored in this disease. Despite advances in insulin delivery and glucose monitoring, disease-modifying options remain limited for patients. These findings support the need for focused, proof-of-concept studies in well-characterized patient populations to better understand this signal, its durability, and the underlying biology.
An important next step will be examining the interplay between beta cell effects and the autoimmunity inherent in type 1 diabetes, and whether combination approaches with immunomodulatory therapies could further enhance or stabilize these beta cell effects.



Jason Gaglia, MD, MMSc

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL | STAFF PHYSICIAN, JOSLIN DIABETES CENTER – ONE OF THE WORLD'S LEADING DIABETES CENTERS

"While insulin therapy is life saving for people with Type 1 diabetes, chronic exogenous insulin use is not without consequence. Over time, it is associated with well recognized iatrogenic risks, including hypoglycemia, diabetic ketoacidosis, weight gain, lipohypertrophy, and increased cardiovascular burden. Targeting menin with icovamenib represents a fundamentally new therapeutic approach in diabetes. Rather than simply replacing insulin, it seeks to improve endogenous beta cell function. The early results we are seeing in Type 1 diabetes are highly encouraging.
I am excited to explore longer dosing periods to fully assess the potential of enabling patients to regain their own beta cell–mediated glucose control which is something no current therapy has been able to achieve. If this approach is confirmed, this could represent a meaningful step towards allowing patients to live their daily lives with greater physiological stability and far less constant fear of their disease.



Ralph DeFronzo, MD

ENDOCRINOLOGIST, PROFESSOR OF MEDICINE UTHSCSA



ICOVAMENIB

First-in-class menin targeting agent in development for the treatment of diabetes - TYPE 2 DIABETES

biomea FUSION™

Opportunity - Type 2 Diabetes

Biomea is aiming to be the first approved beta cell restorative agent targeting menin in Type 2 Diabetes

- Icovamenib is the first-in-class beta cell restorative therapy in development in diabetes
- Icovamenib is potentially the best-in-class oral agent addressing diabetes at the root cause level – the depleted pool of beta cells
- Preclinical on target evidence of direct impact on beta cells, their proliferation and insulin productivity
- Over 500 patients dosed to date with icovamenib, demonstrating at the effective dosing scheme a safety profile that mirrors placebo
- Two ongoing Phase II Type 2 diabetes studies (addressing approximately 30% of Type 2 diabetes patients) reading out with their primary endpoints in 1H 27
- Registrational studies targeted for 1H 28 initiation

Restoring beta-cell health to delay insulin dependence

and reduce complications and disease burden

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Early-Stage

β-cell stress

Insulin deficiency/resistance

Metabolic dysregulation

Mid-Stage

Microvascular disease

Diabetes nephropathy (early)

Peripheral neuropathy

Autonomic neuropathy (early)

Late-Stage

Macrovascular disease

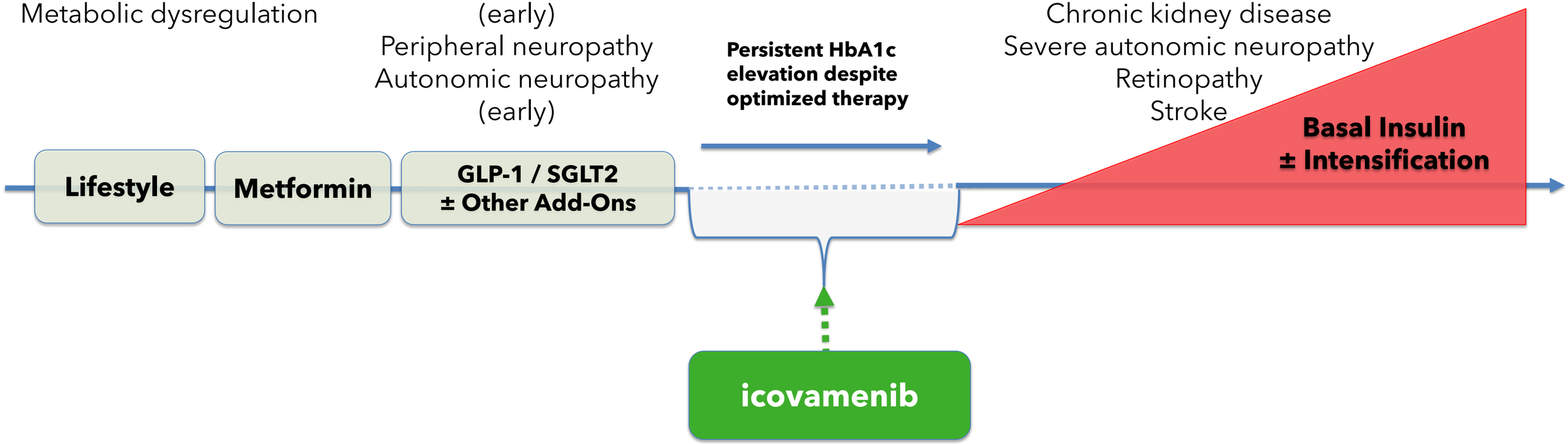
Coronary artery disease

Chronic kidney disease

Severe autonomic neuropathy

Retinopathy

Stroke



In the U.S., >50% of patients with diabetes remain above HbA1c targets ≥7%[1]

Depending on the GLP-1 RA agent, 15-45% do not achieve HbA1c < 7% in clinical trials[2]

1.NHANES analyses of glycemic control among U.S. adults with diabetes (JAMA; Diabetes Care); 2.SUSTAIN, AWARD, and SURPASS clinical trial programs for GLP-1 receptor agonists

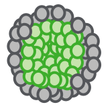
Icovamenib's mechanism of action

Icovamenib promotes selective and partial reduction in menin levels



Lowering menin levels releases the break on beta cell proliferation

Induction of beta cell proliferation



Pancreatic islet

IMPROVED BETA CELL MASS & FUNCTION FOR TYPE 1 AND TYPE 2 DIABETES

- Increase in insulin/C-peptide
- Decrease in blood glucose (HbA1c)

Baseline demographics & characteristics

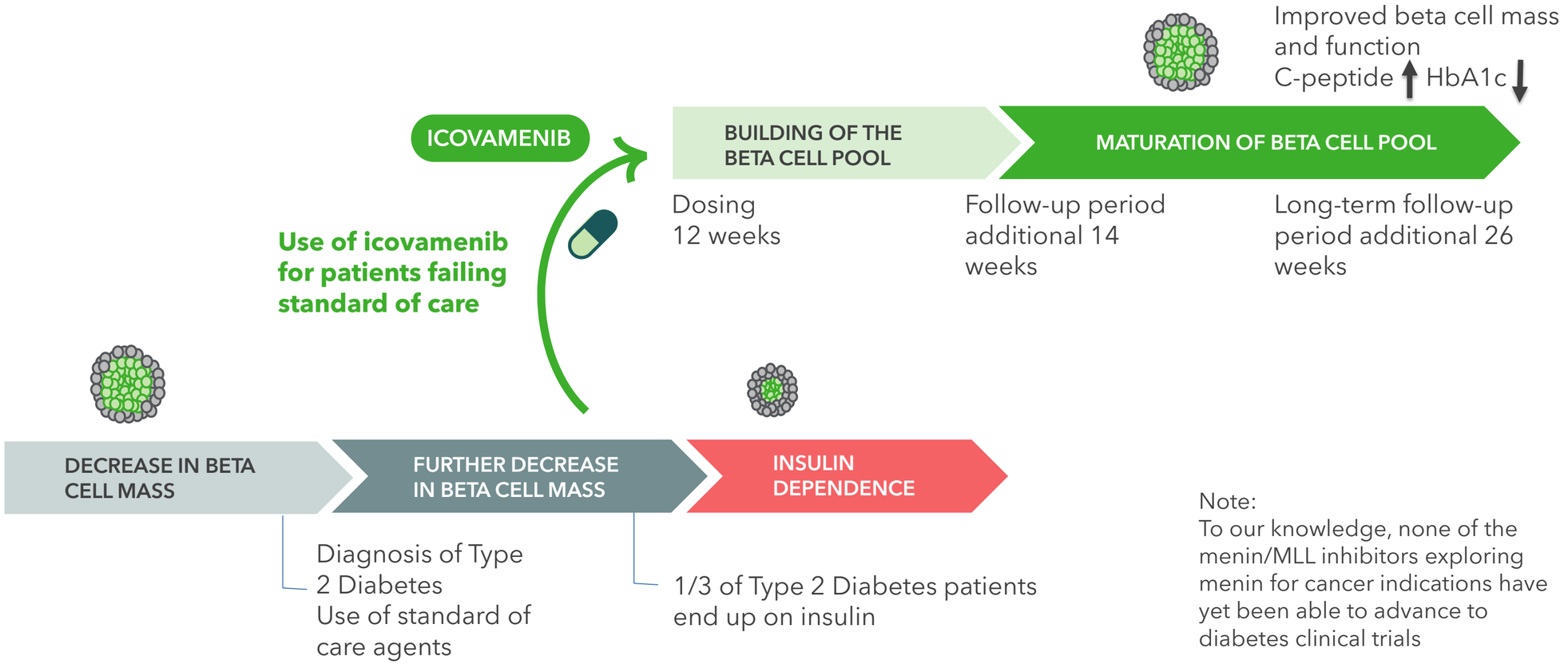
Per Protocol Population* on 1 or More Antihyperglycemic Agents at Baseline (N=163)

Parameter Mean (SD) or %	Arm A icovamenib (8 wks 100mg QD) (N=45)	Arm B icovamenib (12 wks 100 mg QD) (N=36)	Arm C icovamenib (8 wks 100 mg QD then 4 wks of 100 mg BID) (N=33)	Combined Arms icovamenib (N=114)	Combined Arms placebo (N=49)
Age (yr)	55 (7)	56 (6)	51 (10)	54 (8)	55 (7)
Duration of T2D Diagnosis (yr)	4.3 (1.8)	4.7 (1.8)	4.2 (2.2)	4.4 (1.9)	4.3 (2.0)
Sex (% Female)	(31)	(56)	(36)	(40)	(43)
HbA1c % (SD)	8.3 (1.1)	8.3 (1.0)	8.0 (0.8)	8.2 (1.0)	8.3 (1.0)
Fasting C-peptide (ng/mL)	3.4 (1.2)	3.8 (1.5)	3.7 (1.8)	3.6 (1.5)	3.5 (1.4)
BMI (kg/m^2)	30.9 (4.7)	32.7 (4.5)	32.4 (4.9)	31.9 (4.7)	32.6 (4.2)
BMI <30 kg/m^2 (%)	(49)	(22)	(30)	(35)	(27)
BMI ≥30 kg/m^2 (%)	(51)	(75)	(70)	(64)	(73)
Number of T2D Medications, n (%)					
1	39 (87)	23 (64)	23 (70)	85 (75)	41 (84)
2	4 (9)	11 (31)	7 (21)	22 (19)	6 (12)
3	2 (4)	2 (6)	3 (9)	7 (6)	2 (4)

Frias, et al. Metabolism, Volume 177, Supplement,2025

*Per the COVALENT-111 Protocol the population analyzed includes only subjects who received ≥80% of their planned dosing. A clinical hold interrupted the dosing. Patients were also excluded if they had significant protocol deviation.

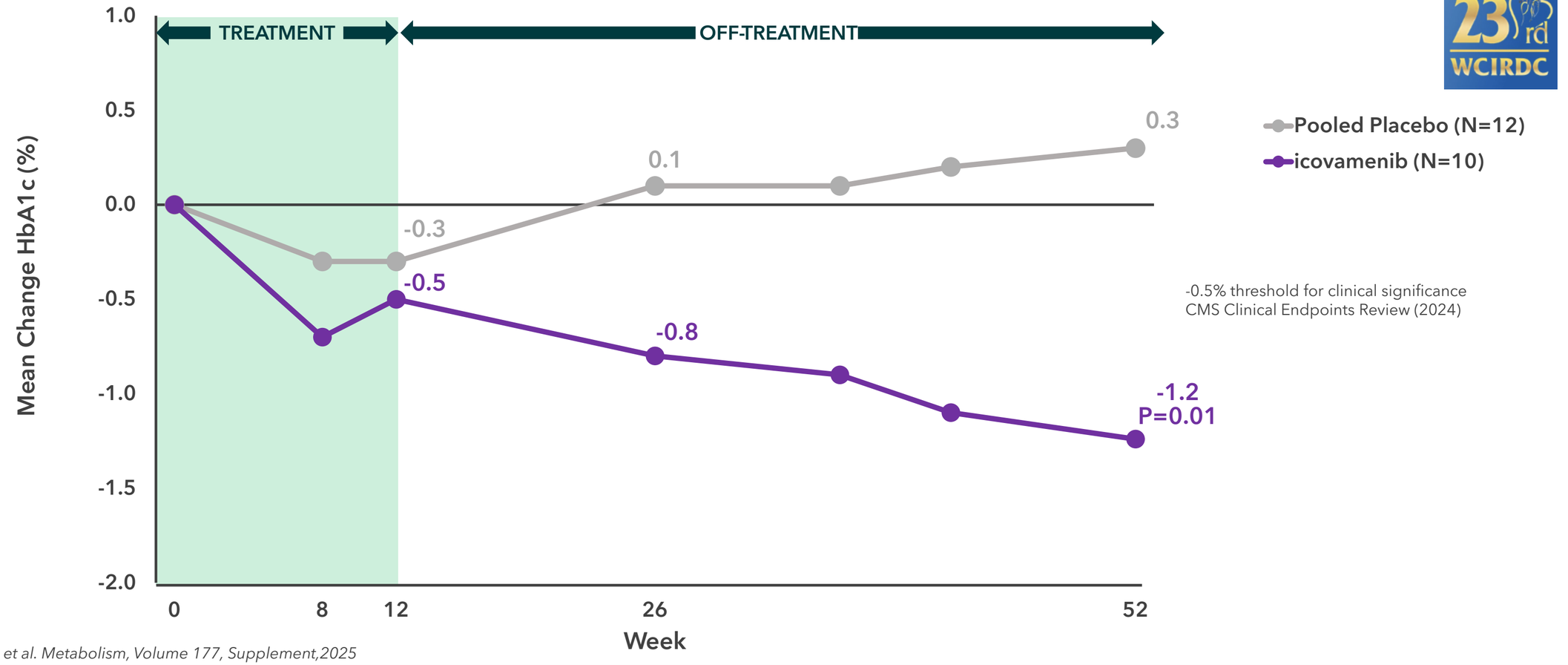
Icovamenib increased beta cell quantity, function & GLP-1 receptor expression following a short treatment period



Note:
To our knowledge, none of the menin/MLL inhibitors exploring menin for cancer indications have yet been able to advance to diabetes clinical trials

ICOVAMENIB | COVALENT-111

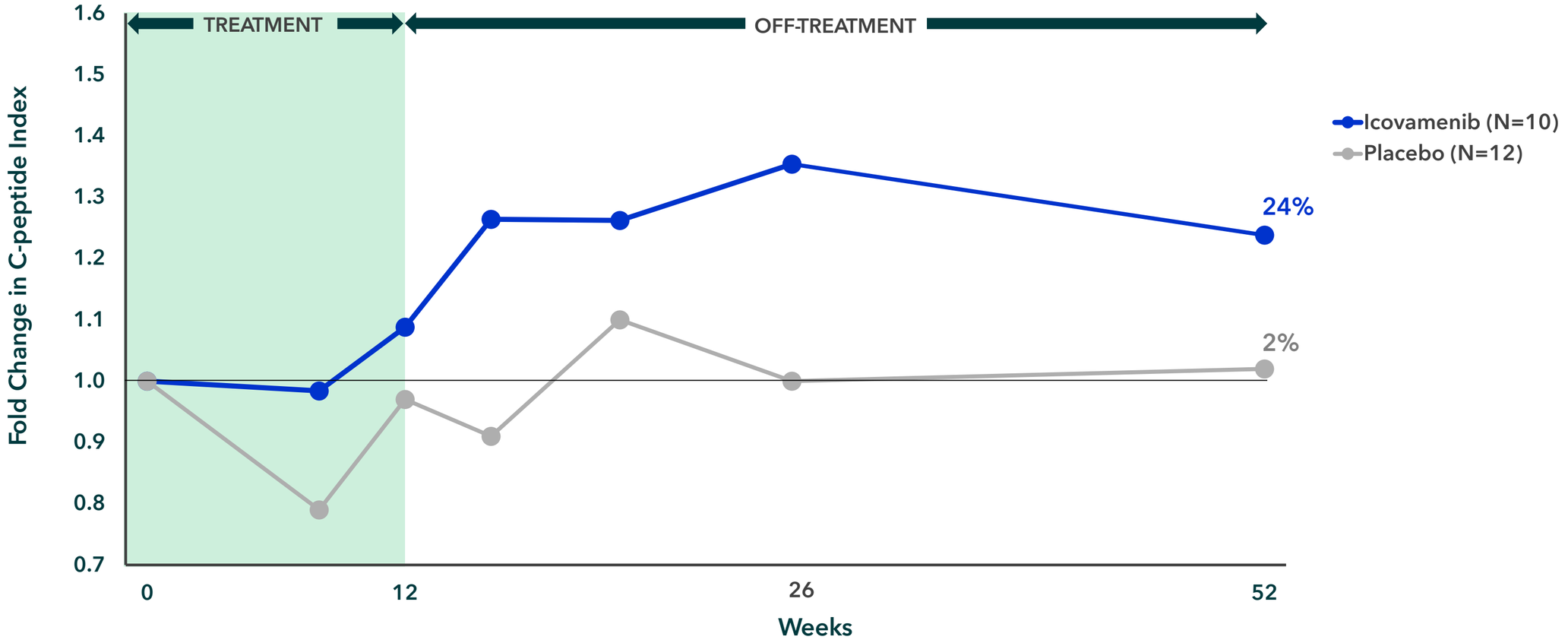
12 weeks of dosing (arms B&C) delivered lasting benefit through 52 weeks for severe insulin-deficient diabetes patients



Frias, et al. Metabolism, Volume 177, Supplement,2025

Arm A was excluded from this analysis because it included only 8 weeks of dosing which the company is not planning to pursue.

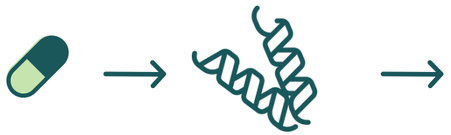
Icovamenib increased insulin secretion as measured by C-peptide index in severe insulin-deficient patients (arms B&C)



Data censored at onset of rescue medication, defined as any modification in antihyperglycemic therapy

Icovamenib's mechanism of action

Icovamenib promotes selective and partial reduction in menin levels





Lowering menin levels releases the break on beta cell proliferation and GLP-1 and GLP-1 receptor expression

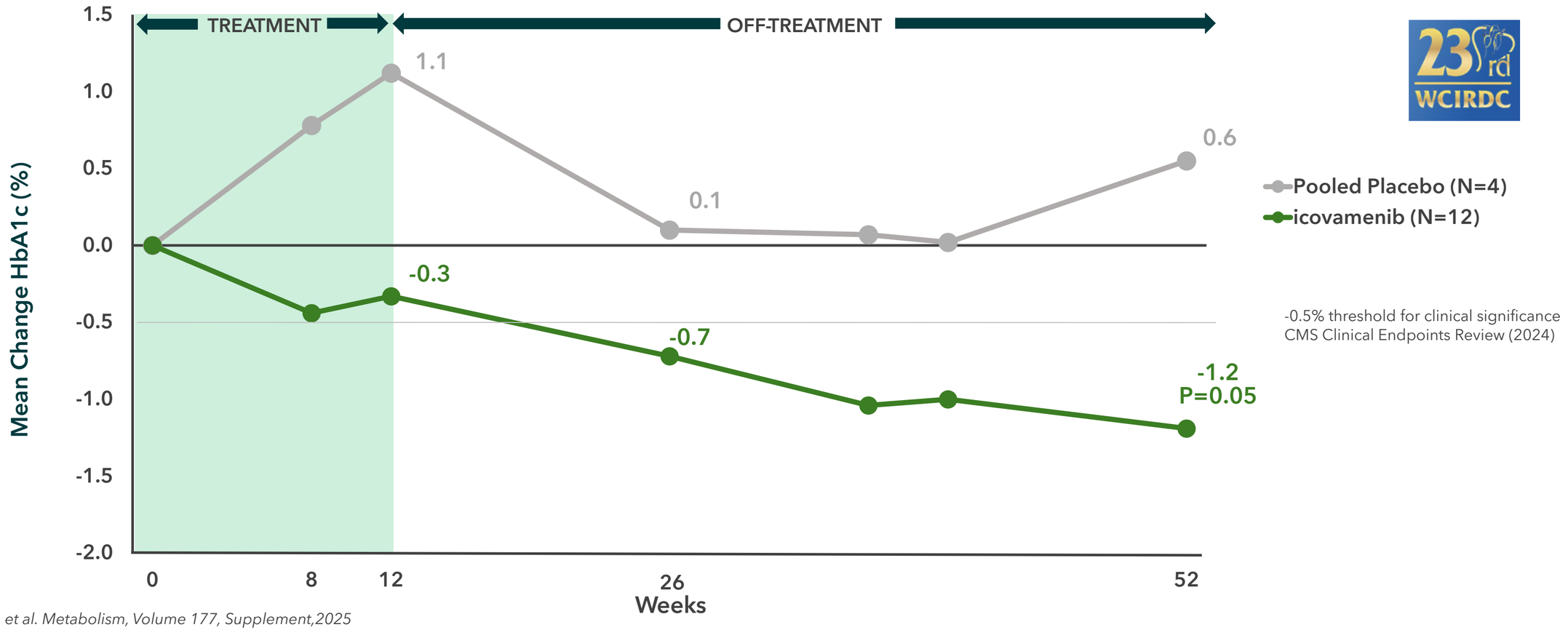
Increased expression of
- **GLP-1**
- **GLP-1 receptor**

IMPROVED INCRETIN EFFECTS

- Improved beta cell function
- Decrease in blood glucose (HbA1c)
- Synergistic with GLP-1 based therapies
- Potential for weight loss
- Potential for lean mass/muscle preservation

ICOVAMENIB | COVALENT-111

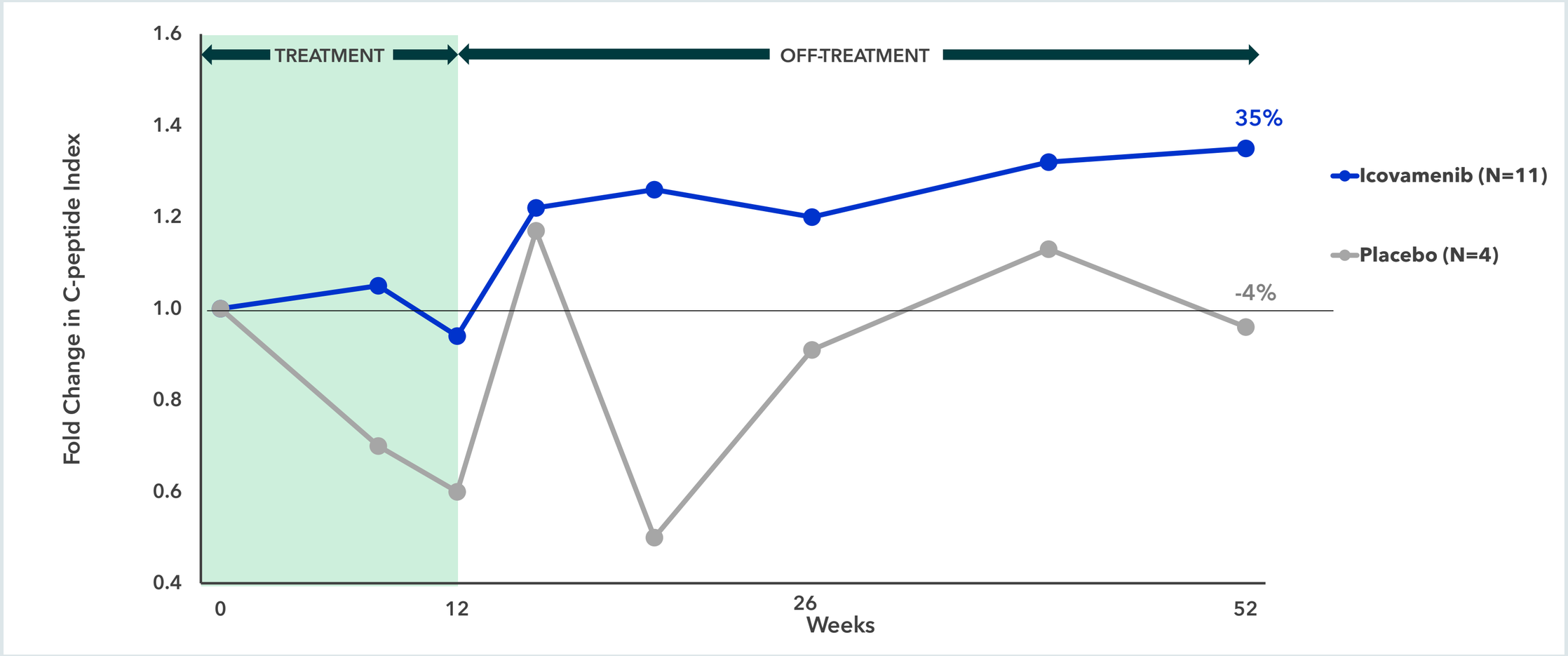
Patients on a GLP-1 based therapy at enrollment showed durable & clinically meaningful response in reduction of blood sugar (HbA1c)



Frias, et al. Metabolism, Volume 177, Supplement,2025

ICOVAMENIB | COVALENT-111

Icovamenib increased insulin secretion as measured by C-peptide index in GLP-1 RA treated patients – 9 months post last dose



Data censored at onset of rescue medication, defined as any modification in antihyperglycemic therapy

ICOVAMENIB | COVALENT-111

Favorable 52-week safety profile

Parameter	Arm A icovamenib (N=67)	Arm B icovamenib (N=67)	Arm C icovamenib (N=67)	Combined Arms icovamenib (N=201)	Combined Arms placebo (N=66)
Patients with ≥1 TEAE, N (%)	19 (28)	22 (33)	14 (21)	55 (27)	18 (27)
Treatment-Related SAEs, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs*, N (%)	1 (1)	0 (0)	1 (1)	2 (1)	1 (1)
Treatment Discontinuation due to TEAE, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Study Discontinuation due to TEAE, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ALT increase, N (%)	3 (4)	0	2 (3)	5 (3)	0
AST increase, N (%)	3 (4)	0	1 (1)	4 (2)	0
Resolution of ALT/AST w/o treatment interruption (%)	100	100	100	100	N/A
Deaths, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Frias, et al. Metabolism, Volume 177, Supplement,2025

Data are n (%) TEAE = Treatment Emergent Adverse event. SAE = Serious Adverse Event. Data are n (%) of TEAE with ≥5% frequency in any arm. ALT (alanine aminotransferase) or AST (aspartate aminotransferase) increase irrespective of incidence %.

*Arm A had an SAE of atrial fibrillation, unrelated to study treatment and occurred during the treatment period.

*Arm C had an SAE of COVID-19. Unrelated to study treatment and occurred during the treatment period.

*Placebo Arm had an SAE of nephrolithiasis. Unrelated to study treatment and occurred during the treatment period.

ALT increase: In the icovamenib arms, 4 of the 5 events were Grade 1 and 1 event was Grade 2.

AST increase: In the icovamenib arms, all 4 events were Grade 1.

All incidences of ALT and AST elevations resolved without interruption.

Note:
In AML studies icovamenib demonstrated a well-tolerated safety profile across all dose levels, with up to 500 mg QD / 325 mg BID, and dose durations extending over 1 year

ICOVAMENIB | COVALENT-111

Short treatment with icovamenib delivered HbA1c reductions comparable to chronic injectable & oral standards of care

Comparing icovamenib to currently approved type 2 diabetes agents with chronic dosing

THERAPY	DOSING REGIMEN	ADMINISTRATION ROUTE	OBSERVATION PERIOD	MEAN HbA1c REDUCTION (PLACEBO ADJ. %)
Ozempic (GLP-1 Agonist)	**Chronic dosing**	Injectable	Week 52 (SUSTAIN 8)	-1.5 (1mg)
Mounjaro (GLP-1/GIP Agonist)	**Chronic dosing**	Injectable	Week 40 (SURPASS 1)	-1.9 (5mg) -2.1 (15 mg)
Jardiance (SGLT2 Inhibitor)	**Chronic dosing**	Oral	Week 52 (Extension study)	-0.6 (10mg) -0.6 (25mg)
Januvia (DPP4 Inhibitor)	**Chronic dosing**	Oral	Week 52 (Sitagliptin)	-0.5 (100mg)
Icovamenib (menin inhibitor)	**12 weeks dosing**	**Oral**	**Week 52 (COVALENT-111)**	**-1.5% to -1.8%* (100 mg)**

Ozempic FDA Label; Mounjaro FDA Label; Jardiance FDA Label; Januvia FDA Label

*Icovamenib data are from a Phase II study in selected populations: insulin deficient diabetes patients and GLP-1 inadequate responders.

Disclaimer: The data presented above are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities and differences. The values shown in the cross-study comparisons are directional and may not be directly comparable.

ICOVAMENIB | T2D

Optimal dose, dose-duration, target population identified for phase IIb program

Phase IIa key derisking-insights:

- ✓ Optimal dose selected, 100 mg
- ✓ Food Effect Study confirmed optimal PK exposure of icovamenib within 30 minutes after a meal
- ✓ 12-week treatment observed to drive durable and lasting effects, no chronic treatment required
- ✓ Strong clinical activity in insulin-deficient and GLP-1 inadequate responder populations
- ✓ Treatment-emergent AEs comparable to placebo

COVALENT-211

Phase II trial in type 2 insulin deficient diabetes patients failing standard of care

- Adult participants with T2D who were treated with 1-3 antidiabetic medications
- HbA1c 7.5%-10.5% and BMI ≤ 32 kg/m^2
- Background therapy maintained unless rescue required

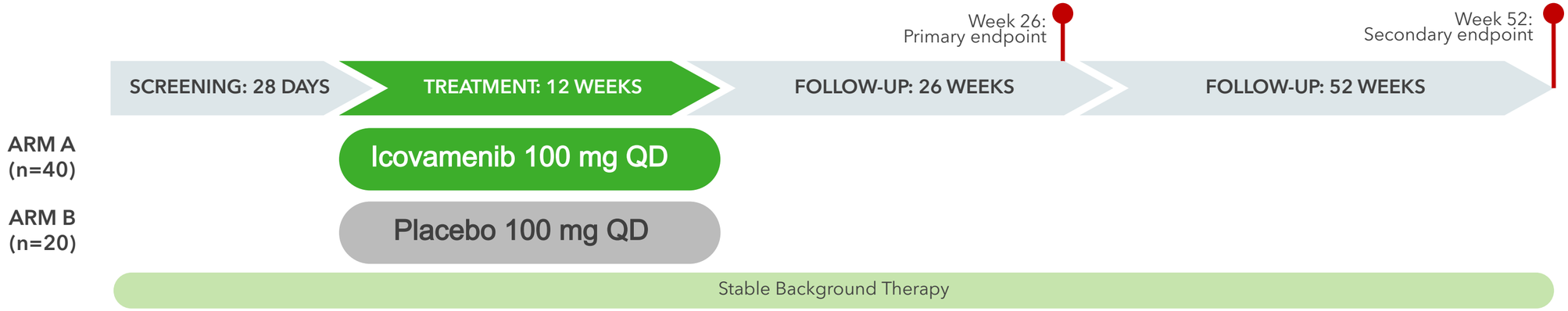
COVALENT-212

Phase II trial in type 2 diabetes patients failing standard of care while on a GLP-1 RA

- Adult participants with T2D who are not achieving glycemic targets despite GLP-1-based therapy
- HbA1c ≥7.0% and ≤10.5% and BMI 25 to 45 kg/m^2
- Background therapy maintained unless rescue required

A Phase II trial of icovamenib in T2D insulin deficient participants who are not achieving glycemic targets

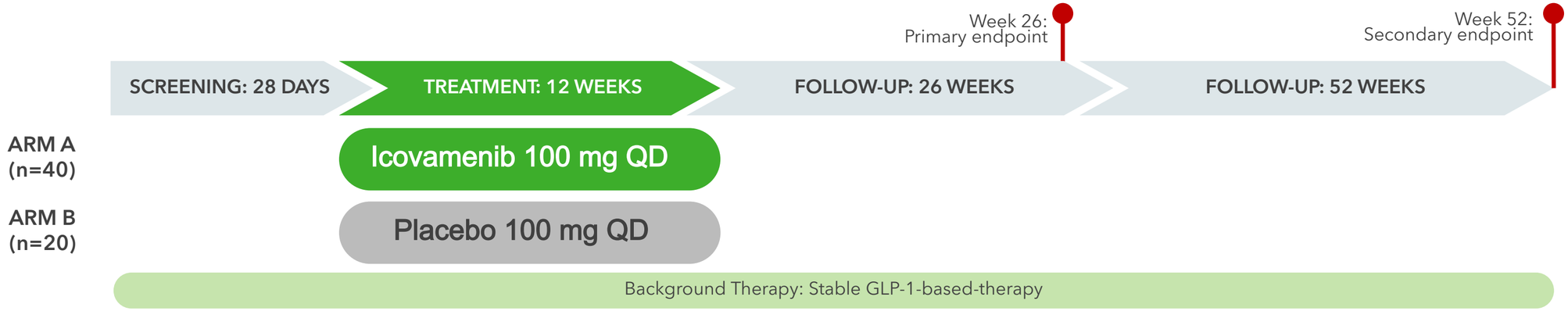
Objectives	Endpoints	Inclusion Criteria
To demonstrate that icovamenib 100 mg once daily for 12 weeks is superior to placebo for glycemic control at Week 26 and Week 52	• Mean change in HbA1c from baseline at Week 26 and 52 • Mean change in fasting plasma glucose (FPG) from baseline at Week 26 • Safety	• Adult participants with Type 2 Diabetes who were treated with 1-3 antidiabetic medications • HbA1c 7.5%-10.5% • BMI ≤ 32 kg/m^2 • Background therapy maintained unless rescue required



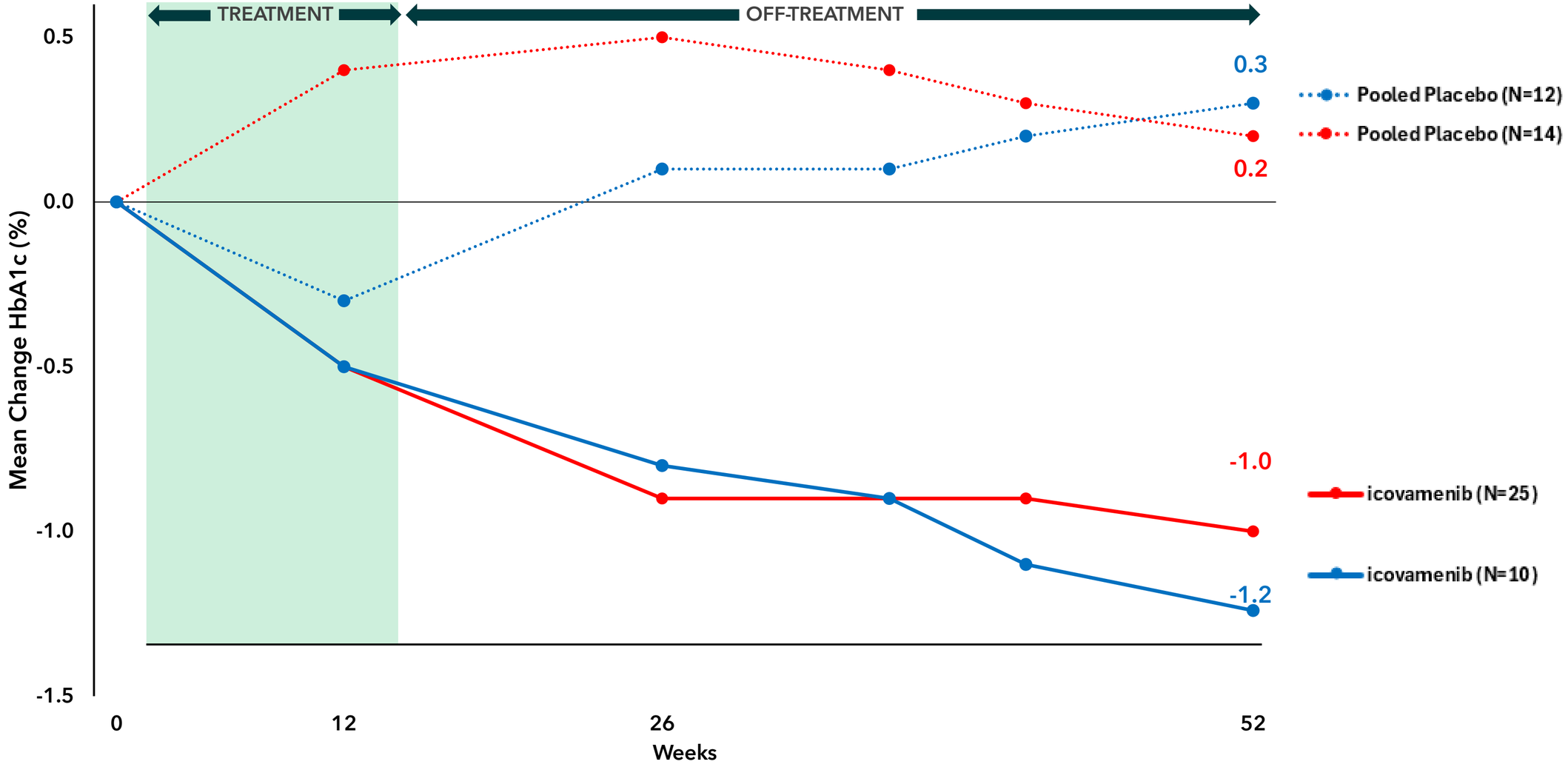
ICOVAMENIB | COVALENT-212

Phase II trial of icovamenib in participants with T2D who are not achieving glycemic targets while using GLP -1-based therapy

Objectives	Endpoints	Inclusion Criteria
To demonstrate that icovamenib 100 mg once daily for 12 weeks is superior to placebo for glycemic control at Week 26 and Week 52	• Mean change in HbA1c from baseline at Week 26 and 52 • Mean change in fasting plasma glucose (FPG) from baseline at Week 26 • Safety	• Adult participants with T2D who are not achieving glycemic targets despite GLP-1-based therapy • HbA1c ≥7.0% and ≤10.5% • BMI 25 to 45 kg/m^2 • Background therapy maintained unless rescue required



Applying enrollment criteria of COVALENT-211 (red) vs published results in SIDDs dosed in COVALENT-111 (blue)





ICOVAMENIB

First-in-class menin targeting agent in development for the treatment of diabetes – PRECLINICAL RESULTS

biomea FUSION™

Menin is naturally inhibited during pregnancy and breastfeeding

- allowing for adaptive beta cell mass increase & reduced diabetes risk

biomea FUSION

- Physiologic states such as pregnancy and lactation suppress menin, enabling beta-cell expansion and increased insulin output

- Preclinical and human data consistently link reduced menin signaling to improved beta-cell mass and function.

First in a 2005 paper in Proceedings of the National Academy of Sciences (PNAS) by Satyajit K. Karnik et al. titled "**Menin regulates pancreatic islet growth** by promoting histone methylation and expression of genes encoding p27^Kip1 and p18^INK4c"

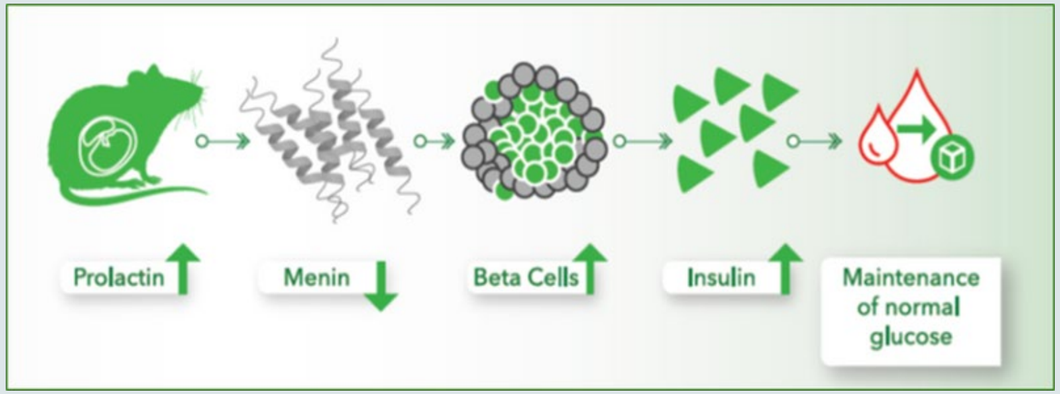
- Icovamenib has been shown to directly inhibit menin, aiming to pharmacologically replicate a naturally occurring, validated biologic process

Science AAAS

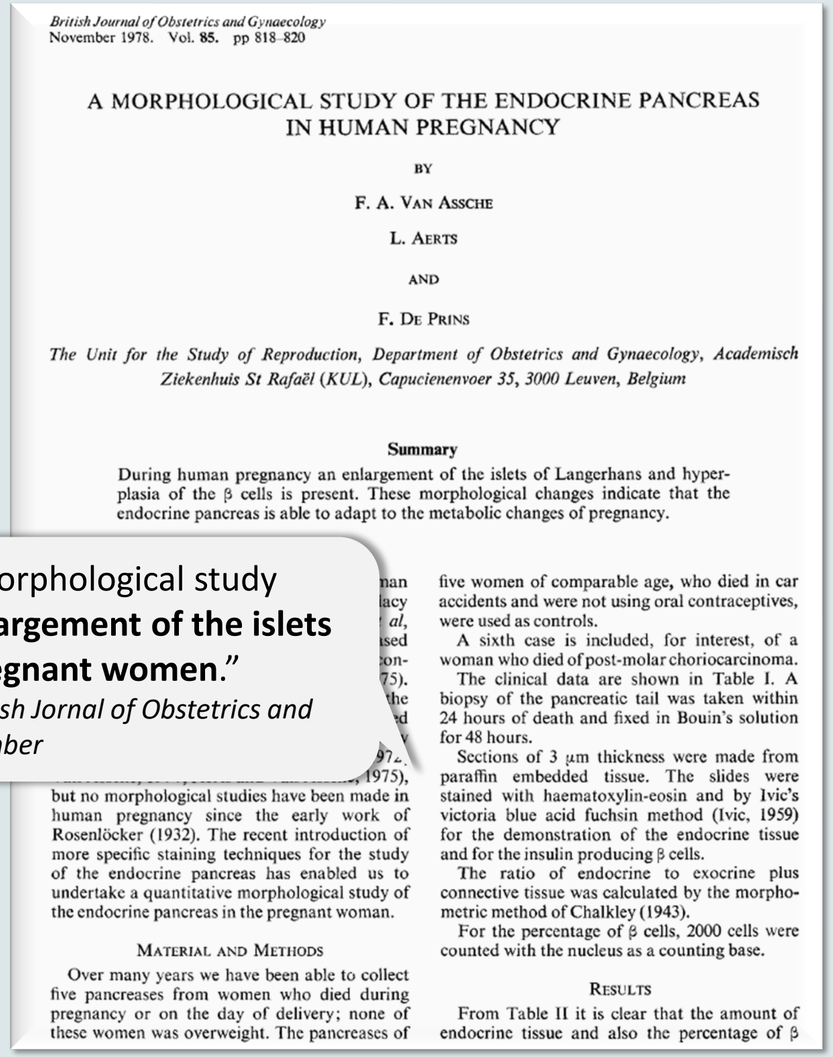
Menin Controls Growth of Pancreatic β-Cells in Pregnant Mice and Promotes Gestational Diabetes Mellitus

Satyajit K. Karnik,[1] Hainan Chen,[1*] Graeme W. McLean,[1*] Jeremy J. Heit,[1*] Xueying Gu,[1] Andrew Y. Zhang,[1] Magali Fontaine,[2] Michael H. Yen,[1,3] Seung K. Kim[1,3]†

Karnik SK, et al. Science. 2007;318:806-809



Beta Cells Proliferation During Pregnancy



British Journal of Obstetrics and Gynaecology
November 1978. Vol. **85.** pp 818–820

A MORPHOLOGICAL STUDY OF THE ENDOCRINE PANCREAS IN HUMAN PREGNANCY

BY

F. A. VAN ASSCHE

L. AERTS

AND

F. DE PRINS

The Unit for the Study of Reproduction, Department of Obstetrics and Gynaecology, Academisch Ziekenhuis St Rafaël (KUL), Capucienenvoer 35, 3000 Leuven, Belgium

Summary

During human pregnancy an enlargement of the islets of Langerhans and hyperplasia of the β cells is present. These morphological changes indicate that the endocrine pancreas is able to adapt to the metabolic changes of pregnancy.

but no morphological studies have been made in human pregnancy since the early work of Rosenlöcker (1932). The recent introduction of more specific staining techniques for the study of the endocrine pancreas has enabled us to undertake a quantitative morphological study of the endocrine pancreas in the pregnant woman.

MATERIAL AND METHODS

Over many years we have been able to collect five pancreases from women who died during pregnancy or on the day of delivery; none of these women was overweight. The pancreases of five women of comparable age, who died in car accidents and were not using oral contraceptives, were used as controls.

A sixth case is included, for interest, of a woman who died of post-molar choriocarcinoma.

The clinical data are shown in Table I. A biopsy of the pancreatic tail was taken within 24 hours of death and fixed in Bouin's solution for 48 hours.

Sections of 3 μm thickness were made from paraffin embedded tissue. The slides were stained with haematoxylin-eosin and by Ivic's victoria blue acid fuchsin method (Ivic, 1959) for the demonstration of the endocrine tissue and for the insulin producing β cells.

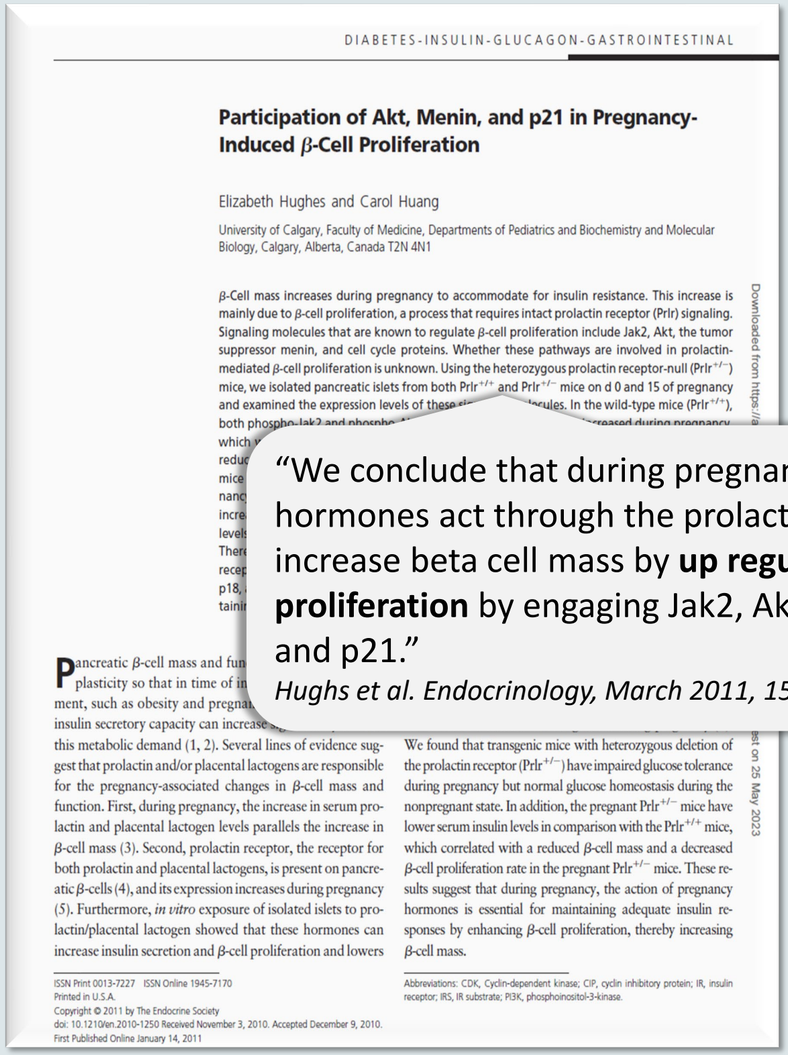
The ratio of endocrine to exocrine plus connective tissue was calculated by the morphometric method of Chalkley (1943).

For the percentage of β cells, 2000 cells were counted with the nucleus as a counting base.

RESULTS

From Table II it is clear that the amount of endocrine tissue and also the percentage of β

"This quantitative morphological study shows a **marked enlargement of the islets of Langerhans in pregnant women**."
F. A. Van Assche et al. British Jornal of Obstetrics and Gynaecology, 1978 November



Participation of Akt, Menin, and p21 in Pregnancy-Induced β-Cell Proliferation

Elizabeth Hughes and Carol Huang

University of Calgary, Faculty of Medicine, Departments of Pediatrics and Biochemistry and Molecular Biology, Calgary, Alberta, Canada T2N 4N1

β-Cell mass increases during pregnancy to accommodate for insulin resistance. This increase is mainly due to β-cell proliferation, a process that requires intact prolactin receptor (Prlr) signaling. Signaling molecules that are known to regulate β-cell proliferation include Jak2, Akt, the tumor suppressor menin, and cell cycle proteins. Whether these pathways are involved in prolactin-mediated β-cell proliferation is unknown. Using the heterozygous prolactin receptor-null ($Prlr^{+/-}$) mice, we isolated pancreatic islets from both $Prlr^{+/+}$ and $Prlr^{+/-}$ mice on d 0 and 15 of pregnancy and examined the expression levels of these si… …lecules. In the wild-type mice ($Prlr^{+/+}$), both phospho-Jak2 and phospho-… …creased during pregnancy, which …reduc… …mice … …nanc… …incre… …level… There… …recep… p18, … …tainir…

…ancreatic β-cell mass and fun… …plasticity so that in time of in… …ment, such as obesity and pregna… …insulin secretory capacity can increase … this metabolic demand (1, 2). Several lines of evidence suggest that prolactin and/or placental lactogens are responsible for the pregnancy-associated changes in β-cell mass and function. First, during pregnancy, the increase in serum prolactin and placental lactogen levels parallels the increase in β-cell mass (3). Second, prolactin receptor, the receptor for both prolactin and placental lactogens, is present on pancreatic β-cells (4), and its expression increases during pregnancy (5). Furthermore, *in vitro* exposure of isolated islets to prolactin/placental lactogen showed that these hormones can increase insulin secretion and β-cell proliferation and lowers

We found that transgenic mice with heterozygous deletion of the prolactin receptor ($Prlr^{+/-}$) have impaired glucose tolerance during pregnancy but normal glucose homeostasis during the nonpregnant state. In addition, the pregnant $Prlr^{+/-}$ mice have lower serum insulin levels in comparison with the $Prlr^{+/+}$ mice, which correlated with a reduced β-cell mass and a decreased β-cell proliferation rate in the pregnant $Prlr^{+/-}$ mice. These results suggest that during pregnancy, the action of pregnancy hormones is essential for maintaining adequate insulin responses by enhancing β-cell proliferation, thereby increasing β-cell mass.

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Copyright © 2011 by The Endocrine Society
doi: 10.1210/en.2010-1250 Received November 3, 2010. Accepted December 9, 2010.
First Published Online January 14, 2011

Abbreviations: CDK, Cyclin-dependent kinase; CIP, cyclin inhibitory protein; IR, insulin receptor; IRS, IR substrate; PI3K, phosphoinositol-3-kinase.

Downloaded from https://a… …est on 25 May 2023

"We conclude that during pregnancy, placental hormones act through the prolactin receptor to increase beta cell mass by **up regulating beta cell proliferation** by engaging Jak2, Akt, **menin**/p18, and p21."
Hughes et al. Endocrinology, March 2011, 152(3):847–855

Beta Cells Proliferation in Obesity

Pancreatic β-Cell Proliferation in Obesity[1,2]

Amelia K. Linnemann,[3] Mieke Baan,[3,4] and Dawn Belt Davis[3,5]*
[3]Division of Endocrinology, Department of Medicine, and [4]School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI; and
[5]William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin

ABSTRACT

Because obesity rates have increased dramatically over the past 3 decades, type 2 diabetes has become increasingly prevalent as well. Type 2 diabetes is associated with decreased pancreatic β-cell mass and function, resulting in inadequate insulin production. Conversely, in nondiabetic obesity, an expansion in β-cell mass occurs to provide sufficient insulin and to prevent hyperglycemia. This expansion is at least in part due to β-cell proliferation. This review focuses on the mechanisms regulating obesity-induced β-cell proliferation in humans and mice. Many factors have potential roles in the regulation of obesity-driven β-cell proliferation, including nutrients, insulin, incretins, hepatocyte growth factor, and recently identified liver-derived secreted factors. Much is still unknown about the regulation of β-cell replication, especially in humans. The extracellular signals that activate proliferative pathways in obesity, the relative importance of each of these pathways, and the extent of cross-talk between these pathways are important areas of future study. *Adv. Nutr. 5: 278–288, 2014.*

Introduction

The rates of obesity worldwide continue to climb because of numerous social, environmental, and perhaps even genetic factors. In the United States, >35% of adults are obese (1). Along with obesity has come increasing prevalence of type 2 diabetes. Notably, however, only 11.3% of adults are estimated to have diagnosed or undiagnosed diabetes (2). These statistics rev… that secondary factors other tha… for diabetes to develop; the 2 a… sity is associated with periphe… of the pathophysiology of typ… hyperglycemia there must be … sulin to meet this increased d… to the pancreatic β-cell, wher… to circulating nutrients and o…

Pancreatic β-cells are foun… small clusters of endocrine… the total pancreatic mass. Th… ple cell types, including in… gon-producing α-cells, and … types producing somatostat… ghrelin. The amount of in…

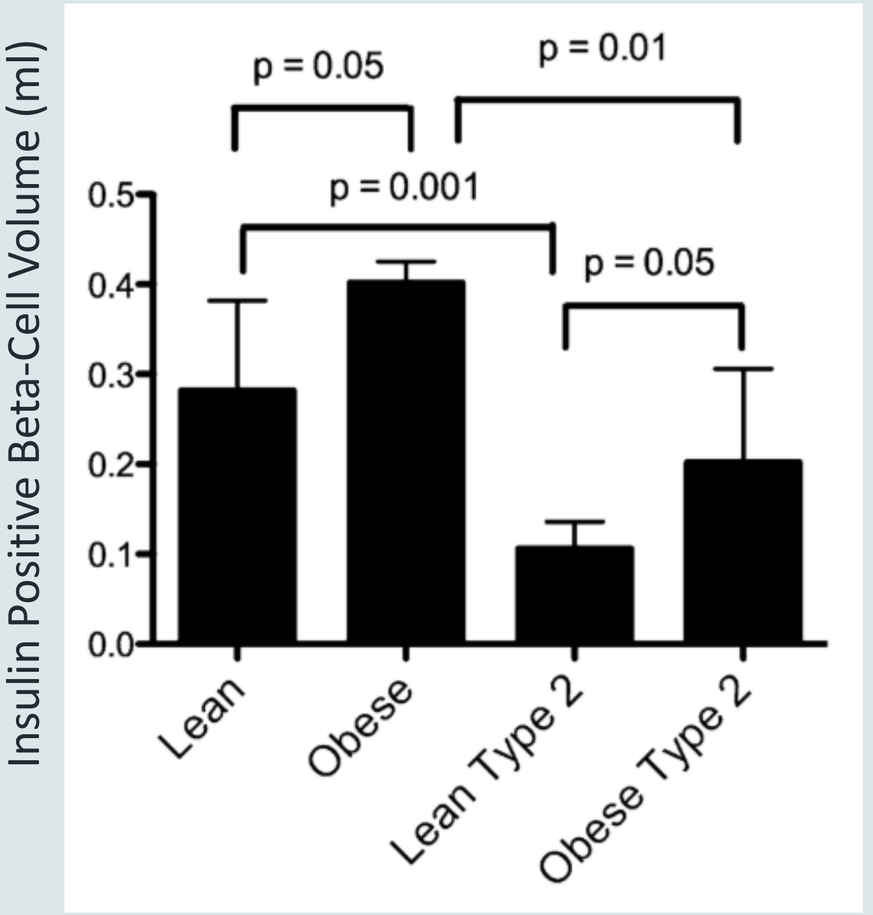
metabolic demand is dependent on numerous factors, including proper sensing of nutrient and hormonal signals, adequate insulin synthesis and secretion, and the overall number of functional β-cells. Although all of these factors are important, this review will focus on the regulation of β-cell … ber. The number of β-cells in a pancreas can … ways by using histologic analysis. To-… specimens revealed 2 key points about β-cell mass in humans (4). First, β-cell mass is increased in nondiabetic obesity, and second, there is decreased β-cell mass in both lean and obese patients diagnosed with type 2 diabetes (Fig. 1).

[1] D.B.D. is supported by National Institute of … (NIDDK) DK083442. M.B. is supported by the N… Service Award Institutional Training Grant T32 RR023916/OD010423 from the National Center for Research Resources. The William S. Middleton Memorial Veterans Hospital provided resources and use of facilities. The contents of this manuscript do not necessarily represent the views of the Department of Veterans Affairs or the U.S. Government.
[2] Author disclosures: A. K. Linnemann, M. Baan, and D. B. Davis, no conflicts of interest.
* To whom correspondence should be addressed. E-mail: dbd@medicine.wisc.edu.

©2014 American Society for Nutrition. Adv. Nutr. 5: 278–288, 2014; doi:10.3945/an.113.005488.

"In nondiabetic **obesity, an expansion in beta cell mass occurs** to provide sufficient insulin and to prevent hyperglycemia. This expansion is at least in part **due to beta cell proliferation**.

Linnmann et al. American Society for Nutrition. Adv. Nutr. 5: 278–288, 2014



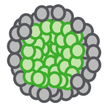
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Induction of beta cell proliferation



Pancreatic islet

Increased expression of
- **GLP-1**
- **GLP-1 receptor**

IMPROVED BETA CELL MASS & FUNCTION FOR TYPE 1 AND TYPE 2 DIABETES

- ↑ Increase in insulin/C-peptide
- ↓ Decrease in blood glucose (HbA1c)

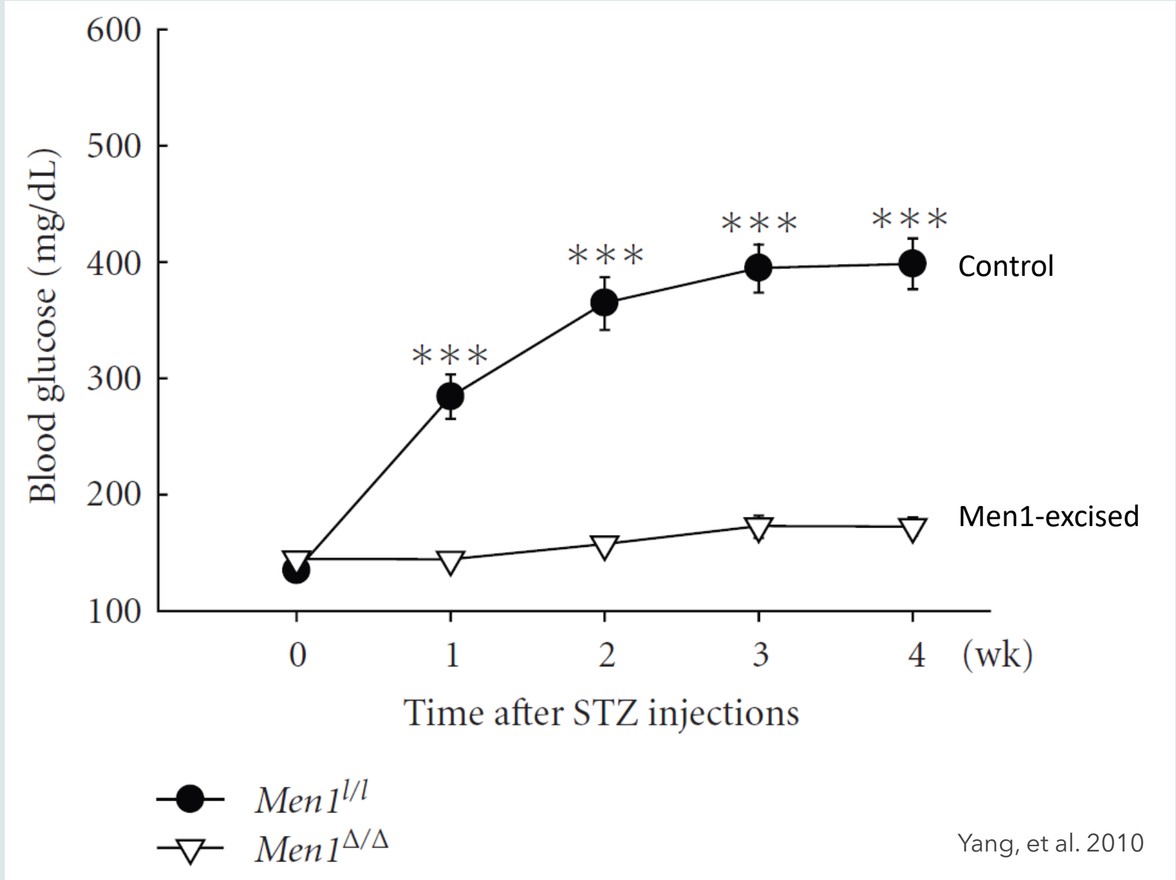
IMPROVED INCRETIN EFFECTS

- ↑ Synergistic with GLP-1 based therapies
- ↑ Improved beta cell function
- ↓ Decrease in blood glucose (HbA1c)
- ↓ Potential for weight loss
- ↑ Potential for lean mass/muscle preservation

Potential for menin inhibition demonstrated by beta cell ablation diabetes model in MEN1-excised mice

MEN1 excision prevents development of STZ-induced hyperglycemia

- Menin is a scaffold protein, encoded by the gene MEN1, that has been recognized for its role in Type 2 Diabetes Mellitus (T2DM) as a key regulator of beta-cell proliferation.
- Men1 knockout mice demonstrate increased beta-cell mass generation (Yang et al., 2010) and menin inhibition has previously been shown to improve glycemic control in high fat induced diabetic mice (Ma et al., 2021).
- Men1-excised mice do not develop hyperglycemia in a Streptozotocin-(STZ) induced rat model, which is a model for impaired beta-cell function and insulin production, demonstrating the role of menin in glycemic control.

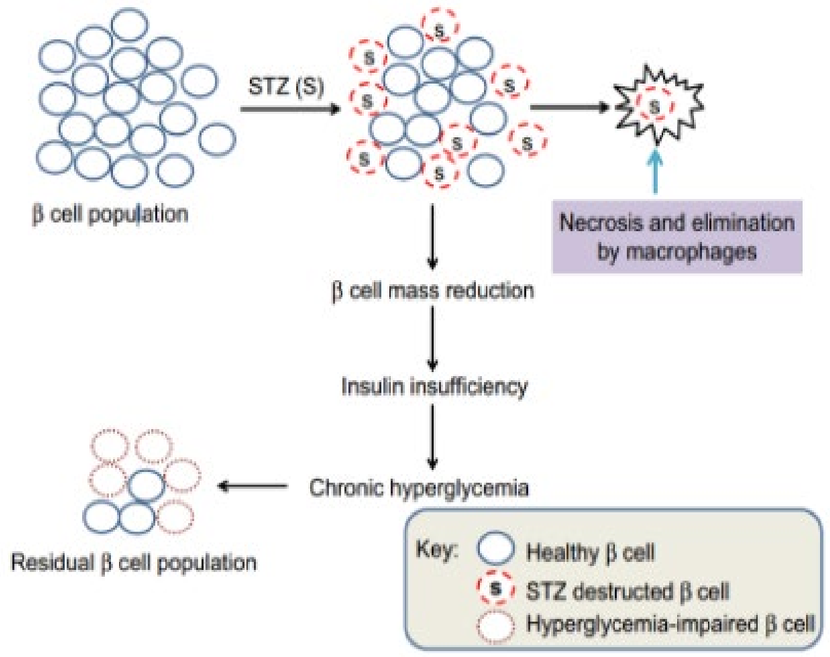


Men1-excised mice did not develop hyperglycemia in the STZ model, which was observed in the control group

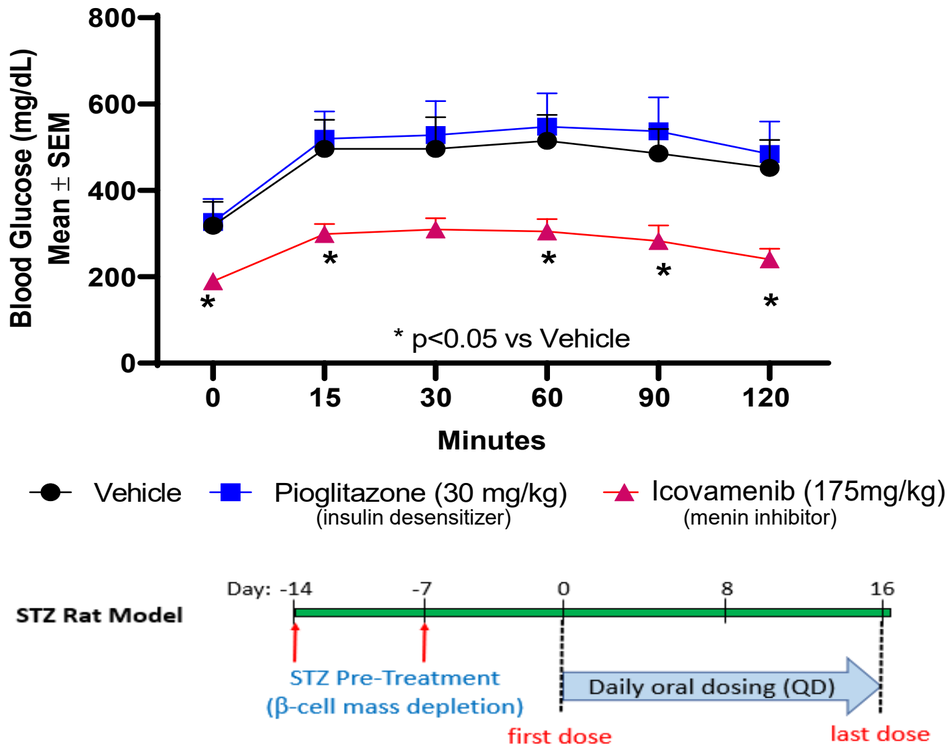
ICOVAMENIB | PRECLINICAL

Icovamenib significantly reduced blood glucose in STZ rats (a model in which only insulin decreases blood glucose levels)

STZ TREATMENT TYPICALLY RESULTS IN ~50% BETA CELL LOSS



ORAL GLUCOSE TOLERANCE TEST (DAY 17)



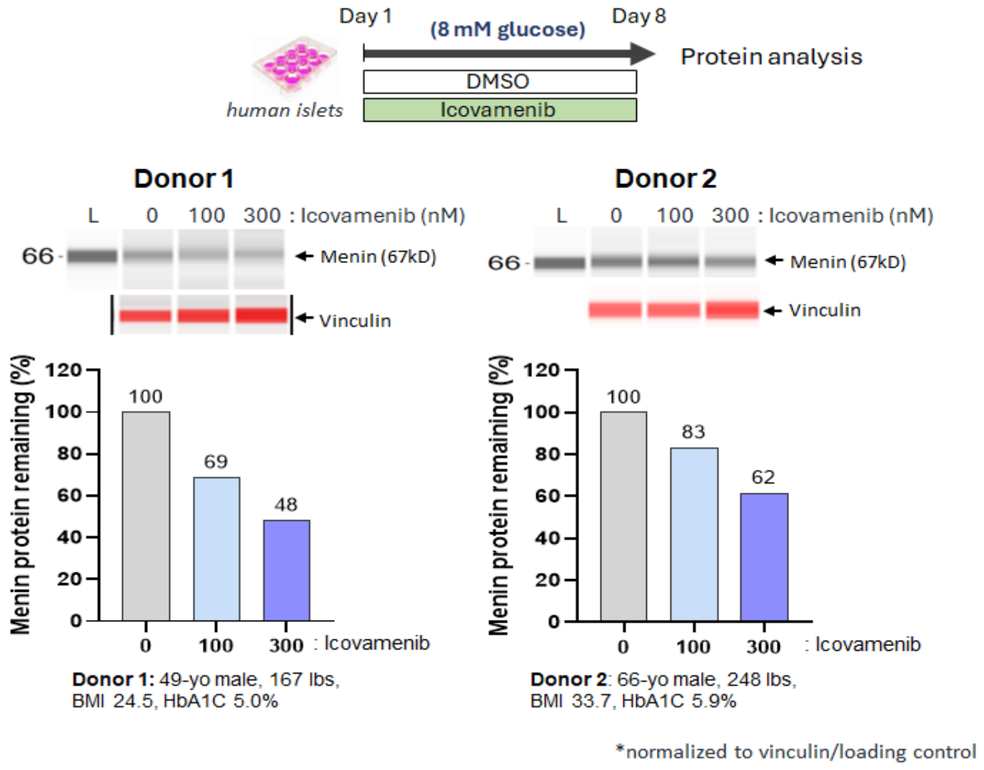
STZ=Streptozotocin, an antibiotic that produces pancreatic islet beta cell destruction and is widely used experimentally to produce a model in diabetes

Butler, et al. (EASD) Diabetologia 65 (Suppl 1), 1–469 (2022) presentation #197

ICOVAMENIB | PRECLINICAL

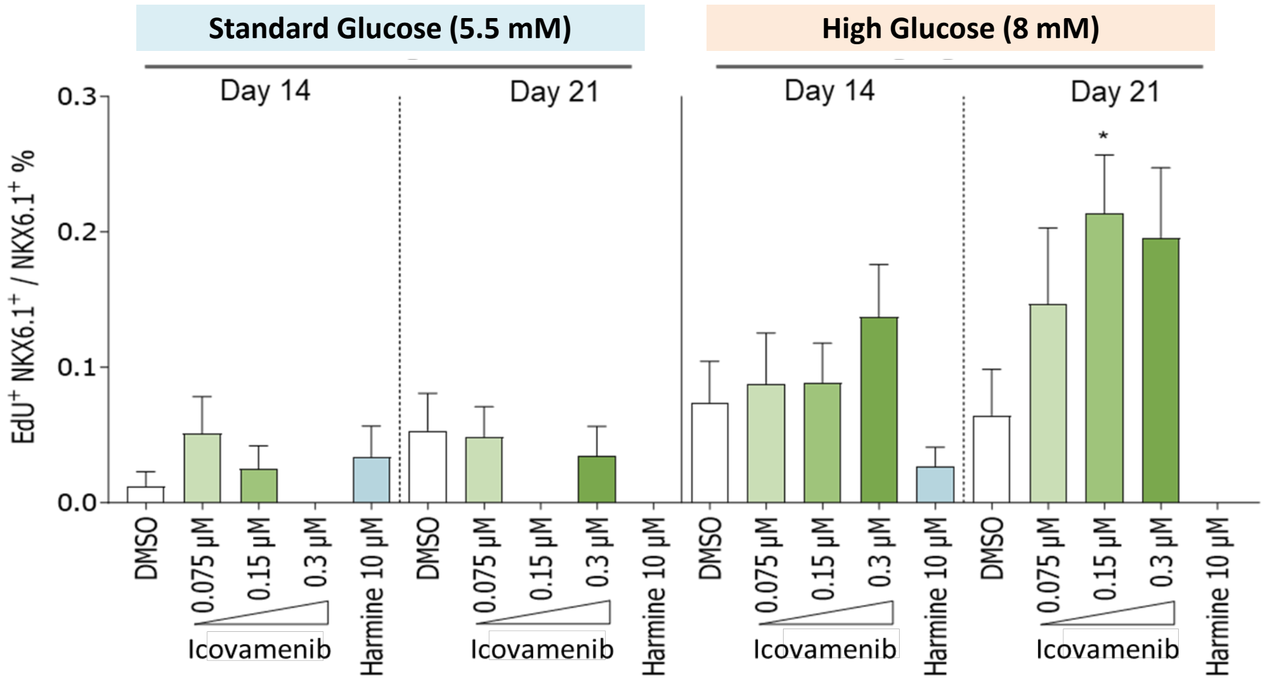
Icovamenib downregulated menin protein levels & promoted beta cell proliferation in ex vivo human islet cultures

MENIN LEVELS DOWNREGULATED



Somanath, et al. (EASD) Diabetologia 68 (Suppl 1), 1–754 (2025). Oral presentation #66

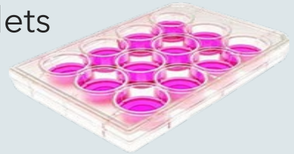
ICOVAMENIB CONDITIONALLY PROMOTED BETA CELL PROLIFERATION ONLY UNDER HYPERGLYCEMIC CONDITIONS



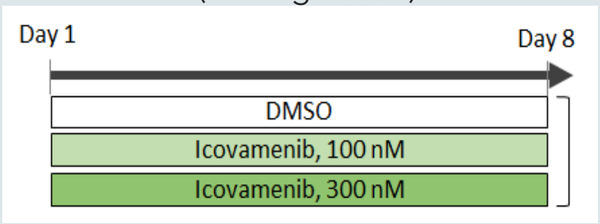
Frias, et al. (WCIRDC) Metabolism,Vol153, Supplement,2023,#88

Icovamenib enhanced GLP-1 receptor & insulin expression in human islets

Cadaver derived human islets

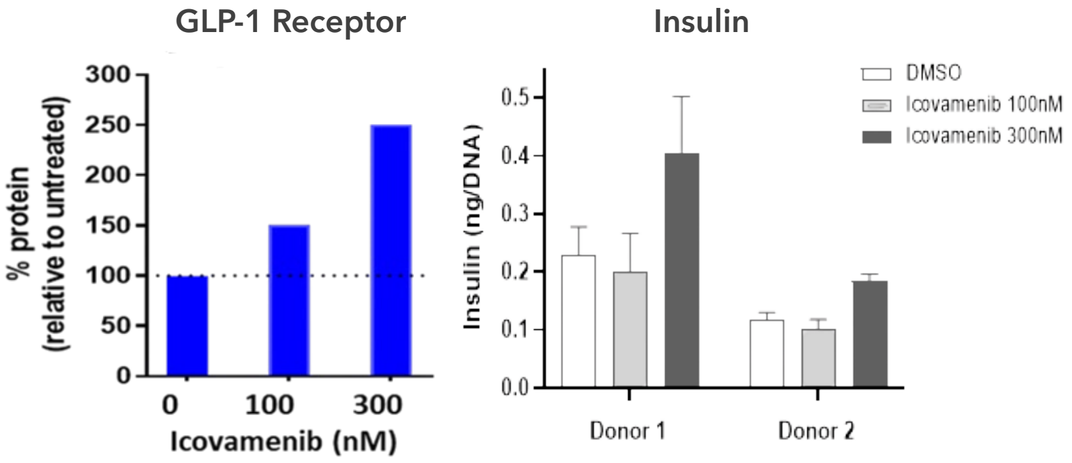


Culture 7 days under glucotox conditions (8mM glucose)



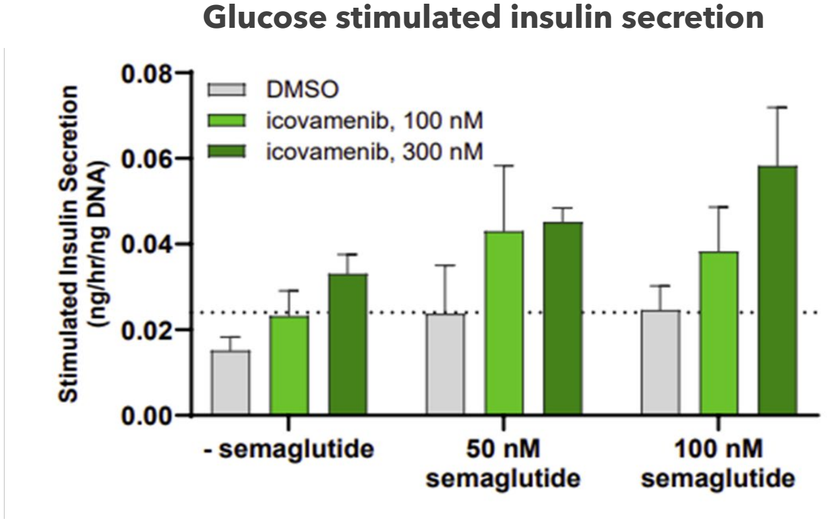
- Gene expression & Protein analysis
- Glucose Stimulated Insulin Secretion -/+ Semaglutide

ICOVAMENIB INCREASED GLP-1 RECEPTOR AND INSULIN PROTEIN LEVELS



Balakrishnan, et al. (WCIRDC) Supplement,2025,156226. Oral presentation

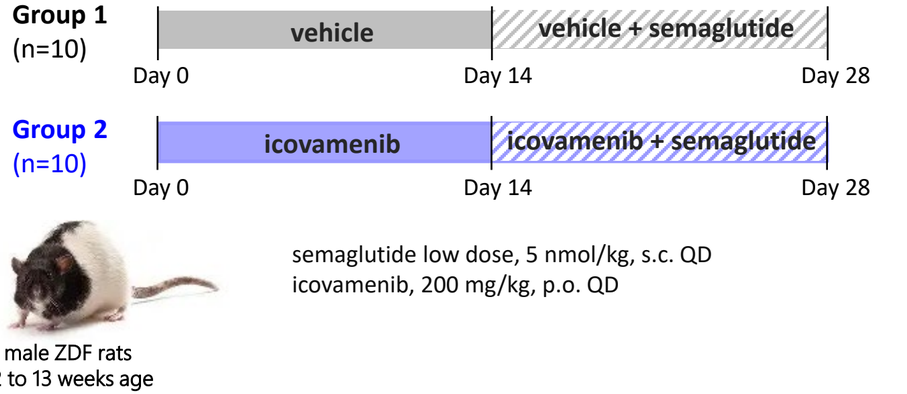
ICOVAMENIB ENHANCES THE RESPONSIVENESS OF HUMAN ISLETS TO GLP-1 RECEPTOR AGONISTS

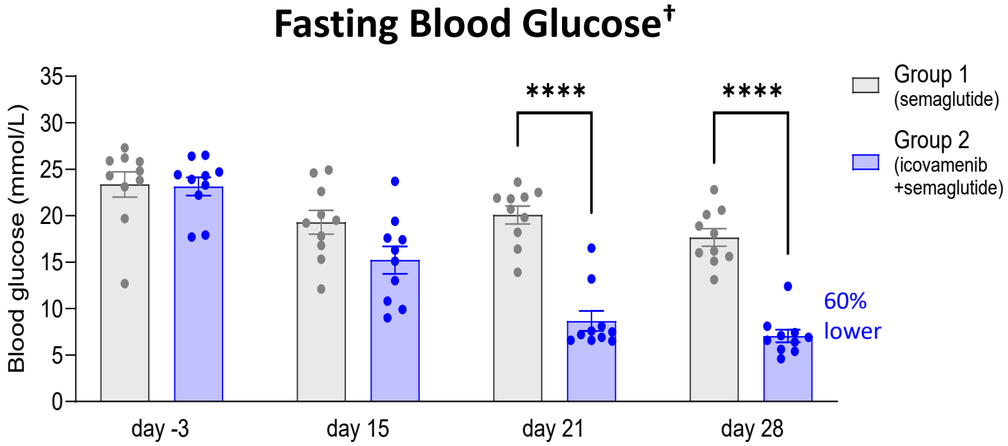


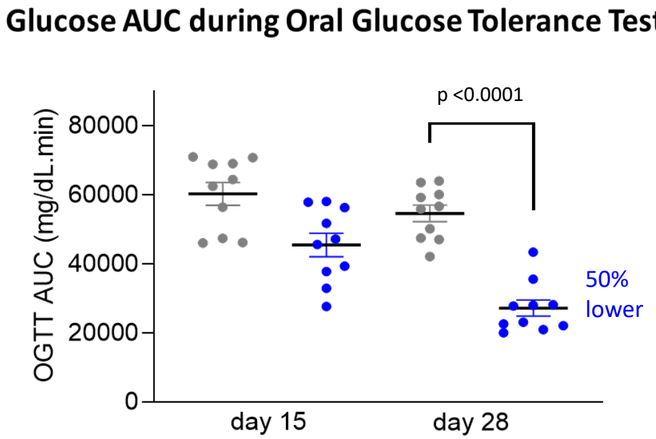
Somanath, et al. (EASD) Diabetologia 68 (Suppl 1), 1–754 (2025). Oral presentation #66

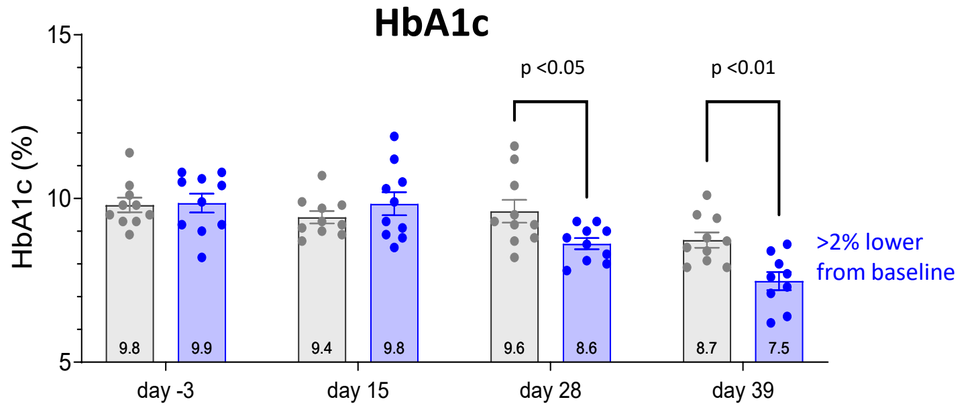
ICOVAMENIB WITH GLP-1RA

Combination treatment of icovamenib & low-dose semaglutide improved glycemic control in ZDF rats









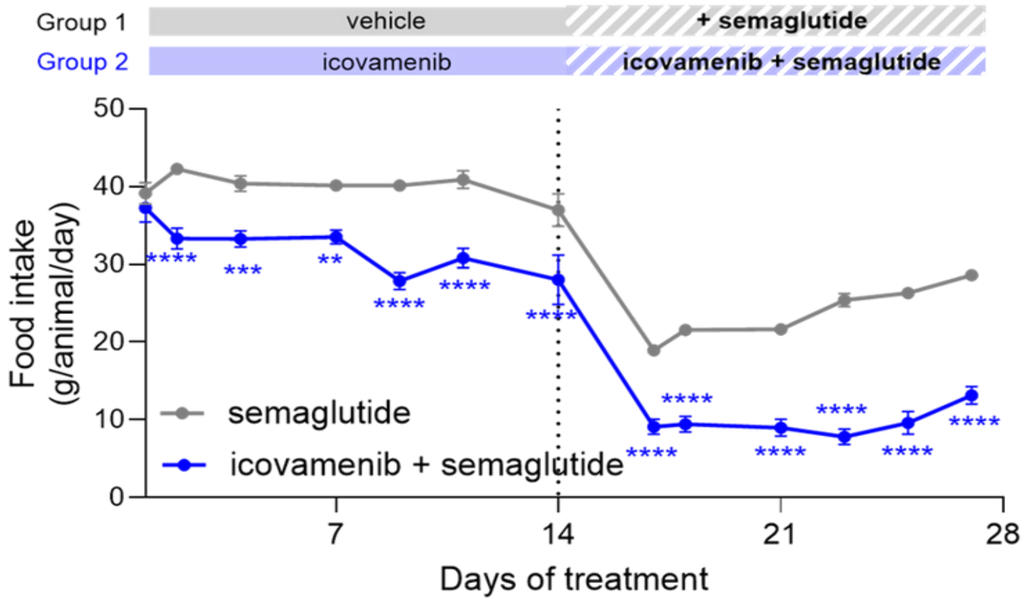
Plots represent mean ± SEM
Dots represent data for individual animal
† 6hr fasting on days -3 and 21, overnight fasting on days 15 and 28.

Somanath, et al. (ADA) Diabetes 2025;74 (Supplement_1):870-P

ICOVAMENIB WITH GLP-1RA

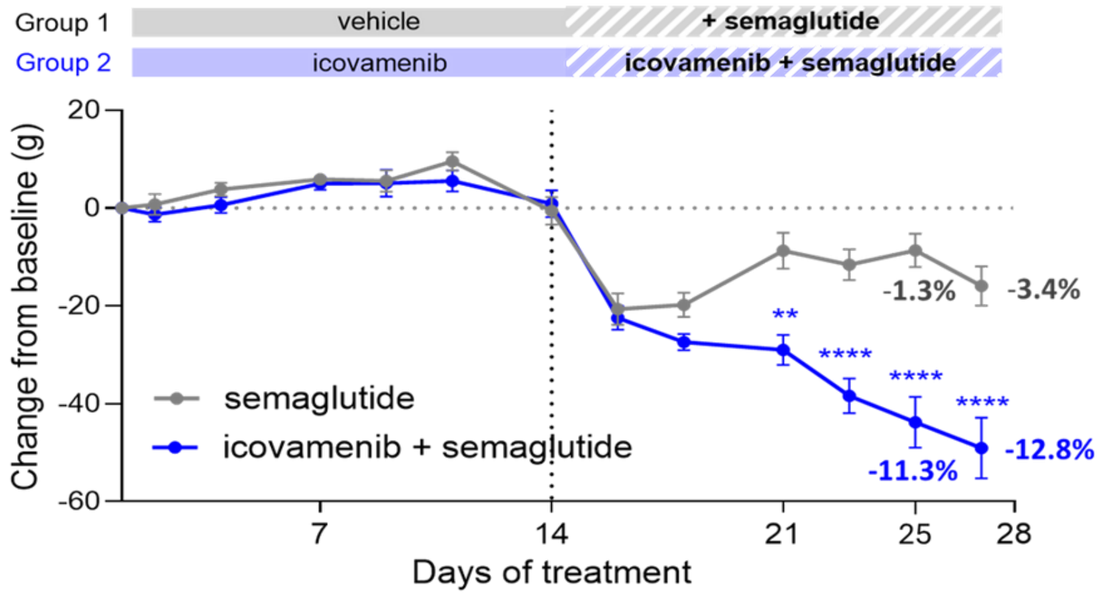
Combination Treatment of Icovamenib & Low-dose Semaglutide Reduces Food Intake & Body Weight

APPETITE SUPPRESSION



Somanath, et al. (ADA) Diabetes 2025;74 (Supplement_1):870-P

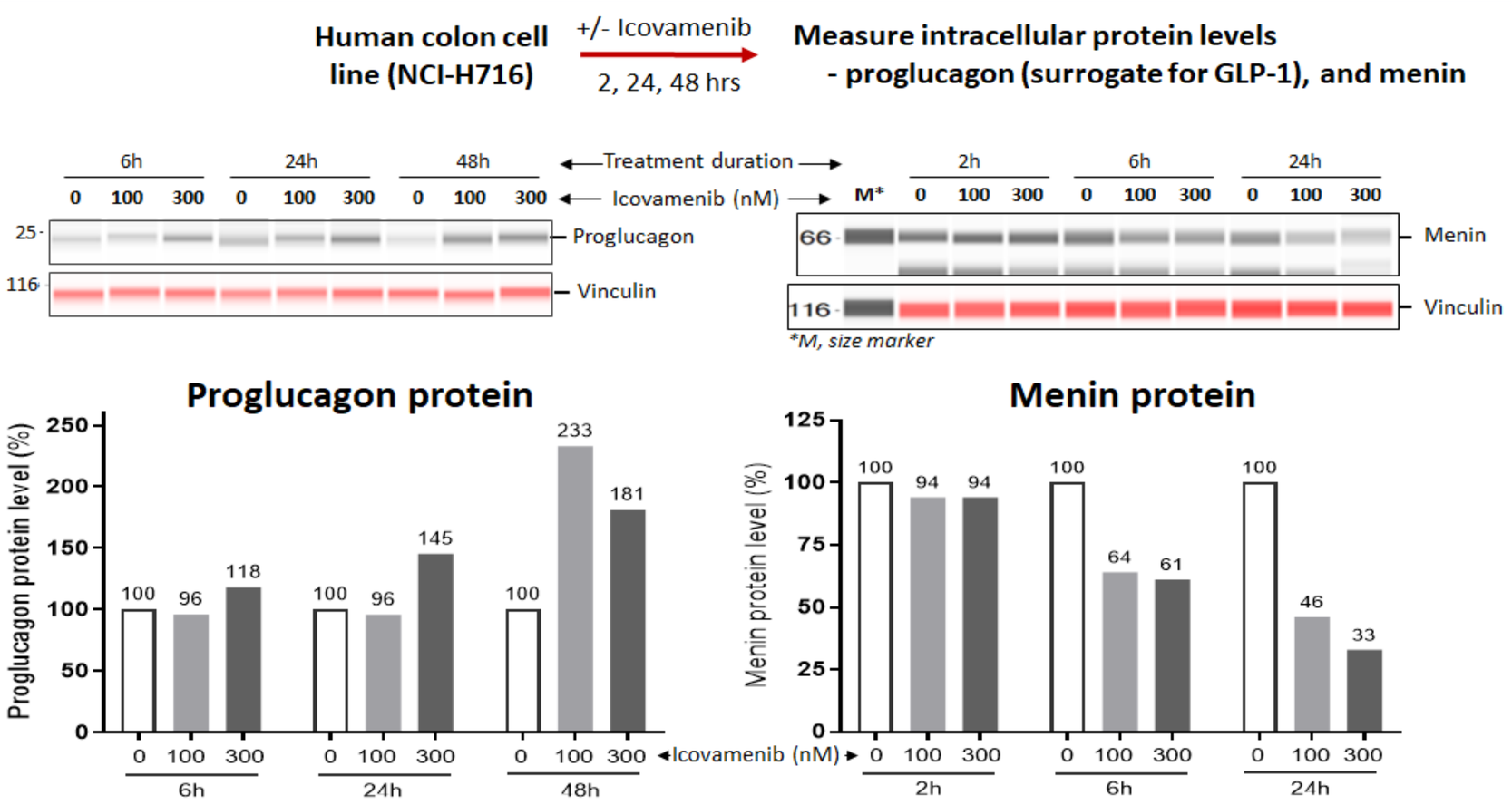
BODY WEIGHT REDUCTION



- ❑ SUPERIOR APPETITE SUPPRESSION WITH ABOUT 10% GREATER BODY WEIGHT REDUCTION THAN LOW-DOSE SEMAGLUTIDE ALONE
- ❑ THE OBSERVED BODY WEIGHT REDUCTION WAS PRIMARILY DUE TO FAT MASS LOSS WITH PRESERVATION OF LEAN MASS

ICOVAMENIB IN COLON CELLS

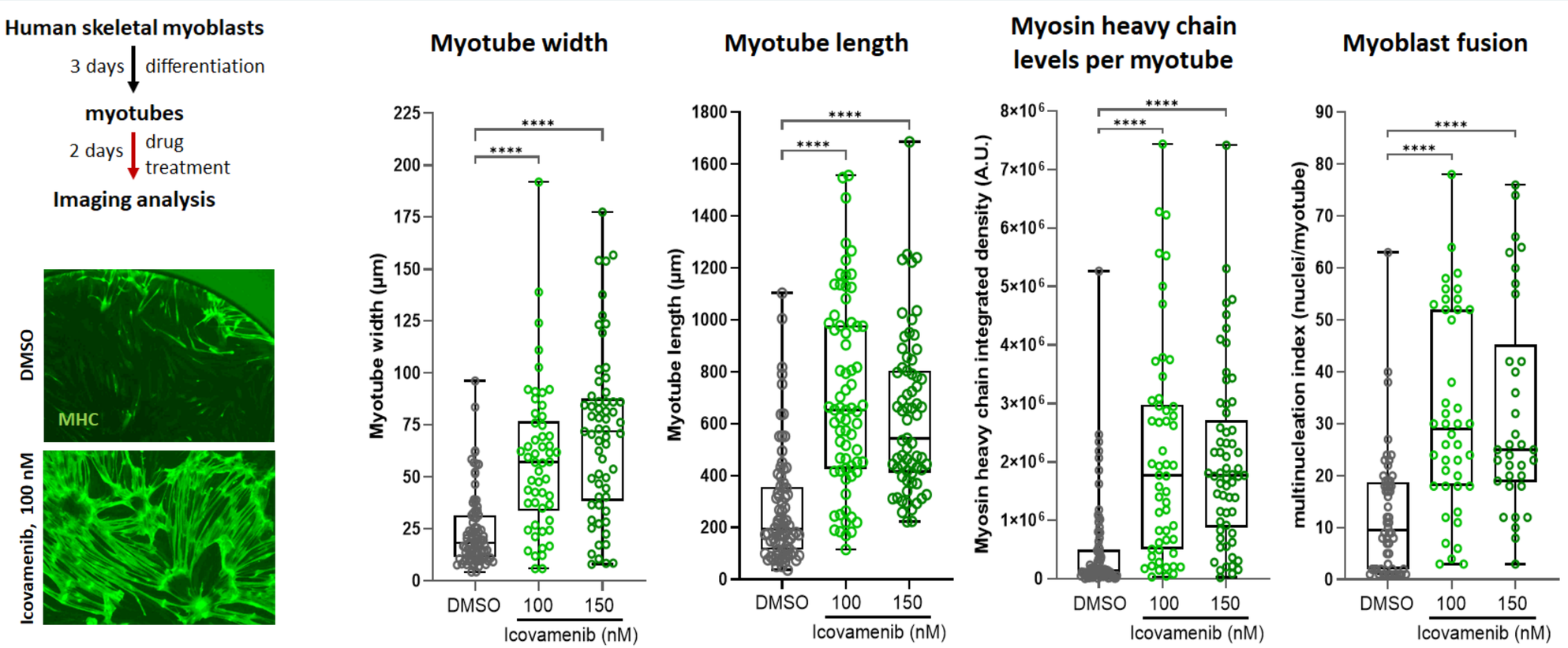
Icovamenib enhanced intracellular proglucagon expression in a human colon L-cell model



Tanataweethum, N. et al. (ADA) Diabetes 2026; 75 (Supplement_1): 2871–LB

ICOVAMENIB IN MYOTUBES

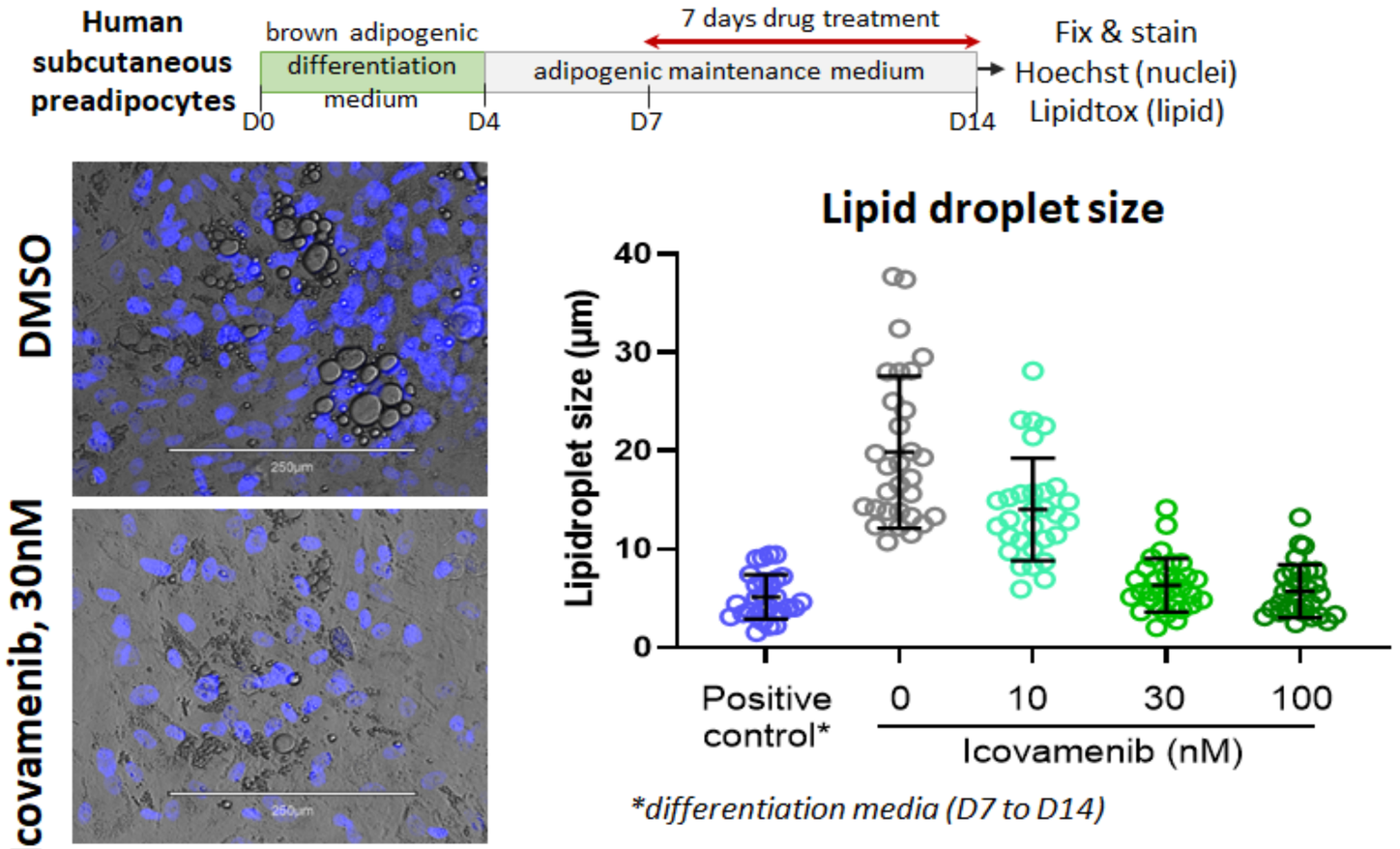
Icovamenib Induced Myogenic Effects in Human Skeletal Myoblast-derived Myotubes



Tanataweethum, N. et al. (ADA) Diabetes 2026; 75 (Supplement_1): 2871–LB

ICOVAMENIB IN ADIPOCYTES

Icovamenib promoted lipolysis in primary human adipocytes

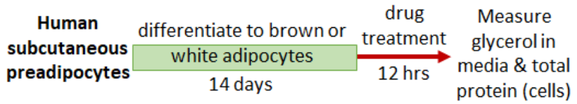


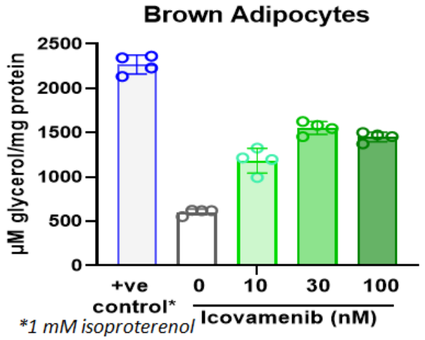
Tanataweethum, N. et al. (ADA) Diabetes 2026; 75 (Supplement_1): 2871–LB

ICOVAMENIB IN ADIPOCYTES

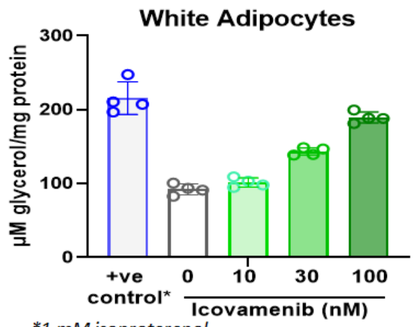
Icovamenib promoted effects indicative of lipolysis and fat browning in primary human adipocytes

Enhanced Glycerol Release



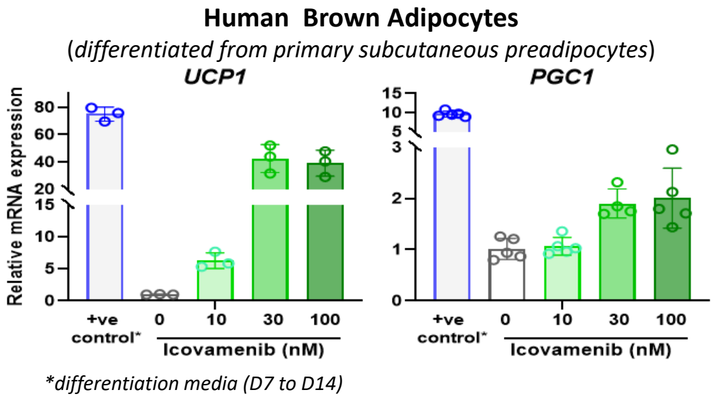


*1 mM isoproterenol

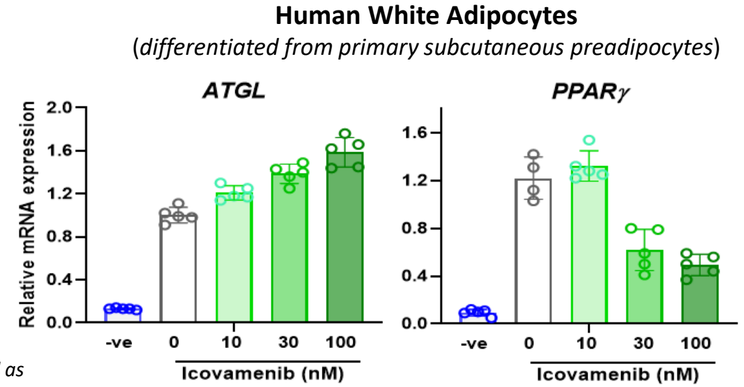


*1 mM isoproterenol

Upregulation of thermogenic and lipolytic genes



*differentiation media (D7 to D14)



Pre-adipocytes

Pre-adipocytes

PPIA (Cyclophilin A) was used as housekeeping gene for normalization of data

Tanataweethum, N. et al. (ADA) Diabetes 2026; 75 (Supplement_1): 2871-LB



BMF-650

An investigational next-generation oral GLP-1 receptor agonist for obesity

- PRECLINICAL RESULTS and
- CLINICAL OVERVIEW

biomea FUSION™

BMF-650: A potential best-in-class oral GLP-1 receptor agonist

THE CURRENT GLP-1 MARKET

Injectable GLP-1 RAs

- Some patients averse to injections
- Inconvenient
- Injection site reactions

First Generation Oral GLP-1 RAs

- High rates of GI side effects
- Many do not reach maintenance dose
- High discontinuation rates

Long, complex titration
Typically, 4-8+ steps, which can take 3-9 months depending on product

7 out of 10
Patients **discontinue** GLP-1 therapy due to side effects[1]

BMF-650
Designed for sustainable weight loss management

Next Generation Oral GLP-1 RA

Oral administration
Convenience without injections

Designed for improved GI tolerability
Potential for better tolerability and adherence

Two-step titration
Faster path to maintenance dose

Built to improve persistence
Helping more patients stay on therapy

Chronic therapy in mind
Designed for sustainable weight loss management

THE PROJECTED IMPACT

Weight Loss Management
Better tolerability will lead to continuous weight management

Better Patient Experience
Simpler regimen and fewer GI side effects

Higher Persistence
More patients stay on therapy and reach therapeutic benefit

Long-term Health Benefits
Sustained weight management supports cardiometabolic health

BMF-650 is designed to be the oral GLP-1 RA patients can start, stay on, and have long term benefits from

1.Real-world evidence across multiple GLP-RA studies (e.g. N Engl J Med 2021.385.896-907. JAMA Netw Open 2022.5e223433; Diabetes Obe Metab. 2023.25.1254-1264

BMF-650 was designed to reduce on-target agonism to achieve long-term tolerability

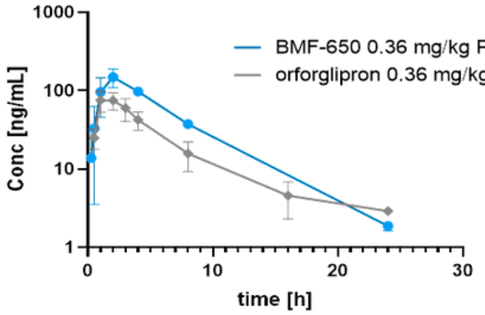
Compound	GLP-1 human EC_{50}	β-arrestin EC_{50}
BMF-650	2.6 nM	> 10 μM
orforglipron	0.1 nM	> 10 μM

- BMF-650 is designed as a biased small molecule GLP-1 receptor agonist, to selectively engage GLP-1 signaling
- Designed with reduced on-target potency to achieve less concentrated agonism
- No off-target activity of concern identified in the counter-screening panels

Wang X, et al. ObesityWeek® 2025; Poster 085.

Pharmacokinetics showed enhanced preclinical bioavailability signals with low variability

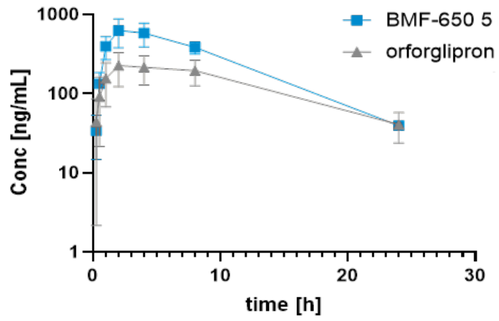
CYNOMOLGUS MONKEY PO PK DATA



BMF-650 showed approx. 2 - fold greater oral bioavailability in comparison to orforglipron

Compound	cyno PO	%F
BMF-650	0.36 mg/kg	54.0
orforglipron	0.36 mg/kg	29.4

SPRAGUE-DAWLEY RAT PO PK DATA



BMF-650 showed approx. 3 - fold greater oral bioavailability in comparison to orforglipron

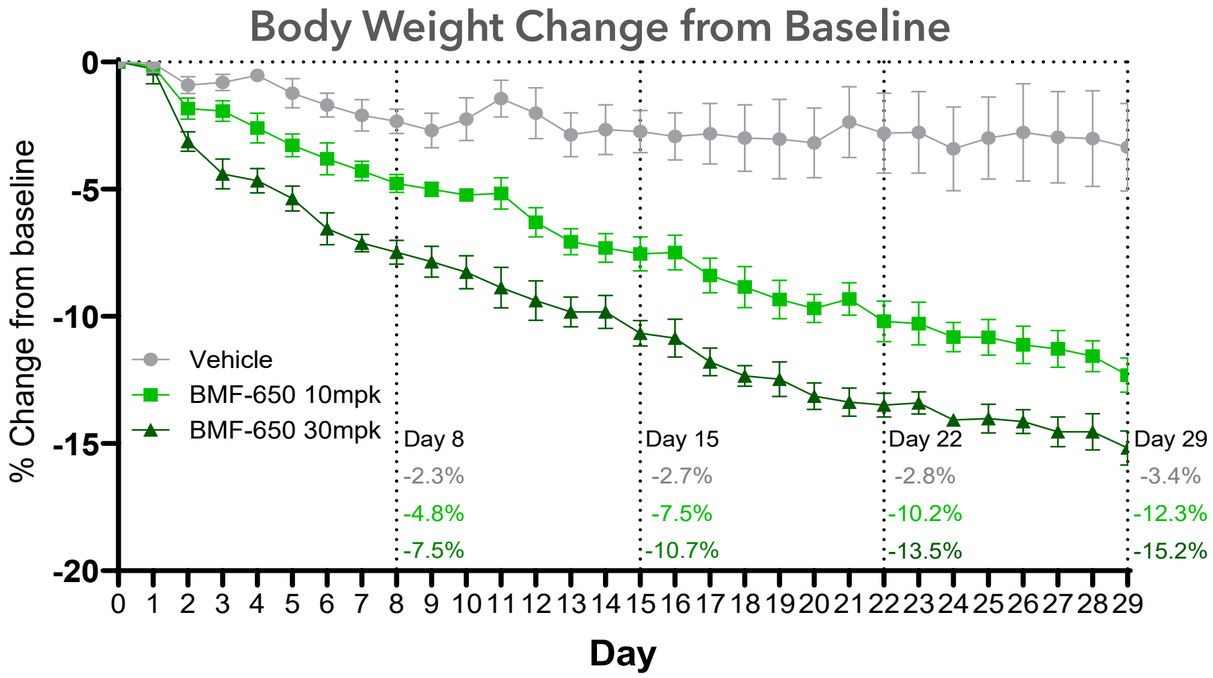
Compound	rat PO	%F
BMF-650	5 mg/kg	32.6
orforglipron	5 mg/kg	11.2

Wang X, et al. ObesityWeek® 2025; Poster 085.

Favorable PK observed across species with high oral bioavailability and long exposure

BMF-650 demonstrated robust, dose-dependent weight loss in obese monkeys with low rates of emesis

BMF-650 up to ~15% body weight reduction after 28 days



Wang, et al. Obesity 2025: 33 Sup 2 Poster #085

Week	Emesis (Vomiting)
1	18.2%*
2	7.0%
3	5.6%
4	1.4%

*One monkey (#3) in the low-dose cohort accounted for 12 of the 23 total events. % calculated for 70 dosing events/week

With 280 active dosing occurrences, there were a total of 23 emesis events (8.2%) balanced across both dosing cohorts.

BMF-650 | Design

A next-generation oral small-molecule GLP-1 RA with a differentiated profile designed to separate GI effects from weight loss

Broader intestinal absorption

Intended to reduce localized concentration peaks within the GI tract, and to promote better tolerated absorption across a broader intestinal surface and time window

Improved oral bioavailability

Intended to achieve systemic exposure with less unabsorbed drug

Gradual, sustained systemic exposure

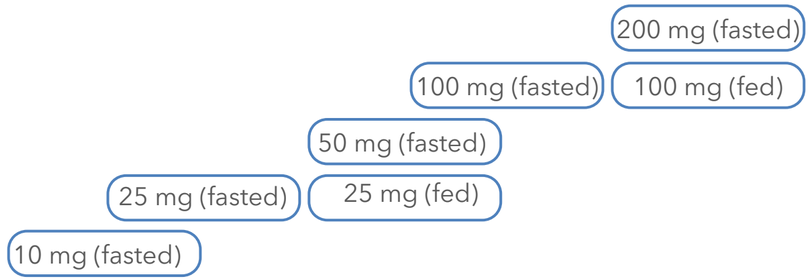
Designed to limit peak-to-trough fluctuations to avoid uneven systemic GLP-1 receptor stimulation

GLP-131: Phase 1 study design

Randomized, double-blind, placebo-controlled study evaluating safety, tolerability, and weight reduction with BMF-650 in overweight or obese participants

	Single Ascending Dose (SAD) Phase 1a	Multiple Ascending Dose (MAD) Phase 1b
Primary & Secondary Objectives	Safety and tolerability, PK, PD, and food effect	Safety and tolerability, and efficacy (weight-loss)
Eligibility	Healthy overweight or obese participants (BMI 25.0–40.0 kg/m²)	Healthy obese participants (BMI 30.0–45.0 kg/m²)
Design	N=40 5 cohorts x 	N=40 4 cohorts x 





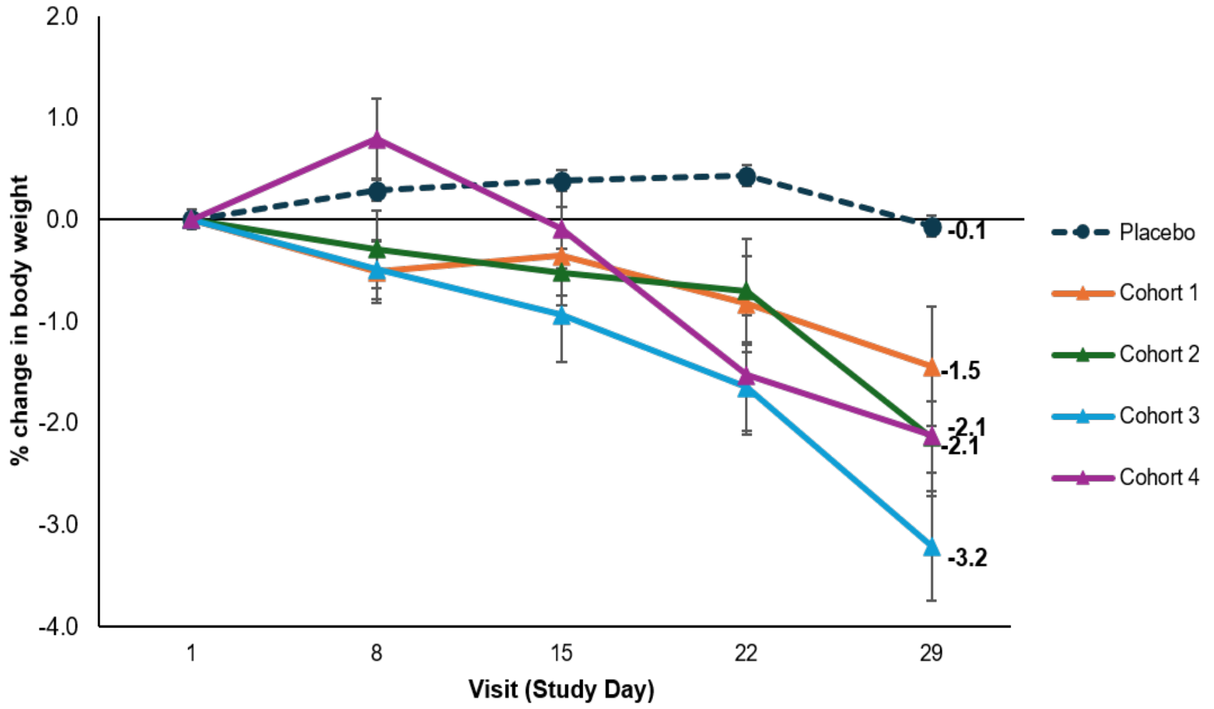
COHORT	Wk 1 → Wk 2 → Wk 3 → Wk 4
4	75 mg → 200 mg → 400 mg → 400 mg
3	75 mg → 150 mg → 300 mg → 300 mg
2	50 mg → 100 mg → 200 mg → 200 mg
1	10 mg → 25 mg → 50 mg → 100 mg

Baseline Demographics & Characteristics

Doses for Weeks 1–4	Active BMF-650					Pooled Placebo (N=8)
	Cohort 1 10/25/50/100 mg (N=8)	Cohort 2 50/100/200/200 mg (N=8)	Cohort 3 75/150/300/300 mg (N=8)	Cohort 4 75/200/400/400 mg (N=8)	MAD Cohorts 1-4 Total (N=32)	
Sex, female, n (%)	**6 (75)**	**6 (75)**	**3 (38)**	**4 (50)**	**19 (59)**	**4 (50)**
Age, years, mean	**49.5**	**45.6**	**49.9**	**42.3**	**46.8**	**40.3**
Weight, kg, mean	**97.0**	**109.1**	**96.1**	**97.6**	**100.0**	**111.1**
BMI, kg/m^2, mean	**34.8**	**36.2**	**31.9**	**34.4**	**34.3**	**35.9**

Clinical efficacy – weight reduction

	Mean percentage change in body weight from baseline at Day 29
Pooled Placebo (n=8)	**-0.1%**
Cohort 1 (n=8) (10/25/50/100 mg)	**-1.5%**
Cohort 2 (n=8) (50/100/200/200 mg)	**-2.1%**
Cohort 3 (n=8) (75/150/300/300 mg)	**-3.2%**
Cohort 4 (n=8) (75/200/400/400 mg)	**-2.1%**



Data are mean ± SE

Analysis of weekly weight reduction

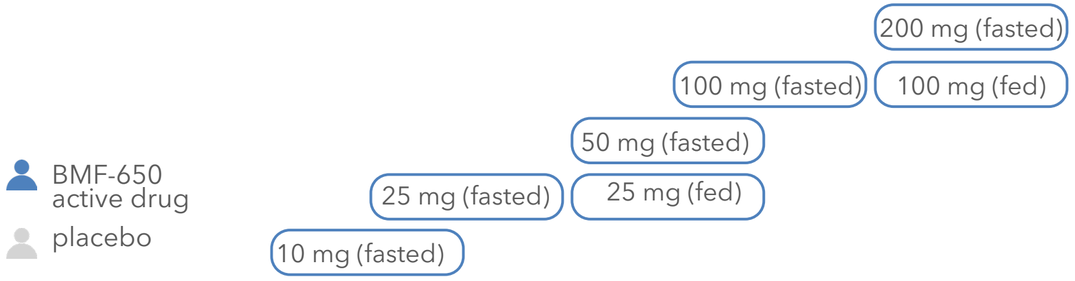
	Pooled PLACEBO n=8	Cohort 1 10 → 25 → 50 → 100	Cohort 2 50 → 100 → 200 → 200	Cohort 3 75 → 150 → 300 → 300	Cohort 4 75 → 200 → 400 → 400
Week 1	+0.33 kg	10 mg -0.47 kg	50 mg -0.41 kg	75 mg -0.45 kg	75 mg +0.76 kg
Week 2	+0.06 kg	25 mg +0.12 kg	100 mg -0.20 kg	150 mg -0.39 kg	200 mg -0.83 kg
Week 3	+0.12 kg	50 mg -0.48 kg	200 mg -0.23 kg	300 mg -0.70 kg	400 mg -1.37 kg
Week 4	-0.82 kg	100 mg -0.63 kg	200 mg -1.57 kg	300 mg -1.47 kg	400 mg -0.63 kg
TOTAL Weight Loss	-0.10 kg	-1.46 kg	-2.41 kg	-3.01 kg	-2.07 kg

- **14 of 16** weekly dosing cohorts showed incremental weekly absolute weight reduction.
- The average weight loss per week when dosed at 200 mg or higher dose was **0.97 kg / week.**
- Placebo achieved a **0.1 kg** weight reduction after 4 weeks. Dose Cohort 3 showed a weight reduction of **3.0 kg after 4 weeks.**
- PK results from Week 1 in Cohort 4 raised suspicion that patients were possibly not taking the drug, so a Cohort 5 was initiated under confinement.

GLP-131: Phase 1 study design + dose cohort 5

Randomized, double-blind, placebo-controlled study, evaluating safety, tolerability, and weight reduction with BMF-650 in overweight or obese participants

	Single Ascending Dose (SAD) Phase 1a	Multiple Ascending Dose (MAD) Phase 1b
Primary & Secondary Objectives	Safety and tolerability, PK, PD and food effect	Safety and tolerability, and efficacy (weight-loss)
Eligibility	Healthy overweight or obese participants (BMI 25.0–40.0 kg/m²)	Healthy obese participants (BMI 30.0–45.0 kg/m²) **Cohort 5 conducted under confinement to evaluate one-step titration regimen**
Design	N=40 5 cohorts x 	N=50 5 cohorts x 



COHORT	Wk 1 → Wk 2 → Wk 3 → Wk 4
5	**200 mg → 400 mg → 400 mg → 400 mg**
4	75 mg → 200 mg → 400 mg → 400 mg
3	75 mg → 150 mg → 300 mg → 300 mg
2	50 mg → 100 mg → 200 mg → 200 mg
1	10 mg → 25 mg → 50 mg → 100 mg

Baseline demographics & characteristics + dose cohort 5

Doses for Weeks 1–4	Active BMF-650						Pooled Placebo (N=10)
	Cohort 1 10/25/50/100 mg (N=8)	Cohort 2 50/100/200/200 mg (N=8)	Cohort 3 75/150/300/300 mg (N=8)	Cohort 4 75/200/400/400 mg (N=8)	Cohort 5 200/400/400/400 mg (N=8)	MAD BMF-650 Total (N=40)	
Sex, female, n (%)	**6 (75)**	**6 (75)**	**3 (38)**	**4 (50)**	**5 (63)**	**24 (60)**	**5 (50)**
Age, years, mean	**49.5**	**45.6**	**49.9**	**42.3**	**41.6**	**45.8**	**37.4**
Weight, kg, mean	**97.0**	**109.1**	**96.1**	**97.6**	**102.1**	**100.4**	**107.2**
BMI, kg/m^2, mean	**34.8**	**36.2**	**31.9**	**34.4**	**34.0**	**34.3**	**35.3**

Analysis of weekly weight reduction

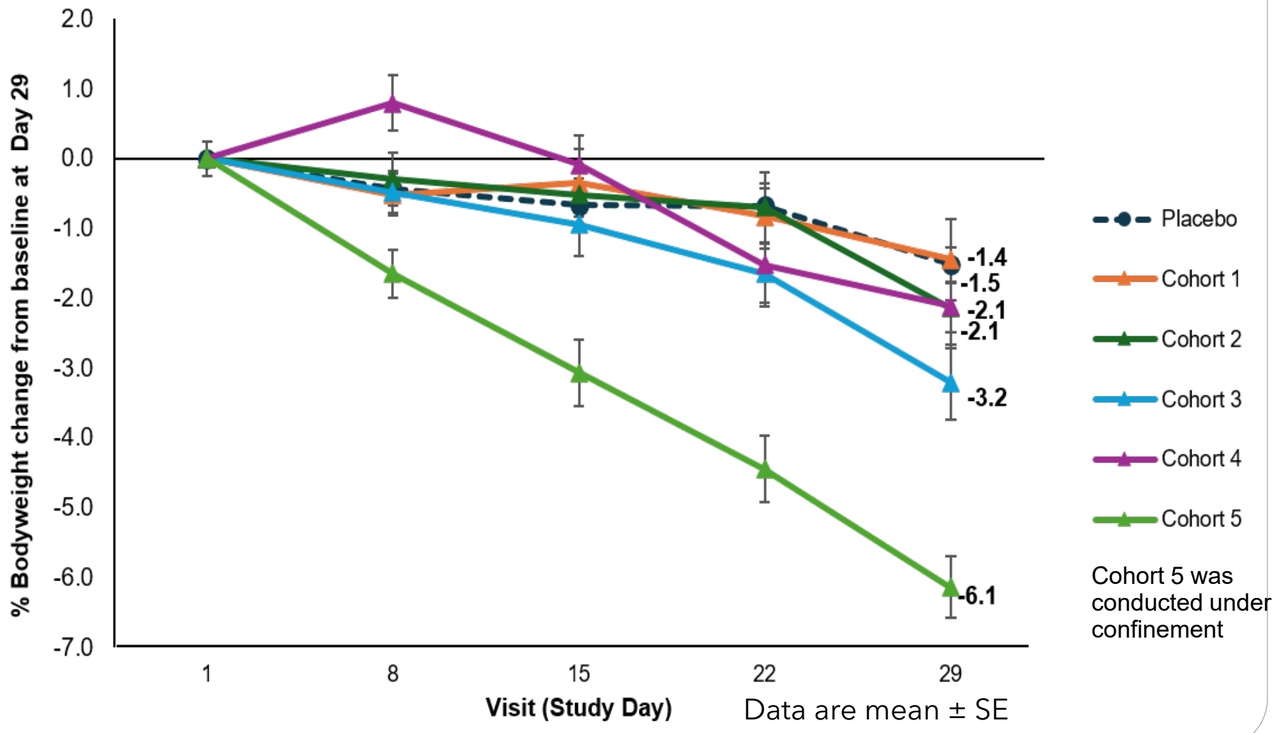
	Pooled PLACEBO n=8	Cohort 1 10 → 25 → 50 → 100	Cohort 2 50 → 100 → 200 → 200	Cohort 3 75 → 150 → 300 → 300	Cohort 4 75 → 200 → 400 → 400	Cohort 5 in-patient confinement: 200 → 400 → 400 → 400
Week 1	+0.33 kg	10 mg -0.47 kg	50 mg -0.41 kg	75 mg -0.45 kg	75 mg +0.76 kg	200 mg -1.72 kg
Week 2	+0.06 kg	25 mg +0.12 kg	100 mg -0.20 kg	150 mg -0.39 kg	200 mg -0.83 kg	400 mg -1.38 kg
Week 3	+0.12 kg	50 mg -0.48 kg	200 mg -0.23 kg	300 mg -0.70 kg	400 mg -1.37 kg	400 mg -1.39 kg
Week 4	-0.82 kg	100 mg -0.63 kg	200 mg -1.57 kg	300 mg -1.47 kg	400 mg -0.63 kg	400 mg -1.71 kg
TOTAL Weight Los	-0.10 kg	-1.46 kg	-2.41 kg	-3.01 kg	-2.07 kg	-6.20 kg

- Cohort 5 used confinement to monitor dosing adherence, with 200 mg once daily for one week, then 400 mg once daily for three weeks.
- Mean weight loss with BMF-650 was **1.55 kg/week**, and similar weight loss with placebo (n=2).
- All participants were provided 2,100 kcal/day. The 2 placebo participants consumed approximately 33% of the presented food, complicating interpretation of weight loss under confinement.

Clinical Efficacy

Weight reduction at Day 29 with participants oral dosing of BMF-650

	Bodyweight % mean change from baseline at Day 29	
Placebo (n=10)	**-1.5%**	
Cohort 1 (n=8) (10/25/50/100 mg)	**-1.4%**	
Cohort 2 (n=8) (50/100/200/200 mg)	**-2.1%**	
Cohort 3 (n=8) (75/150/300/300 mg)	**-3.2%**	
Cohort 4 (n=8) (75/200/400/400 mg)	**-2.1%**	
Cohort 5 (n=8) (200/400/400/400 mg)	**-6.1%**	Exploratory P-value P<0.01



Cohort 5 achieved 6.1% mean weight loss at Day 29
- 75% (6 of 8) participants on BMF-650 in Cohort 5 achieved >5% mean weight loss
- 100% (8 of 8) participants on BMF-650 in Cohort 5 achieved >4% mean weight loss

Primary Endpoint: Overall Treatment-Emergent Adverse Events (TEAEs)

Doses for Weeks 1–4 Participants, n(%)	Active BMF-650						
	Cohort 1 10/25/50/100 mg (N=8)	**Cohort 2** 50/100/200/200 mg (N=8)	**Cohort 3** 75/150/300/300 mg (N=8)	**Cohort 4** 75/200/400/400 mg (N=8)	**Cohort 5** 200/400/400/400 mg (N=8)	MAD BMF-650 Total (N=40)	Pooled Placebo (N=10)
Any TEAE	**6 (75.0)**	**4 (50.0)**	**5 (62.5)**	**6 (75.0)**	**7 (87.5)**	**28 (70.0)**	**4 (40.0)**
Mild (Grade 1)	**3 (37.5)**	**3 (37.5)**	**4 (50.0)**	**5 (62.5)**	**5 (62.5)**	**20 (50.0)**	**4 (40.0)**
Moderate (Grade 2)	**3 (37.5)**	**1 (12.5)**	**1 (12.5)**	**1 (12.5)**	**2 (25.0)**	**8 (20.0)**	**0**

0	**Severe TEAE (Grade 3)**	**0**	**Serious TEAE**	**0**	**TEAE-leading to dose modification**	**0**	**TEAE-leading to study discontinuation**

All TEAEs were mild or moderate and there were no dose modifications or discontinuations related to BMF-650. TEAEs were not associated with dose escalation, dosing cohort, or time at a given dose.

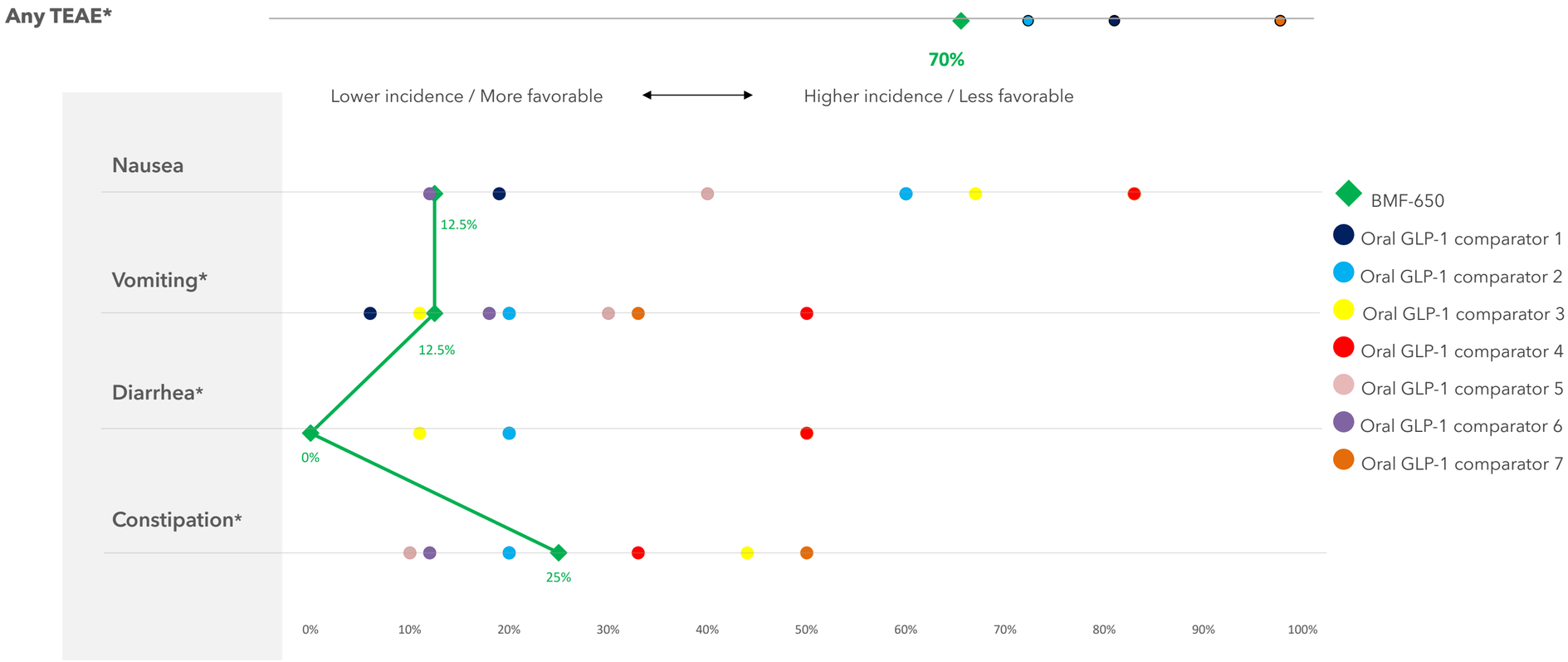
Select Gastrointestinal TEAEs

Doses for Weeks 1–4 **Participants, n (%)**	Active BMF-650						
	Cohort 1 10/25/50/100 mg (N=8)	Cohort 2 50/100/200/200 mg (N=8)	Cohort 3 75/150/300/300 mg (N=8)	Cohort 4 75/200/400/400 mg (N=8)	Cohort 5 200/400/400/400 mg (N=8)	MAD BMF-650 Total (N=40)	Pooled Placebo (N=10)
Nausea	**0**	**3 (37.5)**	**1 (12.5)**	**2 (25.0)**	**1 (12.5)**	**7 (17.5)**	**0**
Constipation	**0**	**1 (12.5)**	**1 (12.5)**	**0**	**2 (25.0)**	**4 (10.0)**	**1 (10.0)**
Vomiting	**1 (12.5)**	**0**	**1 (12.5)**	**0**	**1 (12.5)**	**3 (7.5)**	**0**
Diarrhea	**0**	**1 (12.5)**	**1 (12.5)**	**0**	**0**	**2 (5.0)**	**1 (10.0)**

The select GI-related TEAEs were all Grade 1 AEs in the highest dose level cohort.

BMF-650 at highest dose level vs late-stage oral GLP-1 Phase 1 disclosures

Select GI tolerability



* Not all comparator companies reported this adverse event.

Cross-trial comparisons are descriptive and should be interpreted cautiously due to differences in study design, treatment duration, dose escalation, AE collection and reporting.

Class-like changes in liver enzymes, fasting glucose and heart rate

Doses for Weeks 1–4	Active BMF-650						
	Cohort 1 10/25/50/100 mg (N=8)	Cohort 2 50/100/200/200 mg (N=8)	Cohort 3 75/150/300/300 mg (N=8)	Cohort 4 75/200/400/400 mg (N=8)	Cohort 5 200/400/400/400 mg (N=8)	MAD BMF-650 Total (N=40)	Pooled Placebo (N=10)
Alanine aminotransferase (ALT), U/L	**-1.6**	**-1.4**	**-7.4**	**-9.9**	**-9.4**	**-5.9**	**-6.1**
Aspartate aminotransferase (AST), U/L	**-1.9**	**-1.7**	**-2.8**	**-3.7**	**-3.8**	**-2.8**	**-2.9**
Fasting glucose, mg/dL	**-7.1**	**-5.9**	**-7.2**	**-14.7**	**-11.4**	**-9.2**	**-3.5**
Heart rate, beats/min	**0.6**	**8.1**	**10.4**	**3.7**	**9.0**	**6.4**	**0.8**

Data shown represents mean change from baseline to Day 28

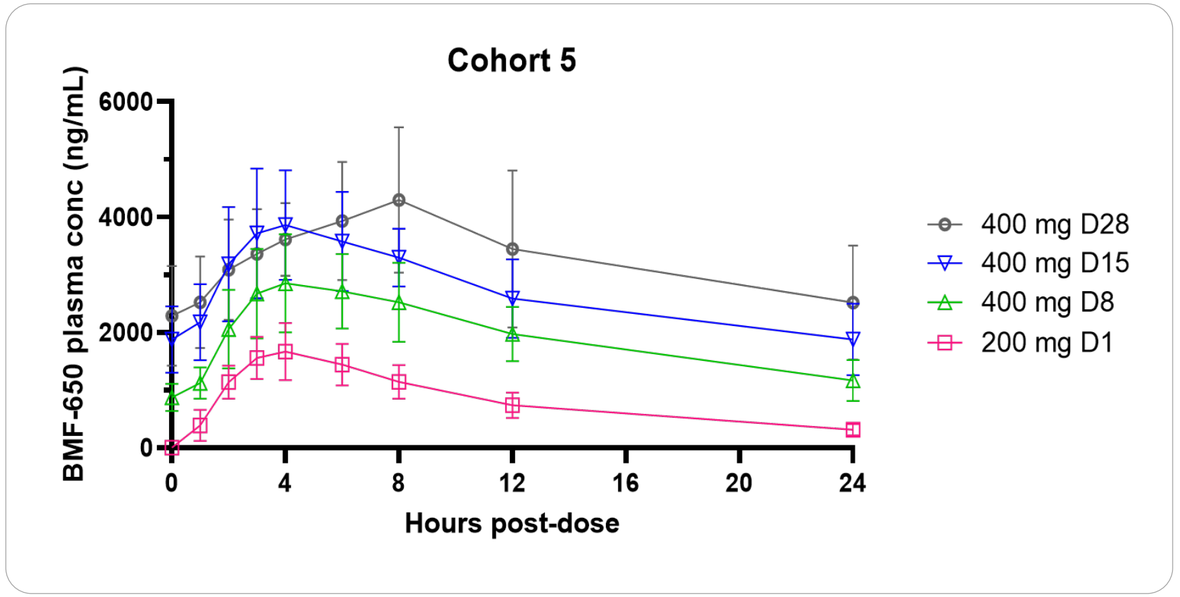
No adverse events involving ALT/AST elevations or heart rate were reported
Reductions in fasting glucose were observed for all doses of BMF-650

BMF-650 delivered target exposure with low peak to trough ratio in human PK

Selected PK parameters for Cohort 5 Day 28

	Cohort 5 Day 28
C_{max} (peak plasma concentration)	4400 ng/mL (± 26.4%)
C_{min} (trough plasma concentration)	2520 ng/mL (± 39.4%)
Peak to trough ratio	1.7
$AUC_{0\text{-}24hrs}$	79000 hr*ng/mL (± 31.8%)

* Preliminary PK analysis (mean).



* Preliminary PK analysis (mean).

Human PK for BMF-650 aligned well with nonclinical predictions and showed low peak/trough ratio
Observed human PK exposure matched favorable monkey exposure in the respective weight-loss study

BMF-650 | Phase 1b MAD

Phase 1 findings provide support for the BMF-650 design hypothesis

Rapid one-step titration to 400 mg is well tolerated

BMF-650 reached the target dose of 400 mg QD via a single titration step design post week 1, supporting a potentially simple and practical dosing paradigm

Sustained and meaningful weight reduction observed at higher dose regimens

Cohort 5 demonstrated mean weight loss at 400 mg across consecutive weeks (−1.4, −1.4 and −1.7 kg/week), reaching 6.1% at week 4, with no evidence of attenuation over the observed treatment period

Encouraging GI tolerability profile

No serious TEAEs, no TEAE-related dose modifications and no TEAE-related study discontinuations occurred across active MAD cohorts, supporting longer-duration evaluation

Next Steps:
Advancing BMF-650 development while optimizing the clinical profile

Clinical Findings	• Highest dose achieved with only a single titration step while maintaining favorable tolerability • Weight loss as expected in line with other GLP-1 agents • Overall, generally well tolerated with no exposure-related safety signals
BMF-650 Next Steps	• Advance Phase 2 development planning incl. a “no-titration” regimen at 400 mg QD • Initiate longer-term toxicology studies to support Phase 2 dosing

THANK YOU

(NASDAQ: BMEA)

For questions or inquiries, please reach out to Meichiel Weiss at ir@biomeafusion.com

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