COVALENT-111: Phase II

First Data Readout of Initial Healthy Volunteer (HV) and Type 2 Diabetes Mellitus (T2DM) Cohorts

March 28, 2023

biomea FUSION™

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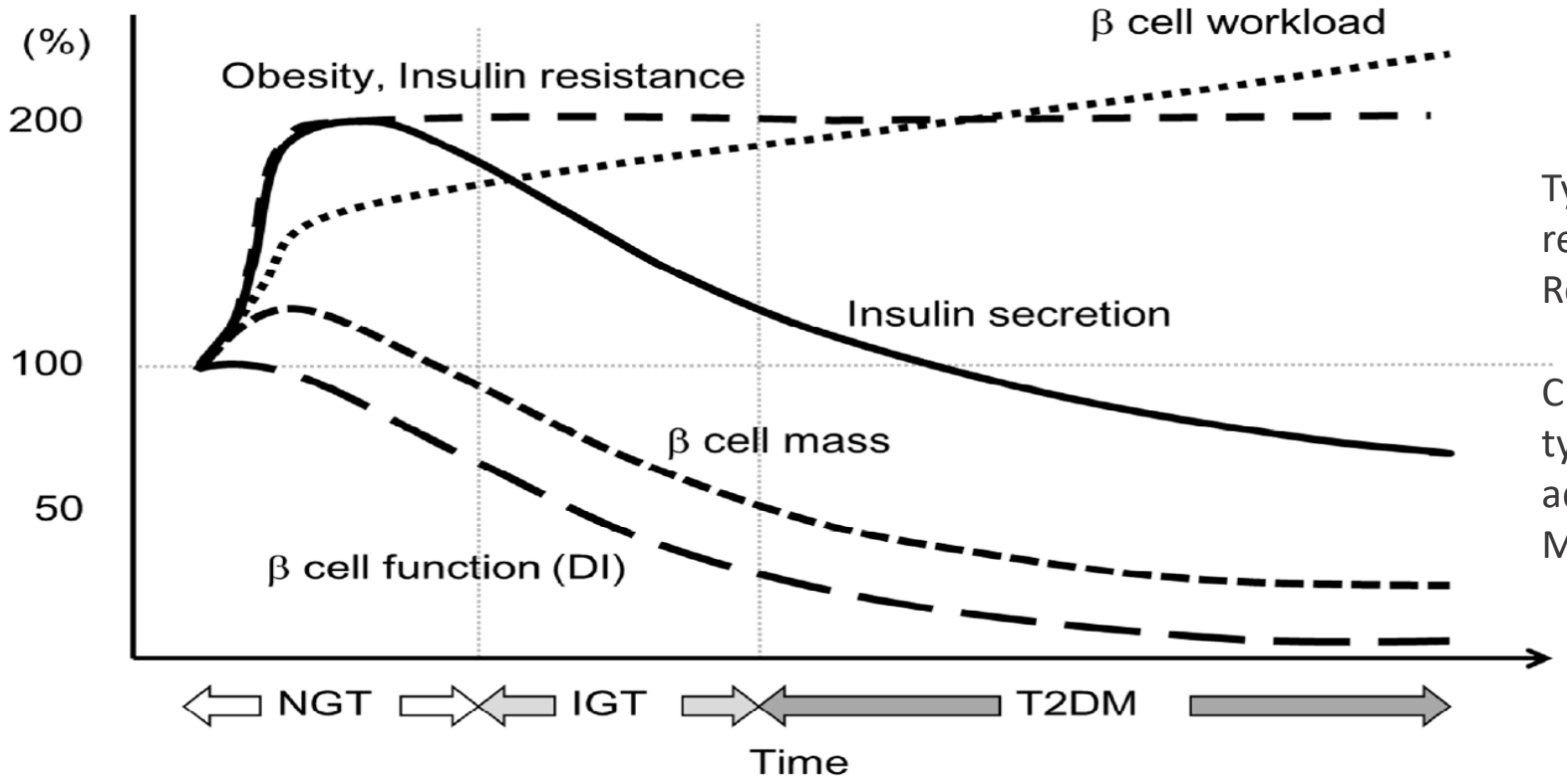
Agenda

Introduction	Ramses Erdtmann *Chief Operating Officer & Co-Founder of Biomea*
Diabetes Background & Overview	Dr. Juan Frias *Medical Director & Principal Investigator of Velocity Clinical Research, Scientific Advisory Board Member of Biomea*
Diabetes & Beta Cell Function	Dr. Rohit Kulkarni *Senior Investigator and Professor of Medicine of Harvard Medical School, Faculty Member, Joslin Diabetes Center, Scientific Advisory Board Member of Biomea*
COVALENT-111 First Study Results	Dr. Steve Morris *Chief Medical Officer of Biomea*
Executive Summary & Outlook	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 typically **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

Menin – Downregulated by Prolactin during Pregnancy

Allowing for beta cell expansion and prevention of gestational diabetes

- Stanford researchers have observed that during pregnancy, maternal pancreatic islets grow to match dynamic physiological demands.
- Menin has been found to control islet growth in pregnant mice. Pregnancy stimulates proliferation of maternal pancreatic islet beta-cells, an effect accompanied by reduced beta-cell levels of menin and its targets.
- Prolactin, a hormonal regulator of pregnancy, represses beta-cell menin levels and stimulates beta-cell proliferation.
- Transgenic expression of menin in maternal beta-cells prevented islet expansion and led to hyperglycemia and impaired glucose tolerance, hallmark features of gestational diabetes.

REPORTS

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

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During pregnancy, maternal pancreatic islets grow to match dynamic physiological demands, but the mechanisms regulating adaptive islet growth in this setting are poorly understood. Here we show that menin, a protein previously characterized as an endocrine tumor suppressor and transcriptional regulator, controls islet growth in pregnant mice. Pregnancy stimulated proliferation of maternal pancreatic islet β-cells that was accompanied by reduced islet levels of menin and its targets. Transgenic expression of menin in maternal β-cells prevented islet expansion and led to hyperglycemia and impaired glucose tolerance, hallmark features of gestational diabetes. Prolactin, a hormonal regulator of pregnancy, repressed islet menin levels and stimulated β-cell proliferation. These results expand our understanding of mechanisms underlying diabetes pathogenesis and reveal potential targets for therapy in diabetes.

Maternal pancreatic islet expansion in rodents and humans (*1–3*) suggests that adaptive islet cell growth is a mechanism for ensuring metabolic balance in pregnancy, a physiological state marked by increased insulin demand. Descriptive studies with rats (*2*, *3*) support the hypothesis that proliferation of insulin-secreting islet β-cells is the principal mechanism of β-cell expansion in pregnancy, but the molecular basis of facultative maternal β-cell proliferation is unknown. Moreover, it is unclear if impaired maternal β-cell proliferation leads to reduced insulin levels and gestational diabetes (*4*).

To investigate the mechanisms controlling maternal islet expansion, we examined β-cell mass in pregnant C57Bl6 mice. We found that maternal β-cell mass increased by twofold (fig. S1A), accommodating increases in maternal body mass (fig. S1B). After parturition, maternal β-cell mass and body mass returned to prepartum levels (fig. S1, A and B). To assess maternal islet cell proliferation, we performed labeling studies with bromodeoxyuridine (BrdU). β-cell proliferation increased in pregnant mice until 15 days postcoitum (dpc) and then declined to prepartum levels (Fig 1, A to C). Thus, maternal islet β-cell expansion and mass are dynamic in mice.

Hyperplasia of the maternal pituitary (*5*) and islets in pregnancy is reminiscent of endocrine proliferation in multiple endocrine neoplasia type I (MEN1), a human cancer syndrome characterized by synchronous tumors of the pituitary, endocrine pancreas, and parathyroid. Most MEN1 cases result from mutation of *Men1*, whose protein product is menin (*6*, *7*). In mice and humans, mutation and pathological *Men1* loss promote neuroendocrine tumors, including islet β-cell tumors in *Men1* (*7*, *8*). Thus, we postulated that physiological changes in *Men1* expression might regulate facultative maternal β-cell growth in pregnancy. Immunohistology, Western blotting, and real-time reverse transcription polymerase chain reaction (RT-PCR) studies of maternal islets isolated during gestation revealed that islet levels of *Men1* mRNA and menin decreased in pregnancy (Fig. 1, D to G), then increased to prepartum levels by 1 week after birth of the pups (Fig. 1, F and G). By contrast, we did not detect changes in maternal islet levels of mRNA encoding mixed lineage leukemia-1 (MLL1), a protein that associates with menin (Fig. 1F). Thus, attenuated *Men1* expression corresponded with increased β-cell proliferation in maternal islets.

Menin functions in a histone methyltransferase protein complex containing MLL (*9*, *10*). This complex promotes trimethylation of histone H3 on lysine 4 (H3K4), an epigenetic mark associated with transcriptionally active chromatin. Menin-dependent histone methylation maintains expression of $p27^{Kip1}$ and $p18^{Ink4c}$ (hereafter, *p27* and *p18*), which encode cyclin-dependent kinase (CDK) inhibitors that prevent islet proliferation (*11–14*). Consistent with our previous findings in islet tumors (*11*), reduced islet menin levels in pregnancy after 8 dpc were accompanied by reduced *p27* and *p18* mRNA and protein levels (Fig. 1G and fig. S1C) and, as revealed by chromatin immunoprecipitation (ChIP), by decreased levels of menin and trimethyl H3K4 associated with *p27* and *p18* (Fig. 1H). Thus, attenuated menin levels and function reduced pancreatic islet *p27* and *p18* expression in pregnant mice.

To determine whether adaptive maternal β-cell proliferation might require reduced *Men1* expression, we generated mice that permitted conditional *Men1* expression in β-cells. Transgenic mice producing hemagglutinin-tagged menin under control of the tetracycline response element (TRE-*Men1*) (*15*) were generated and mated with mice expressing the reverse tetracycline trans-activator (rtTA) in β-cells directed by the rat insulin promoter (RIP) (abbreviated βMen1), administration of doxycycline (Dox) allows rtTA binding to the TRE element and stimulates β-cell expression of *Men1* mRNA and menin protein (fig. S2, A and B). Exposure of RIP-*rtTA* or TRE-*Men1* single transgenic mice to Dox did not induce changes in menin levels (fig. S2, A

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25. We thank K. Birnbaum for the RM1000 data set and B. Parlott and L. Nussaume for providing the J2501 data set, members of the Duke Center for Systems Biology and L. Brady for useful discussions, M. Levesque for assistance

Supporting Online Material
www.sciencemag.org/cgi/content/full/318/5851/801/DC1
Materials and Methods
Figs. S1 to S23
Tables S1 to S14
References
Folders S1 to S6
8 June 2007; accepted 2 October 2007
10.1126/science.1146265

Karnik et al. Science, (2007), 801-806, 318(5851)

Summary of Results

	Cohort 2		Cohort 3	
	BMF-219	**Placebo**	**BMF-219**	**Placebo**
Number of Subjects	10	2	10	2
Exposure: C_{max} (ng/mL)/ AUC (hr*ng/mL)	34.8 / 84.3	-	94.2 / 224	-
Median (Mean) HbA1c % at Baseline	7.9 (8.0)	8.4 (8.4)	7.8 (8.1)	7.8 (7.8)
Median (Mean) Change in HbA1c % at Week 4	**-0.3 (-0.25)**	-0.1 (-0.1)	**-1.0 (-0.81)**	-0.15 (-0.15)

Note: **Cohort 2** – 100 mg BMF-219 or placebo daily for 4 weeks taken with food
Cohort 3 – 100 mg BMF-219 or placebo daily for 4 weeks taken without food

COVALENT-111: A Phase 1/2 Randomized, Double-Blind, Placebo-Controlled Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BMF-219, an Oral Covalent Menin Inhibitor, in Healthy Adult Subjects and in Adult Subjects with Type 2 Diabetes Mellitus (NCT05731544)

Phase 1 (SAD)

SAD C1 to SAD C4 (HVs)
Total N=40
Dose [100, 200, 400, and 600 mg]

Phase 2 (MAD)

MAD C1 (HVs)
Total N = 16

MAD C2 to MAD C8 (T2DM)
Total N=108

Dose [100, 200, 300, 400, 600 mg]

In Phase 2, COVALENT-111 is enrolling subjects with an HbA1c of 7-10% despite being on standard of care (up to three T2DM agents).

Study Treatment: BMF-219

- A covalent small molecule menin inhibitor, administered orally daily in 28 day cycles

Primary Objective:

- Evaluate safety and tolerability of BMF-219

Secondary Objectives:

- Evaluate PK of BMF-219
- Evaluate the effect on BMF-219 on glycemic parameters (HbA1c, PG) and few additional parameters using OGTT, 7-day CGM
- Evaluate the changes in beta cell function
- Evaluate impact on lipid parameters, body weight etc.

Exploratory Objectives:

- To assess the durability of response to glycemic parameters

Dose Escalation Phase (Oral, Daily Dosing X 28 days)

Dosing Scheme

400 mg → Coming soon

200 mg → In progress

100 mg → Completed

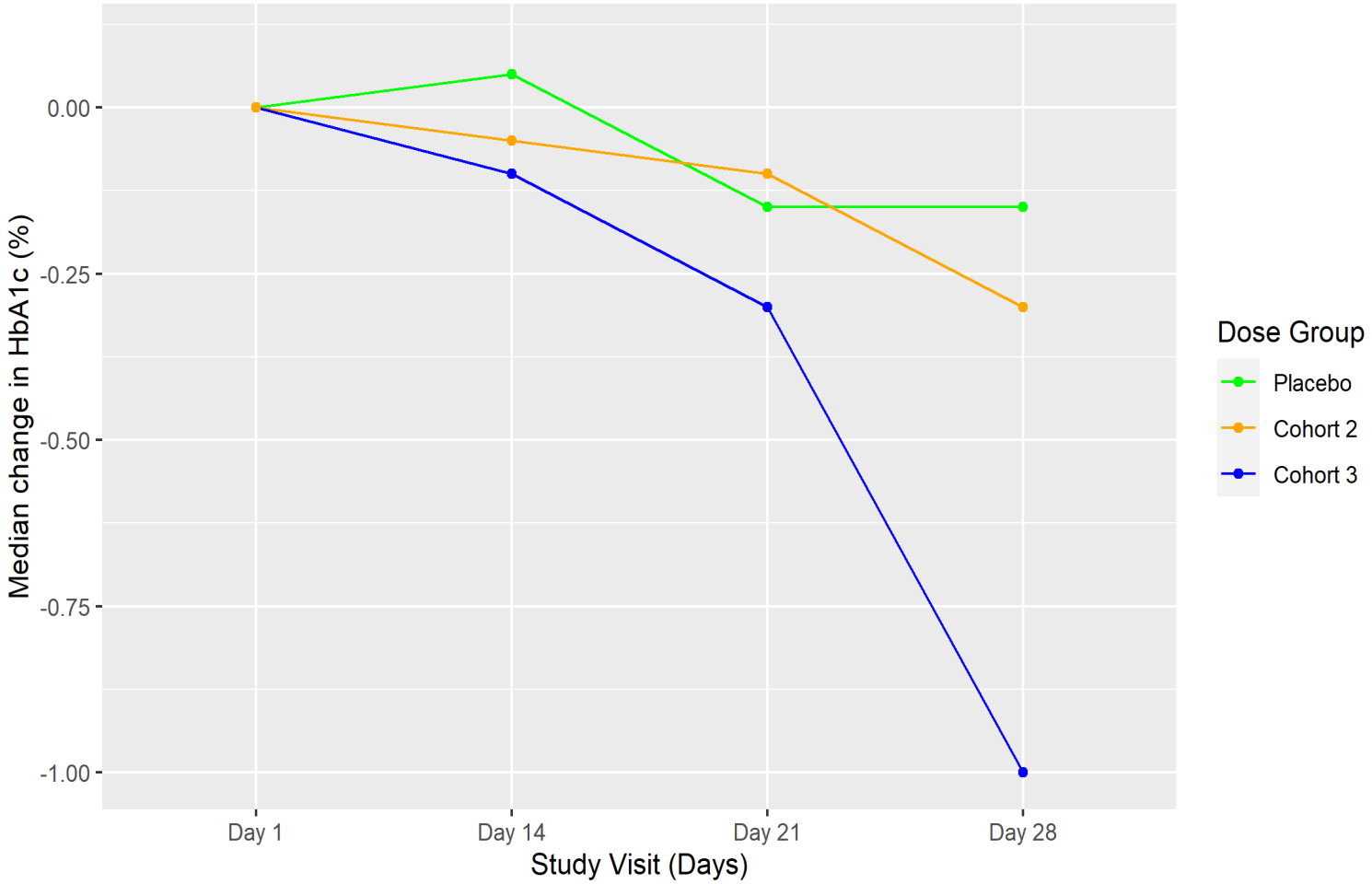
- **Cohort 1** Healthy Volunteer
- **Cohort 2** Taken w/ food
- **Cohort 3** Taken w/o food

- Dose Escalation Phase (Total N) = 60 Type 2 Diabetes
  - Each dose cohort [N=10 active, 2 placebo]
  - Key Inclusion criteria: HbA1c= 7-10%; Time since diagnosis within 15 yrs. on stable anti-diabetic regimen (up to 3 agents) for at least 2 months prior to enrollment.
  - (H.V.) Study treatment duration – once daily dosing for 14 days
  - (T2DM) Study treatment duration – once daily dosing for 28 days
  - Follow-up duration – 5 months post completion of study treatment
- Dose Expansion Phase at two dose levels (Total N) = 24 Type 2 Diabetes

COVALENT-111 Baseline Patient Characteristics

	Cohort 2		Cohort 3	
	BMF-219	**Placebo**	**BMF-219**	**Placebo**
Number of Subjects	10	2	10	2
Age (min, max)	35, 60	40, 53	38, 63	35, 61
Sex (M, F)	7, 3	2, 0	6, 4	2, 0
Time since T2DM diagnosis (min, max)	4 yrs, 14 yrs	~1 yrs, 5 yrs	6 mo, 9 yrs	9 mo, 9 yrs
Concurrent Medications for T2DM	▪ Metformin (7/10) ▪ Janumet (1/10) ▪ Jardiance [Metformin + Empagliflozin] (1/10) ▪ Synjardy [Metformin + Empagliflozin] (1/10)	▪ Metformin alone (1/2) ▪ Janumet [Metformin + Sitagliptin] (1/2)	▪ Metformin alone (9/10) ▪ Janumet and Farxiga [Dapagliflozin] (1/10)	▪ Metformin (2/2)

Observed HbA1c Lowering of BMF-219



Cohort 2

Response Rate

70% of patients responded to BMF-219

HbA1c (all pts)

Median Baseline: 7.9%

Median Δ: - 0.3% (at week 4)

Cohort 3

Response Rate

89% of patients responded to BMF-219

HbA1c (all pts)

Median Baseline: 7.8%

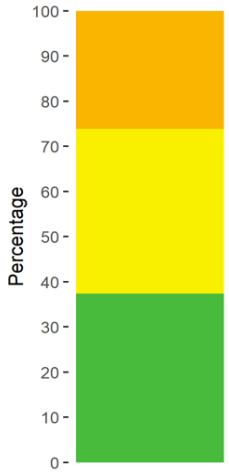
Median Δ: - 1.0% (at week 4)

COVALENT-111 HbA1c Summary Results at Week 4

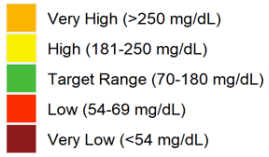
	Cohort 2		Cohort 3	
	BMF-219	**Placebo**	**BMF-219**	**Placebo**
Number of Subjects	10	2	10	2
HbA1c (%) at Baseline	7.1 – 9.1		7.0 – 9.8	
Median HbA1c (Mean) (%) at Baseline	7.9 (8.0)	8.4 (8.4)	**7.8 (8.1)**	7.8 (7.8)
Number of Subjects with Reduction in HbA1c at week 4	7/10 (70%)	1/2	**8/9 (89%)***	1/2
≥0.5% Reduction in HbA1c at Week 4	3/10 (30%)	1/2	**7/9 (78%)***	0
≥1% Reduction in HbA1c at Week 4	0	0	**5/9 (56%)***	0
Median Change in HbA1c at Week 4 (Mean) (%)	-0.3 (-0.25)	-0.1 (-0.1)	**-1.0 (-0.81)**	-0.15 (-0.15)

*Note: The active group denominator in Cohort 3 is 9 because the week 4 sample for one patient was unable to process.

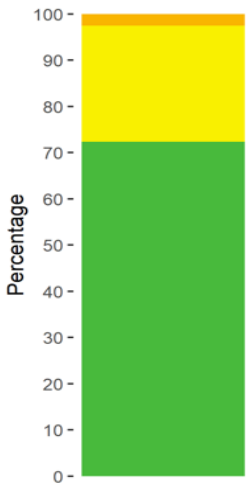
Case Report Cohort 3 Patient Results (Patient A): Glycemic Parameters



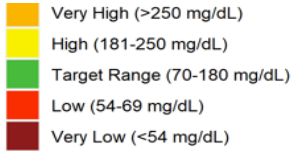
Continuous Glucose Monitoring
Baseline



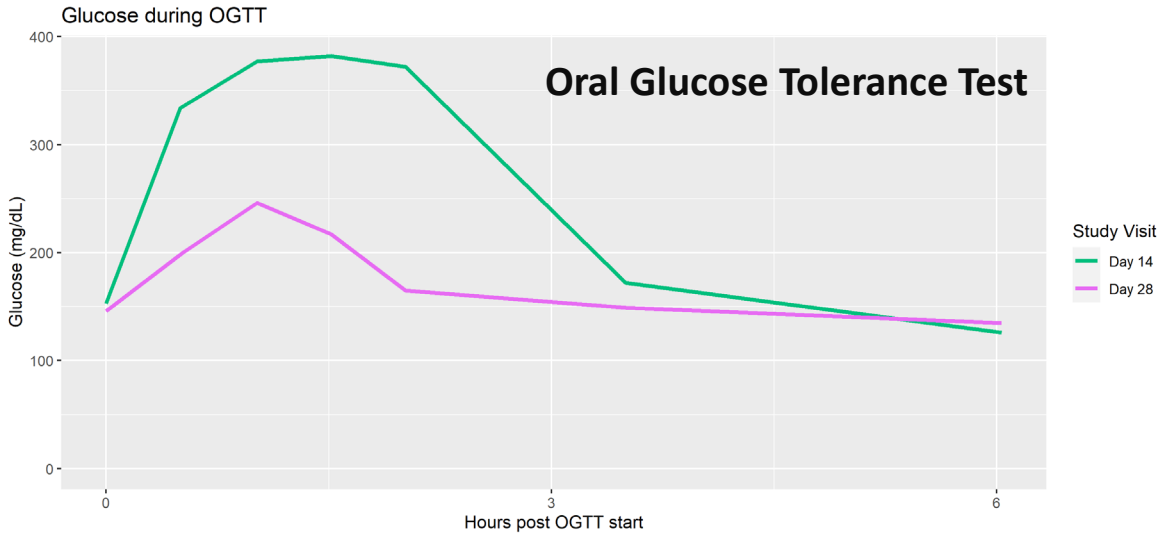
- Average glucose 205 mg/dL
- 37% time in Target Range

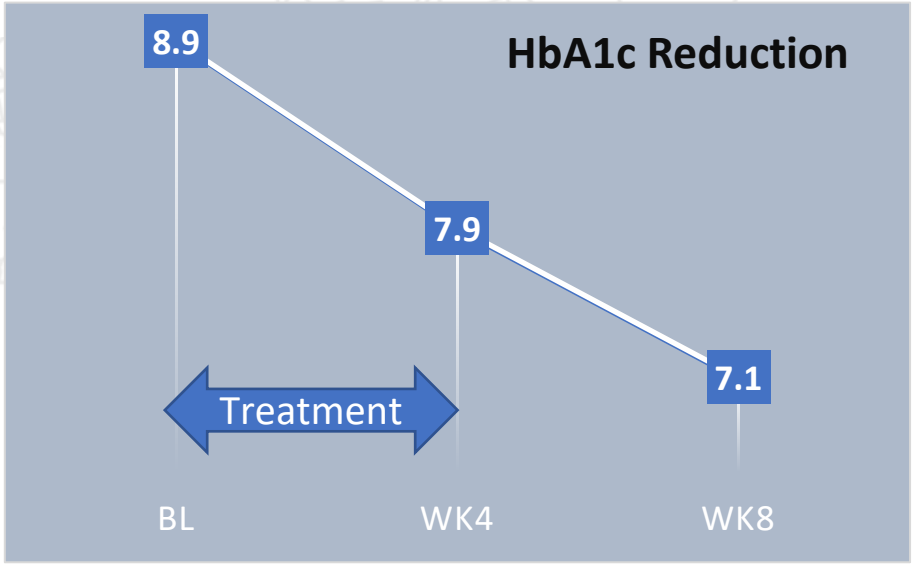


Continuous Glucose Monitoring
Week 4

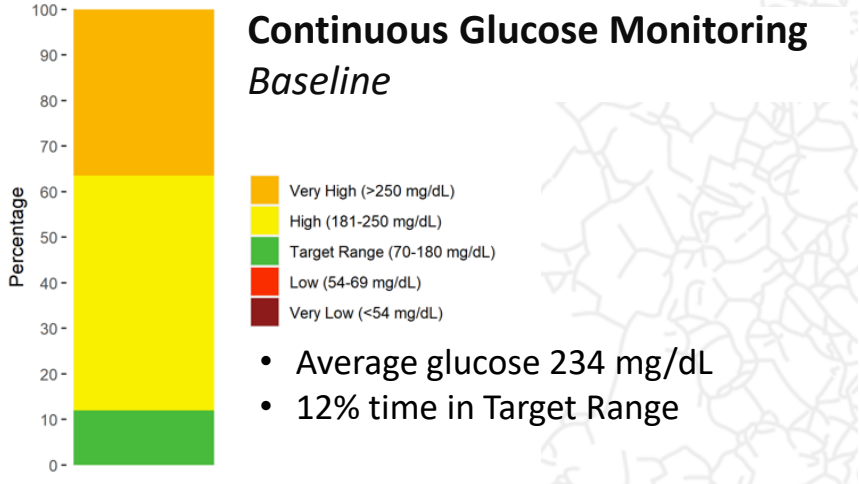


- Average glucose 169 mg/dL
- 72% time in Target Range

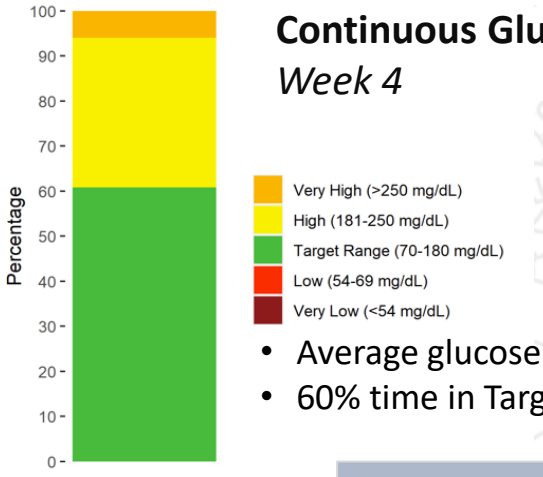




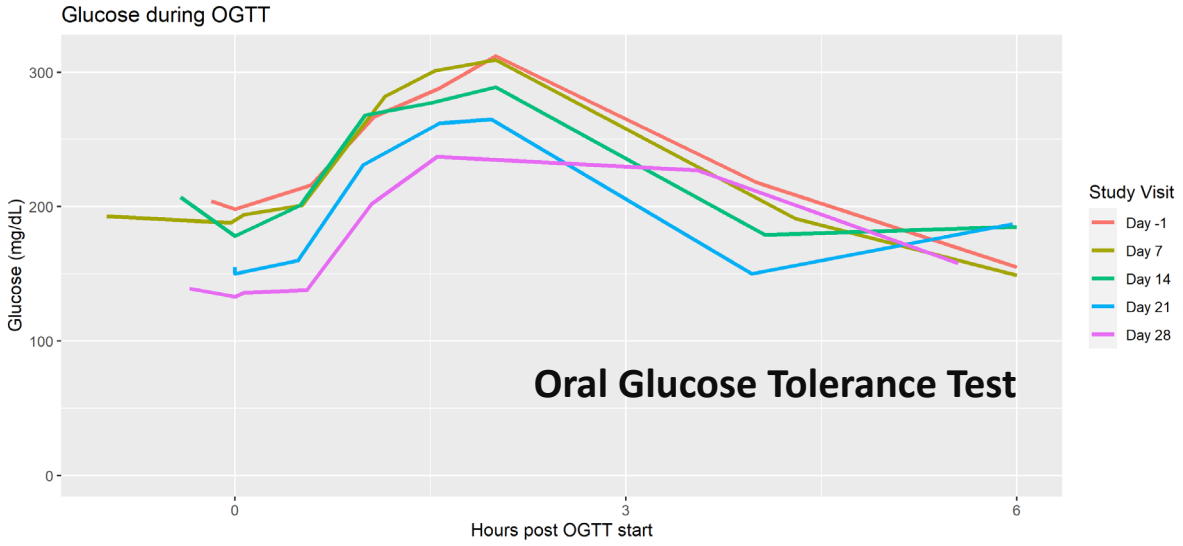
Case Report Cohort 3 Patient Results (Patient B): Glycemic Parameters

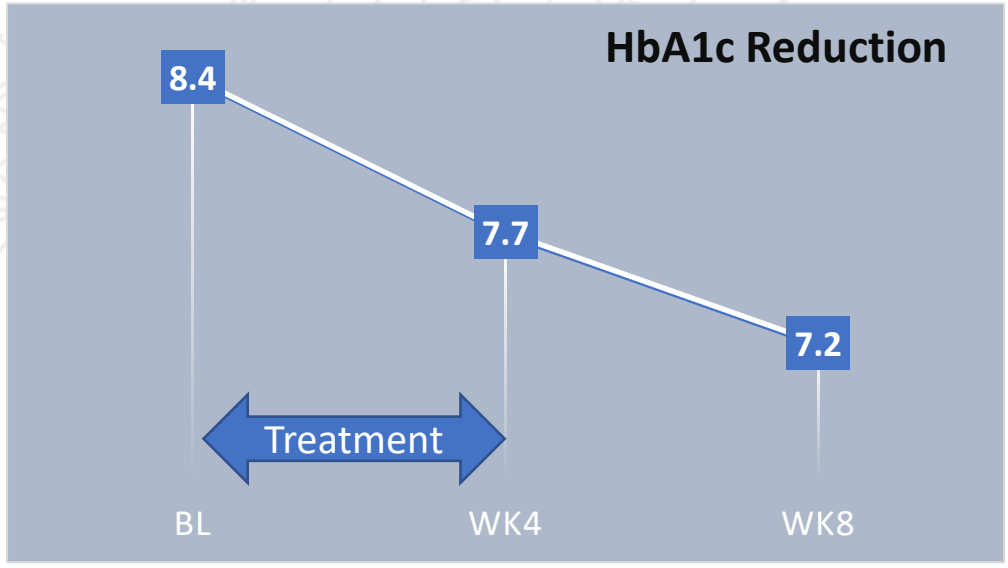


- Average glucose 234 mg/dL
- 12% time in Target Range



- Average glucose 174 mg/dL
- 60% time in Target Range





COVALENT-111 Cohort 1 All Treatment Emergent Adverse Events (TEAEs) (Healthy Volunteers, n=16; *100 mg once daily for 14 days*)

Preferred Term for TEAE	BMF-219 (N=12)	Placebo (N=4)	Total (N=16)
Subjects with ≥1 TEAE	2 (16.7%)	1 (25%)	3 (18.8%)
Headache	1 (8.3%)	1 (25%)	2 (12.5%)
Sharp left eye pain	1 (8.3%)	0	1 (6.3%)

*All TEAEs were Grade 1

COVALENT-111 Cohort 2 & 3 All TEAEs
(Type 2 Diabetes n=24; 100 mg once daily dosing X 4 weeks)

Preferred Term for TEAE	BMF-219 (N=20)	Placebo (N=4)	Total (N=24)
Subjects with ≥1 TEAE	7 (35%)	2 (50%)	9 (38%)
Abdominal bloating	2 (10%)	0	2 (8.4%)
Elevated pancreatic polypeptide in plasma	0	2 (50%)	2 (8.4%)
Cough	1 (5%)	1 (25%)	2 (8.4%)
Elevated GGT	1 (5%)	0	1 (4.2%)
Elevated AST	1 (5%)	0	1 (4.2%)
Elevated ALT	1 (5%)	0	1 (4.2%)
Sore throat	1 (5%)	0	1 (4.2%)
Non-specific GI symptoms	1 (5%)	0	1 (4.2%)
Decreased interleukin-6	1 (5%)	0	1 (4.2%)
Swollen lymph nodes	0	1 (25%)	1 (4.2%)
Elevated lipase	1 (5%)	0	1 (4.2%)
Intermittent headaches	1 (5%)	0	1 (4.2%)
Contact dermatitis	1 (5%)	0	1 (4.2%)

All TEAEs are Grade 1 except Elevated Lipase (Grade 2)

Summary of Data

Safety

- BMF-219 demonstrated a well-tolerated safety profile
- No dose discontinuations
- All 20 subjects completed 4 weeks of treatment and continue in 5-month follow-up period
- No severe or serious TEAEs were observed
- No episodes of symptomatic hypoglycemia occurred in any patients

Efficacy

Cohort 3 highlights

- 89% pts achieved a reduction in HbA1c
- 78% pts achieved ≥ 0.5% reduction in HbA1c
- 56% pts achieved ≥ 1% reduction in HbA1c
- Positive trend in OGTT and CGM parameters

Q & A

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