COVALENT-111: PHASE II

Preliminary Results of Healthy Volunteer (HV) and Type 2 Diabetes Mellitus (T2DM) 100mg Cohorts

June 26, 2023

biomea FUSION

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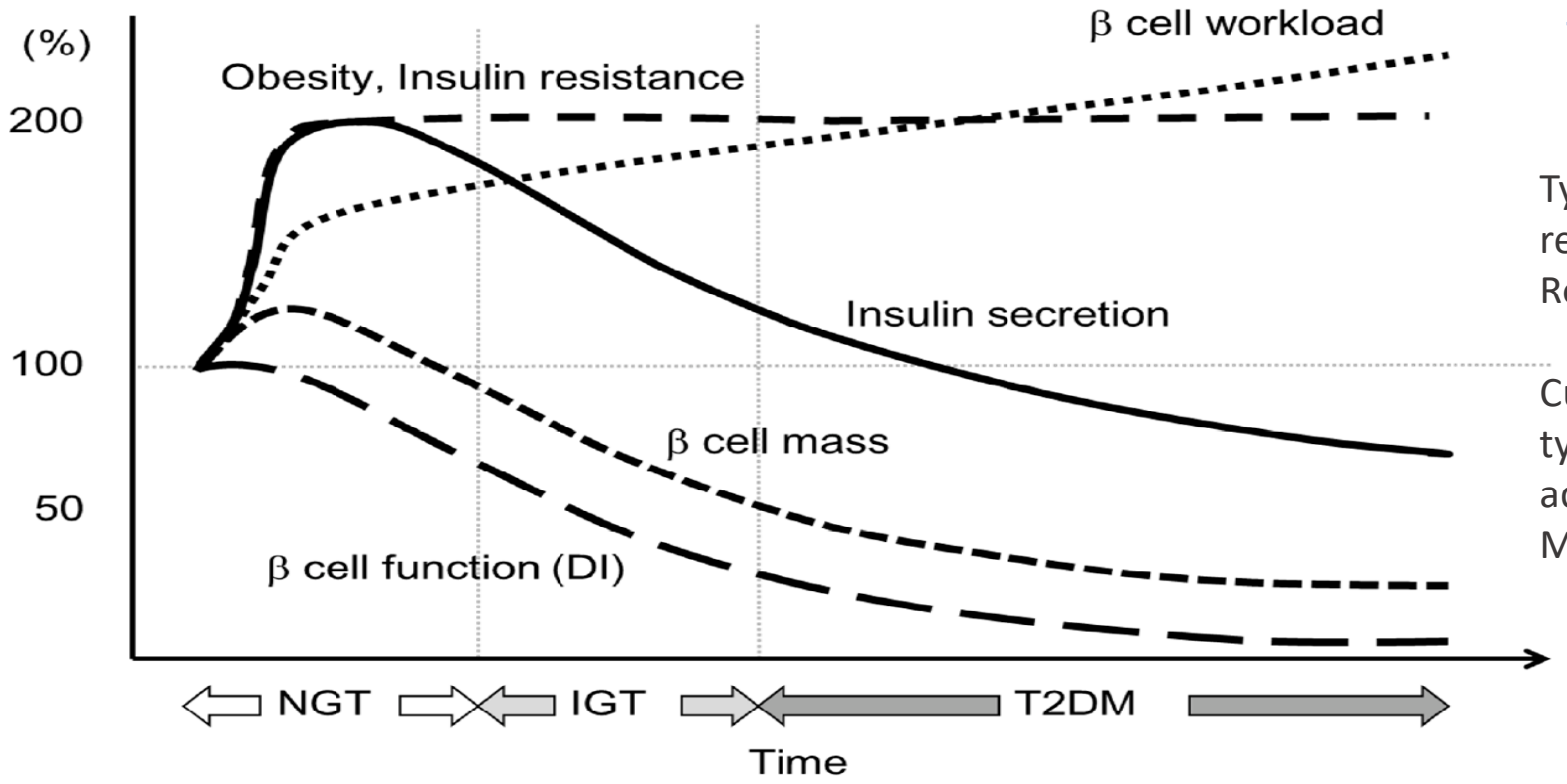
Type 2 Diabetes Progression is Driven by Loss of Beta Cell Mass



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

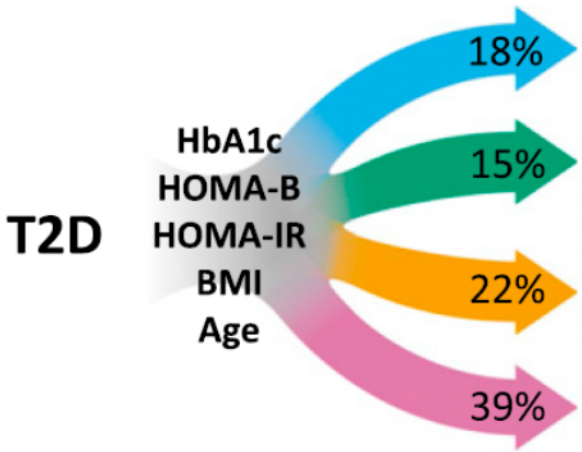
Normal Glucose Tolerance (NGT) followed by Impaired Glucose Tolerance (IGT) followed by Type 2 Diabetes Mellitus (T2DM) Insulin Resistance has been observed to lead to an increase in Beta Cell Workload which may ultimately lead to Beta Cell Failure and Death, and the Progression of Type 2 Diabetes.

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

Diabetes Patient Subtype Characteristics

Pre-Diabetes

Initial Decline in Glycemic Control
Increasing HbA1c, Increasing Insulin Resistance
Decreasing beta cell numbers and function



	Patient Population
SIDD = Severe Insulin Deficient Diabetes Low insulin secretion, poor metabolic control, increased risk of retinopathy and neuropathy	~6M
SIRD = Severe Insulin Resistant Diabetes Insulin resistance, obesity, late onset, increased risk of nephropathy and fatty liver	~5M
MOD = Mild Obesity-Related Diabetes Obesity, early onset	~8M
MARD = Mild Age-Related Diabetes Late onset, low risk of complications	~14M

T1D

Initial Diagnosis/Disease – Stage 2/Stage 3
Increasing HbA1c, Initial Reduction in Insulin
Significant Decrease in beta cell numbers

~1.5M

E. Ahlqvist,1 et., Diabetes 2020;69:2086–2093

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

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]†

Downloaded from http://science.sciencemag.org/ on August 15, 2019

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

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 for 28 days)

Dosing Scheme

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

Table 1: Results Summary at Week 12

	Cohort 2		Cohort 3	
	BMF-219	**Placebo**	**BMF-219**	**Placebo**
Number of Patients	10	2	10	2
HbA1c (%) at Baseline	7.1 – 9.1		7.0 – 9.8	
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)
Number of Patients with Reduction in HbA1c at **Week 12**	6/10 (60%)	1/2	9/10 (90%)*	1/2
≥0.5% Reduction in HbA1c at **Week 12** (%)	4/10 (40%)	1/2	8/10 (80%)*	0
≥1% Reduction in HbA1c at **Week 12** (%)	3/10 (30%)	0	4/10 (40%)*	0
Median (Mean) Change in HbA1c at **Week 12**	-0.1 (-0.1)	0.2 (0.2)	-0.8 (-1.0)	0 (0)
Top 50% Mean Change in HbA1c at **Week 12**	-0.9	NA	-1.5	NA

*Note: Linear imputation used for single data point with results available before and after missing data.
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

Table 1 The top 50% of patients in Cohort 2 had a mean reduction in HbA1c of 0.9% at week 12 while the top 50% of Cohort 3 patients demonstrated a mean reduction of 1.5%. Cohort 2 patients had ~3 fold lower BMF-219 exposure than Cohort 3 patients.

Figure 1: HbA1c Results in Cohort 1 (HVs)

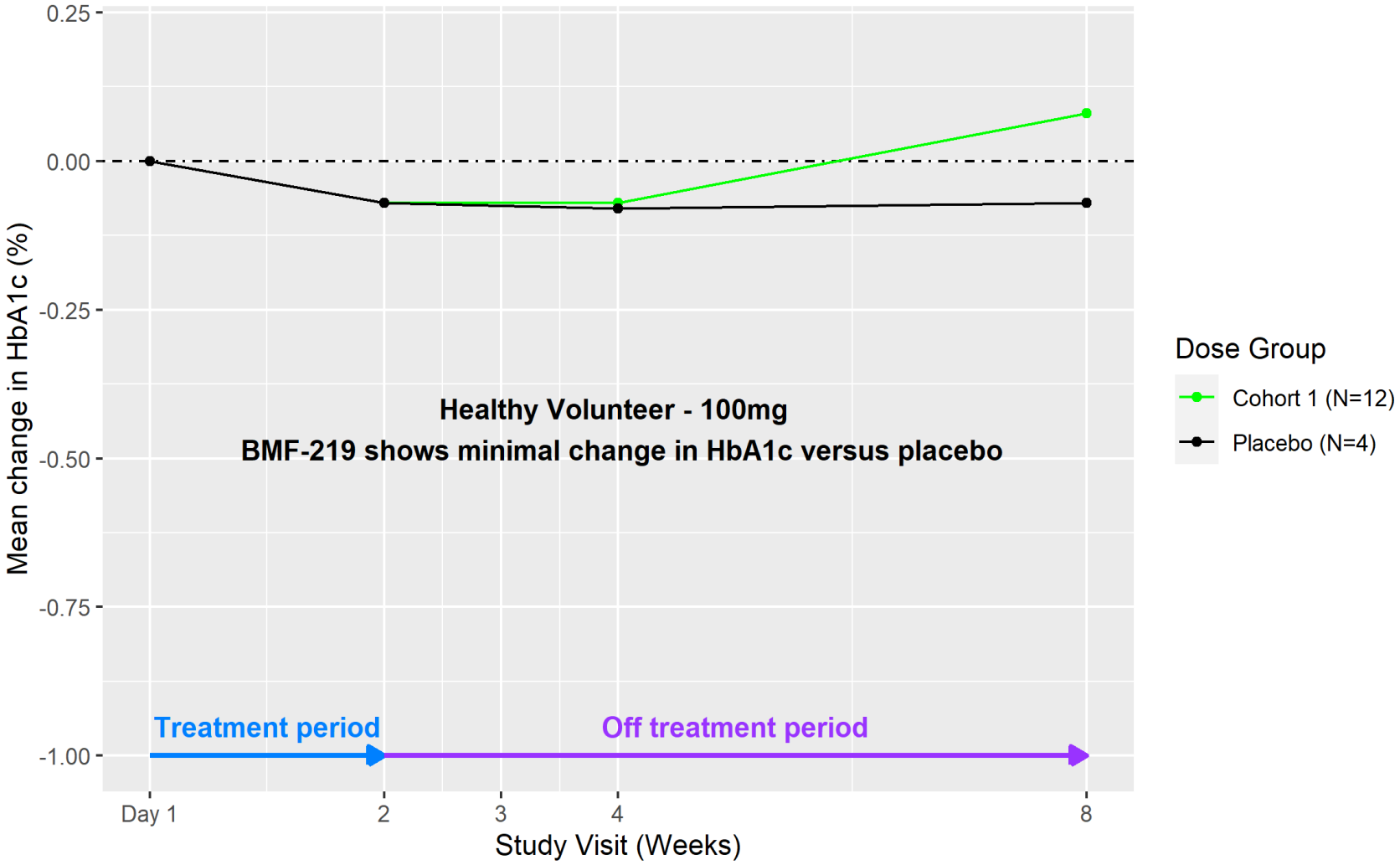


Figure 1. Minimal change was observed in HbA1c in healthy volunteers (HVs) during 14 days of treatment and 6-week follow-up.

Figure 2: Change in HbA1C for all patients and Top 50% at Week 12

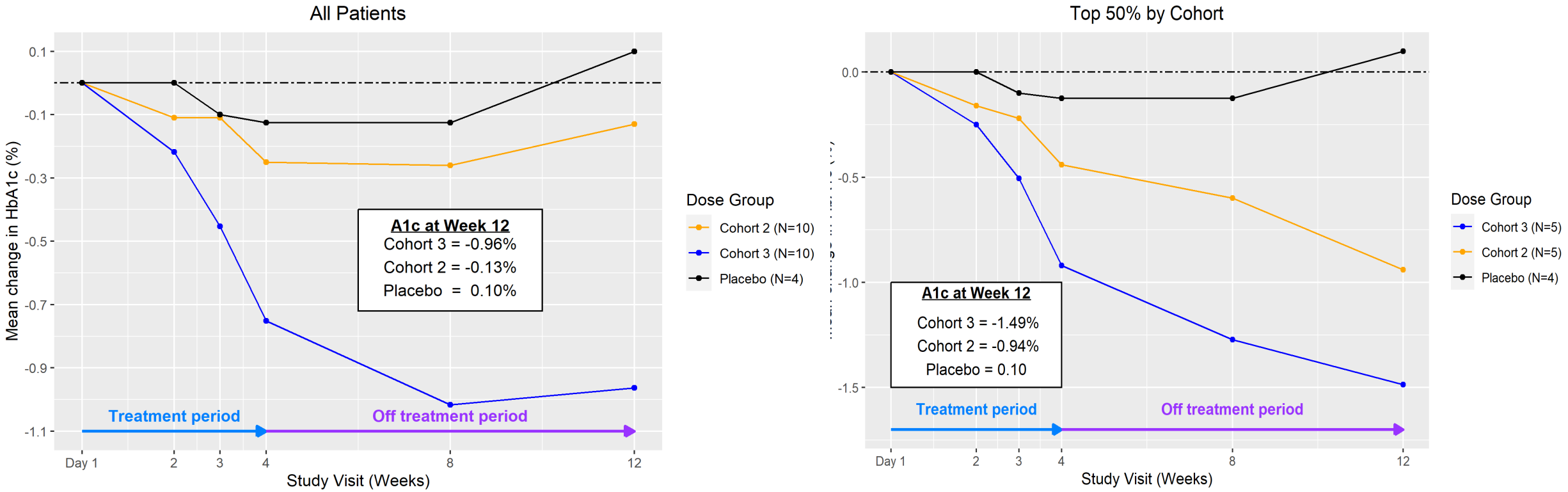


Figure 2 The top 50% of responders after 4-weeks of treatment in Cohorts 2 and 3 demonstrated durable and ongoing reduction in HbA1c while off treatment up to Week 12; a continued reduction in HbA1c was observed in Cohort 2 (additional 114%) and in Cohort 3 (additional 62%).

Figure 3: Patients achieving an HbA1c reduction to ≤ 7% during 4-week treatment and 8-week follow-up

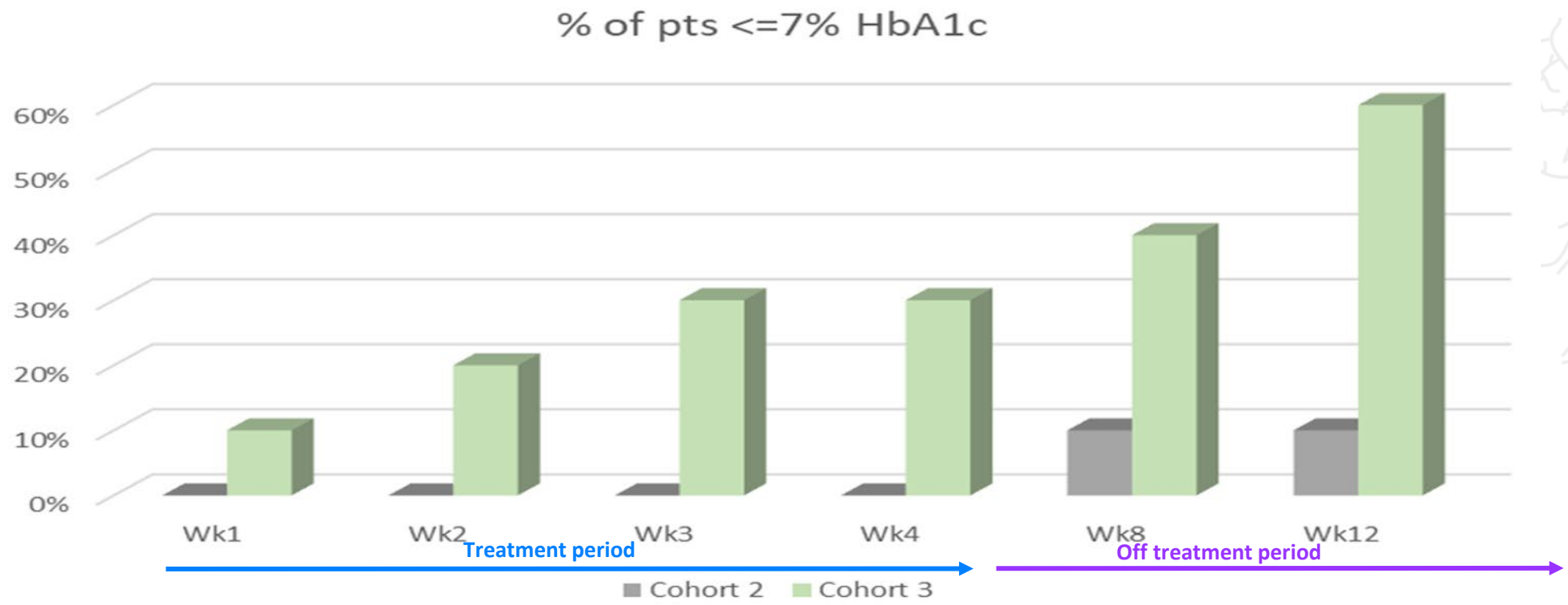


Figure 3. After 4-weeks of BMF-219 once daily dosing both cohorts demonstrated an increasing proportion of patients achieving a target HbA1c ≤ 7% and maintained through Week 12.

Figure 4: Mean AUC of C-peptide and HOMA-B during OGTT

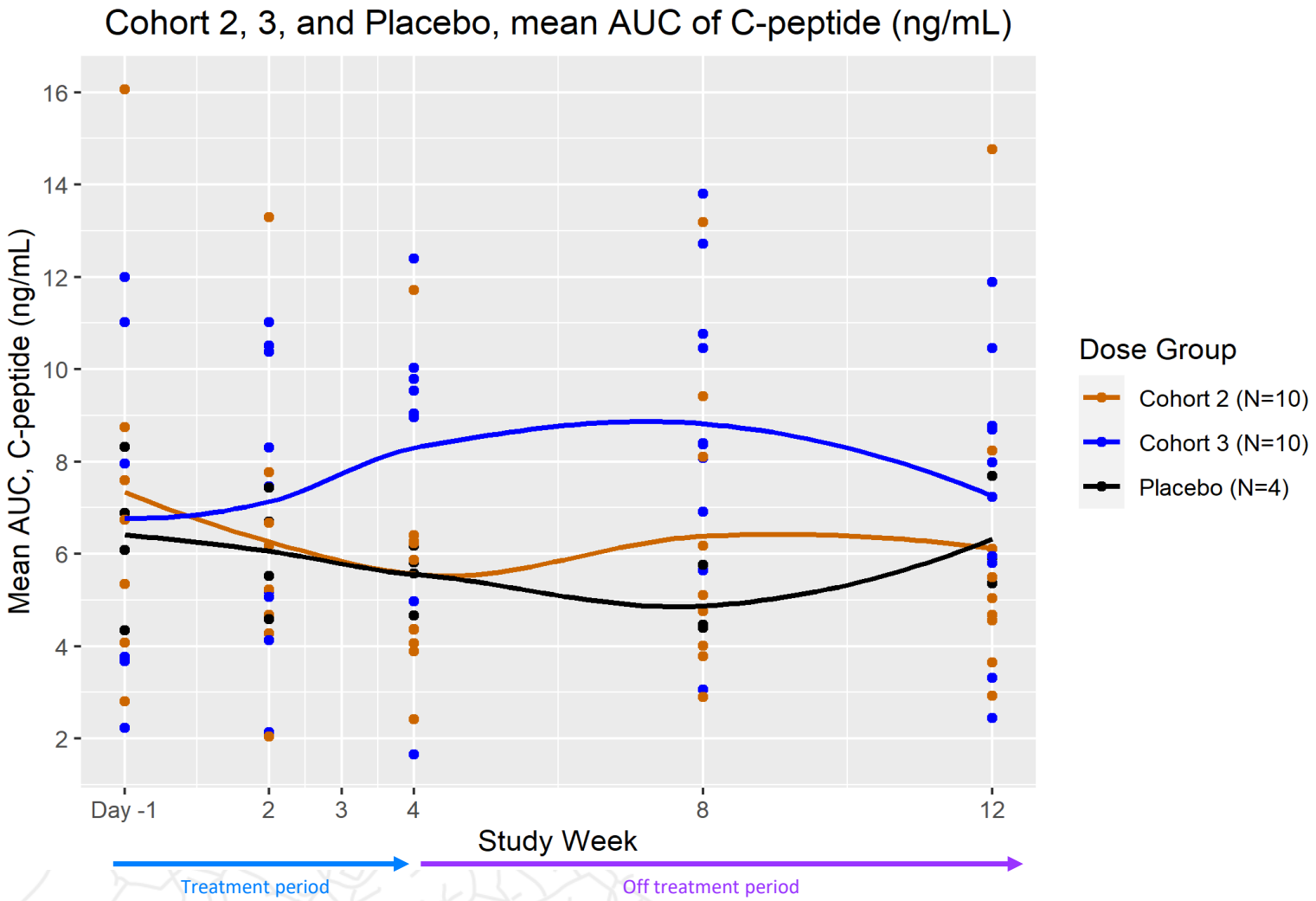


Figure 4.
Top panel (Left) The mean AUC of C-peptide increased during OGTT for Cohort 3 compared to placebo.

Figure 4: Mean AUC of C-peptide and HOMA-B during OGTT

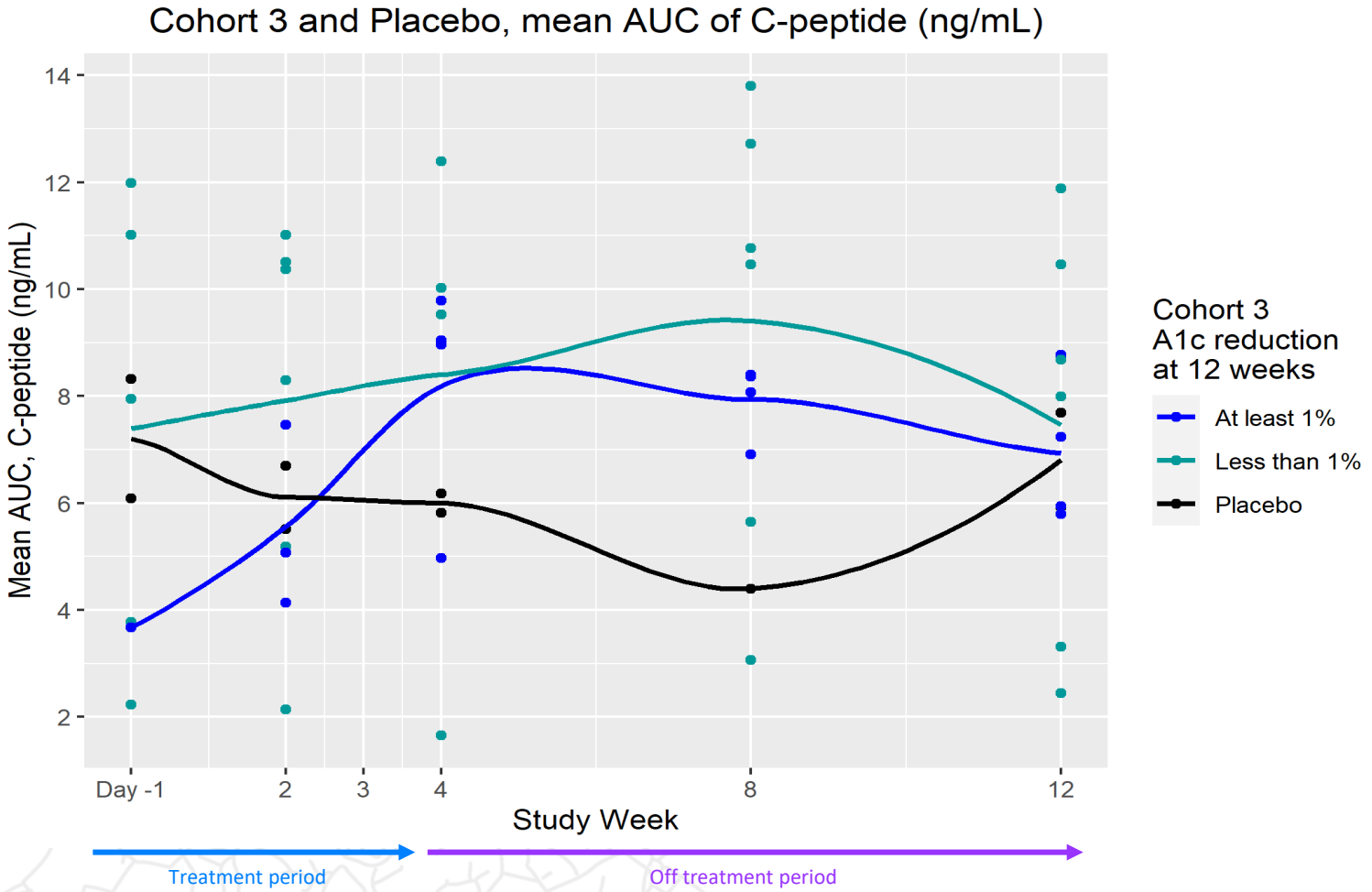


Figure 4.
Top panel (Right) Cohort 3 patients with ≥1% reduction in HbA1c showed a greater increase in C-peptide production

Figure 4: Mean AUC of C-peptide and HOMA-B during OGTT

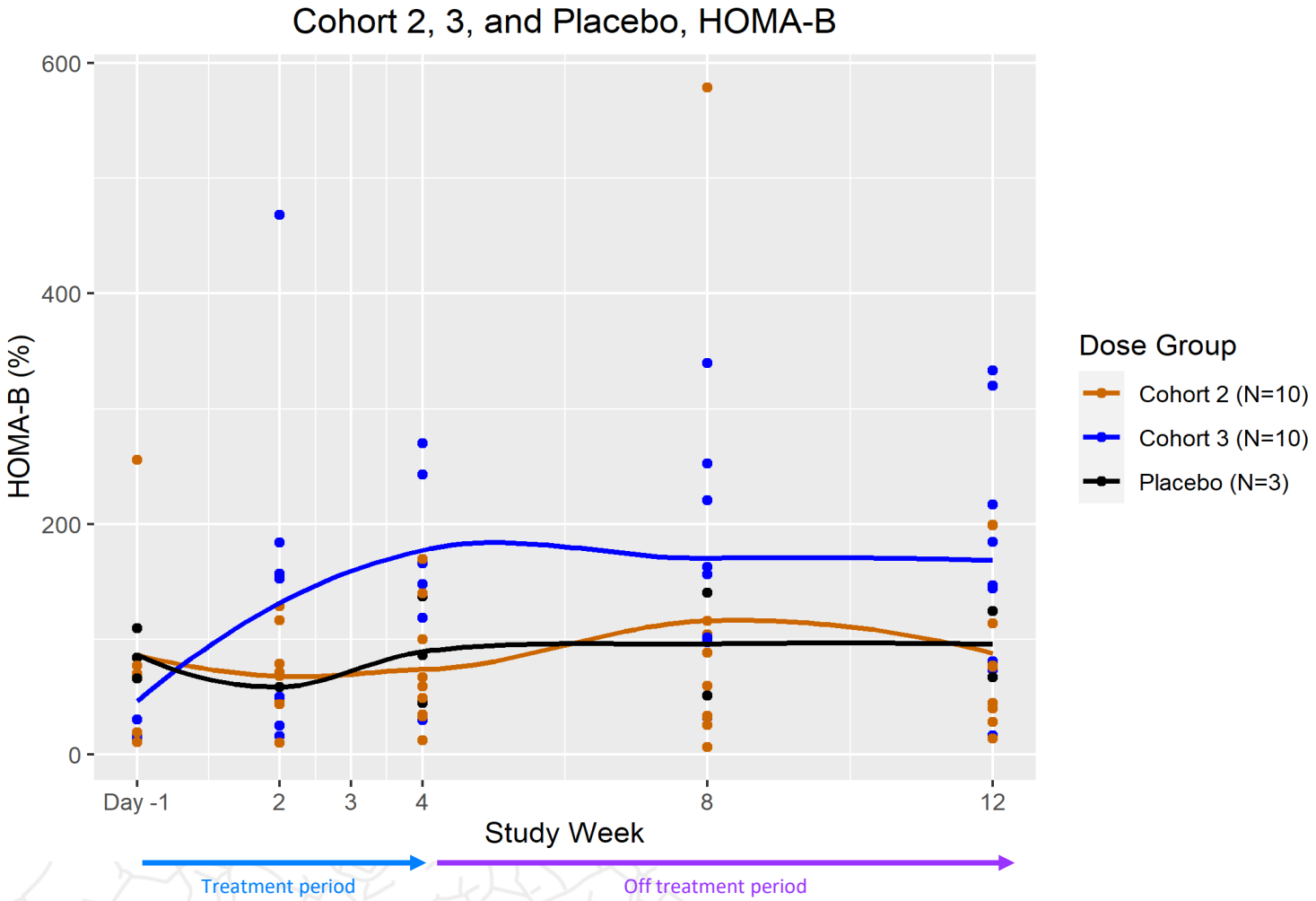


Figure 4.
Lower panel An increase in HOMA B was observed in Cohort 3

Figure 5: Change in HbA1c ordered by Baseline HbA1c, BMI, and Time since Diagnosis (Weeks 4 and 12)

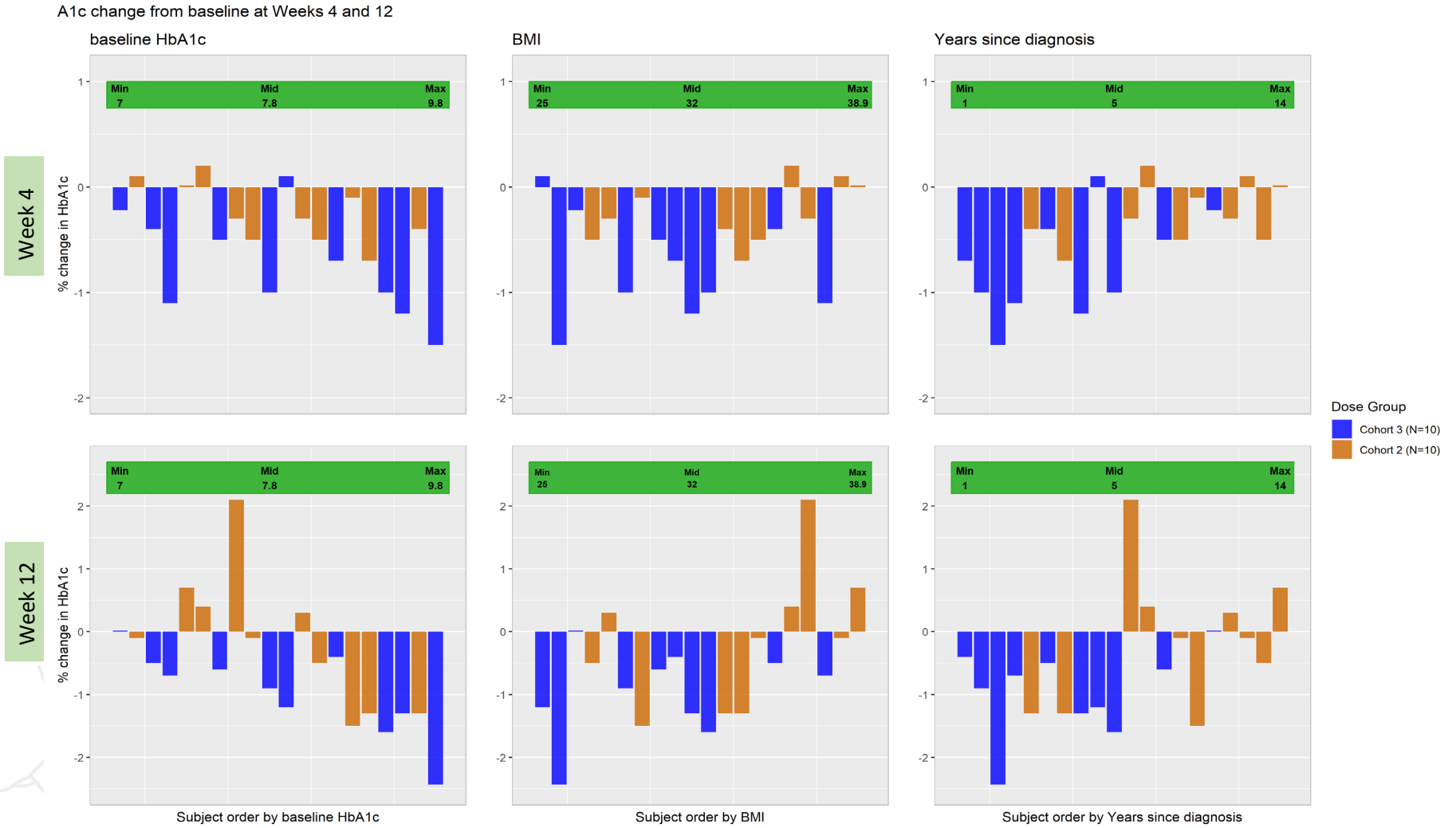
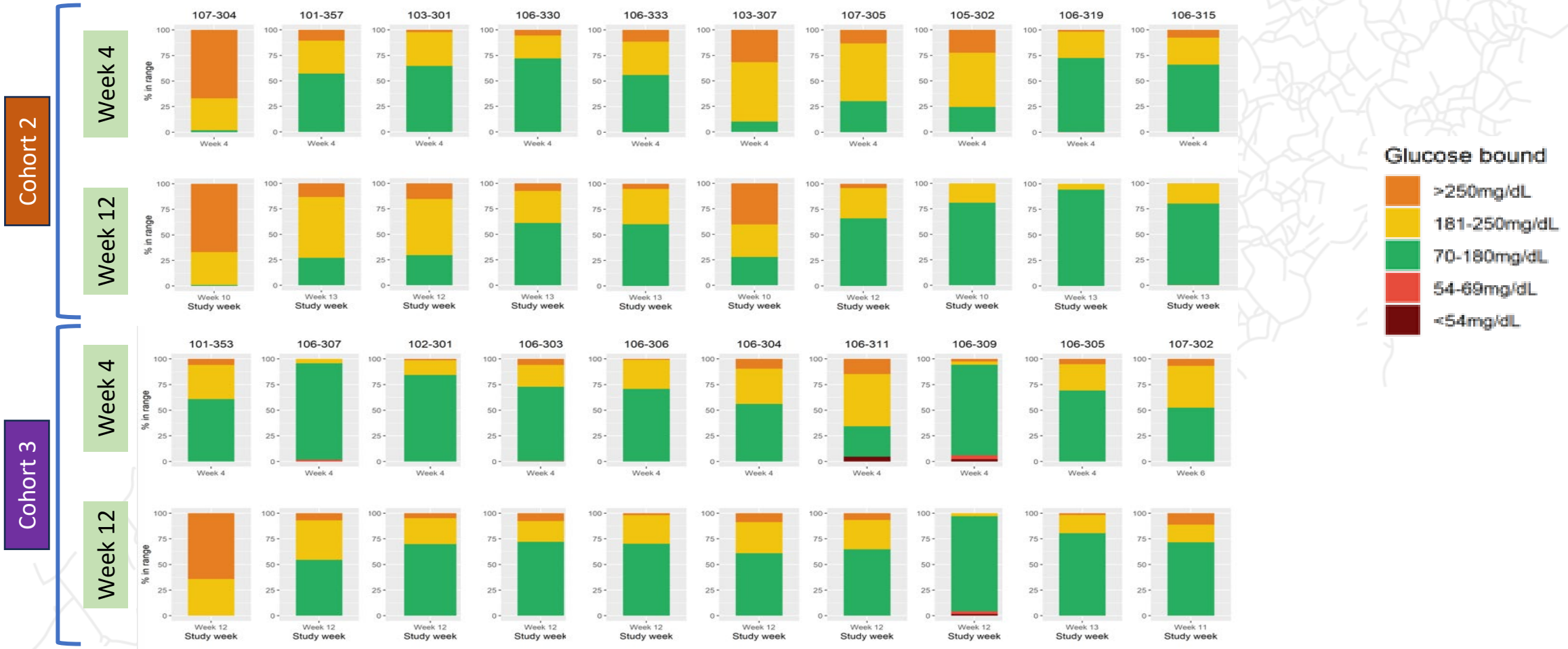


Figure 5.
Left panels. Patients with higher baseline HbA1c tended to have a greater reduction.
Middle panels. Patients in Cohort 3 tended to have lower BMI and a greater reduction in HbA1c.
Right panels. Patients in Cohort 3 tended to have more recently diagnosed T2D (≤5 yrs) and had a greater reduction in HbA1c.

Figure 6: CGM Time In Range (TIR) at Weeks 4 and 12 (Cohorts 2 and 3) (normal glucose range 70 to 180 mg/dL)



Upper Panel (Cohort 2) 6 of 10 (60%) patients maintained or improved TIR while off treatment.
Lower Panel (Cohort 3) 7 of 10 (70%) patients maintained or improved TIR while off treatment.

Figure 7: Change in lipid levels at Weeks 4 and 12

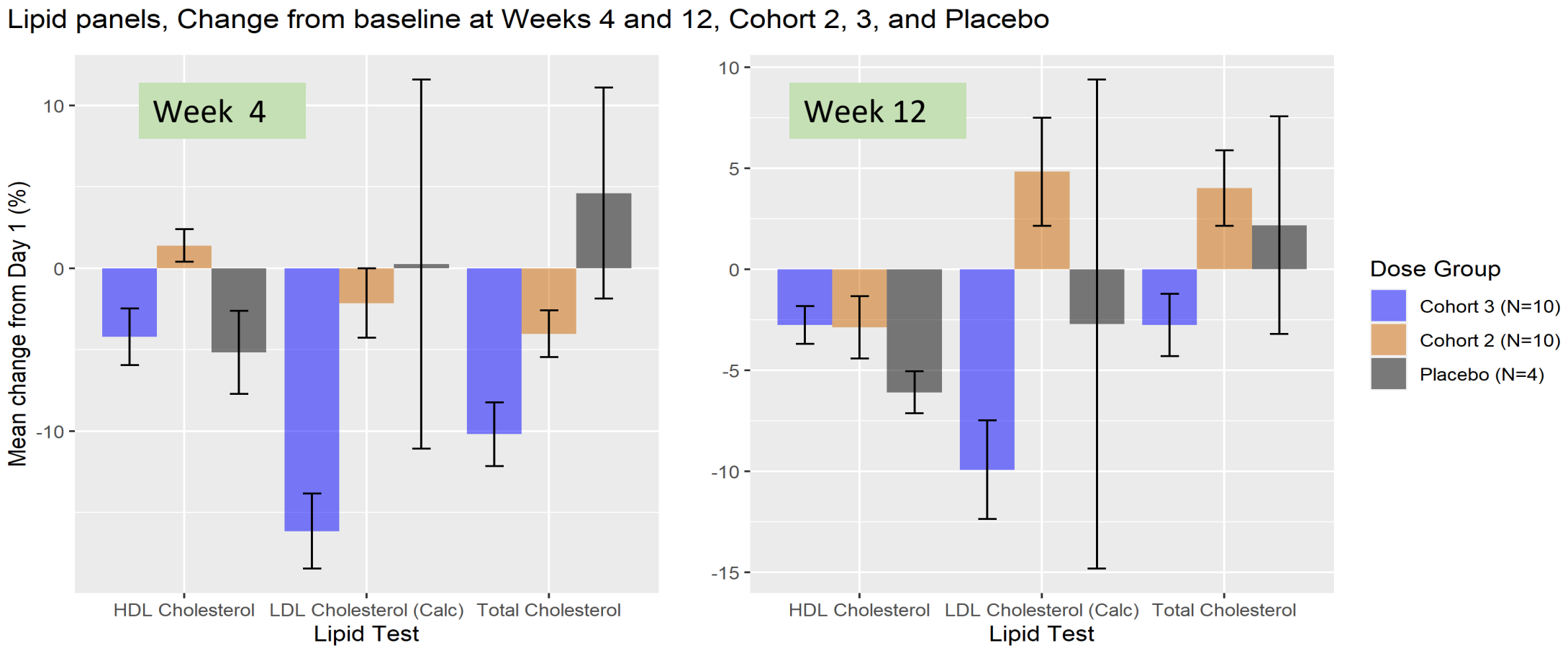


Figure 7. A positive trend was observed in both LDL and total cholesterol levels in Cohort 3.

Summary of Data

Efficacy Data: At Week 12 (8 weeks after completion of 28 days of treatment), BMF-219 demonstrated:

- The majority of patients continued to show a reduction in HbA1c, despite cessation of therapy. During the off-treatment period, both cohorts demonstrated a continued improvement in the proportion of patients [Cohort 2 (10%) and Cohort 3 (60%)] with a target HbA1c ≤7% through week 12.
- Top 50% of patients after 28-day dosing, achieved an HbA1c reduction of 1.49% in Cohort 3 (100 mg fasted) and 0.94% in Cohort 2 (100 mg fed) from baseline
- BMF-219 elicited increases in C-peptide and HOMA-B during the treatment and off-treatment period
- While off treatment, the majority of patients experienced a durable overall improvement in Time In Range in CGM (6/10 in Cohort 2 and 7/10 in Cohort 3)
- No meaningful change in weight relative to baseline
- Favorable trend in LDL and total cholesterol in Cohort 3

Safety Data:

- BMF-219 demonstrated a generally well-tolerated safety profile with no severe or serious AEs
- No symptomatic hypoglycemia
- No dose discontinuation or modification
- No meaningful change in hemoglobin levels

Next Steps:

- Complete dose escalation, identify optimal dose levels, and initiate dose expansion
- Explore longer duration of treatment (for up to 12 weeks)

THANK YOU

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