BMF-219: A Novel Therapeutic Agent to Reestablish Functional Beta Cells and Provide Long-Term Glycemic Control

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All authors are employees of Biomea Fusion

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Background

- **Menin is a scaffold protein** with multiple functions, including the **regulation of gene transcription and cellular signaling**
- Through interacting with its binding partners, menin acts as an important regulator of glycemic control, whereby **inhibition of menin activity enhances beta cell proliferation and function**
- **BMF-219 is an oral covalent menin inhibitor** in clinical development for the management of T2D and T1D
- In **preclinical models of diabetes**, BMF-219 showed durable glycemic control following short-term treatment in ZDF and STZ rat models[1,2]
- In a **multiple ascending dose (MAD) cohorts in patients with T2D**, 4 weeks of BMF-219 100 mg once daily improved glycemic control at Week 12 (8 weeks after the final dose) and was generally safe and well tolerated[3]

1. Butler T. et al. *Diabetes.* 2022; 71 (Supplement_1): 851–P.
2. Somanath P. et al. *Diabetes.* 2022; 71 (Supplement_1): 113–LB.
3. Rodriguez J. et al. *Diabetes.* 2023; 72(Supplement_1): 91-LB

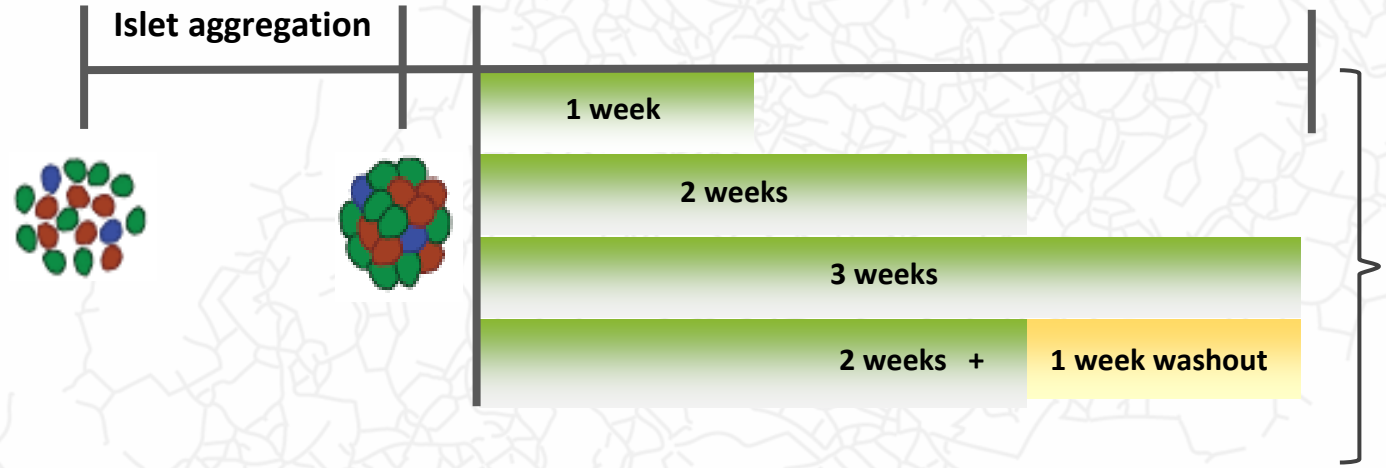
Aims

- To assess the effects of BMF-219 in human donor islet microtissues
- To assess the safety and efficacy of BMF-219 100 mg once daily for 4 weeks at Week 26 (22 weeks after final dose)

Ex-vivo human islet microtissues: Study design

Cadaver-derived human islets (without diabetes)

- BMF-219, harmine, or vehicle control for 1-3 weeks (+/- washout)
- Assayed under standard (5.5 mM) and high (8.0 mM) glucose

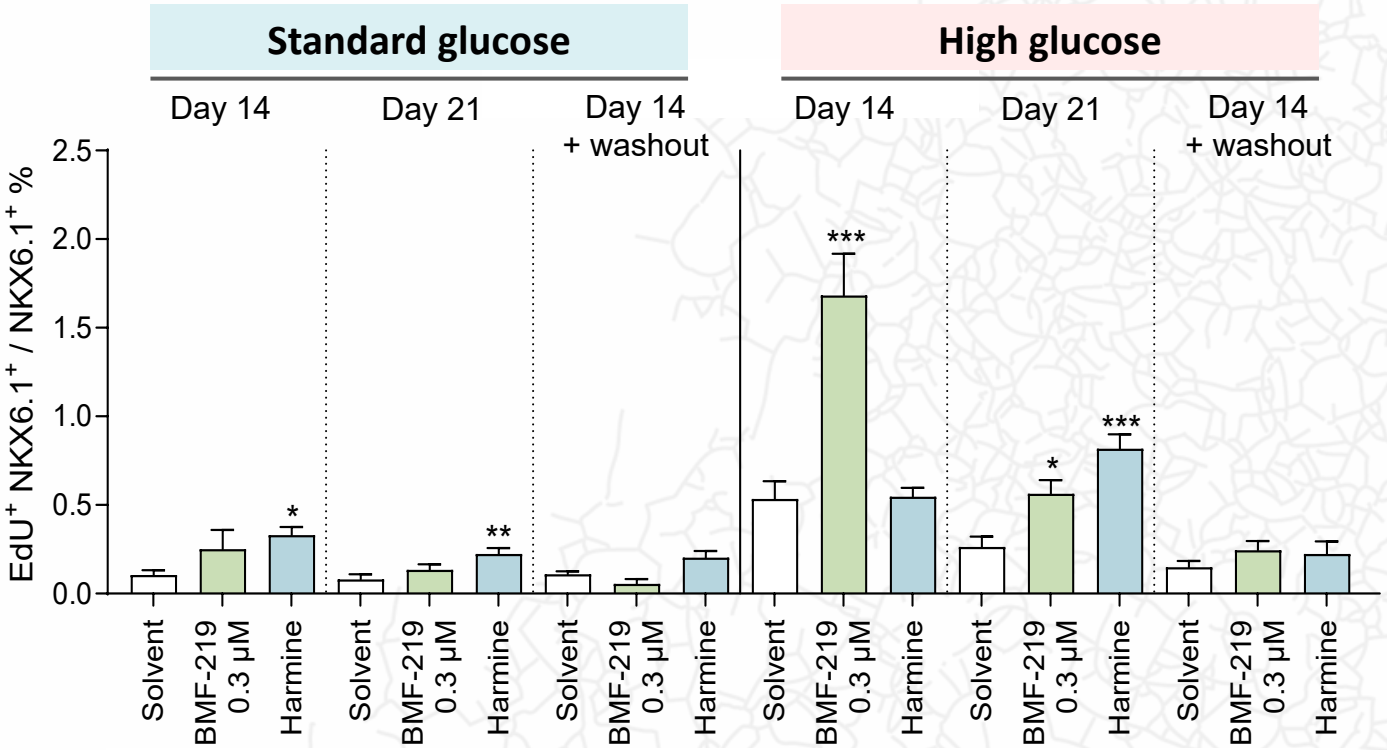


- Beta cell proliferation
- Beta cell insulin content

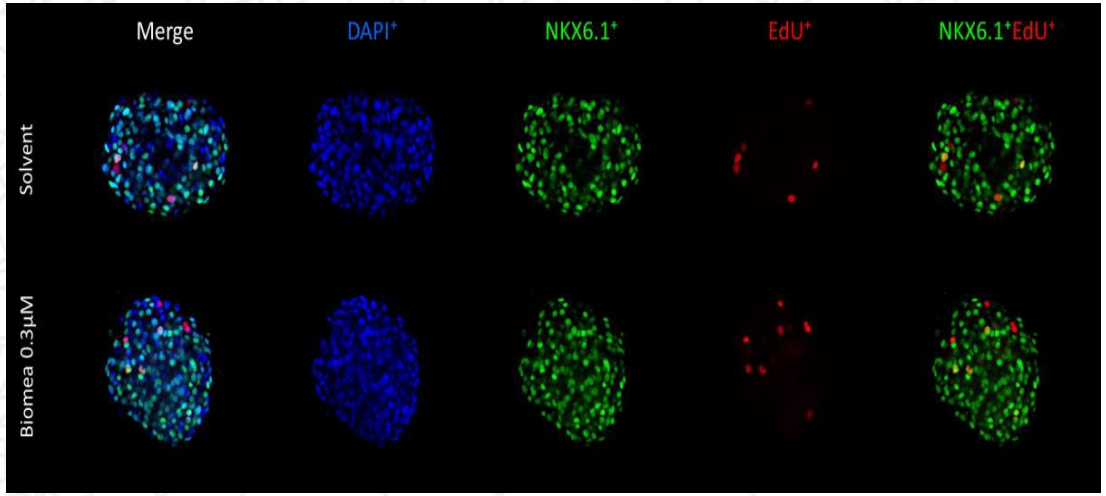
BMF-219 – Human islet microtissues

Human islet microtissues: Beta cell proliferation (Donor 1)

Proliferating beta cells as a fraction of total beta cells



Day 14, high glucose



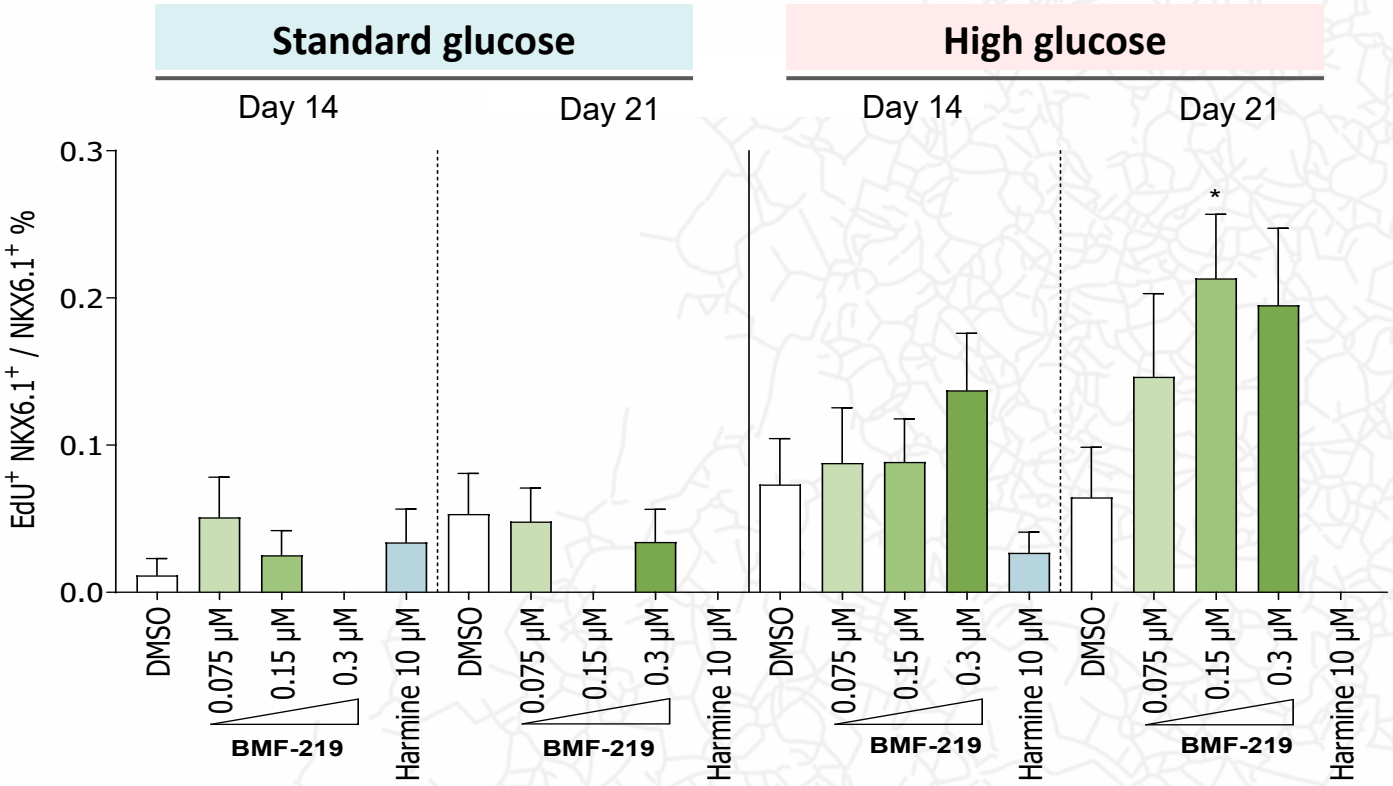
Data represent mean ±SEM of 1 donor with n = 6-10 technical replicates.
One-way ANOVA with Dunnett's post hoc test rel. to DMSO control. *p < 0.05, **p < 0.01, ***p < 0.001

Donor 1	Age	BMI	HbA_{1c}
	19	23.2	5.8

Proliferation observed only under elevated glucose conditions and with continuous drug exposure

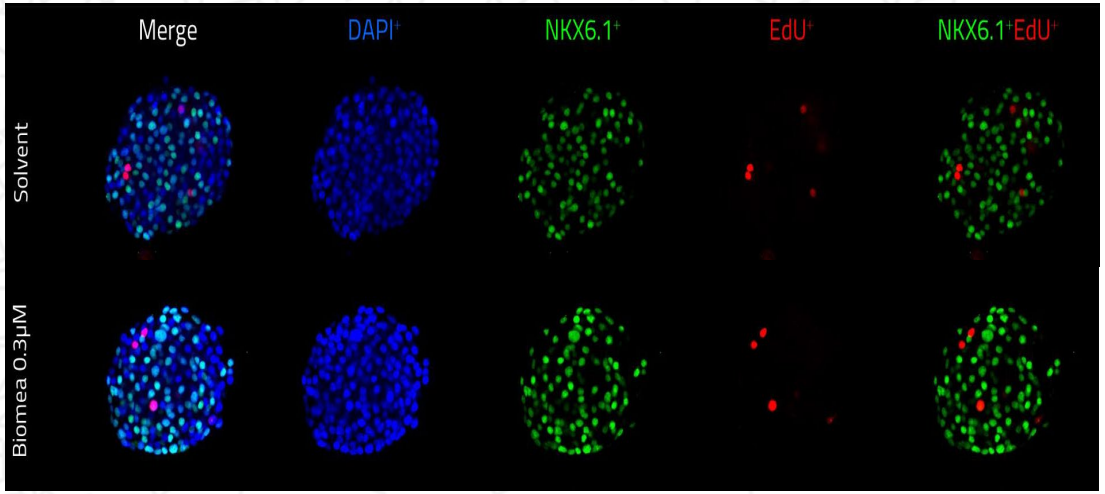
Human islet microtissues: Beta cell proliferation (Donor 2)

Proliferating beta cells as a fraction of total beta cells



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

Day 14, High glucose

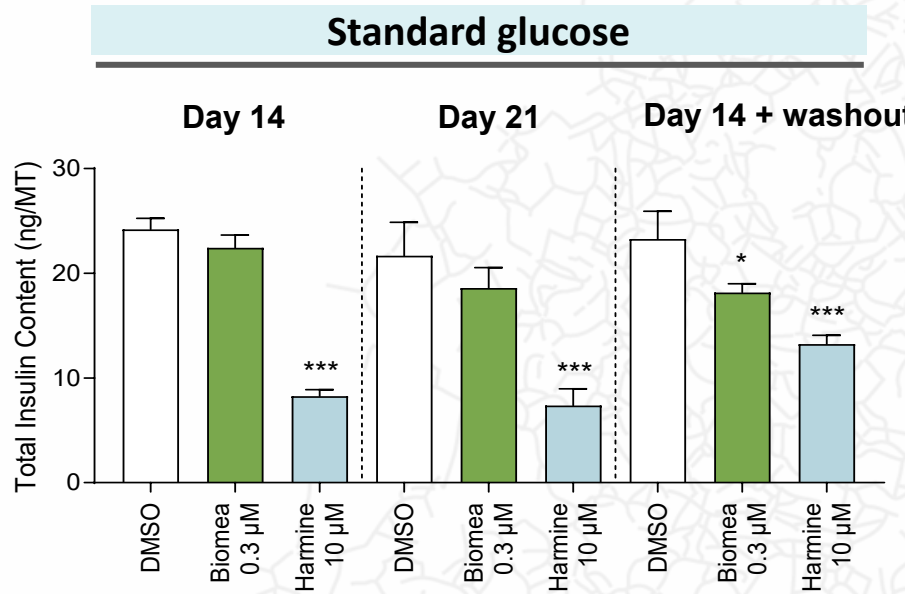


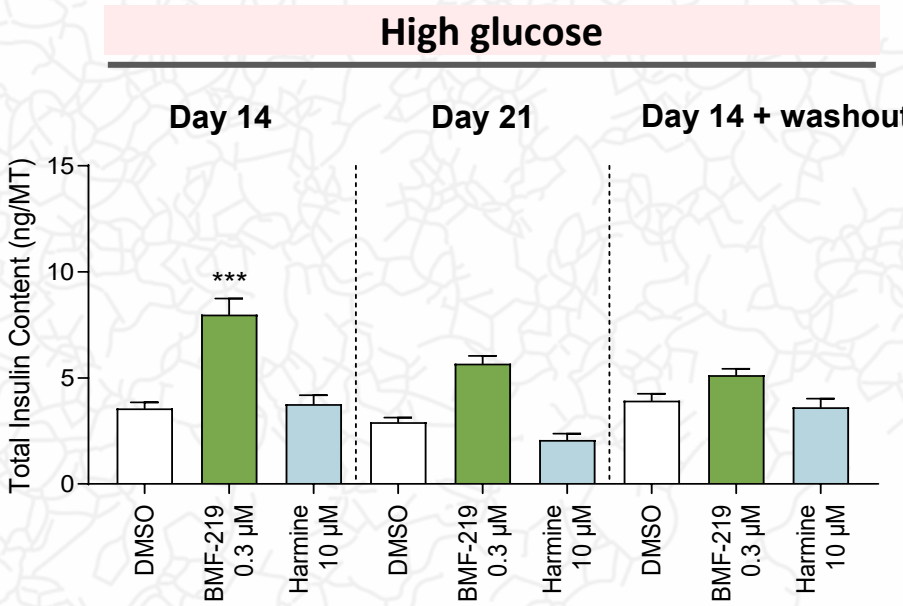
Donor 2	Age	BMI	HbA_{1c}
	32	25.0	5.2

Proliferation observed only under elevated glucose conditions and with continuous drug exposure

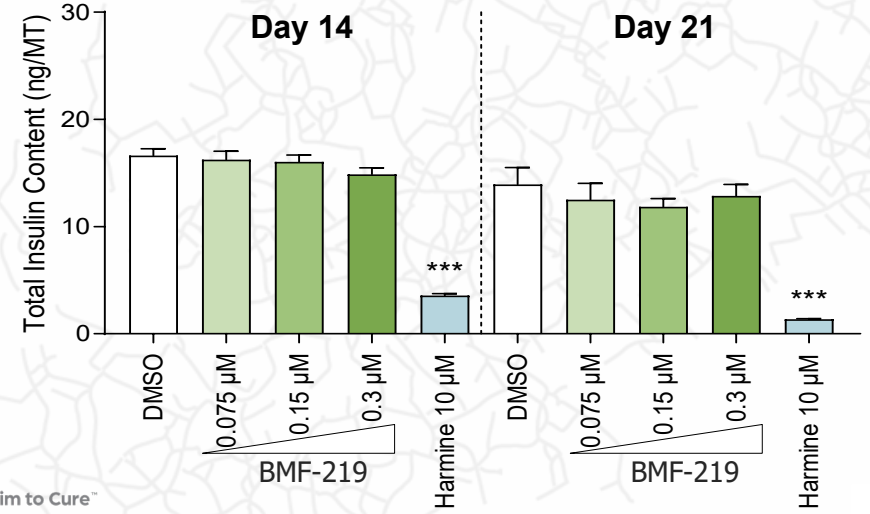
Human islet microtissues: Beta cell insulin content

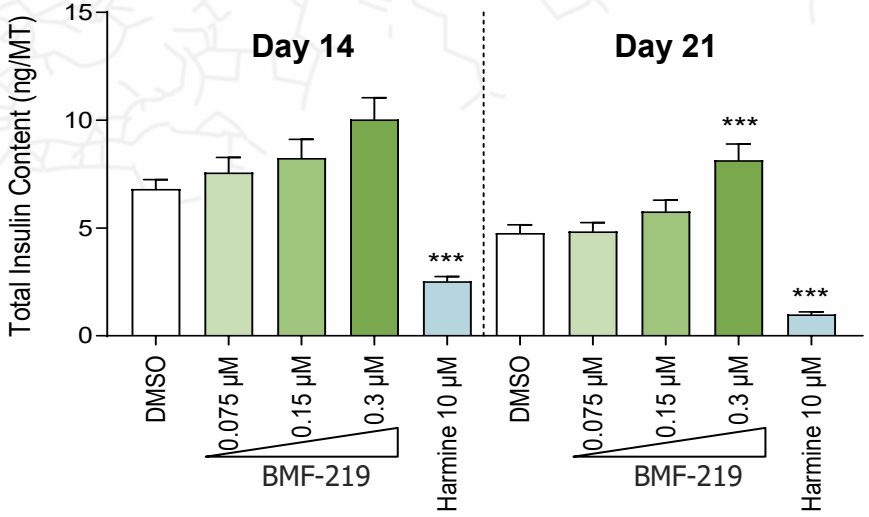
Donor 1





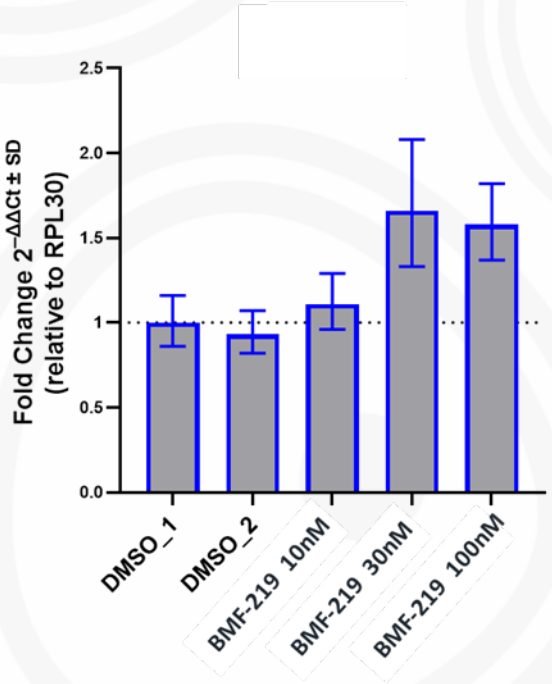
Donor 2



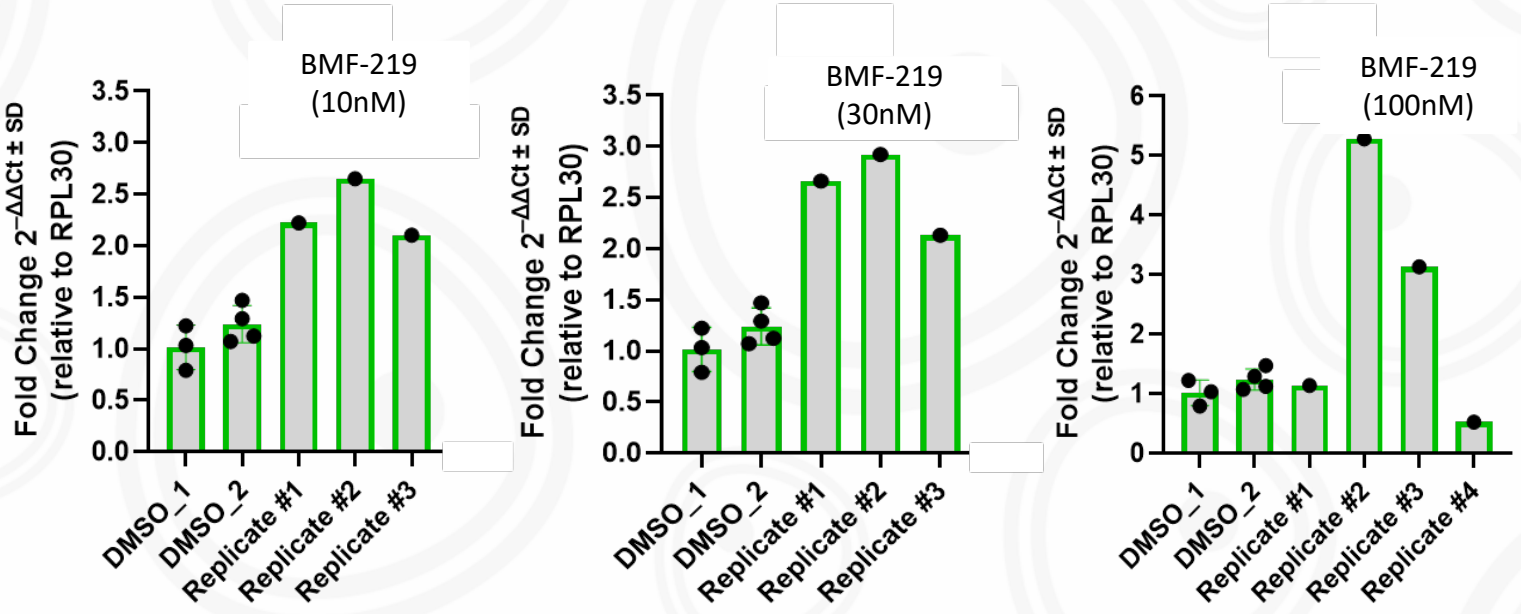


Human islets: CCNA2 and PbK gene expression

CCNA2 gene expression



PbK gene expression



- BMF-219 resulted in **increased CCNA2 and PbK expression**, similar to literature results from menin knockdown experiments
- **CCNA2 and PbK expression** have been shown to **support proliferation of beta cells**, resulting in an increase in beta cell mass

Covalent-111 Study

Key eligibility criteria and study design

Eligibility Criteria

- T2D, age 18-65 yr
- Duration of diabetes 15 yr or less
- HbA_{1c} 7.0-10.0%, inclusive
- Treated with diet/exercise ± up to 3 antihyperglycemic agents (insulin secretagogues and insulin excluded)

COVALENT-111 T2D MAD Cohorts

50 mg QD, without food
x 4 weeks

100 mg QD, without food
x 4 weeks

100 mg QD, with food
x 4 weeks

BMF-219 (n=10) and placebo (n=2) per cohort

200 mg QD, without food
x 4 weeks

200 mg QD, with food
x 4 weeks

100 mg BID, without food
x 4 weeks

200 mg QD x 2 weeks	**400 mg QD** x 2 weeks

without food

4 weeks dosing + 22 weeks follow-up

Study objectives of T2D multiple ascending dose cohorts

Primary Objective:

To assess the **safety and tolerability** of multiple ascending oral doses of BMF-219

Key Secondary Objectives:

- To determine the **pharmacokinetics** following multiple ascending doses of BMF-219
- To determine the impact of multiple ascending doses of BMF-219 on **glycemic parameters**
- To assess changes in **beta-cell function** after multiple ascending doses of BMF-219

Covalent-111 Study

Baseline characteristics and demographics

	BMF-219 100mg QD without food (n=10)	BMF-219 100mg QD with food (n=10)	Placebo (n=6)
Age (year, min-max)	52 (38-63)	51 (35-60)	46 (31-61)
Sex (n, M/F)	6/4	7/3	6/0
Duration of diabetes (year, min-max)	4.2 (0.5-9.0)	8.7 (4.0-14.0)	4.2 (1.0, 10.0)
HbA_{1c} (%-point, SD)	8.1 (0.9)	8.0 (0.6)	8.3 (0.7)
Diet and exercise alone (n, %)	0 (0%)	1 (10%)	0 (0%)
1 antihyperglycemic agent (n, %)	9 (90%)	7 (70%)	5 (83%)
2 antihyperglycemic agent (n, %)	0 (0%)	2 (20%)	1 (17%)
3 antihyperglycemic agent (n, %)	1 (10%)	0	0 (0%)

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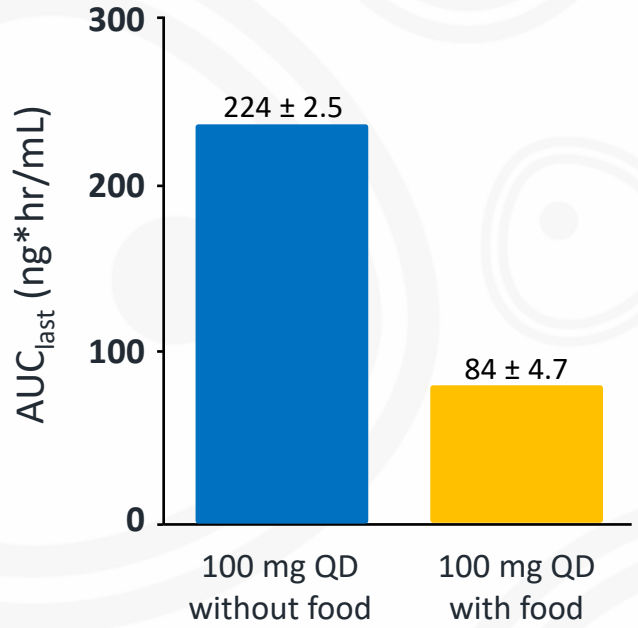
Greater BMF-219 exposure at Week 4 resulted in greater reduction in HbA_{1c} at Week 26

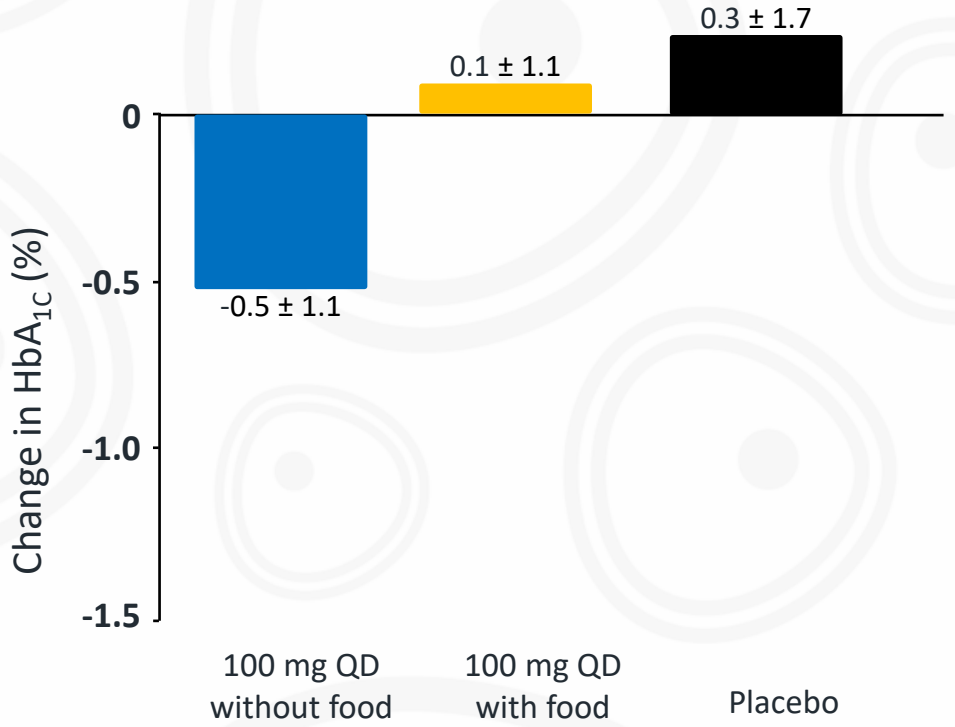
100 mg QD without food

100 mg QD with food

BMF-219 mean AUC_{last} at Week 4



Change in HbA_{1c} at Week 26



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Glycemic results summary at Week 26

	BMF-219 100mg QD without food (n=10)	BMF-219 100mg QD with food (n=10)	Placebo (n=6)
Mean change in HbA_{1c}	-0.5%	0.1%	0.3%
Placebo adjusted mean change in HbA_{1c}	-0.8%	-0.2%	-
Percent of participants with ≥1.0% reduction in HbA_{1c}	20%	20%	0%

Percent of participants with any reduction in HbA_{1c}: 80% (BMF-219 100mg QD without food) and 40% (BMF-219 100mg QD with food)

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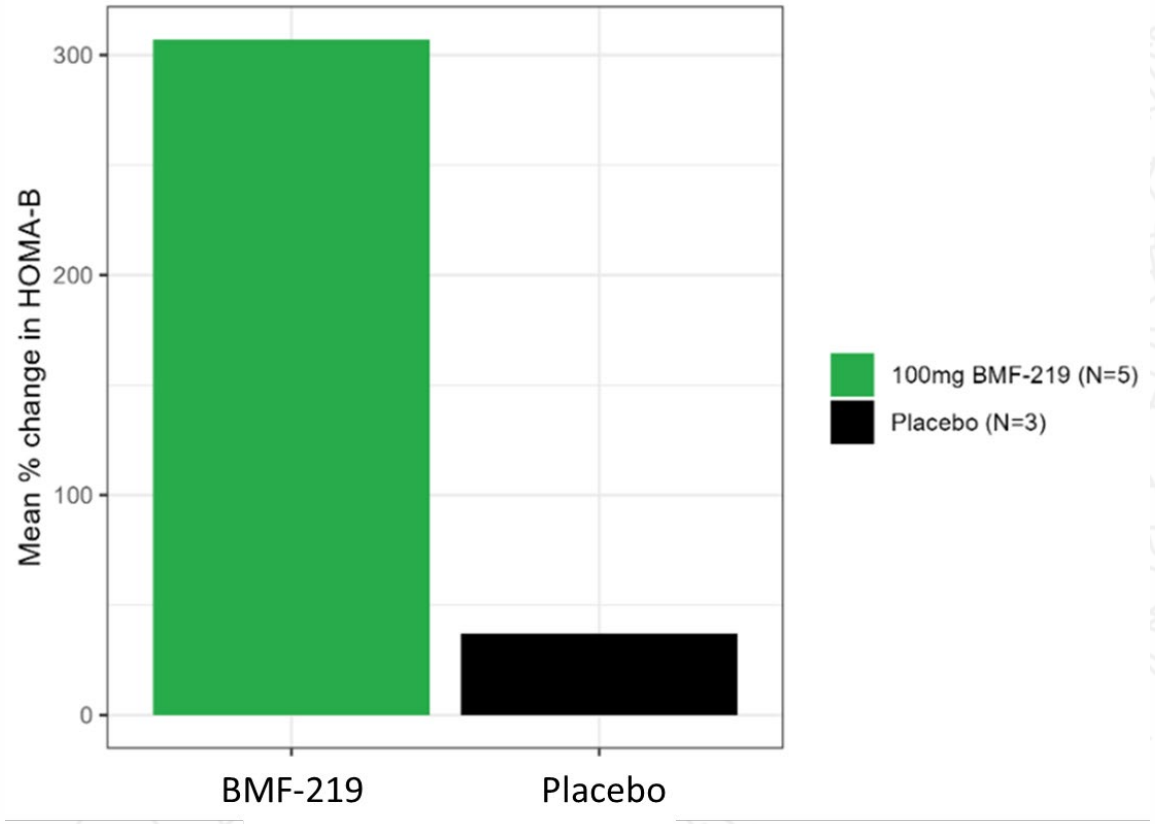
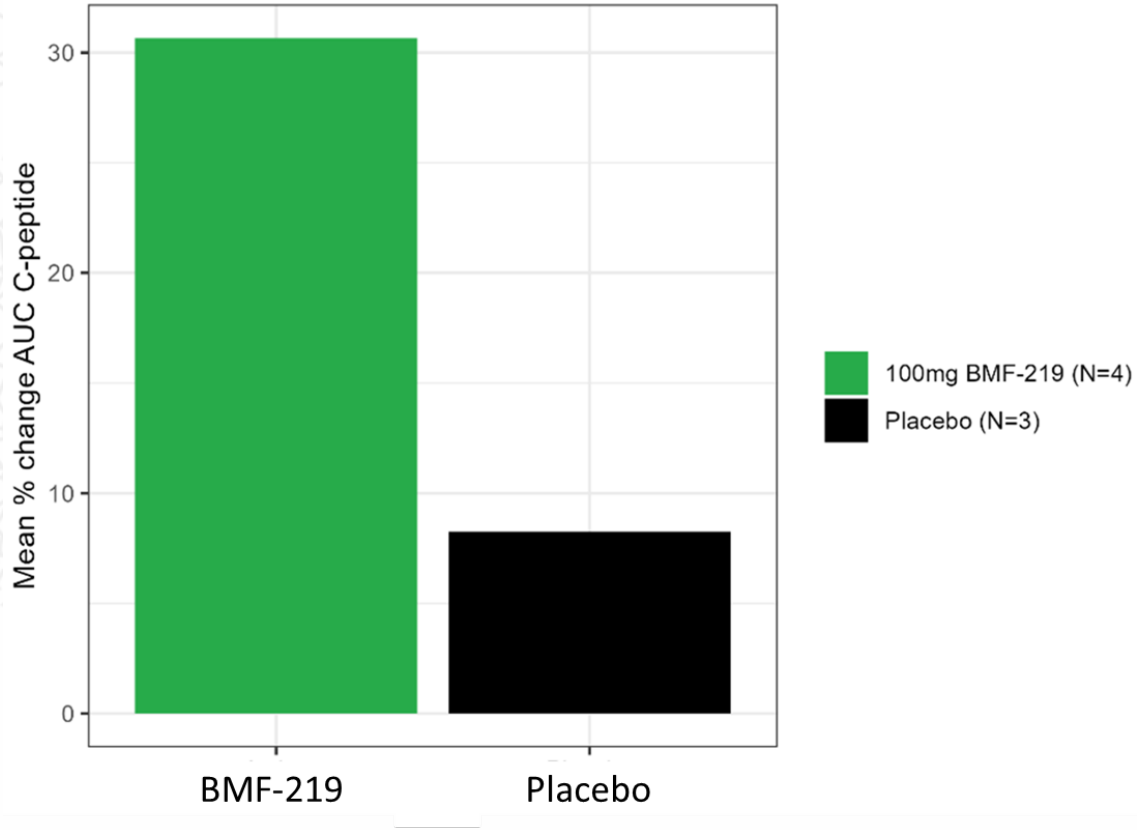
% increase in HOMA-B and C-peptide AUC in responders

Patients with HbA_{1c} reduction ≥0.5% at Week 26 and baseline HOMA-B <200

% change HOMA-B



% change C-peptide AUC



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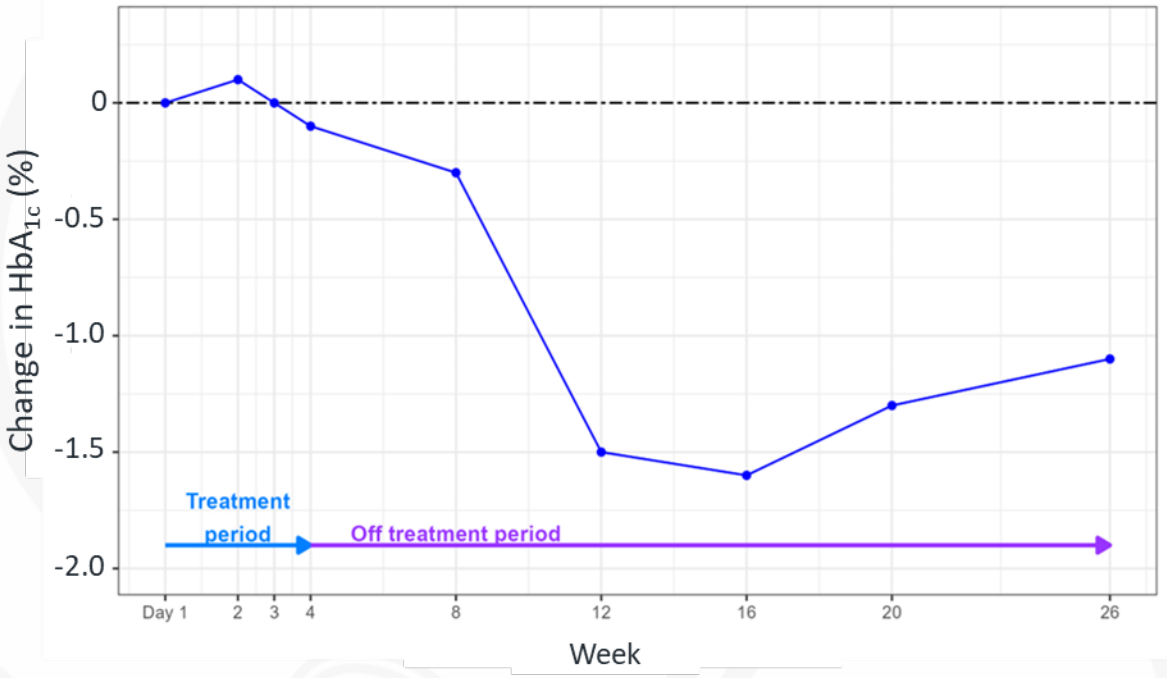
Case Study 1: 45-year-old man with 9-year history of T2D

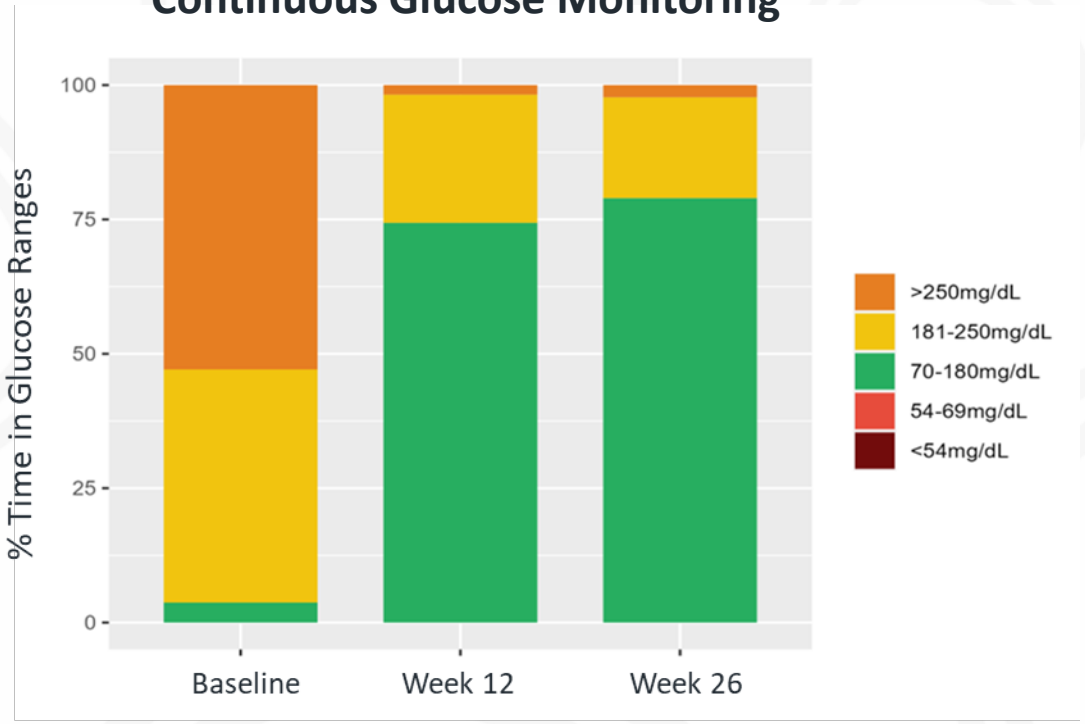
- 45-year-old man with 9-year history of T2D
- Metformin 500 mg BID
- HbA_{1c} 8.4%; FPG 216 mg/dL; BMI 29.6 kg/m^2

- BMF-219 100 mg once daily with food for 4 weeks
- CGM at Week 26 with >75% $TIR_{70\text{-}180\ mg/dL}$
- No tolerability issues or related adverse events

Change in HbA_{1c} (%)



Continuous Glucose Monitoring



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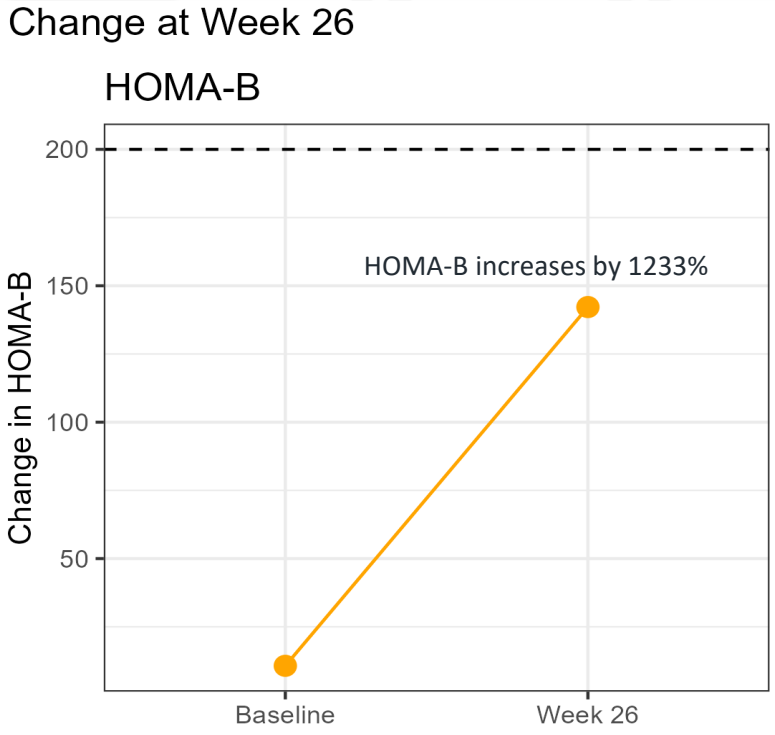
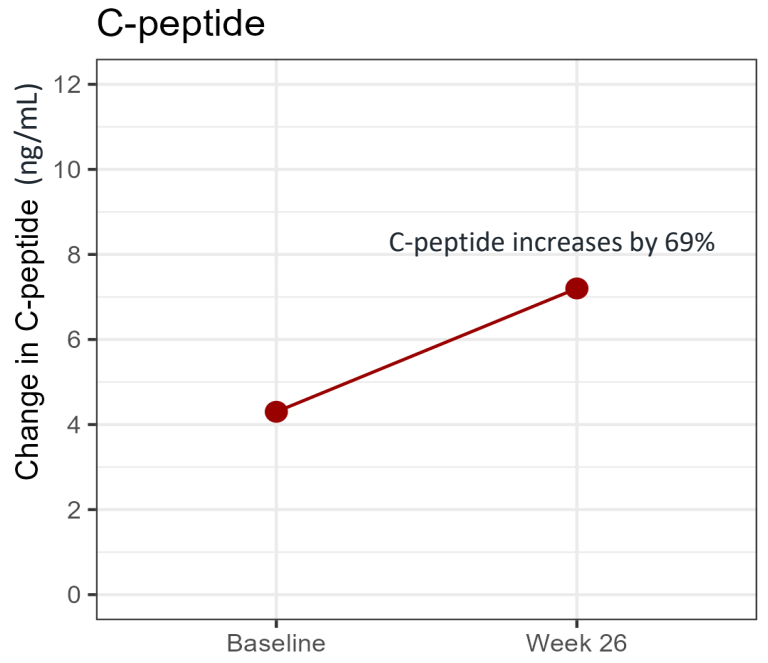




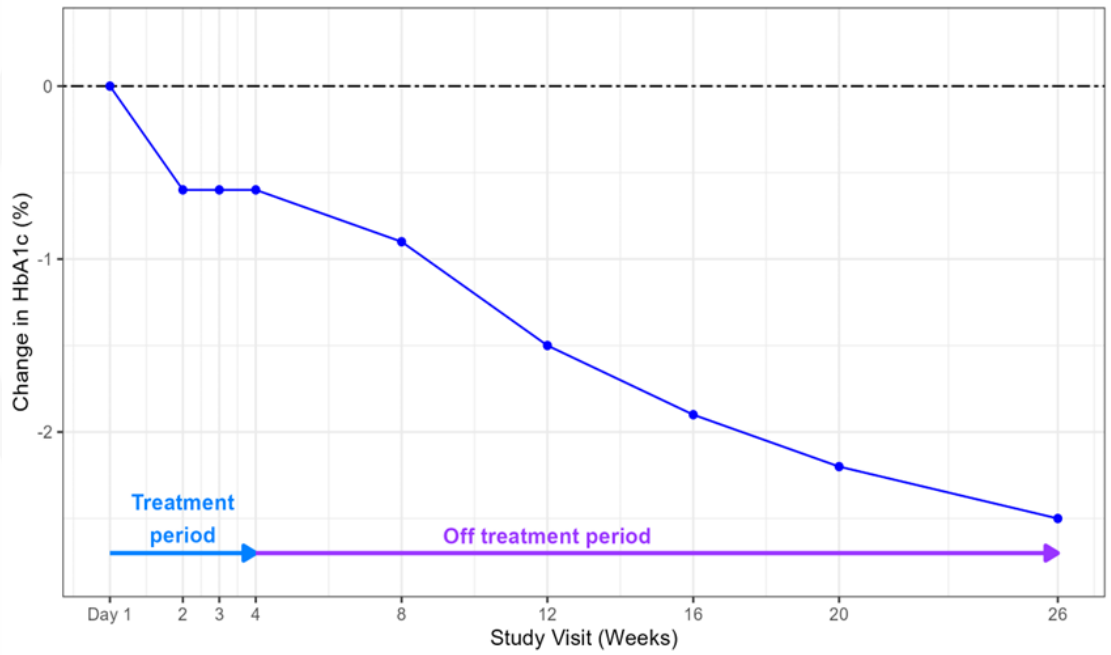
COVALENT-111 Study

Case Study 2: 29-year-old man with 4-year history of T2D

- 29-year-old man with 4-year history of T2D
- Metformin and empagliflozin
- HbA_{1c} 9.5%; FPG 146 mg/dL; BMI 25.6 kg/m^2

- BMF-219 200 mg once daily without food for 4 weeks
- CGM at Week 21 with ~90% $TIR_{70\text{-}180\ mg/dL}$
- No tolerability issues or related adverse events

Change in HbA_{1c} (%)



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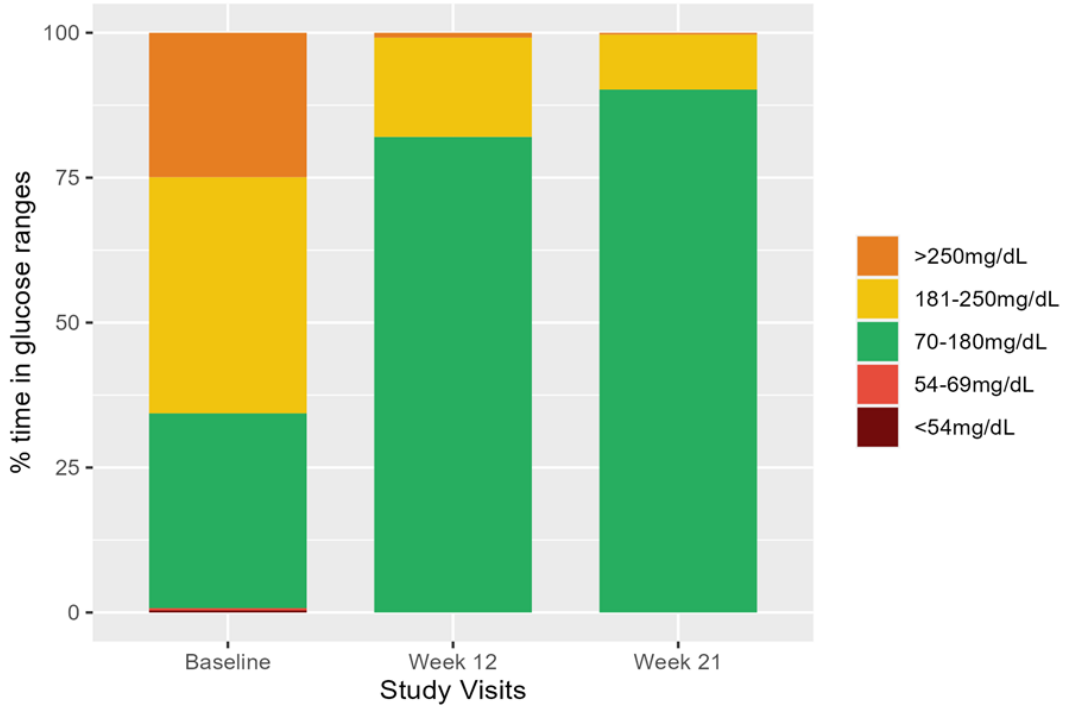

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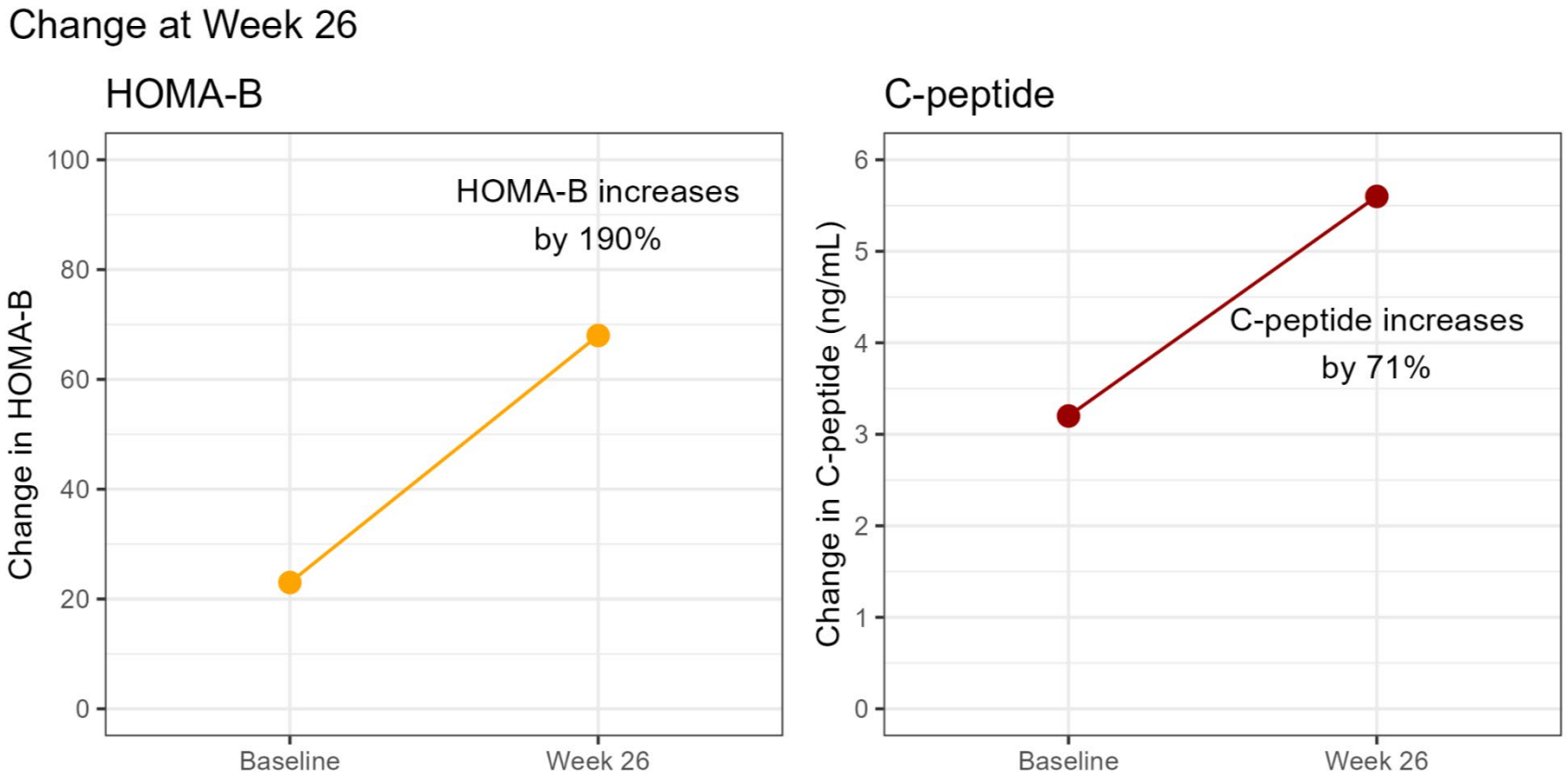

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Safety and tolerability

- BMF-219 was generally well tolerated and safe
- There were no severe or serious adverse events reported
- No dose discontinuations or modifications
- No symptomatic or clinically significant hypoglycemia
- All patients completed 4 weeks of dosing and followed through Week 26

Summary and Conclusions

- In ex-vivo cultured human islet microtissues, BMF-219 enhanced beta cell proliferation and increased beta cell insulin content in a glucose-dependent manner
- In patients with T2D, 4 weeks of BMF-219 100 mg once-daily resulted in clinically meaningful improvements in glycemic control at Week 26 (22 weeks after the final dose)
- These combined results support BMF-219's key mechanism of action of beta cell proliferation and support the novel disease-modifying potential of short-term BMF-219 therapy
- At Week 26, BMF-219 200 mg once-daily for 4 weeks resulted in approximately 40% (4/11) of participants achieving ≥1.0% reduction in HbA_{1c} (nearly doubling the effect achieved at Week 26 with the 100 mg dose)
- Next steps: Higher BMF-219 doses and longer exposure (8-12 weeks) are being assessed in an ongoing Phase 2 trial in T2D and a study in T1D has been initiated

Thank you

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