Abstract # 0088

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

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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 type 2 and type 1 diabetes
- 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 type 2 diabetes, 4 weeks of BMF-219 100mg once daily was shown to improve glycemic control at Week 12 (8 weeks after the final dose) and was generally safe and well tolerated[3]

Aim

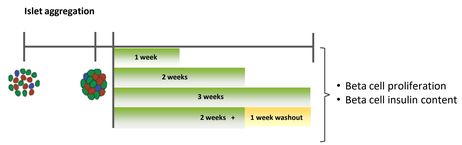
- To assess the effects of BMF-219 on donor human islet microtissue
- To assess the safety and efficacy of BMF-219 100 mg once daily for 4 weeks at Week 26 (22 weeks after final dose)

Study Designs

Ex-Vivo Human Islet: 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 mM) glucose



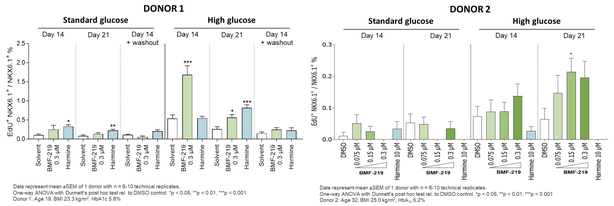
- Beta cell proliferation
- Beta cell insulin content

Covalent-111: Study Design

- Covalent-111 (NCT05731544) is an ongoing Phase 1/2 randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of BMF-219 in patients with T2D
- 12 T2D patients (10 active, 2 placebo) received 100 mg BMF-219 without food and 12 patients (10 active, 2 placebo) received 100 mg BMF-219 taken with food, once daily for 4 weeks. Patients were then followed for 22 weeks off BMF-219
- Key eligibility criteria: Adults with T2D treated with up to 3 antidiabetic agents (excluding insulin secretagogues and insulin), HbA_{1c} 7%-10%, diabetes duration <15 years
- Primary endpoint: Safety and tolerability
- Secondary endpoints included measures of glycemic control (HbA_{1c}, CGM metrics), measures of beta cell function (HOMA-B and stimulated c-peptide), and durability of glycemic response

Ex-Vivo Human Islet: Beta Cell Proliferation

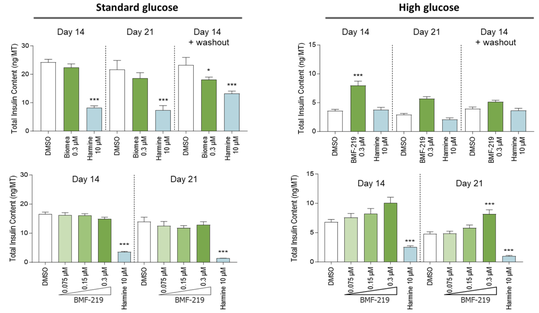
Proliferating beta cells as a fraction of total beta cells



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 19, BMI 23.3 kg/m², HbA1c 6.8%
Donor 2: Age 32, BMI 25.0 kg/m², HbA_{1c} 5.2%

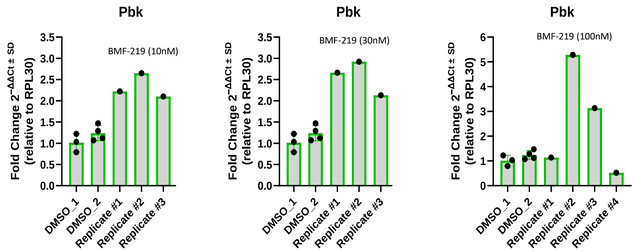
Proliferation observed only under elevated glucose conditions and with continuous drug exposure

Ex-Vivo Human Islet: Beta Cell Insulin Content



BMF-219 induced a glucose-dependent enhancement in beta cell insulin content

Ex-Vivo Human Islet: PbK Gene Expression

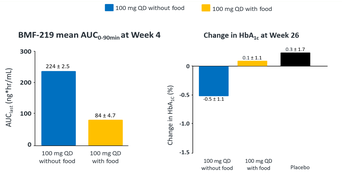


BMF-219 treatment results in an increase in PbK (PDZ-binding kinase) expression, similar to results seen in literature describing Menin knockdown experiments. PbK expression has been shown to help drive proliferation of beta cells, resulting in an increase in beta cell mass and function. PbK expression is regulated by menin binding partner JunD, in a glucose dependent manner.

Covalent –111: Baseline Characteristics and Demographics

	BMF-219 100mg QD w/o food (n=10)	BMF-219 100mg QD w/ 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 (1.0, 10.0)	8.7 (3.0, 14.0)	4.2 (1.0, 10.0)
HbA_{1c} (%-point, SD)	8.10 (0.92)	7.96 (0.62)	8.25 (0.71)
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 (0%)

Covalent-111: Pharmacokinetics and HbA1C response



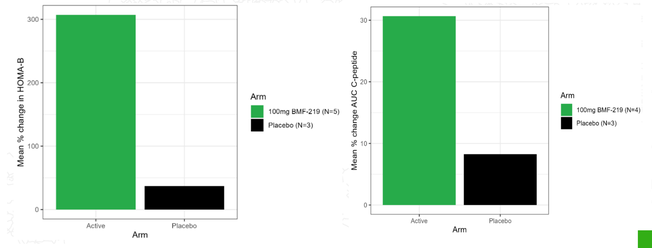
- 100mg QD without food resulted in approximately 2.7-fold higher BMF-219 exposure than 100mg QD with food
- Higher exposure resulted in greater reduction in HbA_{1c}

Covalent-111: 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 HbA1c: 80% (BMF-219 100mg QD without food), 40% (BMF-219 100mg QD with food)

Covalent-111: Increase from Baseline in HOMA-B and AUC C-Peptide

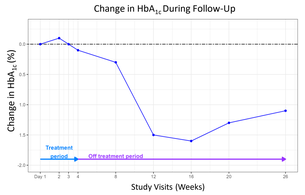


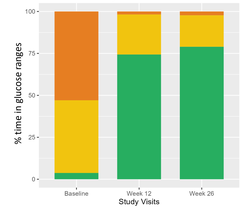
After 4 weeks of once daily BMF-219, responders (HbA_{1c} reduction ≥0.5% at Wk 26) with baseline HOMA-B <200 (below upper limit) across both cohorts achieved a greater increase in HOMA-B (307%) and stimulated C-peptide AUC (31%) vs placebo at Week 26

Case Study

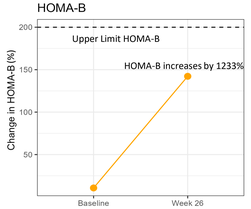
- 45-year-old man with 9-year history of T2D
- Metformin 500 mg BID
- HbA_{1c} 8.4%; FPG 216 mg/dL; BMI 29.6 kg/m²

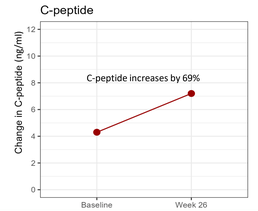
- BMF-219 100 mg once daily with food for 4 weeks
- CGM at Week 26 in Normal Range
- No tolerability issues or related adverse events





Change at Week 26





Summary and Conclusions

- Ex-vivo human islets:
  - BMF-219 improved human beta-cell function and proliferation
  - BMF-219 upregulated known genetic regulators of beta cell replication and improved beta-cell proliferation and function
- Covalent 111 trial data: At Week 26 (22 weeks after completion of 4-weeks of treatment), with an initial dose of 100 mg, BMF-219 elicited:
  - A placebo adjusted mean reduction in HbA1c of 0.8% compared to 0.7% at Week 4
  - An increase in C-peptide and HOMA-B during the treatment and off-treatment period
  - Durable HbA_{1c} reduction (≥1.0%) in 20% of patients at Week 26 with only 4 weeks of treatment
  - A generally well-tolerated safety profile with no severe or serious AEs
  - No symptomatic or clinically significant hypoglycemia
  - No dose discontinuation or modification
- These combined results support BMF-219's core mechanism of action of beta-cell proliferation, and ability to drive clinically significant increase in beta cell function and glycemic control in patients with T2D
- These data support further assessment of BMF-219 as short-term treatment for the management of patients with diabetes

Next Steps:

- Explore multiple doses for longer duration of BMF-219 treatment (up to 12 weeks) in patients with T2D and T1D

References

1. Butler T. et al. Oral Long-Acting Menin Inhibitor Normalizes Type 2 Diabetes Mellitus (T2DM) in Two Rat Models. Diabetes 1 June 2022; 71 (Supplement_1): 851–P.
2. Somanath P. et al. Oral Menin Inhibitor, BMF-219, Displays a Significant and Durable Reduction in HbA1c in a Type 2 Diabetes Mellitus Rat Model. Diabetes 1 June 2022; 71 (Supplement_1): 113–LB.
3. Rodriguez J. et al. COVALENT-111, A Phase 1/2 Trial of BMF-219, an Oral Covalent Menin Inhibitor, in Patients with Type 2 Diabetes Mellitus – Preliminary Results. Diabetes 20 June 2023; 72(Supplement_1): 91-LB

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