DURABLE GLYCEMIC CONTROL WITH BMF-219 DURING OFF-TREATMENT PERIOD AT WEEK 26: A PHASE 1/2 TRIAL OF BMF-219 IN PATIENTS WITH TYPE 2 DIABETES (COVALENT-111)

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Background

- T2D is characterized by hyperglycemia due to a progressive decline in beta-cell function
- Menin, a scaffold protein, is an important regulator of glycemic control, whereby inhibition of menin 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 diabetes ZDF and STZ rat models, BMF-219 showed durable glycemic control following short-term treatment [1,2]
- In multiple ascending dose (MAD) cohorts in patients with T2D, 4 weeks of BMF-219 100 and 200mg once daily dosing improved glycemic control at Week 26 (22 weeks after the final dose)[3]

Aim

- To assess the safety and efficacy of 4 weeks of once daily BMF-219 at Week 26 (22 weeks after final dose)

Methods

- COVALENT-111 (NCT05731544) is an ongoing Phase 1/2 randomized, double-blind, placebo controlled, MAD study evaluating BMF-219 in patients with inadequately controlled T2D who receive once-daily BMF-219 (50, 100, 200, 400mg) for 4 weeks and are followed until Week 26.
- Key eligibility criteria: Adults with T2D treated with up to 3 antidiabetic agents (excluding SU, insulin), HbA1c 7%-10.5%, T2D duration ≤ 15 years
- Primary endpoint: Safety and tolerability
- Secondary endpoints: Measures of glycemic control (HbA1c, CGM), beta cell function (HOMA-B and C-peptide), and durability of glycemic response

Study Design

Baseline Characteristics and Demographics

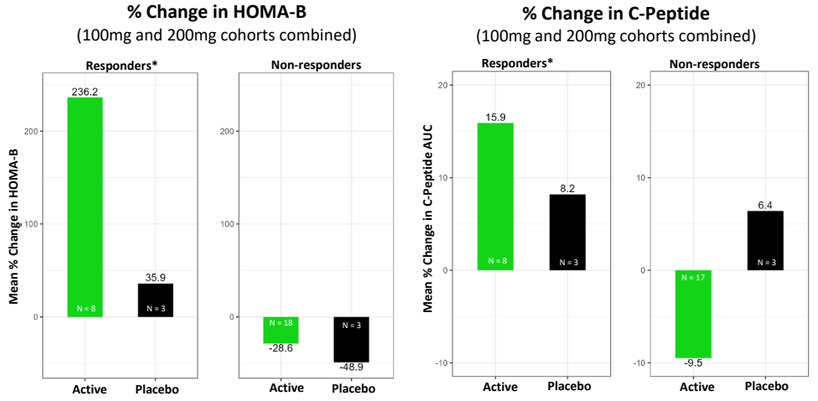
Characteristics[1]	100mg without Food N = 10	200mg without Food N = 10	100mg with Food N = 10	200mg with Food N = 2	Placebo N = 6
Age (yrs)	52 (38,63)	50 (25,64)	51 (35,60)	61 (60,61)	46 (31,61)
Female	4 (40%)	4 (40%)	3 (30%)	2 (100%)	0 (0%)
Male	6 (60%)	6 (60%)	7 (70%)	0 (0%)	6 (100%)
Duration of diabetes (yrs)	4.3 (0.3,9.3)	4.9 (0.5,11.7)	8.3 (2.6,13.6)	11.3 (9.7,12.8)	3.9 (0.7,9.5)
Baseline HbA1c (%)	8.1 (0.92)	7.85 (0.82)	7.96 (0.62)	8.35 (0.64)	8.25 (0.71)
Baseline therapy					
Metformin only	9 (90%)	6 (60%)	5 (50%)	0 (0%)	5 (83%)
Other	1 (10%)	2 (20%)	4 (40%)	2 (100%)	1 (17%)
None	0 (0%)	2 (20%)	1 (10%)	0 (0%)	0 (0%)

[1]Mean (Minimum, Maximum); n (%); Mean (SD)

Glycemic Results Summary at Week 26 (22 Weeks After Last Dose of BMF-219)

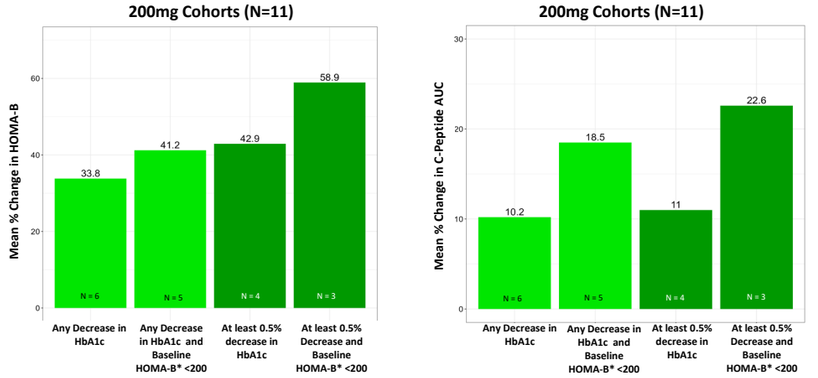
	BMF-219 100mg Without Food N = 10	BMF-219 200mg Without Food N = 9	BMF-219 100mg With Food N = 10	BMF-219 200mg With Food N = 2	Placebo N = 6
Mean change in HbA1c	-0.5%	-0.1%	0.1%	-1.1%	0.3%
Placebo Adjusted Mean Change in HbA1c	-0.8%	-0.4%	-0.2%	-1.4%	--
Percent of Participants with ≥ 1.0 reduction in HbA1c at Week 26	2/10 (20%)	2/9 (22%)	2/10 (20%)	2/2 (100%)	0/6 (0%)

Increase in HOMA-B and C-Peptide at Week 26



After 4 weeks of once-daily dosing, responders across both 100 and 200mg cohorts had a greater increase in HOMA-B and C-peptide AUC when compared to non-responders and placebo.

*** Responders have baseline HOMA-B <200 and have achieved at least 0.5% decrease in HbA1c at Week 26**



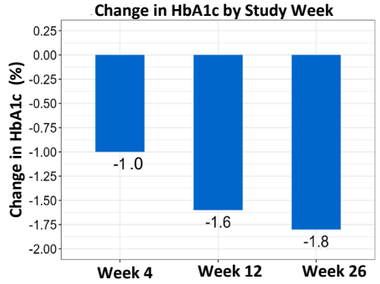
HOMA-B and C-peptide at Week 26 increases with magnitude of reduction in HbA1C and in patients with baseline HOMA-B <200 with BMF-219 200 mg once daily dosing for 4 weeks.

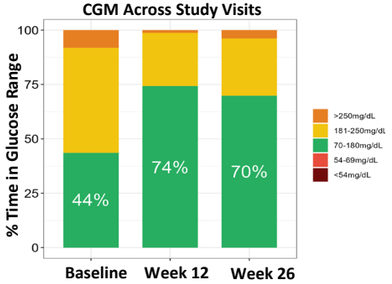
*** HOMA-B <200 is considered beta cell deficient**

Case Study

- 51-year-old man with 5-year history of T2D
- Metformin 500mg BID
- HbA_{1c} 8.9%; FPG 184mg/dL; BMI 32.1 kg/m^2

- BMF-219 100mg QD without food for 4 weeks
- Metformin continued
- No adverse events reported





A case study demonstrating continued improvement in HbA1C and improved Time In Range on CGM (after completion of 4 weeks of once daily oral treatment), indicating a durable glycemic control.

Summary and Conclusion

- At Week 26 (22 weeks after completion of a 4-week regimen) 100 and 200 mg BMF-219 resulted in:
  - Durable glycemic response (≥1.0% HbA1C reduction in 20% and 36% of patients in once daily 100 and 200mg cohorts, respectively)
  - Durable increase in C-peptide at Week 26 (22 weeks off treatment) for BMF-219 responders
  - Patients who demonstrated the greatest HbA1c reduction at Week 26, had greatest improvement in beta cell function as measured by HOMA-B and C-peptide
  - A generally well tolerated safety profile with no serious adverse events and no adverse event-related study discontinuations
  - No symptomatic or clinically significant hypoglycemia
- Robust durable responses seen in many patients after 4 weeks of BMF-219 and the demonstration of improvement in beta-cell function which correlates with this glycemic response, support the assessment of longer duration of therapy (8-12 weeks) with BMF-219
- Subsequent study cohorts are currently assessing BMF-219 administration for up to 12 weeks, with follow-up until Week 52

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. Frias J. et al. BMF-219: A Novel Therapeutic Agent to Re-Establish Functional Beta Cells and Provide Long-Term Glycemic Control. Metabolism May 2023; 142 (Supplement): Abstract#0088

Biomea Fusion sincerely acknowledges and thanks all the COVALENT-111 participants and their families, as well as the site Principal Investigators and staff for their hard work and dedication.

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