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COVALENT-111, A Phase 1/2 Trial of BMF-219, an Oral Covalent Menin Inhibitor, in Patients with Type 2 Diabetes Mellitus – Preliminary Results

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Background

- T2D is a metabolic condition characterized by impaired glycemic control caused by progressive beta-cell loss and inadequate insulin secretion.
- Menin is a scaffold protein, encoded by the MEN1 gene, that plays a key role in beta-cell proliferation and function, as evidenced by increased beta-cell mass generation in conditional Men1 knockout mice.[1]

BMF-219

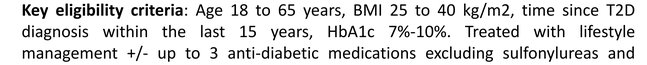
BMF-219 is an oral, selective, investigational, covalent menin inhibitor that has demonstrated durable glycemic control following short course treatments in both Zucker Diabetic Fatty (ZDF) Rat and Streptozotocin-induced (STZ) T2D rat models.[2,3]

COVALENT-111: Study Overview & Design

Covalent-111 (NCT05731544) is a Phase 1/2 randomized, double-blind, placebo-controlled, Single and Multiple Ascending Dose (SAD and MAD) study evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of BMF-219 in healthy adults and in patients with Type 2 Diabetes Mellitus (T2D).

16 healthy volunteers (12 active, 4 placebo) participated in Cohort 1 and received 100 mg BMF-219 or placebo without food, once daily for 2 weeks with follow up until Week 8.

12 T2D patients (10 active, 2 placebo) participated in each Cohorts 2 (100 mg with food) and 3 (100 mg without food) of BMF-219 or placebo, once daily for 4 weeks with follow up until Week 26.



The primary endpoint is safety while secondary endpoints are to assess the effect on glycemic parameters (FPG, HbA1c, OGTT, 7-day CGM), changes in beta-cell function (HOMA-B), and the durability of glycemic control.

Key eligibility criteria: Age 18 to 65 years, BMI 25 to 40 kg/m2, time since T2D diagnosis within the last 15 years, HbA1c 7%-10%. Treated with lifestyle management +/- up to 3 anti-diabetic medications excluding sulfonylureas and insulin.

Results

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.

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)

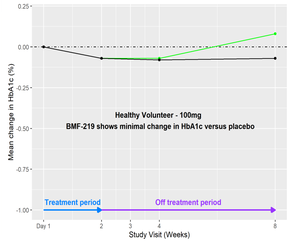
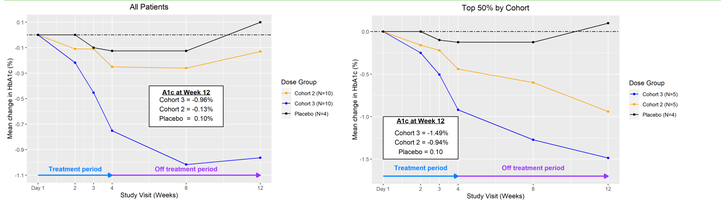


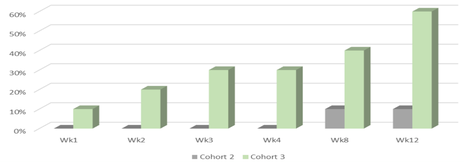
Figure 1 (HbA1c trend in Cohort 1). Minimal change was observed in HbA1c in healthy volunteers (HVs) during 14 days of treatment and 6-week follow-up.

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



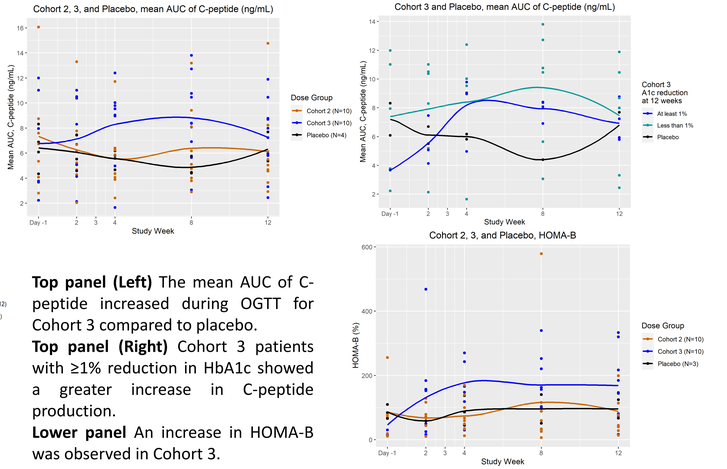
The top 50% of responders after 4-weeks of treatment in Cohorts 2 and 3 demonstrated durable and ongoing reduction in HbA1c while off treatment up to Week 12; a continued reduction in HbA1c was observed in Cohort 2 (additional 114%) and in Cohort 3 (additional 62%).

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



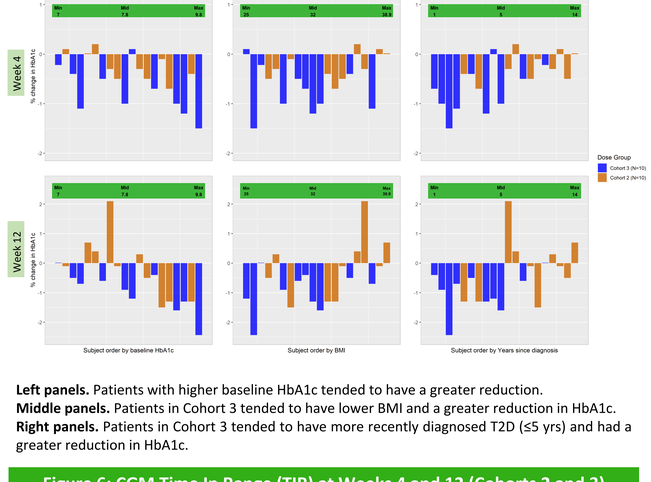
After 4-weeks of BMF-219 once daily dosing both cohorts demonstrated an increasing proportion of patients achieving a target HbA1c ≤ 7% and maintained through Week 12.

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



Top panel (Left) The mean AUC of C-peptide increased during OGTT for Cohort 3 compared to placebo.
Top panel (Right) Cohort 3 patients with ≥1% reduction in HbA1c showed a greater increase in C-peptide production.
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)

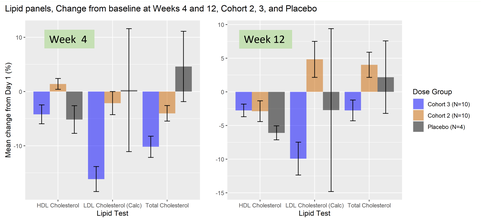


Left panels. Patients with higher baseline HbA1c tended to have a greater reduction.
Middle panels. Patients in Cohort 3 tended to have lower BMI and a greater reduction in HbA1c.
Right panels. Patients in Cohort 3 tended to have more recently diagnosed T2D (≤5 yrs) and had a greater reduction in HbA1c.

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



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

Conclusions

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)

References

1. Yang Y. et al. Reversal of preexisting hyperglycemia in diabetic mice by acute deletion of the Men 1 gene. Proc Natl Acad Sci USA. 2010 Nov 23;107(47):20358-63.
2. 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.
3. 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.

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