KEY OBSERVATIONS FROM THE DOSE-ESCALATION PORTION OF COVALENT-111, A PHASE 1/2 TRIAL OF THE COVALENT MENIN INHIBITOR BMF-219 IN PATIENTS WITH TYPE 2 DIABETES

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Background

- T2D is characterized by hyperglycemia due to a progressive decline in beta-cell function
- Menin, a scaffold protein, is as 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 diabetes ZDF and STZ rat models, BMF-219 showed durable glycemic control following 2-4 weeks of treatment [1,2]
- In multiple ascending dose (MAD) cohorts in patients with T2D, 4 weeks of BMF-219 100 and 200mg once daily improved glycemic control at Week 26 (22 weeks after the final dose)[3]
- Here we present key observations from COVALENT-111, a trial assessing BMF-219 in patients with T2D

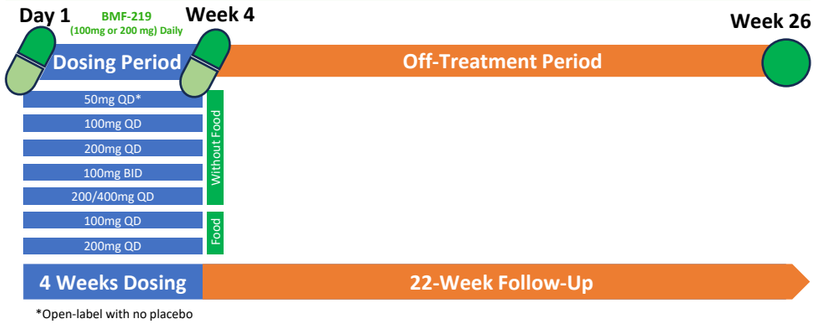
Aim

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

Methods

- In COVALENT-111, adults with T2D received BMF-219 daily (with or without food) for 4 weeks in multiple ascending dose cohorts (50, 100, 200, 400 mg) with follow-up until Week 26
- Key eligibility: Adults with T2D treated with up to 3 antidiabetic agents (excluding SU and 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

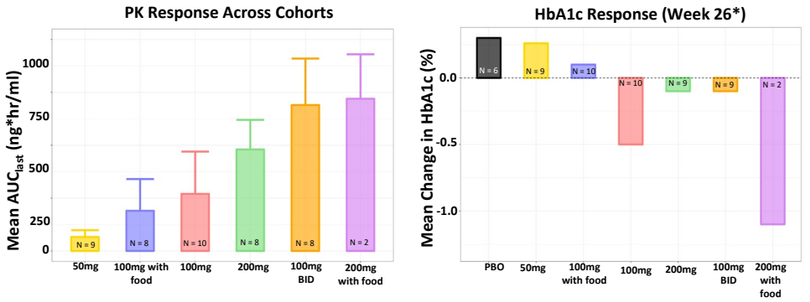


*Open-label with no placebo

Results

Across initial cohorts (n=31; 100 and 200mg with or without food), 39% of patients had a ≥0.5% HbA1c reduction at Week 26. Importantly, with higher BMF-219 exposure observed in the 200mg with food cohort, patients (n=2) diagnosed >7 years and failing dual- or triple-agent therapy at baseline (including GLP1 RA and/or SGLT2i) had a robust HbA1c response to BMF-219 (-0.5%, -1.1%, and -1.1% at Weeks 4, 12, and 26, respectively).

PK at Week 4 and Corresponding HbA1c Response at Week 26

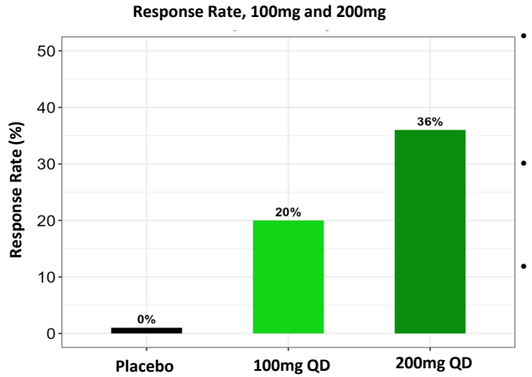


(Left) Dose-dependent PK response among 100 and 200mg cohorts with the 200mg dose taken with food resulting in the highest PK exposure

(Right) HbA1c response across cohorts at Week 26* (22 weeks after final BMF-219 dose), suggesting durability of response

*Data depicted for 50mg cohort reflects Week 20 values, the most recent timepoint for which information is available

Proportion of Patients with ≥1% HbA1c Reduction at Week 26

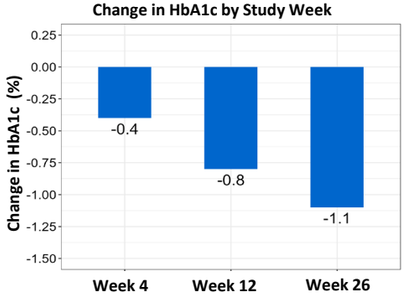


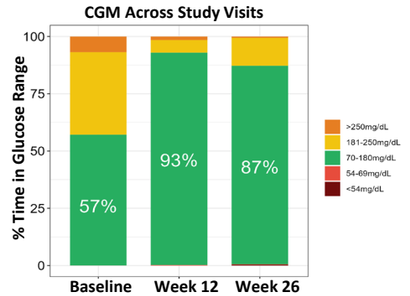
- 20% of patients across 100mg QD cohorts and 36% patients across 200 mg QD cohorts demonstrated ≥1.0% HbA1c reduction at Week 26 (22 weeks after the final dose).
- Across 100 and 200mg cohorts (N=31), 39% of patients had ≥0.5% HbA1c reduction at Week 26, with a mean HbA1c reduction of 1.3%.
- Across 100 and 200mg cohorts (N=31), 26% of patients had ≥1.0% HbA1c reduction at Week 26, with a mean HbA1c reduction of 1.5%.

Case Study

- 61-year-old woman with 10-year history of T2D
- Metformin 500 mg BID; liraglutide 1.2mg QD (GLP-1 RA); canagliflozin 500 mg QD (SGLT2i)
- HbA_{1c} 7.9%; FPG 163 mg/dL; BMI 29.4 kg/m^2

- BMF-219 200 mg QD with food for 4 weeks
- Metformin, liraglutide (GLP-1 RA), and canagliflozin (SGLT2i) continued
- No serious adverse events reported





A patient with a 10-year history of T2D and on triple-agent regimen (metformin, GLP1 RA, and SGLT2i) at baseline, experienced a 1.1% reduction in HbA1c and an increase of 30% in TIR compared to baseline at Week 26

Summary and Conclusions

At Week 26 (22 weeks after completion of 4 weeks of treatment):

- Patients in COVALENT-111 are displaying improved glycemic control while off therapy, supporting improved pancreatic function following BMF-219 treatment
- A higher proportion of patients treated with 200mg QD achieved a clinically significant reduction in HbA1c compared to 100mg QD dosing
- A durable glycemic response (≥1.0% HbA1C reduction) was seen in 20% and 36% of patients in once daily 100 mg and 200 mg cohorts, respectively
- Across 100mg QD, 200mg QD, and 100mg BID cohorts (N=40), 38% of patients had ≥0.5% HbA1c reduction with a mean HbA1c reduction of 1.2%, and 23% of patients had ≥1.0% HbA1c reduction with a mean HbA1c reduction of 1.5% at Week 26
- Patients with >7 years duration of diabetes and failing dual- or triple-agent therapy (including GLP1 RA and/or SGLT2i) also demonstrated improved glycemic control (HbA1c -0.4%, -1.1%, and -1.1% at Weeks 4, 12, and 26, respectively) with BMF-219 200mg with food
- A generally well tolerated safety profile with no SAEs was observed

- These data demonstrate the novel disease-modifying potential of short-term BMF-219 therapy in patients with T2D
- The expansion phase of COVALENT-111 aims to further optimize long-term glycemic control, dosing BMF-219 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

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