QUICK FACTS - BMF-219 in Diabetes

Biomea's investigational covalent menin inhibitor

Overview of diabetes

Diabetes is considered a chronic health condition that affects how the body turns food into energy. This occurs in part because the body doesn't produce enough insulin, a hormone produced by beta cells in the pancreas that regulates blood sugar, because those beta cells become damaged or destroyed. As a result, glucose cannot enter the cells of the body efficiently, leading to an accumulation of sugar in the bloodstream. Over time, this dysregulated blood sugar can cause serious health problems and damage vital organs, and as a result, most people with any type of diabetes have a shorter life expectancy than those without. The CDC estimates about 2 in 5 of the adult population in the USA are now expected to develop type 2 diabetes during their lifetime[1], and more than 37 million people of all ages (about 11% of the US population) have diabetes today[2]. Moreover, 96 million adults (more than 1 in 3) have pre-diabetes[2], which is defined as blood sugar levels that are higher than normal, but not yet high enough to be classified as diabetes. In addition, diabetes is one of the largest economic burdens on the United States health care system, with $1 out of every $4 in US health care costs being spent on caring for people with diabetes[3]. Despite the availability of current standard-of-care medications, diabetes remains a largely uncontrolled disease with roughly 50% of patients not at the ADA recommended A1c goal while on treatment[4]. There is a significant need for the improved treatment and care of people with diabetes.

What is the biological driver of diabetes?

Loss of functional beta cell mass is a core component in disease progression in both types of diabetes — type 1 diabetes (mediated by autoimmune dysfunction) and type 2 diabetes (mediated by metabolic dysfunction)[5]. Beta cells are found in the pancreas and are responsible for the synthesis and secretion of insulin, which is a hormone that helps the body use glucose for energy and control blood glucose levels. In people with diabetes, the beta cell mass and function are diminished, leading to insufficient insulin secretion and hyperglycemia. Currently, there are no approved therapies for the treatment of what is thought to be an underlying root cause of the disease.

What is the role of menin in diabetes?

Menin is thought to act as a control on beta cell turnover / beta cell growth[6], supporting the notion that inhibition of menin could lead to the reactivation, protection, and regeneration of beta cells, which could potentially be a disease-modifying approach to treat diabetes. Notably, it has previously been shown that knocking out the gene responsible for the production of menin (MEN1) results in profound glycemic control in diabetic animal models[7].

Is there a natural occurrence that resembles the inhibition of menin?

During pregnancy, the numbers of beta cell islets, the individual islet size, and the total number of beta cells can increase[8]. It has been shown in preclinical models that, during pregnancy, prolactin down-regulates menin, which results in the expansion of maternal pancreatic beta cells and improved glycemic control for the mother and fetus, therefore preventing gestational diabetes. We believe the ability of BMF-219 to inhibit menin pharmacologically could recapitulate this physiologic mechanism. In a Stanford study conducted by Karnik and coworkers, an article published by *Science* journal from 2007, beta cell proliferation rate was shown to increase when menin function was decreased due to prolactin.

What is BMF-219's mechanism of action in addressing diabetes?

BMF-219 was designed to specifically inhibit menin's capacity to interact with transcriptional partners that drive the expression of cell cycle protein regulators, including those that prevent the replication and expansion of beta-cells. Biomea is exploring the potential for BMF-219-mediated menin inhibition as a viable therapeutic approach to improve glycemic control in patients with type 1 and type 2 diabetes. In preclinical studies, BMF-219 has been observed to improve beta cell mass and function in diabetic animal models. Biomea is exploring the potential of BMF-219 as a viable therapeutic approach that aims to potentially halt or reverse progression of diabetes by covalently inhibiting menin to potentially achieve:

- Proliferation of new beta cells,
- Reactivation of a pool of inactive beta cells, and
- Preservation of existing beta cells

This mechanism of action is expected to be complementary to all currently approved treatments in diabetes.

About COVALENT-111 (NCT05731544) – BMF-219 in type 2 diabetes

COVALENT-111 is a multi-site, randomized, double-blind, placebo-controlled Phase I/II study, clinically investigating Biomea's covalent menin inhibitor, BMF-219, in adults with type 2 diabetes uncontrolled by current therapies. In March 2023, Biomea announced initial positive safety and efficacy data for the first two cohorts of patients with type 2 diabetes enrolled in the Phase II portion of the trial. After 4 weeks of once-daily 100 mg dosing with the investigational oral covalent menin inhibitor, BMF-219, 89% of patients achieved a reduction in A1c, 78% of patients achieved at least a 0.5% reduction in A1c, and 56% achieved at least a 1% reduction in A1c. Later in June 2023, Biomea reported updated clinical data from the first two cohorts of the ongoing Phase II COVALENT-111 study at the American Diabetes Association (ADA) 83rd Scientific Sessions, showing positive continued and durable patient improvements while being off therapy, 8 weeks after the last dose.

Principal clinical findings reported in June, 2023

- Summary of efficacy data at week 12 - 8 weeks after the last treatment with BMF-219 (two 100 mg dosing cohorts (n=12 per cohort; 10 patients on BMF-219: 2 patients on placebo)[9]: For patients who received BMF-219 100 mg once daily without food for 4 weeks, 50% (n=5/10) saw a continued improvement in HbA1c with a mean reduction in HbA1c of 1.49% at Week 12, compared to the mean reduction of 0.9% at the end of the dosing period at Week 4; 60% (n=6/10) achieved an HbA1c of 7% or below at the end of Week 12, compared to 30% (n=3/10) at the end of dosing period (Week 4) and 10% (n=1/10) at the end of Week 1; the average C-peptide and HOMA-B expression increased through Week 8 and stabilized thereafter. As measured by continuous glucose monitoring (CGM), 7 of 10 (70%) of these patients maintained or improved time in range while off treatment.
- BMF-219 demonstrated a well-tolerated safety profile. No patients on BMF-219 discontinued dosing and all patients completed 4 weeks of treatment. During the off-treatment period (Week 5 to Week 12), no severe or serious TEAEs were noted.

Key clinical and preclinical findings reported in December, 2023

- Update on escalation portion of BMF-219 in Type 2 diabetes: At Week 26, 22 weeks after the last dose of BMF-219, participants in the 100 mg QD (without food) cohort saw an improved placebo adjusted mean reduction in HbA1c of 0.8% with 20% of patients achieving a durable HbA1c reduction of 1% or more. Observed HbA1C

reduction was supported by an increase from baseline in placebo adjusted mean HOMA-B (+270%) and in mean stimulated C-peptide AUC (+22%) at Week 26 in responders with normal HOMA-B baseline. The 200 mg cohorts near doubled the percentage of patients (~40%) with durable HbA1c reduction of 1% or more compared to the 100 mg cohorts. BMF-219 leads to lasting improvements of A1c after 6 months of follow up OFF THERAPY, demonstrated by the results of these first dosing cohorts (after only 4 weeks of dosing). BMF-219 was well-tolerated, with no severe or serious AEs and no symptomatic or clinically significant hypoglycemia and no dose discontinuation or modification. The combined clinical results shown at WCIRDC support BMF-219's mechanism of action of beta-cell preservation, reactivation, and proliferation.

- Important data on ex-vivo human islet experiment, validating the MoA of 219: Dependent on dose concentration and dose duration, BMF-219 was observed to increase beta cell mass and function, as well as promote controlled proliferation and enhance insulin content in beta cells. Proliferation was observed only under elevated glucose conditions, which mimics diabetic levels, and with continuous drug exposure. BMF-219 was observed to upregulate the expression of key cell-cycle proteins, PbK and CCNA2 (Cyclin A2) in a glucose-dependent fashion, which are gene expression changes consistent with published literature.

About COVALENT-112 (NCT06152042) – BMF-219 in type 1 diabetes

Biomea also recently initiated COVALENT-112, a multi-site, randomized, double-blind, placebo-controlled Phase II study, clinically investigating BMF-219, in participants with type 1 diabetes.

1. CDC: Hispanic or Latino People and Type 2 Diabetes.
2. CDC: National Diabetes Statistics Report - Estimates of Diabetes and Its Burden in the United States.
3. CDC: Health and Economic Benefits of Diabetes Interventions.
4. Hankosky et al. Tirzepatide reduces the predicted risk of developing type 2 diabetes in people with obesity or overweight: Post hoc analysis of the SURMOUNT-1 trial. Diabetes Obes Metab. 2023;25:3748–3756. doi: 10.1111/dom.15269
5. Cernea et al. Biochem Med (Zagreb). 2013 Oct; 23(3): 266–280. doi: 10.11613/BM.2013.033
6. Hughs et al. Endocrinology, March 2011, 152(3):847–855
7. Yang et al. Reversal of preexisting hyperglycemia in diabetic mice by acute deletion of the Men1 gene. PNAS, 2010 https://doi.org/10.1073/pnas.1012257107
8. Dr. Kim, S.K. et al., Science. 2007 Nov 2. doi: 10.1126/science.1146812
9. Rodriguez 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. ADA 2023 Late Breaking Poster.