QUICK FACTS - BMF-219 in Diabetes

Overview of diabetes

Diabetes is one of the largest economic burdens on the US health care system and the 7th leading cause of death in the US. According to the CDC, worldwide 463 million adults have diabetes. In the United States alone, 34.2 million adults have diabetes – 10.5% of the population. Further, 96 million adults (more than 1 in 3) in the US have pre-diabetes. In the United States, $1 out of every $4 in US health care costs is being spent on caring for people with diabetes. In 2021, the US spent $380 billion to treat diabetes. Today, diabetes is an uncontrolled disease despite the availability of current standard-of-care medications. There is a significant need for the improved treatment and care of diabetes patients.

What is the biologic 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). Both type 1 and type 2 diabetes patients continue to lose glycemic control because of the continued loss of beta cells. 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 patients 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 a root cause of the underlying disease.

What is the role of menin in diabetes?

Menin is thought to act as a brake on beta cell turnover / beta cell growth, supporting the notion that inhibition of menin could lead to the regeneration of normal healthy beta cells, which could be a disease-modifying approach to treat type 2 diabetes. Notably, it has previously been shown that knocking out the gene responsible for the creation of menin (MEN1) results in profound glycemic control in diabetic animal models. (Yang 2010 https://doi.org/10.1073/pnas.1012257107) Over expression of menin may prevent the body from restoring pancreatic function.

Is there a natural occurrence that resembles the inhibition of menin with 219?

It has been shown that during pregnancy, prolactin down regulates menin, which results in the proliferation of maternal pancreatic islets and continued maintenance of glucose control for the mother and fetus (therefore preventing gestational diabetes). Prolactin has been observed to prevent menin from engaging in transcription so that there is less menin in the nucleus. Prolactin has been demonstrated to repress beta cell menin levels and to stimulate beta cell proliferation. We believe the ability of BMF-219 to inhibit menin pharmacologically recapitulates this physiologic mechanism that happens during pregnancy. The numbers of beta cell islets, the individual islet size, and the total number of beta cells increase during pregnancy as a result of this physiologic compensatory mechanism potentially based on the down regulation of menin. In Stanford research conducted by Karnik and coworkers, Science article from 2007, beta cell proliferation rate was shown to increase when menin function was decreased due to prolactin. This enhanced proliferation was at least in part due to a reduction in the levels in the beta cells of the cyclin-dependent kinase inhibitors considered (DOI: 10.1126/science.1146812).

What is the potential mechanism of action of BMF-219 – Biomea's investigational covalent menin inhibitor in addressing type 2 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 that aims to potentially halt or reverse progression of type 2 diabetes. In preclinical studies BMF-219 has been observed to restore and balance beta cell mass in multiple animal models of diabetes.

Biomea is exploring the potential of BMF-219 as a viable therapeutic approach that aims to potentially halt or reverse progression of type 2 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 currently approved treatments.

About COVALENT-111 (NCT05731544)

COVALENT-111 is a multi-site, randomized, double-blinded, placebo-controlled Phase I/II study. In the completed Phase I portion of the trial, healthy subjects were enrolled in single ascending dose cohorts. As previously reported, the Phase I portion of COVALENT-111 has been completed, and BMF-219 was generally well tolerated with an encouraging PK and PD profile in healthy volunteers. The Phase II portion, ongoing in Canada and the U.S., consists of multiple ascending dose cohorts enrolling adult patients with type 2 diabetes uncontrolled by current therapies. COVALENT-111 is designed to examine the capacity of BMF-219 to potentially provide long-term glycemic control to patients by restoring their pool of beta cells**.**