QUICK FACTS – BMF-219 in Oncology

Biomea's investigational covalent menin inhibitor

What is BMF-219?

BMF-219 is an investigational oral small molecule covalent inhibitor, rationally designed by Biomea to be a potent and selective inhibitor of the menin protein. Menin is a critical regulator known to play a direct role in oncogenic signaling in multiple cancers[1]. Covalent inhibitors bind to target proteins to form a permanent bond with them and optimized covalent binding molecules like BMF-219 can pose high potency with lower systemic exposure, allowing for a larger therapeutic window than what many reversible drugs typically achieve.

What is menin?

Menin is a scaffold protein that impacts multiple cellular processes, including cell cycle control and proliferation, apoptosis, and gene expression through interactions with dozens of different binding partners. It plays an essential role in oncogenic signaling in multiple cancer types[2].

How does BMF-219 work?

In oncology, BMF-219 is being examined for the potential treatment of cancers that are highly dependent on menin, like certain types of liquid (leukemias and lymphomas) and solid (lung, pancreas, colon) malignancies. BMF-219 is designed to form a **covalent** bond with menin permanently blocking its interaction between numerous binding partners involved in cancer, which could lead to pronounced beneficial effects. In fact, BMF-219 has shown in preclinical models to modulate the expression of target oncogene expression including NPM1, MYC, HOX, MEIS1, BCL2 and KRAS.

What is the advantage of BMF-219 covalently binding to menin?

Covalent drugs have shown the potential to offer superior safety, tolerability, and efficacy over conventional, reversible drugs. Specifically, covalent binding may offer three distinct advantages: higher target selectivity, deeper target inactivation, and a greater therapeutic window. BMF-219 is a covalently binding small molecule inhibitor designed to form a permanent bond directly with menin and in so doing continue to disable its role in cancer progression even after the body has cleared the drug. Other investigational menin inhibitors are typically designed to block the interaction between menin and one of its binding partners, MLL1, through a reversible mechanism. Unfortunately, these reversible inhibitors undergo continuous cycles of binding and release from their target, requiring continuous and high systemic exposure in the body to achieve reliable inhibition. This can pose safety and tolerability challenges.

[1] Agarwal SK, et al. *Horm Metab Res* 2005. DOI: 10.1055/s-2005-870139

[2] Matkar S, et al. *Trends Biochem. Sci*. 2013 DOI: 10.1016/j.tibs.2013.05.005

Which oncology programs have been started with BMF-219?

BMF-219 is a covalent menin inhibitor being developed for the treatment of cancers that are highly dependent on menin, with Biomea's current cancer pipeline including treatment of MLL1-r AML, NPM1 mutant AML, high-risk CLL, MYC driven/addicted liquid tumors (e.g., DLBCL, MM), as well as KRAS mutant colorectal, lung, and pancreatic tumors. When taken together, BMF-219 is currently being evaluated in up to 8 liquid and solid tumor types across two ongoing clinical trials.

COVALENT-101 is a Phase 1 clinical trial to explore the safety and efficacy of BMF-219 in patients with relapsed/refractory AML and ALL, including those with MLL/ KMT2A gene arrangements or NPM1 mutations. The study includes various cohorts of patients to explore the potential utility of BMF-219 across a range of menin-dependent hematologic malignancies including MM, DLBCL, and CLL (NCT05153330).

Principal clinical findings reported in December, 2023

- BMF-219 demonstrated early signs of clinical activity to achieve durable complete responsed with minimal residual disease negativity in AML, with pharmacodynamic data further supporting the MoA of BMF-219 as a menin inhibitor; in-line with preclinical models, BMF-219 downregulated key leukemogenic genes (e.g. HOXA9, MEIS1) as well as MEN1.
- BMF-219 was well tolerated with no dose-limiting toxicities observed and without adverse event related treatment discontinuations.

We have also initiated and are enrolling **COVALENT-102**, a Phase 1/1b clinical trial of BMF-219 in patients with unresectable, locally advanced, or metastatic non-small cell lung cancer (NSCLC), colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC) with an activating KRAS mutation (NCT05631574).