Oral Menin Inhibitor, BMF-219, displays a significant and durable reduction in HbA1c in a Type 2 Diabetes Mellitus Rat Model

Priyanka Somanath, PhD 1, Sachintha Mursya, MD 1, Weiqun Li, PhD 1, Brian Law, BS 1, Tenley Archer, PhD 1, Daniel Li, MS 1, Tripa Raghavan, Latha Kumar, Taiwei Kinoshita, PhD 1, Ming Dalakatschan, PhD 1, and Thomas Butler, MSC MBA 1

1 Biomea Fusion, Inc. Redwood City, CA

Introduction

- Menin is a scaffold protein encoded by the gene, MEN1, that regulates diverse cellular processes in a tissue-context dependent manner.
- Menin plays a key role in beta-cell proliferation and function, as previously demonstrated though increased beta-cell mass generation in Mnt-deleted mice (Ma et al., 2021).
- The menin-MLL interaction also plays a role in suppressing islet cell growth through control of cell cycle inhibitor expression.
- Importantly, menin inhibition has been shown to improve β-cell proliferation and glycemic control in high-fat-induced diabetic mouse model (Ma et al., 2021).
- BMF-219 is an orally bioavailable, selective, covalent menin inhibitor that elicits a broad impact on the complexes surrounding menin, which direct its biological function.

- Here, we demonstrate the marked potential of an oral menin inhibitor, BMF-219, in achieving durable glycemic control following a short course treatment in a Type 2 Diabetes Mellitus (T2DM) Zucker Diabetic Fatty Rat model.

Methods

Zucker Diabetic Fatty (ZDF) rats were dosed daily with BMF-219, liraglutide or vehicle for 28 days (n=10 per group) and monitored for an additional 28 days post last dose as shown in scheme below. Group 1 (40 mg/kg) was treated with BMF-219 Day 17-28 PO on day 17 for rest of the dosing phase. Fasting blood glucose, insulin, C-peptide levels, HbA1c, oral glucose tolerance test (OGTT) and body weight were monitored during and post-treatment.

Results

BMF-219 significantly reduces HbA1c and controls blood glucose levels in a 4-week dosing study in ZDF rats

Figure 2 shows the 4-week effect of BMF-219 treatment on HbA1c and fasting glucose levels in ZDF rats. BMF-219 significantly reduces HbA1c and fasting glucose levels in ZDF rats. BMF-219 treatment resulted in a reduction of HbA1c and fasting glucose levels in a dose-dependent manner. BMF-219 significantly reduced HbA1c levels compared to vehicle and control groups.

Figure 3. BMF-219 exerts strong glycemic control over 28-days of treatment in ZDF rats. OGTT was conducted on day 25 on rats treated with BMF-219 at indicated doses, liraglutide or vehicle control. Data represent mean ± SEM for the dose group.

Conclusions

- BMF-219 was tested in rats at clinically relevant exposures.
- All animals tolerated BMF-219 well throughout the study, displaying high activity.
- BMF-219 mid and high-dose arms showed reduction in fasting blood glucose levels similar to Liraglutide. On day 29 (one day after treatment stop), BMF-219 high dose group showed sustained and significant reduction in fasting glucose.
- BMF-219 treatment reduced HbA1c levels by Day 21 of treatment. Absolute amounts were lower than vehicle group by 3.5% (33% reduced from vehicle) and lower than liraglutide group by 1.8% (20% reduced from vehicle) on day 29, and remained reduced throughout the study, including post-treatment.
- All BMF-219 dose groups showed improved glycemic control by oral glucose tolerance test (OGTT) on day 25, in comparison to vehicle-treated group, with the high dose treatment group showing improved response vs. liraglutide.
- Fasting insulin and C-peptide levels were elevated in BMF-219 treated animals up to the last day of dosing, with the effects lasting well into two weeks post last dose.
- BMF-219 induced significant reductions in HbA1c at all doses tested, with the effects lasting 15 days after the last dose.
- Of note, animals in this study, including vehicle group, displayed progressive increase in body weight and fasting blood glucose levels over time, likely from very high food intake. This compromises meaningful data interpretation beyond day 43.
- Collectively, these data demonstrate the novel long-acting potential of BMF-219 as an oral treatment for T2DM, in maintaining glycemic control after short-term dosing.

References