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

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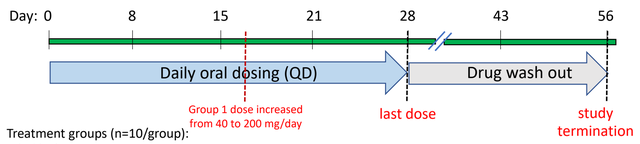
Introduction

- 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 *Men1* knockout 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 mice (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 dose (40 mg/kg) was increased to 200 mg/kg 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.



Treatment groups (n=10/group):

1. Vehicle
2. BMF-219 40 mg/kg days 1-16, 200 mg/kg days 17-28
3. BMF-219 85 mg/kg
4. BMF-219 170 mg/kg
5. Liraglutide 0.2 mg/kg

Rats monitored through dosing and washout phases:

- Body weight, fasting blood glucose, blood insulin, C-peptide, HbA1c and OGTT

Results

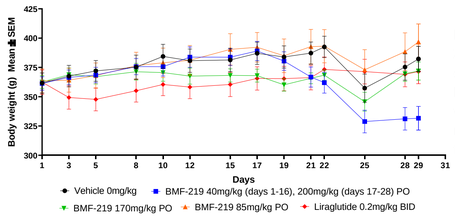


Figure 1. Body weight of ZDF rats during the 28 days of treatment with BMF-219, liraglutide, or vehicle control. Data represents mean SEM for the dose group.

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

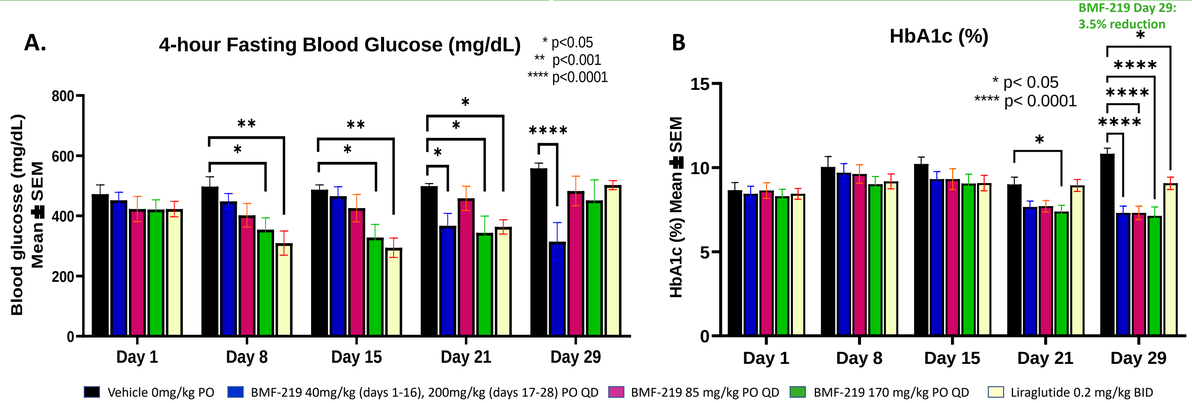


Figure 2. Reduction in fasting blood glucose and HbA1c levels in BMF-219 treated ZDF rats. Rats treated with BMF-219 at indicated doses, liraglutide, or vehicle control were monitored for 4-hour fasting glucose (A) and HbA1c (B) was calculated for treated animals weekly over a 28-day treatment. Changes in blood glucose or HbA1c were compared to vehicle control to calculate statistical significance.

BMF-219 maintains a significant reduction of HbA1c two weeks after the last dose

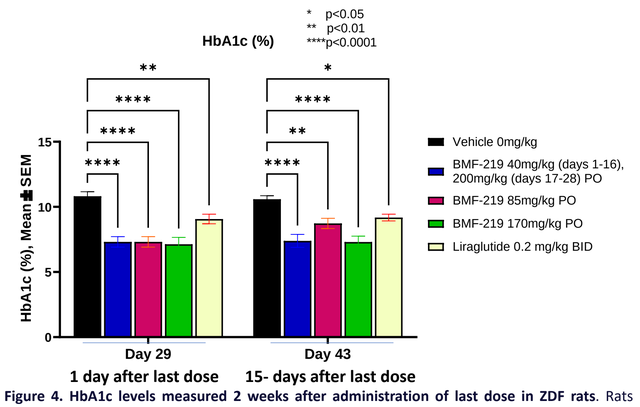


Figure 4. HbA1c levels measured 2 weeks after administration of last dose in ZDF rats. Rats treated for 28 days with BMF-219 at indicated doses, liraglutide or vehicle control were monitored for HbA1c levels on day 1 and day 15 post-dosing. Drug-treated groups are compared to vehicle control to calculate statistical significance by two-way ANOVA.

BMF-219 displays durable glycemic control over 4 weeks of dosing

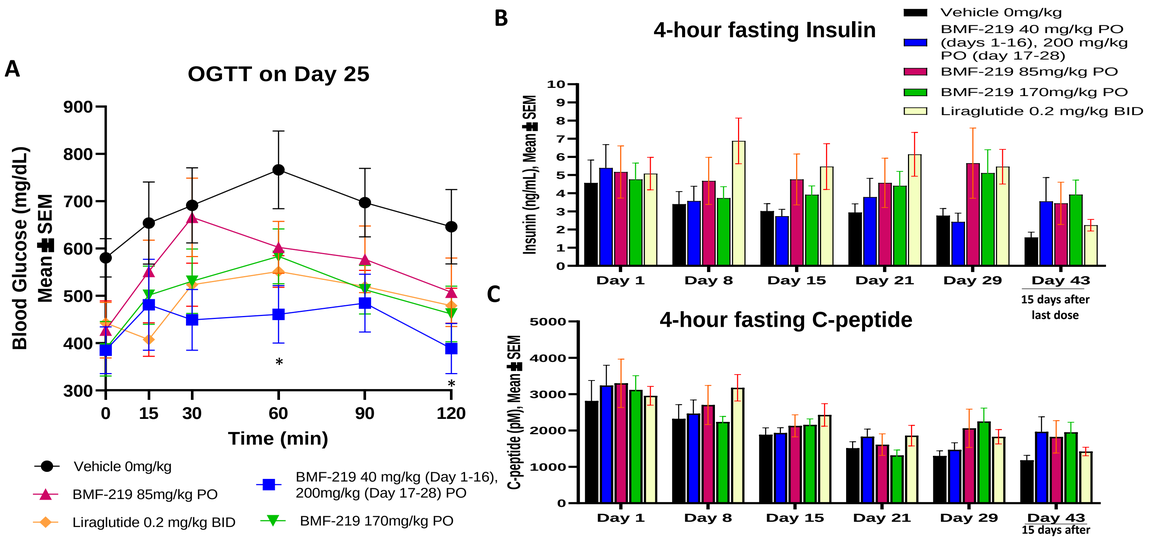


Figure 3. BMF-219 exerts strong glycemic control over 28-days of treatment in ZDF rats. OGTT was conducted on day 25 on rats treated with BMF-219 at indicated doses, liraglutide or vehicle control by measurement of blood glucose at 15 and 30 minute intervals up to 2 hours (A). Fasting insulin (B) and C-peptide (C) levels were measured weekly over 28 days in rats treated with BMF-219 at indicated doses, liraglutide, or vehicle control. Insulin and C-peptide levels were also measured on day 43 (15 days after the last dose was administered).

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 blood 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-treated 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

Ma, J. et al. Menin-regulated Pbk controls high fat diet-induced compensatory beta cell proliferation. *EMBO Mol Med*. 2021; 13(5):e13524.

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