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

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**Menin: A novel target for beta-cell homeostasis**

### Potential Mechanism of Menin in Diabetes

- Menin is an epigenetic protein that plays a key role in regulating beta-cell proliferation and function.
- Menin inhibition has previously been shown to improve glycemic control in high fat induced diabetic mice (Ma et al., 2021).
- Inhibition of menin/JunD complex reduces the expression of Cyclin Dependent Kinase Inhibitors (CDKIs), allowing CDKs to drive beta-cell proliferation.

### BMF-219: A selective covalent menin inhibitor

BMF-219 covalent binding to menin disrupts menin complexes, resulting in global change of function.

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**Menin regulation of beta-cell quiescence**

- Menin inhibition by BMF-219 allows for beta-cell restoration and glucose homeostasis.

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*Figure adapted from Issa et al. Leukemia 35, 2482–2495 (2021).*
The ZDF rat is a model of pancreatic exhaustion and insulin resistance, thus mimicking some aspects of human diabetes.

The ZDF rat is a translatable model for studying the development of T2D.

**Study Objective**

Measure the ability of BMF-219 in restoring glycemic control in Zucker Diabetic Fatty (ZDF) Rat over a 4-week dosing study.

**Treatment Scheme of ZDF Rat Model**

- **Study Objective**
  Measure the ability of BMF-219 in restoring glycemic control in Zucker Diabetic Fatty (ZDF) Rat over a 4-week dosing study.

- **Treatment groups (n=10/group):**
  1. Vehicle
  2. BMF-219 40 mg/kg days 1-16, 200 mg/kg days 17-28 (QD, PO)
  3. BMF-219 85 mg/kg (QD, PO)
  4. BMF-219 170 mg/kg (QD, PO)
  5. Liraglutide 0.2 mg/kg (BID, SC)

- **Drug wash out**
  Rats monitored through dosing and washout phases:
  - Fasting blood glucose, insulin, OGTT, HbA1c, body weight, blood lipemic levels

- **Image Source:** Charles River Laboratories, 2001.
BMF-219 substantially controls blood glucose levels in a 4-week dosing study in ZDF rats.
BMF-219 substantially controls blood glucose levels in a 4-week dosing study in ZDF rats

**4hr Fasting Blood Glucose**

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Day 21</th>
<th>Day 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SEM</td>
<td></td>
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</tbody>
</table>

**4hr Fasting Insulin**

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Day 21</th>
<th>Day 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (ng/mL)</td>
<td><strong>2</strong></td>
<td><em>1</em></td>
<td><strong>2</strong></td>
<td><em>1</em></td>
<td><strong>2</strong></td>
</tr>
<tr>
<td>Mean</td>
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</tr>
<tr>
<td>SEM</td>
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</tbody>
</table>

**OGTT - Day 25**

- Vehicle 0mg/kg
- BMF-219 200mg/kg PO
- BMF-219 170mg/kg PO
- Liraglutide 0.2 mg/kg BID
BMF-219 restores beta-cell function over 4 weeks of treatment

**Severity Grading Assessment for Pancreatic Beta-Cell Function**

<table>
<thead>
<tr>
<th></th>
<th>HOMA-B Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate (normal state)</td>
<td>≥ 201.00</td>
</tr>
<tr>
<td>Mild deficiency</td>
<td>134.00 to 200.99</td>
</tr>
<tr>
<td>Moderate deficiency</td>
<td>67.00 to 133.99</td>
</tr>
<tr>
<td>Severe deficiency</td>
<td>0.00 to 66.99</td>
</tr>
</tbody>
</table>

BMF-219 significantly reduces HbA1c (-3.5%) during treatment and maintains lowering effect during 2 weeks of drug washout.

**Hemoglobin A1c (%)**

- BMF-219 Day 29: 3.5% HbA1c reduction

**Legend:**
- Vehicle 0mg/kg
- BMF-219 40mg/kg (days 1-16), 200mg/kg (days 17-28) PO
- BMF-219 170mg/kg PO
- Liraglutide 0.2 mg/kg BID

- * p<0.05
- ** p<0.01
- **** p<0.0001

**Graph:**
- Day: 0  8  15  21  28  43  56
- Daily oral dosing (QD) → Drug wash out
- HbA1c reduction in BMF-219 treated groups maintained through washout period
BMF-219 treated groups display body weight and cholesterol reduction

**BMF-219 200 mg/kg group reduces body weight during treatment in ZDF rats**

**BMF-219 reduces blood lipemic levels measured on Day 29**

- **Total Cholesterol**
  - *** p<0.0005
  - **** p<0.0001

- **Triglycerides**

**Body weight**

13% body weight reduction on Day 29
BMF-219 displays significant glycemic control in ZDF rats, outperforming liraglutide in reduction of fasting blood glucose by Day 29 and by OGTT on day 25.

BMF-219 significantly reduces HbA1c levels (-3.5%) during treatment and drug washout.

BMF-219 treatment restores HOMA-B scores to normal state indicating restored beta-cell function.

BMF-219 treated groups have significant reductions in body weight (13% at 4 weeks of treatment) and reduced blood lipemic levels.

Collectively, these data demonstrate the novel long-acting potential of BMF-219 as an orally administered short-term treatment in achieving and maintaining glycemic control in T2DM.
THANK YOU