The Menin Inhibitor Ziftomenib Induces Insulin Production and Improves Insulin Sensitivity in a Rat Model of Type 2 Diabetes Mellitus (T2DM)

#845-P

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BACKGROUND

- Menin is a scaffold protein known to regulate epigenetic gene expression in several cell types. Genetic menin loss (MEN1 syndrome) is associated with insulinemia due to upregulated pancreatic β-cell proliferation.
- Inhibiting menin could be a viable option to enhance pancreatic function in diabetic patients.
- Ziftomenib is an orally available, potent, and selective menin inhibitor currently undergoing a registration-enabling, Phase 2 clinical trial in *NPM1*-mutated acute myeloid leukemia.
- **The highly diabetic Zucker Diabetic Fatty (ZDF) rat model of T2DM was used to evaluate ziftomenib.**

RESULTS

Study Design

ZDF male rats (obese, fa/fa)

- **Vehicle**: QD, PO
- **Ziftomenib**: 2x (mpk), QD, PO; reduced to 1x (mpk), QD, PO, on Day 10
- **Semaglutide**: step-wise dose escalation; 6.25, 12.5, 25, 50 nmol/kg, Q3D, SC

Ziftomenib reduces blood glucose and %HbA1C levels and improves insulin sensitivity

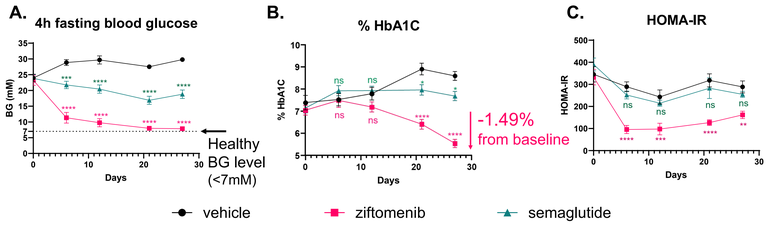


Figure 1. Ziftomenib significantly reduced 4h FBG levels and %HbA1C within 27 days of treatment. Rats (11 rats per group) received treatments for 27 days. **A/B.** The 4h FBG levels and %HbA1C levels were measured ~weekly. **C.** HOMA-IR was calculated as (fasting insulin (μU/mL) x FBG (nM)/22.5). ns, not significant; *, p<0.05; **, p<0.01; ***, p<0.005; ****, p<0.001. Data presented as mean +/- SEM.

Ziftomenib stimulates insulin production

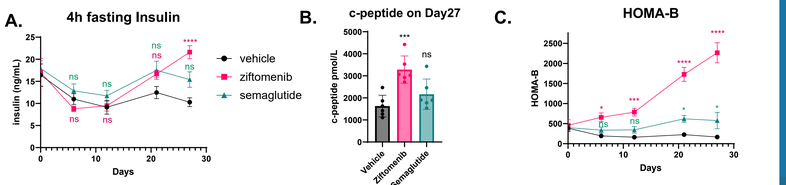


Figure 2. Ziftomenib significantly increased serum insulin and c-peptide levels, indicating significant improvement to steady-state β-cell function. Rats (11 rats per group) received treatments for 27 days. **A.** The 4h fasting serum insulin levels were measured ~weekly. **B.** Serum c-peptide levels were measured on Day 27 (6 rats per group). **C.** HOMA-B was calculated as (20 x fasting insulin (μU/mL)) / (fasting glucose (mmol/L) - 3.5). ns, not significant; *, p<0.05; **, p<0.01; ***, p<0.005; ****, p<0.001. Data presented as mean +/- SEM.

Ziftomenib improves postprandial glucose control

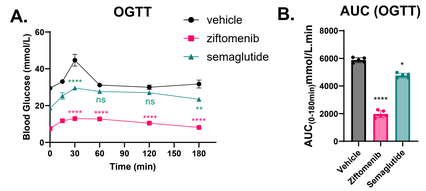


Figure 3. Ziftomenib significantly reduced BG during the glucose challenge after 27 days of treatment. **A.** OGTT was performed on Day 27 (5 rats per group). **B.** AUC was calculated. ns, not significant; *, p<0.05; **, p<0.01; ***, p<0.005; ****, p<0.001. Data presented as mean +/- SEM.

In model of more advanced disease, ziftomenib reduces FBG and improves insulin production with continued effects during wash-out period

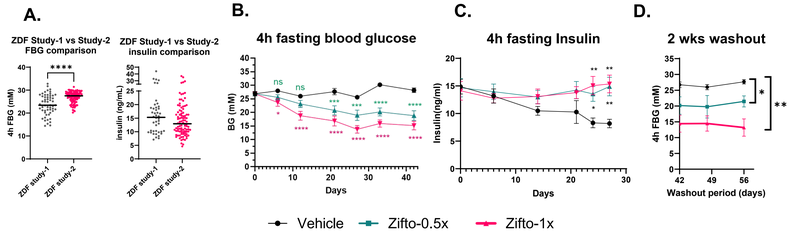
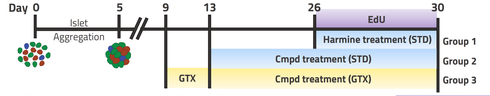


Figure 4. Ziftomenib maintained meaningful activity during the wash-out period, suggesting restoration of β-cell mass. 12 rats were treated with 0.5x or 1x mpk ziftomenib (QD) for 42 days, and 4 rats were observed for 2 weeks after the dosing stop. **A.** In this study, rats had more progressed disease status at randomization. **B/C.** 4h FBG and serum insulin levels were measured during the dosing period. **D.** The 4h FBG of 4 rats was measured weekly after dosing was stopped. ns, not significant; *, p<0.05; **, p<0.01; ***, p<0.005; ****, p<0.001. Data presented as mean +/- SEM.

Study Design (Human islet microtissue platform)



- Ziftomenib: 1x (nM) or 5x (nM)
- Harmine: 10 μM (only used in STD, toxic under GTX)
- Proliferating β-cells: NKX6.2+, EdU+
- Proliferating non-β-cells: NKX6.2-, EdU+

Donor information

	Donor-1	Donor-2
Age	33	33
Sex	Female	Male
BMI	28.84	33.15
HbA1c	5.5%	5.7%
Islet classified (normal or T2D)	Normal	Normal

Ziftomenib stimulates β-cell proliferation with minimal effects on non-β-cells in human pancreatic islet microtissues

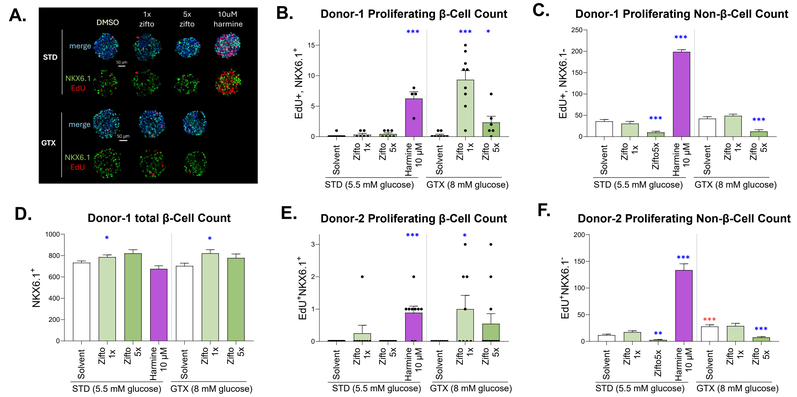


Figure 5. Ziftomenib stimulated the proliferation of β-cells specifically in both donor samples. A. Representative fluorescent confocal images of Donor-1 MT samples (merge: DAPI/NKX6.1/EdU). **B, C, E, and F.** The number of proliferating β-cells/MT or the number of proliferating non-β-cells was counted. **D.** Total β-cell number of Donor-1 was counted. Data presented as mean + SEM of 1 donor with 5 to 6 technical replicates. *, p<0.05; **, p<0.01; ***, p<0.001.

CONCLUSIONS

- Ziftomenib induced β-cell proliferation in human islet microtissues. Induction of non-β-cell proliferation was not detectable, indicating menin is a viable target for β-cell mass specific expansion.
- Ziftomenib treatment showed consistent progressive improvement in both insulin sensitivity and insulin production in ZDF rats.
- The efficacy was fully maintained after dosing discontinuation, likely due to the restoration of pancreatic β-cell mass.
- Ziftomenib is currently in a registration-enabling, Phase 2 clinical investigation in *NPM1*-mutated acute myeloid leukemia. Further study of ziftomenib and next-generation menin inhibitors in T2DM is warranted.

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Abbreviations: Av, Average; BG, blood glucose; FBG, fasting blood glucose; GTX, glucotoxic conditions; mpk, mg/kg; MT, microtissue; *NPM1*, *nucleophosmin-1*; PO, orally; QD, once per day; Q3D, once every 3 days; SC, subcutaneous; STD, standard.