

Next-Generation Menin Inhibitor KO-7246 Regenerates β Cell Mass in Diabetic Rodent and Human Islet Models

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Overview

- Menin is a validated regulator of β -cell mass and function in rodent and human
- Pharmacologic menin inhibition may have the potential to normalize glycemic control in patients with diabetes by restoring endogenous insulin-producing capacity
- Treatment of diabetes with a menin inhibitor could require longer-term treatment than oncology indications, potentially in combination with other modalities such as insulin or GLP-1 agents
- KO-7246 has the potential to be a next-generation/best-in-class menin inhibitor for diabetes
 - Potent and selective menin inhibitor
 - Robust activity in complementary diabetes models, including human β cells
 - Specifically designed for requirements of chronic use in a cardiometabolic disease setting
 - Currently undergoing IND-enabling studies with initial clinical evaluation planned thereafter

Multiple Lines of Evidence Support Disease-Modifying Potential for Menin Inhibitors in the Treatment of Diabetes

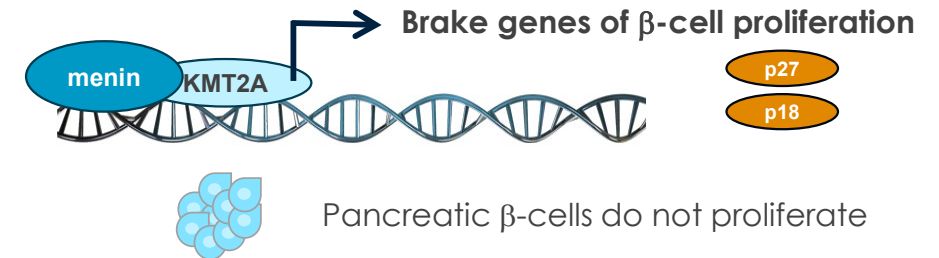
- **Mammalian physiology:** Pregnancy demonstrates that lowering menin signaling is associated with adaptive β -cell expansion.¹
- **Human Genetics:** MEN1 loss establishes that reduced menin activity can profoundly increase pancreatic β -cell proliferation.²
- **Pharmacologic Validation:** Several chemically distinct menin inhibitors now provide a way to control this pathway reversibly.
- **Implication:** These observations support pharmacologic menin inhibition as a strategy to restore functional β -cell capacity in both T1D and T2D.

¹Karnik S.K. *et al. Science* 2007, 318(5851): 806-809.

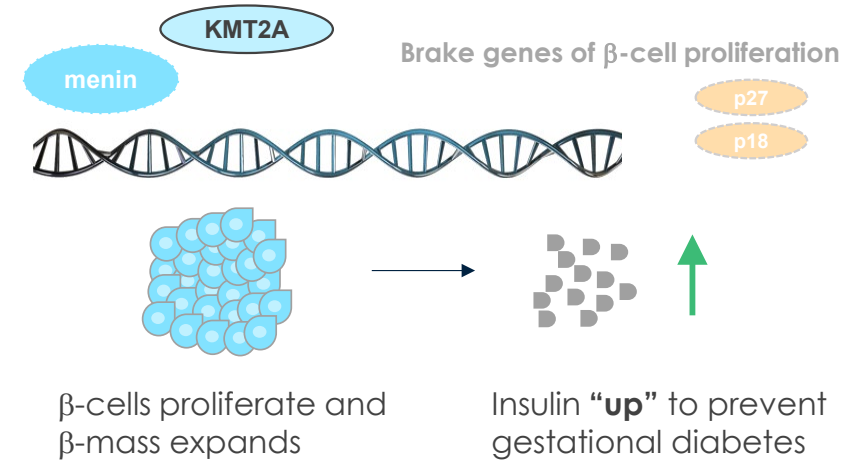
²Agarwal S *et al Ann N Y Acad Sci.* 2004 1014:189-98..

Menin as an epigenetic molecular brake of β -cell proliferation

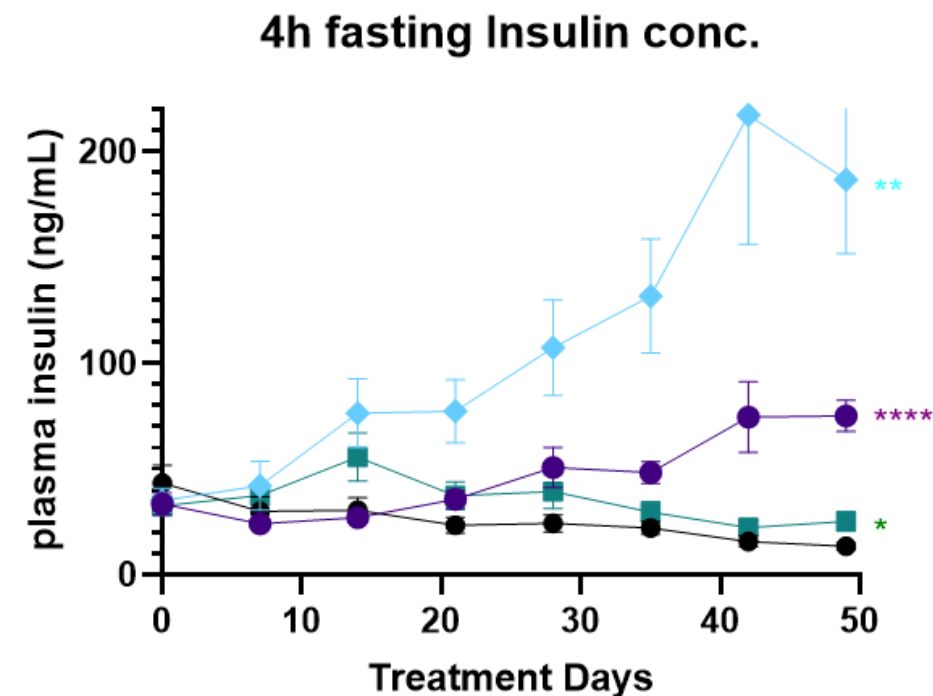
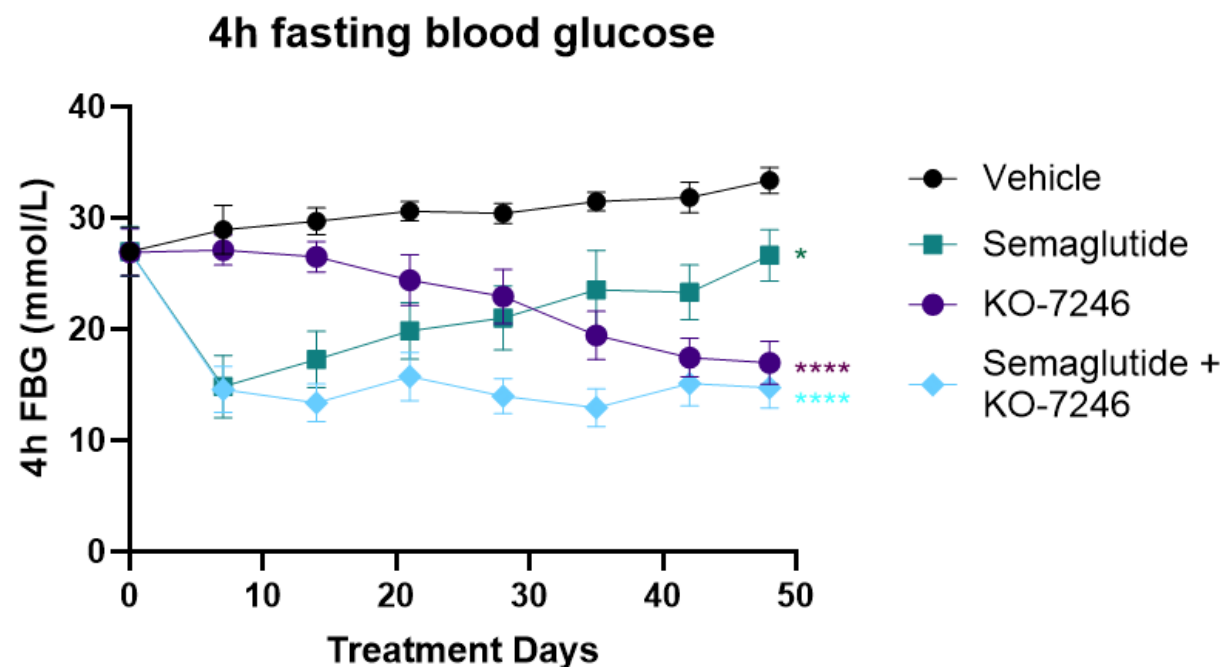
i) Under normal physiological conditions



ii) During pregnancy



KO-7246 Provides Durable Glycemic Control and Complements GLP-1 Therapy in db/db Mouse Model of Type 2 Diabetes

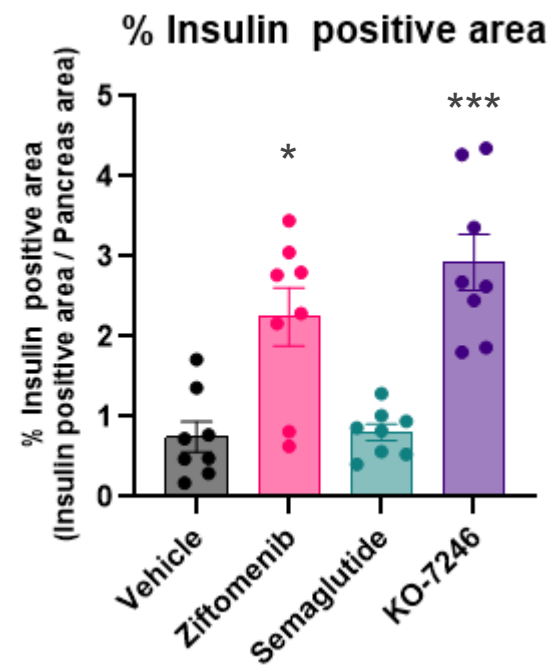
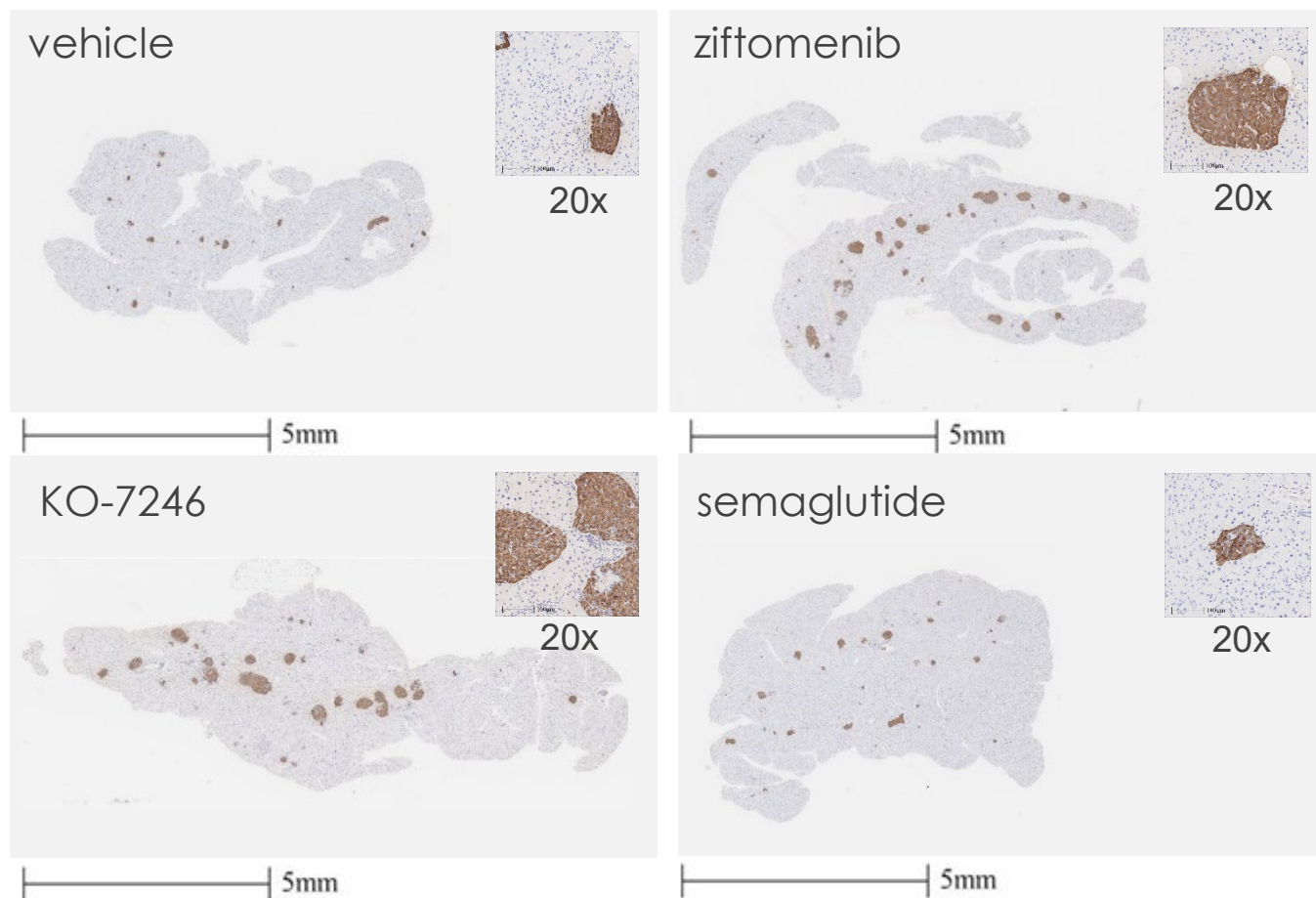


- Semaglutide reduced blood glucose levels rapidly but transiently
- KO-7246 significantly reduced FBG and elevated insulin levels over a 7-week period
 - First-generation menin inhibitor ziftomenib produced similar results¹
- No hypoglycemia observed in any KO-7246-treated animals

KO-7246 Expands Pancreatic β -Cell Mass in db/db Preclinical Models

Expansion provides direct evidence supporting proposed regenerative mechanism

Insulin IHC (β -cell signals in **brown**)

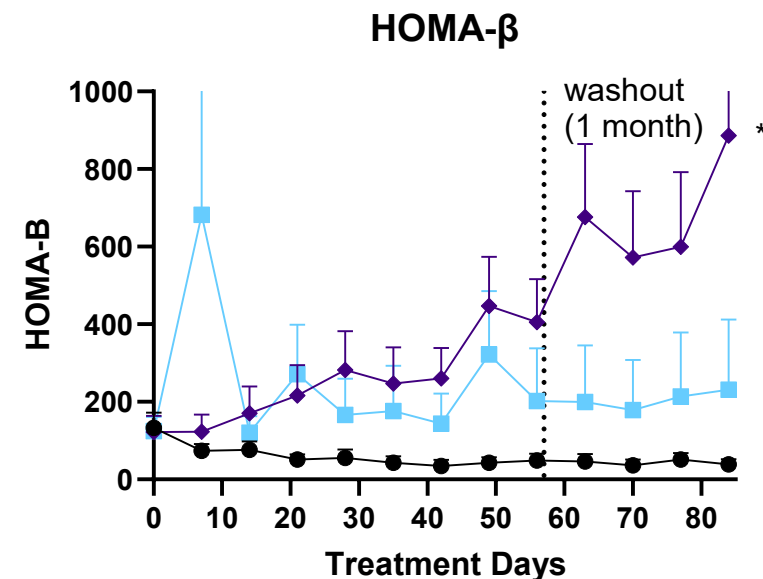
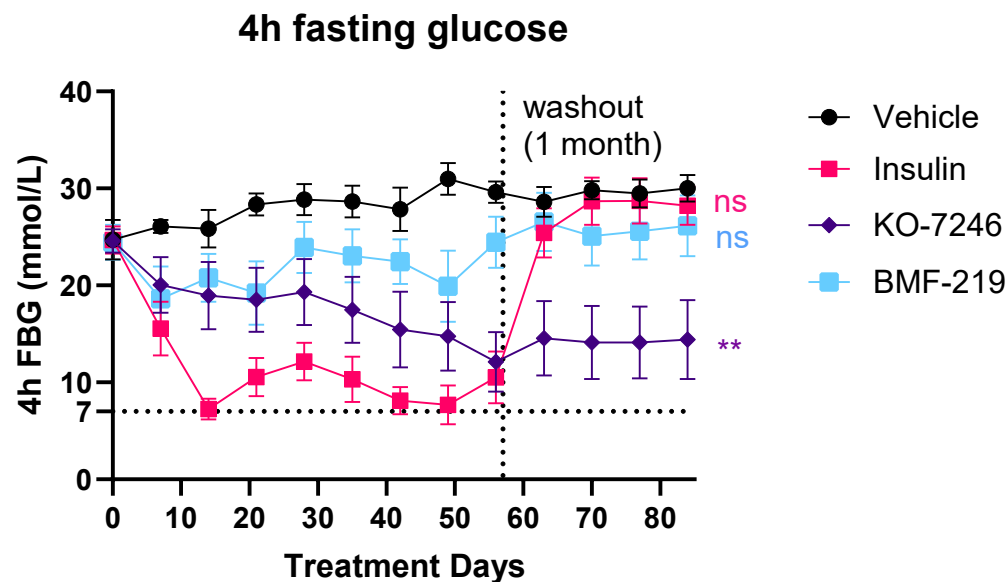


10 mice/group, 49d treatment period;
each point represents the average of
three slices/mouse

*, $p < 0.05$; ***, $p < 0.005$

KO-7246 Demonstrated Robust, Durable Glucose Reduction Activity in STZ Rat Model of Type 1 Diabetes

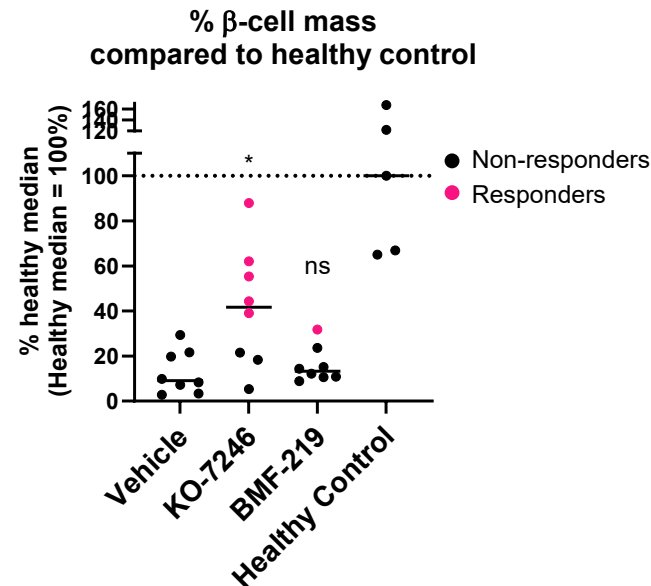
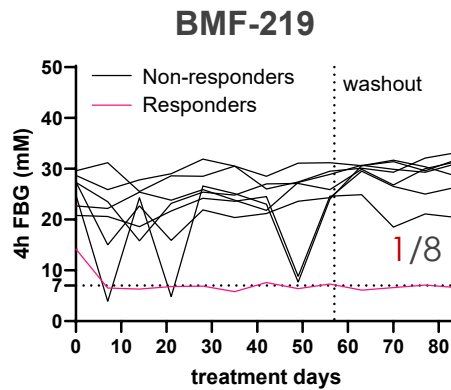
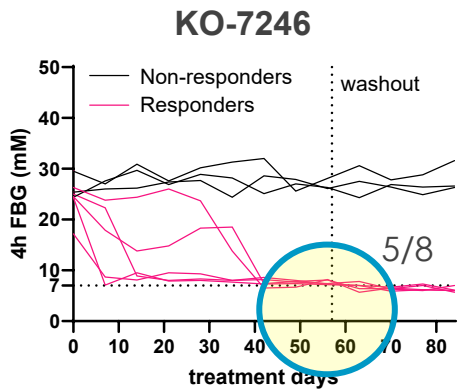
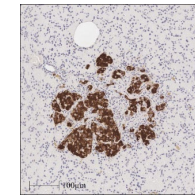
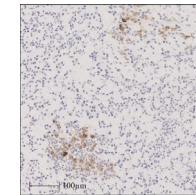
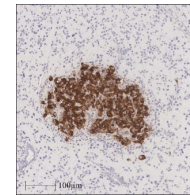
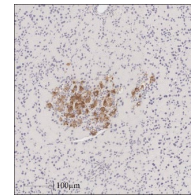
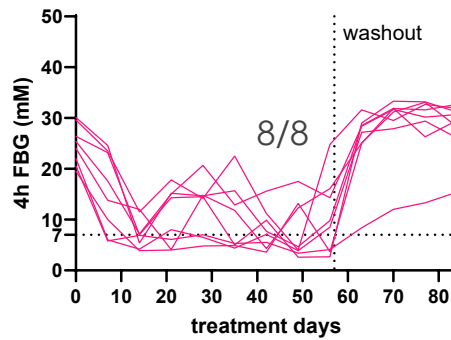
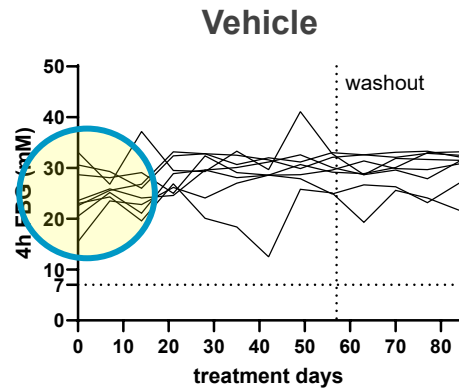
Full restoration of glycemic control achieved in model of insulin insufficiency



- KO-7246 robustly and durably reduced FBG and enhanced HOMA-β, comparing favorably to BMF-219
- Kinetics and post-dose stability of activity support β-cell mass regeneration MOA of KO-7246

KO-7246, but not BMF-219, Fully Restored Islet Function in STZ T1D Rat Model

Response appeared dependent on residual β -cell capacity, consistent with regenerative mechanism



- Responders all achieved and maintained complete glycemic control
- Islets regenerated to 40-90% of healthy controls by Day 56
- BMF-219 did not reduce FBG or increase β -cell mass

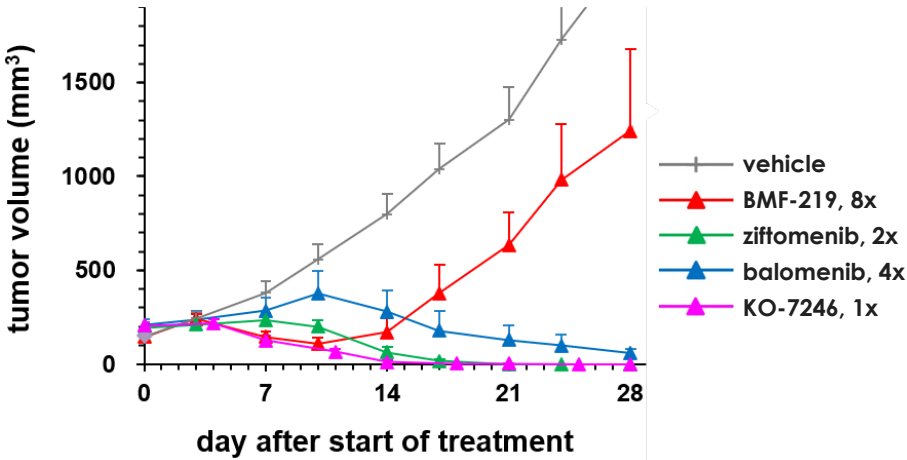
ns; not significant; *, $p < 0.05$

KO-7246 and Balomenib are Differentiated from BMF-219

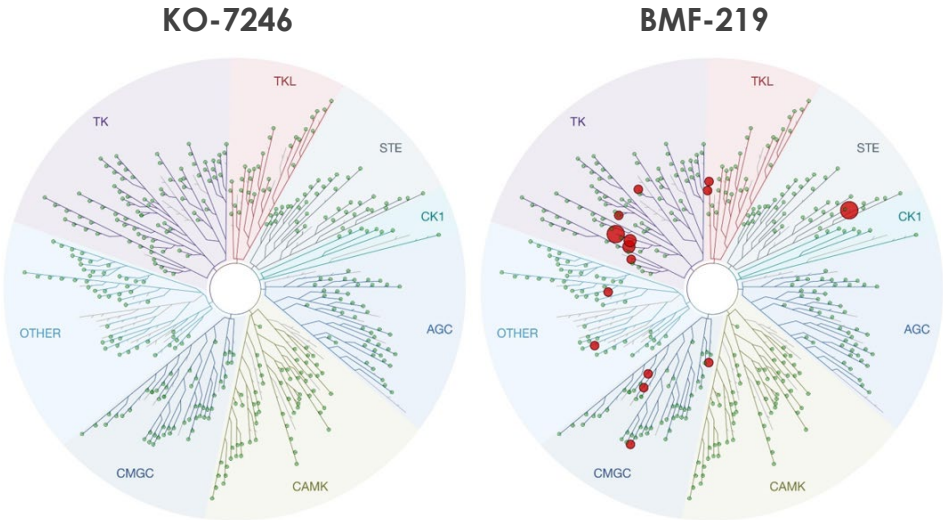
	KO-7246	balomenib	icovamenib (BMF-219)
menin-MLL FP IC ₅₀ (nM)	7.7	23.1	>10,000
MV4-11 CTG IC ₅₀ (nM)	7.9	28.1	218
mouse MV4-11 CDX model	robust efficacy	efficacy at 4x daily dose	no efficacy even at 8x daily dose
CDK9 %inhibition at 1.0 μM	0	not tested	>80 (IC ₅₀ =19.1 nM)

- KO-7246 and balomenib are validated menin inhibitors, but KO-7246 is more active in vitro and in vivo
- BMF-219/Icovamenib inhibits several kinases, including CDK9, but has no discernable activity towards menin

Menin-Dependent AML Model



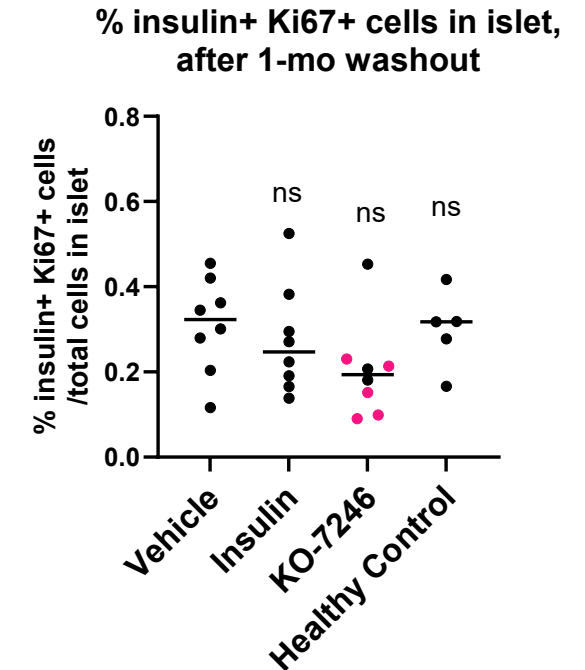
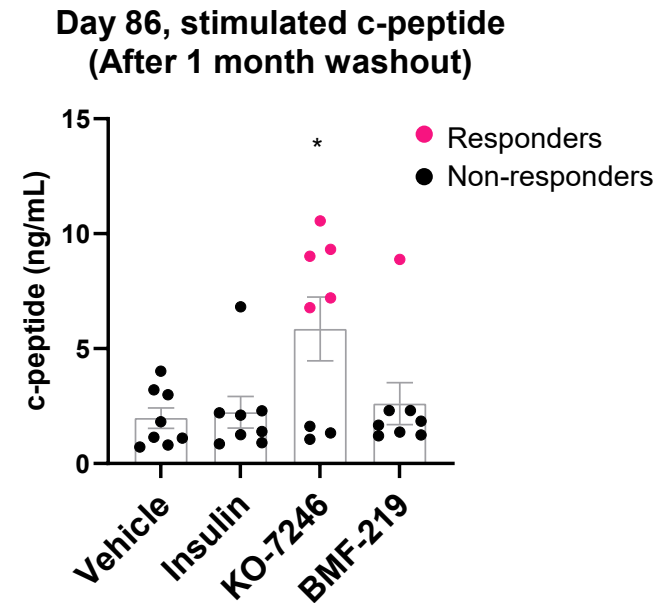
Kinase Family Tree



Transient Pharmacologic Menin Inhibition Is Fundamentally Different from Lifelong MEN1 Loss

Enhanced endogenous insulin production persists after β -cell proliferation

- MEN1 Syndrome patients develop proliferative insulinomas after years/decades of biallelic MEN1 loss
 - More than 500 AML patients have been dosed daily with menin inhibitors for multiple years – no MEN1 Syndrome symptoms
- Animals dosed to Day 56 and observed to Day 86
 - C-peptide significantly elevated after one month washout (indicating greater β -cell mass)
 - Negligible levels of residual cell proliferation in all groups (indicating limited active cell division)

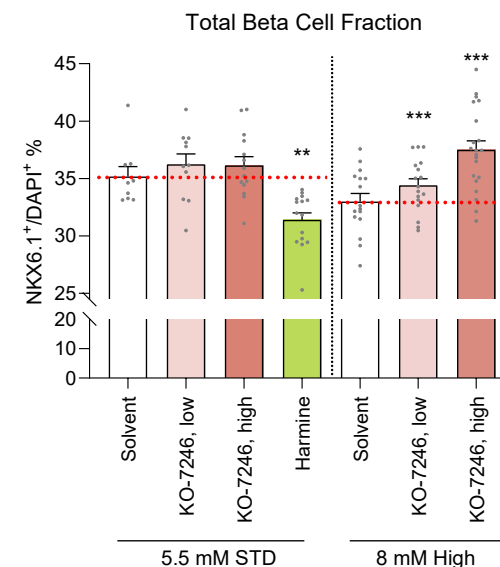
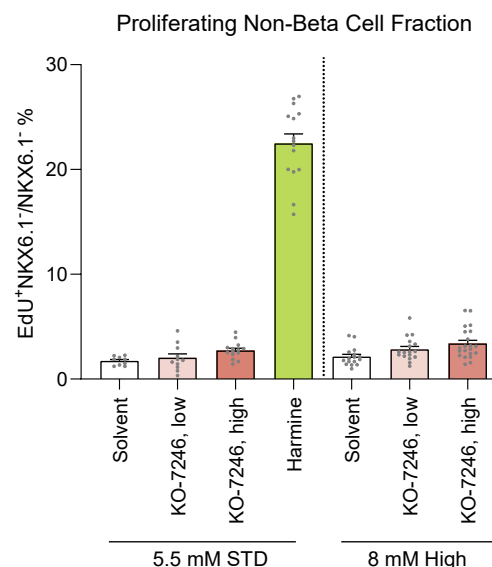
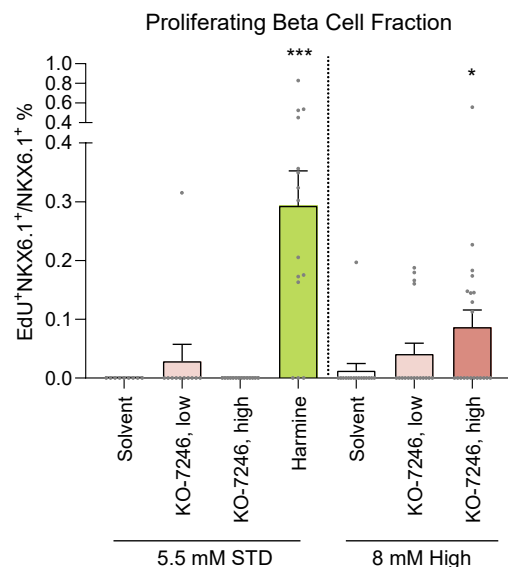
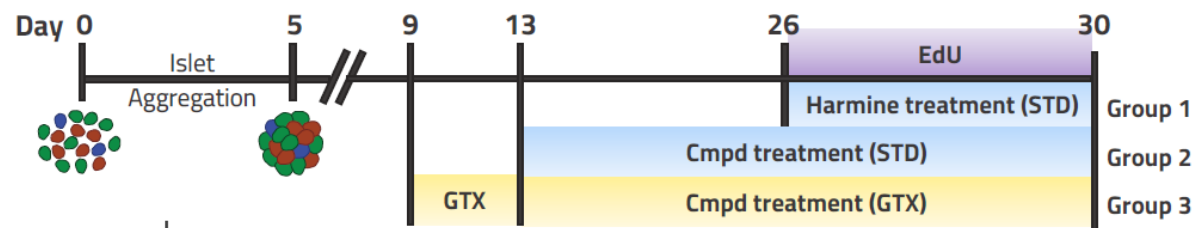


ns; not significant; *, $p < 0.05$

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KO-7246 Induced Proliferation of Human β -Cells

KO-7246 induced β -cell proliferation in multiple donor samples



- KO-7246 dose-dependently induced β -cell proliferation under glucotox conditions
- DYRK1A inhibitor harmine was unselective

- Harmin also induced proliferation of non- β -cells
- KO-7246 had no effect on non- β -cell proliferation

- KO-7246 dose-dependently increased the β -cell fraction under glucotox conditions
- Harmin had a net negative effect on the β -cell fraction

KO-7246 Has Potential to be a Disease-Modifying Therapy for Patients with Type 1 or Type 2 Diabetes

- Menin inhibition has the potential to restore endogenous β -cell capacity in patients with Type 1 and Type 2 diabetes
- KO-7246 combines a validated menin-based mechanism of action with robust, disease-modifying pharmacology across a range of diabetes models
 - Potent menin inhibition demonstrated in multiple *in vitro* and *in vivo* menin-dependent models
 - Produced durable glycemic control through β -cell regeneration in multiple preclinical diabetes models
- IND-enabling development of this potential best-in-class menin inhibitor underway with initial clinical evaluation planned thereafter

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