Backgrounder

Preclinical Results of BMF-219 in Diabetes

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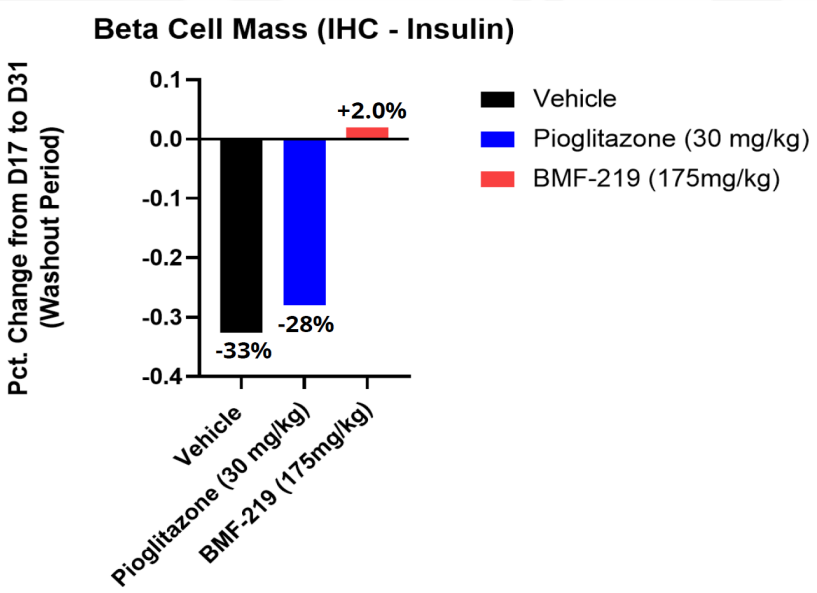
Pre-Clinical Summary Highlights in Type 2 Diabetes with BMF-219

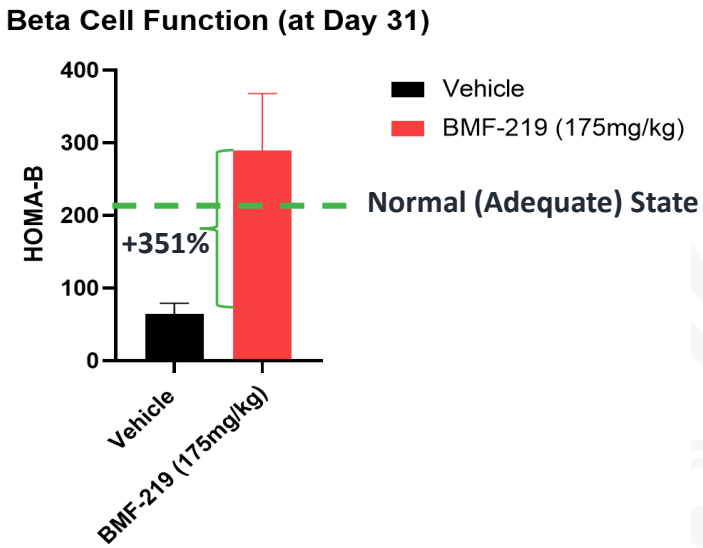
BMF-219 Regenerated, Preserved and Reactivated Beta Cells in Preclinical Studies

Preservation



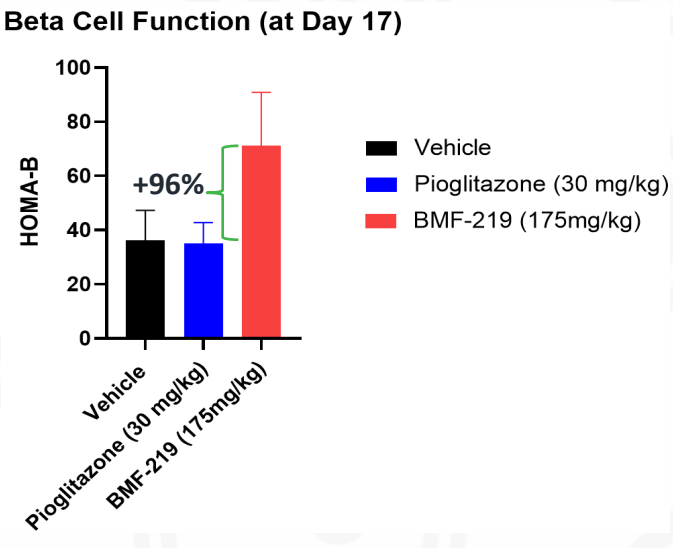
Quantitative Analysis of pancreatic islet tissue cross sections shows BMF-219 treated **ZDF** animals show novel effects in Beta Cell Mass growth and maintenance. BMF-219 was able to maintain Beta Cell function and prevent Beta Cell Mass loss in a model of insulin resistance. Importantly, Beta Cell Mass is maintained, despite cessation of dosing.

Reactivation



BMF-219 demonstrated a significant level of beta cell function compared to vehicle at day 31 in an insulin resistant type 2 diabetes animal model (**ZDF**). Homa B, a measurement of Beta Cell function, was analyzed using 4 h fasting glucose and insulin levels. It increased up to ~351% versus vehicle, despite cessation of therapy.

Proliferation

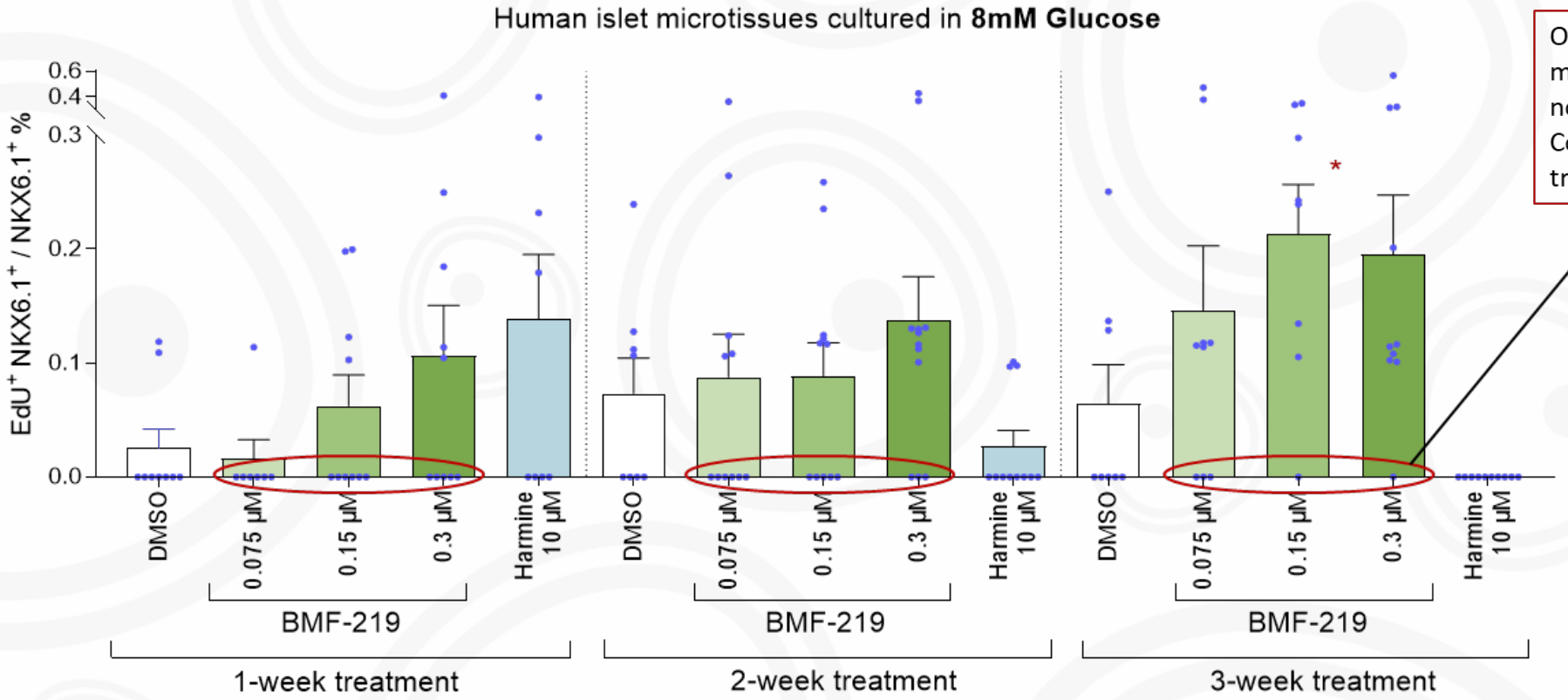


BMF-219 increased HOMA-B by 96% in a type 2 animal model (STZ = 50% Beta Cell destruction). Homa B, a measurement of Beta Cell function, was analyzed using 4 h fasting glucose and insulin levels. BMF-219 in ex-vivo Human Donor Islets (Ex-Vivo) statistically significant increased beta cells with BMF-219.

Butler et al. Oral long-acting menin inhibitor normalizes type 2 diabetes in two rat models; Ex-vivo Human Islets data EASD 2022

Longer Dosing is Predicted to Generate an Increase in Responder Rates Based on Human Donor Islet Experiments - Dose Expansion Study will dose patients for 8-weeks and 12-weeks

Proliferating beta cells plotted as fraction of total beta cells



Data represent mean ±SEM of 1 donor with n = 9-12 technical replicates.
One-way ANOVA with Dunnett's post hoc test rel. to DMSO control. *p < 0.05, **p < 0.01, ***p < 0.001

BMF-219: An Oral Menin Inhibitor in Clinical Development as a Short-Term Treatment to Address the Root Cause of Diabetes, Beta-Cell Dysfunction

December 7, 2023 WCIRDC

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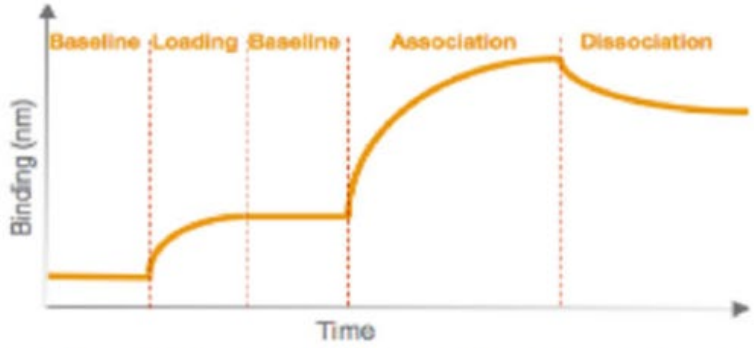
Target Engagement (Kd)

Biomea Compounds Tested against Menin

BMF-219 Target Engagement (Kd) with Menin

Compound	Kd (nM)
BMF-203	250
BMF-219 (Compound D)	<0.001
BMF-222	1,250
BMF-224	1,804
BMF-5	3,191

*Compound D displays a K_{dis} rate that supports covalent engagement



Measuring the shift over time enables the determination of binding

Comments:
Samples A-F were tested by Octet BMIA for affinity to Menin-Biotin.
SA sensors were loaded with Menin-Biotin
Binding constants were calculated for association and dissociation of 7 dilutions of each compound.
1:1 Curve Fits were applied and Global Fits were calculated as:

Analyte ID	K_D	k_{on}	k_{dis}	R^2
Compound A	1.478E-06	8.101E+02	1.197E-03	0.718
Compound B	9.965E-05	7.179E+02	7.154E-02	0.977
Compound C	2.274E-07	1.698E+03	3.861E-04	0.568
Compound D	<1.0E-12	4.009E+02	<1.0E-07	0.713
Compound E	7.049E-06	3.367E+03	2.373E-02	0.636
Compound F	9.461E-05	4.085E+02	3.865E-02	0.987

Covalent Adduct Formation

Peptide Mapping with BMF-219

BMF-219 Binding to Single Specific Cysteine in Menin

Overview: PROTEIN METRICS by Dotmatics (CRO) Identify attachment site(s) of BMF-219 to Human rMenin

Experimental Summary:

- Incubated rMenin and BMF-219
- After incubation, treat with solution to digest Tryp/Lys-C to split rMenin into singular cysteine fragments (potential binding sites) .
- Identify rMenin fragments that bound to BMF-219

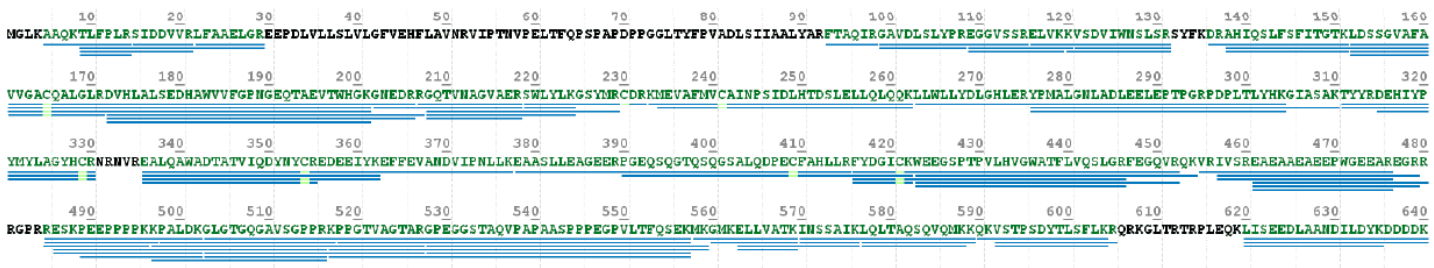
PROTEIN METRICS

Export of: C:\Users\wkittleman\Desktop\25Oct22 Biomea rMenin BMF219 rxns WK\25Oct22 Biomea rMenin BMF219 HEPES 2hr cntrl HEPES 2hr 1 to 50 two missed cleavages.blgc
Creation time: 2022.12.07 15:10:19
Created by: wkittleman
Protein sequence:

Origene_Human_rMenin_TP312368_with_CMycDDK_tag Coverage: (547 of 641) 85.34%

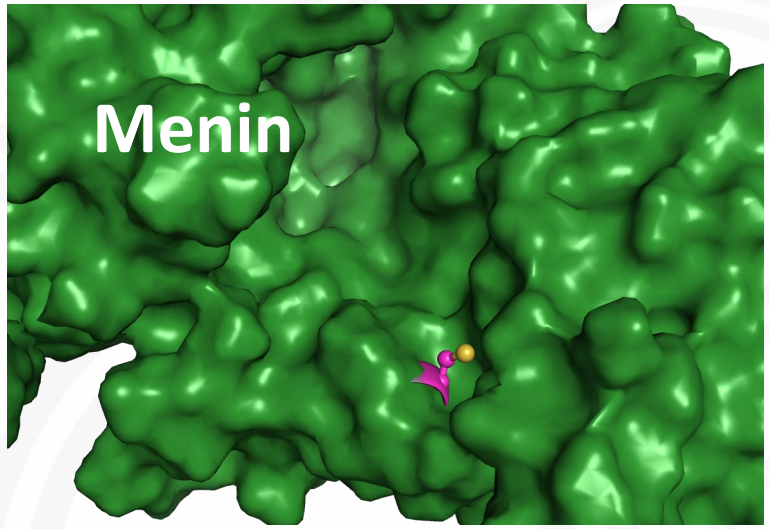
MGLKAAQKTLFPLRSIDDVVRLFAAELGREEPDLVLLSLVLGFVEHFLAVNRVIPTNVPELTFQPSPAPDPPGGLTYFPVADLSIIAALYARFTAQIRGAVDLSLYPREGGVSSRELVKKVSDVIWNSLSRSYFKDRAHIQSLFSFITGTKLDSSGVAFAVVGACQALGLRDVHLALSEDHAWVVFGPNGEQTAEVTWHGKGNEDRRGQTVNAGVAERSWLYLKGSYMRCDRK
MEVAFMVCAINPSIDLHTDSLELLQLQQKLLWLLYDLGHLERYPMALGNLADLEELEPTPGRPDPLTLYHKGIASAKTYYRDEHIYP
EAEEPWGEEAREGRRRGPRRESKPEEPPPPKKPALDKGLGTGQGAVSGPPRKPPGTVAGTARGPEGGSTAQVPAPAASPPPEGPVLTFQSEKMKGMKELLVATKINSSAIKLQLTAQSQVQMKKQKVSTPSDYTLSFLKRQRKGLTRTRPLEQKLISEEDLAANDILDYKDDDDKV

Protein coverage:
Origene_Human_rMenin_TP312368_with_CMycDDK_tag



- All cysteine fragments identified
- Overall sequence coverage of 85.34%

BMF-219 Binding to Specific Cysteine in Menin



Targetable Cysteine	Binding Selectivity
CYS1	100.0%
CYS2	0.0%
CYS3	0.0%
CYS4	0.0%
CYS5	0.0%
CYS6	0.0%

Peptide Mapping Data

BMF-219 binds only to single, desired target cysteine

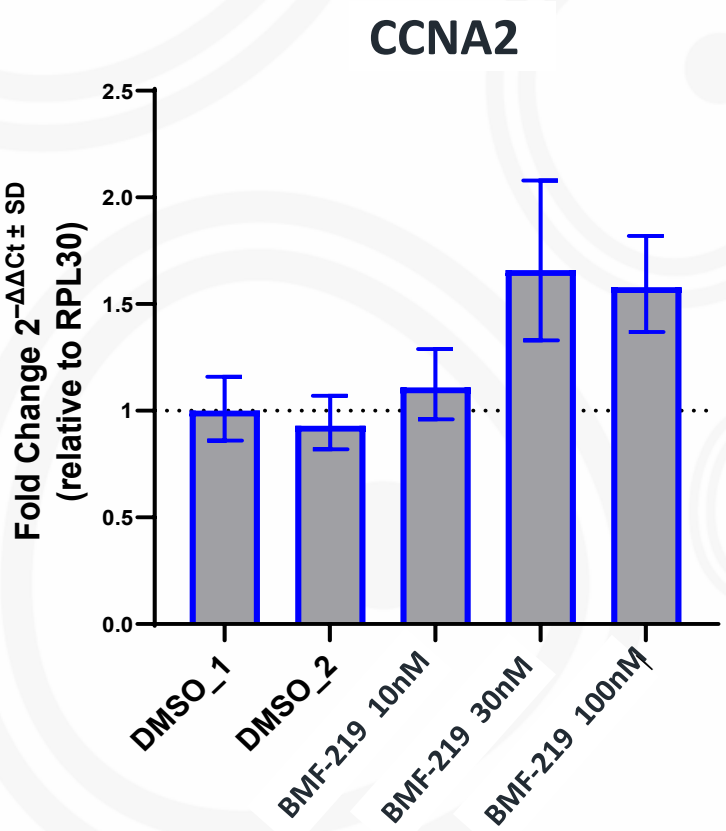
Peptide Mapping Results Summary

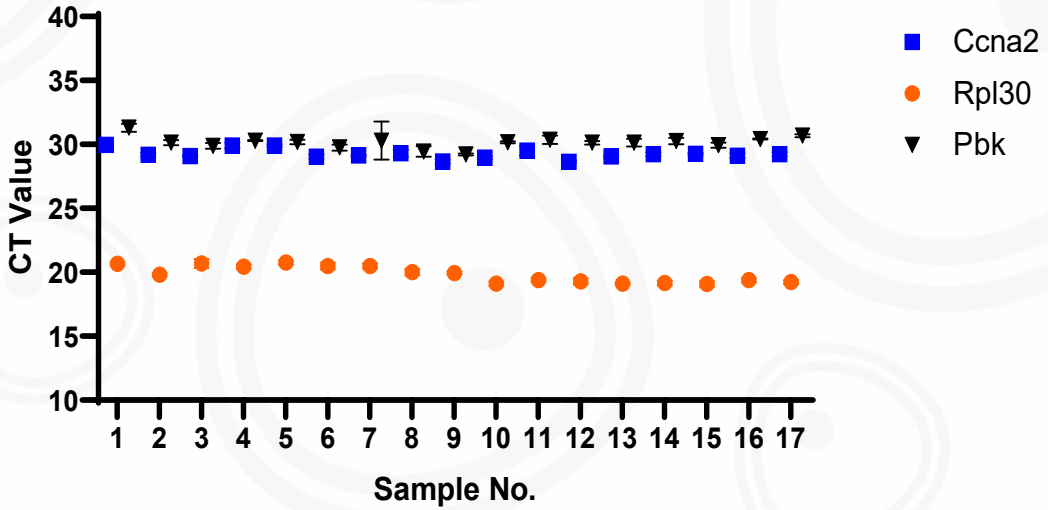
- Analyzed all reactions through Freestyle
- Only observed BMF-219 attached to Cys1 (Biomea numbering)
- Did not observe BMF-219 attached to any other cysteine

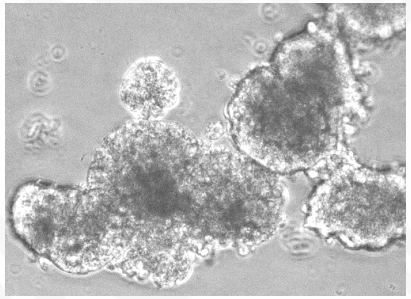
Gene Expression – Human Islets

BMF-219 Impact on Menin Gene Signatures

Ex-Vivo Experiments – Human Islets (CCNA2 encodes Cyclin A2)







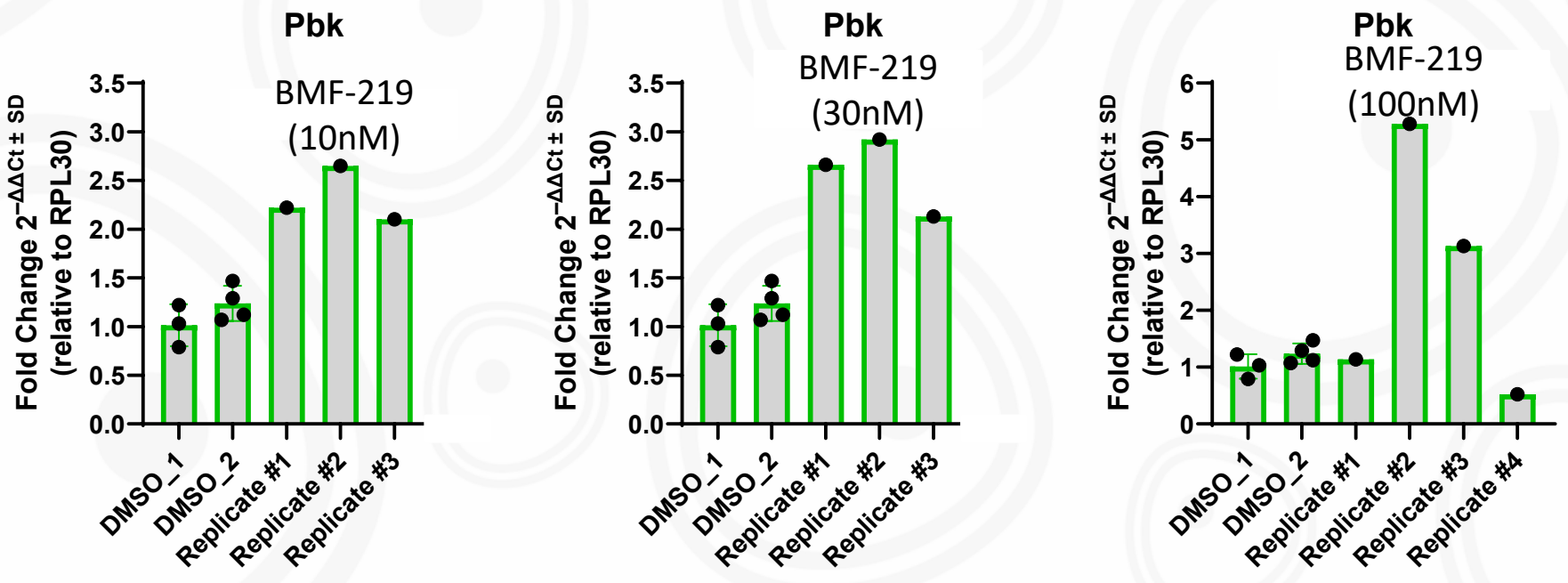
Human pancreatic islet

Treatment for 5 days

Examine gene expression by Q-PCR

BMF-219 treatment results in an increase in CCNA2 expression, similar data in published literature results of Menin knockdown experiments. CCNA2 expression has been shown to support proliferation of beta cells, resulting in an increase in beta cell mass. CCNA2, the gene for Cyclin A2, is known to be regulated by the menin binding pathway Pbk/JunD, which are glucose controlled.

Ex-Vivo Experiments – Human Islets



BMF-219 treatment results in an increase in PbK (PDZ-binding kinase) expression, similar to results seen in literature describing Menin knockdown experiments. PbK expression has been shown to help drive proliferation of beta cells, resulting in an increase in beta cell mass and function. PbK expression is regulated by menin binding partner JunD, in a glucose dependent manner.

BMF-219 in Animal Models of Diabetes

Durable Improvement in Beta-cell Function and Glycemic Control

Priyanka Somanath, PhD
Associate Director, Translational Drug Discovery & Development
Biomea Fusion

Study Design: Zucker Diabetic Fatty (ZDF) Rat Model of T2D

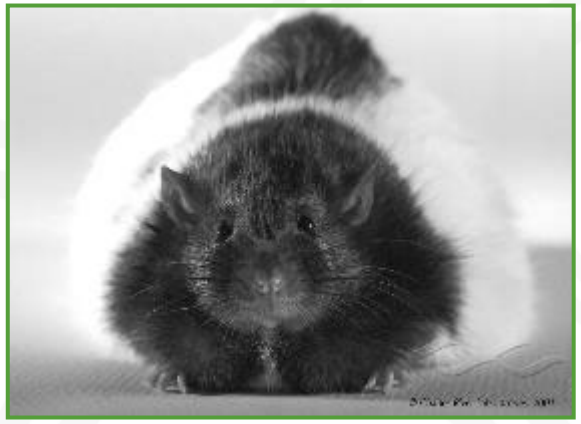


Image Source: Charles River Laboratories, 2001

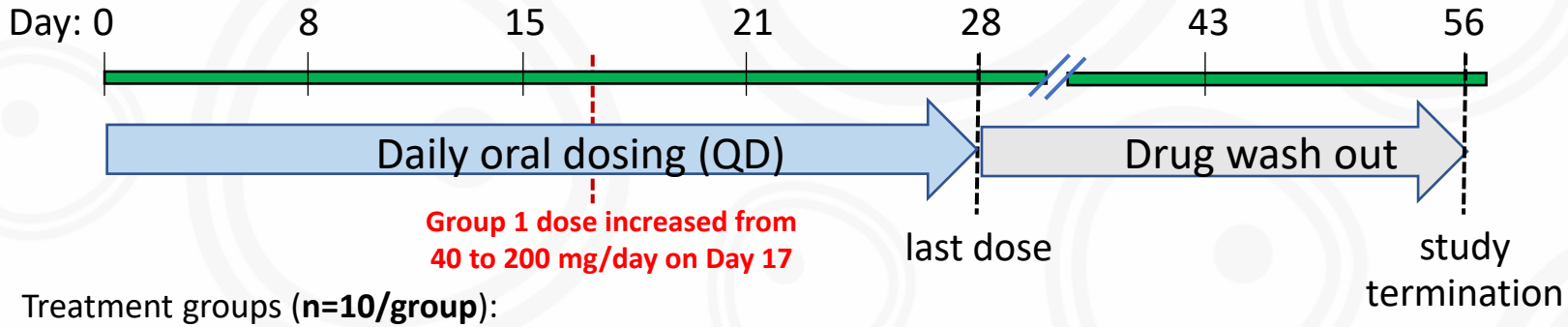
- The ZDF rat is a model of pancreatic exhaustion and insulin resistance, thus mimicking some aspects of human diabetes.
- The ZDF rat is a translatable model for studying the development of T2D.

Age: 11-12 weeks old male rats

Study Objective

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

Treatment Scheme of ZDF Rat Model



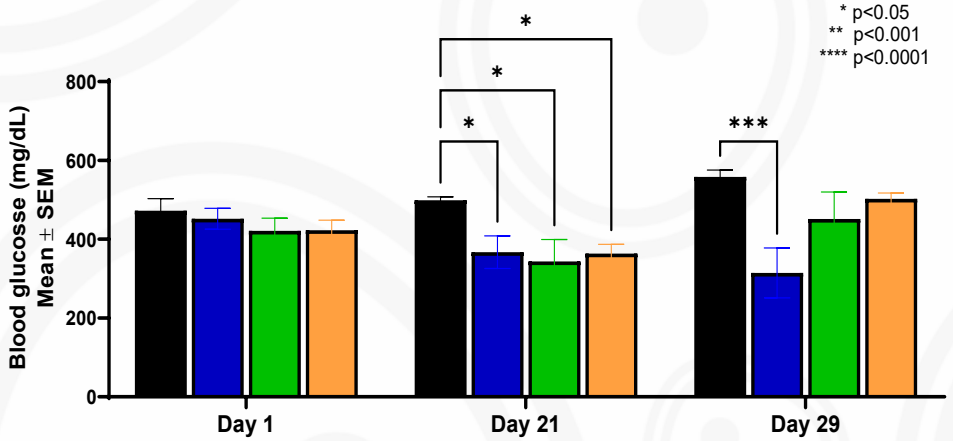
Treatment groups (**n=10/group**):

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)

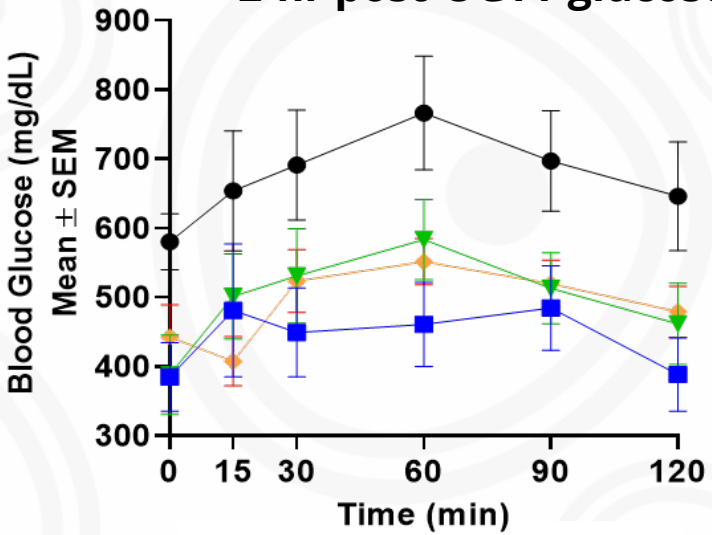
Rats monitored through dosing and washout phases: Fasting blood glucose, insulin, OGTT, HbA1c, body weight, blood lipemic levels

BMF-219 Substantially Controlled Blood Glucose Levels in a 4-Week Dosing Study

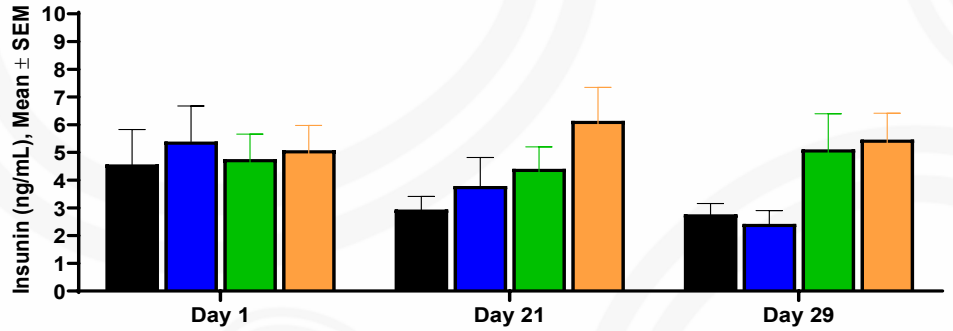
4-hr Fasting Blood Glucose



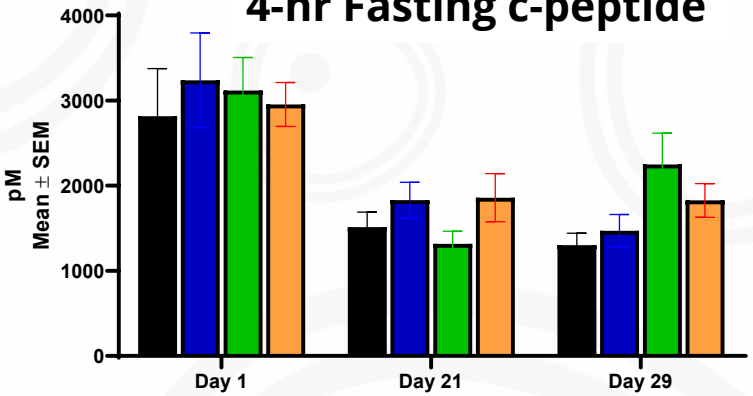
2-hr post-OGTT glucose



4-hr Fasting Insulin



4-hr Fasting c-peptide



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

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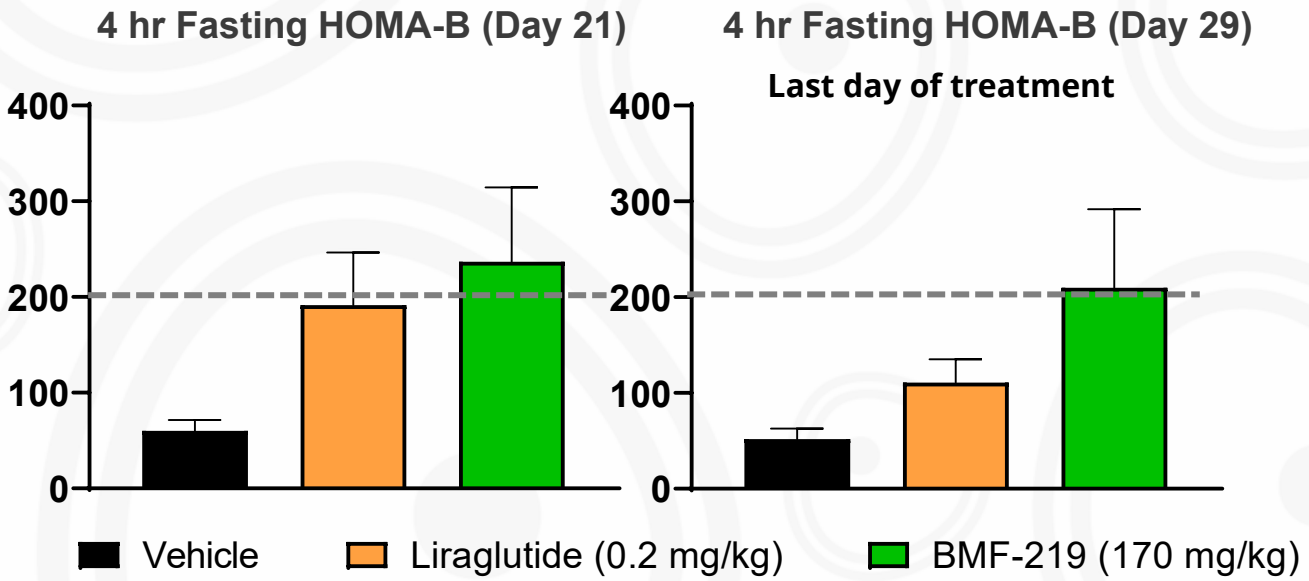
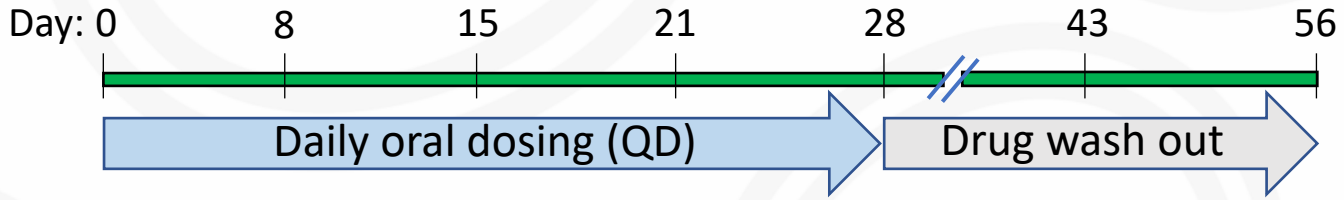
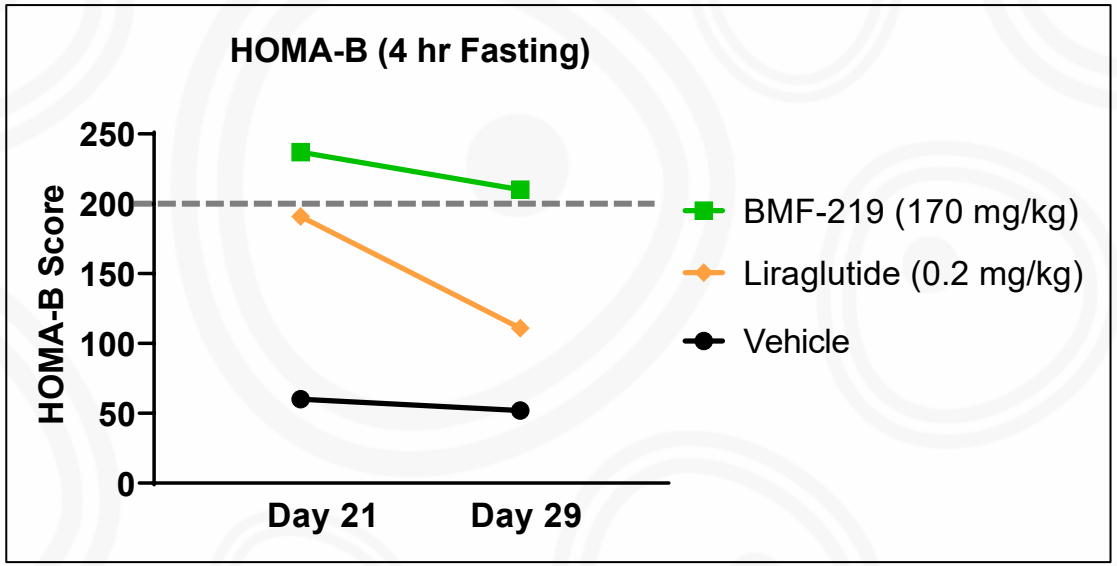
BMF-219 Restores Beta-Cell Function over 4 Weeks of Treatment





Group 1 dose increased from 40 to 200 mg/kg day on Day 17

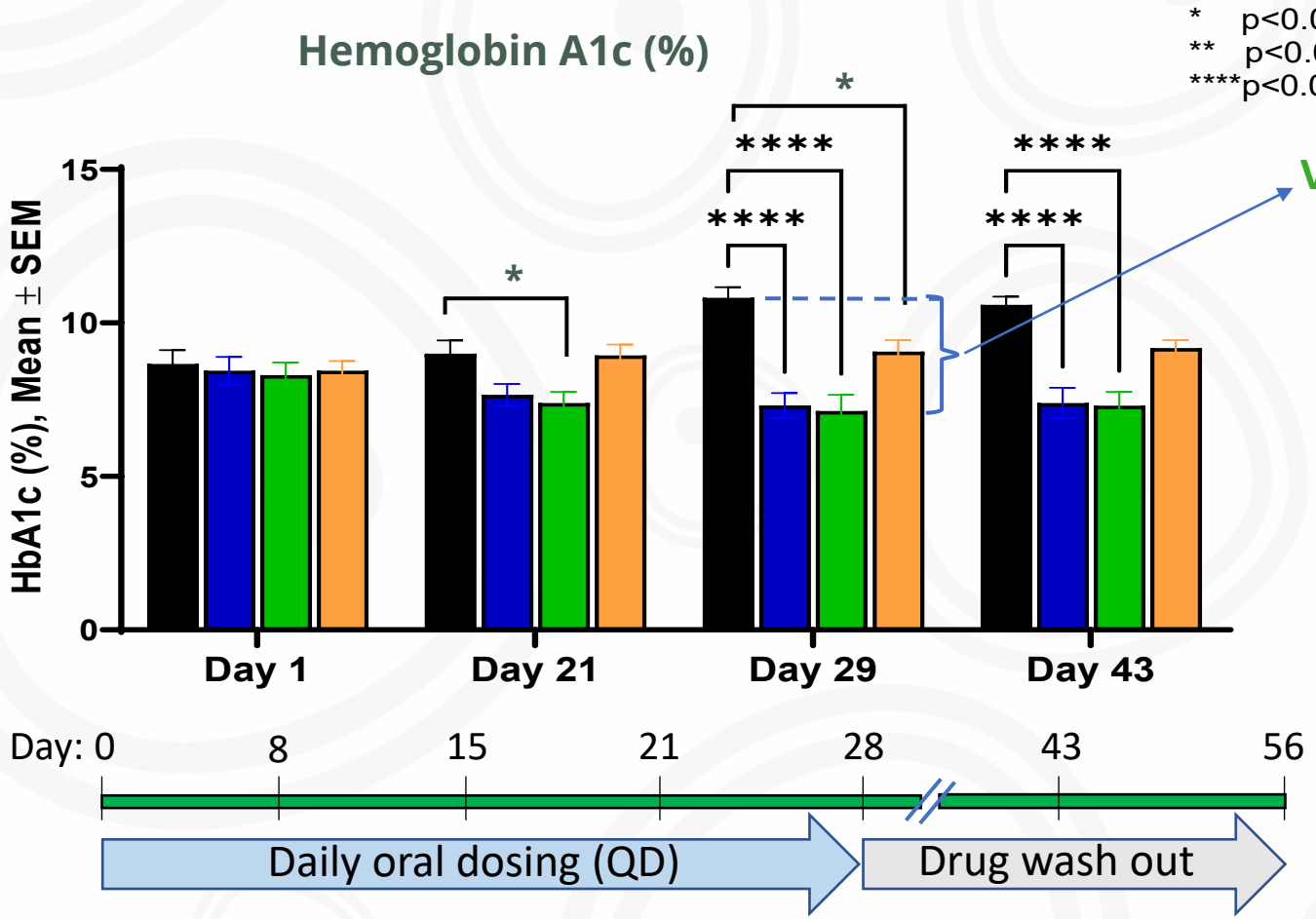
BMF-219 restores and maintains HOMA-B index to normal state (>201) over 4 weeks of treatment



Severity Grading Assessment for Pancreatic Beta-Cell Function	HOMA-B Index
Adequate (normal state)	≥ 201.00
Mild deficiency	134.00 to 200.99
Moderate deficiency	67.00 to 133.99
Severe deficiency	0.00 to 66.99

Table Source: Fasipe JO et al. 2020. Can J Diabetes 44 (2020) 663e669.

BMF-219 Significantly Reduces HbA1c (-3.5%) vs. Vehicle during Treatment and Maintains Lowering Effect during 2 Weeks of Drug Washout



Vehicle vs BMF-219: HbA1c delta = 3.5%

- 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

HbA1c reduction in BMF-219 treated groups maintained through washout period

Group 1 dose increased from 40 to 200 mg/kg/day

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Summary of Key Animal Data

- BMF-219 was well-tolerated in all animals.
- BMF-219 displayed 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 reduced HbA1c levels (-3.5%) relative to vehicle control during treatment and during drug washout.
- Collectively, these data suggest a durable effect of BMF-219 on glycemic control and beta cell function, enabling further clinical studies.

Joslin Diabetes

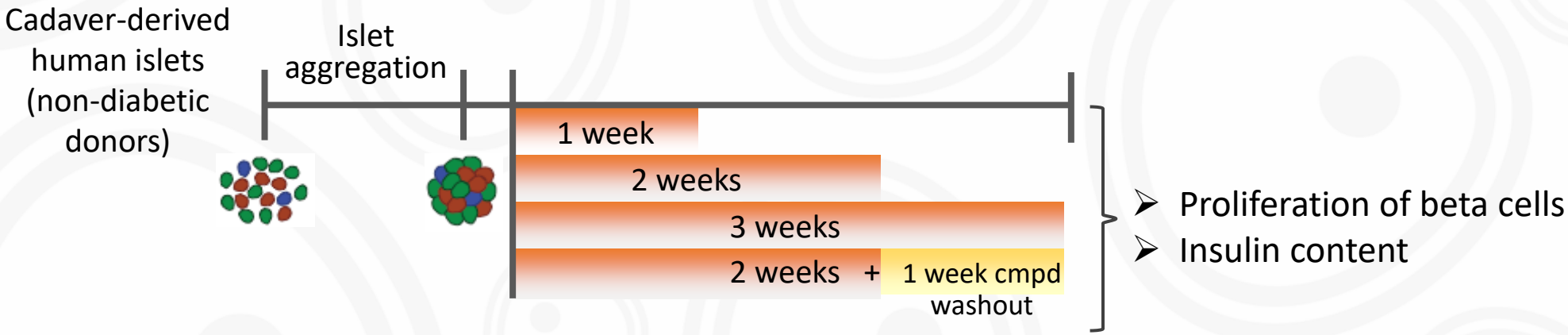
Harvard Medical School

Menin Inhibition: What May Explain the Effects of BMF-219 on β-Cell Function and Glycemic Control?

Rohit N. Kulkarni MD PhD

Ex-Vivo Human Islet Microtissues: Assay Set-Up and Read Outs

- Compound treatment 1-3 weeks (+/- compound washout)
- Assayed under standard (5.5 mM) and high (8.0 mM) glucose

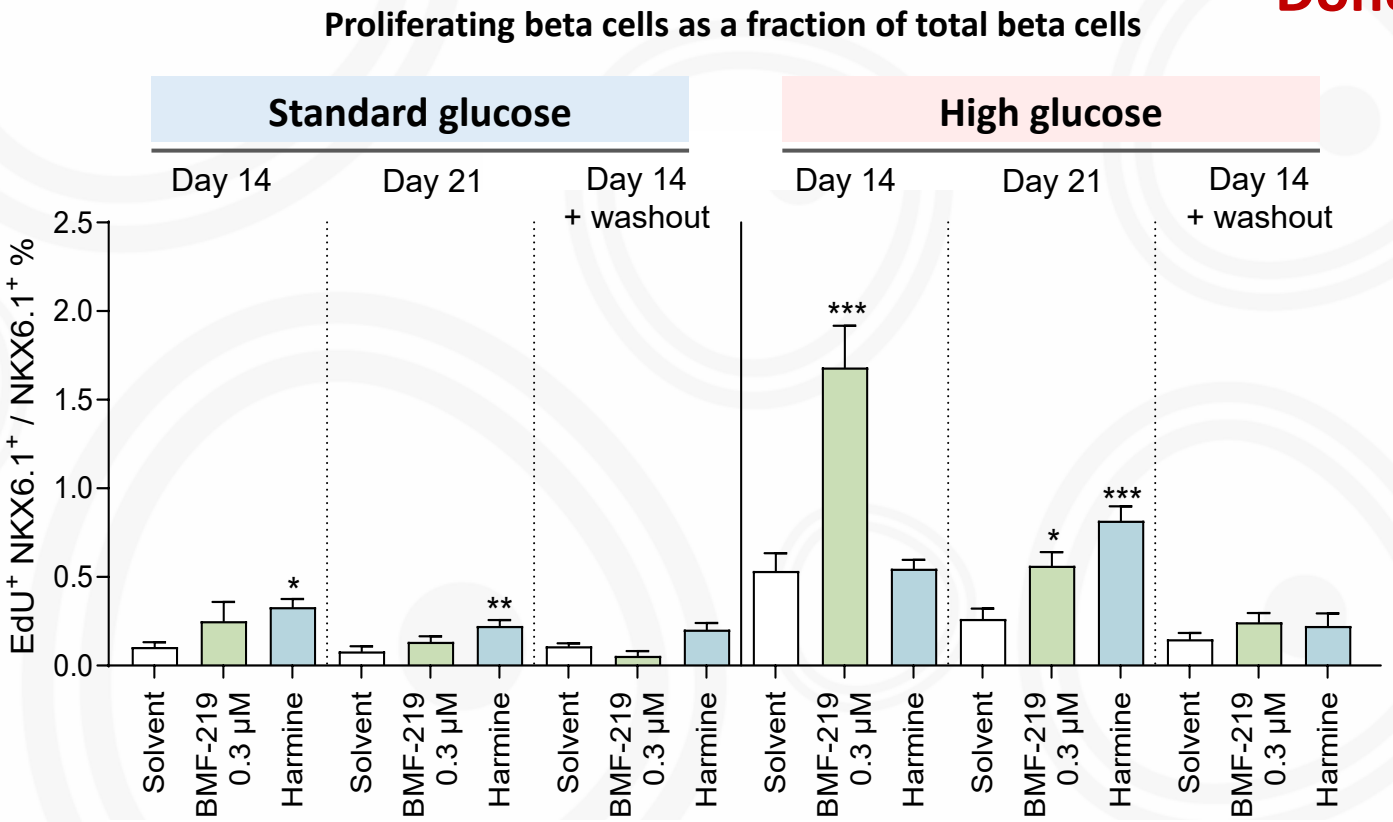


Donor characteristics:

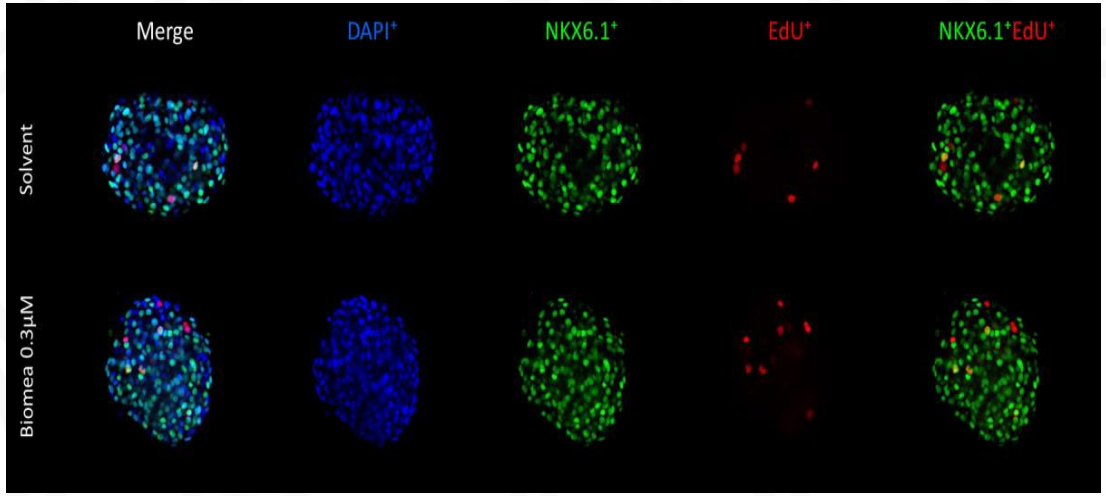
Donor	Age	BMI	HbA1c
#1	19	23.2	5.8
#2	32	25.0	5.2

BMF-219 Induced a Glucose-Dependent Enhancement in β-Cell Proliferation

Donor 1



Donor 1; Day 14, High glucose



Data represent mean ±SEM of 1 donor with n = 6-10 technical replicates.
One-way ANOVA with Dunnett's post hoc test rel. to DMSO control. *p < 0.05, **p < 0.01, ***p < 0.001

Donor #1	Age	BMI	HbA1c
White	19	23.2	5.8

Proliferation observed only under elevated glucose conditions, which mimic diabetic levels, and with continuous drug exposure.

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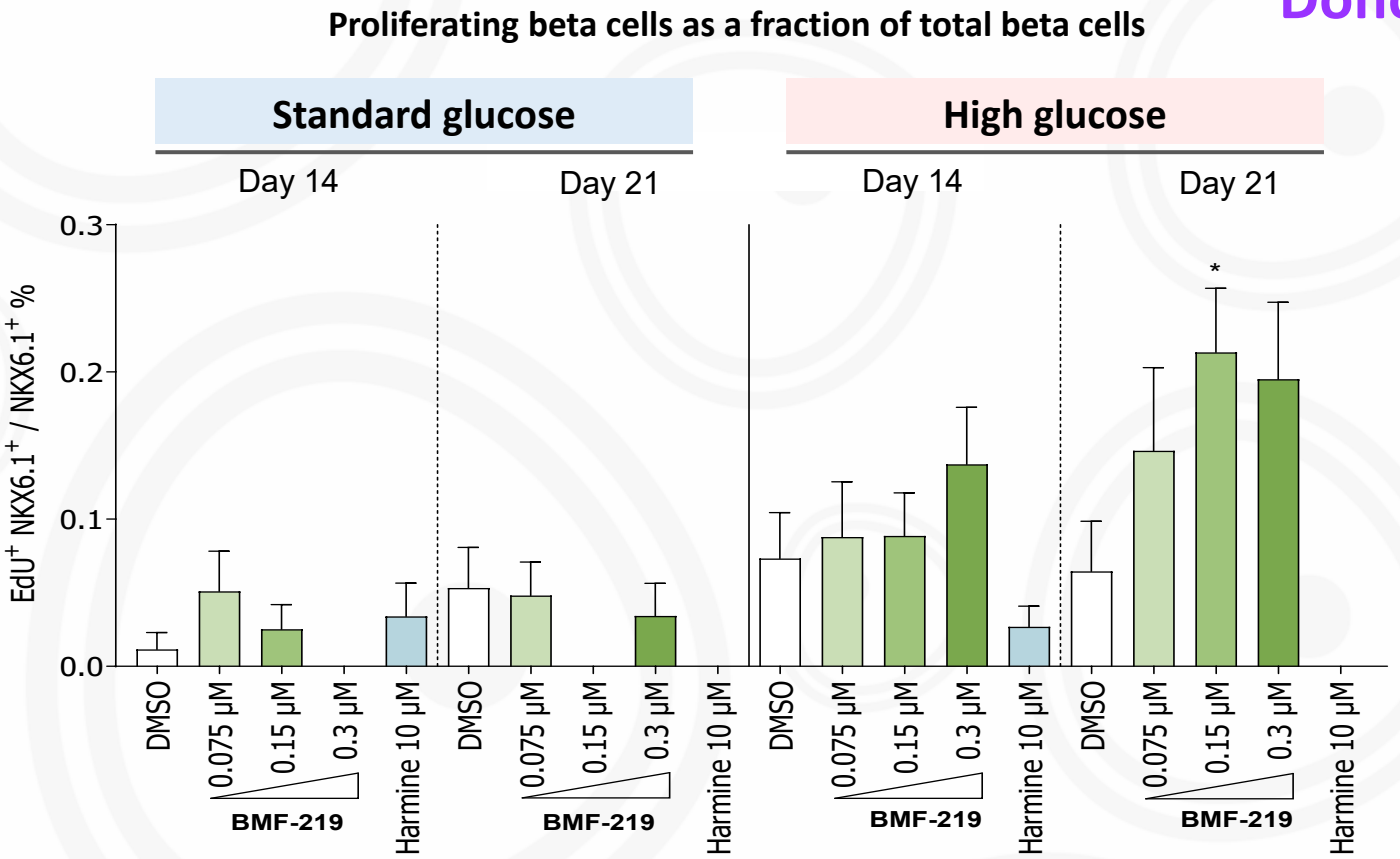
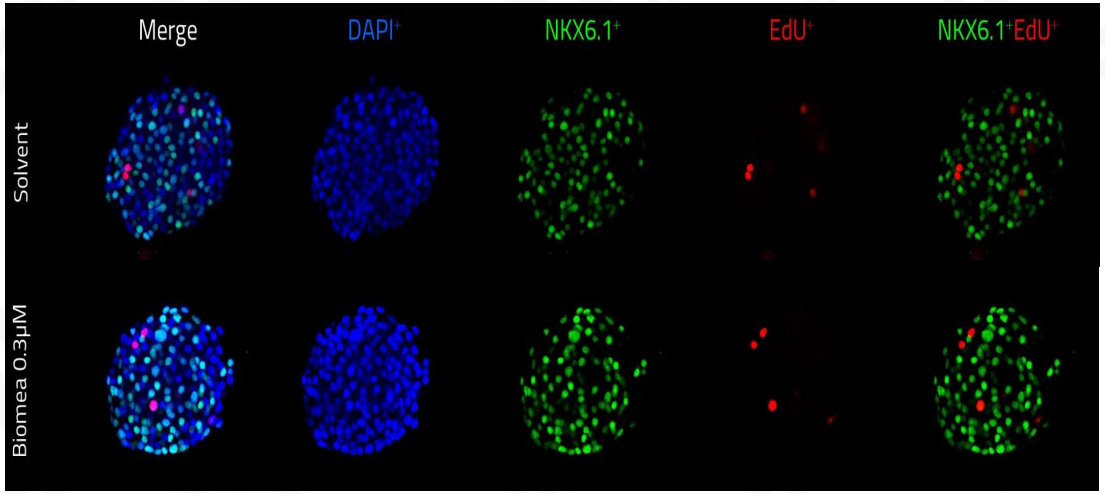
BMF-219 Induced a Glucose-Dependent Enhancement in β-Cell Proliferation

Donor 2





Data represent mean ±SEM of 1 donor with n = 9-12 technical replicates.
One-way ANOVA with Dunnett's post hoc test rel. to DMSO control. *p < 0.05, **p < 0.01, ***p < 0.001

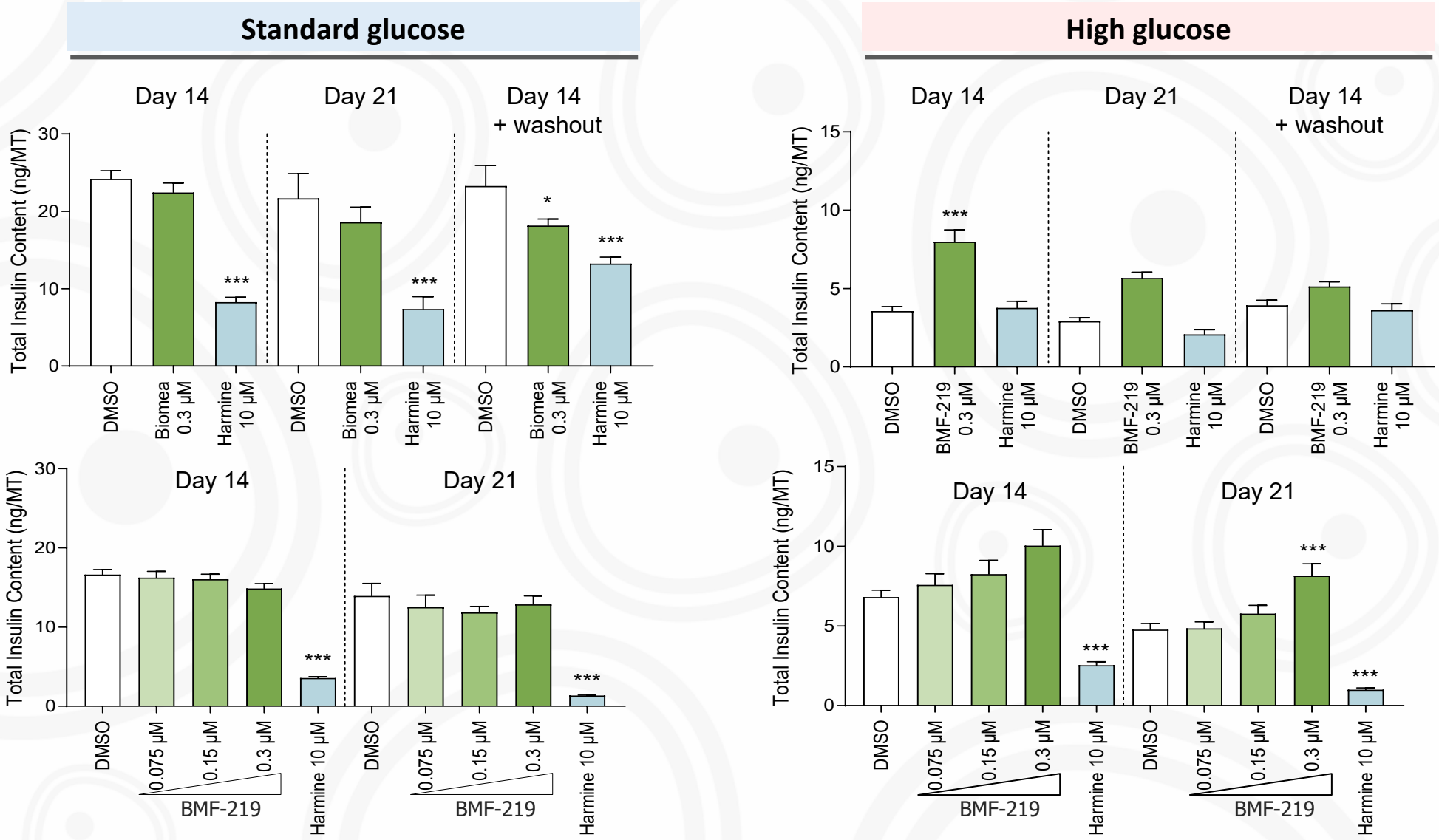
Donor 2	Age	BMI	HbA1c
Caucasian	32	25.0	5.2

Proliferation observed only under elevated glucose conditions, which mimic diabetic levels.

BMF-219 Induced a Glucose-Dependent Enhancement in β-Cell Insulin Content

Donor 1

Donor 2



Summary and Ongoing Studies on BMF219

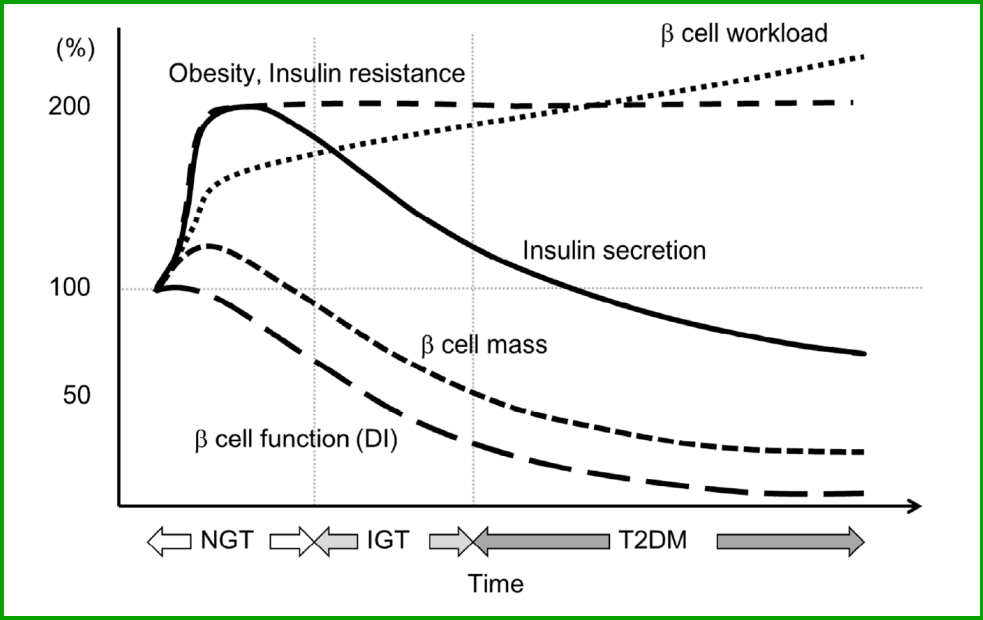
- BMF-219 promotes controlled proliferation and enhances insulin content in β-cells in human islets *ex vivo* in a glucose- and dose-dependent manner
- Data suggests induction of β-cell proliferation as a mechanism for the improved glycemic control in BMF-219-treated patients with diabetes
- Ongoing studies aim to explore changes in gene and protein signatures of human β-cells treated with BMF-219 using RNA sequencing and proteomics to dissect signaling pathways for the safe activation and re-activation of human β-cell cycle proliferation

Oral long-acting menin inhibitor normalizes type 2 diabetes in two rat models

September 22, 2024 EASD

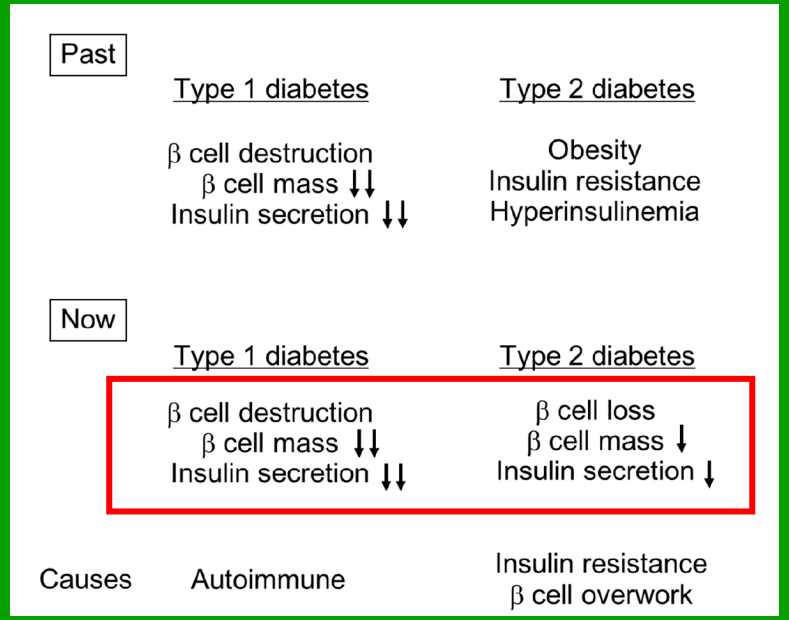
Our understanding of diabetes has evolved; Progression of type 1 and type 2 diabetes are both driven by beta cell loss

Progression of Type 2 Diabetes



*Insulin Resistance leads to an increase in Beta Cell Workload, which ultimately leads to Beta Cell Failure and Death and the progression of Type 2 Diabetes.

"Understanding of Diabetes has evolved"



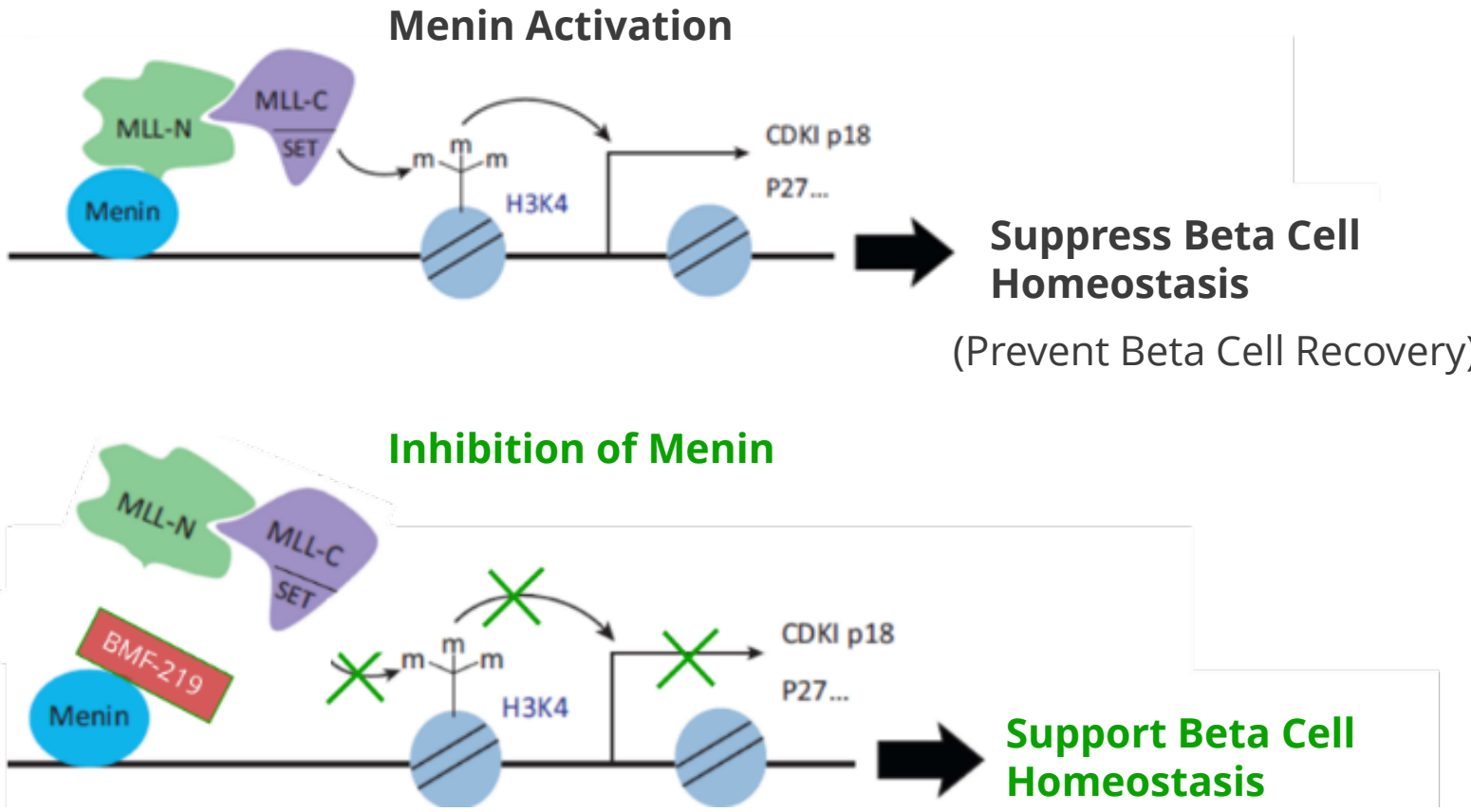
*Both Type 1 Diabetes and Type 2 Diabetes disease results in Beta Cell loss and reduction in Beta Cell Mass

Disease Modifying Potential: BMF-219 drives Beta Cell Proliferation

*Int. J. Mol. Sci. 2016, 17, 744; doi:10.3390/ijms17050744

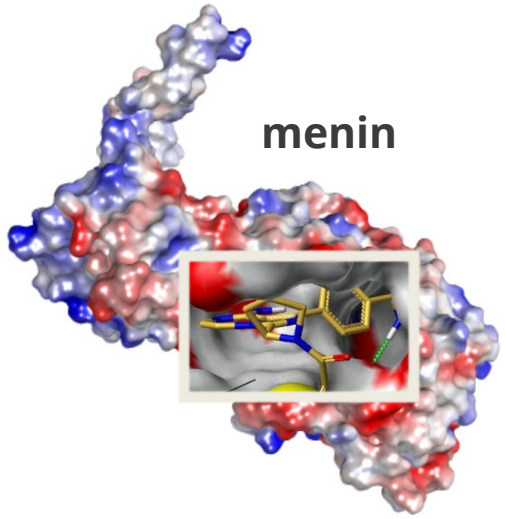
Menin: A key checkpoint for beta cell homeostasis; an important target for type 1 and type 2 diabetes

- Menin functions in a histone methyltransferase protein complex containing MLL
- This complex promotes trimethylation of histone H3 on lysine 4 (H3K4), which is associated with transcriptionally active chromatin and..
- Menin dependent histone methylation maintains expression of p27 and p18, two key members of cyclin-dependent kinase (CDK) inhibitor family that prevent β-cell proliferation.

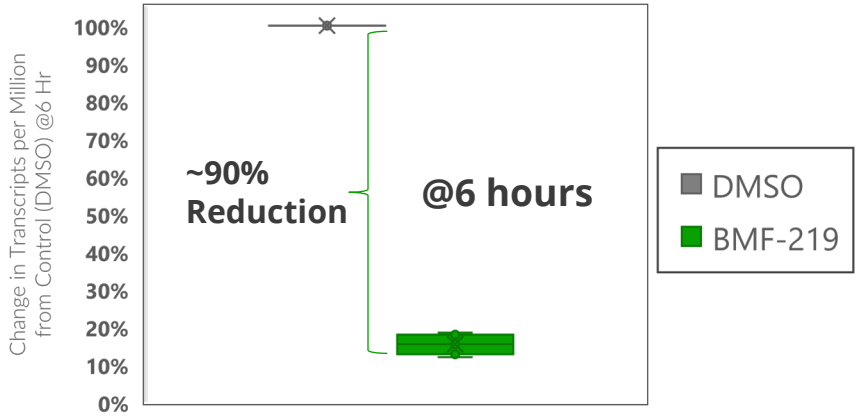


Sources: Karnik et al., Science, Nov 2007, Vol 318 P806-809

BMF-219, A potent & selective covalent menin inhibitor

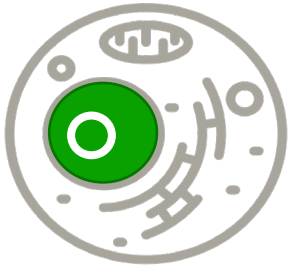


MEN1 Gene Expression Decreases w/ BMF-219 Treatment



BMF-219 exerts transient changes in Menin Protein

Menin Half Life Varies By Compartment



Half Life in Cytoplasm: <1hr

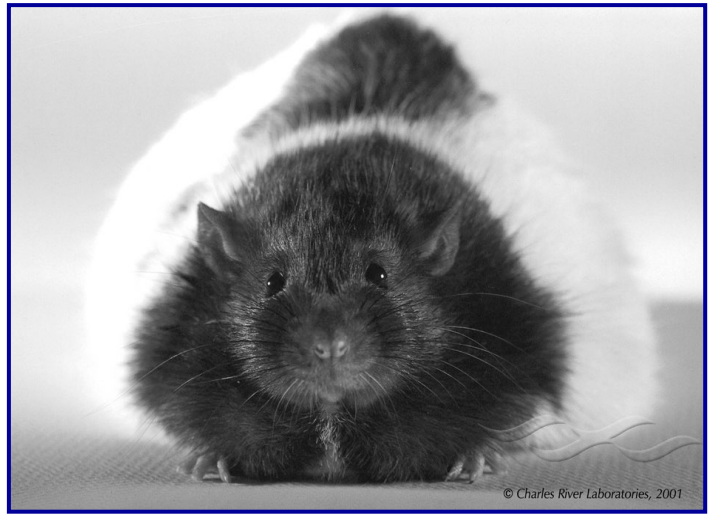
Half Life in Nucleus: 6-8 hrs

Menin's half-life in nucleus is most relevant for pharmacological intervention

- BMF-219 produces **robust decrease in expression of target protein** (Menin)
- **Effect continues beyond established nuclear half-life** of menin, indicating robust effect that is not impacted by protein turnover

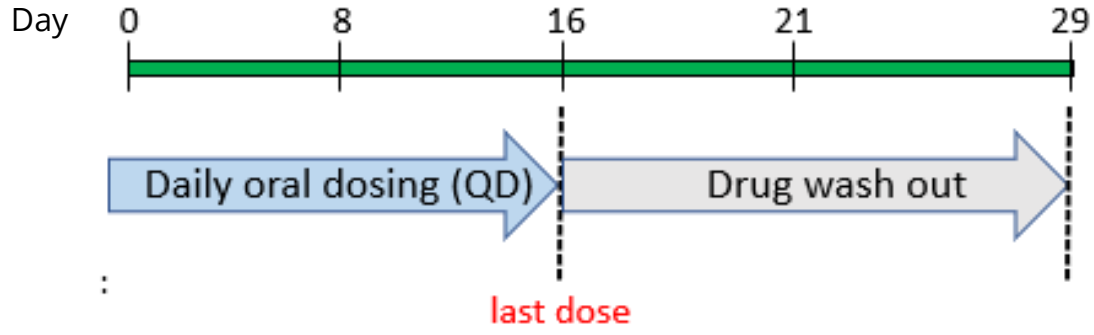
Zucker Diabetic Fatty Rat –A model of insulin resistance

THE ZDF RAT



- The ZDF rat is a model of pancreatic exhaustion, thus mimicking some aspects of human diabetes.
- Pioglitazone and metformin provide therapeutic efficacy in this model.
- The ZDF rat is a translatable model for studying the development of T2D.

Study Design

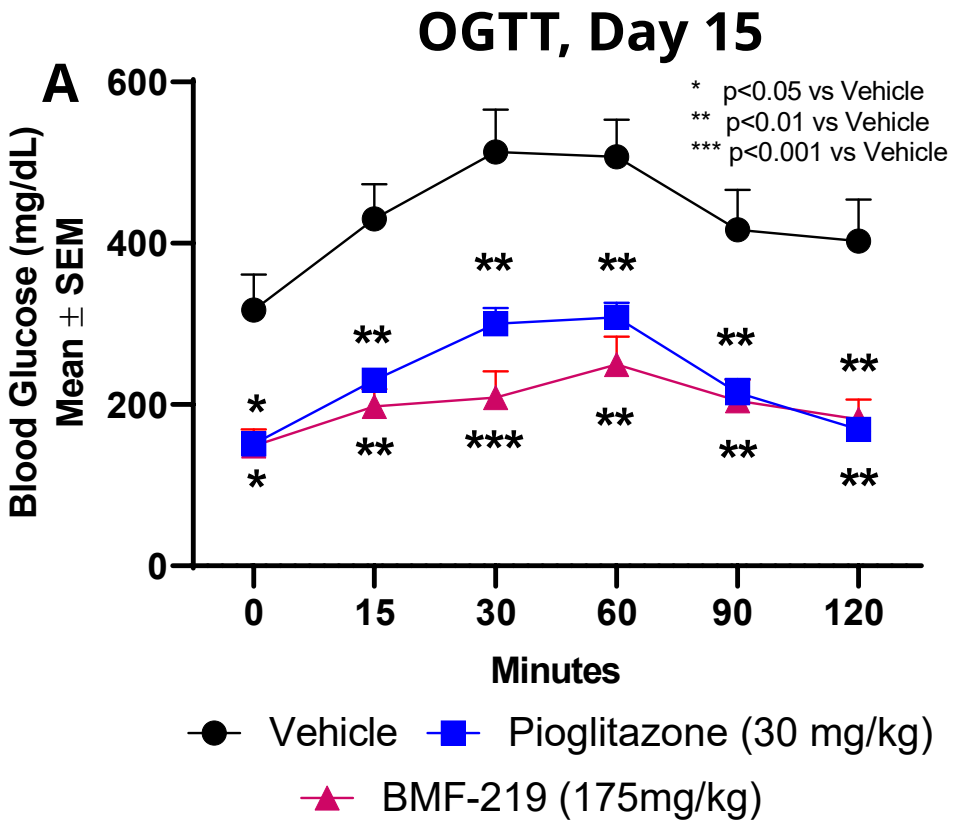


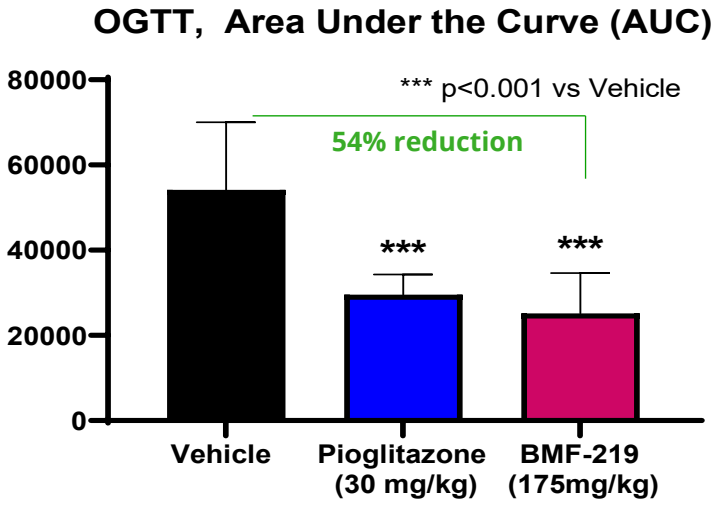
Rats monitored for the following parameters through dosing and washout phases include:
Body weight, fasting blood glucose, blood insulin, C-peptide, and OGTT

Treatment groups (n=10/group):

1. Vehicle
2. BMF-219 175 mg/kg
3. Pioglitazone 30 mg/kg

BMF-219 significantly reduces blood glucose by Oral Glucose Tolerance Test (OGTT) in ZDF rats

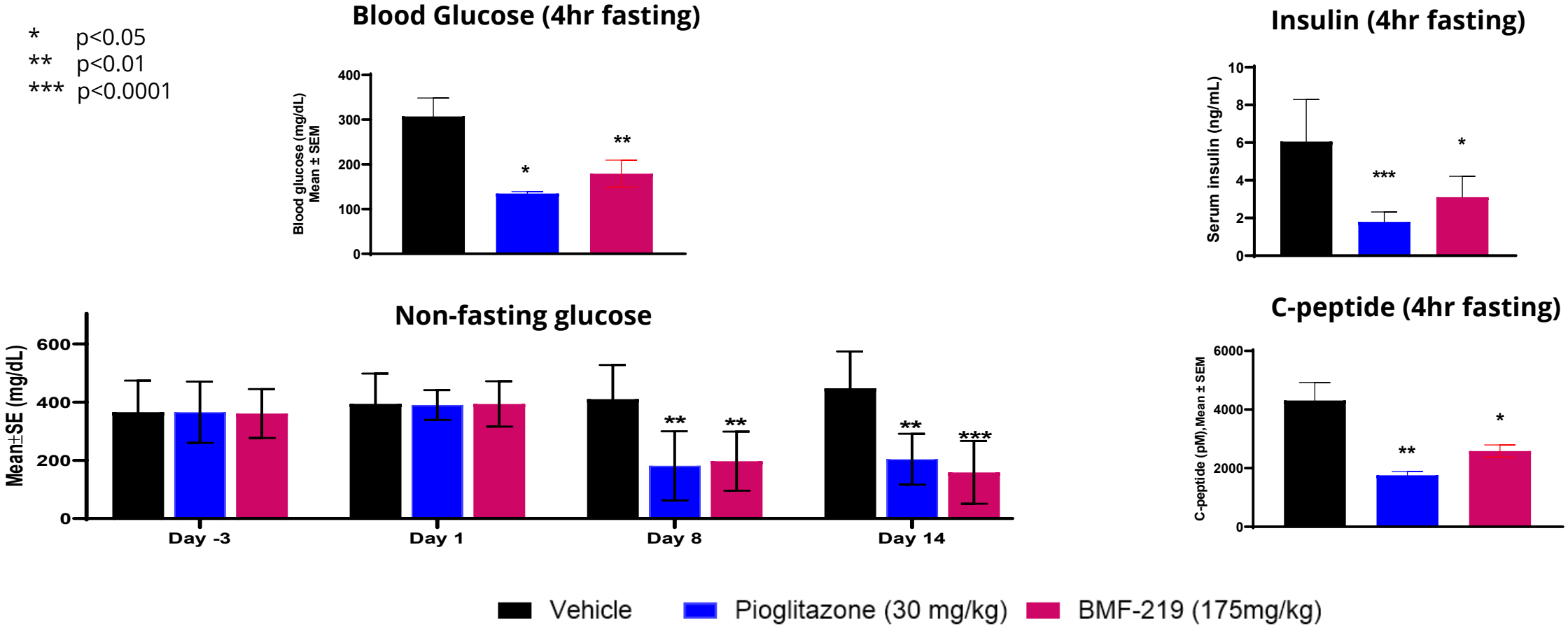




BMF-219 significantly reduces blood glucose levels by OGTT at Day 15 of treatment

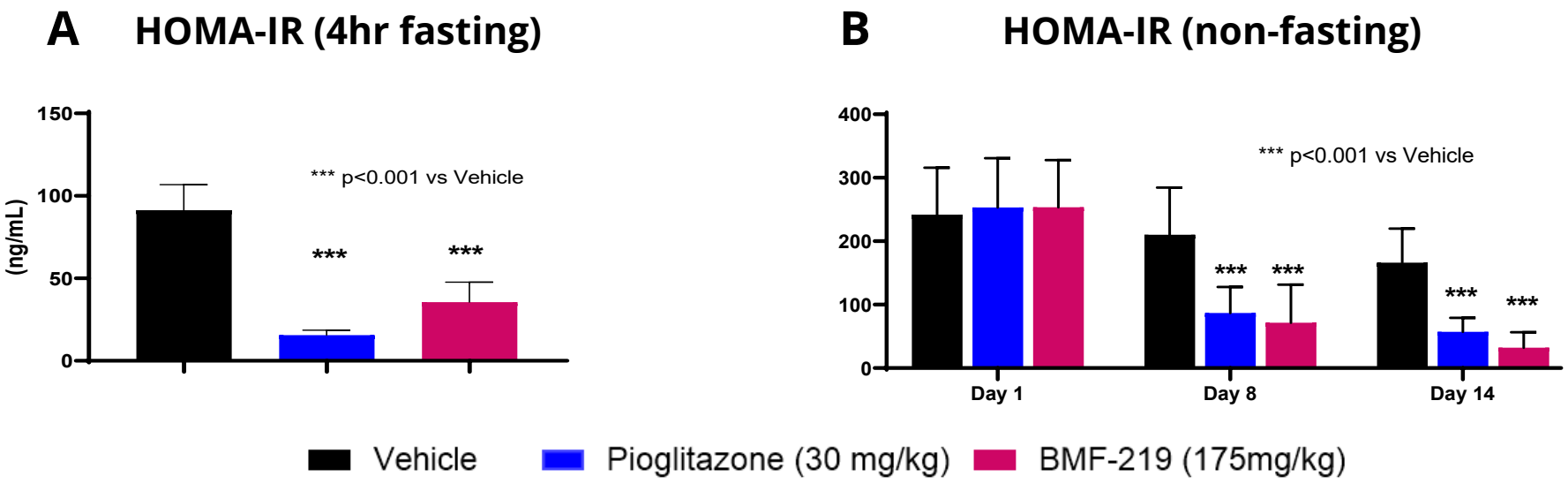
BMF-219 significantly reduces blood glucose, insulin, and c-peptide levels in ZDF Rats (After 2 Weeks of Dosing)

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



BMF-219 significantly reduces blood glucose levels and alters serum insulin and C-peptide levels in ZDF rats @ Day 17

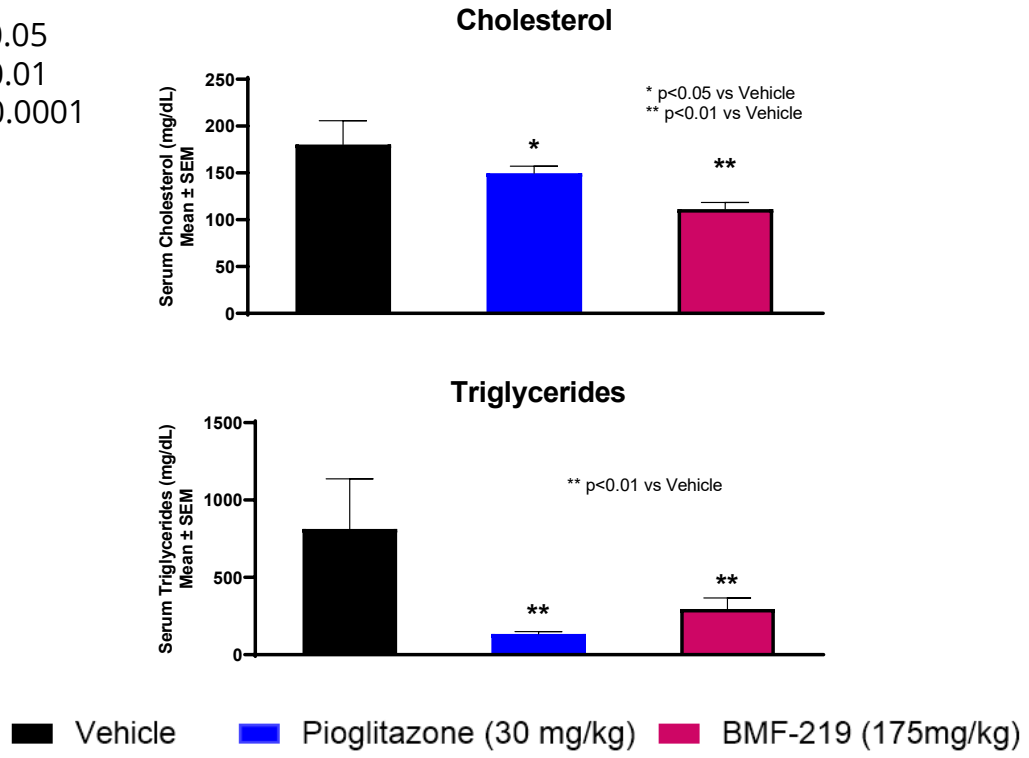
BMF-219 increases insulin sensitivity in ZDF rats

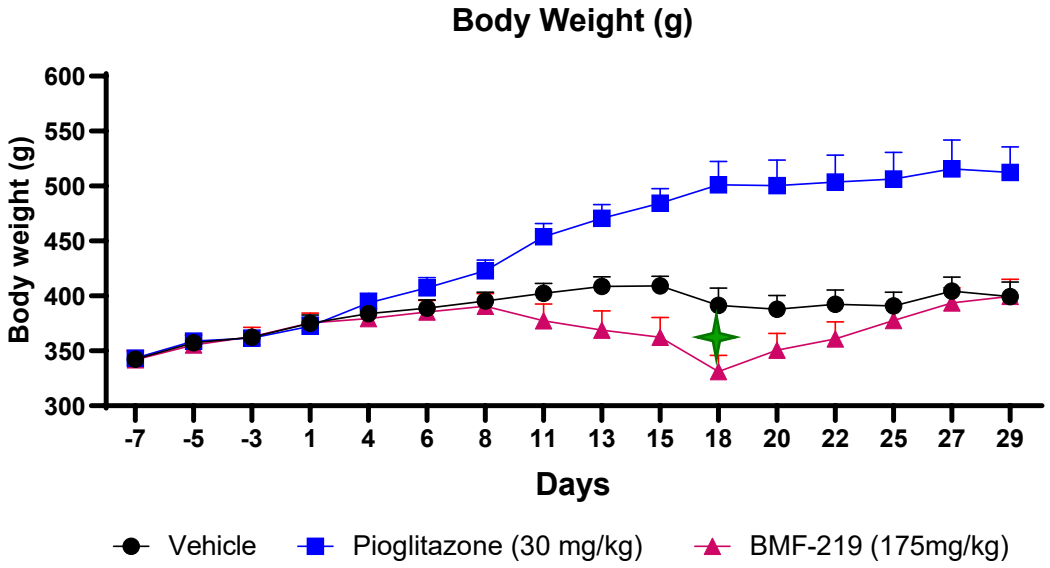


Measurement of HOMA-IR in rats treated with BMF-219 for 16 Days

BMF-219 significantly reduces blood lipemic levels and reduces body weight at day 17

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



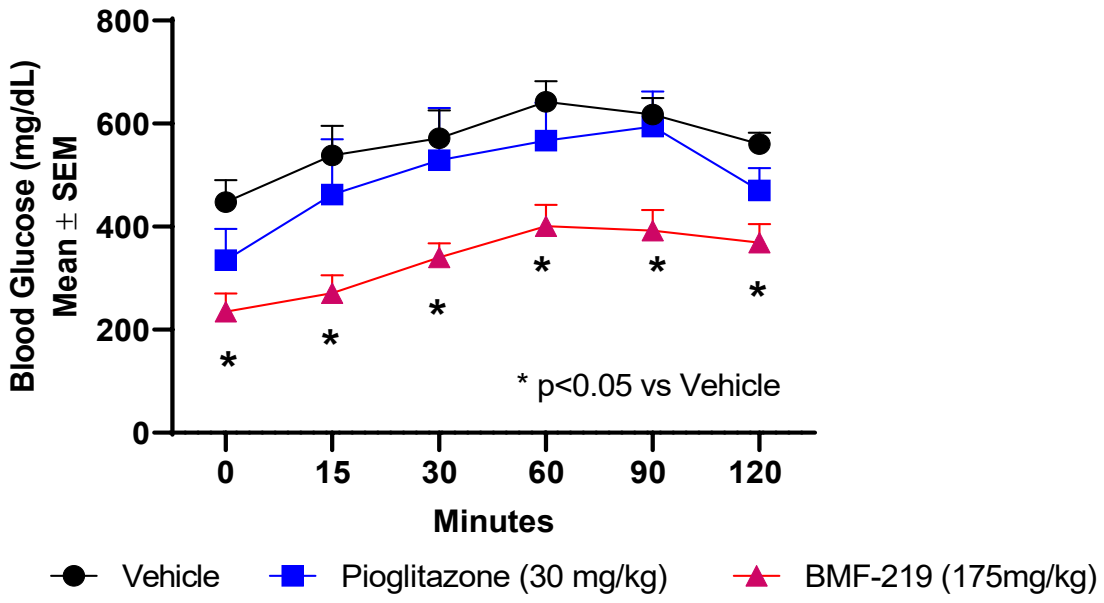


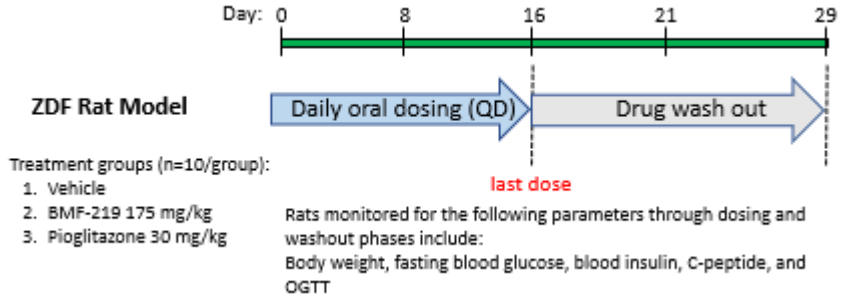
15% reduction after 2 weeks dosing

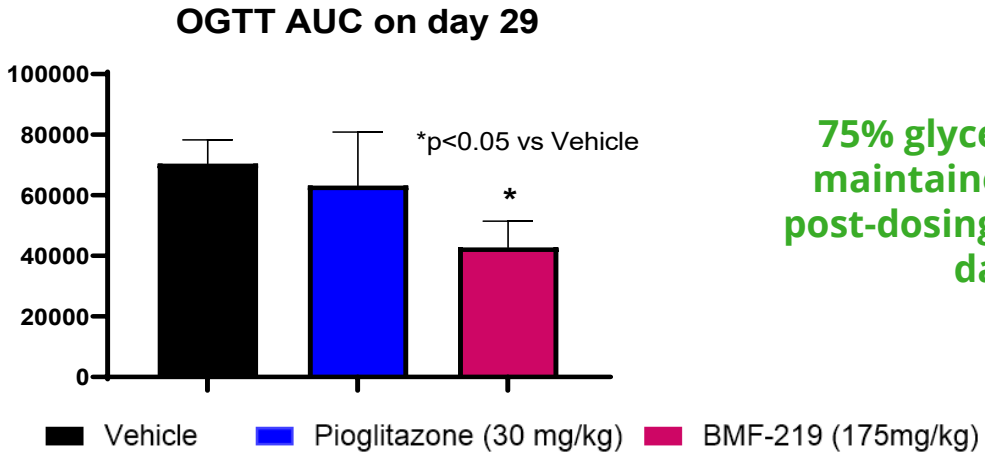
Measurement of cholesterol, triglycerides and body weight in BMF-219 treated rats for 16 days. (Animals continued to eat a high caloric diet until Day 31).

BMF-219 displays durable glycemic control during drug washout, two weeks after the last dose

After 2-week Drug Washout





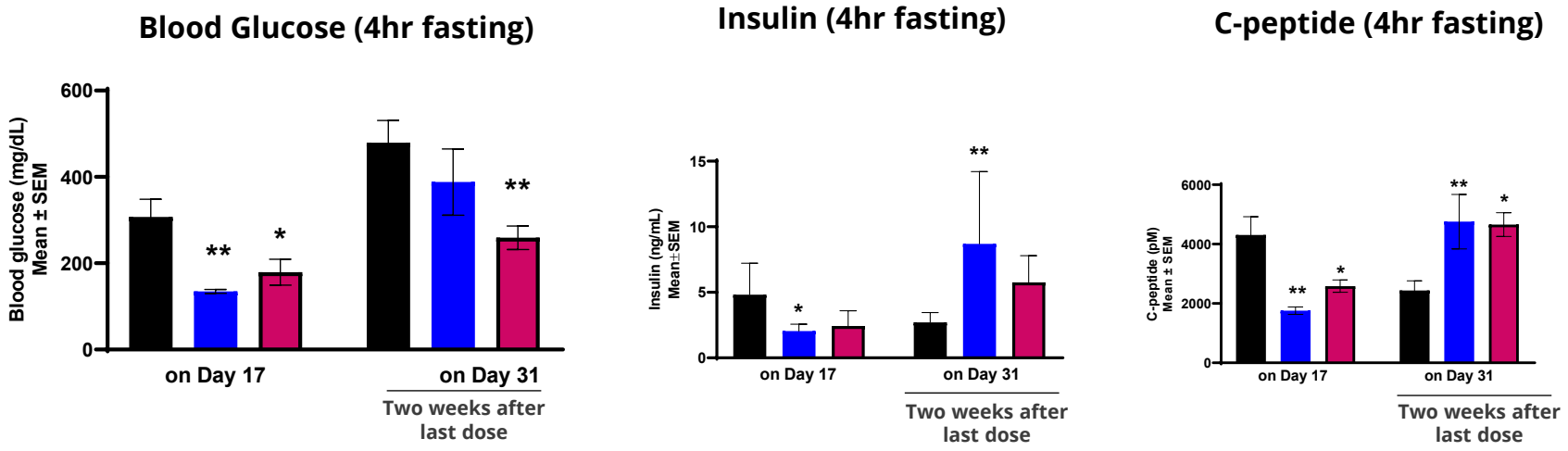


75% glycemic control maintained on day 29 post-dosing compared to day 15

ZDF rats treated with BMF-219, pioglitazone or vehicle control for 16 days were monitored for blood glucose levels by OGTT on day 29, ~2 weeks after administration of the last dose, displaying an AUC reduction of 40%, (p<0.05).

BMF-219 maintains a strong impact on blood glucose, insulin and c-peptide levels during drug washout, two weeks after the last dose

Day 31: After 2-week Drug Washout



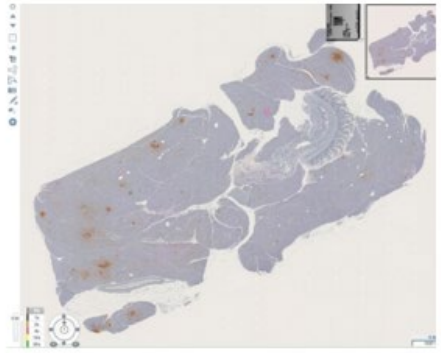
* p<0.05
** p<0.01
*** p<0.0001

BMF-219 maintains significant impact on blood glucose, insulin and c-peptide levels during drug washout (two weeks after last dose)

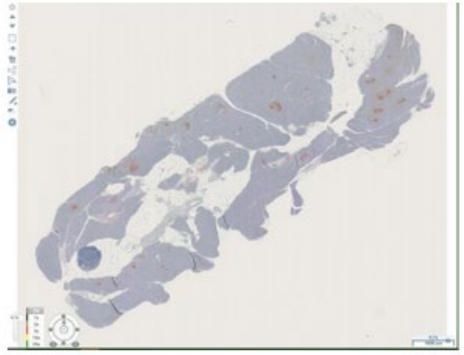
(Animals continued to eat a high caloric diet until Day 31)

BMF-219 increases β-islets in pancreas sections of ZDF diabetic model

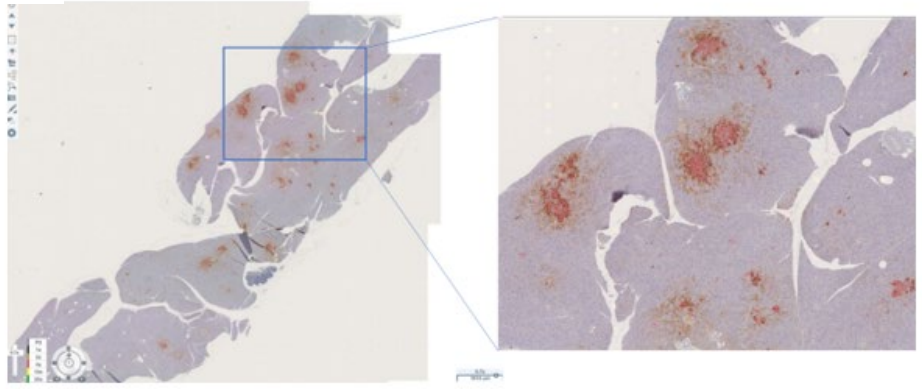
A. Vehicle; Day 31



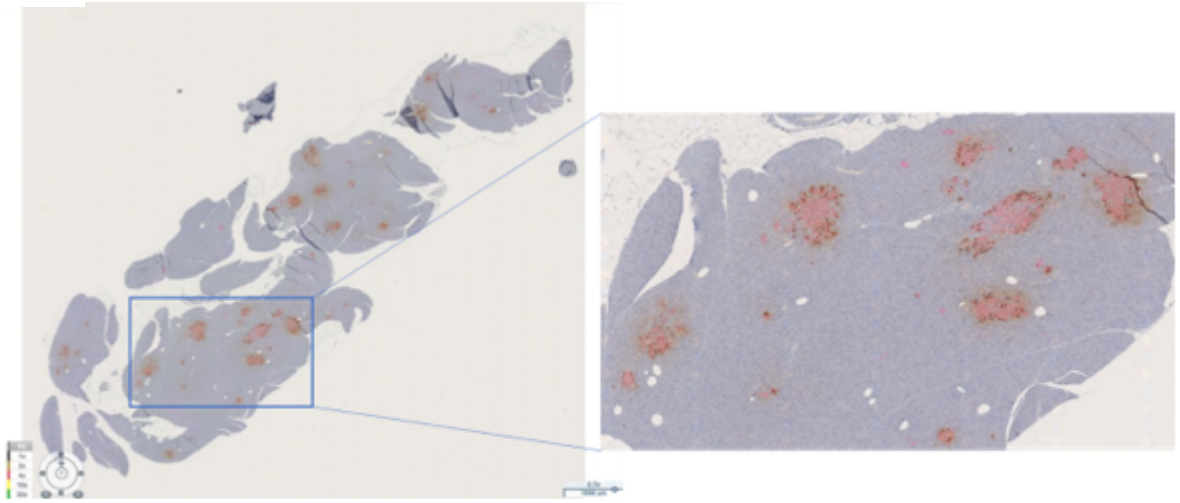
B. Pioglitazone; Day 17



C. BMF-219; Day 17

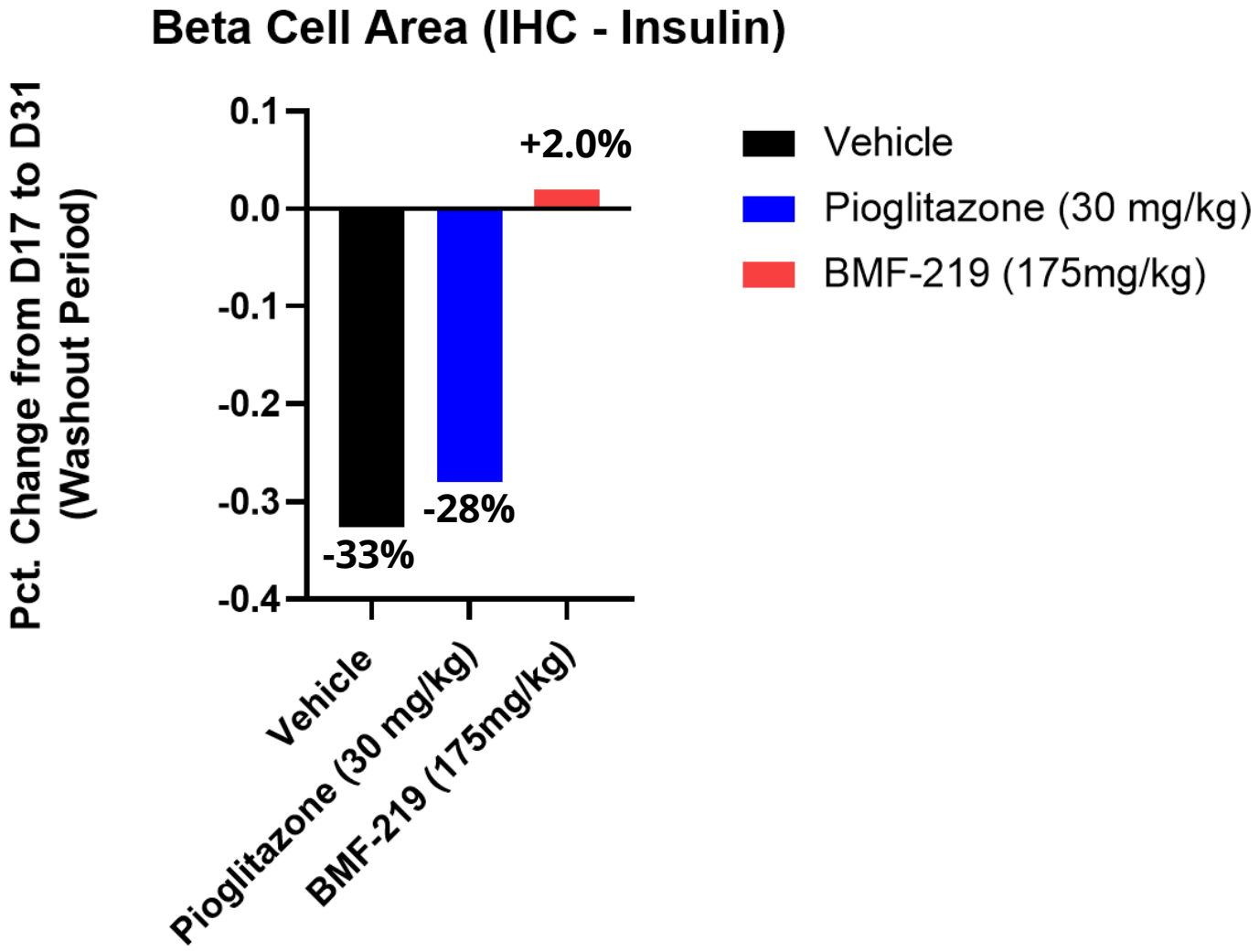


D. BMF-219; Day 31



A) Vehicle-treated animal, Day 31. Beta islets display low congregation and growth, while alpha cells dominate. **B)** Pioglitzaone-treated animal, Day 17. Beta islets display congregation and growth. **C)** BMF-219 treated animal, Day 17. In contrast to the pioglitazone-treated animal shown in Panel B, note that BMF-219 treatment results in high congregation and growth of the beta islets. **D)** BMF-219 treated animal, Day 31. Beta islets display high congregation and continue to increase and mature. Red is insulin-beta islets, brown is glucagon-alpha cells.

BMF-219 increases β-islets in pancreas sections of ZDF diabetic model

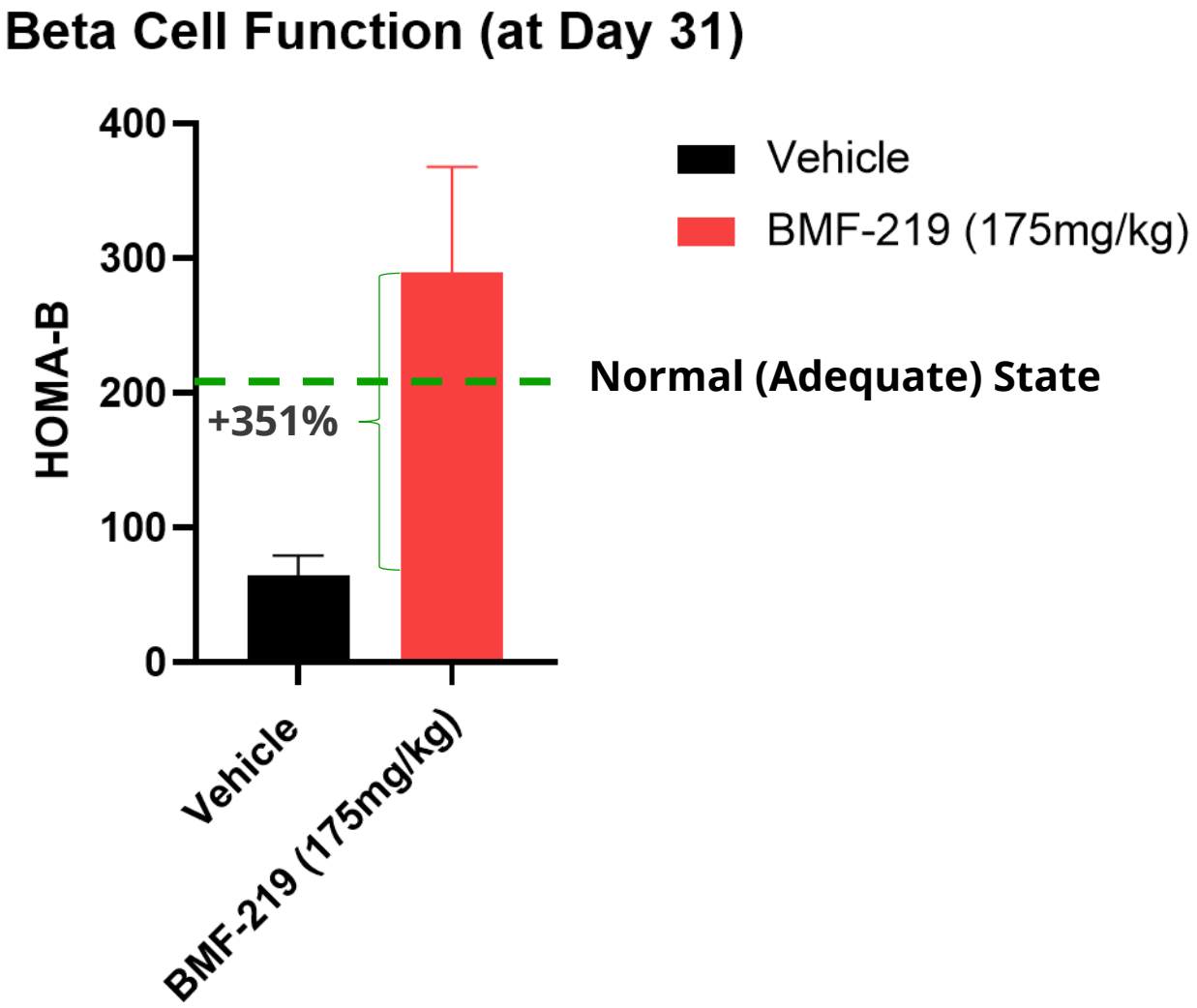


Quantitative Analysis of pancreatic islet tissue cross sections shows BMF-219 treated animals show novel effects in Beta Cell Area growth and maintenance.

BMF-219 was able to maintain Beta Cell function and prevent Beta Cell Area Loss in an Insulin Resistance Type 2 Diabetes Model.

Importantly, Beta Cell Area is maintained, despite cessation of dosing.

BMF-219 demonstrates strong β-cell activity, supporting quantitative analysis



HOMA-Beta, a measurement of Beta Cell Function, was analyzed using 4-hr fasting glucose and insulin levels in animal plasma.

BMF-219 displayed a significant level of Beta Cell function compared to vehicle at Day 31 in an Insulin Resistance Type 2 Diabetes Model.

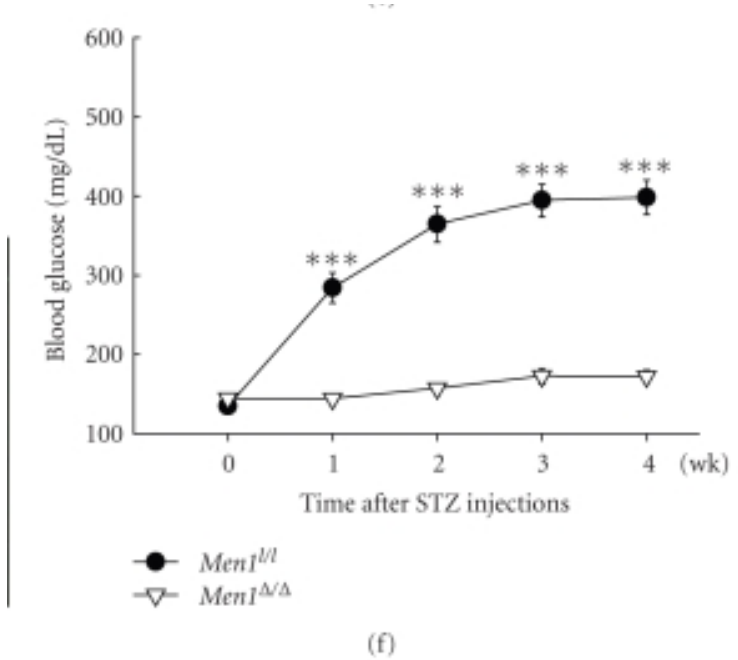
This data supports the observed results from the Beta Cell Area Quantitative Analysis using IHC. Importantly, Beta Cell Function is observed despite cessation of dosing.

O.J. Fasipe et al. / Can J Diabetes 44 (2020) 663e669

Streptozotocin (STZ) Rat, A type 2 diabetes model of beta cell loss

MEN1 Excision Prevents Development of STZ-induced Hyperglycemia

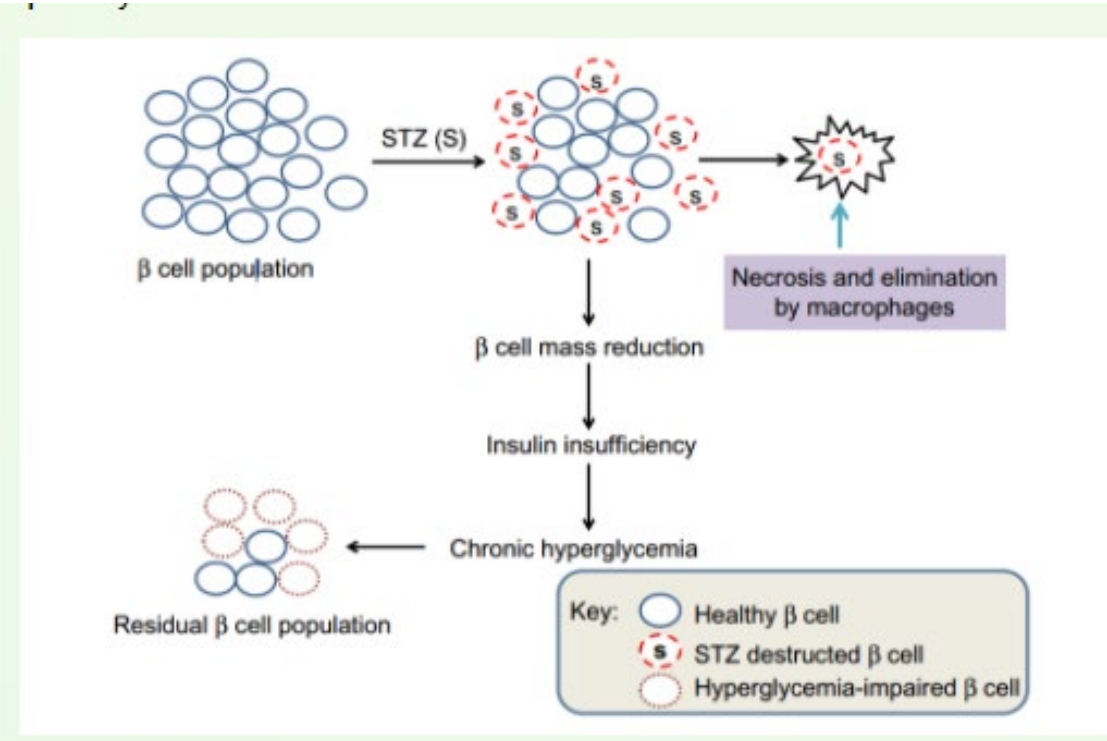
- Menin is a scaffold protein, encoded by the gene *MEN1*, that has been recently recognized for its role in Type 2 Diabetes Mellitus (T2DM) as a key regulator of b-cell proliferation.
- *Men1* knockout mice demonstrate increased B-cell mass generation (Yang et al., 2010) and menin inhibition has previously been shown to improve glycemic control in high fat induced diabetic mice (Ma et al., 2021).
- Men1-excised mice do not develop hyperglycemia in a Streptozotocin-(STZ) induced rat model, which is a model for impaired beta-cell function and insulin production, demonstrating the role of menin in glycemic control.



***Men1*-excised mice did not develop hyperglycemia in STZ model, which was observed in the control group**

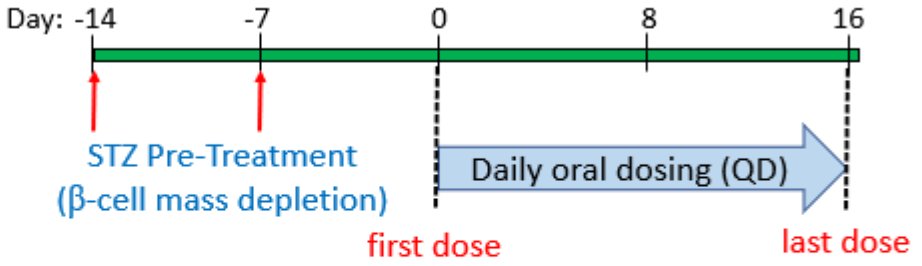
STZ Rat Model- Study Design

The Streptozotocin (STZ)-Induced Rat Model
Only direct insulin injection shows an effect in this model



Study Design

STZ Rat Model with high fat diet



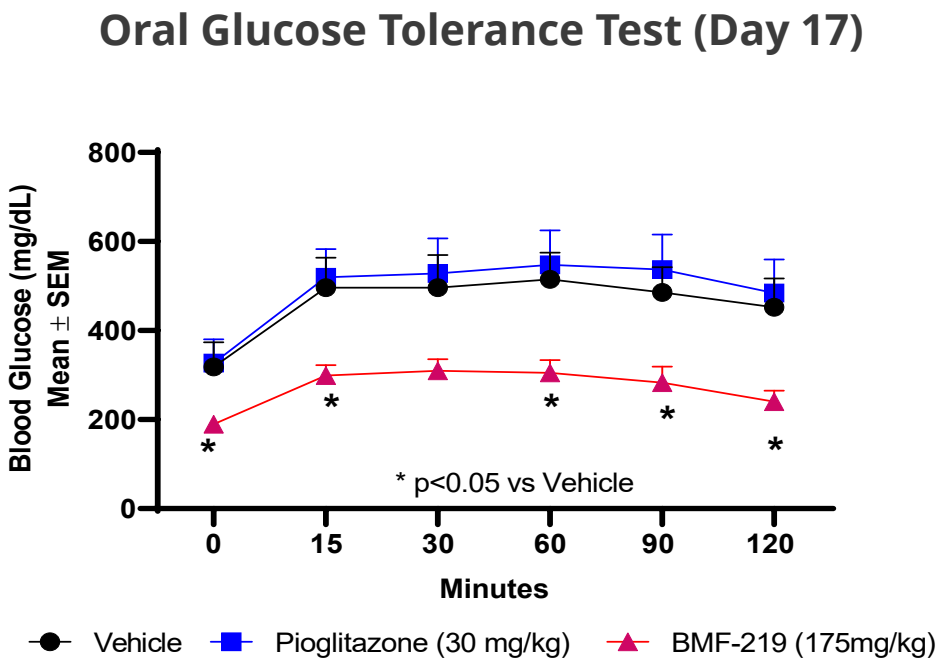
Treatment groups (n=10/group):

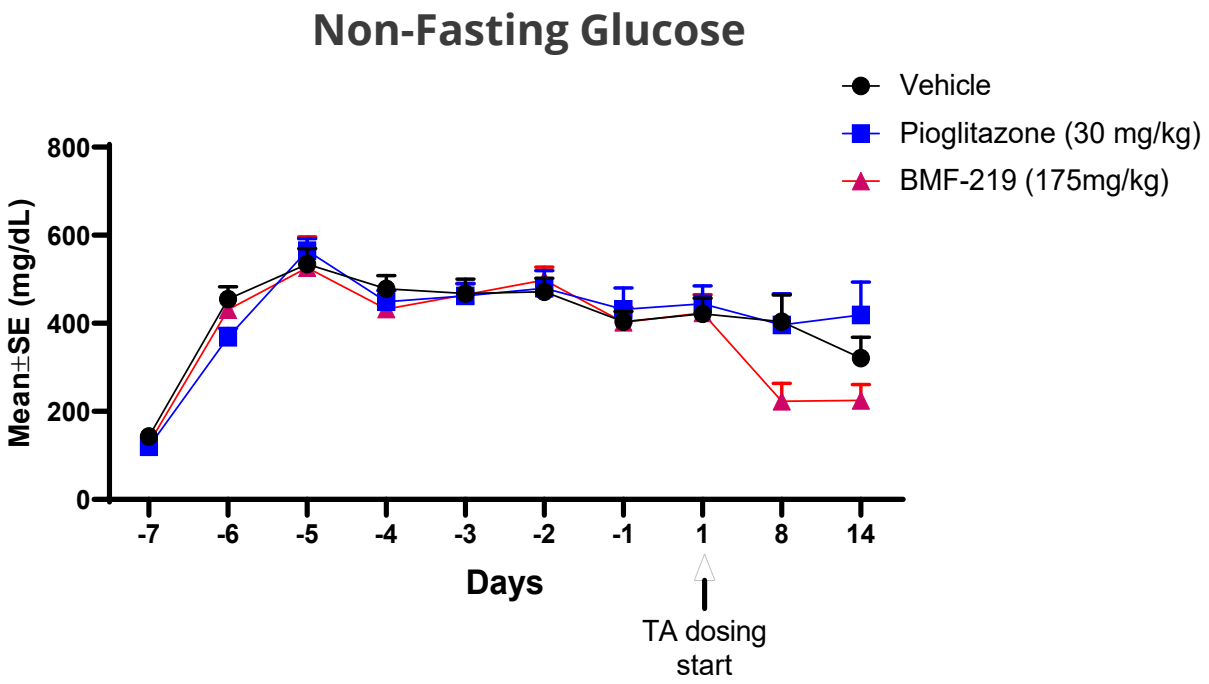
1. Vehicle
2. BMF-219 175 mg/kg
3. Pioglitazone 30 mg/kg

Rats monitored for the following parameters through dosing include: OGTT, blood glucose levels

STZ treatment typically results in ~50% Beta Cell Loss

BMF-219 significantly reduced blood glucose by Oral Glucose Tolerance Test (OGTT) in an STZ-induced rat model

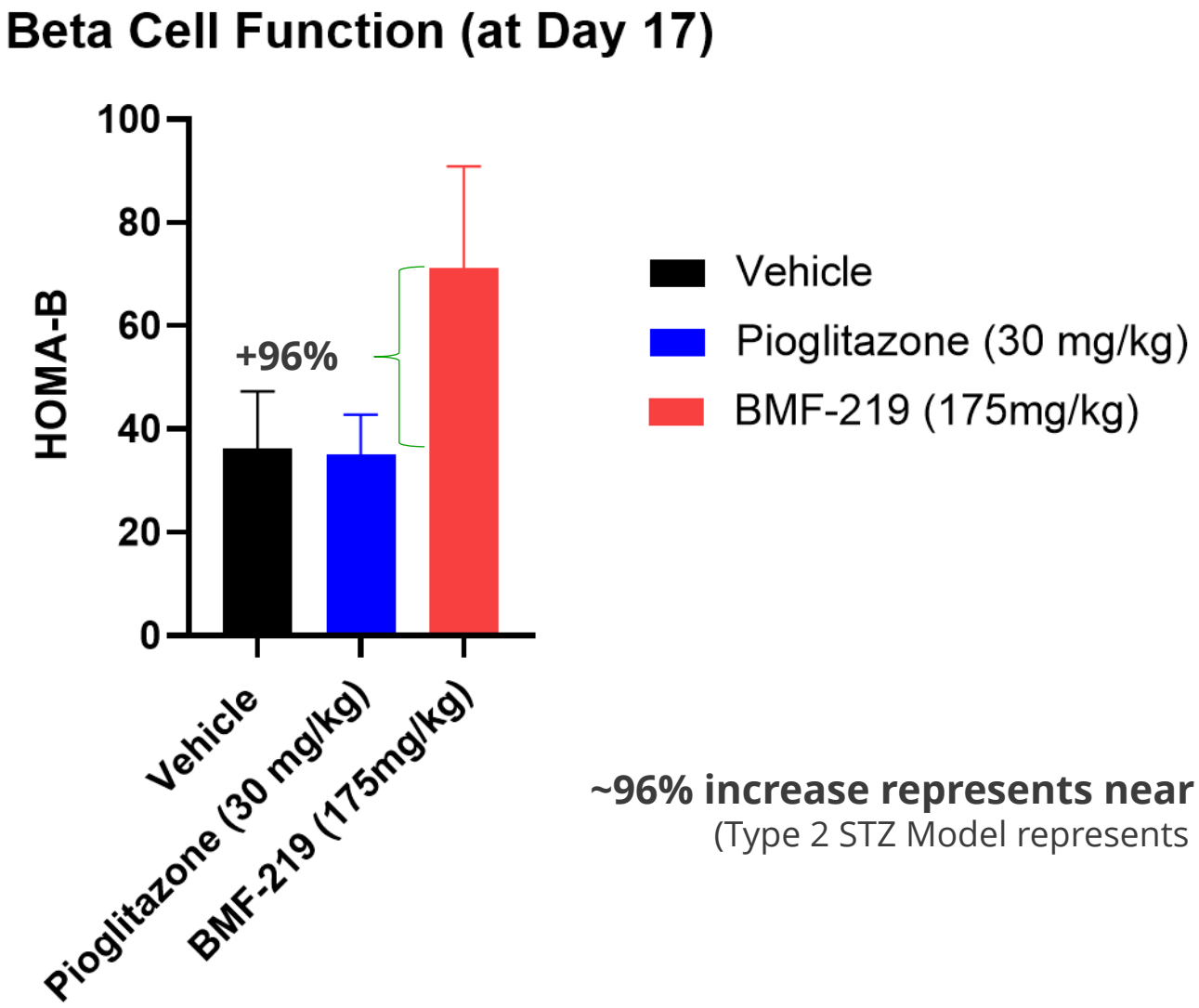




Only BMF-219 significantly reduces blood glucose by OGTT in STZ rats

Only BMF-219 lowered non-fasting glucose in STZ rats

BMF-219 demonstrates recovery of β-cell activity



HOMA-Beta, a measurement of Beta Cell Function, was analyzed using 4-hr fasting glucose and insulin levels in animal plasma.

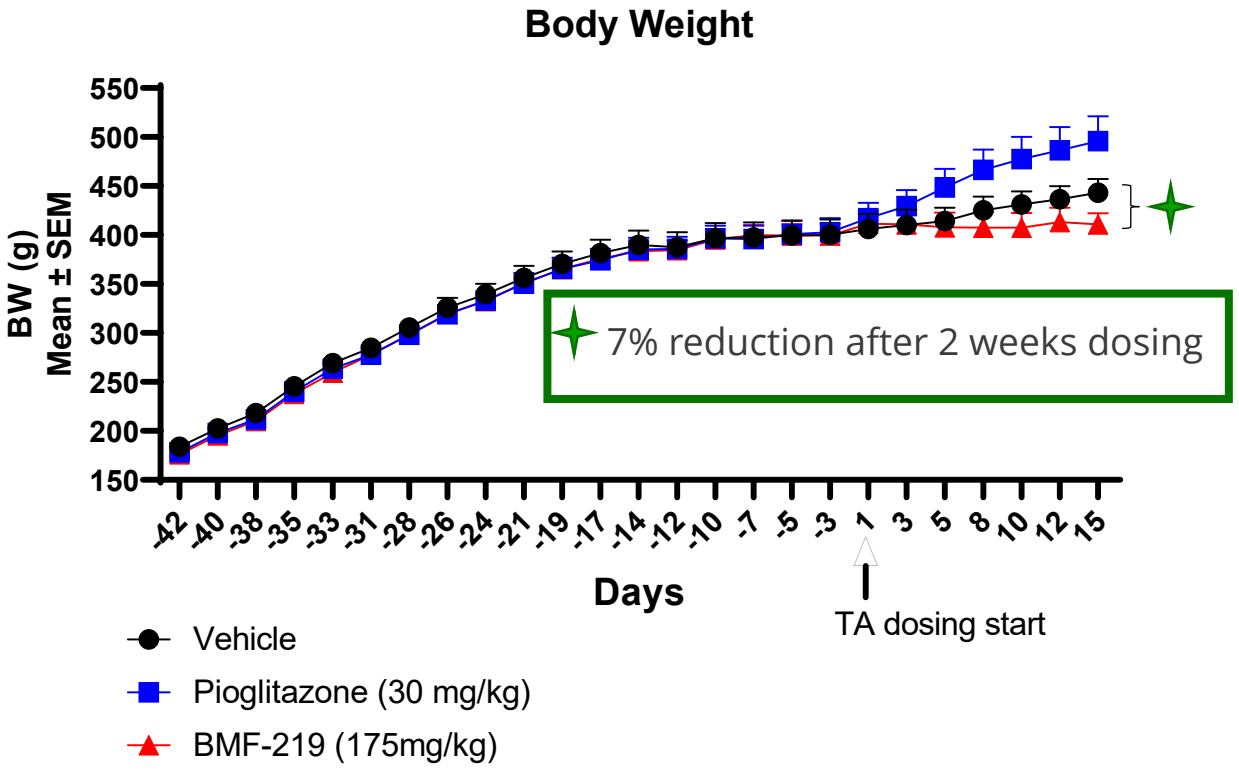
BMF-219 displayed a significant level of Beta Cell function compared to vehicle at Day 17 in a Beta Cell Type 2 Diabetes Model.

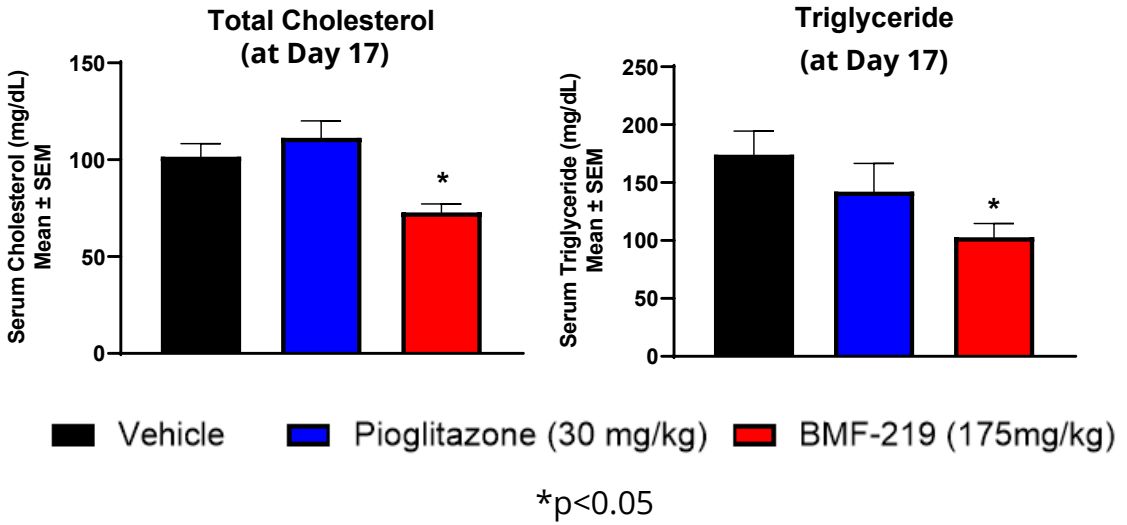
This data supports the observed results from the Beta Cell Mass Quantitative Analysis using IHC. Importantly, Beta Cell Function is observed despite cessation of dosing.

~96% increase represents near doubling of beta cell function

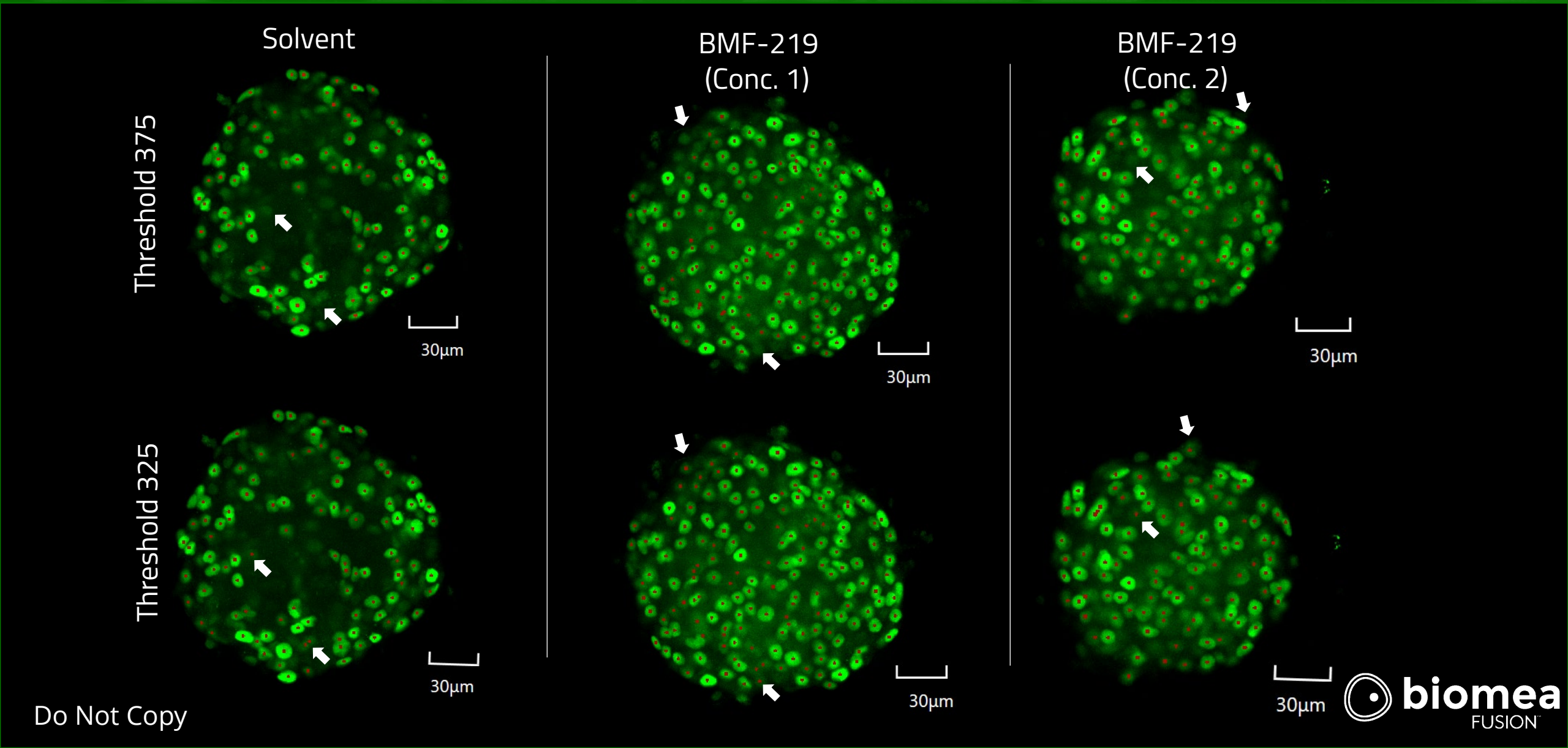
(Type 2 STZ Model represents ~ 50% Beta Cell Destruction)

BMF-219 significantly reduces blood lipemic levels and body weight in STZ rats





Human Donor Islets (Ex-Vivo): Statistically significant increase in beta cells with BMF-219



biomea FUSION

Conclusions & Next Steps

- BMF-219 was tested in two type 2 diabetic in-vivo models at clinically relevant exposures.

BMF-219 treatment in STZ-induced diabetic rat model:

- Improved glucose metabolism (OGTT AUC reduction 41%, $p<0.05$) and reduction in blood lipemic levels and body weight. Minimal efficacy for pioglitazone.
- BMF-219 but not pioglitazone increased HOMA-B.

BMF-219 treatment in ZDF rat model:

- Significant reduction (~50%) in fasting and non-fasting blood glucose levels,
- Significant reduction in serum insulin, C-peptide ($p<0.05$), and HOMA-IR ($p<0.001$) after two weeks of treatment.
- Prolonged glycemic control as evidenced by decreased OGTT glucose levels on day 15 (AUC reduction of 54%, $p<0.001$) and on day 29 (AUC reduction of 40%, $p<0.05$, ~2 weeks after the last dose).
- Significant reductions in blood lipemic levels ($p<0.01$) and body weight.

- Next Steps: Type 1 Model – Can BMF-219 re-establish Beta Cells from a severely diminished pool?

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

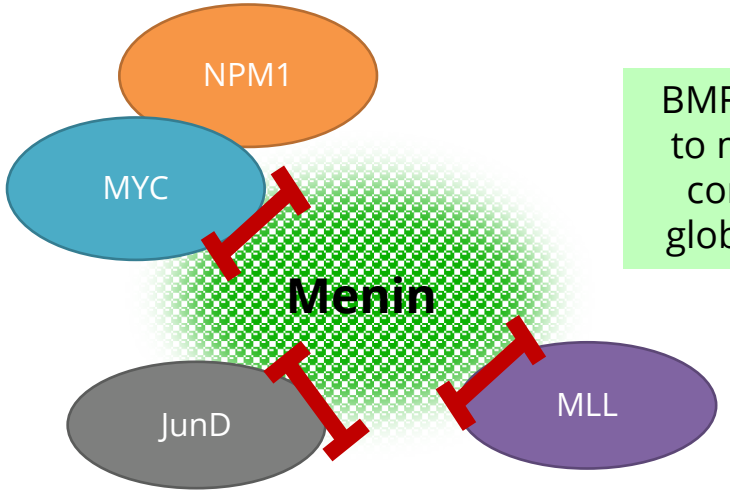
September 20, 2022

Menin: A novel target for beta-cell homeostasis

Potential Mechanism of Menin in Diabetes

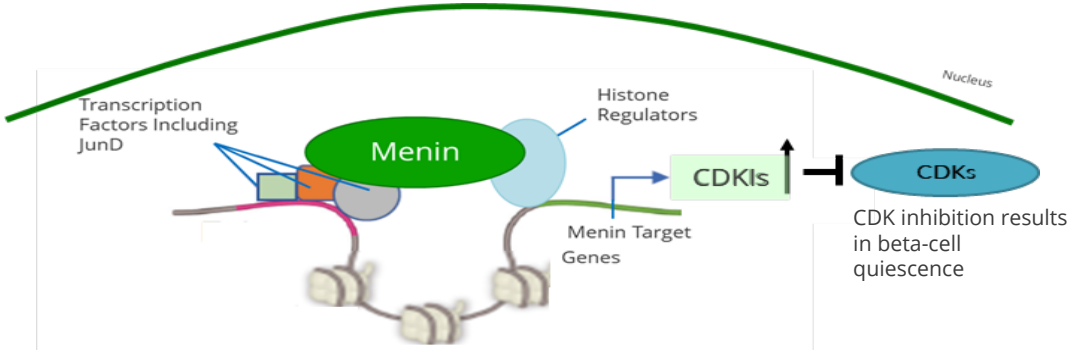
- Menin is an epigenetic protein that plays a key role in regulating beta-cell proliferation and function.
- Menin inhibition has previously been shown to improve glycemic control in high fat induced diabetic mice (Ma et al., 2021).
- Inhibition of menin/JunD complex reduces the expression of Cyclin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

Menin regulates beta-cell quiescence



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

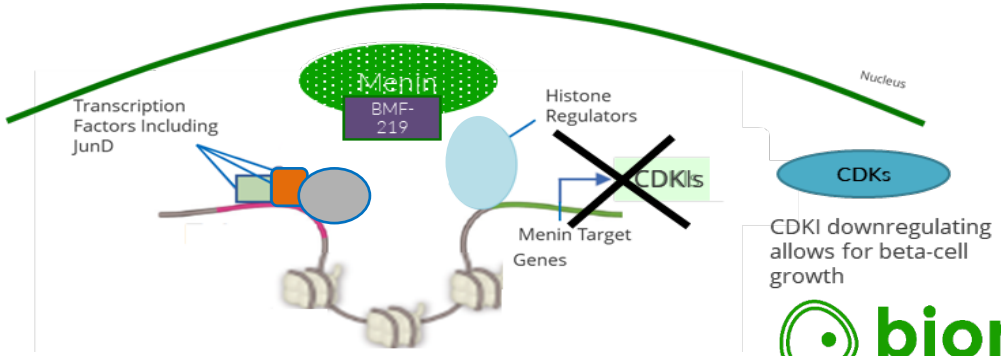


Figure adapted from Issa et al. *Leukemia* **35**, 2482–2495 (2021).

Study Design: Zucker Diabetic Fatty (ZDF) rat model of T2DM

THE ZDF RAT

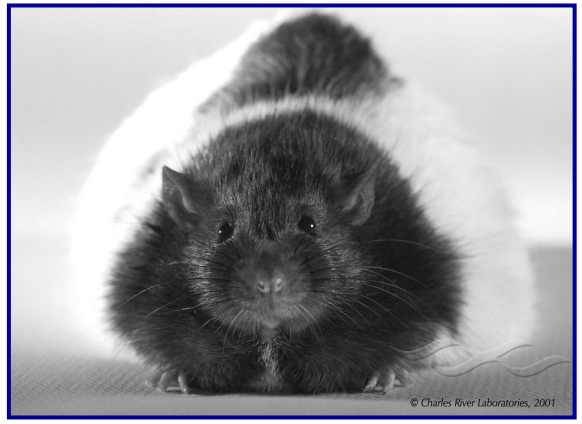
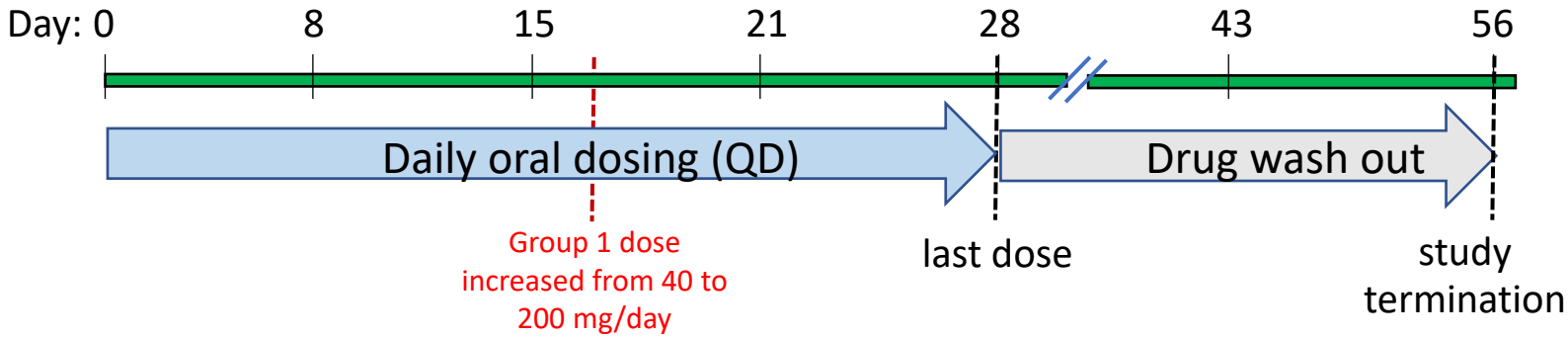


Image Source: Charles River Laboratories, 2001.

- 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.

Treatment Scheme of ZDF Rat Model



Treatment groups (n=10/group):

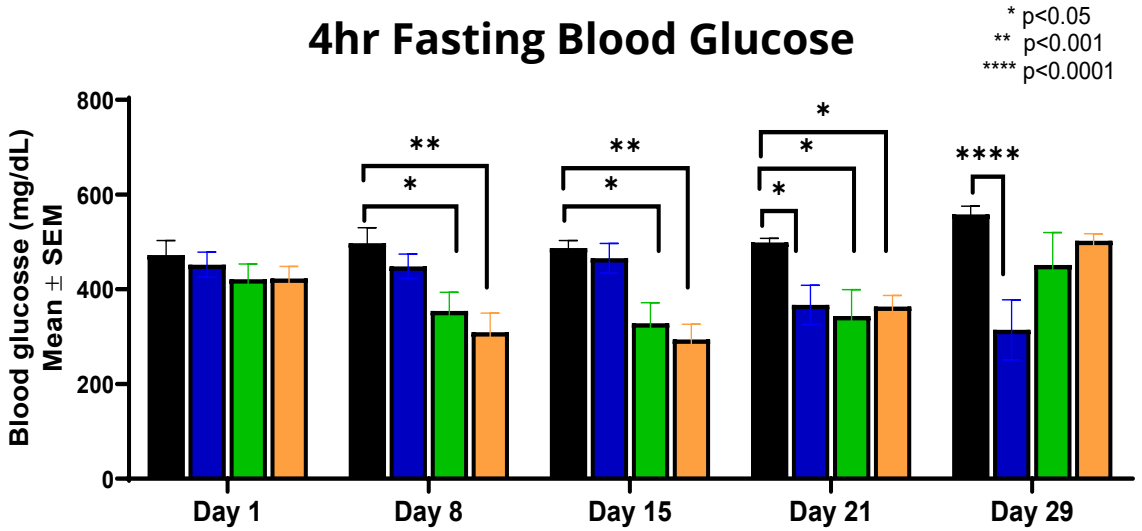
1. Vehicle
2. BMF-219 40 mg/kg days 1-16, 200 mg/kg days 17-28 (QD, PO)
3. BMF-219 85 mg/kg (QD, PO)
4. BMF-219 170 mg/kg (QD, PO)
5. Liraglutide 0.2 mg/kg (BID, SC)

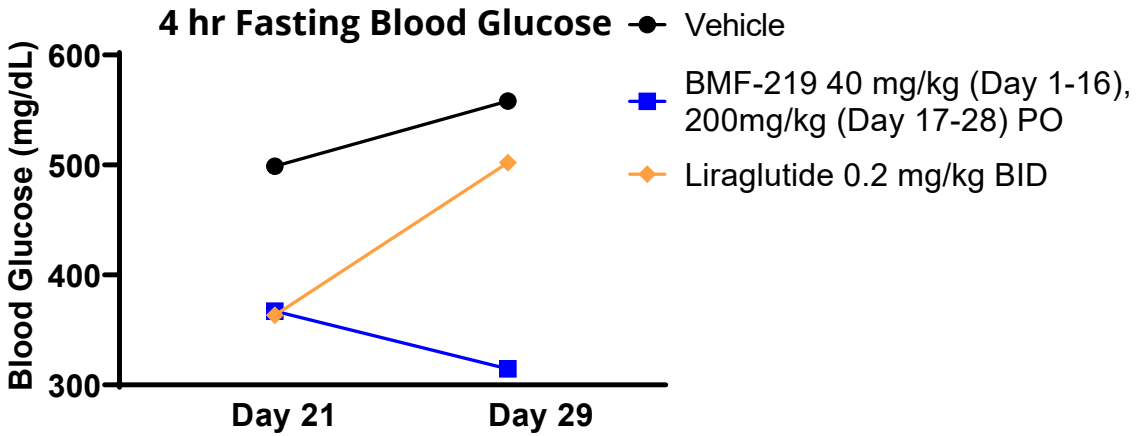
Rats monitored through dosing and washout phases:
Fasting blood glucose, insulin, OGTT, HbA1c, body weight, blood lipemic levels

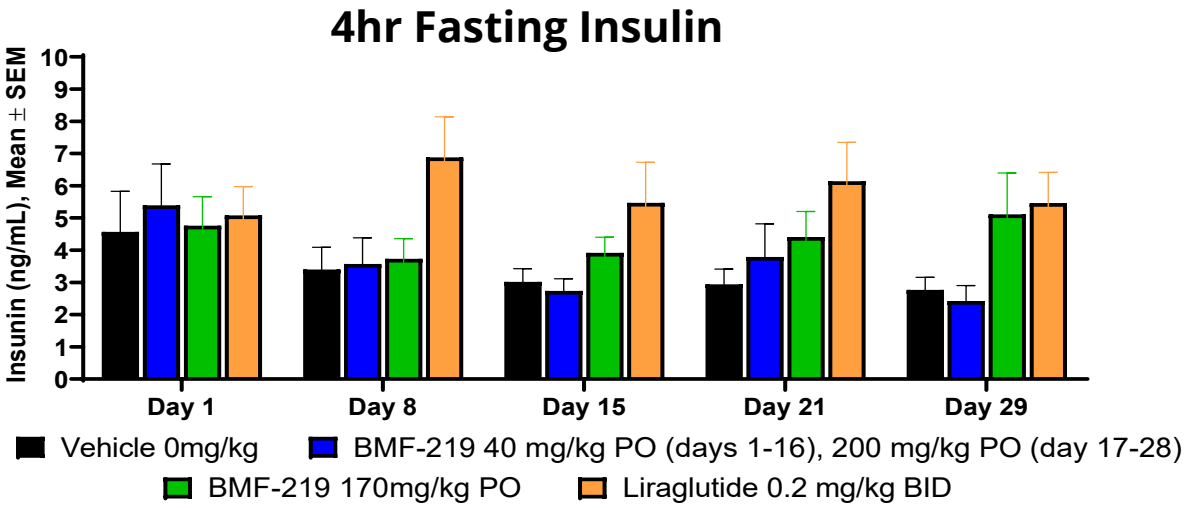
Study Objective

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

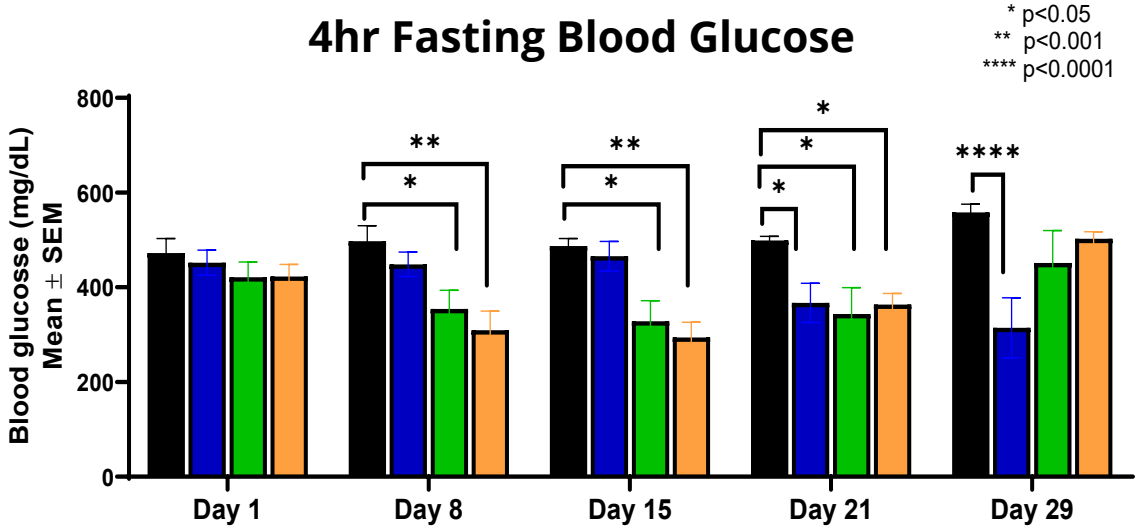
BMF-219 substantially controls blood glucose levels in a 4-week dosing study in ZDF rats

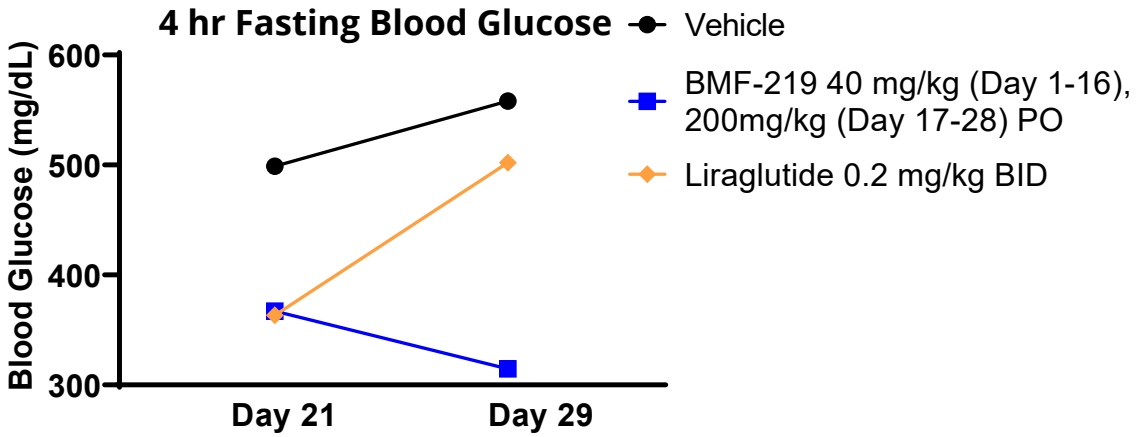


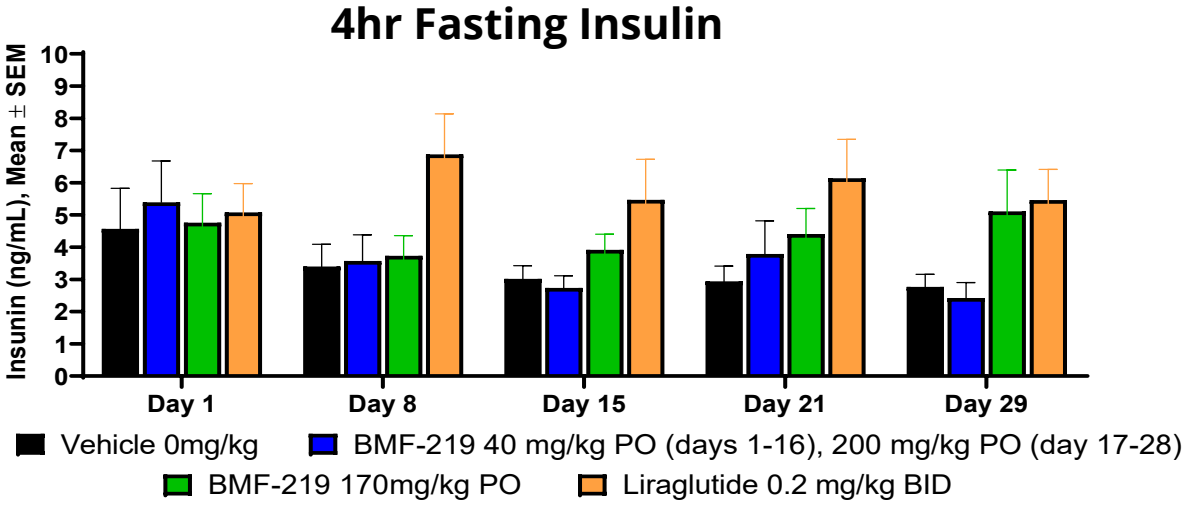


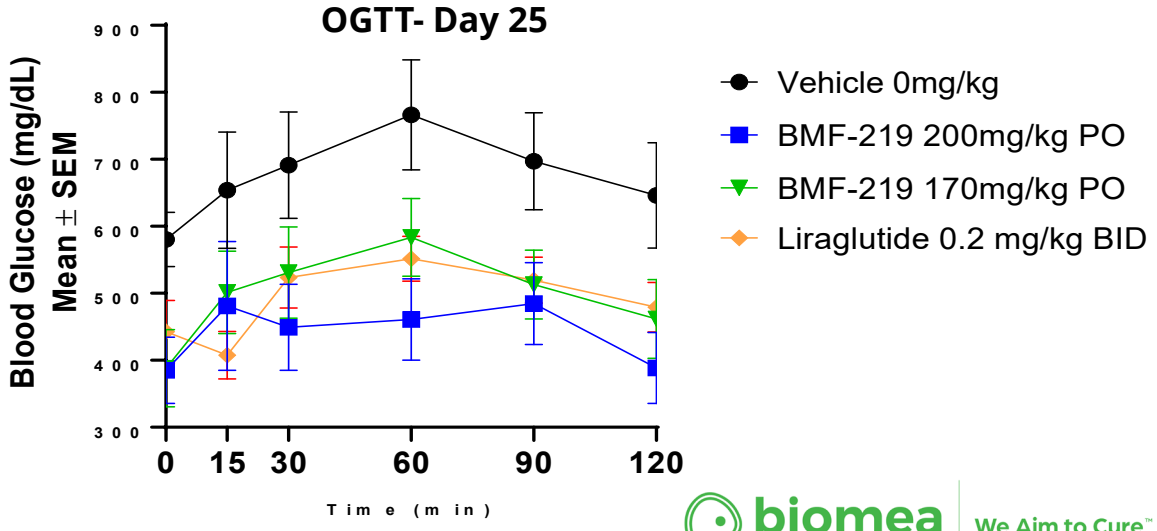


BMF-219 substantially controls blood glucose levels in a 4-week dosing study in ZDF rats

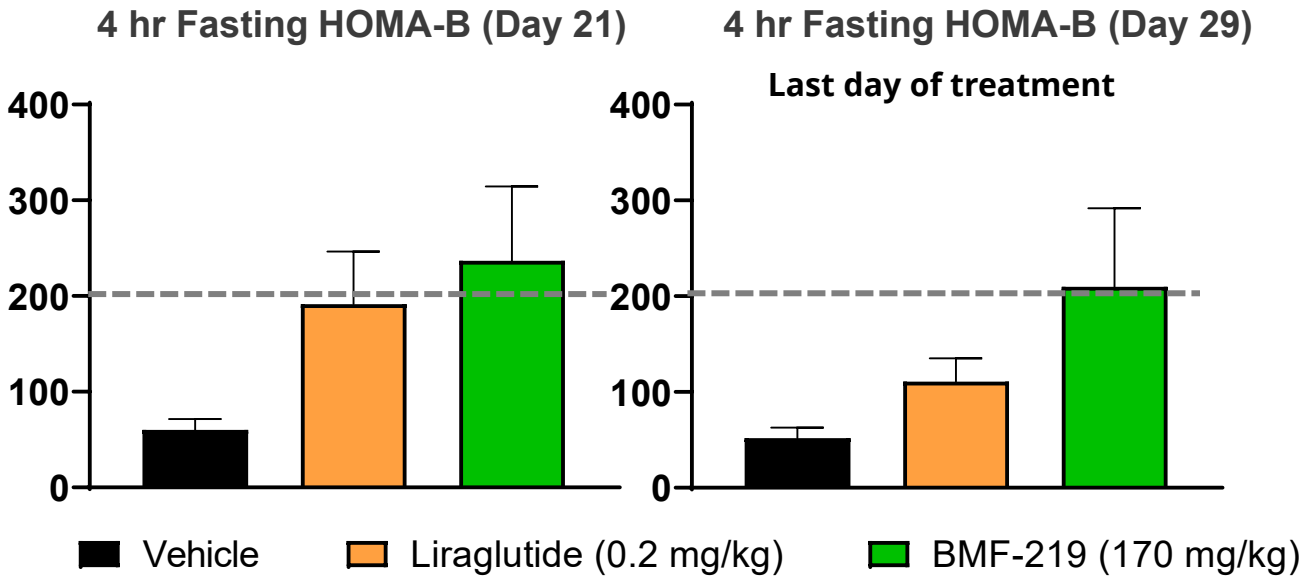








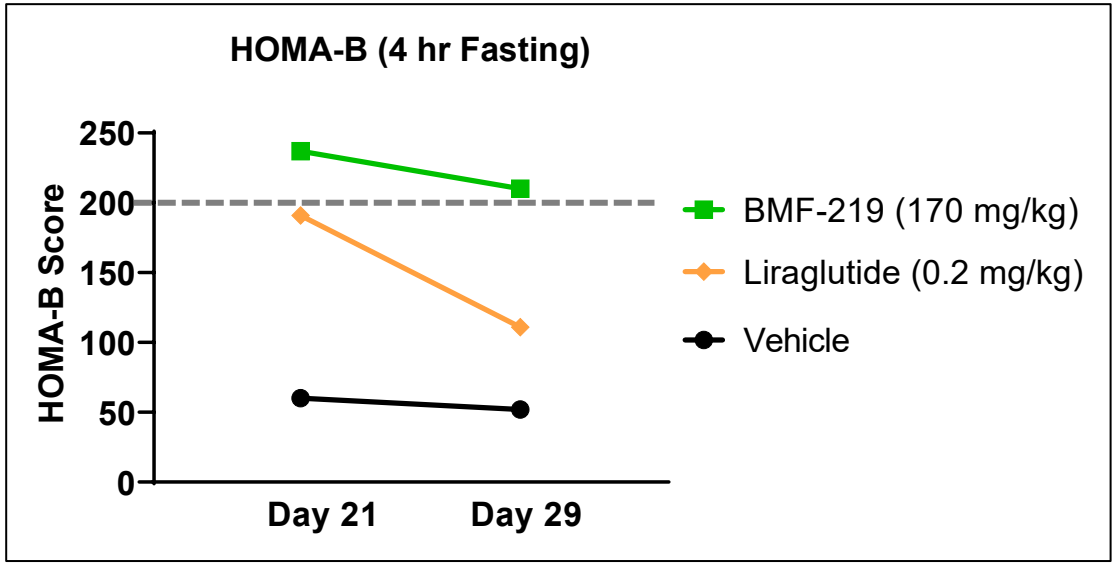
BMF-219 restores beta-cell function over 4 weeks of treatment



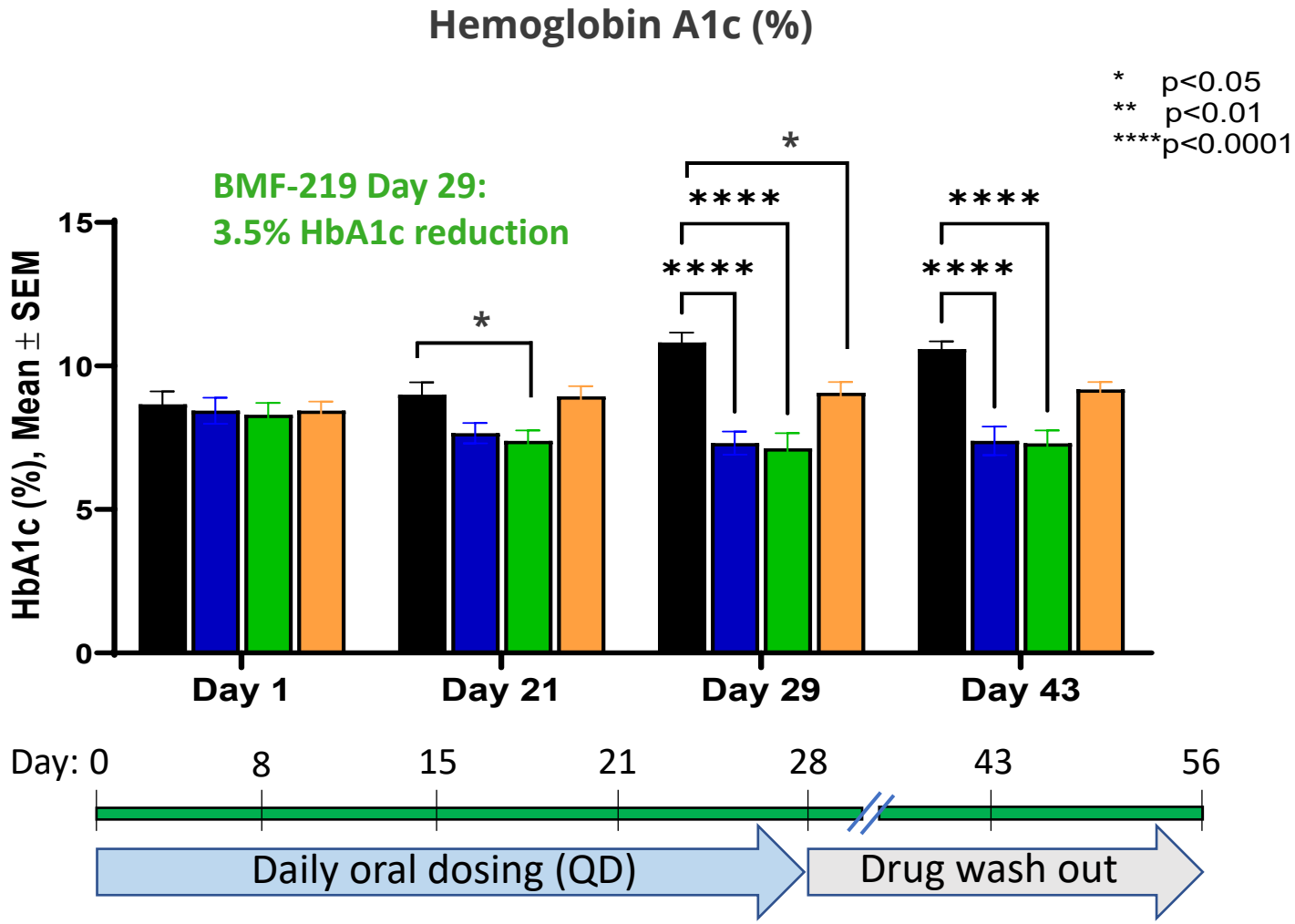
Severity Grading Assessment for Pancreatic Beta-Cell Function	HOMA-B Index
Adequate (normal state)	≥ 201.00
Mild deficiency	134.00 to 200.99
Moderate deficiency	67.00 to 133.99
Severe deficiency	0.00 to 66.99

Table Source: Fasipe JO et al. 2020. Can J Diabetes 44 (2020) 663e669.

BMF-219 restores and maintains HOMA-B index to normal state (>201) over 4 weeks of treatment



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

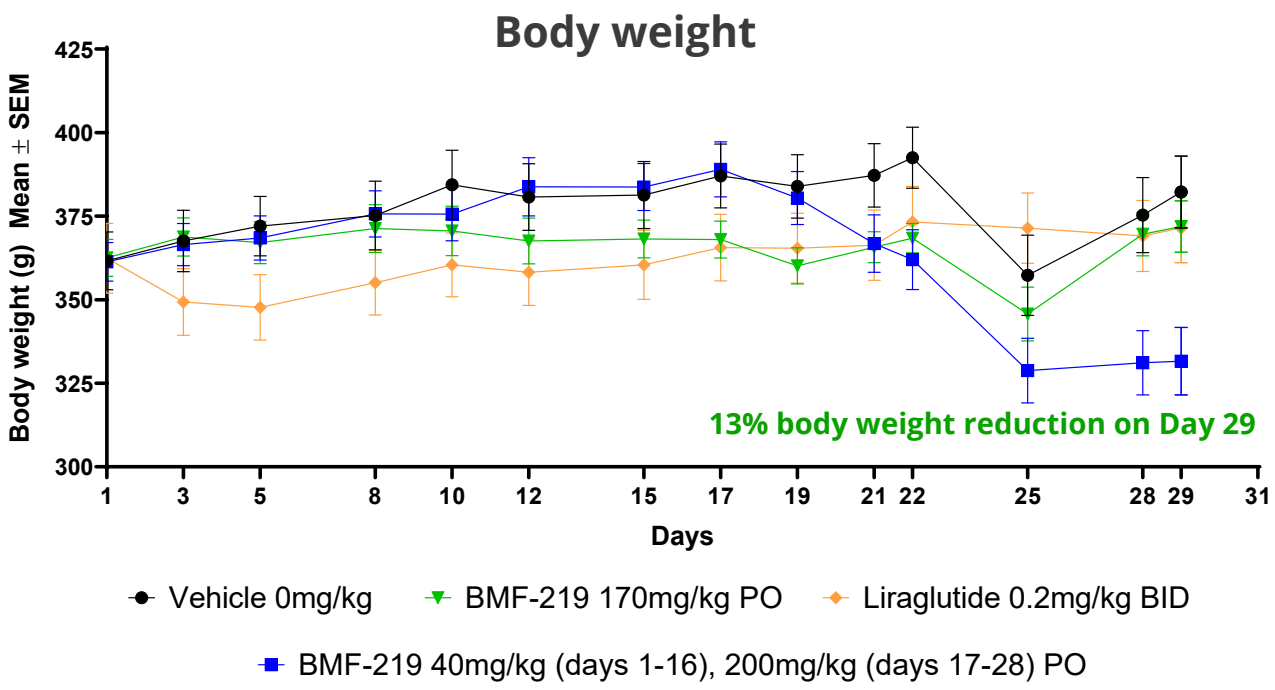


- Vehicle 0mg/kg
- BMF-219 40mg/kg (days 1-16), 200mg/kg (days 17-28) PO
- BMF-219 170mg/kg PO
- Liraglutide 0.2 mg/kg BID

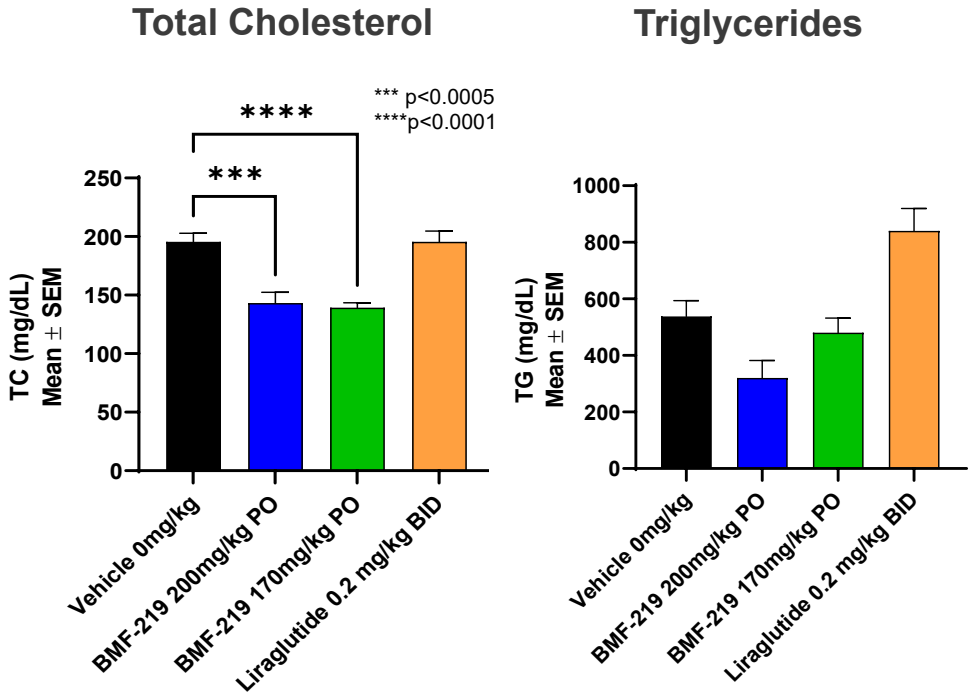
HbA1c reduction in BMF-219 treated groups maintained through washout period

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

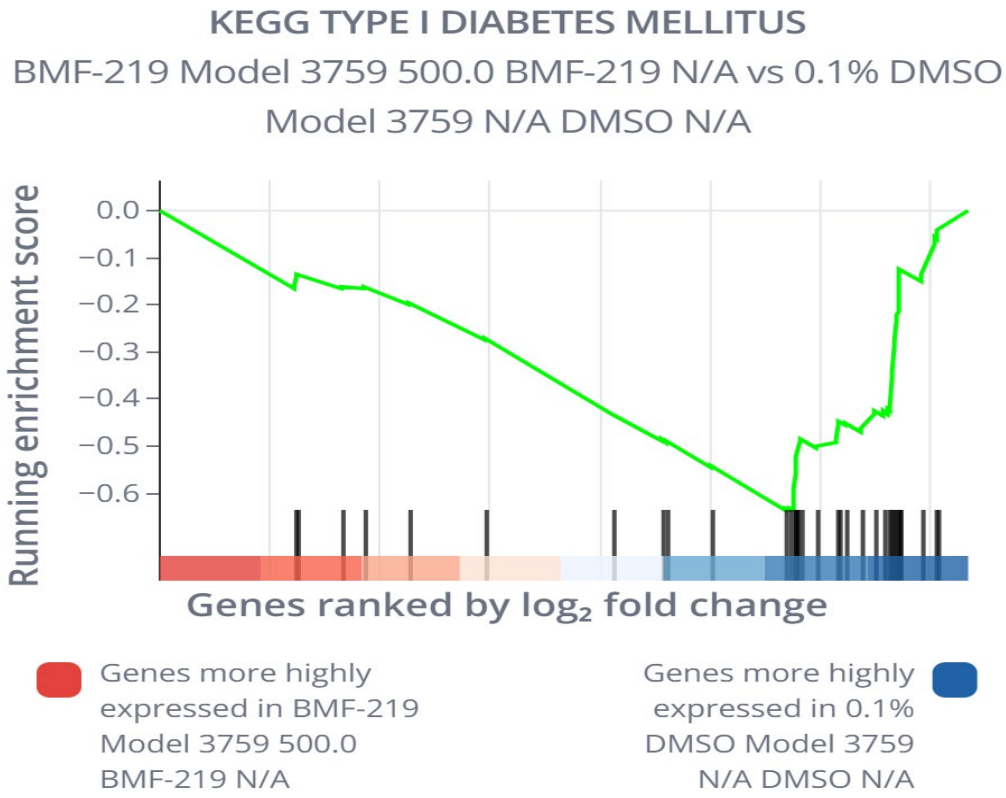


Summary and Conclusions

- **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.

BMF-219 downregulates Type 1 Autoimmune Pathways in CLL patient samples



BMF-219 downregulates notable pathways including autoimmune function pathways such as Type 1 Diabetes Mellitus, with reduction of IL1B

Somanath P., et al. AACR 2023 (#473)

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THANK YOU

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