21st WCIRDC

FRACTYL health

Single-dose GLP-1-based Pancreatic Gene Therapy Maintains Weight Loss After Semaglutide Withdrawal in a Murine Model of Obesity

Alice Liou Fitzpatrick, Suya Wang, Emily Cozzi, Randy Seeley, Timothy Kieffer, Jay Caplan, Harith Rajagopalan

December 8th, 2023

Disclosure Statement

Authors

Harith Rajagopalan, Alice Liou Fitzpatrick, Suya Wang, Emily Cozzi, Timothy Kieffer and Jay Caplan are employees and shareholders of Fractyl Health, Inc. Randy Seeley is a paid consultant for and received research support from Novo Nordisk, Fractyl Health, Congruence, and Eli Lilly; is a paid consultant for CinRx and Crinetics; and received research support from Amgen, Astra Zeneca, and Bullfrog AI.

Pancreatic Gene Therapy (PGTx) is in early development and has not been assessed by any regulatory body for investigational or commercial use.

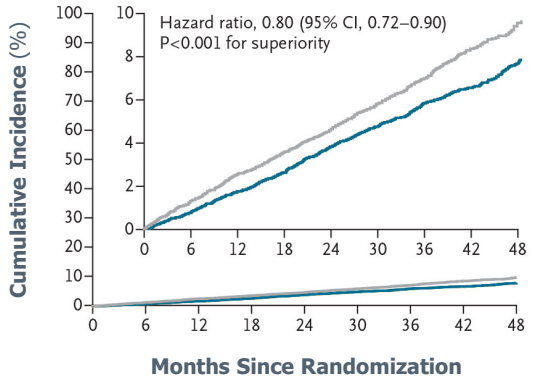
Incretin Therapies: T2D, Obesity, and Beyond

Broad-based benefit on surrogate biomarkers and hard endpoints

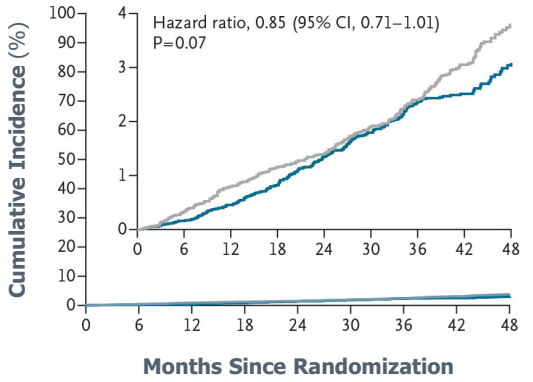
GLP-1RAs can reduce mortality in individuals with obesity and a history of cardiovascular disease

Compounding effect from cumulative exposure in up to 4 years of follow up

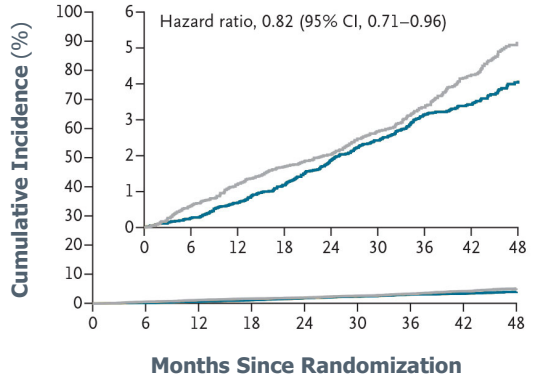
A) Primary Cardiovascular Composite End Point



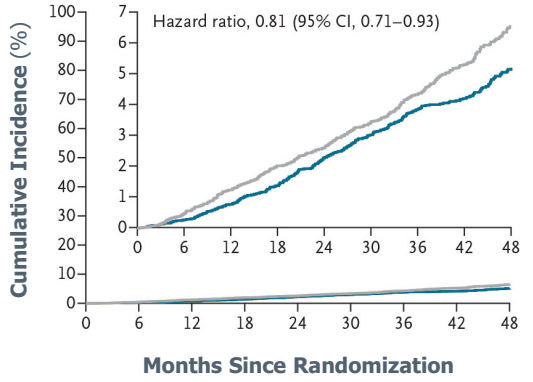
B) Death from Cardiovascular Causes



C) Heart Failure Composite End Point



D) Death from Any Cause



Placebo

Semaglutide

Figures adapted from Lincoff et al. N Engl J Med. 2023 Nov 11. doi: 10.1056/NEJMoa2307563. Online ahead of print. CI=confidence interval, GLP-1RA=glucagon-like peptide 1 receptor agonist

Incretin Therapies: Real-world Discontinuation Rates are High

Majority of patients discontinue therapy within first year

Despite proven clinical efficacy in obesity and T2D,[1,2] **up to 2/3rds of patients discontinue** weekly GLP-1RA therapy within 1 year[3-6]

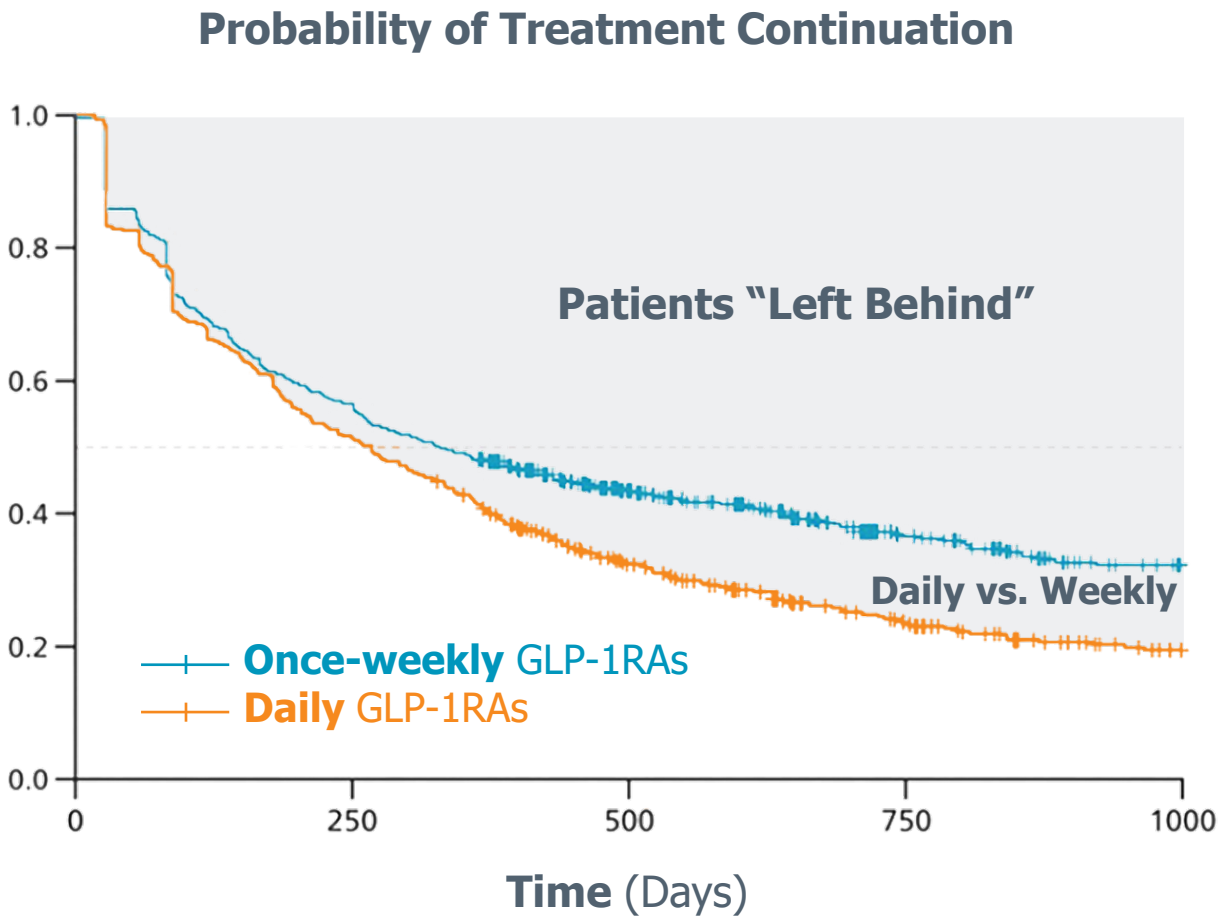


Figure adapted from Polonsky et al. Diabetes Ther. 2022 13:175–1871. 1. Nauck et al. Mol Metab. 2021 46:101102. 2. Campbell and Drucker. Cell Metab. 2013 17:819-837. 3. Polonsky et al. Diabetes Ther. 2022 13:175–1871. 4. Weiss. Patient Prefer Adherence. 2020 14:2337-2345. 5. Polonsky et al. Diabetes Spectr. 2021 34:175-183. 6. Terhune. Reuters. 2023 July 11. GLP-1=glucagon-like peptide 1, GLP-1RA=GLP-1R agonist

Incretin Therapies: Metabolic Rebound Now Well Described

Current GLP-1RAs do not durably alter metabolic setpoint

Discontinuation of therapy leads to **near total loss of metabolic benefit[1]**

GLP-1RA therapies support weight loss and glucose control, **but how do we maintain these effects?**

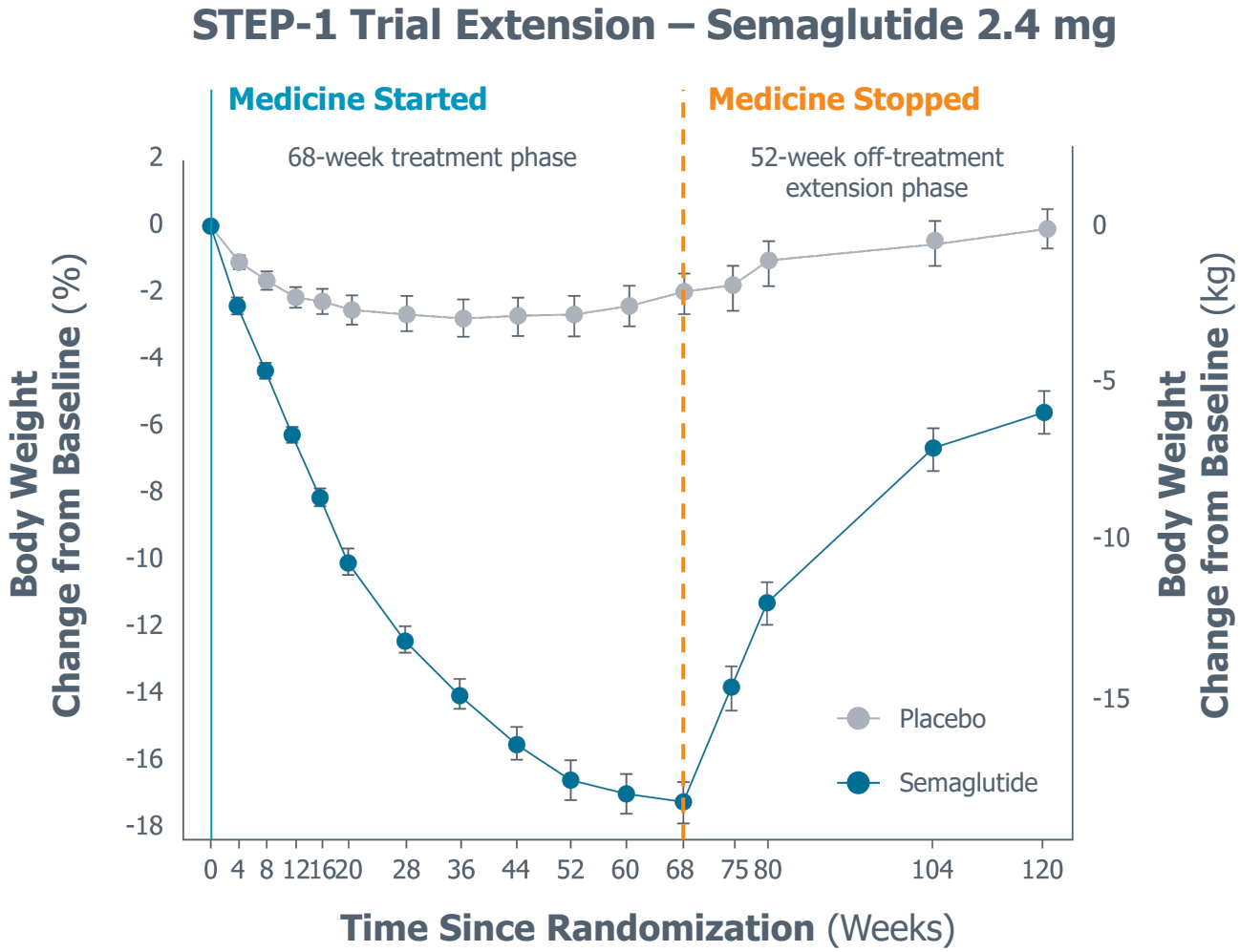


Figure adapted from Wilding et al. Diabetes Obes Metab. 2022 24:1553-1564. 1. Wilding et al. Diabetes Obes Metab. 2022 24:1553-1564. GLP-1RA=glucagon-like peptide 1 receptor agonist

Pancreatic Gene Therapy (PGTx) to Modify Islet Function

Potential for durable improvement in metabolic health

Islet cells terminally differentiated,[1] making adeno-associated virus (AAV) a suitable means of durable genetic modification

β-cell machinery can be leveraged to produce nutrient-stimulated hormones that modify systemic metabolic function[2,3]

GLP-1-based PGTx, driven by the insulin promoter, may offer differentiated benefit via durable local production of GLP-1RA

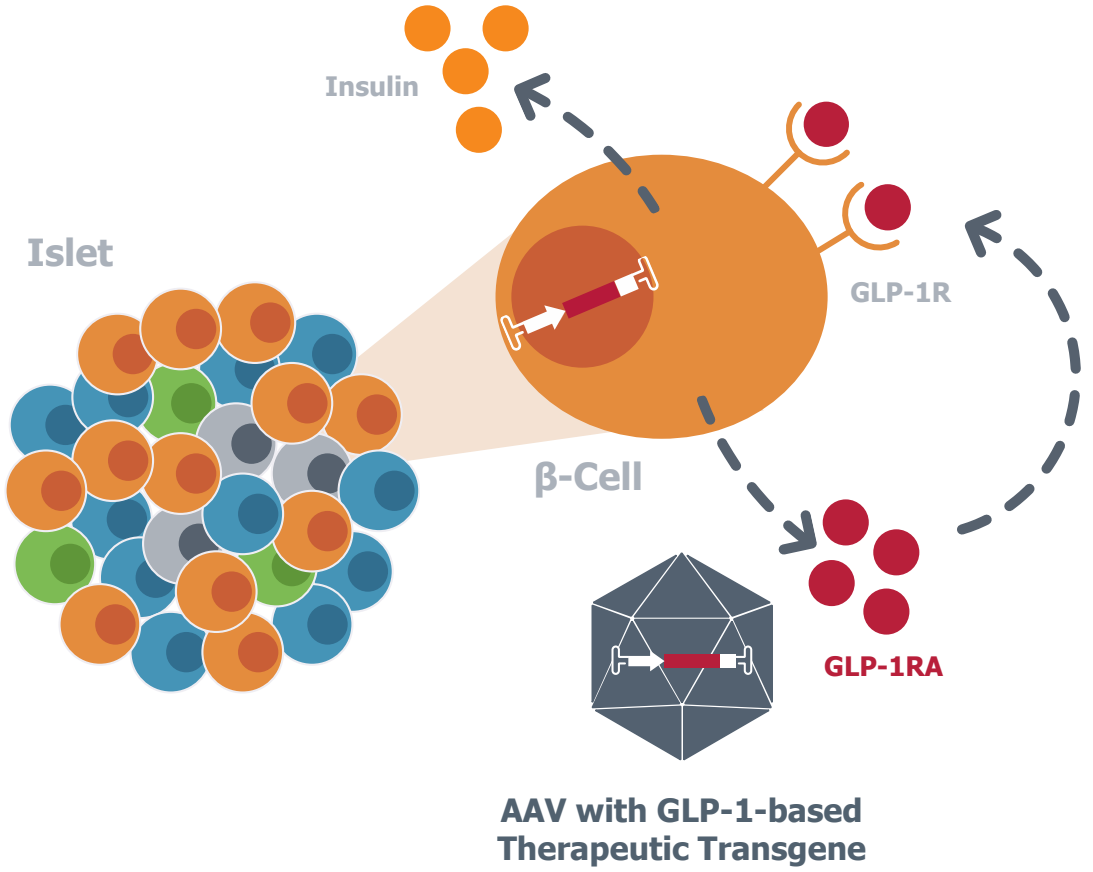
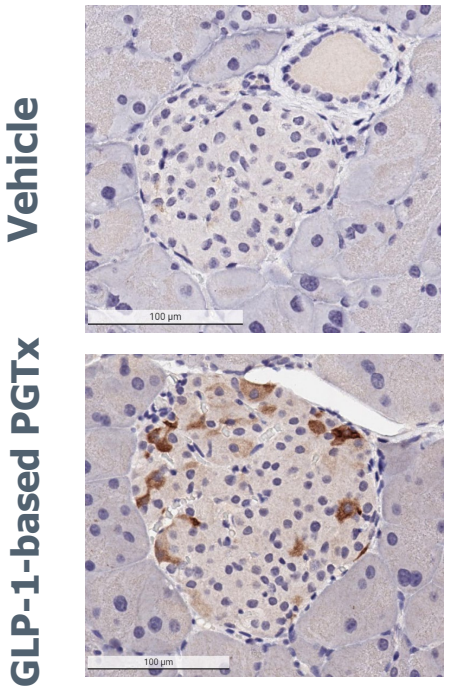


Figure adapted from Saikia et al. JCI Insight. 2021 6:e1418511. 1. Perl et al. J Clin Endocrinol Metab. 2010 95: E234–E239. 2. Lubaczeuski et al. Keystone 2023 oral presentation. Poster no. 1025. 3. Rajagopalan et al. ADA 2023 oral presentation. Abstract no. 181-OR. AAV=adeno-associated virus, GLP-1=glucagon-like peptide 1, GLP-1R=GLP-1 receptor, GLP-1RA=GLP-1R agonist, PGTx=pancreatic gene therapy

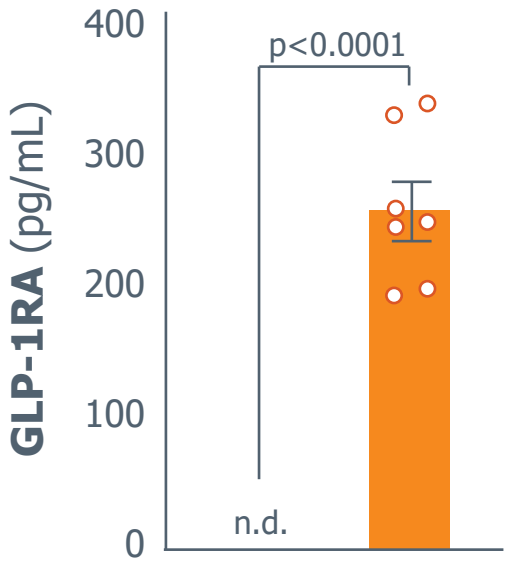
GLP-1-based PGTx Improves Insulin Production and GSIS in Islets

Metabolic improvements in isolated *db/db* islets 10 weeks after PGTx

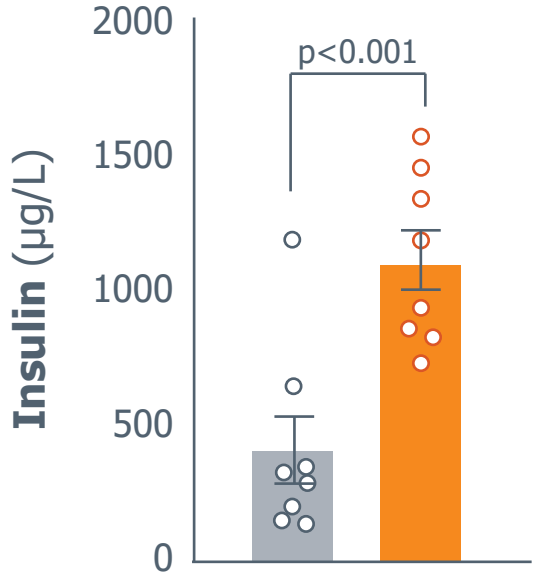
A) Islet Transduction



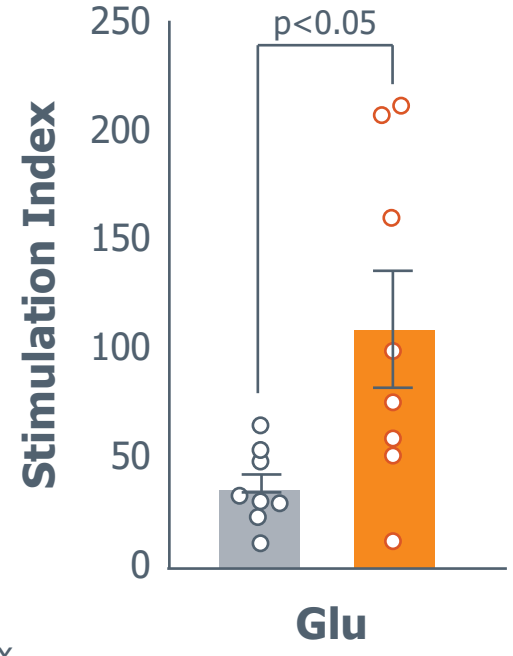
B) GLP-1RA Protein Content



C) Insulin Content



D) Glucose-Stimulated Insulin Secretion (GSIS)



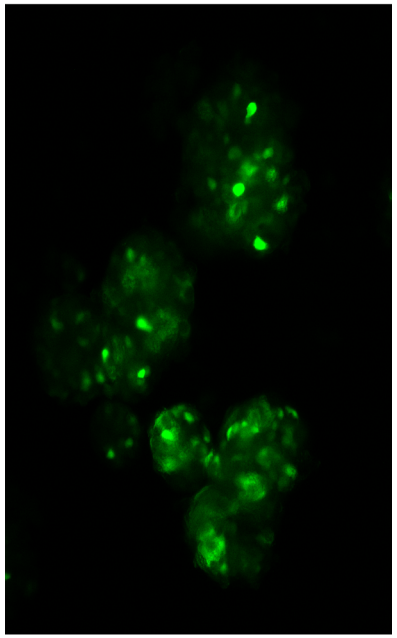
Islet Transduction → **GLP-1RA Expression** → **Insulin Production** → **Glucose Stimulation**

Mean ± SD shown; n=8 per group. D) Glucose stimulation of 16.7 mM +/- IBMX from 2.8 mM baseline. Rajagopalan et al. ADA 2023 oral presentation. Abstract no. 181-OR. GLP-1=glucagon-like peptide 1, GLP-1RA=GLP-1 receptor agonist, Glu=glucose, GSIS=glucose-stimulated insulin secretion, n.d.=not detectable, PGTx=pancreatic gene therapy

GLP-1-based PGTx Improves GSIS in Human Islets and β-cell Line

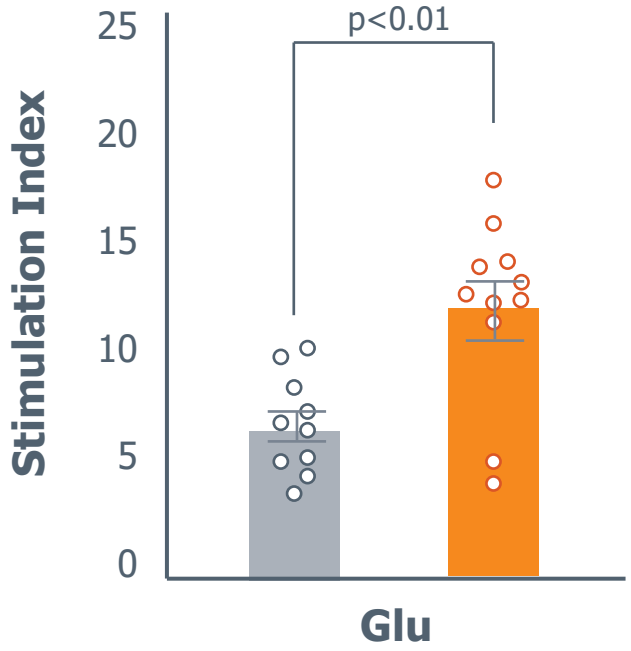
Improved GSIS mediated by GLP-1R activation

A) Human Islet Transduction

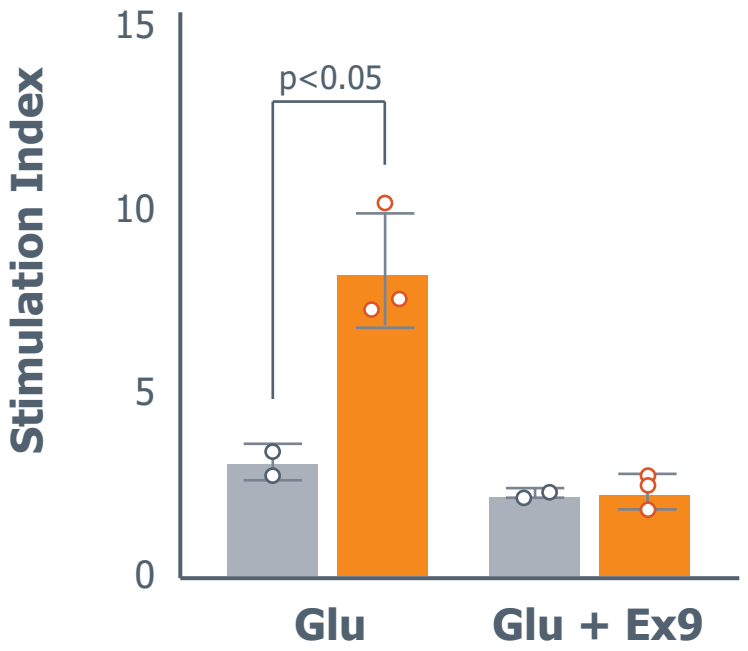


GFP Expression

B) Human Islet GSIS



C) Human β-cell Line GSIS ± Ex9 (GLP-1R Antagonist)

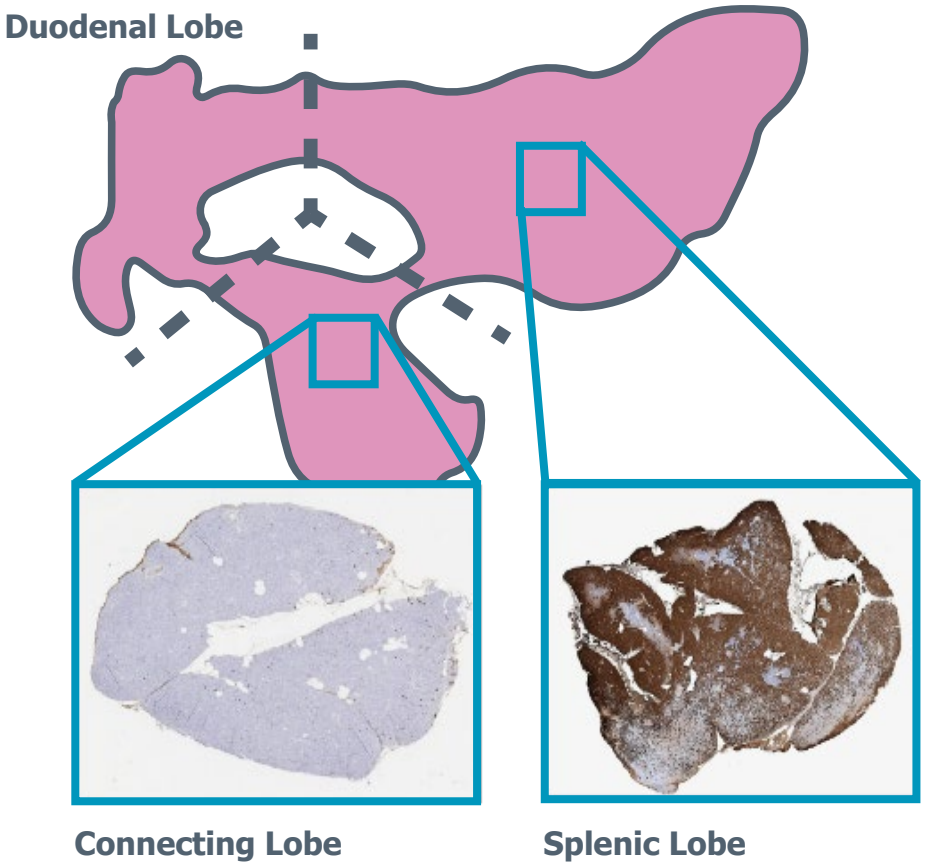


Mean ± SEM shown; n=2-11 per group. B) Glucose stimulation of 16.7 mM from 2.8 mM baseline, C) Glucose stimulation of 11 mM from 0 mM baseline. Rajagopalan et al. ADA 2023 oral presentation. Abstract no. 181-OR. Ex9=Exendin-9, GFP=green fluorescent protein, GLP-1=glucagon-like peptide 1, GLP-1R=GLP-1 receptor, Glu=glucose, GSIS=glucose-stimulated insulin secretion, PGTx=pancreatic gene therapy

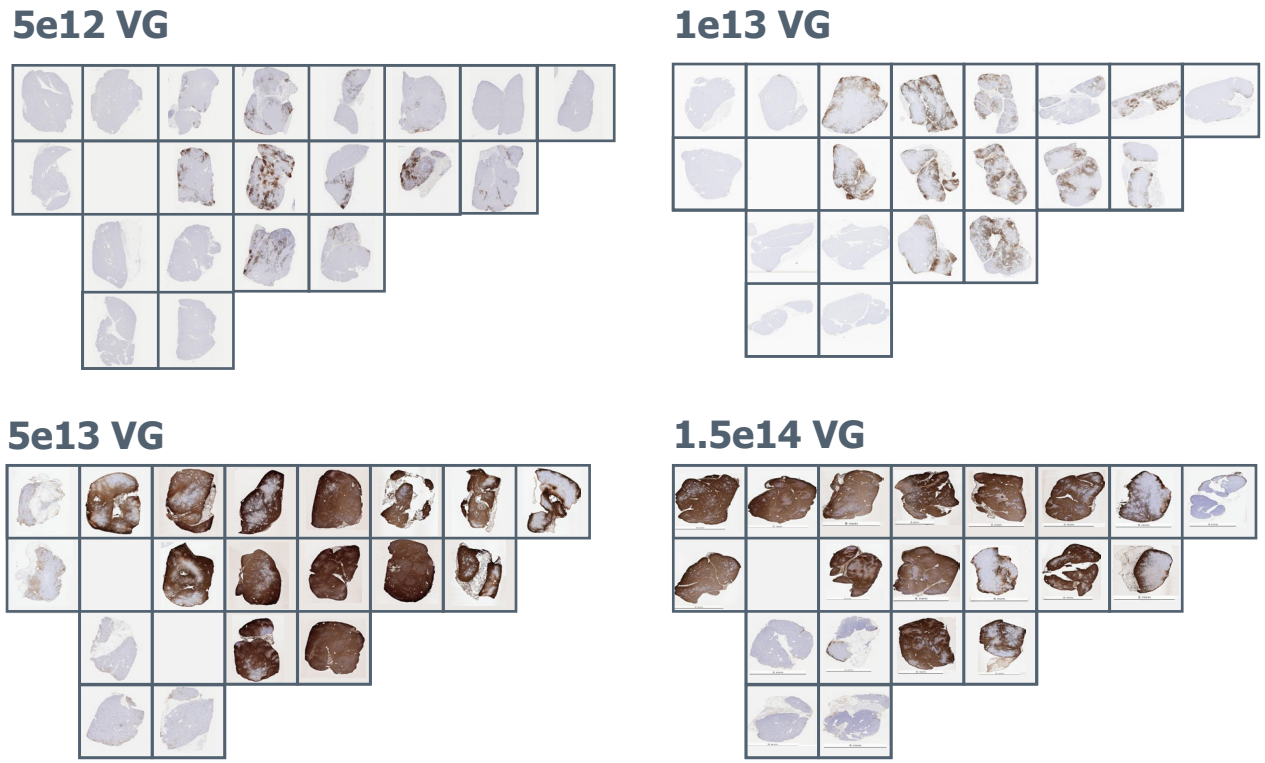
Proprietary Local Endoscopic Delivery System Extensively Tested

Dose-dependent transduction throughout porcine splenic lobe

A) Extensive GFP in Splenic Lobe



B) VG Dose-dependent GFP in Pancreas

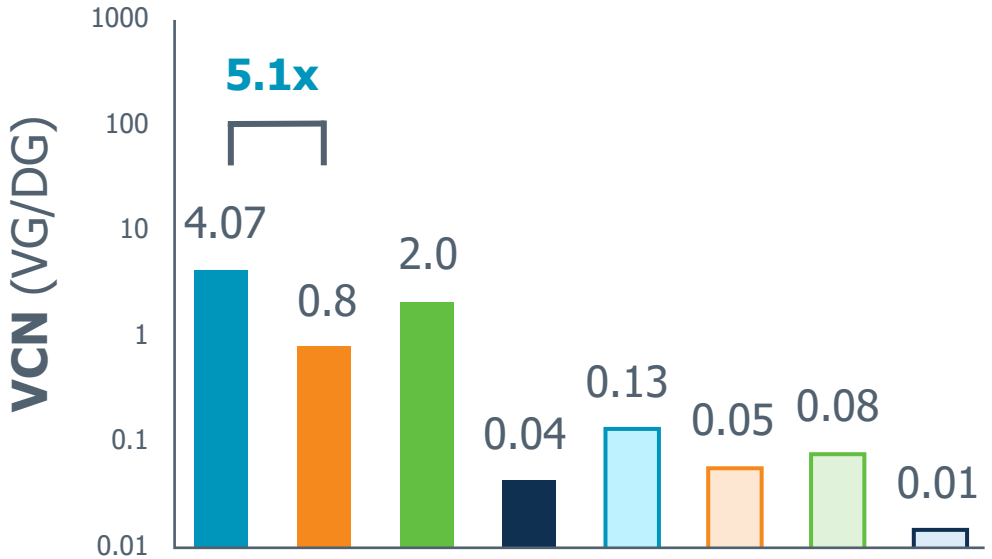


Rajagopalan et al. ASGCT 2023 oral presentation. Abstract no. 191. GFP=green fluorescent protein, VG=vector genomes

Local Endoscopic Delivery Allows High Expression

Dramatically limits systemic exposure to AAV in porcine model

A) Local Delivery (4.2e12 VG/kg)



B) I.V. (8.3e12 VG/kg)[2]

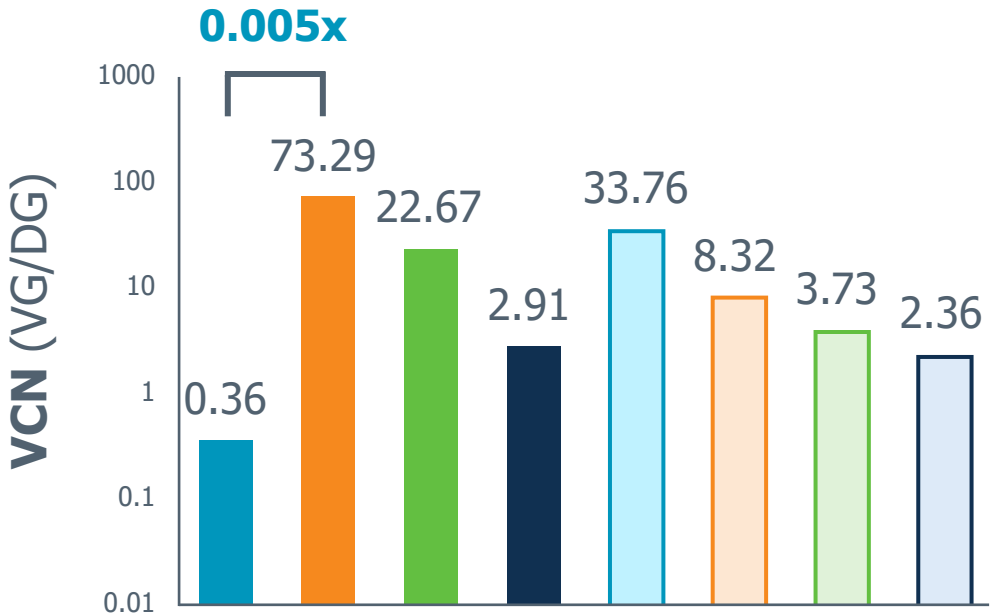
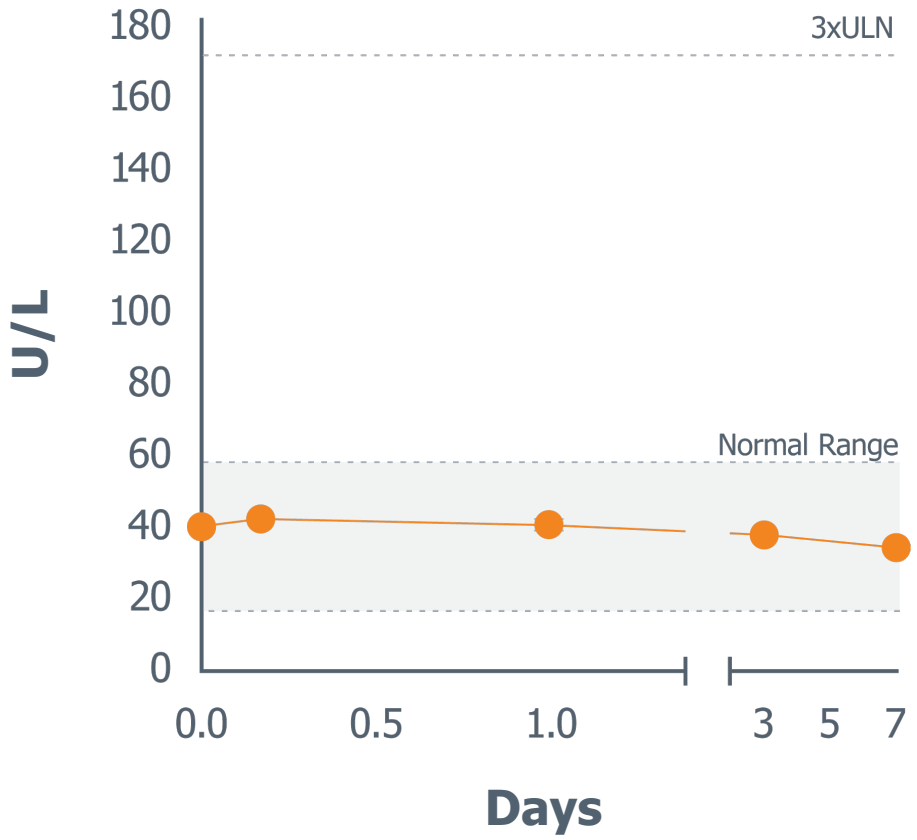


Figure B) adapted from Li et al. Physiol Genomics 54: 261–272, 2022. EUS, N=4; I.V., N=2. 1. Rajagopalan et al. ASGCT 2023 oral presentation. Abstract no. 312. 2. Li et al. Physiol Genomics 54: 261–272, 2022. AAV=adeno-associated virus, VCN=vector copy number, VG=vector genomes, DG=diploid genomes, I.V.=intravenous

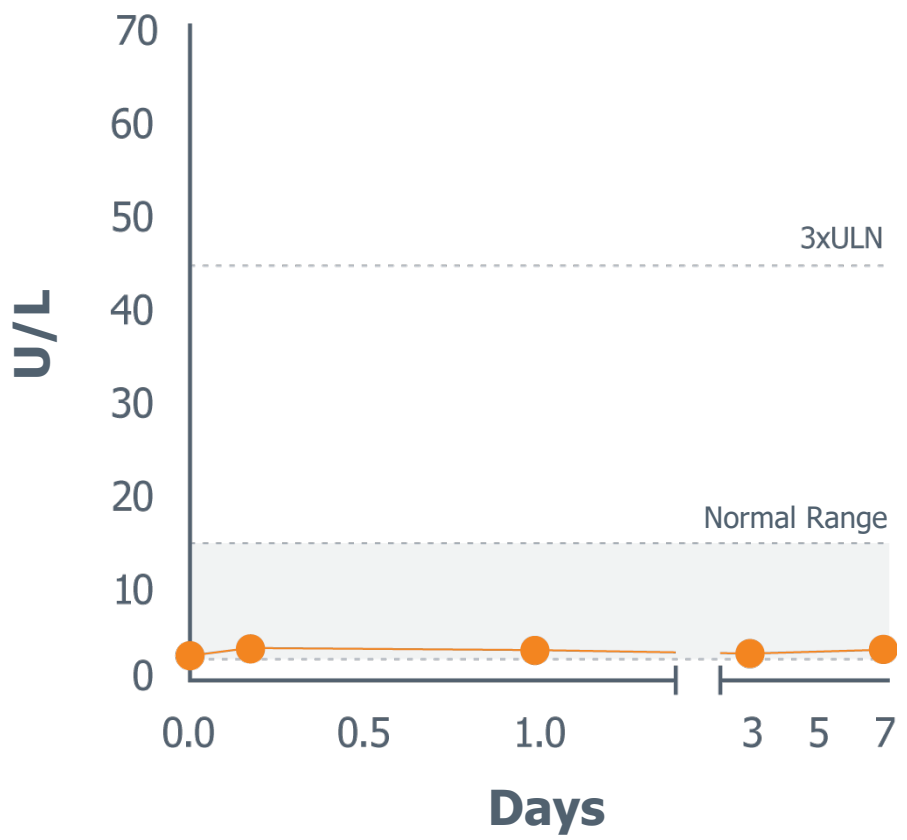
Proof-of-principle Safety with Local Endoscopic Delivery System

ALT and lipase levels remained within normal range across all timepoints

A) 7-day ALT



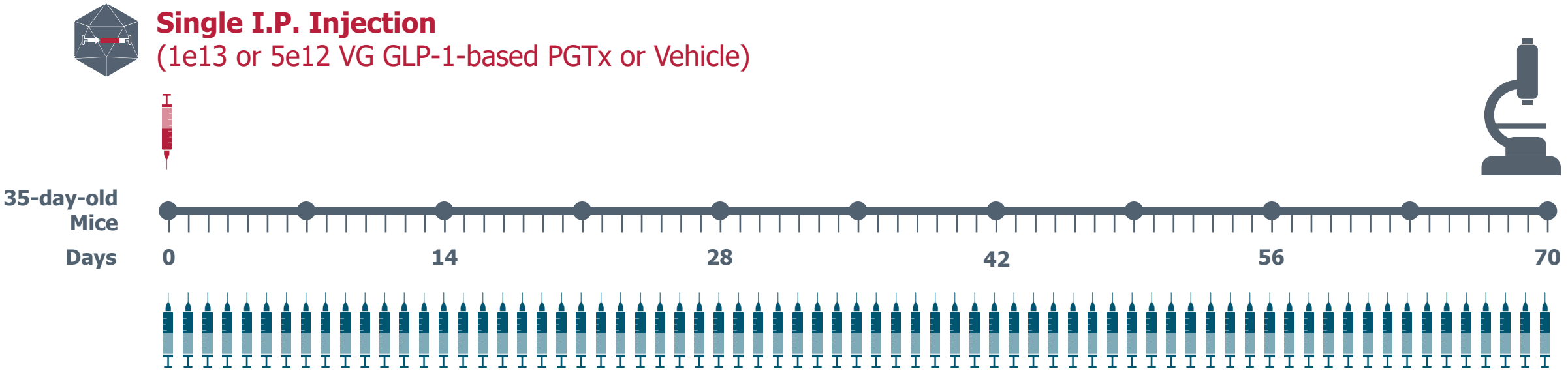
B) 7-day Lipase



Mean ± SEM shown; n=28. 1. Thompson et al. UEGW 2023 poster presentation. Abstract no. AS-UEG-2023-02238. ALT=alanine transaminase, ULN=upper limit of normal

GLP-1-based PGTx T2D Efficacy Study: Head-to-head vs. Semaglutide

db/db murine model is *de facto* standard for T2D development



Daily S.C. Injections
Semaglutide (10 nmol/kg/d)
or Vehicle

Efficacy/MOA (Day 0-70)
Weekly Fasting Blood Glucose
Biweekly Insulin
Weight

Sacrifice (Days 58-70)
Organ Histology
Pancreatic GLP-1RA Protein
Serum GLP-1RA Protein

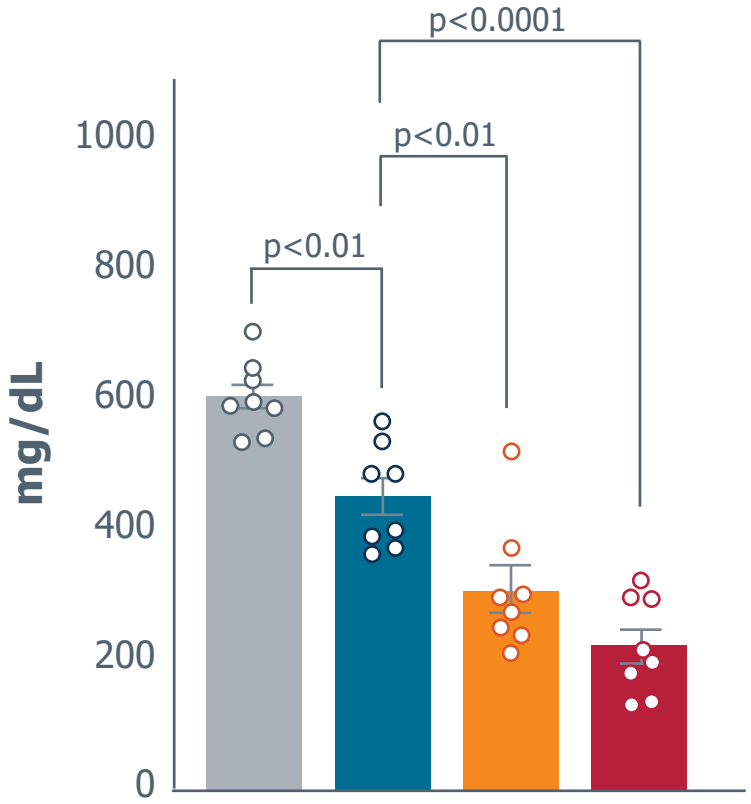
GLP-1=glucagon-like peptide 1, GLP-1RA= GLP-1 receptor agonist, I.P.=intraperitoneal, MOA=mechanism of action, PGTx=pancreatic gene therapy, S.C.=subcutaneous, VG=vector genomes

Glucose-lowering Efficacy in *db/db* Murine Model

GLP-1-based PGTx improves fasting glucose vs. daily semaglutide

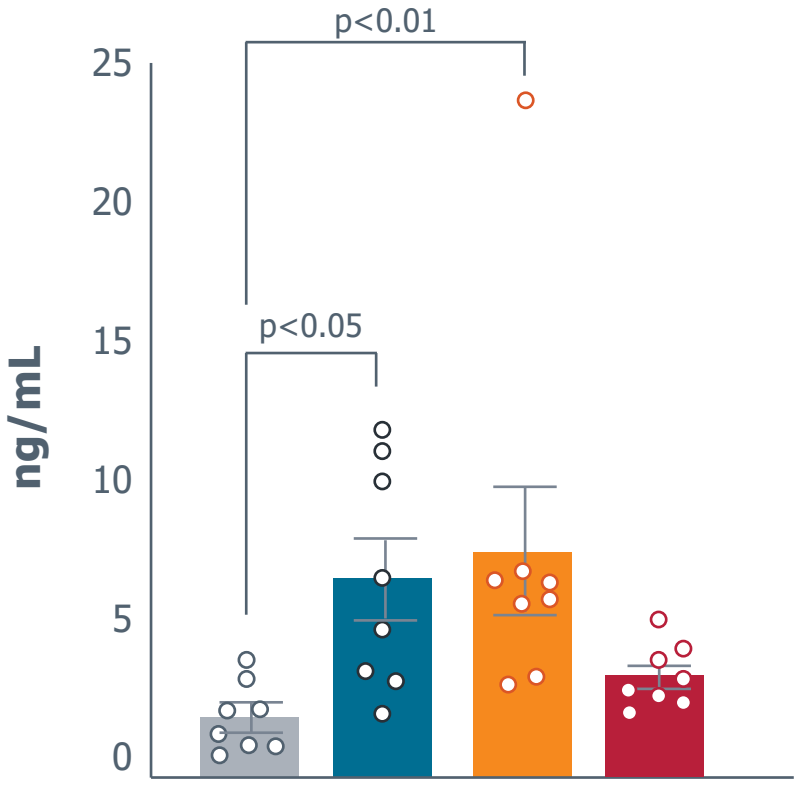
A) Fasting Blood Glucose

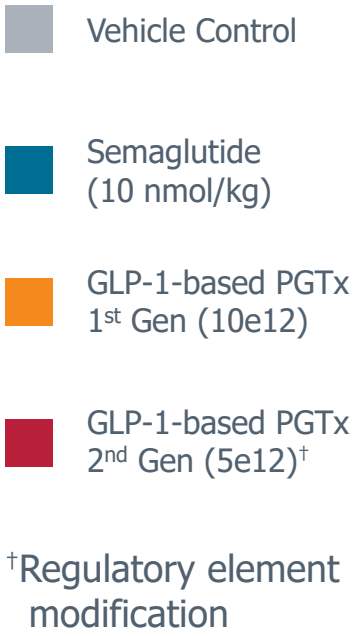
(Week 8, 4-6 Hours Fasted)



B) Fasting Insulin

(Week 8, 4-6 Hours Fasted)





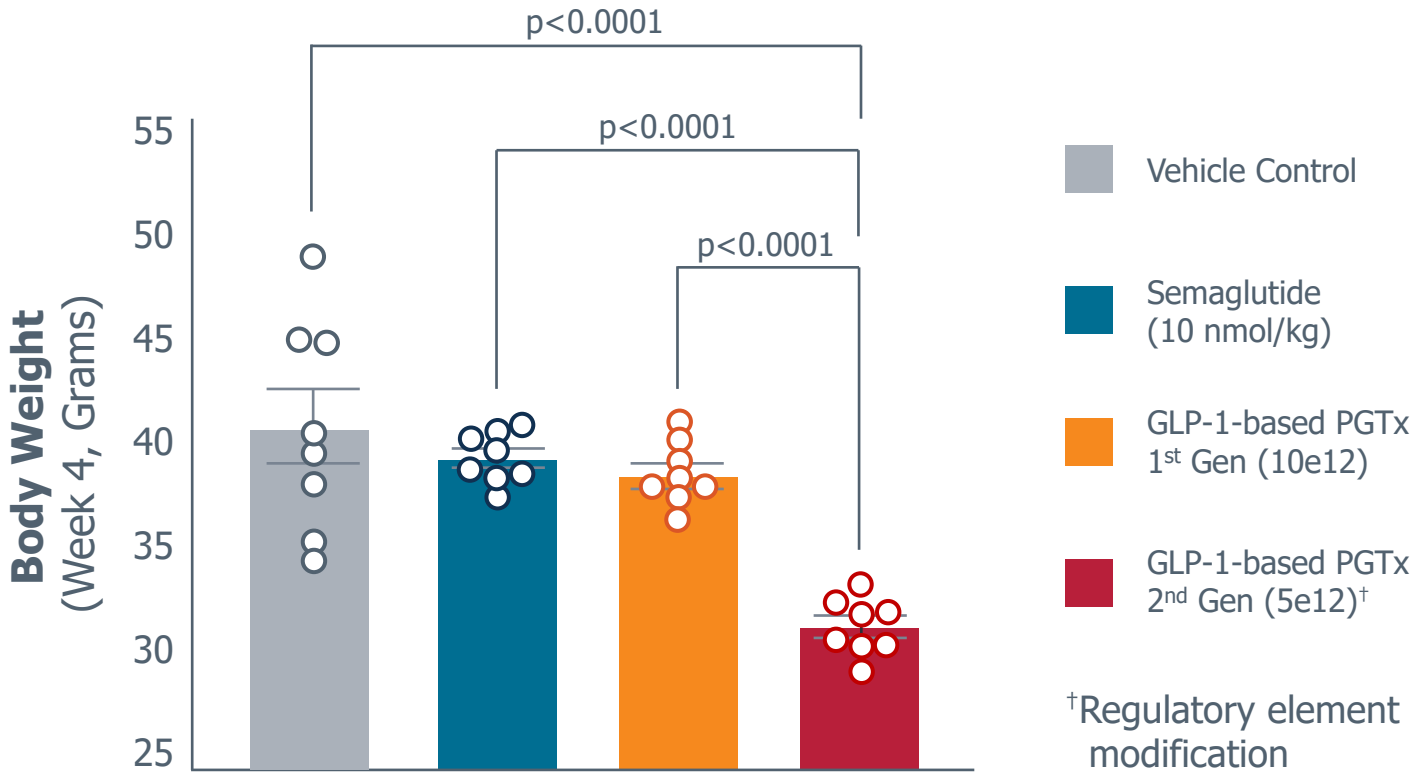
Mean ± SEM shown; n=8 per group. Rajagopalan et al. ADA 2023 oral presentation. Abstract no. 181-OR. Gen=generation, GLP-1=glucagon-like peptide 1, PGTx=pancreatic gene therapy

Body Weight Change in *db/db* Murine Model

GLP-1-based PGTx prevents weight gain vs. daily semaglutide

23% lower total body weight with PGTx compared to vehicle

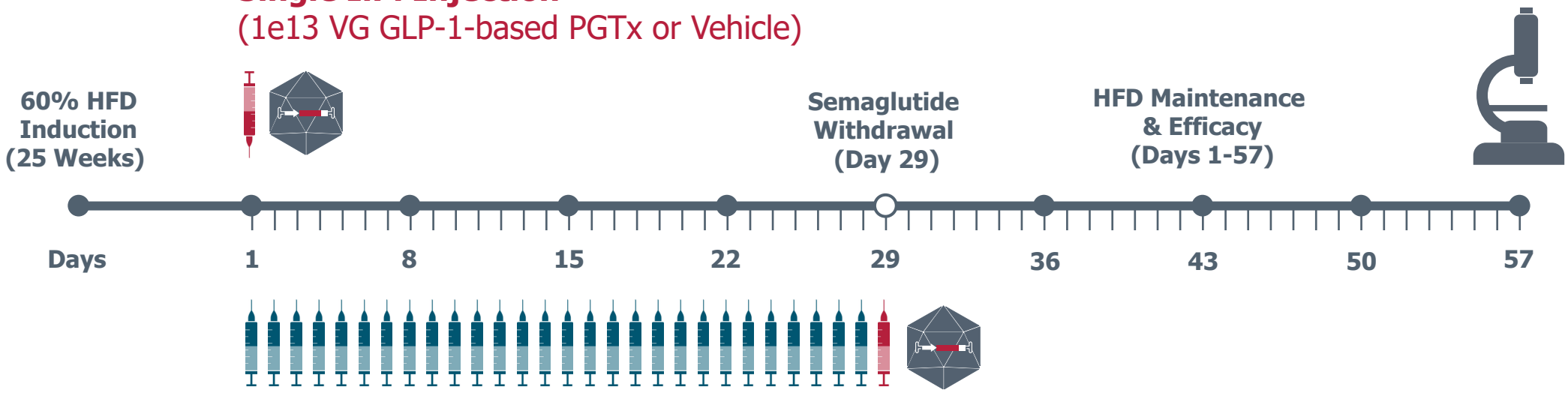
20% lower total body weight with PGTx compared to semaglutide



Mean ± SEM shown; n=8 per group. Rajagopalan et al. ADA 2023 oral presentation. Abstract no. 181-OR. AAV=adeno-associated virus, Gen=generation, GLP-1= glucagon-like peptide 1, PGTx=pancreatic gene therapy

GLP-1-based PGTx T2D Efficacy Study: Head-to-head vs. Semaglutide

DIO murine model is *de facto* standard for obesity development

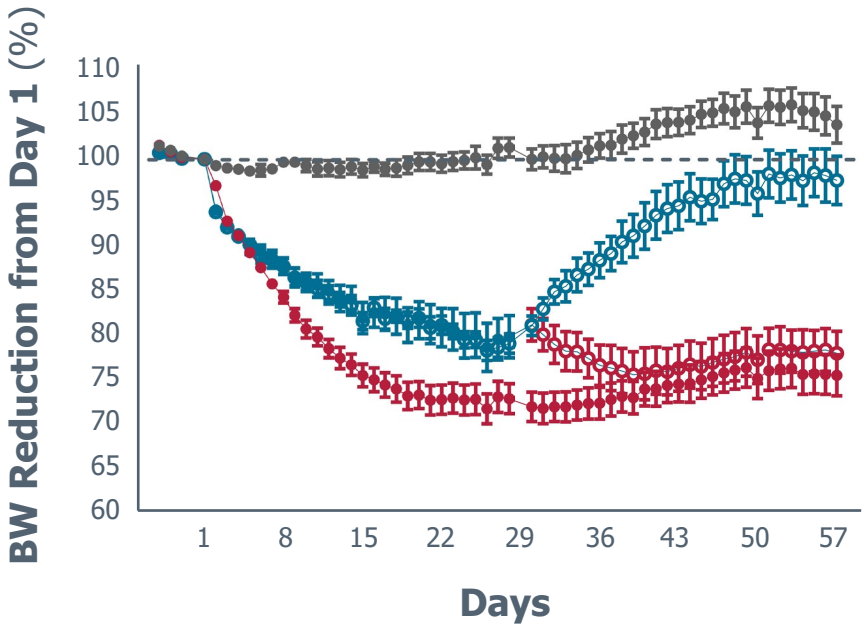


GLP-1=glucagon-like peptide 1, HFD=high fat diet, I.P.=intraperitoneal, PGTx=pancreatic gene therapy, S.C.=subcutaneous, VG=vector genomes

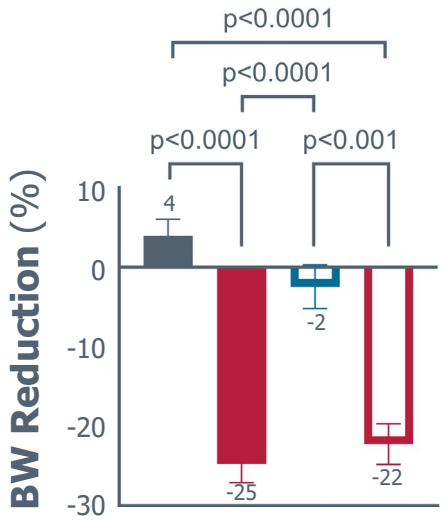
Body Weight and Food Intake Change in DIO Murine Model

Single-dose GLP-1-based PGTx sustains weight loss after semaglutide withdrawal

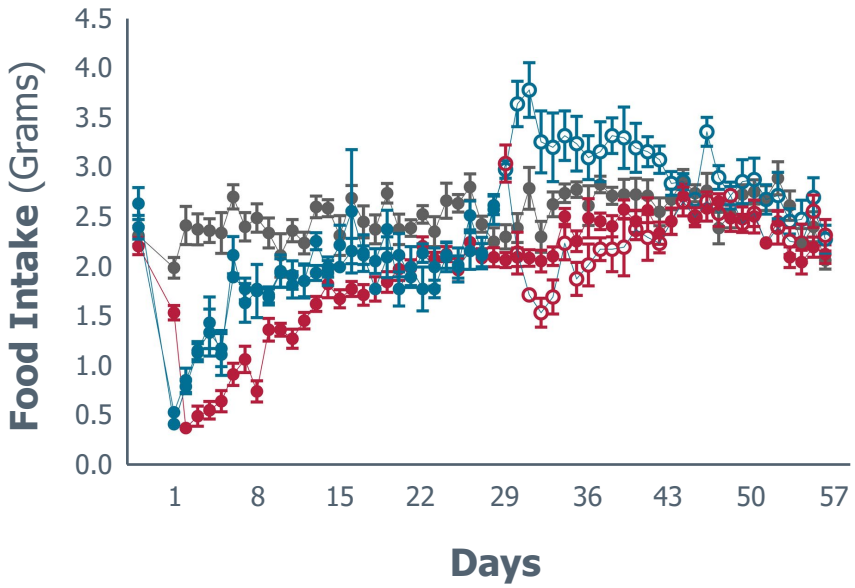
A) Change in BW Over Time



B) End of Study BW Change



C) Food Intake Over Time



GLP-1-based PGTx (1e13 VG)

Sema Withdrawal + Vehicle

Vehicle Control

Sema (10 nmol/kg/d)

Sema Withdrawal + GLP-1-based PGTx (5e12 VG)

Mean ± SEM shown; n=8-10 per group. BW=body weight, DIO=diet-induced obesity, GLP-1=glucagon-like peptide 1, PGTx=pancreatic gene therapy, VG=vector genomes

GLP-1-based PGTx Safety and Feasibility Studies in Model Systems

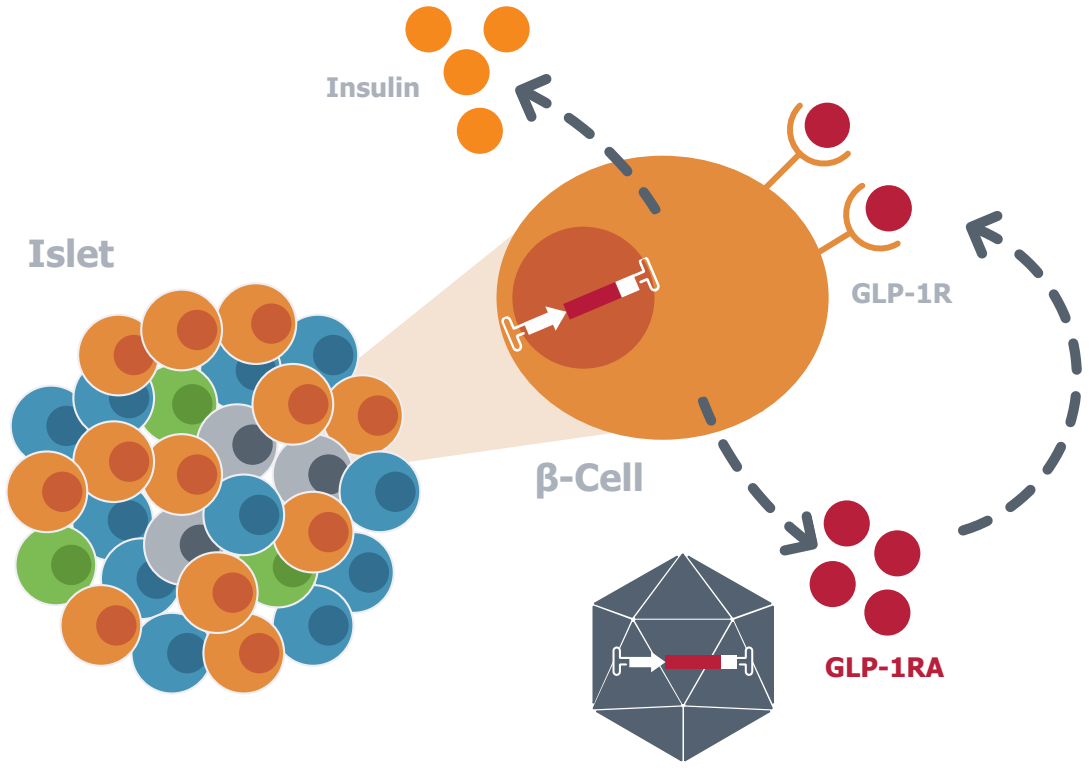
Conclusions to date

Early safety and feasibility observations in *db/db* and DIO mice and Yucatan pigs are encouraging

Compared to chronic semaglutide, single-dose PGTx **improves fasting glucose and prevents weight gain in *db/db* model of T2D**

Single-dose PGTx can lead to **durable weight loss and maintenance of weight loss** after semaglutide withdrawal in DIO mice

PGTx lead optimization demonstrates **potential for superior potency in T2D and obesity with low pancreatic dose**



AAV=adeno-associated virus, DIO=diet-induced obesity, GLP-1=glucagon-like peptide 1, GLP-1R=GLP-1 receptor, GLP-1RA=GLP-1R agonist, PGTx=pancreatic gene therapy

Thank You
Acknowledgements

Shimyn Slomovic, PhD
Sr. Director, Head of R&D

Design and *in vitro* screening

Lin Quek, PhD
Assoc. Director

Gary White, MS
Sr. Scientist

Suya Wang, PhD
Scientist II

Keiko Ishida, BS
Sr. Assoc. Scientist

ex vivo and animal studies

Alice Fitzpatrick, DVM, PhD
Assoc. Director

Rebecca Reese, Assoc.
Scientist I

Camila Lubaczeuski, PhD
Scientist I

Nicole Picard, BS
Assoc. Scientist

Device Engineering

Mike Biasella, BS
Sr. Engineer Manager

Jake Wainer, BS
Sr. Biomedical Engineer

Tech Ops and Research Ops

Eric Horowitz, PhD
Exec. Director

Bill Monahan, BS
Assoc. Director

FRACTYL® health

ERASE Task Force and Advisors

Randy Seeley, PhD
Michigan School of Medicine

Alan Cherrington, PhD
Vanderbilt University School of Medicine

Dave D'Alessio, MD
Duke University School of Medicine

Geltrude Mingrone, MD, PhD
Kings College London and Gemelli Hospital Rome

Jon Campbell, PhD
Duke University School of Medicine