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

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DDW2024
Digestive Disease Week®
MAY 18–21, 2024 | WASHINGTON, D.C.
EXHIBIT DATES: MAY 19–21, 2024
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Disclosure Statement

We disclose the following financial relationship(s) with a commercial interest:

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: Type 2 Diabetes, Obesity, and Beyond

Emerging benefit in MASLD and MASH

Clinical studies suggest that GLP-1RAs can **improve steatohepatitis, liver function, and fibrosis biomarkers**[1]

GLP-1RAs can **resolve MASH without worsening fibrosis** in individuals with biopsy-proven MASH and fibrosis[2]

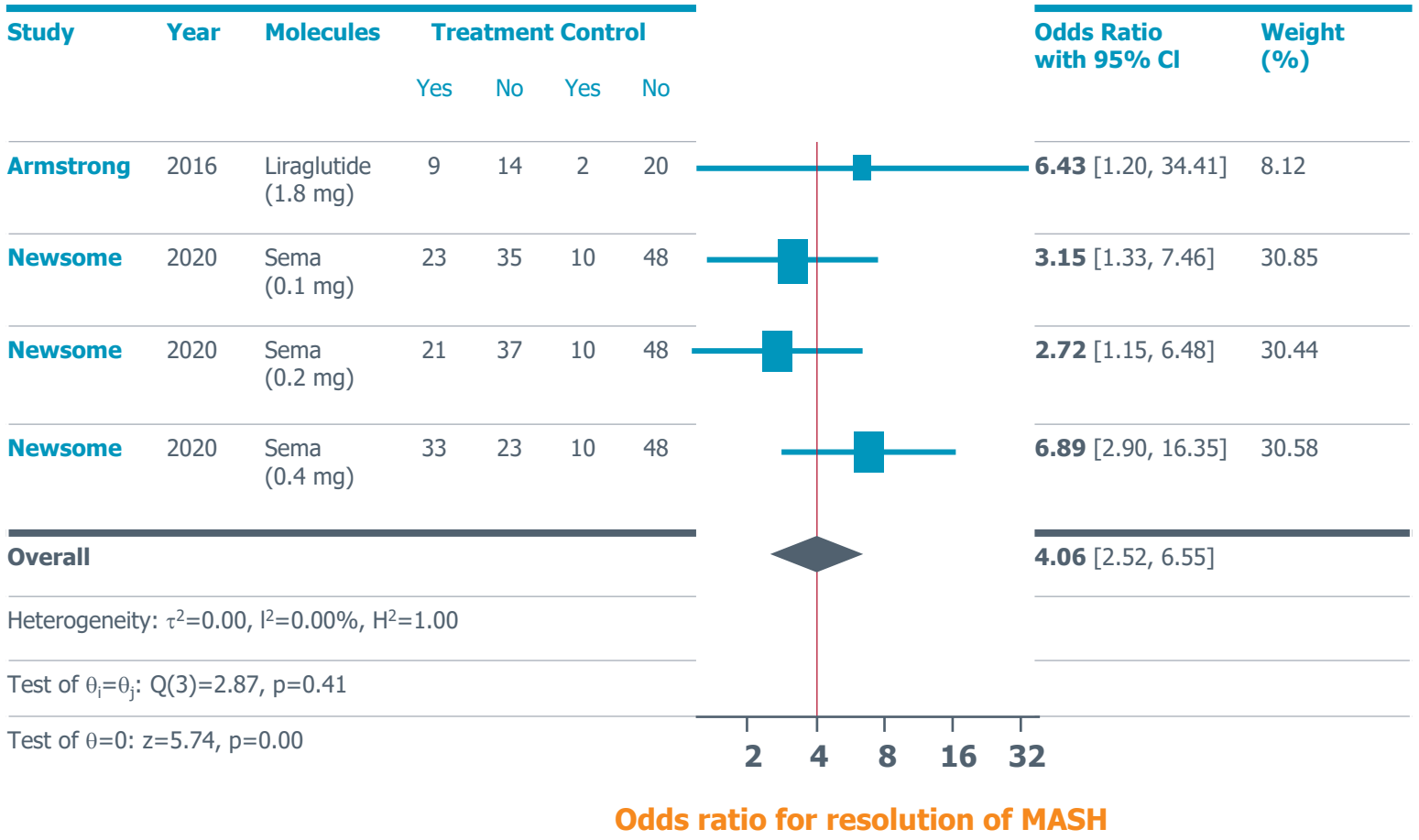


Figure adapted from Mantovani et al. Metabolites 2021 11:73. 1. Abdelmalek et al. Diabetes Obes Metab. 2024 26:2001-2016. 2. Mantovani et al. Metabolites 2021 11:73. CI=confidence interval, GLP-1RA=glucagon-like peptide 1 receptor agonist, MASH=metabolic dysfunction-associated steatohepatitis, MASLD=metabolic dysfunction-associated steatotic liver disease

Incretin Therapies: Real-world Discontinuation Rates are High

Majority of patients discontinue therapy within first year

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

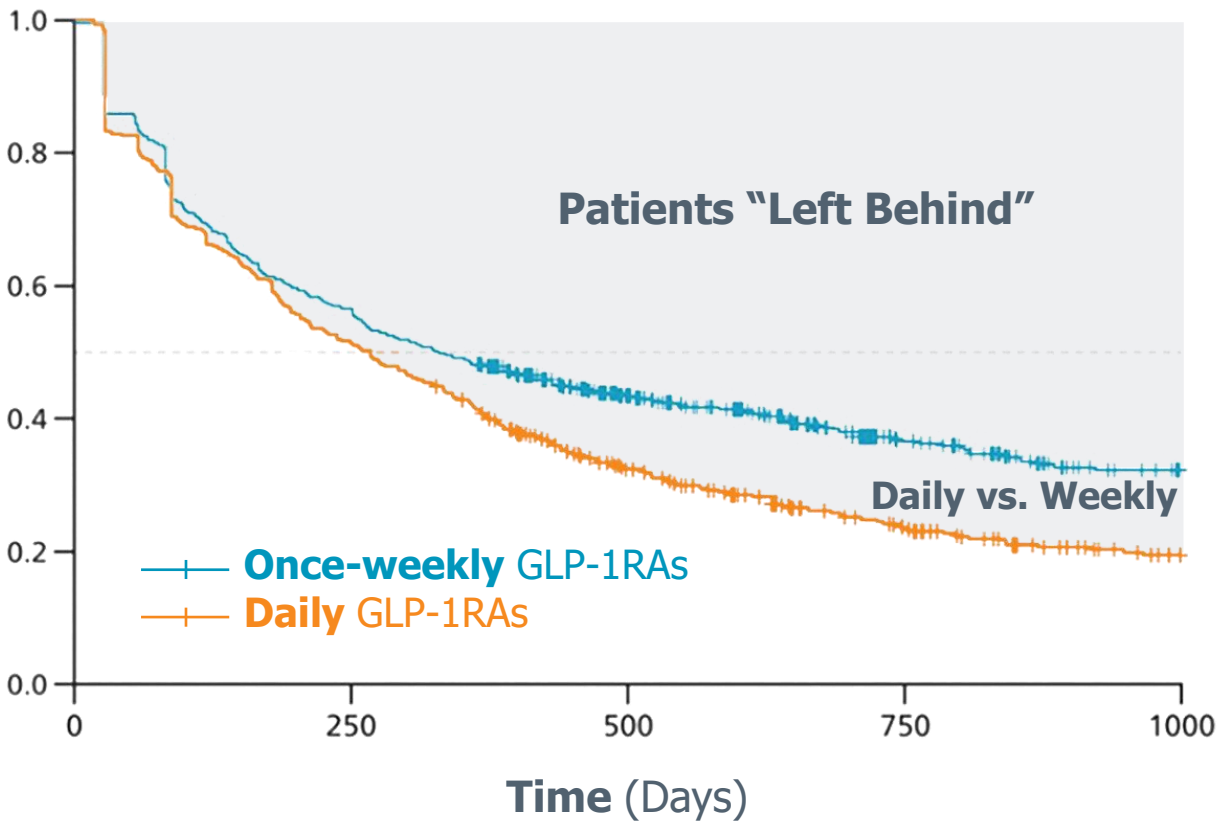


Figure adapted from Polonsky et al. Diabetes Ther. 2022 13:175–1871. 1. Nauck et al. Mol Metab. 2021 46:101102. 2. Campbell and Drucker. Cell Metab. 2013 17:819-837. 3. Polonsky et al. Diabetes Ther. 2022 13:175–1871. 4. Weiss et al. Patient Prefer Adherence. 2020 14:2337-2345. 5. Polonsky et al. Diabetes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

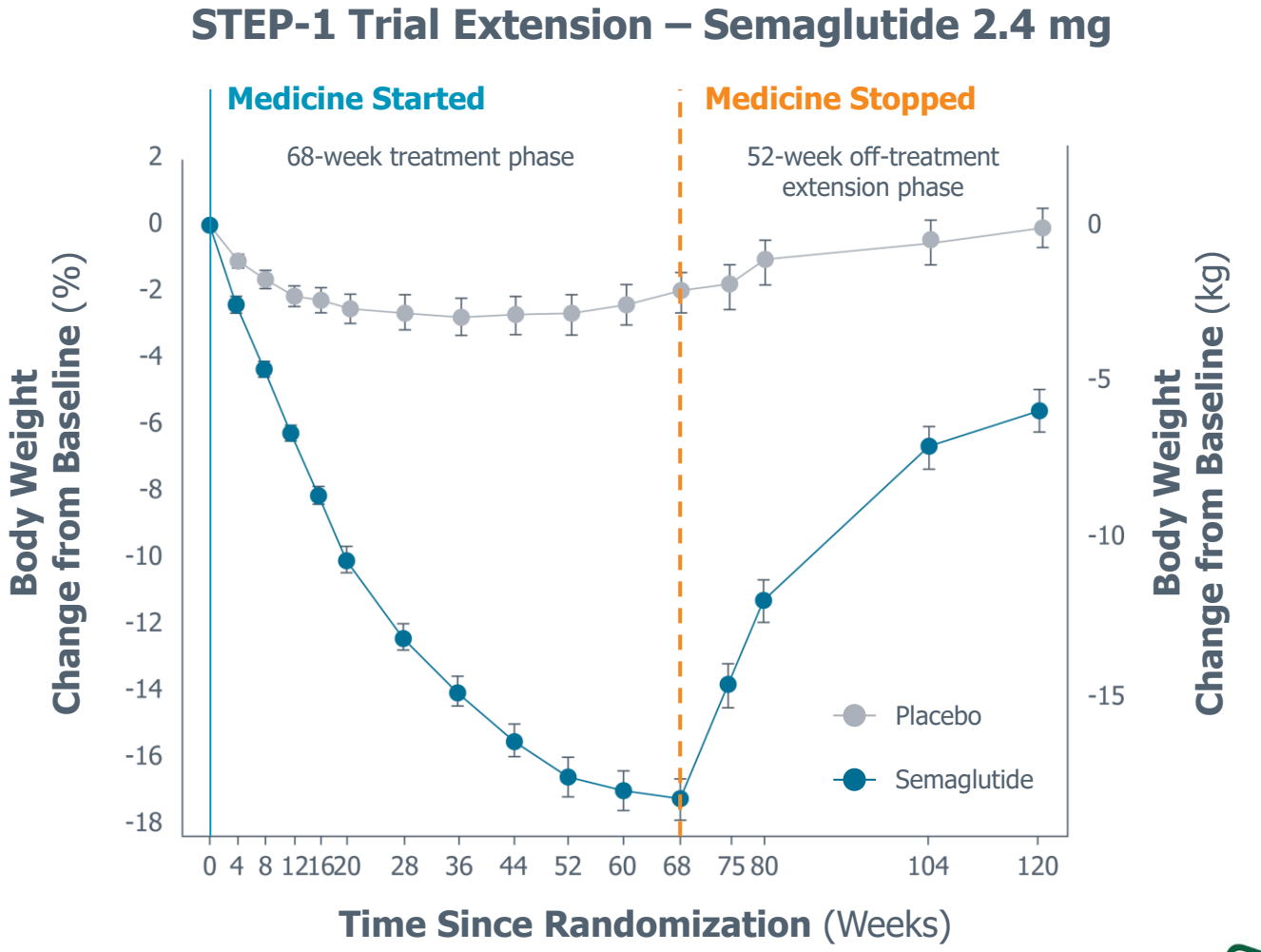


Figure adapted from Wilding et al. Diabetes Obes Metab. 2022 24:1553-1564. 1. Wilding et al. Diabetes Obes Metab. 2022 24:1553-1564.
GLP-1RA=glucagon-like peptide 1 receptor agonist

Pancreatic Gene Therapy (PGTx) to Modify Islet Function

Potential for durable improvement in metabolic health

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

Pancreas is readily accessible via endoscopic ultrasound, and local delivery enables PGTx feasibility and safety

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

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

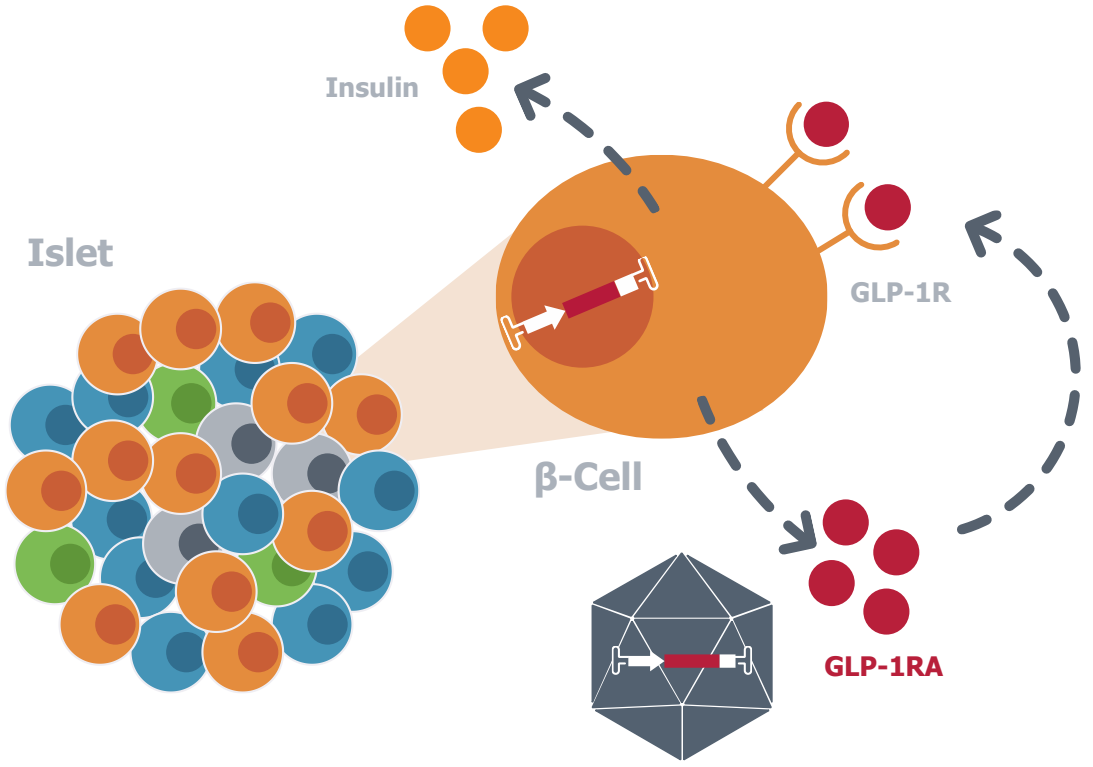


Figure adapted from Saikia et al. JCI Insight. 2021 6:e1418511. 1. Perl et al. J Clin Endocrinol Metab. 2010 95: E234–E239. 2. Lubaczeuski et al. Keystone 2023 oral presentation. Poster no. 1025. 3. Rajagopalan et al. ADA 2023 oral presentation. Abstract no. 181-OR. AAV=adeno-associated virus, GLP-1R=glucagon-like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

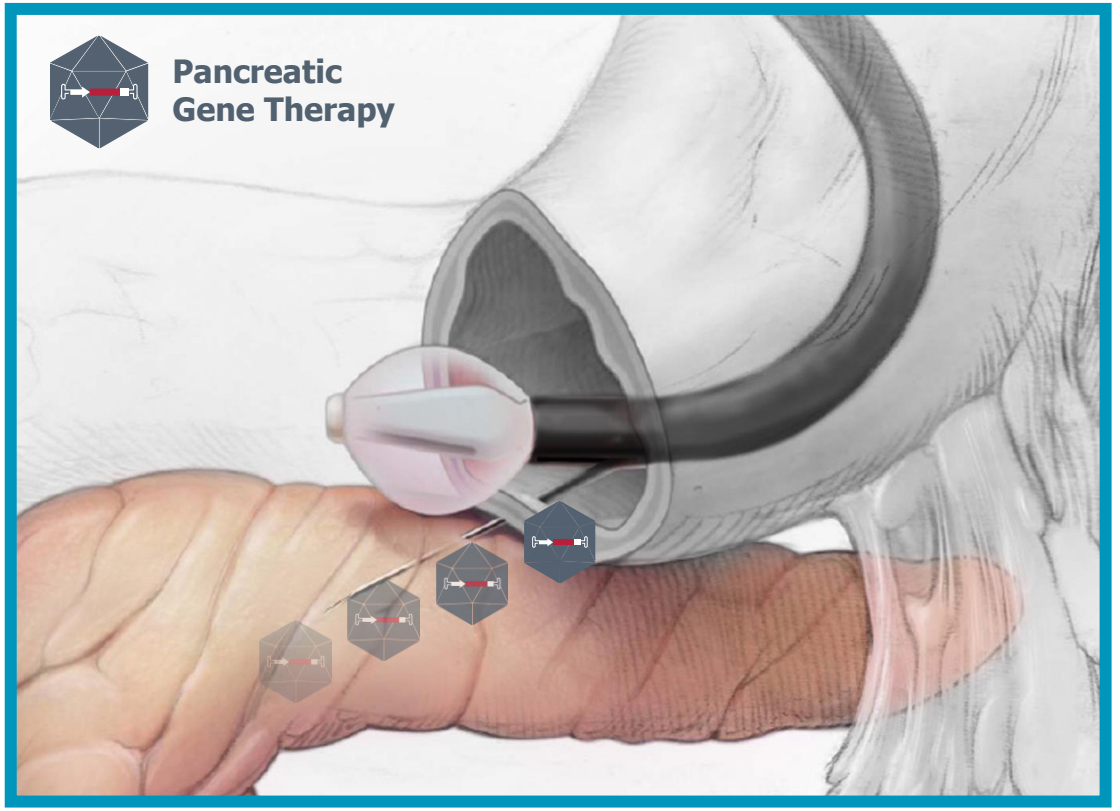
Gene Therapy Route of Administration to Pancreas

Islets are most easily accessed via endoscopic ultrasound

Islets are predominantly in body and tail of pancreas, most easily accessible via endoscopic ultrasound (EUS)[1,2]

Upper EUS is routine and straightforward (~300K patients per year in US[3])

Procedural risk can be mitigated with device and procedure steps



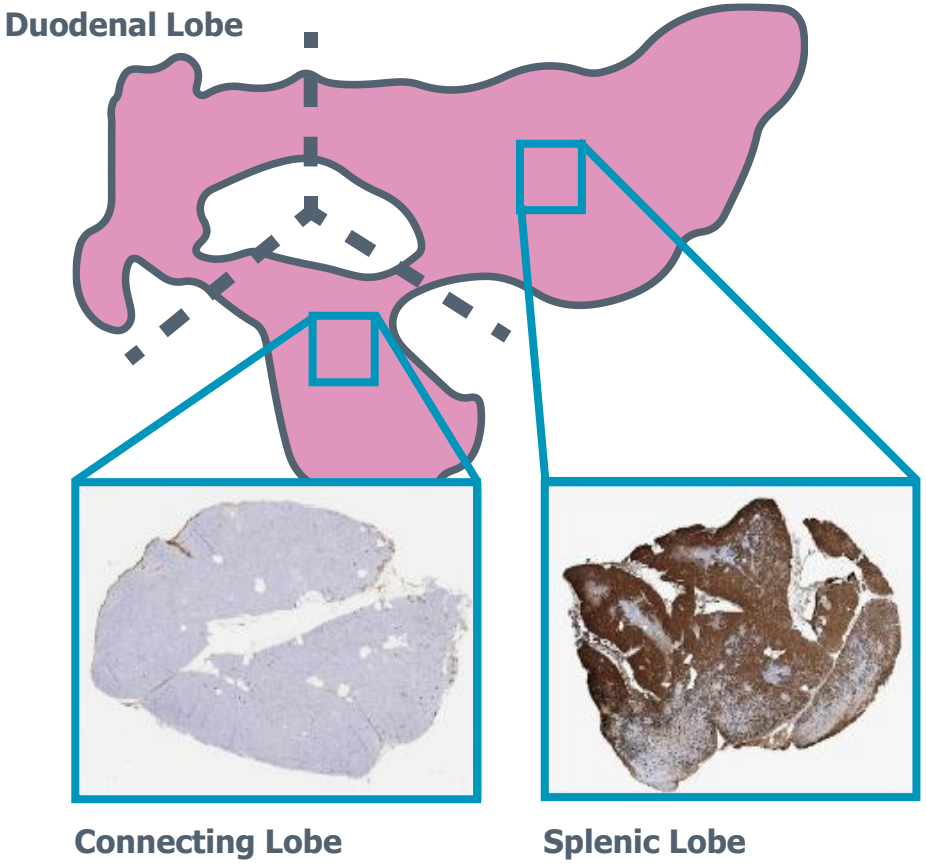
Endoscopic Procedure & AAV Delivery

1. Docherty et al. Encyclopedia of Tissue Engineering and Regenerative Medicine. 2019. 2. Ravi et al. Medicine (Baltimore). 2021 Apr 30;100(17):e25642.
3. Peery et al. Gastroenterology 2022 Feb: 162(2):621-644. AAV=adeno-associated virus, EUS=endoscopic ultrasound

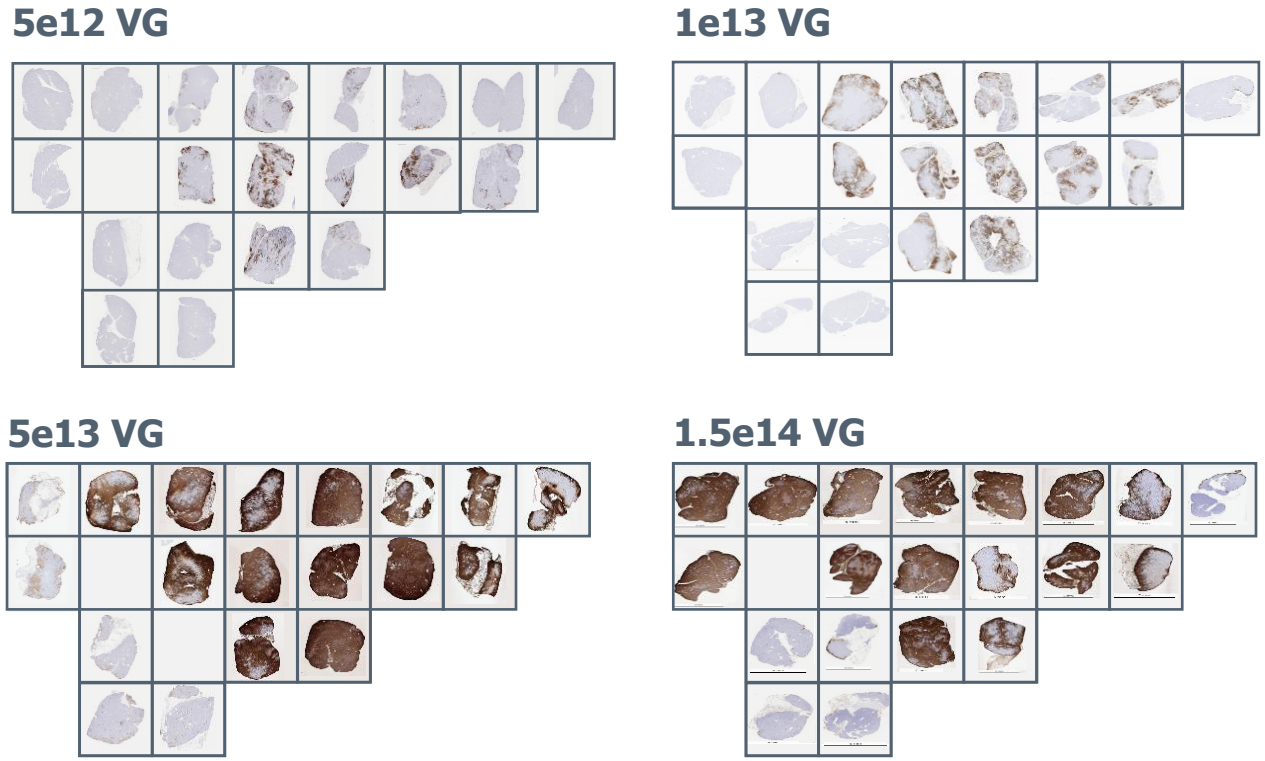
Proprietary Local Endoscopic Delivery System Extensively Tested

Dose-dependent transduction throughout porcine splenic lobe

A) Extensive GFP in Splenic Lobe



B) VG Dose-dependent GFP in Pancreas

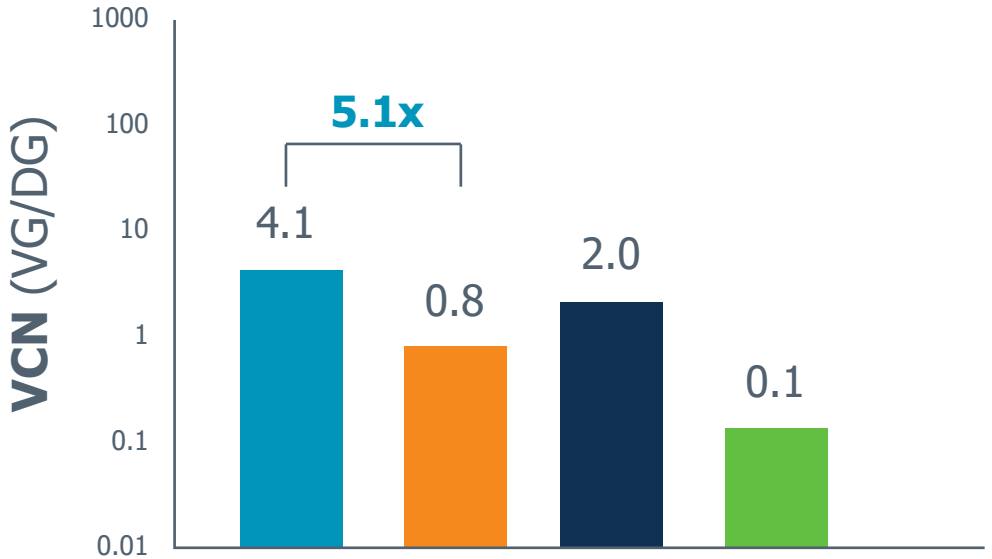


Rajagopalan et al. ASGCT 2023 oral presentation. Abstract no. 191. GFP=green fluorescent protein, VG=vector genomes

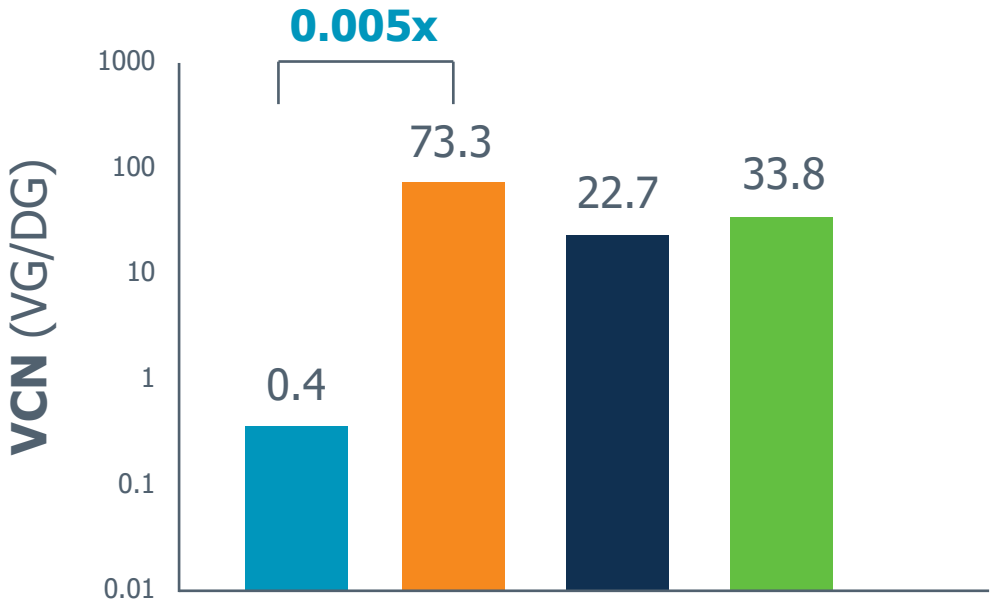
Local Endoscopic Delivery Allows High Expression

Dramatically limits systemic exposure to AAV in porcine model

A) Local Delivery[1] (4.2e12 VG/kg)



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



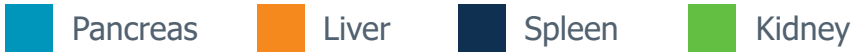
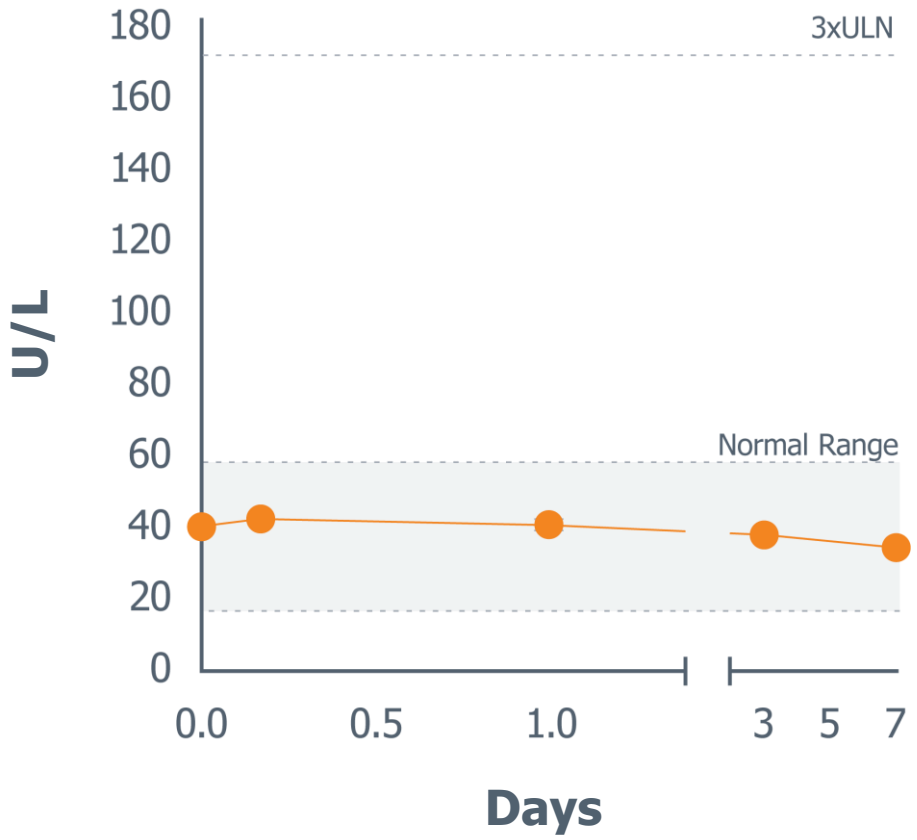


Figure A) adapted from Rajagopalan et al. ASGCT 2023 oral presentation. Abstract no. 312. Figure B) adapted from Li et al. Physiol Genomics 54: 261–272, 2022. EUS, N=4; I.V., N=2. 1. Rajagopalan et al. ASGCT 2023 oral presentation. Abstract no. 312. 2. Li et al. Physiol Genomics 54: 261–272, 2022. AAV=adeno-associated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

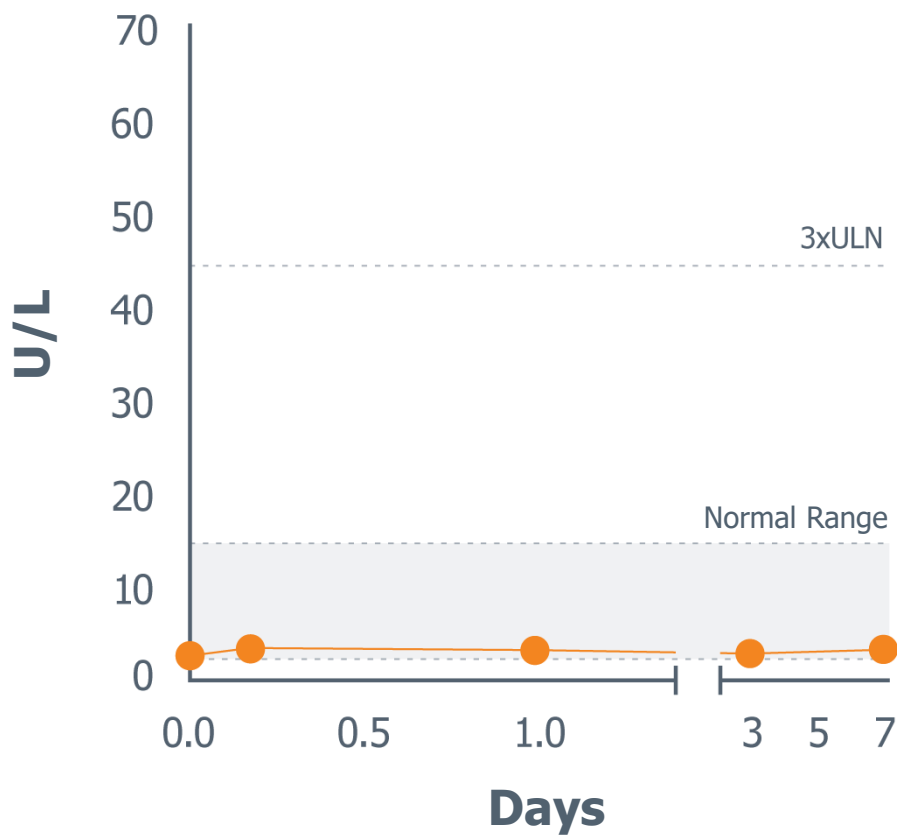
Proof-of-principle Safety with Local Endoscopic Delivery System

Mean ALT and lipase levels remained within normal range across all timepoints

A) 7-day ALT



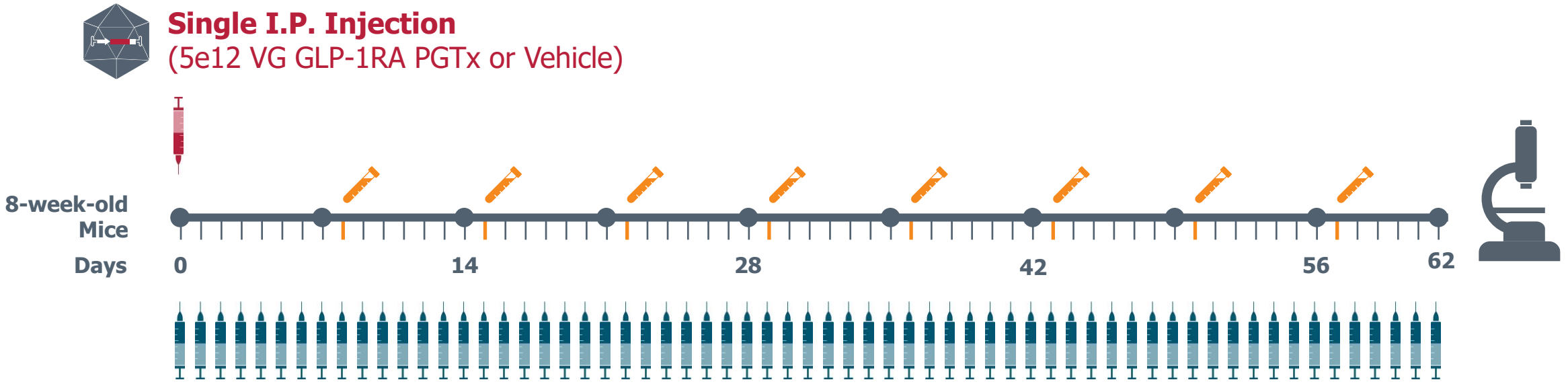
B) 7-day Lipase



Mean 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-1RA PGTx T2D Efficacy Study: Head-to-head vs. Semaglutide

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

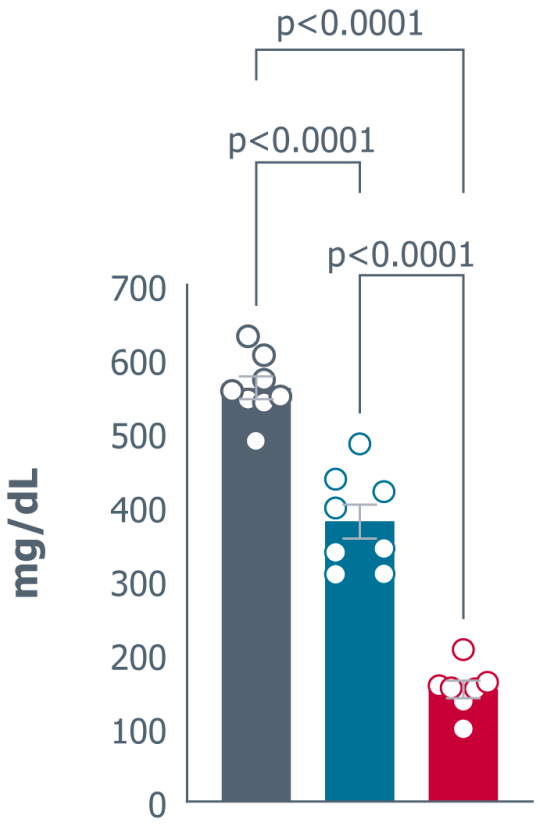


AAV=adeno-associated virus, GLP-1RA=glucagon-like peptide 1 receptor agonist, INS=insulin promoter, I.P.=intraperitoneal, MOA=mechanism of action, PGTx=pancreatic gene therapy, S.C.=subcutaneous, VG=vector genomes

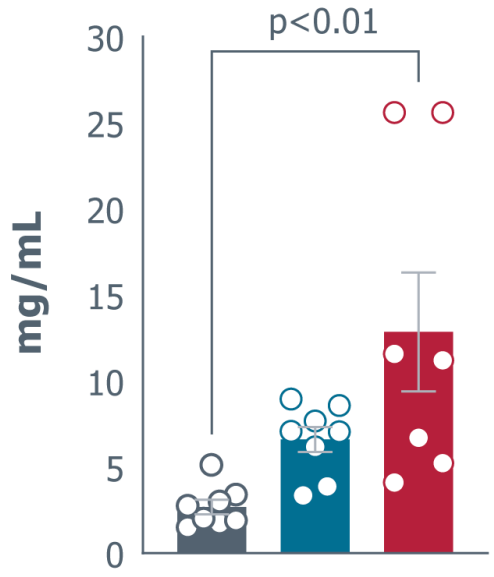
Glucose-lowering Efficacy in *db/db* Murine Model

GLP-1RA PGTx improves glucose, insulin, and weight vs. daily semaglutide

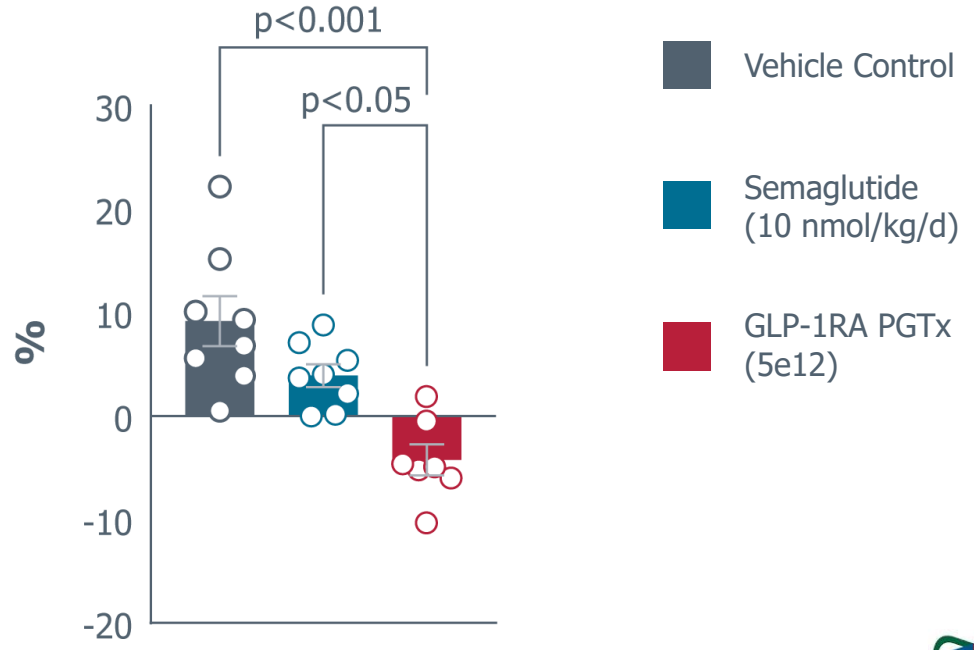
A) Fasting Blood Glucose
(Day 29, 4-6 Hours Fasted)



B) Fasting Plasma Insulin
(Day 29, 4-6 Hours Fasted)



C) Body Weight Change from Baseline
(Day 29, 4-6 Hours Fasted)



Mean ± SEM shown; n=7-8 per group. GLP-1RA=glucagon-like peptide 1 receptor agonist, PGTx=pancreatic gene therapy

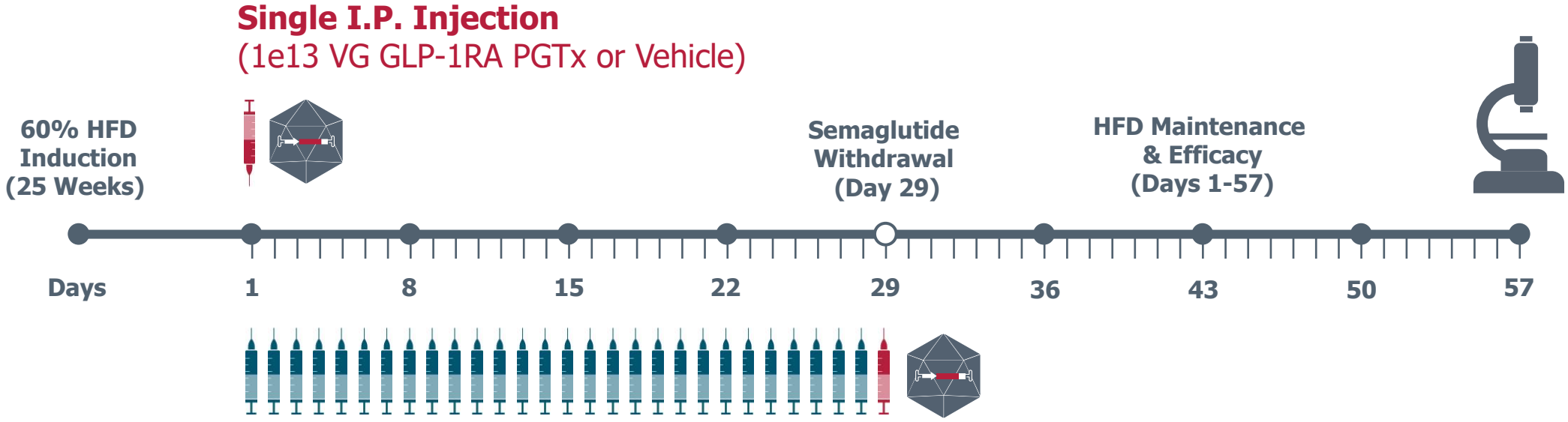
In Diet-induced Obesity, Compared to Chronic Semaglutide, Can One-time GLP-1-based PGTx:

Improve body weight?

Improve MASLD?

GLP-1RA PGTx Obesity Efficacy Study: Head-to-head vs. Semaglutide

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

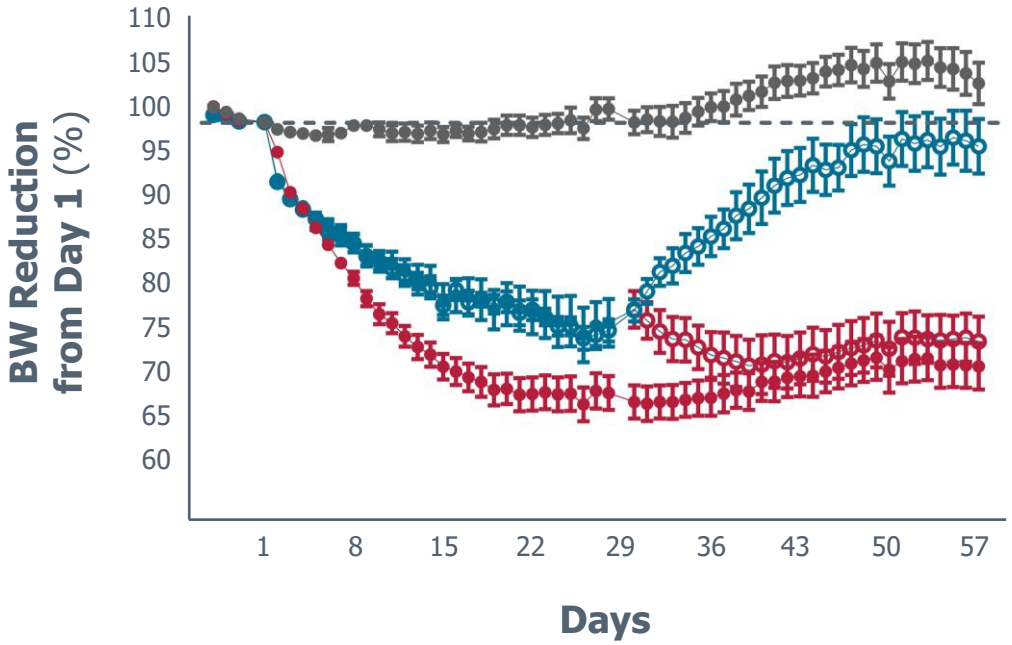


DIO=diet-induced obesity, GLP-1RA=glucagon-like peptide 1 receptor agonist, HFD=high fat diet, I.P.=intraperitoneal, PGTx=pancreatic gene therapy, S.C.=subcutaneous, VG=vector genomes

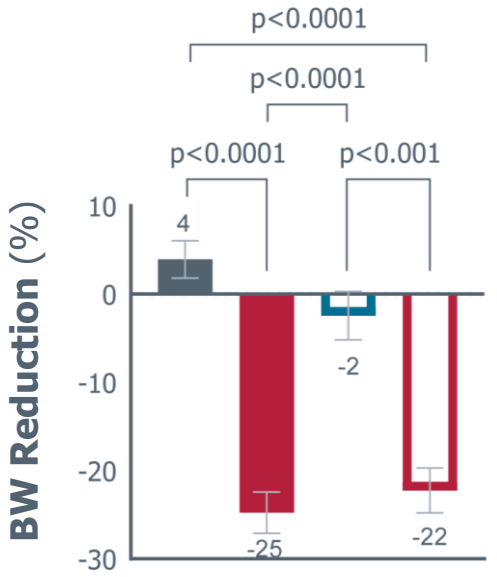
Body Weight Change in DIO Murine Model

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

A) Change in BW Over Time



B) End of Study BW Change



Vehicle Control

Sema (10 nmol/kg/d)

GLP-1RA PGTx (1e13 VG)

Sema Withdrawal + Vehicle

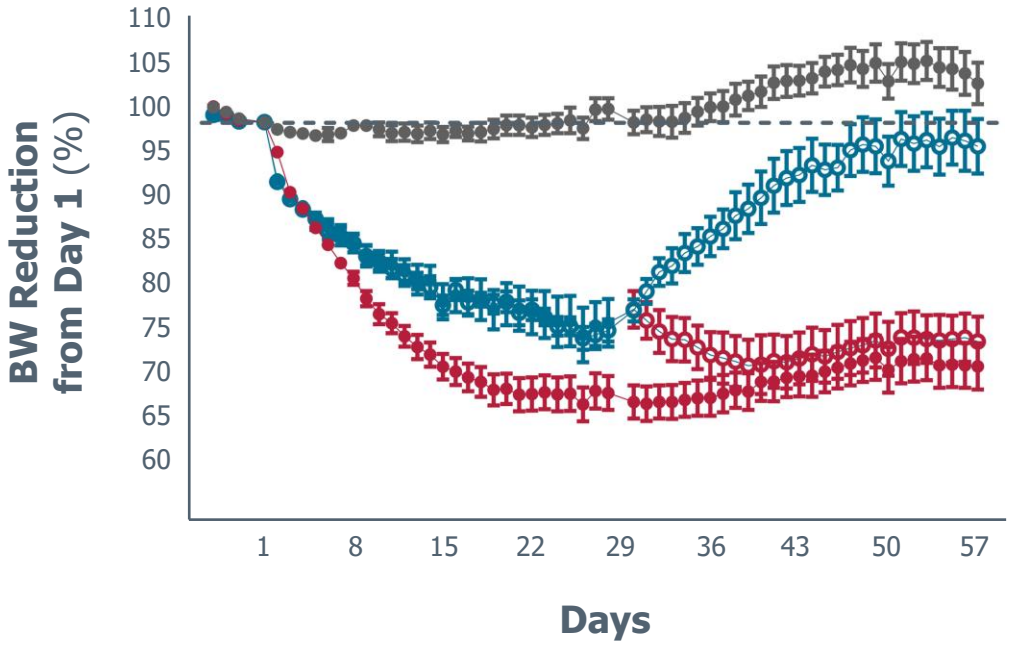
Sema Withdrawal + GLP-1RA PGTx (5e12 VG)

Mean ± SEM shown; n=5-10 per group. Fitzpatrick et al. WCIRDC 2023 oral presentation. Abstract no. 0077. BW=body weight, DIO=diet-induced obesity, GLP-1RA=glucagon-like peptide 1 receptor agonist, PGTx=pancreatic gene therapy, Sema=semaglutide, VG=vector genomes

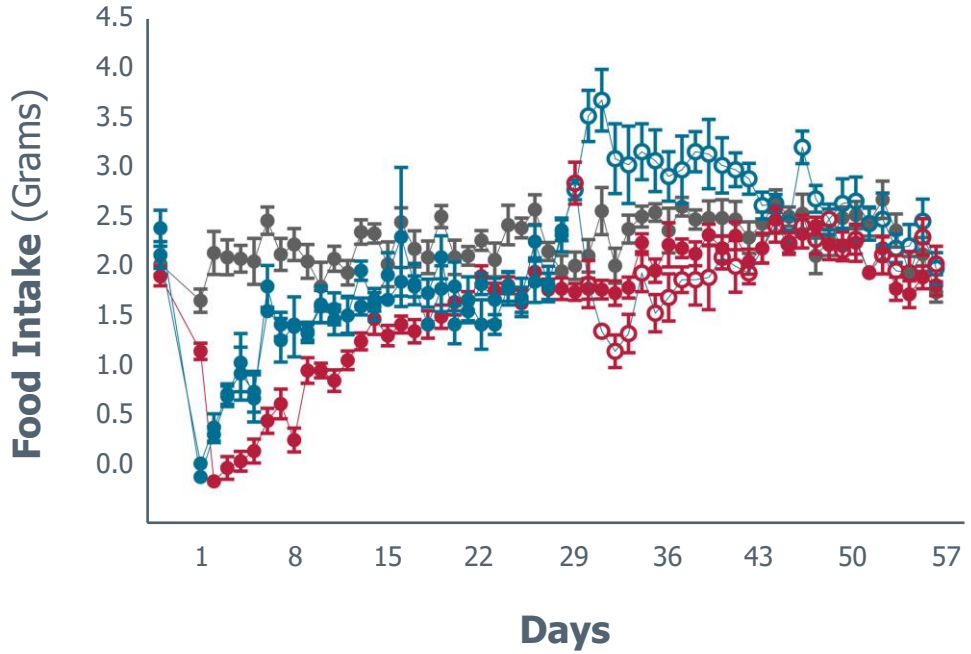
Food Intake Change in DIO Murine Model

Body weight changes are reflected by alterations in food intake

A) Change in BW Over Time



B) Food Intake Over Time



Vehicle Control

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

Mean ± SEM shown; n=5-10 per group. Fitzpatrick et al. WCIRDC 2023 oral presentation. Abstract no. 0077. BW=body weight, DIO=diet-induced obesity, GLP-1RA=glucagon-like peptide 1 receptor agonist, PGTx=pancreatic gene therapy, Sema=semaglutide, VG=vector genomes

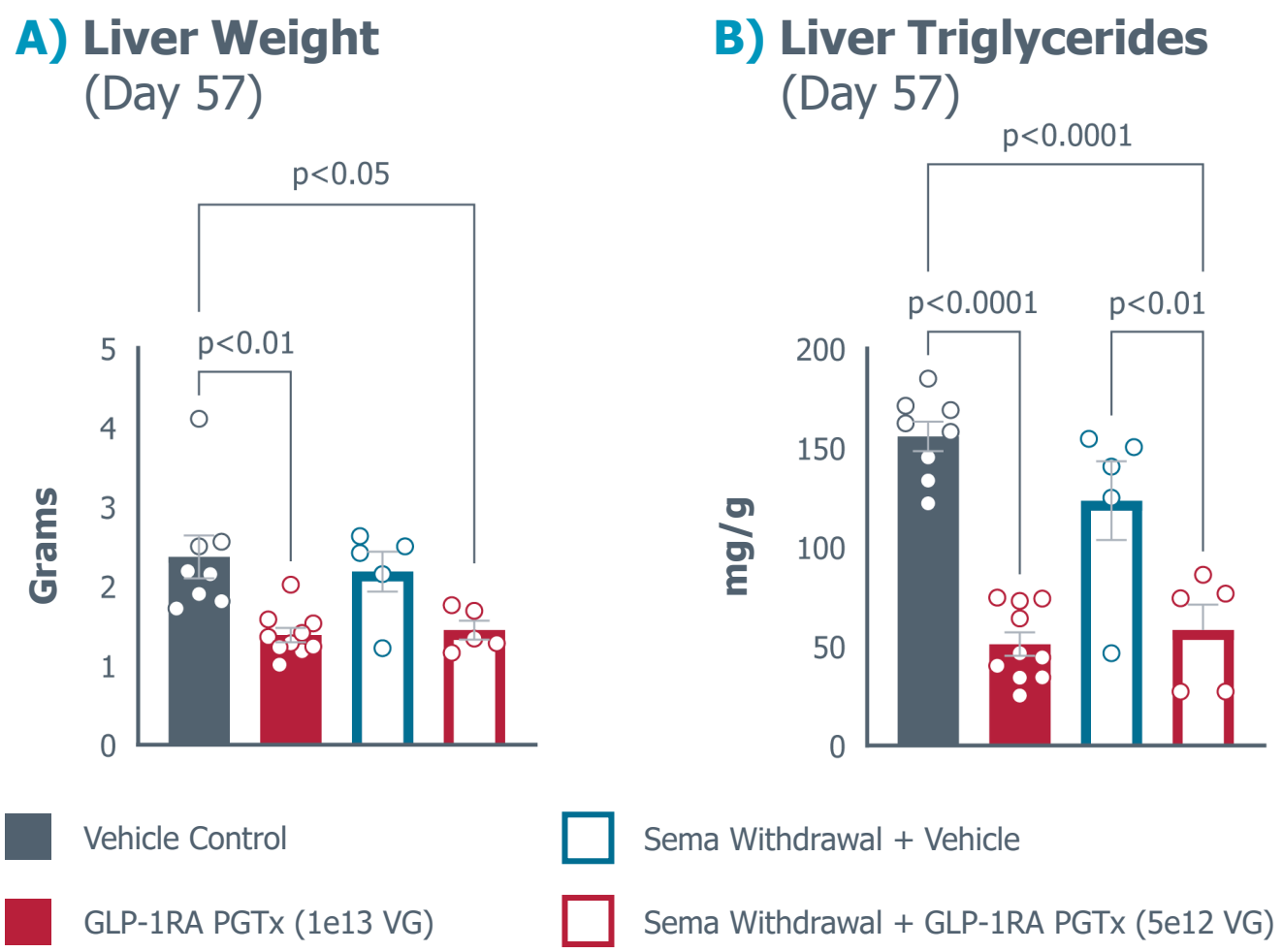
Liver Weight and Triglyceride Change in DIO Murine Model

Single-dose GLP-1RA PGTx reduced liver weight and triglycerides

42% lower liver weight with PGTx compared to vehicle

67% lower liver triglycerides with PGTx compared to vehicle

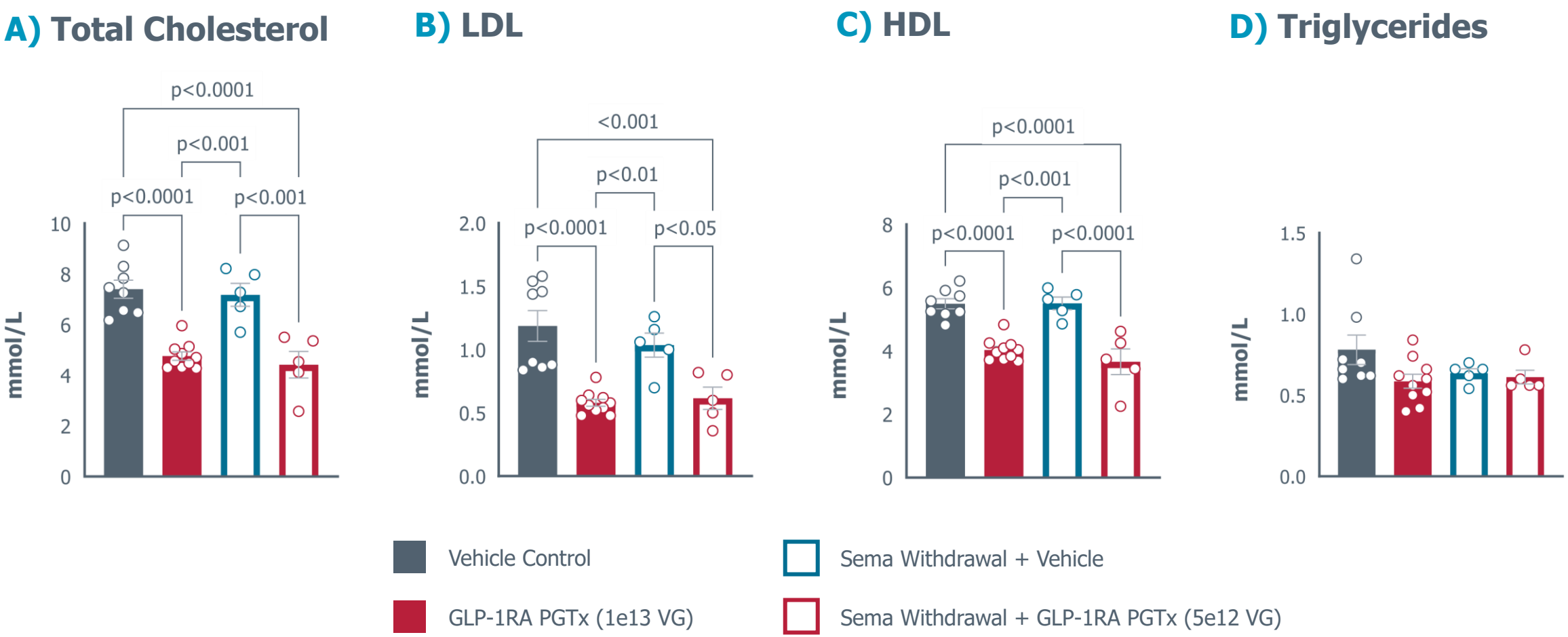
Sema withdrawal consistent with vehicle control



Mean ± SEM shown; n=5-10 per group. DIO=diet-induced obesity, GLP-1RA= glucagon-like peptide 1 receptor agonist, PGTx=pancreatic gene therapy, VG=vector genomes

Plasma Cholesterol and Triglyceride Change in DIO Murine Model

Single-dose GLP-1RA PGTx reduced total cholesterol



Mean ± SEM shown; n=5-10 per group. DIO=diet-induced obesity, GLP-1RA= glucagon-like peptide 1 receptor agonist, PGTx=pancreatic gene therapy, LDL=low-density lipoprotein, HDL=high density lipoprotein, VG=vector genomes

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

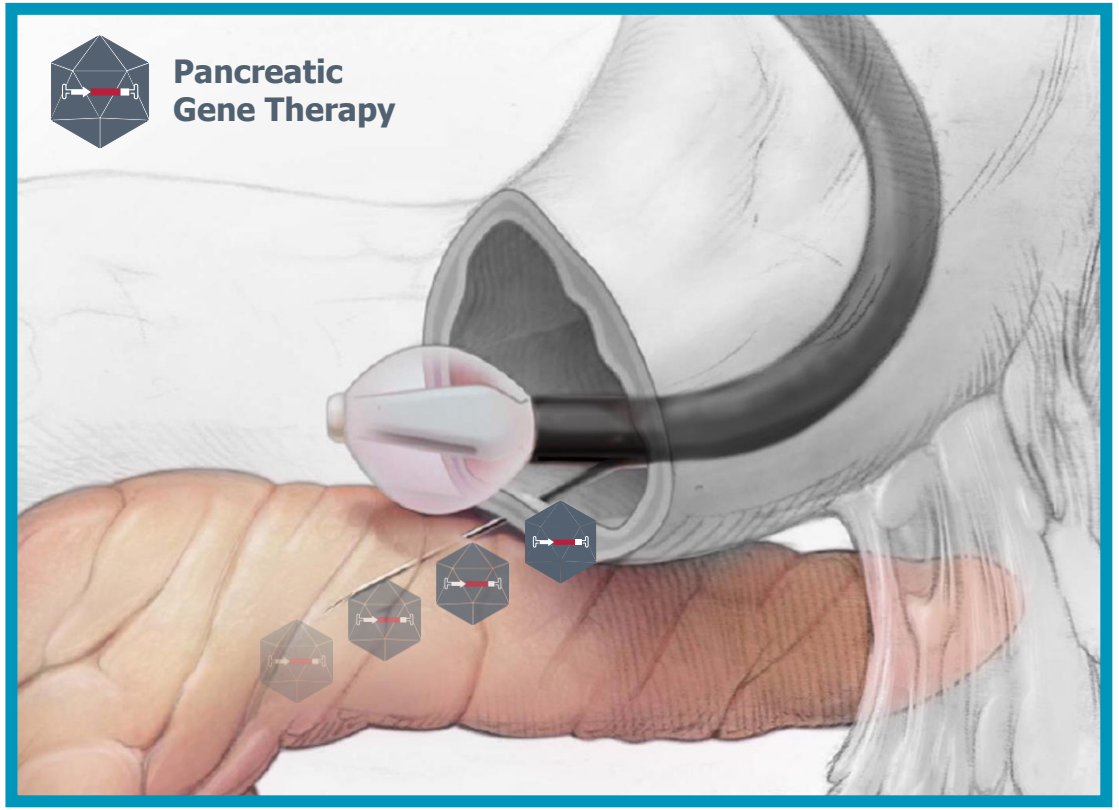
Conclusions to date

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 the *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 can **improve steatohepatitis and systemic lipid profile** in DIO mice



DIO=diet-induced obesity, GLP-1RA=glucagon-like peptide 1 receptor agonist, PGTx=pancreatic gene therapy

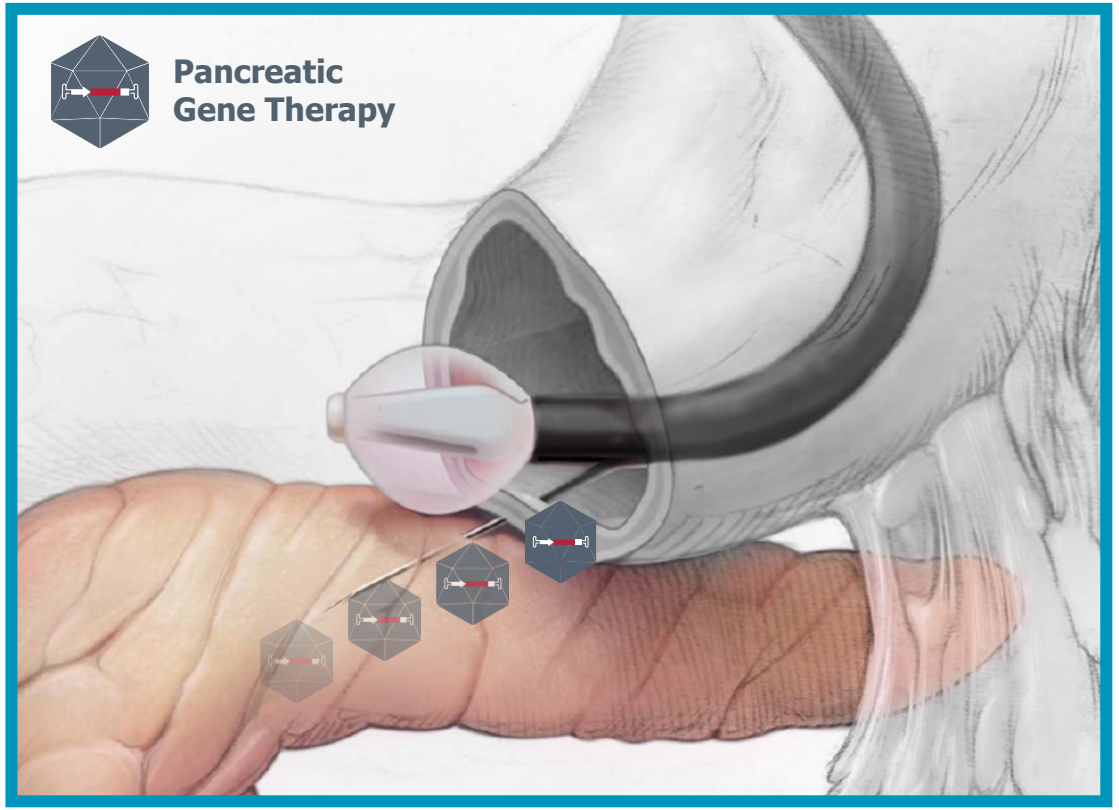
GLP-1RA PGTx Safety and Feasibility Studies

Next Steps

First GLP-1 PGTx, RJVA-001, nominated as development candidate

IND-enabling, preclinical studies are underway

Anticipate initiating **first-in-human trial in type 2 diabetes** in the first half of 2025



DIO=diet-induced obesity, GLP-1RA=glucagon-like peptide 1 receptor 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

Lindsay Schulman, MS
Senior Associate Scientist

ex vivo and animal studies

Alice Fitzpatrick, DVM, PhD
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