FRACTYL® health

Developing Breakthrough Therapies for Obesity and Diabetes

Corporate Presentation | June 2024

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Leadership team and BOD

Experience spanning biotechnology and medical technology

Management Team

Harith Rajagopalan, MD, Ph.D.
Co-founder & CEO

Jay Caplan
Co-founder, President, Chief Product Officer

Lisa Davidson
Chief Financial Officer

Tim Kieffer, Ph.D.
Chief Scientific Officer

Arian Kimber
Chief Commercial Officer

Sarah Toomey
General Counsel and Corporate Secretary

Jon Fitzgerald
Quality Assurance and Regulatory Affairs

Len Rosberg
Manufacturing

Kelly White, PharmD
Clinical and Medical Affairs

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Co-founder & CEO, Fractyl Health

Marc Elia
Founder of M28 Capital

Amy Schulman
Partner, Polaris Partners

Kelly Barnes
Former Partner, PwC

Sam Conaway
President of Boston Scientific U.S. Cardiology Sales and Chair of Close the Gap

Clive Meanwell, MB, CHB, MD
Executive Chairman and Founder of Population Health Partners

Ajay Royan
Co-founder and Managing General Partner, Mithril

Addressing the major unmet need in obesity

Differentiated, substantial opportunity with multiple near-term catalysts

Obesity: 100M in US with obesity today[1]

GLP-1 drugs have transformed the treatment landscape

Weight maintenance has emerged as the new, significant unmet need

Revita: potentially offers long-term weight maintenance after GLP-1

Weight maintenance data expected starting in Q4 2024

T2D Pivotal study topline readout expected mid-2025

Rejuva: potential remission of metabolic disease via pancreatic gene therapy

Candidate nomination for obesity planned H2 2024

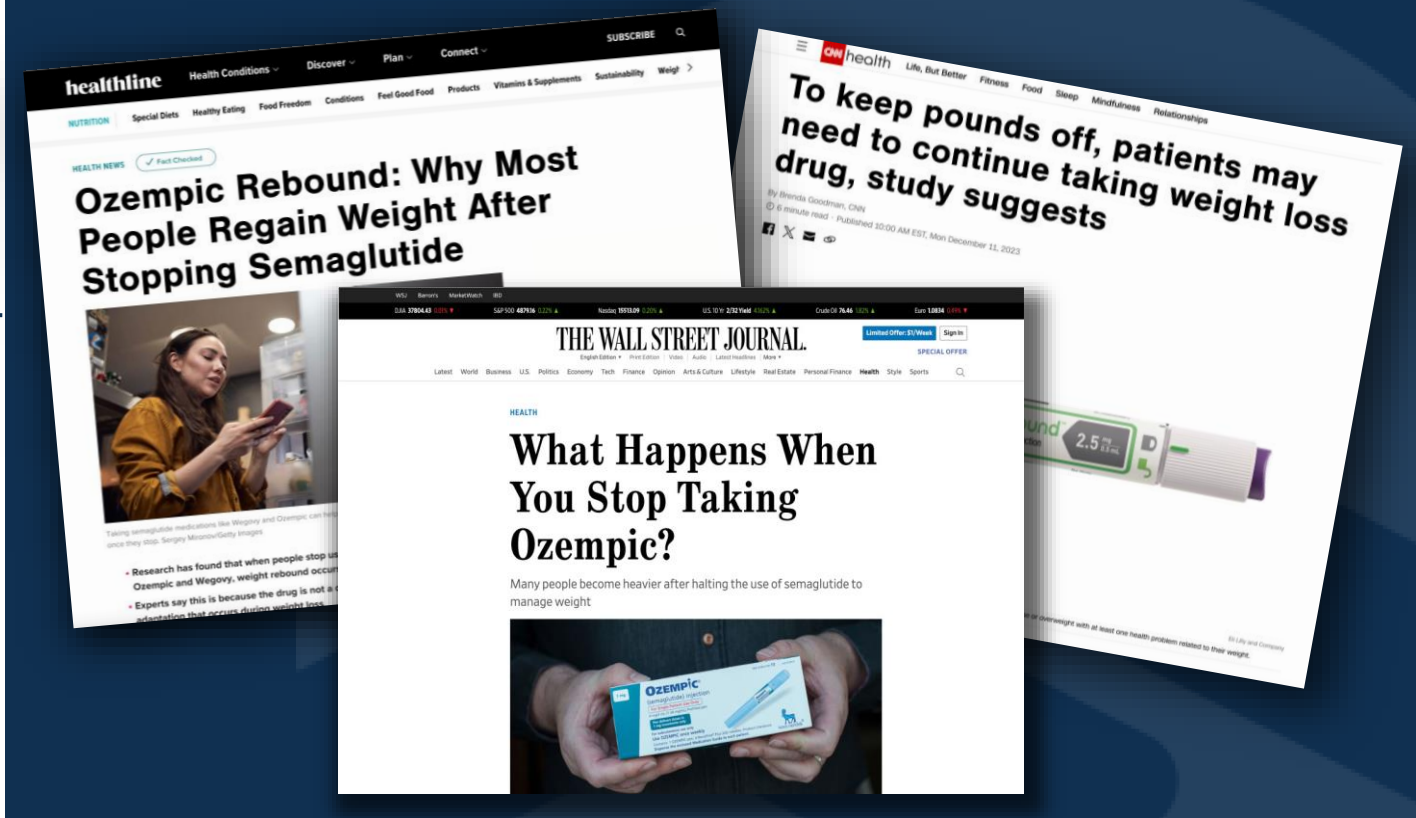
FIH study for T2D planned H1 2025

1. CDC

Obesity:
Acute healthcare crisis with untapped market potential

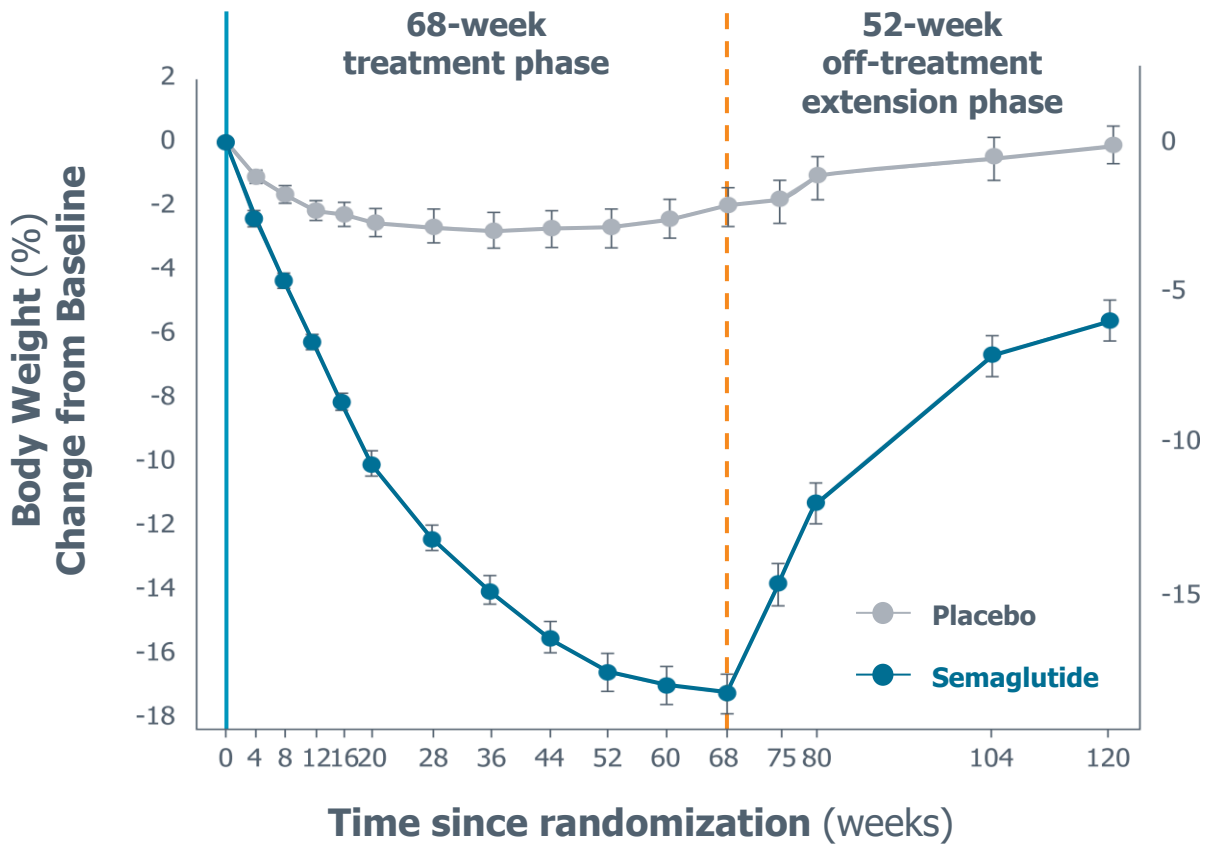
Today's GLP-1 Therapies: Unprecedented Market Successes with Significant Limitations

Leading to the Key Question Today: How to Prevent Weight Rebound?



67% weight regain after one year[1]

Novo Nordisk STEP 1 trial extension



> **One year after withdrawal …participants regained two-thirds of their prior weight loss…**

John P H Wilding et al
Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension[1]

1. Wilding JPH, Diabetes Obes Metab.2022;24:1553–1564 (Funded by Novo Nordisk)

GLP-1 drugs have a persistence problem

BCBS data show 50% GLP-1 drug discontinuation within 3 months

Private insurer survey of ~170K unique GLP-1 drug users for weight loss from January 2014 to December 2023[1]

Only 42% of users still on therapy at 12 weeks of follow up

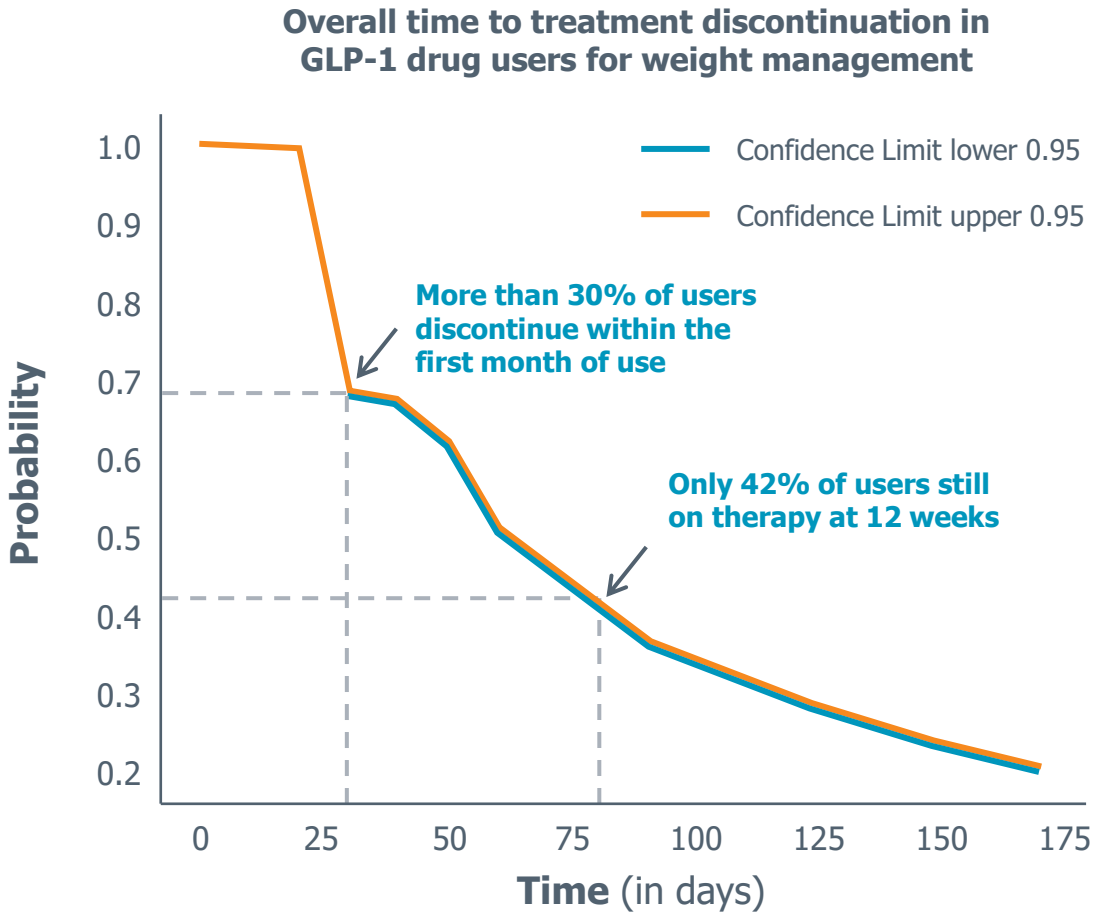


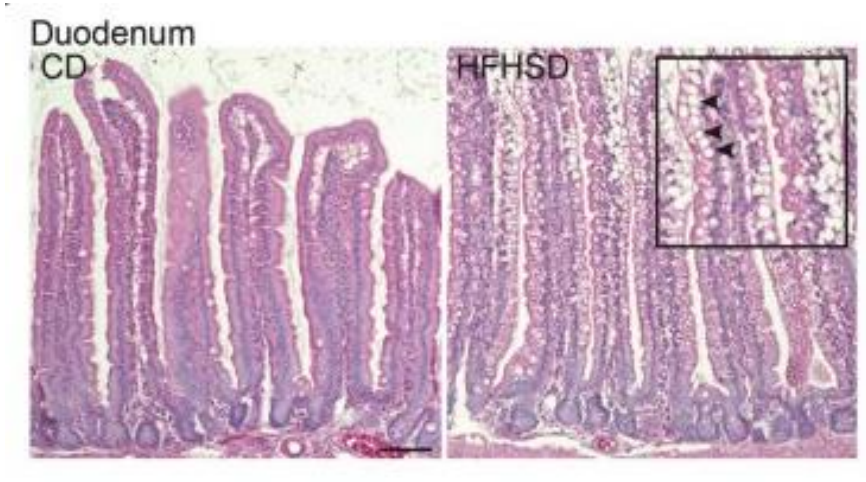
Figure adapted from Blue Health Intelligence, Issue Brief May 2024. 1. Blue Health Intelligence, Issue Brief May 2024. BCBS=Blue Cross Blue Shield, GLP-1RA=glucagon-like peptide 1 receptor agonist, PCP=primary care physician

Revita

Fractyl's potential solution to the problem of weight regain

Gut dysfunction is a root cause of obesity & T2D[1]

Altered metabolic setpoint caused by high fat and sugar diets[2]



High fat and high sugar diets cause structural and functional changes to the gut lining

Chronic high fat and high sugar diets cause gut dysfunction → **Gut dysfunction alters gut-brain signaling[1-2]** → **Altered metabolic setpoint drives obesity and T2D[2]**

[1]Aliluev et al Nat Metab. 2021 3:1202-1216 [2]Duca et al Cell Metab. 2015 22:367-380 CD = Chow Diet HFHSD = High Fat High Sugar Diet

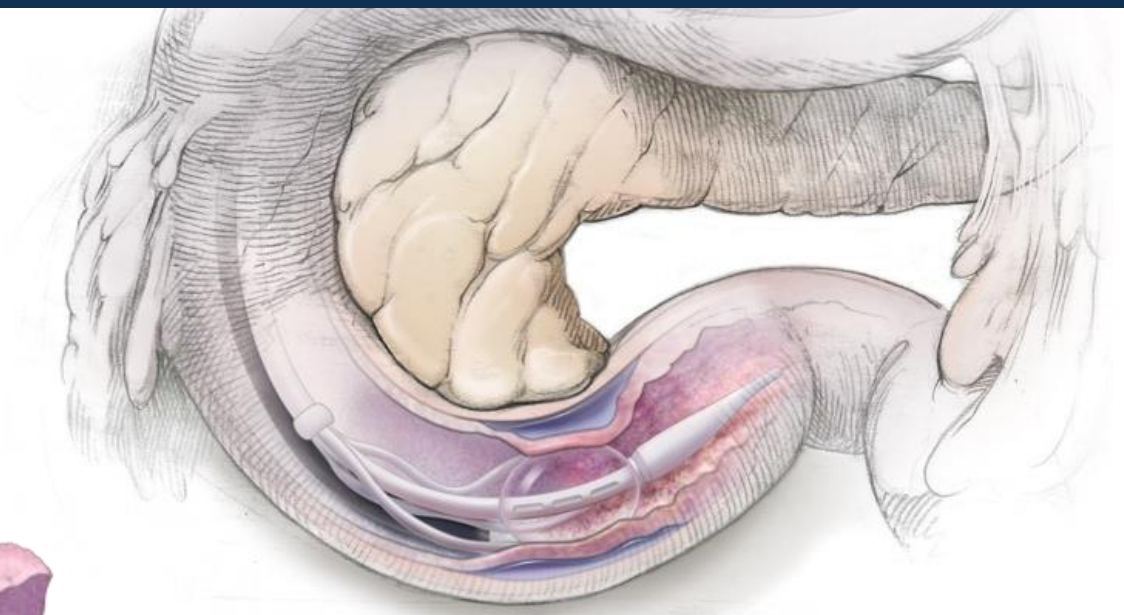
Revita targets gut dysfunction

First potential opportunity for a durable metabolic reset[1-4]

Outpatient endoscopic procedural therapy

Clinical trials in > 300 participants

2-year durable improvements in weight and glucose[4-10]



1. Mah AT et al. Endocrinology. 2014 155:3302-3314. 2. Mao J et al. Diabetes. 2013 62:3736-3746. 3. de Moura EGH et al. Endosc Int Open. 2019 7:E685-E690. 4. Haidry RJ, et al. Gastrointest Endosc. 2019 90:673-681.e2. 5. van Baar ACG, et al. Endosc Int Open. 2020 8:E1683-E1689. 6. Rajagopalan H, et al Diabetes Care. 2016 39:2254-2261. 7. van Baar ACG, et al. Gut. 2020 69:295-303. 8. Mingrone G, et al. Gut. 2022 71:254-264. 9. van Baar ACG, et al. Gastrointest Endosc. 2021 94:111-120.e3. 10. van Baar et al. Diabetes Res. Clin. Pract. 2022 184:109194

Revita console and catheter system

Designed to seamlessly integrate into high volume endoscopy workflow

Designed for durable and repeatable metabolic improvement

80+ issued patents covering methods, systems, devices

CE Mark in EU/UK

Reimbursed and marketed in Germany

Breakthrough Designation from FDA in insulin-treated T2D

Control console

Single-use catheter

Real-time sensors

½ day training
< 1 hour procedure time
< 4 cases for proficiency

Revita is for investigational use only in the United States. Revita has a CE mark in the European Union. Prototype rendering

Revita weight maintenance results

Pooled weight loss data in T2D including overweight participants[1]

Patient population

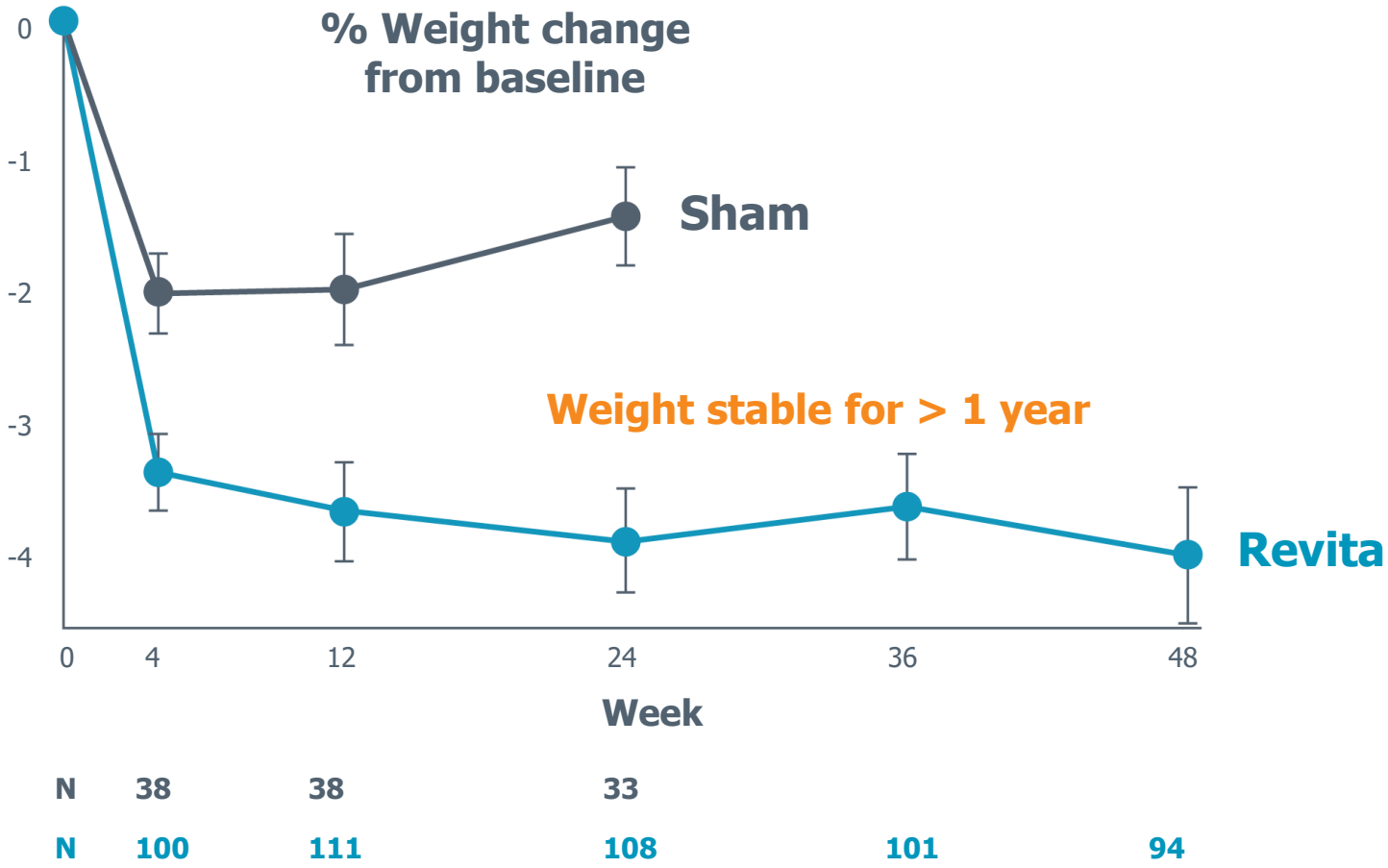
Patients with advanced T2D on multiple GLAs

Baseline Demographics

Baseline 93 kg (BMI 31.1)

HbA1c 8.3%

T2D duration 10 years



Ozempic 1 mg demonstrated similar body weight loss (~ 5% at wk 30) in similar T2D patients[2]

1. Fractyl Health, Data on File
2. Sorli C et al. The Lancet Diabetes & Endocrinology 2017; 5(4)251-260. ; we have not conducted any head-to-head studies of Revita with Ozempic

Post-market registry ongoing in Germany

Weight loss and glucose control in real world experience[1]

Patient population

Patients with T2D on at least 1 GLA at baseline

Baseline demographics

62 years age
64% male
13 years duration T2D
BMI 32.1 kg/m^2

Anticipated timing

Quarterly open label data updates

	Baseline n=14 **Median** (min,max)	**6 Month n=14** **Median** (min,max)
Weight (kg)	**111** (66,139)	**102** (62,127)
HbA1c (%)	**9.2** (7.3,12.8)	**7.6** (6.0,13.2)
FPG (mg/dL)	**153** (101,355)	**116** (79,198)

- The DMR procedure was well tolerated in registry participants with no DMR-related serious adverse events reported to date.

1. Fractyl Health, Data on File as of May 2024 NCT06256497 GLAs = Glucose Lowering Agents

REVEAL-1/REMAIN-1 Program
Can Revita prevent weight regain after GLP-1 drug discontinuation?

Reveal-1 weight maintenance study[1]

Open label study for patients who need to stop GLP-1s

Patient population	Primary endpoint	Key secondary endpoints	Design	Anticipated timing
Obese patients (BMI 30) without T2D and achieving at least 15% TBW loss with tirzepatide or semaglutide and cannot continue drug Up to 20 participants	Change from baseline in weight compared to historical controlled studies of GLP-1 withdrawal	Glucose, CV risk factors	Single-arm, open-label, cohort study of Revita after GLP-1 drug discontinuation Diet and lifestyle counseling throughout	**Open label study updates expected starting in Q4 2024**

TBW = total body weight 1. Reveal-1 is an open label cohort as part of the Remain-1 pivotal IDE. Participants may either already be taking GLP-1 based semaglutide or tirzepatide and have achieved at least 15% TBW loss or will initiate tirzepatide to achieve at least 15% TBW loss before Revita

Remain-1 pivotal study in weight maintenance

Planned mid-point data analysis anticipated in Q2 2025

Patient population

Obese patients (BMI 30) without T2D and GLP-1 drug naive

At least 315 participants

Planned mid-point data analysis after 45 participants randomized and followed for 12 weeks

Co-Primary endpoints

Change from baseline in weight to week 24
and
% of Revita participants who maintain at least 5% TBW loss at week 24

Key secondary endpoints

Glucose,
CV risk factors

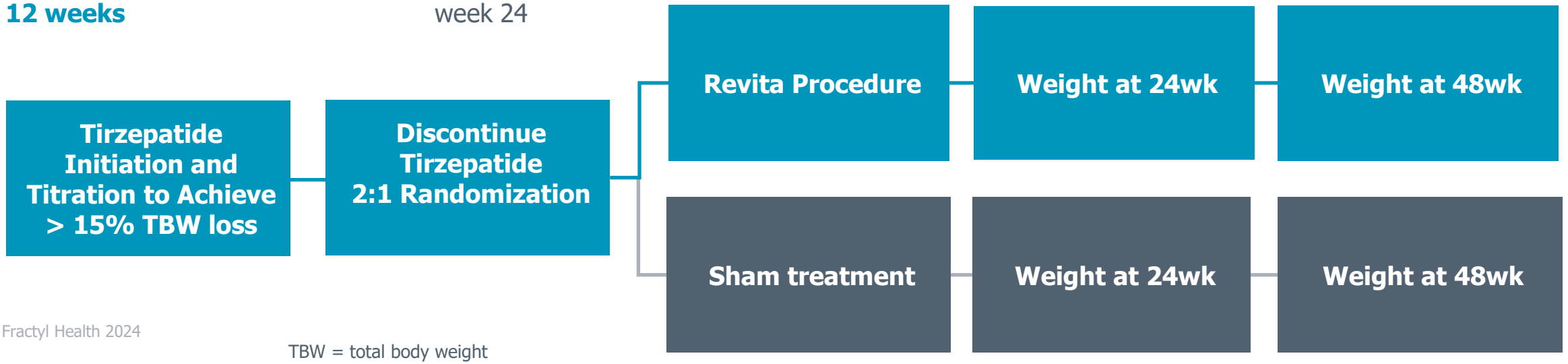
Study Design

Randomized (2:1), double blind, sham controlled after GLP-1 discontinuation

Diet and lifestyle counseling throughout

Anticipated timing

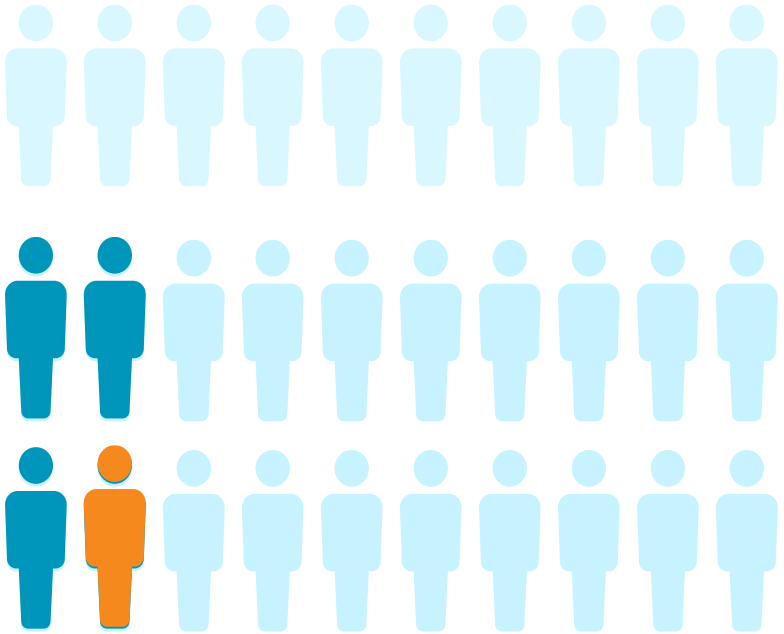
Planned mid-point data analysis expected in Q2 2025



TBW = total body weight

Millions of US patients have taken GLP-1s

Unprecedented number of new prescriptions and discontinuations



"I have been religiously taking a GLP-1 for years and I myself am looking for an option to get off!"
- US Endocrine KOL

100 million people with obesity in the US today who may benefit from GLP-1 drugs[1]

Up to 20% have already tried GLP-1 drugs with CAGR up to 40%[2-3]

> 50% who have started GLP-1s discontinue within one year[4]

Many of those who remain on drug are looking for a viable off-ramp today

1. CDC
2. KFF Health Tracking Poll May 2024
3. TD Cowen estimates
4. Polonsky et al. *Diabetes Ther.* 13, 175–187 (2022)

Revita for T2D

Goal: durably improve glucose control, maintain weight loss, and reduce medication burden for millions of people with inadequately controlled T2D

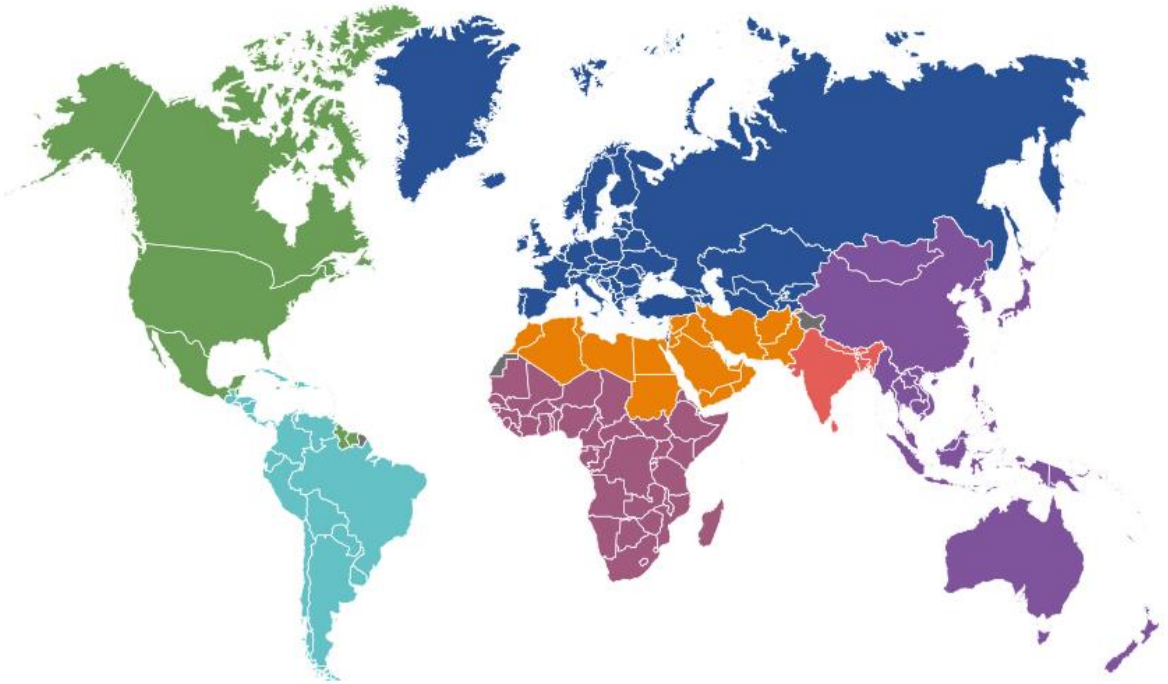
T2D is a high unmet need market opportunity

60+ approved drugs but market continues to grow

> $350B annual cost of T2D in 2022[1]

> $20B in branded GLP-1 sales for T2D in 2022 (15% CAGR)[2]

> 50M in US projected to have diagnosed T2D by 2030[3]



537M with diabetes globally in 2021[4]

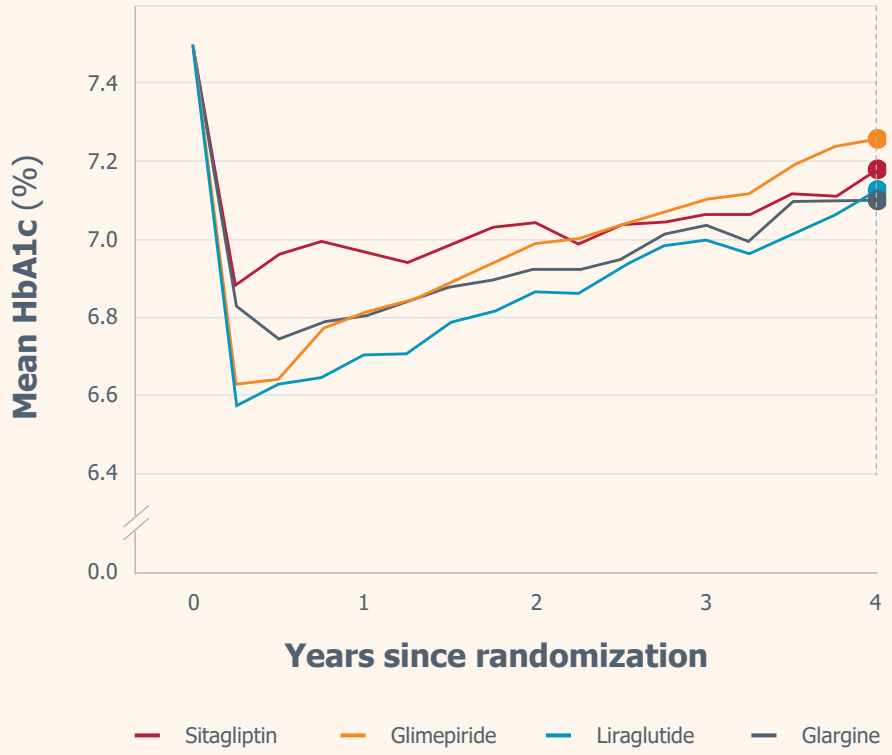
Map: Number of people with diabetes worldwide and per IDF Region in 2021–2045 (20–79 years)

1. CDC 2. TD Cowen estimates 3. Rowley et al Pop Health Mgmt 2017 4. IDF Diabetes Atlas 2021

Diminishing effectiveness of T2D therapies

Need more effective and durable therapies for T2D

Lack of durability of current therapies drives need for medication escalation[1]



There is no drug approved for T2D today that can halt or reverse progression of disease

Adapted from: 1. GRADE Study 2022 HbA1c=hemoglobin A1c, IU=international units, OR=odds ratio, *p<0.05

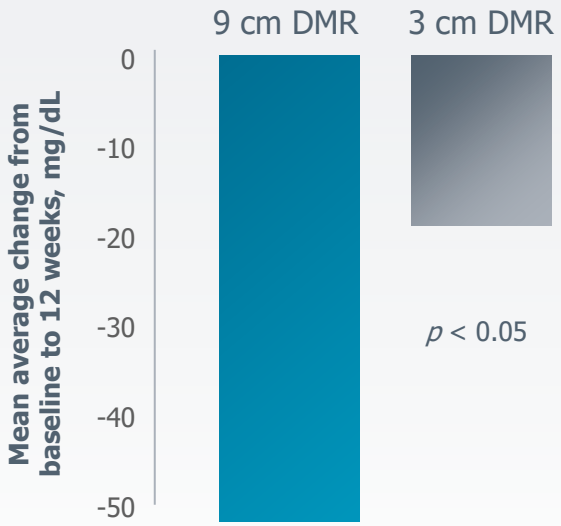
Revita T2D clinical program overview

Consistent effects on blood glucose across clinical studies

Revita FIH[1]

Dose-dependent glucose lowering

Dose-Dependent Efficacy

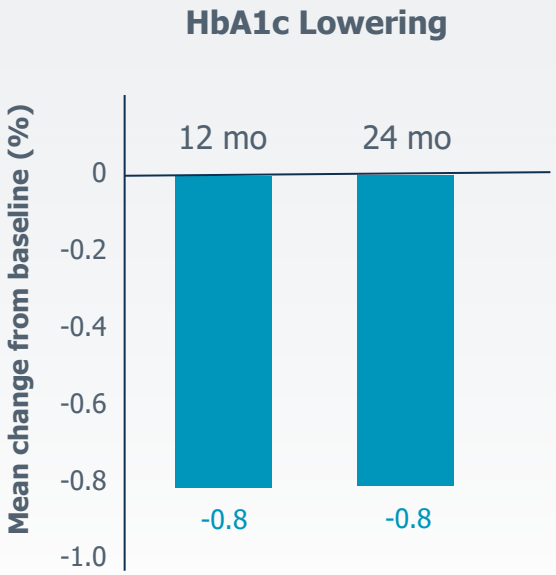


Axial length of treated intestine = treatment dose

Revita-1 Open Label[2]

2-year glucose lowering and weight control

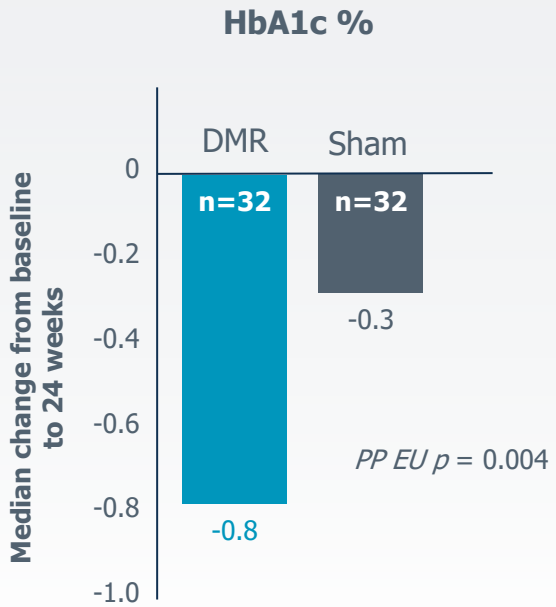
Durable Metabolic Improvements



Revita-2 Sham-Controlled[3]

Sham-controlled efficacy pilot study

Sham-Controlled Efficacy

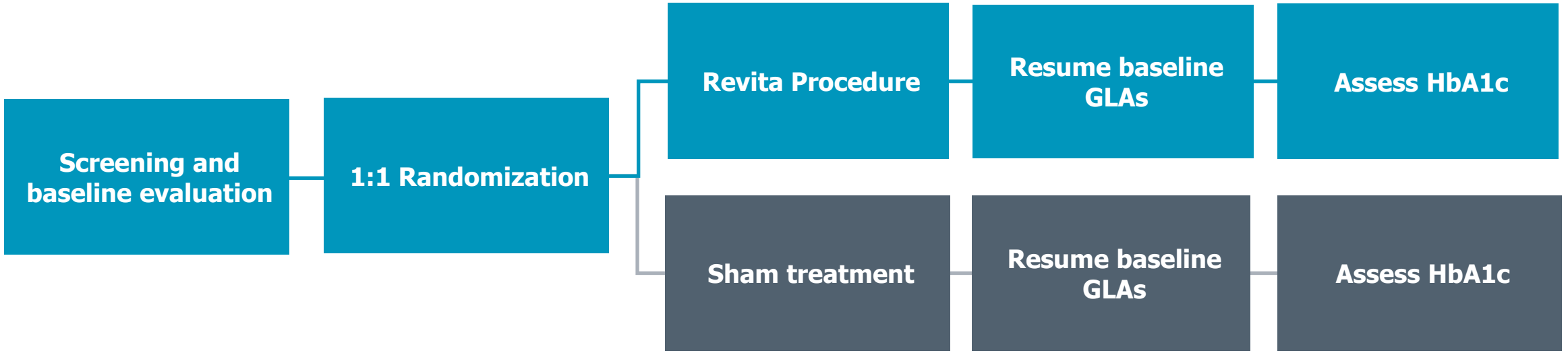


1. Rajagopalan et al Diabetes Care 2016 2. van Baar et al. Diabetes Res Clin Pract. 2022 184:109194 3. Mingrone et al. Gut 2022 71:254-264

Revitalize-1 pivotal study underway

FDA Breakthrough Device designation and CMS reimbursement support

Patient population	Primary endpoint	Key secondary endpoints	Design	Anticipated timing
Inadequately controlled T2D (HbA1c > 7.5) despite use of at least 1 glucose lowering agent (GLA)	Change from baseline in HbA1c at 24 weeks	HbA1c targets weight loss, insulin requirement	Randomized (1:1) double blind sham controlled	**Topline data mid-2025**



Revitalize 1 Study; ClinicalTrials.gov Identifier: NCT04419779

Rejuva
Our potential solution for remission of obesity and T2D

RJVA-001 for T2D

Nutrient-responsive GLP-1 via intrapancreatic gene therapy

High Unmet Medical Need

- Highly variable tolerability to GLP-1 drugs
- Frequent injections
- Patient/physician adherence issues
- Incomplete responders

Epidemiology: US

- ~ 27M prevalence

Product Design

- Vector: AAV9
- Transgene: human GLP-1
- Promoter: insulin
- Delivery: Endoscopic needle

Differentiation

Effectively transduces pancreatic islets
One-time intrapancreatic administration
Nutrient-responsive GLP-1 expression

Status

IND-enabling studies

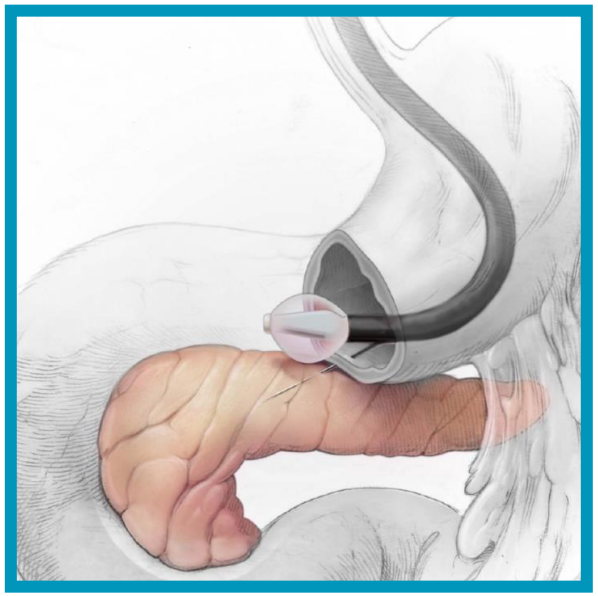
Expected Milestone

Initiate Clinical Study in H1 2025

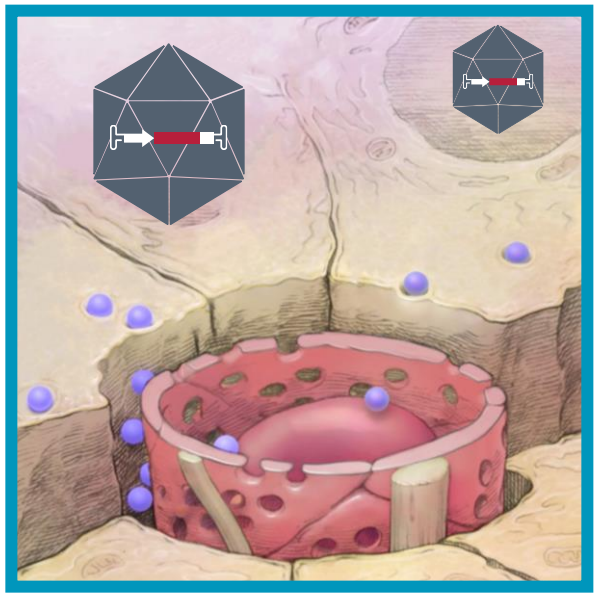
GLP-1-based pancreatic gene therapy (PGTx)

Designed to mimic human physiology

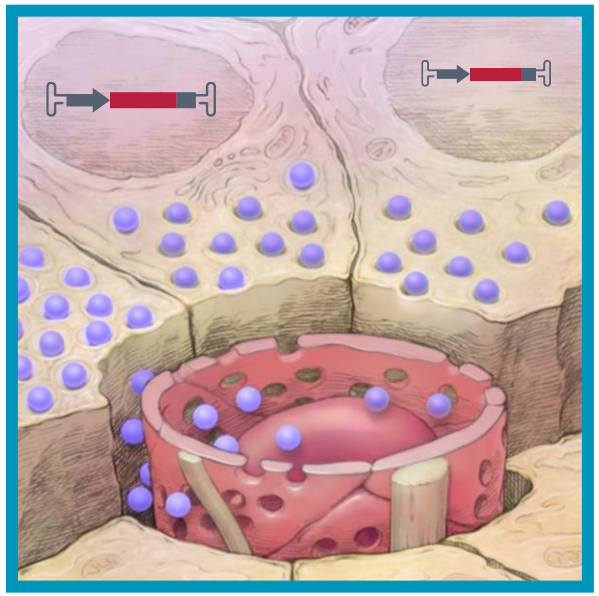
1. Local delivery



2. Low-dose AAV9



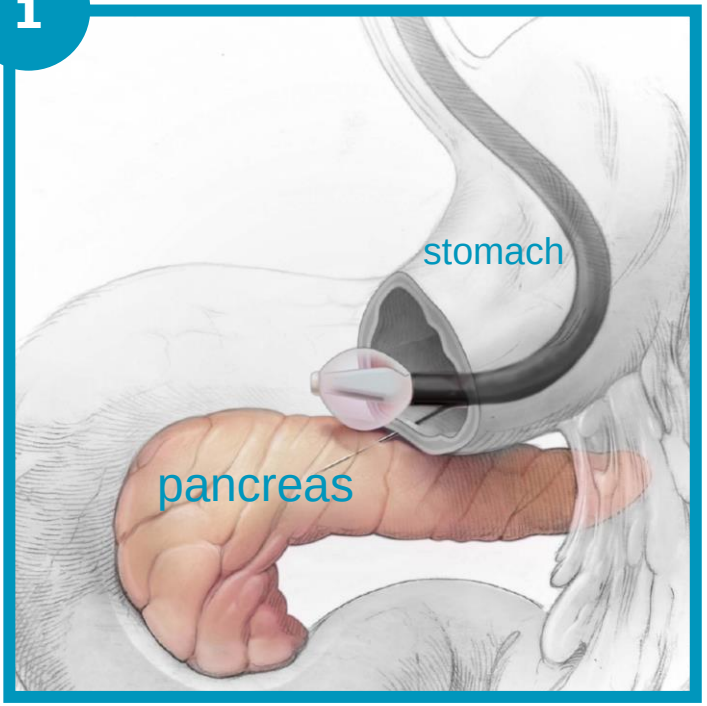
3. GLP-1 transgenes



Rejuva delivery device

Designed to reduce procedural risk of pancreatic injection

1 Local Delivery



Endoscopic ultrasound-based needle injection is already a standard diagnostic tool for pancreatic lesions[1]

Rejuva procedure designed to reduce risk with key device design elements (needle gauge, pressure regulation) and procedure steps (directed at tail of pancreas, avoiding pancreatic duct)

Proprietary device and endoscopic procedure enabled by Revita system[2,3]

1. Cazacu et al. Endosc Ultrasound. 2018 May-Jun; 7(3): 141–160 2. Thompson et al. DDW 2023 poster presentation. Control no. 3862948.
3. Rajagopalan et al. ASGCT 2023 oral presentation. Abstract no. 191

Local, AAV-delivered PGTx designed to improve islet function

AAV can achieve durable genetic modification of islet cells[1,2]

Intra-islet GLP-1 can restore beta cell health and function[3,4]

GLP-1-based PGTx (driven by the insulin promoter) may offer differentiated benefit by high local levels of GLP-1 with low systemic exposure

Proprietary platform encompasses methods, delivery systems, and gene constructs

2 Low-dose AAV9

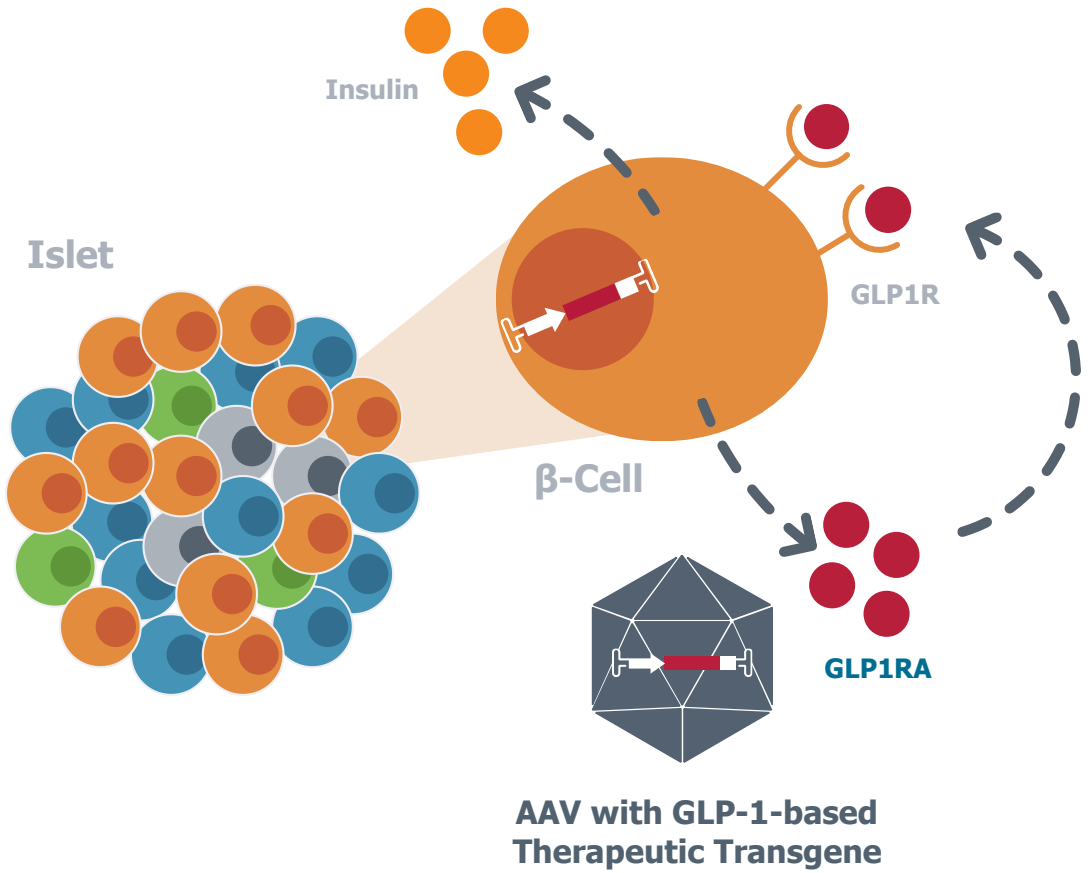


Figure adapted from Saikia et al. JCI Insight. 2021 6:e1418511. 1. Ju et al. Diabetologia. 1998 41:736-739. 2. Kapturczak et al. Mol Ther. 2002 5:154-160. 3. Campbell and Drucker. Cell Metab. 2013 17:819-837. 4. Riedel et al. Gene Ther. 2010 Feb; 17(2):171-80. AAV=adeno-associated virus, GLP1=glucagon-like peptide 1, GLP1R=GLP1 receptor, GLP1RA=GLP1R agonist, PGTx=pancreatic gene therapy

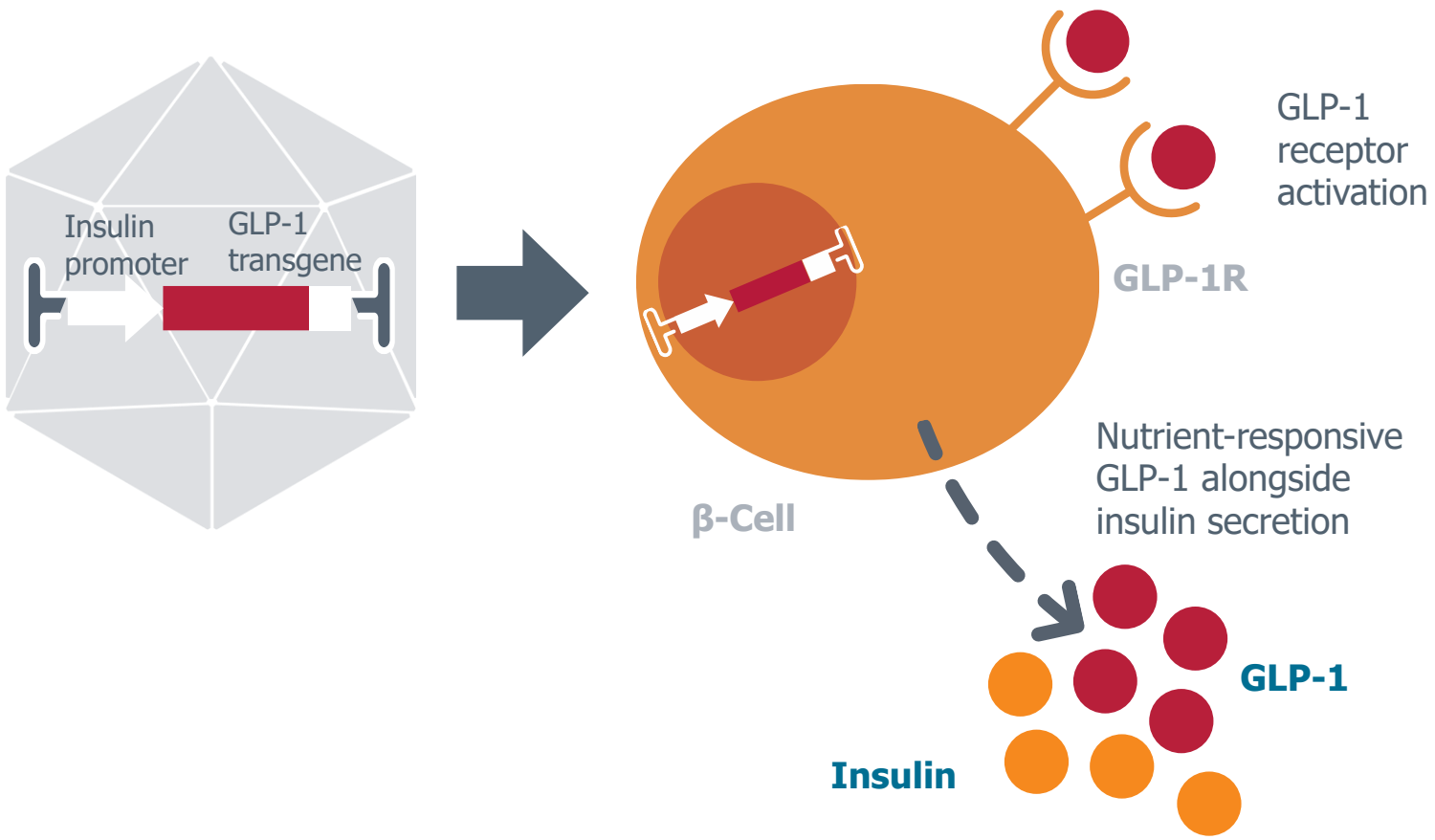
RJVA-001 for T2D

Insulin promoter designed to mimic human physiology

3 Insulin promoter

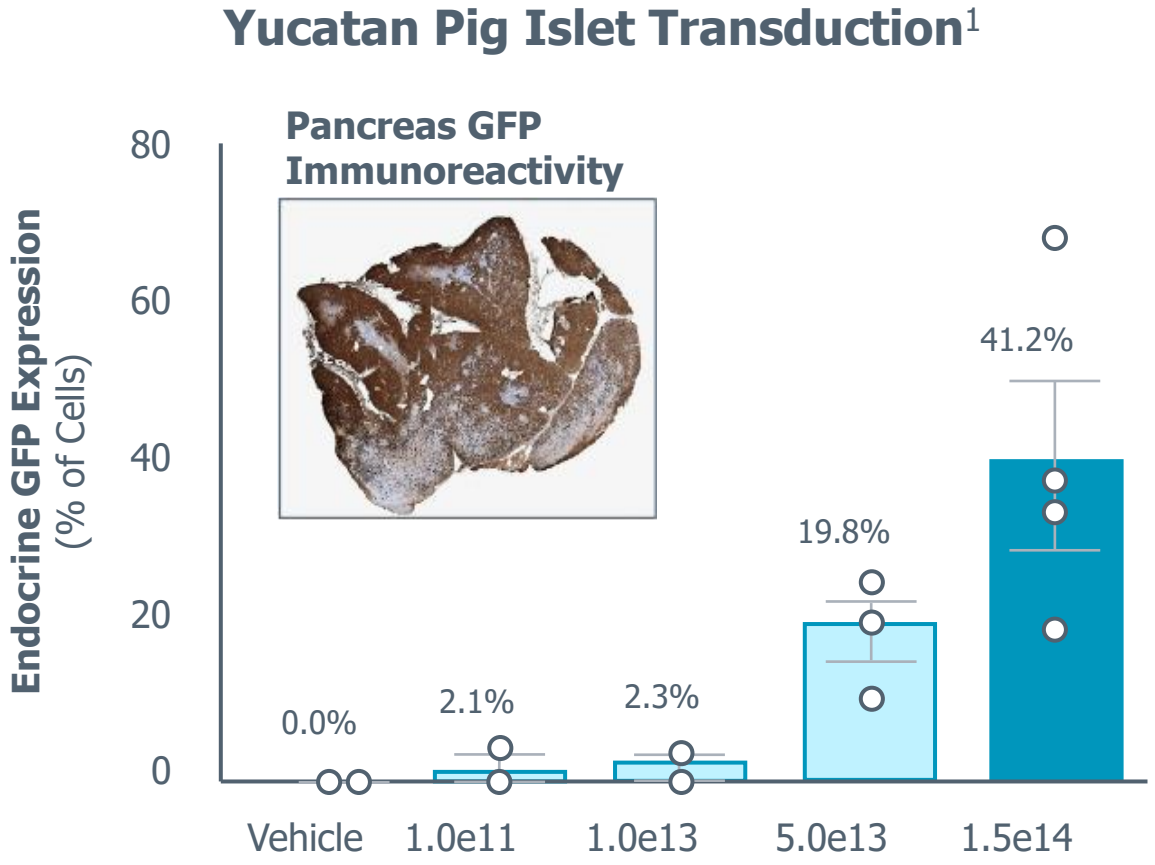
Insulin promoter and regulatory elements designed to maximize benefit and minimize risk:

- Beta cell-restricted transgene expression
- Rapid and tightly regulated secretion
- Glucose concentration-dependent transgene expression
- Augmented, autoregulated, native GLP-1 signaling designed to mimic healthy physiology



Intrapancreatic delivery of AAV9

5.0e13 total VG in Yucatan pig ~ 5e11 VG/kg human dose



>50 animals treated with 100% technical success;
no adverse safety signals to date

Low viral genome dose with limited systemic virus exposure[1]

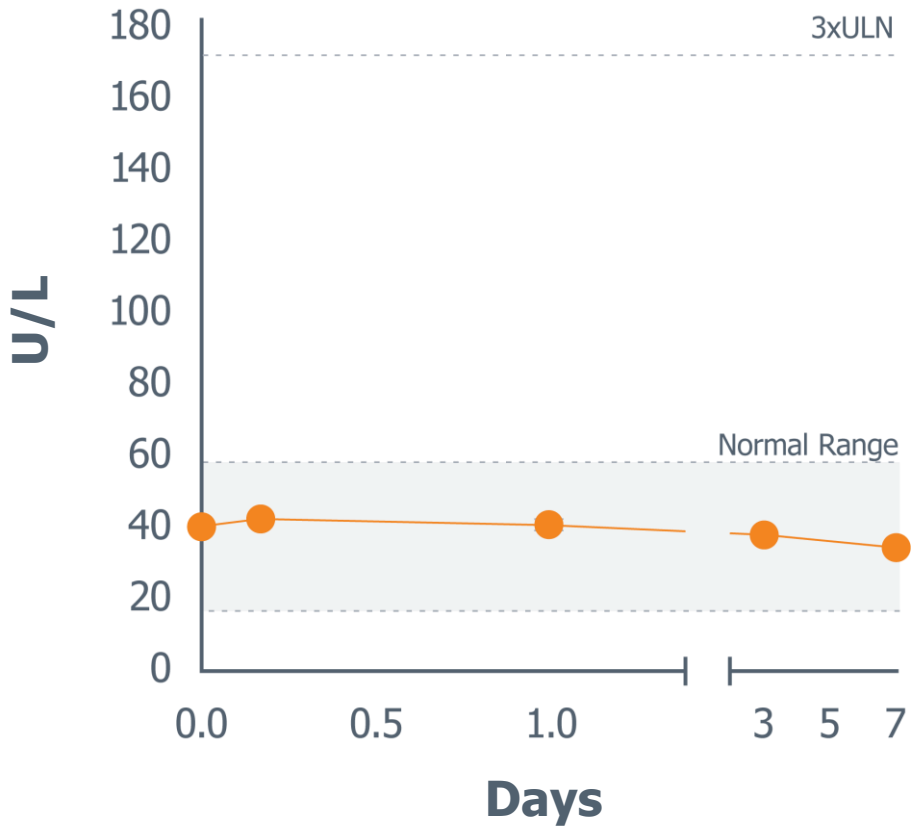
Designed to be 2-3 orders of magnitude less AAV9 than used in Zolgensma®

Mean ± SD shown; n=2-4 per group. 1. Presented at Rajagopalan et al. ASGCT 2023. Abstract no. 191. Oral Presentation

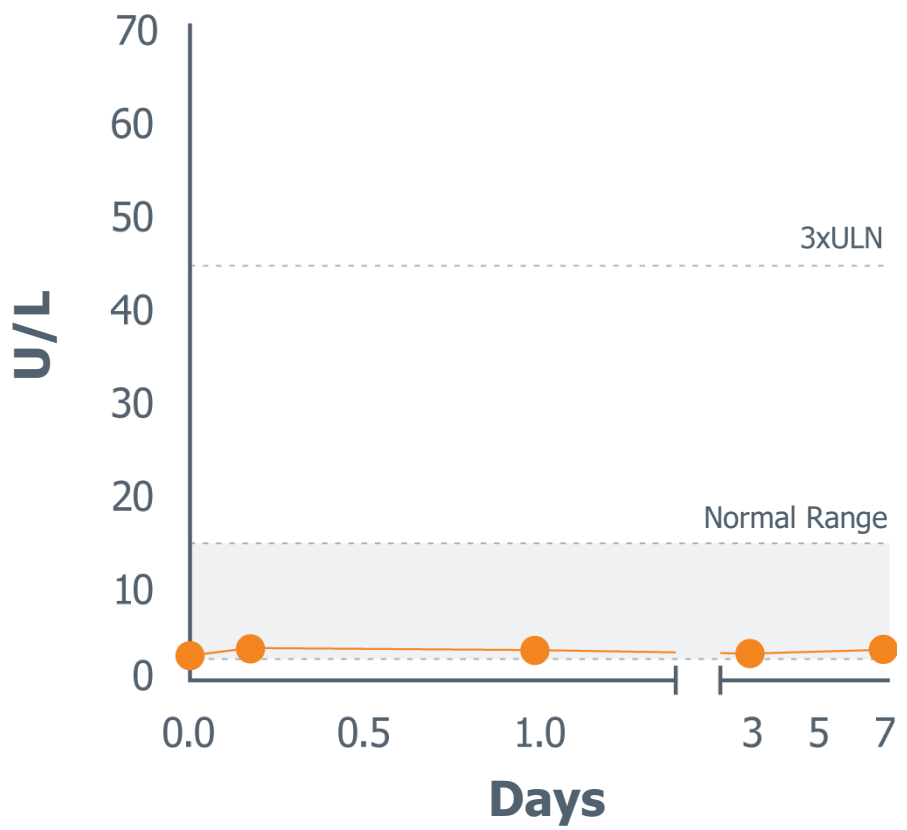
Intrapancreatic AAV9: Toxicology

ALT and lipase levels within normal range across all timepoints

A) 7-day ALT



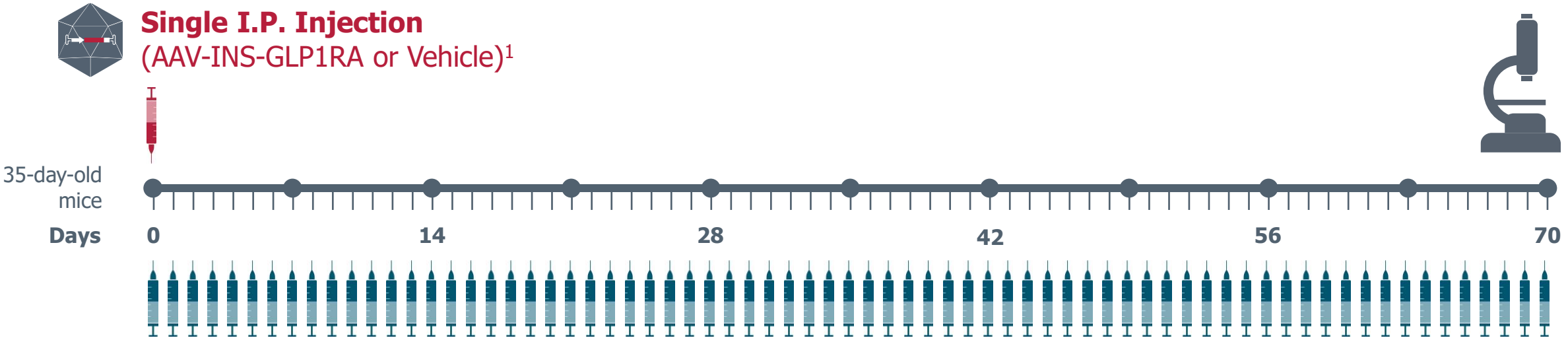
B) 7-day Lipase



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

RJVA-001 prototype* vs. semaglutide

Design of POC efficacy study in db/db mouse (standard T2D model)



Daily S.C. Injection
Semaglutide (10 nmol/kg*) or Vehicle[1]

*Semaglutide dose selected for glucose-lowering optimization[2]

Efficacy/MOA (day 0-70)
Weekly Fasting Blood Glucose
Biweekly Insulin
Weight[1]

Sacrifice (days 58-70)
Organ Histology
Pancreatic GLP-1RA Protein
Serum GLP-1RA Protein[1]

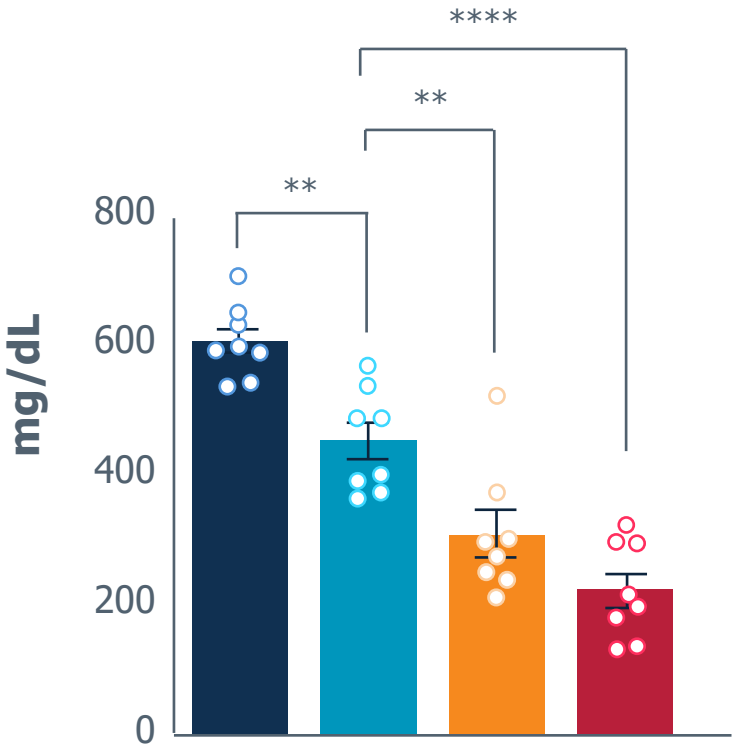
1. Rajagopalan et al. ADA 2023 oral presentation. Control #2023-A-3216-Diabetes 2. CDER (2017) Semaglutide NDA Application (209637Orig1s000), Section 4.4 Nonclinical Pharmacology/Toxicology. AAV=adeno-associated virus, GLP-1=glucagon-like peptide 1, GLP-1RA= GLP-1 receptor agonist, INS=insulin promoter, I.P.=intraperitoneal, MOA=mechanism of action, PGTx=pancreatic gene therapy, S.C.=subcutaneous

RJVA-001 prototype* vs. semaglutide

Glucose and insulin levels after 8 weeks in db/db mice

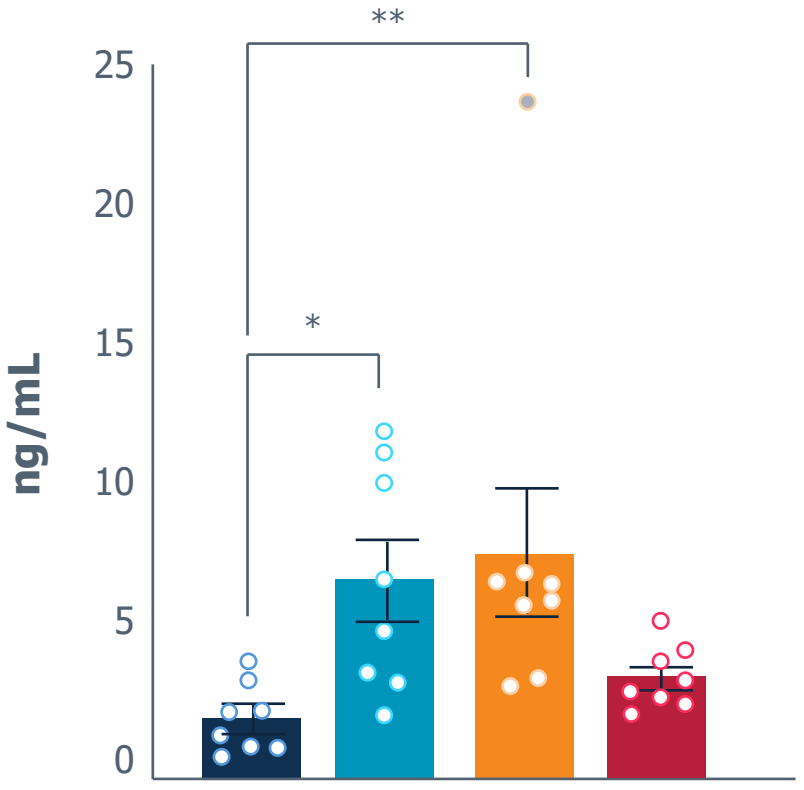
A) Fasting Blood Glucose

(Week 8, 4–6 hour fasted)[1]



B) Fasting Insulin

(Week 8, 4–6 hours fasted)[1]



Vehicle Control

Semaglutide (10 nmol/kg)

AAV-INS-GLP1RA 1st Gen (10e12)

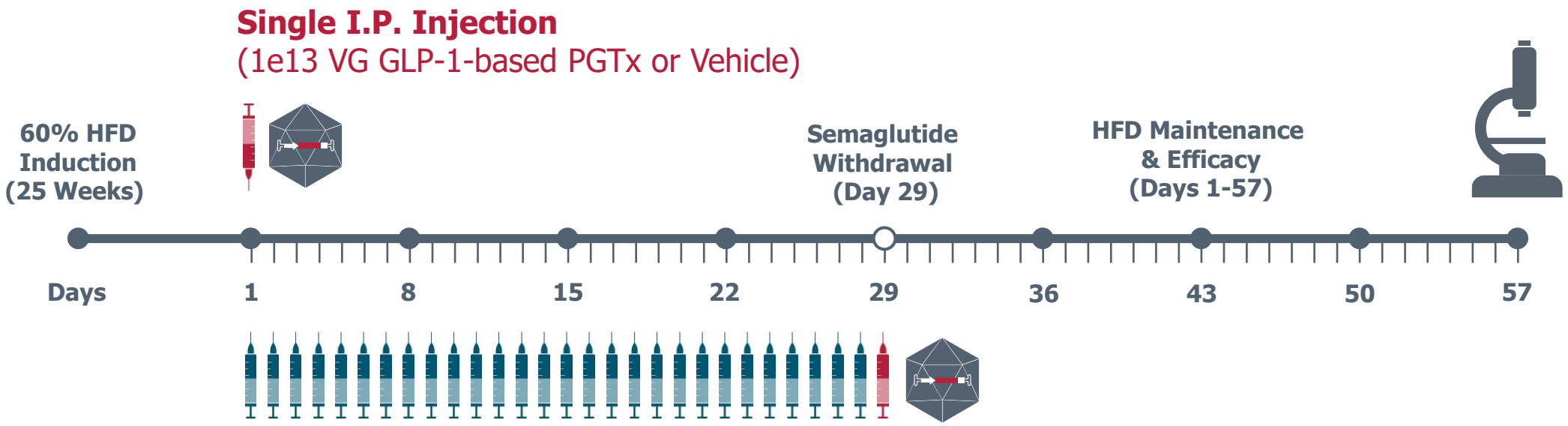
AAV-INS-GLP-1RA 2nd Gen (5e12)†

†Regulatory element modification

1. Rajagopalan et al. ADA 2023 oral presentation. Control #2023-A-3216-Diabetes. Mean ± SEM shown; *p<0.05, **p<0.01, ****p<0.0001; n=8 per group. AAV=adeno-associated virus, Gen=generation, GLP-1=glucagon-like peptide 1, GLP-1RA=GLP1 receptor agonist, INS=insulin promoter, PGTx=pancreatic gene therapy

RJVA-001 prototype* vs. semaglutide

Design of POC efficacy study in DIO mouse (standard obesity model)

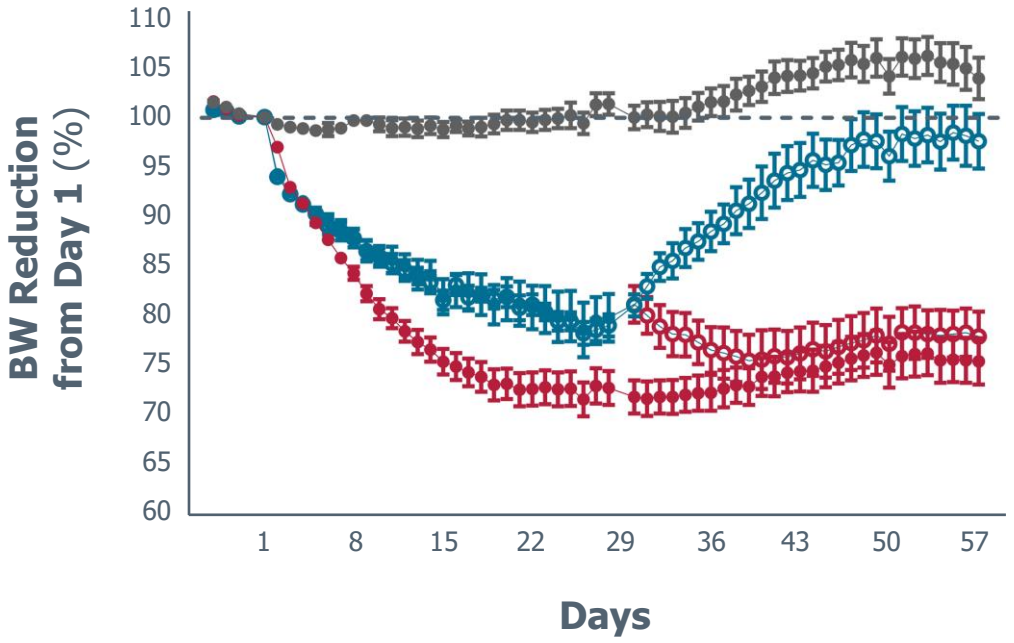


Fitzpatrick AL et al. WCIRDC 2023 oral presentation; AAV=adeno-associated virus, BW=body weight, BWL=body weight loss, DIO=diet-induced obesity, GLP1=glucagon-like peptide 1, GLP1RA= GLP1 receptor agonist, HFD=high fat diet, INS=insulin promoter, I.P.=intraperitoneal, PGTx=pancreatic gene therapy, S.C.=subcutaneous

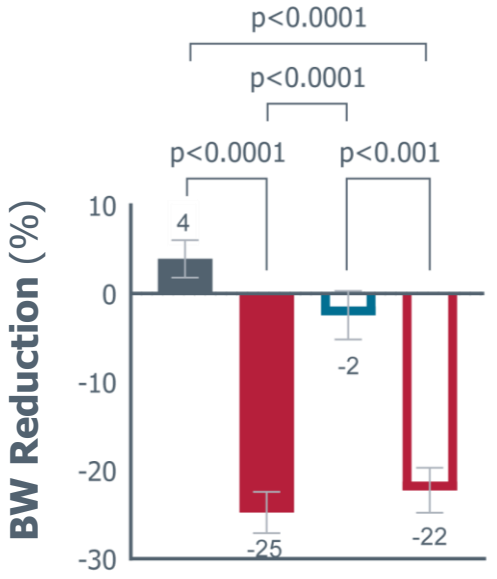
RJVA-001 prototype* vs. semaglutide

Weight loss and food intake in DIO mouse model

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

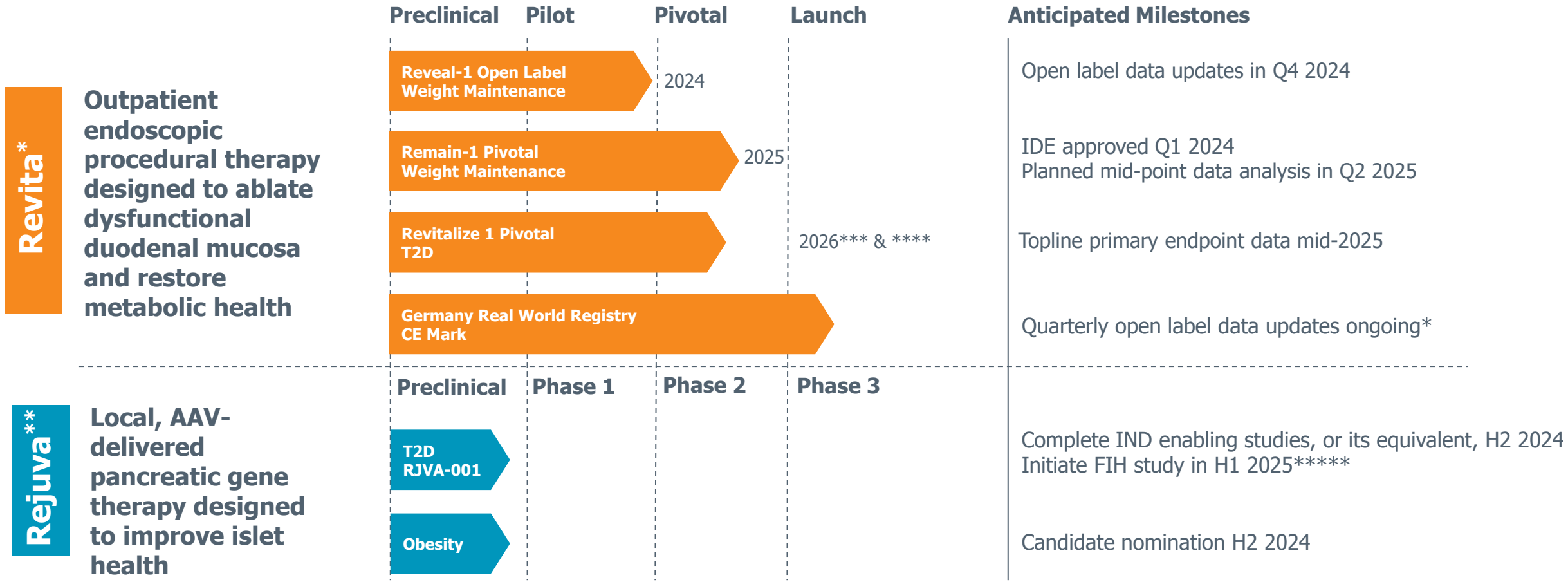
RJVA-001 summary

Nutrient-responsive GLP-1 via intrapancreatic gene therapy

- Utilizes Fractyl's proprietary intrapancreatic delivery system – invented to enable local delivery of pancreatic gene therapy vectors
- Designed for improved potency and tolerability compared to other approaches
- Efficacy in db/db and DIO mouse models of T2D and obesity superior to chronic semaglutide
- Regulatory alignment on IND-enabling studies for T2D FIH study
- RJVA-001 candidate nominated in H1 2024
- Clinical trial initiation in T2D expected in H1 2025

Well-funded with recent IPO proceeds of $110M

Financed to support operations through multiple near-term milestones



*Revita has been granted Breakthrough Device designation for the hydrothermal ablation of the duodenal mucosa to improve glycemic control and eliminate insulin needs in T2D patients inadequately controlled on long-acting insulin; and CE mark obtained from EU and UK in 2016 for Revita for the improvement of glycemic control in patients with inadequately controlled T2D despite oral and/or injectable glucose lowering medications and/or long-acting insulin; **Product candidates under our Rejuva gene therapy platform will undergo Phase 1, Phase 2 and Phase 3 clinical trials ***The Revitalize-1 study is a pivotal study in patients with inadequately controlled T2D on any glucose lowering agent; ****If PMA approved *****subject to IND approval

IND = Investigational New Drug Application with FDA or comparable regulatory body; IDE = Investigational Device Exemption with FDA or comparable regulatory body; FIH = first-in-human; PMA = Premarket Approval

Addressing the major unmet need in obesity

Differentiated, substantial opportunity with multiple near-term catalysts

Obesity: 100M in US with obesity today[1]

GLP-1 drugs have transformed the treatment landscape

Weight maintenance has emerged as the new, significant unmet need

Revita: potentially offers long-term weight maintenance after GLP-1

Weight maintenance data expected starting in Q4 2024

T2D Pivotal study topline readout expected mid-2025

Rejuva: potential remission of metabolic disease via pancreatic gene therapy

Candidate nomination for obesity planned H2 2024

FIH study for T2D planned H1 2025

1. CDC

Investor Relations
Stephen Jasper
Gilmartin Group
stephen@gilmartinir.com
619.949.3681

Lisa Davidson
Chief Financial Officer
IR@fractyl.com
781.902.8800