Revita for Weight Maintenance: FDA IDE Approval for Remain-1 Pivotal and Reveal-1 Open-Label Studies

Corporate Presentation | April 2024

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Our purpose

To defend humanity from metabolic disease

Our mission

To develop transformative therapies that can prevent and hopefully cure metabolic disease

Remain-1 Pivotal Study Executive Summary

Revita aims to be a treatment option for durable weight maintenance after GLP-1 discontinuation

- Use of GLP-1 based drugs predicted to rapidly expand in the coming years
- Discontinuation of these drugs is frequent and multifactorial, often due to intolerability, and frequently leading to regain of weight and worsening of glucose, cardiometabolic risk factors, and body composition[1]
- Standard of care today for weight maintenance after GLP-1 discontinuation is diet and exercise
- 2/3^{rds} of those initially interested in taking a prescription weight loss drug subsequently lose interest when informed about risk of weight regain[2]
- Revita is an outpatient endoscopic procedural therapy targeting the duodenal mucosa, which is a root cause of obesity and T2D
- The Remain-1 study is the first approved pivotal IDE of a potential weight maintenance therapy after discontinuation of GLP-1 based drugs

1. Wilding JPH, Diabetes Obes Metab.2022;24:1553–1564 and Aronne et al JAMA. 2024;331(1):38-48 2. Source: KFF Health Tracking Poll (July 11-19 2023)

Metabolic diseases are a massive market

With significant CAGR

Highly potent drugs in GLP-1RA class are now available for T2D, obesity, and CV mortality

$65B in annual pharmaceutical spend on T2D and obesity in 2022

However, conventional GLP-1RA therapies limited by need for chronic administration and high discontinuation rates

- Over 50% discontinue within 1 year[1]
- Patients who discontinue are unlikely to experience durable benefit from GLP-1RA Rx[2]

Lowering glucose and weight is now easy, **but keeping it off is still hard**

Estimated Worldwide Market For Diabetes / Obesity Drugs By Class ($MM, Net Sales)[3]

	2022	2028	'22 – '28
Drug Class	**Market**	**Market**	**% CAGR**
Injectable Incretin Diabetes	**$18,769**	**$44,514**	**15%**
Injectable Incretin Obesity	**$2,519**	**$20,134**	**41%**
Oral Incretin Diabetes	**$1,657**	**$5,363**	**22%**

1. Rowley et al Population Health Mgmt 2017 2. Wilding JPH, Diabetes Obes Metab.2022;24:1553–1564 and Aronne et al JAMA. 2024;331(1):38-48
3. Source: TD Cowen estimates

Obesity is the largest metabolic disease market opportunity

Unmet need has shifted from weight loss to weight maintenance

> 40%

of adult US population is obese[1]

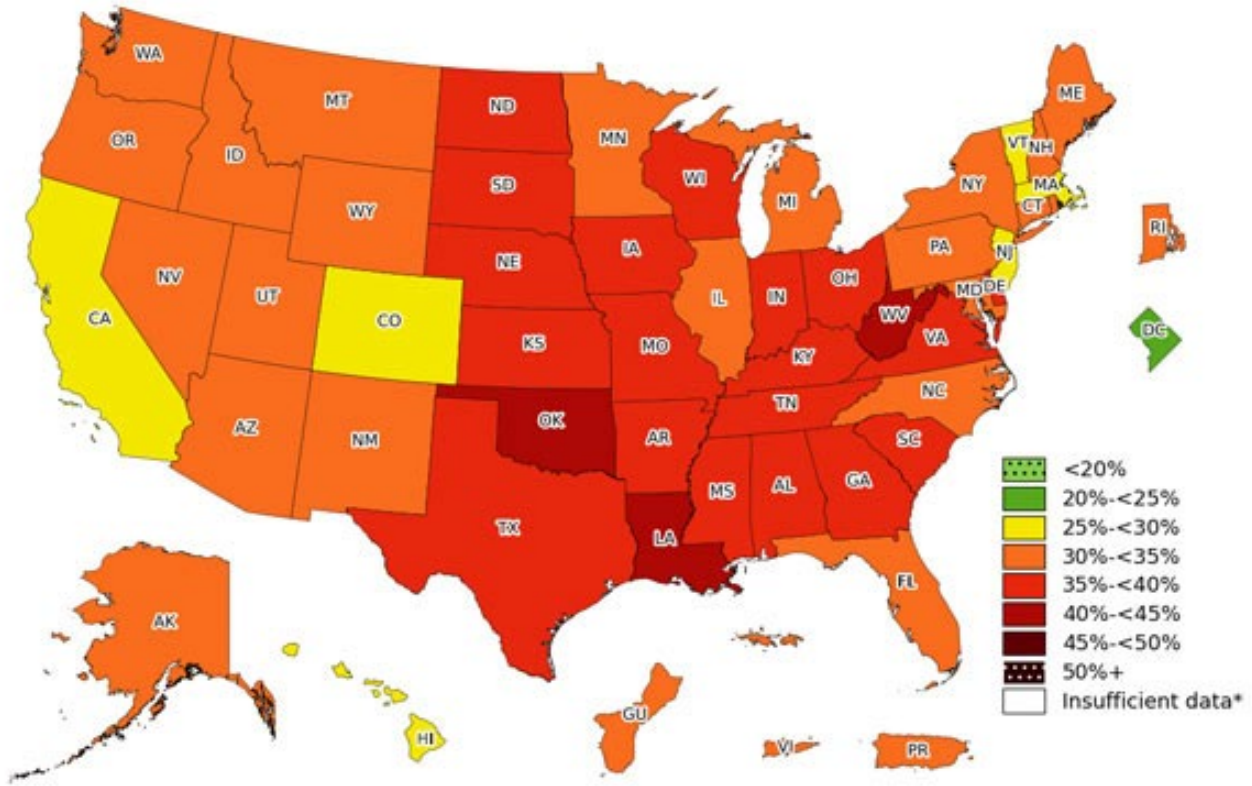
$2.5B

in branded GLP-1 drug sales in 2022 with 41% CAGR[2]

> 50%

who start GLP-1RAs discontinue within 1 year[3]

CDC 2022 Adult Obesity Prevalence[1]



1. CDC 2. TD Cowen estimated 3. Polonsky et al. Diabetes Ther. 13, 175–187 (2022)

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HEALTH NEWS ✓ Fact Checked

Ozempic Rebound: Why Most People Regain Weight After Stopping Semaglutide

Taking semaglutide medications like Wegovy and Ozempic can help once they stop. Sergey Mironov/Getty Images

- Research has found that when people stop using Ozempic and Wegovy, weight rebound occurs
- Experts say this is because the drug is not a
adaptation that occurs during weight loss

CNN health

Life, But Better · Fitness · Food · Sleep · Mindfulness · Relationships

To keep pounds off, patients may need to continue taking weight loss drug, study suggests

By Brenda Goodman, CNN

6 minute read · Published 10:00 AM EST, Mon December 11, 2023

e or overweight with at least one health problem related to their weight.

Eli Lilly and Company

WSJ · Barron's · MarketWatch · IBD

DJIA 37804.43 0.01% ▼ · S&P 500 4879.16 0.22% ▲ · Nasdaq 15513.09 0.20% ▲ · U.S. 10 Yr 2/32 Yield 4.162% ▲ · Crude Oil 76.46 1.82% ▲ · Euro 1.0834 0.49% ▼

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HEALTH

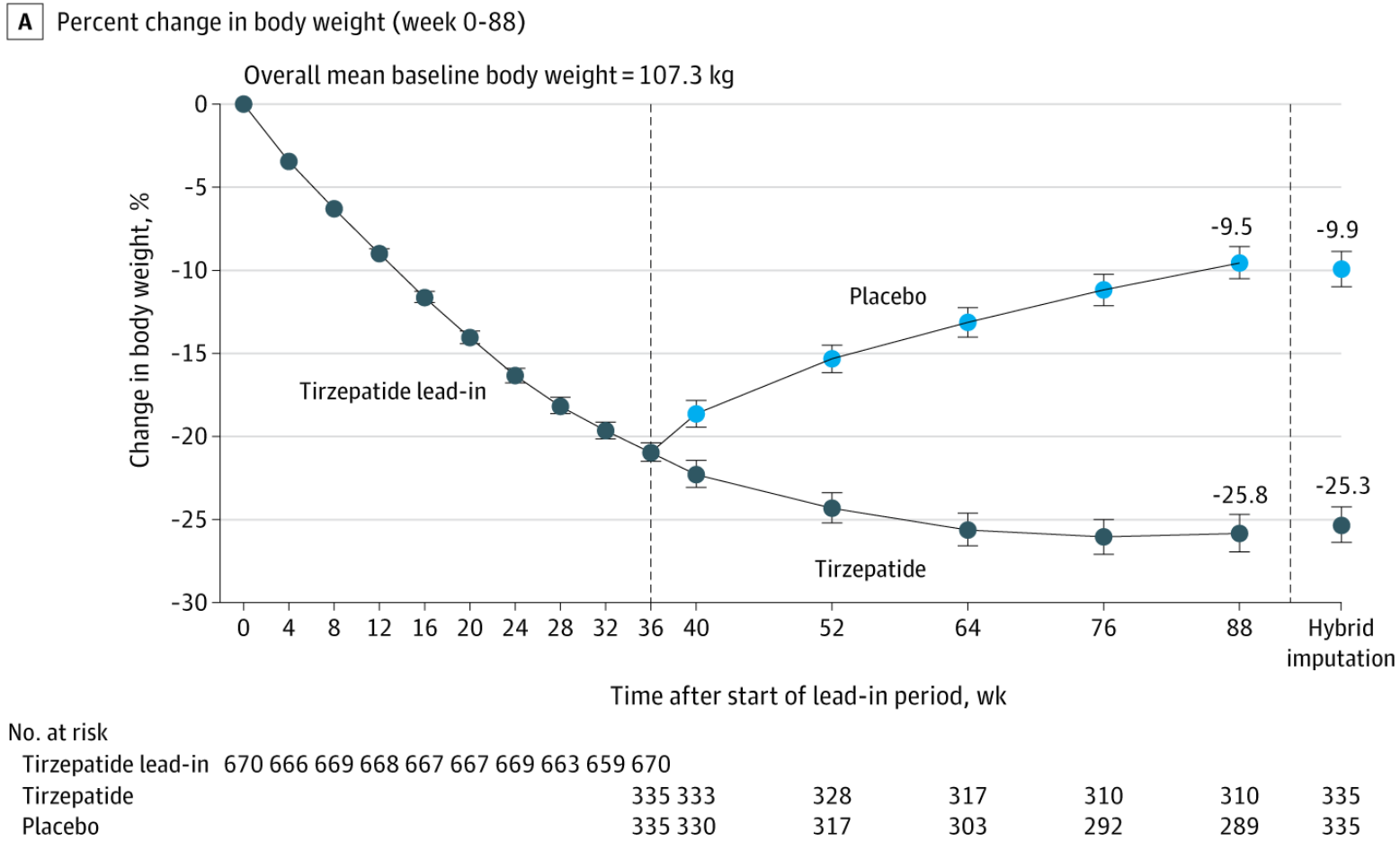
What Happens When You Stop Taking Ozempic?

Many people become heavier after halting the use of semaglutide to manage weight

Surmount-4: Blueprint for Design of Remain-1

"Withdrawing tirzepatide led to substantial regain of lost weight"[1]

- Initial open-label tirzepatide lead-in period over 36 weeks (as adjunct to reduced calorie diet and increased physical activity)
- Double-blind treatment period with tirzepatide withdrawal ("placebo") vs ongoing tirzepatide MTD
- > 20% TBW loss by week 36 but significant regain of lost weight 1 year after discontinuation

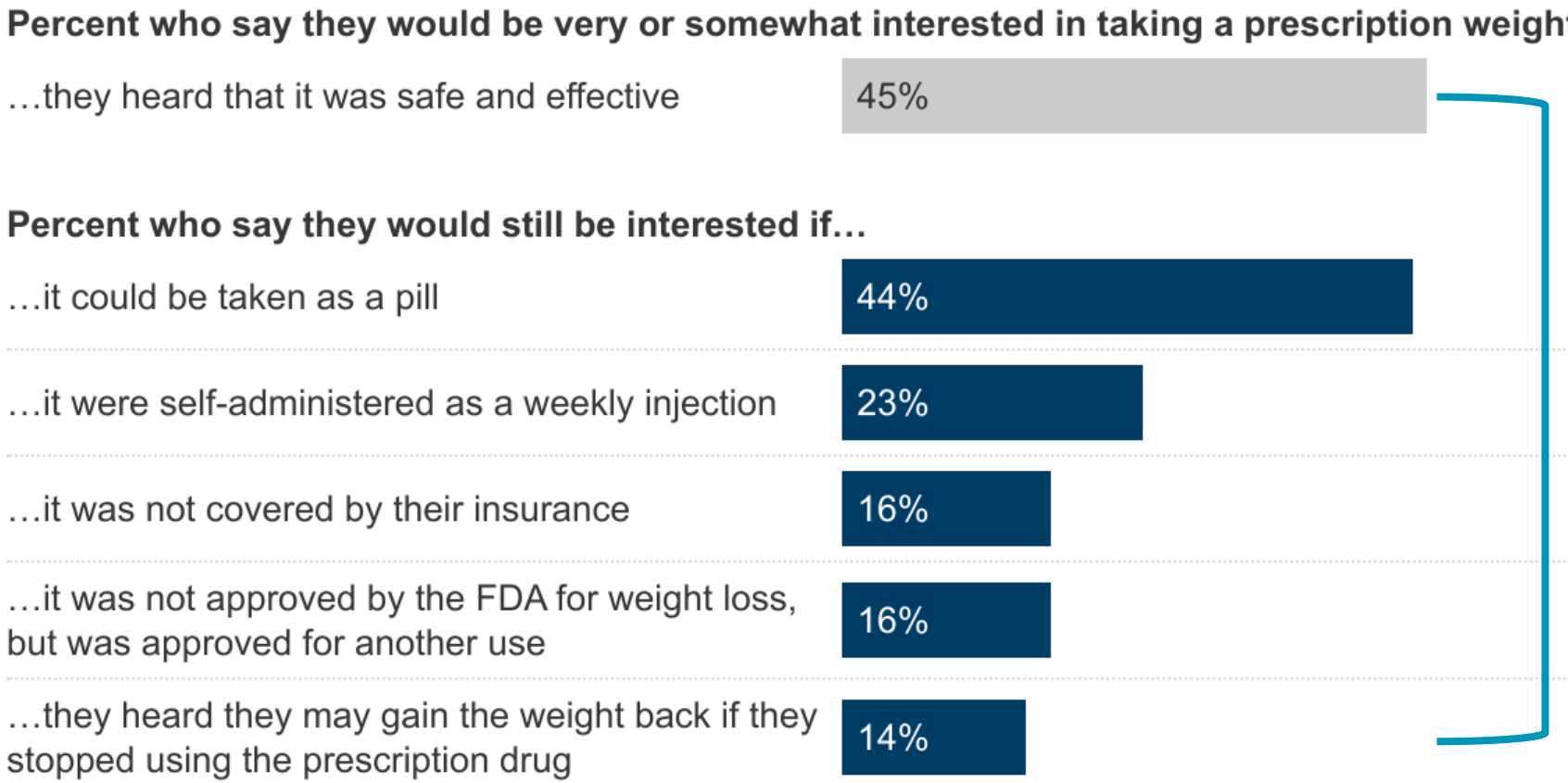


MTD = Maximally Tolerated Dose

1. Aronne et al JAMA. 2024;331(1):38-48.

Patients Are Concerned About Weight Regain

Only 14% are interested in starting weight loss drugs if appropriately informed about risk of weight regain after stopping the drugs



2/3rds of those initially interested in taking a prescription weight loss drug subsequently **lose interest when informed about risk of weight regain**

SOURCE: KFF Health Tracking Poll (July 11-19, 2023)

Revita for obesity

Goal: Provide durable, effortless weight maintenance for millions of people with obesity

Revita Weight Maintenance in Prior Studies

Pooled weight loss data demonstrated sustained weight maintenance in T2D[1]

Patient population

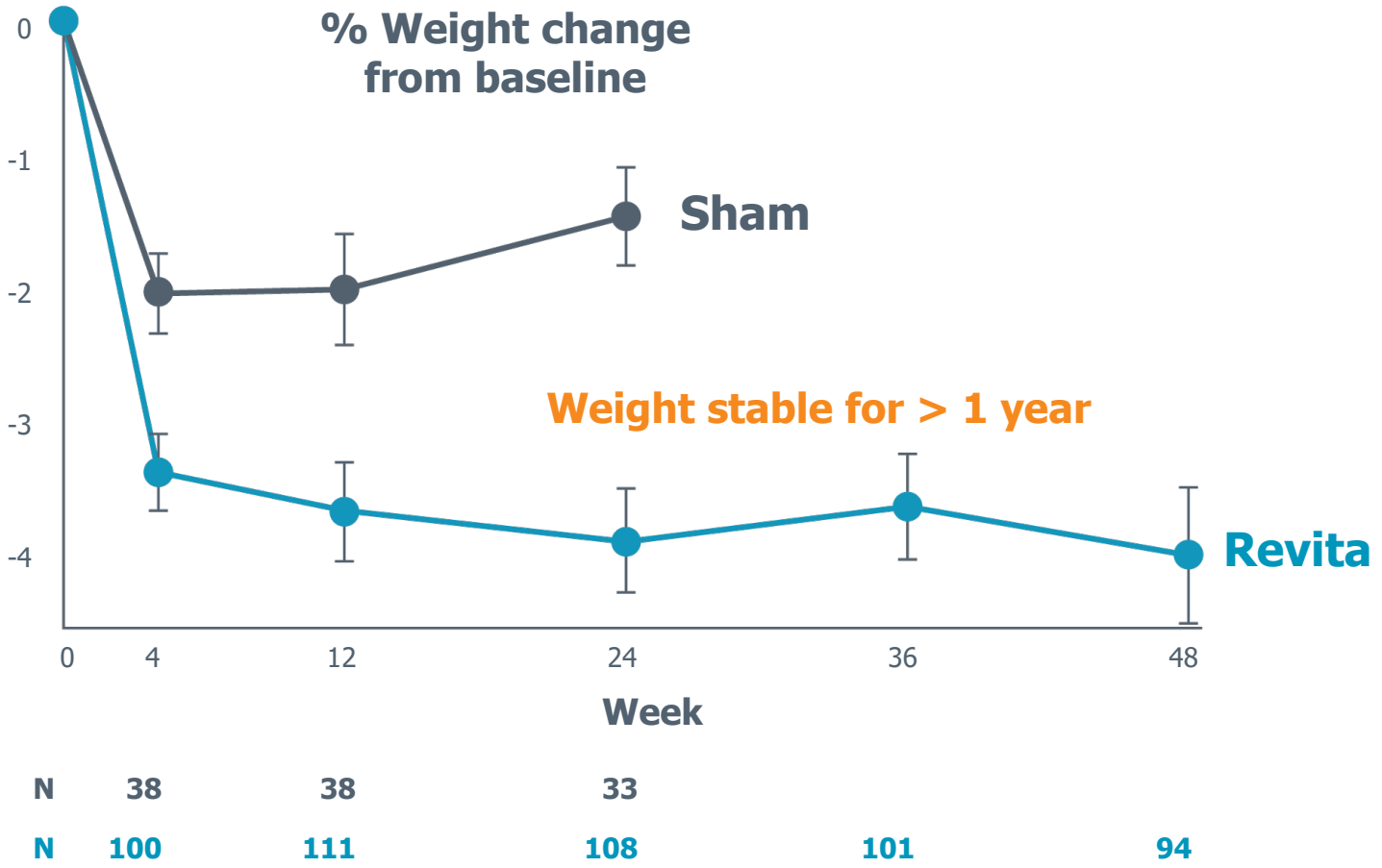
Patients with advanced T2D on multiple ADAs

Baseline Demographics

Baseline 93 kg (BMI 31.1)

HbA1c 8.3%

T2D Duration 10 years



Ozempic 1mg 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

Latest Real-World Registry Data Show Weight Loss

Weight loss and glucose control in people with T2D treated with Revita + diet/lifestyle intervention[1]

Patient population

Patients with T2D on at least 1 ADA at baseline

Baseline demographics

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

	Baseline n=14 Median (min,max)	**3 Month n=14 Median** (min,max)	**Change from Baseline to 3 Month Median Results**
Weight (lbs)	**244.7** (145.5, 306.4)	**227.1** (136.7, 291)	**- 17.6 lbs**
HbA1c (%)	**9.2** (5.6,12.8)	**7.3** (5.7,15.8)	**- 1.9 %**

1. Fractyl Health, Data on File ADAs = Anti-diabetic agents

Tirzepatide Withdrawal Worsens Metabolic Profile

Benefits on weight, glucose, CV parameters while on treatment all worsen upon withdrawal

Surmount-4[1]

Tirzepatide MTD vs Tirzepatide withdrawal ("placebo")

Weight regain, glucose and cardiometabolic risk factors worsen after withdrawal

eTable 3. Primary and secondary end points (efficacy estimand)[a]

	Estimate (95% CI)			
	Tirzepatide MTD (N=335)	Placebo (N=335)	Absolute difference[b] (95% CI)	P value
Primary end point[c]				
Percent change in body weight (week 36 to 88), %	-6.7 (-7.7 to -5.7)	14.8 (13.8 to 15.8)	-21.4 (-22.9 to -20.0)	<.001
Key secondary end points[c,d]				
Change in body weight (week 36 to 88), kg	-5.7 (-6.5 to -4.9)	11.9 (11.1 to 12.7)	-17.6 (-18.8 to -16.4)	<.001
Change in waist circumference (week 36 to 88), cm	-4.6 (-5.4 to -3.8)	8.3 (7.4 to 9.2)	-12.9 (-14.1 to -11.7)	<.001
Participants maintaining ≥80% of body weight lost (week 88), No. (%)	310 (93.4)	44 (13.5)	95.9 (54.7 to 168.1)	<.001
Participants achieving body weight reduction (week 0 to 88), No. (%)				
≥5%	327 (98.5)	227 (69.0)	47.3 (18.3 to 122.0)	<.001
≥10%	312 (94.0)	146 (44.4)	71.5 (34.5 to 148.4)	<.001
≥15%	289 (87.1)	79 (24.0)	80.0 (42.1 to 152.1)	<.001
≥20%	241 (72.6)	38 (11.6)	140.8 (66.1 to 300.3)	<.001
Percent change in body weight (week 36 to 64), %	-6.0 (-6.7 to -5.3)	9.9 (9.2 to 10.6)	-15.9 (-16.9 to -14.9)	<.001
Additional secondary end points[e] **(week 36 to 88)**				
Change in BMI	-2.1 (-2.4 to -1.8)	4.3 (4.0 to 4.6)	-6.4 (-6.8 to -6.0)	<.001
Change in hemoglobin A_{1c}, %	-0.08 (-0.11 to -0.05)	0.25 (0.22 to 0.28)	-0.33 (-0.38 to -0.28)	<.001
Change in fasting glucose, mg/dL	-0.9 (-1.9 to 0.1)	7.7 (6.6 to 8.8)	-8.6 (-10.1 to -7.2)	<.001
Percent change in fasting insulin, %[f]	-15.4 (-21.0 to -9.8)	23.3 (14.7 to 31.9)	-31.4 (-37.7 to -24.4)	<.001
Percent change in lipid levels, %[f]				
Total cholesterol	2.3 (0.6 to 4.0)	8.3 (6.5 to 10.2)	-5.5 (-7.8 to -3.3)	<.001
Non-HDL-C	-4.0 (-6.1 to -1.9)	5.5 (3.1 to 7.9)	-9.0 (-11.9 to -6.1)	<.001
HDL-C	18.3 (16.2 to 20.4)	14.6 (12.5 to 16.7)	3.2 (0.6 to 5.8)	.014
LDL-C	-3.4 (-5.8 to -1.0)	3.4 (0.7 to 6.1)	-6.6 (-9.9 to -3.2)	<.001
VLDL-C	-7.8 (-11.3 to -4.3)	14.7 (10.2 to 19.3)	-19.7 (-24.0 to -15.1)	<.001
Triglycerides	-8.2 (-11.8 to -4.7)	15.6 (10.9 to 20.3)	-20.6 (-24.9 to -16.0)	<.001
Free fatty acids	-13.4 (-18.4 to -8.4)	-2.9 (-8.7 to 2.9)	-10.8 (-17.9 to -3.0)	.008

1. Aronne et al JAMA. 2024;331(1):38-48.

Reveal-1 Open-Label Cohort[1]

Weight maintenance after GLP-1RA discontinuation

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 *or* GLP-1 drug naïve with run-in period to achieve at least 15% TBW loss with tirzepatide ~ 50 participants	Change from baseline in weight	Glucose, CV risk factors	Single-arm, open-label, cohort study of Revita after GLP-1RA discontinuation Diet and lifestyle counseling throughout	Open-label study updates starting H2 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

Aim to reduce weight regain from baseline by at least 50% compared to sham at 24 and 48 weeks

Patient population

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

Run-in period to achieve at least 15% TBW loss with tirzepatide

315 participants with sample size re-estimation after 75% of participants randomized

Co-Primary endpoints

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

Key secondary endpoints

Glucose,
CV risk factors

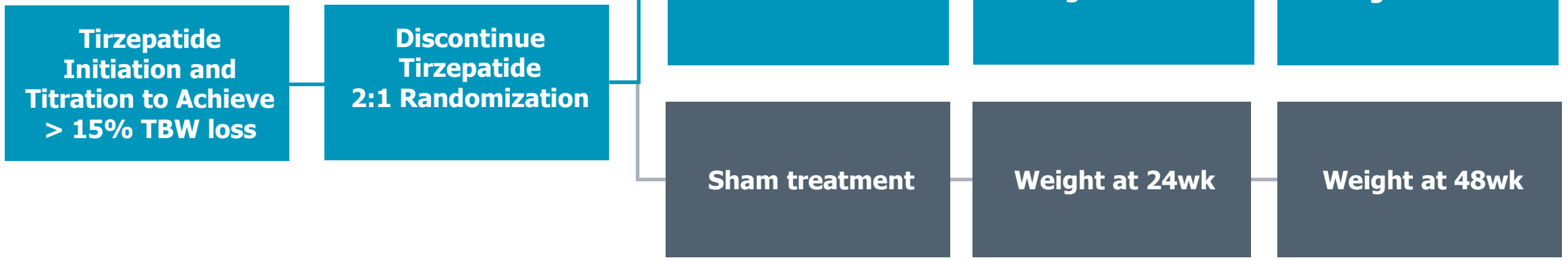
Study Design

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

Diet and lifestyle counseling throughout

Anticipated timing

IDE approved Q1 2024
Study initiation H2 2024



TBW = total body weight

Study Design Comparisons

Surmount-4, Remain-1, Reveal-1 key similarities and differences

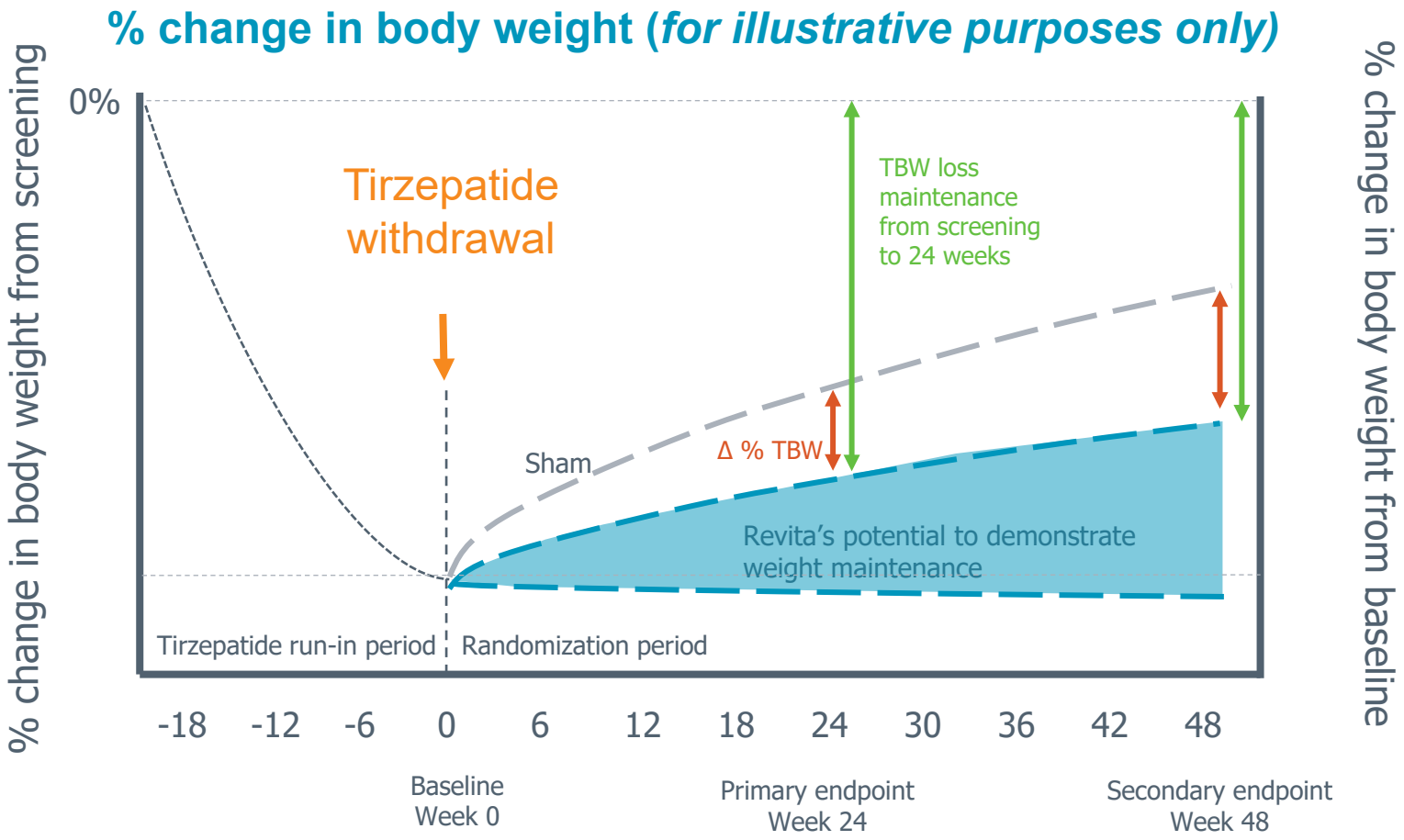
	Surmount-4[1]	Remain-1 Randomized	Reveal-1 Open-Label Cohort
Patient Population	BMI ≥ 30 or BMI ≥ 27 with at least 1 weight-related comorbidity	BMI ≥ 30	BMI ≥ 30 prior to GLP-1RA therapy
GLP-1RA Status	GLP-1RA naive	GLP-1RA naïve	GLP-1RA naïve or already achieved at least 15% TBW loss with GLP-1RA[2]
Study Design	Open label run-in titration period of 36 weeks followed by double blind randomized withdrawal vs continuation	Open label run-in titration period to achieve at least 15% TBW loss, followed by withdrawal, double-blind randomization Revita vs sham (2:1)	Open-label run-in titration on tirzepatide only if not already achieving GLP-1RA-mediated at least 15% TBW loss, followed by withdrawal and open-label Revita
Concurrent Treatment	Reduced calorie diet and increased physical activity	Reduced calorie diet and increased physical activity	Reduced calorie diet and increased physical activity
Primary Endpoints Timing	52 weeks after baseline randomization	24 weeks after baseline randomization (blinding maintained through 48 weeks)	Ongoing open-label assessments
Secondary Endpoints	Glucose, cardiometabolic, quality of life	Glucose, cardiometabolic, quality of life	Glucose, cardiometabolic, and quality of life

1. Aronne et al JAMA. 2024;331(1):38-48. Sponsored by Eli Lilly 2. Semaglutide and tirzepatide only acceptable GLP-1RAs

Potential Results from Remain-1 Pivotal Study

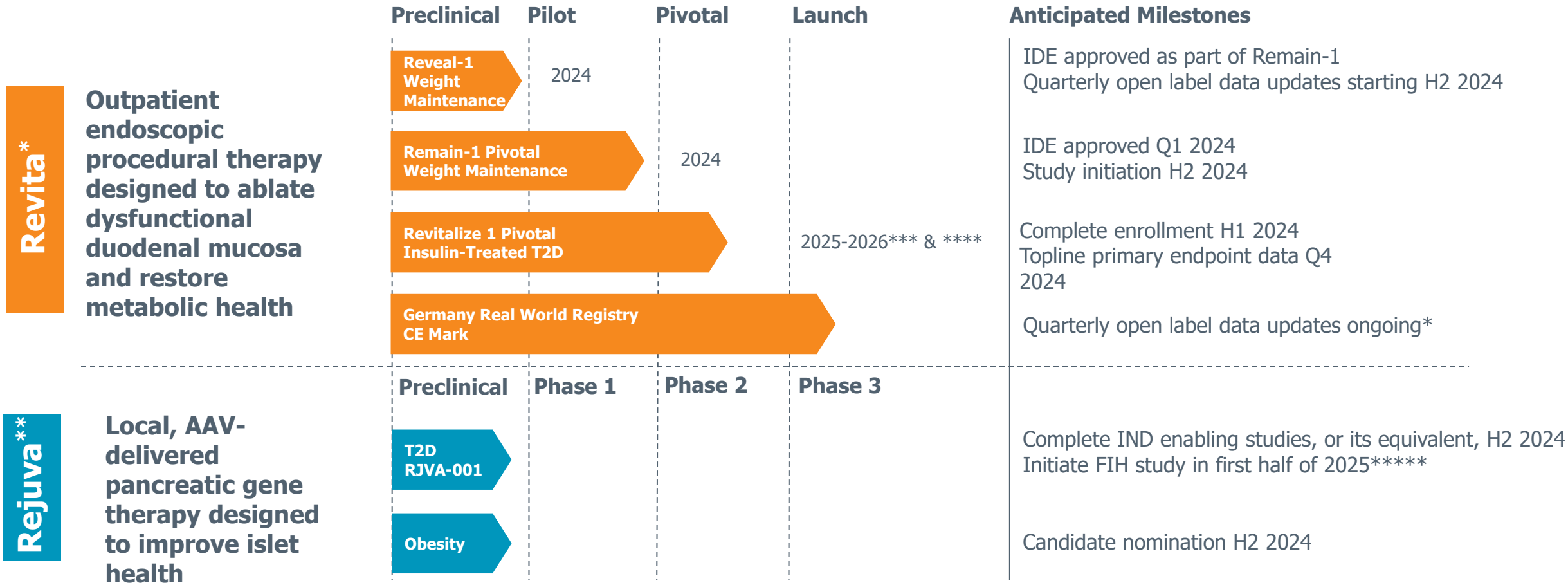
Co-primary endpoints will evaluate change from baseline in total body weight through 24 weeks

- **Co-primary endpoint #1:** % Change in body weight from baseline to week 24, Revita vs sham (success criteria: statistical superiority of Revita > sham)
- **Co-primary endpoint #2:** % of Revita participants who maintain at least 5% TBW loss from screening to week 24 (success criteria: > 50% response rate in Revita arm)
- **Sample size and powering assumptions:** n=315 participants with 2:1 allocation to Revita:sham. Sample size re-estimation after 200 participants are randomized (up to 500 participants)



Revita and Rejuva clinical pipeline

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 despite being on up to three ADAs and daily insulin; ****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

Revita Background Information

Mechanism of Action, Device and Procedure Description, Safety Summary

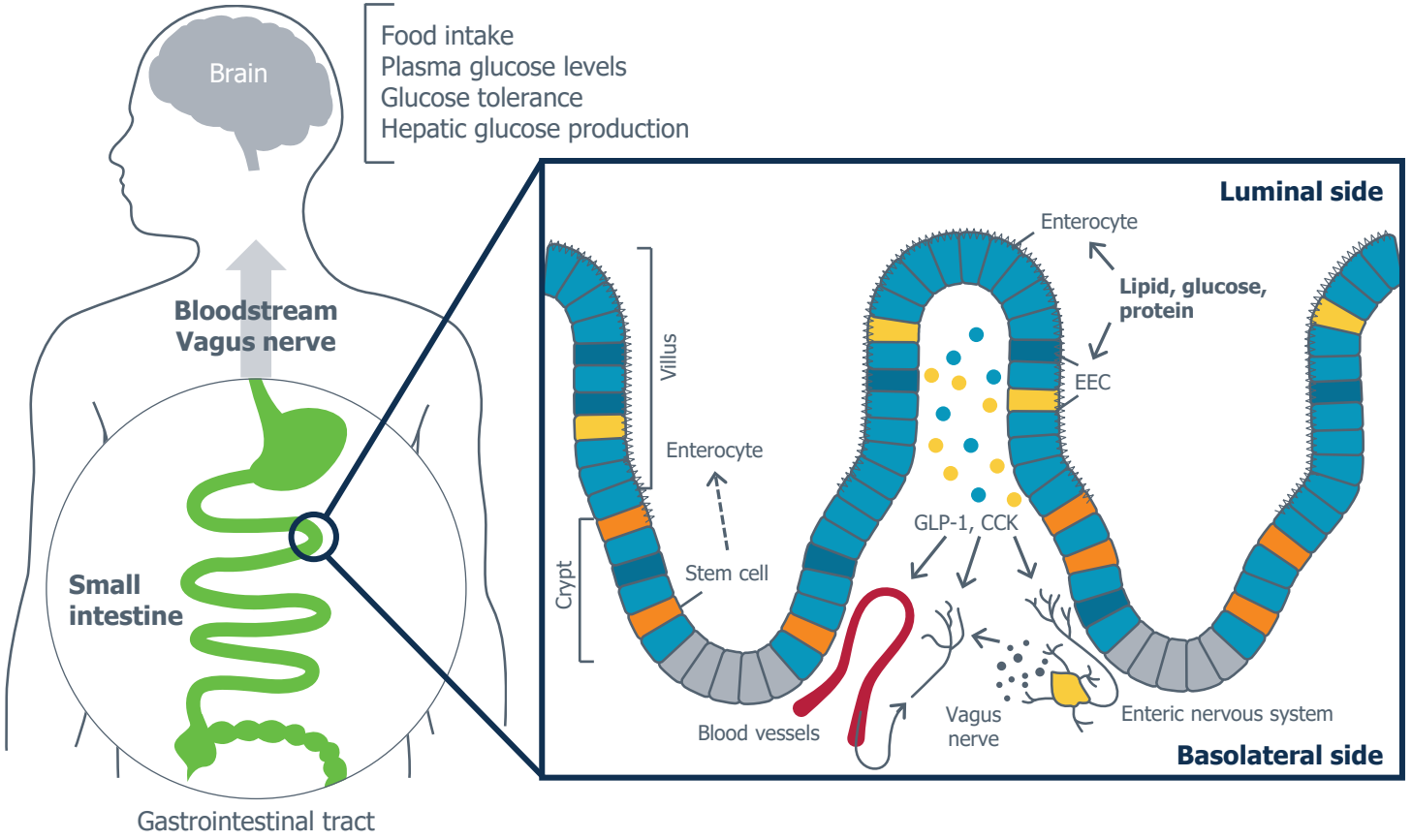
Duodenum is a central regulator of metabolic control

Key nutrient sensor and signaling beacon for brain

Duodenum is a critical neuro-endocrine organ

- First part of small intestine and key site for absorption, sensing, and signaling
- Blood + nerve signaling pathways from duodenal surface to brain
- Brain then regulates appetite and blood sugar

Known beneficial effects of duodenal bypass on weight maintenance and glucose control

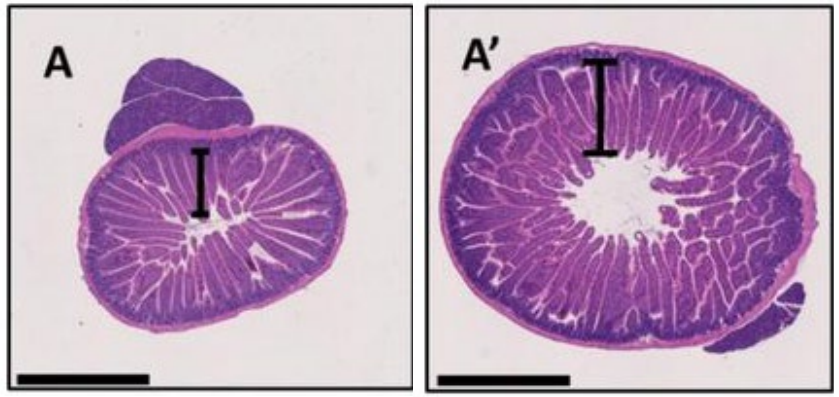


Adapted from Duca et al Cell Metab. 2015 22:367-380

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

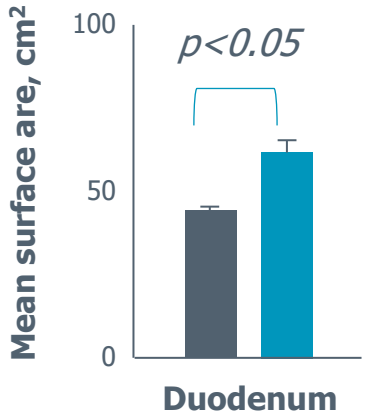
Driven by chronic exposure to high fat and high sugar diets[2]

HFHSD causes duodenal hyperplasia[3]

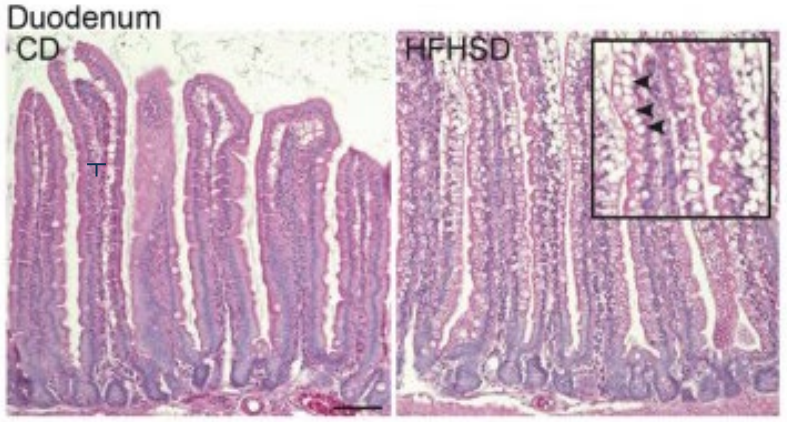


Normal diet HFHSD

50% greater mucosal surface area[3]



Increased enteroendocrine cell types[1]



Chronic high fat and high sugar diets cause gut dysfunction

Gut dysfunction alters gut-brain signaling[1-2]

Altered gut-brain signaling 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 [3] West et al bioRxiv 822122; CD = Chow Diet HFHSD = High Fat High Sugar Diet

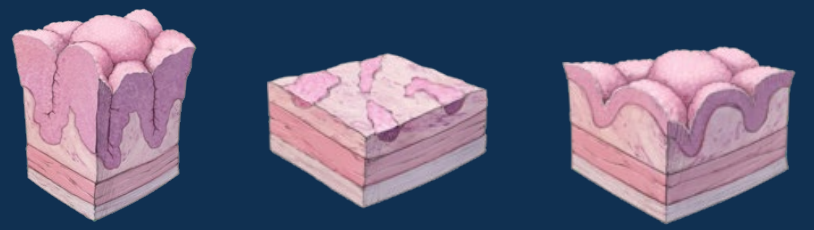
Revita summary

Revita is an outpatient endoscopic procedure that targets the duodenum to reverse pathology in the duodenal lining that is a root cause of obesity and T2D

CE mark in EU; reimbursement authorization in Germany

Initiated pilot commercial launch and Real World Registry study in 1H 2023 in Germany

Registrational studies underway in the U.S.



Revita aims to be the non-drug alternative to control weight and glucose by targeting the gut

In **obesity**, Revita is a potential non-drug alternative that can offer durable weight maintenance and other metabolic benefits for patients after discontinuing GLP-1RA therapies

In **T2D**, Revita is a potential non-drug alternative for patients with inadequately controlled T2D despite standard of care, who need to improve metabolic control while reducing insulin burden

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 in Germany

Breakthrough Designation from FDA in insulin-treated T2D

Control console with user-friendly touch screen interface automates majority of procedure

Real-time sensors designed to monitor procedure and ensure technical success and safety

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

Single-use catheter optimized with over 300 clinical procedures to date

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

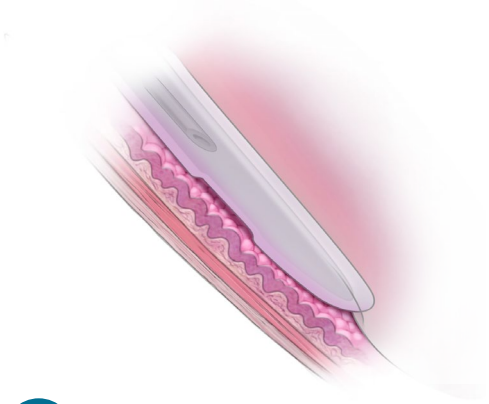
Revita endoscopic procedural therapy

Procedure designed to provide a thermal protection before ablation

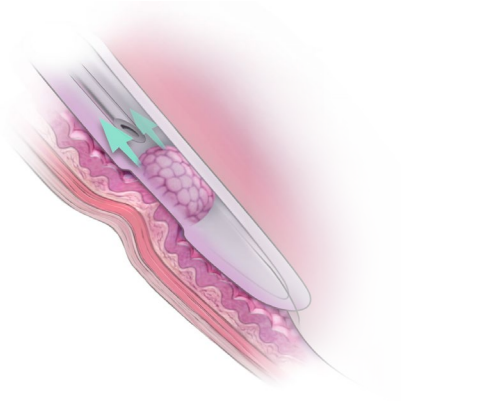
Thermal protection designed to protect deeper layers before ablation (or potentially repeat treatments)

Sequence progresses from Ampulla of Vater to end of duodenum (> 10-14 cm)

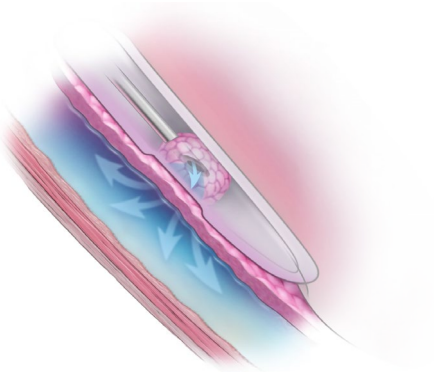
Conducted under direct endoscopic visualization of entire procedure



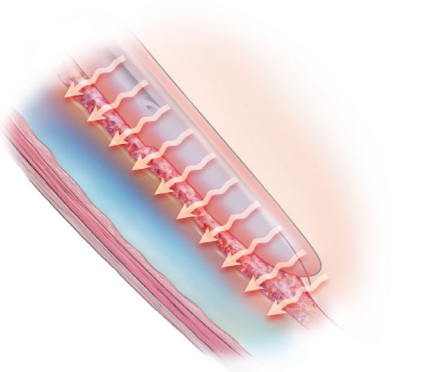
1 Revita catheter engages duodenal lining



2 Catheter port vacuums mucosa and advances needle into submucosa



3 Needles inject saline circumferentially into submucosa



4 Hydrothermal ablation follows in thermally protected area

Encouraging tolerability and AE profile

Well validated experience in > 300 trial participants and multiple centers

- No long-term device or procedure-related AEs
- Gastrointestinal AEs infrequent, mild and transient in nature
- Typically lasting 1-2 days and mostly mild in severity
- Consistent with routine upper endoscopic procedures
- Abdominal pain, abdominal distention, nausea, and diarrhea most commonly reported
- Few hypoglycemic events were mild in severity and only associated with medicines known to cause hypoglycemia
- No clinical or laboratory signs or reports of malabsorption, nutrient deficiency, pancreatitis, or infection

AE = adverse event

Thank you!

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