올해 8월 국내 출시 예정인 비만치료의 게임체인저

Tirzepatide 핵심포인트

Recent Evidence on the Once-Weekly Incretin Therapy

Department of Family Medicine, Dong-A University Hospital
Shine Bo Kyung

Content Overview

- **Pharmacotherapies for Weight Management and MoA of Tirzepatide**

- **Highlights From Clinical Trials of Emerging Anti-Obesity Medications**
  - Tirzepatide: SURMOUNT Studies
    1. SURMOUNT-1
    2. SURMOUNT-5

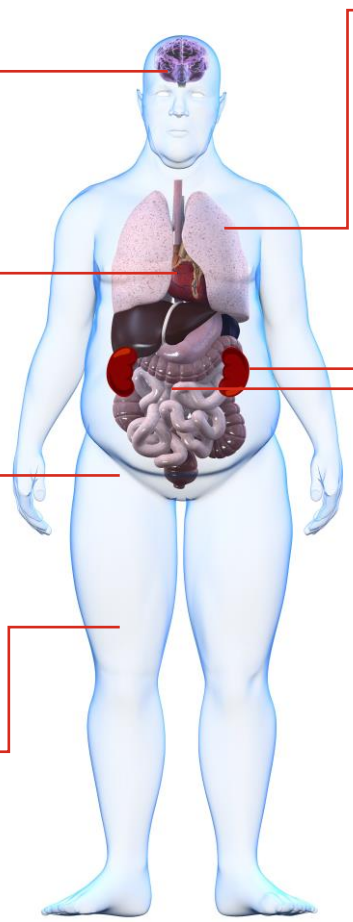
Obesity is a Multisystem Disease Associated With Comorbidities[1,2]

Neurological and Psychological
Stroke, vision loss, diabetic neuropathy, pseudo-tumor cerebri, dementia, depression, anxiety, eating disorders, migraine, and social stigmatization

Cardiovascular
Hypertension, heart diseases (CAD, PAD, atrial fibrillation, heart attack, congestive HF), high cholesterol, poor circulation, venous stasis, leg and ankle swelling, thromboembolism, and blood clots

Genitourinary
Women: Reduced fertility, PCOS, urinary stress incontinence, irregular menses, and pregnancy complications
Men: Reduced fertility, benign prostatic hypertrophy, hypogonadism, and erectile dysfunction

Musculoskeletal
Osteoarthritis (especially knees, hips, and ankles), gout, lower back pain, and vertebral disk disease



Pulmonary
OSA, asthma, OHS, pulmonary hypertension, restrictive lung disease, and respiratory failure

Renal
Nephrolithiasis, proteinuria, CKD

Gastrointestinal
Gallbladder disease, NAFLD, Gastro-esophageal reflux, cholelithiasis, NASH, and hepatic steatosis

Endocrine: prediabetes, T2D, dyslipidemia

Cancers: colorectal, postmenopausal breast, endometrial, gastrointestinal, liver

Infections: sensitivity to influenza, skin, and soft tissue infections

CAD=Coronary Artery Disease; CKD=Chronic Kidney Disease; HF=Heart Failure; NAFLD=Nonalcoholic Fatty Liver Disease; NASH=Nonalcoholic Steatohepatitis; OHS=Obesity Hypoventilation Syndrome; OSA=Obstructive Sleep Apnea; PAD=Peripheral Artery Disease; PCOS=Polycystic Ovarian Syndrome; T2D=Type 2 Diabetes.

1. Tsai AG, Bessesen DH. *Ann Intern Med*. 2019;170(5):ITC33-ITC48. 2. Sarma S, et al. *Diabetes Obes Metab*. 2021;23(Suppl. 1):3-16.

Weight Loss of ≥5% Can Improve Most Adiposity-Related Complications in Patients with Overweight or Obesity

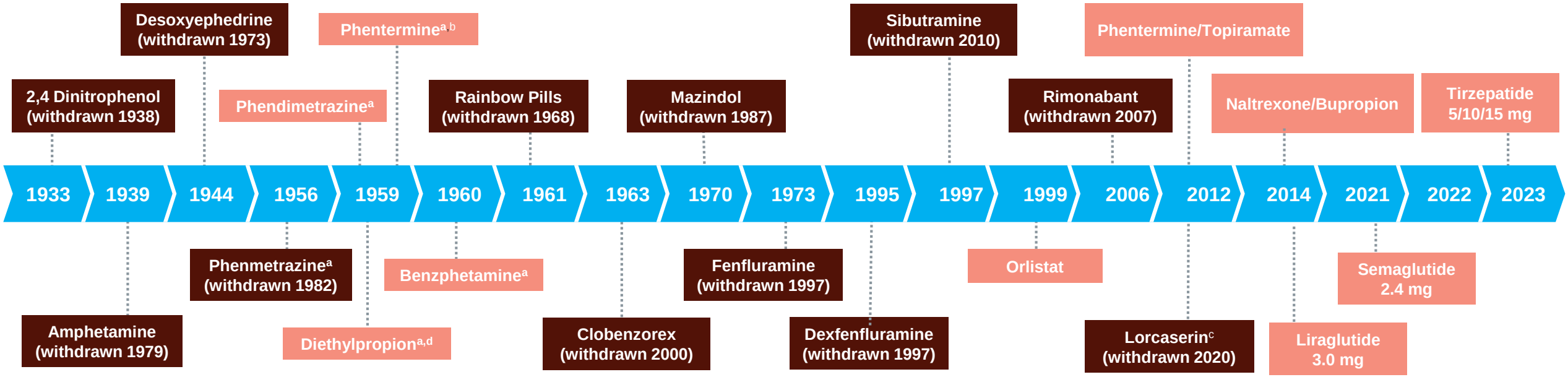
Weight-Related Comorbidity		Weight Loss Goal	Clinical Goals
Prediabetes		10%	• Prevention of type 2 diabetes
Type 2 diabetes		5 to ≥15%	• Reduction in HbA1c • Reduction in number and/or doses of glucose-lowering medications
Hypertension		5 to ≥15%	• Reduction in systolic and diastolic blood pressure • Reduction in number and/or doses of a anti-hypertensive medications
Obstructive sleep apnea		7 to ≥11%	• Improved symptoms • Reduction in apnea-hypopnea index
Osteoarthritis		≥10%	• Improved symptoms • Increased function
Dyslipidemia		5 to ≥15%	• Lower non-HDL-C and TGs • Higher HDL-C
Metabolic syndrome		10%	• Prevention of type 2 diabetes
Metabolic Dysfunction-Associated Steatotic Liver Disease	Steatosis	≥5%	• Reduction in intrahepatocellular lipid
	Steatohepatitis	10-40%	• Reduction in inflammation and fibrosis

HbA1c=Glycated Hemoglobin; HDL-C=High-Density Lipoprotein Cholesterol; TG=Triglyceride.

Garvey WT, et al. *Endocr Pract*. 2016;22(3):1-203.

Chronology of AOMs

Based on First Approval

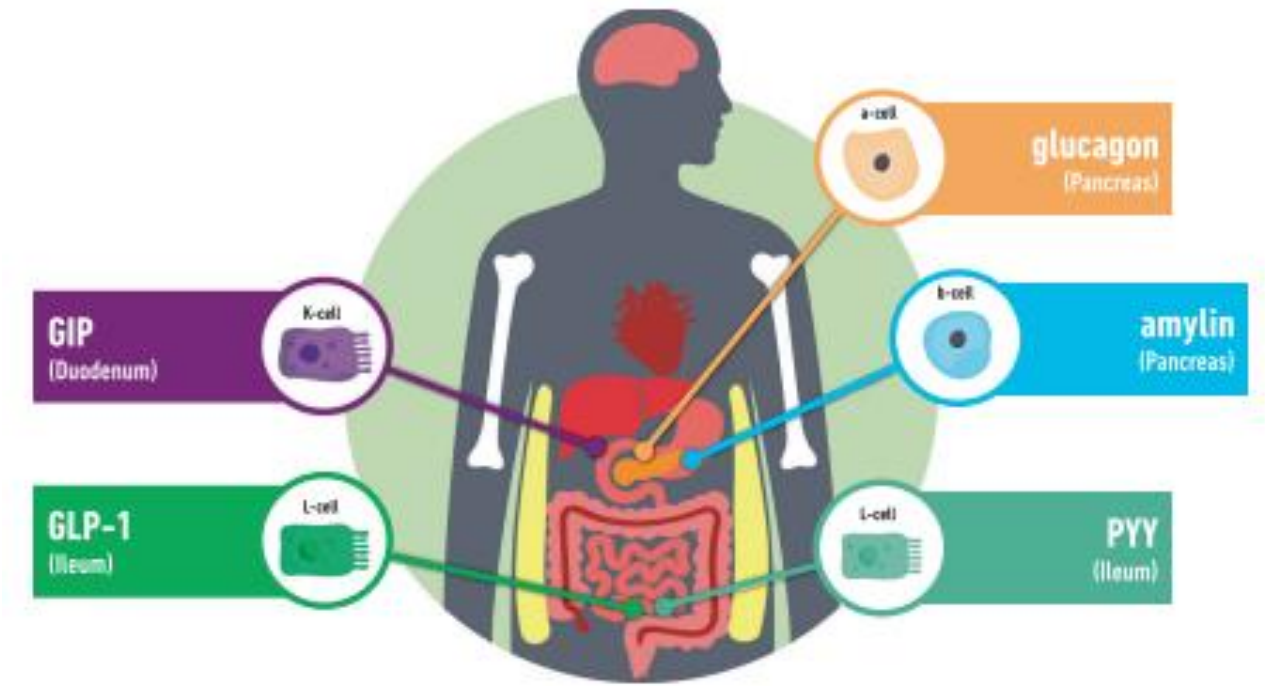


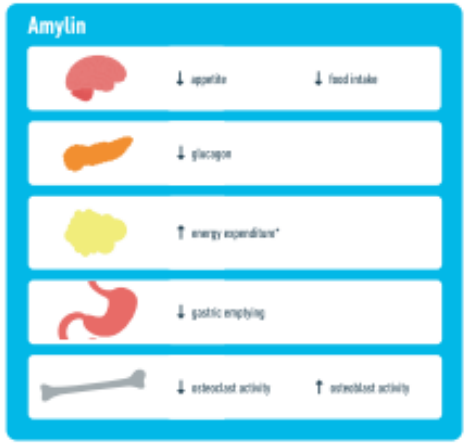
[a]Approved for short-term use in the United States. [b]Withdrawn in 1981 in Sweden, United Arab Emirates, Mauritius, Turkey, Oman, United Kingdom, Venezuela. [c]Withdrawn from market in February 2020 for safety issue related to increased cancer incidence. [d]Withdrawn in 1975 in Sweden, Norway, United Arab Emirates, Turkey, Oman, United Kingdom, Venezuela, France, and Brazil.

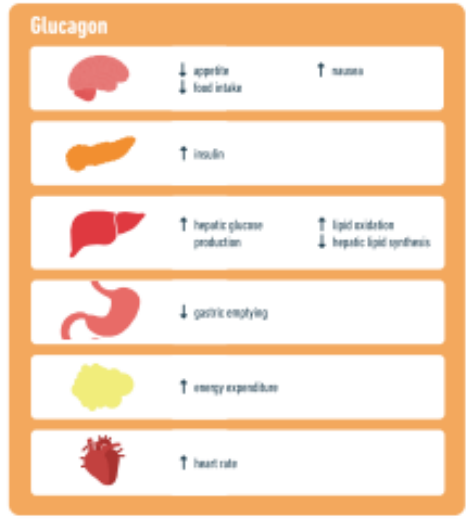
AOM=Anti-Obesity Medication.

1. Pilitsi E, et al. *Metabolism*. 2019;92:170-192. 2. Müller TD, et al. *Nat Rev Drug Discov.* 2021;1-23. 3. Onakpoya IJ, et al. *BMC Med*. 2016;14:191. 4. Zepbound [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024.

What is the pipeline for future medications for obesity?



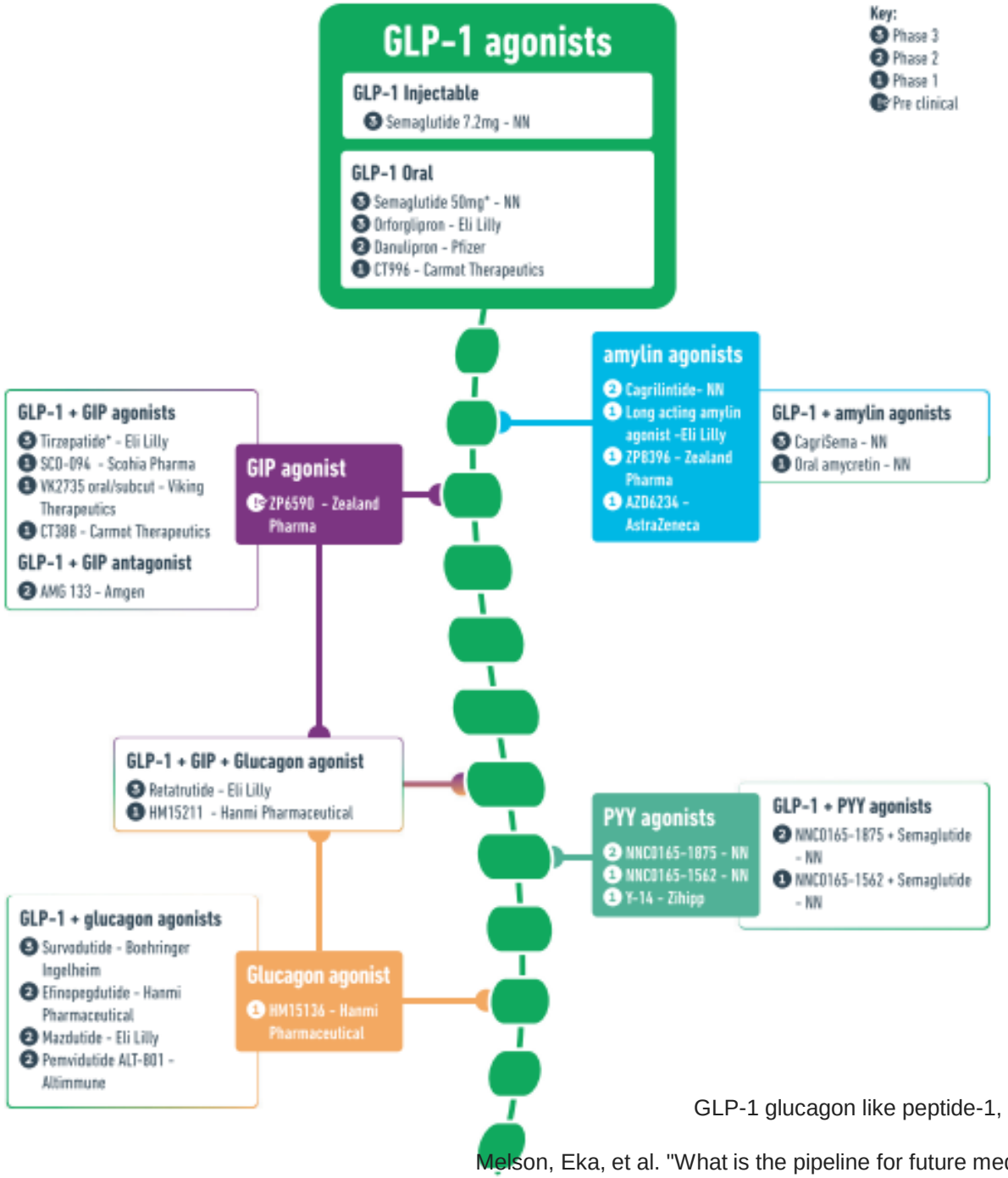




GLP-1 glucagon like peptide-1, GIP glucose-dependent insulinotropic polypeptide, PYY peptide YY,

.

Melson, Eka, et al. "What is the pipeline for future medications for obesity?." *International Journal of Obesity* (2024): 1-19.



GLP-1 glucagon like peptide-1, GIP glucose-dependent insulinotropic polypeptide, PYY peptide YY,

.

Melson, Eka, et al. "What is the pipeline for future medications for obesity?." *International Journal of Obesity* (2024): 1-19.

Table 1. Pipeline for future obesity medications.

Name	Dose	Administration	Mechanism of action	Company	Expected completion date	Clinical Trials gov	Other indication(s)
Phase 3 obesity trials							
Semaglutide*	50 mg	PO, OD	GLP-1 RA	Novo Nordisk	Completed	NCT05035095	Phase 3 - T2D
Orforglipron	NA	PO, OD	GLP-1 RA	Eli Lilly	September-2027	NCT05869903	Phase 3 - T2D, CV outcomes in T2D
Semaglutide	7.2 mg	SC, OW	GLP-1 RA	Novo Nordisk	NA	NA	NA
Tirzepatide*	5–15 mg	SC, OW	GLP-1 RA + GIP RA	Eli Lilly	Completed	NCT04184622	Phase 3 - T2D, HFpEF, OSA, CV outcomes in T2D, morbidity and mortality in obesity Phase 2 - MASH, CKD
CagriSema	2.4 mg/2.4 mg	SC, OW	GLP-1 RA + Amylin RA	Novo Nordisk	October-2026	NCT05567796	Phase 3 - T2D, CV outcomes
Survodutide	3.6–6 mg	SC, OW	GLP-1 RA + GCG RA	Boehringer Ingelheim	Completed	NCT04667377	Phase 2 - T2D, MASH
Mazdutide	4–6 mg	SC, OW	GLP-1 RA + GCG RA	Innovent Biologics	April-2024	NCT05607680	Phase 3 - T2D Phase 1 CKD
Mazdutide	9 mg	SC, OW	GLP-1 RA + GCG RA	Innovent Biologics	September 2025	NCT06164873	NA
Retatrutide	4–12 mg	SC, OW	GLP-1 RA + GIP RA + GCG RA	Eli Lilly	May-2026	NCT05929066	Phase 3 - T2D, OA Phase 2 - CKD
Phase 2 obesity trials							
Danuglipron	40–200 mg	PO, BD	GLP-1 RA	Pfizer	Completed	NCT04707313	NA
Cagrilintide	0.3–4.5 mg	SC, OW	Amylin RA	Novo Nordisk	Completed	NCT03856047	Phase 1 - MASH
PYY 1875	0.03–2.4 mg	SC, NA	PYY RA	Novo Nordisk	Completed	NCT03707990	NA
Efinopegdutide	5–10 mg	SC, OW	GLP-1 RA + GCG RA	Hanmi Pharmaceutical	Completed	NCT03486392	Phase 2 - T2D, MASH, MASLD
Pemvidutide	1.2–2.4 mg	SC, OW	GLP-1 RA + GCG RA	Altimmune	Completed	NCT05295875	Phase 2 - MASH, MASLD Phase 1 – T2D
AMG 133	NA	SC, once monthly	GLP-1 RA + GIP receptor antagonist	Amgen	January-2025	NCT05669599	NA
NNC0165-1875 + Semaglutide	1–2 mg + 2.4 mg	SC, every 2 to 4 weeks	GLP-1 RA + PYY RA	Novo Nordisk	Completed	NCT04969939	NA
Dapiglutide	4–6 mg	SC, OW	GLP-1 RA + GLP2 RA	Zealand Pharma	August-2024	NCT05788601	NA
Bimagrumab + Semaglutide	30 mg/kg + 1–2.4 mg	IV, every 4 weeks (Bimagrumab) + SC, OW	Activin receptor II inhibition + GLP-1 RA	Versanis Bio	September-2025	NCT05616013	NA
S-309309	NA	PO, OD	MGAT2	Shionogi	May-2024	NCT05925114	NA
Phase 1 obesity trials							
CT-996	NA	PO, OD	GLP-1 RA	Carmot Therapeutics	November-2024	NCT05814107	NA

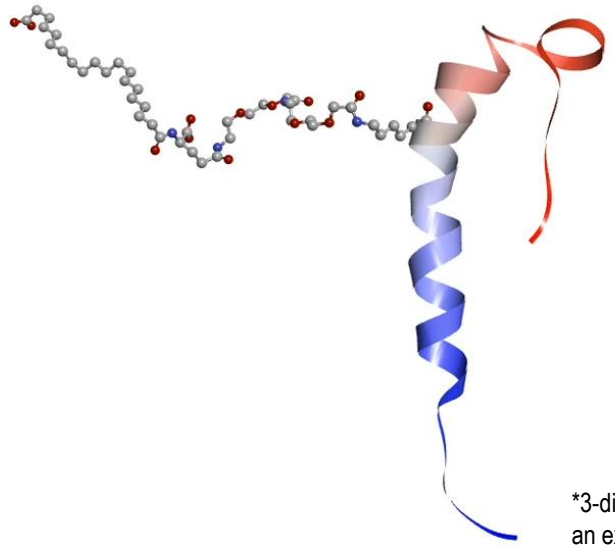
Name	Dose	Administration	Mechanism of action	Company	Expected completion date	Clinical Trials gov	Other indication(s)
Long-acting amylin agonist	NA	NA	Amylin RA	Eli Lilly	NA	NA	NA
AZD6234	NA	SC, OW	Amylin RA	AstraZeneca	December-2023	NCT05511025	NA
ZP8396	NA	SC, OW	Amylin RA	Zealand Pharma	May-2024	NCT05613387	NA
HM15136	NA	SC, frequency not stated	Glucagon RA	Hanmi Pharmaceutical	Completed	NCT04032782	NA
NNC0165-1562	NA	SC, OW	PYY RA	Novo Nordisk	Completed	NCT02568306	NA
Y-14	9-36mg	SC, OW/every 2 weeks	PYY RA	Zihipp	Completed	NCT0367311	NA
VK2735	NA	PO, frequency not stated	GLP-1 RA + GIP RA	Viking Therapeutics	NA	NA	Phase 1 – MASH
VK2735	NA	SC, OW	GLP-1 RA + GIP RA	Viking Therapeutics	December-2023	NCT05203237	Phase 1 – MASH
SCO-094	NA	PO, frequency not stated	GLP-1 RA + GIP RA	Scohia Pharma	NA	NA	Phase 1 - T2D, MASH
CT-388	5–12 mg	SC, OW	GLP-1 RA + GIP RA	Carmot Therapeutics	Completed	NCT04838405	Phase 1 - T2D
Amycretin (NNC0487-0111)	1–100 mg	PO, OD	GLP-1 RA + Amylin RA	Novo Nordisk	November-2024	NCT05369390	NA
Dacra QW II	NA	NA	Amylin RA + calcitonin RA	Eli Lilly	NA	NA	NA
NNC0165-1562 and Semaglutide	NA	SC, OW	PYY RA + GLP-1RA	Novo Nordisk	Completed	NCT03574584	NA
HM15211	NA	SC, OW	GLP-1 RA + GIP RA + GCG RA	Hanmi Pharmaceutical	Completed	NCT03374241	Phase 2 – MASH
NNC0247-0829	NA	SC, OW	GDF15 analogue	Novo Nordisk	Completed	NCT04010786	NA
JNJ-9090/CIN-109	NA	SC, OW/Twice weekly	GDF15 analogue	CinRx Pharma	NA	NA	NA
SCO-267	NA	PO, OD	G-protein-coupled receptor 40	Scohia Pharma	Completed	JapicCTI-195057	Phase 1 - MASH
Preclinical status							
ZP6590	NA	NA	GIP RA	Zealand Pharma	NA	NA	NA

*Completed phase 3 trials for obesity

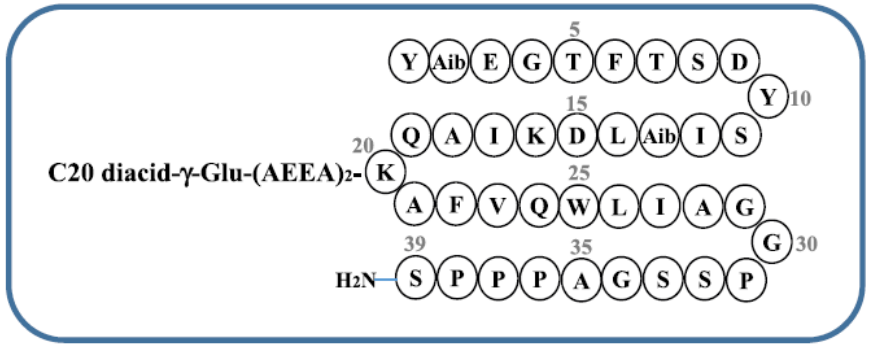
T2D type 2 diabetes, *HFpEF* heart failure with preserved ejection fraction, *MASH* metabolic dysfunction-associated steatohepatitis, *MASLD* metabolic dysfunction-associated steatotic liver disease, *CKD* chronic kidney disease, *CV* cardiovascular, *OA* osteoarthritis, *OSA* obstructive sleep apnoea, *RA* receptor agonist, *GLP-1* glucagon-like peptide-1, *GIP* glucose-dependent insulinotropic polypeptide, *GCG* glucagon, *PYY* peptide YY, *GDF15* Growth/differentiation factor-15, *MGAT2* Monoacylglyceroltransferase 2, *SC* subcutaneous, *PO* oral, *IV* intravenous, *OD* once-daily, *BD* twice daily, *OW* once-weekly, *NA* data not available.

Tirzepatide: Molecular structure and properties

- Tirzepatide is a dual GIP and GLP-1 receptor agonist
- 39 amino acids sequence including a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life[1]
- Mean half-life of approximately 5 days (116.7 h), enabling once-weekly dosing[1]
- Its plasma concentrations in patients with renal and hepatic impairment do not differ from those in healthy people



*3-dimensional rendering of tirzepatide is not an exact reproduction of the molecule and should be used for representative purposes only.

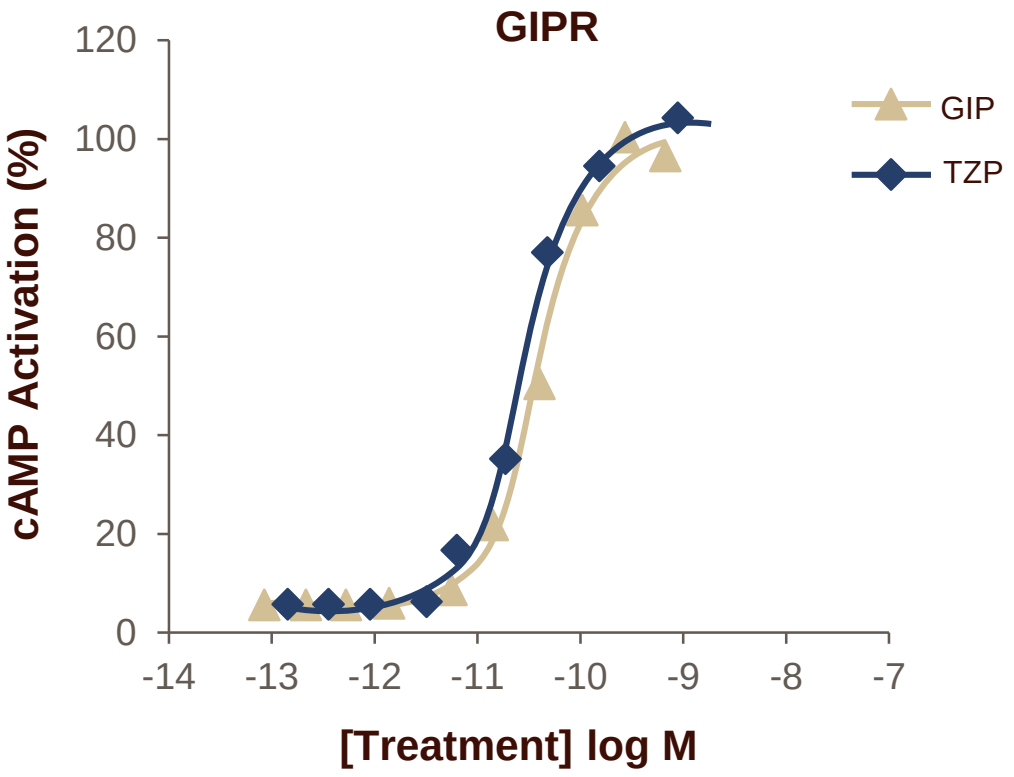


GIP=Glucose-Dependent Insulinotropic Polypeptide; GIPR=Glucose-Dependent Insulinotropic Polypeptide Receptor; GLP-1R=Glucagon-Like Peptide-1 Receptor.

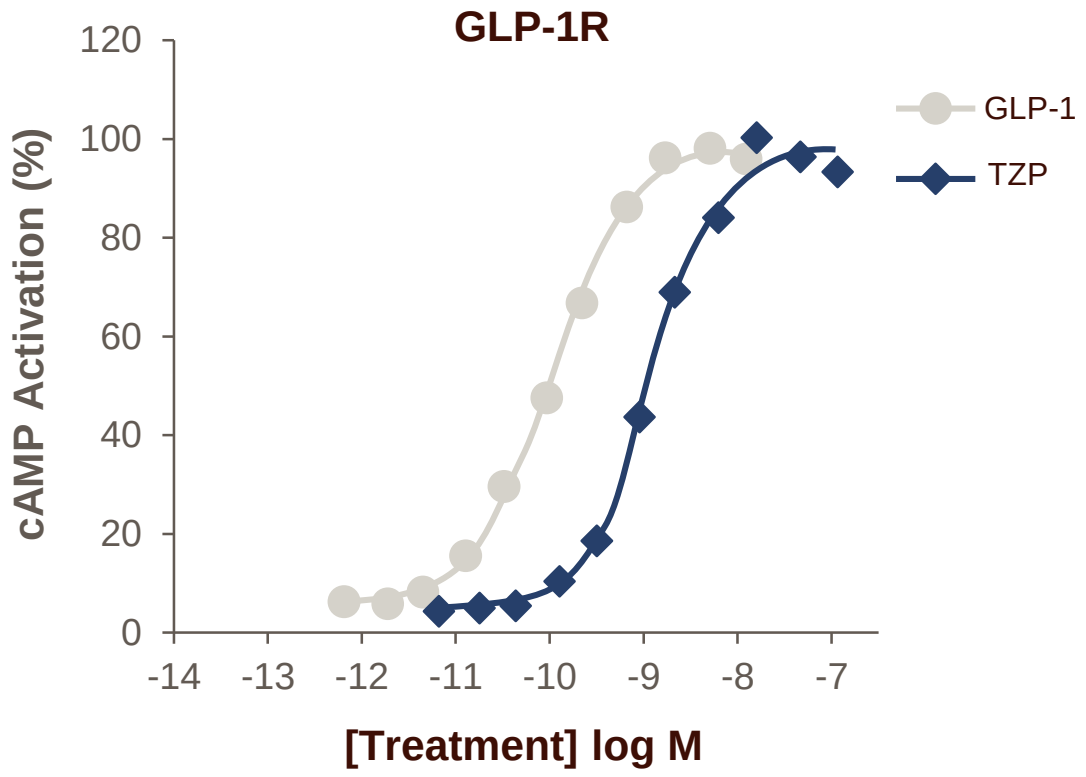
1. Coskun T, et al. *Mol Metab*. 2018;18:3-14; 2. Urva S, et al. *Clin Pharmacokinet*. 2021 Aug;60(8):1049-1059; 3. Urva S, et al. *Clin Pharmacokinet*. 2022 Jul;61(7):1057-1067.

Tirzepatide: A Once-Weekly GIP/GLP-1 Receptor Agonist

Tirzepatide potency at the GIPR is similar to native GIP*



Tirzepatide potency at the GLP-1R is weaker than native GLP-1*



*In overexpressed HEK cells.
cAMP = cyclic adenosine monophosphate; GIP = glucose-dependent insulinotropic polypeptide; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1 = glucagon-like peptide-1; GLP-1R = glucagon-like peptide-1 receptor; HEK = human embryonic kidney; TZP = tirzepatide.
Coskun T, et al. *Mol Metab*. 2018;18:3-14.

Potential Actions of GIP and GLP-1 Based on Clinical and Preclinical Research

GLP-1 Receptor Agonism

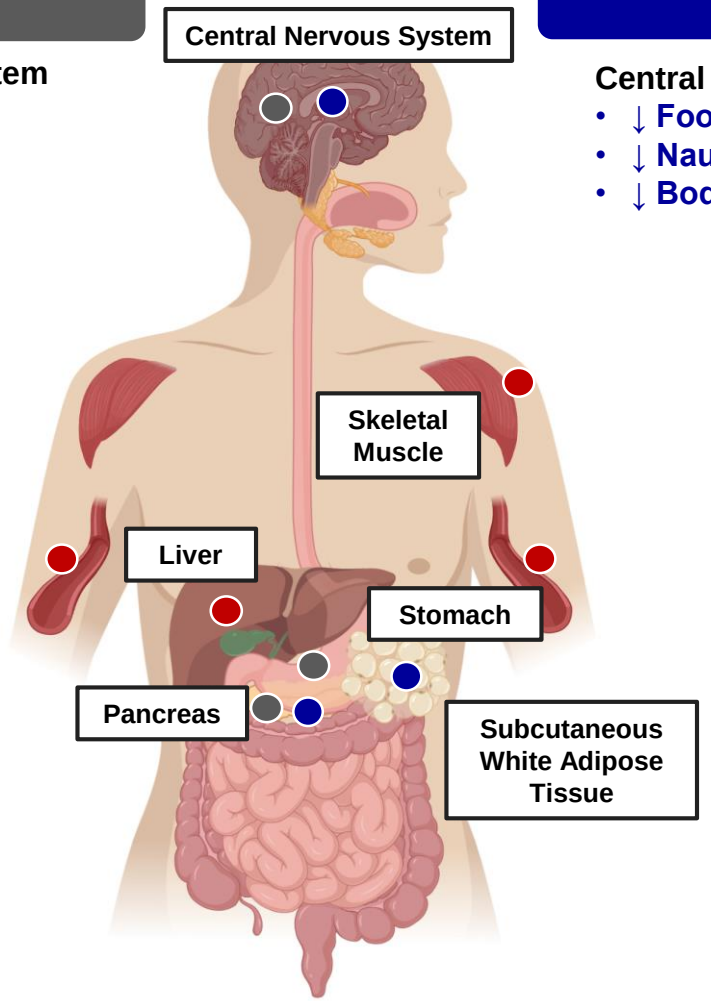
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation



- GLP-1 Receptor Agonism
- GIP Receptor Agonism
- Indirect Action

GIP Receptor Agonism

Central Nervous System
- ↓ Food intake
- ↓ Nausea
- ↓ Body weight

Pancreas
- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia, Dietary Triglyceride

Skeletal Muscle
- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation

Adapted from: Samms RJ, et al. *Trends Endocrinol Metab*. 2020;31(6):410-421

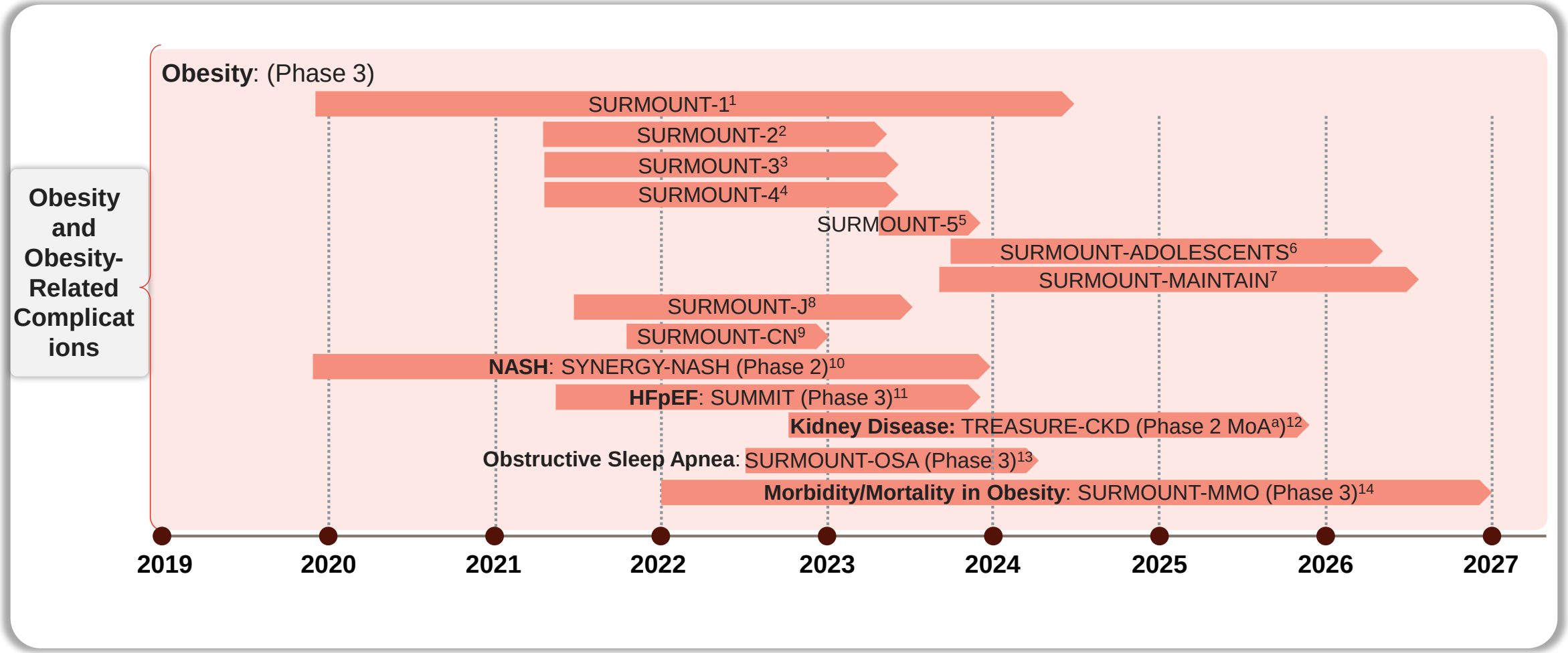
GIP = glucose-dependent insulinotropic polypeptide; GLP-1R = glucagon-like peptide-1 receptor; MOA = mechanism of action

SURMOUNT Studies

Investigating Tirzepatide
for Chronic Weight Management

Tirzepatide Clinical Development Program

For Obesity and Obesity-Related Metabolic Complications



[a]Not an outcomes study.

Abbreviations and references are listed in speaker notes section below.

SURMOUNT: Tirzepatide in People With Obesity

Phase 3 Global Clinical Trials Overview

Phase 3 SURMOUNT Program

	SURMOUNT-1: Weight Management[1]	SURMOUNT-2: Weight Management in T2D[2]	SURMOUNT-3: Weight Management After Intensive Lifestyle Intervention[3]	SURMOUNT-4: Maintenance of Weight Loss[4]	SURMOUNT-5: Weight Management in Participants With Weight-Related Comorbidities[5]
Primary completion date:	April 2022	April 2023	May 2023	May 2023	November 2024 (Ongoing)
Number of study participants:	2539	938	806	783	700
Treatment duration:	72 weeks → **Prediabetes Extension to 176 Weeks**	72 weeks	72 weeks	88 weeks (36 weeks open-label treatment followed by 52 weeks double-blind treatment)	72 weeks
Intervention/ treatment:	TZP 5, 10, 15 mg QW; PBO QW	TZP 10, 15 mg QW; PBO QW	TZP MTD (10 or 15 mg) QW; PBO QW	TZP MTD (10 or 15 mg) QW; PBO QW	TZP QW; SEMA QW

Abbreviations and references are listed in speaker notes section below.

Tirzepatide Once Weekly for the Treatment of Obesity

SURMOUNT-1

Background

- Obesity is a complex, multi-component, metabolic disease of energy homeostasis[1]
- Several clinical guidelines recommend pharmacotherapy for people with obesity or overweight with weight-related comorbidities[1]
- Tirzepatide, a novel once-weekly GIP and GLP-1 receptor agonist, is approved by FDA for the treatment of adults with type 2 diabetes[2]. TZP demonstrated significant weight reduction in phase 2[2] and phase 3 studies[4-8] in people with diabetes
- Tirzepatide is in phase 3 development for adults with obesity or overweight with weight-related comorbidities[1]
- SURMOUNT-1, a multicenter, phase 3 randomized, double-blind, parallel, placebo-controlled trial aimed to determine the efficacy and safety of tirzepatide in participants without T2D who have obesity or are overweight with weight-related comorbidities[1]

FDA = Food and Drug Administration; GIP = Glucose-dependent Insulinotropic Polypeptide; GLP = Glucagon-like Peptide-1; TZP = Tirzepatide.

1. Jastreboff AM, et al. *N Engl J Med.* 2022;387(3):205-216. 2. https://www.fda.gov/news-events/press-announcements/FDA Approves Novel, Dual-Targeted Treatment for Type 2 Diabetes | FDA. Accessed May 13, 2022. 3. Frias JP, et al. *Lancet*. 2018;392(10160):2180-2193. 4. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 5. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 6. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 7. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 8. Dahl D, et al. *JAMA*. 2021;327(6):534-545.

Endpoints

Primary and key secondary

Primary Endpoints

To demonstrate tirzepatide 10 mg and/or 15mg once-weekly is/are superior to placebo at 72 weeks for:

- percent change in body weight, and
- percentage of participants with ≥5% body weight reduction

Key Secondary Endpoints

To demonstrate pooled tirzepatide 10 mg and 15 mg, QW is superior to placebo for:

- mean change in body weight at 20 weeks

To demonstrate tirzepatide (10 mg and/ or 15 mg, QW) is/are superior to placebo for:

- percentage of participants who achieved ≥10%, ≥15%, or ≥20% body weight reduction at 72 weeks

To demonstrate tirzepatide (5 mg, QW) is superior to placebo at 72 weeks for:

- percent change in body weight, and
- percentage of participants with ≥5% body weight reduction

QW = Once Weekly; SF-36v2 = Short Form Health Survey (SF-36) Version 2.

Jastreboff AM, et al. *N Engl J Med.* 2022;387(3):205-216.

Endpoints (Contd.)

Key Secondary and Additional Secondary Endpoints

Cardiometabolic Risk Factors/Physical Function

To demonstrate that pooled tirzepatide (5 mg, 10 mg, 15 mg) is superior to placebo at 72 weeks for:

- mean change in triglycerides, non-HDL cholesterol, HDL cholesterol
- mean change in systolic blood pressure
- mean change in fasting insulin

To demonstrate that pooled tirzepatide (10 mg and 15 mg) is superior to placebo at 72 weeks for:

- mean change in SF-36v2 physical functioning domain score

To demonstrate that tirzepatide 10 mg and/or 15 mg is/are superior to placebo at 72 weeks for:

- mean change in waist circumference

Additional secondary endpoints

- Participants with weight reduction ≥25% at week 72
- Change in diastolic blood pressure
- Percent change in total cholesterol, LDL cholesterol, VLDL cholesterol, free fatty acids

HDL = High-Density Lipoprotein; LDL = Low-density Lipoprotein; SF-36v2 = Short Form Health Survey Version 2; VLDL = Very-low-density Lipoprotein.

Jastreboff AM, et al. *N Engl J Med.* 2022;387(3):205-216.

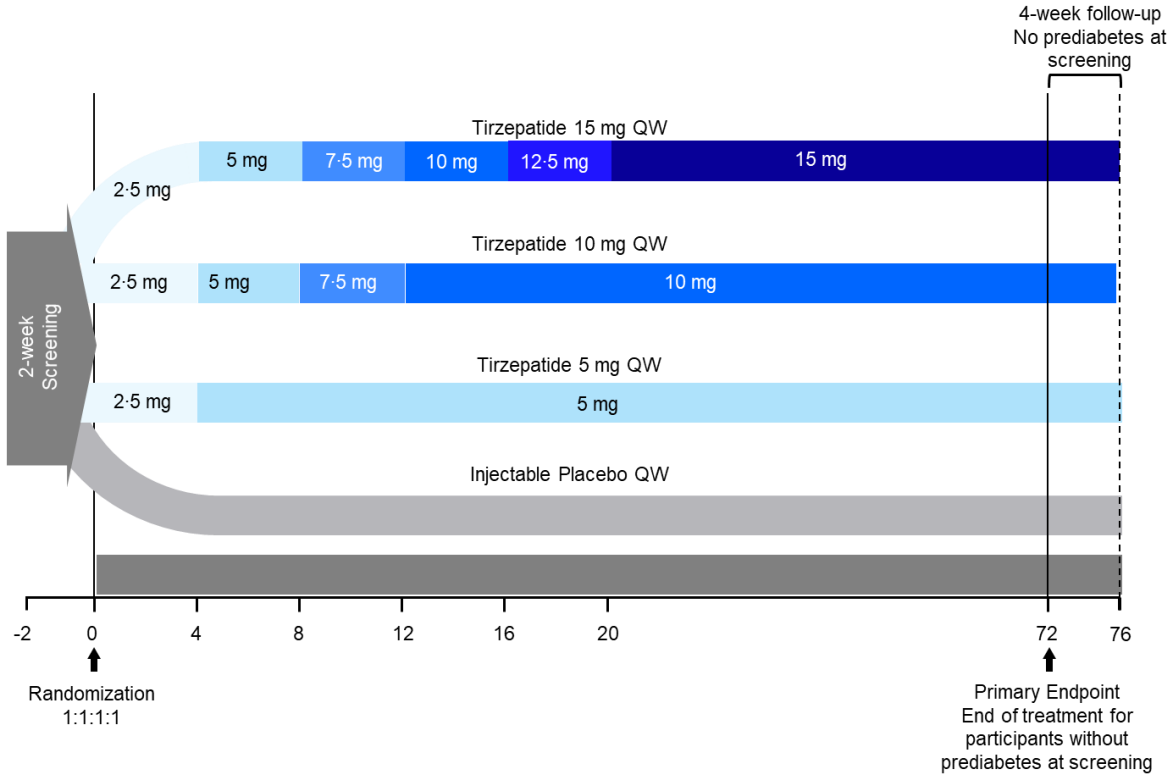
Study Design and Inclusion Criteria of Participants

1 Key Inclusion Criteria

- Age ≥18 years
- BMI ≥30 kg/m^2 or ≥27 kg/m^2 and ≥1 weight-related comorbidities (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease)
- History of ≥1 self-reported unsuccessful dietary efforts to lose body weight

2 Key Exclusion Criteria

- Type 1 or Type 2 Diabetes mellitus
- Change in body weight >5 kg within 3 months prior to screening
- Obesity induced by other endocrinologic disorders or monogenetic or syndromic forms of obesity
- History of pancreatitis



Key Methods and Assessments

- Efficacy and safety endpoints were analyzed using data from all randomly assigned participants (intention-to-treat [ITT] population)
- Two estimands were used to assess treatment efficacy from different perspectives

Treatment regimen estimand

Representing the average treatment effect of tirzepatide relative to placebo, regardless of treatment discontinuation

Efficacy estimand

Representing the average treatment effect of tirzepatide relative to placebo if the treatment was taken as intended

Jastreboff AM, et al. *N Engl J Med.* 2022;387(3):205-216.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)	Total (N=2539)
Age — yr	45.6±12.7	44.7±12.4	44.9±12.3	44.4±12.5	44.9±12.5
Female sex — no. (%)	426 (67.6)	427 (67.1)	425 (67.5)	436 (67.8)	1714 (67.5)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	56 (8.9)	58 (9.1)	59 (9.4)	58 (9.0)	231 (9.1)
Asian	68 (10.8)	71 (11.2)	66 (10.5)	71 (11.0)	276 (10.9)
Black or African American	48 (7.6)	47 (7.4)	51 (8.1)	55 (8.6)	201 (7.9)
White	447 (71.0)	452 (71.1)	443 (70.3)	450 (70.0)	1792 (70.6)
Native Hawaiian or other Pacific Islander	2 (0.3)	2 (0.3)	3 (0.5)	2 (0.3)	9 (0.4)
Multiple	9 (1.4)	6 (0.9)	8 (1.3)	7 (1.1)	30 (1.2)
Hispanic or Latino — no. (%)	308 (48.9)	297 (46.7)	299 (47.5)	310 (48.2)	1214 (47.8)
Duration of obesity — yr	14.0±10.81	14.7±11.05	14.8±10.75	14.0±10.71	14.4±10.83
Body weight — kg	102.9±20.71	105.8±23.32	105.6±22.92	104.8±21.37	104.8±22.12
Mean body-mass index	37.4±6.63	38.2±7.01	38.1±6.69	38.2±6.89	38.0±6.81
Body-mass index category — no. (%)					
<30	38 (6.0)	38 (6.0)	40 (6.3)	24 (3.7)	140 (5.5)
≥30 to <35	241 (38.3)	209 (32.9)	199 (31.6)	227 (35.3)	876 (34.5)
≥35 to <40	174 (27.6)	187 (29.4)	179 (28.4)	180 (28.0)	720 (28.4)
≥40	177 (28.1)	202 (31.8)	212 (33.7)	212 (33.0)	803 (31.6)
Waist circumference — cm	113.2±14.25	114.8±15.80	114.4±15.59	114.0±14.92	114.1±15.16

Jastreboff AM, et al. *N Engl J Med.* 2022;387(3):205-216.

Blood pressure — mm Hg					
Systolic	123.6±12.45	123.8±12.77	123.0±12.94	122.9±12.77	123.3±12.73
Diastolic	79.3±8.14	79.9±8.32	79.3±8.23	79.6±7.95	79.5±8.16
Pulse — beats per min	72.3±9.60	71.8±9.57	72.5±9.95	72.9±9.27	72.4±9.60
Lipid levels — geometric mean mg/dl (coefficient of variation, %)					
Total cholesterol	187.1 (21.1)	190.7 (19.9)	187.4 (19.9)	186.4 (20.3)	187.9 (20.3)
HDL cholesterol	47.6 (26.6)	47.5 (26.1)	47.5 (25.5)	46.5 (26.9)	47.3 (26.3)
LDL cholesterol	108.7 (30.2)	111.5 (30.3)	109.5 (30.0)	108.4 (30.5)	109.5 (30.2)
Triglycerides	128.9 (51.7)	126.5 (51.5)	127.9 (47.5)	130.5 (49.2)	128.4 (50.0)
Estimated GFR — ml/min/1.73 m^2 ‡	97.6±17.87	98.3±18.26	98.2±17.67	98.1±18.28	98.1±18.02
Prediabetes, no. (%)	247 (39.2)	262 (41.2)	253 (40.2)	270 (42.0)	1032 (40.6)
Glycated hemoglobin — %	5.6±0.36	5.6±0.37	5.6±0.41	5.6±0.38	5.6±0.38
Fasting glucose — mg/dl	95.4±9.7	95.5±10.7	95.3±10.3	95.7±9.5	95.5±10.1
Fasting insulin — mIU/liter	13.6±10.0	14.1±12.2	14.4±9.3	14.3±9.9	14.1±10.4
SF-36 physical function score	49.6±8.3	49.6±7.5	49.6±7.8	49.7±7.7	49.6±7.8

Jastreboff AM, et al. *N Engl J Med.* 2022;387(3):205-216.

Efficacy of Tirzepatide

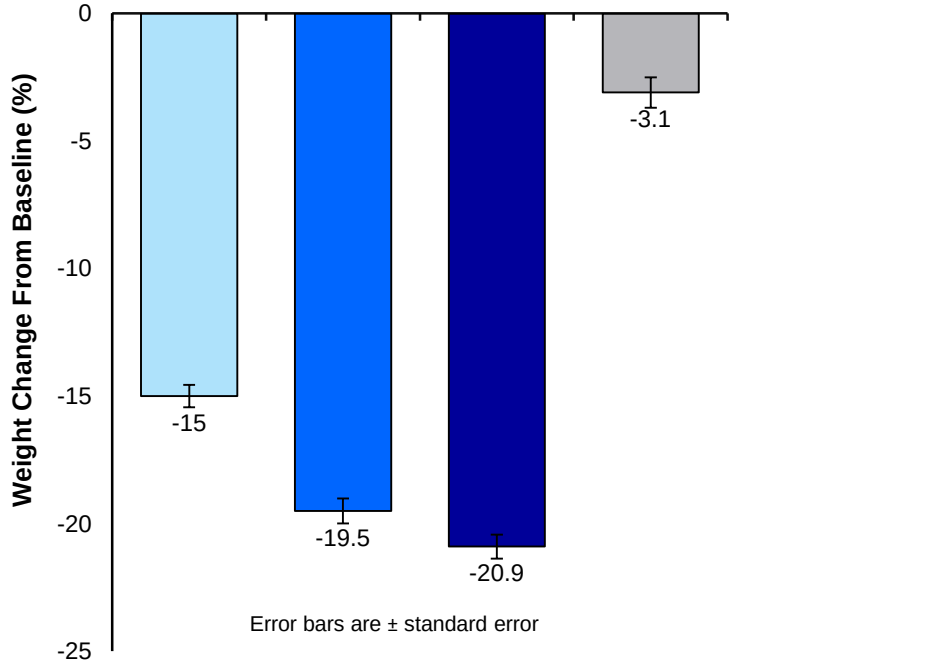
SURMOUNT-1

Percent Change in Body Weight From Baseline to 72 Weeks

Treatment-Regimen Estimand

Tirzepatide 5 mg Tirzepatide 10 mg

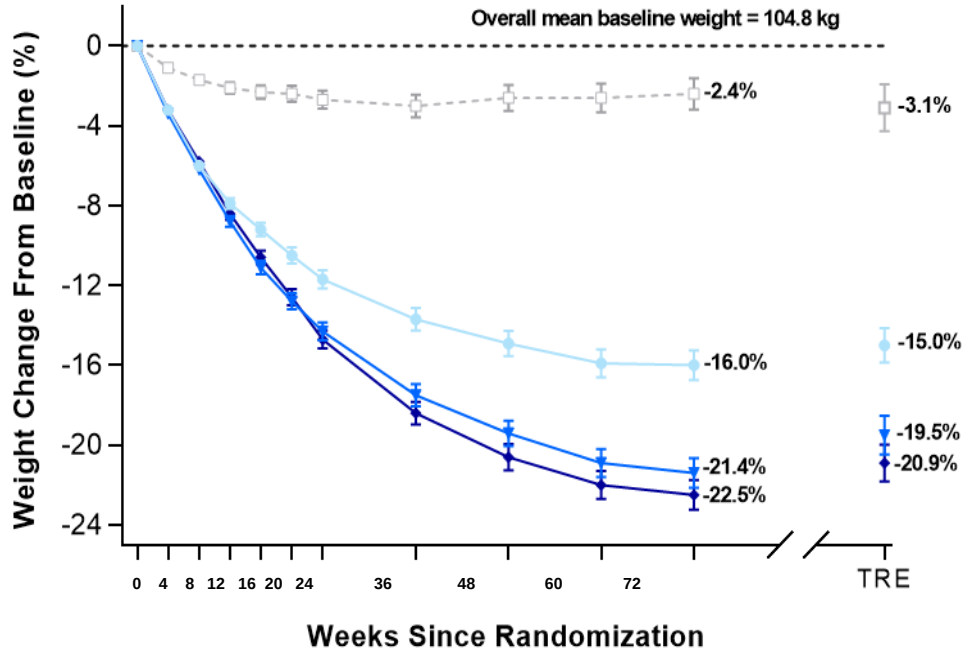
	TZP 5 mg vs PBO*	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	-11.9 (-13.4, -10.4)	-16.4 (-17.9, -14.8)	-17.8 (-19.3, -16.3)
P value		<.001	



Efficacy Estimand

Tirzepatide 15 mg Placebo

	TZP 5 mg vs PBO*	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	−13.5 (−14.6 to −12.5)	−18.9 (−20.0, −17.8)	−20.1 (−21.2, −19.0)
P value		<.001	

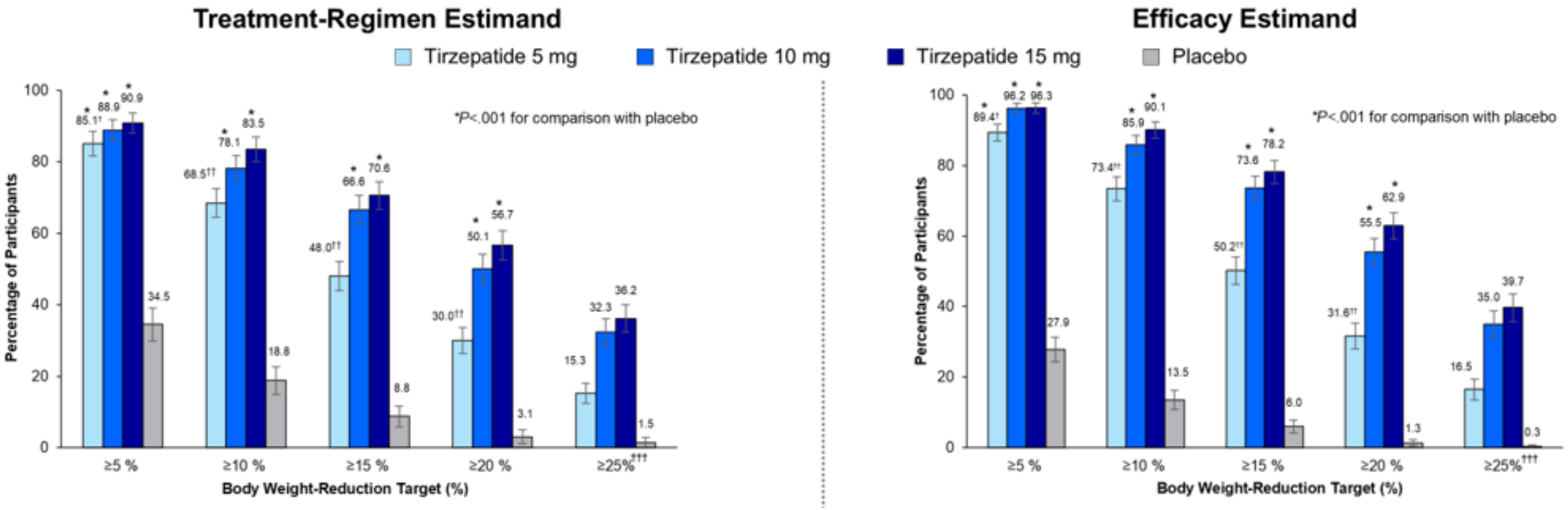


Comparison of Weight Loss Effects Among Major Anti-Obesity Medications

Study	Medication	Maximum Weight Reduction Effect	Placebo-Adjusted Effect
SCALE (56 week)	Liraglutide 3.0mg (Saxenda)	-8.0%	-5.4%
SEQUEL (108 week)	Phentermine/Topiramate (Qsymia 15/92mg)	-10.5%	-8.7%
STEP-1 (68 week)	Semaglutide 2.4mg (Wegovy)	-14.9%	-12.4%
SURMOUNT-1 (72 week)	Tirzepatide 15mg (Mounjaro)	-22.5%	-20.1%

SURMOUNT-1

Percent of Participants Achieving Body Weight Reduction Targets



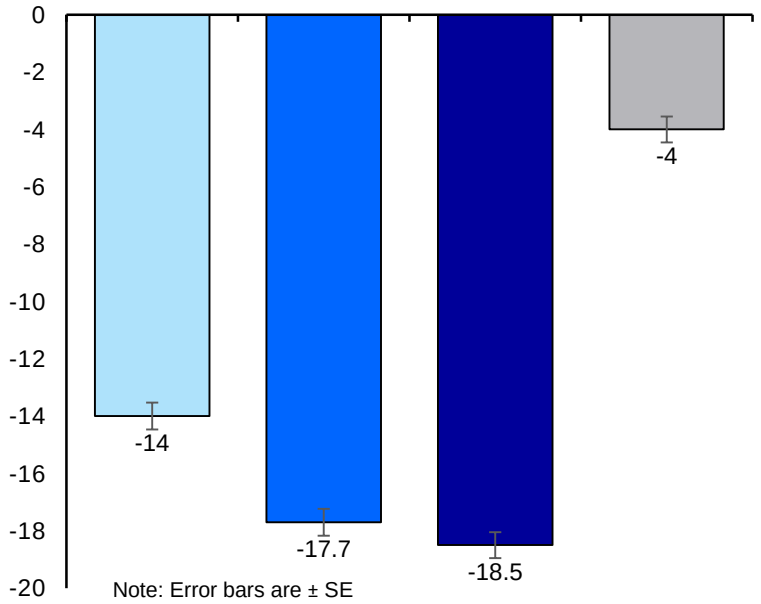
Comparison of Body Weight Reduction Achievements: Tirzepatide vs. Semaglutide

Body Weight Reduction Targets	Tirzepatide 15mg (SURMOUNT-1)	Semaglutide 2.4mg (STEP-1)
≥5%	96%	86%
≥10%	91%	75%
≥15%	84%	55%
≥20%	66%	30%
≥25%	36.2%	NA

Change in Waist Circumference From Baseline to 72 Weeks

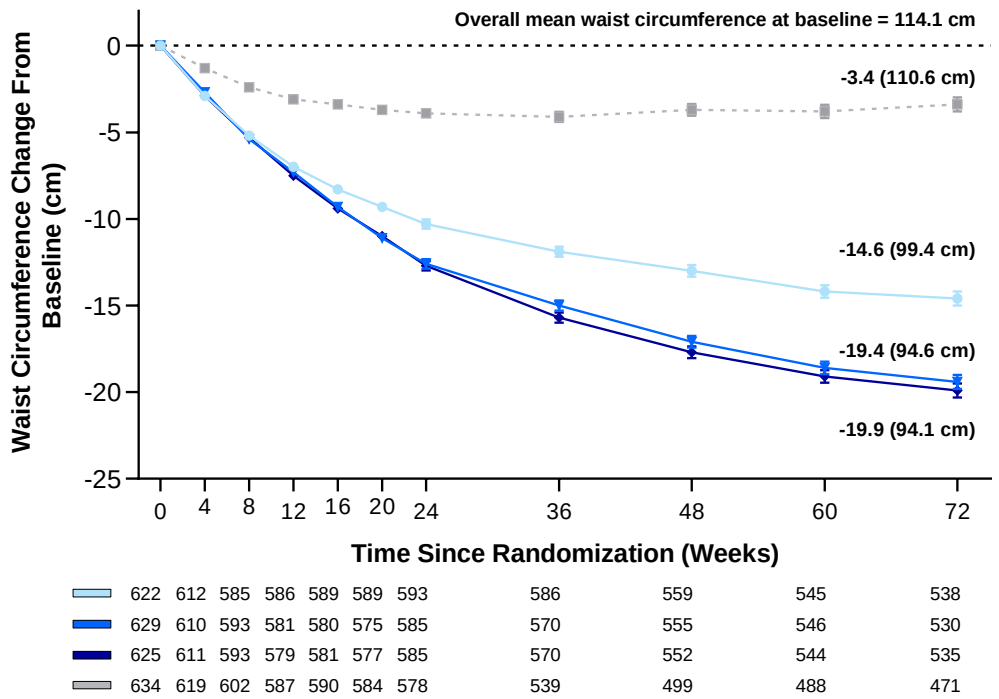
Treatment Regimen Estimand

	TZP 5 mg vs PBO	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	-10.1 (-11.6, -8.6)	-13.8 (-15.2, -12.3)	-14.5 (-15.9, -13.0)
P value		<.001	



Note: Error bars are ± SE

Efficacy Estimand



Change in Key Secondary Endpoints

Treatment Regimen Estimand

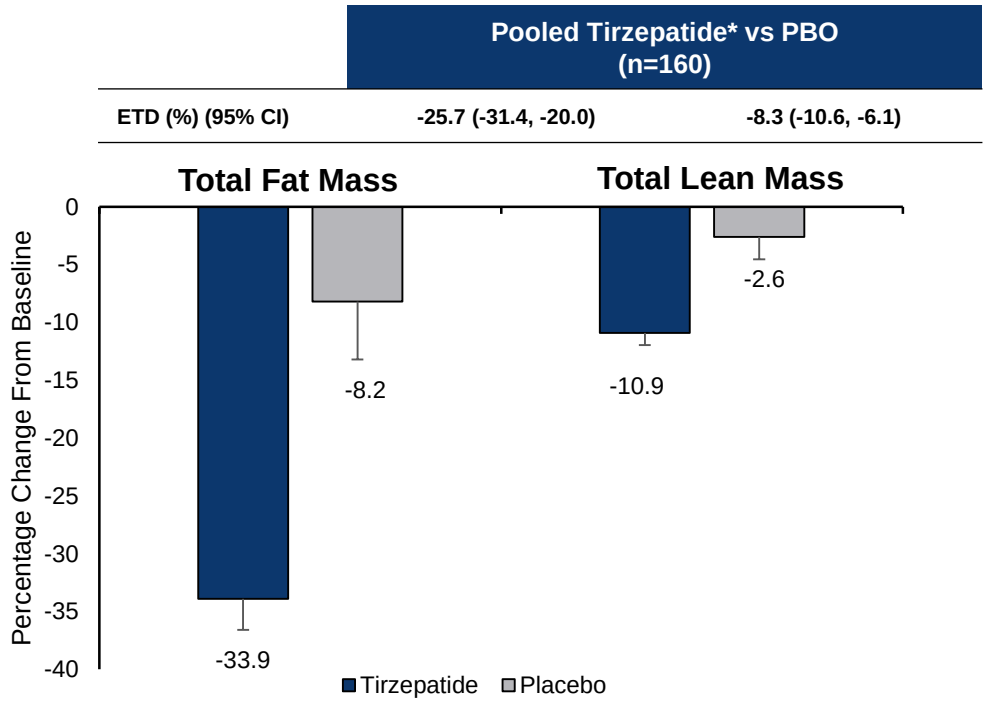
Table 3. Key Secondary and Additional Secondary End Points for Pooled Tirzepatide Dose Groups (Treatment-Regimen Estimand).*

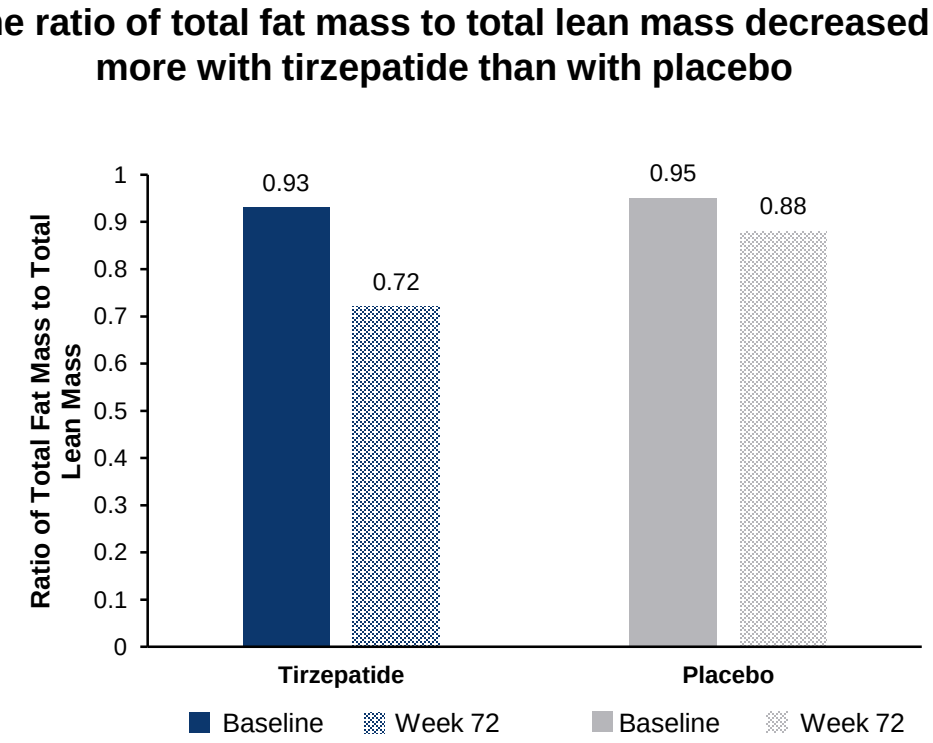
End Points	Pooled Tirzepatide Groups†	Placebo (N=643)	Estimated Treatment Difference from Placebo (95% CI)
	least-squares mean (95% CI)		
Key secondary end points‡			
Change from baseline to week 20 in body weight — kg§	−12.8 (−13.1 to −12.5)	−2.7 (−3.2 to −2.2)	−10.1 (−10.7 to −9.6)
Change in measure			
SF-36 physical function score§¶	3.6 (3.2 to 4.0)	1.7 (0.8 to 2.6)	1.9 (1.0 to 2. 9)
Systolic blood pressure — mm Hg	−7.2 (−7.8 to −6.7)	−1.0 (−2.3 to −0.3)	−6.2 (−7.7 to −4.8)
Percentage change in level‖			
Triglycerides — mg/dl	−24.8 (−26.3 to −23.1)	−5.6 (−10.0 to −1.2)	−20.3 (−24.3 to −16.1)
Non-HDL cholesterol — mg/dl	−9.7 (−10.7 to −8.6)	−2.3 (−4.9 to −0.2)	−7.5 (−10.1 to −4.9)
HDL cholesterol — mg/dl	8.0 (6.9 to 9.1)	−0.7 (−2.9 to 1.5)	8.8 (6.1 to 11.5)
Fasting insulin — mIU/liter**	−42.9 (−44.9 to −40.9)	−6.6 (−15.3 to 2.2)	−38.9 (−44.8 to −32.4)
Additional secondary end points††			
Change in diastolic blood pressure — mm Hg	−4.8 (−5.2 to −4.4)	−0.8 (−1.6 to 0.0)	−4.0 (−4.9 to −3.1)
Percentage change in level‖			
Total cholesterol — mg/dl	−4.8 (−5.6 to −4.0)	−1.8 (−3.7 to 0.1)	−3.1 (−5.2 to −1.0)
LDL cholesterol — mg/dl	−5.8 (−6.9 to −4.6)	−1.7 (−4.6 to 1.3)	−4.2 (−7.2 to −1.0)
VLDL cholesterol — mg/dl	−24.4 (−25.9 to −22.9)	−4.8 (−9.2 to −0.4)	−20.6 (−24.6 to −16.4)
Free fatty acids — mmol/liter	−7.5 (−10.7 to −4.3)	9.5 (3.8 to 15.3)	−15.6 (−20.8 to −9.9)

Jastreboff AM, et al. *N Engl J Med.* 2022;387(3):205-216.

Change in Body Composition

Efficacy Estimand





Note: Pooled tirzepatide refers to pooled tirzepatide 5 mg, 10 mg, and 15 mg groups, unless otherwise indicated.
The percentage change in total body fat mass from baseline to week 72 was assessed in a subset of participants who **underwent dual-energy X-ray absorptiometry (enrolled n=255; completers with both baseline and week 72 DXA n=160).**

Comparison of Body Composition Changes: Tirzepatide vs. Semaglutide

Metric	Tirzepatide 15mg (SURMOUNT-1)	Semaglutide 2.4mg (STEP-1)
Total Fat Mass Change (%)	-33.9%	-21.4%
Total Lean Mass Change (%)	-10.9%	-6.9%
Fat-to-Lean Mass Ratio Change	0.93 → 0.72	0.92 → 0.82

Safety

Table 4. Adverse Events and Safety.

Variable	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)
	number (percent)			
Participants with ≥1 adverse event during treatment period	510 (81.0)	520 (81.8)	497 (78.9)	463 (72.0)
Serious adverse events	40 (6.3)	44 (6.9)	32 (5.1)	44 (6.8)
Death*	4 (0.6)	2 (0.3)	1 (0.2)	4 (0.6)
Adverse events leading to discontinuation of trial drug or placebo†	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)
Nausea	6 (1.0)	7 (1.1)	12 (1.9)	2 (0.3)
Diarrhea	2 (0.3)	5 (0.8)	3 (0.5)	0
Abdominal pain	0	2 (0.3)	3 (0.5)	0
Vomiting	0	4 (0.6)	0	0
Adverse events occurring in at least 5% of participants in any treatment group†				
Nausea	155 (24.6)	212 (33.3)	195 (31.0)	61 (9.5)
Diarrhea	118 (18.7)	135 (21.2)	145 (23.0)	47 (7.3)
Covid-19	94 (14.9)	98 (15.4)	82 (13.0)	90 (14.0)
Constipation	106 (16.8)	109 (17.1)	74 (11.7)	37 (5.8)
Dyspepsia	56 (8.9)	62 (9.7)	71 (11.3)	27 (4.2)
Vomiting	52 (8.3)	68 (10.7)	77 (12.2)	11 (1.7)
Decreased appetite	59 (9.4)	73 (11.5)	54 (8.6)	21 (3.3)
Headache	41 (6.5)	43 (6.8)	41 (6.5)	42 (6.5)
Abdominal pain	31 (4.9)	34 (5.3)	31 (4.9)	21 (3.3)
Alopecia	32 (5.1)	31 (4.9)	36 (5.7)	6 (0.9)
Dizziness	26 (4.1)	35 (5.5)	26 (4.1)	15 (2.3)
Eructation	24 (3.8)	33 (5.2)	35 (5.6)	4 (0.6)
Injection-site reaction‡	18 (2.9)	36 (5.7)	29 (4.6)	2 (0.3)

Adverse Events of Special Interest

Adverse events of special interest				
Hepatic events§	2 (0.3)	2 (0.3)	0	0
Cancer	9 (1.4)	3 (0.5)	5 (0.8)	7 (1.1)
Pancreatitis (adjudication-confirmed)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Major adverse cardiovascular events (adjudication-confirmed)	4 (0.6)	5 (0.8)	0	5 (0.8)
Cardiac disorders¶	0	1 (0.2)	2 (0.3)	1 (0.2)
Severe or serious gastrointestinal events	11 (1.7)	20 (3.1)	21 (3.3)	7 (1.1)
Gallbladder disease§	5 (0.8)	11 (1.7)	6 (1.0)	5 (0.8)
Renal events§	2 (0.3)	2 (0.3)	2 (0.3)	1 (0.2)
Major depressive disorder or suicidal ideation§	1 (0.2)	2 (0.3)	2 (0.3)	0
Hypersensitivity‖	0	1 (0.2)	1 (0.2)	0
Hypoglycemia (blood glucose <54 mg/dl)	9 (1.4)	10 (1.6)	10 (1.6)	1 (0.2)
Other adverse events of interest that emerged during treatment period†				
Cholelithiasis	7 (1.1)	9 (1.4)	4 (0.6)	6 (0.9)

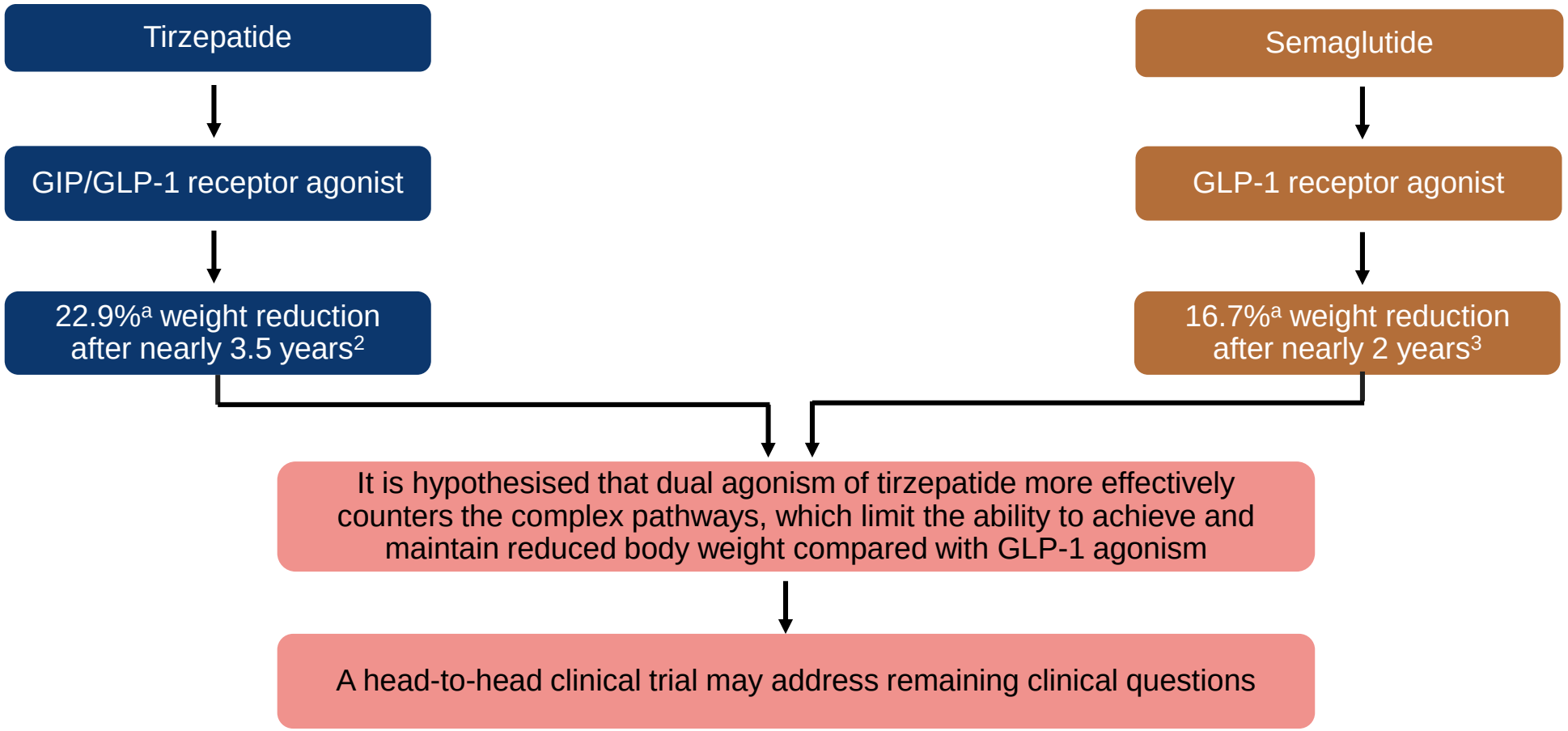
Conclusions

- In the SURMOUNT-1 trial, treatment with tirzepatide 5mg, 10 mg, and 15 mg resulted in significant and substantial degree of weight reductions in participants with obesity, or overweight with ≥1 weight related comorbidities
- Up to 96% of participants achieved >5% weight reduction, with up to 63% of patients achieving ≥20% weight reduction
- ~40% of patients achieved the prespecified exploratory endpoint of >25% weight reduction with TZP 15 mg
- Tirzepatide improved cardiometabolic risk factors and physical function, including waist circumference, systolic and diastolic blood pressure, lipids, fasting insulin, and SF-36v2 physical functioning domain score
- All doses of once-weekly tirzepatide were well-tolerated, with no new safety signal identified
- Findings of SURMOUNT-1 may advance the therapeutic potential of medical treatment options for people living with obesity

Tirzepatide as Compared With Semaglutide for the Treatment of Obesity

SURMOUNT-5

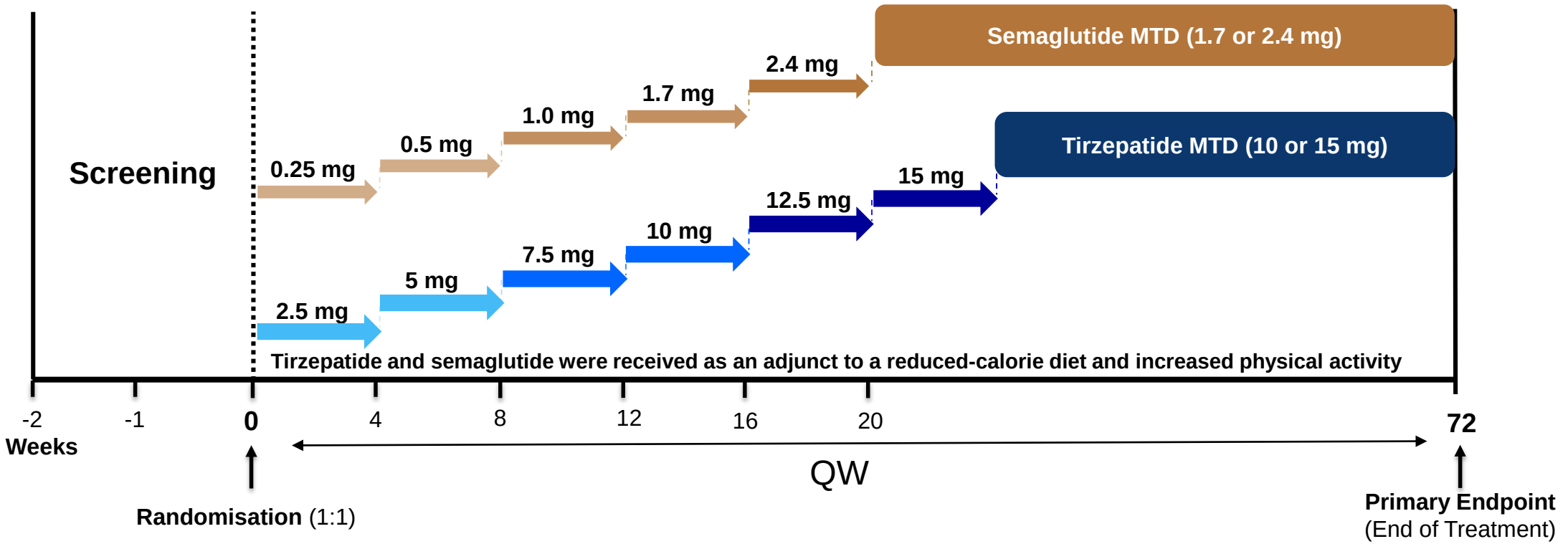
Background



- [a]Based on efficacy estimand.
- GIP=Glucose-Dependent Insulinotropic Polypeptide; GLP-1=Glucagon-Like Peptide-1.
- 1. Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394 2. Jastreboff AM, et al. *N Engl J Med.* 2025;392:958-971. 3. Wilding JPH, et al. *N Engl J Med.* 2021;384:989-1002.

Study Design

- A Phase 3b, 72-Week, Multicenter, Randomized, Controlled, Parallel-Arm, Open-Label Trial



Additional relevant design details:

- A total of 32 sites in United States and Puerto Rico
- Female participant allocation was restricted to a maximum 70% to allow adequate male representation in the trial
- Stratification factors: prediabetes status at randomization, sex, and BMI at randomization <35 vs. ≥35 kg/m^2

- MTD=Maximum Tolerated Dose; QW=Once Weekly
- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

Primary and Key Secondary Endpoints

Primary endpoint

Percent change from baseline in body weight at 72 weeks

Key secondary endpoints

Body weight reduction from baseline of:

- ≥10%
- ≥ 15%
- ≥ 20%, and
- ≥ 25%

Change from baseline in waist circumference (cm) at 72 weeks

- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

Additional Secondary and Tertiary Endpoints

Additional secondary endpoints

Change in body weight (kg) from baseline at Week 72

Body weight reduction from baseline of ≥ 30% at Week 72

Change in BMI (kg/m^2) from baseline at Week 72

Tertiary endpoints

Change from baseline at Week 72 in SBP, DBP, triglycerides (mg/dL), VLDL (mg/dL), non-HDL (mg/dL), fasting insulin (pmol/L), LDL (mg/dL), HDL cholesterol (mg/dL), and HbA1c (%)

- BMI=Body Mass Index; DBP=Diastolic Blood Pressure; HbA1c=Glycated Haemoglobin; HDL=High-Density Lipoprotein; VLDL=Very-Low-Density Lipoprotein.
- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

Key Inclusion and Exclusion Criteria

- Adults ≥18 years of age
- BMI: ≥30 kg/m^2 or ≥27 kg/m^2 with at least 1 prespecified obesity-related complication: hypertension, dyslipidemia, OSA, or CVD
- At least 1 unsuccessful dietary effort to lose body weight

- Diagnosis of diabetes or screening laboratories suggesting diabetes
- Change in body weight >5 kg within 3 months prior to screening
- Obesity induced by other endocrinologic disorders or monogenic or syndromic forms of obesity
- History of pancreatitis or MTC or MEN-2
- Use of GLP-1RA or anti-obesity medication within 3 months of screening

BMI=Body Mass Index; CVD=Cardiovascular Disease; GLP-1RA=Glucagon-Like Peptide-1 Receptor Agonist; MEN-2=Multiple Endocrine Neoplasia Syndrome Type 2; MTC=Medullary Thyroid Carcinoma; OSA=Obstructive Sleep Apnea.

- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

Estimands and Statistical Analysis

Modified Treatment-Regimen Estimand

What is the treatment difference in **mean percent change in body weight from baseline** after Week 72 of treatment**, regardless of treatment discontinuation and other anti-obesity medication** (except for switching to non-study tirzepatide or semaglutide)

- This estimand assumed that participants who had bariatric surgery or another weight loss procedure did not get any benefit from their randomized study treatment

Efficacy Estimand

What is the treatment difference in **mean percent change in body weight from baseline** after Week 72 of treatment assuming that **participants had stayed on treatment and not taken other anti-obesity therapies**

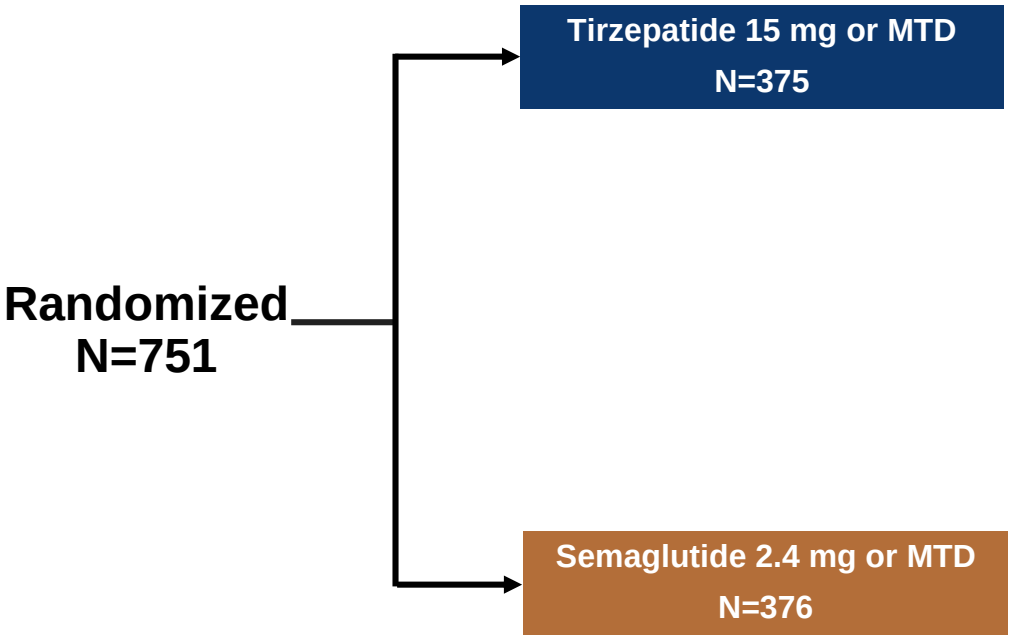
- Other weight management drugs, bariatric surgery, or other weight management procedures

- Efficacy and safety analyses included all patients who took at least 1 dose of the study drug
- The modified treatment regimen estimand uses the full analysis set, and the efficacy estimand uses the efficacy analysis set
- Multiplicity adjustment was conducted separately for each of the estimand

- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

Participant Disposition

- Randomized Population



	Discontinued study treatment	Discontinued study
Adverse events	23 (6.1%)	6 (1.6%)
Inadvertent enrollment	5 (1.3%)	5 (1.3 %)
Lost to follow-up	14 (3.7%)	16 (4.3%)
Non-compliance with study drug	1(0.3%)	1 (0.3%)
Pregnancy	1 (0.3%)	1 (0.3%)
Withdrawal by subject	25 (6.7%)	27 (7.2%)

Completed Treatment=306 (81.6%)
Completed Study=319 (85.1%)

	Discontinued study treatment	Discontinued study
Adverse events	30 (8.0%)	6 (1.6%)
Inadvertent enrollment	3 (0.8%)	3 (0.8%)
Lost to follow-up	16 (4.3%)	18 (4.8%)
Non-compliance with study drug	1 (0.3%)	1 (0.3%)
Other	2 (0.5%)	1 (0.3%)
Pregnancy	1 (0.3%)	2 (0.5%)
Withdrawal by subject	27 (7.2%)	26 (6.9%)

Completed Treatment=296 (78.7%)
Completed Study=319 (84.8%)

- Note: Participants in either treatment group who discontinued the study treatment did not switched treatments or received bariatric surgery during the study.
- MTD=Maximum Tolerated Dose; N=Number of Participants in Population.
- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

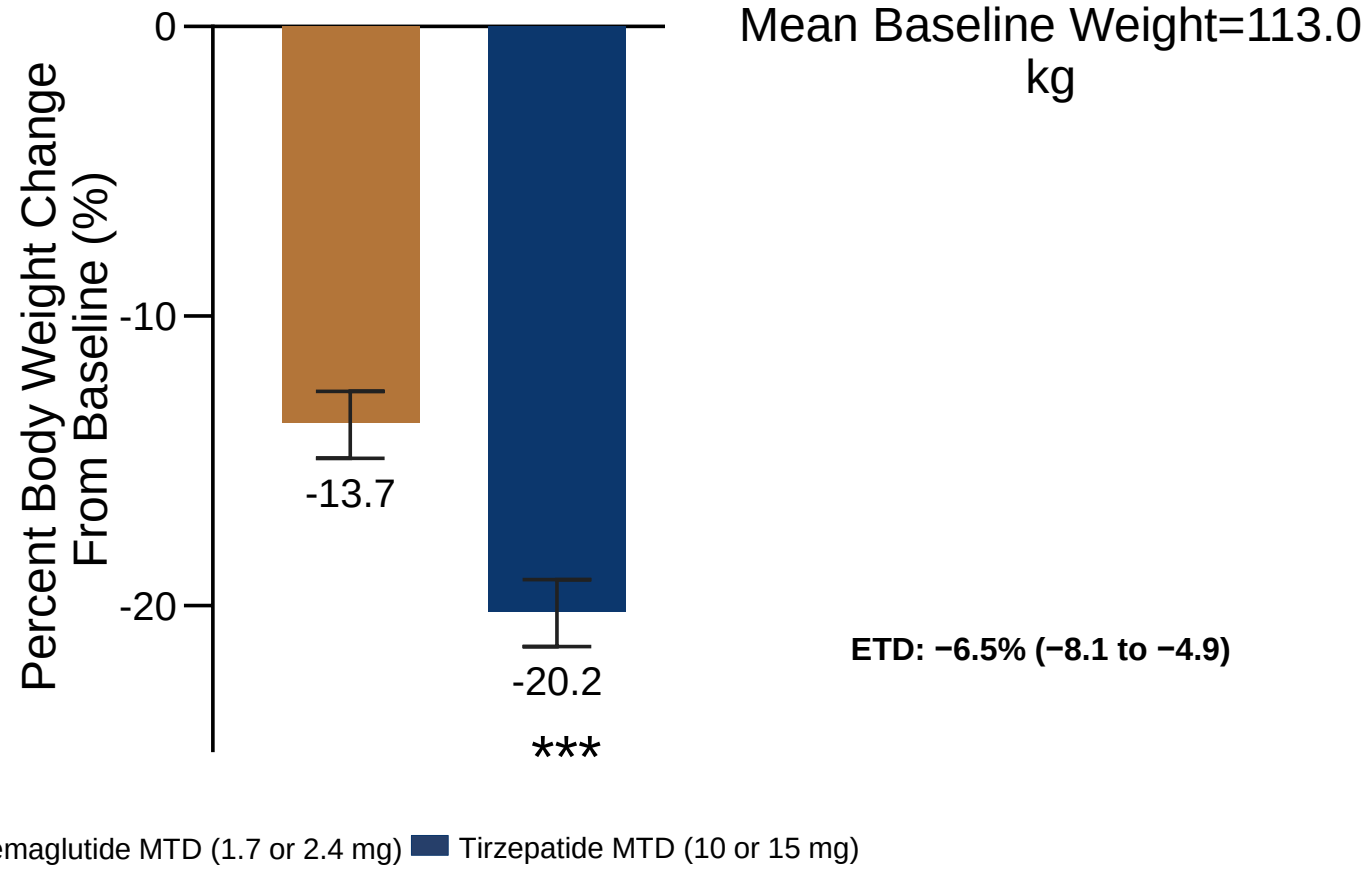
Characteristic	Tirzepatide (N=374)	Semaglutide (N=376)	Total (N=750)
Age — yr	45.0±12.9	44.4±12.7	44.7±12.8
Age categories — no. (%)			
<65 yr	342 (91.4)	349 (92.8)	691 (92.1)
≥65 yr	32 (8.6)	27 (7.2)	59 (7.9)
Female sex — no. (%)	242 (64.7)	243 (64.6)	485 (64.7)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	6 (1.6)	0	6 (0.8)
Asian	11 (2.9)	7 (1.9)	18 (2.4)
Black	77 (20.6)	67 (17.8)	144 (19.2)
White	276 (73.8)	295 (78.5)	571 (76.1)
Multiple	4 (1.1)	7 (1.9)	11 (1.5)
Hispanic or Latino	93 (24.9)	103 (27.4)	196 (26.1)
Prediabetes at randomization — no. (%)	215 (57.5)	210 (55.9)	425 (56.7)
Duration of obesity — yr	16.4±11.6	14.7±11.0	15.6±11.3
Body weight — kg	112.7±24.8	113.4±26.3	113.0±25.6
Body-mass index‡	39.4±7.4	39.4±7.7	39.4±7.6
Waist circumference — cm	117.7±16.1	118.8±17.6	118.3±16.9
Body-mass index category — no. (%)‡			
<35	115 (30.7)	118 (31.4)	233 (31.1)
≥35	259 (69.3)	258 (68.6)	517 (68.9)
Participants with multiple obesity-related complications — no. (%)§	187 (50.0)	189 (50.3)	376 (50.1)

Aronne, Louis J., et al. "Tirzepatide as Compared with Semaglutide for the Treatment of Obesity." New England Journal of Medicine (2025).

Efficacy Results

Primary Endpoint: Percentage Change in Body Weight From Baseline to 72 Weeks

- Modified Treatment Regimen Estimand (FAS)

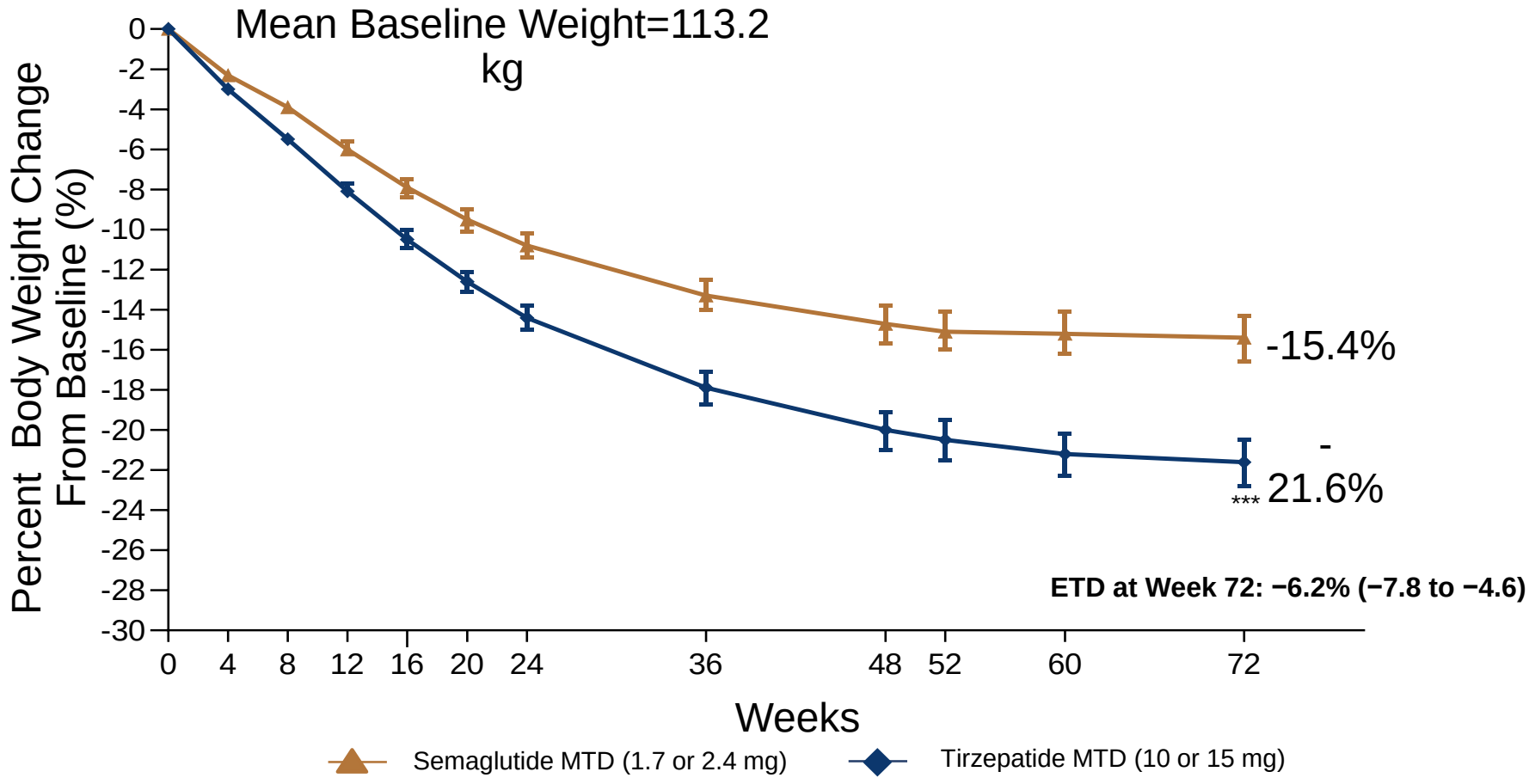


***p<.001 vs. semaglutide.
Data are LSM (95% CI).
CI=Confidence Interval; ETD=Estimated Treatment Difference; FAS=Full Analysis Set; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose.

- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

Primary Endpoint: Percentage Change in Body Weight From Baseline to 72 Weeks

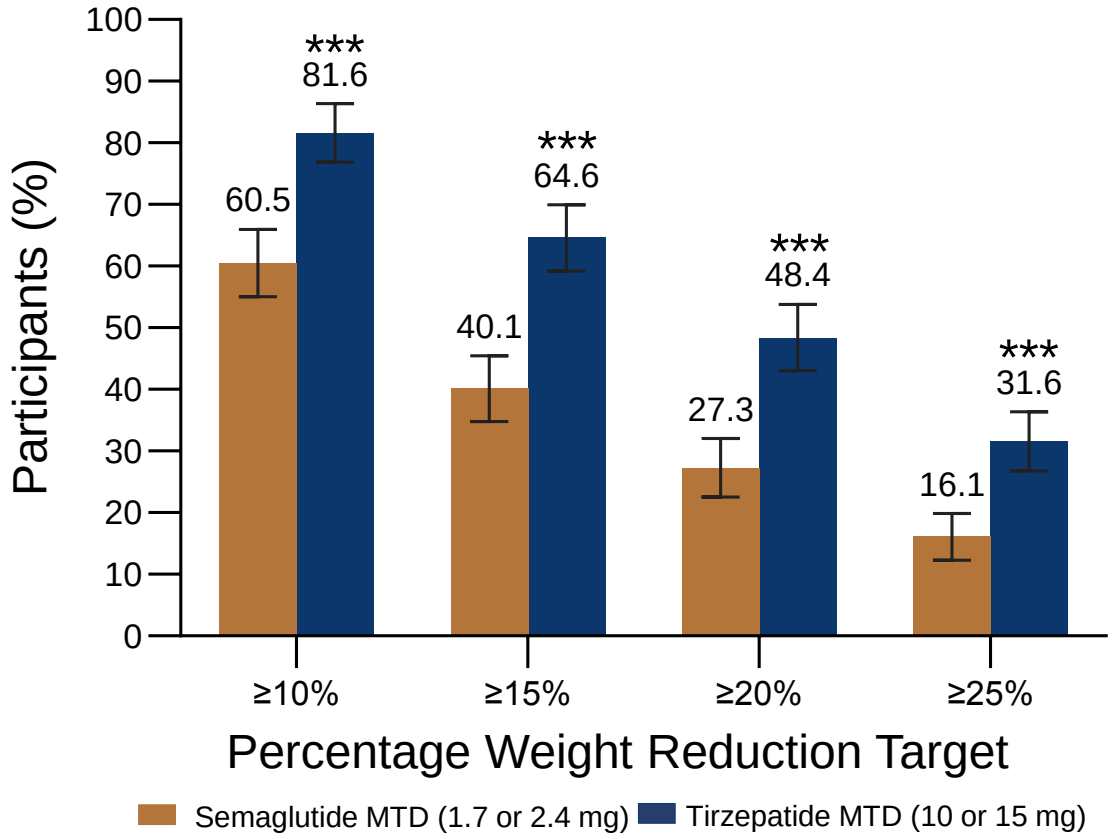
- Efficacy Estimand (EAS)



- ***p<.001 vs. semaglutide.
- Data are LSM (95% CI). Data is derived from MMRM analysis for the efficacy estimand. Only the Week 72 timepoint was pre-specified and controlled for multiplicity.
- CI=Confidence Interval; EAS=Efficacy Analysis Set; ETD=Estimated Treatment Difference; LSM=Least Squares Mean; MMRM=Mixed-Model for Repeated Measures; MTD=Maximum Tolerated Dose.
- 1. Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394 2. Data on File, Eli Lilly and Company.

Key Secondary Endpoints: Percentage of Participants Achieving Body Weight Reduction Targets

- Modified Treatment Regimen Estimand (FAS)

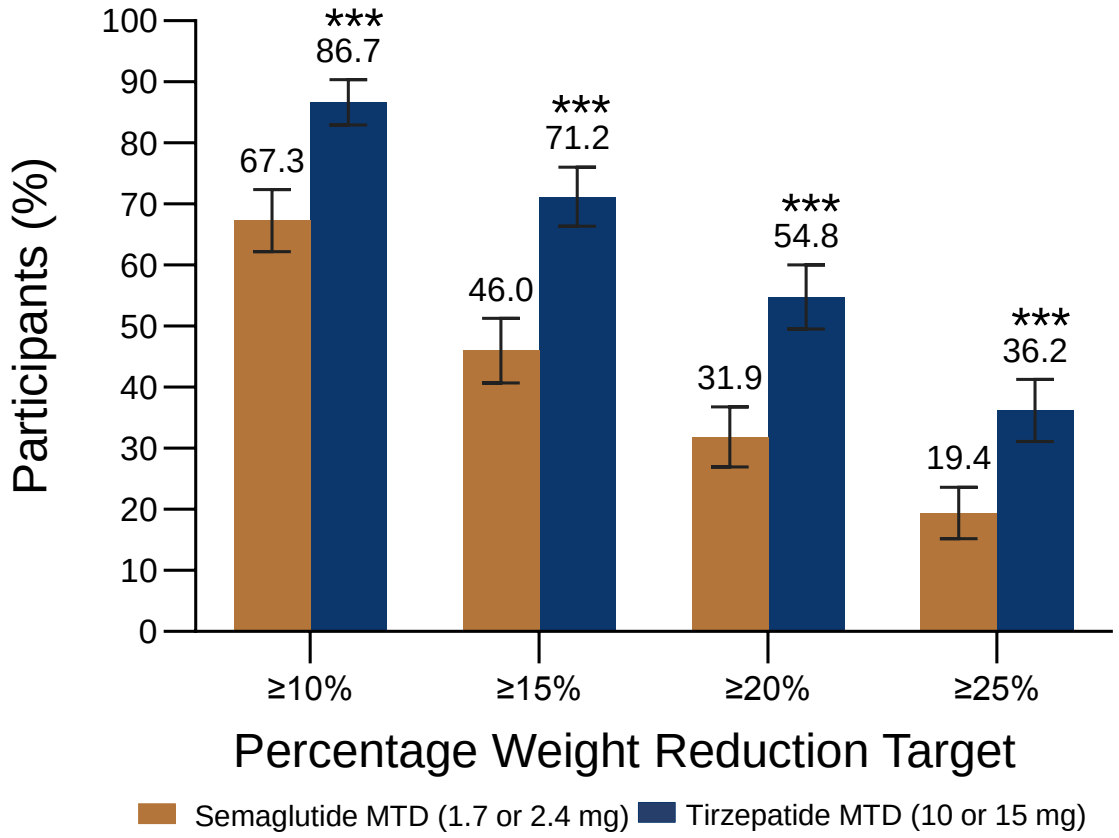


***p<.001 vs. semaglutide.
Data are LSM (95% CI). Percentages were calculated with the use of Rubin's rules by combining the percentage of participants who met the target in imputed data sets.
CI=Confidence Interval; FAS=Full Analysis Set; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose.

- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

Key Secondary Endpoints: Percentage of Participants Achieving Body Weight Reduction Targets

- Efficacy Estimand (EAS)

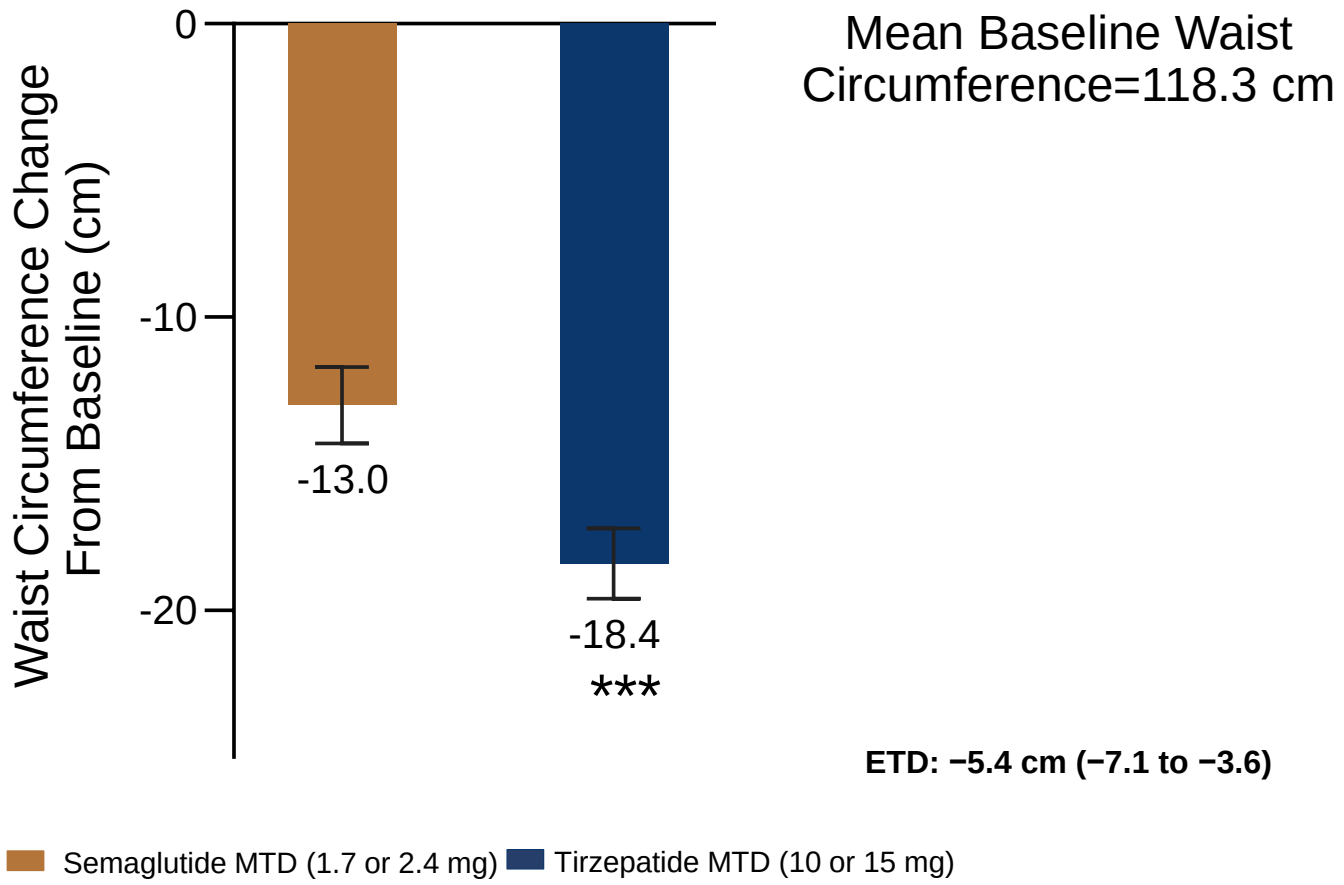


***p<.001 vs. semaglutide.
Data are LSM (95% CI). Percentages were calculated with the use of Rubin's rules by combining the percentage of participants who met the target in imputed data sets.
CI=Confidence Interval; EAS=Efficacy Analysis Set; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose.

- 1. Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394 2. Data on File, Eli Lilly and Company.

Key Secondary Endpoints: Change in Waist Circumference (cm) From Baseline to 72 Weeks

- Modified Treatment Regimen Estimand (FAS)

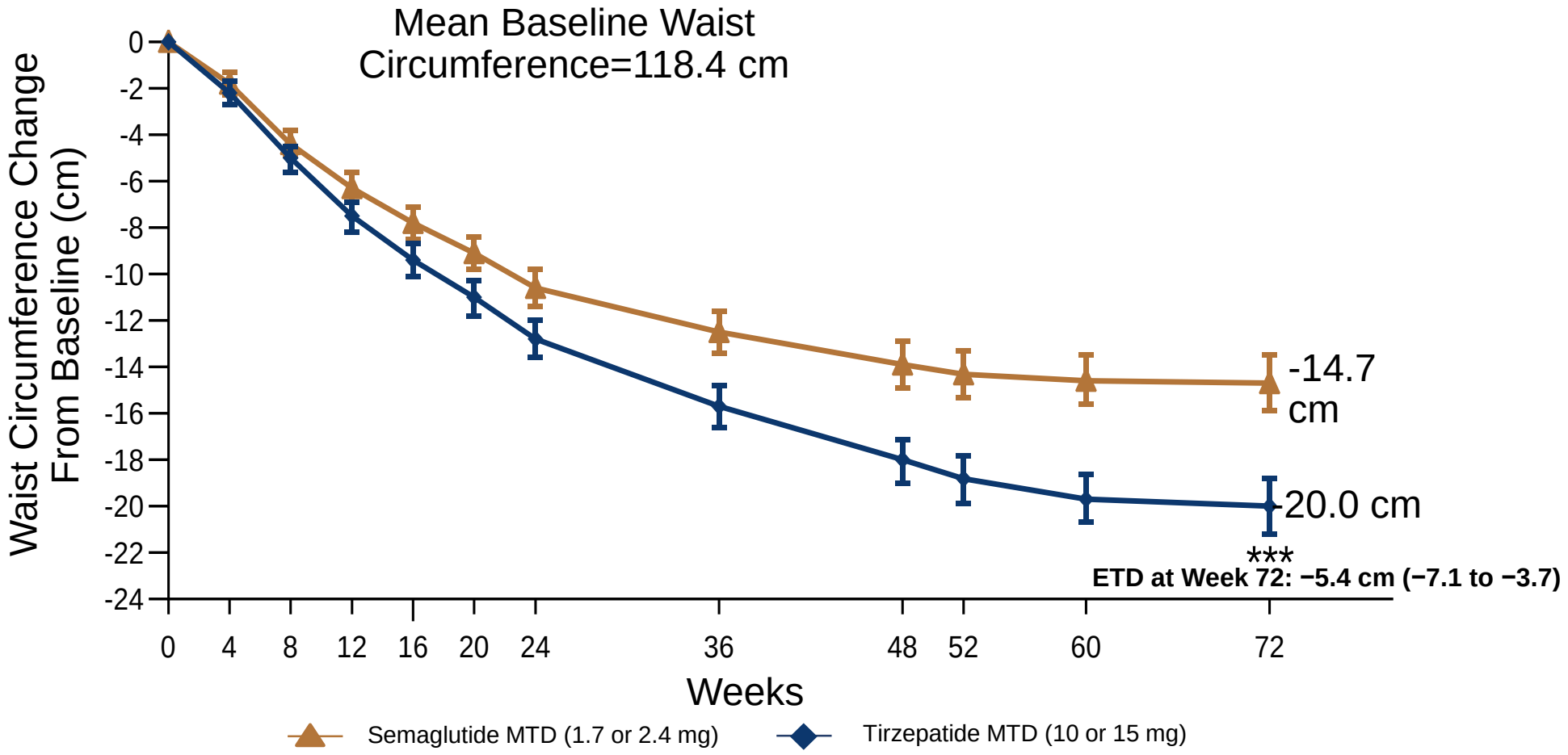


***p<.001 vs. semaglutide.
Data are LSM (95% CI).
CI=Confidence Interval; ETD=Estimated Treatment Difference; FAS=Full Analysis Set; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose.

- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

Key Secondary Endpoints: Change in Waist Circumference (cm) From Baseline to 72 Weeks

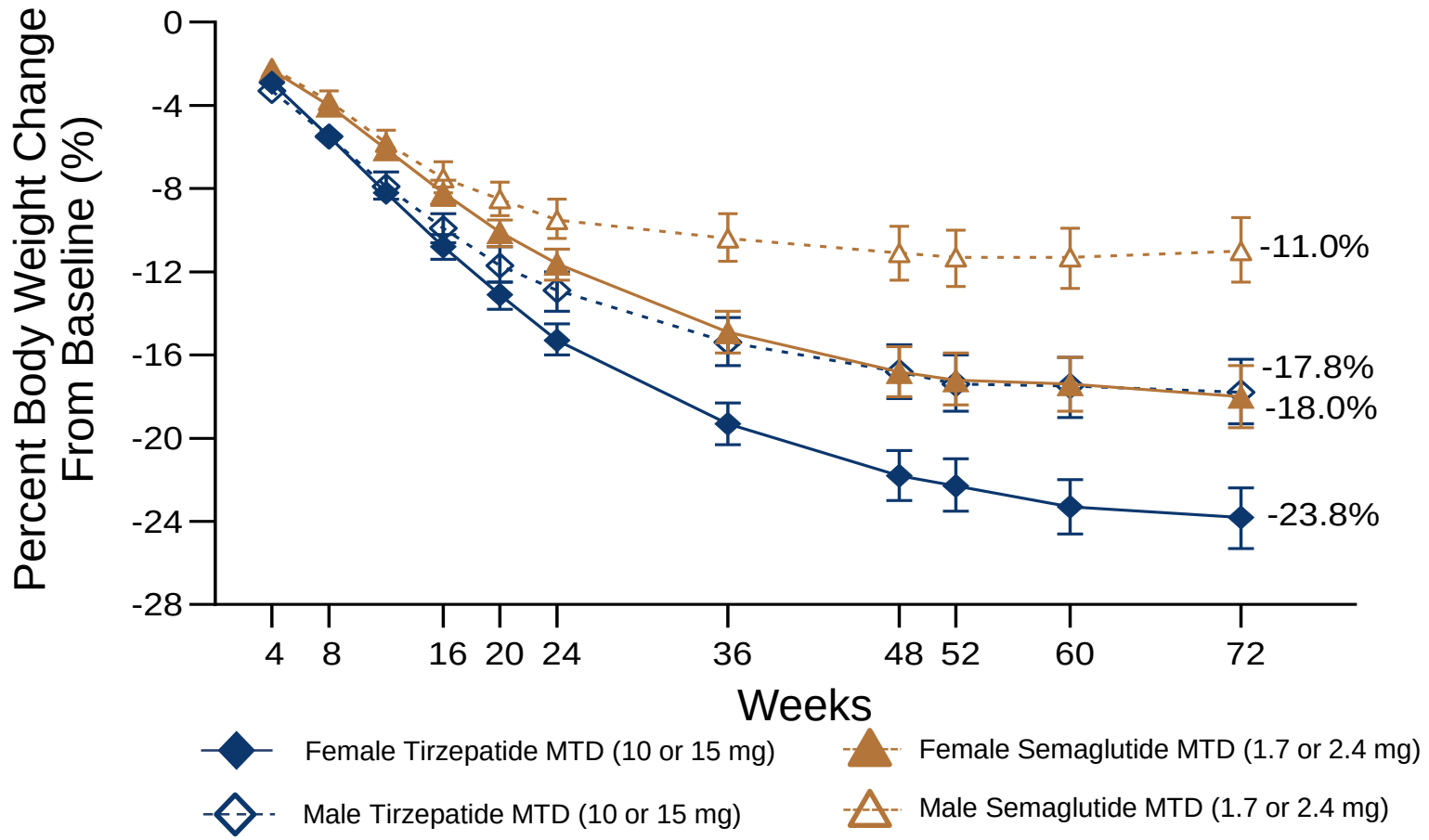
- Efficacy Estimand (EAS)



- ***p<.001 vs. semaglutide.
- Data are LSM (95% CI). Data is derived from MMRM analysis for the efficacy estimand. Only the Week 72 timepoint was pre-specified and controlled for multiplicity.
- CI=Confidence Interval; EAS=Efficacy Analysis Set; ETD=Estimated Treatment Difference; LSM=Least Squares Mean; MMRM=Mixed-Model for Repeated Measures; MTD=Maximum Tolerated Dose.
- 1. Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394 2. Data on File, Eli Lilly and Company.

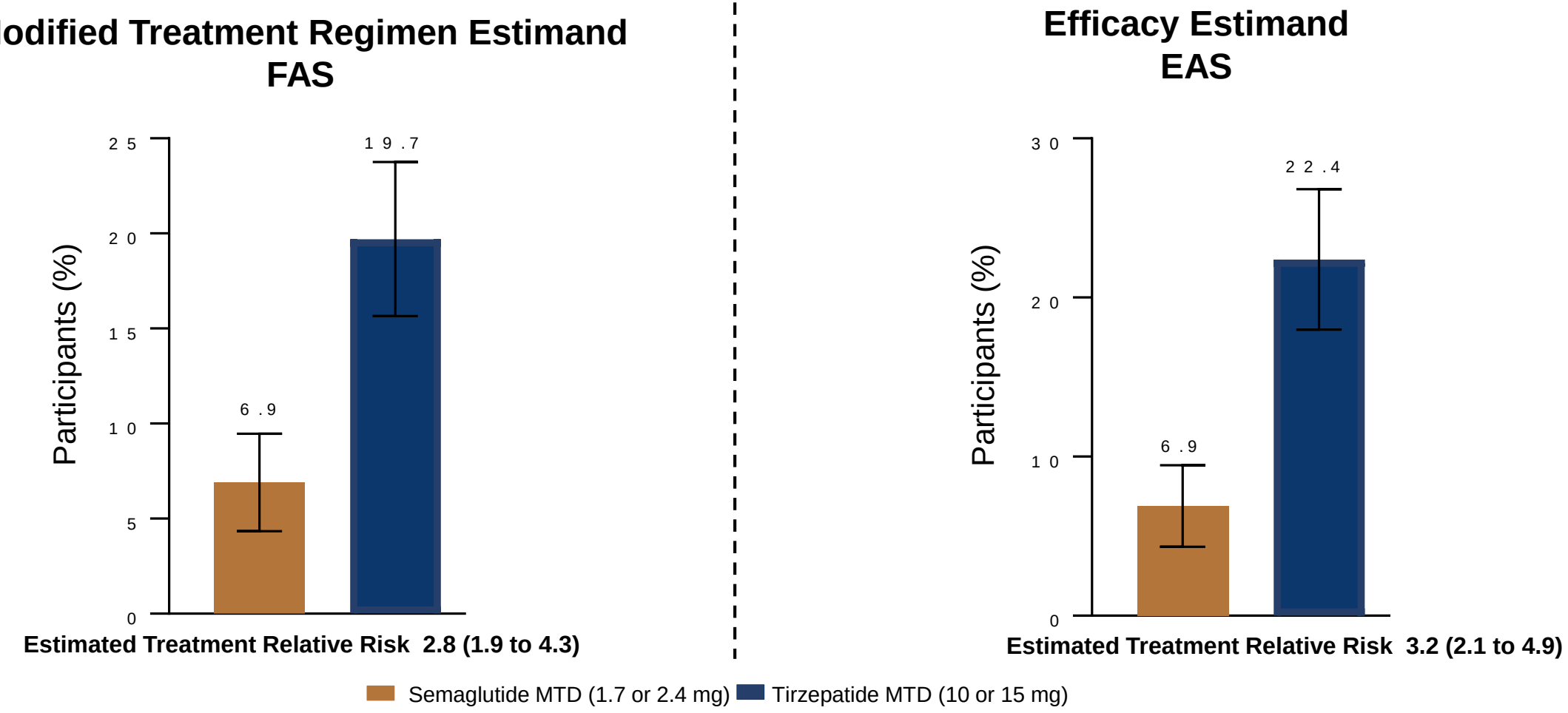
Percentage Change in Body Weight by Sex

- Efficacy Estimand



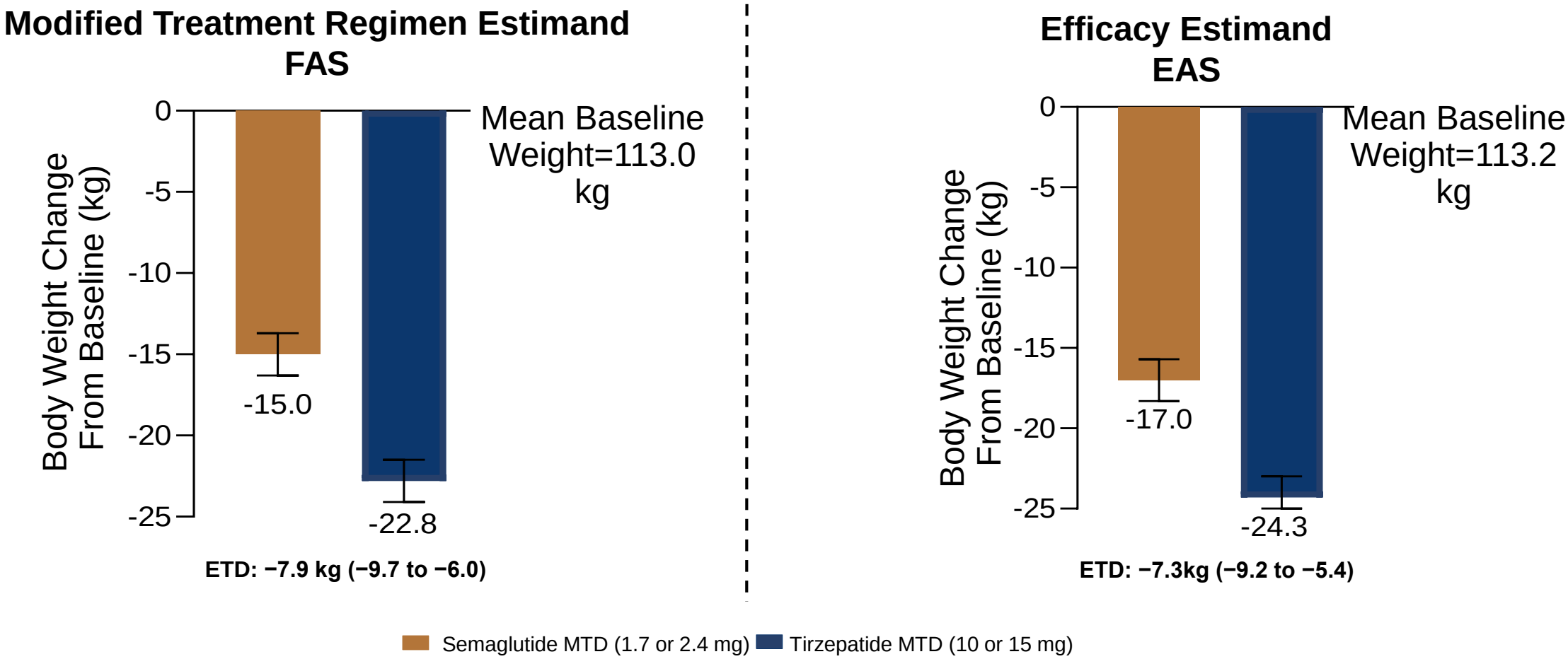
- Data are LSM (95% CI). Derived from a MMRM analysis for efficacy estimand. This was a prespecified analysis and the confidence interval for this endpoint was not adjusted for multiplicity and should not be used to make inferences.
- LSM=Least Squares Mean; MMRM=Mixed-Model for Repeated Measures; MTD=Maximum Tolerated Dose.
- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

Additional Secondary Endpoint: Weight Reduction of ≥ 30%



- Data are LSM (95% CI). Confidence intervals for this endpoint have not been adjusted for multiplicity and should not be used to make inferences.
- Percentages were calculated with the use of Rubin's rules by combining the percentage of participants who met the target in imputed data sets..
- CI=Confidence Interval; EAS=Efficacy Analysis Set; FAS=Full Analysis Set; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose.
- 1. Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394 2. Data on File, Eli Lilly and Company.

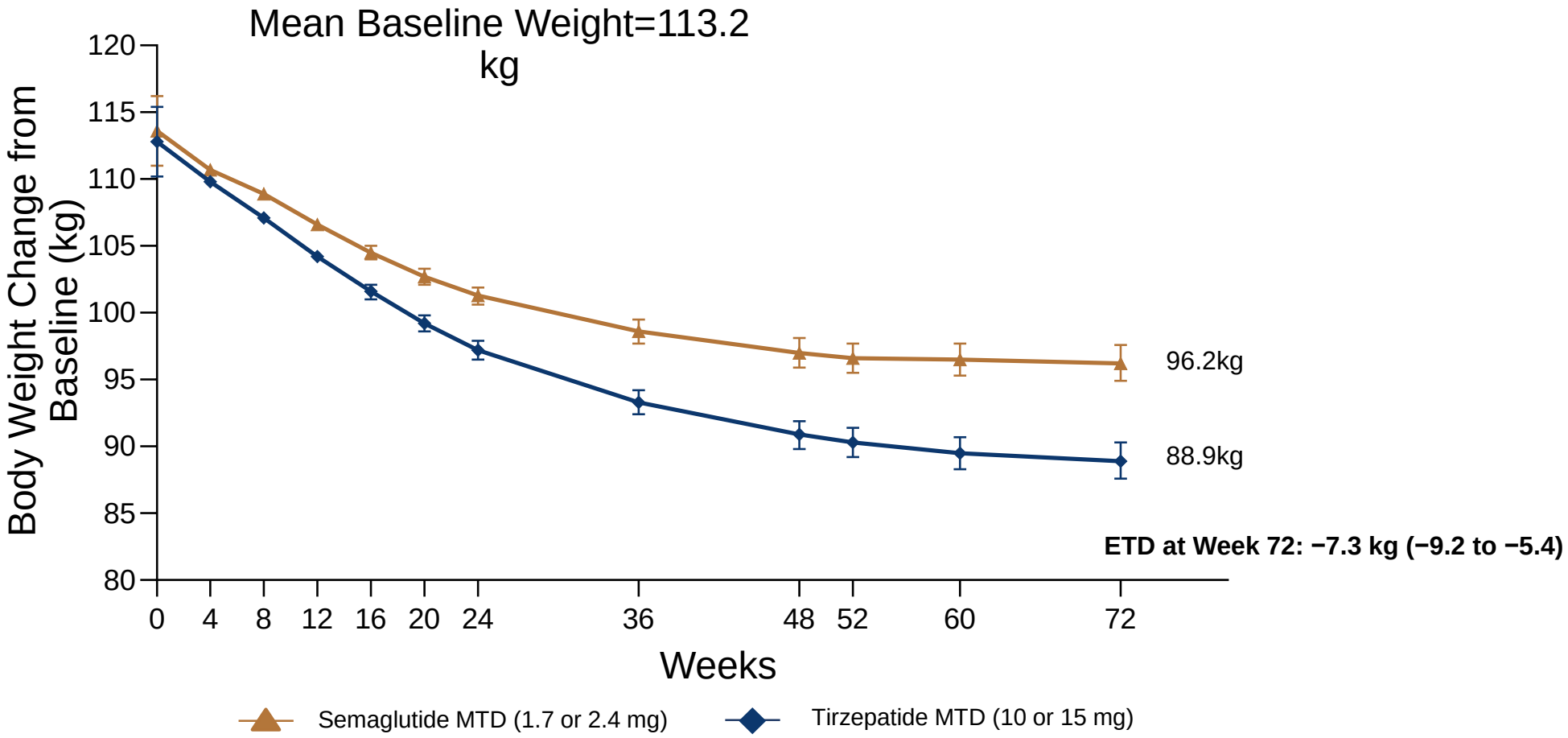
Additional Secondary Endpoint: Change in Body Weight (kg)



- Data are LSM (95% CI). Confidence intervals for this endpoint have not been adjusted for multiplicity and should not be used to make inferences.
- CI=Confidence Interval; EAS=Efficacy Analysis Set; ETD=Estimated Treatment Difference; FAS=Full Analysis Set; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose.
- 1. Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394 2. Data on File, Eli Lilly and Company.

Additional Secondary Endpoint: Change in Body Weight (kg) From Baseline to 72 Weeks

- Efficacy Estimand (EAS)



- Data are LSM (95% CI). Data is derived from MMRM analysis for the efficacy estimand. CIs for this endpoint have not been adjusted for multiplicity and should not be used to make inferences.
- Only participants with non-missing baseline value and at least 1 non-missing post-baseline value of the of the response variable were included in analysis.
- CI=Confidence Interval; EAS=Efficacy Analysis Set; ETD=Estimated Treatment Difference; LSM=Least Squares Mean; MMRM=Mixed-Model for Repeated Measures; MTD=Maximum Tolerated Dose.
- 1. Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394 2. Data on File, Eli Lilly and Company.

Tertiary Endpoints

- Efficacy Estimand

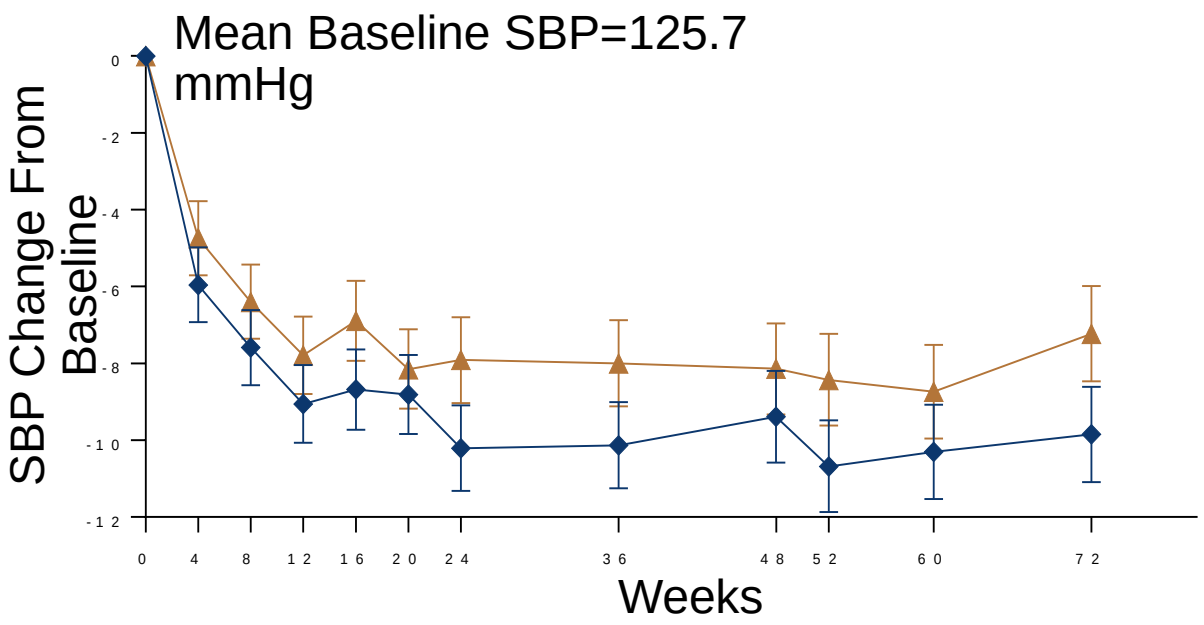
Endpoints	Semaglutide MTD	Tirzepatide MTD	Estimated treatment difference (95% CI)
Change in systolic blood pressure, mmHg	−7.7 (−8.9 to −6.4)	−10.2 (−11.4 to −8.9)	−2.5 (−4.2 to −0.7)
Change in diastolic blood pressure, mmHg	−3.2 (−4.0 to −2.3)	−4.6 (−5.5 to −3.8)	−1.5 (−2.7 to −0.3)
Change in HbA1c, %	−0.39 (−0.42 to −0.36)	−0.50 (−0.53 to −0.47)	−0.10 (−0.15 to −0.06)
Change in fasting serum glucose, mg/dL	−11.6 (−12.4 to −10.7)	−13.4 (−14.2 to −12.5)	−1.8 (−3.1 to −0.6)
Change in fasting insulin, pmol/L	−35.0 (−39.5 to −30.1)	−53.0 (−56.2 to −49.5)	−27.7 (−34.7 to −20.0)
Change in triglycerides, mg/dL	−27.5 (−30.9 to −24.1)	−34.9 (−38.0 to −31.8)	−7.4 (−12.0 to −2.8)
Change in VLDL cholesterol, mg/dL	−5.3 (−6.0 to −4.6)	−6.8 (−7.4 to −6.2)	−1.5 (−2.4 to −0.6)
Change in non-HDL cholesterol, mg/dL	−12.8 (−15.7 to −9.9)	−15.6 (−18.4 to −12.7)	−2.7 (−6.8 to 1.3)
Change in LDL cholesterol, mg/dL	−5.9 (−8.6 to −3.2)	−7.8 (−10.4 to −5.2)	−1.9 (−5.6 to 1.9)
Change in HDL cholesterol, mg/dL	2.9 (2.0 to 3.8)	5.7 (4.8 to 6.7)	2.8 (1.5 to 4.1)

- The CIs have not been adjusted for multiplicity and should not be used to make inferences. Data are LSM (95% CI).
- CI=Confidence Interval; HbA1c=Glycated Haemoglobin; HDL=High-Density Lipoprotein; LDL=Low-Density Lipoprotein; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose; VLDL=Very-Low-Density Lipoprotein.
- Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394

Change in Blood Pressure

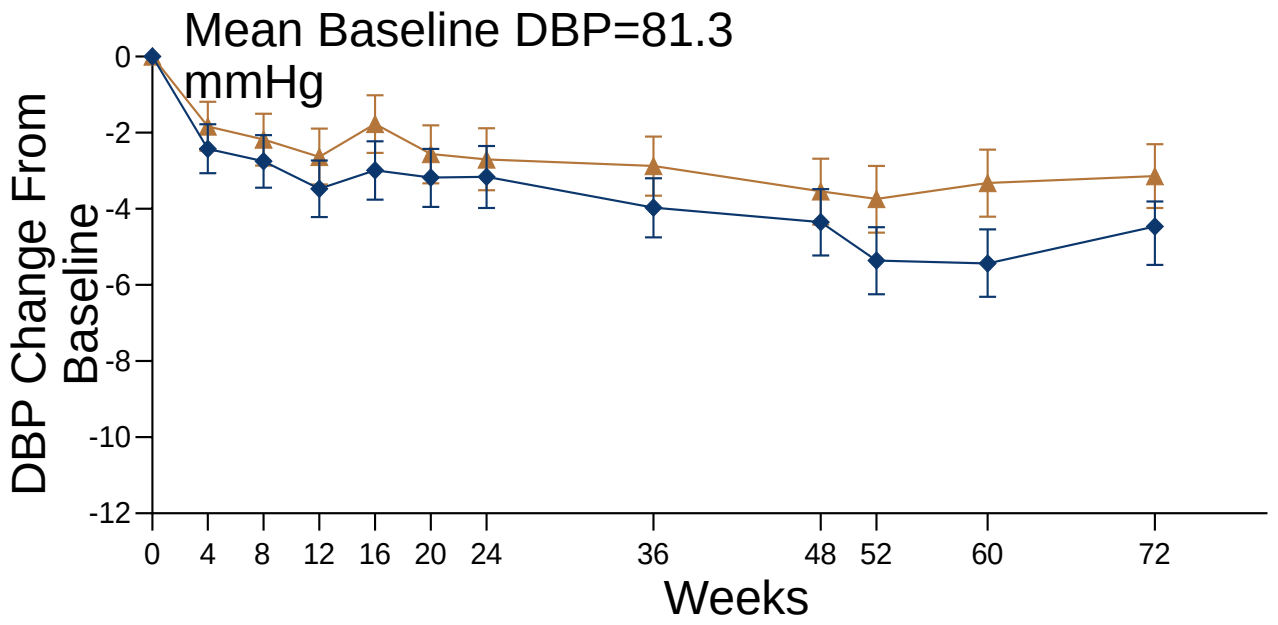
- Efficacy Estimand

Sitting SBP (mmHg)



ETD at Week 72: −2.5 (−4.2 to −0.7)

Sitting DBP (mmHg)



ETD at Week 72: −1.5 (−2.7 to −0.3)

Semaglutide MTD (1.7 or 2.4 mg) Tirzepatide MTD (10 or 15 mg)

- Data are derived from a MMRM analysis for the efficacy estimand. CIs for this endpoint have not been adjusted for multiplicity and should not be used to make inferences. Data are LSM (95% CI).
- CI=Confidence Interval; DBP=Diastolic Blood Pressure; ETD=Estimated Treatment Difference; LSM=Least Squares Mean; MMRM=Mixed-Model Repeated Measures; MTD=Maximum Tolerated Dose; SBP=Systolic Blood Pressure.

1. Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394 2. Data on File, Eli Lilly and Company.

- Tirzepatide is not approved for improvement of blood pressure

Summary of Efficacy

- In the SURMOUNT 5 trial, all primary and key secondary endpoints were met for both the mTRE and EE
- Over 72 weeks, tirzepatide MTD was statistically and clinically superior to semaglutide MTD for weight reduction
  - mTRE: −20.2% vs. −13.7% (ETD −6.5%)
  - EE: −21.6% vs. −15.4% (ETD −6.2%)
- A higher percentage of participants achieved all weight reduction targets with tirzepatide MTD compared with semaglutide MTD, including that nearly two times more participants achieved the 25% or more weight reduction target with tirzepatide
- Participants on tirzepatide MTD achieved statistically and clinically superior reduction in waist circumference compared with those on semaglutide MTD, with mean estimated treatment difference 5.4 cm for both estimands

EE=Efficacy Estimand; ETD=Estimated Treatment Difference; mTRE=Modified Treatment Regimen Estimand; MTD=Maximum Tolerated Dose.

1. Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394 2. Data on File, Eli Lilly and Company.

Safety

Table 3. Adverse Events and Safety.*

Variable	Tirzepatide (N=374)	Semaglutide (N=376)	Total (N=750)
	number of participants (percent)		
Adverse events that occurred or worsened during the treatment period	287 (76.7)	297 (79.0)	584 (77.9)
Serious adverse events	18 (4.8)	13 (3.5)	31 (4.1)
Adverse events leading to death	0	0	0
Discontinuation from the trial because of adverse events	6 (1.6)	6 (1.6)	12 (1.6)
Discontinuation of the trial treatment because of adverse events	23 (6.1)	30 (8.0)	53 (7.1)
Discontinuation of the trial treatment because of gastrointestinal adverse events	10 (2.7)	21 (5.6)	31 (4.1)
Adverse events occurring in ≥5% of participants in either group†			
Nausea	163 (43.6)	167 (44.4)	330 (44.0)
Constipation	101 (27.0)	107 (28.5)	208 (27.7)
Diarrhea	88 (23.5)	88 (23.4)	176 (23.5)
Vomiting	56 (15.0)	80 (21.3)	136 (18.1)
Coronavirus disease 2019	51 (13.6)	47 (12.5)	98 (13.1)
Fatigue	39 (10.4)	46 (12.2)	85 (11.3)
Eructation	37 (9.9)	29 (7.7)	66 (8.8)
Injection-site reaction	32 (8.6)	1 (0.3)	33 (4.4)
Upper respiratory tract infection	32 (8.6)	43 (11.4)	75 (10.0)
Alopecia	31 (8.3)	23 (6.1)	54 (7.2)
Abdominal distention	27 (7.2)	24 (6.4)	51 (6.8)
Headache	27 (7.2)	27 (7.2)	54 (7.2)
Abdominal pain	24 (6.4)	26 (6.9)	50 (6.7)
Dizziness	24 (6.4)	18 (4.8)	42 (5.6)
Gastroesophageal reflux disease	23 (6.1)	40 (10.6)	63 (8.4)
Dyspepsia	22 (5.9)	28 (7.4)	50 (6.7)
Decreased appetite	17 (4.5)	19 (5.1)	36 (4.8)
Nasopharyngitis	17 (4.5)	23 (6.1)	40 (5.3)
Sinusitis	11 (2.9)	21 (5.6)	32 (4.3)
Adverse events leading to discontinuation of the trial treatment‡			
Nausea	5 (1.3)	7 (1.9)	12 (1.6)
Vomiting	3 (0.8)	4 (1.1)	7 (0.9)
Constipation	1 (0.3)	2 (0.5)	3 (0.4)
Diarrhea	1 (0.3)	2 (0.5)	3 (0.4)
Fatigue	1 (0.3)	1 (0.3)	2 (0.3)
Cholelithiasis	0	2 (0.5)	2 (0.3)

Aronne, Louis J., et al. "Tirzepatide as Compared with Semaglutide for the Treatment of Obesity." New England Journal of Medicine (2025).

Conclusion

- In the SURMOUNT 5 trial, tirzepatide was statistically and clinically superior to semaglutide for the primary endpoint of percent body weight reduction at Week 72
  - 6.5% mean estimated treatment difference for the modified Treatment Regimen Estimand and
  - 6.2% mean estimated treatment difference for the efficacy estimand
- Additionally, tirzepatide was statistically and clinically superior for all key secondary endpoints including:
  - Percentage of participants achieving weight reduction targets of ≥10%, ≥15%, ≥20%, and ≥25%
  - Change from baseline in waist circumference, 5.4 cm greater reduction
- The overall safety and tolerability profile of tirzepatide and semaglutide in participants with obesity are consistent with the known safety profile of each medication

1. Aronne LJ, et al. *N Engl J Med*. 2025; doi: 10.1056/NEJMoa2416394 2. Data on File, Eli Lilly and Company.

Thank you for your attention