

JAMA | Original Investigation

Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity

The SURMOUNT-4 Randomized Clinical Trial

Louis J. Aronne, MD; Naveed Sattar, MD; Deborah B. Horn, DO, MPH; Harold E. Bays, MD; Sean Wharton, MD; Wen-Yuan Lin, MD, PhD; Nadia N. Ahmad, MD, MPH; Shuyu Zhang, MSc; Ran Liao, PhD; Mathijs C. Bunck, MD, PhD; Irina Jouravskaya, MD, PhD; Madhumita A. Murphy, MD; for the SURMOUNT-4 Investigators

IMPORTANCE The effect of continued treatment with tirzepatide on maintaining initial weight reduction is unknown.

OBJECTIVE To assess the effect of tirzepatide, with diet and physical activity, on the maintenance of weight reduction.

DESIGN, SETTING, AND PARTICIPANTS This phase 3, randomized withdrawal clinical trial conducted at 70 sites in 4 countries with a 36-week, open-label tirzepatide lead-in period followed by a 52-week, double-blind, placebo-controlled period included adults with a body mass index greater than or equal to 30 or greater than or equal to 27 and a weight-related complication, excluding diabetes.

INTERVENTIONS Participants (n = 783) enrolled in an open-label lead-in period received once-weekly subcutaneous maximum tolerated dose (10 or 15 mg) of tirzepatide for 36 weeks. At week 36, a total of 670 participants were randomized (1:1) to continue receiving tirzepatide (n = 335) or switch to placebo (n = 335) for 52 weeks.

MAIN OUTCOMES AND MEASURES The primary end point was the mean percent change in weight from week 36 (randomization) to week 88. Key secondary end points included the proportion of participants at week 88 who maintained at least 80% of the weight loss during the lead-in period.

RESULTS Participants (n = 670; mean age, 48 years; 473 [71%] women; mean weight, 107.3 kg) who completed the 36-week lead-in period experienced a mean weight reduction of 20.9%. The mean percent weight change from week 36 to week 88 was -5.5% with tirzepatide vs 14.0% with placebo (difference, -19.4% [95% CI, -21.2% to -17.7%]; $P < .001$). Overall, 300 participants (89.5%) receiving tirzepatide at 88 weeks maintained at least 80% of the weight loss during the lead-in period compared with 16.6% receiving placebo ($P < .001$). The overall mean weight reduction from week 0 to 88 was 25.3% for tirzepatide and 9.9% for placebo. The most common adverse events were mostly mild to moderate gastrointestinal events, which occurred more commonly with tirzepatide vs placebo.

CONCLUSIONS AND RELEVANCE In participants with obesity or overweight, withdrawing tirzepatide led to substantial regain of lost weight, whereas continued treatment maintained and augmented initial weight reduction.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT04660643](https://clinicaltrials.gov/ct2/show/study/NCT04660643)

JAMA. 2024;331(1):38-48. doi:10.1001/jama.2023.24945
Published online December 11, 2023.

- [+ Visual Abstract](#)
- [+ Supplemental content](#)
- [+ CME Quiz at \[jamacmelookup.com\]\(https://jamacmelookup.com\)](#)

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The SURMOUNT-4 Investigators are listed in Supplement 5.

Corresponding Author: Louis J. Aronne, MD, Comprehensive Weight Control Center, Division of Endocrinology, Diabetes, and Metabolism, Weill Cornell Medicine, 1305 York Ave, Fourth Floor, New York, NY 10065 (ljaronne@med.cornell.edu).

Obesity is a serious chronic, progressive, and relapsing disease.¹ Lifestyle interventions are a cornerstone of obesity management; however, sustaining weight reduction achieved through lifestyle-based caloric restriction is challenging.

Therefore, current guidelines recommend adjunctive antiobesity medications to promote weight reduction, facilitate weight maintenance, and improve health outcomes in people with obesity.²⁻⁴ Randomized withdrawal studies of antiobesity medications to date have consistently demonstrated clinically significant body weight regain with cessation of therapy.^{5,6} There is also evidence that antiobesity medications, including long-acting glucagon-like peptide-1 (GLP-1) receptor agonists, naltrexone/bupropion, phentermine/topiramate, and orlistat, may help maintenance of achieved weight reduction.^{5,7-12}

Tirzepatide is a single molecule that combines glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonism¹³ resulting in synergistic effects on appetite, food intake, and metabolic function.¹⁴⁻¹⁶ Tirzepatide is approved in many countries, including the US, EU, and Japan, as a once-weekly subcutaneous injectable for type 2 diabetes and for the treatment of obesity in the US and UK.¹⁶⁻¹⁸ In a placebo-controlled trial of participants with obesity or overweight without diabetes, tirzepatide led to mean reductions in body weight up to 20.9% after 72 weeks of treatment.^{17,18}

The aim of the SURMOUNT-4 trial was to investigate the effect of continued treatment with the maximum tolerated dose (ie, 10 or 15 mg) of once-weekly tirzepatide, compared with placebo, on the maintenance of weight reduction following an initial open-label lead-in treatment period in participants with obesity or overweight.

Methods

Study Design

SURMOUNT-4 was a phase 3 randomized withdrawal study with a 36-week, open-label tirzepatide lead-in period followed by a 52-week, double-blind, placebo-controlled period conducted at 70 sites in Argentina, Brazil, Taiwan, and the US. The trial started on March 29, 2021, and finished on May 18, 2023. The study protocol (Supplement 1) was approved by the ethical review board at each site and was followed according to local regulations and the principles of the Declaration of Helsinki, Council of International Organizations of Medical Sciences International Ethical Guidelines, and Good Clinical Practice guidelines. Written informed consent was obtained from all participants before participation in this study.

Participants

Eligible participants (18 years or older) had a body mass index (BMI) greater than or equal to 30 or greater than or equal to 27 and at least 1 weight-related complication (ie, hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease). Key exclusion criteria included diabe-

Key Points

Question Does once-weekly subcutaneous tirzepatide with diet and physical activity affect maintenance of body weight reduction in individuals with obesity or overweight?

Findings After 36 weeks of open-label maximum tolerated dose of tirzepatide (10 or 15 mg), adults (n = 670) with obesity or overweight (without diabetes) experienced a mean weight reduction of 20.9%. From randomization (at week 36), those switched to placebo experienced a 14% weight regain and those continuing tirzepatide experienced an additional 5.5% weight reduction during the 52-week double-blind period.

Meaning In participants with obesity/overweight, withdrawing tirzepatide led to substantial regain of lost weight, whereas continued treatment maintained and augmented initial weight reduction.

tes, prior or planned surgical treatment for obesity, and treatment with a medication that promotes weight loss within 3 months prior to enrollment. Full eligibility criteria are shown in eAppendix 1 in Supplement 2. The study was not designed to represent the racial diversity of each of the participating countries. Race and ethnicity were self-reported by participants in this study using fixed selection categories.

Procedures

Tirzepatide was administered once weekly as a subcutaneous injection. During the 36-week, open-label lead-in period, the starting dose of tirzepatide was 2.5 mg and was increased by 2.5 mg every 4 weeks until a maximum tolerated dose of 10 or 15 mg was achieved (eFigure 1 in Supplement 2). Throughout the study, gastrointestinal symptoms were managed by dietary counseling, symptomatic medications per the investigator's discretion, or skipping of a single dose of treatment as described in the protocol (Supplement 1). During the lead-in period, if these mitigations were not successful, a cycle of tirzepatide dose deescalation and reescalation (in 2.5-mg increments) was allowed. At the end of the lead-in period, participants who attained the maximum tolerated dose of tirzepatide (10 or 15 mg) were randomized in a 1:1 ratio by a computer-generated random sequence using an interactive web-response system to either continue receiving the maximum tolerated dose of tirzepatide or switch to matching placebo for an additional 52 weeks. Randomization was stratified by country, sex, maximum tolerated dose of tirzepatide, and percent weight reduction at week 36 (<10% vs ≥10%). Dose adjustments were not permitted during the double-blind treatment period.

All participants received lifestyle counseling by a qualified health care professional throughout the study to encourage adherence to a healthy 500 kcal/d deficit diet and at least 150 minutes of physical activity per week. The use of concomitant medications is described in eAppendix 2 in Supplement 2.

Outcomes

The primary end point was the percent change in body weight from randomization (week 36) to week 88. Key secondary end points capturing weight maintenance and regain, respectively, were the proportion of participants at week 88 maintaining at least 80% of the body weight loss during the 36-week open-label period and time during the 52-week double-blind treatment period to first occurrence of participants returning to greater than 95% baseline body weight for those who lost at least 5% during the open-label lead-in period. Key secondary end points also included change in absolute body weight and waist circumference during the double-blind period (week 36 to 88) and the proportion of participants achieving weight reduction thresholds of at least 5%, at least 10%, at least 15%, and at least 20% since enrollment (week 0 to 88); the proportion of participants achieving at least 25% weight reduction from week 0 to 88 was a prespecified exploratory end point.

Additional secondary end points included change from randomization (week 36) to week 88 and from enrollment (week 0) to week 88 in cardiometabolic risk factors including glycemic parameters, fasting insulin, lipids, blood pressure, and patient-reported outcomes measured by the Short Form-36 Version 2 Health Survey (SF-36 v2) acute form and Impact of Weight on Quality of Life-Lite-Clinical Trials Version (IWQOL-Lite-CT).

Safety assessments included treatment-emergent adverse events, serious adverse events, and early discontinuation of study drug due to adverse events during the tirzepatide lead-in treatment period (weeks 0-36), the double-blind period (weeks 36-88), and safety follow-up period. Cases of major adverse cardiovascular events, acute pancreatitis, and deaths were reviewed by an independent external adjudication committee.

Sample Size Calculation

A sample size of 600 randomized participants provided greater than 90% power to demonstrate superiority of maximum tolerated dose of tirzepatide vs placebo for the primary end point at a 2-sided significance level of .05 using a 2-sample *t* test. The calculation assumed a dropout rate of up to 25%, a difference between treatment groups of at least 6% in mean percent change in body weight from randomization (week 36) to week 88, and a common SD of 8% based on data from 2 phase 2 trials.^{19,20}

Statistical Analysis

Unless stated otherwise, efficacy end points were analyzed using the full analysis set (data obtained during the double-blind period, regardless of adherence to study drug) and the efficacy analysis set (data obtained during the double-blind period, excluding data after discontinuation of study drug). Assessment of adverse events and laboratory parameters used the safety analysis set (data obtained during the double-blind period and safety follow-up period, regardless of adherence to study drug). All results from statistical analyses were accompanied by 2-sided 95% CIs and corresponding *P* values (statistical significance was defined as

P < .05). Statistical analyses were performed using SAS version 9.4 (SAS Institute).

Two estimands (treatment regimen estimand and efficacy estimand) were used to assess efficacy from different perspectives and accounted for intercurrent events and missing data.²¹ The treatment regimen estimand was conducted on the full analysis set representing the mean treatment effect of tirzepatide relative to placebo for all participants who had undergone randomization, regardless of treatment adherence. If intercurrent events led to missing data, the missingness was assumed to be related to treatment, except for intercurrent events solely due to COVID-19, for which missing at random was assumed. The efficacy estimand was conducted on the efficacy analysis set representing the mean treatment effect of tirzepatide relative to placebo for all participants who had undergone randomization if the treatment was administered as intended (ie, excluding the data collected after study drug discontinuation). Continuous end points were analyzed using an analysis of covariance model for the treatment regimen estimand and a mixed model for repeated measures for the efficacy estimand, and categorical end points were analyzed by logistic regression for both estimands (treatment difference was assessed by odds ratio). Details on statistical analysis methods, estimands, and handling of missing values are provided in eAppendix 3 in Supplement 2 and the statistical analysis plan (Supplement 3). All reported results are for the treatment regimen estimand unless stated otherwise. The type I error rate was controlled within each estimand independently for evaluation of primary and key secondary end points with a graphical approach (eAppendix 3 in Supplement 2). Because of the potential for type I error due to multiple comparisons, findings for analyses of additional secondary end points should be interpreted as exploratory.

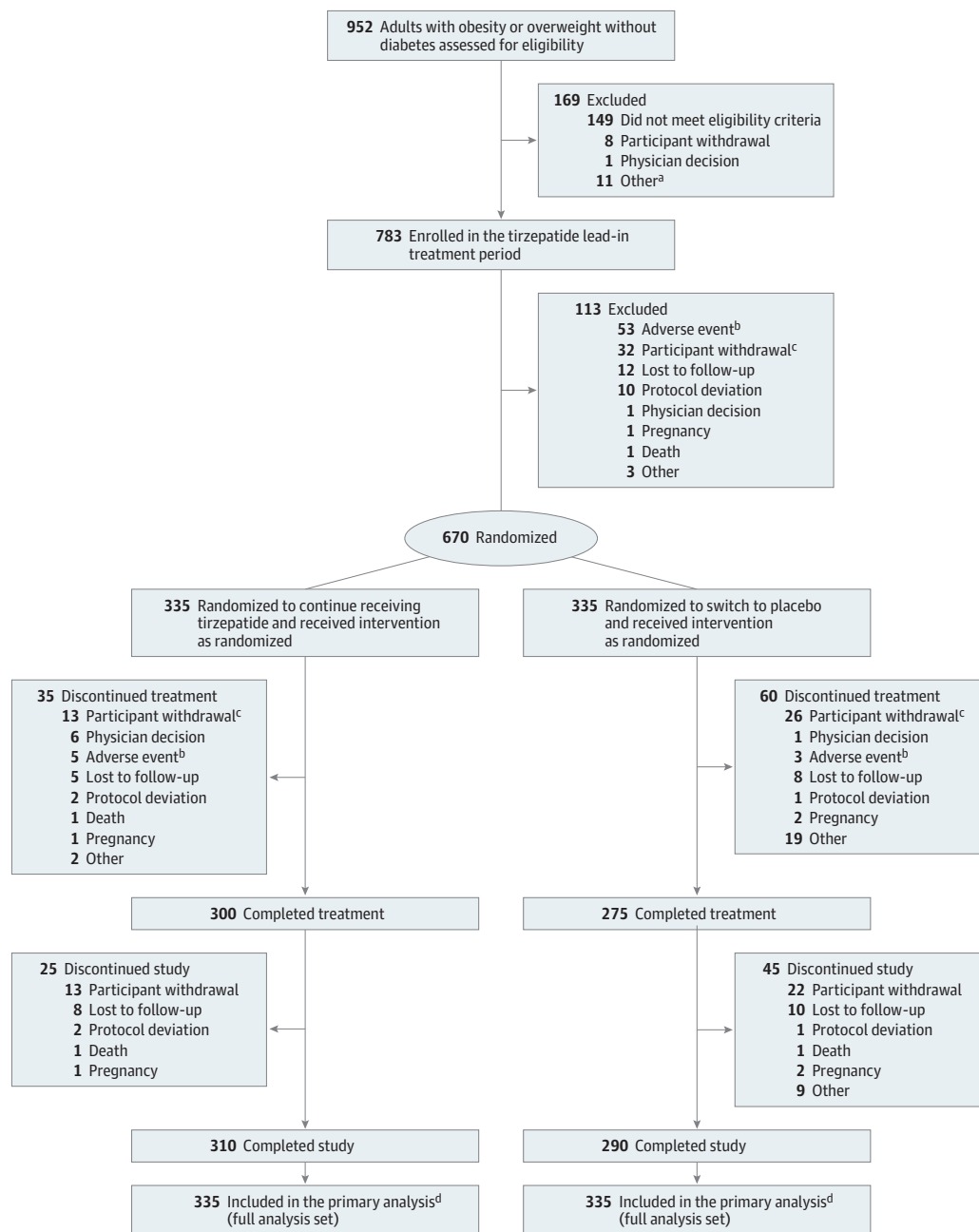
Results

Study Participants

A total of 952 patients were screened and 783 were enrolled in the 36-week open-label tirzepatide lead-in treatment period. Among enrolled participants, 113 discontinued the study drug during the lead-in period, most commonly due to an adverse event or participant withdrawal (Figure 1). A total of 670 participants (92.7% achieved a maximum tolerated dose of 15 mg and 7.3% achieved a maximum tolerated dose of 10 mg) were randomized to continue receiving the maximum tolerated dose of tirzepatide (*n* = 335) or switch to receiving placebo (*n* = 335). Of the randomized participants, 600 (89.6%) completed the study and 575 (85.8%) completed the study while receiving the study drug. Withdrawal and "other" (mainly in the placebo group as lack of efficacy) were the most common reasons for premature study drug discontinuation during the double-blind period (Figure 1).

Most randomized participants were women (70.6%) and White (80.1%), with an overall mean age of 48 years, body weight of 107.3 kg, BMI of 38.4, and waist circumference of

Figure 1. Flow of Participants in the SURMOUNT-4 Trial



^a Includes 10 individuals for whom the site enrollment closed and 1 who was lost to follow-up.

^b See Table 3 and eTable 4 in Supplement 2 for the details of the adverse events that led to treatment discontinuation.

^c The most common reasons for participant withdrawal included participant no longer wished to participate, participant unavailable to attend visits, participant moved out of state or country, and personal or family issues.

^d Guided by the treatment regimen estimand.

115.2 cm at enrollment (week 0; Table 1). The mean duration of obesity was 15.5 years and 69.4% participants had 1 or more weight-related complication (eTable 1 in Supplement 2), with hypertension and dyslipidemia being the most prevalent (Table 1). Demographics and clinical characteristics at randomization (week 36) were similar across tirzepatide

and placebo groups, with overall mean body weight of 85.2 kg, BMI of 30.5, and waist circumference of 97.5 cm.

Open-Label Lead-In Period

During the open-label tirzepatide lead-in period (week 0 to 36), randomized participants achieved a mean weight

Table 1. Demographics and Clinical Characteristics of the Randomized Population

Characteristic	Mean (SD)		
	Week 0 (start of tirzepatide lead-in treatment period) (N = 670)	Week 36 (randomization)	
		Tirzepatide (n = 335)	Placebo (n = 335)
Age, y	48 (13)	49 (13)	48 (12)
Age category, No. (%)			
<65	603 (90.0)	296 (88.4)	302 (90.1)
≥65	67 (10.0)	39 (11.6)	33 (9.9)
Sex, No. (%)			
Women	473 (70.6)	236 (70.4)	237 (70.7)
Men	197 (29.4)	99 (29.6)	98 (29.3)
Race, No. (%) ^a			
Asian	48 (7.2)	26 (7.8)	22 (6.6)
Black or African American	75 (11.2)	39 (11.6)	36 (10.7)
Native Hawaiian or Other Pacific Islander	2 (0.3)	1 (0.3)	1 (0.3)
White	537 (80.1)	264 (78.8)	273 (81.5)
Multiple	8 (1.2)	5 (1.5)	3 (0.9)
Hispanic or Latino, No. (%) ^a	296 (44.2)	141 (42.1)	155 (46.3)
Duration of obesity, y ^b	15.5 (11.8)	15.9 (12.1)	15.2 (11.4)
Body weight, kg	107.3 (22.3)	84.6 (19.8)	85.8 (22.3)
BMI	38.4 (6.6)	30.3 (6.0)	30.7 (6.8)
BMI category, No. (%)			
<25	0	59 (17.6)	63 (18.8)
≥25 to <30	18 (2.7)	122 (36.4)	120 (35.8)
≥30 to <35	212 (31.6)	88 (26.3)	75 (22.4)
≥35 to <40	215 (32.1)	41 (12.2)	43 (12.8)
≥40	225 (33.6)	25 (7.5)	34 (10.1)
Waist circumference, cm	115.2 (14.5)	96.8 (14.1)	98.2 (16.0)
Blood pressure, mm Hg			
Systolic	126 (13)	115 (13)	115 (12)
Diastolic	81 (8)	75 (9)	76 (9)
Pulse rate, beats/min	72 (9)	77 (9)	78 (9)
Hemoglobin A _{1c} , %	5.54 (0.36)	5.07 (0.30)	5.04 (0.31)
Fasting glucose, mg/dL	94.8 (10.9)	85.1 (7.4)	85.0 (7.8)
Fasting insulin, mIU/L	13.9 (10.7)	7.4 (5.2)	8.0 (6.3)
Lipid levels, mg/dL			
Total cholesterol	192.3 (39.6)	179.9 (36.8)	180.2 (37.3)
Non-HDL-C	140.8 (37.5)	130.8 (34.5)	131.7 (36.2)
HDL-C	51.5 (13.1)	49.1 (11.6)	48.8 (11.5)
LDL-C	113.8 (32.9)	111.0 (32.4)	113.2 (33.6)
VLDL-C	60.3 (27.7)	45.3 (20.7)	41.4 (16.4)
Triglycerides	136.2 (80.9)	99.1 (45.1)	93.0 (44.3)
Free fatty acids, mEq/L	0.53 (0.22)	0.48 (0.20)	0.51 (0.22)
eGFR, mL/min/1.73 m ²	97.8 (17.2)	96.4 (18.8)	97.9 (17.9)
eGFR category, No. (%)			
≥30 to <45	2 (0.3)	2 (0.6)	1 (0.3)
≥45 to <60	12 (1.8)	7 (2.1)	7 (2.1)
≥60 to <90	189 (28.2)	108 (32.2)	89 (26.6)
≥90	467 (69.7)	218 (65.1)	238 (71.0)

(continued)

Table 1. Demographics and Clinical Characteristics of the Randomized Population (continued)

Characteristic	Mean (SD)		
	Week 0 (start of tirzepatide lead-in treatment period) (N = 670)	Week 36 (randomization)	
		Tirzepatide (n = 335)	Placebo (n = 335)
Comorbidities, No. (%) ^c			
Hypertension	236 (35.2)	119 (35.5)	117 (34.9)
Dyslipidemia	212 (31.6)	113 (33.7)	99 (29.6)
Anxiety/depression	151 (22.5)	73 (21.8)	78 (23.3)
Osteoarthritis	133 (19.9)	70 (20.9)	63 (18.8)
Obstructive sleep apnea	81 (12.1)	40 (11.9)	41 (12.2)
Asthma/COPD	69 (10.3)	34 (10.1)	35 (10.4)
Nonalcoholic fatty liver disease	48 (7.2)	22 (6.6)	26 (7.8)
Atherosclerotic cardiovascular disease	41 (6.1)	18 (5.4)	23 (6.9)
Polycystic ovary syndrome ^d	23 (4.9)	9 (3.8)	14 (5.9)
Gout	24 (3.6)	15 (4.5)	9 (2.7)
SF-36 v2 scores ^e			
Physical functioning domain	47.6 (8.2)	53.4 (5.8)	53.2 (6.5)
Role-physical domain	50.1 (7.8)	54.5 (4.9)	53.7 (6.5)
Role-emotional domain	49.5 (8.9)	52.4 (7.0)	52.2 (7.2)
Mental health domain	52.6 (7.8)	54.6 (6.8)	54.8 (6.8)
IWQOL-Lite-CT physical function composite score ^f	59.1 (24.5)	80.7 (17.2)	81.6 (17.8)

SI conversions: To convert HDL-C, LDL-C, and total cholesterol to mmol/L, multiply by 0.0259; glucose to mmol/L, multiply by 0.055; triglycerides to mmol/L, multiply by 0.0113.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol.

^a Race and ethnicity were recorded in this study and were determined by the participant according to fixed selection categories.

^b Duration of obesity was self-reported by participants.

^c Medical conditions were assessed through a review of participant's medical history at week 0.

^d Percentage is based on total number of female participants in the respective treatment group.

^e The Short Form-36 Version 2 Health Survey, acute form (SF-36 v2) measures health-related quality of life and general health status. The SF-36 v2 scores are norm-based scores, ie, scores transformed to a scale in which the 2009 US general population has a mean score of 50 and an SD of 10. An increase in score represents an improvement in health status.

^f The Impact of Weight on Quality of Life-Lite-Clinical Trials Version (IWQOL-Lite-CT) measures weight-specific health-related quality of life. All items are rated on either a 5-point frequency scale ("never" to "always") or a 5-point truth scale ("not at all true" to "completely true"). Scores are transformed to a scale of 0 to 100, with higher scores reflecting better levels of functioning.

reduction of 20.9%, with reductions in BMI and waist circumference and improvements in blood pressure, glycaemic parameters, lipid levels, and patient-reported outcomes (eTable 2 in Supplement 2).

Double-Blind Period

Primary End Point

For the treatment regimen estimand, the mean percent change in weight from week 36 to week 88 was -5.5% with tirzepatide vs 14.0% with placebo (difference, -19.4% [95% CI, -21.2% to -17.7%]; $P < .001$; Table 2; eFigure 2A in Supplement 2). For the efficacy estimand, corresponding changes were -6.7% with tirzepatide vs 14.8% with placebo (difference, -21.4% [95% CI, -22.9% to -20.0%]; $P < .001$; eTable 3 and eFigure 3 in Supplement 2).

Key Secondary End Points

At week 88, a significantly greater percentage of participants who continued receiving tirzepatide vs placebo maintained at least 80% of the body weight loss during the 36-week open-label tirzepatide lead-in treatment period (89.5% vs 16.6% ; $P < .001$; treatment regimen estimand; Table 2; eFigure 2B in

Supplement 2). Consistent results were observed when using the efficacy estimand (eTable 3 in Supplement 2). Time-to-event analysis showed that continued tirzepatide treatment during the double-blind period reduced the risk of returning to greater than 95% baseline body weight for those who had already lost at least 5% since week 0 by approximately 98% compared with placebo (hazard ratio, 0.02 [95% CI, 0.01 to 0.06]; $P < .001$) for the treatment regimen estimand, which was consistent with the results for the efficacy estimand (eFigure 4 in Supplement 2). The mean change from week 36 to week 88 in body weight and waist circumference is presented in Table 2 for the treatment regimen estimand and in eTable 3 in Supplement 2 for the efficacy estimand.

Additional Secondary End Points

Relative to placebo, tirzepatide was associated with significant improvements from randomization at week 36 to week 88 in BMI, hemoglobin A_{1c}, fasting glucose, insulin, lipid levels, and systolic and diastolic blood pressure ($P < .001$ for all except $P = .014$ for high-density lipoprotein cholesterol and $P = .008$ for free fatty acids) (eTable 3 in Supplement 2; efficacy estimand). Significant improvements were observed in

Table 2. Primary and Secondary End Points (Treatment Regimen Estimand)^a

Outcome	Least-squares mean (95% CI)		Absolute difference (95% CI) ^b	P value
	Tirzepatide (n = 335)	Placebo (n = 335)		
Primary end point ^c				
Change in body weight from wk 36 to 88, %	-5.5 (-6.8 to -4.2)	14.0 (12.8 to 15.2)	-19.4 (-21.2 to -17.7)	<.001
Key secondary end points ^{c,d}				
Change in body weight from wk 36 to 88, kg	-4.7 (-5.7 to -3.6)	11.1 (10.1 to 12.2)	-15.8 (-17.3 to -14.3)	<.001
Change in waist circumference from wk 36 to 88, cm	-4.3 (-5.3 to -3.2)	7.8 (6.9 to 8.8)	-12.1 (-13.5 to -10.6)	<.001
Participants maintaining ≥80% of body weight lost during 36-wk lead-in at wk 88, No. (%)	300 (89.5)	55 (16.6)	44.0 (24.9 to 77.5)	<.001
Participants achieving body weight reduction from wk 0 to 88, No. (%)				
≥5%	326 (97.3)	235 (70.3)	20.3 (7.7 to 53.3)	<.001
≥10%	309 (92.1)	155 (46.2)	26.1 (12.6 to 54.1)	<.001
≥15%	282 (84.1)	87 (25.9)	32.6 (16.4 to 64.8)	<.001
≥20%	233 (69.5)	42 (12.6)	46.1 (20.7 to 102.9)	<.001
Change in body weight from wk 36 to 64, %	-5.4 (-6.3 to -4.6)	10.0 (9.0 to 11.0)	-15.4 (-16.8 to -14.1)	<.001
Exploratory end point ^e				
Participants achieving ≥25% body weight reduction from wk 0 to 88, No. (%)	183 (54.5)	17 (5.0)	61.5 (25.9 to 146.1)	<.001

^a Treatment regimen estimand (corresponding analyses used the full analysis set) evaluated treatment effects regardless of treatment adherence. Missing values were imputed using method of multiple imputation guided by hybrid approach. For continuous variables, analysis of covariance model was used, and logistic regression was used for categorical end points, both with terms of treatment, stratification factors (country, sex, maximum tolerated dose of tirzepatide at randomization, and percent weight reduction at randomization [except for analyses related to weight]), and corresponding outcome value at randomization (and outcome value at week 0 if measured since week 0) as covariates. See eTable 3 in Supplement 2 for corresponding data for the efficacy estimand.

^b Data are absolute differences between mean changes unless stated otherwise.

The differences between mean percent changes in body weight are expressed in percentage points. Data for participants maintaining or achieving certain criteria are proportions of participants and estimated odds ratio (95% CI).

^c Tested for superiority, controlled for type I error.

^d Key secondary end points include the time, during the 52-week double-blind period (week 36 to 88 in the entire study), to first occurrence of participant returning to >95% baseline body weight if already lost ≥5% since week 0. See eFigure 4 in Supplement 2 for corresponding data for the treatment regimen and efficacy estimand.

^e Not controlled for type I error.

the SF-36 v2 physical functioning, role-physical, role-emotional, and mental health domain scores and IWQOL-Lite-CT physical function composite scores with tirzepatide vs placebo from week 36 to week 88 ($P < .001$ for all except $P = .015$ for SF-36 v2 role-physical score and $P = .001$ for SF-36 v2 role-emotional score) (eTable 3 in Supplement 2; efficacy estimand).

Entire Study

Key Secondary End Points

A significantly greater percentage of participants continuing tirzepatide vs placebo met the weight reduction thresholds of at least 5% (97.3% vs 70.3%), at least 10% (92.1% vs 46.2%), at least 15% (84.1% vs 25.9%), and at least 20% (69.5% vs 12.6%) from week 0 to week 88 ($P < .001$ for all; treatment regimen estimand; Table 2; eFigure 2C in Supplement 2). Consistent results were observed when using the efficacy estimand (eTable 3 in Supplement 2).

Additional Secondary End Points

Compared with placebo, tirzepatide was associated with improvements throughout the entire study (from week 0 to

week 88) in body weight, BMI, cardiometabolic parameters (waist circumference, hemoglobin A_{1c}, fasting glucose, insulin, lipid levels, and systolic and diastolic blood pressure), and patient-reported outcomes ($P < .001$ for all except $P = .004$ for free fatty acids and $P = .064$ for high-density lipoprotein cholesterol) (Figure 2 and eTable 3, eFigure 3, and eFigure 5-8 in Supplement 2).

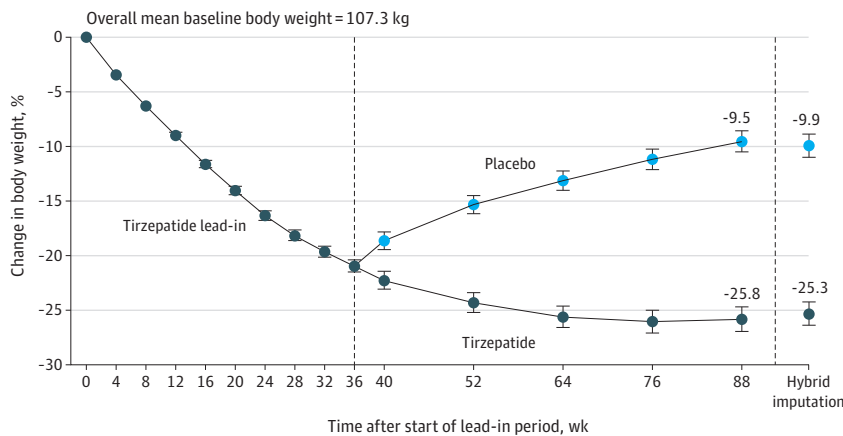
A greater percentage of participants continuing tirzepatide vs placebo achieved the prespecified exploratory end point of at least 25% weight reduction from week 0 to week 88 with the treatment regimen estimand (54.5% vs 5.0%; $P < .001$; Table 2 and eFigure 2C in Supplement 2) and the efficacy estimand (eTable 3 in Supplement 2).

Adverse Events and Tolerability

A total of 81.0% of participants reported at least 1 treatment-emergent adverse event during the tirzepatide lead-in treatment period, with the most frequent events being gastrointestinal (nausea [35.5%], diarrhea, [21.1%], constipation [20.7%], and vomiting [16.3%]; eTable 4 in Supplement 2). During the double-blind period, 60.3% of participants continuing tirzepatide reported at least 1 treatment-emergent

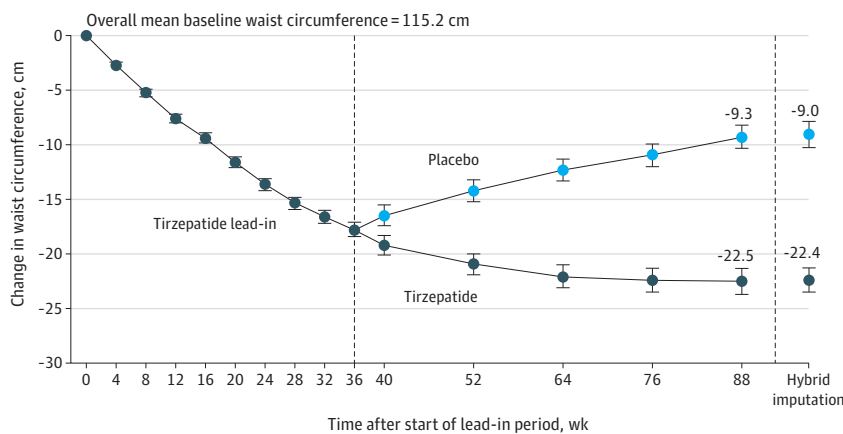
Figure 2. Effect of Tirzepatide vs Placebo on Body Weight and Waist Circumference

A Percent change in body weight (week 0-88)



No. at risk	Tirzepatide lead-in	670	666	669	668	667	669	663	659	670					
Tirzepatide		335	333							328	317	310	310	335	
Placebo		335	330							317	303	292	289	335	

B Change in waist circumference (week 0-88)



No. at risk	Tirzepatide lead-in	670	666	669	668	666	667	669	663	659	670				
Tirzepatide		335	333							328	317	310	310	335	
Placebo		335	328							318	303	292	289	335	

Observed mean values from the full analysis set are shown. Error bars represent 95% CI for the mean. The dashed vertical line at week 36 represents the randomization point. Analysis of covariance using the full analysis set with hybrid imputation least-square mean values at week 88 is also shown on the right. See eTable 3 in Supplement 2 for corresponding data for the efficacy estimand.

adverse event compared with 55.8% of participants who switched to placebo (Table 3). The most frequent treatment-emergent adverse events during the double-blind period were COVID-19 and gastrointestinal disorders. Gastrointestinal events were more common in the tirzepatide group than in the placebo group (diarrhea, 10.7% vs 4.8%; nausea, 8.1% vs 2.7%; and vomiting, 5.7% vs 1.2%; Table 3). Most gastrointestinal events were mild to moderate in severity, and incidence of new events decreased over time in tirzepatide-treated participants during the lead-in period and leveled off during the double-blind period (eFigure 9 and eFigure 10 in Supplement 2).

Treatment discontinuation due to an adverse event occurred in 7.0% of enrolled participants during the tirzepatide lead-in treatment period, mainly due to gastrointestinal events

(eTable 4 in Supplement 2). During the double-blind period, treatment discontinuation due to an adverse event occurred in 1.8% of participants in the tirzepatide group and 0.9% in placebo group (Table 3).

Overall, 16 participants (2.0%) reported serious adverse events during the lead-in period (eTable 4 in Supplement 2) and 10 (3.0%) during the double-blind period, with similar percentages across treatment groups (Table 3). There was 1 death reported during the tirzepatide lead-in treatment period due to COVID-19 pneumonia and 2 deaths reported during the double-blind period (1 in the tirzepatide group due to congestive heart failure and 1 in the placebo group due to adenocarcinoma of the colon; eTable 6 in Supplement 2). None of the deaths were considered by investigators to be related to the study drug.

Table 3. Adverse Events During the Double-Blind (Week 36 to 88) and Safety Follow-Up Period (Safety Analysis Set)

Adverse events	No. (%)	
	Tirzepatide (n = 335)	Placebo (n = 335)
Participants with ≥1 adverse event	202 (60.3)	187 (55.8)
Serious adverse events	10 (3.0)	10 (3.0)
Death ^{a,b}	1 (0.3)	1 (0.3)
Adverse events leading to treatment discontinuation ^c	6 (1.8)	3 (0.9)
Diarrhea	2 (0.6)	0
Cardiac failure congestive	1 (0.3)	0
Abdominal pain	1 (0.3)	0
Vomiting	1 (0.3)	0
Pancreatic enzymes increased	1 (0.3)	0
Adenocarcinoma of colon	0	1 (0.3)
Colorectal cancer	0	1 (0.3)
Non-Hodgkin Lymphoma	0	1 (0.3)
Adverse events occurring in ≥5% of participants in any treatment group ^c		
COVID-19	47 (14.0)	50 (14.9)
Diarrhea	36 (10.7)	16 (4.8)
Nausea	27 (8.1)	9 (2.7)
Vomiting	19 (5.7)	4 (1.2)
Upper respiratory tract infection	8 (2.4)	18 (5.4)
Adverse events of special interest		
Severe or serious hepatic events	0	0
Malignancies	3 (0.9)	3 (0.9)
Adjudicated pancreatitis ^b	0	0
Adjudicated major adverse cardiovascular events ^b	3 (0.9)	0
Severe or serious arrhythmias and cardiac conduction disorders	0	0
Severe or serious gastrointestinal events ^d	6 (1.8)	1 (0.3)
Severe or serious acute gallbladder disease	0	3 (0.9)
Severe or serious kidney disorders	0	0
Severe or serious major depressive disorder or suicidal ideation	0	0
Severe or serious hypersensitivity	0	0
Hypoglycemia (blood glucose <54 mg/dL)	2 (0.6)	0
Other adverse events of interest ^c		
Cholelithiasis	1 (0.3)	1 (0.3)
Acute cholecystitis	0	3 (0.9)

^a Deaths are also included as serious adverse events and discontinuations due to adverse event.

^b Deaths and potential cases of acute pancreatitis and major adverse cardiovascular events were reviewed by an independent external adjudication committee.

^c Adverse events are listed according to Medical Dictionary for Regulatory Activities, version 26.0, preferred terms.

^d Includes 6 serious gastrointestinal events in 3 tirzepatide-treated participants (intestinal obstruction, abdominal pain, nausea, peptic ulcer, small intestinal obstruction, and vomiting) and 1 serious gastrointestinal event in the placebo group (intestinal obstruction).

There were no adjudication-confirmed cases of pancreatitis reported during the study (Table 3; eTable 4 in Supplement 2). Cholelithiasis was reported in 7 participants (0.9%)

during the tirzepatide lead-in treatment period (eTable 4 in Supplement 2) and in 1 participant (0.3%) in both the tirzepatide group and placebo group during the double-blind period (Table 3). Acute cholecystitis was reported in 4 participants (0.5%) during the tirzepatide lead-in treatment period (eTable 4 in Supplement 2) and in 3 (0.9%) in the placebo group during the double-blind period (Table 3). No cases of medullary thyroid carcinoma or pancreatic cancer were reported.

Other adverse events of special interest are described in Table 3 and eTable 4 in Supplement 2 and additional safety variables are described in eTable 7 and eTable 8 in Supplement 2.

Discussion

The SURMOUNT-4 trial results emphasize the need to continue pharmacotherapy to prevent weight regain and ensure the maintenance of weight reduction and its associated cardiometabolic benefits.²² At least 5 trials (including the present study) across various classes of medications, including potent antiobesity medications such as semaglutide, have demonstrated that weight is substantially regained after cessation of pharmacotherapy.^{5,6,23,24}

The consistency of these data across therapeutic classes spanning more than 2 decades suggests that obesity is a chronic metabolic condition similar to type 2 diabetes and hypertension requiring long-term therapy in most patients.

A notable finding in the SURMOUNT-4 trial is that after switching to placebo for 1 year, participants ended the study with substantial body weight reduction (9.9%). However, much of their initial improvement in cardiometabolic risk factors had been reversed. Further studies are needed to understand the potential long-term benefits and risks (ie, legacy effects) of such short-term therapy.

The health benefits seen with continued treatment with the maximum tolerated dose of tirzepatide during this study were achieved with a safety profile consistent with that previously reported in SURMOUNT and SURPASS trials and in studies of incretin-based therapies approved for the treatment of obesity and overweight.^{18,25-32}

The strengths of this study include its large sample size and the randomized withdrawal design. The duration of the open-label lead-in period allowed the study to assess the maintenance of body weight reduction. Dose escalation protocols during the open-label lead-in period helped to maximize tolerability and reflect dose adjustment strategies that may be helpful to future prescribers.

Limitations

This study has limitations. First, the design of this study did not allow dose adjustments after randomization and did not evaluate the effects of intensive behavioral therapy on the maintenance of body weight reduction. Second, those who tolerated initial treatment with 10-mg or 15-mg tirzepatide may represent a subgroup of the general population.

Conclusions

After achieving clinically meaningful weight reduction during a 36-week tirzepatide lead-in treatment period, adults

with obesity or overweight who continued treatment with maximum tolerated dose tirzepatide for an additional 52 weeks demonstrated superior weight maintenance and continued weight reduction compared to those who switched to placebo.

ARTICLE INFORMATION

Accepted for Publication: November 11, 2023.

Published Online: December 11, 2023.
doi:10.1001/jama.2023.24945

Author Affiliations: Comprehensive Weight Control Center, Division of Endocrinology, Diabetes, and Metabolism, Weill Cornell Medicine, New York, New York (Aronne); BHF Glasgow Cardiovascular Research Centre, School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, United Kingdom (Sattar); University of Texas Center for Obesity Medicine and Metabolic Performance, Department of Surgery, University of Texas McGovern Medical School, Houston (Horn); Louisville Metabolic and Atherosclerosis Research Center, Louisville, Kentucky (Bays); McMaster University, and Wharton Weight Management Clinic, York University, Toronto, Ontario, Canada (Wharton); Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan (Lin); Eli Lilly and Company, Indianapolis, Indiana (Ahmad, Zhang, Liao, Bunck, Murphy); Eli Lilly and Company, Moscow, Russia (Jouravskaya).

Author Contributions: Dr Aronne had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Aronne, Lin, Ahmad, Zhang, Bunck, Murphy.

Acquisition, analysis, or interpretation of data: Aronne, Sattar, Horn, Bays, Wharton, Ahmad, Liao, Bunck, Jouravskaya, Murphy.

Drafting of the manuscript: Aronne, Ahmad, Liao, Bunck, Murphy.

Critical review of the manuscript for important intellectual content: Aronne, Sattar, Horn, Bays, Wharton, Lin, Ahmad, Zhang, Bunck, Jouravskaya, Murphy.

Statistical analysis: Ahmad, Zhang, Liao, Bunck.

Obtained funding: Bunck.

Administrative, technical, or material support: Bays, Lin, Bunck, Murphy.

Supervision: Aronne, Horn, Ahmad, Bunck, Murphy.

Other - Served as a principal investigator in the trial: Horn.

Other - Responsible medical officer for the SURMOUNT program: Bunck.

Conflict of Interest Disclosures: Dr Aronne reported receiving grants or personal fees from Altimmune, AstraZeneca, Boehringer Ingelheim, Eli Lilly, ERX, Gelesis, Intellihealth, Jamieson Wellness, Janssen, Novo Nordisk, Optum, Pfizer, Senda Biosciences and Versanis and being a shareholder of Allurion, ERX Pharmaceuticals, Gelesis, Intellihealth, and Jamieson Wellness. Dr Sattar reported receiving personal fees or grants from Abbott Laboratories, Amgen, AstraZeneca, Boehringer, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche, and Sanofi outside the submitted work. Dr Horn reported research funding from Lilly and Novo Nordisk during the conduct of the study and personal fees from Eli Lilly, Novo Nordisk, and Gelesis outside the submitted work.

Dr Bays reported receiving grants from Eli Lilly during the conduct of the study and grants from 89 Bio, Alon Medtech/Epitomee, Altimmune, Amgen, Boehringer Ingelheim, Kallyope, Novo Nordisk, Pfizer, Shionogi, Viking, and Vivus and personal fees from Altimmune, Amgen, Boehringer Ingelheim, and Eli Lilly outside the submitted work.

Dr Wharton reported receiving nonfinancial support from Eli Lilly during the conduct of the study and personal fees from Novo Nordisk, Boehringer Ingelheim, Biohaven, Bausch Health Canada, and Eli Lilly outside the submitted work. Dr Ahmad reported being an employee and shareholder of Eli Lilly and Company during the conduct of the study. Dr Zhang reported being an employee and shareholder of Eli Lilly and Company during the conduct of the study. Dr Liao reported being an employee and shareholder of Eli Lilly and Company during the conduct of the study. Dr Bunck reported being an employee and shareholder of Eli Lilly and Company during the conduct of the study. Dr Murphy reported being an employee and shareholder of Eli Lilly and Company during the conduct of the study. No other disclosures were reported.

Funding/Support: This study was sponsored by Eli Lilly and Company.

Role of the Funder/Sponsor: Eli Lilly and Company was involved in the study design and conduct; data collection, management, analyses, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The sponsor did not have the right to veto publication or to control the decision regarding to which journal the manuscript was submitted. Final decisions resided with the authors, which included employees of the sponsor.

Group Information: The SURMOUNT-4 Investigators are listed in [Supplement 5](#).

Meeting Presentation: Part of the data from this study was presented at the 59th European Association for Study of Diabetes; October 2-6, 2023.

Data Sharing Statement: See [Supplement 4](#).

Additional Contributions: We thank the participants and the study coordinators who cared for them. We thank Amelia Torcello Gomez, PhD, for her writing and editorial assistance, for which she was compensated as part of her salary as an employee of Eli Lilly and Company.

REFERENCES

1. Kushner R. Obesity 2021: current clinical management of a chronic, serious disease. *J Fam Pract*. 2021;70(6S):S35-S40. doi:10.12788/jfp.0221
2. Apovian CM, Aronne LJ, Bessesen DH, et al; Endocrine Society. Pharmacological management of obesity: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-362. doi:10.1210/jc.2014-3415

3. Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. *CMAJ*. 2020;192(31):E875-E891. doi:10.1503/cmaj.191707

4. Garvey WT, Mechanick JI, Brett EM, et al; Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(suppl 3):1-203. doi:10.4158/EPI161365.GL

5. Rubino D, Abrahamsson N, Davies M, et al; STEP 4 Investigators. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA*. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224

6. James WP, Astrup A, Finer N, et al. Effect of sibutramine on weight maintenance after weight loss: a randomised trial: Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet*. 2000;356(9248):2119-2125. doi:10.1016/S0140-6736(00)03491-7

7. Wadden TA, Hollander P, Klein S, et al; NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized trial. *Int J Obes (Lond)*. 2013;37(11):1443-1451. doi:10.1038/ijo.2013.120

8. Garvey WT, Batterham RL, Bhatta M, et al; STEP 5 Study Group. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. *Nat Med*. 2022;28(10):2083-2091. doi:10.1038/s41591-022-02026-4

9. le Roux CW, Fils-Aimé N, Camacho F, Gould E, Barakat M. The relationship between early weight loss and weight loss maintenance with naltrexone-bupropion therapy. *EclinicalMedicine*. 2022;49:101436. doi:10.1016/j.eclinm.2022.101436

10. Neoh SL, Sumithran P, Haywood CJ, Houlihan CA, Lee FT, Proietto J. Combination phentermine and topiramate for weight maintenance: the first Australian experience. *Med J Aust*. 2014;201(4):224-226. doi:10.5694/mja13.00193

11. Sjöström L, Rissanen A, Andersen T, et al; European Multicentre Orlistat Study Group. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *Lancet*. 1998;352(9123):167-172. doi:10.1016/S0140-6736(97)11509-4

12. Hill JO, Hauptman J, Anderson JW, et al. Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a 1-y study. *Am J Clin Nutr*. 1999;69(6):1108-1116. doi:10.1093/ajcn/69.6.1108

13. Coskun T, Sloop KW, Loghin C, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. *Mol Metab*. 2018;18:3-14. doi:10.1016/j.molmet.2018.09.009

14. Samms RJ, Coghlan MP, Sloop KW. How May GIP Enhance the Therapeutic Efficacy of GLP-1?

- Trends Endocrinol Metab.* 2020;31(6):410-421. doi:10.1016/j.tem.2020.02.006
15. Hammoud R, Drucker DJ. Beyond the pancreas: contrasting cardiometabolic actions of GIP and GLP1. *Nat Rev Endocrinol.* 2023;19(4):201-216. doi:10.1038/s41574-022-00783-3
16. Heise T, DeVries JH, Urva S, et al. Tirzepatide reduces appetite, energy intake, and fat mass in people with type 2 diabetes. *Diabetes Care.* 2023; 46(5):998-1004. doi:10.2337/dc22-1710
17. le Roux CW, Zhang S, Aronne LJ, et al. Tirzepatide for the treatment of obesity: rationale and design of the SURMOUNT clinical development program. *Obesity (Silver Spring).* 2023;31(1):96-110. doi:10.1002/oby.23612
18. Jastreboff AM, Aronne LJ, Ahmad NN, et al; SURMOUNT-1 Investigators. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med.* 2022;387(3):205-216. doi:10.1056/NEJMoa2206038
19. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet.* 2018; 392(10160):2180-2193. doi:10.1016/S0140-6736(18)32260-8
20. Frias JP, Nauck MA, Van J, et al. Efficacy and tolerability of tirzepatide, a dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes: a 12-week, randomized, double-blind, placebo-controlled study to evaluate different dose-escalation regimens. *Diabetes Obes Metab.* 2020;22(6):938-946. doi:10.1111/dom.13979
21. International Council for Harmonisation. Addendum on Estimands and Sensitivity Analysis in Clinical Trials To The Guideline on Statistical Principles for Clinical Trials E9(R1). Accessed June 5, 2023. https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf
22. Aronne LJ, Hall KD, Jakicic MJ, et al. Describing the weight-reduced state: physiology, behavior, and interventions. *Obesity (Silver Spring).* 2021;29(Suppl 1):S9-S24. doi:10.1002/oby.23086
23. Smith SR, Weissman NJ, Anderson CM, et al; Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med.* 2010;363(3):245-256. doi:10.1056/NEJMoa0909809
24. Wilding JPH, Batterham RL, Davies M, et al; STEP 1 Study Group. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab.* 2022;24(8):1553-1564. doi:10.1111/dom.14725
25. Garvey WT, Frias JP, Jastreboff AM, et al; SURMOUNT-2 investigators. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2023;402(10402):613-626. doi:10.1016/S0140-6736(23)01200-X
26. Rosenstock J, Wysham C, Frias JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet.* 2021;398(10295):143-155. doi:10.1016/S0140-6736(21)01324-6
27. Frias JP, Davies MJ, Rosenstock J, et al; SURPASS-2 Investigators. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med.* 2021;385(6):503-515. doi:10.1056/NEJMoa2107519
28. Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet.* 2021;398(10300):583-598. doi:10.1016/S0140-6736(21)01443-4
29. Del Prato S, Kahn SE, Pavo I, et al; SURPASS-4 Investigators. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet.* 2021;398(10313):1811-1824. doi:10.1016/S0140-6736(21)02188-7
30. Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. *JAMA.* 2022;327(6):534-545. doi:10.1001/jama.2022.0078
31. Wilding JPH, Batterham RL, Calanna S, et al; STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med.* 2021;384(11):989-1002. doi:10.1056/NEJMoa2032183
32. Pi-Sunyer X, Astrup A, Fujioka K, et al; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med.* 2015;373(1):11-22. doi:10.1056/NEJMoa1411892