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# Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity
## The SURMOUNT-4 Randomized Clinical Trial

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**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

Visual Abstract

Supplemental content

CME Quiz at jamacmelookup.com

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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 agonism[13] 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.

### 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.

## 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 diabetes, 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.

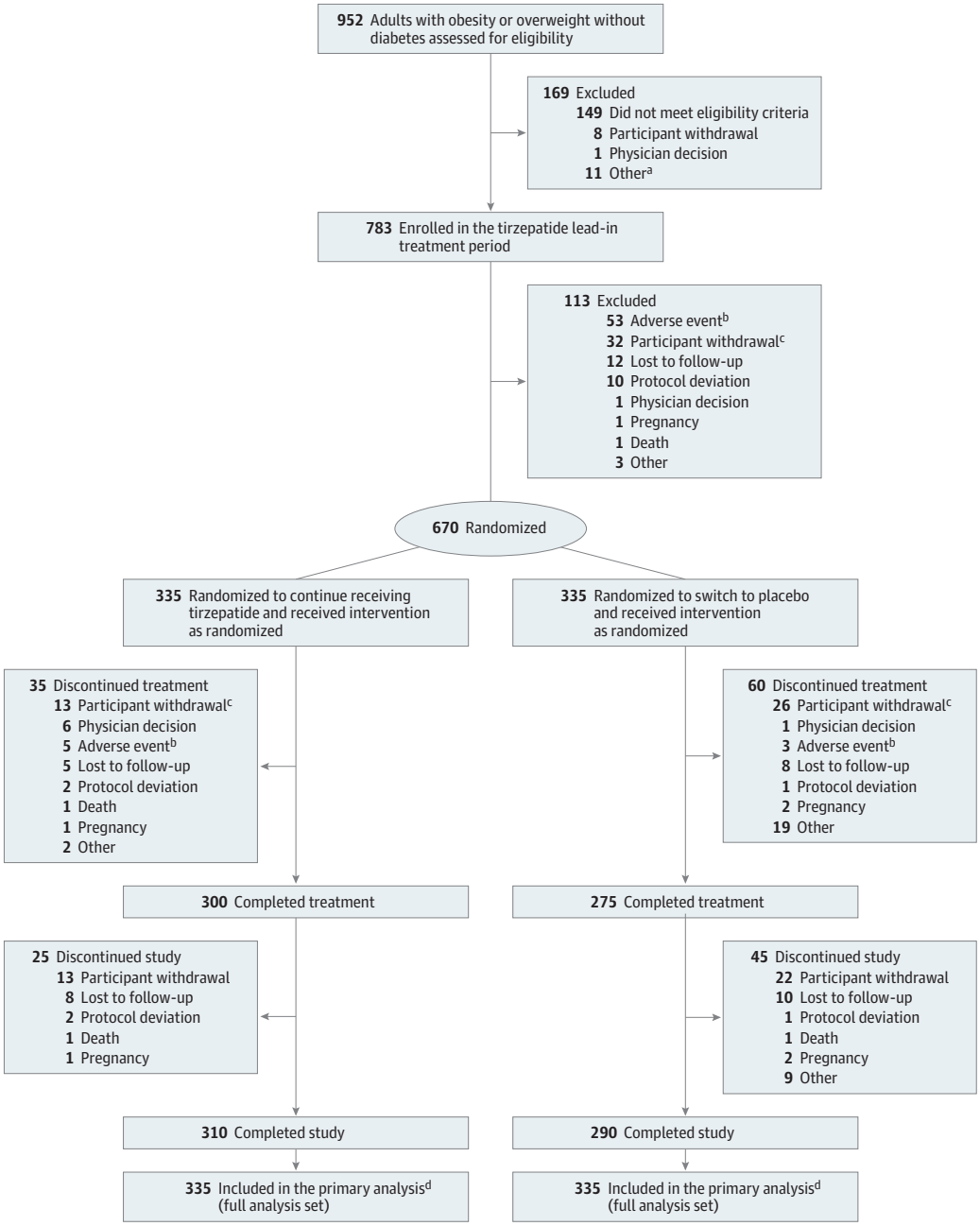
## Results

### 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, glycemic 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 to11.0) | −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

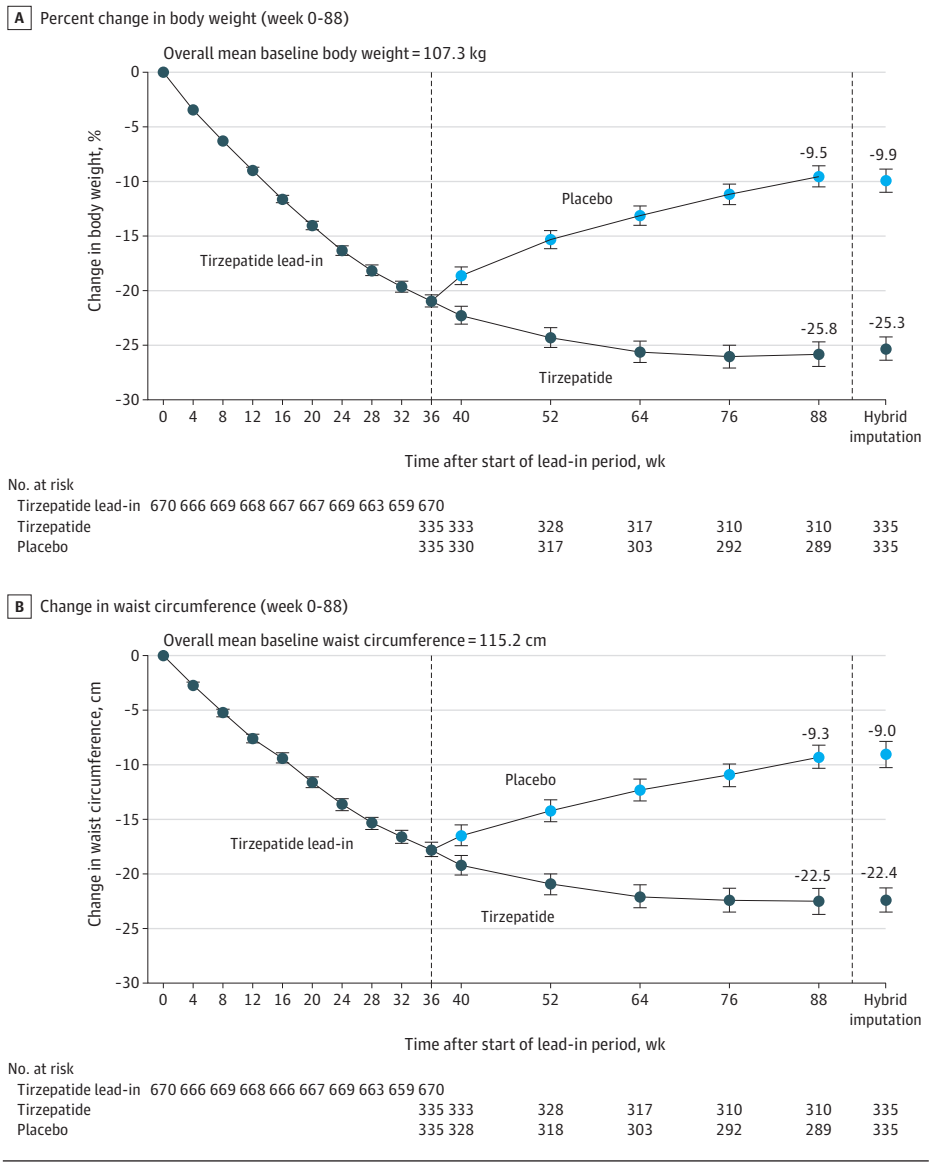
Compared with placebo, tirzepatide was associated with improvements throughout the entire study (from week 0 to week 88) in body weight, BMI, cardiometabolic parameters (waist circumference, hemoglobin $A_{1c}$, fasting glucose, insulin, lipid levels, and systolic and diastolic blood pressure), and patient-reported 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**




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

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**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.
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