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Tirzepatide Once Weekly for the Treatment of Obesity

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ABSTRACT

BACKGROUND

Obesity is a chronic disease that results in substantial global morbidity and mortality. The efficacy and safety of tirzepatide, a novel glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, in people with obesity are not known.

METHODS

In this phase 3 double-blind, randomized, controlled trial, we assigned 2539 adults with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or more, or 27 or more and at least one weight-related complication, excluding diabetes, in a 1:1:1:1 ratio to receive once-weekly, subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 72 weeks, including a 20-week dose-escalation period. Coprimary end points were the percentage change in weight from baseline and a weight reduction of 5% or more. The treatment-regimen estimand assessed effects regardless of treatment discontinuation in the intention-to-treat population.

RESULTS

At baseline, the mean body weight was 104.8 kg, the mean BMI was 38.0, and 94.5% of participants had a BMI of 30 or higher. The mean percentage change in weight at week 72 was -15.0% (95% confidence interval [CI], -15.9 to -14.2) with 5-mg weekly doses of tirzepatide, -19.5% (95% CI, -20.4 to -18.5) with 10-mg doses, and -20.9% (95% CI, -21.8 to -19.9) with 15-mg doses and -3.1% (95% CI, -4.3 to -1.9) with placebo ($P < 0.001$ for all comparisons with placebo). The percentage of participants who had weight reduction of 5% or more was 85% (95% CI, 82 to 89), 89% (95% CI, 86 to 92), and 91% (95% CI, 88 to 94) with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and 35% (95% CI, 30 to 39) with placebo; 50% (95% CI, 46 to 54) and 57% (95% CI, 53 to 61) of participants in the 10-mg and 15-mg groups had a reduction in body weight of 20% or more, as compared with 3% (95% CI, 1 to 5) in the placebo group ($P < 0.001$ for all comparisons with placebo). Improvements in all prespecified cardiometabolic measures were observed with tirzepatide. The most common adverse events with tirzepatide were gastrointestinal, and most were mild to moderate in severity, occurring primarily during dose escalation. Adverse events caused treatment discontinuation in 4.3%, 7.1%, 6.2%, and 2.6% of participants receiving 5-mg, 10-mg, and 15-mg tirzepatide doses and placebo, respectively.

CONCLUSIONS

In this 72-week trial in participants with obesity, 5 mg, 10 mg, or 15 mg of tirzepatide once weekly provided substantial and sustained reductions in body weight. (Supported by Eli Lilly; SURMOUNT-1 ClinicalTrials.gov number, NCT04184622.)

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OBESITY IS THE MOST PREVALENT chronic disease worldwide, affecting approximately 650 million adults.¹ Excess adiposity and its numerous complications, including cardiovascular disease and type 2 diabetes, impose a considerable economic burden and constitute major contributors to global morbidity and mortality.²⁻⁴ Treatments that result in substantial weight reductions may improve outcomes for people living with obesity.

Historically, the treatment of obesity focused almost exclusively on lifestyle-based approaches. However, evidence that diet and exercise prompt physiological counterregulatory mechanisms that limit weight reduction and impede weight maintenance has led to the realization that obesity is a complex, multicomponent metabolic disease of energy homeostasis involving central and peripheral mechanisms.⁵ Once obesity is present, those mechanisms render a return to lower weight difficult.⁶ Accordingly, several clinical guidelines now recommend treatment with anti-obesity medications for people with obesity or for those with overweight and weight-related complications.^{7,8} Recent studies with long-acting glucagon-like peptide-1 (GLP-1) receptor agonists demonstrated that greater efficacy with acceptable safety could be achieved by targeting the pathways of endogenous nutrient-stimulated hormones.^{9,10} Glucose-dependent insulinotropic polypeptide (GIP), another nutrient-stimulated hormone, regulates energy balance through cell-surface receptor signaling in the brain and adipose tissue.¹¹ A molecule that combines both GIP and GLP receptor agonism theoretically may lead to greater efficacy in weight reduction.

Tirzepatide is a once-weekly subcutaneous injectable peptide (approved by the Food and Drug Administration [FDA] for type 2 diabetes) engineered from the native GIP sequence, with agonist activity at both the GIP and GLP-1 receptors.¹² Preclinical data demonstrated that the affinity of tirzepatide for GIP receptors was equal to the affinity of native GIP for GIP receptors, whereas tirzepatide bound GLP-1 receptors with affinity approximately five times weaker than native GLP-1 bound GLP-1 receptors.¹² GIP activation appeared to act synergistically with GLP-1 receptor activation to allow greater weight reduction in mice than that achieved with GLP-1 receptor monoagonism.¹² In phase 2 studies in

people with type 2 diabetes, tirzepatide induced clinically relevant weight reduction, warranting further investigation for the treatment of obesity. The present trial, SURMOUNT-1, evaluated the efficacy and safety of tirzepatide in adults with obesity or overweight who did not have diabetes.

METHODS

TRIAL DESIGN

This phase 3 multicenter, double-blind, randomized, placebo-controlled trial was conducted at 119 sites in nine countries (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol is available at NEJM.org. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by an independent ethics committee or institutional review board at each trial site. All the participants provided written, informed consent before participation. The sponsor (Eli Lilly) designed and oversaw the conduct of the trial; trial site investigators were responsible for data collection, and the sponsor undertook site monitoring, data collation, and data analysis. All the authors participated in interpretation of the data and in critical review of the manuscript. The investigators worked under confidentiality agreements with the sponsor; all the authors had full access to the trial data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PARTICIPANTS

Adults who were 18 years of age or older, with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30 or more, or a BMI of 27 or more and at least one weight-related complication (e.g., hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease), and who reported one or more unsuccessful dietary effort to lose weight were eligible to participate. Key exclusion criteria were diabetes, a change in body weight of more than 5 kg within 90 days before screening, previous or planned surgical treatment for obesity, and treatment with a medication that promotes weight loss within 90 days before screening. A full list of eligibility criteria is provided in the Supplementary Appendix.

PROCEDURES

After a 2-week screening period, participants were randomly assigned in a 1:1:1:1 ratio to receive tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or placebo, administered subcutaneously once weekly for 72 weeks as an adjunct to lifestyle intervention. Lifestyle intervention included regular lifestyle counseling sessions, delivered by a dietitian or a qualified health care professional, to help the participants adhere to healthful, balanced meals, with a deficit of 500 calories per day, and at least 150 minutes of physical activity per week.

Treatment randomization was stratified by country, sex, and the presence or absence of prediabetes, as defined by the 2019 American Diabetes Association Standards of Medical Care in Diabetes¹³ (see the Supplementary Appendix). All randomly assigned participants were to undergo a planned 72-week treatment period that included a dose-escalation period of up to 20 weeks. Tirzepatide was initiated at a dose of 2.5 mg once weekly (or matching placebo) and was increased by 2.5 mg every 4 weeks during the dose-escalation period to reach a maintenance dose of up to 15 mg once weekly by week 20 (Fig. S1). After the 72-week treatment period, participants who had been without prediabetes at randomization proceeded to a 4-week safety follow-up period; those with prediabetes at randomization continued in their original treatment group for an additional 2-year trial treatment period. This article reports findings from the 72-week treatment phase (the primary trial period) and the 4-week safety follow-up.

END POINTS AND ASSESSMENTS

The coprimary end points were the percentage change in body weight from baseline to week 72 and a weight reduction of 5% or more at week 72. Key secondary end points included weight reduction of 10% or more, 15% or more, and 20% or more at week 72; the change in weight from baseline to week 20; and the change from baseline to week 72 in waist circumference, systolic blood pressure, fasting insulin and lipid levels, and the physical function score on the 36-Item Short Form Health Survey (SF-36), version 2, acute form. The percentage change in total body-fat mass from baseline to week 72 was assessed in a subgroup

of 255 participants who underwent dual-energy x-ray absorptiometry.

Safety assessments included adverse events and serious adverse events that occurred during the reporting period. Laboratory assessments were conducted according to the protocol (see the Supplementary Appendix).

STATISTICAL ANALYSIS

We calculated that a sample size of 2400 participants would provide an effective power of greater than 90% to demonstrate the superiority of tirzepatide (10 mg, 15 mg, or both) to placebo, relative to the coprimary end points, each at a two-sided significance level of 0.025. The sample-size calculation assumed at least an 11-percentage-point difference in the mean percentage weight reduction from baseline at 72 weeks for tirzepatide (10 mg, 15 mg, or both) as compared with placebo, a common standard deviation of 10%, and a dropout rate of 25%.

Both efficacy and safety end points were analyzed with data from all randomly assigned participants (intention-to-treat population). Two estimands were used to assess treatment efficacy from different perspectives and accounted for intercurrent events differently: first, the “treatment regimen” estimand, for which we used the treatment policy strategy in the ICH E9 (International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] Statistical Principles for Clinical Trials [E9]) addendum on estimands and sensitivity analysis in clinical trials (R1)¹⁴, representing the average treatment effect of tirzepatide relative to placebo for all participants who had undergone randomization, regardless of treatment discontinuation, and second, the “efficacy” estimand, representing the average treatment effect of tirzepatide relative to placebo for all participants who had undergone randomization, if the treatment was administered as intended (according to the hypothetical strategy in the ICH E9 [R1] addendum¹⁴).

Details on estimands, handling of missing values, and statistical analysis methods are provided in the Supplementary Appendix. All reported results are for the treatment-regimen estimand unless stated otherwise. The type I error rate was strongly controlled within each estimand independently for evaluation of coprimary

and key secondary end points with a graphical approach.

RESULTS

PARTICIPANTS

The trial was conducted from December 2019 through April 2022 and included 2539 participants (Table 1). Overall, 86.0% of participants completed the primary trial treatment period (88.4% to 89.8% across the tirzepatide groups and 77.0% in the placebo group) and 81.9% adhered to the treatment or placebo as assigned (83.5% to 85.7% across the tirzepatide groups and 73.6% in the placebo group) (Fig. S2). Treatment discontinuations due to adverse events were 4.3%, 7.1%, and 6.2% with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and 2.6% with placebo.

Demographic and clinical baseline characteristics were generally similar across treatment groups (Table 1). The mean age of the participants was 44.9 years; most were female (67.5%) and White (70.6%); the mean body weight was 104.8 kg, the mean BMI was 38.0, and the mean waist circumference was 114.1 cm; 94.5% of the participants had a BMI of 30 or higher. Participants reported an average duration of obesity of 14.4 years; 40.6% had prediabetes at baseline, and nearly two thirds had one or more weight-related complications (Table 1 and Table S1). Enrollment data according to country, U.S.-specific demographic data, and information on the representativeness of the trial participants are presented in Tables S1, S2, and S3, respectively.

CHANGE IN BODY WEIGHT

For the treatment-regimen estimand, the mean change in weight at week 72 was -15.0% (95% CI, -15.9 to -14.2) with a 5-mg weekly dose of tirzepatide, -19.5% (95% CI, -20.4 to -18.5) with a 10-mg dose, and -20.9% (95% CI, -21.8 to -19.9) with a 15-mg dose and -3.1% (95% CI, -4.3 to -1.9) with placebo (Fig. 1A and Table 2). All three tirzepatide doses were superior to placebo, with estimated treatment differences relative to placebo of -11.9 percentage points (95% CI, -13.4 to -10.4) for the 5-mg dose, -16.4 percentage points (95% CI,

-17.9 to -14.8) for the 10-mg dose, and -17.8 percentage points (95% CI, -19.3 to -16.3) for the 15-mg dose ($P < 0.001$ for all comparisons). At 20 weeks after randomization, treatment with tirzepatide resulted in a significantly greater weight reduction than that with placebo (Table 3).

For the efficacy estimand, the mean change in weight at week 72 with tirzepatide was -16.0% (95% CI, -16.8 to -15.2), a weight reduction of 16.1 kg (35.5 lb), with the 5-mg dose; -21.4% (95% CI, -22.2 to -20.6), a reduction of 22.2 kg (48.9 lb), with the 10-mg dose; and -22.5% (95% CI, -23.3 to -21.7), a reduction of 23.6 kg (52.0 lb) with the 15-mg dose, and the mean change with placebo was -2.4% (95% CI, -3.2 to -1.6), a reduction of 2.4 kg (5.3 lb) (Fig. 1B). The corresponding estimated treatment differences with tirzepatide relative to placebo were -13.5 percentage points (95% CI, -14.6 to -12.5), -18.9 percentage points (95% CI, -20.0 to -17.8), and -20.1 percentage points (95% CI, -21.2 to -19.0) for the 5-mg, 10-mg, and 15-mg doses, respectively (Fig. 1B and Figs. S3, S4, and S5).

With the treatment-regimen estimand, 85% (95% CI, 82 to 89), 89% (95% CI, 86 to 92), and 91% (95% CI, 88 to 94) of participants in the 5-mg, 10-mg, and 15-mg tirzepatide groups, respectively, had a body weight reduction of 5% or more at 72 weeks, as compared with 35% (95% CI, 30 to 39) of participants in the placebo group ($P < 0.001$ for all comparisons with placebo). With use of the efficacy estimand, the respective percentages were 89% (95% CI, 87 to 92), 96% (95% CI, 95 to 98), 96% (95% CI, 95 to 98), and 28% (95% CI, 24 to 31).

At week 72, more participants in the tirzepatide groups had reductions in body weight of 10% or more, 15% or more, and 20% or more from baseline than participants in the placebo group ($P < 0.001$) (Fig. 1C and 1D). In addition, for the prespecified exploratory end point of a reduction in body weight of 25% or more, 15% (95% CI, 12 to 18), 32% (95% CI, 29 to 36), and 36% (95% CI, 32 to 40) of participants in the 5-mg, 10-mg, and 15-mg tirzepatide groups, respectively, met this target, as compared with 1.5% (95% CI, 0 to 3) of participants in the placebo group (Table 2).

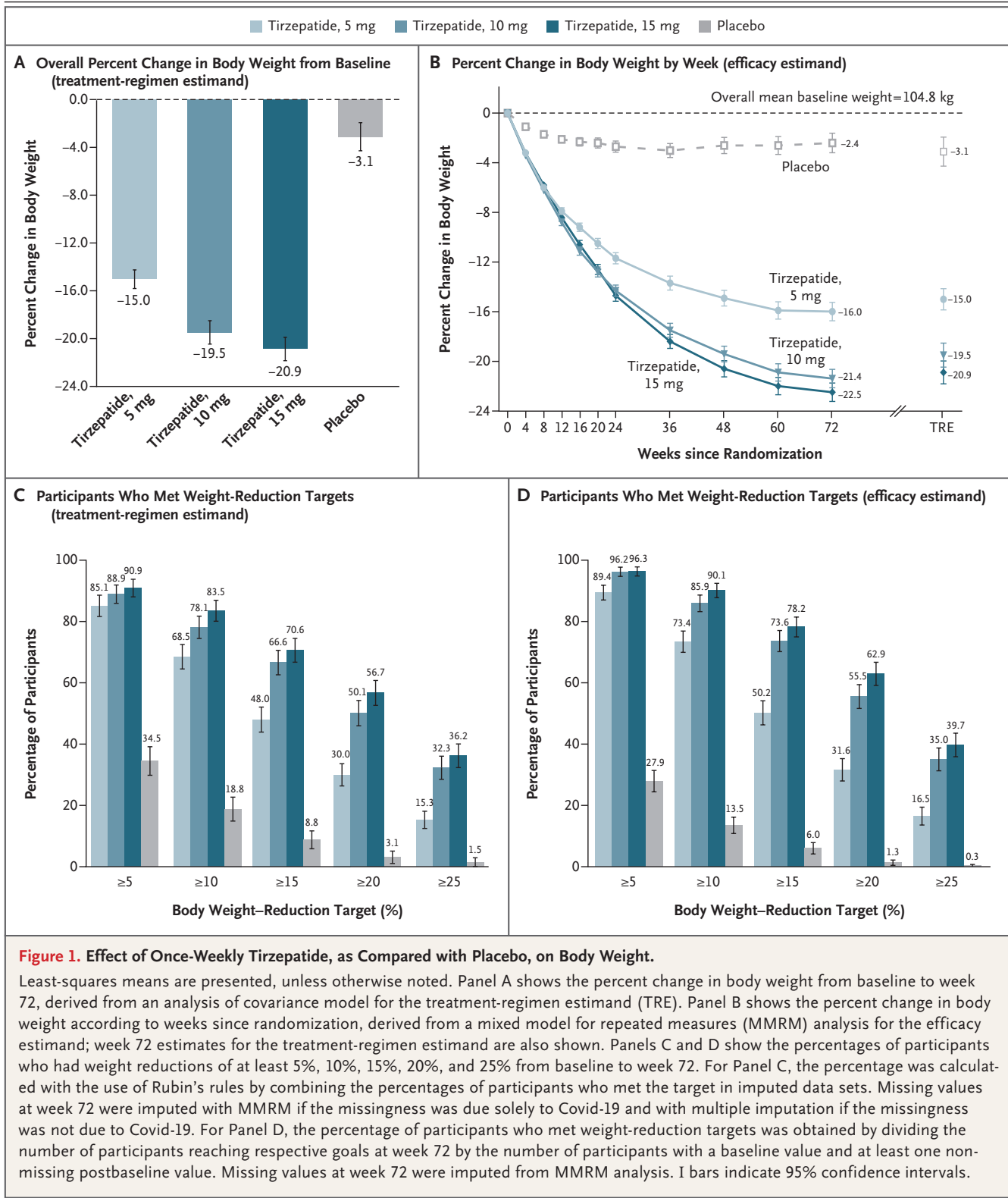
Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

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
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

* Plus-minus values are mean±SD. GFR denotes glomerular filtration rate, HDL high-density lipoprotein, LDL low-density lipoprotein, and SF-36 Short Form Health Survey, version 2, acute form.

† Race or ethnic group was reported by the participants.

‡ The estimated GFR was calculated with use of the serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation.



CARDIOMETABOLIC RISK FACTORS AND PHYSICAL FUNCTION

Benefits with tirzepatide were noted with respect to changes in waist circumference, systolic

and diastolic blood pressure, fasting insulin level, and lipid levels (Table 2, Table 3, and Figs. S6 and S7). At week 72, most (95.3%) of the participants with prediabetes at baseline in the

Table 2. Primary and Secondary End Points for the Treatment-Regimen Estimand.*

End Points	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)
	<i>least-squares mean (95% CI)</i>			
Copriary end points†				
Percentage change in body weight‡	-15.0 (-15.9 to -14.2)	-19.5 (-20.4 to -18.5)	-20.9 (-21.8 to -19.9)	-3.1 (-4.3 to -1.9)
Difference from placebo in percentage change in body weight — percentage points‡	-11.9 (-13.4 to -10.4)	-16.4 (-17.9 to -14.8)	-17.8 (-19.3 to -16.3)	—
Weight reduction of 5% or more at week 72 — percentage of participants‡§	85.1 (81.6 to 88.6)	88.9 (85.9 to 91.9)	90.9 (88.0 to 93.8)	34.5 (29.8 to 39.2)
Key secondary end points†				
Weight reduction of 10% or more at week 72 — percentage of participants§¶	68.5 (64.5 to 72.5)	78.1 (74.4 to 81.7)	83.5 (80.0 to 86.9)	18.8 (14.9 to 22.7)
Weight reduction of 15% or more at week 72 — percentage of participants§¶	48.0 (43.9 to 52.1)	66.6 (62.6 to 70.6)	70.6 (66.7 to 74.5)	8.8 (5.9 to 11.7)
Weight reduction of 20% or more at week 72 — percentage of participants§¶	30.0 (26.4 to 33.6)	50.1 (46.0 to 54.2)	56.7 (52.6 to 60.8)	3.1 (1.1 to 5.1)
Change in waist circumference — cm¶	-14.0 (-14.9 to -13.1)	-17.7 (-18.7 to -16.8)	-18.5 (-19.3 to -17.6)	-4.0 (-5.1 to -2.8)
Difference from placebo in change in waist circumference — cm ¶	-10.1 (-1.6 to -8.6)	-13.8 (-15.2 to -12.3)	-14.5 (-15.9 to -13.0)	—
Additional secondary end point				
Weight reduction of 25% or more at week 72 — percentage of participants §	15.3 (12.5 to 18.1)	32.3 (28.5 to 36.1)	36.2 (32.3 to 40.1)	1.5 (0.1 to 2.9)

* All changes are from baseline to week 72.

† The primary and key secondary end points were tested under a type 1 error-control procedure, and all comparisons with placebo were significant at $P < 0.001$.

‡ The change in body weight in the tirzepatide 5-mg group was not a copriary end point and was analyzed as a key secondary end point.

§ The percentage was calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets.

¶ The specified weight-reduction targets and the change in waist circumference in the tirzepatide 5-mg group were not key secondary end points and were analyzed as additional secondary end points. Hypothesis testing was not conducted; confidence intervals were not adjusted for multiplicity, and no definite conclusions can be drawn.

|| This was an exploratory end point not controlled for type 1 error; therefore, hypothesis testing was not conducted. Confidence intervals were not adjusted for multiplicity, and no definite conclusions can be drawn.

tirzepatide groups had reverted to normoglycemia, as compared with 61.9% of participants in the placebo group.

The SF-36 physical function scores increased more with tirzepatide than with placebo, an indication that participants' perspective on their physical functioning was more likely to improve with tirzepatide (Table 3).

Treatment with tirzepatide was associated with greater improvements from baseline than that with placebo in all key secondary end points (Table 2 and Table 3). Additional efficacy data for the efficacy estimand are presented in Table S4.

CHANGE IN BODY COMPOSITION

The mean reduction in total body fat mass was 33.9% with tirzepatide, as compared with 8.2%

with placebo, for an estimated treatment difference relative to placebo of -25.7 percentage points (95% CI, -31.4 to -20.0) in the subgroup of participants who underwent dual-energy x-ray absorptiometry (efficacy estimand that included the 160 of 255 participants in the subgroup who had evaluable data at both baseline and week 72) (Fig. S8). The ratio of total fat mass to total lean mass decreased more with tirzepatide (from 0.93 at baseline to 0.70 at week 72) than with placebo (from 0.95 to 0.88).

SAFETY

Overall, 78.9 to 81.8% of participants treated with tirzepatide reported at least one adverse event that emerged during the treatment period, as compared with 72.0% of participants in the

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)
	<i>least-squares mean (95% CI)</i>		
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)

* All changes are from baseline to week 72, unless otherwise indicated. VLDL denotes very-low-density lipoprotein.

† “Pooled tirzepatide groups” refers to pooled data for the 5-mg, 10-mg, and 15-mg groups unless otherwise indicated.

‡ The key secondary end points were tested under type 1 error-control procedure, and all tests had $P < 0.001$ versus placebo.

§ Data are for the pooled 10-mg and 15-mg tirzepatide groups.

¶ The change from baseline in the SF-36 physical function score was assessed with use of an analysis of covariance model, with terms for baseline SF-36 physical function score, treatment, and stratification factors.

|| The estimated treatment differences from placebo in the percentage changes in levels are expressed as percentage-points. Lipid and fasting insulin levels were analyzed with the use of log transformation. Data shown represent model-based estimates and 95% confidence intervals.

** Results of absolute values for the change in fasting insulin, fasting glucose, and glycated hemoglobin are included in Table S4.

†† For additional secondary end points, the widths of confidence intervals were not adjusted for multiplicity, and these may not be used in place of hypothesis tests.

placebo group (Table 4). The most frequently reported adverse events were gastrointestinal (nausea, diarrhea, and constipation). These adverse events occurred in more participants in the tirzepatide groups than in the placebo group, were transient and mild to moderate in severity, and occurred primarily during the dose-escalation period (Fig. S9).

Serious adverse events were reported by 160 participants (6.3%) overall. Similar percentages of participants in the tirzepatide and placebo groups reported serious adverse events (Table 4). Overall, approximately 21% of serious adverse events were considered to be related to coronavirus disease 2019 (Covid-19), which affected

participants in all treatment groups (Table S5). Eleven deaths were reported: 4 (0.6%) in the 5-mg tirzepatide group, 2 (0.3%) in the 10-mg group, 1 (0.2%) in the 15-mg group, and 4 (0.6%) in the placebo group (Table S6).

There were four reported cases of adjudication-confirmed pancreatitis, evenly distributed across treatment groups, including the placebo group (Table 4). None were adjudicated as severe. No cases of medullary thyroid cancer were reported. The reported incidence of cholelithiasis was similar among the tirzepatide and placebo groups. Cholecystitis and acute cholecystitis were reported more frequently in the tirzepatide groups than in the placebo group,

although the incidences were low ($\leq 0.6\%$) (Table 4). Additional safety variables are described in Table 4 and Table S7.

DISCUSSION

In the present trial, adults with obesity had average weight reductions of 19.5% and 20.9% with 10-mg and 15-mg doses of tirzepatide, respectively, as compared with a 3.1% weight reduction with placebo (treatment-regimen estimand). This is an unusually substantial degree of weight reduction in response to an antiobesity medication as compared with findings reported in other phase 3 clinical trials. Given that tirzepatide is both a GIP receptor and GLP-1 receptor agonist, we speculate that there may be additive benefit in targeting multiple endogenous nutrient-stimulated hormone pathways that have been implicated in energy homeostasis.

A body-weight reduction of 5% or more has long been considered the threshold for clinically meaningful effect on the basis of improvement in metabolic health.¹⁵ It is remarkable that in this trial, the majority (89% to 91%) of participants receiving 10-mg or 15-mg doses of tirzepatide achieved this benchmark. Weight reductions of 10% or more, 15% or more, and 20% or more yield additional clinical benefits,^{15,16} may be required for improvement in certain weight-related complications,¹⁷ and are often more desired therapeutic goals in clinical practice. The majority of participants reached these three higher weight-loss targets (78–84%, 67–71%, and 50–57%, respectively), across the 10-mg and 15-mg dose groups.

For perspective: the average placebo-adjusted weight reductions with older antiobesity medications that are currently approved by the FDA for the treatment of obesity are approximately 3.0 to 8.6%,¹⁸ whereas a recently introduced antiobesity medication, semaglutide (2.4 mg), resulted in a placebo-adjusted weight reduction of 12.4%, with nearly one third of persons having a weight reduction of 20% or more.¹⁰ In the current trial, participants receiving the lowest maintenance dose of tirzepatide (5 mg) had a mean placebo-adjusted weight reduction of 11.9% from baseline, with 30% of participants reaching the weight-loss target of 20% or more. It is important to note that no direct comparison of these trials can be made, since trial populations and

designs differed. Finally, bariatric surgery results in weight reduction of approximately 25 to 30% at 1 to 2 years.^{19,20} In the current trial, 36.2% of participants in the 15-mg tirzepatide group met the prespecified exploratory end point of weight reduction of 25% or more. With substantial observed weight reductions at all three doses, tirzepatide may serve as an important tool in the medical management of obesity.

The 10-mg and 15-mg tirzepatide groups were similar in mean percentage weight reduction, yet a higher proportion of participants in the 15-mg group met the 10% or more, 15% or more, and 20% or more weight-loss targets. The incidence of adverse events was similar in the 10-mg and 15-mg groups. This finding suggests that the 15-mg dose may confer additional benefits in some patients, without added safety concerns. It will be important to identify which patients may garner the greatest degree of benefit from various doses of tirzepatide.

In the present trial, weight reduction with tirzepatide was accompanied by greater improvements with respect to all measured cardiovascular and metabolic risk factors, including waist circumference, systolic and diastolic blood pressure, and fasting insulin, lipid, and aspartate aminotransferase levels, than placebo. Participants treated with tirzepatide had a percent reduction in fat mass approximately three times greater than the reduction in lean mass, resulting in an overall improvement in body composition. The ratio of fat-mass loss to lean-mass loss was similar to that reported with lifestyle-based and surgical treatments for obesity.²¹ In addition, nearly all participants (>95%) treated with tirzepatide who had prediabetes at baseline had converted to normoglycemia by the end of the primary trial period, as compared with 62% of participants who received placebo. These improvements may translate to reduced risk of cardiovascular disease, chronic kidney disease, nonalcoholic fatty liver disease, and type 2 diabetes, among other outcomes.^{15,16,22} Future trials are needed to test this hypothesis.

The safety profile of tirzepatide was consistent with previous findings in the SURPASS clinical trials in patients with type 2 diabetes,²³⁻²⁷ and similar to other incretin-based therapies for the treatment of obesity.^{9,10,28-30} As typically observed with these medications, transient, mostly mild-to-moderate gastrointestinal events

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)
	<i>number (percent)</i>			
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				
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)

Table 4. (Continued.)

Variable	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)
	<i>number (percent)</i>			
Cholecystitis	4 (0.6)	3 (0.5)	0	0
Acute cholecystitis	1 (0.2)	4 (0.6)	1 (0.2)	0
Chronic cholecystitis	1 (0.2)	1 (0.2)	3 (0.5)	3 (0.5)

* All deaths were adjudicated by an external committee of physicians, who determined whether the death was cardiovascular-related.

† Adverse events are listed according to *Medical Dictionary for Regulatory Activities*, version 24.1, preferred terms.

‡ None of the events were reported as severe or serious.

§ Events were classified as severe or serious adverse events.

¶ Events were classified as severe or serious supraventricular arrhythmias and cardiac conduction disorders.

|| Hypersensitivity includes immediate (≤ 24 hours after administration of tirzepatide or placebo) and nonimmediate (> 24 hours after administration of tirzepatide or placebo) severe or serious hypersensitivity events.

were the most frequently reported adverse events, occurring primarily during the dose-escalation period.

Although there was no difference observed in reported cholelithiasis between recipients of tirzepatide and placebo, cholecystitis was observed more frequently with tirzepatide. Overall, the incidence in the current trial was low ($\leq 0.6\%$), making causal conclusions difficult. Gallbladder-related events have been reported to increase in persons with considerable weight reduction and are also observed with other obesity therapies, such as bariatric surgery and treatment with GLP-1 receptor agonists.^{9,10,31}

Because the present trial was initiated in December 2019 and conducted almost entirely during the Covid-19 pandemic, there was an expected impact on the incidence of adverse events. Close to 20% of participants tested positive for infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or had symptomatic Covid-19 during the reporting period. There were 160 participants with serious adverse events in this trial. More than 20% of these participants had serious adverse events judged to be related to Covid-19. Nearly one third of the 11 deaths were directly attributed to Covid-19 (Table S5).

Our trial had several strengths. Its global nature, large sample size, and overall high completion rate make the findings relatively generalizable. Overall, 86% (approximately 90% across the tirzepatide groups) of the participants completed the trial, despite the Covid-19 pandemic. The weight reduction in the placebo group was similar to results observed with pla-

cebo in other recent obesity pharmacotherapy trials and is likely to reflect a similar level of adherence to the lifestyle intervention.^{9,10} Finally, the duration of the trial (72 weeks) enabled participants to reach a weight plateau in the 5-mg group and near-plateaus in the 10-mg and 15-mg groups; the additional 2-year treatment period for participants with prediabetes should provide further insight into the maximum and long-term weight-lowering effect of tirzepatide in people with prediabetes.

This trial had certain limitations. The enrolled participants with obesity and overweight may represent a subpopulation with a greater commitment to weight-management efforts than the general population with obesity. Furthermore, the measured baseline cardiometabolic risk factors in the trial population, such as blood pressure and lipids, were relatively normal, possibly attenuating the potential to show improvement, though meaningful changes in these variables were observed. Overall, only 5.5% of trial participants with overweight (BMI of 27 to < 30) were included; further studies would be needed in such patients.

In the present trial, all three doses of once-weekly tirzepatide demonstrated substantial and sustained weight reduction in adults with obesity.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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