ORIGINAL ARTICLE

Tirzepatide as Compared with Semaglutide for the Treatment of Obesity

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ABSTRACT

BACKGROUND

Tirzepatide and semaglutide are highly effective medications for obesity management. The efficacy and safety of tirzepatide as compared with semaglutide in adults with obesity but without type 2 diabetes is unknown.

METHODS

In this phase 3b, open-label, controlled trial, adult participants with obesity but without type 2 diabetes were randomly assigned in a 1:1 ratio to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or the maximum tolerated dose of semaglutide (1.7 mg or 2.4 mg) subcutaneously once weekly for 72 weeks. The primary end point was the percent change in weight from baseline to week 72. Key secondary end points included weight reductions of at least 10%, 15%, 20%, and 25% and a change in waist circumference from baseline to week 72.

RESULTS

A total of 751 participants underwent randomization. The least-squares mean percent change in weight at week 72 was –20.2% (95% confidence interval [CI], –21.4 to –19.1) with tirzepatide and –13.7% (95% CI, –14.9 to –12.6) with semaglutide (P<0.001). The least-squares mean change in waist circumference was –18.4 cm (95% CI, –19.6 to –17.2) with tirzepatide and –13.0 cm (95% CI, –14.3 to –11.7) with semaglutide (P<0.001). Participants in the tirzepatide group were more likely than those in the semaglutide group to have weight reductions of at least 10%, 15%, 20%, and 25%. The most common adverse events in both treatment groups were gastrointestinal, and most were mild to moderate in severity and occurred primarily during dose escalation.

CONCLUSIONS

Among participants with obesity but without diabetes, treatment with tirzepatide was superior to treatment with semaglutide with respect to reduction in body weight and waist circumference at week 72. (Funded by Eli Lilly; SURMOUNT-5 ClinicalTrials.gov number, NCT05822830.)

Tirzepatide and semaglutide are part of a new generation of highly effective medications for the management of obesity.[1] Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist,[2] and semaglutide is a long-acting GLP-1 receptor agonist.[3]

Clinically meaningful weight reductions occur with both medications, with reported mean weight reductions of up to 22.9% after nearly 3.5 years of treatment with tirzepatide[4] and of 16.7% after nearly 2 years of treatment with semaglutide.[3] Both treatments decrease appetite and regulate food-related behaviors,[5,6] presumably through expression of their respective receptor targets in subcortical regions of the brain that regulate food intake. The patterns of central expression of GIP receptors do not fully overlap with those of GLP-1 receptors,[7,8] and this variation is hypothesized to contribute to the higher weight reduction that has been noted with the dual agonism of GIP and GLP-1 receptors than with agonism of either receptor alone in preclinical models.[9] In addition, although adipocytes lack functional GLP-1 receptors, they do have functional GIP receptors that are hypothesized as being responsible for the direct regulation of adipocytes by tirzepatide.[10] The additional mechanisms of action provided by the dual agonism of tirzepatide are posited to counter more effectively than monoagonism the complex pathways that limit a person's ability to reduce body weight and maintain this reduction.[11] To address this concept, a head-to-head clinical trial that evaluates the remaining clinical equipoise is warranted. Therefore, we conducted a 72-week, randomized, controlled trial to evaluate the efficacy and safety of the maximum tolerated dose of tirzepatide (10 mg or 15 mg) as compared with the maximum tolerated dose of semaglutide (1.7 mg or 2.4 mg) in adults with obesity.

METHODS

TRIAL DESIGN

This phase 3b, multicenter, parallel-arm, open-label, randomized, controlled trial was conducted during 72 weeks at 32 sites in the United States and Puerto Rico (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol (available at NEJM.org) was approved by an ethics review board at each site, and the trial was conducted in accordance with the principles of the Declaration of Helsinki and with the Good Clinical Practice guidelines of the International Council for Harmonisation. All the participants provided written informed consent before enrollment.

The sponsor (Eli Lilly) and the first two authors designed the trial. The trial-site investigators were responsible for data collection, and the sponsor undertook site monitoring, data collation, and data analysis. The first draft of the manuscript was written by the first and last authors. The investigators worked under confidentiality agreements with the sponsor. All the authors participated in the interpretation of the data and the critical review of the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

A Quick Take is available at NEJM.org

PARTICIPANTS

Participants were included if they were 18 years of age or older, had a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30 or higher or a BMI of 27 or higher and at least one prespecified obesity-related complication (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease), and reported at least one unsuccessful dietary effort for weight reduction. Key exclusion criteria included a diagnosis of diabetes, previous or planned surgical treatment for obesity, treatment with a medication for weight reduction or a GLP-1 receptor agonist within 90 days before screening, or a change in body weight of more than 5 kg within 90 days before screening. A full list of eligibility criteria is provided in the Supplementary Appendix.

PROCEDURES

Participants were randomly assigned in a 1:1 ratio to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or the maximum tolerated dose of semaglutide (1.7 mg or 2.4 mg). Treatment was administered subcutaneously by the participants once weekly for 72 weeks. Randomization was performed with the use of an interactive Web-response system and was stratified according to baseline BMI (<35 or ≥35), sex, and prediabetes status as determined from laboratory tests performed at screening after the participants had fasted.[12]

Tirzepatide was initiated at a dose of 2.5 mg once weekly, and the dose was increased by 2.5 mg every 4 weeks until a maximum tolerated dose of 10 mg or 15 mg was reached (Fig. S1 in the Supplementary Appendix). Semaglutide was initiated at a dose of 0.25 mg once weekly, and the dose was increased every 4 weeks in accordance with recommended dosing (from 0.25 mg to 0.5 mg, 1.0 mg, 1.7 mg, and 2.4 mg) until the 2.4-mg dose was reached. If unacceptable side effects were associated with the 2.4-mg dose, the participant could continue receiving the 1.7-mg dose as a maintenance dose, an approach consistent with the STEP 1 (Semaglutide Treatment Effect in People with Obesity) trial.[13] Similar to the protocols for the previous SURMOUNT trials,[14] the protocol for the current trial provided the investigators with guidance on mitigating gastrointestinal symptoms. Participants who had unacceptable side effects while taking tirzepatide at a dose of 10 mg or 15 mg or while taking semaglutide at a dose of 1.7 mg or 2.4 mg, including after no more than two cycles of de-escalation of treatment followed by re-escalation, discontinued the trial intervention and were encouraged to remain in the trial for continued follow-up. All the participants received counseling on nutrition and physical activity.

If a participant's BMI decreased to 22 during the course of trial treatment, efforts were made to maintain body weight at that level; counseling included advice to adjust caloric intake. Furthermore, the investigator had the option to reduce the dose (e.g., decreasing the tirzepatide dose from 15 mg to 10 mg or from 10 mg to 5 mg or decreasing the semaglutide dose from 2.4 mg to 1.7 mg).

END POINTS AND ASSESSMENTS

The primary end point was the percent change in body weight from baseline to week 72 with tirzepatide as compared with semaglutide. The key secondary end points were a weight reduction of at least 10%, 15%, 20%, and 25% and a change in waist circumference from baseline to week 72. Additional secondary and tertiary end points are described in the Supplementary Appendix.

Safety assessments included adverse events and serious adverse events that occurred during the reporting period, including adverse events that led to the discontinuation of tirzepatide or semaglutide. Major adverse cardiovascular events, pancreatitis, and deaths were reviewed by an independent external adjudication committee.

STATISTICAL ANALYSIS

We estimated that a sample size of 700 participants (350 per group) would provide approximately 90% power to show that tirzepatide was superior to semaglutide with respect to the mean percent change in body weight from baseline to week 72. We used the following assumptions: a two-sample t-test with a two-sided significance level of 0.05; a trial-drug discontinuation rate of 20%, with a resultant common standard deviation of 12%; and a between-group difference in the percent change in body weight of 3 percentage points.

Data from all the participants who received at least one dose of the trial drug were used to analyze the efficacy and safety end points. Two estimands were used to assess the primary and key secondary end points from different perspectives. The primary estimand for the trial was the modified treatment-regimen estimand, whereas the secondary estimand was the efficacy estimand. Although the primary and key secondary end points were adjusted for multiplicity within each estimand, inferences regarding the treatment effects in this article apply only to the primary estimand. The modified treatment-regimen estimand evaluated the treatment effect regardless of premature discontinuation of the trial drug or initiation of other medications for obesity management (unless a participant who had been assigned to tirzepatide initiated semaglutide outside the trial or a participant assigned to semaglutide initiated tirzepatide outside the trial). This estimand also assumed that participants who underwent any surgical weight-reduction procedures had not benefited from their randomly assigned trial treatment or possibly had an increase in body weight; therefore, the highest trial weight recorded before the participants underwent the surgical procedure would be applied as the end point. The efficacy estimand is described in the Supplementary Appendix. All results are reported for the modified treatment-regimen estimand unless otherwise specified. For the primary and key secondary end points, the type I error rate was controlled at a two-sided alpha level of 0.05 within each estimand by means of a graphical testing procedure.[15]

Statistical analyses of continuous end points

for the modified treatment-regimen estimand were conducted with the use of an analysis-of-covariance model. Model terms included treatment, stratification factors (prediabetes status at randomization, sex, and BMI category at randomization [<35 vs. ≥35]), and baseline values as covariates. Continuous end points for the efficacy estimand were conducted with the use of a mixed model for repeated measures. Categorical variables were evaluated with the use of a logistic-regression analysis with treatment, stratification factors, and baseline values as covariates. Full details on each estimand, handling of missing data, and statistical analysis methods are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

The trial was conducted between April 21, 2023, and November 13, 2024. Of 948 participants assessed for trial eligibility, 751 underwent randomization, and 750 received at least one dose of tirzepatide or semaglutide (Fig. S3).

Overall, 85.0% of the participants completed the trial (85.1% in the tirzepatide group and 84.8% in the semaglutide group) and 80.2% completed the 72 weeks of trial treatment (81.6% in the tirzepatide group and 78.7% in the semaglutide group). The trial treatment was discontinued because of adverse events by 6.1% of the participants in the tirzepatide group and 8.0% of those in the semaglutide group. In the tirzepatide group, 89.3% of the participants received at least one 15-mg dose, and in the semaglutide group, 92.8% received at least one 2.4-mg dose.

In general, demographic and clinical characteristics of the participants were similar in the two groups (Table 1 and Table S1). The mean age of the participants was 44.7 years; the majority were women (64.7%) and White (76.1%). The mean body weight was 113.0 kg, the mean BMI 39.4, and the mean waist circumference 118.3 cm. The average reported duration of obesity was 16 years; 50.1% of the participants had at least two obesity-related complications (Table 1).

CHANGE IN BODY WEIGHT

The least-squares mean percent change in body weight from baseline to week 72 was –20.2% with tirzepatide (95% confidence interval [CI], –21.4 to –19.1) and –13.7% with semaglutide (95% CI, –14.9 to –12.6) (Fig. 1A and Table 2). Tirzepatide was superior to semaglutide with respect to weight reduction (estimated treatment difference, –6.5 percentage points; 95% CI, –8.1 to –4.9; P<0.001). Results for the efficacy estimand are provided in Figure 2A and Table S2.

The least-squares mean change in body weight from baseline to week 72 was –22.8 kg with tirzepatide (95% CI, –24.1 to –21.5) and –15.0 kg with semaglutide (95% CI, –16.3 to –13.7) (Table 2). The results for the efficacy estimand are provided in Figure S5.

More participants treated with tirzepatide than those treated with semaglutide had reductions in body weight of at least 10%, 15%, 20%, and 25% from baseline (P<0.001) (Fig. 1B, Fig. S4, and Table 2). Participants treated with tirzepatide were 1.3, 1.6, 1.8, and 2.0 times more likely than participants treated with semaglutide to have weight reductions of at least 10%, 15%, 20%, and 25%, respectively. A total of 19.7% of the participants in the tirzepatide group had a reduction in body weight of at least 30% (an exploratory end point) as compared with 6.9% of those in the semaglutide group, which indicated that the likelihood of meeting this weight-reduction target with tirzepatide was 2.8 times as high as that with semaglutide (Table 2). In both trial-treatment groups, the weight reduction was approximately 6 percentage points greater among women than among men (Table S12).

CHANGE IN WAIST CIRCUMFERENCE AND CARDIOMETABOLIC RISK FACTORS

The least-squares mean change in waist circumference from baseline to week 72 was –18.4 cm with tirzepatide (95% CI, –19.6 to –17.2) and –13.0 cm with semaglutide (95% CI, –14.3 to –11.7) (Fig. 1C and Table 2). Tirzepatide was superior to semaglutide with respect to reduction in waist circumference (estimated treatment difference, –5.4 cm; 95% CI, –7.1 to –3.6; P<0.001). The results for the efficacy estimand are provided in Figure 2B.

Systolic blood pressure showed improvements with tirzepatide (least-squares mean change, –10.2 mm Hg; 95% CI, –11.4 to –8.9) and with semaglutide (least-squares mean change, –7.7 mm Hg; 95% CI, –8.9 to –6.4) (Table S4). Diastolic blood pressure also showed improvements with both treatments. Glycated hemoglobin, fasting serum glucose, and lipid levels improved with both trial

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

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

* Plus–minus values are means ±SD.
† Race or ethnic group was reported by the participants.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Participants were considered to have multiple obesity-related complications if they had two or more complications related to obesity, including a history of conditions reported at screening.

treatments, which is consistent with previous trials.[13,14] For both trial treatments, a comparison of weight-reduction categories (<10%, 10 to <20%, 20 to <30%, and ≥30%) showed that higher categorical weight reductions were associated with greater improvements in each cardiometabolic risk factor (Table S5).

SAFETY

Overall, 76.7% of the participants treated with tirzepatide and 79.0% of those treated with semaglutide reported at least one adverse event that occurred or worsened during the treatment period (Table 3). The most frequently reported adverse events were gastrointestinal (e.g., nausea, constipation, diarrhea, and vomiting). Most gastrointestinal adverse events were mild to moderate in severity and occurred primarily during dose escalation, with some variation in pattern between the two trial-treatment groups with respect to incidence and prevalence (Figs. S8 and S9). Gastrointestinal events were the most common adverse events leading to treatment discontinuation and were observed more often in the semaglutide group (21 participants [5.6%]) than in the tirzepatide group (10 participants [2.7%]). Injection-site reactions were more common in the tirzepatide group than in the semaglutide group (8.6% vs. 0.3%).

Serious adverse events were reported by 31 participants (4.1%) overall, with a similar occurrence in the tirzepatide group (4.8%) and the semaglutide group (3.5%) (Table 3). One adjudication-confirmed case of pancreatitis was re-

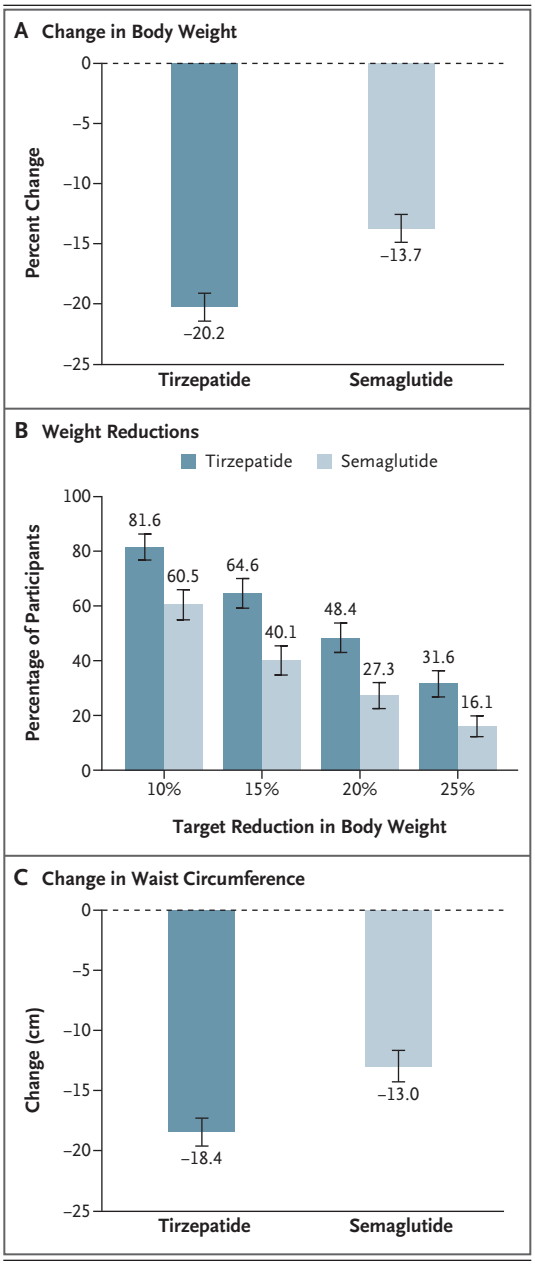

Figure 1. Effect of Tirzepatide as Compared with Semaglutide on Body Weight and Waist Circumference.

Shown is the effect of once-weekly tirzepatide (maximum tolerated dose, 10 mg or 15 mg) as compared with once-weekly semaglutide (maximum tolerated dose, 1.7 mg or 2.4 mg) on body weight and waist circumference. Panel A shows the least-squares mean percent change from baseline to week 72 in body weight, which was derived with the use of an analysis-of-covariance model for the modified treatment-regimen estimand (which evaluated the treatment effect regardless of premature discontinuation of the trial drug or initiation of other medications for obesity management). Panel B shows the percentages of participants who had weight reductions of at least 10%, 15%, 20%, and 25% from baseline to week 72, as calculated for the modified treatment-regimen estimand. The percentages were calculated with the use of Rubin's rules by combining the percentages of participants who met each target in imputed data sets. Panel C shows the least-squares mean change from baseline to week 72 in waist circumference (in centimeters), which was derived with the use of an analysis-of-covariance model for the modified treatment-regimen estimand. I bars indicate 95% confidence intervals.

ported in the semaglutide group. No adjudication-confirmed major cardiovascular events, deaths, cases of medullary thyroid cancer, or cases of pancreatic cancer were reported. Additional measures of safety are reported in Table S9. The results with respect to adverse events of special interest were consistent with those of previous trials.[3,13,14]

DISCUSSION

In our trial, adults with obesity but without diabetes had a 20.2% reduction in weight at 72 weeks when receiving tirzepatide, as compared with a 13.7% reduction when receiving semaglutide. Weight reduction was approximately 6 percentage points lower among men than among women in both treatment groups, a finding that is believed to explain the slightly lower weight reduction in the current trial than in previous trials. The current trial included a higher percentage of men (35%) than previous trials, especially when compared with the STEP trials involving persons without diabetes, in which 19 to 26% of the participants were men.[3,17] The current findings align with results reported in the SURMOUNT[14,18-20] and STEP trials[21] as well as in a recent cohort study that showed greater weight reduction with tirzepatide than with semaglutide.[22]

The complexity of energy-balance regulation has been a major impetus for the development of therapeutic agents with multiple mechanisms of action. The combination of pharmacotherapies that have different mechanisms results in greater weight reduction than the use of a single component, as seen with phentermine combined with extended-release topiramate[23] and with bupropion combined with naltrexone.[24] Although it is a single molecule, tirzepatide pharmacologically acti-

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

End Point	Tirzepatide (N=374)	Semaglutide (N=376)	Treatment Difference or Relative Risk (95% CI)*
Primary end point			
Least-squares mean percent change in body weight (95% CI)	−20.2 (−21.4 to −19.1)	−13.7 (−14.9 to −12.6)	−6.5 (−8.1 to −4.9)
Key secondary end points			
Least-squares mean change in waist circumference — cm	−18.4 (−19.6 to −17.2)	−13.0 (−14.3 to −11.7)	−5.4 (−7.1 to −3.6)
Weight reduction of ≥10% — no. (%)†	304 (81.6)	227 (60.5)	1.3 (1.2 to 1.5)
Weight reduction of ≥15% — no. (%)†	241 (64.6)	151 (40.1)	1.6 (1.4 to 1.9)
Weight reduction of ≥20% — no. (%)†	181 (48.4)	103 (27.3)	1.8 (1.5 to 2.2)
Weight reduction of ≥25% — no. (%)†	118 (31.6)	60 (16.1)	2.0 (1.5 to 2.6)
Additional secondary end points‡			
Weight reduction of ≥30% — no. (%)†	74 (19.7)	26 (6.9)	2.8 (1.9 to 4.3)
Least-squares mean change in body weight — kg	−22.8 (−24.1 to −21.5)	−15.0 (−16.3 to −13.7)	−7.9 (−9.7 to −6.0)
Least-squares mean change in body-mass index	−8.0 (−8.5 to −7.5)	−5.3 (−5.8 to −4.8)	−2.7 (−3.3 to −2.0)

* Values are shown as the estimated percentage-point treatment difference between groups with the exception of the weight-reduction categories of at least 10%, 15%, 20%, 25%, and 30%, which are shown as the relative risk. Relative risk was calculated with the use of G-computation methods[16] on the basis of logistic regression. P<0.001 for all primary and key secondary end points.

† The number and percentage were calculated according to imputed data. The number was calculated by averaging the number of participants who achieved the target weight reduction across imputed data sets and then rounding to the integer; the percentage was calculated by combining the percentage of participants who achieved the target weight reduction in imputed data sets with the use of Rubin's rule.

‡ The confidence intervals for the additional secondary end points have not been adjusted for multiplicity and should not be used to make inferences.

vates two metabolic receptors, GIP and GLP-1, which have both overlapping and nonoverlapping expression and function.[2] This dual-agonism activity of tirzepatide may contribute to the greater weight reduction observed with tirzepatide than with semaglutide, a monoagonist used in the current trial.

Currently recommended magnitudes of weight reduction often lead to a threshold effect with respect to abatement in specific obesity-related complications,[25] because the magnitude that may contribute to remission or partial remission of many obesity-related complications is difficult to achieve or has not been defined. In persons with type 2 diabetes, a linear relationship between the incidence of early disease remission and a weight reduction of up to approximately 10 to 15% has been established,[26] yet recommendations supporting weight-reduction targets of this magnitude are limited.[27] In two recent clinical trials, 42 to 50% of participants with moderate-to-severe obstructive sleep apnea and obesity who received tirzepatide had a decrease in disease activity to mild disease without sleepiness or had remission with mean weight reductions of 18 to 20%.[28] A weight reduction of this magnitude is substantially greater than the approximate 7 to 11% reduction recommended in guidance for patients with obesity-related obstructive sleep apnea.[25] With a new generation of medications for obesity management, higher magnitudes of weight reduction become more readily achievable and sustainable, which provides the opportunity to modify recommendations to a treat-to-target approach.[1]

With both treatments in our trial, as weight reduction increased, greater improvements occurred in cardiometabolic risk factors, including blood pressure, glycemia, and lipid levels, which is consistent with the findings in previous reports.[17] The mean differences between tirzepatide and semaglutide in the cardiometabolic risk factors may be clinically relevant considering that reductions in systolic blood pressure of 2 to 5 mm Hg have been shown to reduce the risk of cardiovascular events.[29] The evaluation of the effect of greater weight reduction on decreases in cardiometabolic risk factors may translate to improved shared decision making by assisting with the selection of treatment goals. For example, among the participants who had a weight reduc-

tion of at least 20% while receiving treatment and had available data at week 72 (46.5% of participants in the tirzepatide group and 26.1% in the semaglutide group), the mean reduction in systolic blood pressure ranged from 9.1 to 17.5 mm Hg, as compared with 3.4 to 6.7 mm Hg among those who had a weight reduction of less than 10%. Whereas semaglutide has shown a benefit with respect to cardiovascular outcomes in persons with obesity and a history of cardiovascular disease in the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial,[30] the ongoing SURMOUNT-MMO trial (ClinicalTrials.gov number, NCT05556512) with tirzepatide may provide data regarding prevention of cardiovascular disease in persons with obesity with a history of cardiovascular disease and those at high risk for cardiovascular disease. Greater weight reduction, including during treatment with semaglutide[31] and tirzepatide,[32] generally improves quality of life, mostly through an improvement in physical functioning.[33] Although some patients will not require the higher magnitudes of weight reduction, the findings of improved health with greater magnitudes of weight reduction lend support to the clinical relevance of the current trial because the majority of the participants who received tirzepatide had a weight reduction of at least 15%, and nearly a third had a reduction of at least 25%, as compared with 16.1% of the participants who received semaglutide. The additional 5.4-cm reduction in waist circumference with tirzepatide as compared with semaglutide is also clinically relevant. In a large pooled analysis of waist circumference and mortality, each 5-cm increase in waist circumference predicted a 7% increase in mortality among men and a 9% increase among women.[34] In alignment with these data, published guidance has emphasized the importance of treating patients with abdominal obesity[25] and aiming for a reduction of at least 4 cm.[35]

Patient preferences are an essential component of shared decision making;[36] however, older guidelines detailed patients' weight-reduction goals as often not realistic[37] and were from an era when available interventions led to weight reductions of only 5 to 10%.[38] Recently, the OBSERVE study reported that adults with obesity may have weight-reduction goals of greater than 10%, especially those with class II and III obesity who have preferred weight-reduction goals of 20% or higher.[39] In the study, the preferred weight reductions were not clinically excessive, given that approximately 85% of respondents were projected to continue to have obesity or overweight according to BMI after reaching their goal weight.[39] Treatment that aligns with patient preferences may lead to increased adherence with better treatment outcomes.[39]

Both tirzepatide and semaglutide had safety profiles consistent with those in previous trials.[13,14,18-20] As typically observed with incretin-based therapies, gastrointestinal adverse events were predominantly mild to moderate in severity, occurred mostly during dose escalation, and led to treatment discontinuation more often with

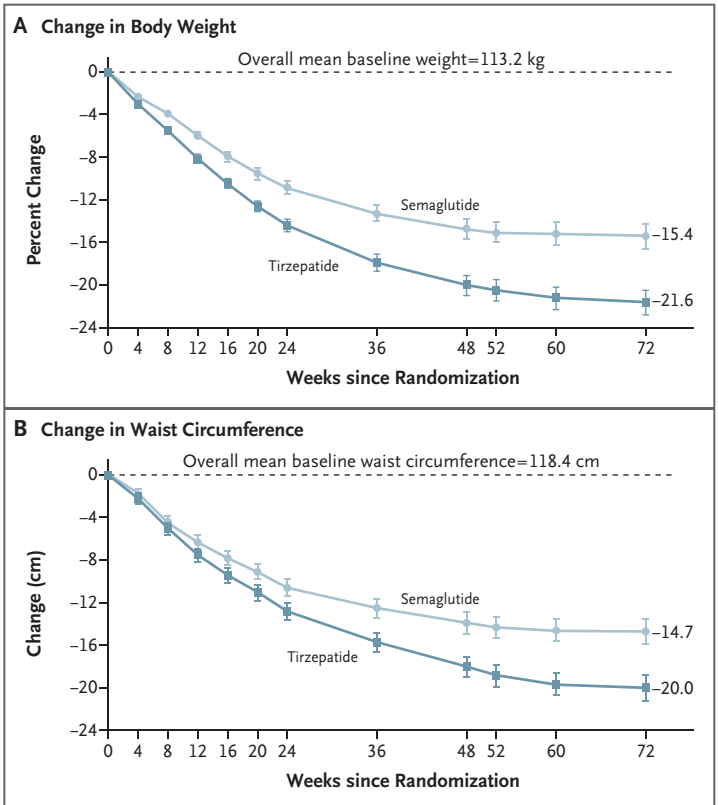

Figure 2. Change in Body Weight and Waist Circumference from Baseline to Week 72 (Efficacy Estimand).

Shown are the least-squares mean percent changes in body weight (Panel A) and the least-squares mean changes in waist circumference (Panel B) according to weeks since randomization. Values were derived with the use of a mixed-model-for-repeated-measures analysis for the efficacy estimand (described in the Supplementary Appendix). I bars indicate 95% confidence intervals.

Table 3. Adverse Events and Safety.*

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

* Safety end points were analyzed with the use of data from participants regardless of whether participants adhered to treatment, initiated other antiobesity medication, or underwent bariatric surgery.
† Adverse events are listed according to preferred terms in the *Medical Dictionary for Regulatory Activities*, version 24.1.
‡ Shown are adverse events that were reported more than once.

semaglutide than with tirzepatide. The tirzepatide group had more injection-site reactions than the semaglutide group, which is consistent with other SURMOUNT trials.[14,20] In the current trial, no participants were reported to have had severe or serious injection-site reactions nor to have discontinued trial treatment because of such reactions.

This trial has certain strengths and limitations. One strength is the diversity of the participants, with 19% reporting their race as Black and 26% reporting their ethnic group as Hispanic or Latino, which is representative of the populations living with obesity (Table S6). By evaluating the maximum tolerated dose for both treatments, the trial addressed a potentially more meaningful real-world question than would have been addressed with a fixed-dose approach. A limitation is that the trial was not blinded; however, the consistency of the current findings with those from previous blinded trials supports their generalizability.

In this trial, treatment with tirzepatide, a dual GIP and GLP-1 receptor agonist, was superior to treatment with semaglutide, a selective GLP-1 receptor agonist, with respect to reduction in body weight and waist circumference.

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