ORIGINAL ARTICLE

Tirzepatide for Obesity Treatment and Diabetes Prevention

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ABSTRACT

BACKGROUND

Obesity is a chronic disease and causal precursor to myriad other conditions, including type 2 diabetes. In an earlier analysis of the SURMOUNT-1 trial, tirzepatide was shown to provide substantial and sustained reductions in body weight in persons with obesity over a 72-week period. Here, we report the 3-year safety outcomes with tirzepatide and its efficacy in reducing weight and delaying progression to type 2 diabetes in persons with both obesity and prediabetes.

METHODS

We performed a phase 3, double-blind, randomized, controlled trial in which 2539 participants with obesity, of whom 1032 also had prediabetes, were assigned in a 1:1:1:1 ratio to receive tirzepatide at a once-weekly dose of 5 mg, 10 mg, or 15 mg or placebo. The current analysis involved the participants with both obesity and prediabetes, who received their assigned dose of tirzepatide or placebo for a total of 176 weeks, followed by a 17-week off-treatment period. The three key secondary end points, which were controlled for type I error, were the percent change in body weight from baseline to week 176 and onset of type 2 diabetes during the 176-week and 193-week periods.

RESULTS

At 176 weeks, the mean percent change in body weight among the participants who received tirzepatide was –12.3% with the 5-mg dose, –18.7% with the 10-mg dose, and –19.7% with the 15-mg dose, as compared with –1.3% among those who received placebo (P<0.001 for all comparisons with placebo). Fewer participants received a diagnosis of type 2 diabetes in the tirzepatide groups than in the placebo group (1.3% vs. 13.3%; hazard ratio, 0.07; 95% confidence interval [CI], 0.0 to 0.1; P<0.001). After 17 weeks off treatment or placebo, 2.4% of the participants who received tirzepatide and 13.7% of those who received placebo had type 2 diabetes (hazard ratio, 0.12; 95% CI, 0.1 to 0.2; P<0.001). Other than coronavirus disease 2019, the most common adverse events were gastrointestinal, most of which were mild to moderate in severity and occurred primarily during the dose-escalation period in the first 20 weeks of the trial. No new safety signals were identified.

CONCLUSIONS

Three years of treatment with tirzepatide in persons with obesity and prediabetes resulted in substantial and sustained weight reduction and a markedly lower risk of progression to type 2 diabetes than that with placebo. (Funded by Eli Lilly; SURMOUNT-1 ClinicalTrials.gov number, NCT04184622.)

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CME

Improving health is the overarching goal of obesity treatment. Nearly 1 billion people are living with obesity,[1] and of those, approximately two thirds have prediabetes.[2] Characterized by insulin resistance and beta-cell dysfunction, prediabetes increases the risk of developing type 2 diabetes by as much as 70% over a lifetime.[3]

Obesity is a chronic neuroendocrine disease and a major risk factor for both prediabetes and type 2 diabetes.[4] Initially, studies involving persons with obesity and prediabetes investigated whether lifestyle interventions,[5-7] pharmacotherapeutics,[8-10] or bariatric surgery[11] prevent or delay the onset of type 2 diabetes. Later studies centered on reversion to normoglycemia, given that prediabetes itself predisposes to many adverse health consequences, including microvascular and macrovascular complications.[3,8,9] Pharmacotherapeutic interventions that directly target both obesity and dysglycemia may have unique advantages. Clinically meaningful, sustained weight reduction improves insulin sensitivity, and the direct effects on pancreatic islets enhance glucose-dependent insulin secretion; these two effects work in concert to improve metabolic homeostasis.[12] Such pharmacologic interventions can be used to treat obesity, prevent prediabetes from progressing to type 2 diabetes, and provide the opportunity for reversion to normoglycemia, thereby maximizing health gains.

Tirzepatide is a unique glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that has been approved by the Food and Drug Administration and the European Medicines Agency for the treatment of obesity as well as type 2 diabetes. Tirzepatide therapy has resulted in significant weight reduction, glycemic control, and improvements in other metabolic measures in persons with obesity with or without type 2 diabetes.[13,14] In the first 72-weeks of the SURMOUNT-1 trial (the primary period of this trial), participants with obesity who received the 15-mg dose of tirzepatide lost on average more than 20% of their total body weight, with an accompanying 0.51% reduction in the glycated hemoglobin level.[13] Here, we report the 3-year safety and efficacy outcomes with tirzepatide, including its effect on achieving and sustaining longer-term weight reduction and preventing type 2 diabetes in participants with prediabetes at baseline.

Methods

Trial Design

SURMOUNT-1 was an international, phase 3, double-blind, randomized, placebo-controlled trial of tirzepatide in persons with obesity (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[13,15] The duration of treatment was determined according to glycemic status (prediabetes or normoglycemia) at randomization. Participants with obesity and without prediabetes at baseline were offered treatment for 72 weeks, whereas participants with obesity and prediabetes at baseline were offered treatment for 176 weeks (Fig. S1). The results reported here are for the participants with prediabetes at baseline.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines and was approved by an independent ethics committee or institutional review board at each trial site. Written informed consent was obtained from all the participants. The sponsor (Eli Lilly) designed and oversaw the conduct of 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 author. 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, available at NEJM.org.

Participants

In the current analysis, the trial participants had a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of at least 30 or at least 27 with at least one obesity-related complication, and all had prediabetes.[13] The diagnosis of prediabetes was based on the results of at least two measurements (the glycated hemoglobin level, the fasting serum glucose level, or the serum glucose level in a 2-hour oral glucose tolerance test, with cutoff points established by the American Diabetes Association [ADA][16]) at a single visit or two different visits. A key exclusion criterion was diabetes mellitus. Comprehensive eligibility criteria are provided in the Supplementary Appendix.

A Quick Take is available at NEJM.org

PROCEDURES AND ASSESSMENTS

The 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 176 weeks, followed by a 17-week off-treatment period (safety follow-up), for a total trial duration of 193 weeks. All groups received lifestyle intervention, including regular lifestyle counseling sessions with a dietitian or a qualified health care professional with a focus on healthful, balanced meals, with a 500-kcal deficit per day, and at least 150 minutes of physical activity per week.[15]

Glycemic status was assessed by measuring the glycated hemoglobin and fasting serum glucose levels at baseline and every 12 to 13 weeks throughout the treatment period and by measuring the serum glucose level in a 2-hour oral glucose tolerance test at baseline and at weeks 72, 124, and 176. All three glycemic assessments were also performed after the 17-week off-treatment period. The diagnosis of diabetes was based on ADA guidelines[16] and confirmed by an independent adjudication committee (see the Supplementary Appendix). Additional assessments included cardiometabolic risk factors such as blood pressure, lipid levels, and health-related quality of life (measured with the 36-Item Short Form Health Survey [SF-36], version 2, acute form, and the Impact of Weight on Quality of Life–Lite Clinical Trials Version [IWQOL-Lite-CT] questionnaire). Norm-based scores were used for the SF-36 domains, with higher scores indicating better levels of function, better health, or better health and function. Each SF-36 domain was scored individually on Likert scales of varying lengths (3-point scale, 5-point scale, or 6-point scale). IWQOL-Lite-CT total and composite scores range from 0 to 100, with higher scores indicating better health-related quality of life and functioning.

END POINTS

The results for the coprimary end points (percent change in body weight and percentage of participants with ≥5% weight reduction) and key secondary end points (controlled for type I error) for 72-week outcomes have been published.[13] The three key secondary end points that were assessed in the current analysis, with control for type I error, were the percent change in body weight from baseline to week 176 (assessed in the 10-mg and 15-mg tirzepatide groups and the placebo group) and onset of type 2 diabetes during the 176-week and 193-week periods (assessed in the pooled tirzepatide groups and the placebo group). Safety assessments included adverse events and serious adverse events that occurred through week 193.

STATISTICAL ANALYSIS

We estimated that our sample size would provide the trial with approximately 90% power to show the superiority of tirzepatide (with pooled data from the three dose groups) over placebo for delaying the onset of diabetes. Our estimation was based on the assumptions that 1.6% of the participants receiving tirzepatide and 6% of those receiving placebo will have progression to diabetes and that 49% of the participants will withdraw from the trial.[8] Efficacy and safety end points were analyzed with data from the participants with prediabetes who had undergone randomization (the intention-to-treat population).

Two estimands were used to assess efficacy from different perspectives and accounted for intercurrent events differently. For the treatment-regimen estimand, we used the treatment policy strategy in the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E9 (R1) addendum on estimands and sensitivity analysis in clinical trials.[17] This estimand represented the treatment effect of tirzepatide relative to placebo for all the participants who had undergone randomization, regardless of discontinuation of tirzepatide or placebo. The efficacy estimand represented the average treatment effect of tirzepatide relative to placebo among all the participants who had undergone randomization, if the treatment or placebo was administered as intended.[17] All reported results are for the treatment-regimen estimand unless stated otherwise.

The type I error was strongly controlled at a two-sided alpha of 0.05 within each estimand independently with a graphical approach, including adjustment for multiple end points and multiple doses as compared with placebo. To assess how much the end point of weight reduction contributed to the treatment effect on progression to type 2 diabetes, a post hoc mediation analysis was performed, in which path-specific effects, expressed as differences or ratios of survival probabilities, were examined.[18] Details on estimands, handling of missing values, and statistical analysis methods, including the evaluation of reversion

to normoglycemia and glycemic status according to weight-loss thresholds, are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

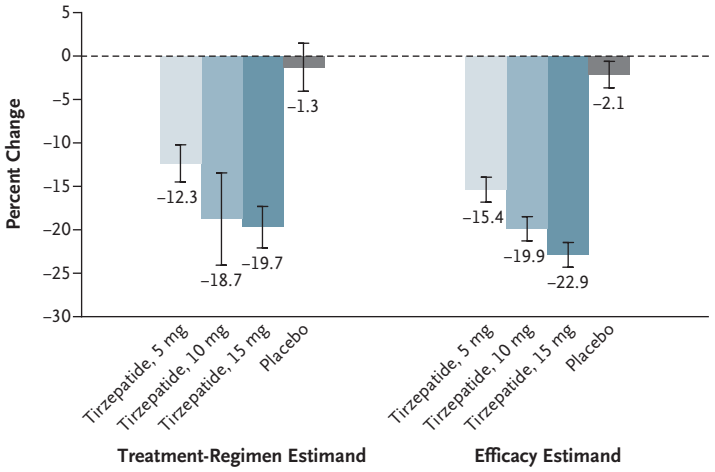
The trial was conducted from December 2019 through July 2024. Among the 2539 participants in the SURMOUNT-1 trial, 1032 (40.6%) had prediabetes at baseline (Table 1) and were included in the current analyses. Overall, 677 participants (65.6%) completed the trial through 193 weeks, and 662 (64.1%) adhered to the treatment or placebo regimen as assigned. Overall, 101 participants (9.8%) with prediabetes who had undergone randomization withdrew from the trial before week 72; an additional 124 participants (12.0%) withdrew from the trial at week 72 or at the subsequent 4-week safety follow-up visit, and 130 (12.6%) withdrew from the trial during the subsequent 2 years. The disposition of the

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

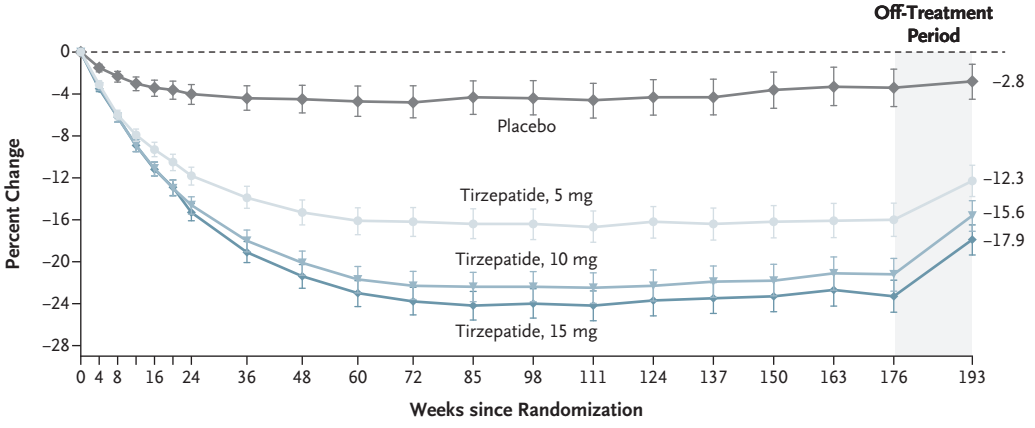
Variable *	Tirzepatide, 5 mg (N=247)	Tirzepatide, 10 mg (N=262)	Tirzepatide, 15 mg (N=253)	Placebo (N=270)	Total (N=1032)
Age — yr	49.3±12.2	47.4±11.6	48.4±11.7	47.7±11.9	48.2±11.8
Female sex — no. (%)	160 (64.8)	168 (64.1)	161 (63.6)	170 (63.0)	659 (63.9)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	18 (7.3)	20 (7.6)	19 (7.5)	18 (6.7)	75 (7.3)
Asian	22 (8.9)	27 (10.3)	26 (10.3)	30 (11.1)	105 (10.2)
Black	19 (7.7)	15 (5.7)	20 (7.9)	23 (8.5)	77 (7.5)
White	182 (73.7)	198 (75.6)	185 (73.1)	193 (71.5)	758 (73.4)
Native Hawaiian or other Pacific Islander	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	4 (0.4)
Multiple	5 (2.0)	1 (0.4)	2 (0.8)	5 (1.9)	13 (1.3)
Hispanic or Latino	118 (47.8)	120 (45.8)	117 (46.2)	127 (47.0)	482 (46.7)
Body weight — kg	104.6±21.91	108.9±23.88	108.6±25.44	107.3±21.97	107.3±23.36
Body-mass index‡	37.8±6.63	39.0±7.15	39.2±7.43	39.1±7.10	38.8±7.10
Waist circumference — cm	115.0±14.54	117.4±15.53	116.6±16.73	117.1±15.42	116.5±15.58
Glycated hemoglobin level — %	5.79±0.30	5.74±0.33	5.76±0.39	5.77±0.33	5.76±0.34
Fasting glucose level — mg/dl	101.2±9.04	101.8±10.06	101.0±9.54	101.3±9.61	101.3±9.57
Fasting insulin level — mIU/liter	16.0±12.83	16.3±16.12	16.5±9.39	17.1±10.49	16.5±12.47
Systolic blood pressure — mm Hg	126.9±12.13	125.3±13.14	125.4±12.73	124.8±12.75	125.6±12.71
Diastolic blood pressure — mm Hg	80.8±7.98	80.4±8.73	80.3±8.11	80.8±7.80	80.6±8.16
Pulse — beats/min	72.9±9.42	71.9±9.73	73.2±10.13	73.5±9.40	72.8±9.68
Lipid levels — mg/dl					
Total cholesterol	190.8±39.55	193.0±37.10	190.0±38.66	192.1±39.77	191.5±38.74
HDL cholesterol	48.4±11.90	48.4±12.63	48.6±12.76	46.0±11.11	47.8±12.14
LDL cholesterol	112.9±34.05	115.3±31.95	111.2±32.82	115.3±34.48	113.7±33.34
Triglycerides	150.5±81.23	149.1±81.78	152.6±77.31	156.5±88.67	152.2±82.39
Estimated GFR — ml/min/1.73 m^2§	93.8±17.51	95.0±18.65	96.2±17.21	95.1±18.37	95.1±17.95

* Plus–minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.
† Race and ethnic group were reported by the participants.
‡ The body-mass index (the weight in kilograms divided by the square of the height in meters) among the participants at baseline ranged from 27.0 to 69.9.
§ The estimated glomerular filtration rate (GFR) was calculated with use of the serum creatinine–based Chronic Kidney Disease Epidemiology Collaboration equation.

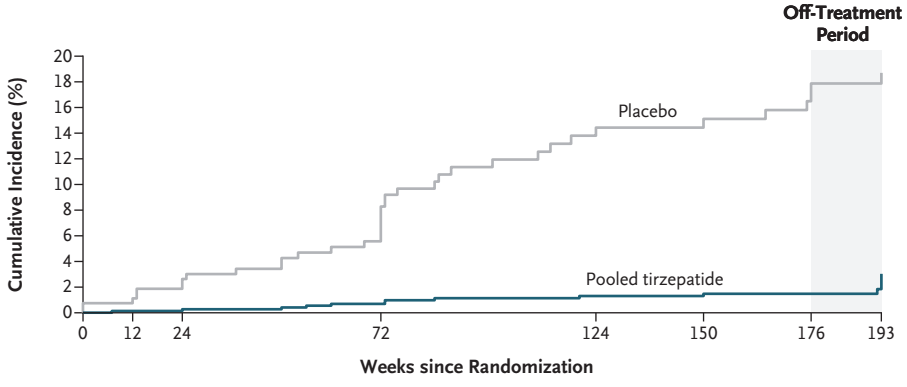
A Change in Body Weight from Baseline to Week 176



B Change in Body Weight



C Incidence of Type 2 Diabetes



No. at Risk								
Placebo	270	266	257	209	137	126	121	99
Pooled tirzepatide	762	751	742	700	581	570	557	494
No. of Participants with Diagnosis								
Placebo	2	3	7	20	31	32	36	37
Pooled tirzepatide	0	1	2	5	9	10	10	18

Figure 1 (facing page). Effect of Once-Weekly Tirzepatide on Body Weight and Progression to Type 2 Diabetes.

Panel A shows the percent change in body weight from baseline to week 176, as derived from an analysis of covariance model for the treatment-regimen estimand and from a mixed-model-for-repeated-measures analysis for the efficacy estimand. The change in body weight in the 5-mg tirzepatide group was a prespecified end point but not a key secondary end point that was controlled for type I error. Panel B shows the percent change in body weight according to weeks since randomization, derived from a mixed-model-for-repeated-measures analysis in the safety analysis population (which included the same patients as those in the intention-to-treat population). The shaded gray area represents the 17-week off-treatment follow-up period. Only participants who had weight measured at both weeks 176 and 193 were included in this analysis. In Panel A and B, least-squares mean changes are presented, and the I bars indicate 95% confidence intervals. Panel C shows Kaplan–Meier estimates of the percentage of participants in the safety analysis population who received a diagnosis of type 2 diabetes during the course of the trial (during the 176-week treatment period and during the 17-week off-treatment period).

participants and the reasons for discontinuation of tirzepatide or placebo and trial withdrawal are shown in Figure S2. Details on country-specific enrollment and the representativeness of participants are provided in Tables S1 and S2, respectively.

The demographic and clinical characteristics of the participants at baseline were generally similar across the trial groups (Table 1 and Table S3). The mean age of the participants was 48.2 years, and most were female (63.9%) and White (73.4%). The mean body weight was 107.3 kg, the mean BMI 38.8, and the mean waist circumference 116.5 cm; 37.2% of the participants had a BMI of 40 or greater (Table 1).

CHANGE IN BODY WEIGHT

For the treatment-regimen estimand, the mean percent change in body weight from randomization to week 176 among the participants who received tirzepatide was –12.3% (95% confidence interval [CI], –14.5 to –10.2) with the 5-mg dose (mean weight reduction, 12.4 kg), –18.7% (95% CI, –24.1 to –13.4) with the 10-mg dose (mean weight reduction, 20.0 kg), and –19.7% (95% CI, –22.1 to –17.3) with the 15-mg dose (mean weight reduction, 21.4 kg), as compared with –1.3% (95% CI, –4.0 to 1.5) among the participants who received placebo (mean weight reduction, 0.9 kg) (Fig. 1A and Table 2). All tirzepatide doses were superior to placebo with respect to weight reduction, with estimated treatment differences relative to placebo of –11.1% (95% CI, –14.4 to –7.8) with the 5-mg dose, –17.5% (95% CI, –23.6 to –11.3) with the 10-mg dose, and –18.4% (95% CI, –22.2 to –14.7) with the 15-mg dose ($P<0.001$ for all comparisons). The results for the efficacy estimand are provided in Figure 1A, Figures S3 and S4, Table S4, and the Supplemental Results section in the Supplementary Appendix.

PREVENTION OR DELAY OF TYPE 2 DIABETES

For the treatment-regimen estimand, onset of type 2 diabetes occurred in 10 participants (1.3%) who received tirzepatide (in 4 [1.5%] with the 5-mg dose, in 5 [2.0%] with the 10-mg dose, and in 1 [0.4%] with the 15-mg dose) and in 36 participants (13.3%) who received placebo (hazard ratio [pooled tirzepatide vs. placebo], 0.07; 95% CI, 0.0 to 0.1; $P<0.001$) (Table 2, Fig. 1C, and Fig. S5A). The results for the efficacy estimand are provided in the Supplemental Results section and in Figure S5B.

WEIGHT REDUCTION THRESHOLDS AND CHANGE IN GLYCEMIC STATUS

The percentages of participants reaching body-weight reduction thresholds of at least 5%, at least 10%, at least 15%, at least 20%, and at least 25% are shown in Figure 2A and 2B and Table 2. For the treatment-regimen estimand, among the participants who received tirzepatide, reversion to normoglycemia at week 176 was observed in 222 participants (89.9%) who received the 5-mg dose, in 239 (91.2%) who received the 10-mg dose, and in 236 (93.3%) who received the 15-mg dose, as compared with 159 participants (58.9%) who received placebo (Fig. 2C). The results for the efficacy estimand and for the analysis that used pooled data from the tirzepatide groups are provided in the Supplemental Results section and in Figure S6A, respectively.

Among the participants with body-weight reductions of at least 5% and at least 10% at week 176, reversion to normoglycemia was observed in

Table 2. Key Secondary and Prespecified Additional End Points for the Treatment-Regimen Estimand.

End Point	Tirzepatide, 5 mg (N=247)	Tirzepatide, 10 mg (N=262)	Tirzepatide, 15 mg (N=253)	Pooled Tirzepatide (N=762)	Placebo (N=270)
Key secondary end points at week 176 *†					
Least-squares mean change in body weight — % (95% CI)	−12.3 (−14.5 to −10.2)	−18.7 (−24.1 to −13.4)	−19.7 (−22.1 to −17.3)	—	−1.3 (−4.0 to 1.5)
Least-squares mean difference from placebo — percentage points (95% CI)	−11.1 (−14.4 to −7.8)	−17.5 (−23.6 to −11.3)	−18.4 (−22.2 to −14.7)	—	—
New onset type 2 diabetes — no. (%)‡	—	—	—	10 (1.3)	36 (13.3)
Hazard ratio, pooled tirzepatide vs. placebo (95% CI)‡	—	—	—	0.07 (0.0 to 0.1)	
Key secondary end point at week 193*‡§					
New onset type 2 diabetes — no. (%)	—	—	—	18 (2.4)	37 (13.7)
Hazard ratio, pooled tirzepatide vs. placebo (95% CI)	—	—	—	0.12 (0.1 to 0.2)	
Additional secondary end points at week 176¶					
Weight reduction of ≥5% — % of participants (95% CI)‖	77.7 (70.9 to 84.5)	84.6 (75.7 to 93.5)	86.9 (79.6 to 94.1)	—	29.5 (20.3 to 38.6)
Least-squares mean change in SF-36 physical-function score — points (95% CI)‡**	—	—	—	4.4 (2.3 to 6.4)	1.7 (0.0 to 3.5)
Least-squares mean difference from placebo — points (95% CI)‡	—	—	—	2.6 (0.0 to 5.3)	—

* The key secondary end points were tested under a type I error–control procedure, and all comparisons with placebo were significant at P<0.001.
† The change in body weight in the 5-mg tirzepatide group was analyzed as an additional secondary end point (not a key secondary end point) and was not controlled for type I error.
‡ Data are for pooled tirzepatide groups (5 mg, 10 mg, and 15 mg).
§ Week 193 data are from the safety analysis population.
¶ Additional secondary end points were not tested under a type I error–control procedure.
‖ 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.
** Norm-based scores were used for the 36-Item Short Form Health Survey (SF-36), version 2, acute form. 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. Possible scores on the SF-36 physical-function scale range from 19.0 to 57.6, with higher scores indicating better levels of function, better health, or better health and function.

486 (96%) and 440 (97%), respectively, of those who received tirzepatide and in 39 (83%) and 17 (81%), respectively, of those who received placebo. Among the participants with body-weight reductions of at least 15%, at least 20%, or at least 25% at week 176, reversion to normoglycemia was observed in 360 (98%), 271 (99%), and 184 (99%), respectively, of those who received tirzepatide and in 11 (100%), 6 (100%), and 4 (100%), respectively, of those who received placebo. Among the participants who did not have at least a 5% reduction in weight at week 176, reversion to normoglycemia was observed in 38 (81%) of those who received tirzepatide and in 47 (49%) of those who received placebo (Fig. 2D and S6B). Data on the mean glycated hemoglobin and fasting serum glucose levels over time are provided in Figures S7 and S8.

The results for fasting serum glucose and plasma insulin levels in a 2-hour oral glucose tolerance test are provided in Figure S9. The post hoc mediation analysis showed that 38.9% and 55.2% of the reduction in the risk of type 2 diabetes (for the treatment-regimen estimand and the efficacy estimand, respectively) during the 176-week treatment period was mediated through the percent reduction in body weight.

OFF-TREATMENT FOLLOW-UP PERIOD

At week 193 after the 17-week off-treatment period, weight regain was observed in the groups that had previously received tirzepatide (Fig. 1B and Table S5). During the 17-week off-treatment period, an additional 8 participants who received tirzepatide had adjudication-confirmed type 2 diabetes, for a total of 18 participants (2.4%) with new type 2 diabetes in the tirzepatide groups, as compared with 37 participants (13.7%) in the placebo group (hazard ratio [pooled tirzepatide vs. placebo], 0.12; 95% CI, 0.1 to 0.2; P<0.001) (Fig. 1C). In terms of glycemic status at week 193, among the participants who received tirzepatide, reversion to normoglycemia was observed in 182 (73.7%) with the 5-mg dose, in 215 (82.1%) with the 10-mg dose, and in 196 (77.5%) with the 15-mg dose; prediabetes was observed in 58 (23.5%), 39 (14.9%), and 54 (21.3%), respectively; and type 2 diabetes was observed in 7 (2.8%), 8 (3.1%), and 3 (1.2%), respectively (Fig. 2C). In comparison, 151 participants (55.9%) in the placebo group had normoglycemia, 82 (30.4%) had prediabetes, and 37 (13.7%) had type 2 diabetes.

CARDIOMETABOLIC RISK FACTORS AND HEALTH-RELATED QUALITY OF LIFE

Tirzepatide therapy resulted in improvements in waist circumference, systolic and diastolic blood pressure, and lipid levels that were sustained through week 176 (Table 2 and Figs. S10, S11, and S12). The change from baseline in the SF-36 physical-function domain score was 2.6 points higher with tirzepatide than with placebo (Table 2 and Fig. S13A). In addition, the changes from baseline in the SF-36 domain scores for mental health, role-emotional, role-physical, bodily pain, and general health perception were higher with tirzepatide than with placebo (Fig. S13B), as were the changes from baseline in the IWQOL-Lite-CT physical-function, physical, and psychosocial composite scores (Fig. S13C).

ADVERSE EVENTS AND SAFETY

Data regarding treatment discontinuation due to adverse events and the percentage of participants reporting at least one adverse event are provided in Table 3. Other than coronavirus disease 2019 (Covid-19), the most frequently reported adverse events were gastrointestinal (nausea, constipation, and diarrhea) (Table S6). These adverse events were generally mild to moderate in severity. Nausea and diarrhea were typically transient and occurred primarily during the dose-escalation period (Fig. S14).

Serious adverse events were reported by 135 participants (31 to 38 [13 to 15%] in the tirzepatide groups and by 32 [12%] of those in the placebo group) (Table 3). Among the 1032 participants, 17 (1.6%) had serious adverse events that were related to Covid-19 (Table S7). A total of 10 deaths were reported, with 7 occurring in the tirzepatide groups (2 [0.8%] with the 5-mg dose, 3 [1.1%] with the 10-mg dose, and 2 [0.8%] with the 15-mg dose) and 3 (1.1%) in the placebo group (Table 3 and Table S8). Four cases of adjudication-confirmed pancreatitis were reported (three across the tirzepatide groups and one in the placebo group) (Table 3). Cholelithiasis was reported in 5 to 9 participants (2.1 to 3.6%) across the tirzepatide groups and in 5 participants (1.9%) in the placebo group. Cholecystitis or acute cholecystitis was reported in 1 to 3 participants (0.4 to 1.1%) across the tirzepatide groups and in 1 participant (0.4%) in the placebo group (Table S9). The outcomes for additional safety variables, including liver enzyme levels, are reported in Table 3, Table S10, and Figure S15.

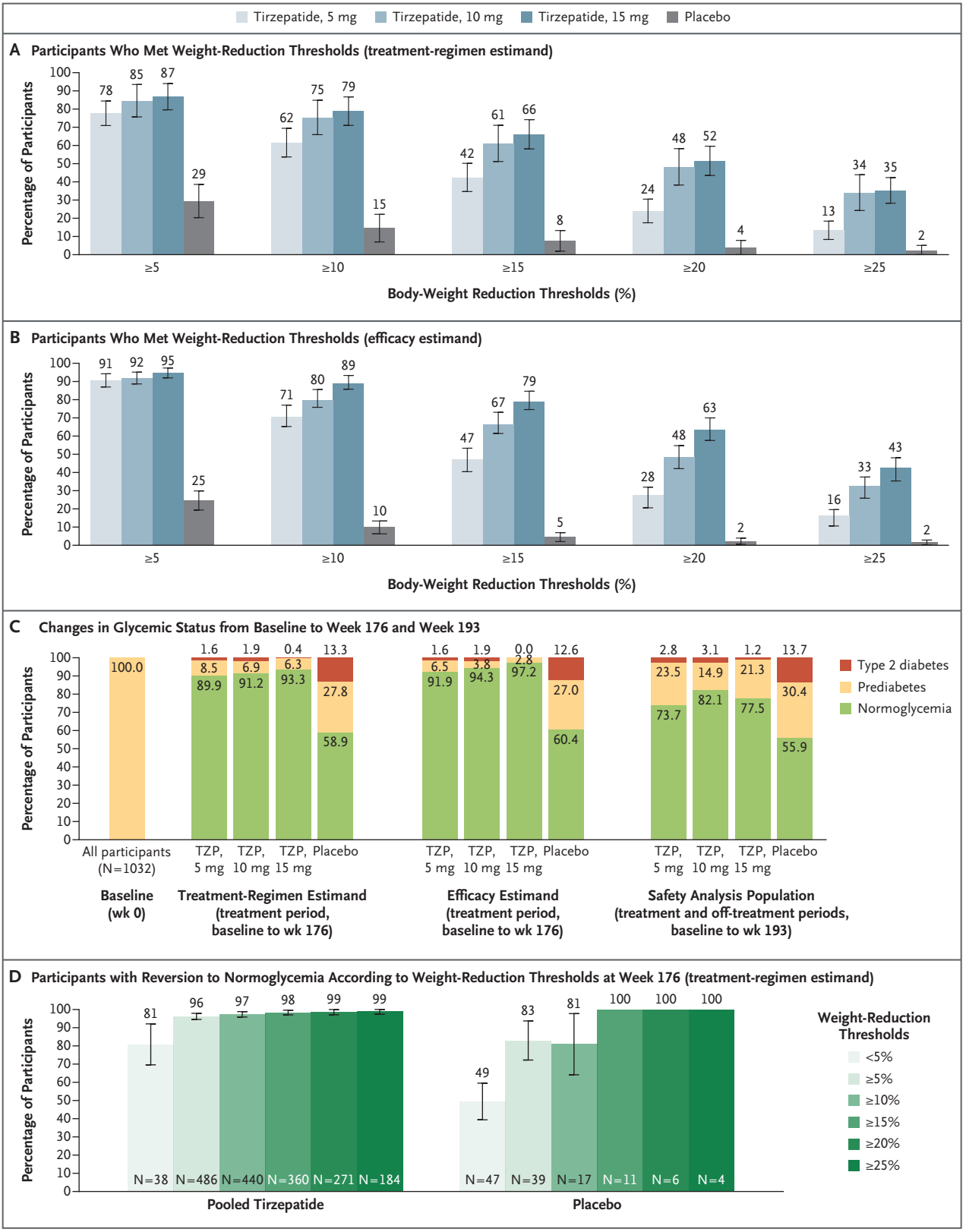


Figure 2 (facing page). Effect of Tirzepatide on Reaching Body-Weight Reduction Thresholds, Change in Glycemic Status, and Reversion to Normoglycemia.

Panels A and B show the percentages of participants who had weight reductions of at least 5%, 10%, 15%, 20%, and 25% from baseline to week 176. I bars indicate 95% confidence intervals. In Panel A, the percentage was calculated with the use of Rubin's rules by combining the percentages of participants who met the thresholds in imputed data sets. Missing values at week 176 were imputed with a mixed model for repeated measures if the missingness was due solely to coronavirus disease 2019 (Covid-19) and with multiple imputation if the missingness was not due to Covid-19. In Panel B, the percentage of participants who met weight-reduction thresholds was obtained by dividing the number of participants reaching respective thresholds at week 176 by the number of participants with a baseline value and at least one nonmissing postbaseline value. Missing values at week 176 were imputed with a mixed model for repeated measures. Panel C shows the shift in glycemic status from baseline (week 0) to the end of treatment period at week 176 and to end of the off-treatment period at week 193 (safety follow-up) with tirzepatide (TZP; 5 mg, 10 mg, and 15 mg) and placebo for the treatment-regimen estimand and efficacy estimand (data from week 193 are from the safety analysis population). Panel D shows the percentage of participants with reversion to normoglycemia according to body-weight reduction thresholds at week 176, as estimated for the treatment-regimen estimand. The subgroup of participants with a weight reduction of less than 5% comprised those who either gained body weight or lost less than 5% of body weight during the 176-week treatment period.

DISCUSSION

In this trial involving persons with obesity and prediabetes, those who were assigned to receive tirzepatide had a mean body-weight reduction of up to 20%, which was sustained over more than 3 years (176 weeks), and the risk of progression to type 2 diabetes was markedly lower than that with placebo. In absolute terms, nearly 99% (752 of 762) of the participants who received tirzepatide remained diabetes-free, an impressive result that shows a substantial benefit over more than 3 years with a pharmacologic intervention in a clinical trial.

Treatment that simultaneously targets adiposity and dysglycemia is important in persons with prediabetes, both to prevent progression to type 2 diabetes and to induce reversion to normoglycemia,[19] which potentially mitigates the risk of cardiovascular disease.[20] Nutrient-stimulated hormone–based therapies (e.g., liraglutide, semaglutide, and tirzepatide)[21,22] improve glycemic regulation through multiple mechanisms, including direct effects on glucose-dependent insulin secretion[22] and attenuation of insulin resistance through centrally mediated body weight reduction.[21,22] Observed reductions in dysglycemia in persons with prediabetes and obesity appear to track with the efficacy of these medications in terms of weight reduction. In a 3-year trial, liraglutide resulted in a body-weight reduction of 6.1%, which was associated with a hazard ratio for progression to type 2 diabetes of 0.34, with 65.9% of participants having reversion to normoglycemia.[8] Across several studies ranging from 1 to 5 years in duration, semaglutide resulted in a mean weight reduction of 9.7 to 15.2%, which was associated with a hazard ratio for developing type 2 diabetes of 0.27, with a number needed to treat to prevent one case of diabetes of 18.5; among those with prediabetes, 69.5 to 81% had reversion to normoglycemia.[9,23-25] In the current 3-year study of tirzepatide, a mean body-weight reduction of up to 20% was accompanied by a hazard ratio for progression to type 2 diabetes of 0.07, with a number needed to treat to prevent one case of diabetes of 9, and 92% of the participants had reversion to normoglycemia, findings that support the hypothesis that greater weight reduction yields greater metabolic benefits.

To understand the contribution of weight reduction more completely, we conducted a post hoc mediation analysis, the results of which suggested that up to half the observed effect in the delay to onset of type 2 diabetes with tirzepatide was mediated by medication-induced weight reduction. These results highlight the sustained metabolic health benefits that may be attained with antiobesity medications that combine proximal effects on islet function with long-term weight reduction that increases insulin sensitivity and reduces beta-cell workload in persons with prediabetes and obesity.

The durability of the glycemic effects with tirzepatide throughout the treatment period in the current trial, with a resulting glycated hemoglobin level of 5.1% (with the 15-mg dose) at the 176-week time point, is noteworthy, given the progressive nature of prediabetes. In the Diabetes Prevention Program trial involving persons with prediabetes, lifestyle intervention and metformin

Table 3. Adverse Events and Safety.

Event*	Tirzepatide, 5 mg (N=247)	Tirzepatide, 10 mg (N=262)	Tirzepatide, 15 mg (N=253)	Placebo (N=270)
Any adverse events during treatment period — no. (%)	210 (85.0)	230 (87.8)	219 (86.6)	223 (82.6)
Serious adverse events — no. (%)	31 (12.6)	38 (14.5)	34 (13.4)	32 (11.9)
Deaths — no. (%)†	2 (0.8)	3 (1.1)	2 (0.8)	3 (1.1)
Adverse events leading to discontinuation of tirzepatide or placebo — no. (%)‡				
Any event	18 (7.3)	25 (9.5)	31 (12.3)	16 (5.9)
Nausea	2 (0.8)	2 (0.8)	6 (2.4)	1 (0.4)
Diarrhea	1 (0.4)	3 (1.1)	4 (1.6)	0
Constipation	1 (0.4)	2 (0.8)	1 (0.4)	0
Adverse events of special interest — no. (%)‡				
Hepatic events§	1 (0.4)	1 (0.4)	1 (0.4)	0
Cancer	8 (3.2)	4 (1.5)	6 (2.4)	4 (1.5)
Pancreatitis, adjudication-confirmed	2 (0.8)	1 (0.4)	0	1 (0.4)
MACE, adjudication-confirmed¶	2 (0.8)	7 (2.7)	2 (0.8)	7 (2.6)
Cardiac disorders‖	3 (1.2)	3 (1.1)	3 (1.2)	1 (0.4)
Thyroid malignant condition or C-cell hyperplasia**	0	0	2 (0.8)	1 (0.4)
Medullary thyroid carcinoma	0	0	0	0
Gastrointestinal event§	6 (2.4)	15 (5.7)	6 (2.4)	5 (1.9)
Gallbladder disease§	3 (1.2)	10 (3.8)	9 (3.6)	2 (0.7)
Renal event§	2 (0.8)	1 (0.4)	2 (0.8)	0
Major depressive disorder or suicidal ideation§	0	1 (0.4)	0	0
Hypersensitivity††	0	2 (0.8)	1 (0.4)	0
Hypoglycemia with a blood glucose level <54 mg/dl	8 (3.2)	6 (2.3)	5 (2.0)	0

* Safety end points were analyzed with data from all the participants with prediabetes at baseline who underwent randomization and took at least one dose of tirzepatide or placebo. To convert the value for glucose to millimoles per liter, multiply by 0.05551. Covid-19 denotes coronavirus disease 2019.
† 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 27.0, preferred terms.
§ Events were classified as severe or serious adverse events.
¶ Four deaths (reported causes: multiple injuries in one, Covid-19 in one, acute heart failure in one, and cerebrovascular accident in one) were adjudicated as having an undetermined cause and were documented as major adverse cardiovascular events (MACE).
‖ Events were classified as severe or serious supraventricular arrhythmias and cardiac conduction disorders.
** The reported thyroid malignant conditions were papillary cancer.
†† 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 each superior to placebo in reducing the risk of type 2 diabetes; however, glycemic measures continued to rise in all trial groups over 4 years.[10,26] In the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial involving persons with cardiovascular disease and obesity, despite reducing the risk of developing type 2 diabetes and maintaining weight reduction, treatment with semaglutide did not slow progression of dysglycemia over time.[9,10] Collectively, these and other data[8,24,25,27] show that persons with prediabetes have a progressive decline in beta-cell function over time, irrespective of active treatment or placebo. Although direct comparisons cannot be made among the trials owing to the different populations and methods,

the current trial showed a sustained effect of tirzepatide on glycemia over 3 years of treatment. In addition, the tirzepatide-treated participants who lost less than 5% of body weight still garnered glycemic benefit, a finding that suggests possible direct effects of treatment, even in the absence of clinically significant weight reduction. Tirzepatide has previously been shown to improve markers of beta-cell function and insulin sensitivity in persons with type 2 diabetes.[28] Furthermore, recent data suggest long-acting GIP-receptor agonism may improve insulin sensitivity independent of weight reduction.[29] The placebo group in the current trial did not show the expected worsening in glycemic measures during the continued lifestyle intervention. Differences in population, lifestyle intervention, and participant attrition, as compared with previous trials, may have been contributing factors.

The maintenance of weight reduction and durability of glycemic benefit began to dissipate during the off-treatment follow-up period, which was seen in other trials[8,25,30-32] and was therefore expected. An estimated mean weight regain of 7% was observed over the 17-week off-treatment period, and reversion from normoglycemia to prediabetes was observed in 15.5% of the participants who received tirzepatide; an additional 1.2% of the participants received a diagnosis of type 2 diabetes. Collectively, these findings support the concept that to maintain weight reduction and glycemic improvements, therapies would need to be continued long-term, as is done for other chronic diseases.

Cardiometabolic factors improved throughout this 3-year trial, including blood pressure, lipid levels, and alanine aminotransferase and aspartate aminotransferase levels. These findings are consistent with the results of shorter trials of tirzepatide[13,14,31] and seem to be meaningful for persons with prediabetes who are at risk of cardiovascular disease even in the absence of progression to diabetes.[33] Quality of life also improved to a greater extent in tirzepatide-treated participants than in those who received placebo, with improvements in all domains of the SF-36 and the IWQOL-Lite-CT, most notably physical function. These findings reinforce that effective, long-term management of obesity can affect quality of life beyond metabolic benefit.[10,34-37]

This trial also collected more than 3 years of data on safety and adverse events with tirzepatide in participants with obesity. The incidence of gastrointestinal adverse events with tirzepatide use decreased over the duration of the trial, a finding that supports the safety of long-term use. Reports of vomiting with tirzepatide were rare, whereas mild constipation was more frequently reported, especially in the group that received the 5-mg dose of tirzepatide. The frequency of adverse events was similar to that seen in previous trials with nutrient-stimulated hormone–based therapies,[21,22] and there were no unexpected serious adverse events. As with other treatments for obesity that resulted in significant weight reduction,[38-40] the incidence of gallbladder-related events was higher among the participants who received tirzepatide than among those who received placebo.[13]

The strengths of the current trial are its long duration (193 weeks [3.7 years]), which provides longer-term data on safety and substantial efficacy data with tirzepatide. The sample size of participants with obesity and prediabetes was relatively large, and more stringent criteria were used for prediabetes (at least two abnormal findings among three measures [the fasting glucose level, the glycated hemoglobin level, and the glucose level on a 2-hour oral glucose tolerance test] rather than one) to capture baseline risk. Application of the ADA diagnostic criteria for type 2 diabetes and adjudication of the potential onset of type 2 diabetes enabled more rigorous outcome assessment than detecting diabetes on the basis of a single glycated hemoglobin value.

A limitation of the trial was participant attrition with respect to both discontinuation of the trial drug or placebo and withdrawal from the trial (especially in the placebo group). The percentage of participants who withdrew from the trial was similar to that in a previous trial investigating weight and glycemic outcomes over a 3-year period,[8] lower than that in a previous trial investigating treatment for obesity over a 4-year period,[41] and higher than that in a recent trial investigating cardiovascular outcomes in persons with obesity,[42] in which participants were not recruited with the intent for weight reduction. The current trial design included a 72-week primary phase, which may have influenced attrition.

In this randomized, controlled trial involving persons with obesity and prediabetes, tirzepatide therapy resulted in sustained weight reduction that was accompanied by a markedly lower risk

of progression to type 2 diabetes than that with placebo.

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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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