Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Eligibility criteria

Inclusion and exclusion criteria
Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, were not permitted.

Inclusion criteria
Participants were eligible to be included in the study only if they met all of the following criteria:

Type of participant and disease characteristics

- Have a body mass index (BMI) of:
    - ≥30 kg/m^2 or
    - ≥27 kg/m^2 and previously diagnosed with at least 1 of the following weight-related complications:
        - Hypertension: treated or with systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg
        - Dyslipidaemia: treated or with low-density lipoprotein (LDL) ≥160 mg/dL (4.1 mmol/L) or triglycerides ≥150 mg/dL (1.7 mmol/L), or high-density lipoprotein (HDL) <40 mg/dL (1.0 mmol/L) for men or HDL <50 mg/dL (1.3 mmol/L) for women
        - Obstructive sleep apnoea
        - Cardiovascular disease (for example, ischemic cardiovascular disease, New York Heart Association [NYHA] Functional Classification Class I-III heart failure)
- Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight
- In the investigator's opinion, are well-motivated, capable, and willing to:
    - learn how to self-inject study drug, as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug)
    - inject study drug (or receive an injection from a trained individual if visually impaired or with physical limitations)
    - follow study procedures for the duration of the study, including, but not limited to, following lifestyle advice (for example, dietary restrictions, exercise plan), maintaining a study diary, and completing required questionnaires

Participant characteristics

- Are at least 18 years of age and age of majority per local laws and regulations
    - Male participants:
        - Male participants with partners of childbearing potential should be willing to use reliable contraceptive methods throughout the study and for 5 half-lives of study drug plus 90 days, corresponding to 4 months after the last injection
    - Female participants:
        - Female participants not of childbearing potential may participate and include those who are:
            - infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation) or congenital anomaly (such as Mullerian agenesis)

            or

            - Postmenopausal – defined as either:
                - A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause AND a follicle stimulating hormone (FSH) >40 mIU/mL; women in this category must test negative in pregnancy test prior to study entry

                or

                - A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea

                or

                - A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy

        - Female participants of childbearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must
            - test negative for pregnancy at Visit 1 based on a serum pregnancy test
            - if sexually active, agree to use 2 forms of effective contraception, where at least 1 form is highly effective for the duration of the trial plus 30 days, corresponding to 2 months after the last injection, and
            - not be breastfeeding
- ***Note:*** Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed consent

- Capable of giving signed informed consent to participate in this study in accordance with local regulations and the Ethical Review Board governing the study site

Exclusion criteria

Participants were excluded from study enrollment if they meet any of the following criteria:

Medical conditions

Diabetes-related

- Have type 1 or type 2 diabetes, history of ketoacidosis, or hyperosmolar state/coma
- Have at least 1 laboratory value suggestive of diabetes during screening, including 1 or more of: HbA_{1c} ≥6.5% (≥48 mmol/mol), fasting glucose ≥126 mg/dL (≥7.0 mmol/L), and random glucose ≥200 mg/dL (≥11.1 mmol/L)

Obesity-related

- Have a self-reported change in body weight >5 kg within 3 months prior to screening
- Have a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty if performed >1 year prior to screening)
- Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months prior to screening (for example, mucosal ablation, gastric artery embolization, intragastric balloon, or duodenal-jejunal endoluminal liner)

Other medical

- Have renal impairment measured as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory during screening
- Have a known clinically significant gastric emptying abnormality (for example, severe gastroparesis or gastric outlet obstruction) or chronically take drugs that directly affect gastrointestinal motility
- Have a history of chronic or acute pancreatitis
- Have thyroid-stimulating hormone (TSH) outside of the range of 0.4 to 6.0 mIU/L at the screening visit
  Note: Participants receiving treatment for hypothyroidism may be included, provided their thyroid hormone replacement dose has been stable for at least 3 months and their TSH at screening falls within the range indicated above.
  Note: Participants with a history of subclinical hypothyroidism but a TSH at screening within the range indicated above, may be included if, in the investigator's opinion, the patient is unlikely to require initiation of thyroid hormone replacement during the course of the study.
- Have obesity induced by other endocrinologic disorders (for example, Cushing syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, Melanocortin 4 Receptor deficiency or Prader Willi Syndrome)
- Have a history of significant active or unstable major depressive disorder (MDD) or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years
  Note: Participants with MDD or generalized anxiety disorder whose disease state is considered stable for the past 2 years and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.
- Have a lifetime history of suicide attempt
- Have a Patient Health Questionnaire-9 (PHQ-9) score of 15 or more on or before Visit 2
- On the Columbia-Suicide Severity Rating Scale (C-SSRS) on or before Visit 2:
    - a "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS

or

- a "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS

or

- a "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C-SSRS

and

- the ideation or behavior occurred within the past month

- Have uncontrolled hypertension (systolic blood pressure above or equal to 160 mmHg and/or diastolic blood pressure above or equal to 100 mmHg)
- Have any of the following cardiovascular conditions within 3 months prior to Visit 2: acute myocardial infarction, cerebrovascular accident (stroke), unstable angina, or hospitalization due to congestive heart failure (CHF)
- Have NYHA Functional Classification Class IV CHF
- Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease (NAFLD), or any of the following, as determined by the central laboratory during screening:
  - alanine aminotransferase (ALT) level >3.0X upper limit of normal (ULN) for the reference range
  - alkaline phosphatase (ALP) level >1.5X ULN for the reference range, or
  - total bilirubin (TBL) level >1.2X ULN for the reference range (except for cases of known Gilbert's Syndrome)

  Note: Participants with NAFLD <u>are eligible</u> to participate in this trial if their ALT level is ≤3.0X ULN for the reference range.
- Have a serum calcitonin level (at Visit 1) of:
  - ≥20 ng/L, if eGFR ≥60 mL/min/1.73 m^2
  - ≥35 ng/L, if eGFR <60 mL/min/1.73 m^2
- Have a family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia (MEN) syndrome type 2
- Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years
- Have any other condition not listed in this section (for example, hypersensitivity or intolerance) that is a contraindication to glucagon-like peptide-1 (GLP-1) receptor agonists
- Have a history of any other condition (such as known drug or alcohol abuse, diagnosed eating disorder, or other psychiatric disorder) that, in the opinion of the investigator, may preclude the participant from following and completing the protocol
- Have history of use of marijuana or tetrahydrocannabinol (THC)-containing products within 3 months of enrollment or unwillingness to abstain from marijuana or THC-containing products use during the trial

  Note: If a participant has used cannabidiol oil during the past 3 months but agrees to refrain from use for the duration of the study, the participant can be enrolled.
- Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant
- Have any hematological condition that may interfere with HbA_{1c} measurement (for example, hemolytic anemias, sickle cell disease)

Prior/concomitant therapy

- Are receiving or have received within 3 months prior to screening chronic (>2 weeks or >14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) or have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that has required (within the last 3 months) or is likely to require, in the opinion of the investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) during the course of the study
- Have current or history of (within 3 months prior to Visit 2) treatment with medications that may cause significant weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotics, and mood stabilizers

  Note: Selective serotonin reuptake inhibitors other than paroxetine are permitted.

- Have taken, within 3 months prior to Visit 2, medications (prescribed or over-the-counter) or alternative remedies that promote weight loss
  Note: Use of metformin or any other glucose-lowering medication, whether prescribed for polycystic ovary syndrome (PCOS) or diabetes prevention, is not permitted.
- Have started implantable or injectable contraceptives (such as Depo Provera®) within 18 months prior to screening

Prior/concurrent clinical study experience

- Are currently enrolled in any other clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study
- Within the last 30 days, have participated in a clinical study and received treatment, whether active or placebo. If the study involved an IP, 5 half-lives or 30 days, whichever is longer, should have passed
- Have previously completed or withdrawn from this study or any other study investigating tirzepatide after receiving at least 1 dose of IP

Other exclusions

- Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
- Are Eli Lilly and Company employees

eAppendix 2. Concomitant medications

Participants were permitted to use concomitant medications that they required during the study, except certain excluded medications that may have interfered with the assessment of efficacy and safety characteristics of the study drugs. Participants developing diabetes during the study were allowed to initiate medication for glucose control, with the exception of dipeptidyl-peptidase-4 (DPP 4) inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists. Initiation of metformin for the treatment of diabetes was permitted, but metformin should not have been initiated during the study for the treatment of other metabolic conditions.

eAppendix 3. Statistical analyses

Treatment regimen estimand

The treatment regimen estimand reflects efficacy regardless of the adherence to treatment and was conducted on the full analysis set using an analysis of covariance for continuous outcomes and logistic regression for binary outcomes. Both models included terms of treatment group, stratification factors (country, sex, tirzepatide maximum tolerated dose [MTD] at randomization, and percent weight reduction at randomization [except for analyses related to weight]), and corresponding outcome value at randomization (and outcome value at week 0 if measured since week 0) as covariates. Missing data were imputed using a hybrid approach; thus, this estimand is also referred to as "hybrid" estimand in the study protocol (Supplement 1). Missing data solely due to a pandemic or natural disaster were considered missing at random and imputed by predictions using observed data of the outcome from the same treatment group through a mixed model for repeated measures (MMRM) analysis model adjusting for baseline and stratification factors. Missing data due to all other intercurrent events were imputed based on retrieved dropouts in the same treatment group, defined as observed outcome measurements from participants in the same treatment group who had their efficacy measure at week 88 assessed after early discontinuation of study drug. Analysis was conducted with multiple imputations of missing data. A total of 100 imputed datasets were generated. There were 25 participants in the tirzepatide group and 46 participants in the placebo group with missing weight data at the primary end point.

Efficacy estimand

The efficacy estimand reflects efficacy in participants who were adherent to study drug and was conducted on the efficacy analysis set. For continuous outcomes, a MMRM was used. The independent variables were treatment group, visit, treatment-by-visit interaction, stratification factors (country, sex, tirzepatide MTD at randomization, and percent weight reduction at randomization [except for analyses related to weight]) as fixed effects, and corresponding outcome value at randomization (and outcome value at week 0 if measured since week 0) as

covariate(s). For categorical outcomes, a logistic regression model was used that included the following covariates: treatment group, stratification factors, and corresponding outcome value at randomization (and outcome value at week 0 if measured since week 0), where missing end points were dichotomized after they were predicted from the continuous end point mixed model for repeated measures analysis explained above. There were 35 participants in the tirzepatide group and 62 participants in the placebo group with missing weight data at the primary end point.

	Treatment regimen estimand	**Efficacy estimand**
Treatment condition of interest	Tirzepatide MTD versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, regardless of study drug adherence	Tirzepatide MTD versus placebo, as an adjunct to a reduced-calorie diet and increased physical activity, excluding data after discontinuation of study drug
Population to which the results apply	Adult participants with obesity, or with overweight and at least 1 weight-related complication irrespective of the compliance to planned course of treatment.	Adult participants with obesity, or with overweight and at least 1 weight-related complication, if they stay on the treatment planned.
Intercurrent events (ICEs)	The ICEs leading to treatment discontinuation solely due to COVID-19 were addressed by the treatment condition of interest attribute and handled by the *hypothetical strategy.* The ICEs leading to treatment discontinuation for any other reasons were addressed by the treatment condition of interest attribute and handled by *treatment policy strategy* as described in the International Council for Harmonisation (ICH) E9 (R1)	The ICEs leading to treatment discontinuation for any reason were addressed by the treatment condition of interest attribute and handled by the *hypothetical strategy* as described in the International Council for Harmonisation (ICH) E9 (R1)

Type 1 error rate control strategy for primary and key secondary efficacy objectives

Both treatment regimen estimand and efficacy estimand were used to assess the primary and key secondary objectives. As they are intended for different purposes, no multiplicity adjustments were made for conducting separate analysis relative to the two estimands. In addition, no multiplicity adjustments were made for evaluating additional secondary and exploratory objectives and safety assessments. The alternative hypothesis for the primary objective is as follows:

H1(wgt_pchg_wk36): once-weekly (QW) tirzepatide MTD is superior to placebo for percent change from randomization (week 36) in body weight at 88 weeks.

The alternative hypotheses for the key secondary objectives controlling for type 1 error rate are the following:

H2(wgt_chg_wk36): QW tirzepatide MTD is superior to placebo for change from randomization (week 36) in body weight (kg) at 88 weeks.

H3(wc_chg_wk36): QW tirzepatide MTD is superior to placebo for change from randomization (week 36) in waist circumference (cm) at 88 weeks.

H4(maintain80): QW tirzepatide MTD is superior to placebo for percentage of participants who maintain ≥80% of the body weight lost during the open-label lead-in period at 88 weeks.

H5(return95): QW tirzepatide MTD is superior to placebo for delaying time (in weeks), during the 52-week double-blind treatment period, to first occurrence of participants returning to >95% Visit 2 (week 0) body weight among participants who lost ≥5% body weight during the open-label lead-in period.

H6(wgt5_wk0): QW tirzepatide MTD is superior to placebo for percentage of participants who achieve ≥5% body weight reduction from Visit 2 (week 0) at 88 weeks.

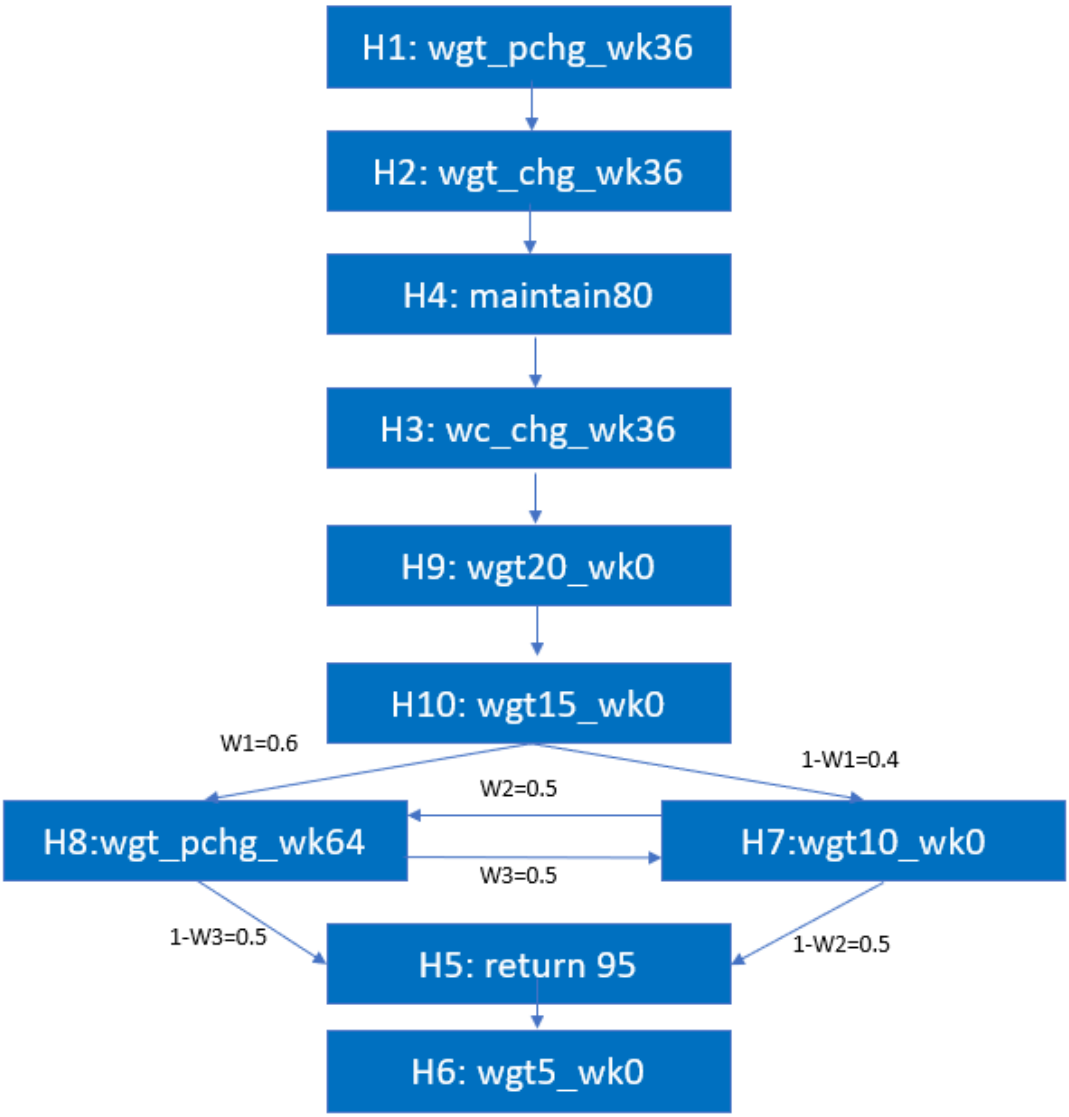
H7(wgt10_wk0): QW tirzepatide MTD is superior to placebo for percentage of participants who achieve ≥10% body weight reduction from Visit 2 (week 0) at 88 weeks.

H8(wgt_pchg_wk64): QW tirzepatide MTD is superior to placebo for percent change from randomization (week 36) in body weight at 64 weeks.

H9(wgt15_wk0): QW tirzepatide MTD is superior to placebo for percentage of participants who achieve ≥15% body weight reduction from Visit 2 (week 0) at 88 weeks.

H10(wgt20_wk0): QW tirzepatide MTD is superior to placebo for percentage of participants who achieve ≥20% body weight reduction from Visit 2 (week 0) at 88 weeks.

***Figure*: Type 1 error control strategy for primary and key secondary efficacy end points**



eTable 1. Additional demographics and clinical characteristics (randomized population)

	Total (N=670)	Tirzepatide MTD (N=335)	Placebo (N=335)
Country, No. (%)			
Argentina	111 (16.6)	55 (16.4)	56 (16.7)
Brazil	89 (13.3)	43 (12.8)	46 (13.7)
Taiwan	38 (5.7)	21 (6.3)	17 (5.1)
United States	432 (64.5)	216 (64.5)	216 (64.5)
Number of complications, No. (%)[a]			
None	205 (30.6)	98 (29.3)	107 (31.9)
1	195 (29.1)	99 (29.6)	96 (28.7)
2	112 (16.7)	59 (17.6)	53 (15.8)
3	76 (11.3)	39 (11.6)	37 (11.0)
4	52 (7.8)	26 (7.8)	26 (7.8)
≥5	30 (4.5)	14 (4.2)	16 (4.8)

Abbreviations: MTD, maximum tolerated dose (10 or 15 mg).

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

eTable 2. Changes during the tirzepatide lead-in treatment period (randomized population)

Characteristics	Mean change (SD) from week 0 to 36		
	Total (N=670)	Tirzepatide MTD (N=335)	Placebo (N=335)
Body weight, %	-20.9 (7.3)	-21.1 (7.0)	-20.8 (7.6)
BMI	-8.0 (3.0)	-8.0 (2.8)	-7.9 (3.1)
Waist circumference, cm	-17.8 (8.5)	-18.2 (8.3)	-17.4 (8.7)
Blood pressure, mmHg			
Systolic	-11.2 (12.5)	-11.8 (12.4)	-10.5 (12.6)
Diastolic	-5.1 (9.1)	-5.4 (9.1)	-4.9 (9.1)
Pulse rate, beats/min	5.0 (9.0)	5.2 (9.1)	4.8 (9.0)
Hemoglobin A_{1c}, %	-0.5 (0.3)	-0.5 (0.3)	-0.5 (0.3)
Fasting glucose, mg/dL	-9.8 (10.3)	-10.2 (10.7)	-9.3 (9.9)
Fasting insulin, %	-35.2 (42.2)	-37.3 (39.2)	-33.1 (44.9)
Lipid levels, %			
Total cholesterol	-5.2 (16.5)	-5.6 (16.3)	-4.8 (16.7)
Non-HDL-C	-4.7 (22.9)	-5.2 (22.5)	-4.2 (23.3)
HDL-C	-3.7 (15.4)	-3.6 (15.8)	-3.7 (15.1)
LDL-C	2.0 (34.9)	2.5 (40.9)	1.4 (27.6)
VLDL-C	-21.6 (30.0)	-22.4 (29.0)	-20.8 (31.1)
Triglycerides	-22.1 (29.4)	-23.1 (27.8)	-21.2 (31.0)
Free fatty acids	10.2 (125.3)	11.1 (158.3)	9.3 (79.8)
eGFR, ml/min/1.73 m^2	-0.7 (10.5)	-1.1 (10.4)	-0.3 (10.7)
SF-36 v2 scores[a]			
Physical functioning domain	5.7 (7.4)	5.9 (7.4)	5.5 (7.5)
Role-physical domain	4.0 (7.4)	4.5 (7.0)	3.5 (7.7)
Role-emotional domain	2.7 (8.8)	2.3 (8.6)	3.2 (9.0)
Mental health domain	2.1 (7.7)	1.8 (7.1)	2.5 (8.3)
IWQOL-Lite-CT physical function composite score[b]	22.1 (22.6)	22.0 (22.2)	22.2 (23.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MTD, maximum tolerated dose (10 or 15 mg); VLDL-C, very low-density lipoprotein cholesterol.

SI conversions: To convert glucose to millimoles per liter, multiply by 0.055.

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

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

eTable 3. Primary and secondary end points (efficacy estimand)[a]

	Estimate (95% CI)			
	Tirzepatide MTD (N=335)	**Placebo (N=335)**	**Absolute difference[b] (95% CI)**	**P value**
Primary end point[c]				
Percent change in body weight (week 36 to 88), %	-6.7 (-7.7 to -5.7)	14.8 (13.8 to 15.8)	-21.4 (-22.9 to -20.0)	<.001
Key secondary end points[c,d]				
Change in body weight (week 36 to 88), kg	-5.7 (-6.5 to -4.9)	11.9 (11.1 to 12.7)	-17.6 (-18.8 to -16.4)	<.001
Change in waist circumference (week 36 to 88), cm	-4.6 (-5.4 to -3.8)	8.3 (7.4 to 9.2)	-12.9 (-14.1 to -11.7)	<.001
Participants maintaining ≥80% of body weight lost (week 88), No. (%)	310 (93.4)	44 (13.5)	95.9 (54.7 to 168.1)	<.001
Participants achieving body weight reduction (week 0 to 88), No. (%)				
≥5%	327 (98.5)	227 (69.0)	47.3 (18.3 to 122.0)	<.001
≥10%	312 (94.0)	146 (44.4)	71.5 (34.5 to 148.4)	<.001
≥15%	289 (87.1)	79 (24.0)	80.0 (42.1 to 152.1)	<.001
≥20%	241 (72.6)	38 (11.6)	140.8 (66.1 to 300.3)	<.001
Percent change in body weight (week 36 to 64), %	-6.0 (-6.7 to -5.3)	9.9 (9.2 to 10.6)	-15.9 (-16.9 to -14.9)	<.001
Additional secondary end points[e] (week 36 to 88)				
Change in BMI	-2.1 (-2.4 to -1.8)	4.3 (4.0 to 4.6)	-6.4 (-6.8 to -6.0)	<.001
Change in hemoglobin A_{1c}, %	-0.08 (-0.11 to -0.05)	0.25 (0.22 to 0.28)	-0.33 (-0.38 to -0.28)	<.001
Change in fasting glucose, mg/dL	-0.9 (-1.9 to 0.1)	7.7 (6.6 to 8.8)	-8.6 (-10.1 to -7.2)	<.001
Percent change in fasting insulin, %[f]	-15.4 (-21.0 to -9.8)	23.3 (14.7 to 31.9)	-31.4 (-37.7 to -24.4)	<.001
Percent change in lipid levels, %[f]				
Total cholesterol	2.3 (0.6 to 4.0)	8.3 (6.5 to 10.2)	-5.5 (-7.8 to -3.3)	<.001
Non-HDL-C	-4.0 (-6.1 to -1.9)	5.5 (3.1 to 7.9)	-9.0 (-11.9 to -6.1)	<.001
HDL-C	18.3 (16.2 to 20.4)	14.6 (12.5 to 16.7)	3.2 (0.6 to 5.8)	.014
LDL-C	-3.4 (-5.8 to -1.0)	3.4 (0.7 to 6.1)	-6.6 (-9.9 to -3.2)	<.001
VLDL-C	-7.8 (-11.3 to -4.3)	14.7 (10.2 to 19.3)	-19.7 (-24.0 to -15.1)	<.001
Triglycerides	-8.2 (-11.8 to -4.7)	15.6 (10.9 to 20.3)	-20.6 (-24.9 to -16.0)	<.001
Free fatty acids	-13.4 (-18.4 to -8.4)	-2.9 (-8.7 to 2.9)	-10.8 (-17.9 to -3.0)	.008

	Estimate (95% CI)			
	Tirzepatide MTD (N=335)	**Placebo (N=335)**	**Absolute difference[b] (95% CI)**	**P value**
Change in blood pressure, mmHg				
Systolic	2.1 (0.9 to 3.3)	8.4 (7.2 to 9.7)	-6.4 (-8.1 to -4.6)	<.001
Diastolic	-0.4 (-1.2 to 0.4)	3.2 (2.3 to 4.1)	-3.6 (-4.8 to -2.4)	<.001
Change in SF-36 v2 scores[g]				
Physical functioning domain	0.8 (0.2 to 1.4)	-1.8 (-2.4 to -1.2)	2.6 (1.8 to 3.5)	<.001
Role-physical domain	0.1 (-0.5 to 0.7)	-0.9 (-1.5 to -0.3)	1.1 (0.2 to 1.9)	.015
Role-emotional domain	0.6 (-0.2 to 1.4)	-1.2 (-2.0 to -0.4)	1.9 (0.8 to 3.0)	.001
Mental health domain	0.3 (-0.4 to 1.0)	-2.1 (-2.9 to -1.3)	2.4 (1.4 to 3.5)	<.001
Change in IWQOL-Lite-CT physical function composite score[g]	4.3 (2.5 to 6.1)	-5.1 (-6.9 to -3.3)	9.4 (6.9 to 12.0)	<.001
Additional secondary end points[e] (week 0 to 88)				
Change in body weight, kg	-27.6 (-28.4 to -26.8)	-10.0 (-10.8 to -9.2)	-17.6 (-18.8 to -16.4)	<.001
Percent change in body weight, %	-26.0 (-26.8 to -25.2)	-9.5 (-10.3 to -8.7)	-16.4 (-17.5 to -15.4)	<.001
Change in BMI	-10.0 (-10.3 to -9.7)	-3.6 (-3.9 to -3.3)	-6.4 (-6.8 to -6.0)	<.001
Change in waist circumference, cm	-22.8 (-23.8 to -21.8)	-9.1 (-10.1 to -8.1)	-13.6 (-15.1 to -12.2)	<.001
Change in hemoglobin A_{1c}, %	-0.57 (-0.60 to -0.54)	-0.22 (-0.26 to -0.18)	-0.34 (-0.39 to -0.29)	<.001
Change in fasting glucose, mg/dL	-10.6 (-11.6 to -9.6)	-1.7 (-2.8 to -0.6)	-8.9 (-10.4 to -7.4)	<.001
Percent change in fasting insulin, %[f]	-54.1 (-57.2 to -51.0)	-29.8 (-34.7 to -24.9)	-34.6 (-40.6 to -27.9)	<.001
Percent change in lipid levels, %[f]				
Total cholesterol	-5.0 (-6.6 to -3.4)	2.2 (0.4 to 4.0)	-7.0 (-9.3 to -4.7)	<.001
Non-HDL-C	-11.5 (-13.5 to -9.5)	-0.8 (-3.2 to 1.6)	-10.8 (-13.7 to -7.8)	<.001
HDL-C	12.3 (10.2 to 14.4)	9.4 (7.3 to 11.5)	2.6 (-0.1 to 5.4)	.064
LDL-C	-5.2 (-7.6 to -2.8)	2.6 (-0.1 to 5.3)	-7.6 (-10.9 to -4.2)	<.001
VLDL-C	-32.6 (-35.3 to -29.9)	-15.6 (-19.2 to -12.0)	-20.1 (-24.7 to -15.3)	<.001
Triglycerides	-33.3 (-36.0 to -30.6)	-15.3 (-18.9 to -11.7)	-21.2 (-25.8 to -16.4)	<.001
Free fatty acids	-20.4 (-25.0 to -15.8)	-9.7 (-15.2 to -4.2)	-11.8 (-19.0 to -4.1)	.004
Change in blood pressure, mmHg				
Systolic	-9.3 (-10.5 to -8.1)	-2.4 (-3.7 to -1.1)	-6.9 (-8.7 to -5.1)	<.001
Diastolic	-5.5 (-6.4 to -4.6)	-1.7 (-2.6 to -0.8)	-3.8 (-5.1 to -2.6)	<.001

	Estimate (95% CI)			
	Tirzepatide MTD (N=335)	**Placebo (N=335)**	**Absolute difference[b] (95% CI)**	**P value**
Change in SF-36 v2 scores[g]				
Physical functioning domain	6.4 (5.7 to 7.1)	3.7 (3.0 to 4.4)	2.8 (1.8 to 3.7)	<.001
Role-physical domain	4.2 (3.6 to 4.8)	2.6 (2.0 to 3.2)	1.7 (0.8 to 2.6)	<.001
Role-emotional domain	3.2 (2.4 to 4.0)	1.3 (0.5 to 2.1)	1.9 (0.8 to 3.0)	<.001
Mental health domain	2.4 (1.6 to 3.2)	0.2 (-0.6 to 1.0)	2.2 (1.1 to 3.3)	<.001
Change in IWQOL-Lite-CT physical function composite score[g]	26.0 (24.1 to 27.9)	16.7 (14.7 to 18.7)	9.3 (6.6 to 12.0)	<.001
Exploratory end point[e] (week 0 to 88)				
Participants achieving ≥25% body weight reduction, No. (%)	188 (56.6)	13 (4.0)	172.2 (71.0 to 417.6)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite-Clinical Trials; LDL-C, low-density lipoprotein cholesterol; MTD, maximum tolerated dose (10 or 15 mg); SF-36 v2, Short Form-36 Version 2 Health Survey; VLDL-C, very low-density lipoprotein cholesterol.

SI conversions: To convert glucose to millimoles per liter, multiply by 0.055.

[a]All parameters are expressed as least squares mean unless stated otherwise. Efficacy estimand (corresponding analyses used the efficacy analysis set) evaluated treatment effects using on-treatment data prior to discontinuation of study drug. Mixed model for repeated measures was used (unless stated otherwise) with treatment, visit, treatment × visit interaction, and stratification factors (country, sex, tirzepatide maximum tolerated dose at randomization, and percent weight reduction at randomization [except for analyses related to weight]) as fixed effects, and corresponding outcome value at randomization (and outcome value at week 0 if measured since week 0; or outcome value at week 0 if measured since week 0 for laboratory measures and waist circumference) as covariate(s). For categorical outcomes, a logistic regression model was used with treatment, stratification factors, and corresponding outcome value at randomization (and outcome value at week 0 if measured since week 0) as covariates.

[b]Data are absolute differences between mean changes unless stated otherwise. The differences between mean percent changes in body weight, fasting insulin, and lipid levels are expressed in percentage points. Data for participants maintaining or achieving certain criteria are proportions of participants and estimated odds ratio (95% CI).

[c]Tested for superiority, controlled for Type 1 error.

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

[e]Tested for significant difference, not controlled for Type 1 error.

[f]These parameters were log-transformed before analysis to account for their skewed distribution and estimated ratio to baseline were transformed back for interpretation expressed as percent change from week 36 to week 88 or from week 0 to week 88 and estimated percent difference from placebo.

[g]Analysis of covariance model was used with treatment, all stratifications factors, and corresponding outcome value at randomization (or at week 0 if measured since week 0) as covariates. Missing data were imputed using last observation carried forward.

eTable 4. Adverse events during the tirzepatide lead-in treatment period (week 0 to 36)[a]

Adverse events	No. (%)
	Tirzepatide lead-in (N=783)
Participants with ≥1 adverse event	634 (81.0)
Serious adverse events	16 (2.0)
Death[b,c]	1 (0.1)
Adverse events leading to treatment discontinuation[d,e,f]	55 (7.0)
Nausea	14 (1.8)
Vomiting	8 (1.0)
Abdominal pain	4 (0.5)
Constipation	4 (0.5)
Diarrhea	3 (0.4)
Gastroesophageal reflux disease	2 (0.3)
Decreased appetite	2 (0.3)
Headache	2 (0.3)
Adverse events occurring in ≥5% of participants[d]	
Nausea	278 (35.5)
Diarrhea	165 (21.1)
Constipation	162 (20.7)
Vomiting	128 (16.3)
COVID-19	83 (10.6)
Decreased appetite	74 (9.5)
Gastroesophageal reflux disease	69 (8.8)
Injection site reaction	64 (8.2)
Dyspepsia	63 (8.0)
Headache	56 (7.2)
Fatigue	53 (6.8)
Abdominal pain	48 (6.1)
Alopecia	40 (5.1)
Adverse events of special interest	
Severe or serious hepatic events	0
Malignancies	2 (0.3)
Adjudicated pancreatitis[c]	0
Adjudicated major adverse cardiovascular events[c]	1 (0.1)
Severe or serious arrhythmias and cardiac conduction disorders	4 (0.5)
Severe or serious gastrointestinal events[g]	24 (3.1)
Severe or serious acute gallbladder disease	7 (0.9)
Severe or serious renal disorders	1 (0.1)
Severe or serious major depressive disorder or suicidal ideation	0
Severe or serious hypersensitivity	0
Hypoglycemia (blood glucose <54 mg/dL)	1 (0.1)
Other adverse events of interest[d]	
Cholelithiasis	7 (0.9)
Acute cholecystitis	4 (0.5)
Chronic cholecystitis	1 (0.1)

Abbreviations: COVID-19, coronavirus disease 2019.

[a]The safety follow-up period was included for participants who discontinued during open-label period.

[b]Deaths are also included as serious adverse events and discontinuations due to adverse event.

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

[d]Adverse events are listed according to Medical Dictionary for Regulatory Activities, version 26.0, preferred terms.

[e]Only preferred terms with n≥2 are presented.

[f]Treatment discontinuation due to an adverse event included adverse events that occurred in the lead-in period but led to discontinuation in the double-blind period.

[g]Includes 7 serious gastrointestinal events (6 gallbladder-related and 1 malnutrition).

eTable 5. COVID-19-related adverse events

Adverse events	No. (%)		
	Tirzepatide lead-in treatment period (N=783)	Double-blind period and safety follow-up period	
		Tirzepatide MTD (N=335)	Placebo (N=335)
Deaths related to COVID-19[a]	1 (0.1)	0	0
COVID-19 pneumonia	1 (0.1)	0	0
Serious adverse events related to COVID-19	2 (0.3)	0	0
COVID-19	1 (0.1)	0	0
COVID-19 pneumonia	1 (0.1)	0	0
Treatment emergent adverse events related to COVID-19	90 (11.5)	52 (15.5)	53 (15.8)
COVID-19	83 (10.6)	47 (14.0)	50 (14.9)
SARS-CoV-2 test positive	5 (0.6)	4 (1.2)	2 (0.6)
COVID-19 pneumonia	1 (0.1)	0	0
Suspected COVID-19	1 (0.1)	0	0
Coronavirus test positive	0	1 (0.3)	1 (0.3)

Abbreviations: COVID-19, coronavirus disease 2019; MTD, maximum tolerated dose (10 or 15 mg); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Deaths are also included as serious adverse events related to COVID-19.

eTable 6. Reported deaths during the entire study

Patient (age, sex)	Treatment group	Description	Days from first dose of study drug to death	Days from randomization to death	Cause of death as reported by the Adjudication Committee
45 y, male	Tirzepatide lead-in	COVID-19 pneumonia	46	-	COVID-19 pneumonia
63 y, male	Tirzepatide MTD	Cardiac failure congestive	501	249	Cardiovascular
29 y, female	Placebo	Adenocarcinoma of colon	641	388	Non-cardiovascular

Abbreviations: COVID-19, coronavirus disease 2019; MTD, maximum tolerated dose (10 or 15 mg).

eTable 7. Additional safety measures during the double-blind period (safety analysis set)

	Normal range	Estimated mean (SE)	
		Tirzepatide MTD (N=335)	Placebo (N=335)
Pulse rate, beats/min	60–100		
Week 36		77.1 (0.5)	77.8 (0.5)
Week 88		75.2 (0.4)	72.1 (0.4)
Change at week 88		-2.1 (0.4)***	-5.2 (0.4)
Pancreatic-amylase, U/L	3–46		
Week 36		27.9 (0.7)	28.5 (0.8)
Week 88		30.5 (0.5)	25.5 (0.4)
Percent change at week 88		8.1 (1.8)***	-9.7 (1.5)
Lipase, U/L	0–100		
Week 36		40.1 (1.1)	41.3 (1.2)
Week 88		42.5 (0.9)	31.7 (0.7)
Percent change at week 88		4.7 (2.3)***	-21.9 (1.8)
Aspartate aminotransferase, U/L	8–40		
Week 36		17.5 (0.3)	17.4 (0.3)
Week 88		18.6 (0.3)	18.7 (0.3)
Percent change at week 88		6.6 (1.6)	7.2 (1.7)
Alanine aminotransferase, U/L	Female: 4–43; Male: 5–48		
Week 36		16.2 (0.5)	16.6 (0.5)
Week 88		16.6 (0.4)	17.6 (0.4)
Percent change at week 88		1.6 (2.4)	7.2 (2.6)
Calcitonin, ng/L	Female: < 5.0 ng/L (<1.46 pmol/L); Male: < 8.4 ng/L (<2.46 pmol/L)		
Week 36		1.42 (0.06)	1.45 (0.06)
Week 88		1.47 (0.03)	1.33 (0.03)
Percent change at week 88		2.0 (1.9)***	-7.7 (1.7)
Urine albumin-to-creatinine ratio, mg/g	0–30		
Week 36		5.3 (0.3)	5.7 (0.3)
Week 88		5.9 (0.3)	5.0 (0.2)
Percent change at week 88		7.4 (5.0)*	-8.3 (4.3)

Abbreviations: MTD, maximum tolerated dose (10 or 15 mg).

Data are estimated mean (SE). Mixed model for repeated measures was used with treatment, visit, treatment × visit interaction, and stratification factors as fixed effects, and corresponding outcome value at randomization as a covariate. Except for pulse rate, all other measures were analyzed with log-transformation to account for their skewed distribution. *P < .05 and ***P < .001 treatment comparison to placebo.

eTable 8. Vital signs abnormalities during the double-blind period (safety analysis set)

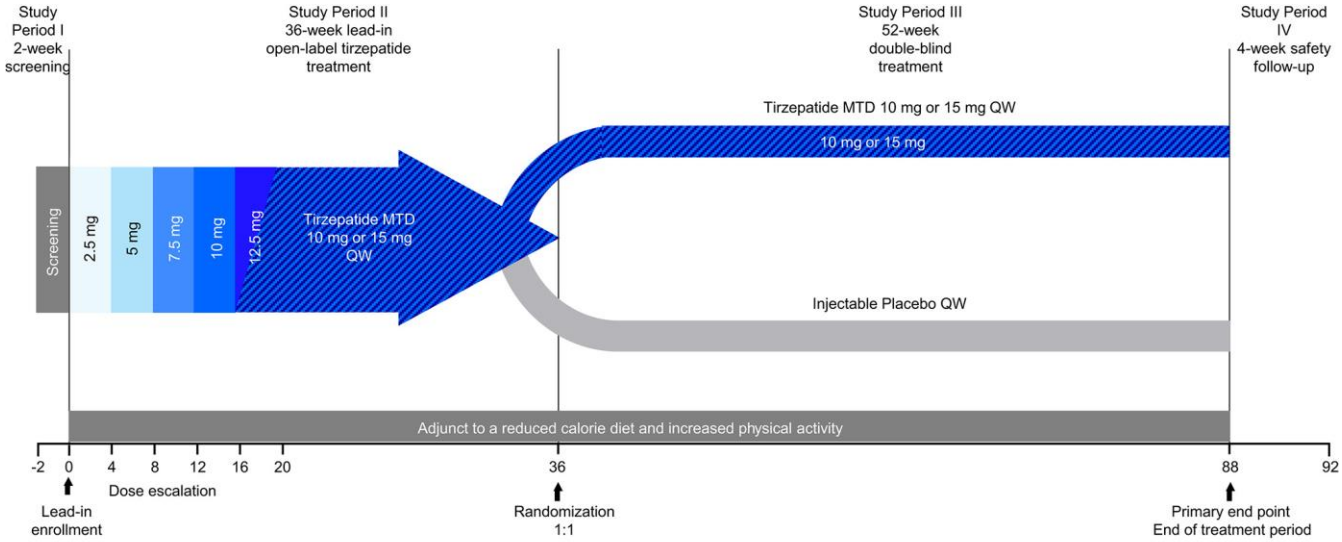
	No. (%)	
	Tirzepatide MTD (N=335)	**Placebo (N=335)**
Randomization (week 36)		
Pulse rate, beats/min		
Low: <50	6 (1.8)	1 (0.3)
High: >100	19 (5.7)	21 (6.3)
Systolic blood pressure, mmHg		
Low: ≤90	18 (5.4)	20 (6.0)
High: ≥129	220 (65.7)	201 (60.0)
High: ≥140	98 (29.3)	84 (25.1)
Diastolic blood pressure, mmHg		
Low: ≤50	2 (0.6)	4 (1.2)
High: ≥90	116 (34.6)	124 (37.0)
Any post-randomization value (including safety follow-up period)		
Pulse rate, beats/min		
Low: <50 and change from week 36 ≤-15	0	1 (0.3)
High: >100 and change from week 36 ≥15	1 (0.3)	0
Systolic blood pressure, mmHg		
Low: ≤90 and change from week 36 ≤-20	0	0
High: ≥129 and change from week 36 ≥20	2 (0.6)	8 (2.4)
High: ≥140 and change from week 36 ≥20	2 (0.6)	6 (1.8)
Diastolic blood pressure, mmHg		
Low: ≤50 and change from week 36 ≤-10	2 (0.6)	2 (0.6)
High: ≥90 and change from week 36 ≥10	3 (0.9)	8 (2.4)

Abbreviations: MTD, maximum tolerated dose (10 or 15 mg).

eFigure 1. SURMOUNT-4 study design

Abbreviations: MTD, maximum tolerated dose; QW, once weekly.

This is a phase 3, multicenter, randomized, placebo-controlled, double-blind, 88-week clinical trial investigating the efficacy and safety of the MTD of tirzepatide (10 or 15 mg), administered subcutaneously QW, compared with placebo, on the maintenance of weight reduction after an initial 36-week open-label tirzepatide lead-in treatment period in participants with BMI ≥30, or ≥27 with obesity-related complications (excluding diabetes).

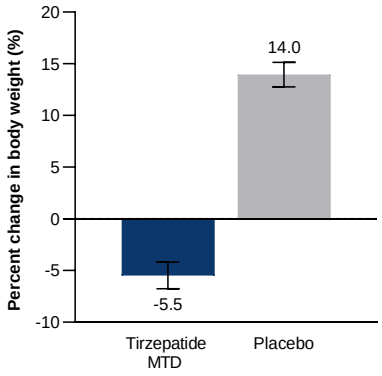


eFigure 2. Effect of tirzepatide maximum tolerated dose (10 or 15 mg) compared with placebo on efficacy outcomes in the SURMOUNT-4 trial

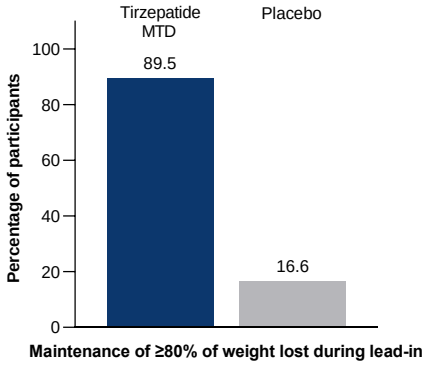
Abbreviations: MTD, maximum tolerated dose.

Error bars represent 95% CI for the mean. A, B, and C, Least squares means. Treatment regimen estimand (corresponding analyses used the full analysis set) evaluated treatment effects regardless of treatment adherence. Missing values were imputed using method of multiple imputation guided by hybrid approach. Analysis of covariance model was used with treatment, stratification factors (country, sex, tirzepatide maximum tolerated dose at randomization), and body weight at randomization (and body weight at week 0 if measured since week 0) as covariates. B and C, Logistic regression was used with the same covariates as that for analysis of covariance model.

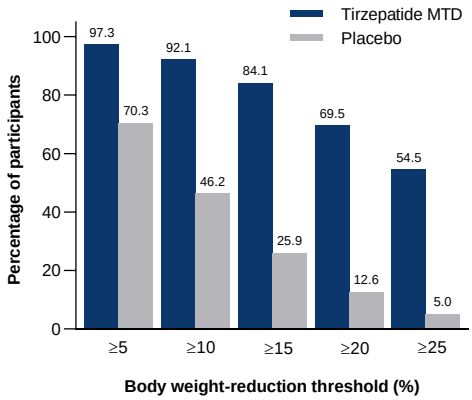
A Percent change in body weight (weeks 36-88; treatment regimen estimand)



B Participants who met weight-maintenance end point (week 88; treatment regimen estimand)



C Participants who met weight-reduction thresholds (weeks 0-88; treatment regimen estimand)



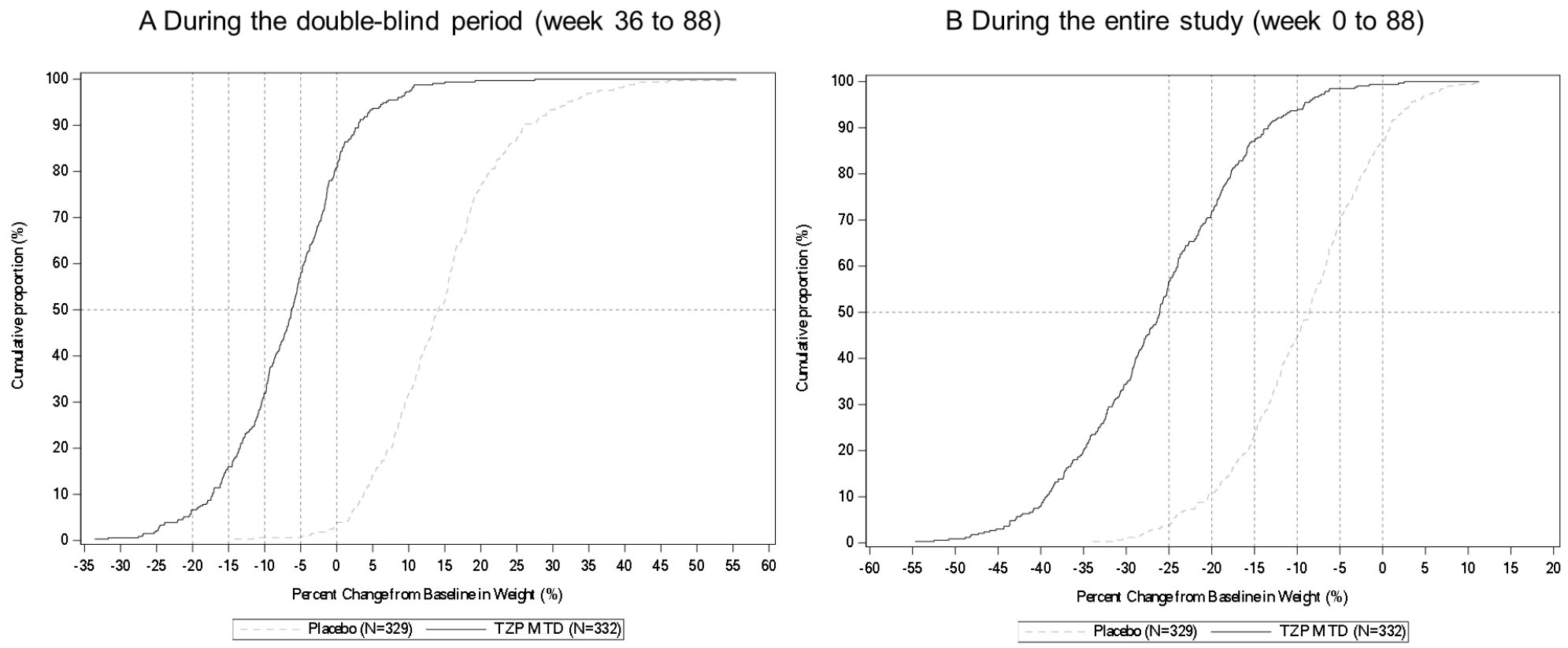
eFigure 3. Cumulative distribution plot of the percent change in weight (efficacy estimand)[a]

Abbreviations: MTD, maximum tolerated dose (10 or 15 mg); TZP, tirzepatide.

Reference values for percent changes (-25%, -20%, - 15%, -10%, -5%, 0%) are marked with gray, dashed lines on the x-axis; 50th percentile is marked with a gray, dashed line on the y-axis. Only participants with non-missing values at week 36 or week 0, respectively, and at least one non-missing post-randomization value of the response variable were included in the plot.

A, During the double-blind period (week 36 to 88). B, During the entire study (week 0 to 88).

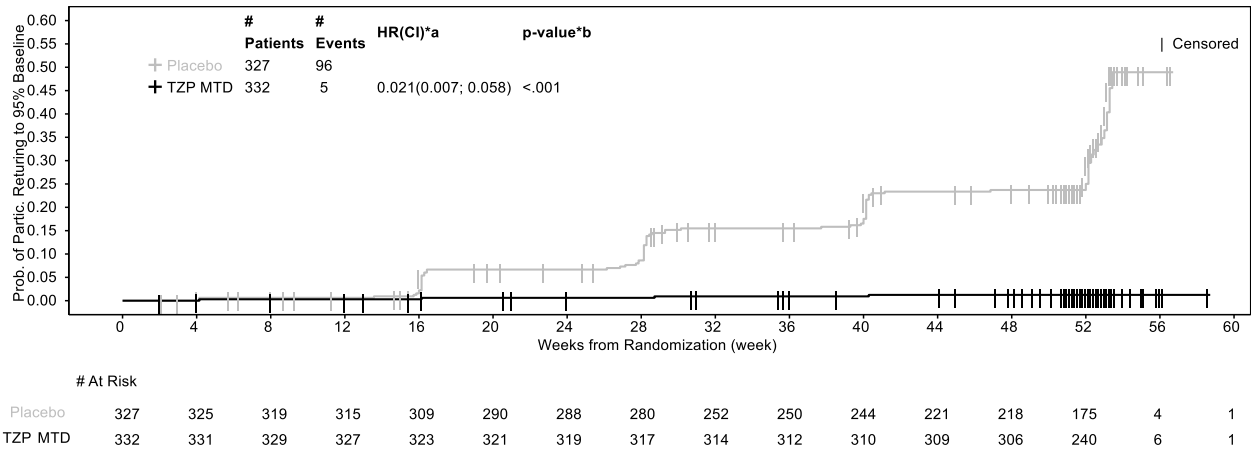
[a]Efficacy estimand (corresponding analyses used the efficacy analysis set) evaluated treatment effects using on-treatment data prior to discontinuation of study drug. Mixed model for repeated measures was used with treatment, visit, treatment × visit interaction, and stratification factors as fixed effects, and corresponding outcome value at randomization and/or at week 0 as a covariate.



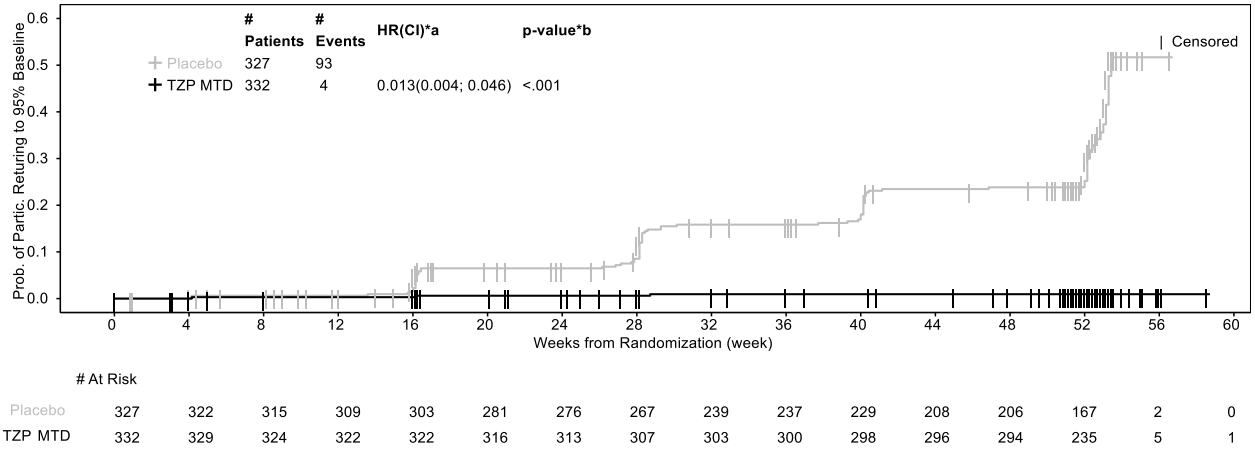
eFigure 4. Time, during the 52-week double-blind period (week 36 to 88 in the entire study), to first occurrence of participant returning to >95% baseline body weight if already lost ≥5% since week 0

Abbreviations: HR, hazard ratio; MTD, maximum tolerated dose (10 or 15 mg); TZP, tirzepatide.
An event is defined as the first occurrence of participant returning to >95% baseline body weight since week 0.
A, Treatment regimen estimand (corresponding analyses used the full analysis set) evaluated treatment effects regardless of treatment adherence and the participant without event is censored at the time of the end of the double-blind treatment period.
B, Efficacy estimand (corresponding analyses used the efficacy analysis set) evaluated treatment effects using on-treatment data prior to discontinuation of study drug and the participant without event is censored at the time of treatment discontinuation.
In both estimands, hazard ratio was computed by Cox proportional hazards model with terms of treatment, country, sex, TZP MTD at randomization (week 36), and weight at randomization (week 36) and at week 0 as covariates.
[a]Unstratified hazard ratio from Cox proportional hazard model and 95% CI.
[b]Log-rank unstratified p-value (2-sided) for comparison of treatment vs placebo.

A Treatment regimen estimand

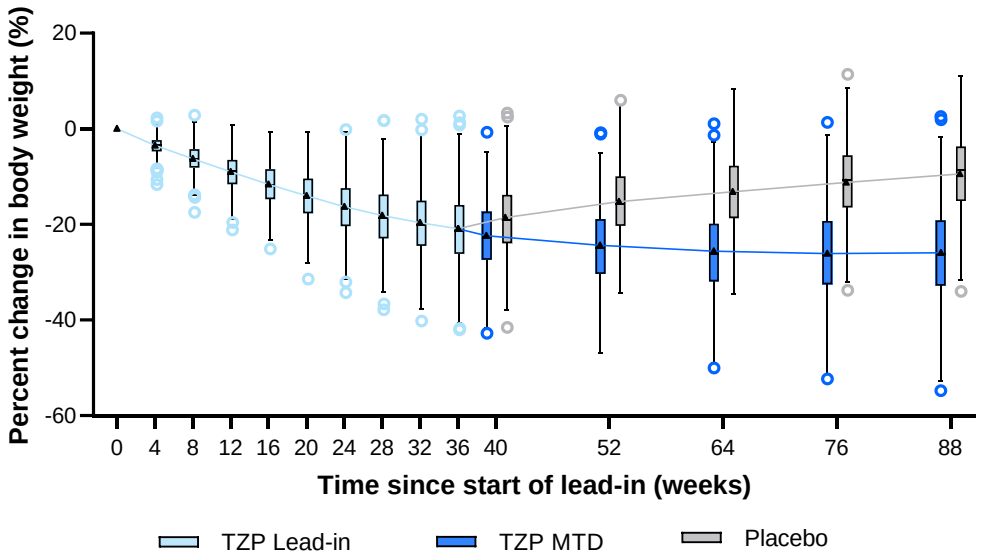


B Efficacy estimand



eFigure 5. Box plot of the percent change in body weight over time during the entire study

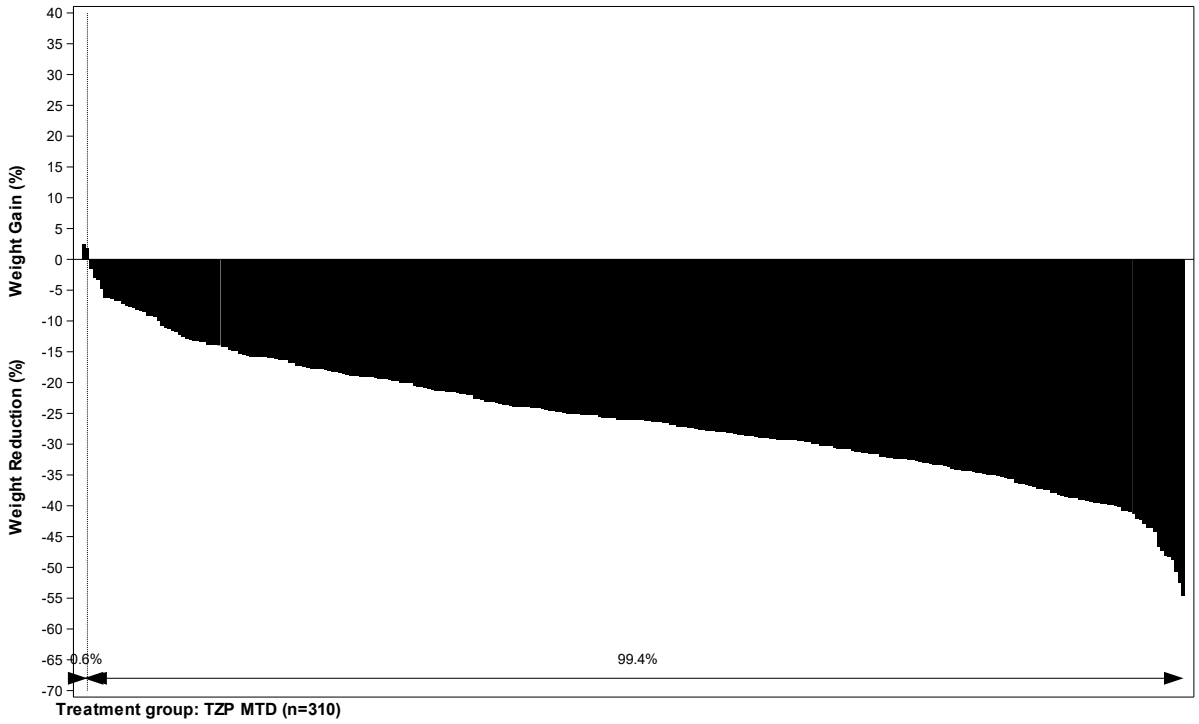
Abbreviations: MTD, maximum tolerated dose (10 or 15 mg); TZP, tirzepatide.
Includes all observed data from full analysis set without imputation. The middle lines within each box represent the median, the triangles in each box represent the mean, the box tops and bottoms represent the interquartile range, the whiskers extend to the most extreme observed values with 1.5 times the interquartile range of the nearer quartile, and the open circles beyond the whiskers represent the observed values outside that range.

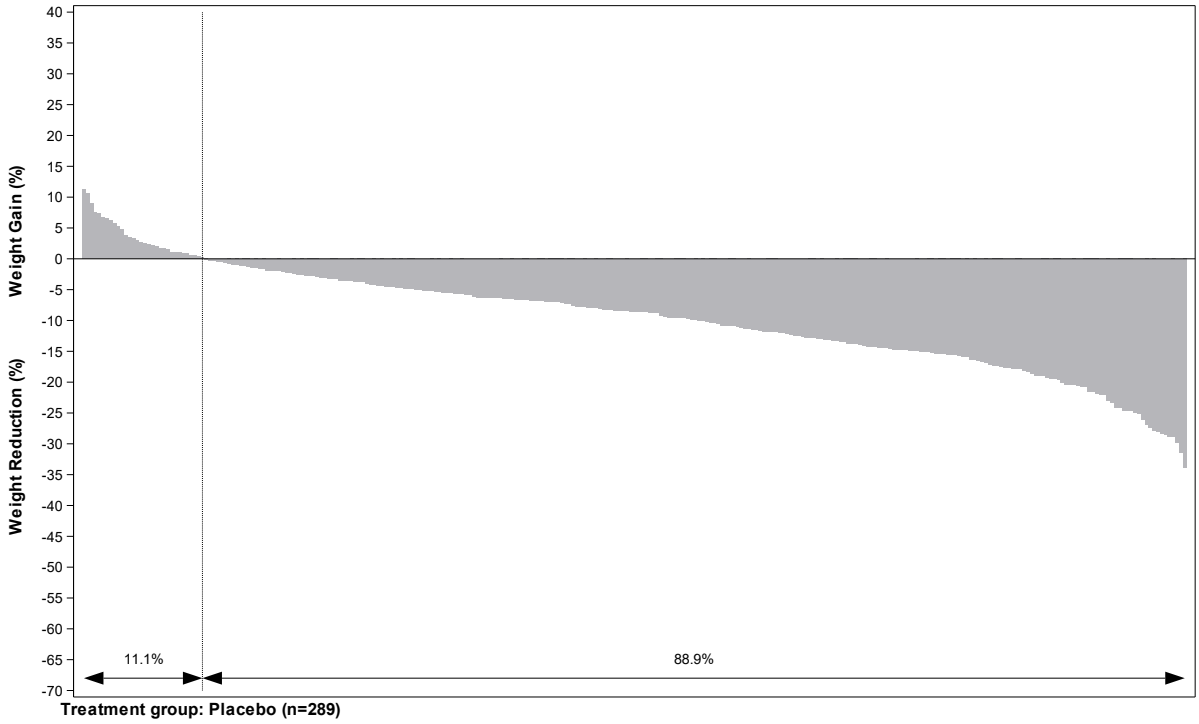


Treatment group	Number of participants at each time point									
Tirzepatide lead-in	670	666	669	668	667	667	669	663	659	669
Tirzepatide MTD							330	325	310	300	299
Placebo							328	309	293	278	273

eFigure 6. Waterfall plot of the percent change in body weight from week 0 to 88

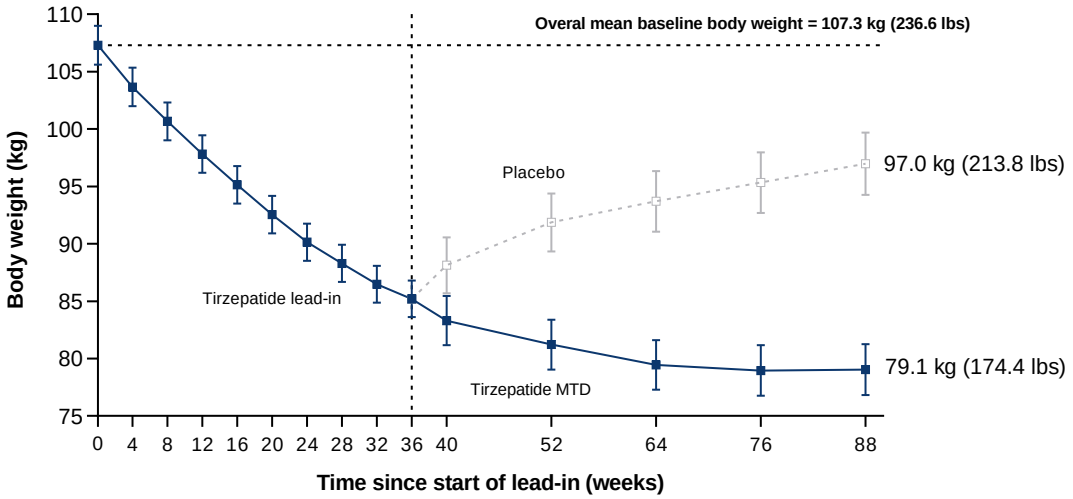
Abbreviations: MTD, maximum tolerated dose (10 or 15 mg); TZP, tirzepatide.
Observed data from full analysis set.





eFigure 7. Body weight over time during the entire study

Abbreviations: MTD, maximum tolerated dose (10 or 15 mg).
Observed mean values (error bars represent 95% CI for the mean). The dashed vertical line at week 36 represents the randomization time point.

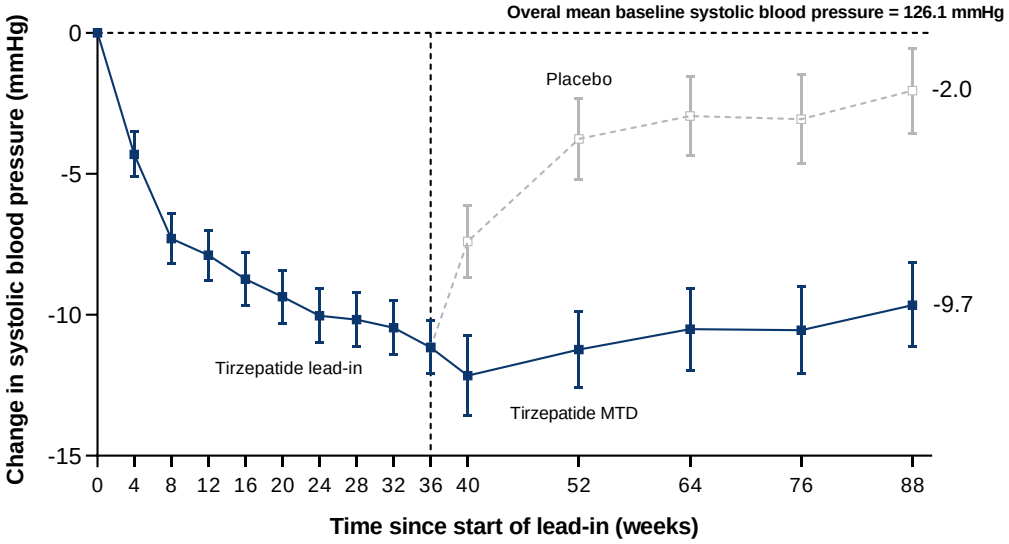


Treatment group	Number of participants at each time point													
Tirzepatide lead-in	670	666	669	668	667	667	669	663	659	670				
Tirzepatide MTD										335	333	328	317	310	310
Placebo										335	330	317	303	292	289

eFigure 8. Change in blood pressure over time during the entire study

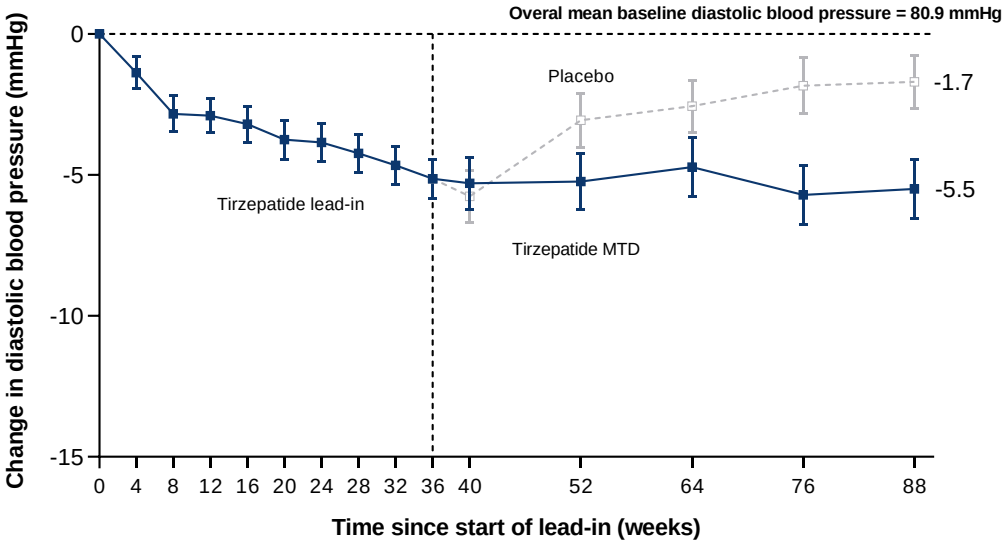
Abbreviations: MTD, maximum tolerated dose (10 or 15 mg).
Observed mean values (error bars represent 95% CI for the mean). The dashed vertical line at week 36 represents the randomization time point.

A Change in systolic blood pressure



Treatment group	Number of participants at each time point									
Tirzepatide lead-in	670	666	669	668	668	667	670	663	659	670
Tirzepatide MTD							335	333	328	317	311	310
Placebo							335	329	319	303	292	288

B Change in diastolic blood pressure

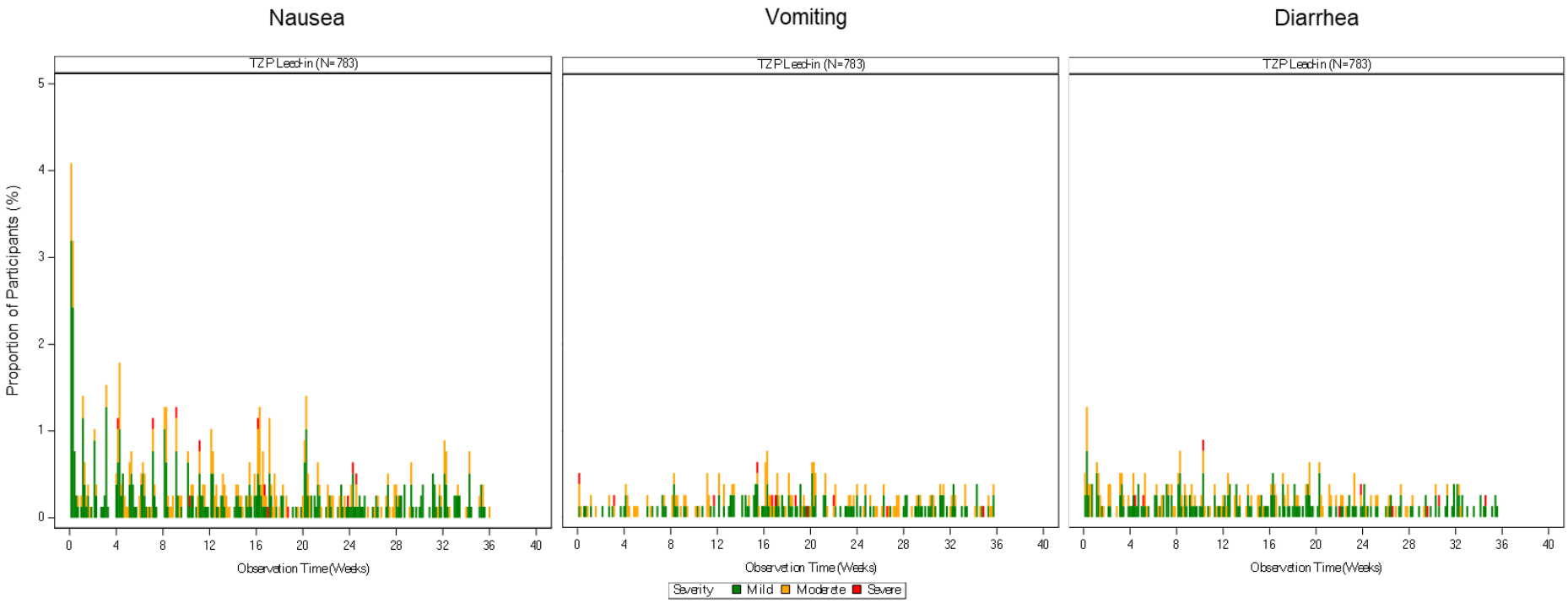


Treatment group	Number of participants at each time point									
Tirzepatide lead-in	670	666	669	668	668	667	670	663	659	670
Tirzepatide MTD							335	333	328	317	311	310
Placebo							335	329	319	303	292	288

eFigure 9. Incidence of nausea, vomiting, and diarrhea over time during the tirzepatide lead-in treatment period

Abbreviations: TZP, tirzepatide.

The percentage of participants receiving tirzepatide who reported nausea (Panel A), vomiting (Panel B), or diarrhea (Panel C) are presented. Percentages are based on number of participants at risk at specific observation time. Events were classed as mild (shown in green), moderate (shown in orange), or severe (shown in red).



eFigure 10. Incidence of nausea, vomiting, and diarrhea over time during the double-blind period (safety analysis set)

Abbreviations: MTD, maximum tolerated dose (10 or 15 mg); TZP, tirzepatide.

The percentage of participants receiving tirzepatide or placebo who reported nausea (Panel A), vomiting (Panel B), or diarrhea (Panel C) are presented. Percentages are based on number of participants at risk at specific observation time. Events were classed as mild (shown in green), moderate (shown in orange), or severe (shown in red).