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Tirzepatide Once Weekly for the Treatment of Obesity

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Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

Background

- Obesity is a complex, multi-component, metabolic disease of energy homeostasis[1]
- Several clinical guidelines recommend pharmacotherapy for people with obesity or overweight with weight-related comorbidities[1]
- Tirzepatide, a novel once-weekly GIP and GLP-1 receptor agonist, is approved by FDA for the treatment of adults with type 2 diabetes[2]. TZP demonstrated significant weight reduction in phase 2[2] and phase 3 studies[4-8] in people with diabetes
- Tirzepatide is in phase 3 development for adults with obesity or overweight with weight-related comorbidities[1]
- SURMOUNT-1, a multicenter, phase 3 randomized, double-blind, parallel, placebo-controlled trial aimed to determine the efficacy and safety of tirzepatide in participants without T2D who have obesity or are overweight with weight-related comorbidities[1]

FDA = Food and Drug Administration; GIP = Glucose-dependent Insulinotropic Polypeptide; GLP = Glucagon-like Peptide-1; TZP = Tirzepatide.

1. Jastreboff AM, et al. *N Engl J Med.* 2022;387(3):205-216. 2. https://www.fda.gov/news-events/press-announcements/FDA Approves Novel, Dual-Targeted Treatment for Type 2 Diabetes | FDA. Accessed May 13, 2022. 3. Frias JP, et al. *Lancet*. 2018;392(10160):2180-2193. 4. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 5. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 6. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 7. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 8. Dahl D, et al. *JAMA*. 2021;327(6):534-545.

Endpoints

Primary and Key Secondary

Primary Endpoints

To demonstrate tirzepatide 10 mg and/or 15mg once-weekly is/are superior to placebo at 72 weeks for:

- percent change in body weight, and
- percentage of participants with ≥5% body weight reduction

Key Secondary Endpoints

To demonstrate pooled tirzepatide 10 mg and 15 mg, QW is superior to placebo for:

- mean change in body weight at 20 weeks

To demonstrate tirzepatide (10 mg and/ or 15 mg, QW) is/are superior to placebo for:

- percentage of participants who achieved ≥10%, ≥15%, or ≥20% body weight reduction at 72 weeks

To demonstrate tirzepatide (5 mg, QW) is superior to placebo at 72 weeks for:

- percent change in body weight, and
- percentage of participants with ≥5% body weight reduction

QW = Once Weekly; SF-36v2 = Short Form Health Survey (SF-36) Version 2.

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Endpoints (Contd.)

Key Secondary and Additional Secondary Endpoints

Cardiometabolic Risk Factors/Physical Function

To demonstrate that pooled tirzepatide (5 mg, 10 mg, 15 mg) is superior to placebo at 72 weeks for:

- mean change in triglycerides, non-HDL cholesterol, HDL cholesterol
- mean change in systolic blood pressure
- mean change in fasting insulin

To demonstrate that pooled tirzepatide (10 mg and 15 mg) is superior to placebo at 72 weeks for:

- mean change in SF-36v2 physical functioning domain score

To demonstrate that tirzepatide 10 mg and/or 15 mg is/are superior to placebo at 72 weeks for:

- mean change in waist circumference

Additional secondary endpoints

- Participants with weight reduction ≥25% at week 72
- Change in diastolic blood pressure
- Percent change in total cholesterol, LDL cholesterol, VLDL cholesterol, free fatty acids

HDL = High-Density Lipoprotein; LDL = Low-density Lipoprotein; SF-36v2 = Short Form Health Survey Version 2; VLDL = Very-low-density Lipoprotein.

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Study Design and Inclusion Criteria of Participants

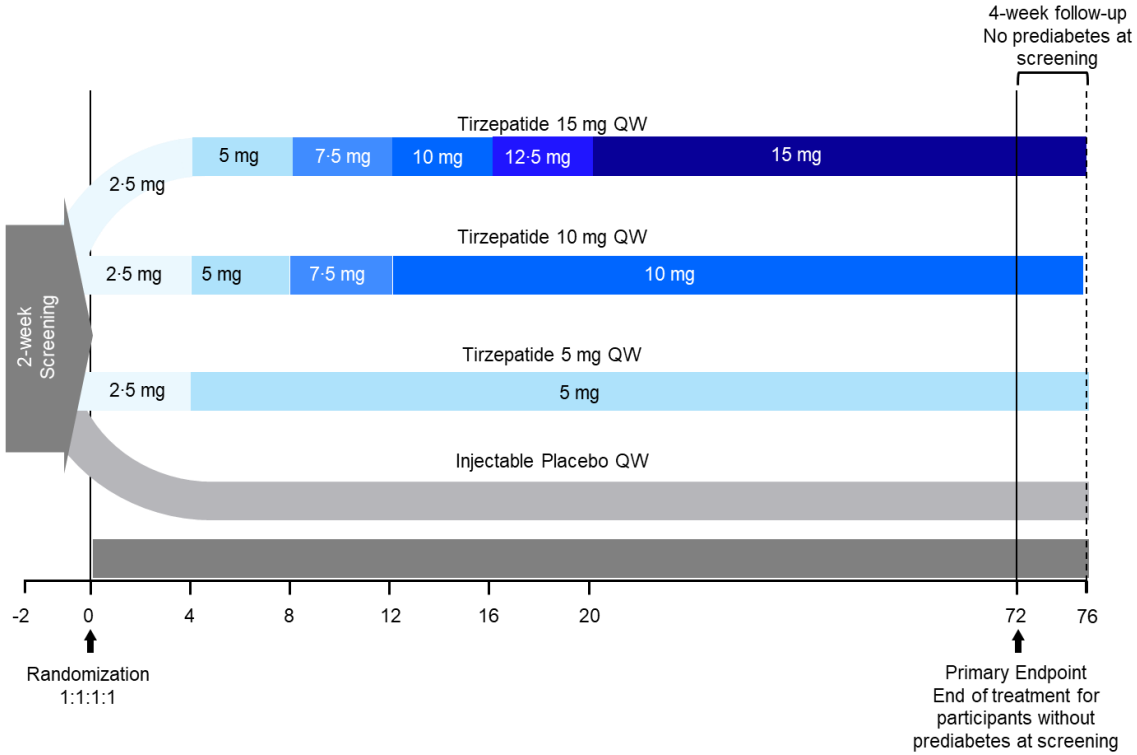
Phase 3, multicenter, randomized, double-blind, placebo-controlled trial at 118 sites in 9 countries (NCT04184622)

1 Key Inclusion Criteria

- Age ≥18 years
- BMI ≥30 kg/m^2 or ≥27 kg/m^2 and ≥1 weight-related comorbidities (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease)
- History of ≥1 self-reported unsuccessful dietary efforts to lose body weight

2 Key Exclusion Criteria

- Type 1 or Type 2 Diabetes mellitus
- Change in body weight >5 kg within 3 months prior to screening
- Obesity induced by other endocrinologic disorders or monogenetic or syndromic forms of obesity
- History of pancreatitis



Note: Tirzepatide was administered once weekly (QW) subcutaneously as an adjunct to a reduced-calorie diet and increased physical activity

BMI = Body Mass Index; QW = Once Weekly.

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Key Methods and Assessments

- Efficacy and safety endpoints were analyzed using data from all randomly assigned participants (intention-to-treat [ITT] population)
- Two estimands were used to assess treatment efficacy from different perspectives

Treatment regimen estimand

Representing the average treatment effect of tirzepatide relative to placebo, regardless of treatment discontinuation

Efficacy estimand

Representing the average treatment effect of tirzepatide relative to placebo if the treatment was taken as intended

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SURMOUNT-1 Study – Country Allocation

- The study was conducted in 9 countries across 4 continents: Argentina, Brazil, China, India, Japan, Mexico, Russian Federation, Taiwan, and the United States
- The United States represented 44% of the study population

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Baseline Demographics

	Tirzepatide 5 mg (N=630)	Tirzepatide 10 mg (N=636)	Tirzepatide 15 mg (N=630)	Placebo (N=643)	Total (N=2539)
Age, years	45.6 ± 12.7	44.7 ± 12.4	44.9 ± 12.3	44.4 ± 12.5	44.9 ± 12.5
Female, n (%)	426 (67.6)	427 (67.1)	425 (67.5)	436 (67.8)	1714 (67.5)
Race*, n (%)					
American Indian or Alaska Native	56 (8.9)	58 (9.1)	59 (9.4)	58 (9.0)	231 (9.1)
Asian	68 (10.8)	71 (11.2)	66 (10.5)	71 (11.0)	276 (10.9)
Black or African American	48 (7.6)	47 (7.4)	51 (8.1)	55 (8.6)	201 (7.9)
White	447 (71.0)	452 (71.1)	443 (70.3)	450 (70.0)	1792 (70.6)
Native Hawaiian or other Pacific Islander	2 (0.3)	2 (0.3)	3 (0.5)	2 (0.3)	9 (0.4)
Multiple	9 (1.4)	6 (0.9)	8 (1.3)	7 (1.1)	30 (1.2)
Hispanic or Latino, n (%)	308 (48.9)	297 (46.7)	299 (47.5)	310 (48.2)	1214 (47.8)
Duration of obesity, years	14.0 ± 10.81	14.7 ± 11.05	14.8 ± 10.75	14.0 ± 10.71	14.4 ± 10.83
Body weight, kg	102.9 ± 20.71	105.8 ± 23.32	105.6 ± 22.92	104.8 ± 21.37	104.8 ± 22.12
BMI, kg/m^2	37.4 ± 6.63	38.2 ± 7.01	38.1 ± 6.69	38.2 ± 6.89	38.0 ± 6.81
BMI category, n (%)					
<30	38 (6.0)	38 (6.0)	40 (6.3)	24 (3.7)	140 (5.5)
≥30 to <35	241 (38.3)	209 (32.9)	199 (31.6)	227 (35.3)	876 (34.5)
≥35 to <40	174 (27.6)	187 (29.4)	179 (28.4)	180 (28.0)	720 (28.4)
≥40	177 (28.1)	202 (31.8)	212 (33.7)	212 (33.0)	803 (31.6)
Waist circumference, cm	113.2 ± 14.25	114.8 ± 15.80	114.4 ± 15.59	114.0 ± 14.92	114.1 ± 15.16

Data are mean ± SD, unless otherwise indicated; *Race or ethnic group was reported by the participants.

BMI = Body Mass Index; SD = Standard Deviation.

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Baseline Clinical Characteristics

	Tirzepatide 5 mg (N=630)	Tirzepatide 10 mg (N=636)	Tirzepatide 15 mg (N=630)	Placebo (N=643)	Total (N=2539)
Systolic blood pressure, mmHg	123.6 ± 12.45	123.8 ± 12.77	123.0 ± 12.94	122.9 ± 12.77	123.3 ± 12.73
Diastolic blood pressure, mmHg	79.3 ± 8.14	79.9 ± 8.32	79.3 ± 8.23	79.6 ± 7.95	79.5 ± 8.16
Pulse, beats/min	72.3 ± 9.60	71.8 ± 9.57	72.5 ± 9.95	72.9 ± 9.27	72.4 ± 9.60
Lipid parameters, geometric mean mg/dL (CV [%])					
Total cholesterol	187.1 (21.1)	190.7 (19.9)	187.4 (19.9)	186.4 (20.3)	187.9 (20.3)
HDL cholesterol	47.6 (26.6)	47.5 (26.1)	47.5 (25.5)	46.5 (26.9)	47.3 (26.3)
Non-HDL cholesterol	137.1 (27.2)	139.9 (26.4)	137.7 (26.2)	137.2 (26.5)	138.0 (26.6)
LDL cholesterol	108.7 (30.2)	111.5 (30.3)	109.5 (30.0)	108.4 (30.5)	109.5 (30.2)
VLDL cholesterol	57.8 (46.1)	57.1 (48.1)	58.1 (45.1)	58.9 (45.9)	58.0 (46.3)
Triglycerides	128.9 (51.7)	126.5 (51.5)	127.9 (47.5)	130.5 (49.2)	128.4 (50.0)
Free fatty acids	0.47 (48.4)	0.48 (42.3)	0.46 (47.5)	0.47 (44.0)	0.47 (45.6)
eGFR‡, mL/min/1.73 m^2	97.6 ± 17.87	98.3 ± 18.26	98.2 ± 17.67	98.1 ± 18.28	98.1 ± 18.02
Prediabetes, n (%)	247 (39.2)	262 (41.2)	253 (40.2)	270 (42.0)	1032 (40.6)
HbA1c, %	5.6 ± 0.36	5.6 ± 0.37	5.6 ± 0.41	5.6 ± 0.38	5.6 ± 0.38
Fasting glucose, mg/dL	95.4 ± 9.7	95.5 ± 10.7	95.3 ± 10.3	95.7 ± 9.5	95.5 ± 10.1
Fasting insulin, mIU/L	13.6 ± 10.0	14.1 ± 12.2	14.4 ± 9.3	14.3 ± 9.9	14.1 ± 10.4
SF-36v2 physical functioning domain score	49.6 ± 8.3	49.6 ± 7.5	49.6 ± 7.8	49.7 ± 7.7	49.6 ± 7.8

Data are mean ± SD, unless otherwise indicated ; *The value of the eGFR was calculated according to the serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

CV = Coefficient of Variation; eGFR = Estimated Glomerular Filtration Rate; HbA1c = Glycated Hemoglobin; HDL = High-density Lipoprotein; LDL = Low-density Lipoprotein; VLDL = Very-low-density Lipoprotein; SD = Standard Deviation; ; SF-36v2 = Short Form Health Survey Version; VLDL = Very-low-density Lipoprotein .

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Efficacy of Tirzepatide

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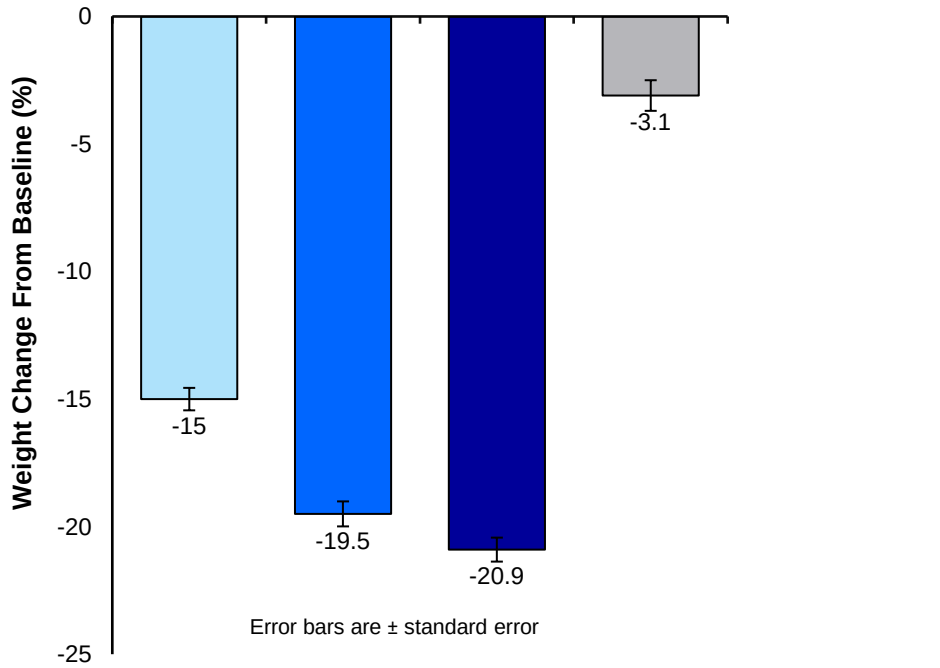
SURMOUNT-1

Percent Change in Body Weight From Baseline to 72 Weeks

- **Statistically significant difference in weight reduction with all tirzepatide doses compared to placebo**
- **Weight reductions of 19.5% and 20.9% with tirzepatide 10 mg and 15 mg, respectively (treatment-regimen estimand)**

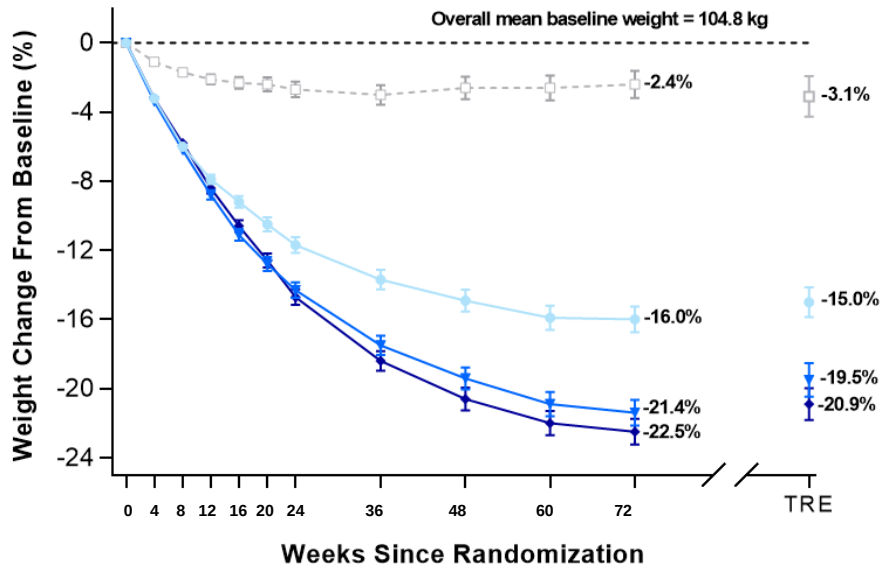
Treatment-Regimen Estimand

	TZP 5 mg vs PBO*	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	-11.9 (-13.4, -10.4)	-16.4 (-17.9, -14.8)	-17.8 (-19.3, -16.3)
P value		<.001	



Efficacy Estimand

	TZP 5 mg vs PBO*	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	−13.5 (−14.6 to −12.5)	−18.9 (−20.0, −17.8)	−20.1 (−21.2, −19.0)
P value		<.001	



Note: Data derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand; week 72 estimates for the treatment-regimen estimand are also shown; Error bars are ± standard error

*Change in body weight in the TZP 5 mg group was not a coprimary endpoint and was analyzed as a key secondary endpoint

CI = Confidence Interval; ETD = Estimated Treatment Difference; TRE = Treatment-Regimen Estimand; TZP = Tirzepatide; PBO = Placebo.

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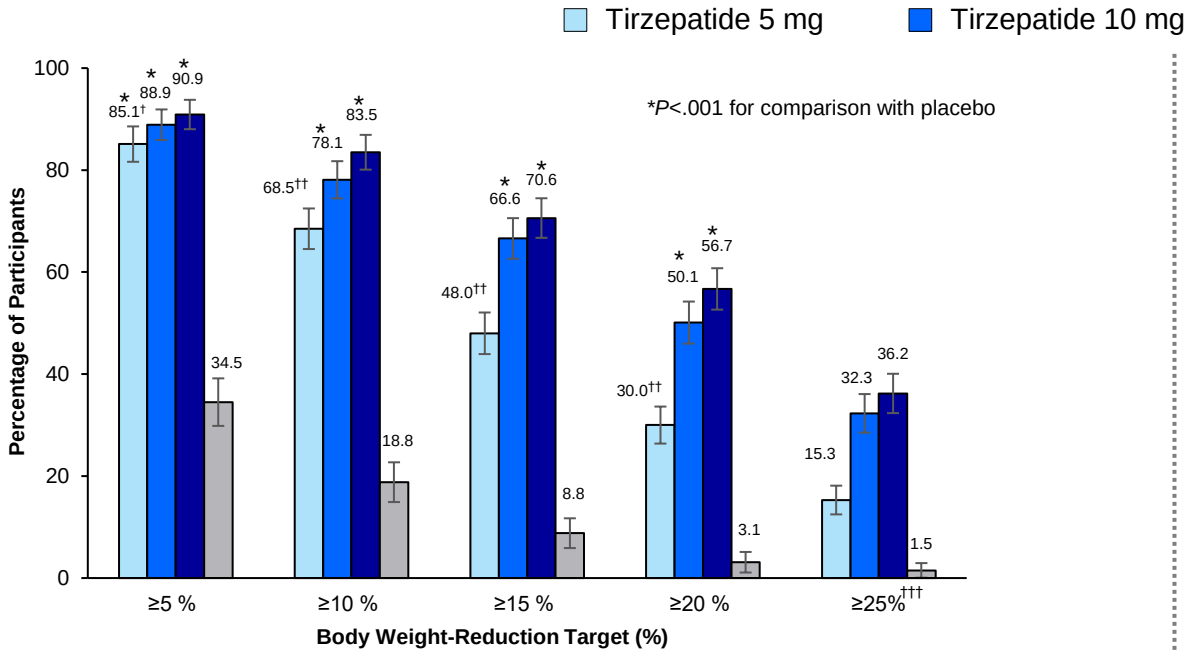
SURMOUNT-1

Percentage of Participants Achieving Body Weight Reductions Targets

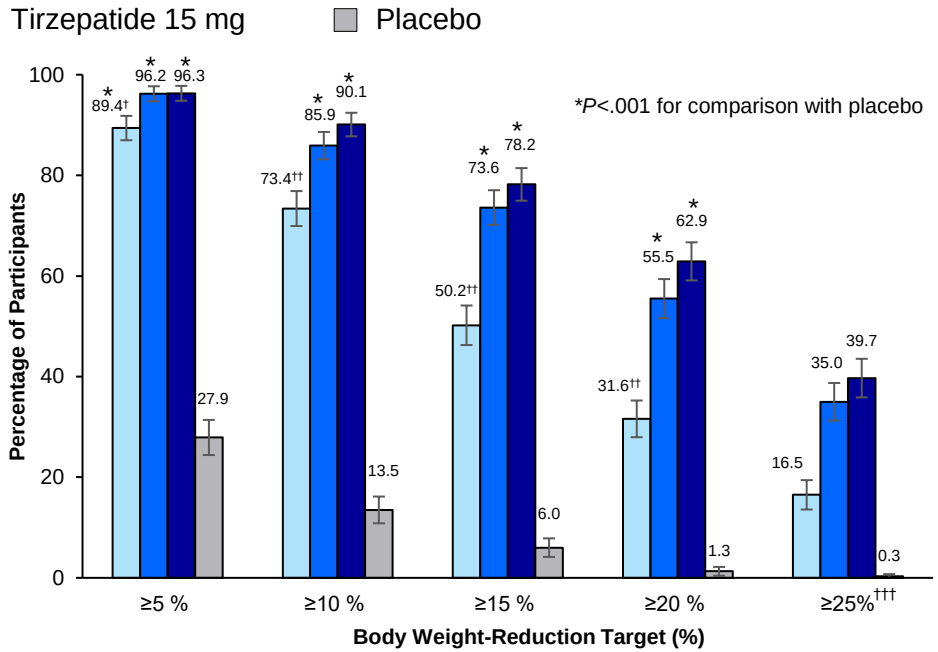
- **Significantly greater proportion of participants on tirzepatide treatment achieved body weight reductions of ≥5%, ≥10%, ≥15%, and ≥20% from baseline than placebo**
- **36.2% of patients achieved pre-specified exploratory endpoint of ≥25% body weight reduction with tirzepatide 15 mg**

Treatment-Regimen Estimand



Note: The percentage was calculated with the use of Rubin's rules by combining the percentages of patients who met the target in imputed data sets. Missing value at week 72 was imputed using MMRM if missing was solely due to COVID-19 and using multiple imputation if missing was not due to COVID-19
Least-squares means are presented for both estimands, unless otherwise noted. Error bars indicate the 95% confidence interval

Efficacy Estimand



Note: The percentage of participants achieving weight loss targets was obtained by dividing the number of participants reaching respective goals at week 72 by the number of participants with baseline value and at least one non-missing postbaseline value. Missing value at week 72 was predicted from MMRM analysis. Logistic regression analysis was used for all comparisons to placebo

† The change in body weight in the tirzepatide 5-mg arm for ≥5% was analyzed as a key secondary end point; †† These were analyzed as additional secondary endpoints and not controlled for type 1 error. Hypothesis testing not conducted/*P*-value not shown
††† Participants with weight reduction ≥25% is an exploratory endpoint and not controlled for type 1 error; therefore, *P* values are not shown.

COVID-19=Coronavirus Disease 2019; MMRM = Mixed-model or Repeated-measures.

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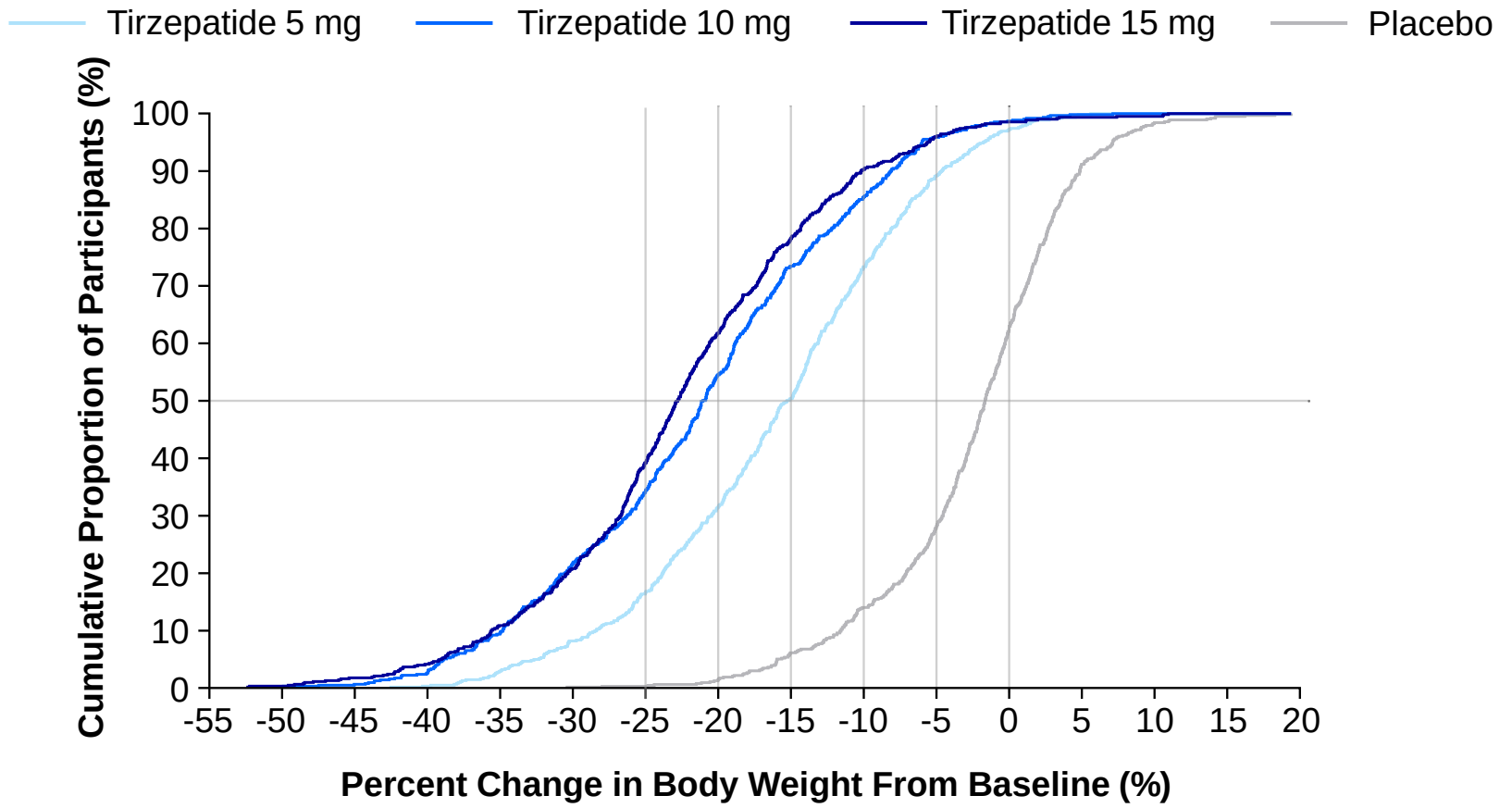
Percent Change in Body Weight From Baseline at Week 72

Cumulative Distribution Plot



Note: Data shown is for efficacy analysis set (including data obtained during treatment period from the intention-to -treat population, excluding data after discontinuation of study drug)
Only subjects with non-missing baseline value and at least one non-missing post-baseline value of the response variable are included in the plot
Missing data was imputed from an MMRM model for post-baseline measures
Reference values for percent changes (-25%, -20%, -15%, -10%, -5%) are marked with gray, solid lines on the x-axis; 50th percentile is marked with a gray, solid line on the y-axis

MMRM = Mixed-model or Repeated-measures.

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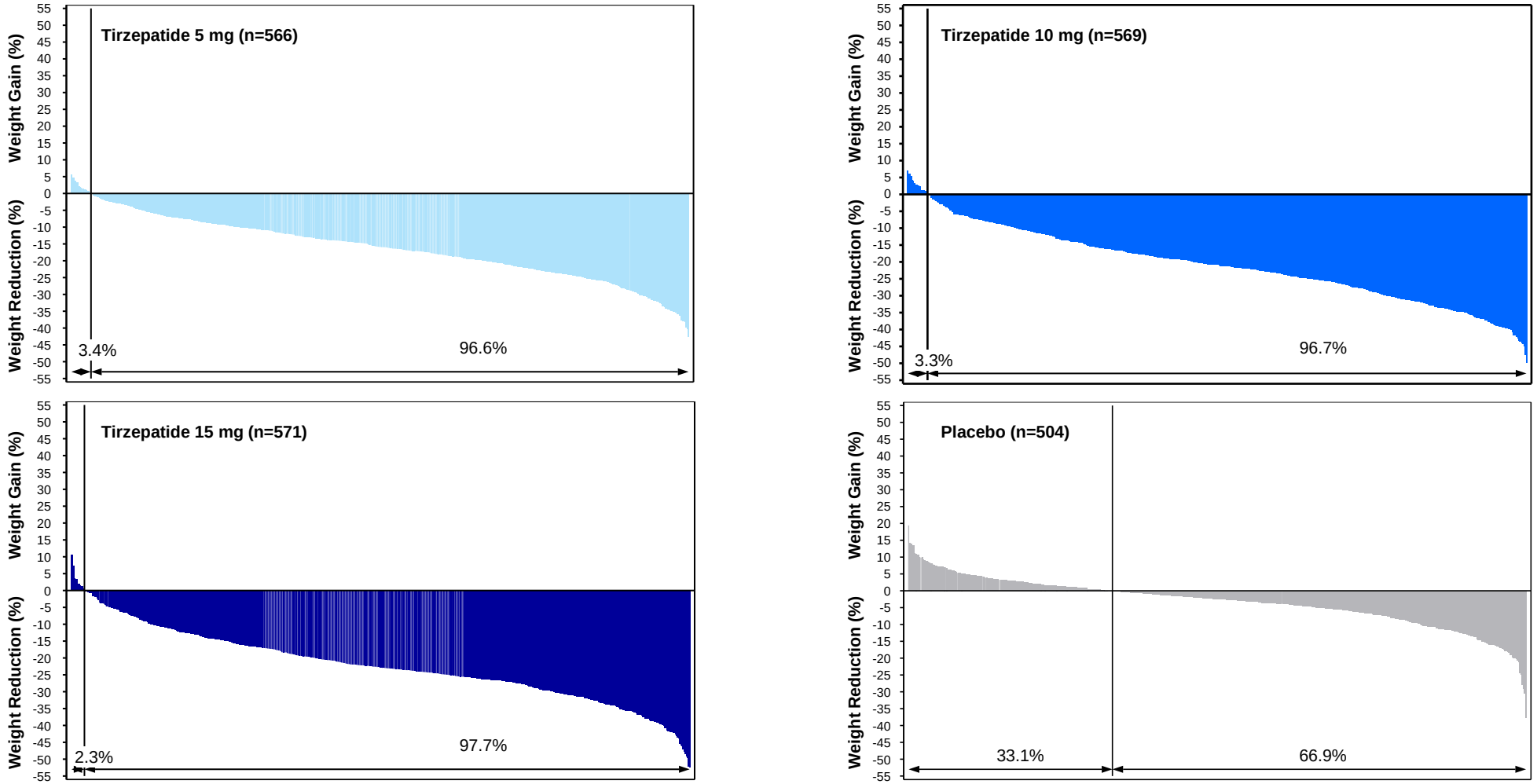
Percent Change in Body Weight at Week 72

Waterfall Plots

Body weight reduction was observed in 96.6%, 96.7% and 97.7% participants of tirzepatide 5 mg, 10 mg, and 15 mg groups respectively, compared to 66.9% of participants in the placebo group



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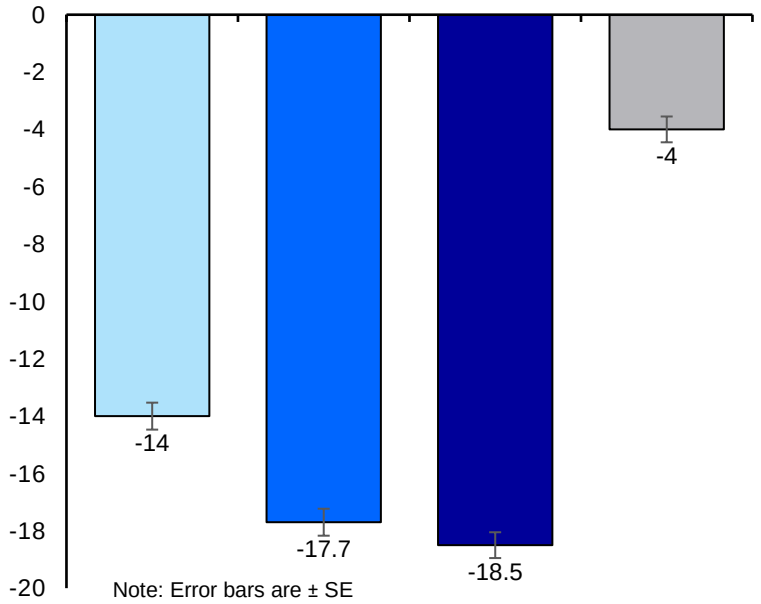
Change in Waist Circumference From Baseline to 72 Weeks

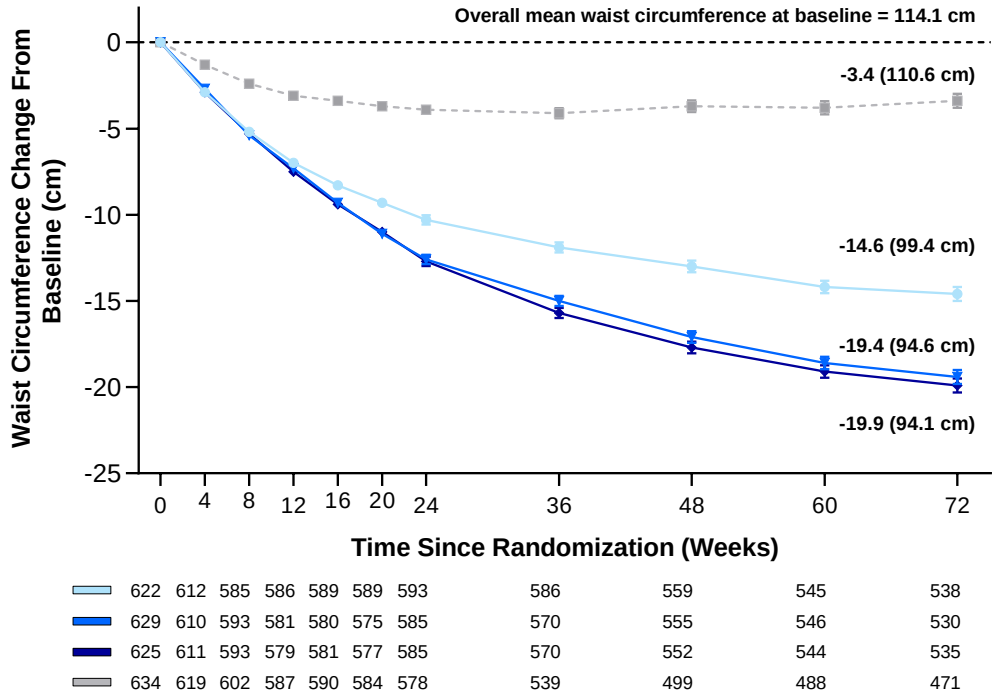
Significant reduction in waist circumference with all tirzepatide doses compared to placebo

Treatment Regimen Estimand

	TZP 5 mg vs PBO	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	-10.1 (-11.6, -8.6)	-13.8 (-15.2, -12.3)	-14.5 (-15.9, -13.0)
P value		<.001	



Efficacy Estimand



Note: Data derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand; Only participants with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis; Values in parentheses are actual waist circumference at week 72.
Error bars are ± standard error.

CI = Confidence Interval; ETD = Estimated Treatment Difference; TZP = Tirzepatide; PBO = Placebo; SE = Standard Error.

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Change in Key Secondary Endpoints

Treatment Regimen Estimand

Treatment with tirzepatide was associated with significantly greater improvements than placebo in all key secondary endpoints

	Pooled Tirzepatide LSM (95% CI)	Placebo (N=643) LSM (95% CI)	ETD versus placebo (95% CI)	*P* value
Change from baseline to week 20 in body weight*, kg	-12.8 (-13.1, -12.5)	-2.7 (-3.2, -2.2)	-10.1 (-10.7, -9.6)	<.001
Change in SF-36v2 physical function score*†	3.6 (3.2, 4.0)	1.7 (0.8, 2.6)	1.9 (1.0, 2.9)	<.001
Change in SBP, mm Hg	-7.2 (-7.8, -6.7)	-1.0 (-2.3, -0.3)	-6.2 (-7.7, -4.8)	<.001
Percent change in††				
Triglycerides, mg/dL	-24.8 (-26.3, -23.1)	-5.6 (-10.0, -1.2)	-20.3 (-24.3, -16.1)	<.001
Non-HDL cholesterol, mg/dL	-9.7 (-10.7, -8.6)	-2.3 (-4.9, -0.2)	-7.5 (-10.1, -4.9)	<.001
HDL cholesterol, mg/dL	8.0 (6.9, 9.1)	-0.7 (-2.9, 1.5)	8.8 (6.1, 11.5)	<.001
Fasting insulin, mIU/L	-42.9 (-44.9, -40.9)	-6.6 (-15.3, 2.2)	-38.9 (-44.8, -32.4)	<.001
Prespecified subgroup analysis				
Percentage of patients reverting to normoglycemia	95.3%	61.9%	NA	NA

Note: Pooled tirzepatide refers to pooled tirzepatide 5 mg, 10 mg, and 15 mg groups, unless otherwise indicated ; *Data are for the pooled tirzepatide 10 mg and 15 mg groups

†Change from baseline in SF-36 score was assessed using analysis of covariance model with terms for baseline SF-36 PF score, treatment, and stratification factors

†† Lipid parameters and fasting insulin were analyzed using log-transformation. Data presented are model-based estimate ± SE

Note: All changes are from baseline to week 72, unless otherwise stated

CI = Confidence Interval;; ETD = Estimated Treatment Difference; HDL = High-density Lipoprotein; LSM = Least Squares Means; NA = Not Applicable; SBP = Systolic Blood Pressure; SD = Standard Deviation; SE = Standard Error; SF-36v2 = Short Form Health Survey (SF-36) Version 2.

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Change in Additional Secondary Endpoints

Treatment Regimen Estimand

Patients treated with tirzepatide showed greater improvements in total cholesterol, LDL cholesterol, VLDL cholesterol, free fatty acids and DBP than those treated with placebo

	Pooled Tirzepatide LSM (95% CI)	Placebo (N=643) LSM (95% CI)	ETD versus placebo (95% CI)
Percent change in			
Total cholesterol, mg/dL	-4.8 (-5.6, -4.0)	-1.8 (-3.7, 0.1)	-3.1 (-5.2, -1.0)
LDL cholesterol, mg/dL	-5.8 (-6.9, -4.6)	-1.7 (-4.6, 1.3)	-4.2 (-7.2, -1.0)
VLDL cholesterol, mg/dL	-24.4 (-25.9, -22.9)	-4.8 (-9.2, -0.4)	-20.6 (-24.6, -16.4)
Free fatty acids, mEq/L	-7.5 (-10.7, -4.3)	9.5 (3.8, 15.3)	-15.6 (-20.8, -9.9)
Change in DBP, mm Hg	-4.8 (-5.2, -4.4)	-0.8 (-1.6, 0.0)	-4.0 (-4.9, -3.1)

Note: Pooled tirzepatide refers to pooled tirzepatide 5 mg, 10 mg, and 15 mg groups, unless otherwise indicated
All changes are from baseline to week 72, unless otherwise stated

CI = Confidence Interval; DBP = Diastolic Blood Pressure; ETD = Estimated Treatment Difference; LDL = Low-density Lipoprotein; LSM = Least Squares Means; SE = Standard Error; VLDL = Very-low-density Lipoprotein.

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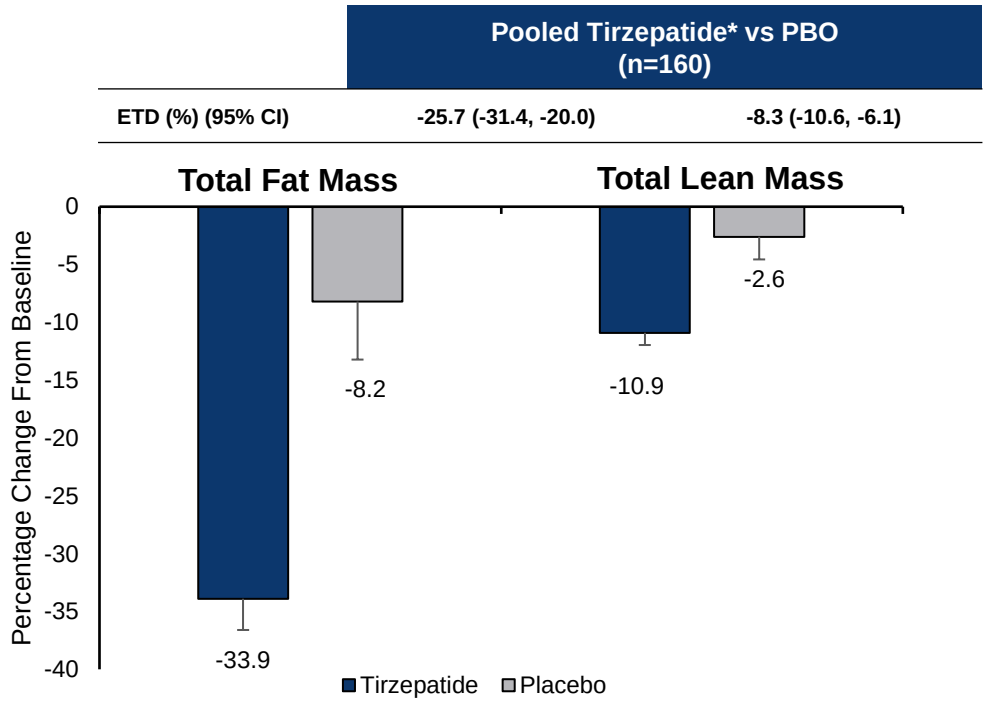
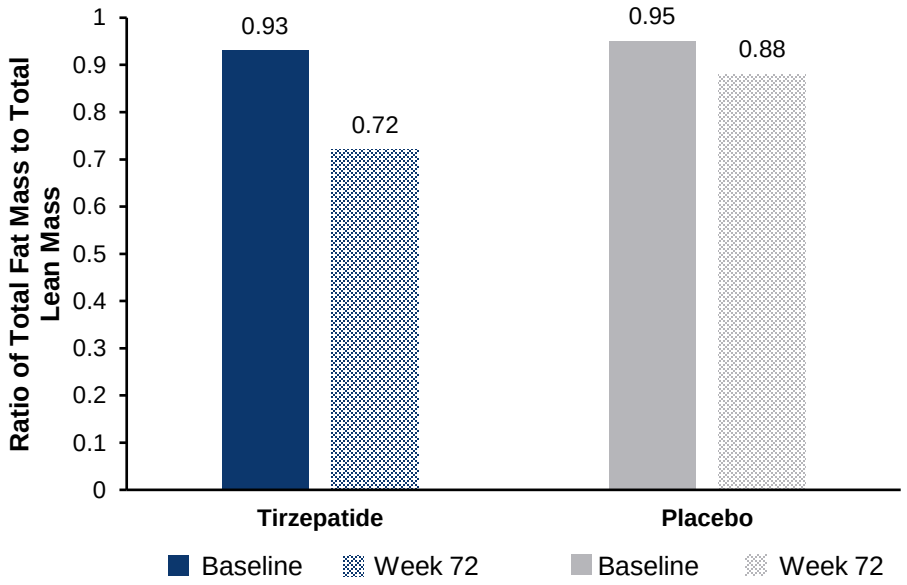
Change in Body Composition

Efficacy Estimand

Treatment with tirzepatide was associated with greater improvements than placebo in total fat mass and total lean mass



The ratio of total fat mass to total lean mass decreased more with tirzepatide than with placebo



Note: Pooled tirzepatide refers to pooled tirzepatide 5 mg, 10 mg, and 15 mg groups, unless otherwise indicated.
The percentage change in total body fat mass from baseline to week 72 was assessed in a subset of participants who underwent dual-energy X-ray absorptiometry (enrolled n=255; completers with both baseline and week 72 DXA n=160).

CI = Confidence Interval; ETD = Estimated Treatment Difference; PBO = Placebo.

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Safety

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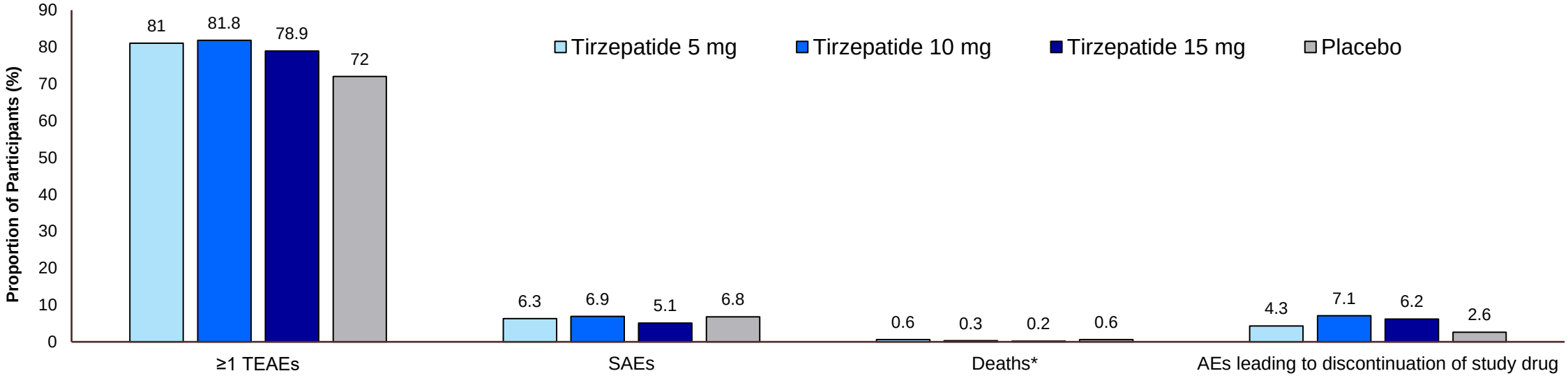
SURMOUNT-1

Overview of Adverse Events



	Tirzepatide 5 mg (N=630)	Tirzepatide 10 mg (N=636)	Tirzepatide 15 mg (N=630)	Placebo (N=643)
Adverse events leading to discontinuation of study drug n (%)	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)
Nausea n (%)	6 (1.0)	7 (1.1)	12 (1.9)	2 (0.3)
Diarrhea n (%)	2 (0.3)	5 (0.8)	3 (0.5)	0
Abdominal pain n (%)	0	2 (0.3)	3 (0.5)	0
Vomiting n (%)	0	4 (0.6)	0	0
Discontinuation of study drug due to gastrointestinal events (%)	1.9	4.4	4.1	0.5

*All deaths were adjudicated by an external committee of physicians; n=4, 2, 1, 4 in tirzepatide 5 mg, 10 mg, 15 mg, and placebo groups, respectively. Three deaths in TZP arms were related to COVID-19 and also included as SAEs.

AE = Adverse Event; SAE = Serious Adverse Event; TEAE = Treatment-emergent Adverse Event; TZP = Tirzepatide.

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Treatment-emergent Adverse Events

Adverse Events n (%)	Tirzepatide 5 mg N=630	Tirzepatide 10 mg N=636	Tirzepatide 15 mg N=630	Placebo N=643
Treatment-emergent adverse events occurring in ≥5% of participants in any treatment group (preferred term)				
Nausea	155 (24.6)	212 (33.3)	195 (31.0)	61 (9.5)
Diarrhea	118 (18.7)	135 (21.2)	145 (23.0)	47 (7.3)
COVID-19	94 (14.9)	98 (15.4)	82 (13.0)	90 (14.0)
Constipation	106 (16.8)	109 (17.1)	74 (11.7)	37 (5.8)
Dyspepsia	56 (8.9)	62 (9.7)	71 (11.3)	27 (4.2)
Vomiting	52 (8.3)	68 (10.7)	77 (12.2)	11 (1.7)
Decreased appetite	59 (9.4)	73 (11.5)	54 (8.6)	21 (3.3)
Headache	41 (6.5)	43 (6.8)	41 (6.5)	42 (6.5)
Abdominal pain	31 (4.9)	34 (5.3)	31 (4.9)	21 (3.3)
Alopecia	32 (5.1)	31 (4.9)	36 (5.7)	6 (0.9)
Dizziness	26 (4.1)	35 (5.5)	26 (4.1)	15 (2.3)
Eructation	24 (3.8)	33 (5.2)	35 (5.6)	4 (0.6)
Injection site reaction	18 (2.9)	36 (5.7)	29 (4.6)	2 (0.3)
Other treatment-emergent adverse events of interest				
Cholelithiasis	7 (1.1)	9 (1.4)	4 (0.6)	6 (0.9)
Cholecystitis	4 (0.6)	3 (0.5)	0	0
Acute cholecystitis	1 (0.2)	4 (0.6)	1 (0.2)	0
Chronic cholecystitis	1 (0.2)	1 (0.2)	3 (0.5)	3 (0.5)

COVID-19 = Coronavirus Disease 2019.

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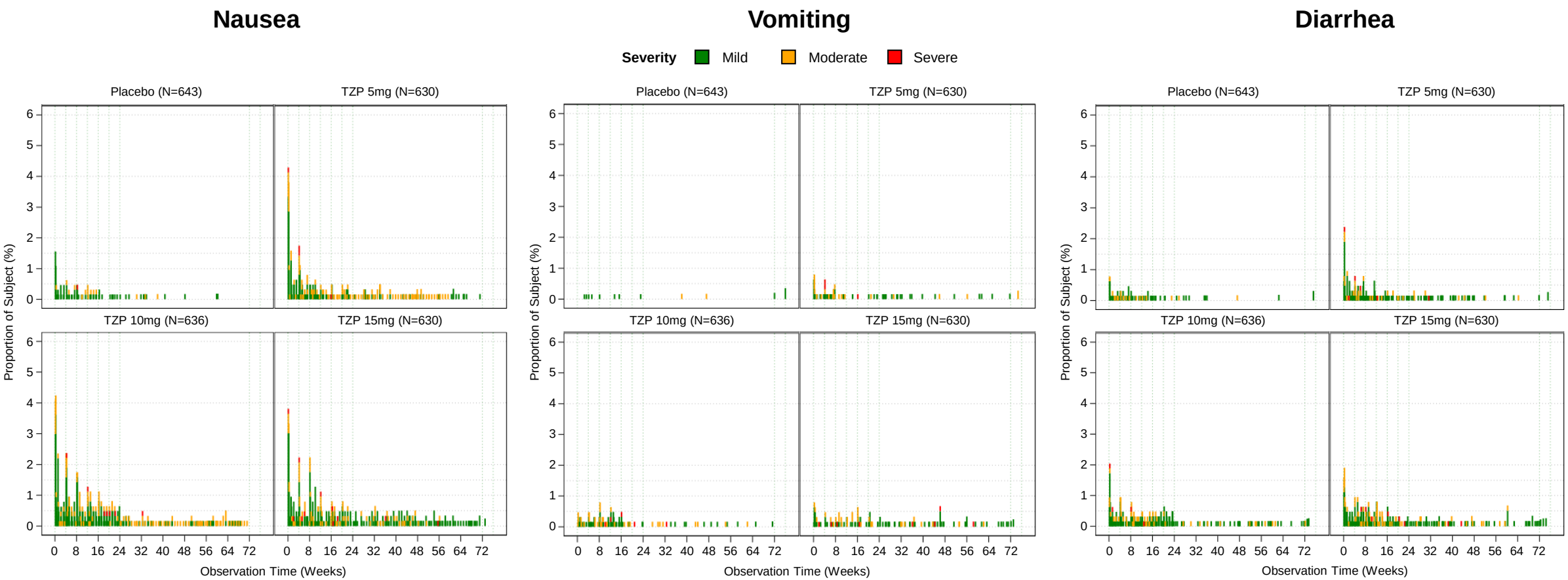
Incidence of Nausea, Vomiting, and Diarrhea Over Time

Most gastrointestinal events were transient, occurring primarily during the dose-escalation period, and were mostly mild to moderate in severity



Note: Percentages are based on number of participants at risk at specific observation time

TZP = Tirzepatide.

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Adverse Events of Special Interest

Adverse events of special interest n (%)	Tirzepatide 5 mg (N=630)	Tirzepatide 10 mg (N=636)	Tirzepatide 15 mg (N=630)	Placebo (N=643)
Hepatic events*	2 (0.3)	2 (0.3)	0	0
Malignancies	9 (1.4)	3 (0.5)	5 (0.8)	7 (1.1)
Pancreatitis (adjudication-confirmed)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
MACE (adjudication-confirmed)	4 (0.6)	5 (0.8)	0	5 (0.8)
Cardiac disorders†	0	1 (0.2)	2 (0.3)	1 (0.2)
Severe or Serious Gastrointestinal Events	11 (1.7)	20 (3.1)	21 (3.3)	7 (1.1)
Gallbladder disease*	5 (0.8)	11 (1.7)	6 (1.0)	5 (0.8)
Renal events*	2 (0.3)	2 (0.3)	2 (0.3)	1 (0.2)
MDD/suicidal ideation*	1 (0.2)	2 (0.3)	2 (0.3)	0
Hypersensitivity‡	0	1 (0.2)	1 (0.2)	0
Hypoglycemia (blood glucose <54 mg/dL)	9 (1.4)	10 (1.6)	10 (1.6)	1 (0.2)

*Events were classified as severe or serious adverse events
†Events were classified as severe or serious supraventricular arrhythmias and cardiac conduction disorders
‡Includes immediate (≤24 hours after trial drug administration) and nonimmediate (>24 hours after trial drug administration) severe or serious hypersensitivity events

MACE = Major Adverse Cardiovascular Events; MDD = Major Depressive Disorder.

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Conclusions

- In the SURMOUNT-1 trial, treatment with tirzepatide 5mg, 10 mg, and 15 mg resulted in significant and substantial degree of weight reductions in participants with obesity, or overweight with ≥1 weight related comorbidities
- Up to 96% of participants achieved >5% weight reduction, with up to 63% of patients achieving ≥20% weight reduction
- ~40% of patients achieved the prespecified exploratory endpoint of >25% weight reduction with TZP 15 mg
- Tirzepatide improved cardiometabolic risk factors and physical function, including waist circumference, systolic and diastolic blood pressure, lipids, fasting insulin, and SF-36v2 physical functioning domain score
- All doses of once-weekly tirzepatide were well-tolerated, with no new safety signal identified
- Findings of SURMOUNT-1 may advance the therapeutic potential of medical treatment options for people living with obesity

SF-36v2 = Short Form Health Survey (SF-36) Version 2.

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Select Supplemental Figures

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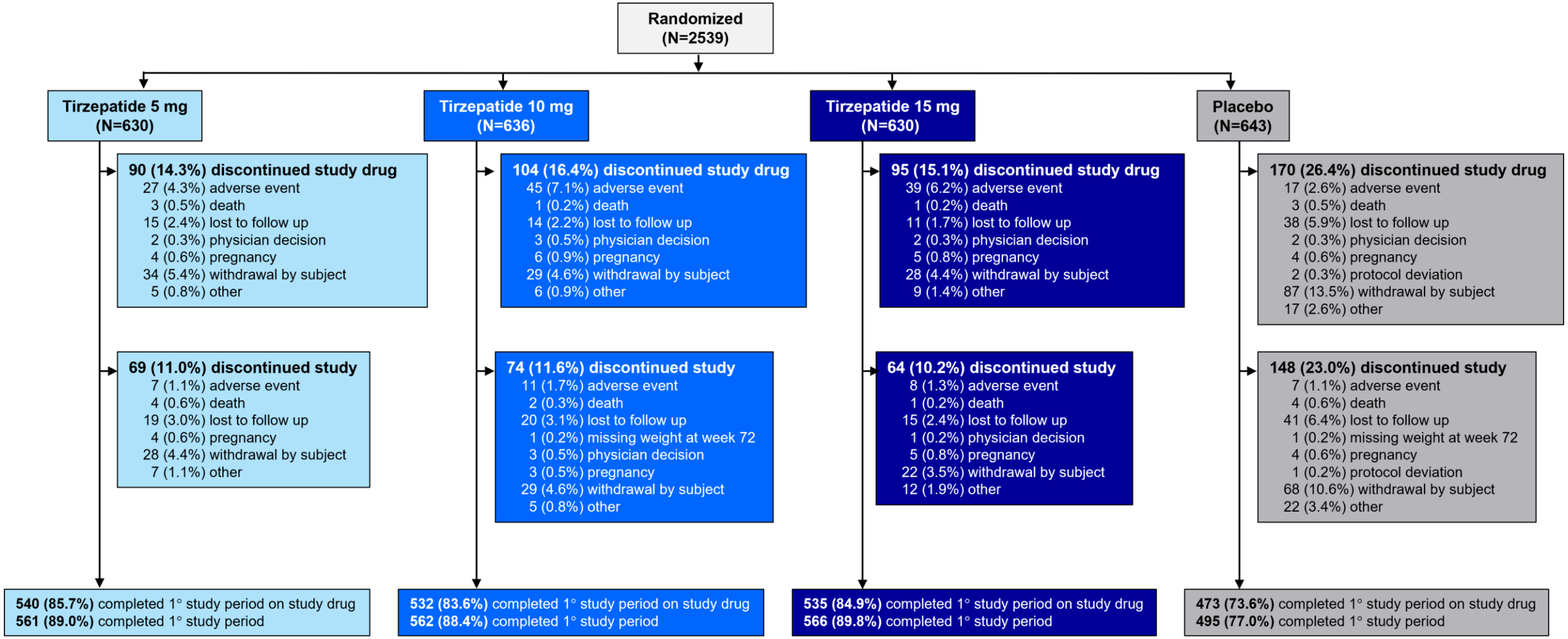
Participant Disposition From Randomization to Primary Endpoint



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Baseline Demographics of US Study Participants

Race/ethnicity of US participants were representative of US demographics

Parameter	TZP 5 mg (N=282)	TZP 10 mg (N=287)	TZP 15 mg (N=284)	Placebo (N=288)	Total (N=1141)
Age, years	48.0 ± 12.7	46.5 ± 12.8	47.2 ± 12.8	46.7 ± 12.6	47.1 ± 12.7
Female, n (%)	197 (69.9)	201 (70.0)	199 (70.1)	201 (69.8)	798 (69.9)
Race*, n (%)					
White	231 (81.9)	231 (80.5)	226 (79.6)	232 (80.6)	920 (80.6)
Black or African American	40 (14.2)	38 (13.2)	43 (15.1)	41 (14.2)	162 (14.2)
Asian	6 (2.1)	10 (3.5)	5 (1.8)	7 (2.4)	28 (2.5)
Multiple	3 (1.1)	6 (2.1)	4 (1.4)	5 (1.7)	18 (1.6)
Native Hawaiian or Other Pacific Islander	2 (0.7)	2 (0.7)	3 (1.1)	2 (0.7)	9 (0.8)
American Indian or Alaska Native	0	0	3 (1.1)	1 (0.3)	4 (0.4)
Ethnicity*, n (%)					
Hispanic or Latino	74 (26.2)	70 (24.4)	75 (26.4)	84 (29.2)	303 (26.6)

*Race and ethnic group were reported by the participants.
Note: Data are mean ± SD, unless otherwise indicated.
In the U.S., where obesity disproportionately affects Black and Hispanic or Latino people, the study population was representative of U.S. demographics, with 14.2% Black and 26.6% Hispanic or Latino participants

TZP = Tirzepatide; US = United States.

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Baseline Clinical Characteristics

Comorbidities

	Tirzepatide 5 mg (N=630)	Tirzepatide 10 mg (N=636)	Tirzepatide 15 mg (N=630)	Placebo (N=643)	Total (N=2539)
Comorbidities, n (%)					
Hypertension	205 (32.5)	208 (32.7)	207 (32.9)	199 (30.9)	819 (32.3)
Dyslipidemia	201 (31.9)	188 (29.6)	182 (28.9)	186 (28.9)	757 (29.8)
ASCVD	16 (2.5)	20 (3.1)	21 (3.3)	21 (3.3)	78 (3.1)
PCOS	7 (1.1)	13 (2.0)	6 (1.0)	13 (2.0)	39 (1.5)
Obstructive sleep apnea	41 (6.5)	51 (8.0)	46 (7.3)	59 (9.2)	197 (7.8)
Osteoarthritis	87 (13.8)	86 (13.5)	77 (12.2)	76 (11.8)	326 (12.8)
Anxiety/Depression	119 (18.9)	101 (15.9)	94 (14.9)	108 (16.8)	422 (16.6)
NAFLD	42 (6.7)	44 (6.9)	48 (7.6)	46 (7.2)	180 (7.1)
Asthma or COPD	72 (11.4)	64 (10.1)	53 (8.4)	78 (12.1)	267 (10.5)
Gout	35 (5.6)	34 (5.3)	32 (5.1)	35 (5.4)	136 (5.4)
Number of comorbidities, n (%)					
None	220 (34.9)	230 (36.2)	249 (39.5)	245 (38.1)	944 (37.2)
1-2	295 (46.8)	294 (46.2)	284 (45.1)	280 (43.6)	1153 (45.4)
3-4	94 (15.0)	96 (15.1)	86 (13.7)	103 (16.1)	379 (14.9)
≥5	21 (3.3)	16 (2.5)	11 (1.7)	15 (2.3)	63 (2.5)
SF-36v2 short form physical functioning domain score	49.6 ± 8.3	49.6 ± 7.5	49.6 ± 7.8	49.7 ± 7.7	49.6 ± 7.8

Data are mean ± SD, unless otherwise indicated; *The value of the eGFR was calculated according to the serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

BMI = Body Mass Index; DBP = Diastolic Blood Pressure; eGFR = Estimated Glomerular Filtration Rate; HbA1c = Glycated Hemoglobin; SBP = Systolic Blood Pressure; SD = Standard Deviation.

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Additional Safety Measures

	Normal range	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
Pulse, bpm	60-100 bpm				
Baseline		72.4 ± 0.38	71.8 ± 0.38	72.4 ± 0.38	72.9 ± 0.38
Week 72		72.8 ± 0.35	74.6 ± 0.35	74.8 ±0.35	72.4 ± 0.37
Change at week 72		0.6 ± 0.35	2.3 ± 0.35	2.6 ± 0.35	0.1 ± 0.37
Pancreatic-amylase, U/L	3-46 U/L				
Baseline		24.1 ± 0.36	23.6 ± 0.35	24.1 ± 0.36	24.2 ± 0.36
Week 72		28.6 ± 0.31	29.2 ± 0.31	28.8 ± 0.31	24.7 ± 0.28
% change at week 72		18.2 ± 1.27	20.8 ± 1.29	19.1 ± 1.27	2.2 ± 1.15
Lipase, U/L	0-100 U/L				
Baseline		29.2 ± 0.47	28.3 ± 0.46	28.4 ± 0.46	28.9 ± 0.46
Week 72		37.2 ± 0.54	38.9 ± 0.56	38.9 ± 0.56	30.4 ± 0.46
% change at week 72		29.2 ± 1.87	35.3 ± 1.96	35.1 ± 1.95	5.6 ± 1.95
Aspartate aminotransferase, U/L	8-40 U/L				
Baseline		20.3 ± 0.29	20.6 ± 0.30	20.8 ± 0.30	20.6 ± 0.30
Week 72		18.3 ± 0.23	18.1 ± 0.23	17.7 ± 0.22	19.3 ± 0.25
% change at week 72		-11.4 ± 1.11	-12.1 ± 1.10	-14.2 ± 1.07	-6.6 ± 1.23
Alanine aminotransferase, U/L	Female: 4-43 U/L; Male: 5-48 U/L				
Baseline		23.1 ± 0.49	23.5 ± 0.50	23.6 ± 0.50	23.5 ± 0.50
Week 72		17.4 ± 0.32	16.8 ± 0.31	16.3 ± 0.30	20.4 ± 0.40
% change at week 72		-25.7 ± 1.37	-28.1 ± 1.33	-30.3 ± 1.29	-12.8 ± 1.69
Calcitonin, ng/L	Female: <5.0 ng/L (<1.46 pmol/L); Male: <8.4 ng/L (<2.46 pmol/L)				
Baseline		1.3 ± 0.03	1.3 ± 0.03	1.3 ± 0.03	1.3 ± 0.03
Week 72		1.4 ± 0.03	1.4 ± 0.03	1.5 ± 0.03	1.3 ± 0.03
% change at week 72		6.9 ± 1.97	10.5 ± 2.04	15.2 ± 2.12	2.8 ± 1.99
Urine Albumin-to-Creatinine Ratio, mg/g	0-30 mg/g				
Baseline		7.6 ± 0.30	7.9 ± 0.31	8.0 ± 0.31	7.6 ± 0.30
Week 72		6.8 ±0.20	6.7 ± 0.20	6.9 ± 0.21	7.4 ± 0.23
% change at week 72		-10.8 ± 2.66	-12.3 ± 2.63	-9.3 ± 2.69	-3.2 ± 3.05

Data are arithmetic mean ± standard error. Note: except for pulse, all other measures were analyzed with log-transformation.

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COVID-19-related Adverse Events

Adverse Events n (%)	Tirzepatide 5 mg (N=630)	Tirzepatide 10 mg (N=636)	Tirzepatide 15 mg (N=630)	Placebo (N=643)	Total (N=2539)
Deaths related to COVID-19*	2 (0.3)	0	1 (0.2)	0	3 (0.1)
Serious adverse events related to COVID-19					
COVID-19 pneumonia	6 (1.0)	3 (0.5)	3 (0.5)	4 (0.6)	16 (0.6)
COVID-19	1 (0.2)	6 (0.9)	1 (0.2)	6 (0.9)	14 (0.6)
Coronavirus infection	1 (0.2)	0	0	0	1 (0.04)
Coronavirus pneumonia	0	1 (0.2)	0	0	1 (0.04)
SARS-CoV-2 test positive	1 (0.2)	0	1 (0.2)	0	2 (0.1)
TEAEs related to COVID-19					
Coronavirus test positive	1 (0.2)	1 (0.2)	0	3 (0.5)	5 (0.2)
COVID-19	94 (14.9)	98 (15.4)	82 (13.0)	90 (14.0)	364 (14.3)
COVID-19 pneumonia	7 (1.1)	5 (0.8)	5 (0.8)	5 (0.8)	22 (0.9)
Suspected COVID-19	2 (0.3)	1 (0.2)	0	2 (0.3)	5 (0.2)
SARS-CoV-2 test positive	5 (0.8)	1 (0.2)	6 (1.0)	6 (0.9)	18 (0.7)
Exposure to SARS-CoV-2	0	1 (0.2)	0	0	1 (0.04)
Coronavirus infection	4 (0.6)	1 (0.2)	0	4 (0.6)	9 (0.4)
Post-acute COVID-19 syndrome	0	0	1 (0.2)	1 (0.2)	2 (0.1)
Coronavirus pneumonia	0	1 (0.2)	0	0	1 (0.04)

Data are number of participants (%). *Deaths are also included as serious adverse events.

COVID-19 = Coronavirus Disease 2019; TEAE = Treatment-emergent Adverse Events; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus-2.

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Deaths Reported During the Study

Eleven deaths reported, 4 in tirzepatide 5 mg group, 2 in tirzepatide 10 mg group, 1 in tirzepatide 15 mg group, and 4 in placebo group

Patient (age, sex)	Treatment Group	Description	Days From Randomization	Days Since Last Dose of Study Drug	Cause of Death as Reported by the Investigator
47 y, male	Placebo	Pulmonary embolism	312	31	Pulmonary embolism
59 y, male	Placebo	Cardiac failure acute	183	5	Acute heart failure
45 y, female	Placebo	Intestinal obstruction	370	299	Intestinal sub-occlusion
76 y, female	Placebo	Ischemic stroke	480	38	Ischemic stroke
45 y, female	Tirzepatide 5 mg	Hepatic failure with polysubstance use* and SARS-CoV-2 infection	318	14	Hepatic failure
59 y, male	Tirzepatide 5 mg	COVID-19 pneumonia	263	94	Acute respiratory distress syndrome (Pneumonia/COVID-19)
62 y, male	Tirzepatide 5 mg	COVID-19 pneumonia	94	44	COVID-19 pneumonia
38 y, male	Tirzepatide 5 mg	Multiple injuries	29	0	Severe polytrauma
36 y, male	Tirzepatide 10 mg	Homicide	260	4	Homicide
68 y, male	Tirzepatide 10 mg	Cerebrovascular accident	325	295	Stroke (suspected)
61 y, male	Tirzepatide 15 mg	SARS-CoV-2 test positive	96	18	COVID-19 positive

*Including alcohol, cocaine, ibuprofen, and opiates.

COVID-19 = Coronavirus Disease 2019; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus-2; y = Years.

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