Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity
The SURMOUNT-4 Randomized Clinical Trial

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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[3-7] in people with diabetes
- TZP is in phase 3 development for adults with obesity or overweight with weight-related comorbidities[1]
- Randomized withdrawal studies with anti-obesity medications to-date have consistently demonstrated clinically significant body weight regain with cessation of therapy[8,9]
- SURMOUNT-4, a Phase 3, randomized withdrawal trial, investigated the effect of continued treatment with maximum tolerated dose, i.e., 10 mg or 15 mg, of once-weekly tirzepatide, compared to placebo, on the maintenance of weight reduction[10]

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

1. Jastreboff AM, et al. *New Engl J Med*. 2022; 387(3):205-216. 2. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-dual-targeted-treatment-type-2-diabetes 3.Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 4. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 5. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 6. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 7. Dahl D, et al. *JAMA*. 2022; 327(6):534-545. 8. Rubino D, et al. *JAMA*. 2021; 325(14):1414-25. 9. James WP, et al. *Lancet.* 2000; 356(9248):2119-25. 10. Aronne LJ, et al. *JAMA.* 2024;331(1):38-48.

Primary and Key Secondary Endpoints

Primary Endpoints

To demonstrate maximum tolerated dose (10 or 15 mg) once weekly is superior to placebo at 88 weeks for:

- Mean percentage change in body weight from randomization (week 36)

Key Secondary Endpoints

To demonstrate maximum tolerated dose (10 or 15 mg) once weekly is superior to placebo for:

- Proportion of participants at week 88 maintaining ≥80% of the body weight lost during the 36-week open-label period
- Time during the 52-week double-blind treatment period to first occurrence of participants returning to >95% baseline body weight for those who had lost at least 5% during the open-label lead-in
- Mean change in absolute body weight (kg) and waist circumference during the double-blind period (week 36 to 88)
- Proportion of participants achieving weight reduction thresholds of ≥5%, ≥10%, ≥15%, and ≥20% since enrollment (week 0 to 88)

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Additional Secondary and Exploratory Endpoints

Additional Secondary Endpoints

To demonstrate maximum tolerated dose (10 or 15 mg) once weekly is superior to placebo for:

- Mean change from randomization (week 36) to week 88 or from enrollment (week 0) to week 88 in
  - Cardiometabolic risk factors including
    - Glycemic parameters
    - Fasting insulin
    - Lipids
    - Blood pressure
  - Patient-reported outcomes measured by SF-36 v2 acute form and IWQOL-Lite-CT Version

Prespecified Exploratory Endpoint

To demonstrate maximum tolerated dose (10 or 15 mg) once weekly is superior to placebo for:

- Proportion of participants achieving ≥25% weight reduction from week 0 to 88

IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite-Clinical Trials Version; SF-36v2=Short Form-36 Version 2.

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Study Design and Inclusion Criteria of Participants

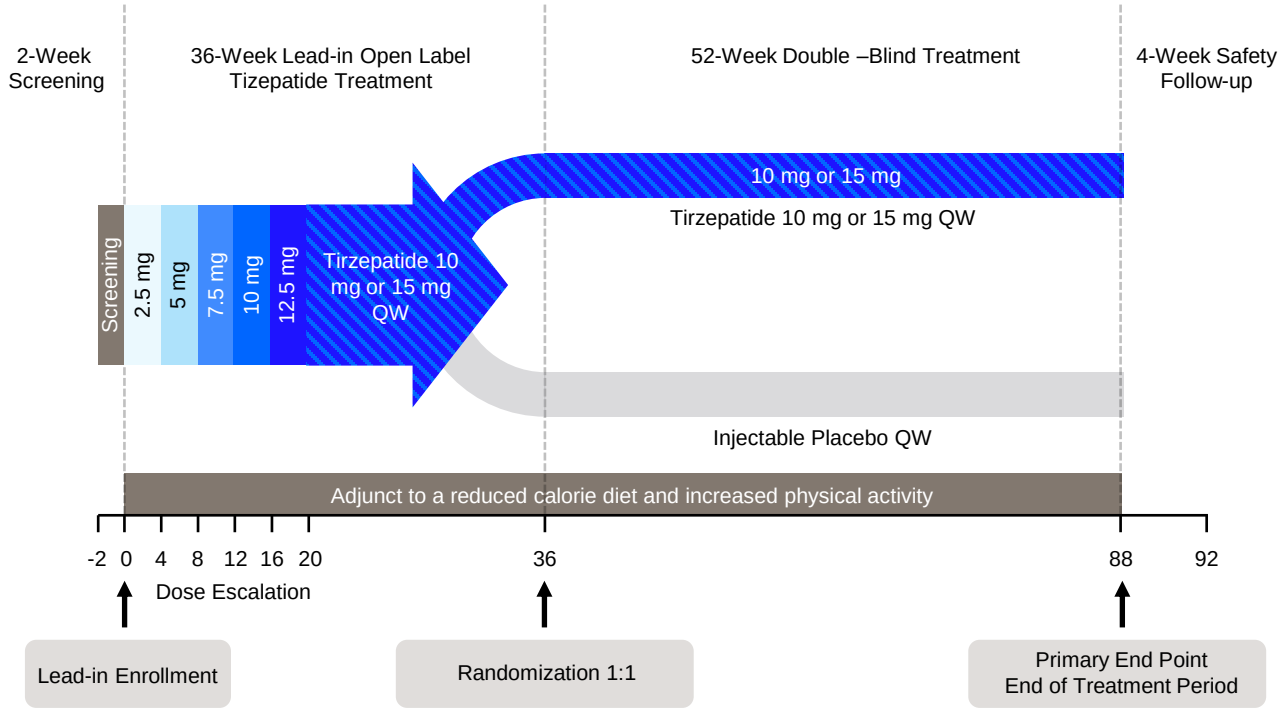
A phase 3, randomized withdrawal study with a 36-week, open-label Tirzepatide lead-in period followed by a 52-week, double-blind, placebo-controlled period conducted at 70 sites in 4 countries

1 Key Inclusion Criteria

- Age ≥18 years
- BMI
  - ≥30 kg/m^2 or
  - ≥27 kg/m^2 and at least 1 weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease)
- History of ≥1 self-reported unsuccessful dietary effort 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
- Prior or planned surgical treatment for obesity
- Treatment with a medication that promotes weight loss < 3 months prior to enrollment



BMI = Body Mass Index; QW = Once Weekly.

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Baseline Demographics and Clinical Characteristics at Week 0 and Week 36 (1 of 4)

	Week 0 (Start of Tirzepatide Lead-In Treatment Period) (N=670)	Week 36 (Randomization)	
		Tirzepatide (N=335)	Placebo (N=335)
Age, years	48 (13)	49 (13)	48 (12)
Age category, n (%)			
<65	603 (90.0)	296 (88.4)	302 (90.1)
≥65	67 (10.0)	39 (11.6)	33 (9.9)
Sex, n (%)			
Female	473 (70.6)	236 (70.4)	237 (70.7)
Male	197 (29.4)	99 (29.6)	98 (29.3)
Race, n (%)[a]			
White	537 (80.1)	264 (78.8)	273 (81.5)
Black or African American	75 (11.2)	39 (11.6)	36 (10.7)
Asian	48 (7.2)	26 (7.8)	22 (6.6)
Multiple	8 (1.2)	5 (1.5)	3 (0.9)
Native Hawaiian or other Pacific Islander	2 (0.3)	1 (0.3)	1 (0.3)
Hispanic or Latino Ethnicity, n (%)[a]	296 (44.2)	141 (42.1)	155 (46.3)
Duration of obesity, years[b]	15.5 (11.8)	15.9 (12.1)	15.2 (11.4)
Body weight, kg	107.3 (22.3)	84.6 (19.8)	85.8 (22.3)

Note=Data are mean ± SD or n (%) from randomized participants unless specified.
[a]Race and ethnicity were recorded in this study and were determined by the participant according to fixed selection categories; [b]Duration of obesity was self-reported by participants.
SD=Standard Deviation.
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Baseline Demographics and Clinical Characteristics at Week 0 and Week 36 (2 of 4)

	Week 0 (Start of Tirzepatide Lead-In Treatment Period) (N=670)	Week 36 (Randomization)	
		Tirzepatide (N=335)	Placebo (N=335)
BMI, kg/m²	38.4 (6.6)	30.3 (6.0)	30.7 (6.8)
BMI category, n (%)			
<25	-	59 (17.6)	63 (18.8)
≥25 to <30	18 (2.7)	122 (36.4)	120 (35.8)
≥30 to <35	212 (31.6)	88 (26.3)	75 (22.4)
≥35 to <40	215 (32.1)	41 (12.2)	43 (12.8)
≥40	225 (33.6)	25 (7.5)	34 (10.1)
Waist circumference, mean (SD), cm	115.2 (14.5)	96.8 (14.1)	98.2 (16.0)
Blood pressure, mean (SD), mmHg			
Systolic	126 (13)	115 (13)	115 (12)
Diastolic	81 (8)	75 (9)	76 (9)
Pulse rate, mean (SD), beats/min	72 (9)	77 (9)	78 (9)
Hemoglobin A_{1c}, mean (SD), %	5.54 (0.36)	5.07 (0.30)	5.04 (0.31)
Fasting glucose, mean (SD), mg/dL	94 .8 (10.9)	85.1 (7.4)	85.0 (7.8)
Fasting insulin, mean (SD), mIU/L	13.9 (10.7)	7.4 (5.2)	8.0 (6.3)

Note=Data are mean ± SD or n (%) from randomized participants unless specified.
BMI=Body Mass Index; SD=Standard Deviation.
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Baseline Demographics and Clinical Characteristics at Week 0 and Week 36 (3 of 4)

	Week 0 (Start of Tirzepatide Lead-In Treatment Period) (N=670)	Week 36 (Randomization)	
		Tirzepatide (N=335)	Placebo (N=335)
Lipid levels, mean (SD), mg/dL			
Total cholesterol	192.3 (39.6)	179.9 (36.8)	180.2 (37.3)
Non-HDL-C	140.8 (37.5)	130.8 (34.5)	131.7 (36.2)
HDL-C	51.5 (13.1)	49.1 (11.6)	48.8 (11.5)
LDL-C	113.8 (32.9)	111.0 (32.4)	113.2 (33.6)
VLDL-C	60.3 (27.7)	45.3 (20.7)	41.4 (16.4)
Triglycerides	136.2 (80.9)	99.1 (45.1)	93.0 (44.3)
Free fatty acids, mEq/L	0.53 (0.22)	0.48 (0.20)	0.51 (0.22)
eGFR, mean (SD), ml/min/1.73 m^2	97.8 (17.2)	96.4 (18.8)	97.9 (17.9)
eGFR category, n (%)			
≥30 to <45	2 (0.3)	2 (0.6)	1 (0.3)
≥45 to <60	12 (1.8)	7 (2.1)	7 (2.1)
≥60 to <90	189 (28.2)	108 (32.2)	89 (26.6)
≥90	467 (69.7)	218 (65.1)	238 (71.0)

Note=Data are mean ± SD or n (%) from randomized participants unless specified.
eGFR=Estimated Glomerular Filtration Rate; HDL-C=High-Density Lipoprotein Cholesterol; IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite-Clinical Trials Version; LDL-C=Low-Density Lipoprotein Cholesterol; SF-36v2=Short Form-36 Version; VLDL-C=Very Low-Density Lipoprotein Cholesterol.
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Baseline Demographics and Clinical Characteristics at Week 0 and Week 36 (4 of 4)

	Week 0 (Start of Tirzepatide Lead-In Treatment Period) (N=670)	Week 36 (Randomization)	
		Tirzepatide (N=335)	Placebo (N=335)
SF-36v2 scores, mean (SD)[c,d]	(N=581)	(N=303)	(N=276)
Physical functioning domain	47.9 (8.1)	53.4 (5.9)	53.4 (6.4)
Role-physical domain	50.4 (7.7)	54.6 (4.9)	53.7 (6.8)
Role-emotional domain	49.8 (8.8)	52.5 (6.9)	52.2 (7.5)
Mental health domain	52.8 (7.6)	54.8 (6.5)	55.3 (6.7)
IWQOL-Lite-CT physical function composite score, mean (SD)[c,e]	59.6 (24.5) (N=581)	81.0 (17.0) (N=301)	81.7 (18.2) (N=278)

Note=Data are mean ± SD or n (%) from randomized participants unless specified. [c]Number of participants for patient-reported outcomes is from the efficacy analysis set, which is different from the number in the randomized population, and the participant numbers are provided; [d]The SF-36 v2 measures health-related quality of life and general health status. The SF-36 v2 scores are norm-based scores, i.e., 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; [e]The 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.

eGFR=Estimated Glomerular Filtration Rate; HDL-C=High-Density Lipoprotein Cholesterol; IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite-Clinical Trials Version; LDL-C=Low-Density Lipoprotein Cholesterol; SF-36v2=Short Form-36 Version; VLDL-C=Very Low-Density Lipoprotein Cholesterol.

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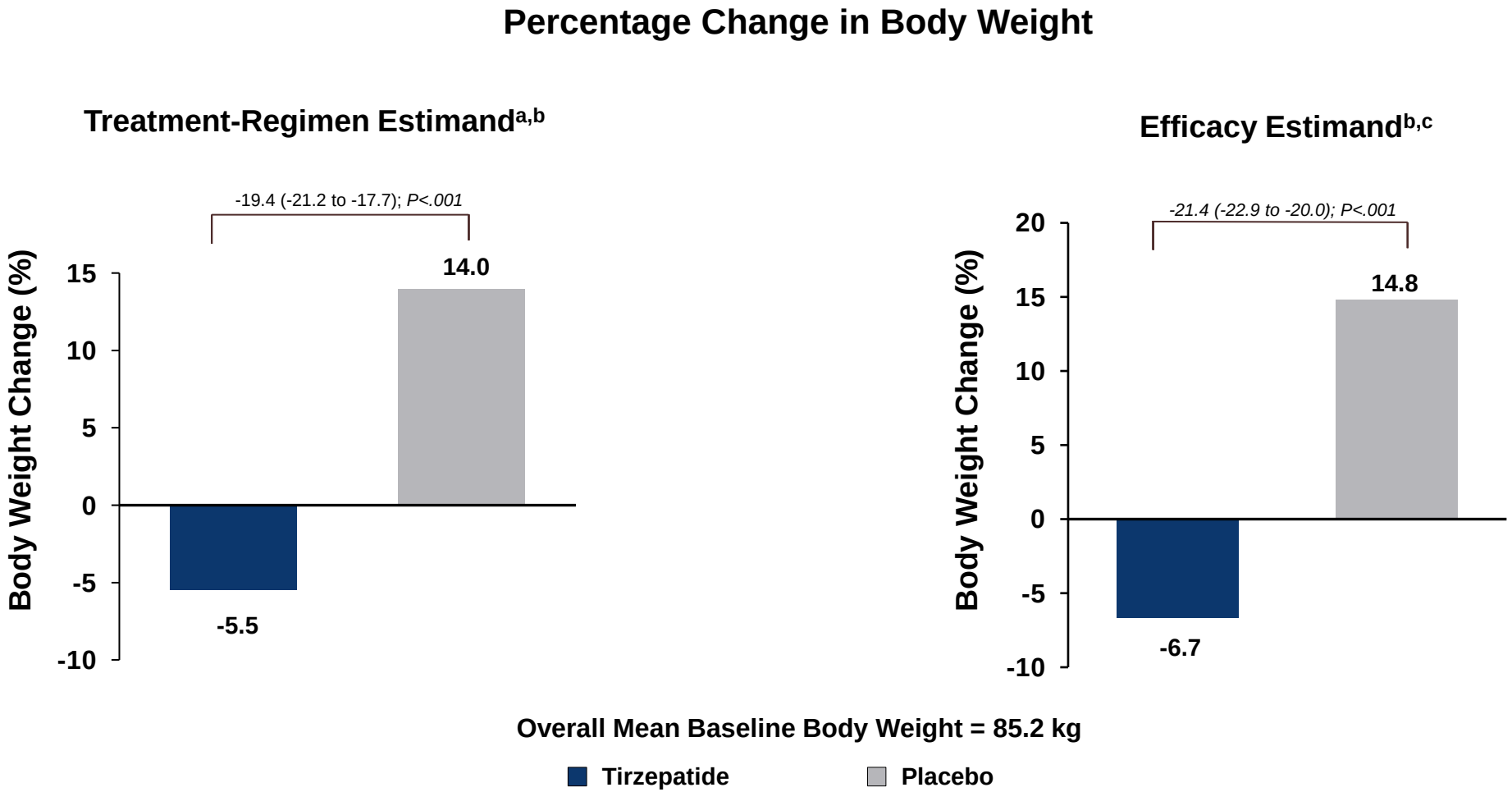
Efficacy outcomes

Change in Body Weight (%) from Week 36 to Week 88



Note=Data are LSM (SE) unless specified.

[a]Treatment regimen estimand (corresponding analyses used the full analysis set) evaluated treatment effects regardless of treatment adherence; [b]Tested for superiority, controlled for Type 1 error; [c]Efficacy estimand (corresponding analyses used the efficacy analysis set) evaluated treatment effects using on-treatment data prior to discontinuation of study drug.

LSM=Least Square MeanSE=Standard Error.

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Change in Body Weight (kg) from Week 36 to Week 88

Note=Data are LSM (SE) unless specified.

[a]Treatment regimen estimand (corresponding analyses used the full analysis set) evaluated treatment effects regardless of treatment adherence; [b]Tested for superiority, controlled for Type 1 error; [c]Efficacy estimand (corresponding analyses used the efficacy analysis set) evaluated treatment effects using on-treatment data prior to discontinuation of study drug.

LSM=Least Square Mean; SE=Standard Error.

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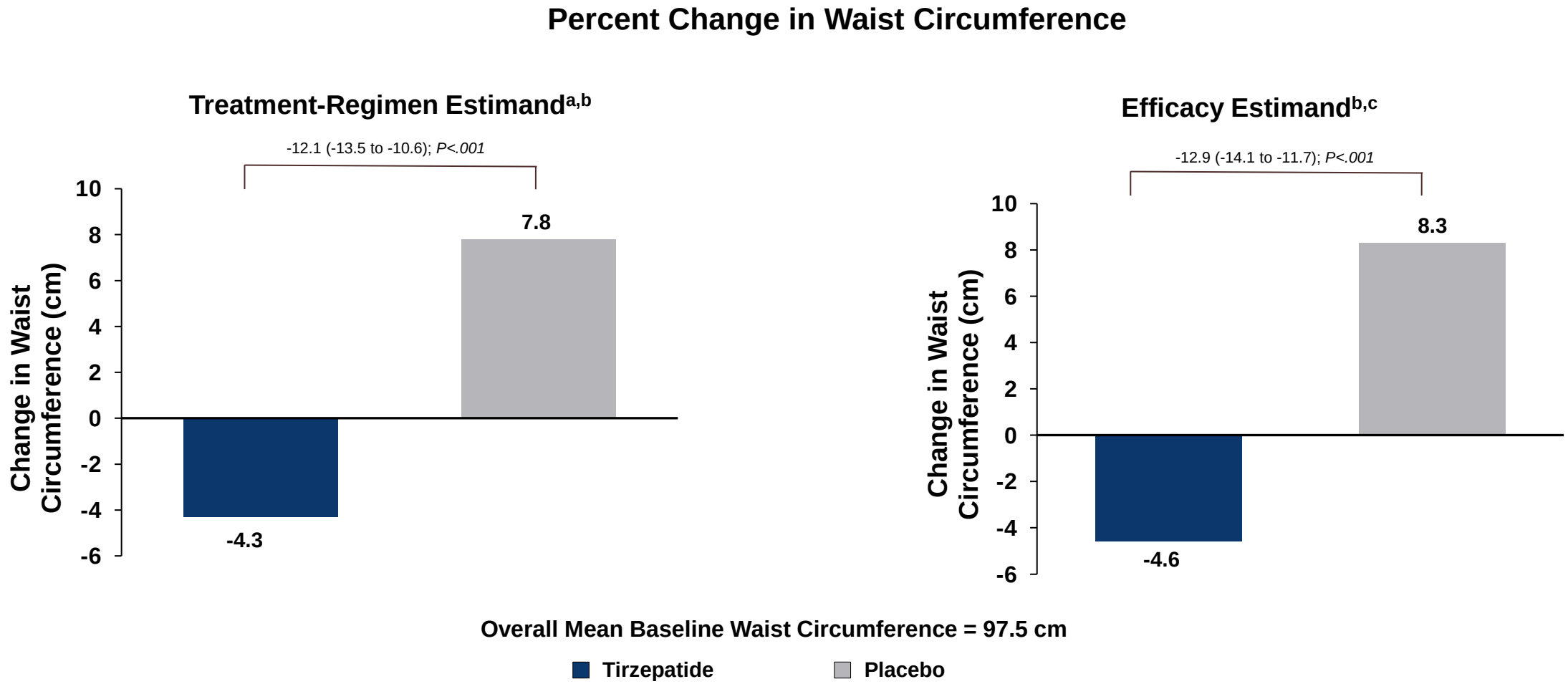
Change in Waist Circumference from Week 36 to Week 88



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LSM=Least Square Mean; SE=Standard Error.
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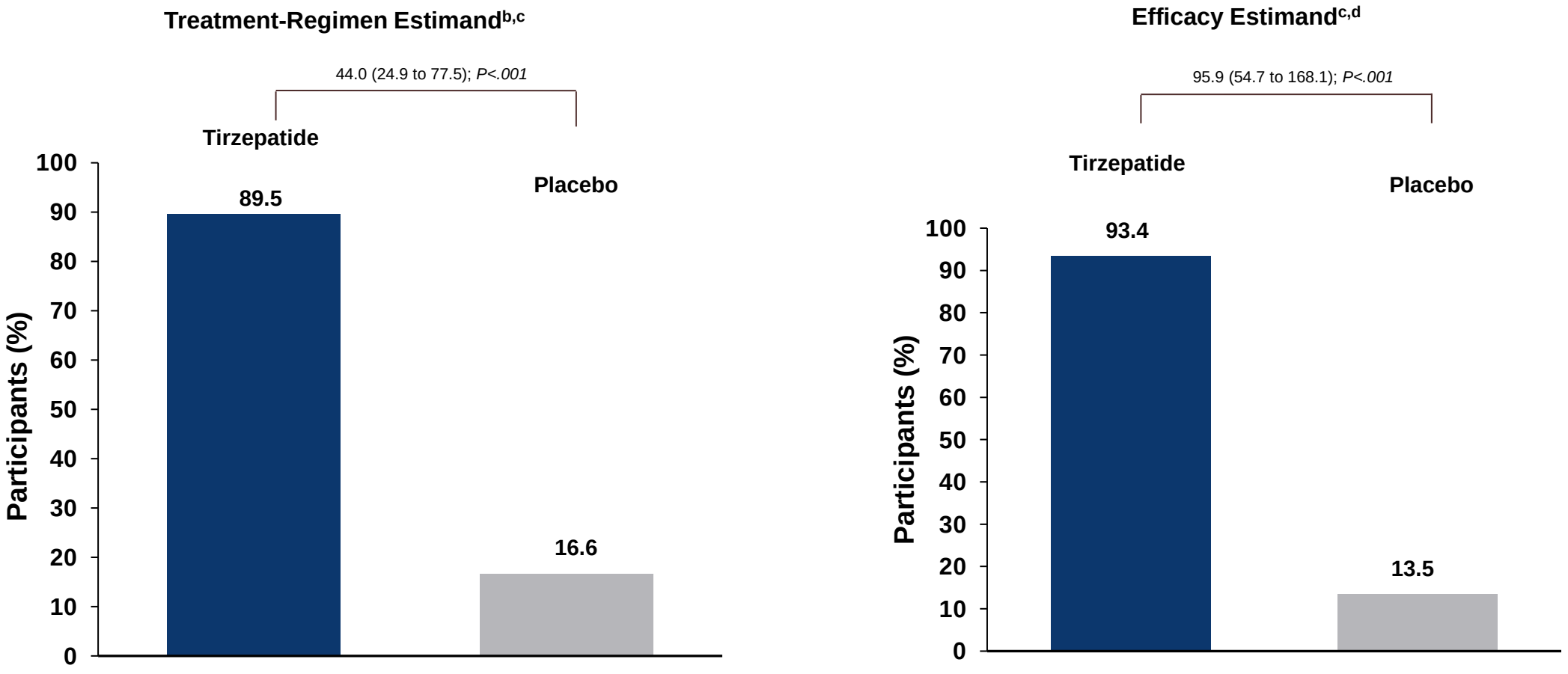
Participants Achieving Weight-Maintenance Target at Week 88[a]

Percent of Participants Maintaining ≥80% of Weight Lost During Lead-In Period



Note=Data are LSM (SE) unless specified.

[a]Participants maintaining ≥80% of body weight lost; [b]Treatment regimen estimand (corresponding analyses used the full analysis set) evaluated treatment effects regardless of treatment adherence; [c]Tested for superiority, controlled for Type 1 error; [d]Efficacy estimand (corresponding analyses used the efficacy analysis set) evaluated treatment effects using on-treatment data prior to discontinuation of study drug.

LSM=Least Square Mean SE=Standard Error.

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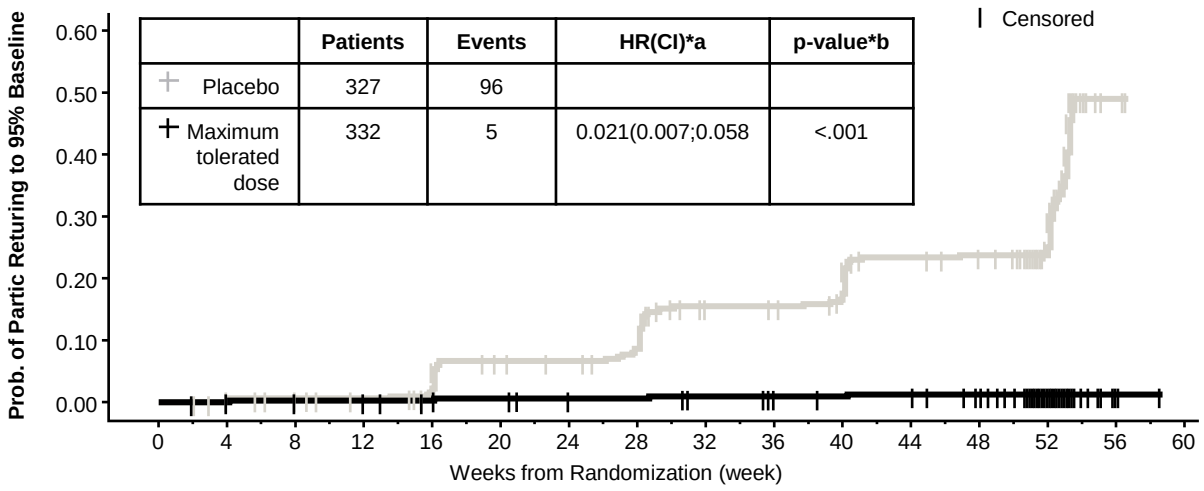
Time to First Occurrence of Participants Returning to >95% Baseline Weight in Those Who Had Lost ≥5% Weight Since Week 0

Time to Event Analysis[c]

Treatment-Regimen Estimand[d,f]

	Patients	Events	HR(CI)*a	p-value*b
Placebo	327	96		
Maximum tolerated dose	332	5	0.021(0.007;0.058	<.001

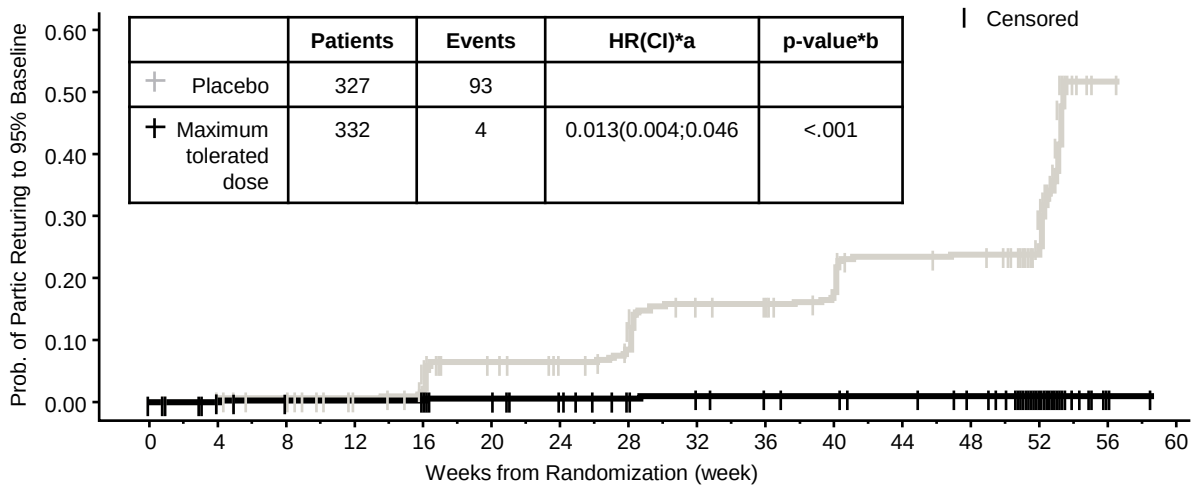


#At Risk

Placebo	327	325	319	315	309	290	288	280	252	250	244	221	218	175	4	1
TZP	332	331	329	327	323	321	319	317	314	312	310	309	306	240	6	1

Efficacy Estimand[e,f]

	Patients	Events	HR(CI)*a	p-value*b
Placebo	327	93		
Maximum tolerated dose	332	4	0.013(0.004;0.046	<.001



#At Risk

Placebo	327	322	315	309	303	281	276	267	239	237	229	208	206	167	2	0
TZP	332	329	324	322	322	316	313	307	303	300	298	296	294	235	5	1

[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. [c]An event is defined as the first occurrence of participant returning to >95% baseline body weight since week 0. [d]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. [e]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. [f]In both estimands, hazard ratio was computed by Cox proportional hazards model with terms of treatment, country, sex, maximum tolerated dose at randomization (week 36), and weight at randomization (week 36) and at week 0 as covariates.

CI=Confidence Interval; HR=Hazard Ratio; TZP= Tirzepatide.

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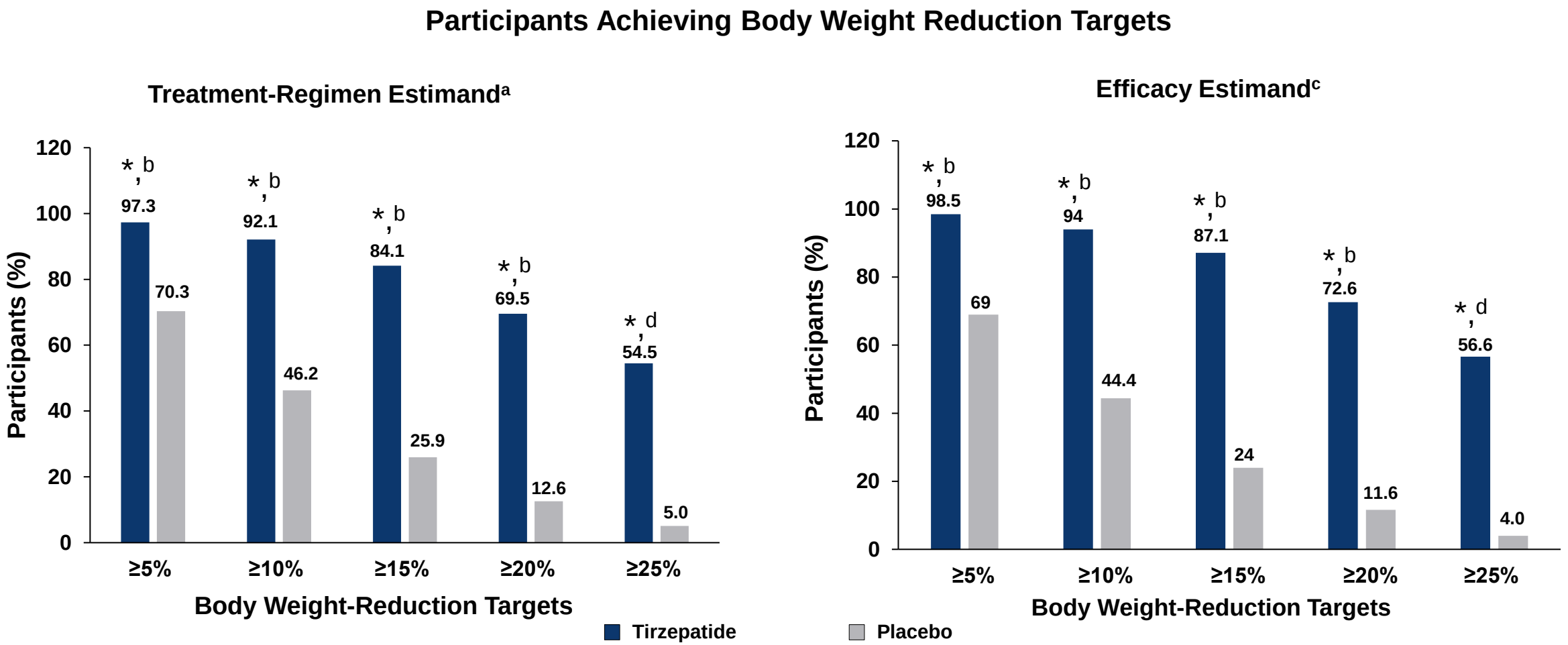
Participants Achieving Weight Reduction Targets from Week 0 to Week 88



Notes=*P<.001; Data are LSM (SE) unless specified.

[a]Treatment regimen estimand (corresponding analyses used the full analysis set) evaluated treatment effects regardless of treatment adherence; [b]Tested for superiority, controlled for Type 1 error; [c]Efficacy estimand (corresponding analyses used the efficacy analysis set) evaluated treatment effects using on-treatment data prior to discontinuation of study drug; [d]Tested for significant difference, not controlled for Type 1 error.

LSM=Least Square Mean; SE=Standard Error

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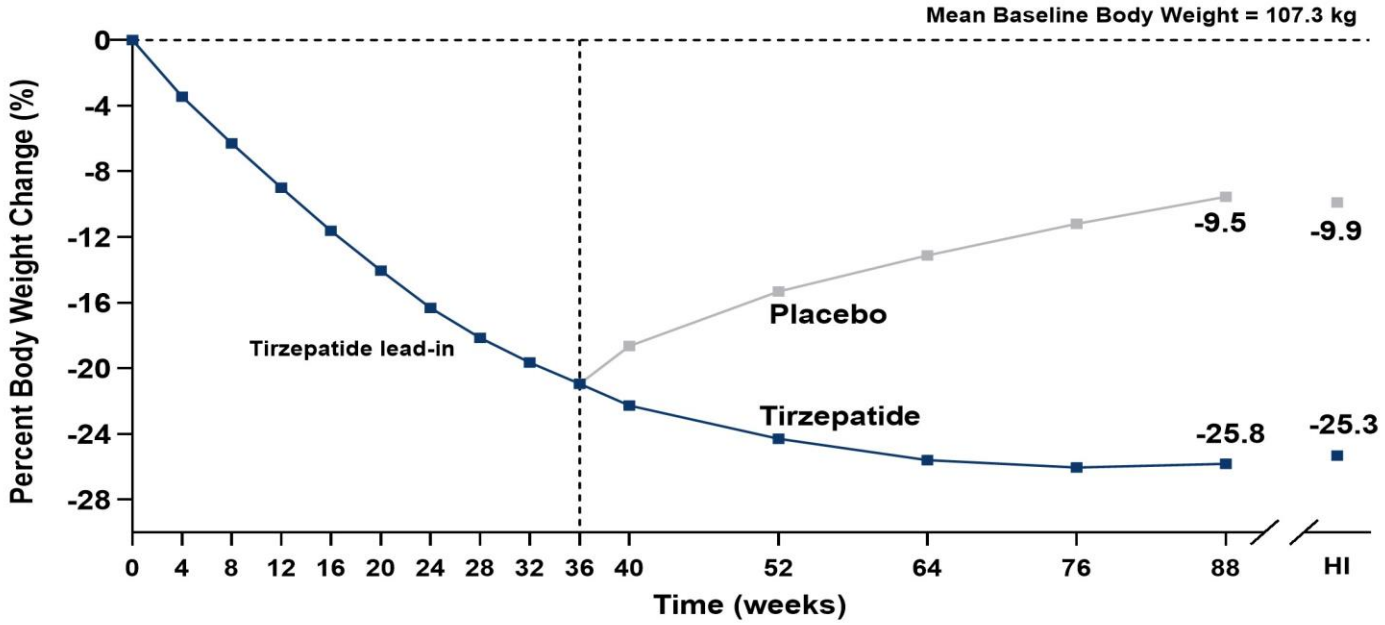
Change in Body Weight from Week 0 to Week 88

Percent Change in Body Weight



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	335
Placebo											335	330	317	303	292	289	335

Notes=Data are observed mean values; The dashed vertical line at week 36 represents the randomization time point; Analysis of covariance with hybrid imputation least square means at week 88 are also shown on the right; The number of participants shown denote those contributing to the mean.
H=Hybrid Imputation;
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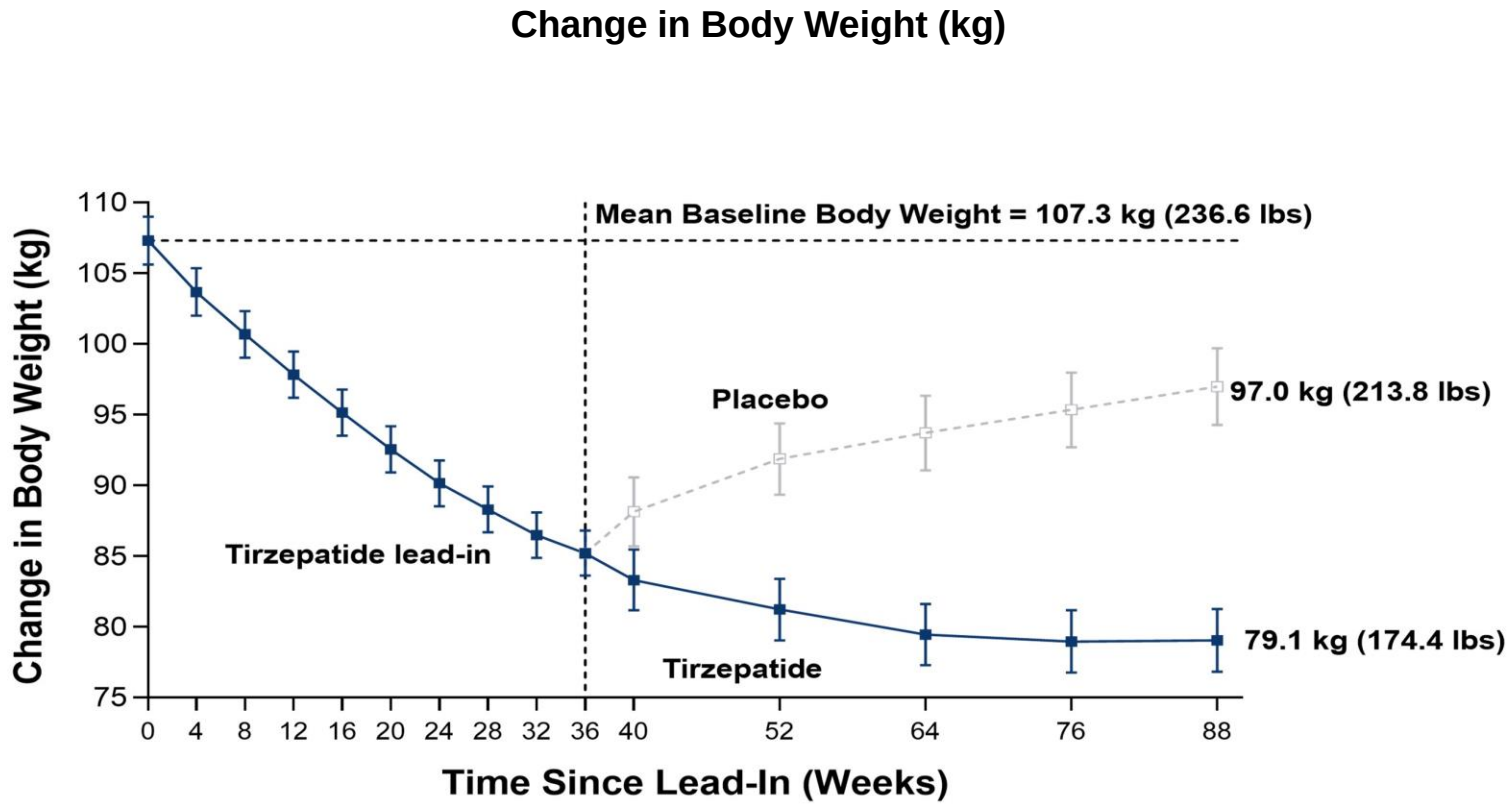
Change in Body Weight from Week 0 to Week 88



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

Notes=Data are observed mean values; The dashed vertical line at week 36 represents the randomization time point.
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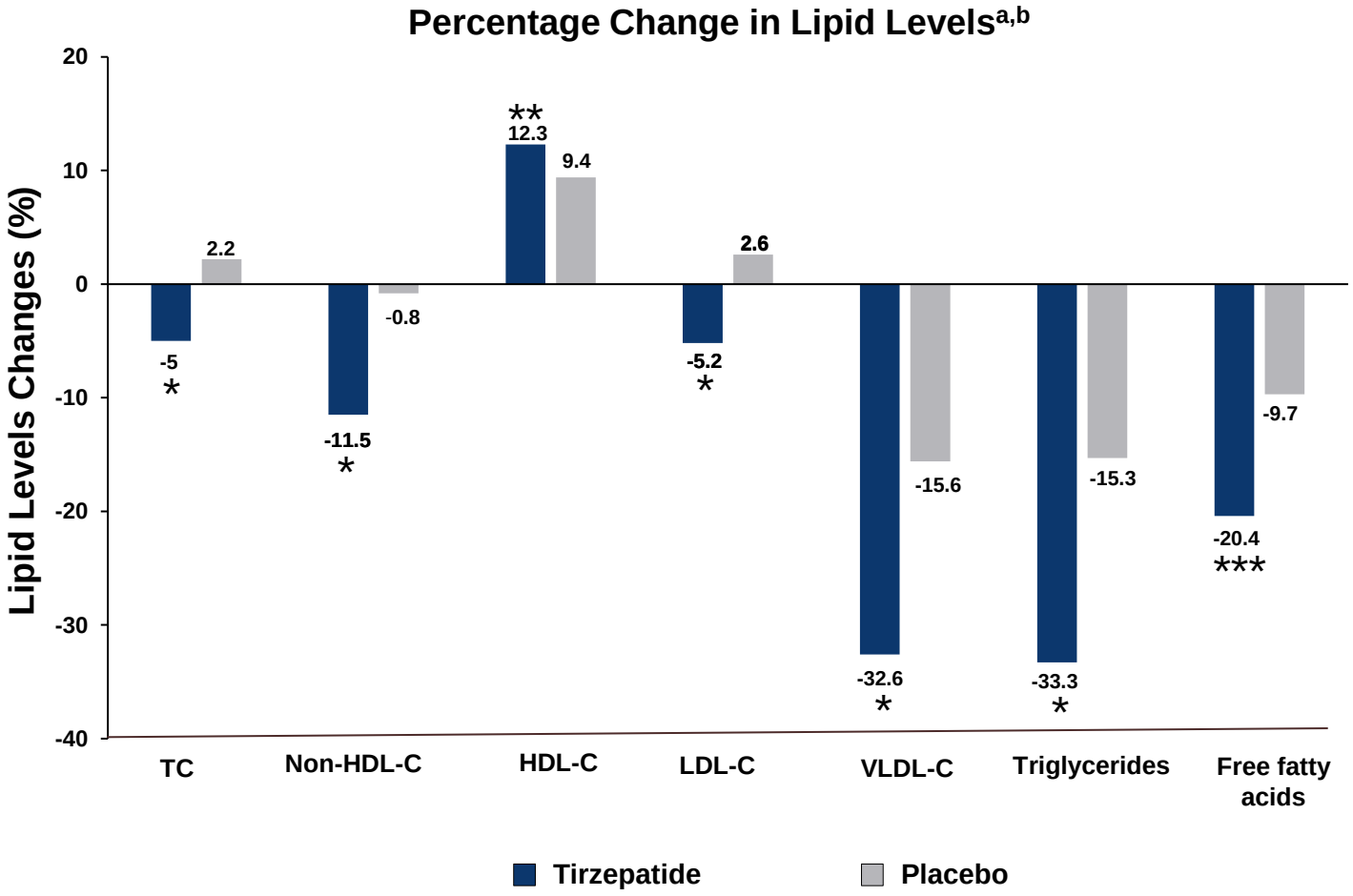
Change in Lipid Levels from Week 0 to Week 88



TC

Notes=*P<.001; **P=.064; ***P=.004; Data are LSM (SE) unless specified.

[a]Tested for significant difference, not controlled for Type 1 error; [b]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.

HDL-C=High-Density Lipoprotein Cholesterol; LDL-C=Low-Density Lipoprotein Cholesterol; LSM=Least Square Mean; SE=Standard Error; TC=Total Cholesterol; VLDL-C=Very Low-Density Lipoprotein cholesterol.

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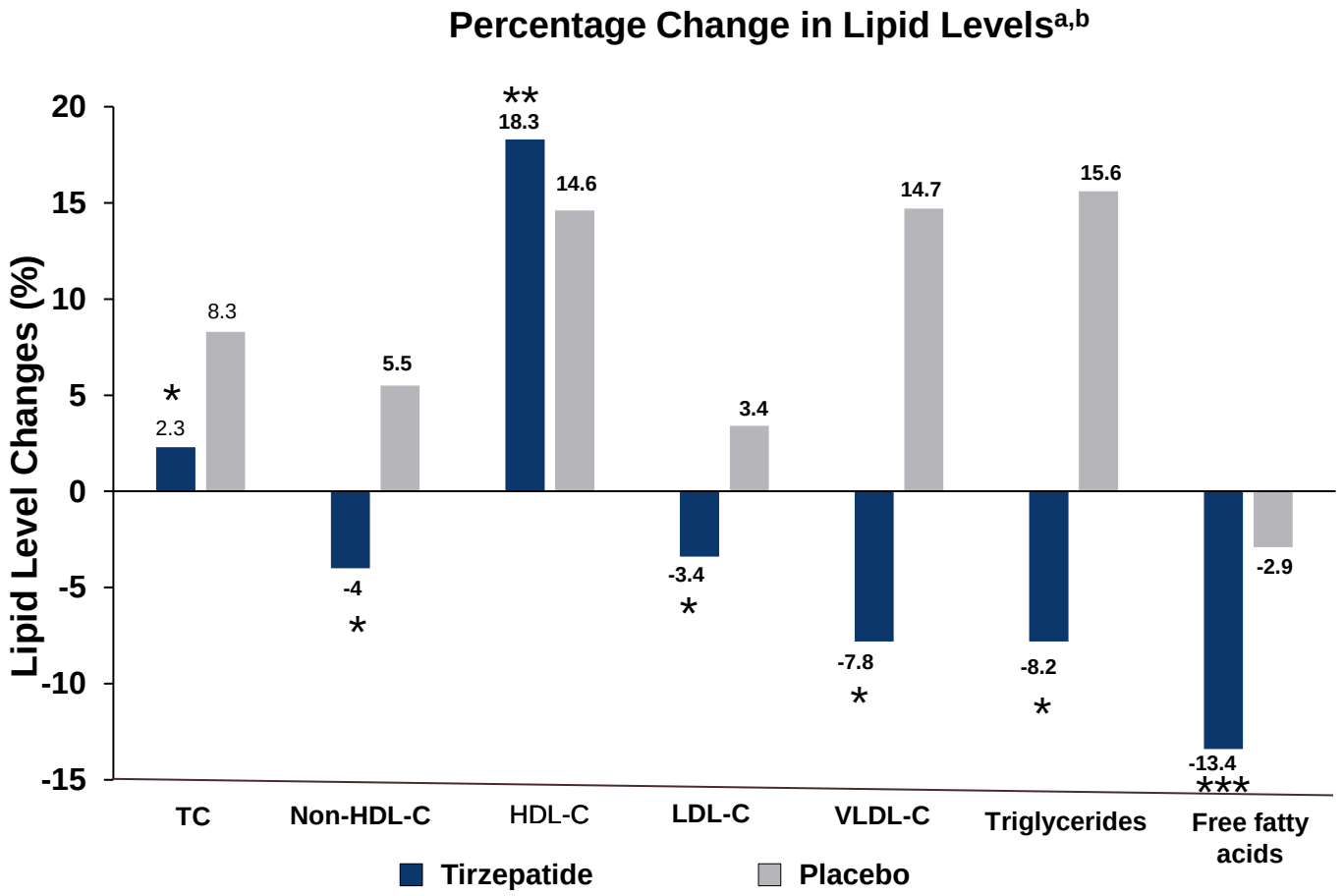
Change in Lipid Levels from Week 36 to Week 88



Notes=*P<.001; **P=.014; ***P=.008. Data are LSM (SE) unless specified.
[a]Tested for significant difference, not controlled for Type 1 error; [b]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.
HDL-C=High-Density Lipoprotein Cholesterol; LDL-C=Low-Density Lipoprotein Cholesterol; LSM=Least Square Mean; SE=Standard Error; TC=Total Cholesterol; VLDL-C=Very Low-Density Lipoprotein cholesterol.
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Change in Cardiometabolic Risk Factors from Week 0 to Week 88[a]

	Tirzepatide (N=335)	Placebo (N=335)	Difference from Placebo[b] (95% CI)	P value
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
Body weight, %	-26.0 (-26.8 to -25.2)	-9.5 (-10.3 to -8.7)	-16.4 (-17.5 to -15.4)	<.001
BMI	-10.0 (-10.3 to -9.7)	-3.6 (-3.9 to -3.3)	-6.4 (-6.8 to -6.0)	<.001
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
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
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
Fasting insulin, % [b]	-54.1 (-57.2 to -51.0)	-29.8 (-34.7 to -24.9)	-34.6 (-40.6 to -27.9)	<.001
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

Notes=Data are LSM (SE) unless specified.
[a]Tested for significant difference, Not controlled for Type 1 error. [b]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.
CI=Confidence Interval; BMI=Body Mass Index; LSM= Least Square Mean; SE=Standard Error.
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Change in Cardiometabolic Risk Factors from Week 36 to Week 88[a]

	Tirzepatide (N=335)	Placebo (N=335)	Difference from Placebo[b] (95% CI)	P value
BMI	-2.1 (-2.4 to -1.8)	4.3 (4.0 to 4.6)	-6.4 (-6.8 to -6.0)	<.001
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
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
fasting insulin, %[b]	-15.4 (-21.0 to -9.8)	23.3 (14.7 to 31.9)	-31.4 (-37.7 to -24.4)	<.001
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

Notes=Data are LSM (SE) unless specified.
[a]Tested for significant difference, not controlled for Type 1 error; [b]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.
CI=Confidence Interval; BMI=Body Mass Index; LSM= Least Square Mean; SE=Standard Error.
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Safety outcomes

Overview of Adverse Events

Double-Blind and Safety Follow-Up Period[a] (1 of 3)

Adverse Events n (%)	Tirzepatide (N=335)	Placebo (N=335)
Participants with ≥1 adverse event	202 (60.3)	187 (55.8)
Serious adverse events	10 (3.0)	10 (3.0)
Death[b]	1 (0.3)	1 (0.3)
Adverse events leading to treatment discontinuation[c]	6 (1.8)	3 (0.9)
Diarrhea	2 (0.6)	0
Cardiac failure congestive	1 (0.3)	0
Abdominal pain	1 (0.3)	0
Vomiting	1 (0.3)	0
Pancreatic enzymes increased	1 (0.3)	0
Adenocarcinoma of colon	0	1 (0.3)
Colorectal cancer	0	1 (0.3)
Non-Hodgkin's lymphoma	0	1 (0.3)
Adverse events occurring in ≥5% of participants in any treatment group[c]		
COVID-19	47 (14.0)	50 (14.9)
Diarrhea	36 (10.7)	16 (4.8)
Nausea	27 (8.1)	9 (2.7)
Vomiting	19 (5.7)	4 (1.2)
Upper respiratory tract infection	8 (2.4)	18 (5.4)

[a]Safety analysis set; [b]Deaths are also included as serious adverse events and discontinuations due to adverse event; [c]Adverse events are listed according to Medical Dictionary for Regulatory Activities, version 26.0, preferred terms.
COVID-19=Coronavirus Disease 2019.

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Overview of Adverse Events

Double-Blind and Safety Follow-Up Period[a] (2 of 3)

Adverse Events n (%)	Tirzepatide (N=335)	Placebo (N=335)
Other adverse events of interest[b]		
Cholelithiasis	1 (0.3)	1 (0.3)
Acute cholecystitis	0	3 (0.9)

[a]Safety analysis set; [b]Adverse events are listed according to Medical Dictionary for Regulatory Activities, version 26.0, preferred terms.

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Overview of Adverse Events

Double-Blind and Safety Follow-Up Period[a] (3 of 3)

Adverse events of special interest n (%)	Tirzepatide (N=335)	Placebo (N=335)
Severe or serious hepatic events	0	0
Malignancies	3 (0.9)	3 (0.9)
Adjudicated pancreatitis[b]	0	0
Adjudicated major adverse cardiovascular events[b]	3 (0.9)	0
Severe or serious arrhythmias and cardiac conduction disorders	0	0
Severe or serious gastrointestinal events	6 (1.8)	1 (0.3)
Severe or serious acute gallbladder disease	0	3 (0.9)
Severe or serious renal disorders	0	0
Severe or serious major depressive disorder or suicidal ideation	0	0
Severe or serious hypersensitivity	0	0
Hypoglycemia (blood glucose <54 mg/dL)	2 (0.6)	0

[a]Safety analysis set; [b]Cases of acute pancreatitis and major adverse cardiovascular events were reviewed by an independent external adjudication committee.

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Overview of Adverse Events

Lead-In Treatment Period (1 of 3)

Adverse Events n (%)[a]	Tirzepatide Lead-In Treatment Period (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]	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)

[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 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.
COVID-19=Coronavirus Disease 2019.
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Overview of Adverse Events

Lead-In Treatment Period (2 of 3)

Adverse Events n (%)[a]	Tirzepatide Lead-In Treatment Period (N=783)
Adverse events occurring in ≥5% of participants[d]	
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)
Other adverse events of interest[d]	
Cholelithiasis	7 (0.9)
Acute cholecystitis	4 (0.5)
Chronic cholecystitis	1 (0.1)

Note=Data are mean ± SD or n (%) from randomized participants unless specified.

[a]The safety follow-up period was included for participants who discontinued during open-label period; [d]Adverse events are listed according to Medical Dictionary for Regulatory Activities, version 26.0, preferred terms.

SD=Standard Deviation.

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Overview of Adverse Events

Lead-In Treatment Period (3 of 3)

Adverse events of special interest n (%)	Tirzepatide Lead-In Treatment Period (N=783)
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 supraventricular arrhythmias and cardiac conduction disorders	4 (0.5)
Severe or serious gastrointestinal events	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)

Data are mean ± SD or n (%) from randomized participants unless specified.

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

SD=Standard Deviation.

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Conclusion

- In this 88-week trial of participants with obesity or overweight with at least one weight-related complication, withdrawing tirzepatide led to weight regain, whereas continued treatment maintained and augmented initial weight reduction
- Tirzepatide met the primary endpoint of superior mean percent change in body weight compared to placebo from 36 weeks to 88 weeks
  - After 36 weeks of receiving open-label tirzepatide titrated to maximum tolerated dose (10 or 15 mg), participants experienced a mean weight reduction of 20.9%
  - From randomization (week 36), those switched to placebo experienced a mean weight regain of 14.8% (11.9 kg) while those continuing tirzepatide experienced an additional 6.7% weight reduction (5.7 kg)
  - The overall mean weight reduction from week 0 to 88 was 25.3% for tirzepatide and 9.9% for placebo
- The percentage of participants at 88 weeks, who maintained ≥80% of the weight lost during the lead-in period, was 89.5% with tirzepatide and 16.6% with placebo
- A significantly greater percentage of participants on tirzepatide met the weight reduction targets of ≥5%, ≥10%, ≥15%, ≥20%, and ≥25%
- The most common adverse events were gastrointestinal-related. These events were reported less frequently during the randomized period and more frequently for tirzepatide compared to placebo

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Back-up

Key Methods and Assessments

- Efficacy end points were analyzed using the full analysis set and the efficacy analysis set
- Assessment of adverse events and laboratory parameters used the safety analysis set
- Two estimands were used to assess treatment efficacy from different perspectives

Treatment-regimen estimand

Represents the average treatment effect of tirzepatide relative to placebo for all participants who had undergone randomization, regardless of treatment discontinuation

Efficacy estimand

Represents the average treatment effect of tirzepatide relative to placebo for all participants who had undergone randomization, if the treatment was administered as intended

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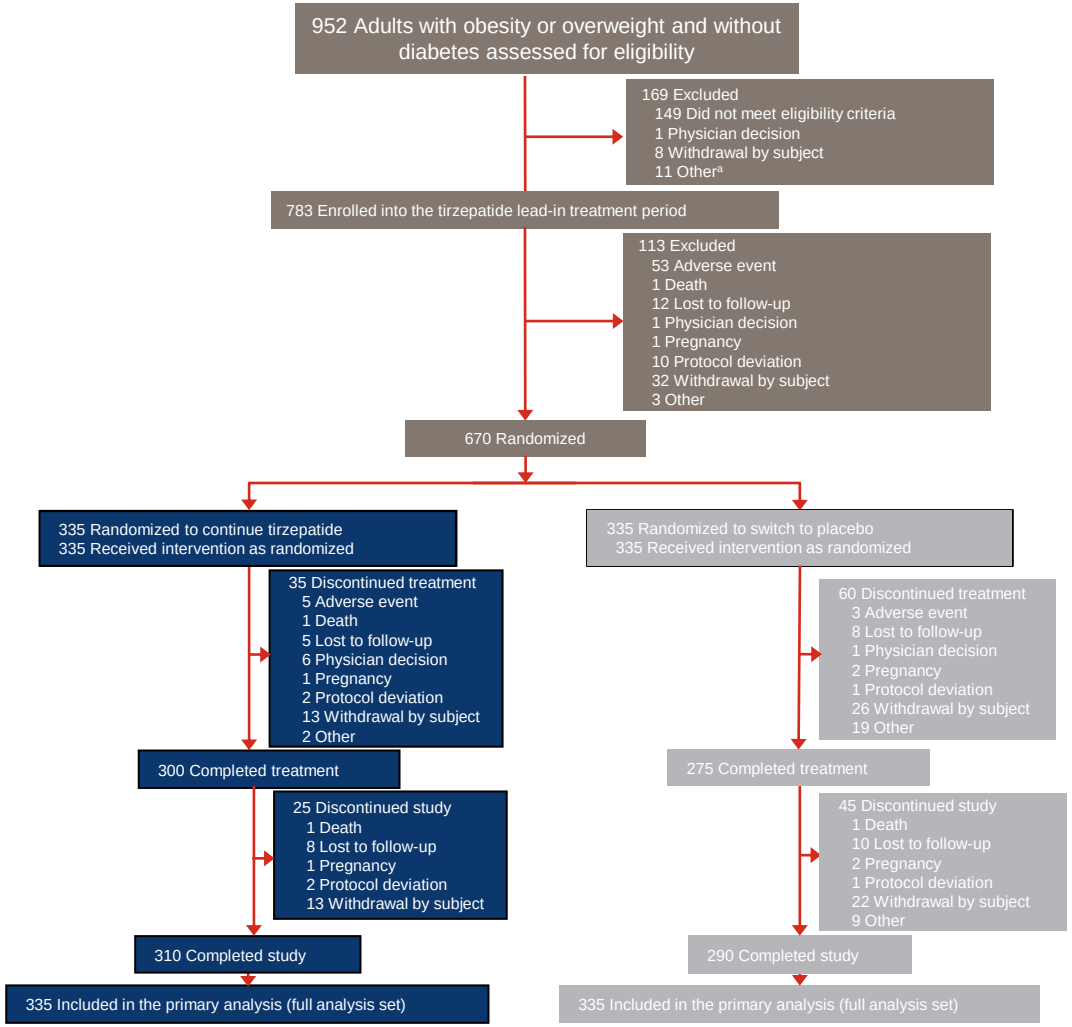
Study Design: Participant Disposition



[a]Includes 10 Site enrollment closed and 1 Lost to follow-up

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Baseline Demographics and Clinical Characteristics at Week 0 and Week 36

	Week 0 (Start of Tirzepatide Lead-In Treatment Period) (N=670)	Week 36 (Randomization)	
		Tirzepatide N=335)	Placebo (N=335)
Complications, n (%)[a]			
Hypertension	236 (35.2)	119 (35.5)	117 (34.9)
Dyslipidemia	212 (31.6)	113 (33.7)	99 (29.6)
Anxiety/Depression	151 (22.5)	73 (21.8)	78 (23.3)
Osteoarthritis	133 (19.9)	70 (20.9)	63 (18.8)
Obstructive sleep apnea	81 (12.1)	40 (11.9)	41 (12.2)
Asthma/COPD	69 (10.3)	34 (10.1)	35 (10.4)
Non-alcoholic fatty liver disease	48 (7.2)	22 (6.6)	26 (7.8)
Atherosclerotic cardiovascular disease	41 (6.1)	18 (5.4)	23 (6.9)
Polycystic ovary syndrome[b]	23 (4.9)	9 (3.8)	14 (5.9)
Gout	24 (3.6)	15 (4.5)	9(2.7)

Note=Data are mean ± SD or n (%) from randomized participants unless specified.
[a]Medical conditions were assessed through a review of participant's medical history at week 0; [b]Percentage is based on total number of female participants in the respective treatment group.
COPD=Chronic Obstructive Pulmonary Disease; SD=Standard Deviation.
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Additional Baseline Demographics and Clinical Characteristics

	Tirzepatide N=335)	Placebo (N=335)	Total (N=670)
Country, n (%)			
Argentina	55 (16.4)	56 (16.7)	111 (16.6)
Brazil	43 (12.8)	46 (13.7)	89 (13.3)
Taiwan	21 (6.3)	17 (5.1)	38 (5.7)
United States	216 (64.5)	216 (64.5)	432 (64.5)
Number of complications, n (%)[a]			
None	98 (29.3)	107 (31.9)	205 (30.6)
1	99 (29.6)	96 (28.7)	195 (29.1)
2	59 (17.6)	53 (15.8)	112 (16.7)
3	39 (11.6)	37 (11.0)	76 (11.3)
4	26 (7.8)	26 (7.8)	52 (7.8)
≥5	14 (4.2)	16 (4.8)	30 (4.5)

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

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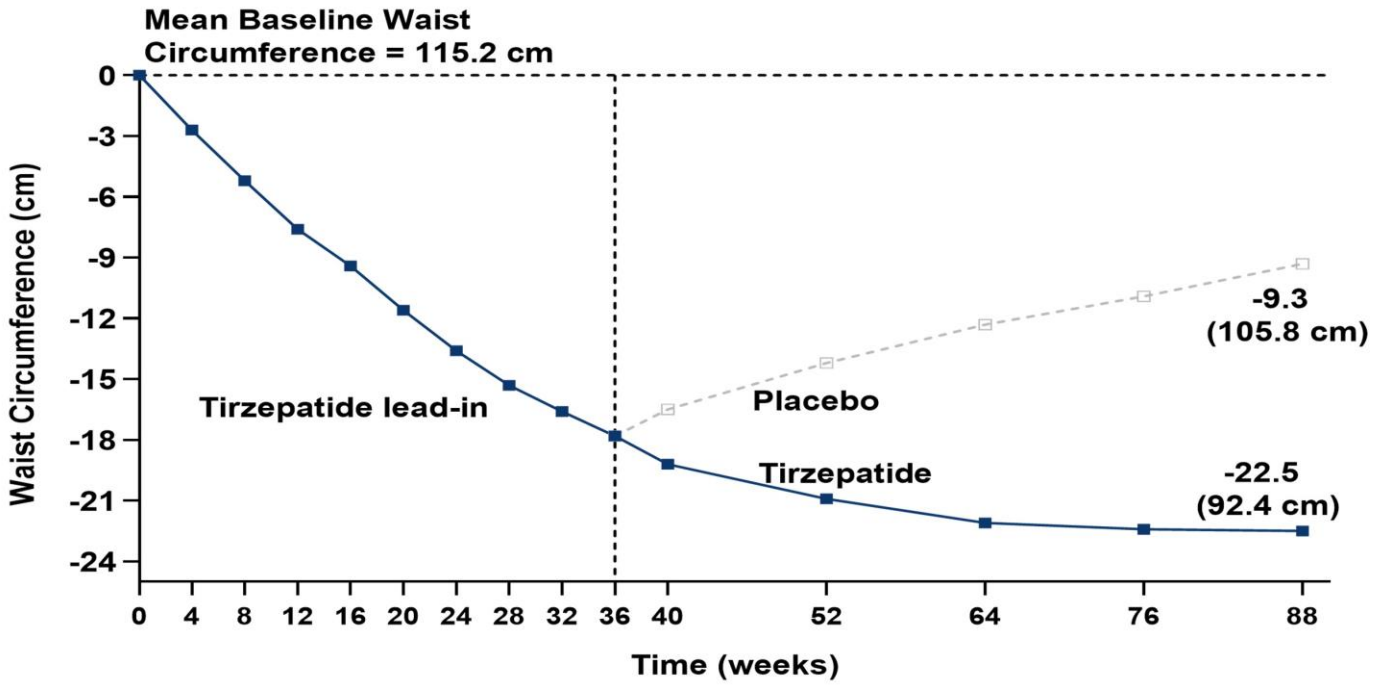
Change in Waist Circumference from Week 0 to Week 88

Mean Change in Waist Circumference



Treatment group	Number of participants at each time point						
Tirzepatide lead-in	670 666 669 668 666 667 669 663 659 670						
Tirzepatide MTD	335	333	328	317	310	310	335(HI)
Placebo	335	328	318	303	292	289	335(HI)

Notes=Data are observed mean values; The dashed vertical line at week 36 represents the randomization time point; Values in parentheses are actual waist circumference at week 88.
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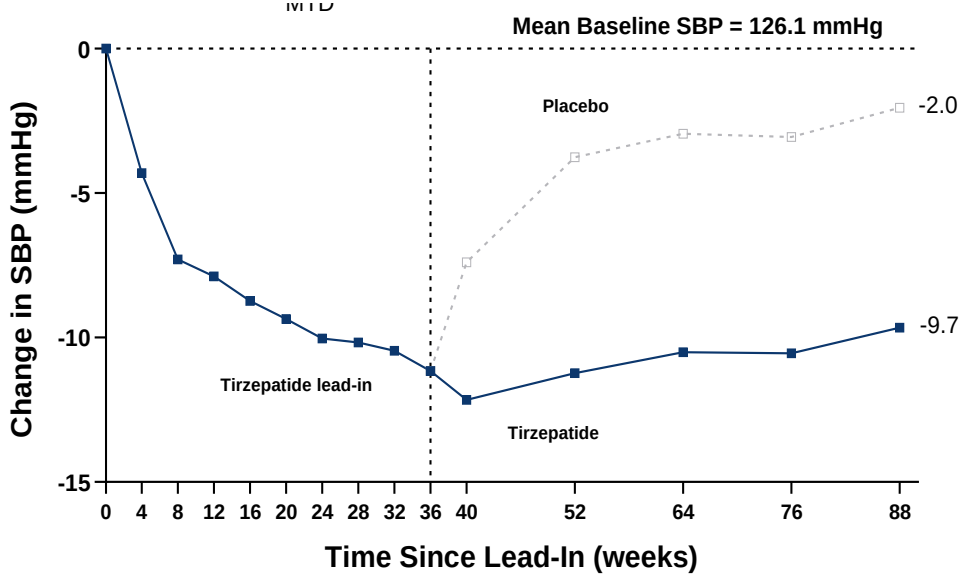
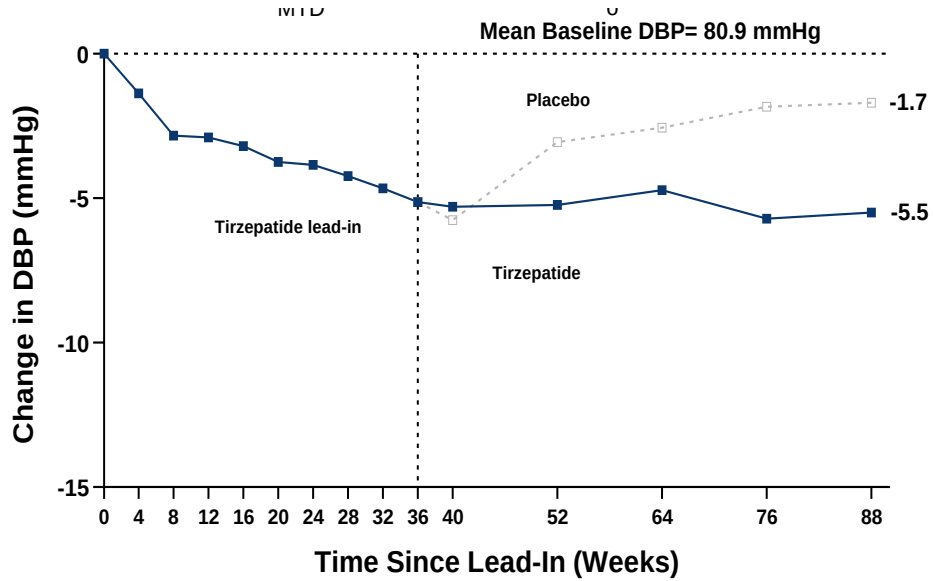
Change in Blood Pressure from Week 0 to Week 88

Mean Change in 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											335	333	328	317	311
Placebo	310														
											335	329	319	303	292
	288														



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

Notes=Data are observed mean values; The dashed vertical line at week 36 represents the randomization time point.
SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure.
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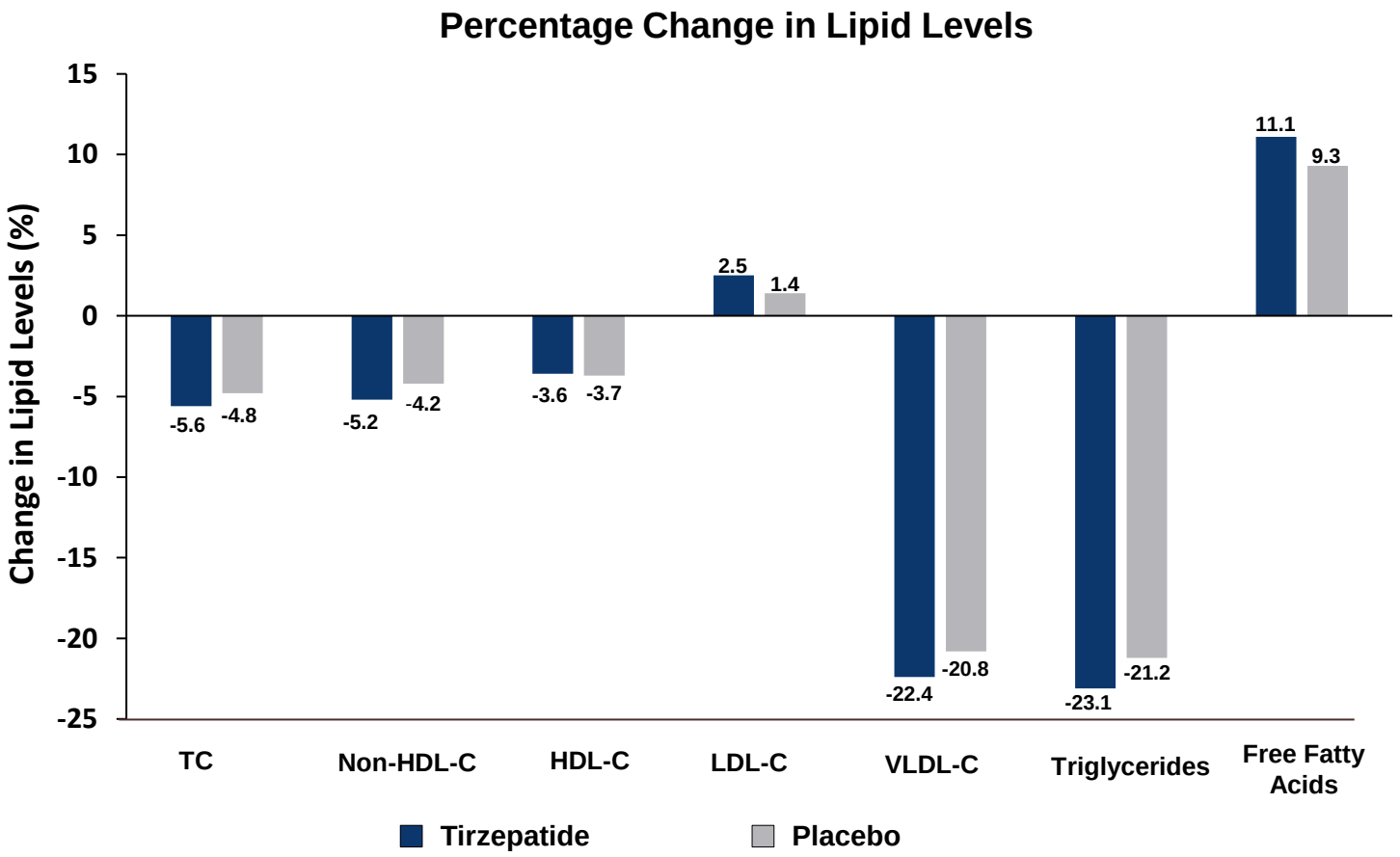
Change in Lipid Levels from Week 0 to Week 36



Note=Data are mean ± SD from randomized participants unless specified.
HDL-C=High-Density Lipoprotein Cholesterol; LDL-C=Low-Density Lipoprotein Cholesterol; SD=Standard Deviation; TC=Total Cholesterol; VLDL-C=Very Low-Density Lipoprotein Cholesterol.
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Change in Cardiometabolic Risk Factors from Week 0 to Week 36

	Tirzepatide (N=335)	Placebo (N=335)	Total (N=670)
Body weight, %	-21.1 (7.0)	-20.8 (7.6)	-20.9 (7.3)
BMI[a]	-8.0 (2.8)	-7.9 (3.1)	-8.0 (3.0)
Waist circumference, cm	-18.2 (8.3)	-17.4 (8.7)	-17.8 (8.5)
Pulse rate, beats/min	5.2 (9.1)	4.8 (9.0)	5.0 (9.0)
Hemoglobin A_{1c}, %	-0.5 (0.3)	-0.5 (0.3)	-0.5 (0.3)
Fasting glucose, mg/dL	-10.2 (10.7)	-9.3 (9.9)	-9.8 (10.3)
Fasting insulin[b], %	-37.3 (39.2)	-33.1 (44.9)	-35.2 (42.2)
eGFR, ml/min/1.73 m^2	-1.1 (10.4)	-0.3 (10.7)	-0.7 (10.5)
Blood pressure, mmHg			
Systolic	-11.8 (12.4)	-10.5 (12.6)	-11.2 (12.5)
Diastolic	-5.4 (9.1)	-4.9 (9.1)	-5.1 (9.1)

Note=Data are mean ± SD or n (%) from randomized participants unless specified.
[a]Calculated as weight in kilograms divided by height in meters squared; [b]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.
BMI=Body Mass Index; eGFR=Estimated Glomerular Filtration Rate; SD=Standard Deviation.
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Change in Patient-Reported Outcomes from Week 0 to Week 36

	Tirzepatide (N=335)	Placebo (N=335)	Total (N=670)
SF -36v2 scores	5.9 (7.4)	5.5 (7.5)	5.7 (7.4)
Physical functioning domain	4.5 (7.0)	3.5 (7.7)	4.0 (7.4)
Role-physical domain	2.3 (8.6)	3.2 (9.0)	2.7 (8.8)
Role-emotional domain	1.8 (7.1)	2.5 (8.3)	2.1 (7.7)
Mental health domain	22.0 (22.2)	22.2 (23.0)	22.1 (22.6)
IWQOL-Lite-CT physical function composite score	22.0 (22.2)	22.2 (23.0)	22.1 (22.6)

Note=Data are mean ± SD or n (%) from randomized participants unless specified.
IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite-Clinical Trials Version; SD=Standard Deviation; SF-36v2=Short Form-36 Version 2
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Change in Patient-Reported Outcomes During Double-Blind Period

	Tirzepatide (N=335)	Placebo (N=335)	Difference from Placebo[b] (95% CI)	P value
From Week 0 to Week 88				
Change in SF-36v2 scores[a]				
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[a]	26.0 (24.1 to 27.9)	16.7 (14.7 to 18.7)	9.3 (6.6 to 12.0)	<.001
From Week 36 to Week 88				
Change in SF-36v2 scores[a]				
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[a]	4.3 (2.5 to 6.1)	-5.1 (-6.9 to -3.3)	9.4 (6.9 to 12.0)	<.001

Note=Data are mean ± SD or n (%) from randomized participants unless specified.
[a]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.
IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite-Clinical Trials Version; SD=Standard Deviation; SF-36v2=Short Form-36 Version 2
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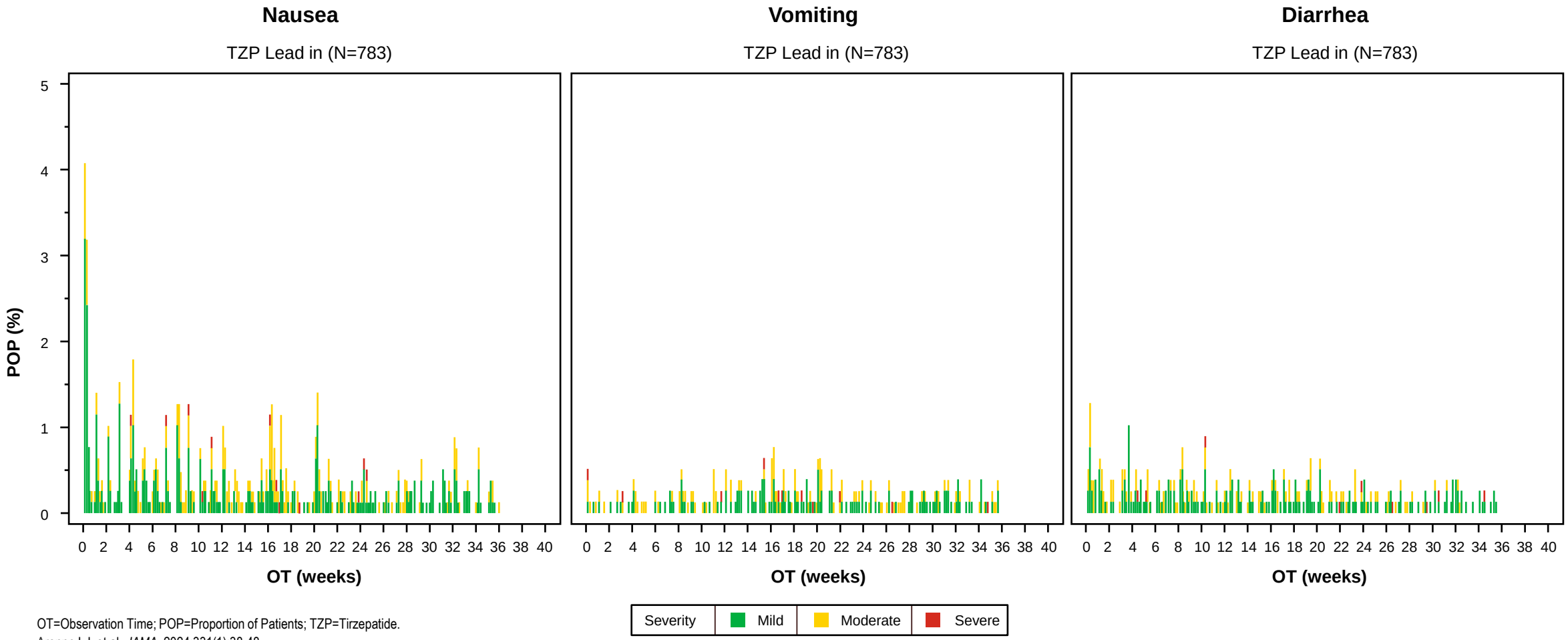
Incidence of Nausea, Vomiting, and Diarrhea During the Tirzepatide Lead-In Treatment Period



OT=Observation Time; POP=Proportion of Patients; TZP=Tirzepatide.

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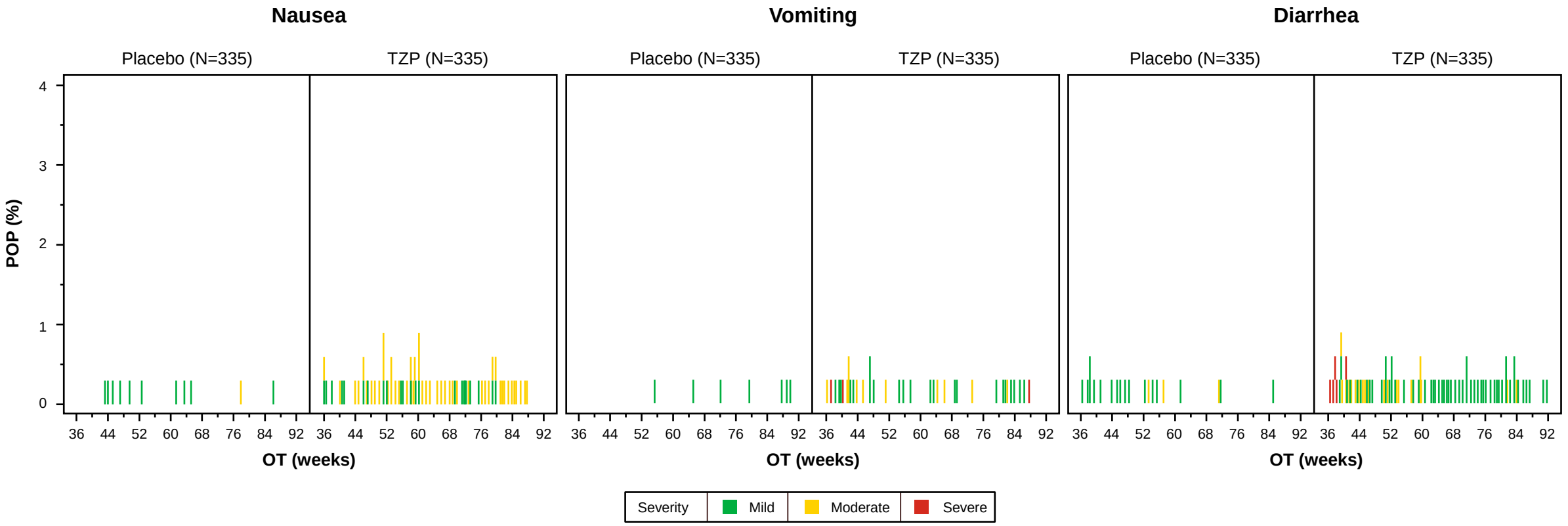
Incidence of Nausea, Vomiting, and Diarrhea During the Double-Blind Period



OT=Observation Time; POP=Proportion of Patients; TZP=Tirzepatide.

Aronne LJ, et al. *JAMA*. 2024;331(1):38-48.