Tirzepatide After Intensive Lifestyle Intervention in Adults With Overweight or Obesity: The SURMOUNT-3 Phase 3 Trial

Thomas A. Wadden[1], Ariana Chao[2], Sriram Machineni[3], Robert Kushner[4], Jamy Ard[5], Gitanjali Srivastava[6,7], Bruno Halpern[8], Shuyu Zhang[9], Jiaxun Chen[9], Mathijs C. Bunck[9], Nadia N. Ahmad[9], & Tammy Forrester[9]

[1]Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [2]Johns Hopkins School of Nursing, Baltimore, MD, USA; [3]Division of Endocrinology and Metabolism, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA; [4]Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [5]Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston Salem, NC, USA; [6]Department of Medicine, Division of Diabetes, Endocrinology & Metabolism, Department of Pediatrics, Department of Surgery, Vanderbilt University School of Medicine, Nashville, TN, USA; [7]Vanderbilt Weight Loss Clinics, Vanderbilt University Medical Center, Nashville, TN, USA; [8]Obesity Group, Department of Endocrinology, Universidade de São Paulo, São Paulo, Brazil; [9]Eli Lilly and Company, Indianapolis, IN, USA

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Background

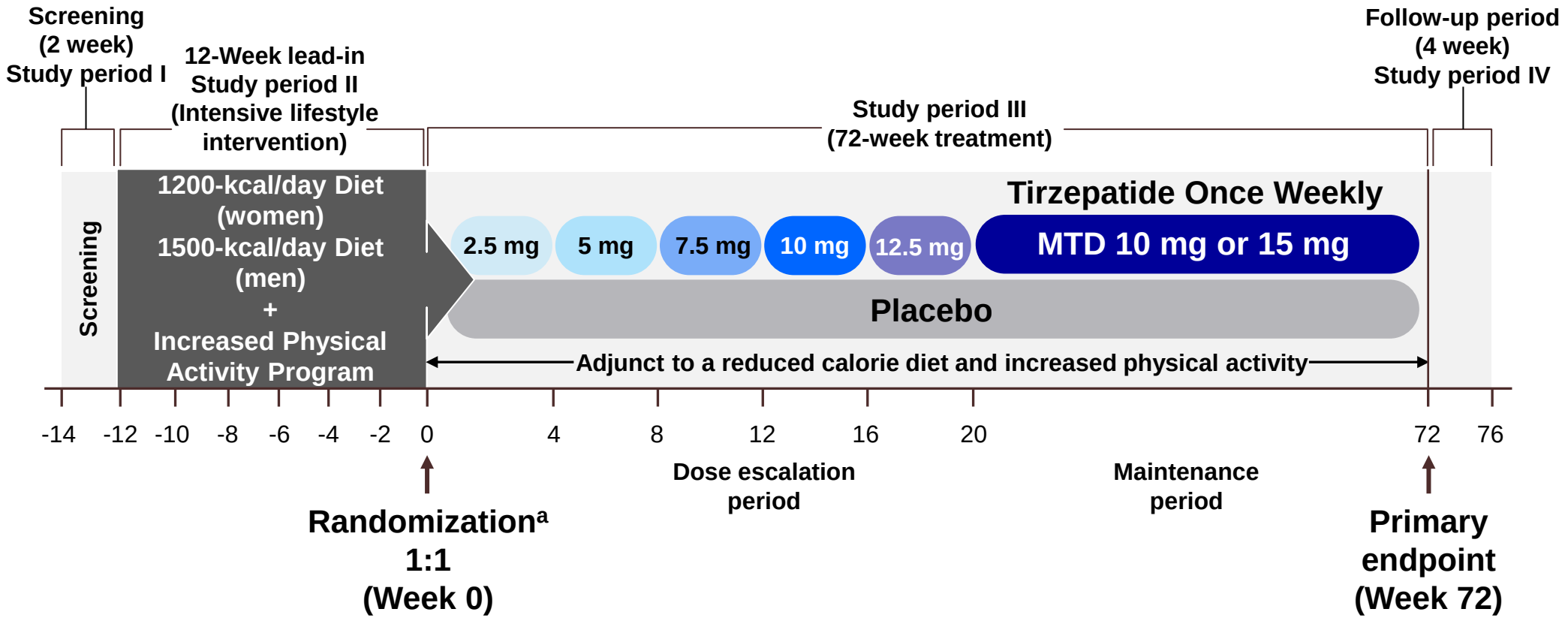
- Obesity is a complex, multifactorial, metabolic disease of dysregulated energy homeostasis. It is often associated with a higher risk of developing multiple comorbidities[1-4]
- Tirzepatide, a novel once-weekly GIP and GLP-1 receptor agonist,[5] has been approved by the FDA and by the EMA for the treatment of T2D and obesity [6-8]
- Tirzepatide has shown significant weight reduction in phase 3 trials in people with obesity (SURMOUNT-1)[9] and obesity with type 2 diabetes (SURMOUNT-2)[10]
- There is a recommendation to use anti-obesity medication after intensive lifestyle intervention which helps provide additional weight reduction, and to prevent weight regain[11-15]
- SURMOUNT-3, a multicenter, phase 3, randomized, double-blind, parallel, placebo-controlled trial, aimed to determine the efficacy and safety of once-weekly tirzepatide after an intensive lifestyle program in people who have obesity or overweight with weight-related comorbidities[16]

EMA=European Medicines Agency; FDA=The US Food and Drug Administration; GIP=Glucose-Dependent Insulinotropic Polypeptide; GLP-1=Glucagon-Like Peptide-1; T2D=Type 2 Diabetes.

1. Lin X, Li H. *Front Endocrinol (Lausanne)*. 2021;12:706978. 2. Yang M, et al. *Healthcare (Basel)*. 2022;10(9):1616. 3. Uranga RM, Keller JN. *Front Neurosci*. 2019;13:513. 4. Wilding JPH, Jacob S. *Obes Rev*. 2021;22(1):e13112. 5. Coskun T, et al. *Mol Metab*. 2018;18:3-14. 6. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-dual-targeted-treatment-type-2-diabetes (Accessed May 22, 2023). 7. https://www.fda.gov/news-events/press-announcements/fda-approves-new-medication-chronic-weight-management (Accessed December 12, 2023). 8. https://www.ema.europa.eu/en/medicines/human/EPAR/mounjaro (Accessed May 22, 2023). 9. Jastreboff AM, et al. *N Eng J Med*. 2022;387(3):205-216. 10. Garvey TM, et al. *Lancet*. 2023;402(10402):613-626. 11. Wharton S, et al. CMAJ. 2020;192(31):E875-E891. 12. Stegenga H, et al. *BMJ*. 2014;349:g6608. 13. Gregg E, et al. *Lancet Diabetes Endocrinol*. 2016;4(11):913-921. 14. Jensen MD, et al. *Obesity (Silver Spring)*. 2014;22(Suppl. 2):S41-410. 15. Garvey WT, et al. *Endocr. Pract*. 2016;22 (Suppl. 3):1-203. 15. Wadden TA, et al. *Am Psychol*. 2020;75(2):235-251. 16. Wadden TA, et al. *Nat Med*. 2023;29(11):2909-2918.

Study Design

Phase 3, randomized, double-blind, multicenter, parallel-group, placebo-controlled trial at 62 sites in 3 countries (NCT04657016)



[a]Only those patients who were able to achieve ≥5% weight reduction at the end of the lead-in period were randomized.
MTD=Maximum Tolerated Dose.
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Primary and Key Secondary Endpoints

Coprimary Endpoints[a]

Superiority of TZP MTD vs. placebo at week 72 from randomization for:

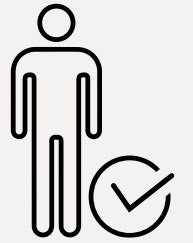
Percent Body Weight Change

Percentage of Participants achieving ≥5% Body Weight Reduction

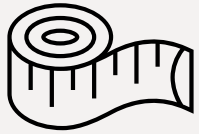
Key Secondary Endpoints[a]
To demonstrate:

TZP MTD is superior to placebo at week 72 from randomization for:

Percentage of Participants who achieve ≥10%, ≥15%, or ≥20% body weight reduction



Percentage of Participants who maintained ≥80% of the body weight loss achieved during the 12-week lead-in period



Mean change in waist circumference

[a]Controlled for type 1 error at a two-sided significance level of 0.05 within each estimand via a graphical testing approach.
MTD=Maximum Tolerated Dose; TZP=Tirzepatide.
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Additional Secondary and Exploratory Endpoints

Additional Secondary Endpoints

To demonstrate that tirzepatide MTD is superior to placebo at 72 weeks for:

- Mean change in body weight and BMI
- Mean change in fasting insulin, fasting glucose, and HbA1c
- Mean change in lipids
- Mean change in blood pressure
- Mean change in SF-36v2 acute form physical functioning domain score and IWQoL-Lite-CT physical function composite score

To demonstrate that tirzepatide MTD is superior to placebo from start of lead-in (week -12) to week 72 for:

- Mean change in absolute and percentage body weight and BMI
- Mean change in waist circumference

Prespecified Exploratory Endpoint

To demonstrate that tirzepatide MTD is superior to placebo at 72 weeks from randomization for:

- Percentage of participants who achieve ≥25% body weight reduction

BMI=Body Mass Index; HbA1c=Glycated Hemoglobin; IWQoL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version; MTD=Maximum Tolerated Dose; SF-36v2=SF-36v2=36-Item Short Form Health Survey Version 2.

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Key Inclusion and Exclusion Criteria of Participants

- Adults ≥18 years of age
- BMI: ≥30 kg/m^2
- BMI ≥27 kg/m^2 with at least 1 weight-related comorbidity: hypertension, dyslipidemia, OSA, or CVD
- At least 1 self-reported unsuccessful dietary effort to lose body weight

- T1DM or T2DM
- Self-reported change in body weight >5 kg within 3 months prior to screening
- Prior or planned surgical treatment for obesity
- Current or prior treatment (within 3 months prior to Visit 2) with medications that may cause weight gain or weight loss

BMI=Body Mass Index; CVD=Cardiovascular Disease; OSA=Obstructive Sleep Apnea; T1DM=Type 1 Diabetes Mellitus; T2DM=Type 2 Diabetes Mellitus.

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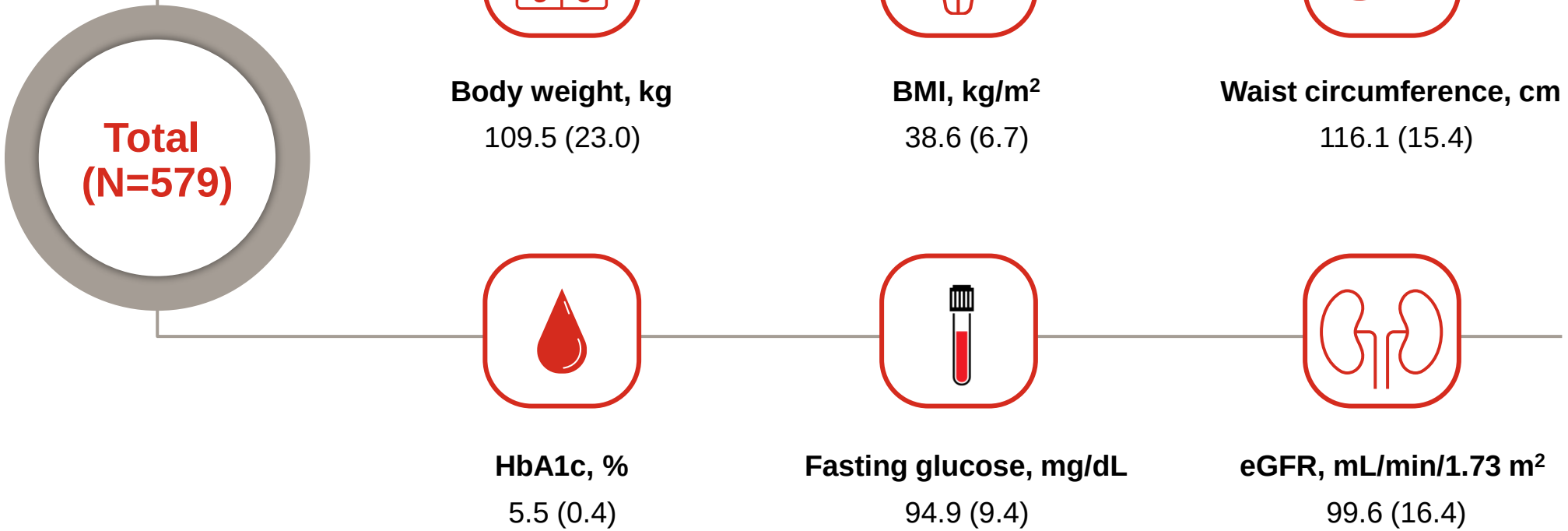
Key Baseline Demographics and Clinical Characteristics

Lead-in Period



Data are mean (SD).
BMI=Body Mass Index; eGFR=Estimated Glomerular Filtration Rate; HbA1c=Glycated Hemoglobin; SD=Standard Deviation.
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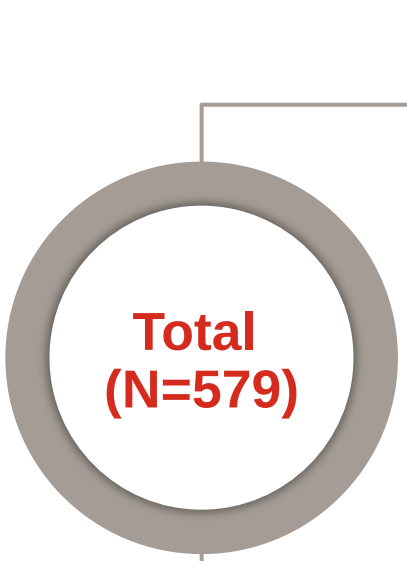
Key Baseline Demographics and Clinical Characteristics

At Randomization



Age, mean (SD), years

45.6 (12.2)

Female, n (%)

364 (62.9)

Race, n (%)

Asian	4 (0.7)
African American	63 (10.9)
Multiple	8 (1.4)
American Indian or Alaskan	6 (1.0)
White	498 (86.0)

Duration of obesity, mean (SD), years[a]

15.1 (11.2)

BMI category, n (%)

<27	17 (2.9)
≥27 to <30	70 (12.1)
≥30 to <35	207 (35.8)
≥35 to <40	174 (30.1)
≥40	111 (19.2)

[a]Duration of obesity was assessed by self-report.
Data are mean (SD).
BMI=Body Mass Index; eGFR=Estimated Glomerular Filtration Rate; HbA1c=Glycated Hemoglobin; SD=Standard Deviation.
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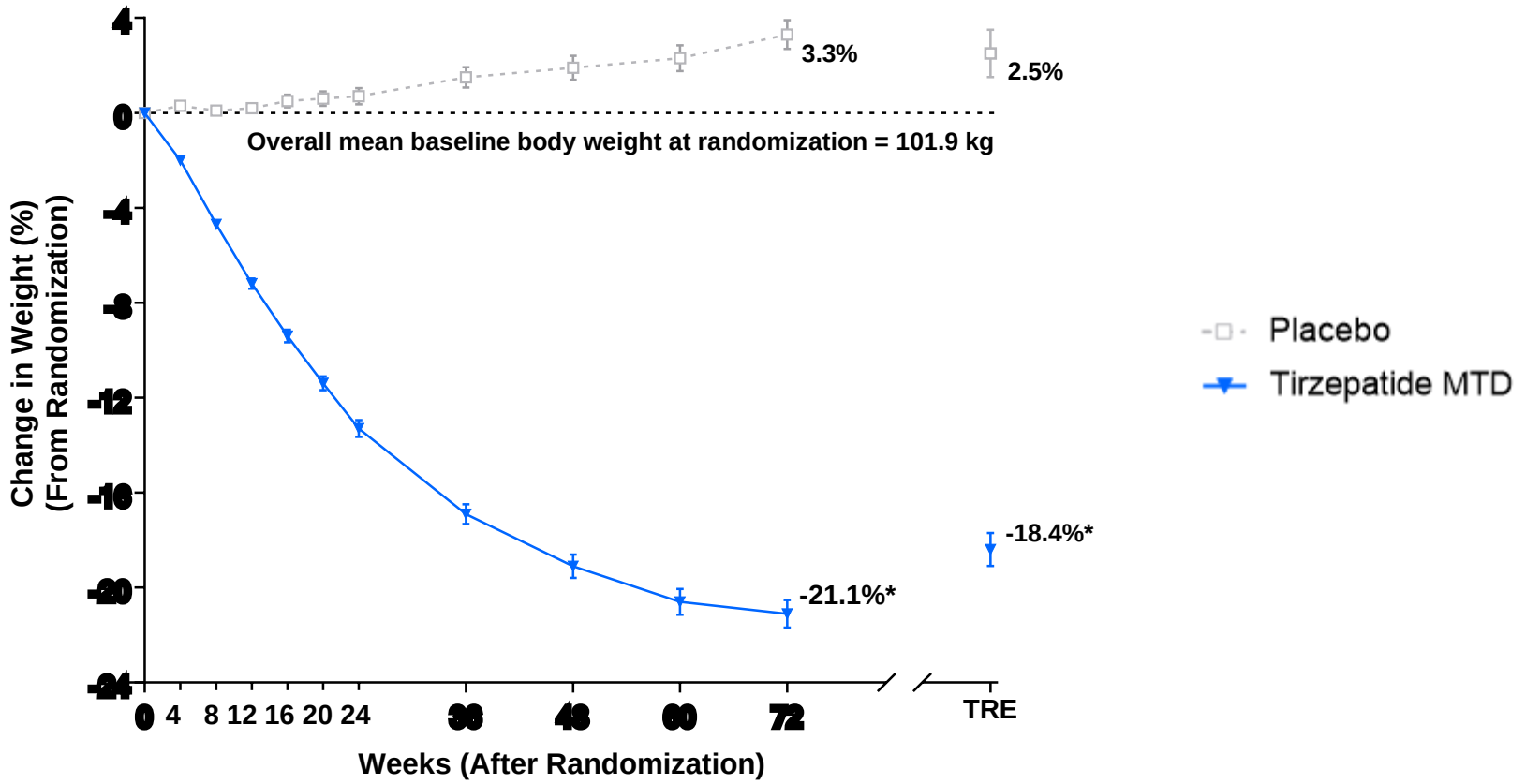
Efficacy of Tirzepatide

Change in Body Weight From Randomization to Week 72

Efficacy Estimand



After ILI, 72 weeks of tirzepatide MTD resulted in additional average body weight reduction of -21.1%

*P<.001 vs. placebo.

Data (percent change) are LSM (SE). MMRM analysis for the efficacy estimand (efficacy analysis set) and ANCOVA analysis for the treatment-regimen estimand (full analysis set).

ANCOVA=Analysis of Covariance; ILI=Intensive Lifestyle Intervention; LSM=Least Squares Mean; MMRM=Mixed Model for Repeated Measures; MTD=Maximum Tolerated Dose; SE=Standard Error; TRE=Treatment-regimen Estimand.

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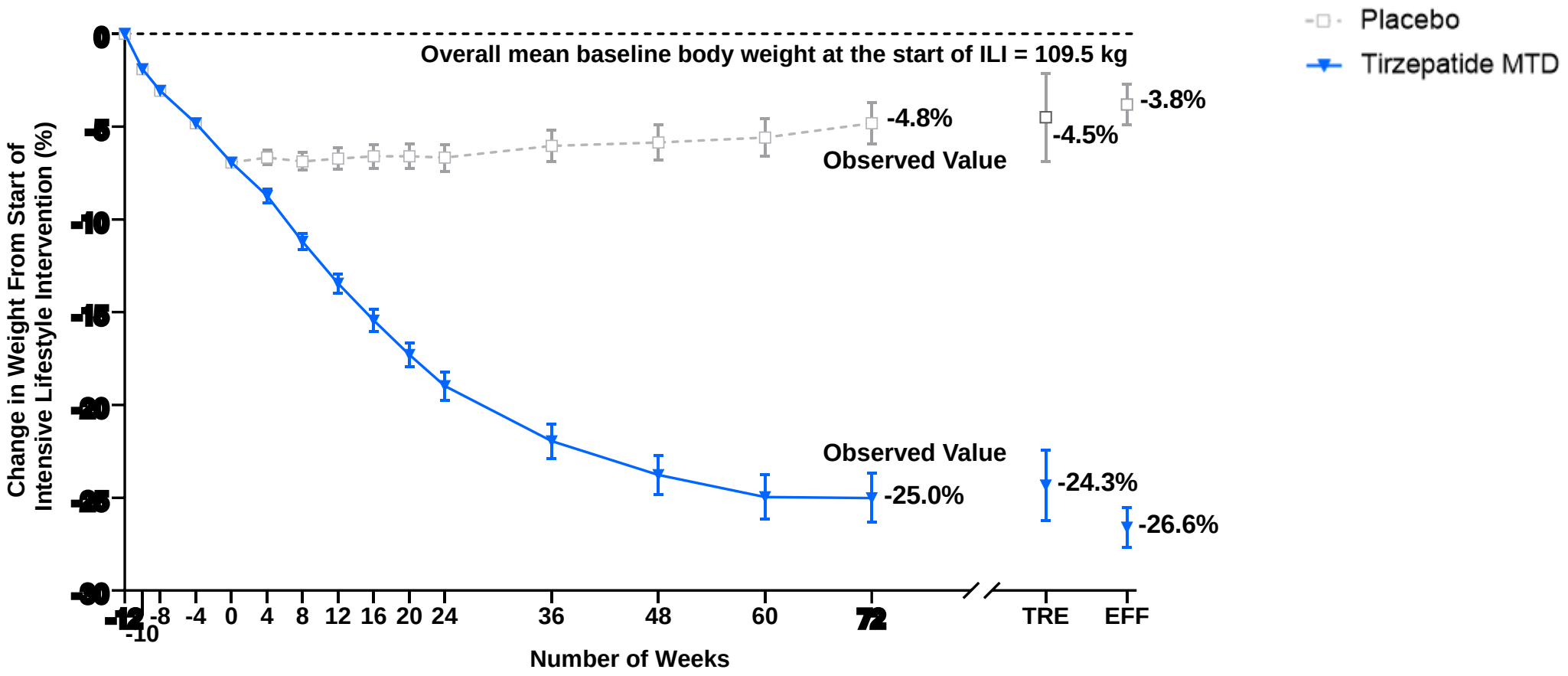
Change in Body Weight From Lead-in Period to Week 72



ILI followed by 72 weeks of tirzepatide MTD resulted in average body weight reductions of -25%

Data derived from observed values, irrespective of treatment adherence. Week 72 estimates for treatment-regimen estimand and efficacy estimand are also shown and both values are LSM (SE).
EFF=Efficacy Estimand; ILI=Intensive Lifestyle Intervention; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose; SE=Standard Error; TRE=Treatment-regimen Estimand.
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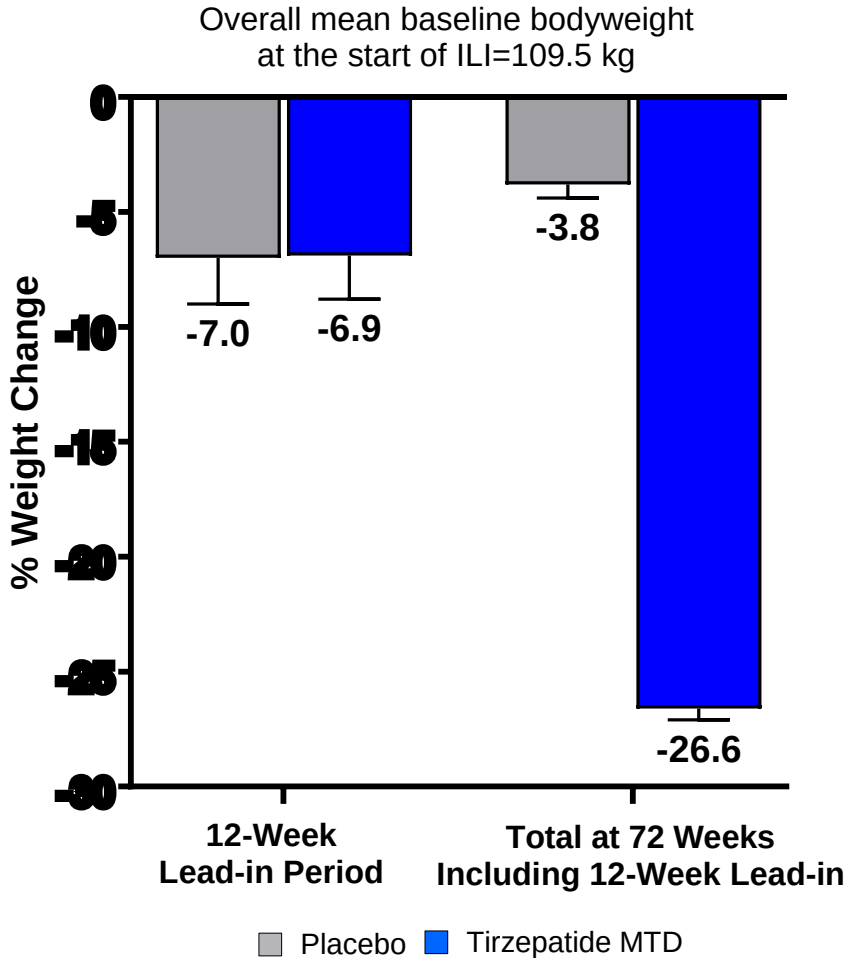
Body Weight Change During Lead-in Period and Total Including Lead-in Period to Week 72



Tirzepatide MTD resulted in greater body weight reduction (-26.6%) at week 84 than placebo

12-Week lead-in data are mean (SD). 84-Week data are LSM (SE).
ILI=Intensive Lifestyle Intervention; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose; SD=Standard Deviation; SE=Standard Error.
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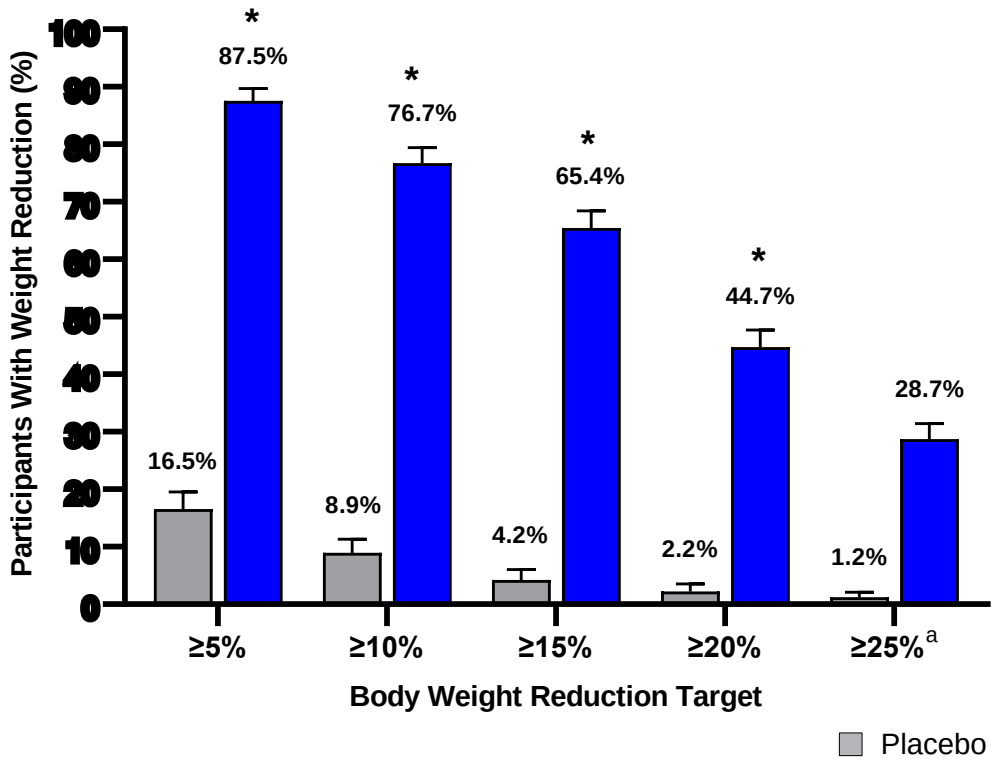
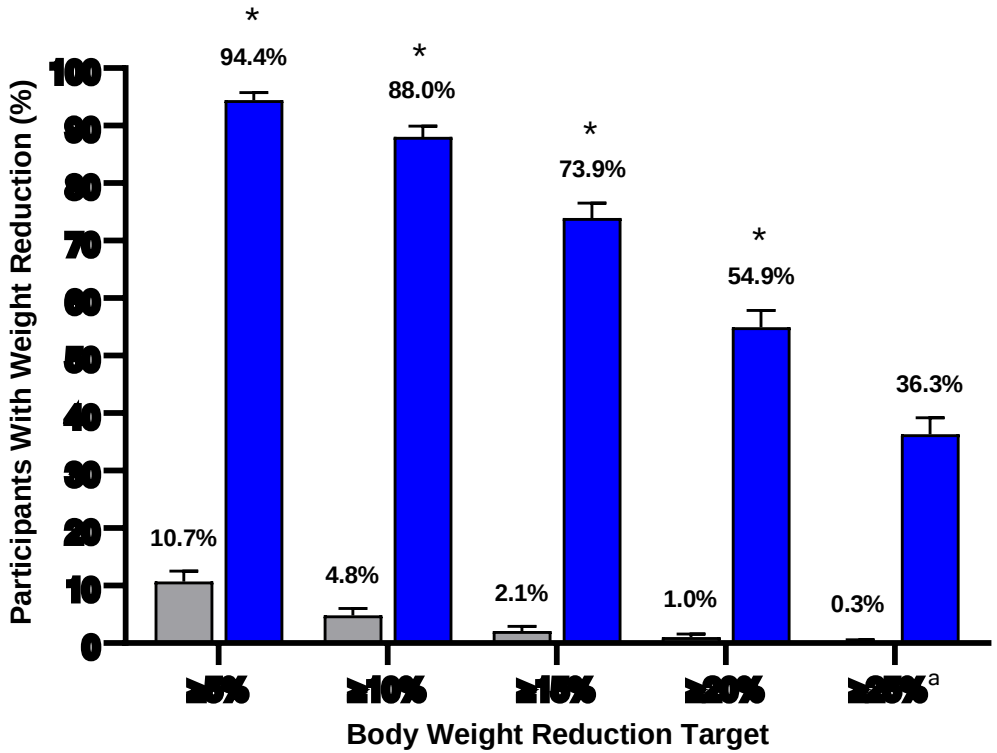
Percentage of Participants Achieving Weight Loss Targets

From Randomization (Week 0) to Week 72

Participants Who Achieved Weight Reduction Targets at Week 72 (Treatment-Regimen Estimand)



Participants Who Achieved Weight Reduction Targets at Week 72 (Efficacy Estimand)



Placebo Tirzepatide MTD

From randomization, tirzepatide MTD resulted in greater proportions of participants achieving weight-reduction thresholds

*P<.001 vs. placebo.

[a]Prespecified exploratory endpoint. Not controlled for type I error.

Data are LSM (SE). Left graph: Treatment-regimen estimand data are from logistic regression with missing values imputed by hybrid imputation. Right graph: Efficacy estimand data are from logistic regression with missing values at week 72 are imputed from MMRM analysis.

LSM=Least Squares Mean; MMRM=Mixed Model for Repeated Measures; MTD=Maximum Tolerated Dose; SE=Standard Error.

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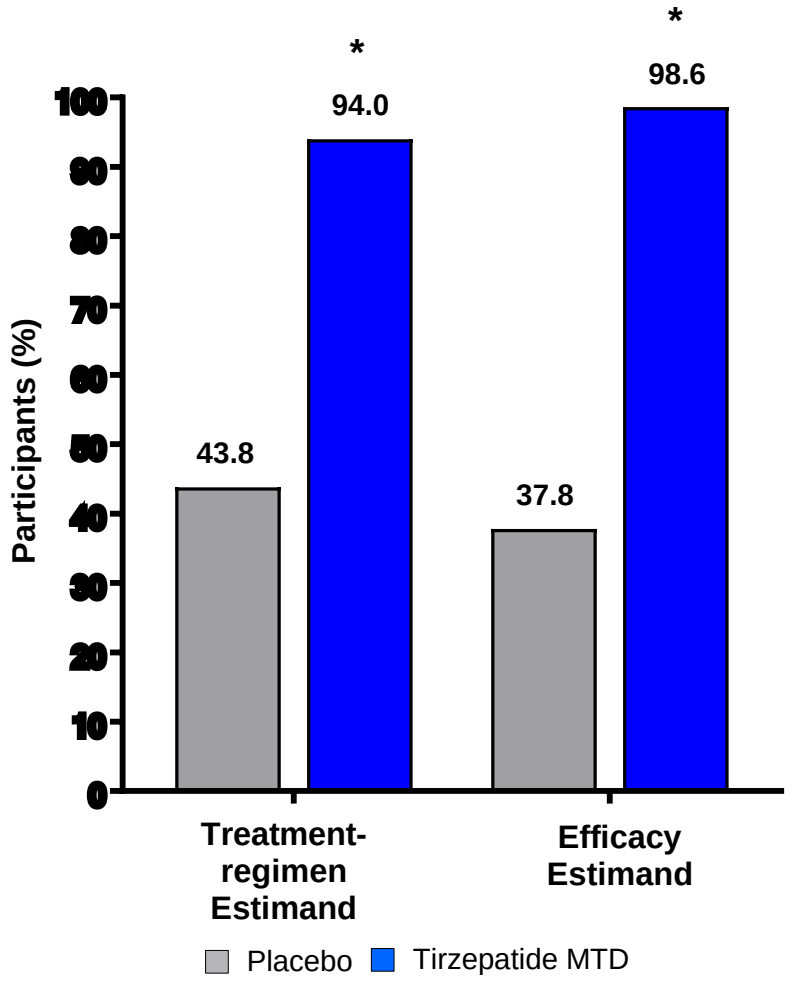
Proportion of Participants Maintaining ≥80% of Body Weight Lost During the 12-week Lead-in Period



*P<.001 vs. placebo.
Data are LSM. Efficacy estimand from efficacy analysis set and treatment-regimen estimand from full analysis set.
LSM=Least Squares Mean; MTD=Maximum Tolerated Dose.
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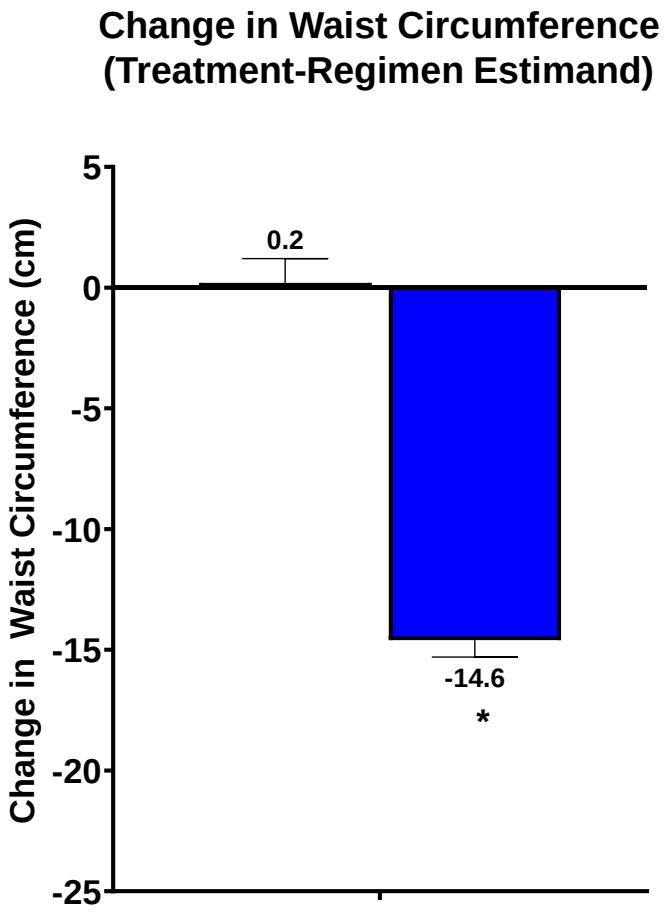
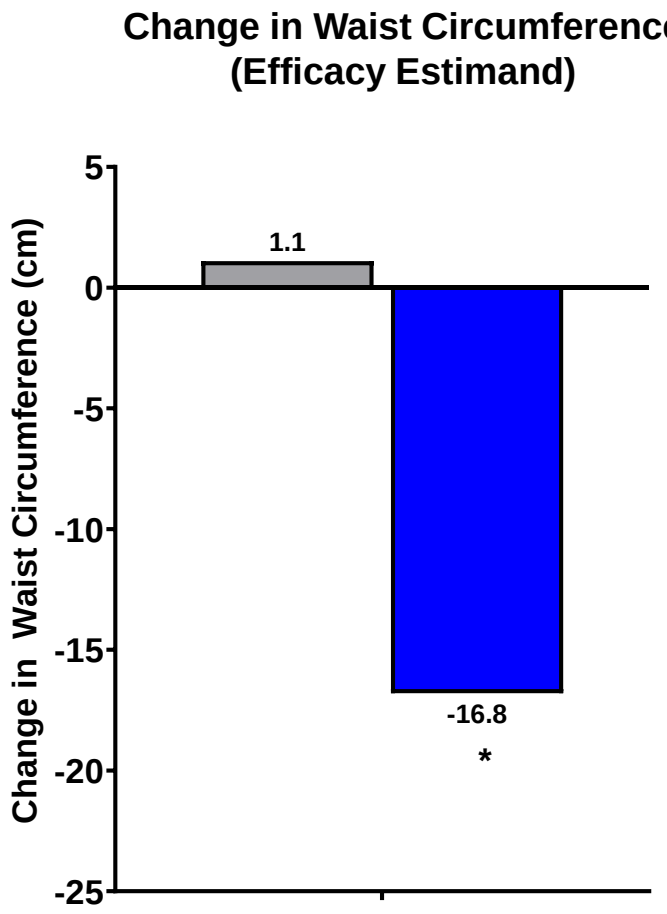
Change in Waist Circumference

From Randomization (Week 0) to Week 72





Placebo Tirzepatide MTD

*P<.001 vs. placebo.

Data are LSM (SE). Left graph: ANCOVA analysis (full analysis set). Right graph: MMRM analysis (efficacy analysis set).

ANCOVA=Analysis of Covariance; LSM=Least Squares Mean; MMRM=Mixed Model for Repeated Measures; MTD=Maximum Tolerated Dose; SE=Standard Error.

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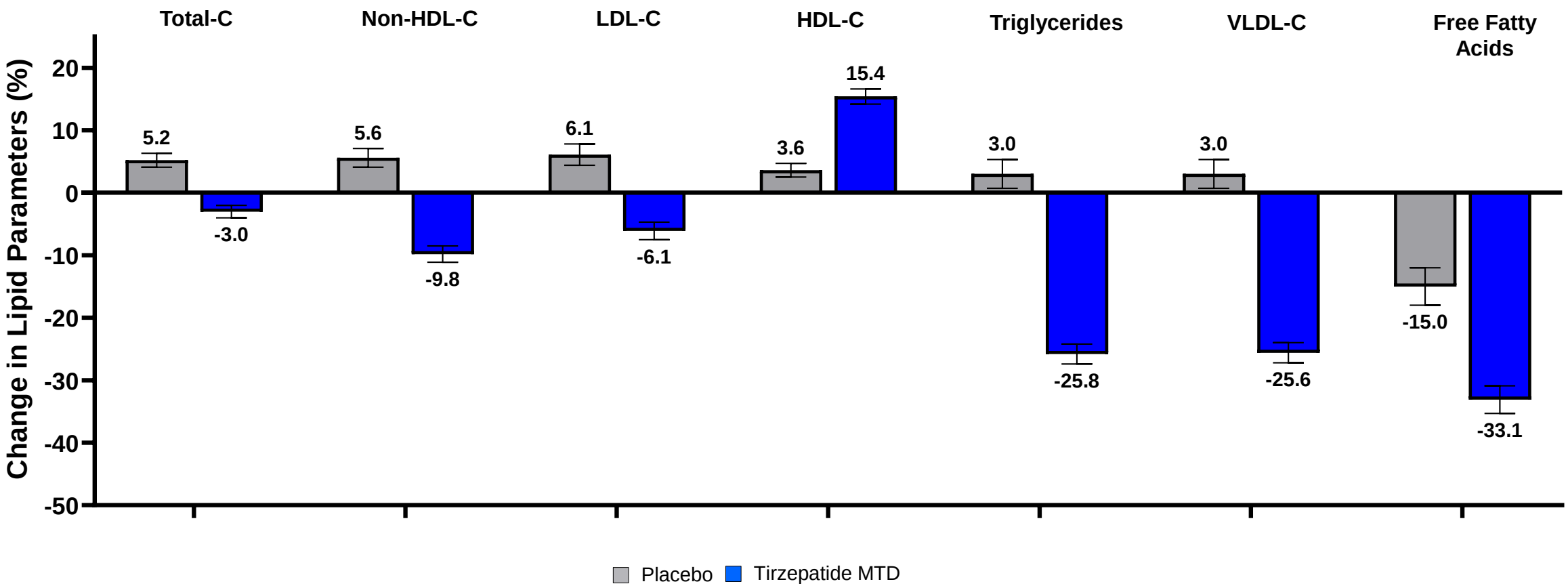
Change in Lipid Parameters

From Randomization (Week 0) to Week 72 – Efficacy Estimand



Data are LSM (SE). Efficacy estimand (efficacy analysis set).

C=Cholesterol; HDL-C=High-density Lipoprotein Cholesterol; LDL-C=Low-density Lipoprotein Cholesterol; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose; SE=Standard Error; VLDL-C=Very Low-density Lipoprotein Cholesterol.

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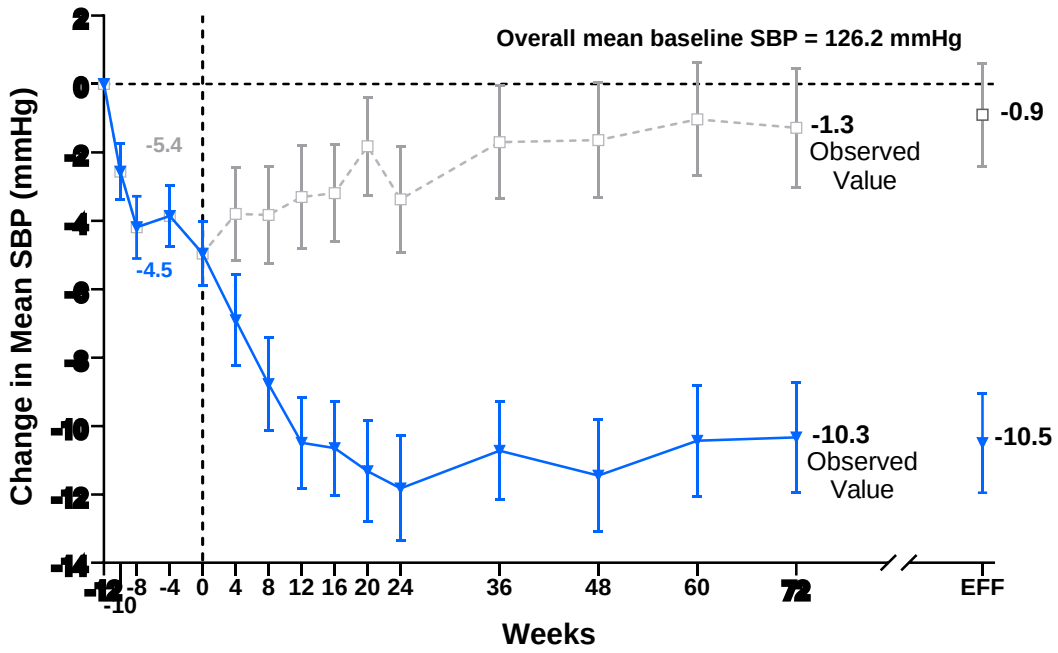
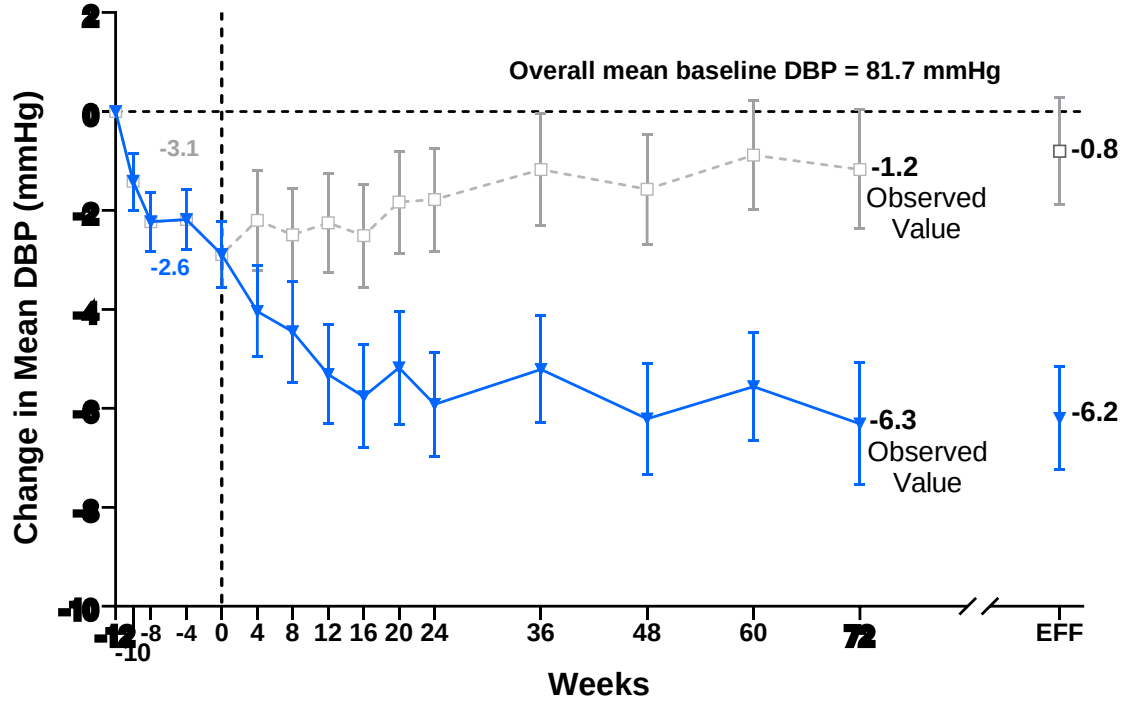
Change in SBP and DBP

From ILI (Week -12) to Week 72

Change in Systolic Blood Pressure



Change in Diastolic Blood Pressure



Placebo

Tirzepatide MTD

Data are observed values. Efficacy estimand values are also shown which are from efficacy analysis set and those values are LSM (SE).

DBP=Diastolic Blood Pressure; EFF=Efficacy Estimand; ILI=Intensive Lifestyle Intervention; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose; SBP=Systolic Blood Pressure; SE=Standard Error.

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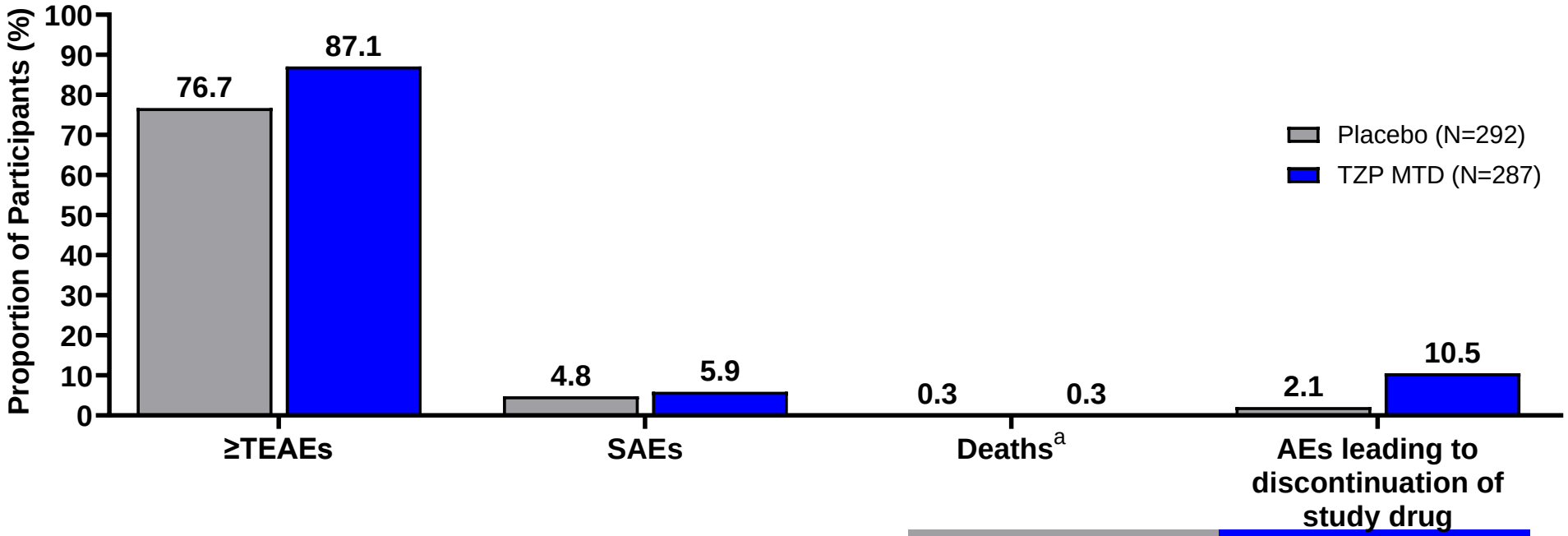
Safety

Overview of Adverse Events



	Placebo (N=292)	Tirzepatide MTD (N=287)
AEs Leading to Treatment Discontinuation[b]	6 (2.1)	30 (10.5)
Nausea, n (%)	4 (1.4)	24 (8.4)
Vomiting, n (%)	0	6 (2.1)
Diarrhea, n (%)	0	3 (1)
Dyspepsia, n (%)	0	3 (1)
Constipation, n (%)	0	2 (0.7)

[a]Deaths are also included as serious adverse events and discontinuations due to adverse event. [b]Only adverse events occurring in ≥2 participants in any treatment group are presented.
Data are from safety analysis set.
AE=Adverse Event; MTD=Maximum Tolerated Dose; SAE=Serious Adverse Event; TEAE=Treatment-emergent Adverse Event.
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Treatment-Emergent Adverse Events

	Placebo (N=292), n (%)	Tirzepatide MTD (N=287), n (%)
Adverse events occurring in ≥5% of participants in any treatment group		
Nausea	41 (14.0)	114 (39.7)
Diarrhoea	27 (9.2)	89 (31.0)
Constipation	20 (6.8)	66 (23.0)
COVID-19	74 (25.3)	66 (23.0)
Vomiting	4 (1.4)	52 (18.1)
Injection site reaction	3 (1.0)	32 (11.1)
Abdominal pain	7 (2.4)	30 (10.5)
Decreased appetite	12 (4.1)	27 (9.4)
Dyspepsia	9 (3.1)	27 (9.4)
Headache	22 (7.5)	27 (9.4)
Upper respiratory tract infection	21 (7.2)	25 (8.7)
Alopecia	4 (1.4)	20 (7.0)
Dizziness	6 (2.1)	20 (7.0)
Fatigue	9 (3.1)	20 (7.0)
Flatulence	8 (2.7)	19 (6.6)
Gastrooesophageal reflux disease	7 (2.4)	19 (6.6)
Back pain	15 (5.1)	17 (5.9)
Eructation	3 (1.0)	16 (5.6)
Influenza	25 (8.6)	12 (4.2)
Urinary tract infection	15 (5.1)	11 (3.8)
Anxiety	19 (6.5)	9 (3.1)
Arthralgia	15 (5.1)	7 (2.4)
Sinusitis	16 (5.5)	6 (2.1)

Values are n (%). Data are from safety analysis set.
COVID-19=Coronavirus Disease 2019; MTD=Maximum Tolerated Dose
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Adverse Events of Special Interest

	Placebo (N=292), n (%)	Tirzepatide MTD (N=287), n (%)
Adverse events of special interest		
Severe or serious gastrointestinal events	5 (1.7)	16 (5.6)
Malignancies	3 (1.0)	5 (1.7)
Severe or serious acute gallbladder diseases	0	2 (0.7)
MACE (adjudication-confirmed)	1 (0.3)	1 (0.3)
Pancreatitis (adjudication-confirmed)	1 (0.3)	1 (0.3)
Severe or serious renal events	0	1 (0.3)
Severe or serious MDD/suicidal behavior and ideation	0	1 (0.3)
Severe or serious arrhythmias and cardiac conduction disorders	1 (0.3)	0
Severe hypoglycemia	0	0
Other adverse events of interest		
Cholelithiasis	3 (1.0)	4 (1.4)
Acute cholecystitis	0	1 (0.3)
Chronic cholecystitis	1 (0.3)	0

Values are n (%). Data are from safety analysis set.
MACE=Major Adverse Cardiovascular Events; MDD=Major Depressive Disorder; MTD=Maximum Tolerated Dose.
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Additional Safety Measures

	Placebo (N=292), n (%)	Tirzepatide MTD (N=287), n (%)
Pulse rate, beats/minute		
Baseline	70.7 (0.62)	72.2 (0.62)
Week 72	72.2 (0.57)	74.0 (0.53)
Change at week 72	0.9 (0.57)	2.7 (0.53)
Pancreatic amylase, IU/L		
Baseline	25.4 (0.56)	24.0 (0.53)
Week 72	24.8 (0.44)	30.3 (0.50)
% Change at week 72	0.6 (1.79)	22.8 (2.03)
Lipase, IU/L		
Baseline	28.4 (0.66)	27.6 (0.63)
Week 72	30.3 (0.78)	41.3 (0.99)
% Change at week 72	7.7 (2.78)	46.6 (3.50)
Alanine aminotransferase, IU/L		
Baseline	20.6 (0.56)	21.4 (0.58)
Week 72	21.1 (0.66)	16.9 (0.49)
% Change at week 72	1.5 (3.17)	-18.9 (2.35)
Aspartate aminotransferase, IU/L		
Baseline	19.3 (0.37)	20.1 (0.38)
Week 72	20.0 (0.46)	18.3 (0.39)
% Change at week 72	2.0 (2.37)	-6.8 (2.00)
Calcitonin, ng/L		
Baseline	1.5 (0.06)	1.6 (0.07)
Week 72	1.6 (0.05)	1.7 (0.05)
% Change at week 72	3.9 (3.30)	12.0 (3.35)
Urine albumin-creatinine ratio, g/kg		
Baseline	6.0 (0.35)	5.8 (0.33)
Week 72	5.4 (0.30)	5.2 (0.26)
% Change at week 72	-8.8 (5.06)	-12.3 (4.47)

Data are model based estimate (standard error) and were analyzed with log transformation, except for pulse rate data.
MTD=Maximum Tolerated Dose.
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Conclusions

- Tirzepatide MTD demonstrated superior and clinically meaningful body weight reduction compared to placebo
  - From randomization: additional -18.4% weight reduction with tirzepatide MTD, vs. 2.5% gain with placebo
  - From start of the ILI lead-in period: -25.0% weight reduction with tirzepatide MTD, vs. -4.8% with placebo
- 87.5% of participants treated with tirzepatide MTD achieved ≥5% weight reduction from randomization
- 28.7% of participants achieved the exploratory endpoint of ≥ 25% weight reduction
- 94.0% of participants treated with tirzepatide MTD maintained ≥80% of weight reduction achieved during the ILI lead-in period
- Tirzepatide led to additional improvements in cardiometabolic risk factors and physical function scores after ILI
- The tolerability and safety profile of tirzepatide in people with obesity/overweight was consistent with the safety profile of the GLP-1 receptor agonist class in people with obesity.
- Gastrointestinal-related adverse events were most frequent, occurring primarily during dose escalation and were mostly mild to moderate.
- Serious adverse events were balanced between placebo and tirzepatide groups

GLP-1=Glucagon-like Peptide-1; ILI=Intensive Lifestyle Intervention; MTD=Maximum Tolerated Dose.

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Back-up Slides

Key Methods and Assessments

- Efficacy and safety endpoints were analyzed using data from all randomized participants (ITT population)
- Safety analyses included all data from the start of treatment to the end of safety follow-up
- Two estimands were used to assess treatment efficacy from different perspectives

Treatment-regimen Estimand

Represents the average treatment effect of tirzepatide compared with placebo, regardless of treatment discontinuation.

Efficacy Estimand

Represents the average treatment effect of tirzepatide compared with placebo if the treatment was taken as intended.

Observed Values

Calculated from actual values measured during the study without imputation for missing data.

ITT=Intention-to-Treat.

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SURMOUNT-3

Country Allocation

The study was conducted across 2 continents in 3 countries: Argentina, Brazil, and the USA

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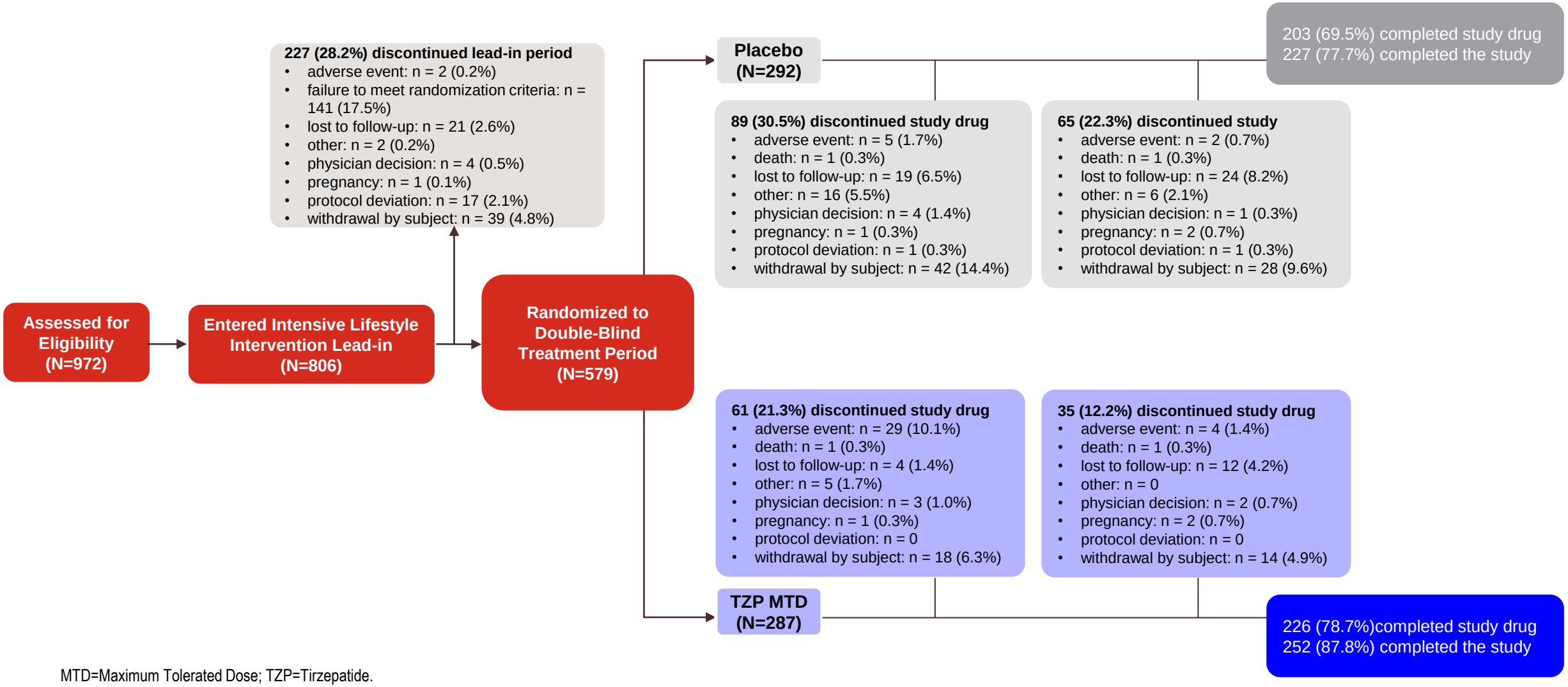
Participant Disposition



MTD=Maximum Tolerated Dose; TZP=Tirzepatide.

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Baseline Demographics and Clinical Characteristics

Lead-in Period

	Tirzepatide MTD (N=287)	Placebo (N=292)	Total (N=579)
Pulse rate, bpm	73.4 (10)	72.2 (9.9)	72.8 (9.9)
Blood pressure, mmHg			
Systolic	125.9 (12.7)	126.0 (13.3)	126.0 (13.0)
Diastolic	81.8 (8.5)	81.2 (8.4)	81.5 (8.5)
Fasting insulin, mIU/L	97.7 (75.3)	93.6 (87.7)	95.6 (81.7)
Lipids, mg/dL			
Total cholesterol	191.4 (36.8)	196.2 (39.0)	193.8 (38.0)
Non-HDL cholesterol	141.9 (35.8)	145.6 (37.5)	143.7 (36.7)
HDL cholesterol	49.6 (14.0)	50.6 (13.8)	50.1 (13.9)
LDL cholesterol	113.7 (30.4)	118.0 (32.4)	115.9 (31.5)
VLDL cholesterol	60.3 (27.2)	62.1 (30.9)	61.2 (29.1)
Triglycerides	141.2 (112.3)	138.2 (73.5)	139.7 (94.7)
Free fatty acids, mEq/L	0.6 (0.2)	0.5 (0.2)	0.5 (0.2)
Patient-reported outcomes			
SF-36 physical functioning domain score[a]	48.9 (7.8)	48.6 (7.8)	48.8 (7.8)
IWQOL-Lite-CT physical function composite score[b]	59.5 (22.7)	57.4 (24.3)	58.4 (23.5)

[a]SF-36v2 measures health-related quality of life and general health status. SF-36v2 scores are norm based—that is, scores are transformed to a scale in which the 2009 US general population has a mean score of 50 and s.d. of 10. An increase in score represents an improvement in health status. [b]IWQOL-Lite-CT measures weight-specific, health-related quality of life. All items are rated on either a five-point frequency scale (‘never’ to ‘always’) or a five-point truth scale (‘not at all true’ to ‘completely true’). Scores are transformed to a scale of 0–100, with higher scores reflecting better levels of functioning.

Data are mean (SD).

HDL=High-density Lipoprotein; IWQoL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version; LDL=Low-density Lipoprotein; MTD=Maximum Tolerated Dose; SD=Standard Deviation; SF-36v2=36-Item Short Form Health Survey Version 2; VLDL=Very Low-density Lipoprotein.

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Baseline Demographics and Clinical Characteristics (1 of 2)

At Randomization

	Tirzepatide MTD (N=287)	Placebo (N=292)	Total (N=579)
Race, n (%)			
Asian	2 (0.7)	2 (0.7)	4 (0.7)
Black or African American	31 (10.8)	32 (11.0)	63 (10.9)
Multiple	6 (2.1)	2 (0.7)	8 (1.4)
American Indian or Alaskan	2 (0.7)	4 (1.4)	6 (1.0)
White	246 (85.7)	252 (86.3)	498 (86.0)
Ethnicity[a], n (%)			
Hispanic or Latino	151 (52.6)	161 (55.1)	312 (53.9)
Not Hispanic or Latino	132 (46.0)	129 (44.2)	261 (45.1)
Not reported	4 (1.4)	2 (0.7)	6 (1.0)
Country, n (%)			
Argentina	43 (15.0)	44 (15.1)	87 (15.0)
Brazil	59 (20.6)	60 (20.5)	119 (20.6)
USA	185 (64.5)	188 (64.4)	373 (64.4)

[a]Race and ethnicity were determined by the participant according to fixed selection categories.
MTD=Maximum Tolerated Dose.
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Baseline Demographics and Clinical Characteristics (2 of 2)

At Randomization

	Tirzepatide MTD (N=287)	Placebo (N=292)	Total (N=579)
Obesity-related complications[a], n (%)			
Hypertension	95 (33.1)	104 (35.6)	199 (34.4)
Dyslipidemia	71 (24.7)	81 (27.7)	152 (26.3)
ASCVD	5 (1.7)	6 (2.1)	11 (1.9)
Polycystic ovarian syndrome	8 (4.4)	8 (4.4)	16 (4.4)
Obstructive sleep apnea	25 (8.7)	34 (11.6)	59 (10.2)
Osteoarthritis	43 (15.0)	48 (16.4)	91 (15.7)
Anxiety/depression	61 (21.3)	55 (18.8)	116 (20.0)
NAFLD	9 (3.1)	16 (5.5)	25 (4.3)
Asthma or COPD	21 (7.3)	31 (10.6)	52 (9.0)
Gout	6 (2.1)	9 (3.1)	15 (2.6)
Number of weight-related complications[a], n (%)			
None	96 (33.4)	100 (34.2)	196 (33.9)
1	102 (35.5)	81 (27.7)	183 (31.6)
2	48 (16.7)	54 (18.5)	102 (17.6)
3	22 (7.7)	36 (12.3)	58 (10.0)
4	14 (4.9)	14 (4.8)	28 (4.8)
≥5	5 (1.7)	7 (2.4)	12 (2.1)

[a]Baseline medical conditions were assessed through a review of participants' medical history.

ASCVD=Atherosclerotic Cardiovascular Disease; COPD=Chronic Obstructive Pulmonary Disease; MTD=Maximum Tolerated Dose; NAFLD=Non-Alcoholic Fatty Liver Disease.

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Change in Clinical Characteristics During ILI

	Change During Lead-in Period		
	Tirzepatide MTD (N=287)	**Placebo (N=292)**	**Total (N=579)**
Body weight, kg	-7.6 (2.9) kg or -6.9 (1.9) %	-7.6 (2.8) kg or -7.0 (2.0) %	-7.6 (2.9) kg or -6.9 (2.0) %
BMI, kg/m²	-2.7 (0.9)	-2.7 (0.9)	-2.7 (0.9)
Waist circumference, cm	-6.6 (5.4)	-6.7 (4.9)	-6.7 (5.2)
Blood pressure, mmHg			
Systolic	-4.5 (11.4)	-5.4 (11.3)	-5.0 (11.4)
Diastolic	-2.6 (8.1)	-3.1 (8.2)	-2.9 (8.1)
Pulse rate, beats/minute	-1.4 (10.2)	-1.8 (9.1)	-1.6 (9.6)
HbA1c, %	-0.1 (0.3)	-0.1 (0.3)	-0.1 (0.3)
Fasting glucose, mg/dL	-3.1 (10.1)	-2.8 (10.0)	-2.9 (10.0)
Fasting insulin, mIU/L	-18.5 (52.9) %	-22.3 (41.3) %	-20.4 (47.4) %
Lipids, mg/dL			
Total cholesterol	-2.5 (13.7) %	-4.9 (12.1) %	-3.7 (13.0) %
Non-HDL cholesterol	-2.3 (18.1) %	-5.5 (15.4) %	-3.9 (16.8) %
HDL cholesterol	-0.8 (13.9) %	-1.5 (13.4) %	-1.2 (13.7) %
LDL cholesterol	0.8 (24.3) %	-3.6 (18.2) %	-1.4 (21.5) %
VLDL cholesterol	-3.8 (33.1) %	-5.5 (34.3) %	-4.7 (33.7) %
Triglycerides	-4.4 (33.4) %	-6.0 (34.1) %	-5.2 (33.8) %
Free fatty acids, mEq/L	23.0 (82.0) %	29.9 (86.3) %	26.5 (84.2) %
eGFR, ml/min/1.73 m²	-3.4 (10.4)	-3.3 (8.9)	-3.3 (9.7)
Patient-reported outcomes			
SF-36 physical functioning domain score[a]	2.7 (7.7)	3.1 (5.8)	2.9 (6.8)
IWQOL-Lite-CT physical function composite score[b]	13.9 (17.6)	13.9 (17.7)	13.9 (17.7)

Data are mean (SD). Description of superscripted a and b are mentioned in speaker note section.

BMI=Body Mass Index; eGFR=Estimated Glomerular Filtration Rate; HbA1c=Glycated Hemoglobin; HDL=High-density Lipoprotein; ILI=Intensive Lifestyle Intervention; IWQoL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version; LDL=Low-density Lipoprotein; MTD=Maximum Tolerated Dose; SD=Standard Deviation; SF-36v2=36-Item Short Form Health Survey Version 2; VLDL=Very Low-density Lipoprotein.

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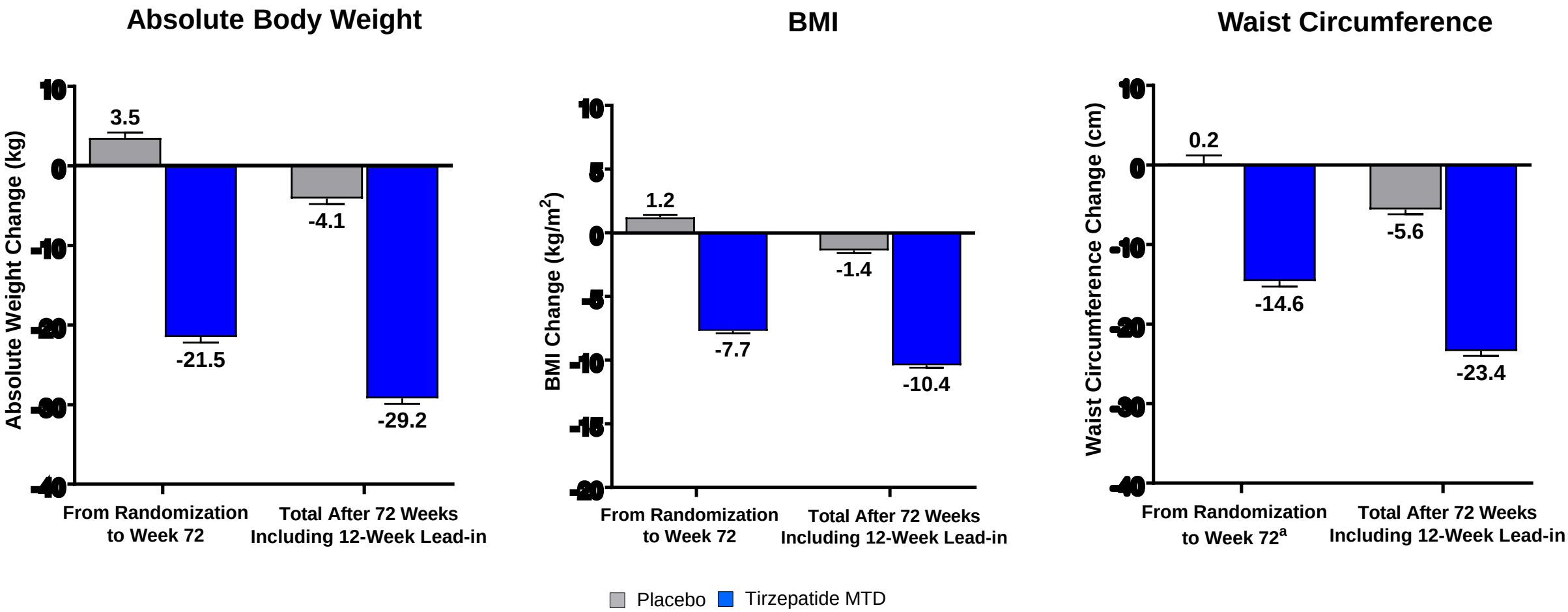
Change in Absolute Body Weight, BMI, and WC

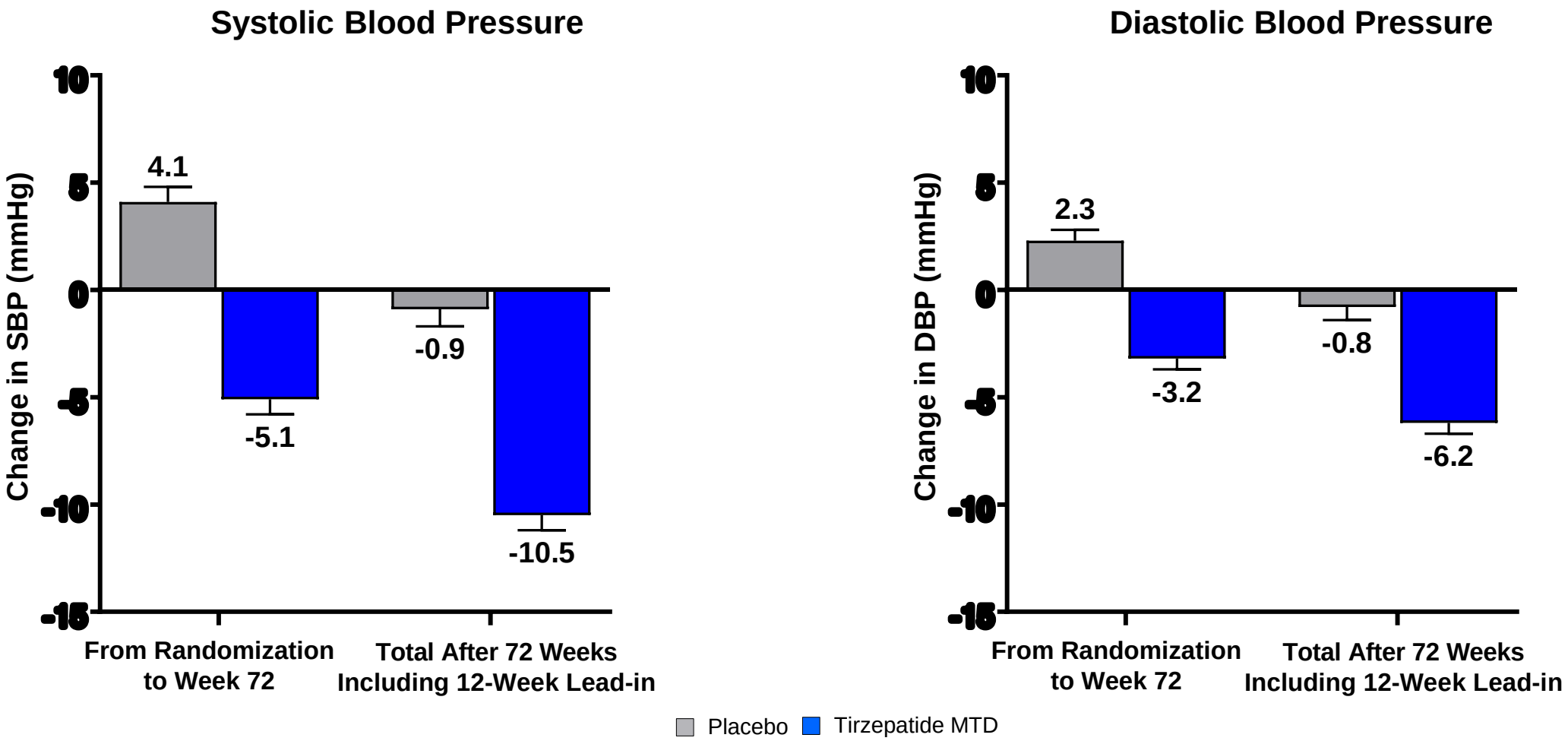
Efficacy Estimand



[a]Treatment-regimen estimand.
Data are LSM (SE).
BMI=Body Mass Index; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose; SE=Standard Error; WC=Waist Circumference.
Wadden TA, et al. *Nat Med*. 2023;29(11):2909-2918.

Change in SBP and DBP

Efficacy Estimand



Data are LSM (SE).

DBP=Diastolic Blood Pressure; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose; SBP=Systolic Blood Pressure; SE=Standard Error.

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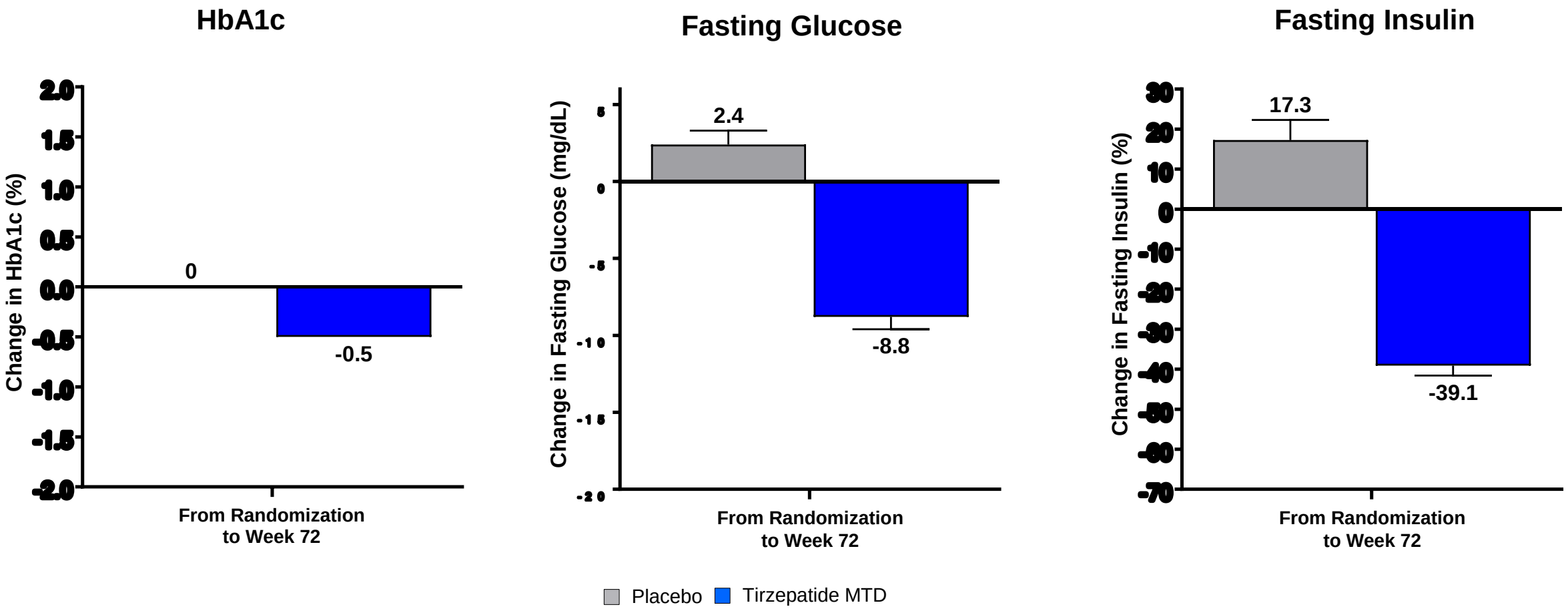
Change in HbA1c, Fasting Glucose, and Fasting Insulin

Efficacy Estimand



Data are LSM (SE).
HbA1c=Glycated Hemoglobin; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose; SE=Standard Error.
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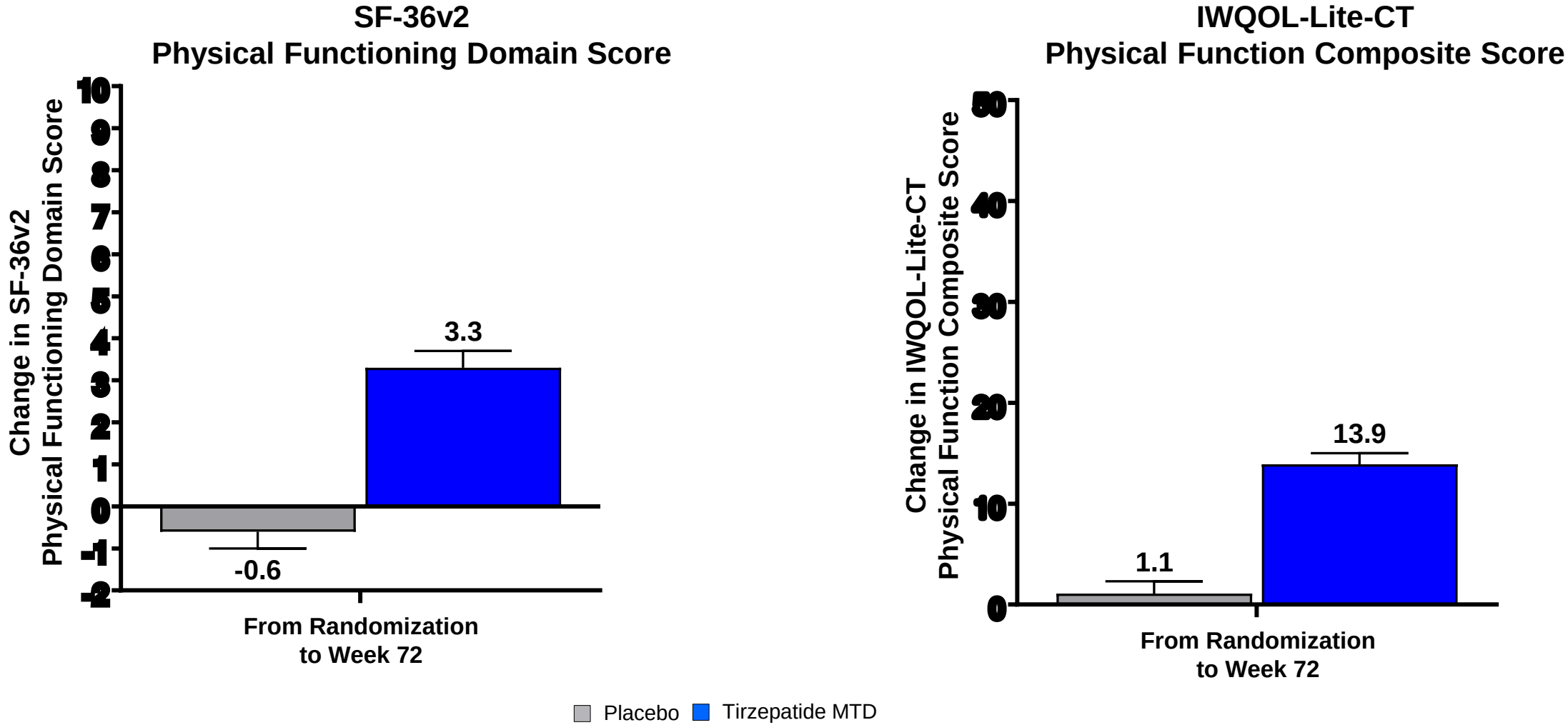
Change in Patient Reported Outcomes



Data are LSM (SE).
IWQoL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version; LSM=Least Squares Mean; MTD=Maximum Tolerated Dose; SE=Standard Error; SF-36v2=36-Item Short Form Health Survey Version 2.
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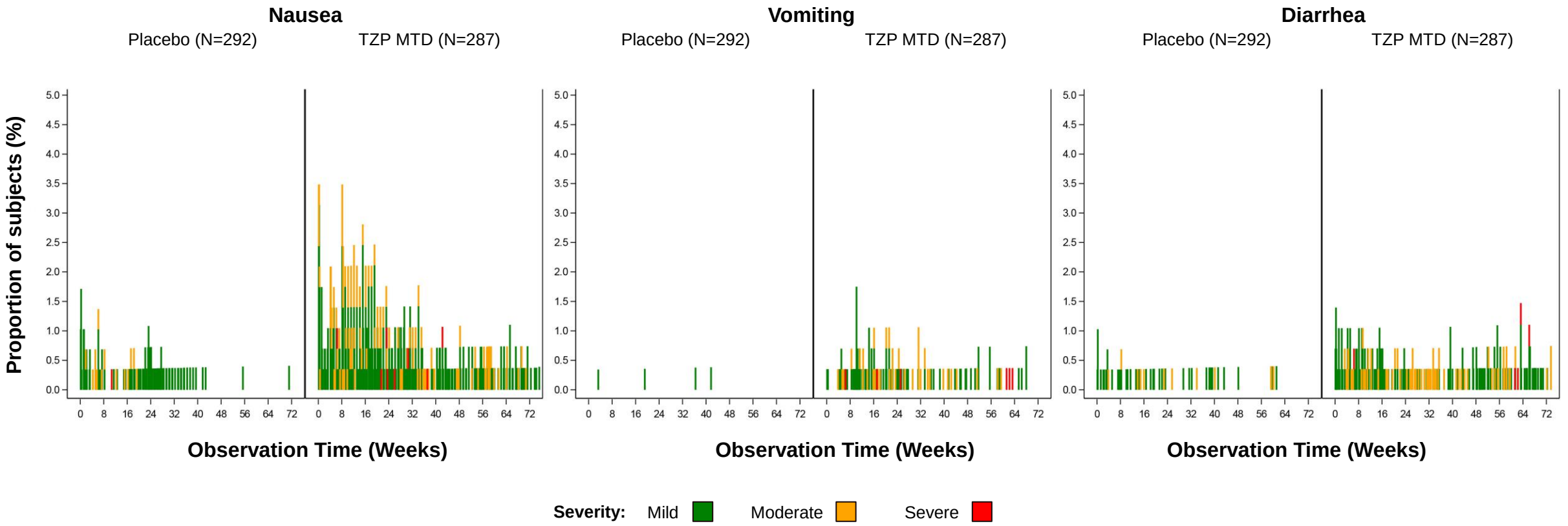
Incidence of Nausea, Vomiting, and Diarrhea



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