SURMOUNT-3
Background & Rationale

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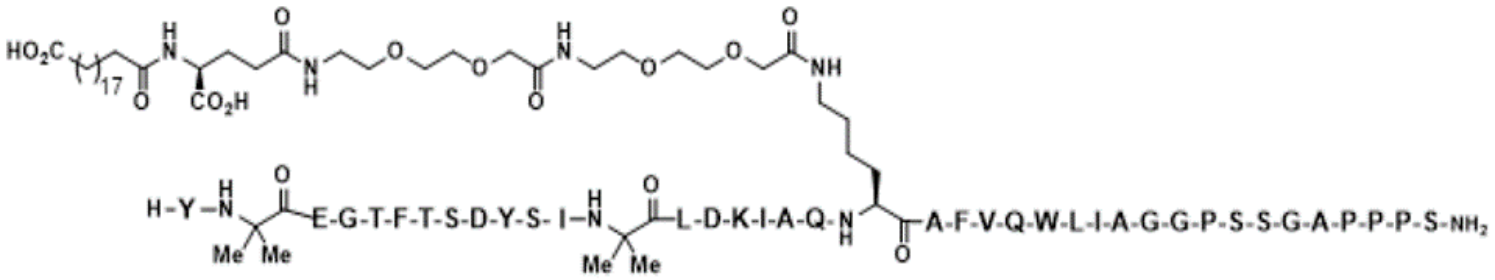
Tirzepatide, a GIP and GLP-1 Dual Receptor Agonist

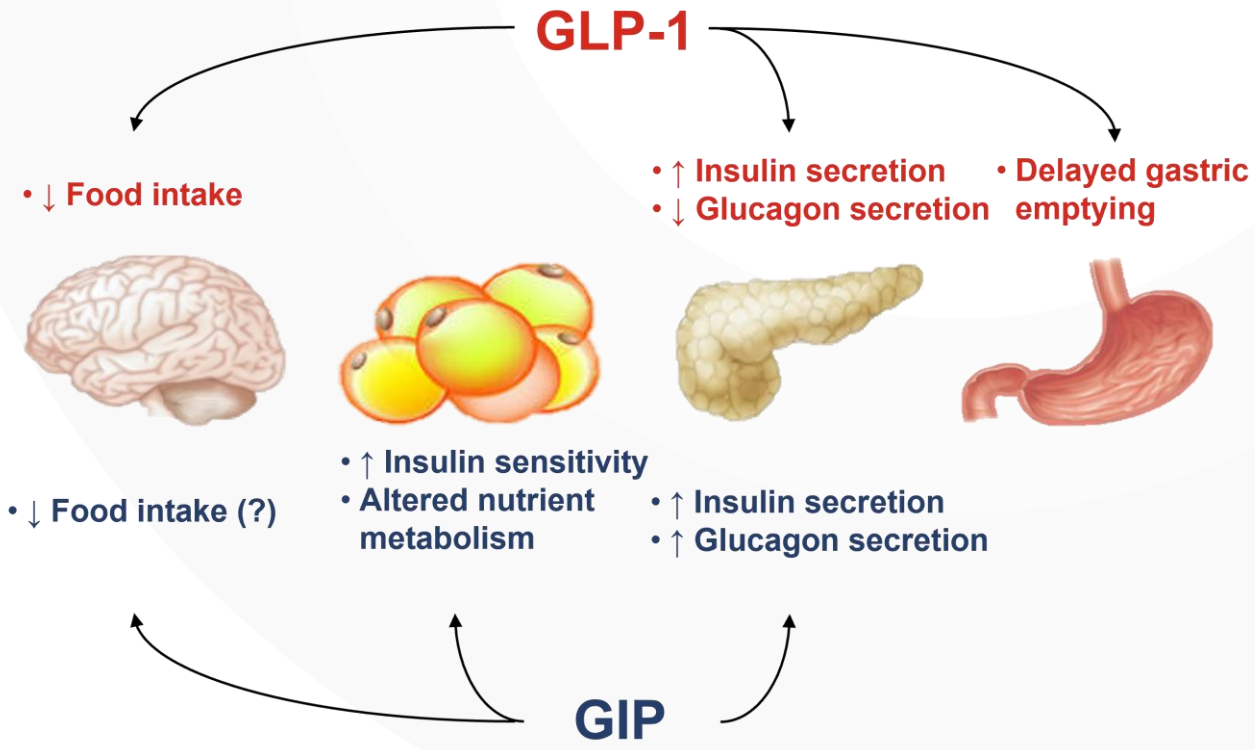
- Tirzepatide is a long-acting GIP receptor and GLP-1 receptor agonist[1]
- It is an amino acid sequence that includes a C20 fatty diacid moiety[1]
- It has a mean half-life of approximately 5 days in humans (116.7 h), supporting once-weekly dosing[1]
- Its plasma concentrations in people with renal and hepatic impairment do not differ from those in healthy people[2,3]



[1]Coskun T, et al. Mol Metab. 2018;18:3-14. [2]Urva S, et al. *Clin Pharmacokinet.* 2021;60:1049–1059. [3]Urva S, et al. *Clin Pharmacokinet.* 2022;61:1057–1067.

GIP and GLP-1 Receptor Agonist: Potential Mechanism of Action

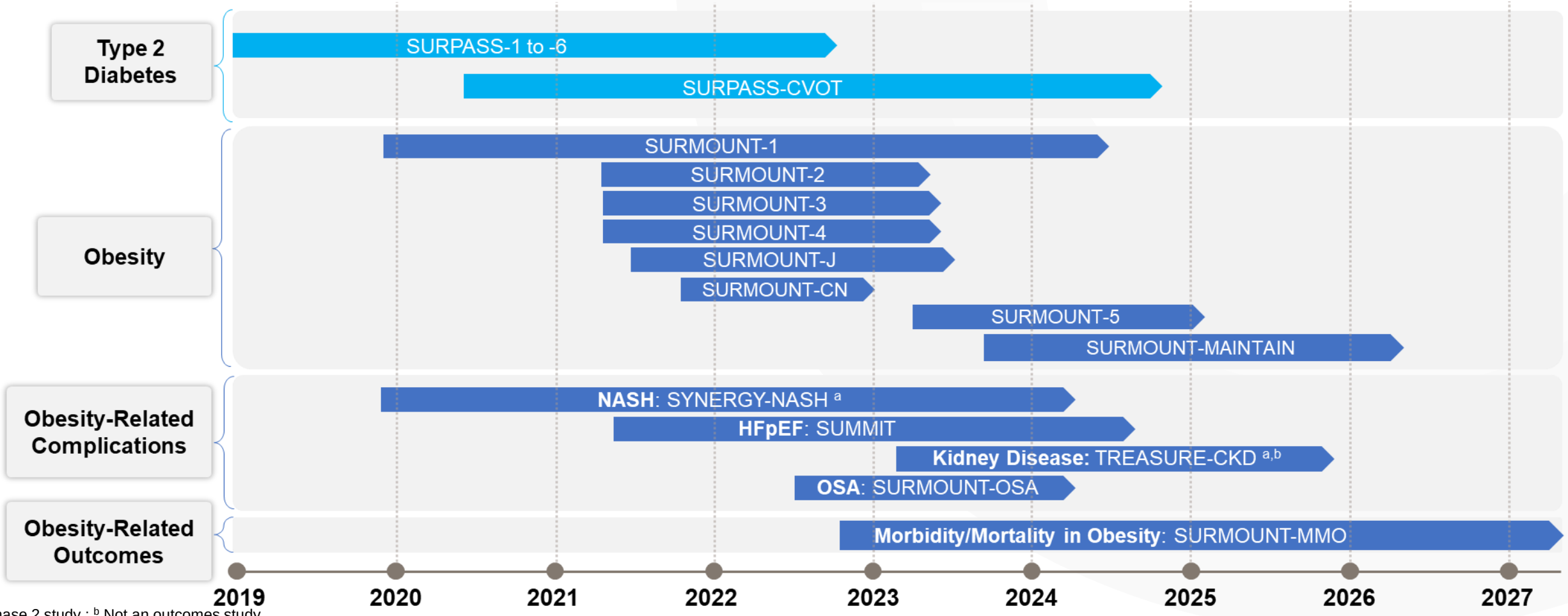
- GLP-1 has suggested direct actions in the CNS, islets, and stomach[1,2]
- GIP has shown potential actions in the CNS (preclinical), and adipose tissue and islets (clinical and preclinical)[2-4]
- A single-molecule GIP/GLP-1 receptor agonist may enable therapeutic actions that are improved over the sum of GIP and GLP-1 single-receptor agonism[5,6]



CNS=central nervous system; GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1.

[1]Müller TD, et al. *Mol Metab*. 2019;30:72-130. [2]Seino Y, et al. *J Diabetes Investig*. 2010;1(1-2):8-23. [3]Fukuda M. *Diabetes*. 2021;70(8):dbi210001. [4]Nauck MA, et al. *Diabetes Obes Metab.* 2021;23(3):5-29. [5]Samms RJ, et al. *Trends Endocrinol Metab*. 2020;31(6):410-421. [6]Bastin M, et al. *Diabetes Metab Syndr Obes*. 2019;12:1973-1985.

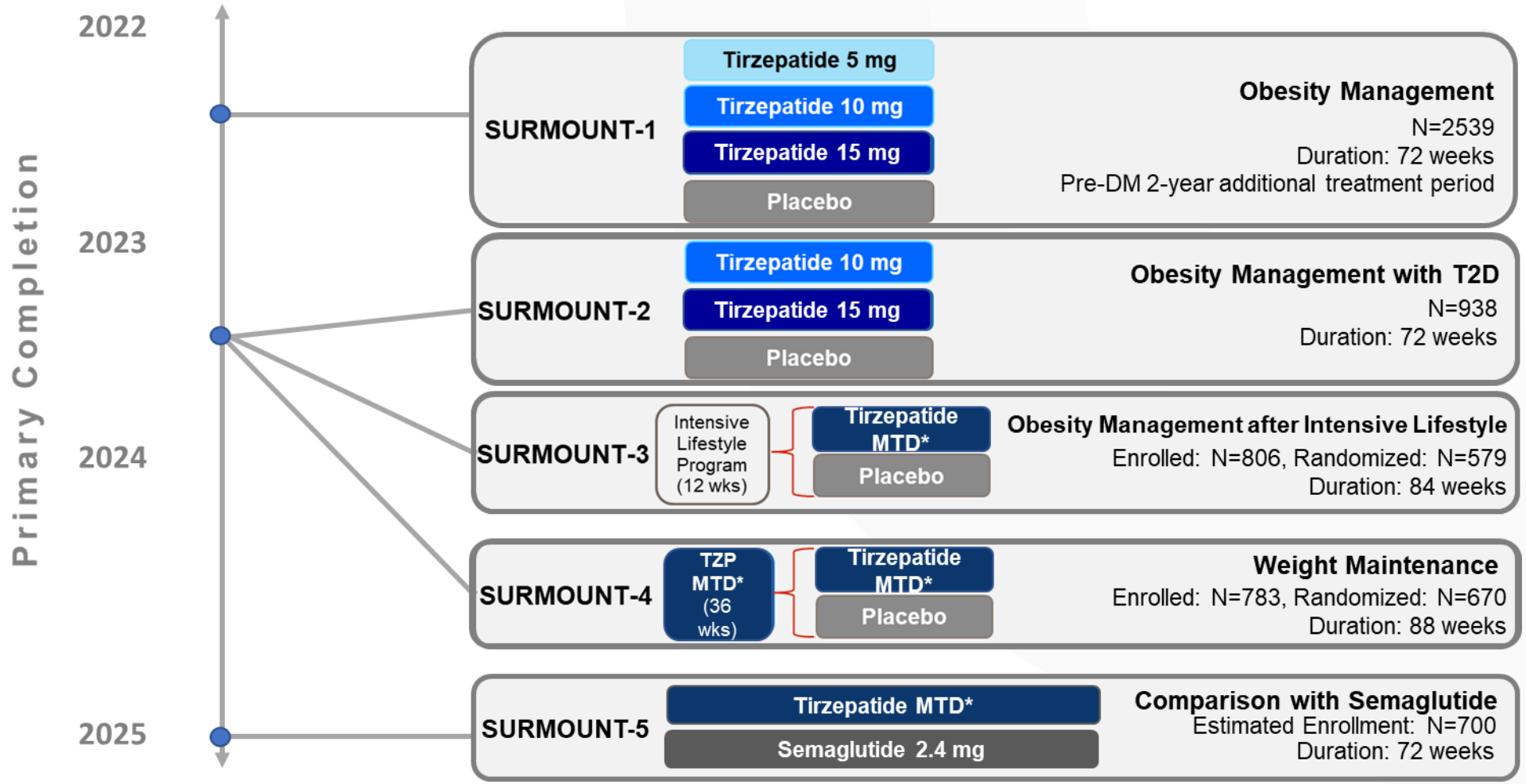
Tirzepatide Clinical Development Program
T2D, Obesity, and Obesity-Related Outcomes



[a] Phase 2 study.; [b] Not an outcomes study.

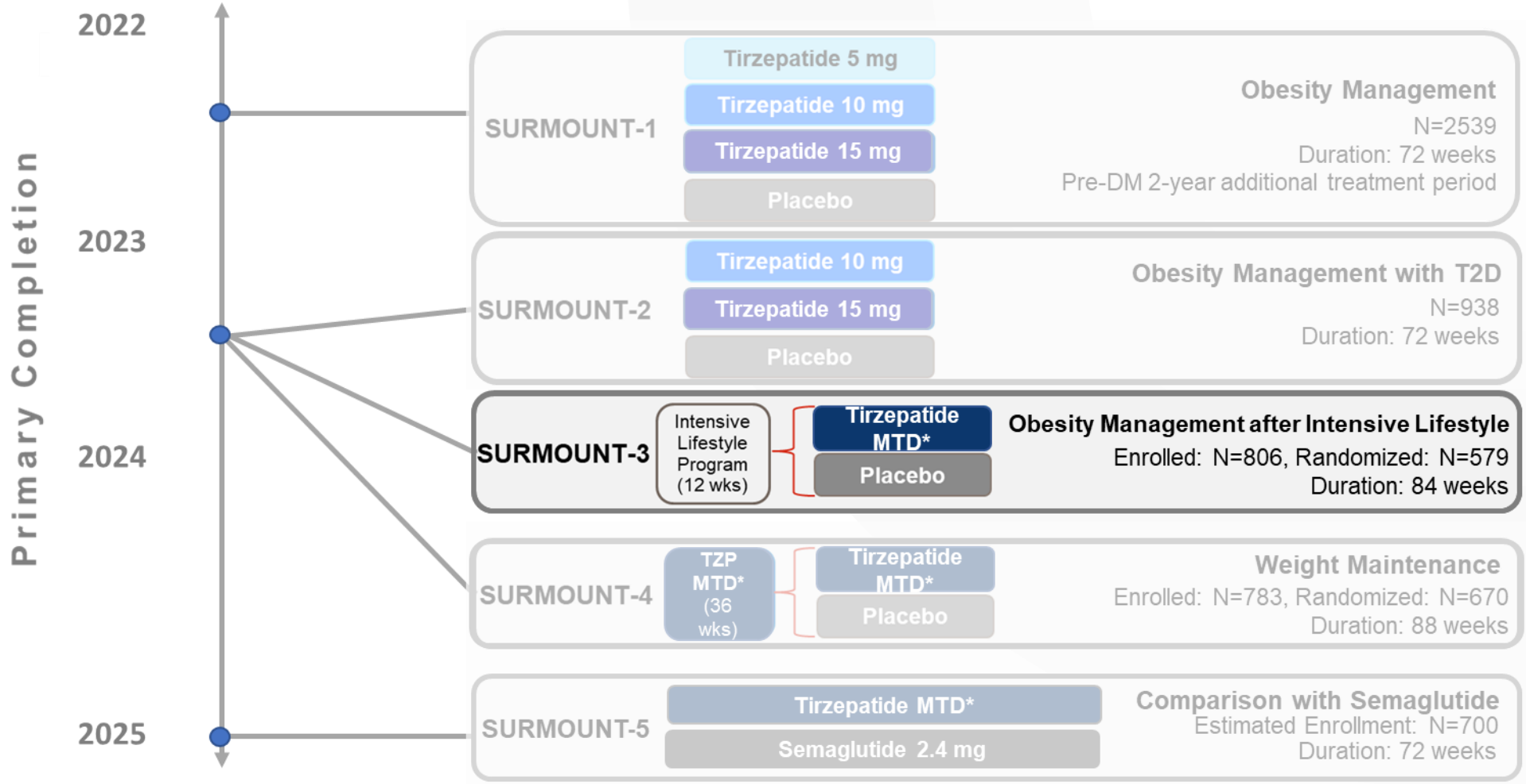
CKD=Chronic Kidney Disease; CVOT=Cardiovascular Outcomes; HFpEF=Heart Failure With Preserved Ejection Fraction; MMO=Morbidity/Mortality in Obesity; MoA=Mechanism of Action; NASH=Non-alcoholic Steatohepatitis; OSA=Obstructive Sleep Apnea.

SURMOUNT: Tirzepatide in People with Obesity
Phase 3 Global Clinical Trials Overview



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

SURMOUNT: Tirzepatide in People with Obesity
Phase 3 Global Clinical Trials Overview

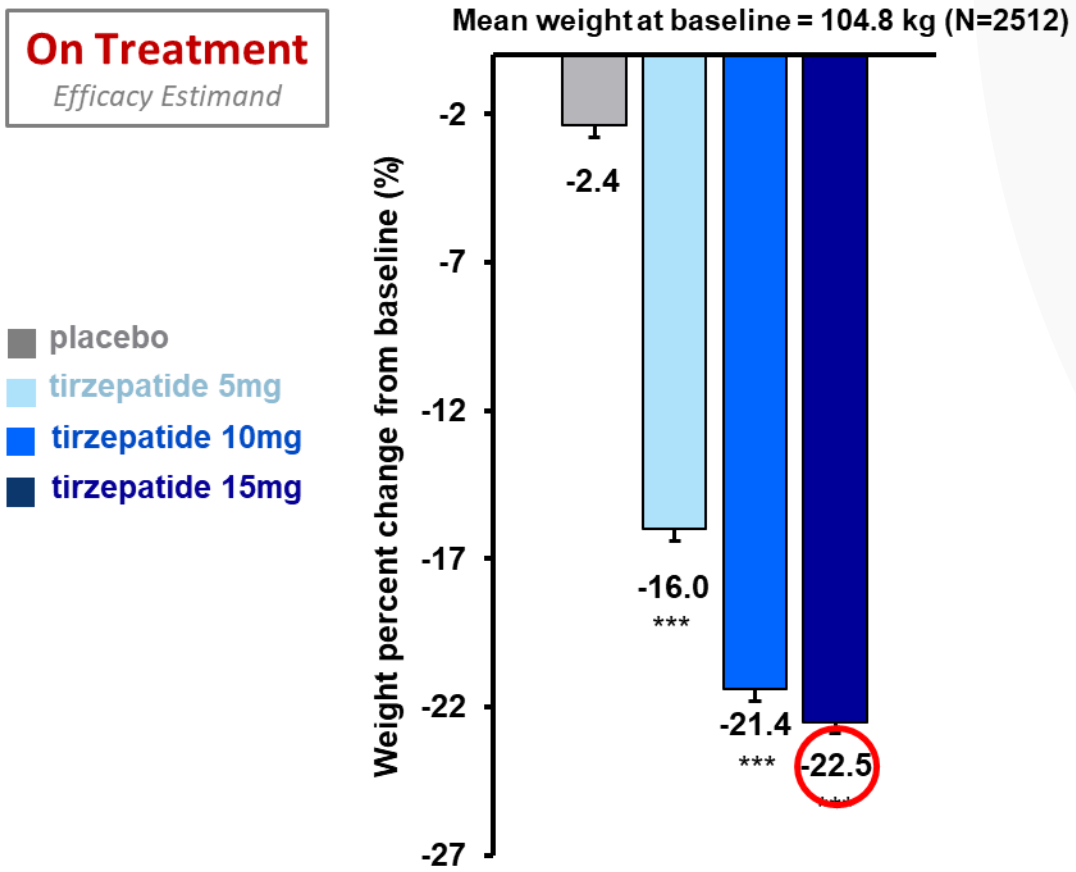


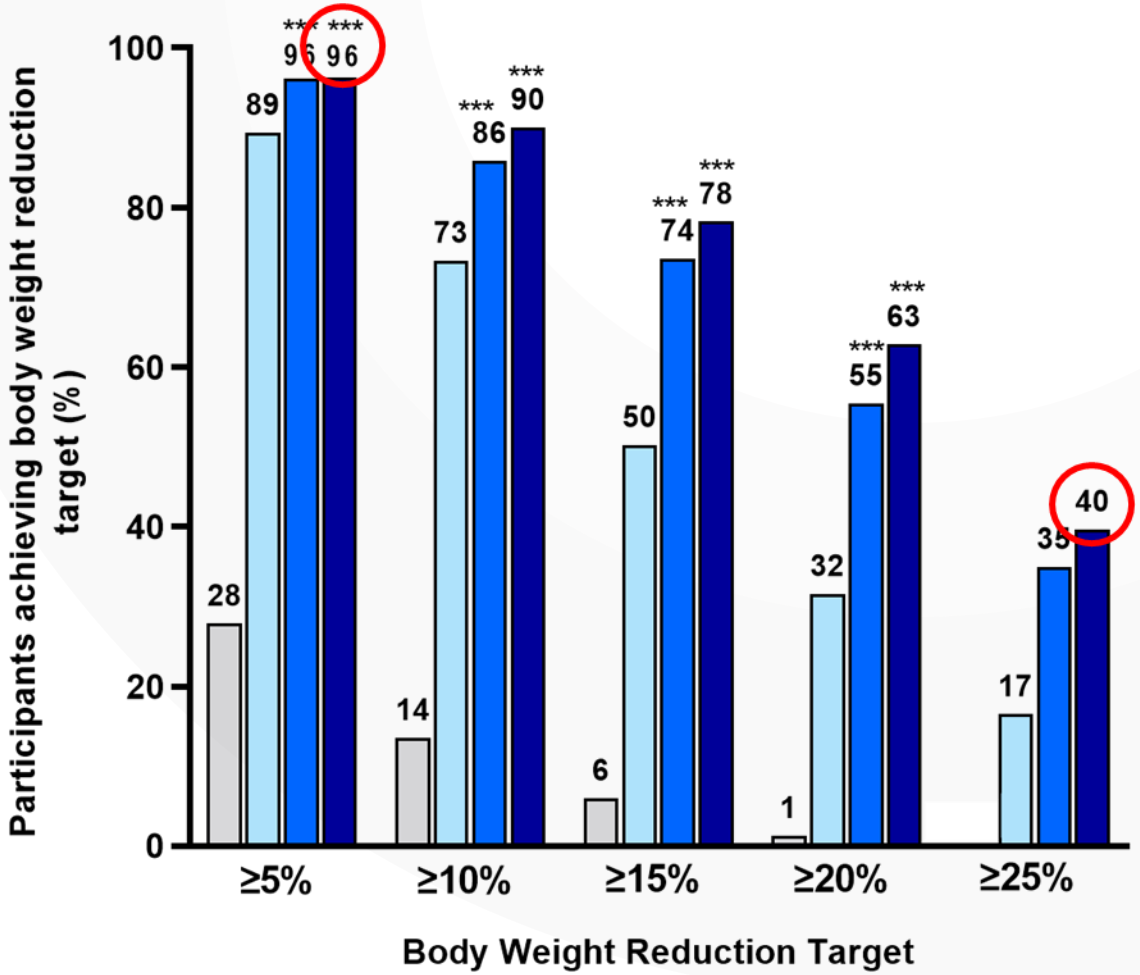
*MTD: maximum tolerated dose (10 mg or 15 mg).

SURMOUNT-1 (Participants Without Type 2 Diabetes)

Percent Body Weight Change and Weight Reduction Thresholds at Week 72

On Treatment
Efficacy Estimand





Placebo vs. tirzepatide: ***p<0.001. All participants received study intervention in adjunct to a reduced calorie diet (500-kcal deficit/day compared to participant's estimated energy expenditure) and 150 min/week of physical activity.
Jastreboff AM, et al. *N Eng J Med*. 2022;387:205-216.

Weight Reduction and Intensive Lifestyle Intervention

- Decreasing body weight by 5-10% reduces the odds of developing T2D and improves obesity-related complications.[1,2]
- Intensive lifestyle intervention (ILI) is considered a cornerstone of obesity management.
  - Reduced-calorie diet, physical activity, and frequent behavioral counseling
  - Mean reductions of 5-8% of baseline weight, with accompanying improvements in health
  - Effectiveness in improving health is limited by two factors
    - ➢ Larger weight reductions are critical for achieving optimal control of obesity-related complications and decreasing cardiovascular mortality.[2]
    - ➢ Patients regain one-third of lost weight in the year after treatment, with increasing weight regain over time.

[1]Jensen MD, et al. *Obesity*. 2014;22:S41-S410. [2]Garvey WT, et al. *Endocr Pract*. 2016;2(3):1-203.

Weight Regain After Diet and Exercise Intervention

- Weight regain after diet and exercise intervention is attributable, in part, to[1-3]
  - persistent metabolic adaptations in which patients' hunger hormones increase, satiety hormones decrease, and
  - energy expenditure declining out of proportion to the amount of weight lost such that an even lower energy intake is needed to maintain the weight-reduced state.

[1]Sumithran P, et al. *N Engl J Med*. 2011;365:1597-1604. [2]Ravussin E & Redman LM. *Am J Clin Nutr*. 2020;112:1653-1654. [3]Rosenbaum M & Leibel RL. *Obesity (Silver Springs)*. 2016;24:1620-1629.

The Use of AOMs After Intensive Lifestyle Intervention

- Expert panels have suggested the use of AOMs after patients lose weight with intensive lifestyle intervention to[1-4]
    1. induce additional weight reduction (which may be needed to achieve optimal control of obesity-related complications)
    2. prevent weight regain.
- The effect of tirzepatide after successful intensive lifestyle intervention is not known.

AOMs = anti-obesity medications

[1]Jensen MD, et al. *Obesity*. 2014;22:S41-S410. [2]Garvey WT, et al. *Endocr Pract*. 2016;2(3):1-203. [3]Wharton S, et al. *Cmaj*. 2020;192:E875-E891. [4]Stegenga H, et al. *BMJ.* 2014;349:g6608.

Conclusions

- In the SURMOUNT-1 trial, tirzepatide 5, 10, and 15 mg provided substantial and sustained reductions in body weight in participants with obesity.
- Decreasing body weight reduces the odds of developing T2D and improves cardiometabolic risk factors and other obesity-related complications.
- Expert panels have suggested the use of AOMs after patients lose weight with intensive lifestyle intervention to induce additional weight reduction or to prevent weight regain.

SURMOUNT-3:
Study Design and Baseline Characteristics

Ania M. Jastreboff, MD, PhD

Associate Professor, Yale University

Endocrinology (Medicine) & Pediatric Endocrinology (Pediatrics)

Director, Yale Obesity Research Center (Y-Weight)

Co-Director, Yale Center for Weight Management

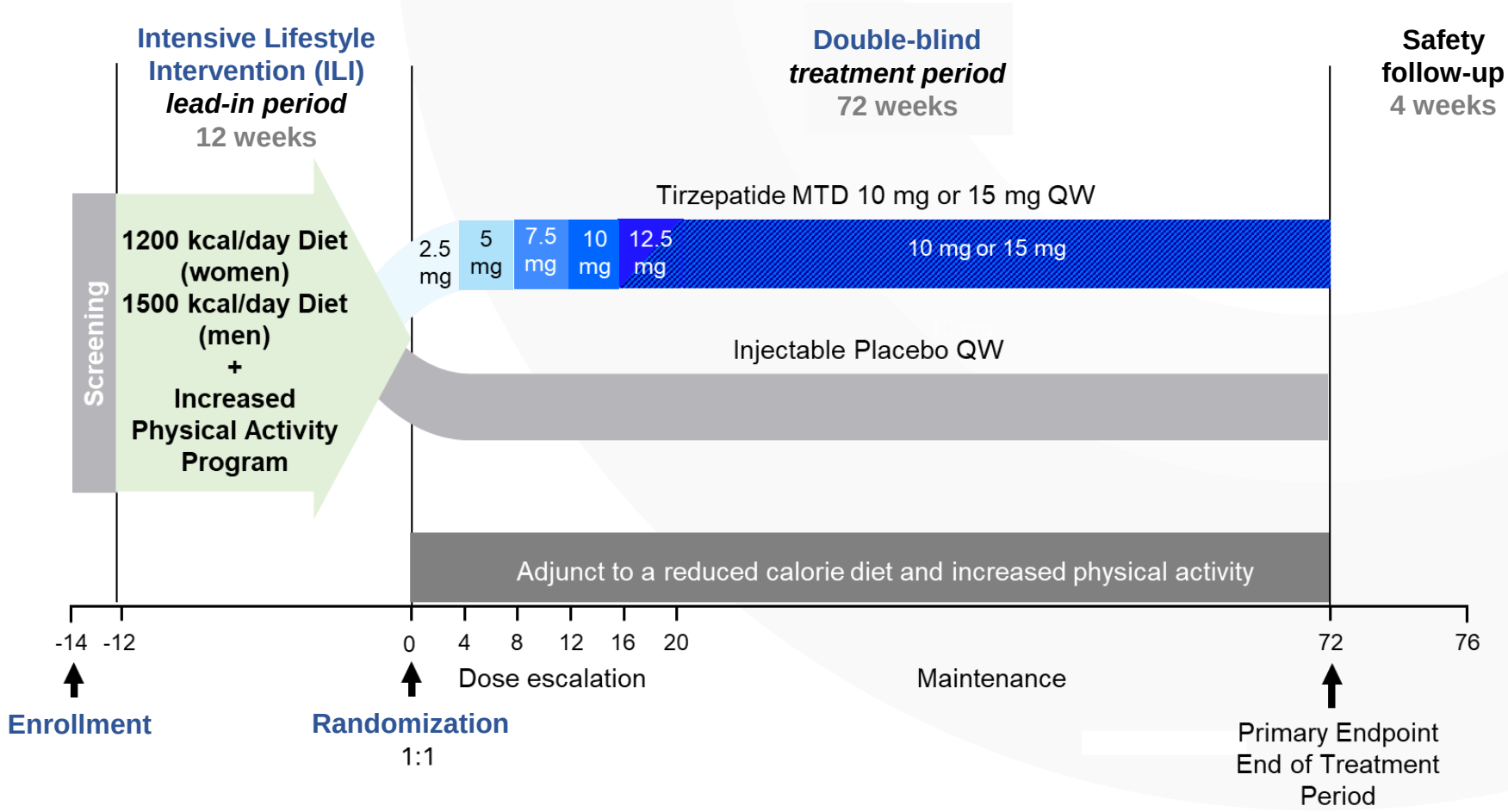
SURMOUNT-3 Study Design

A Randomized, Double-Blind, Multicenter, Placebo-Controlled Trial

Intensive Lifestyle Intervention included:

- in-person lifestyle counseling sessions
- included up to 2 meal replacements per day
- encouraged to engage in at least 150 mins of moderate-intensity physical activity

Participants who achieved ≥5% weight reduction with ILI were randomized



le Roux et al. Obesity. 2023;31(1):96-110. MTD=maximum tolerated dose; QW=once weekly.

SURMOUNT-3 Study Population

- **Key Inclusion Criteria**
  - Age 18 years or older
  - BMI ≥30 kg/m^2, or ≥27 kg/m^2 with at least 1 obesity-related condition (hypertension, dyslipidemia, OSA, or CVD)
  - At least 1 self-reported unsuccessful dietary effort to lose weight
- **Key Exclusion Criteria**
  - Type 1 or type 2 diabetes
  - Self-reported change in body weight >5 kg within 3 months prior to screening
  - Current or prior treatment with medications that may cause weight gain
  - Current or prior treatment with medications intended to promote weight loss
  - Prior or planned surgical treatment for obesity
- **Enrollment**
  - Female participant enrollment capped at 70%

Wadden TA, et al. Nature Medicine. In Press. BMI=body mass index; CVD=cardiovascular disease; OSA=obstructive sleep apnea.

Primary Objective

- To demonstrate that once-weekly **tirzepatide** MTD (10 or 15 mg) is superior to placebo from **randomization to 72 weeks** for:
  - **Percent change in body weight**, AND
  - **Percentage of participants** who achieved **an additional ≥5% body weight reduction**

MTD=maximum tolerated dose.

Key Secondary Objectives (Controlled for Type 1 Error)

- To demonstrate that once-weekly **tirzepatide** MTD (10 or 15 mg) is superior to placebo from randomization to 72 weeks for:
  - **Percentage of participants** who achieved **an additional ≥10%, ≥15%, ≥20%, or ≥25% body weight reduction** (≥25% was a pre-specified exploratory objective)
  - **Percentage of participants** who **maintained ≥80% of the weight lost during the 12-week ILI lead-in period**
  - Mean change in **waist circumference**

MTD=maximum tolerated dose.

Additional Secondary Objectives

- To compare **tirzepatide** MTD to placebo **from randomization to 72 weeks** for mean change in:
  - **Body weight** (kg)
  - **BMI**
  - **Blood pressure**
  - **Lipid parameters**
  - **Glycemic parameters** (fasting glucose, HbA1c, and fasting insulin)
  - **Patient-reported outcomes** (SF-36v2 acute form Physical Functioning domain score and IWQOL-Lite-CT Physical Function composite score)
- To compare **tirzepatide** MTD to placebo **from Week -12 to 72 weeks** for mean change in:
  - **Body weight** (kg and %)
  - **BMI**

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 acute form=Short Form-36 Version 2 Health Survey acute form.

Estimands and Statistical Methods

Observed Value

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

Treatment-Regimen Estimand

The treatment difference <u>regardless of adherence</u> to treatment

- ANCOVA or logistic regression
- All data regardless of study drug discontinuation
- Missing values explicitly imputed

Clinical interpretation

How drug will work in clinical practice across the participants prescribed

(stay ***In Trial***)

Efficacy Estimand

The treatment difference <u>if all participants had remained on treatment</u> for the entire planned treatment period

- MMRM or logistic regression
- Excludes data after discontinuation of study drug

Clinical interpretation

How drug will work in clinical practice across those willing and able to take drug as prescribed

(stay ***On Treatment***)

- All randomized participants took at least 1 dose of study drug, therefore, randomized, mITT, and safety population are the same. All efficacy and safety summaries and analyses are based on the randomized population.

ANCOVA=analysis of covariance; mITT=modified intent-to-treat; MMRM=mixed model repeated measures.

Study and Treatment Completion Rates

Entered Intensive Lifestyle Modification Lead-in
(N=806)

227 (28.2%) discontinued lead-in period
- adverse event: 2 (0.2%)
- did not lose ≥5% body weight: 141 (17.5%)
- lost to follow-up: 21 (2.6%)
- physician decision: 4 (0.5%)
- pregnancy: 1 (0.1%)
- protocol deviation: 17 (2.1%)
- withdrawal by subject: 39 (4.8%)
- other: 2 (0.2%)

Randomized to Double-Blind Treatment Period
(N=579)

Placebo
(N=292)

89 (30.5%) discontinued study drug

65 (22.3%) discontinued study

203 (69.5%) completed on study drug
227 (77.7%) completed the study

TZP MTD
(N=287)

61 (21.3%) discontinued study drug

35 (12.2%) discontinued study

226 (78.7%) completed on study drug
252 (87.8%) completed the study

In tirzepatide-treated participants, 248 (86.4%) had a tirzepatide MTD of 15 mg

Wadden TA, et al. *Nature Medicine.* In Press. MTD=maximum tolerated dose; TZP=tirzepatide.

Summary of Study Drug Discontinuations (Randomized Population)

Parameter	Placebo (N=292)	TZP MTD (N=287)	Total (N=579)
Permanent Discontinuation from Study Drug, n (%)	89 (30.5)	61 (21.3)	150 (25.9)
Adverse Event	5 (1.7)	29 (10.1)	34 (5.9)
Death	1 (0.3)	1 (0.3)	2 (0.3)
Lost to Follow-up	19 (6.5)	4 (1.4)	23 (4.0)
Physician Decision	4 (1.4)	3 (1)	7 (1.2)
Protocol Deviation	1 (0.3)	0 (0)	1 (0.2)
Withdrawal by Subject	42 (14.4)	18 (6.3)	60 (10.4)
Pregnancy	1 (0.3)	1 (0.3)	2 (0.3)
Other	16 (5.5)	5 (1.7)	21 (3.6)

Note: cause of both deaths was myocardial infarction.

The most common reasons for study drug discontinuation in the PBO group were "lost to follow up," "withdrawal by subject" and "other," and in the TZP group were "adverse event" and withdrawal by subject".

Wadden TA, et al. *Nature Medicine.* In Press. MTD=maximum tolerated dose; TZP=tirzepatide.

Baseline Demographics at the Start of the Intensive Lifestyle Intervention Lead-in (Enrolled vs Randomized)

Parameter	Enrolled Population (N=806)	Randomized Population (N=579)
Age (y), mean ± SD	44.9 ± 12.5	45.6 ± 12.2
Female, n (%)	534 (66.3)	364 (62.9)
Race, n (%)		
White	666 (82.6)	498 (86.0)
Black or African American	109 (13.5)	63 (10.9)
Multiple	14 (1.7)	8 (1.4)
American Indian or Alaska Native	10 (1.2)	6 (1.0)
Asian	6 (0.7)	4 (0.7)
Ethnicity, n (%)		
Hispanic or Latino	426 (52.9)	312 (53.9)
Not Hispanic or Latino	369 (45.8)	261 (45.1)
Not Reported	11 (1.4)	6 (1.0)

Baseline demographics at the start of the intensive lifestyle intervention lead-in were similar between the enrolled and randomized populations.

Clinical Characteristics at the Start of the Intensive Lifestyle Intervention Lead-in (Enrolled vs Randomized)

Parameter, mean	Enrolled Population (N=806)	Randomized Population (N=579)
BMI, kg/m^2	38.9	38.6
Body weight, kg	109.7	109.5
Waist circumference, cm	116.2	116.1
Systolic blood pressure, mmHg	125.6	126.0
Total cholesterol, mg/dL	194.6	193.8
Triglycerides, mg/dL	138.2	139.7
Hemoglobin A_{1c}, %	5.5	5.5
Fasting glucose, mg/dL	94.6	94.9
Fasting insulin, mIU/L	95.9	95.6

Clinical Characteristics at the start of the intensive lifestyle intervention lead-in were similar between the enrolled and randomized populations.

Change in Clinical Characteristics in Response to the Intensive Lifestyle Intervention Lead-in (Randomized Population)

	Placebo (N=292)		Tirzepatide MTD (N=287)		Total (N=579)	
	ILI start	Change with ILI	ILI start	Change with ILI	ILI start	Change with ILI
BMI, kg/m^2	38.4	-2.7	38.7	-2.7	38.6	-2.7
Body weight, kg (%)	108.9	-7.6 (-7.0 %)	110.1	-7.6 (-6.9 %)	109.5	-7.6 (-6.9 %)
Waist circumference, cm	116.3	-6.7	115.9	-6.6	116.1	-6.7
Systolic blood pressure, mmHg	126.0	-5.4	125.9	-4.5	126.0	-5.0
Total cholesterol, mg/dL	196.2	-4.9 %	191.4	-2.5 %	193.8	-3.7 %
Triglycerides, mg/dL	138.2	-6.0 %	141.2	-4.4 %	139.7	-5.2 %
Hemoglobin A_{1c}, %	5.5	-0.1	5.5	-0.1	5.5	-0.1
Fasting glucose, mg/dL	94.0	-2.8	95.7	-3.1	94.9	-2.9
Fasting insulin, mIU/L	93.6	-22.3 %	97.7	-18.5 %	95.6	-20.4 %

Clinical characteristics were well-balanced across the treatment groups at the start of the ILI lead-in and randomization. The change during ILI lead-in was consistent in both groups.

Wadden TA, et al. *Nature Medicine.* In Press. BMI=body mass index; MTD=maximum tolerated dose; TZP=tirzepatide.

SURMOUNT-3 Efficacy Results

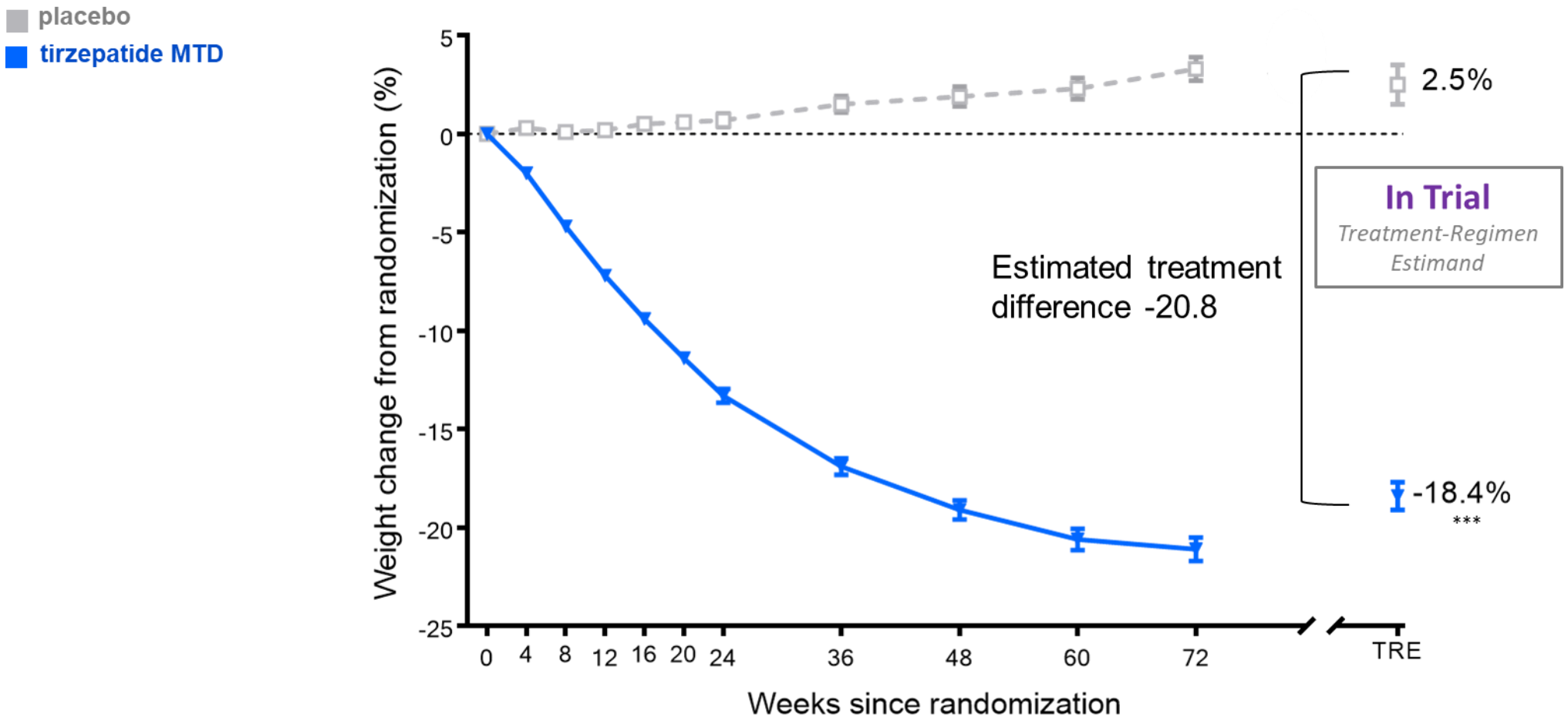
Ariana M. Chao, PhD, CRNP, FNP-BC

Faculty Associate

Johns Hopkins School of Nursing,

Baltimore, MD

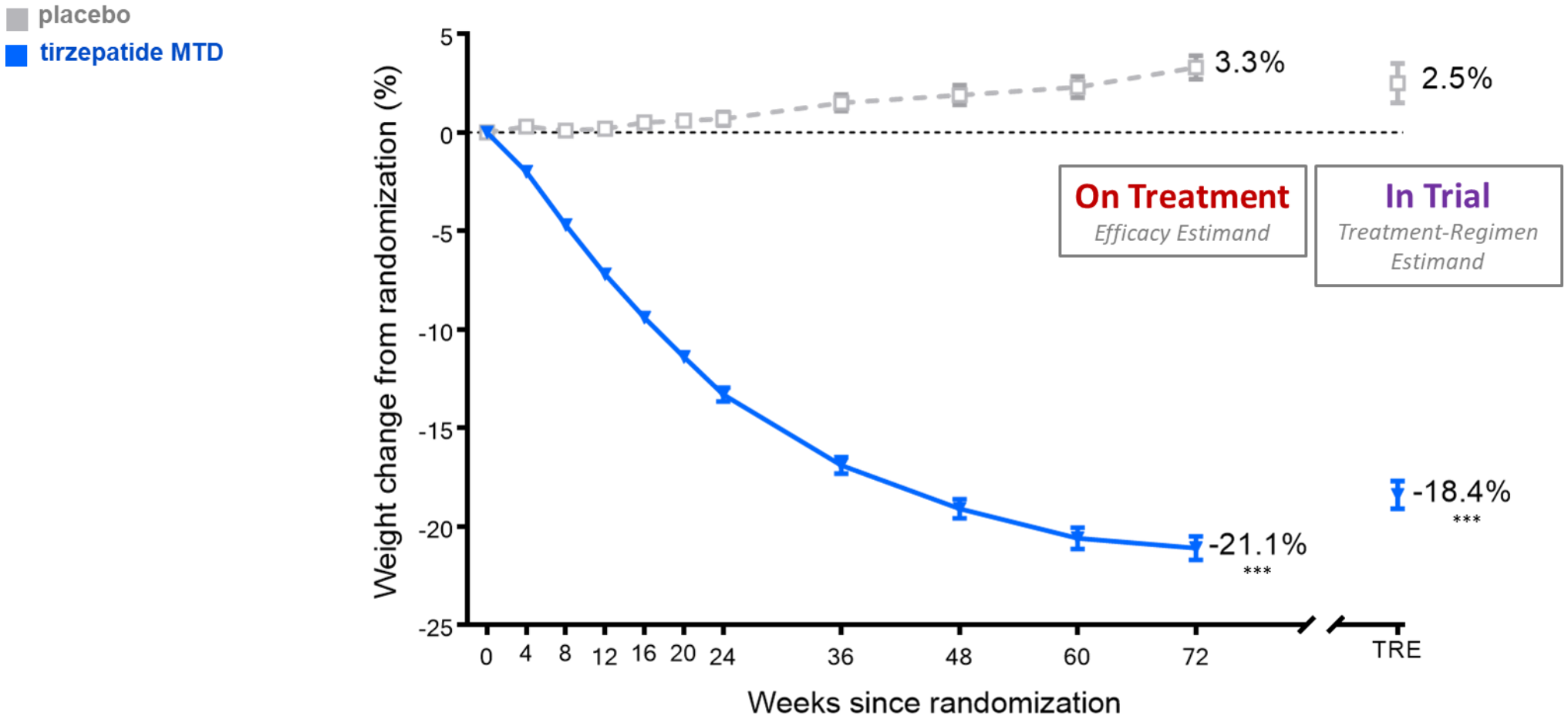
Weight Reduction at 72 Weeks (from randomization, Week 0)



After ILI, 72 weeks of tirzepatide MTD resulted in additional average body weight reduction of 18.4% (TRE).

Wadden TA, et al. *Nature Medicine.* In Press. Data are mean (SE) Placebo vs. tirzepatide ***p<0.001. ILI=intensive lifestyle intervention.

Weight Reduction at 72 Weeks (from randomization, Week 0)



After ILI, 72 weeks of tirzepatide MTD resulted in additional average body weight reduction of 18.4% (TRE).

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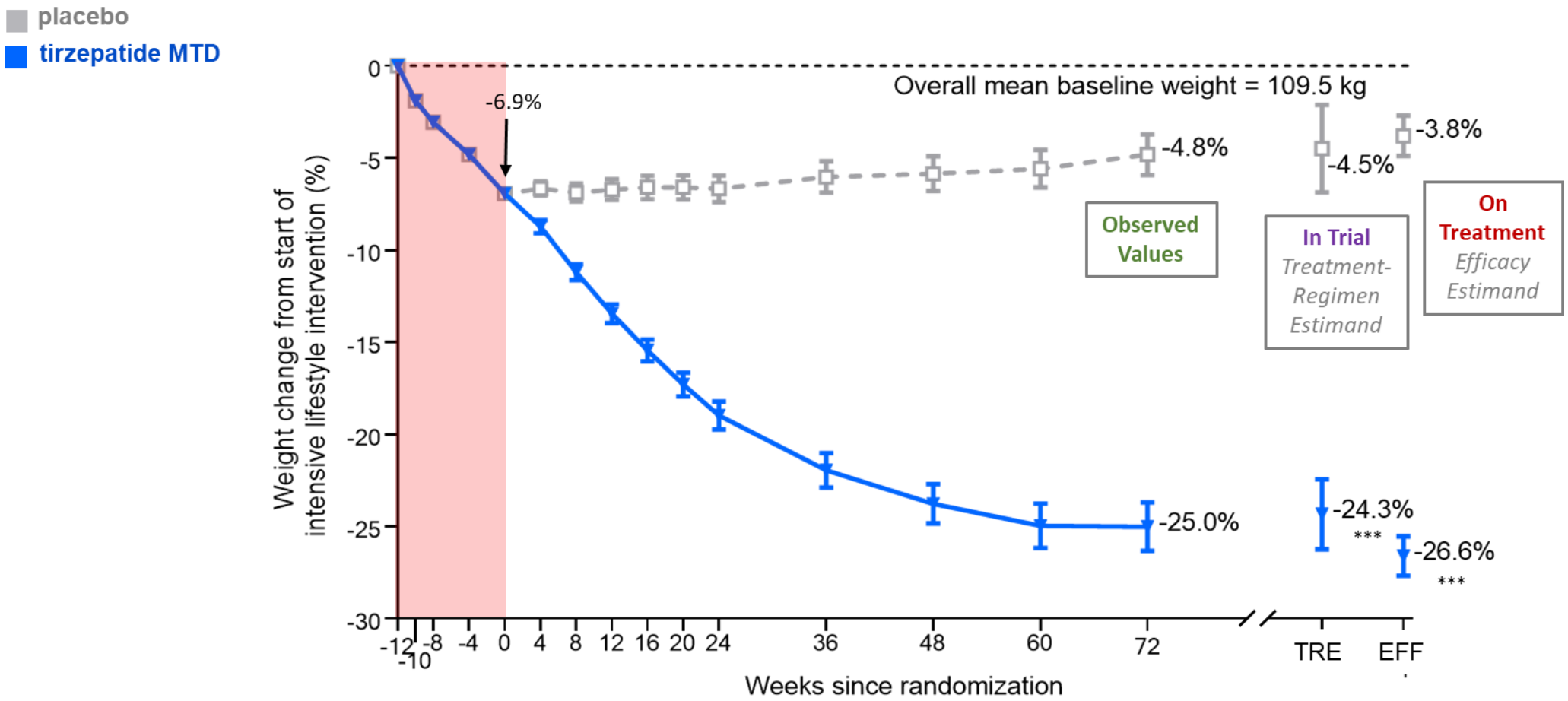
Weight Reduction at 72 Weeks (from start of ILI lead-in, Week -12)



ILI followed by 72 weeks of tirzepatide MTD resulted in average body weight reductions of 24.3% (TRE).

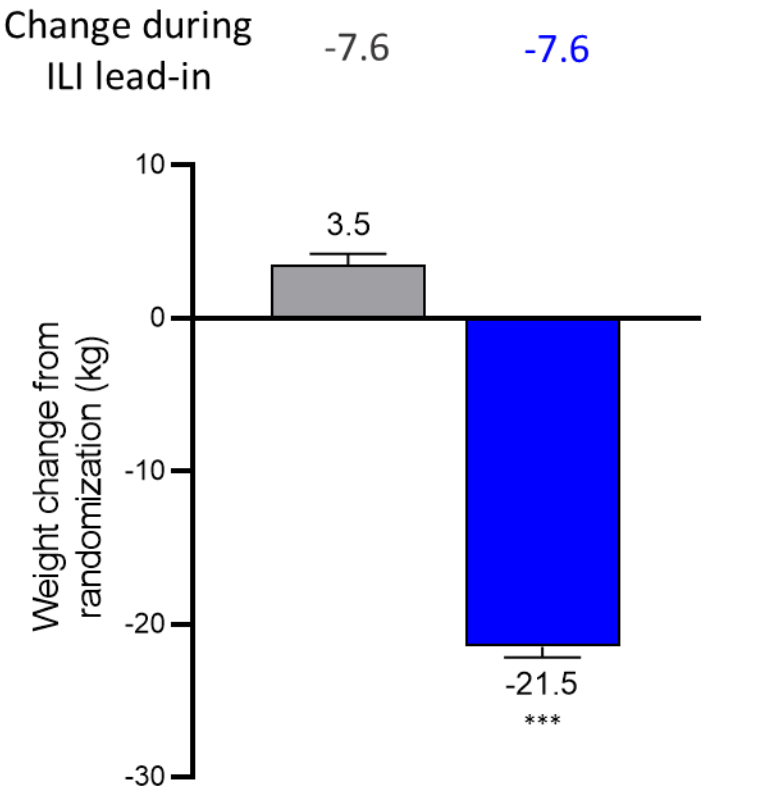
Wadden TA, et al. Nature Medicine. In Press. Time Course Plot: Data are mean (95% CI). Placebo vs. tirzepatide ***p<0.001.

Absolute Change in Weight (kg) at 72 Weeks (from start of ILI lead-in, Week -12)

placebo

tirzepatide MTD

Overall mean
baseline = 109.5 kg
(241.4 lbs)



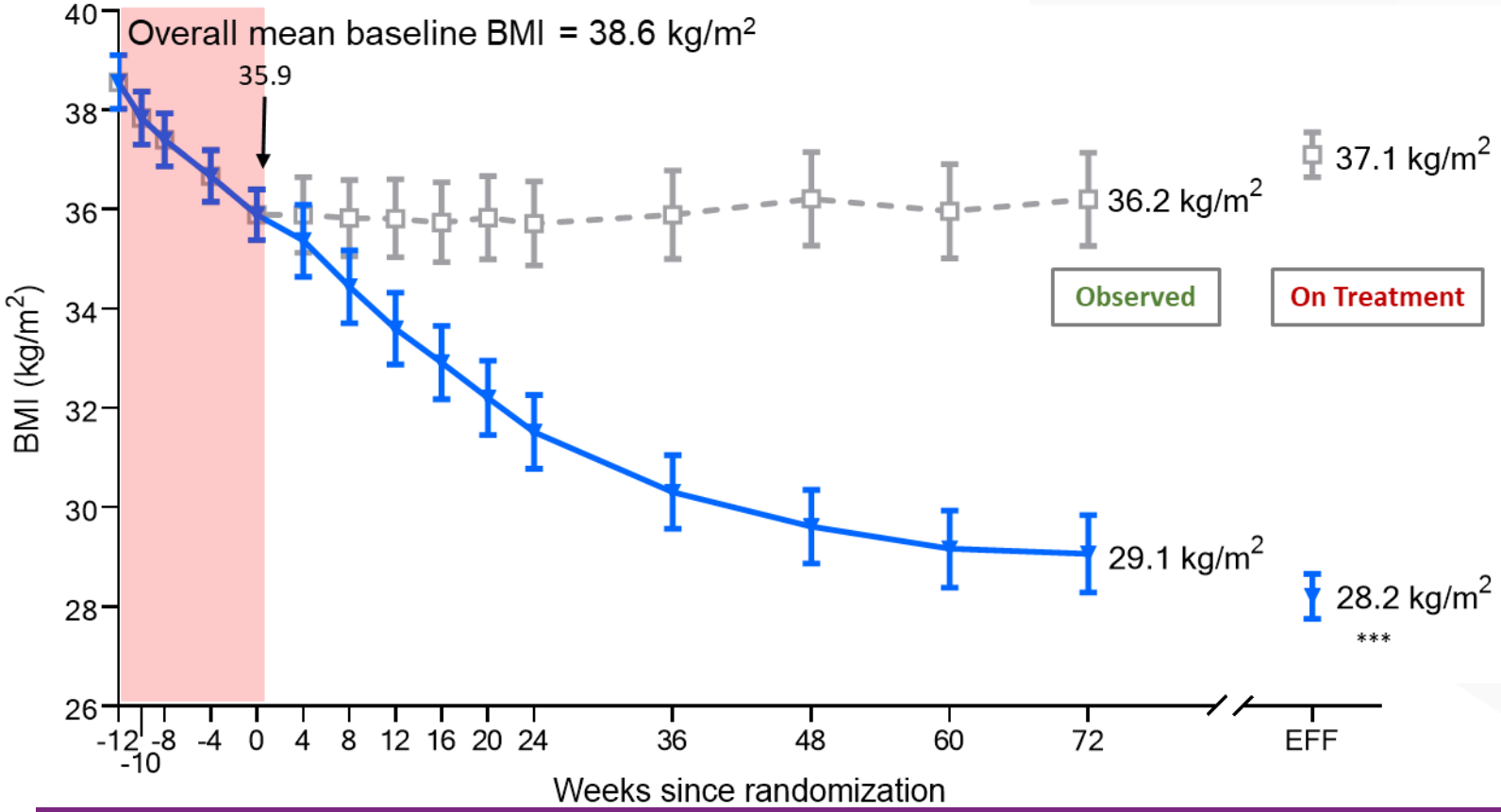
Total change from start of ILI lead-in	-4.1 (-9.0 lbs)	-29.2 (-64.4 lbs)

Wadden TA, et al. Nature Medicine. In Press. Bar Plot: Data are efficacy estimand, mean (SE). Placebo vs. tirzepatide ***p<0.001.

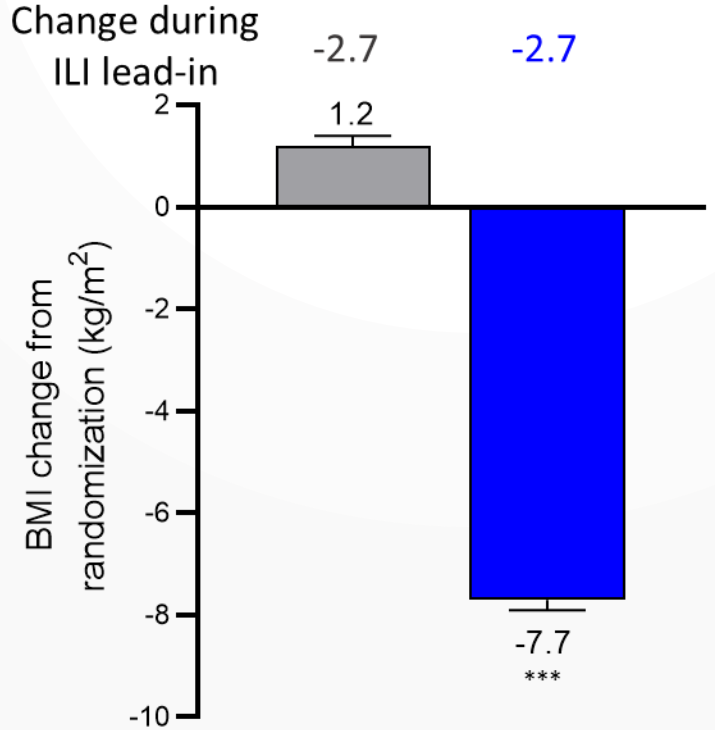
Change in BMI

placebo
tirzepatide MTD

Change from Start of ILI Lead-in (Week -12)



Absolute Change in BMI (kg/m²)



Total change from start of ILI lead-in	-1.4	-10.4

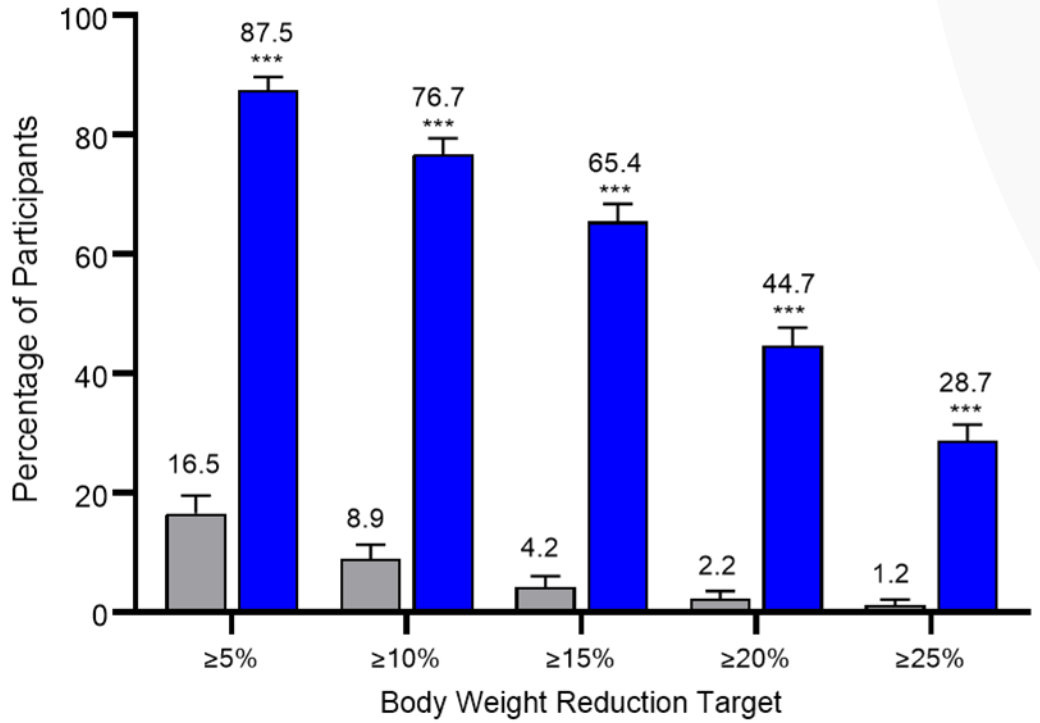
ILI followed by 72 weeks of tirzepatide MTD led to a downward shift of ~2 BMI categories.

Wadden TA, et al. Nature Medicine. In Press. Time Course Plot: Data are mean (95% CI). Bar Plot: Data are efficacy estimand, mean (SE). Placebo vs. tirzepatide ***p<0.001.

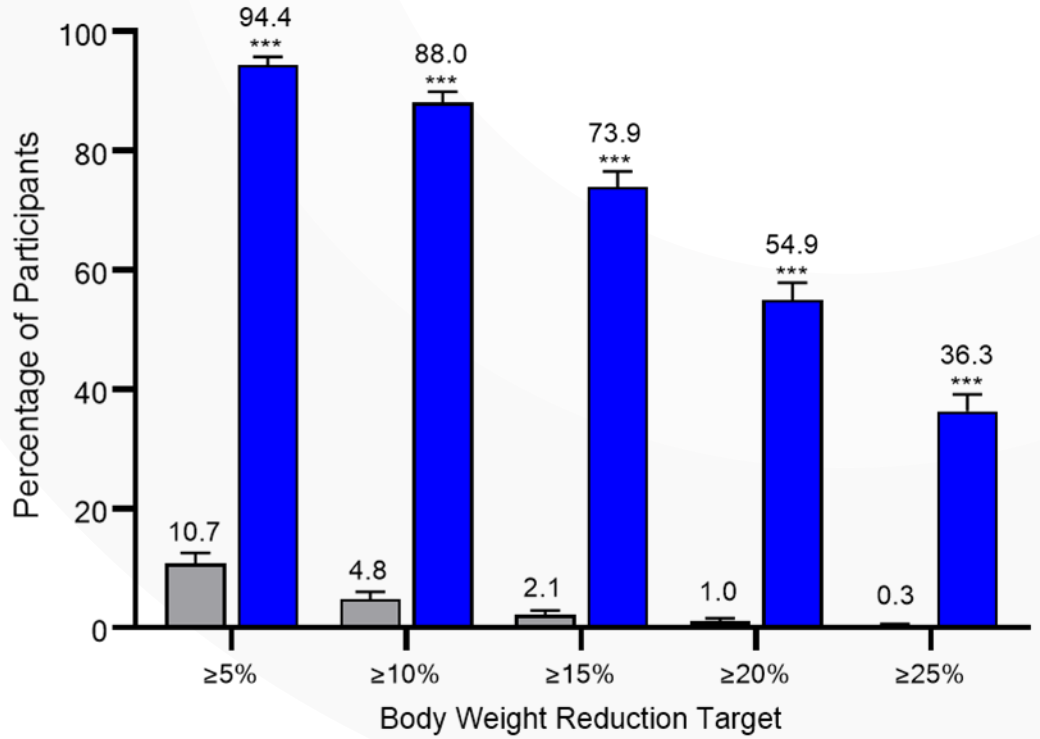
Proportion of Participants Achieving Weight-Reduction Thresholds at 72 Weeks (from randomization, Week 0)

placebo
tirzepatide MTD

In Trial
Treatment-Regimen Estimand



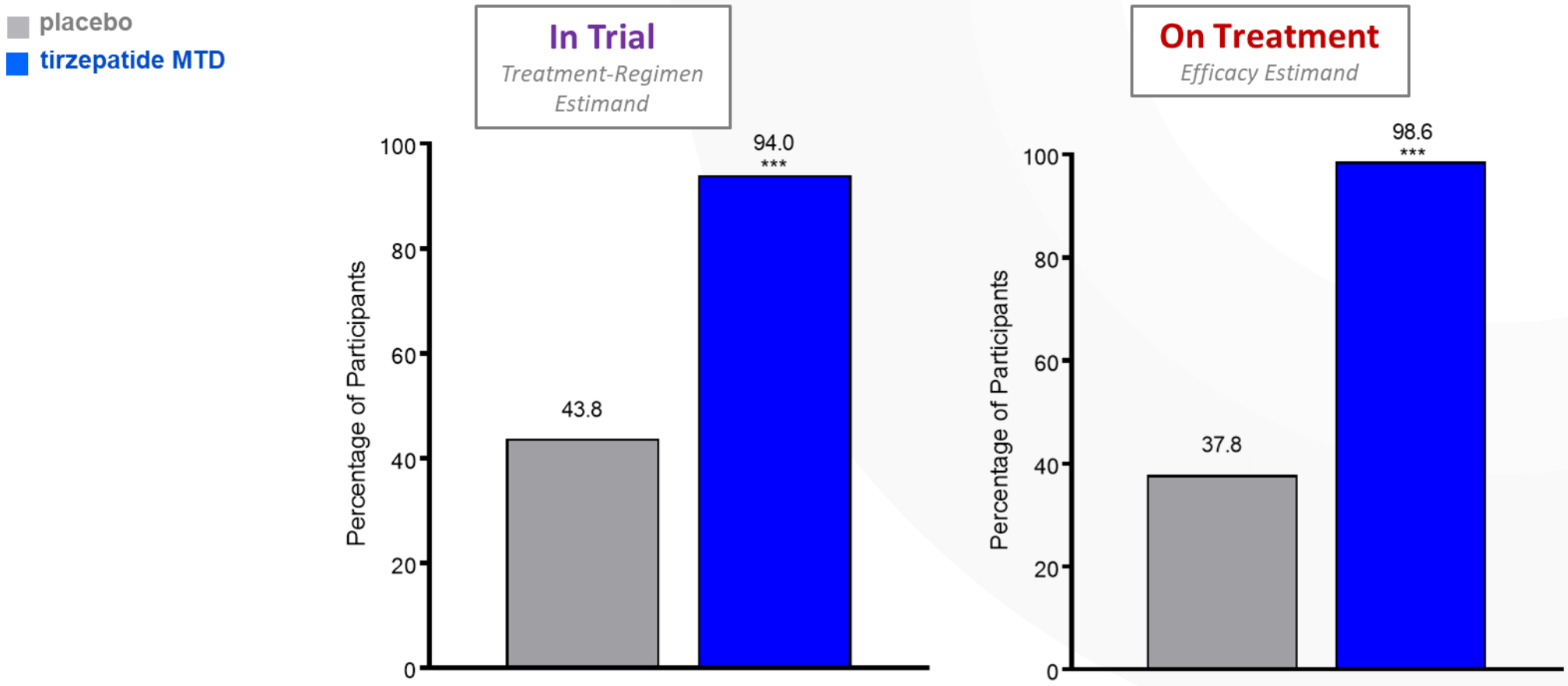
On Treatment
Efficacy Estimand



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

Wadden TA, et al. *Nature Medicine.* In Press. Data are mean (SE). Placebo vs. tirzepatide ***p<0.001.

Proportion of Participants Maintaining ≥80% of Weight Reduction Achieved During ILI Lead-In Period



Almost all participants in the tirzepatide MTD group maintained ≥80% of weight reduction achieved during the lead-in period.

Wadden TA, et al. Nature Medicine. In Press. Data are mean. Placebo vs. tirzepatide ***p<0.001.

Cardiometabolic risk factors and physical function

Change in Waist Circumference (from randomization, Week 0)

placebo

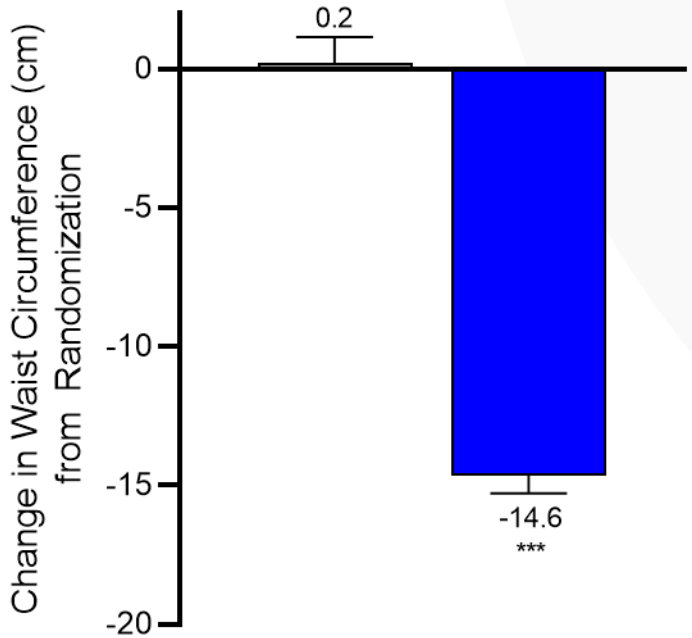
tirzepatide MTD

In Trial
Treatment-Regimen Estimand

Overall mean baseline = 116.1 cm

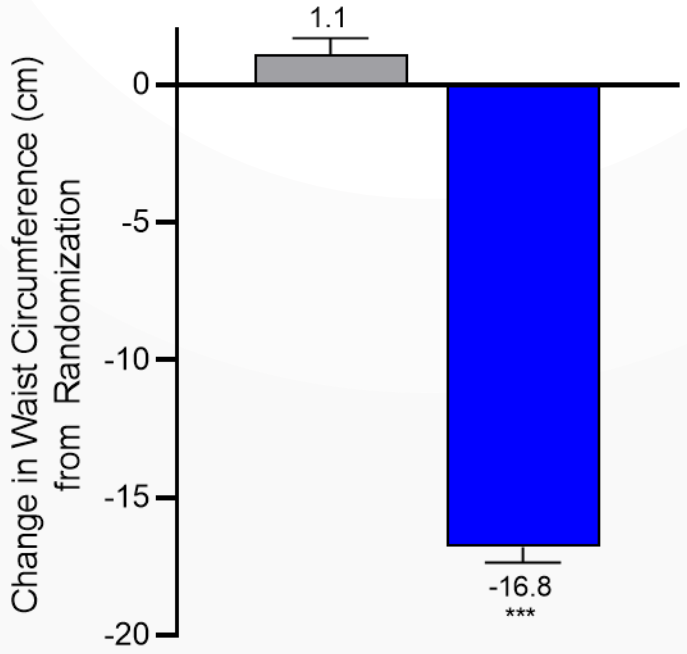
Change during ILI lead-in

-6.7cm -6.6cm



On Treatment
Efficacy Estimand

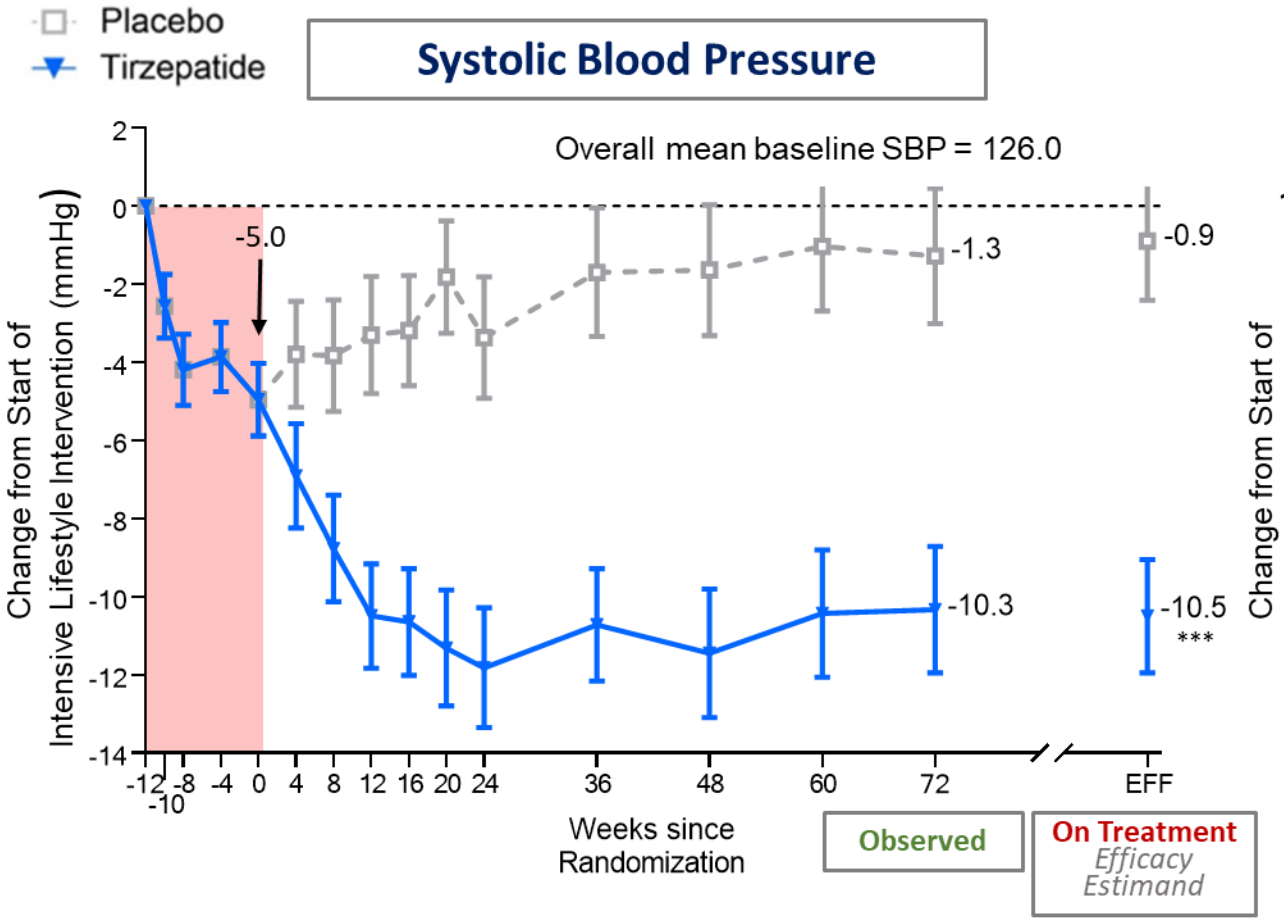
-6.7cm -6.6cm

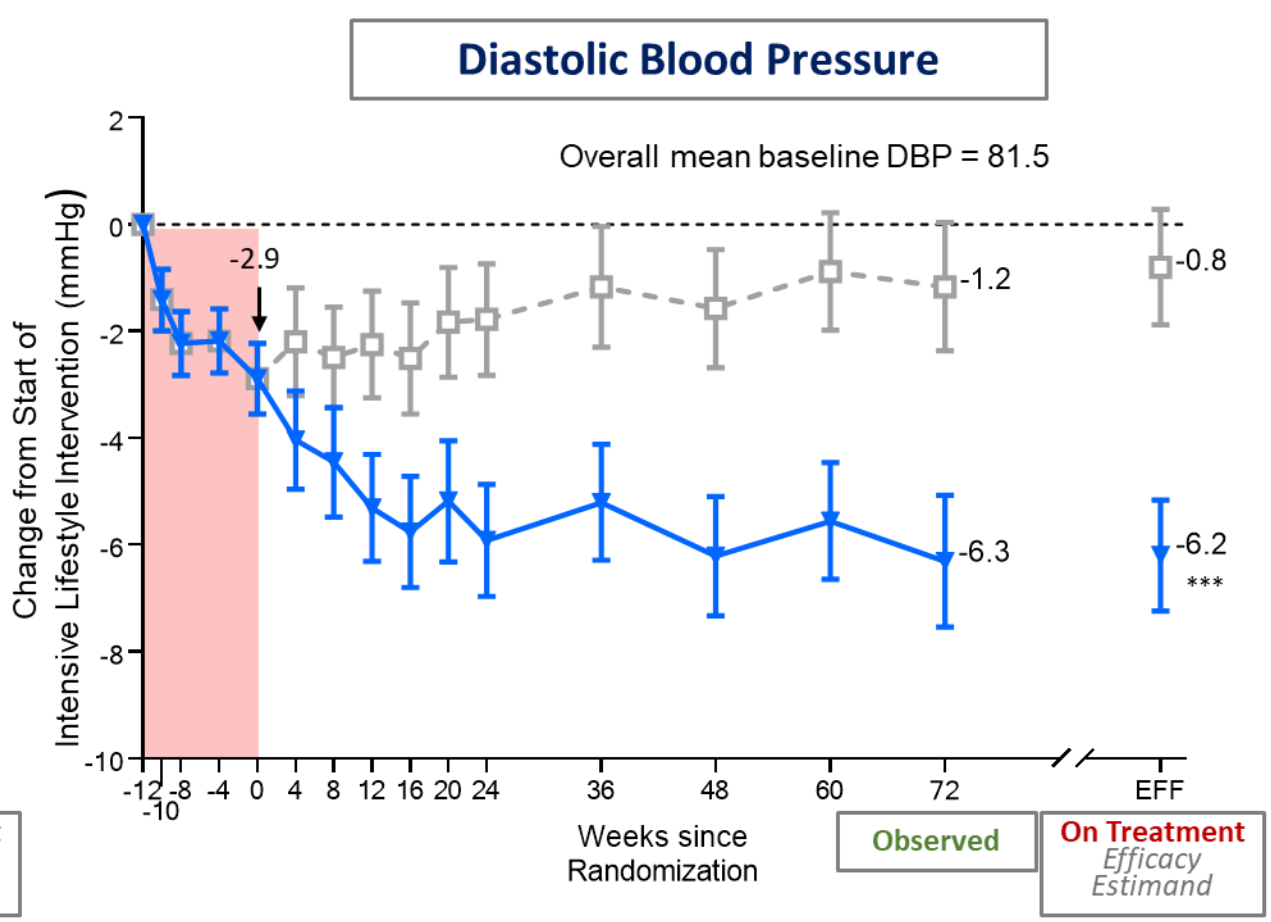


Tirzepatide MTD resulted in superior and clinically meaningful decreases in waist circumference.

Wadden TA, et al. *Nature Medicine.* In Press. Data are mean (SE). Placebo vs. tirzepatide ***p<0.001.

Change in Blood Pressure Over Time (from start of ILI lead-in, Week -12)

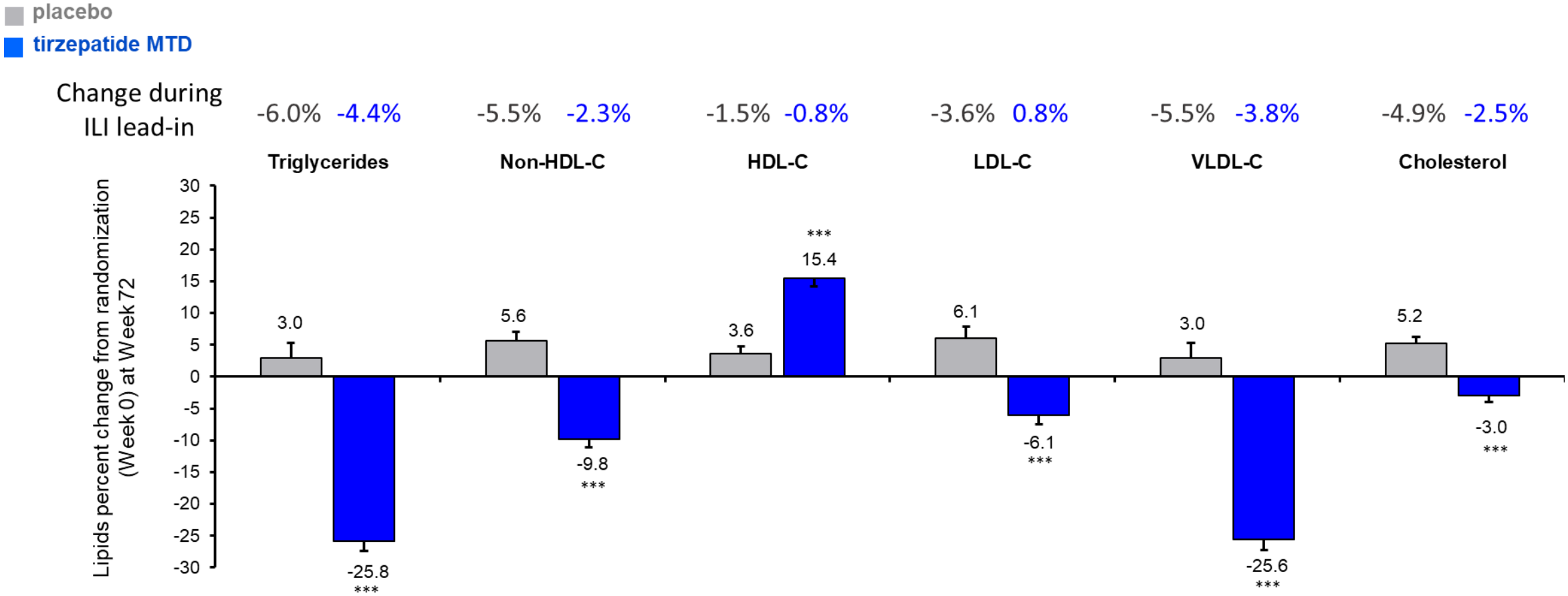




Tirzepatide MTD resulted in decreases to both systolic and diastolic blood pressure.

Wadden TA, et al. *Nature Medicine.* In Press. Data are mean (95% CI). Placebo vs. tirzepatide ***p<0.001.

Percent Change in Lipid Parameters (from randomization, Week 0)



After ILI, tirzepatide MTD resulted in improvements across all fasting lipid levels.

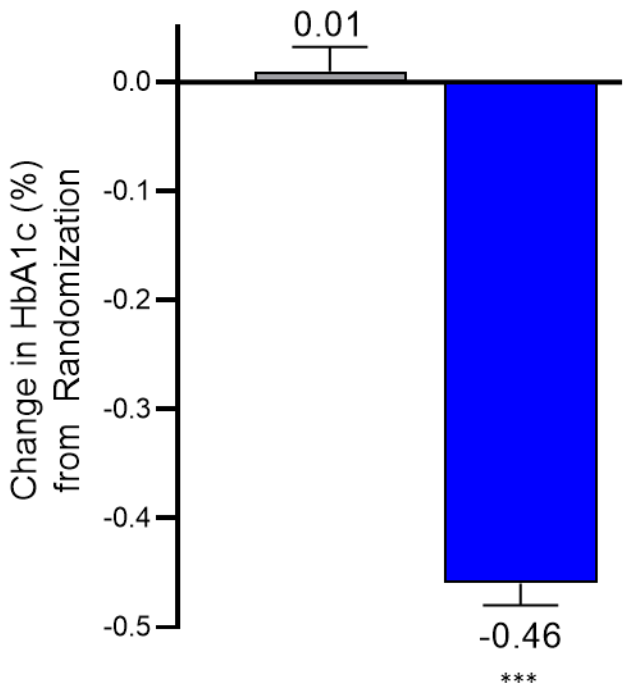
Wadden TA, et al. *Nature Medicine*. In Press. Data are efficacy estimand, mean (SE). Placebo vs. tirzepatide ***p<0.001. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; VLDL-C = very low-density lipoprotein cholesterol

Change in HbA1c, Fasting Glucose, and Fasting Insulin (from randomization, Week 0)

placebo
tirzepatide MTD

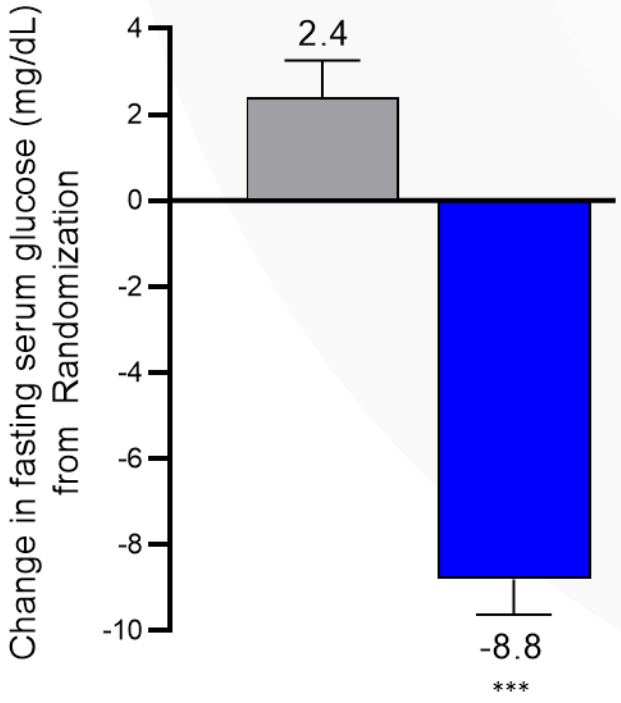
HbA1c

Change during ILI lead-in: -0.1% | -0.1%



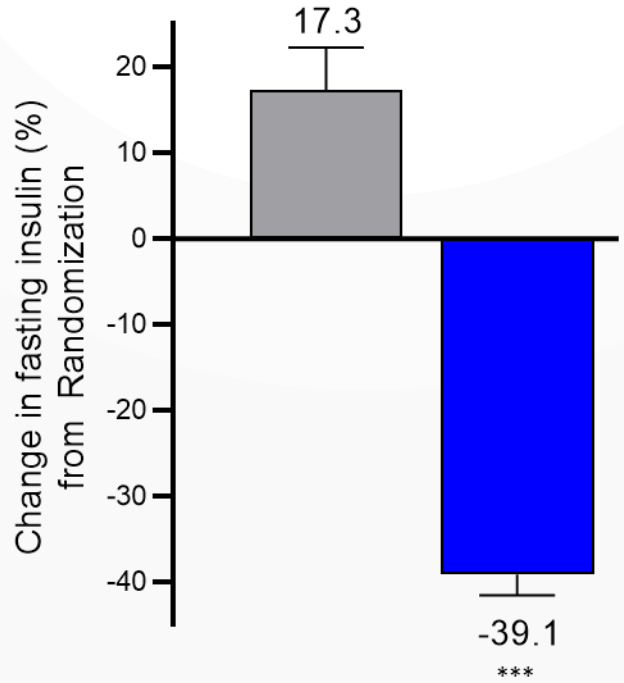
Fasting Serum Glucose

-2.8mg/dL | -3.1mg/dL



Fasting Insulin

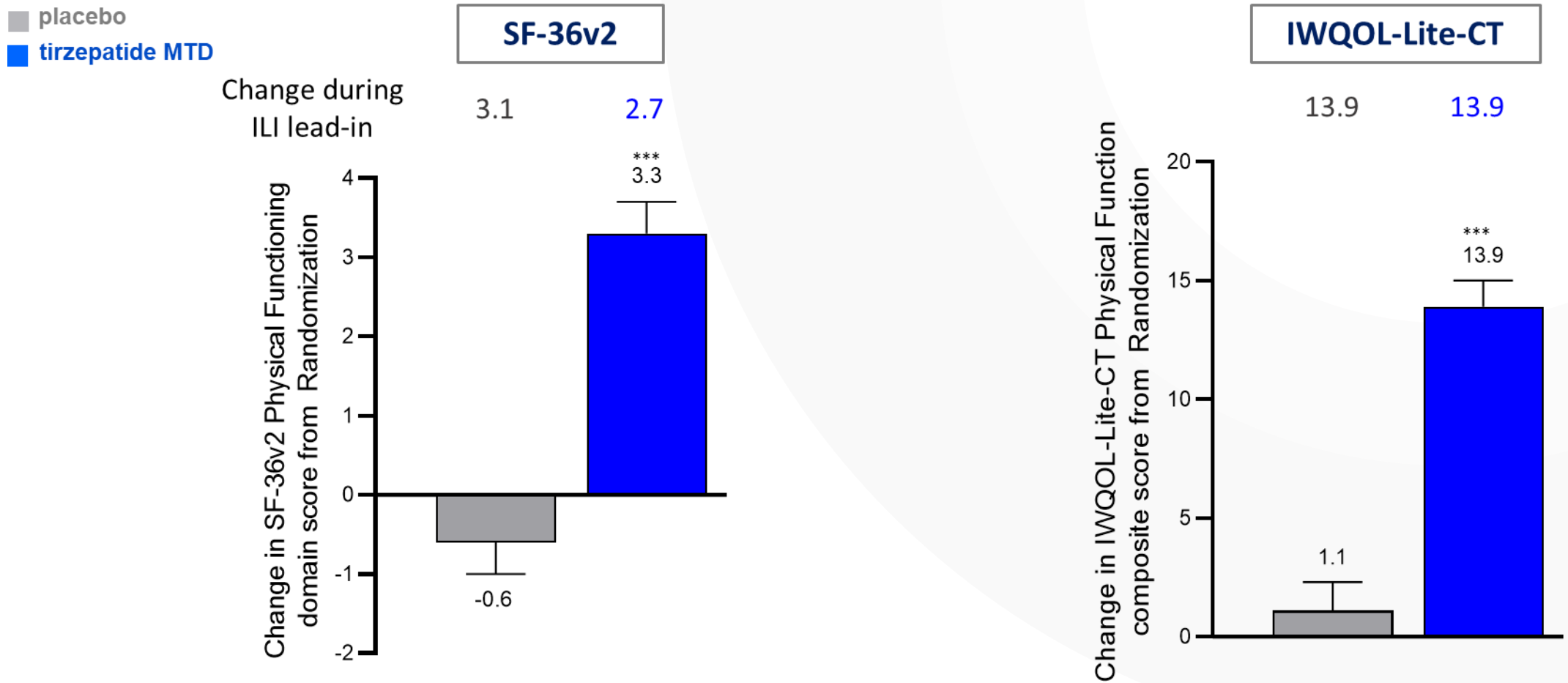
-22.3% | -18.5%



Tirzepatide MTD resulted in additional decreases in HbA1c, fasting glucose, and insulin

Wadden TA, et al. *Nature Medicine.* In Press. Data are efficacy estimand, mean (SE). Placebo vs. tirzepatide ***p<0.001.

Change in Patient-Reported Physical Function (from randomization, Week 0)



Tirzepatide MTD resulted in improvements in health-related quality of life, including physical function.

Wadden TA, et al. *Nature Medicine.* In Press. Data are efficacy estimand, mean (SE). Placebo vs. tirzepatide ***p<0.001.

Summary of Efficacy

- 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*: -24.3% weight reduction with tirzepatide MTD, vs. -4.5% with placebo
    - Overall BMI reduction of 10 kg/m^2 represents a downward shift of about two BMI categories
- 87.5% of participants treated with tirzepatide MTD achieved ≥5% additional weight reduction, *from randomization*
  - 28.7% of participants achieved the exploratory endpoint of ≥25% additional weight reduction
- 94.0% of participants treated with tirzepatide MTD maintained ≥80% of weight reduction achieved during the ILI lead-in period

Summary of Efficacy Continued

- Tirzepatide led to additional improvements in cardiometabolic risk factors and HRQoL after ILI, including:
  - Waist circumference
  - Systolic and diastolic blood pressure
  - Lipid parameters
  - HbA1c, fasting glucose, fasting insulin
  - Patient-reported physical functioning

SURMOUNT-3 Safety Results

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Co-Director, Weight Management Center, Advocate Health Wake Forest Baptist

Overview of Adverse Events

	Placebo (N=292) n (%)	tirzepatide MTD (N=287) n (%)
Number of participants with:		
Treatment-Emergent Adverse Events	224 (76.7)	250 (87.1)
Serious Adverse Events	14 (4.8)	17 (5.9)
Deaths*	1 (0.3)	1 (0.3)
Discontinuation from Study due to AE	3 (1.0)	5 (1.7)
Discontinuation from Study Drug due to AE	6 (2.1)	30 (10.5)

Note: Participants may be counted in more than 1 category. *Deaths are also included as SAEs and discontinuations due to AE.
AE, adverse event; MTD, maximum tolerated dose (tirzepatide 10 mg or 15 mg); SAE, serious adverse event.

TEAEs and discontinuations due to AEs were more frequent in the tirzepatide MTD group compared to placebo. Serious adverse events were similar between the two groups.

Wadden TA, et al. 2023. *Nature Medicine.* In Press.

Serious Adverse Events

System Organ Class	Placebo (N=292)	tirzepatide MTD (N=287)
Participants with ≥1 Serious Adverse Event	14 (4.8)	17 (5.9)
Gastrointestinal disorders	4 (1.4)	5 (1.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	5 (1.7)
Infections and infestations	4 (1.4)	3 (1.0)
Renal and urinary disorders	3 (1.0)	1 (0.3)
Cardiac disorders	1 (0.3)	1 (0.3)
Injury, poisoning and procedural complications	1 (0.3)	1 (0.3)
Hepatobiliary disorders	0	1 (0.3)
Musculoskeletal and connective tissue disorders	0	1 (0.3)
Pregnancy, puerperium and perinatal conditions	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	2 (0.7)	0
General disorders and administration site conditions	1 (0.3)	0

Serious adverse events were balanced between placebo and tirzepatide groups.

Wadden TA, et al. 2023. *Nature Medicine.* In Press.

Serious Adverse Events by Preferred Term

Placebo		tirzepatide MTD	
Abdominal pain	Pancreatitis acute	Acute kidney injury	Malignant melanoma
Appendicitis	Pneumonia	Acute myocardial infarction	Muscle strain
Asthma	Pulmonary thrombosis	Anembryonic gestation	Osteoarthritis
Breast cancer	Pyelonephritis	Bladder transitional cell	Pancreatitis
Cellulitis	Pyrexia	carcinoma	Papillary thyroid cancer
Impaired gastric emptying	Sepsis	Cellulitis	Renal cancer
Limb injury	Small intestinal obstruction	Cholecystitis acute	Sepsis
Myocardial infarction	Urinary tract infection	Colitis microscopic	Small intestinal obstruction
Nephrolithiasis (3)		Colorectal adenoma	Toxoplasmosis
		Haematochezia	Umbilical hernia

Serious adverse events were balanced between placebo and tirzepatide groups.

Wadden TA, et al. 2023. *Nature Medicine.* In Press.

Treatment-Emergent Adverse Events With >5% Frequency in Any Treatment Arm

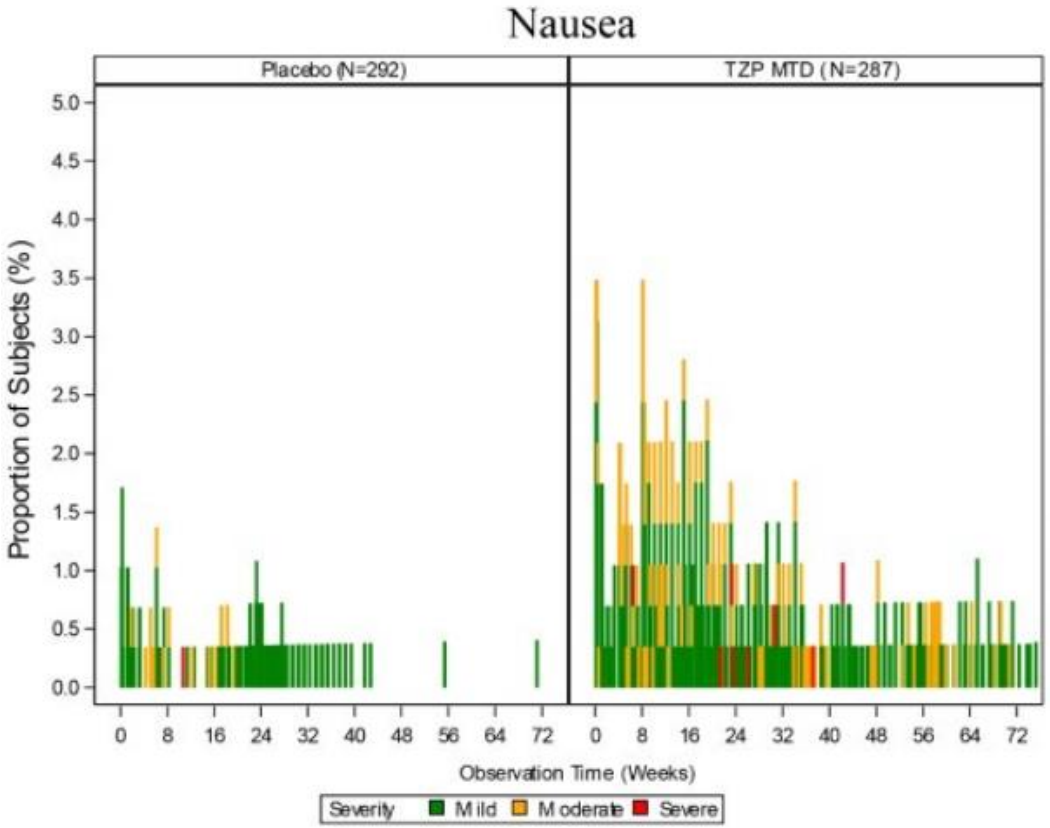
Parameter	Placebo (N=292) n (%)	tirzepatide MTD (N=287) n (%)
Participants with ≥1 TEAE, n(%)	224 (76.7)	250 (87.1)
Nausea	41 (14.0)	114 (39.7)
Diarrhea	27 (9.2)	89 (31.0)
Constipation	20 (6.8)	66 (23.0)
COVID-19	74 (25.3)	66 (23.0)
Vomiting	4 (1.4)	52 (18.1)
Injection site reaction	3 (1.0)	32 (11.1)
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)

Parameter	Placebo (N=292) n (%)	tirzepatide MTD (N=287) n (%)
Participants with ≥1 TEAE, n(%)	224 (76.7)	250 (87.1)
Dizziness	6 (2.1)	20 (7.0)
Fatigue	9 (3.1)	20 (7.0)
Flatulence	8 (2.7)	19 (6.6)
Gastroesophageal 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)

The majority of TEAEs were gastrointestinal in nature and these were greater in the tirzepatide group compared to placebo.

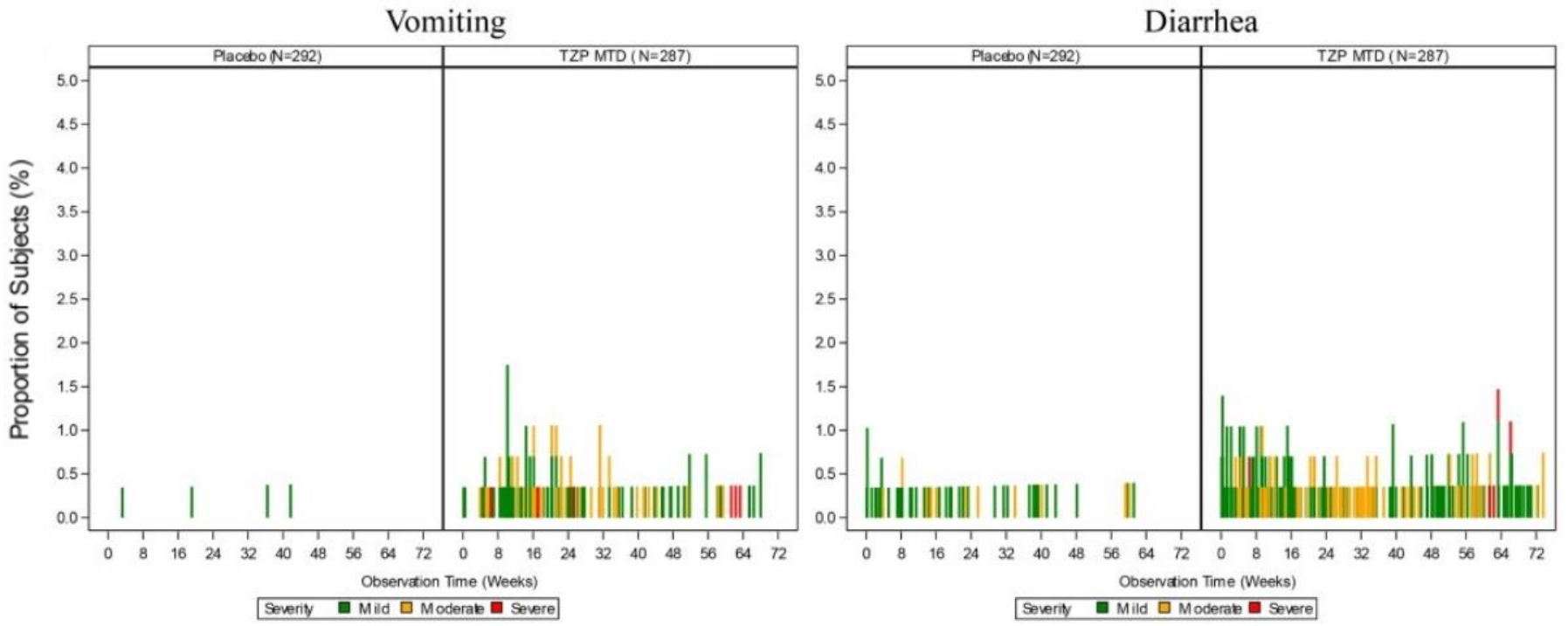
Wadden TA, et al. 2023. *Nature Medicine.* In Press.

Incidence of Nausea Over Time



Wadden TA, et al. 2023. *Nature Medicine.* In Press. Note: Proportions are based on number of participants at risk. MTD = maximum tolerated dose (tirzepatide 10mg or 15 mg); TZP, tirzepatide.

Incidence of Vomiting and Diarrhea Over Time



Note: Proportions are based on number of participants at risk. MTD = maximum tolerated dose (tirzepatide 10mg or 15 mg); TZP, tirzepatide.

Gastrointestinal events occurred primarily during the dose-escalation period, were mostly mild-to-moderate in severity and decreased over time.

Wadden TA, et al. 2023. *Nature Medicine.* In Press.

Adverse Events Reported as Primary Reason for Discontinuation of Study Drug

Parameter	Placebo (N=292) n (%)	tirzepatide MTD (N=287) n (%)
GI Adverse Events	4 (1.4)	24 (8.4)
Nausea	2 (0.7)	6 (2.1)
Vomiting	0	6 (2.1)
Diarrhea	0	3 (1.0)
Dyspepsia	0	3 (1.0)
Constipation	0	2 (0.7)
Abdominal pain upper	1 (0.3)	1 (0.3)
Abdominal pain	0	1 (0.3)
Haematochezia	0	1 (0.3)
Pancreatitis	0	1 (0.3)
Pancreatitis acute	1 (0.3)	0

Parameter	Placebo (N=292) n (%)	tirzepatide MTD (N=287) n (%)
Other Adverse Events	2 (0.7)	6 (2.1)
Acute myocardial infarction	0	1 (0.3)
Blood calcitonin increased	0	1 (0.3)
Cholelithiasis	0	1 (0.3)
Hypotension	0	1 (0.3)
Injection site reaction	0	1 (0.3)
Liver function test abnormal	0	1 (0.3)
Breast cancer	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
All Adverse Events	6 (2.1)	30 (10.5)

GI = Gastrointestinal, MTD = maximum tolerated dose (tirzepatide 10 mg or 15 mg)

Study drug discontinuations due to gastrointestinal adverse events were higher with tirzepatide than placebo.

Wadden TA, et al. 2023. *Nature Medicine.* In Press.

Treatment-Emergent Adverse Events of Interest

Parameter	Placebo (N=292) n (%)	tirzepatide MTD (N=287) n (%)
Severe or serious GI 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

GI, gastrointestinal; MACE, major adverse cardiovascular events; MDD, major depressive disorder; MTD, maximum tolerated dose (tirzepatide 10mg or 15 mg)

Incidence of treatment-emergent adverse events of interest was low and adjudicated events of MACE and pancreatitis were balanced between groups.

Wadden TA, et al. 2023. *Nature Medicine.* In Press.

Pancreatic Enzymes

Safety measure	*Normal range*	Placebo (N=291)	tirzepatide MTD (N=286)
Pancreatic amylase (U/L)	*3 – 46 U/L*		
Baseline		25.4 (0.56)	24.0 (0.53)
Week 72		24.8 (0.44)	30.3 (0.50)
4-Wk Safety Follow-Up		24.7 (0.40)	29.1 (0.44)
% change at week 72		0.6 (1.79)	22.8 (2.03)
Lipase (U/L)	*0 – 100 U/L*		
Baseline		28.4 (0.66)	27.6 (0.63)
Week 72		30.3 (0.78)	41.3 (0.99)
4-Wk Safety Follow-Up		30.4 (0.63)	35.8 (0.70)
% change at week 72		7.7 (2.78)	46.6 (3.50)

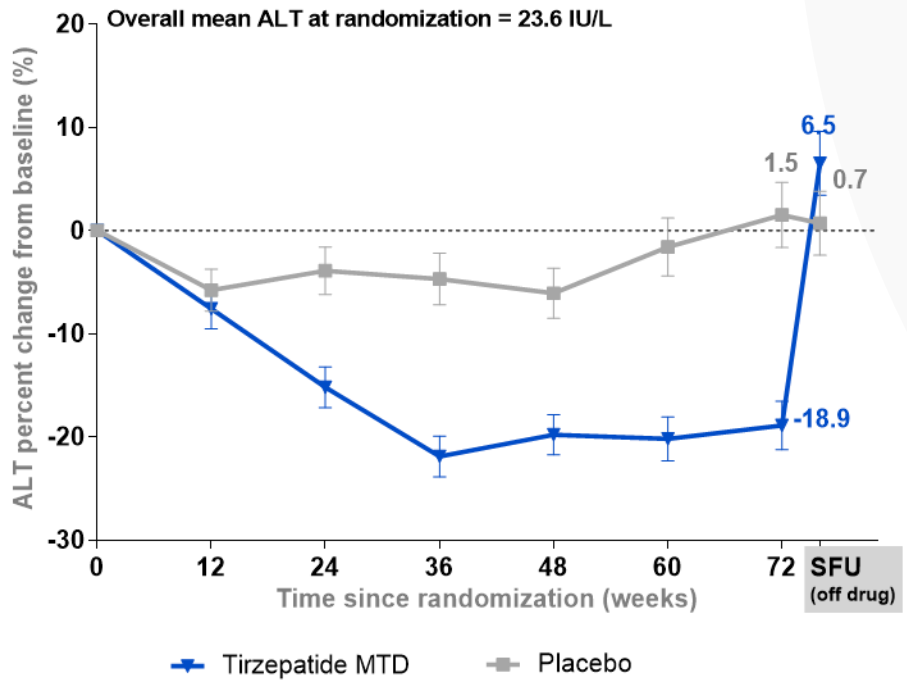
Data are model based estimate (standard error) and were analyzed with log transformation. MTD, maximum tolerated dose (tirzepatide 10 or 15 mg).

Mean pancreatic enzyme activity increased with tirzepatide but remained within the normal range. The finding is consistent with earlier observations with incretin-based therapies for obesity.

Wadden TA, et al. 2023. *Nature Medicine.* In Press.

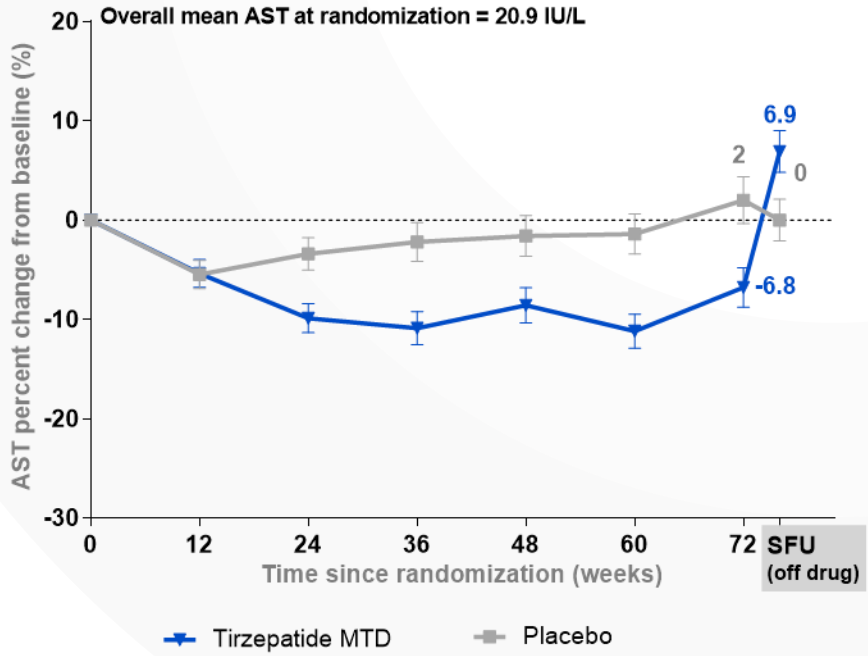
Liver Enzymes

Alanine aminotransferase



Normal range ALT: Female, 4 – 43 U/L; Male, 5 - 48 U/L

Aspartate aminotransferase



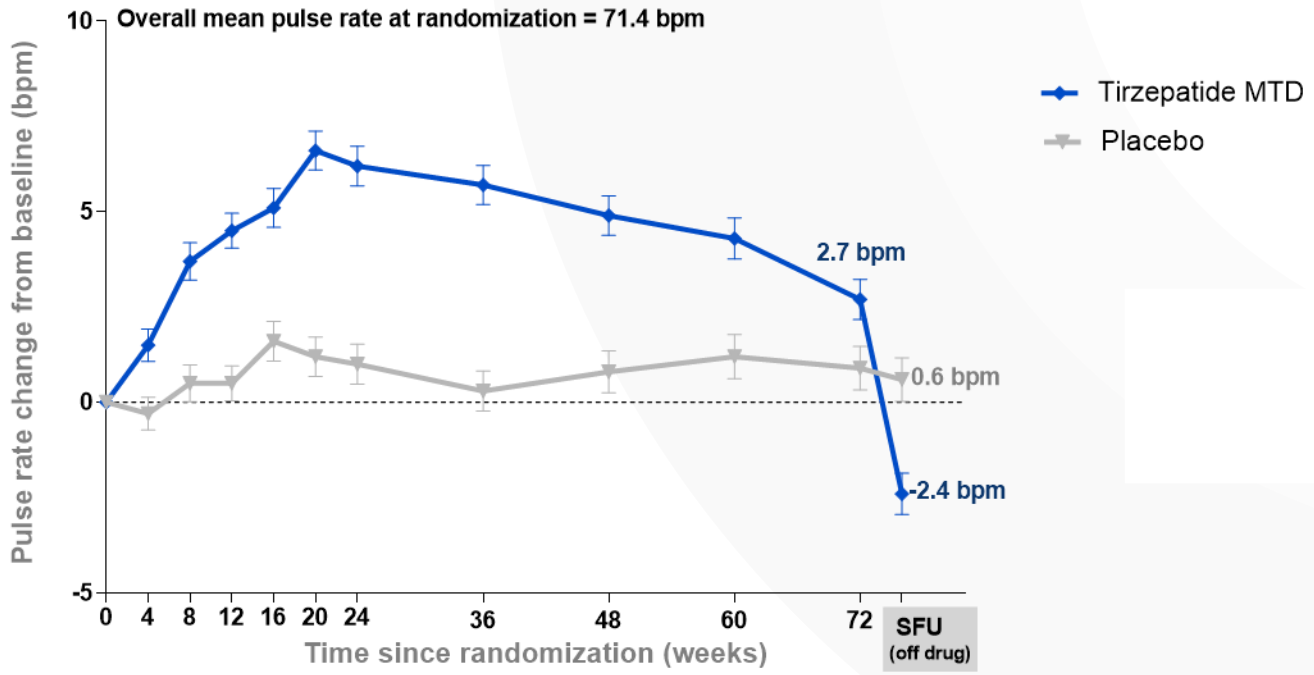
Normal range AST: 8 – 40 U/L

ALT, alanine aminotransferase; AST, Aspartate aminotransferase; MTD = maximum tolerated dose (tirzepatide 10mg or 15 mg); SFU, safety follow-up

Liver enzymes decreased while on treatment in participants receiving tirzepatide.

Wadden TA, et al. 2023. *Nature Medicine.* In Press.

Change from Baseline in Pulse Rate Over Time



MTD = maximum tolerated dose (tirzepatide 10mg or 15 mg); SFU, safety follow-up

Pulse rate increased during tirzepatide dose escalation, with a peak increase of 6.6 bpm at Week 20, then declined. At 72 weeks, pulse rate was 2.7 bpm higher than randomization baseline.

Wadden TA, et al. 2023. *Nature Medicine.* In Press.

Summary of Safety

- 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.
- Small transient increases in mean pulse rate were observed with tirzepatide, consistent with the GLP-1 receptor agonist class.
- Serious adverse events were balanced between placebo and tirzepatide groups.

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Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial | Nature Medicine

QR for this presentation

QR for all Lilly posters and presentations being shared at Obesity Week