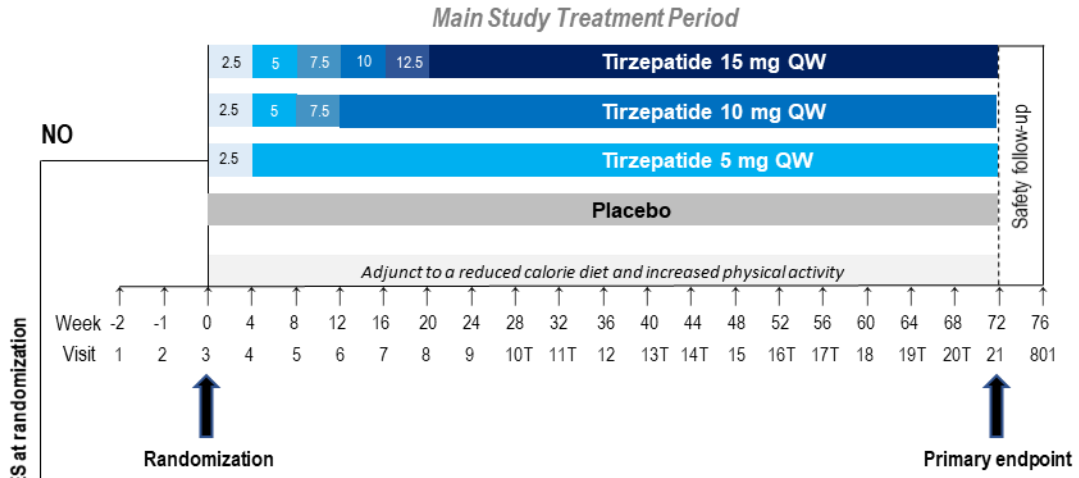
SURMOUNT-1

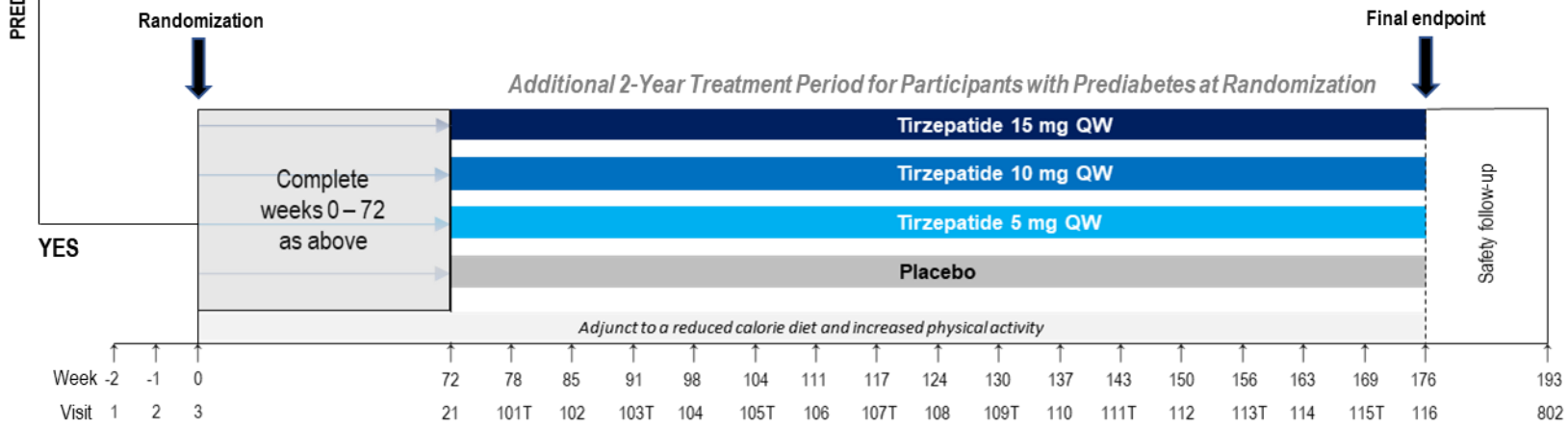
Results of the first Phase 3 Obesity Trial with Tirzepatide, the novel GIP/GLP-1 Receptor Agonist

SURMOUNT-1 Study Design



Key Features:

- N=2539
- 4 arms (1:1:1:1 randomization)
- Randomization stratified by country, sex and prediabetes status (yes, no)
- Study duration dependent on pre-diabetes status: 72/176 weeks
- An upper limit of 70% enrollment of women used to ensure a sufficiently large sample of men
- During the first, 72-week period, one study drug dose reduction per participant was permitted to help manage intolerable gastrointestinal symptoms.



Abbreviations: QW= once weekly; T= telephone visit

Primary Objective

- To demonstrate that tirzepatide 10 mg once-weekly is superior to placebo at 72 weeks for:
  - percent change in body weight, AND
  - percentage of participants with ≥5% body weight reduction

AND/OR

- To demonstrate that tirzepatide 15 mg once-weekly is superior to placebo at 72 weeks for:
  - percent change in body weight, AND
  - percentage of participants with ≥5% body weight reduction

Key Secondary Objectives (Controlled for Type 1 Error)
Body Weight-related

- **Weight reduction targets (categorical objectives)**
  - To demonstrate that tirzepatide 10 mg and/or 15 mg once-weekly is/are superior to placebo at 72 weeks for percentage of participants who achieved body weight reduction targets of:
    - 10% or more
    - 15% or more
    - 20% or more
  - Percentage of participants who achieved ≥25% body weight reduction was a pre-specified exploratory endpoint (not a key secondary endpoint)

- **5-mg objectives**
  - To demonstrate that tirzepatide 5 mg once-weekly is superior to placebo at 72 weeks for:
    - percent change in body weight, AND
    - percentage of participants with ≥5% body weight reduction

Key Secondary Objectives (Controlled for Type 1 Error)
Cardiometabolic Risk Factors

- To demonstrate that pooled tirzepatide (5 mg, 10 mg, 15 mg) is superior to placebo for:
  - mean change in triglycerides, non-HDL cholesterol, HDL cholesterol
  - mean change in systolic blood pressure
  - mean change in fasting insulin

- To demonstrate that tirzepatide 10 mg and/or 15 mg is/are superior to placebo at 72 weeks for:
  - mean change in waist circumference

Baseline Demographics

Parameter	Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)	Total (N=2539)
Age (y)	44.4 ± 12.5	45.6 ± 12.7	44.7 ± 12.4	44.9 ± 12.3	44.9 ± 12.5
Female, n (%)	436 (67.8)	426 (67.1)	427 (67.1)	425 (67.5)	1714 (67.5)
Race, n (%)					
White	450 (70.0)	447 (71.0)	452 (71.1)	443 (70.3)	1792 (70.6)
Asian	71 (11.0)	68 (10.8)	71 (11.2)	66 (10.5)	276 (10.9)
American Indian or Alaska Native	58 (9.0)	56 (8.9)	58 (9.1)	59 (9.4)	231 (9.1)
Black or African American	55 (8.6)	48 (7.6)	47 (7.4)	51 (8.1)	201 (7.9)
Multiple	7 (1.1)	9 (1.4)	6 (0.9)	8 (1.3)	30 (1.2)
Native Hawaiian or Other Pacific Islander	2 (0.3)	2 (0.3)	2 (0.3)	3 (0.5)	9 (0.4)
Ethnicity, n (%)					
Hispanic or Latino	310 (48.2)	308 (48.9)	297 (46.7)	299 (47.5)	1214 (47.8)
Not Hispanic or Latino	281 (43.7)	276 (43.8)	286 (45.0)	280 (44.4)	1123 (44.2)
Not Reported	52 (8.1)	46 (7.3)	53 (8.3)	51 (8.1)	202 (8.0)

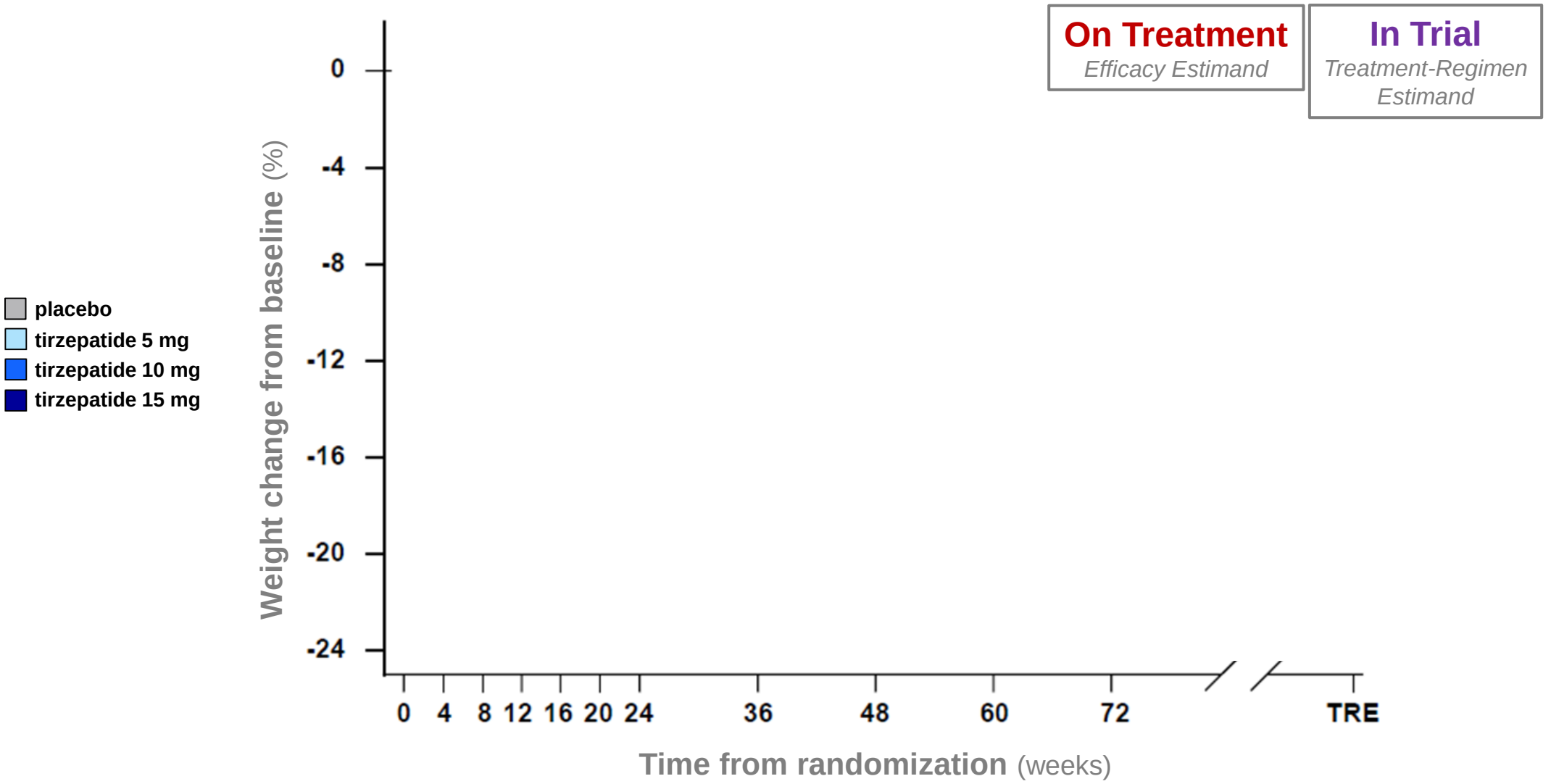
The baseline demographics were well balanced across the treatment groups.

Baseline Clinical Characteristics

Parameter **(mean ± SD, unless otherwise specified)**	**Placebo (N=643)**	**TZP 5 mg (N=630)**	**TZP 10 mg (N=636)**	**TZP 15 mg (N=630)**	**Total (N=2539)**
Weight (kg)	104.8 ± 21.37	102.9 ± 20.71	105.8 ± 23.32	105.6 ± 22.92	104.8 ± 22.12
BMI (kg/m^2)	38.2 ± 6.89	37.4 ± 6.63	38.2 ± 7.01	38.1 ± 6.69	38.0 ± 6.81
Waist circumference (cm)	114.0 ± 14.92	113.2 ± 14.25	114.8 ± 15.80	114.4 ± 15.59	114.1 ± 15.16
Prediabetes, n (%)	270 (42.0)	247 (39.2)	262 (41.2)	253 (40.2)	1032 (40.6)
Systolic blood pressure (mmHg)	122.9 ± 12.77	123.6 ± 12.45	123.8 ± 12.77	123.0 ± 12.94	123.3 ± 12.73
Diastolic blood pressure (mmHg)	79.6 ± 7.95	79.3 ± 8.14	79.9 ± 8.32	79.3 ± 8.23	79.5 ± 8.16
eGFR (CKD-EPI, ml/min/1.73 m^2)	98.1 ± 18.28	97.6 ± 17.87	98.3 ± 18.26	98.2 ± 17.67	98.1 ± 18.02

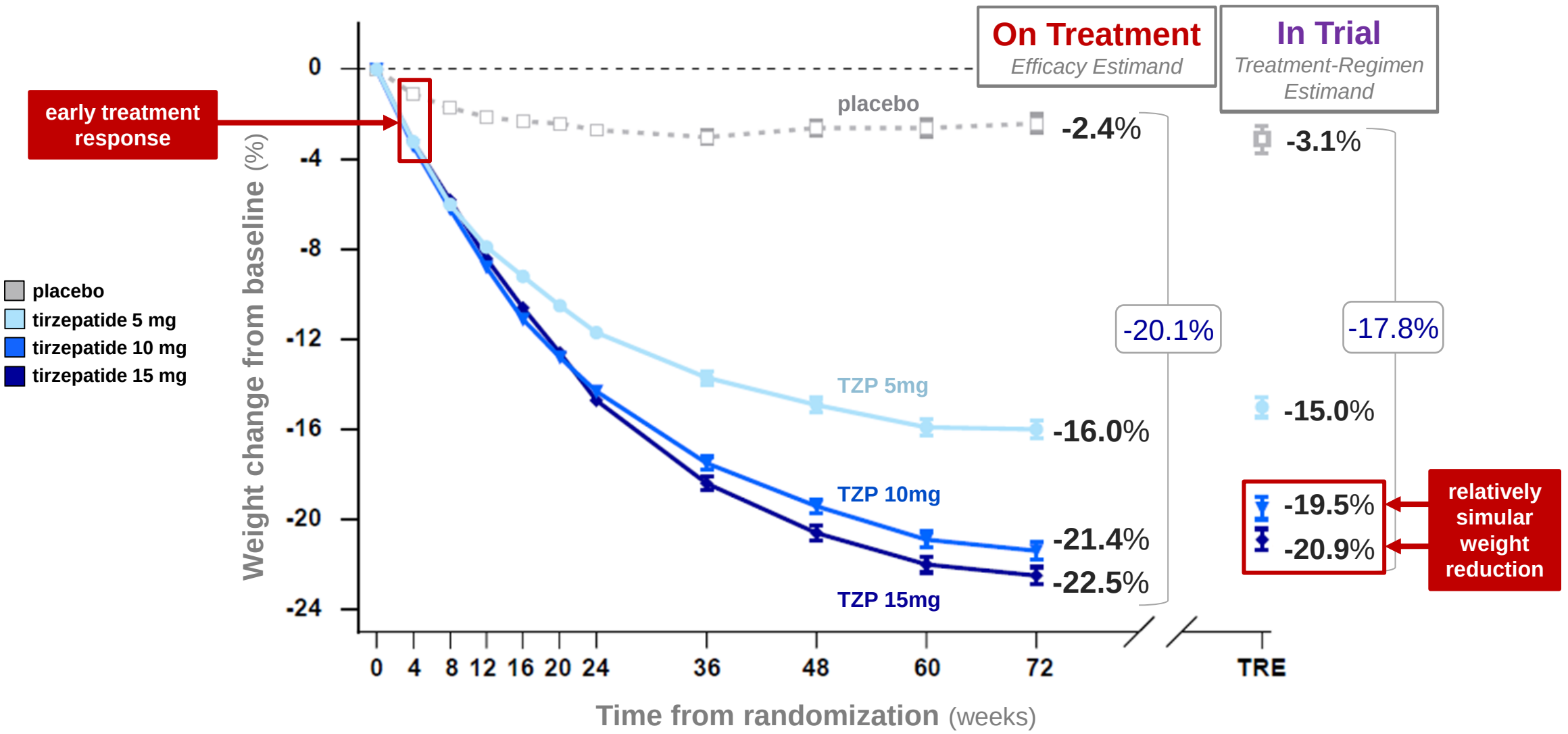
The baseline clinical characteristics were well balanced across the treatment groups.

Weight Reduction Over 72 weeks



Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S et al. NEJM, *in press*

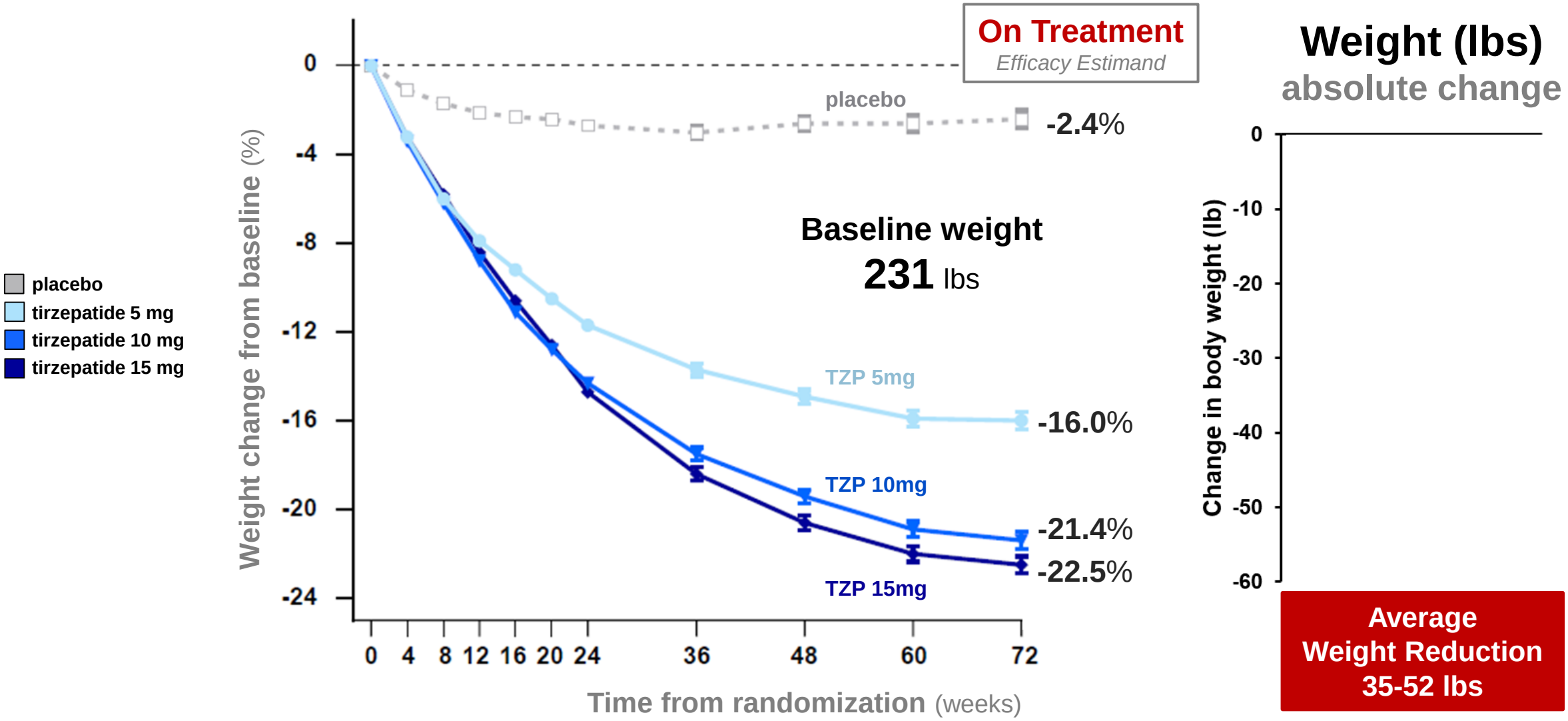
Weight Reduction Over



Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S et al. NEJM, *in press*

Yale SCHOOL OF MEDICINE

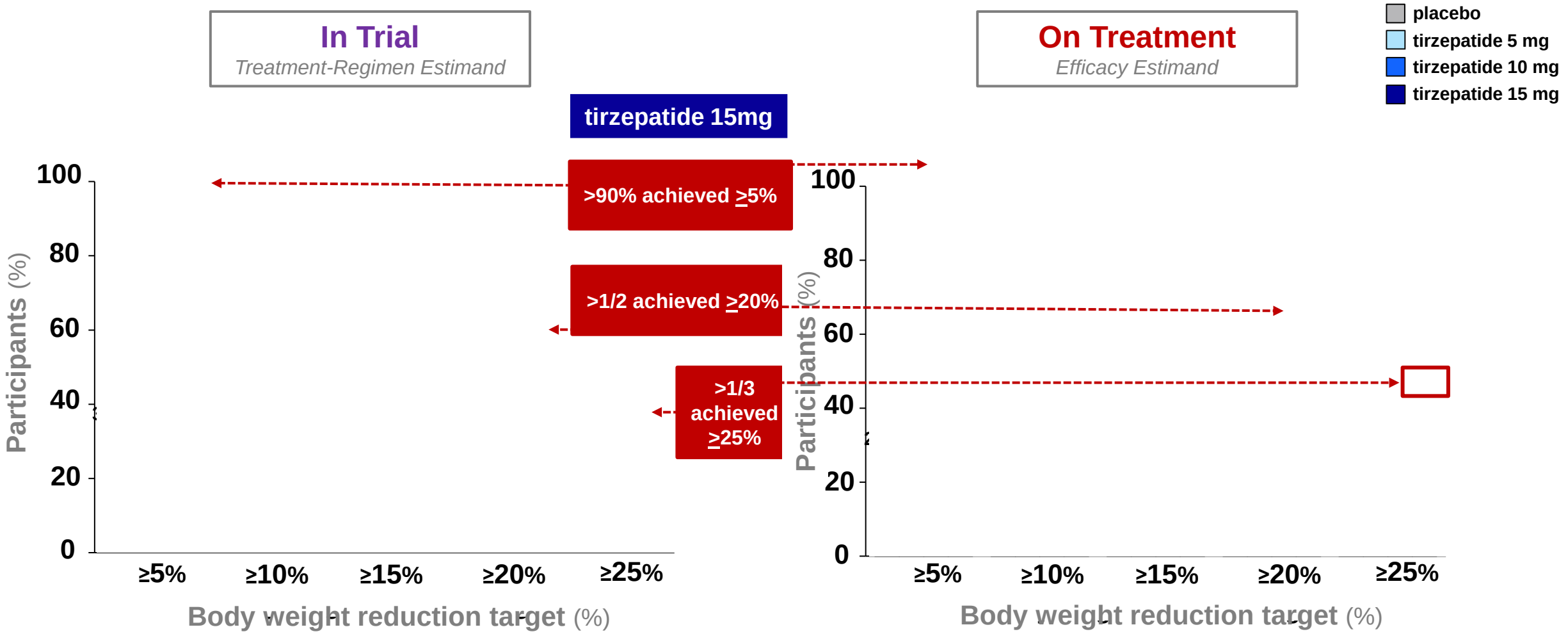
Weight Reduction Over 72 weeks: absolute change



Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S et al. NEJM, *in press*

Yale SCHOOL OF MEDICINE

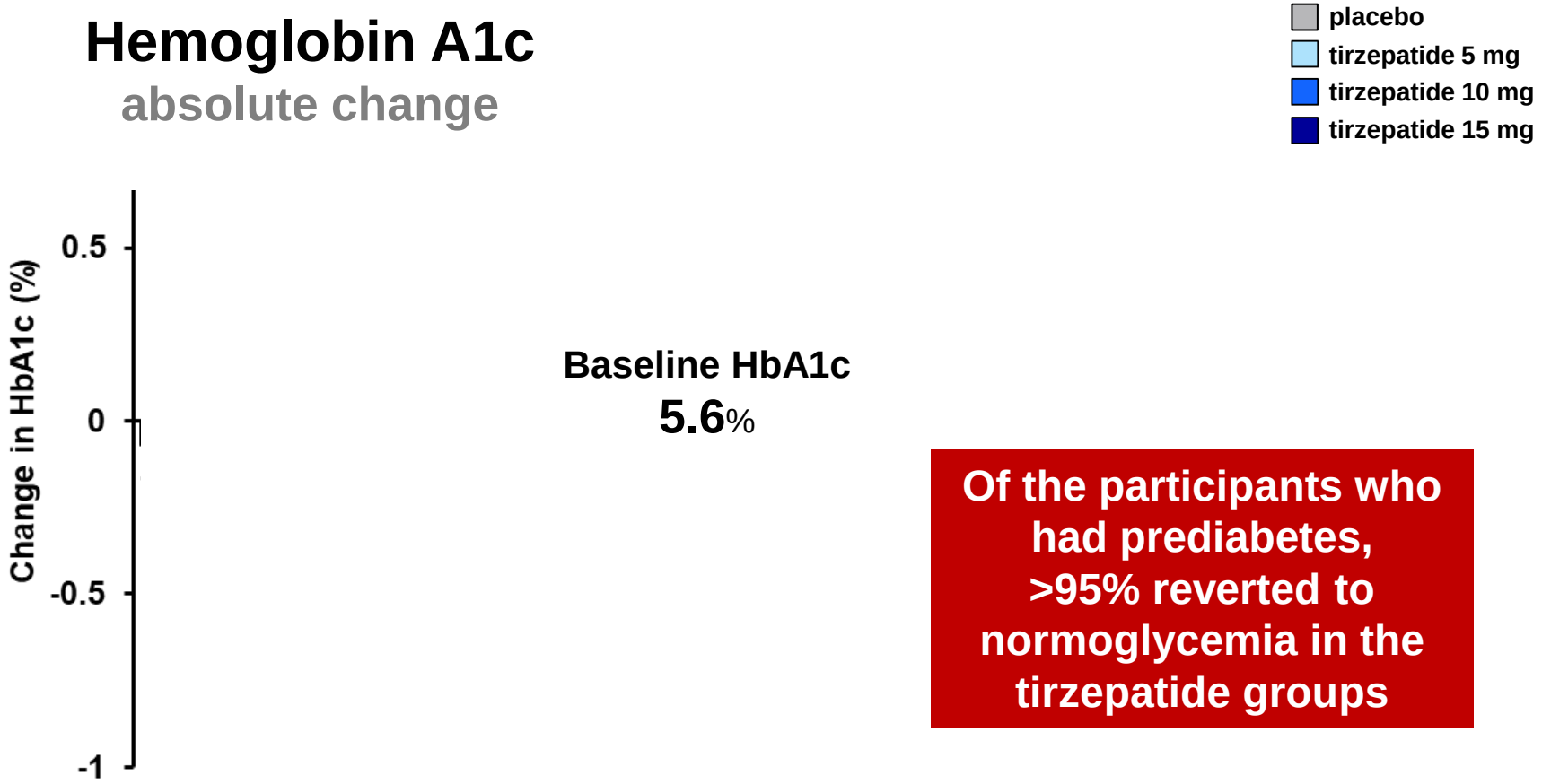
Percent of Participant Reaching Weight-Reduction Targets



Change in HbA1c

On Treatment
Efficacy Estimand

Hemoglobin A1c
absolute change



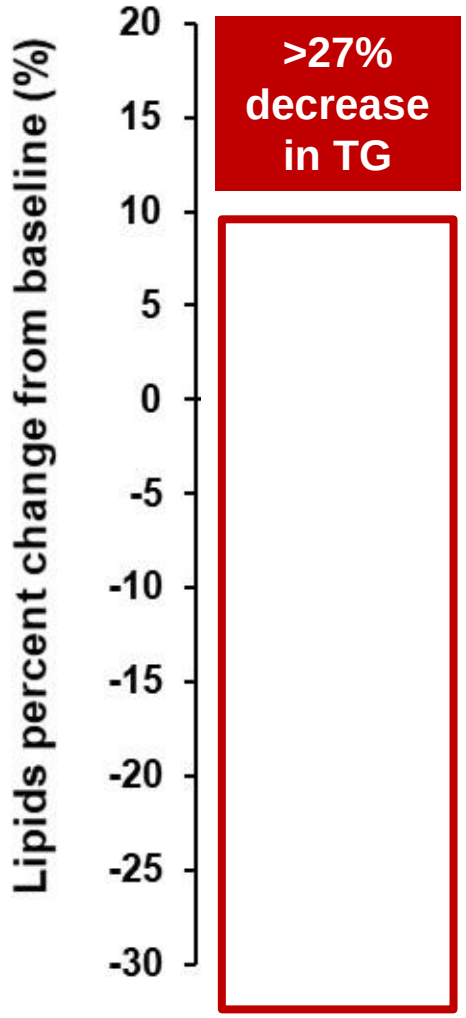
Of the participants who had prediabetes, >95% reverted to normoglycemia in the tirzepatide groups

Decrease in HbA1c by 0.5%

Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S et al. NEJM, *in press*

Change in Lipids

On Treatment
Efficacy Estimand



>27% decrease in TG

placebo
tirzepatide pooled
(5/10/15 mg)

Consistent improvement in all lipid levels

TG = triglycerides
FFA = Free Fatty Acids

Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S et al. NEJM, *in press*

Change in Blood Pressure Over 72 weeks

On Treatment
Efficacy Estimand

Systolic Blood Pressure

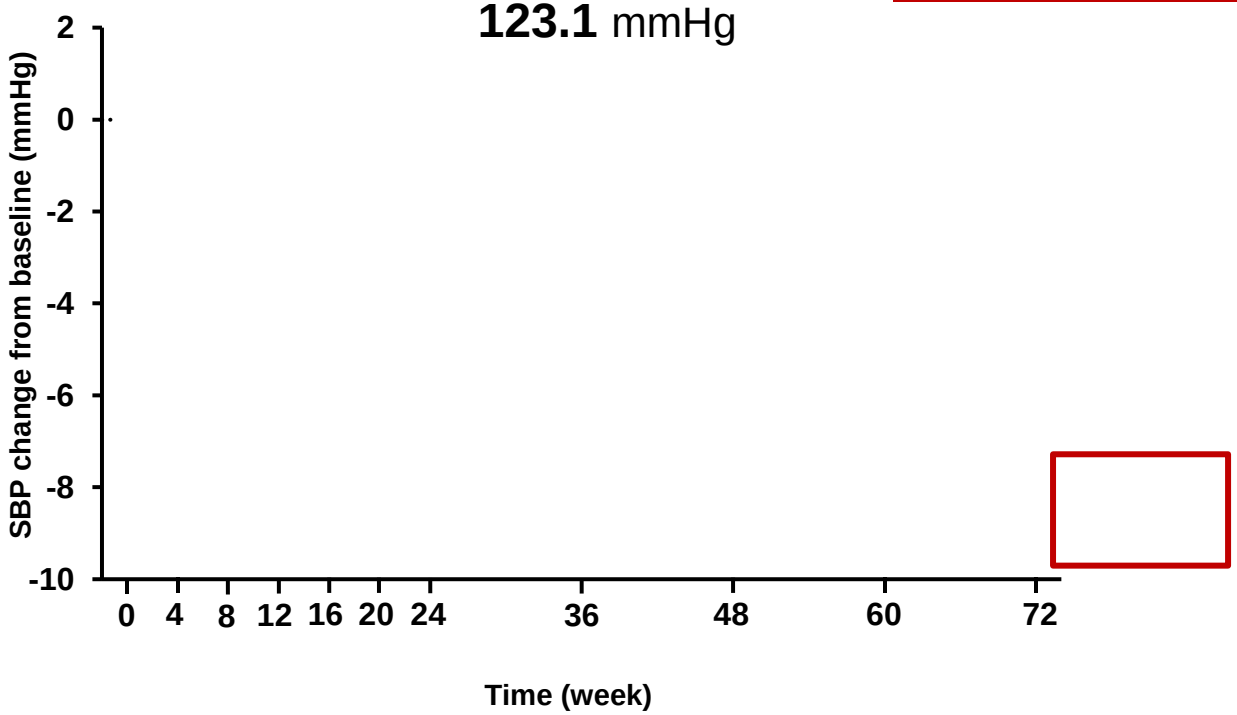
baseline SBP
123.1 mmHg

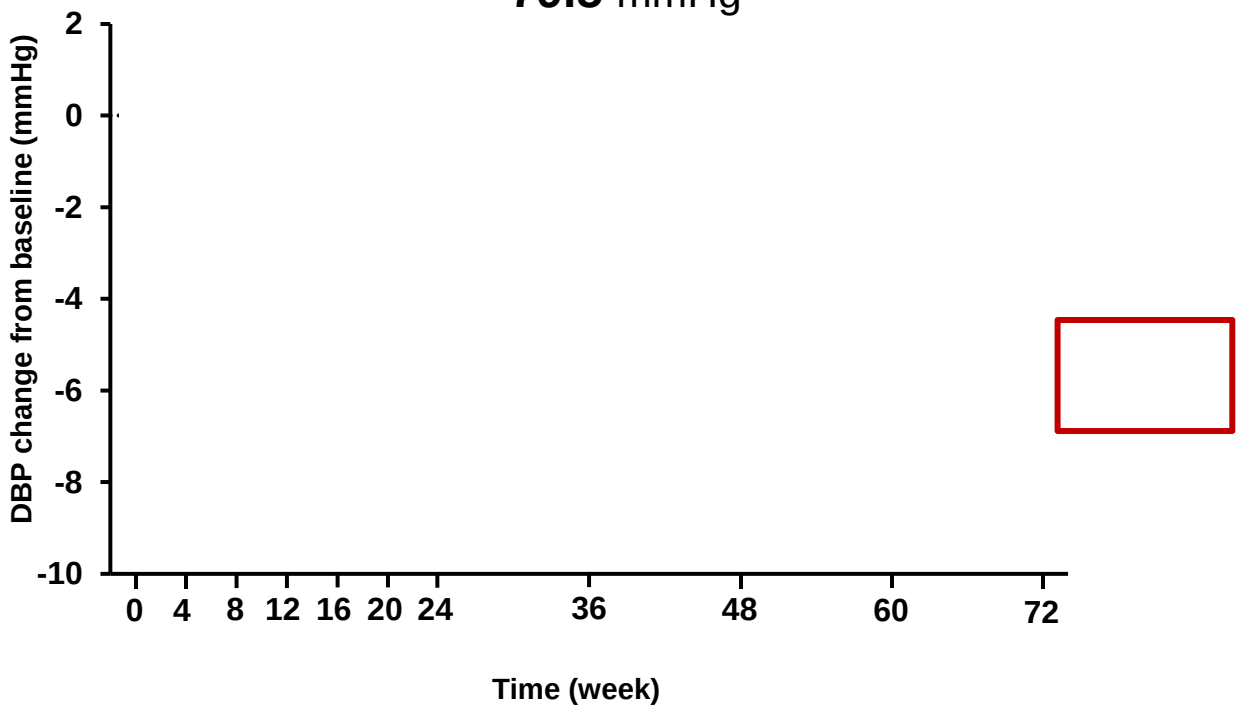
Improvement in blood pressure does not appear to be dependent on the high magnitude of weight reduction

Diastolic Blood Pressure

baseline DBP
79.5 mmHg

placebo
tirzepatide pooled (5/10/15 mg)





Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S et al. NEJM, *in press*

Yale SCHOOL OF MEDICINE

Overview of Adverse Events

Parameter	Placebo (N=643) n (%)	TZP 5 mg (N=630) n (%)	TZP 10 mg (N=636) n (%)	TZP 15 mg (N=630) n (%)
Number of participants with:				
TEAEs	463 (72.0)	510 (81.0)	520 (81.8)	497 (78.9)
SAEs	44 (6.8)	40 (6.3)	44 (6.9)	32 (5.1)
Deaths*	4 (0.6)	4 (0.6)	2 (0.3)	1 (0.2)

*Deaths are also included as SAEs and discontinuations due to AE. Note: Patients may be counted in more than 1 category.
mITT population (safety analysis set); n (%): number (percentage) of participants

Similar percentages of participants in the tirzepatide and placebo groups reported serious adverse events and there was no increase in incidence of death on tirzepatide as compared to placebo.

Treatment Emergent Adverse Events with ≥5% Frequency

Parameter	Placebo (N=643) n (%)	TZP 5 mg (N=630) n (%)	TZP 10 mg (N=636) n (%)	TZP 15 mg (N=630) n (%)
Patients with ≥1 TEAE	463 (72.0)	510 (81.0)	520 (81.8)	497 (78.9)
Nausea	61 (9.5)	155 (24.6)	212 (33.3)	195 (31.0)
Diarrhea	47 (7.3)	118 (18.7)	135 (21.2)	145 (23.0)
COVID-19	90 (14.0)	94 (14.9)	98 (15.4)	82 (13.0)
Constipation	37 (5.8)	106 (16.8)	109 (17.1)	74 (11.7)
Dyspepsia	27 (4.2)	56 (8.9)	62 (9.7)	71 (11.3)
Vomiting	11 (1.7)	52 (8.3)	68 (10.7)	77 (12.2)
Decreased appetite	21 (3.3)	59 (9.4)	73 (11.5)	54 (8.6)
Headache	42 (6.5)	41 (6.5)	43 (6.8)	41 (6.5)
Abdominal pain	21 (3.3)	31 (4.9)	34 (5.3)	31 (4.9)
Hair loss	6 (0.9)	32 (5.1)	31 (4.9)	36 (5.7)
Dizziness	15 (2.3)	26 (4.1)	35 (5.5)	26 (4.1)
Eructation	4 (0.6)	24 (3.8)	33 (5.2)	35 (5.6)
Injection site reaction	2 (0.3)	18 (2.9)	36 (5.7)	29 (4.6)

TEAE, treatment emergent adverse event; Shown in order of decreasing frequency; mITT population (safety analysis set); n (%): number (percentage) of participants

Gastrointestinal Adverse Events Reported as Primary Reason for Discontinuation of the Study Drug

Parameter	Placebo (N=643) n (%)	TZP 5 mg (N=630) n (%)	TZP 10 mg (N=636) n (%)	TZP 15 mg (N=630) n (%)
Participants with Study Drug discontinuation due to Adverse Events	17 (2.6)	27 (4.3)	45 (7.1)	39 (6.2)
Participants with Study Drug discontinuation due to Gastrointestinal Adverse Events	**3 (0.5)**	**12 (1.9)**	**28 (4.4)**	**26 (4.1)**

mITT population (safety analysis set); n (%): number (percentage) of participants

Gastrointestinal adverse events as primary reason for study drug discontinuation were not frequent and were reported in less than 5% of participants on tirzepatide.

Adverse Events of Special Interest

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

[#] reported events classified as severe or serious supraventricular arrhythmias and cardiac conduction disorders
* reported events classified as severe or serious adverse events
[&] includes immediate (≤24 hours after trial drug administration) and nonimmediate (>24 hours after trial drug administration) severe or serious hypersensitivity events.
mITT population (safety analysis set); n (%): number (percentage) of participants; MACE, major adverse cardiovascular disease; MDD, major depressive disorder

There were 4 reported cases of adjudication-confirmed pancreatitis, evenly distributed across treatment groups including placebo.

Key Take aways

- All tirzepatide doses demonstrated superior, clinically meaningful and sustained body weight reduction versus placebo in participants with obesity (with both estimand analyses).
- Participants experienced average weight reductions of 19.5% and 20.9% with tirzepatide 10 mg and 15 mg, respectively (treatment-regimen estimand)
- Treatment with tirzepatide at all doses translated to clinically meaningful improvements in cardiometabolic risk factors.
- The tolerability and safety profile of tirzepatide is consistent with the GLP-1 receptor agonist class in people with obesity.