Tirzepatide for Obesity Treatment and Diabetes Prevention:

SURMOUNT-1 Trial 3-year Weight and Glycemic Outcomes

Obesity Week

November 4, 2024

Tirzepatide for Obesity Treatment and Diabetes Prevention:

SURMOUNT-1 Trial 3-year Weight and Glycemic Outcomes

Introduction

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Global Burden of Diabetes

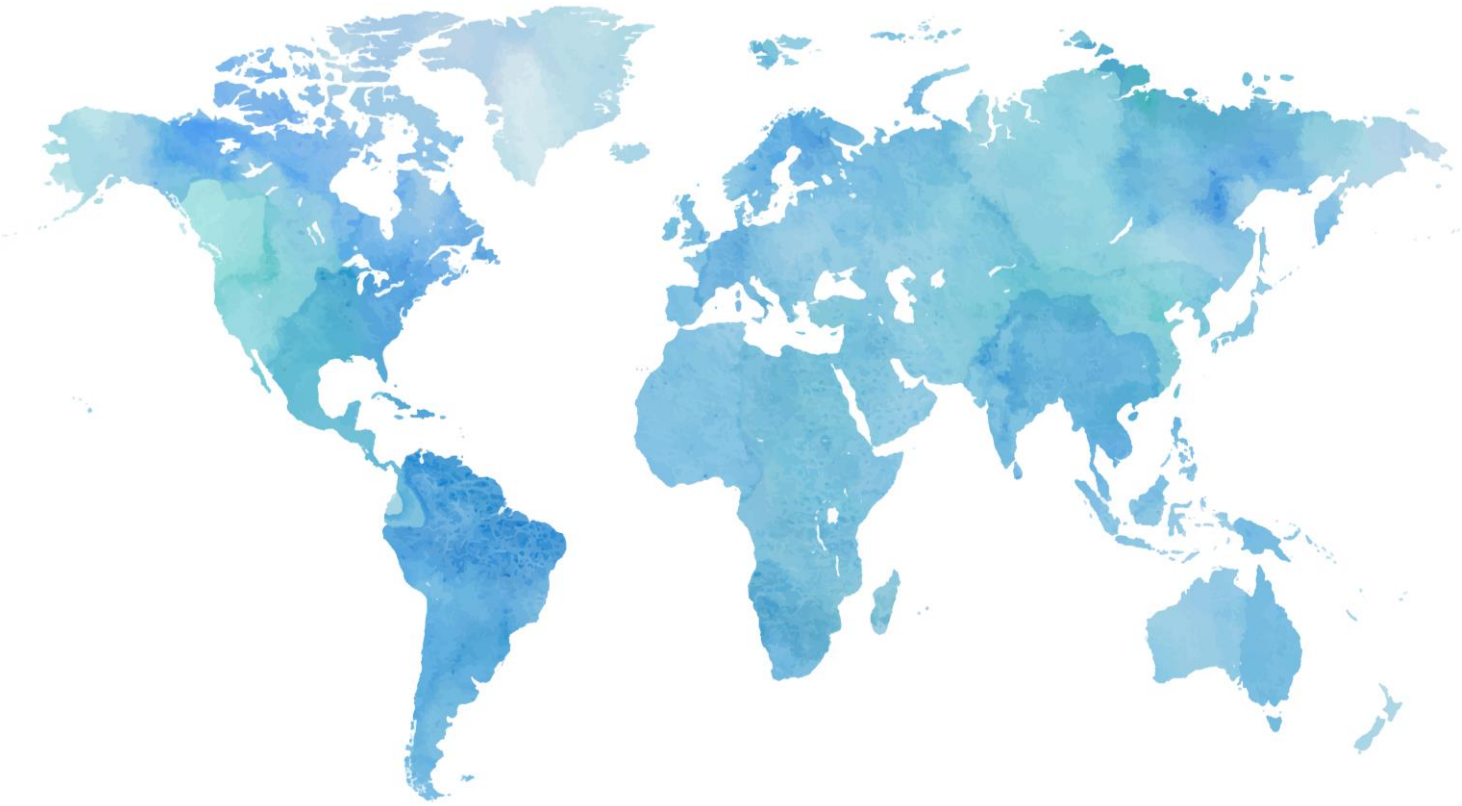
World

2045 **783 million**

2030 **643 million**

2021 **537 million**

46% increase



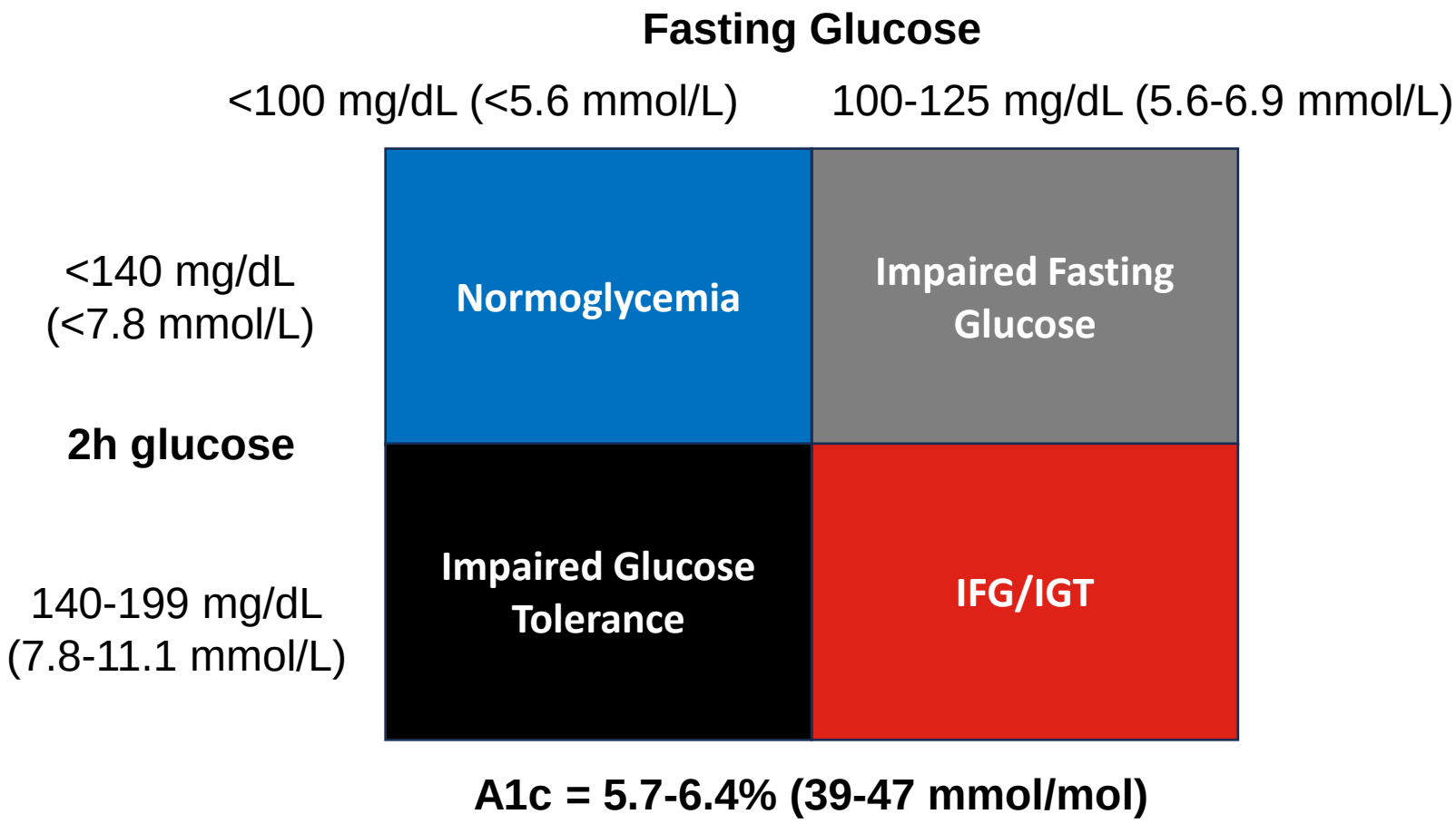
IDF Diabetes Atlas 2021, 10th edition: IDF Diabetes Atlas 2021 | IDF Diabetes Atlas

Global Burden of Diabetes

"An estimated 97.6 million Americans – 38% of the adult population – currently have prediabetes"

- National Diabetes Statistics Report CDC, 2024

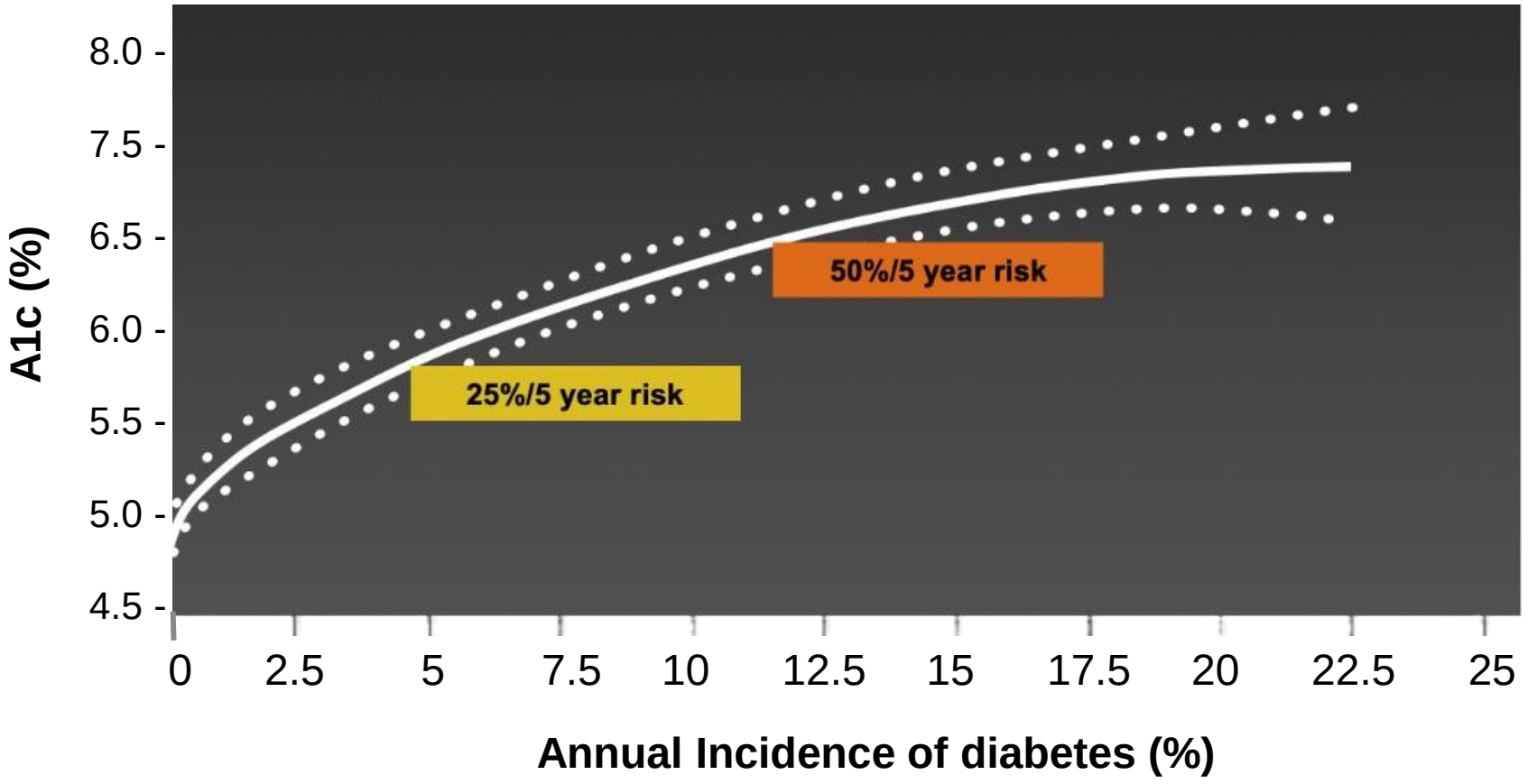
American Diabetes Association: Glucose Criteria for Prediabetes



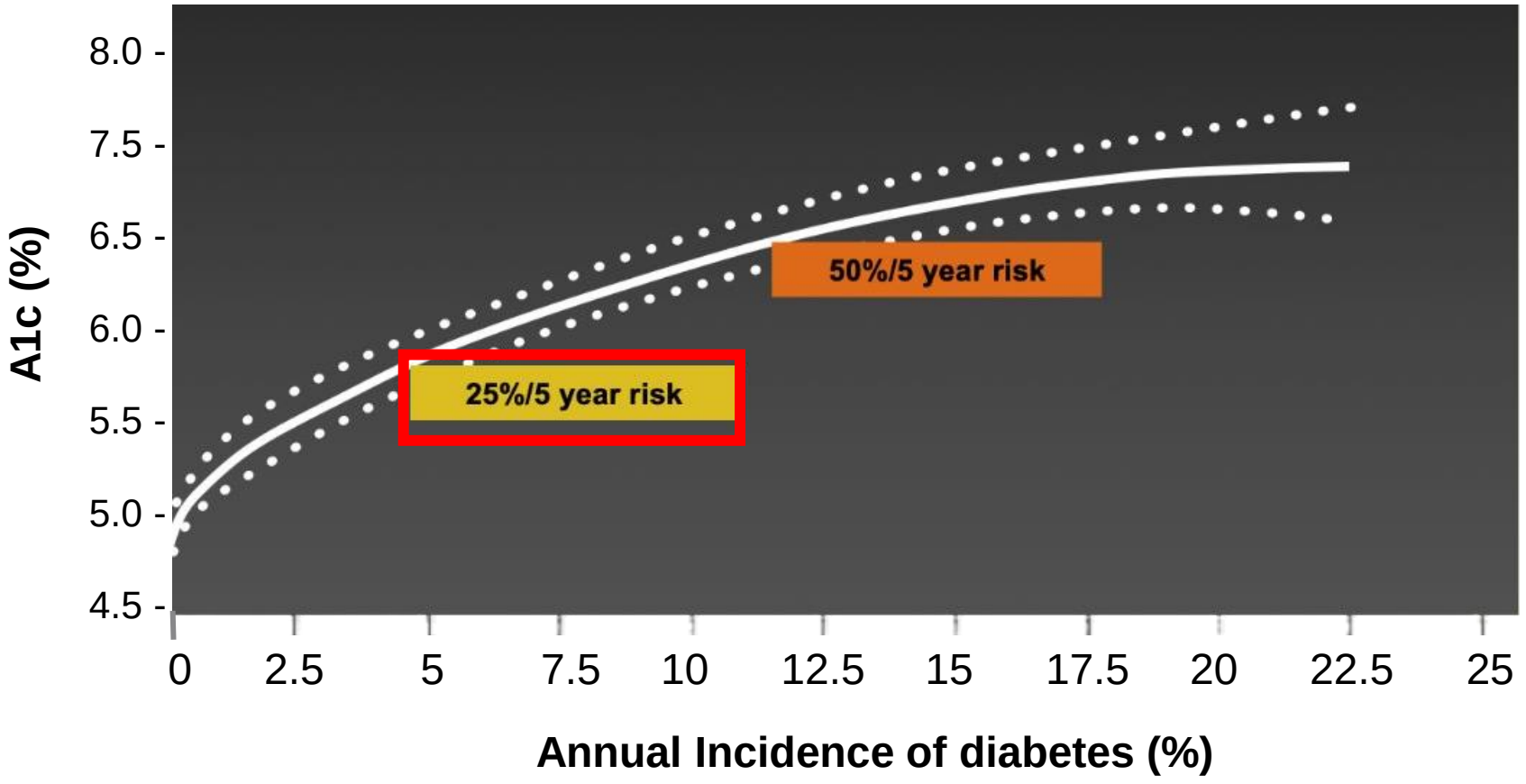
Note: IFG = Impaired Fasting Glycemia , IGT = Impaired Glucose Tolerance

Reference: Diabetes Care 2024;47(Supplement_1):S20–S42 https://doi.org/10.2337/dc24-S002

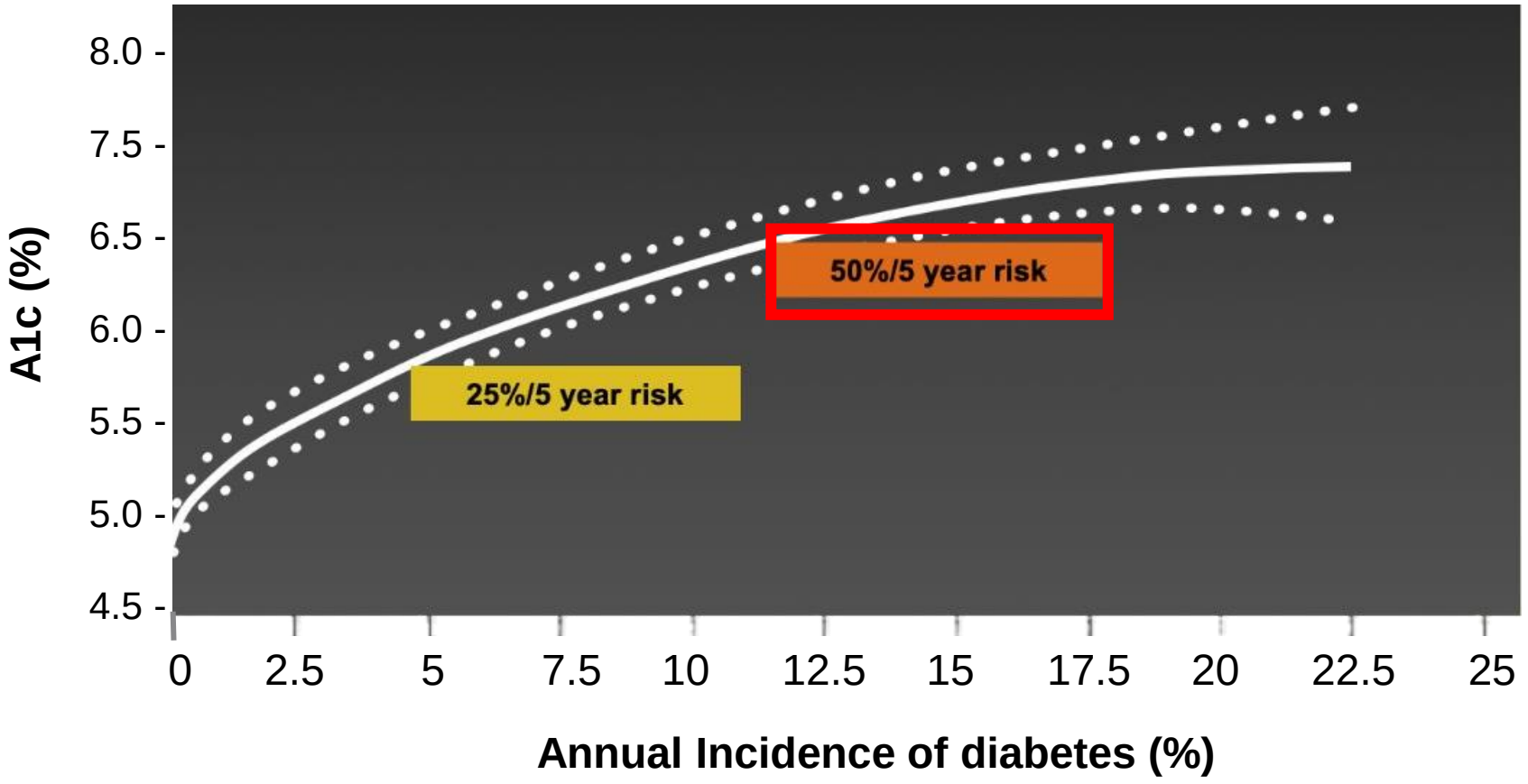
Risk of Diabetes for People with Prediabetes



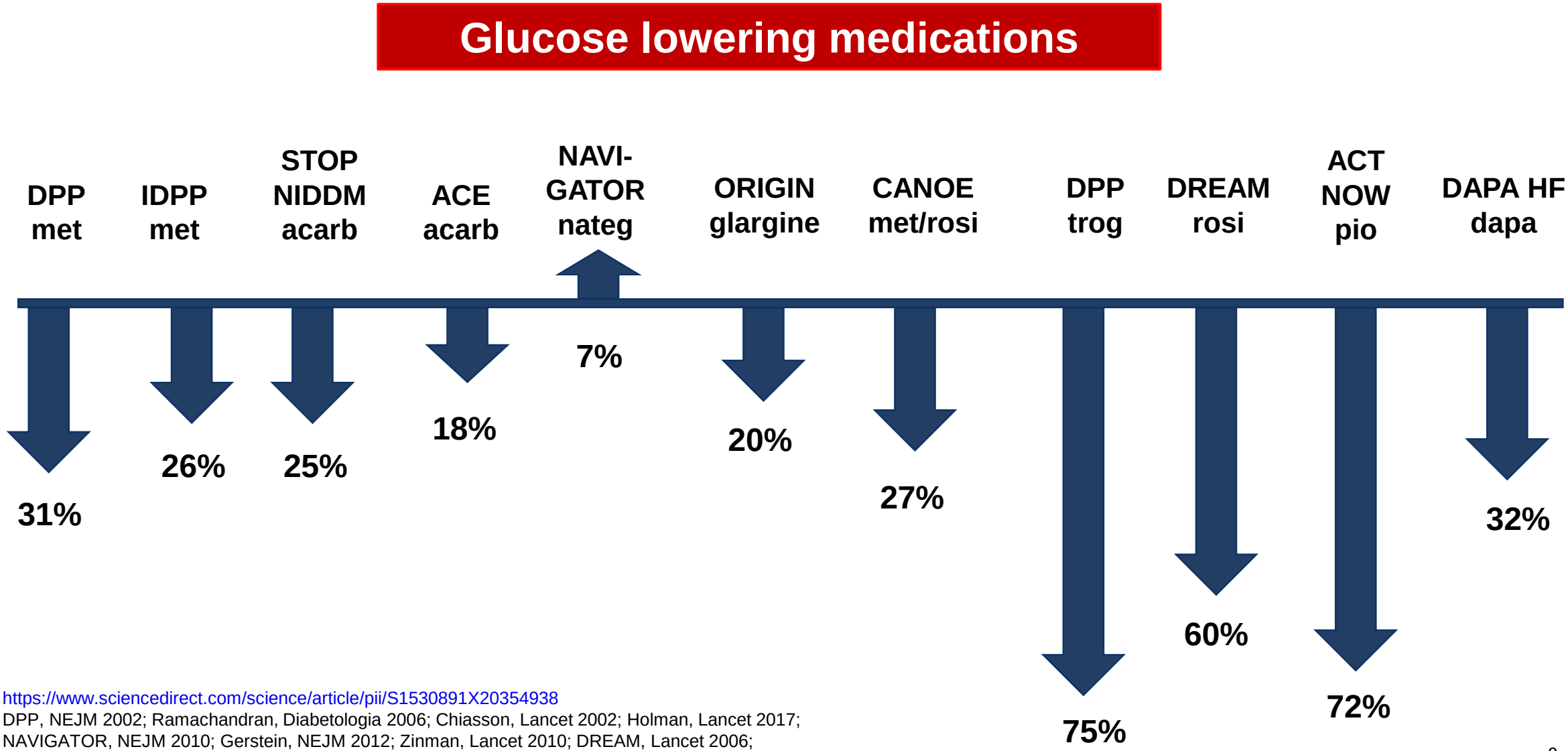
Risk of Diabetes for People with Prediabetes



Risk of Diabetes for People with Prediabetes



Intervention Trials to Reduce Progression of Prediabetes to Type 2 Diabetes

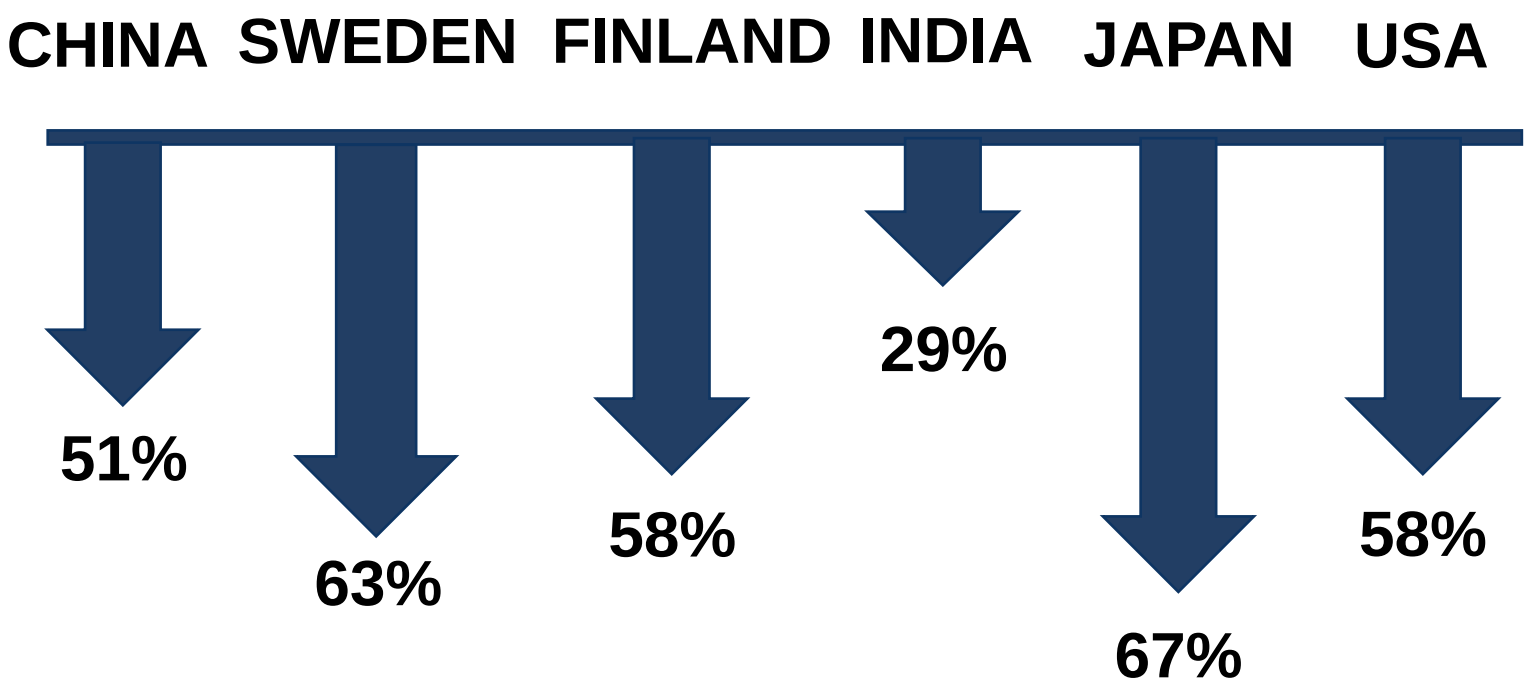


https://www.sciencedirect.com/science/article/pii/S1530891X20354938

DPP, NEJM 2002; Ramachandran, Diabetologia 2006; Chiasson, Lancet 2002; Holman, Lancet 2017; NAVIGATOR, NEJM 2010; Gerstein, NEJM 2012; Zinman, Lancet 2010; DREAM, Lancet 2006; DeFronzo, NEJM 2011; Inzucchi, Diabetes Care 2021

Intervention Trials to Reduce Progression of Prediabetes to Type 2 Diabetes

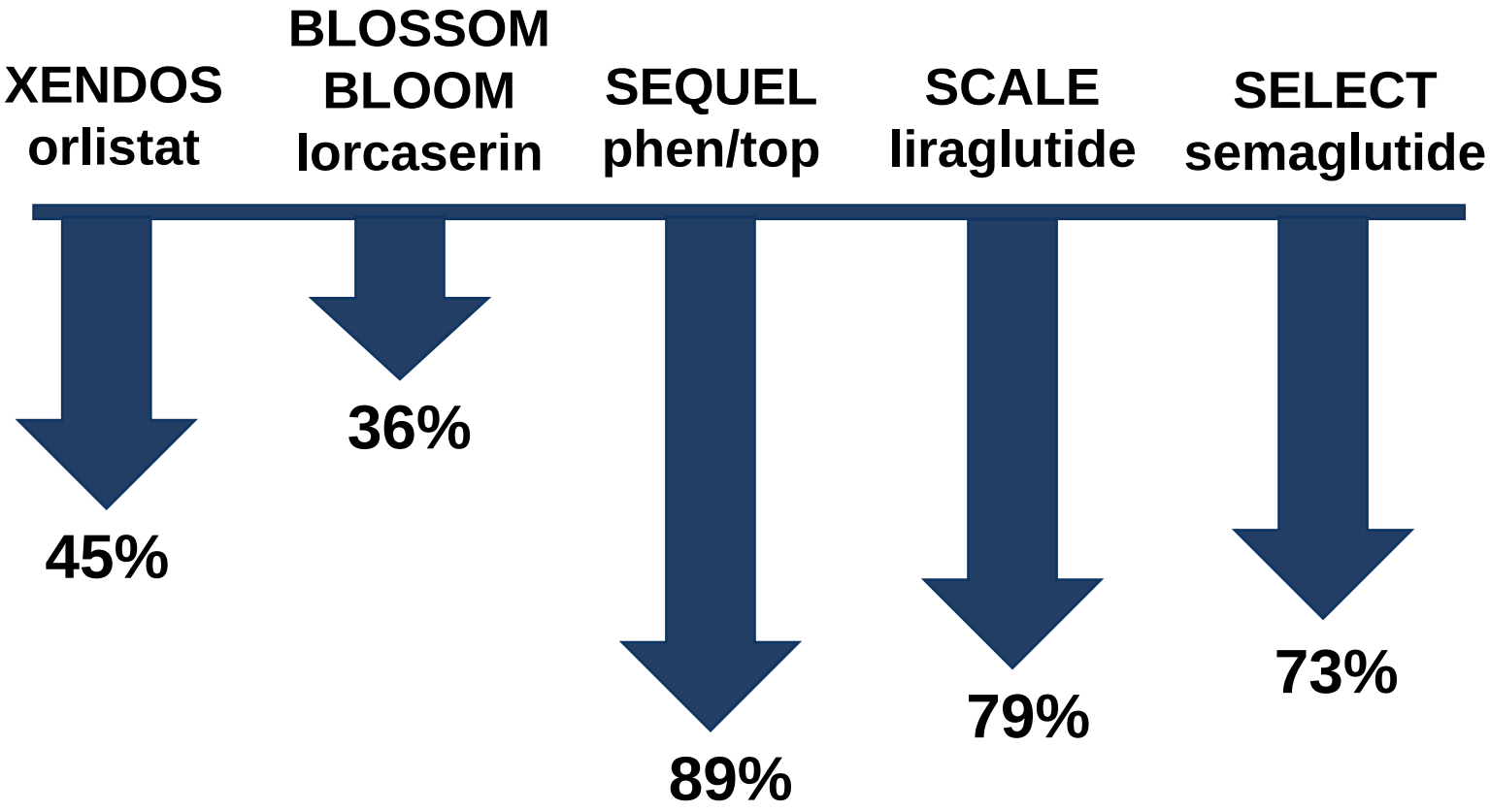
Intensive Lifestyle Intervention



Pan, Diabetes Care 1997; Erikson, Diabetologia 1991; Tuomilhelto, NEJM 2001; Ramachandran, Diabetologia 2006; DPP, NEJM 2002

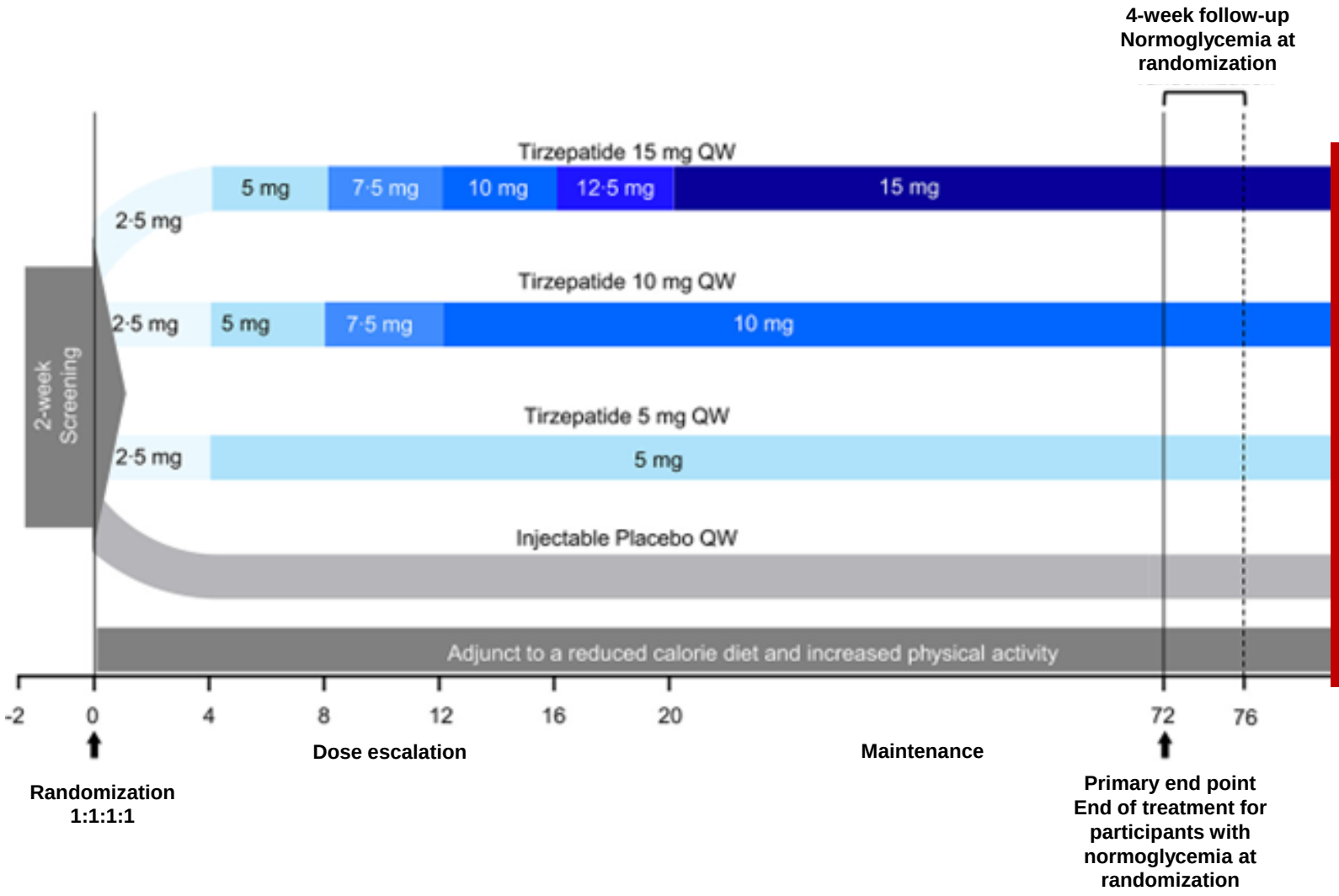
Intervention Trials to Reduce Progression of Prediabetes to Type 2 Diabetes

Anti-obesity Medications



Torgerson, Diabetes Care 2004; Nesto, Postgrad Med 2016; Garvey, Diabetes Care 2014; le Roux, Lancet 2017; Kahn, Diabetes Care 2024

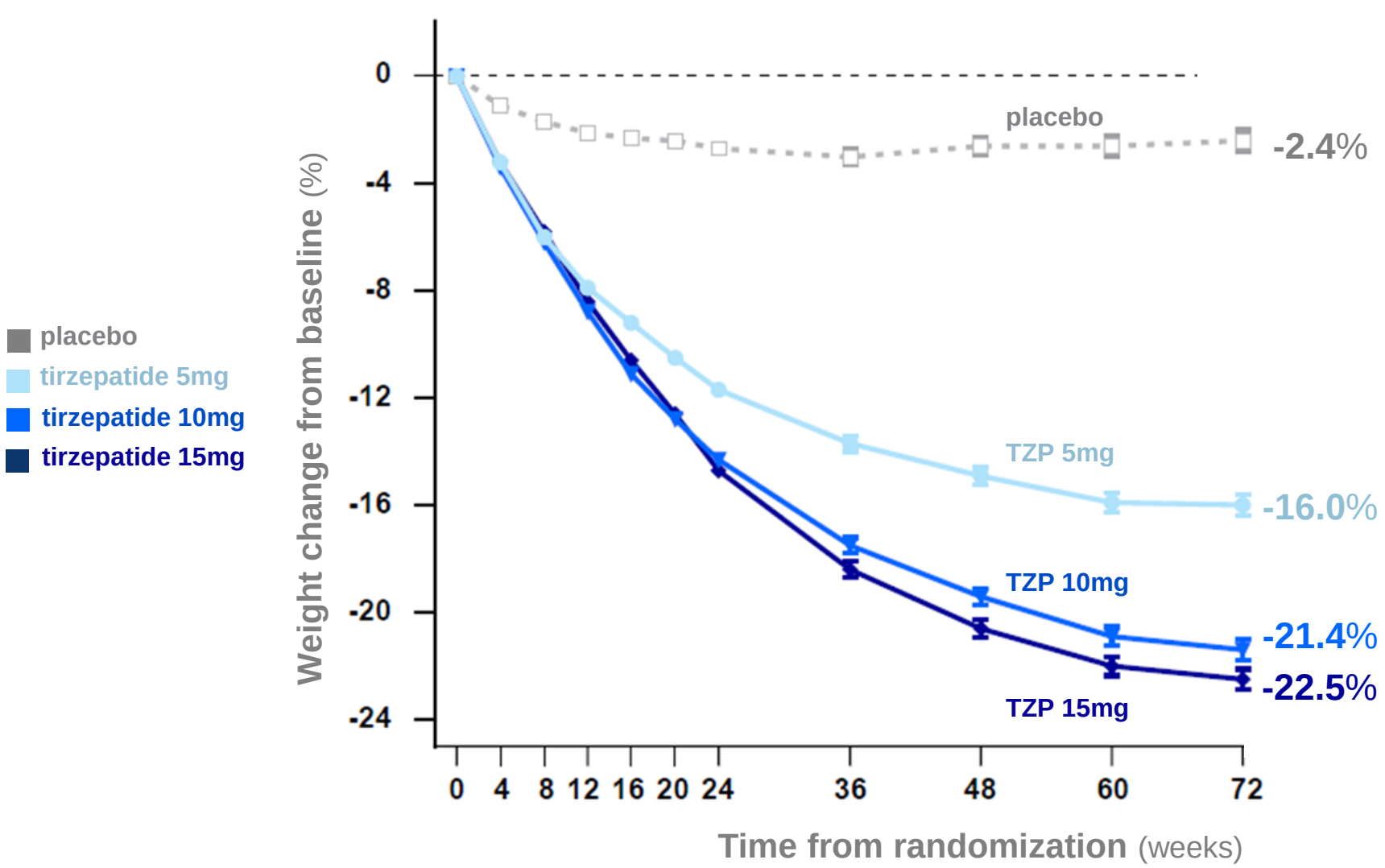
SURMOUNT-1 Study Design



- **N=2539 participants with obesity or overweight, without T2D**
- **Glycemic status assessed at randomization with HbA1c, FSG and 2-hour Oral Glucose Tolerance Test (OGTT)**
- **Participants with normoglycemia at randomization completed the study after 72-weeks of treatment**

Jastreboff, NEJM 2022

Percent Change in Body Weight at Week 72



On Treatment
Efficacy Estimand

Primary Objective

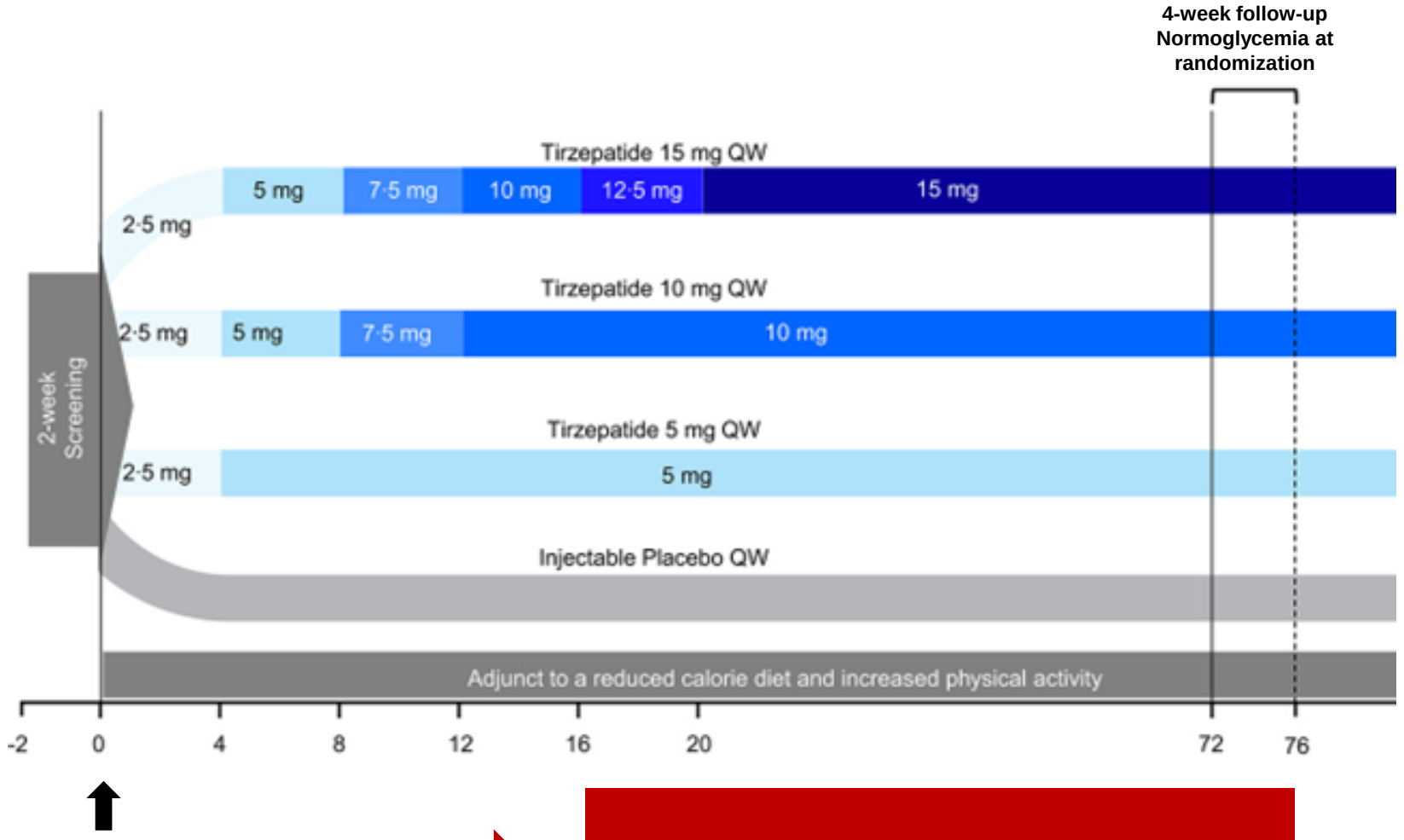
To demonstrate that tirzepatide 10 mg and/or 15 mg once-weekly is superior to placebo at 72 weeks for:

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

Efficacy estimand: MMRM analysis. Data presented over time are least squares means ± standard errors. Tirzepatide vs. placebo at 72 weeks: p<0.001.

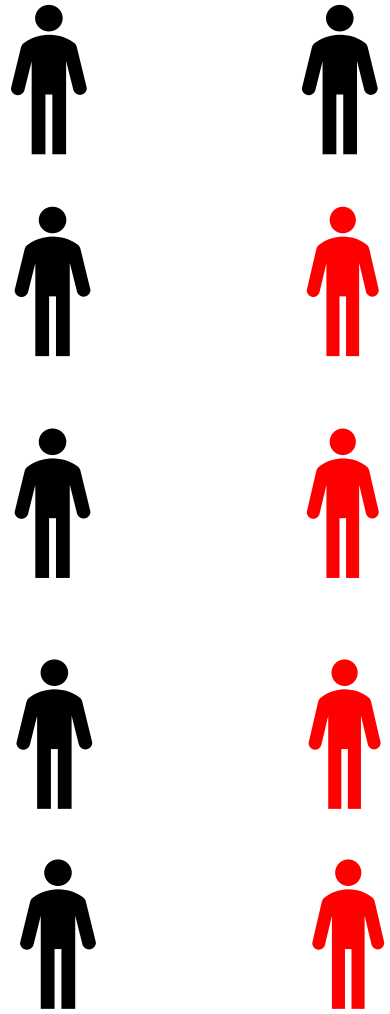
Jastreboff, NEJM 2022

SURMOUNT-1 Study Design



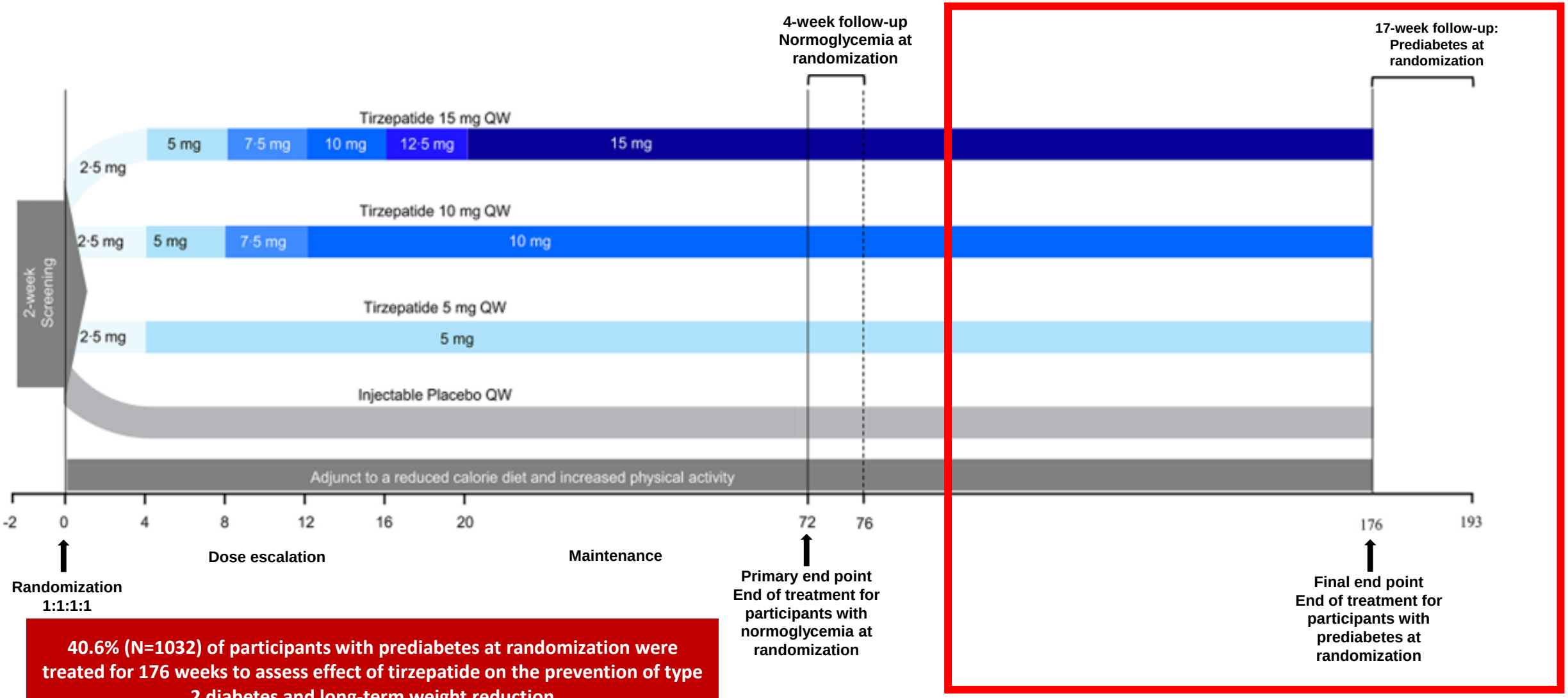
RANDOMIZATION

40.6% (N=1032), presented with prediabetes at randomization



Jastreboff, NEJM 2022

SURMOUNT-1 Study Design



40.6% (N=1032) of participants with prediabetes at randomization were treated for 176 weeks to assess effect of tirzepatide on the prevention of type 2 diabetes and long-term weight reduction

Jastreboff, NEJM. *In press*

Tirzepatide for Obesity Treatment and Diabetes Prevention:

SURMOUNT-1 Trial 3-year Weight and Glycemic Outcomes

Design and Baseline Characteristics

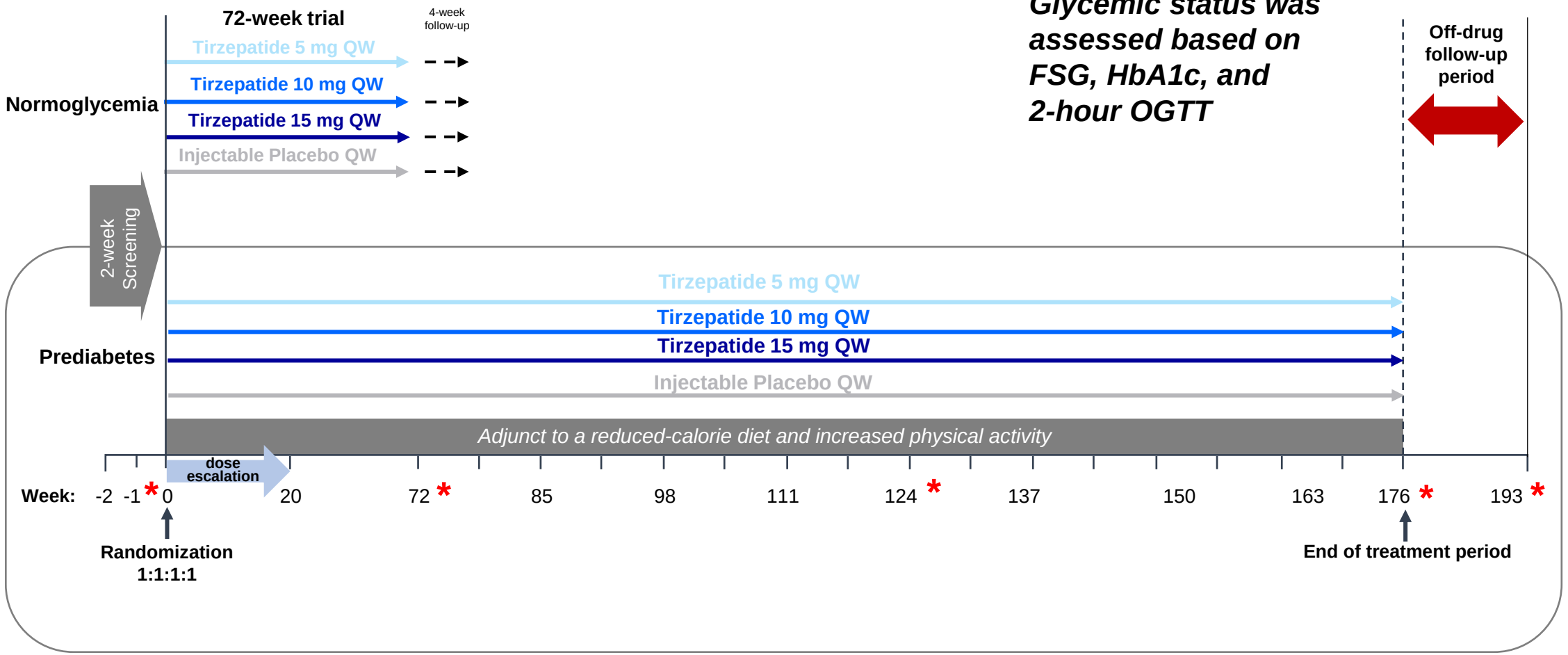
Louis Aronne, MD

Sanford I. Weill Professor of Metabolic Research

Weill-Cornell Medical College, NY, USA

SURMOUNT-1: 3-Year Study Design in People with Prediabetes

Participants with prediabetes at randomization were observed for 176 weeks on treatment, followed by a 17-week off treatment period (193 weeks in total).



* = Visits that included the oral glucose tolerance test (OGTT)

Jastreboff, NEJM. *In press*

SURMOUNT-1: 3-Year Study – Trial Allocation

- **The study was conducted in 9 countries across 4 continents:**

Argentina, Brazil, Mexico, China, Japan, Taiwan, India, Russian Federation, and the United States.

- **The United States represented 45% of the study population.**

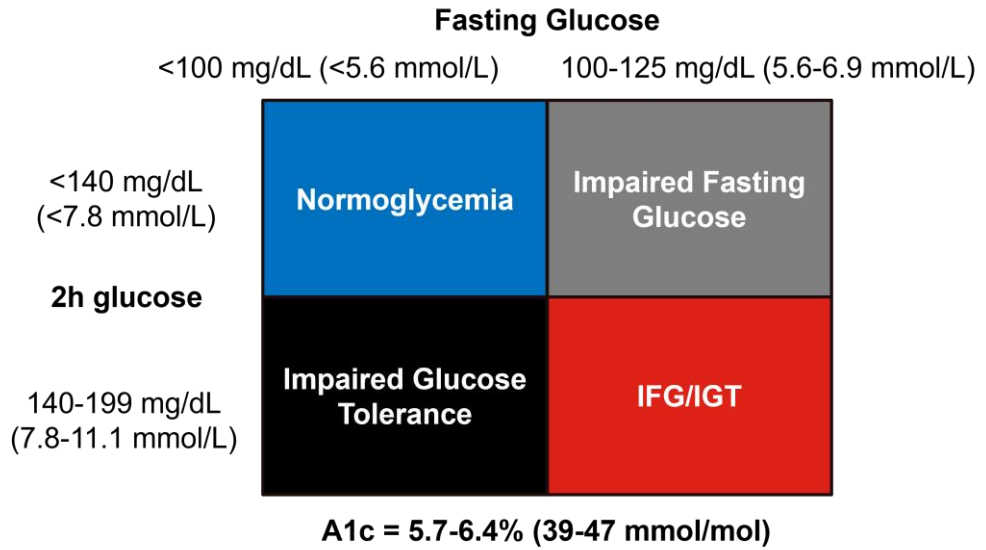
Jastreboff, NEJM. *In press*

Study Design – Inclusion and Exclusion Criteria

Key Inclusion Criteria:

- **Obesity or Overweight:** Adults with BMI ≥30 kg/m^2, or ≥27 kg/m^2 and ≥1 weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease)
- **Prediabetes** at screening (to be eligible for 3-year study)

Diagnosis of prediabetes was defined by the ADA cut-offs and required at least 2 abnormal test results



Key Exclusion Criteria:

- ***Diabetes mellitus***: T1DM or T2DM or laboratory evidence suggesting diabetes mellitus during screening

Jastreboff, NEJM. *In press*

Objectives of the 3-year SURMOUNT-1 Trial

Type 1 error-controlled endpoints

At 176 weeks to demonstrate:

- Tirzepatide 10 mg and/or 15 mg QW doses are superior to placebo for mean percent change in body weight from randomization
- Pooled tirzepatide (all once-weekly doses) is superior to placebo for time to onset of T2D

At 193 weeks (entire study including safety follow up period) to demonstrate:

- Pooled tirzepatide (all once-weekly doses) is superior to placebo for time to onset of T2D

Additional endpoints:

- Reversion to normoglycemia and changes in cardiometabolic risk factors and health-related quality of life were also evaluated at 176 weeks and/or 193 weeks.

QW = Once Weekly; T2DM = Type 2 Diabetes Mellitus

Jastreboff, NEJM. *In press*

Diagnosis of Diabetes During the Study

- **Incident diabetes could be diagnosed when any of the following occurred after randomization (ADA 2019):**
  - any 2 of the following criteria observed at the same visit, or 1 abnormal value observed and subsequently confirmed:
    - **FG ≥126 mg/dL** (7.0 mmol/L)
    - **2-hour glucose ≥200 mg/dL** (11.1 mmol/L) during Oral Glucose Tolerance Test
    - **HbA1c ≥6.5%** (48 mmol/mol)

  OR

  - **random glucose ≥200 mg/dL** (11.1 mmol/L) with signs or symptoms of hyperglycemia (unequivocal hyperglycemia)

  OR

  - **initiation of any medication** for the treatment of diabetes (specifically)

- **All cases of incident diabetes were adjudicated by an independent clinical endpoint committee**

Jastreboff, NEJM. *In press*

Baseline Demographics

Parameter	Placebo (N=270)	TZP 5 mg (N=247)	TZP 10 mg (N=262)	TZP 15 mg (N=253)	Total (N=1032)
Age (y), mean ± SD	47.7 ± 11.9	49.3 ± 12.2	47.4 ± 11.6	48.4 ± 11.7	**48.2 ± 11.8**
Female, n (%)	170 (63.0)	160 (64.8)	168 (64.1)	161 (63.6)	659 (63.9)
Race, n (%)					
American Indian or Alaska Native	18 (6.7)	18 (7.3)	20 (7.6)	19 (7.5)	75 (7.3)
Asian	30 (11.1)	22 (8.9)	27 (10.3)	26 (10.3)	105 (10.2)
Black or African American	23 (8.5)	19 (7.7)	15 (5.7)	20 (7.9)	77 (7.5)
White	193 (71.5)	182 (73.7)	198 (75.6)	185 (73.1)	758 (73.4)
Native Hawaiian or Other Pacific Islander	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	4 (0.4)
Multiple	5 (1.9)	5 (2.0)	1 (0.4)	2 (0.8)	13 (1.3)
Ethnicity, n (%)					
Hispanic or Latino	127 (47.0)	118 (47.8)	120 (45.8)	117 (46.2)	482 (46.7)
Not Hispanic or Latino	122 (45.2)	114 (46.2)	121 (46.2)	113 (44.7)	470 (45.5)
Not Reported	21 (7.8)	15 (6.1)	21 (8.0)	23 (9.1)	80 (7.8)

The baseline demographics were well balanced across the treatment groups.

Randomized population – participants with prediabetes at randomization.
Race and ethnic group were reported by the participants.

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Randomized population – participants with prediabetes at randomization.
Race and ethnic group were reported by the participants.

Baseline Demographics of the Participants in the United States

Parameter	Placebo (N=120)	TZP 5 mg (N=115)	TZP 10 mg (N=116)	TZP 15 mg (N=110)	Total (N=461)
Age (y), mean ± SD	49.5 ± 12.4	51.8 ± 11.8	48.0 ± 12.0	50.2 ± 11.7	**49.9 ± 12.0**
Female sex, n (%)	79 (65.8)	75 (65.2)	78 (67.2)	69 (62.7)	**301 (65.3)**
Race or ethnic group, n (%)					
Asian	2 (1.7)	2 (1.7)	4 (3.4)	2 (1.8)	**10 (2.2)**
Black	18 (15.0)	15 (13.0)	11 (9.5)	16 (14.5)	**60 (13.0)**
White	96 (80.0)	95 (82.6)	99 (85.3)	89 (80.9)	**379 (82.2)**
Native Hawaiian or Other Pacific Islander	1 (0.8)	1 (0.9)	1 (0.9)	1 (0.9)	**4 (0.9)**
Multiple	3 (2.5)	2 (1.7)	1 (0.9)	2 (1.8)	**8 (1.7)**
Hispanic or Latino ethnic group, n (%)	31 (25.8)	27 (23.5)	24 (20.7)	25 (22.7)	**107 (23.2)**

Race/ethnicity of U.S. participants were generally representative of U.S. demographics.

Randomized population – participants with prediabetes at randomization.
Race and ethnic group were reported by the participants.

Baseline Clinical Characteristics

Parameter (mean ± SD, unless otherwise specified)	Placebo (N=270)	TZP 5 mg (N=247)	TZP 10 mg (N=262)	TZP 15 mg (N=253)	Total (N=1032)
Weight (kg)	107.3 ± 21.97	104.6 ± 21.91	108.9 ± 23.88	108.6 ± 25.44	**107.3 ± 23.36**
BMI (kg/m^2)	39.1 ± 7.10	37.8 ± 6.63	39.0 ± 7.15	39.2 ± 7.43	**38.8 ± 7.10**
Waist circumference (cm)	117.1 ± 15.42	115.0 ± 14.54	117.4 ± 15.53	116.6 ± 16.73	**116.5 ± 15.58**
HbA_{1c} (%)	5.8 ± 0.33	5.8 ± 0.30	5.7 ± 0.33	5.8 ± 0.39	**5.8 ± 0.34**
Fasting Glucose (mg/dL)	101.3 ± 9.61	101.2 ± 9.04	101.8 ± 10.06	101.0 ± 9.54	**101.3 ± 9.57**
Fasting insulin (mIU/L)	17.1 ± 10.49	16.0 ± 12.83	16.3 ± 16.12	16.5 ± 9.39	**16.5 ± 12.47**
Systolic blood pressure (mmHg)	124.8 ± 12.75	126.9 ± 12.13	125.3 ± 13.14	125.4 ± 12.73	**125.6 ± 12.71**
Diastolic blood pressure (mmHg)	80.8 ± 7.80	80.8 ± 7.98	80.4 ± 8.73	80.3 ± 8.11	**80.6 ± 8.16**
eGFR (ml/min/1.73 m^2)	95.1 ± 18.37	93.8 ± 17.51	95.0 ± 18.65	96.2 ± 17.21	**95.1 ± 17.95**
Hypertension [yes], n (%)	109 (40.4)	108 (43.7)	105 (40.1)	103 (40.7)	425 (41.2)
Dyslipidemia [yes], n (%)	103 (38.1)	101 (40.9)	77 (29.4)	88 (34.8)	369 (35.8)
Obstructive sleep apnea [yes], n (%)	11 (4.1)	12 (4.9)	18 (6.9)	9 (3.6)	50 (4.8)
Atherosclerotic CVD [yes], n (%)	13 (4.8)	12 (4.9)	11 (4.2)	11 (4.3)	47 (4.6)

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

Randomized population – participants with prediabetes at randomization.

Jastreboff, NEJM. *In press*

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Diastolic blood pressure (mmHg)	80.8 ± 7.80	80.8 ± 7.98	80.4 ± 8.73	80.3 ± 8.11	**80.6 ± 8.16**
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Randomized population – participants with prediabetes at randomization.

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Obstructive sleep apnea [yes], n (%)	11 (4.1)	12 (4.9)	18 (6.9)	9 (3.6)	50 (4.8)
Atherosclerotic CVD [yes], n (%)	13 (4.8)	12 (4.9)	11 (4.2)	11 (4.3)	47 (4.6)

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

Randomized population – participants with prediabetes at randomization.

Jastreboff, NEJM. *In press*

Baseline Clinical Characteristics

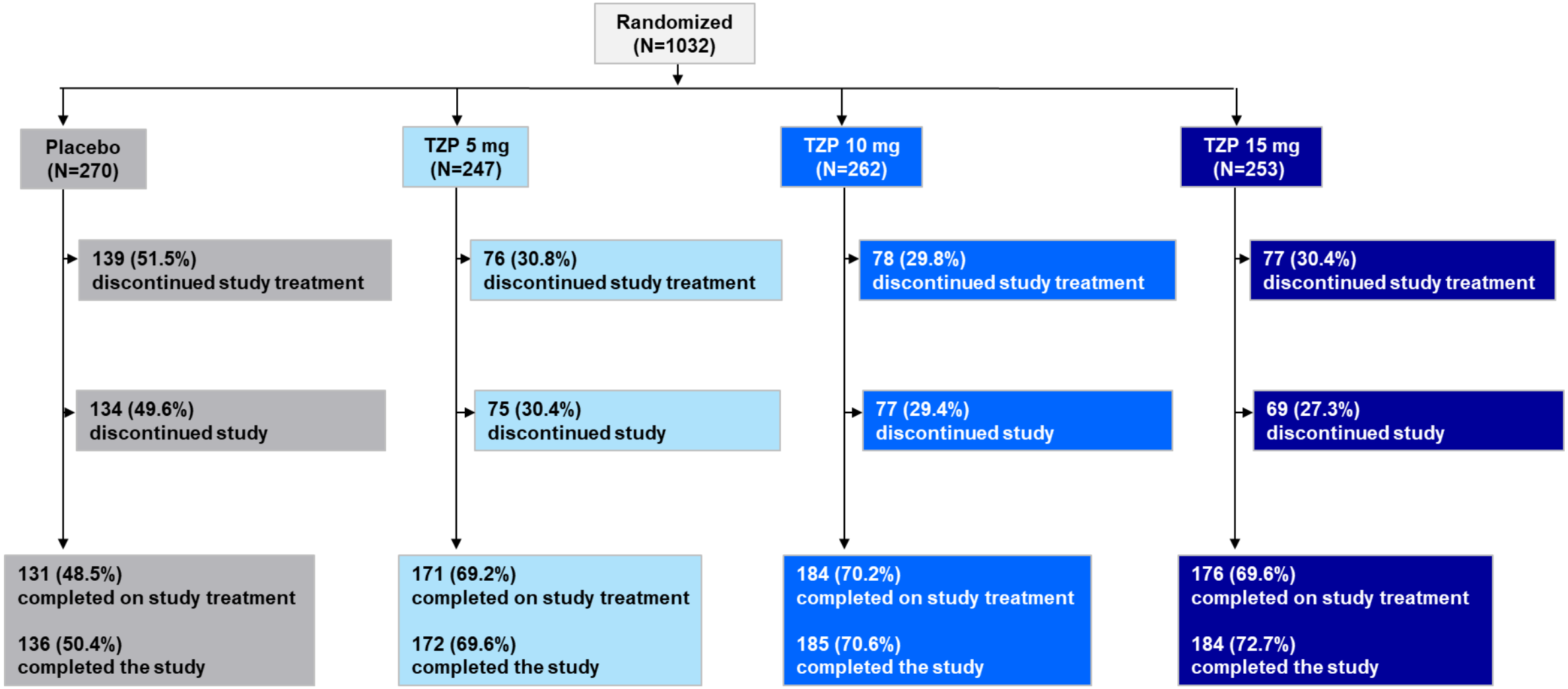
Parameter (mean ± SD, unless otherwise specified)	Placebo (N=270)	TZP 5 mg (N=247)	TZP 10 mg (N=262)	TZP 15 mg (N=253)	Total (N=1032)
Weight (kg)	107.3 ± 21.97	104.6 ± 21.91	108.9 ± 23.88	108.6 ± 25.44	**107.3 ± 23.36**
BMI (kg/m^2)	39.1 ± 7.10	37.8 ± 6.63	39.0 ± 7.15	39.2 ± 7.43	**38.8 ± 7.10**
Waist circumference (cm)	117.1 ± 15.42	115.0 ± 14.54	117.4 ± 15.53	116.6 ± 16.73	**116.5 ± 15.58**
HbA_{1c} (%)	5.8 ± 0.33	5.8 ± 0.30	5.7 ± 0.33	5.8 ± 0.39	**5.8 ± 0.34**
Fasting Glucose (mg/dL)	101.3 ± 9.61	101.2 ± 9.04	101.8 ± 10.06	101.0 ± 9.54	**101.3 ± 9.57**
Fasting insulin (mIU/L)	17.1 ± 10.49	16.0 ± 12.83	16.3 ± 16.12	16.5 ± 9.39	**16.5 ± 12.47**
Systolic blood pressure (mmHg)	124.8 ± 12.75	126.9 ± 12.13	125.3 ± 13.14	125.4 ± 12.73	**125.6 ± 12.71**
Diastolic blood pressure (mmHg)	80.8 ± 7.80	80.8 ± 7.98	80.4 ± 8.73	80.3 ± 8.11	**80.6 ± 8.16**
eGFR (ml/min/1.73 m^2)	95.1 ± 18.37	93.8 ± 17.51	95.0 ± 18.65	96.2 ± 17.21	**95.1 ± 17.95**
Hypertension [yes], n (%)	109 (40.4)	108 (43.7)	105 (40.1)	103 (40.7)	425 (41.2)
Dyslipidemia [yes], n (%)	103 (38.1)	101 (40.9)	77 (29.4)	88 (34.8)	369 (35.8)
Obstructive sleep apnea [yes], n (%)	11 (4.1)	12 (4.9)	18 (6.9)	9 (3.6)	50 (4.8)
Atherosclerotic CVD [yes], n (%)	13 (4.8)	12 (4.9)	11 (4.2)	11 (4.3)	47 (4.6)

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

Randomized population – participants with prediabetes at randomization.

Jastreboff, NEJM. *In press*

Disposition in the 3-Year Study for Participants with Prediabetes



Participants with a non-missing body weight measurement at Week 176 and who attended the safety follow-up visit at Week 193 were considered study completers.

Jastreboff, NEJM. *In press*

Summary of Study Treatment Discontinuations

Parameter	Placebo (N=270)		TZP 5 mg (N=247)		TZP 10 mg (N=262)		TZP 15 mg (N=253)	
	n	(%)	n	(%)	n	(%)	n	(%)
Permanent Discontinuation from Study Treatment	139	(51.5)	76	(30.8)	78	(29.8)	77	(30.4)
Adverse Event	13	(4.8)	16	(6.5)	23	(8.8)	29	(11.5)
Death	3	(1.1)	2	(0.8)	2	(0.8)	2	(0.8)
Lost to Follow-up	23	(8.5)	9	(3.6)	14	(5.3)	9	(3.6)
Physician Decision	2	(0.7)	0	(0)	3	(1.1)	1	(0.4)
Protocol Deviation	3	(1.1)	0	(0)	1	(0.4)	0	
Withdrawal by Subject	73	(27.0)	31	(12.6)	22	(8.4)	25	(9.9)
Pregnancy	3	(1.1)	2	(0.8)	1	(0.4)	3	(1.2)
Site Closed	1	(0.4)	0		1	(0.4)	0	
Other	18	(6.7)	16	(6.5)	11	(4.2)	8	(3.2)

The most common reason for study drug D/C was 'Withdrawal by subject" with higher occurrence in the placebo vs tirzepatide groups.

Randomized population – participants with prediabetes at randomization.

Jastreboff, NEJM. *In press*

Estimands and Clinical Interpretation

Efficacy Estimand
using Efficacy analysis set

Clinical interpretation

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

(stay ***On Treatment***)

The treatment difference if all patients remained on randomized treatment for the entire planned treatment duration (up to 176 weeks).

Treatment-Regimen Estimand
using Full Analysis Set

Clinical interpretation

How drug will work in clinical practice across the patients prescribed.

(stay ***In Trial***)

The treatment difference regardless of adherence to randomized treatment (up to 176 weeks).

Estimand
using Safety Analysis Set

Clinical interpretation

Will the treatment effect persist after discontinuation of drug.

The treatment difference after discontinuation of study drug for at least 17 weeks (up to 193 weeks).

- Graphical approach to strongly control for type 1 error was conducted separately for each of the estimands.
- In this study, all randomized participants with prediabetes at randomization took at least 1 dose of study drug, therefore, the randomized population, mITT population, and safety population are the same.

Tirzepatide for Obesity Treatment and Diabetes Prevention:

SURMOUNT-1 Trial 3-year Weight and Glycemic Outcomes

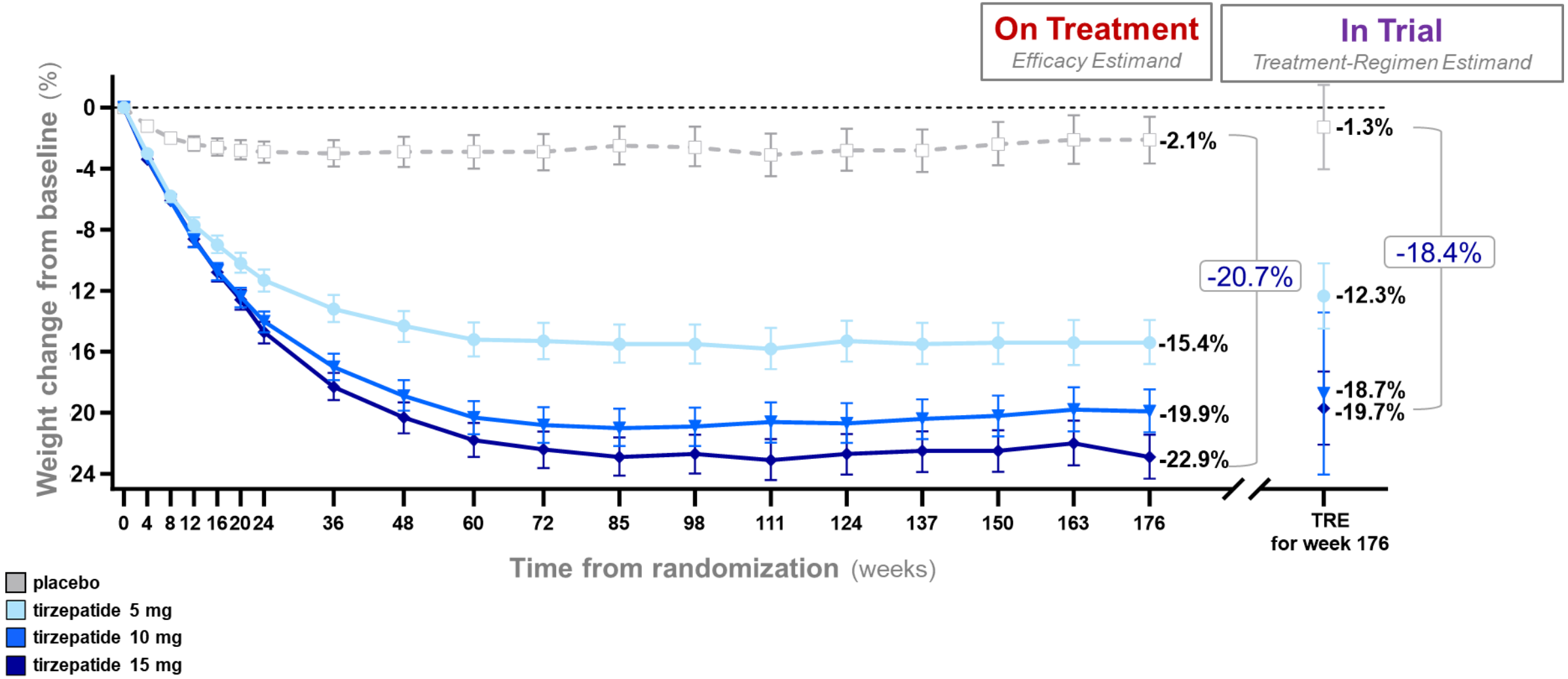
Efficacy Results

Ania M. Jastreboff, MD, PhD
Associate Professor, Medicine & Pediatrics
Endocrinology & Metabolism
Director, Yale Obesity Research Center (Y-Weight)
Yale University School of Medicine

Yale SCHOOL OF MEDICINE

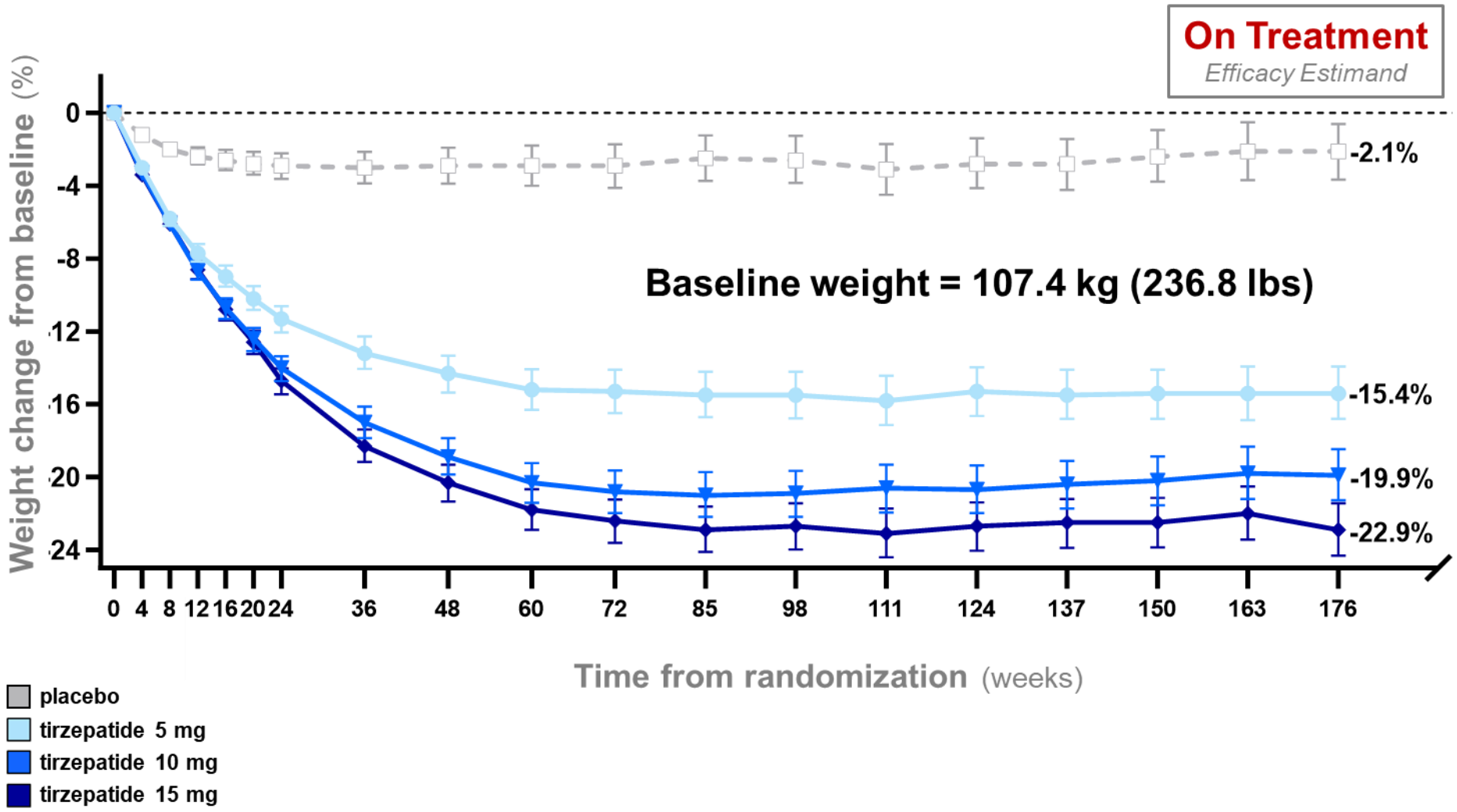
Weight and Glycemic Outcomes
(176 weeks)

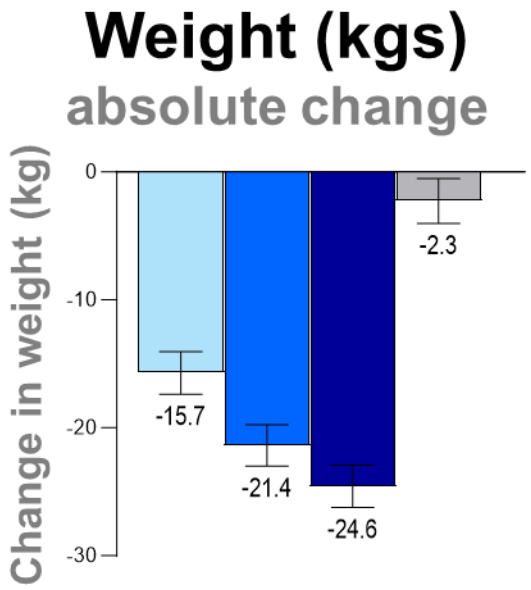
Weight Reduction over 176 weeks (3 yrs 4 mos)



Jastreboff, NEJM. *In press*

Weight Reduction Over 176 weeks: absolute change





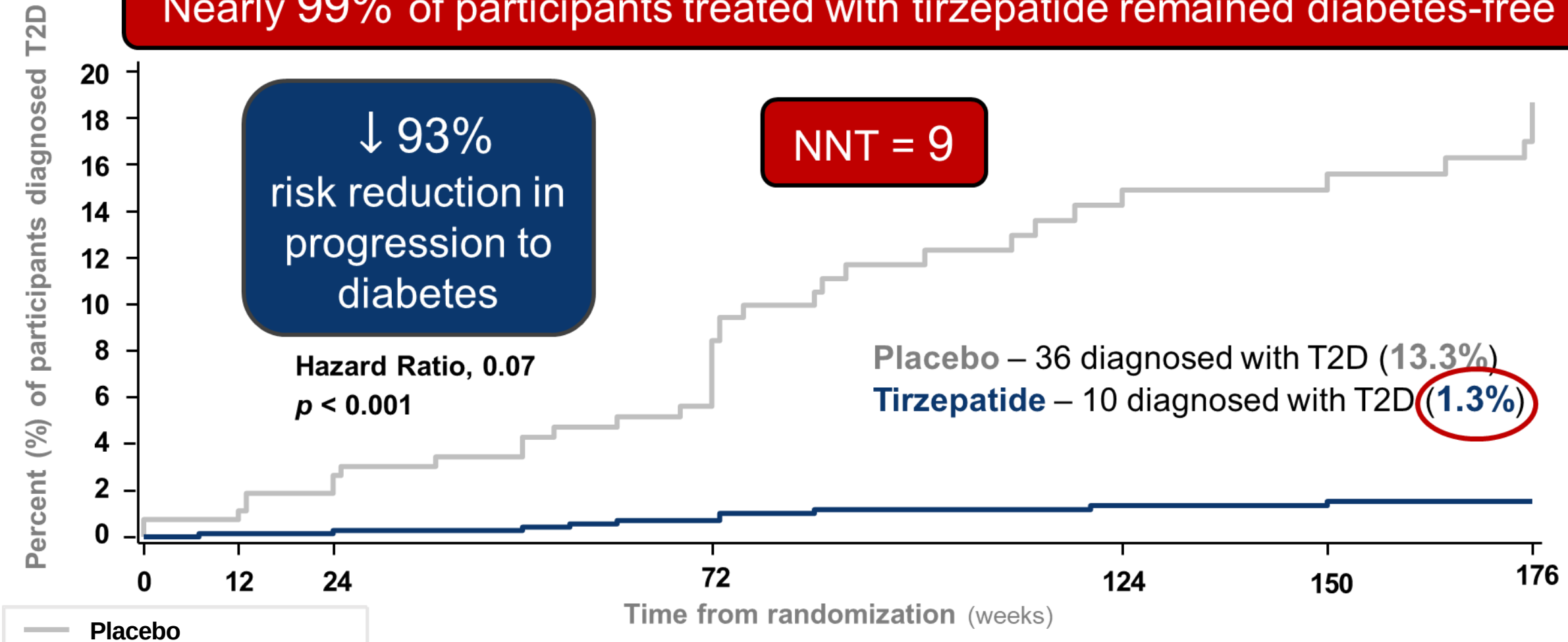
Average Weight Reduction from baseline 34.6-54.2 lbs
(15.7-24.6 kgs)
(range from 5-15 mg TZP dose arms)

Jastreboff, NEJM. *In press*

Proportion of participants diagnosed with T2D over time (pooled tirzepatide doses)

In Trial
Treatment-Regimen Estimand

Nearly 99% of participants treated with tirzepatide remained diabetes-free



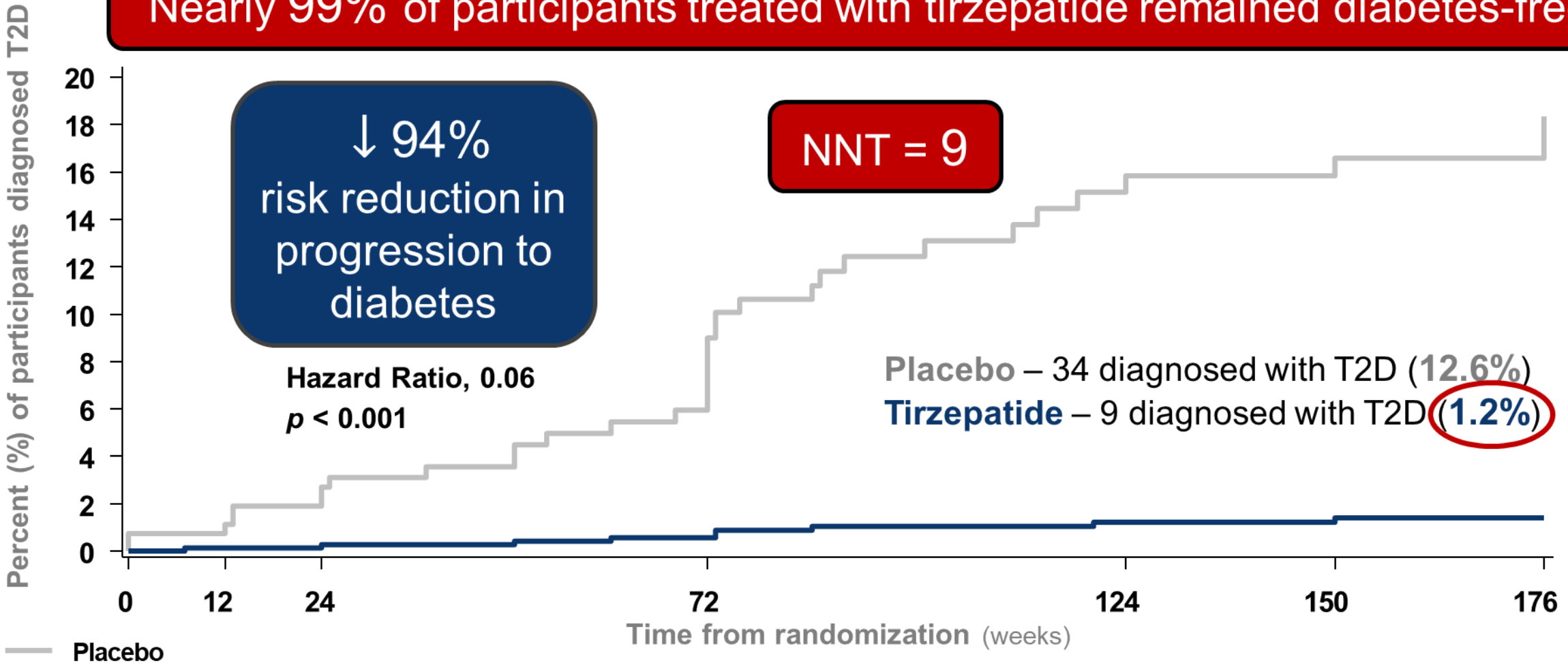
T2D = Type 2 Diabetes
NNT = Number needed to treat to prevent one case of diabetes

Jastreboff, NEJM. *In press*

Proportion of participants diagnosed with T2D over time (pooled tirzepatide doses)

On Treatment
Efficacy Estimand

Nearly 99% of participants treated with tirzepatide remained diabetes-free



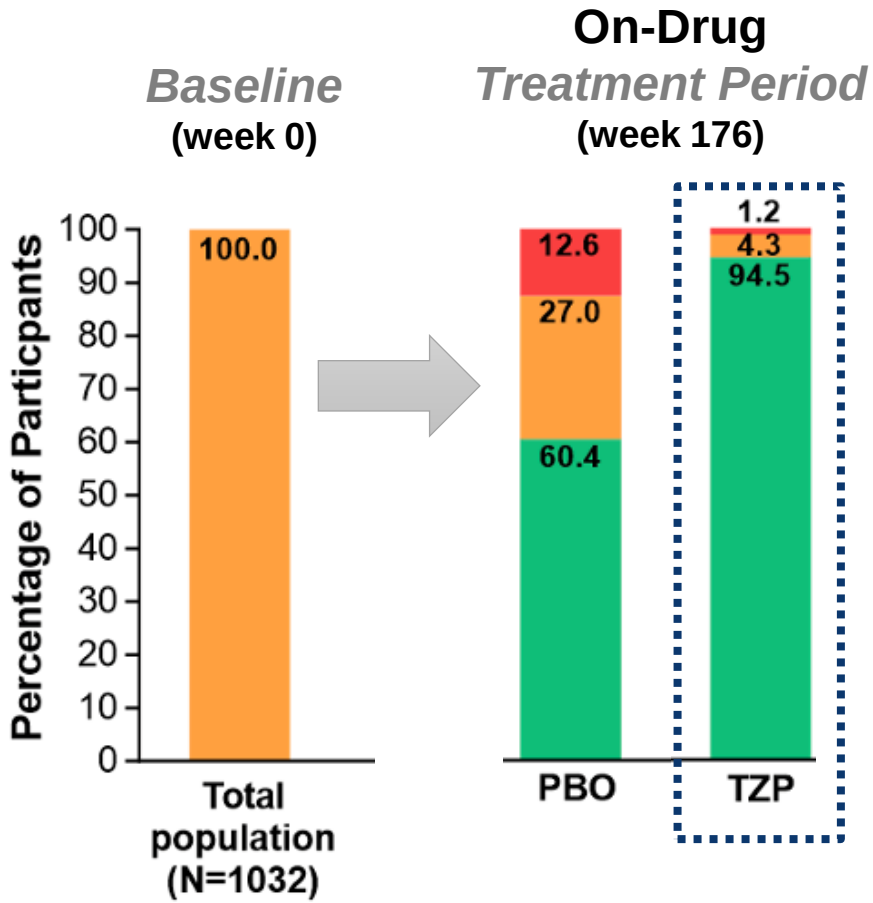
T2D = Type 2 Diabetes
NNT = Number needed to treat to prevent one case of diabetes

Jastreboff, NEJM. *In press*

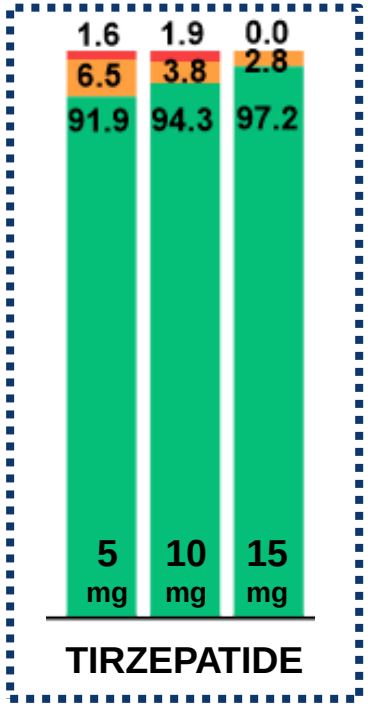
Changes in Glycemic Status at week 176

Normoglycemia
Prediabetes
Type 2 diabetes

On Treatment
Efficacy Estimand



Reversion to normoglycemia was demonstrated in nearly 95% of those who received tirzepatide vs. 60% of those who received placebo



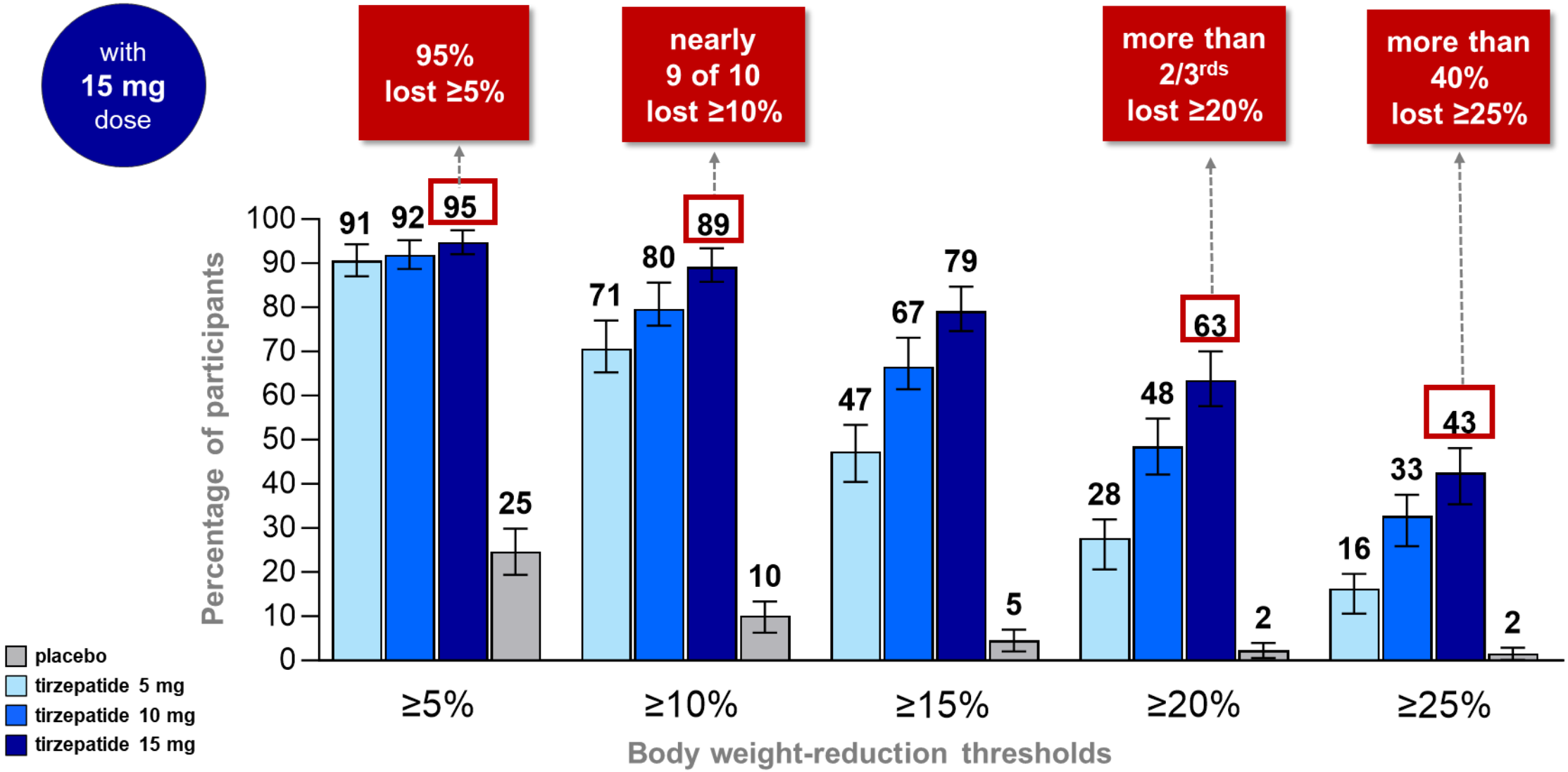
with **15 mg** dose

no participants developed diabetes and 97% reverted from prediabetes to normoglycemia

Jastreboff, NEJM. *In press*

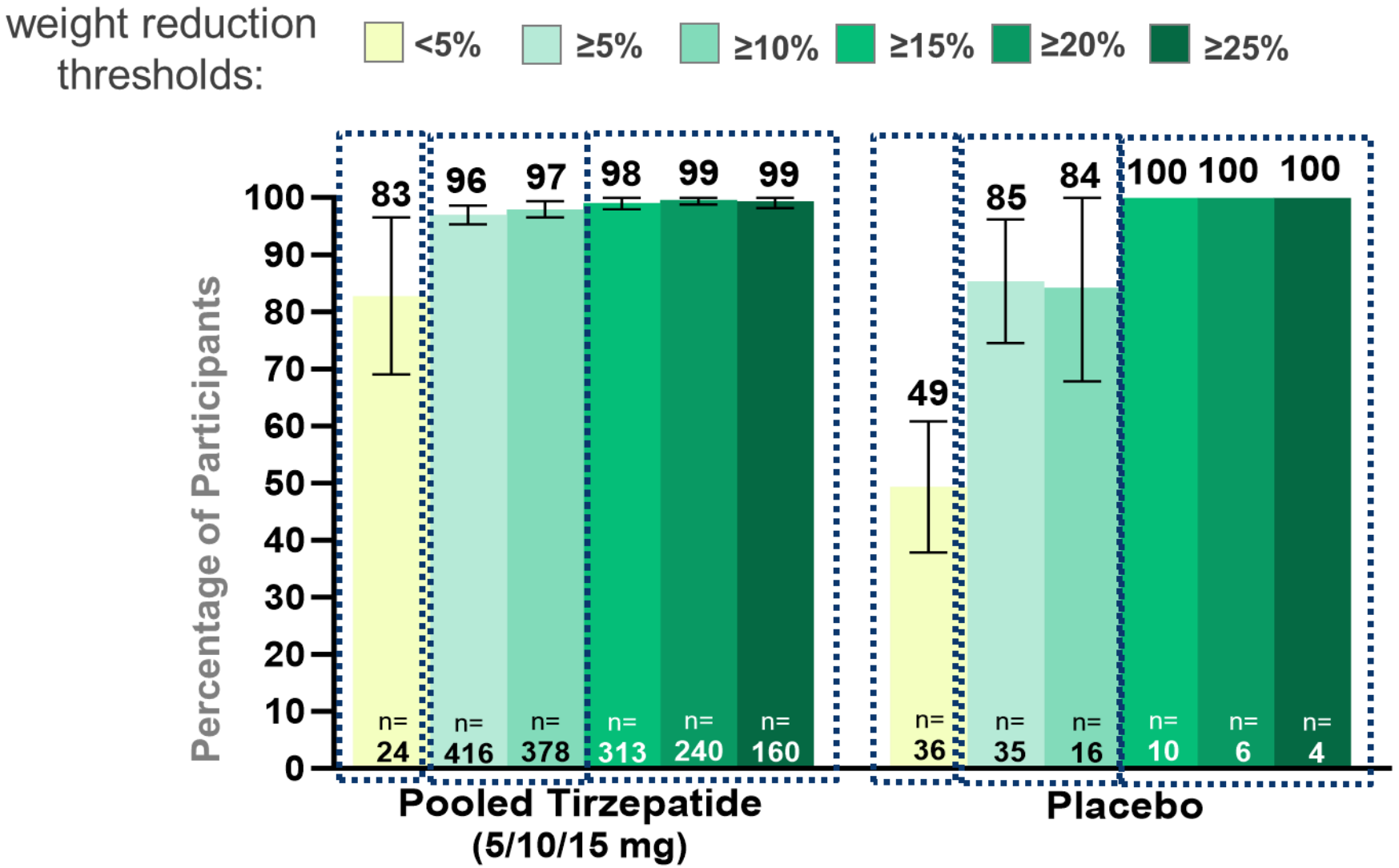
Percent of Participants Reaching Weight Reduction Thresholds (at Week 176)

On Treatment
Efficacy Estimand



Jastreboff, NEJM. *In press*

Proportion of Participants Achieving Normoglycemia by Weight Reduction Thresholds (at Week 176)



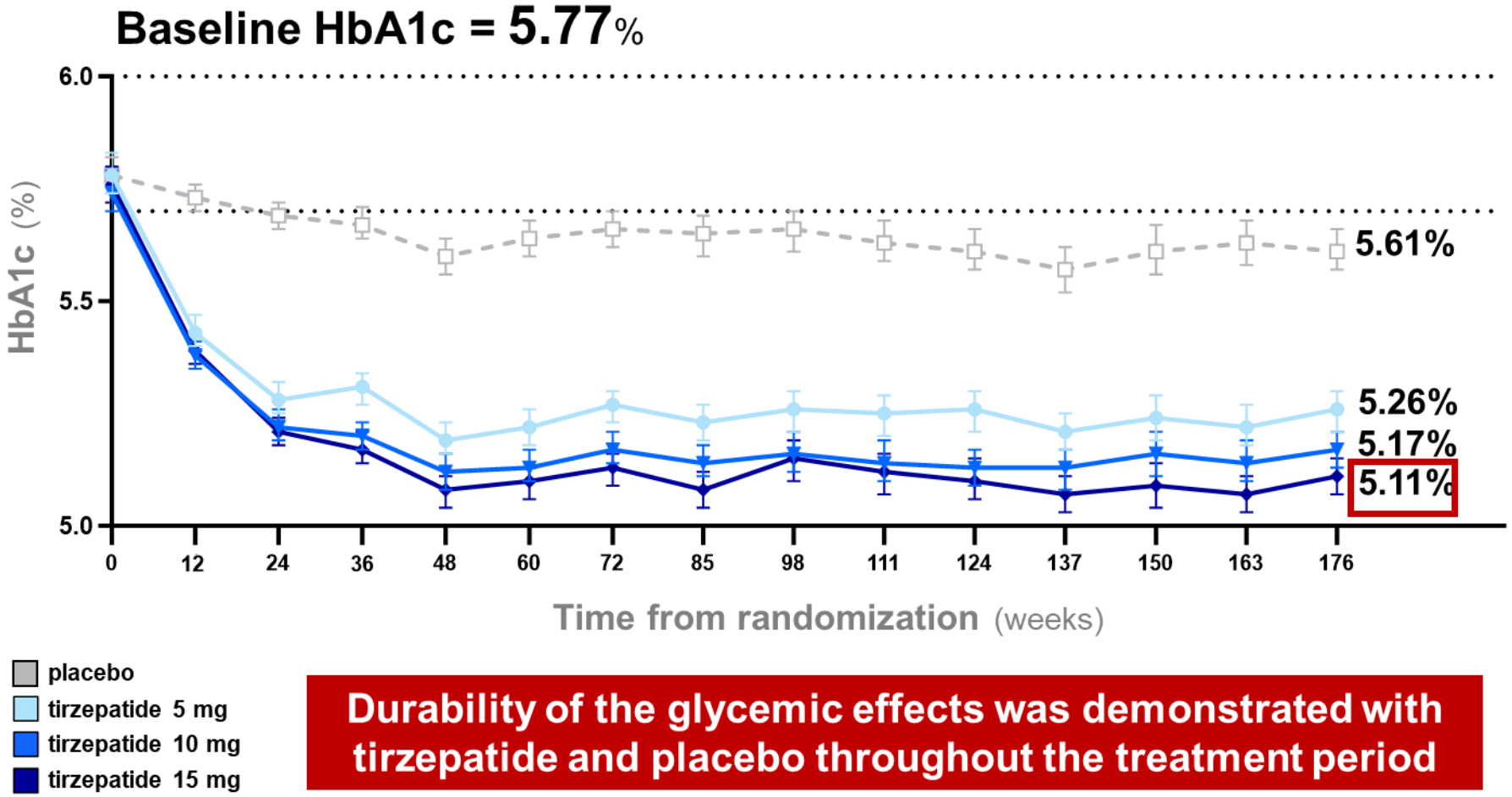
On Treatment
Efficacy Estimand

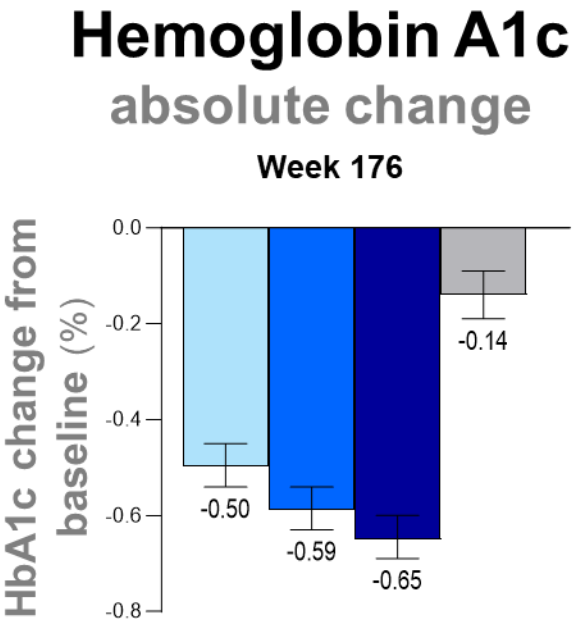
mediation analysis
55.2% of the risk reduction in developing T2D was mediated through body weight reduction
(% weight change)

Jastreboff, NEJM. *In press*

HbA1c: change over 176 weeks

On Treatment
Efficacy Estimand





Durability of the glycemic effects was demonstrated with tirzepatide and placebo throughout the treatment period

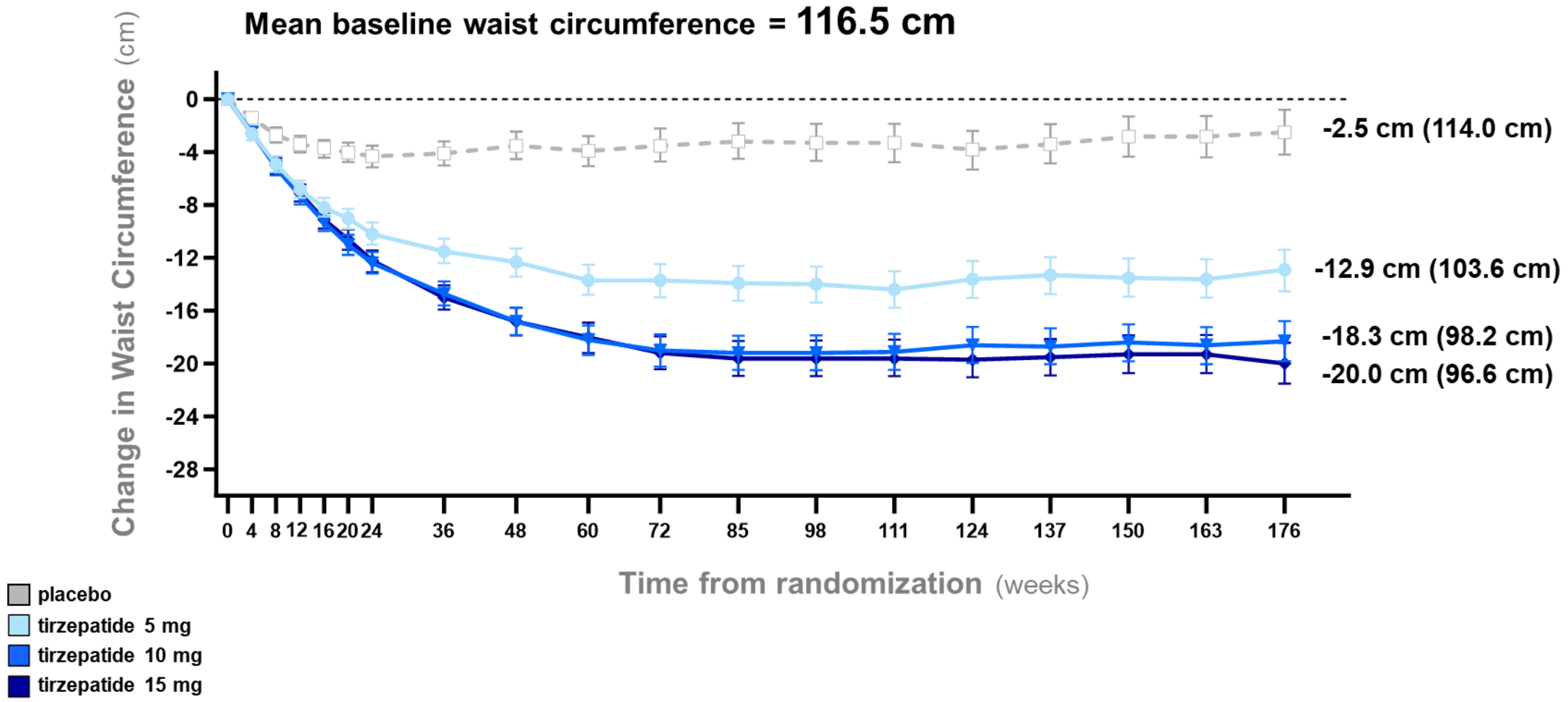
Decrease in HbA1c up to 0.65%

Jastreboff, NEJM. *In press*

Additional Cardiometabolic Outcomes

Waist Circumference: change over 176 weeks

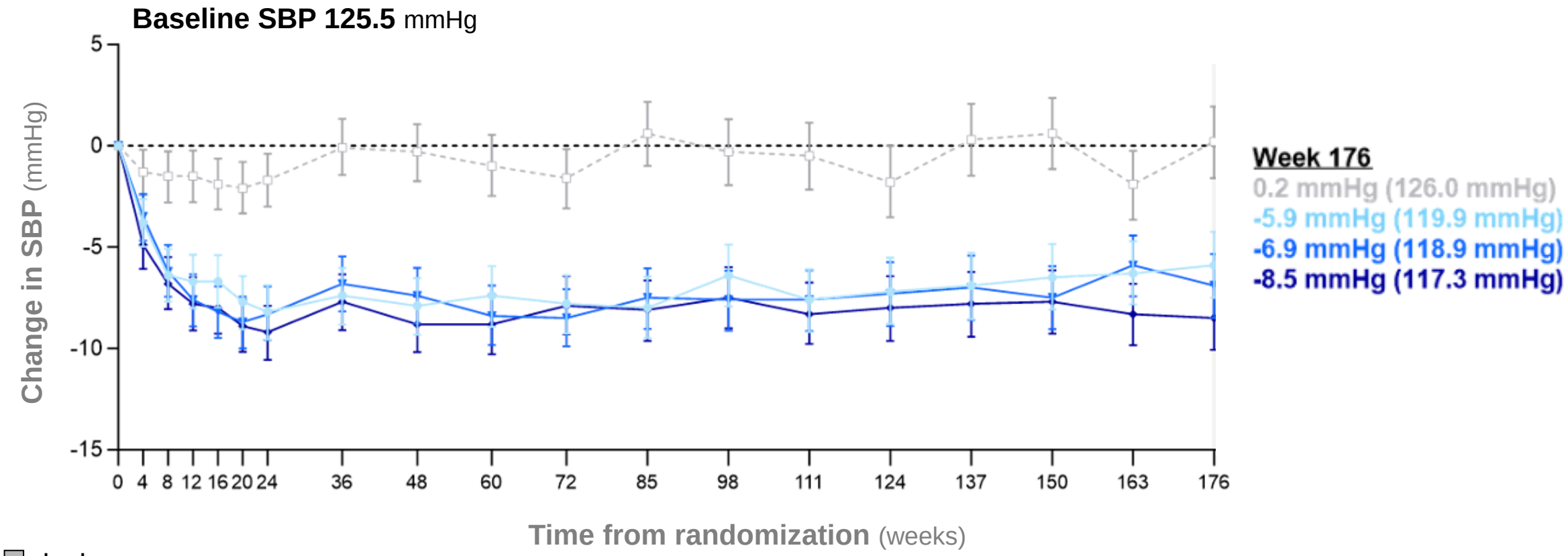
On Treatment
Efficacy Estimand



Jastreboff, NEJM. *In press*

Systolic Blood Pressure: change over 176 weeks

Safety Analysis

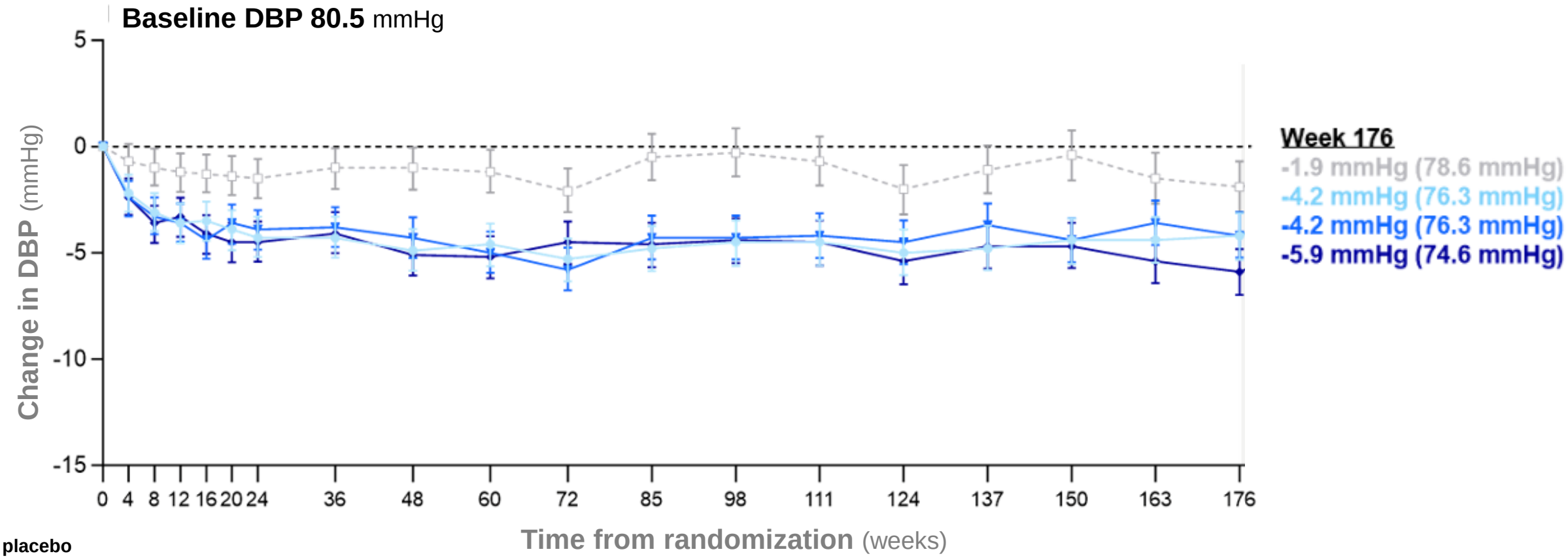


Improvement in systolic blood pressure

Jastreboff, NEJM. *In press*

Diastolic Blood Pressure: change over 176 weeks

Safety Analysis

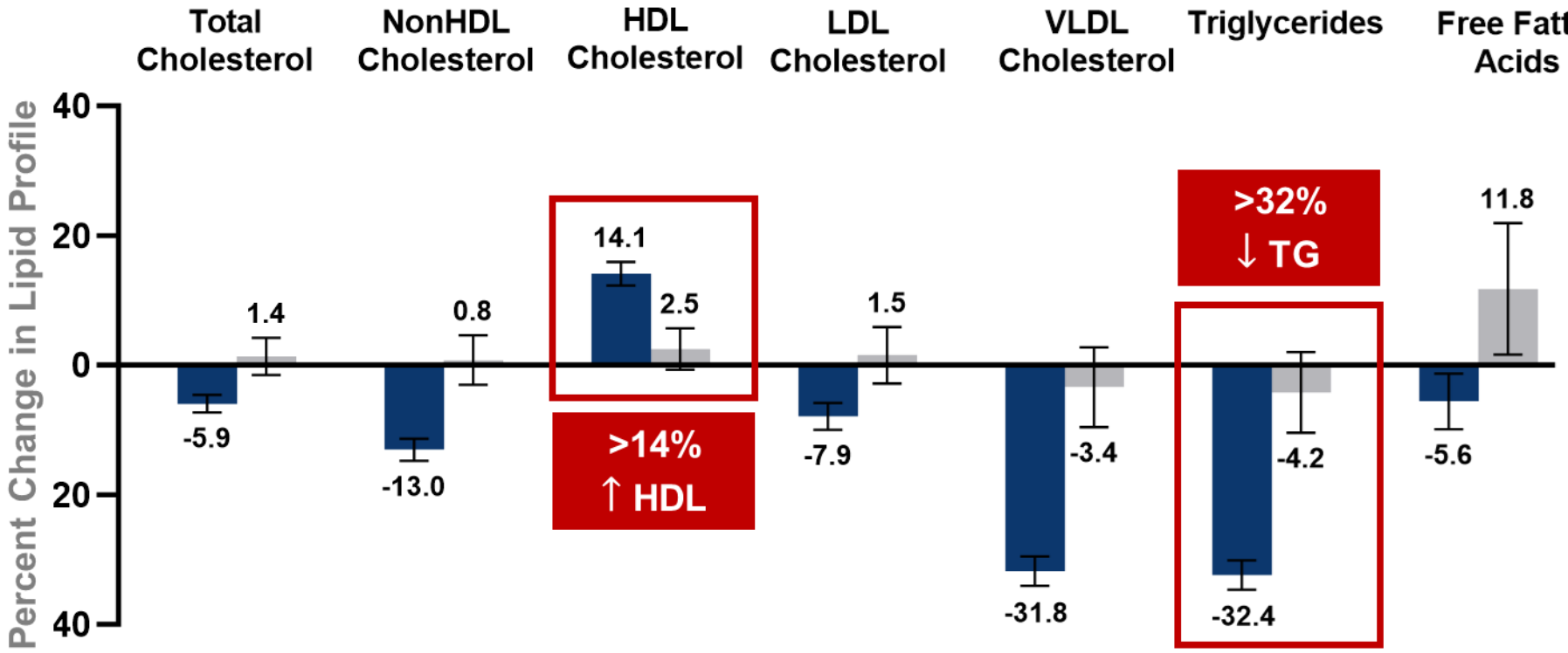


Improvement in dystolic and diastolic blood pressure

Jastreboff, NEJM. *In press*

Lipids: change at Week 176

On Treatment
Efficacy Estimand



placebo
tirzepatide pooled (5/10/15 mg)

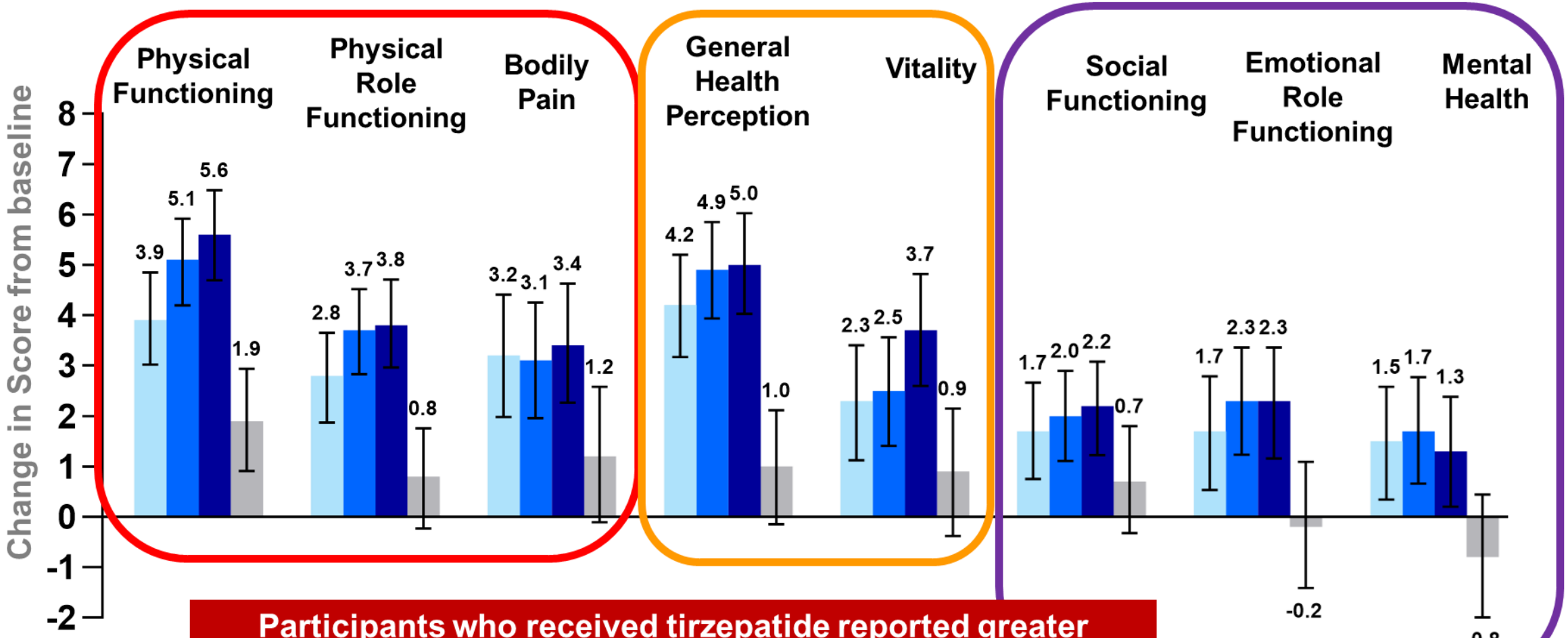
Consistent improvement in all lipid levels

Jastreboff, NEJM. *In press*

Health-Related Quality of Life: Patient Reported Outcomes

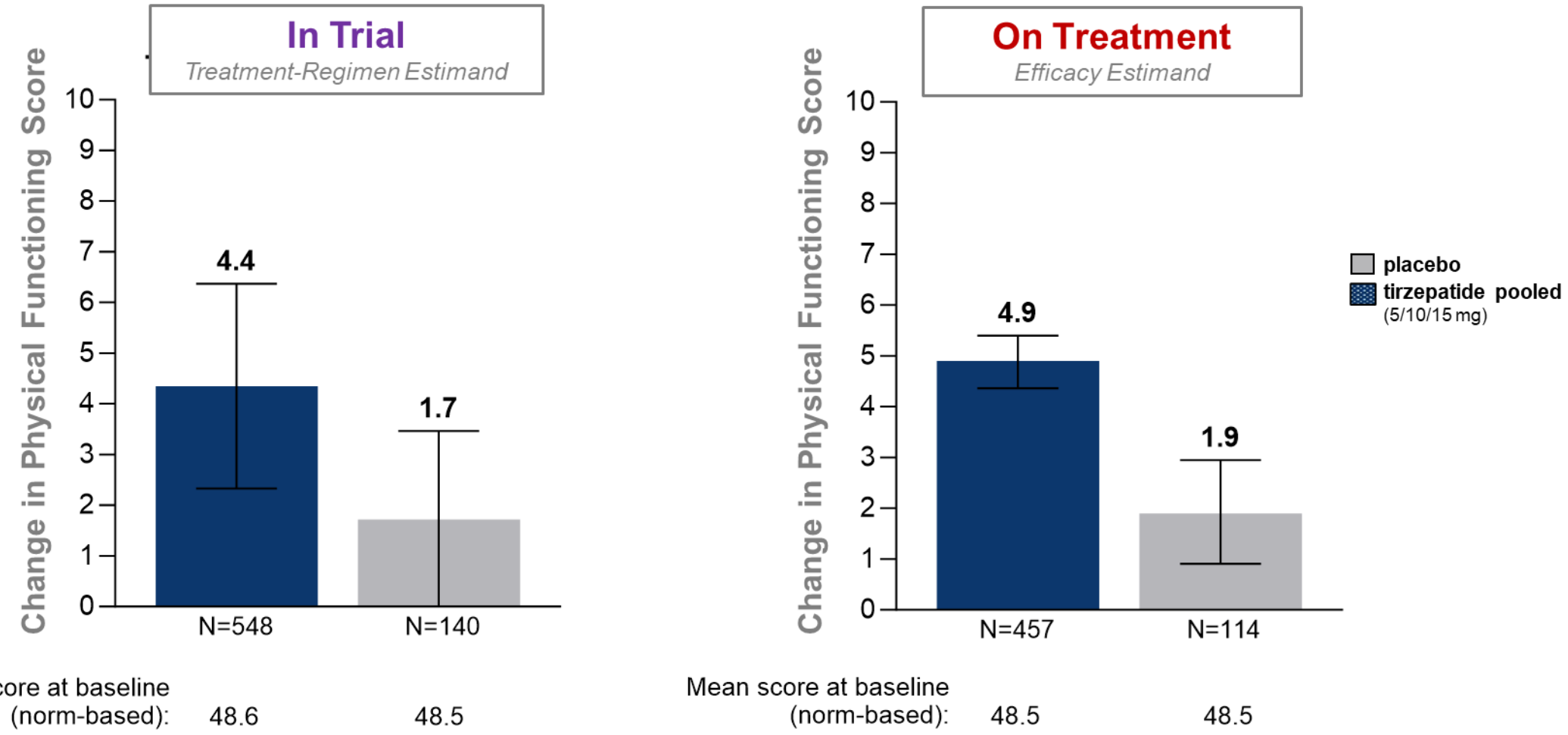
Patient Reported Outcomes:
8 Domains of SF-36 v2

On Treatment
Efficacy Estimand



Participants who received tirzepatide reported greater improvements in all domains of health-related quality of life than those who received placebo

Patient Reported Outcomes (SF-36 v2):
Physical function



Physical functioning scores significantly improved at 176 weeks compared to placebo

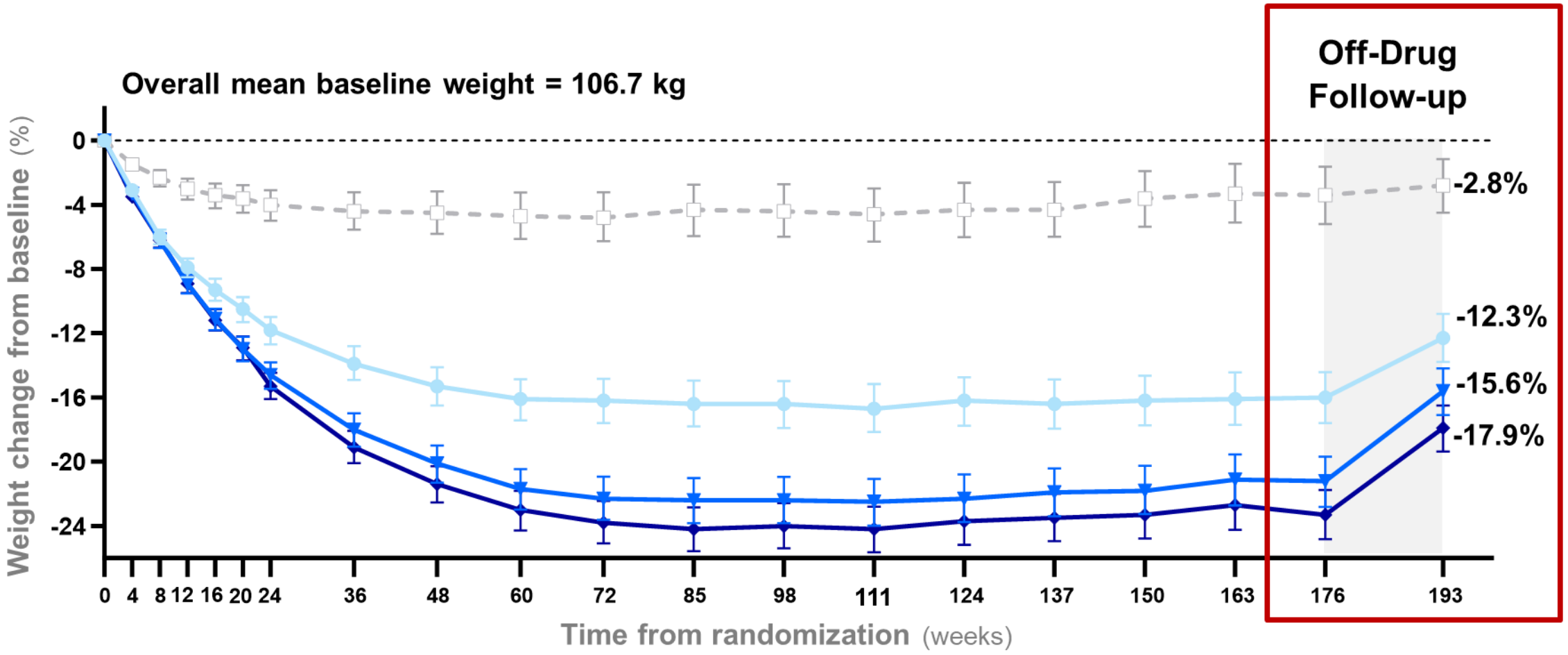
Jastreboff, NEJM. *In press*

Off-drug follow up
(193 weeks)

Off-Drug: Weight Regain
(17-week follow up)

Safety Analysis

(Week 193)



placebo
tirzepatide 5 mg
tirzepatide 10 mg
tirzepatide 15 mg

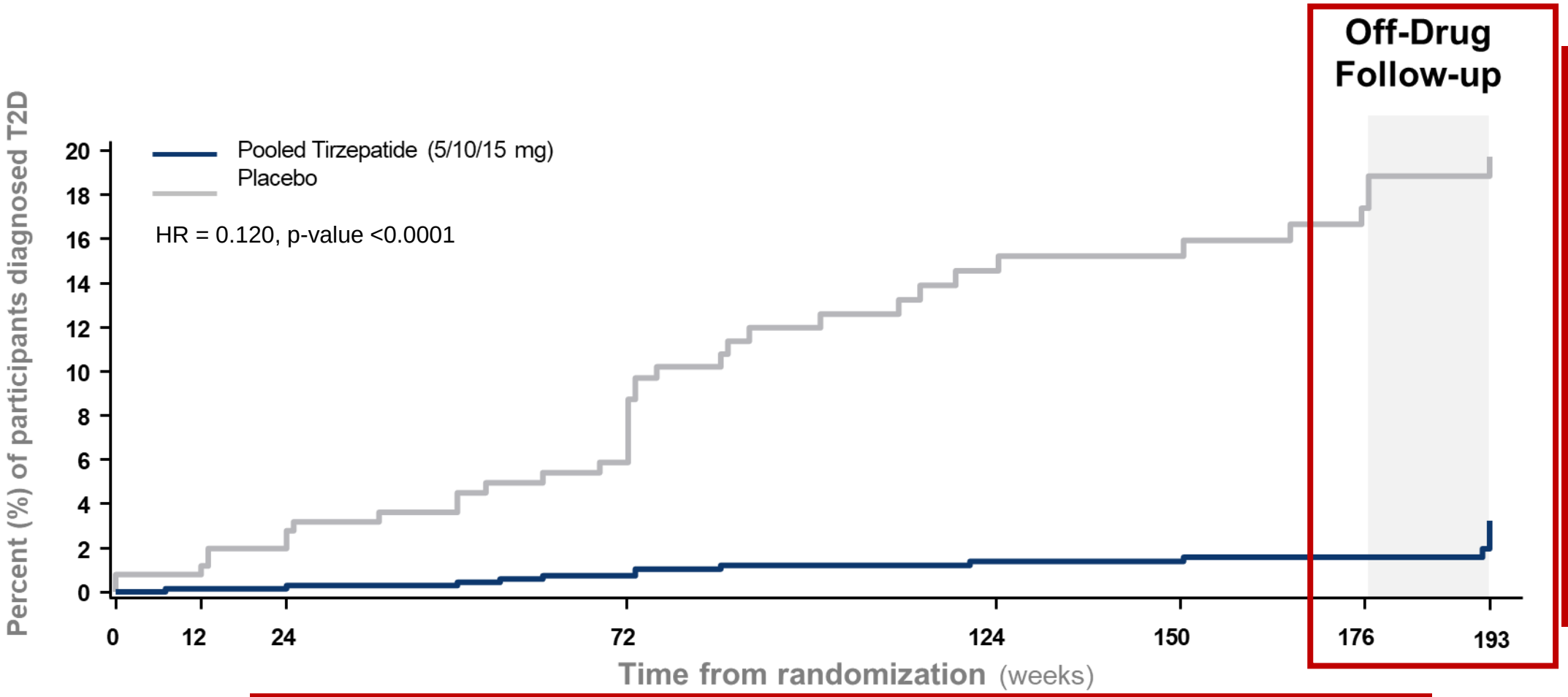
17-weeks off-drug:
Estimated average 7% weight regain

Jastreboff, NEJM. *In press*

Off-Drug: Development of T2D
(17-week follow up)

Safety Analysis

(Week 193)



After the 17-week off-drug safety follow-up, the reduction in risk of progression to adjudication-confirmed T2D was 88% compared with placebo (versus 94% at 176 weeks), possibly related to weight regain in all TZP groups.

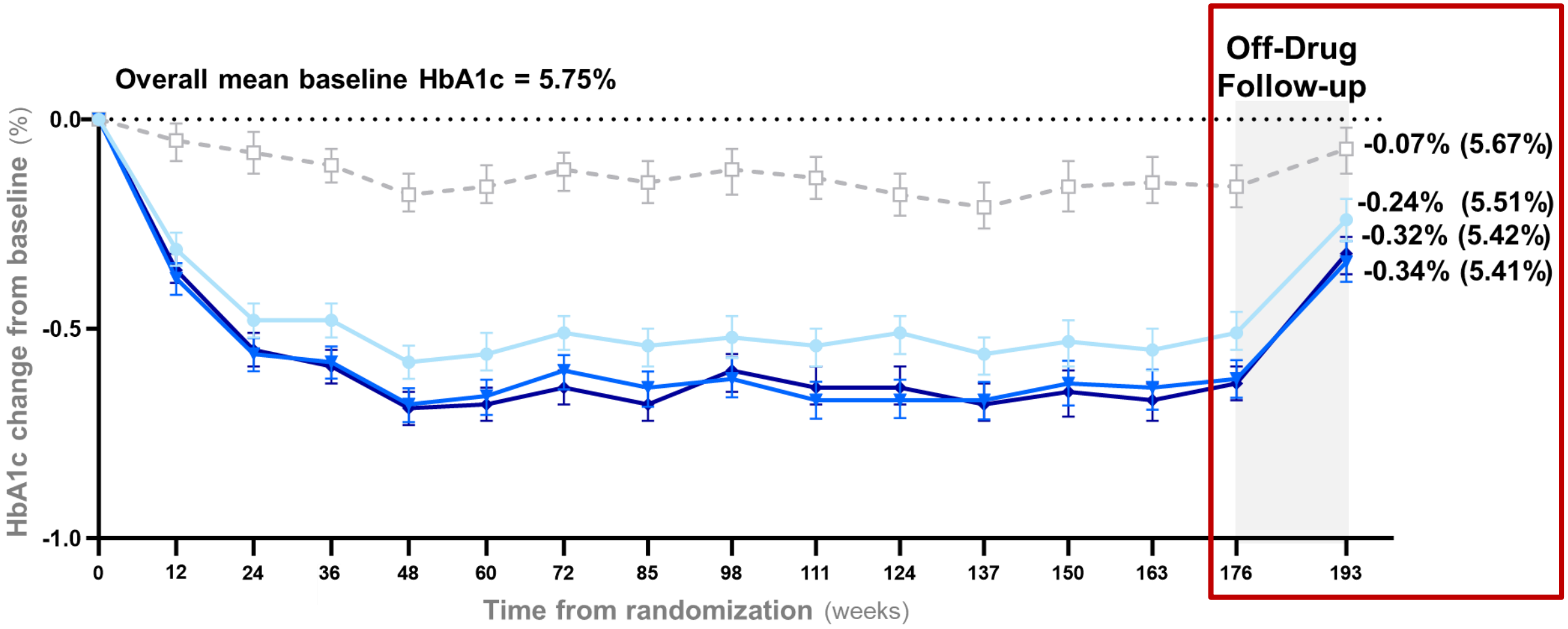
17-weeks off drug:
Eight additional participants in the tirzepatide group developed T2D, nearly doubling the number of individuals with this diagnosis

Jastreboff, NEJM. *In press*

Off-Drug: Increase in HbA1c
(17-week follow up)

Safety Analysis

(Week 193)



placebo
tirzepatide 5 mg
tirzepatide 10 mg
tirzepatide 15 mg

17-weeks off drug:
increases in HbA1c were observed in all groups

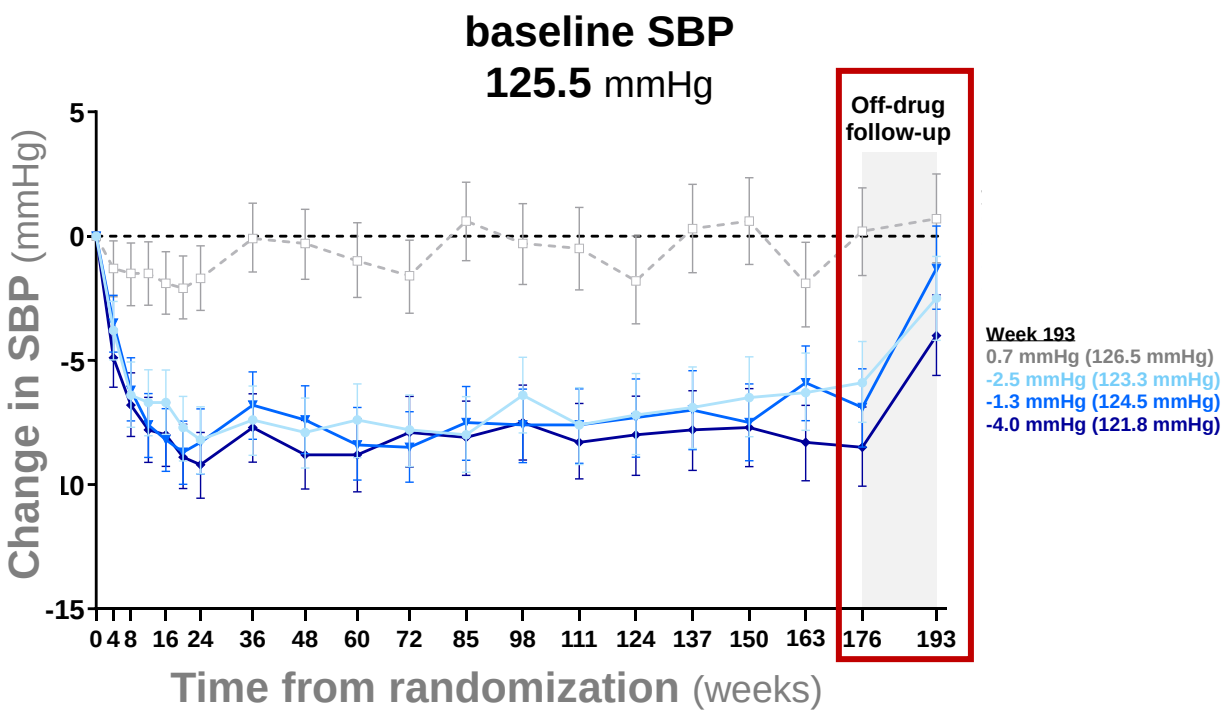
Jastreboff, NEJM. *In press*

Off-Drug: Increase in Blood Pressure
(17-week follow up)

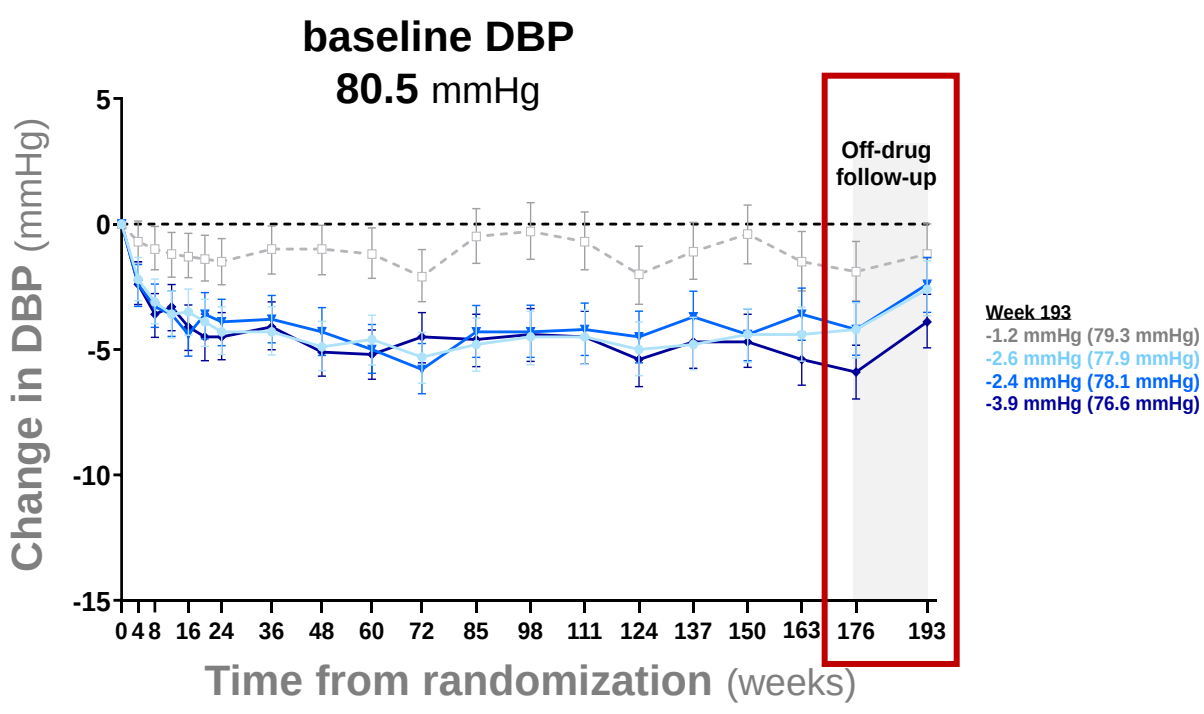
Safety Analysis

(Week 193)

Systolic Blood Pressure



Diastolic Blood Pressure



- placebo
- tirzepatide 5 mg
- tirzepatide 10 mg
- tirzepatide 15 mg

17-weeks off drug:
increases in systolic and diastolic blood pressure

Jastreboff, NEJM. *In press*

SURMOUNT-1: Summary of 3-year efficacy results

On Treatment
Efficacy Estimand

- All 3 doses of tirzepatide demonstrated statistically significant and sustained body weight reduction compared to placebo over more than 3 years

Obesity Treatment with Tirzepatide *over 3 years*

15mg

-22.9%

average absolute weight reduction **54 lbs / 25 kg**

Weight Reduction & Maintenance

more than 60% lost ≥20%

efficacy estimand

Diabetes Prevention with Tirzepatide *over 3 years*

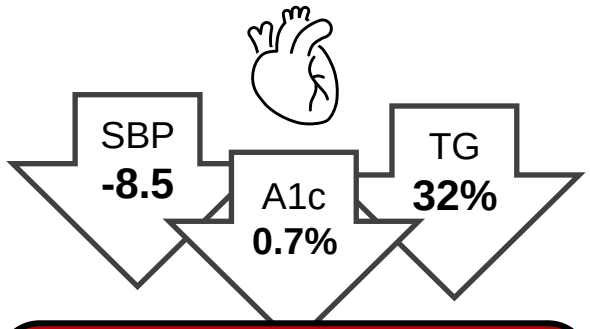
↓ 94% risk reduction in progression to diabetes

NNT = 9

Nearly 99% of participants treated with tirzepatide remained diabetes-free

nearly 95% reverted from prediabetes to normoglycemia

efficacy estimand



All prespecified cardiometabolic measures improved and were maintained

improvements in all domains of health-related quality of life

Off-drug: Weight regain in all tirzepatide groups and accompanied by worsening glycemia and development of T2D

Tirzepatide for Obesity Treatment and Diabetes Prevention:

SURMOUNT-1 Trial 3-year Weight and Glycemic Outcomes

Safety Results

Sean Wharton, MD, PharmD
Assistant Professor, Internal Medicine
University of Toronto, Canada

Overview of Adverse Events

Parameter	Placebo (N=270) n (%)	TZP 5 mg (N=247) n (%)	TZP 10 mg (N=262) n (%)	TZP 15 mg (N=253) n (%)
Treatment Emergent Adverse Events (TEAE)	223 (82.6)	210 (85.0)	230 (87.8)	219 (86.6)
Serious Adverse Events (SAE)	32 (11.9)	31 (12.6)	38 (14.5)	34 (13.4)
Deaths[a]	3 (1.1)	2 (0.8)	3 (1.1)	2 (0.8)

There was no imbalance in incidence of death between the groups.

[a]Deaths are also included as SAEs.
Patients may be counted in more than 1 category.
mITT population (safety analysis set)

Jastreboff, NEJM. *In press*

Summary of Discontinuations due to Adverse Events

Parameter	Placebo (N=270) n (%)	TZP 5 mg (N=247) n (%)	TZP 10 mg (N=262) n (%)	TZP 15 mg (N=253) n (%)
Discontinuations from Study due to Adverse Event (AE)	12 (4.4)	12 (4.9)	15 (5.7)	19 (7.5)
Discontinuations from Study treatment due to Adverse Event (AE)	16 (5.9)	18 (7.3)	25 (9.5)	31 (12.3)

Early discontinuations from study drug due to adverse events were higher in tirzepatide groups compared to placebo.

Deaths are also included as discontinuations due to AE.
mITT population – participants with prediabetes at randomization (safety analysis set)

Jastreboff, NEJM. *In press*

Adverse Events Reported as Primary Reason for Discontinuation from Study Drug

Parameter	Placebo (N=270)		TZP 5 mg (N=247)		TZP 10 mg (N=262)		TZP 15 mg (N=253)	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants with Study Drug DC due to AE or Death	16	(5.9)	18	(7.3)	25	(9.5)	31	(12.3)
Nausea	1	(0.4)	2	(0.8)	2	(0.8)	6	(2.4)
Diarrhea	0		1	(0.4)	3	(1.1)	4	(1.6)
Constipation	0		1	(0.4)	2	(0.8)	1	(0.4)
Abdominal pain	0		0		1	(0.4)	2	(0.8)
Gastrointestinal disorder	0		0		2	(0.8)	1	(0.4)
Pancreatitis acute*	0		3	(1.2)	0		0	
Flatulence	0		0		0		2	(0.8)
Blood calcitonin increased	0		0		2	(0.8)	1	(0.4)
Pulmonary embolism	2	(0.7)	0		0		0	
Rash	0		0		2	(0.8)	0	

GI adverse events were the most common reason for discontinuation from study drug due to AE in tirzepatide groups.

*Reported irrespective of adjudication result.
Only preferred terms with n≥2 in any treatment group are presented.. mITT population – participants with prediabetes at randomization (safety analysis set)

Most Common Adverse Events during Treatment that Occurred in ≥5% of Participants in any Treatment Group — n (%)

Parameter	Placebo (N=270)	TZP 5 mg (N=247)	TZP 10 mg (N=262)	TZP 15 mg (N=253)
COVID-19	62 (23.0)	72 (29.1)	79 (30.2)	67 (26.5)
Nausea	32 (11.9)	60 (24.3)	86 (32.8)	80 (31.6)
Diarrhea	27 (10.0)	49 (19.8)	75 (28.6)	65 (25.7)
Constipation	22 (8.1)	46 (18.6)	57 (21.8)	40 (15.8)
Dyspepsia	15 (5.6)	19 (7.7)	29 (11.1)	36 (14.2)
Decreased appetite	9 (3.3)	26 (10.5)	35 (13.4)	27 (10.7)
Headache	26 (9.6)	21 (8.5)	26 (9.9)	19 (7.5)
Vomiting	4 (1.5)	19 (7.7)	28 (10.7)	36 (14.2)
Upper respiratory tract infection	16 (5.9)	16 (6.5)	19 (7.3)	20 (7.9)
Back pain	13 (4.8)	18 (7.3)	20 (7.6)	16 (6.3)
Arthralgia	16 (5.9)	19 (7.7)	15 (5.7)	16 (6.3)
Urinary tract infection	15 (5.6)	10 (4.0)	19 (7.3)	18 (7.1)
Abdominal pain	9 (3.3)	18 (7.3)	17 (6.5)	13 (5.1)

GI adverse events were the most common AEs in tirzepatide groups.

Treatment-Emergent Adverse Events of Special Interest

Parameter	Placebo (N=270)		TZP 5 mg (N=247)		TZP 10 mg (N=262)		TZP 15 mg (N=253)	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants with ≥1 TEAE of:								
Severe or serious arrhythmias and cardiac conduction disorders	1	(0.4)	3	(1.2)	3	(1.1)	3	(1.2)
Severe or serious gastrointestinal events	5	(1.9)	6	(2.4)	15	(5.7)	6	(2.4)
Severe or serious hepatic events	0		1	(0.4)	1	(0.4)	1	(0.4)
Immediate severe or serious hypersensitivity events	0		0		1	(0.4)	0	
Non-Immediate severe or serious hypersensitivity events	0		0		1	(0.4)	1	(0.4)
Malignancies	4	(1.5)	8	(3.2)	4	(1.5)	6	(2.4)
Severe or serious major depressive disorder or suicidal ideation events	0		0		1	(0.4)	0	
Severe or serious renal disorders	0		2	(0.8)	1	(0.4)	2	(0.8)
C-cell hyperplasia and thyroid malignancies	1	(0.4)	0		0		2	(0.8)
Adjudication-confirmed MACE	7	(2.6)	2	(0.8)	7	(2.7)	2	(0.8)
Adjudication-confirmed pancreatitis	1	(0.4)	2	(0.8)	1	(0.4)	0	
Severe or serious acute gallbladder diseases	2	(0.7)	3	(1.2)	10	(3.8)	9	(3.6)
Hypoglycemia (blood glucose <54 mg/dl)	0		8	(3.2)	6	(2.3)	5	(2.0)

mITT population – participants with prediabetes at randomization (safety analysis set)

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Gallbladder-related Adverse Events – n (%)

Reported as Treatment-Emergent Adverse Events	Placebo (N=270)	TZP 5 mg (N=247)	TZP 10 mg (N=262)	TZP 15 mg (N=253)
Cholelithiasis	5 (1.9)	5 (2.0)	8 (3.1)	9 (3.6)
Cholecystitis	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Acute cholecystitis	1 (0.4)	1 (0.4)	3 (1.1)	1 (0.4)
Chronic cholecystitis	0	1 (0.4)	0	4 (1.6)

Cholelithiasis was observed more frequently with tirzepatide, consistent with other obesity therapies (e.g. metabolic surgery or injectable incretin-based medicines).

mITT population – participants with prediabetes at randomization (safety analysis set)
Safety end points were analyzed with data from all the participants who underwent randomization and took at least one dose of tirzepatide or placebo.
Adverse events are listed according to Medical Dictionary for Regulatory Activities, version 27.0, preferred terms.

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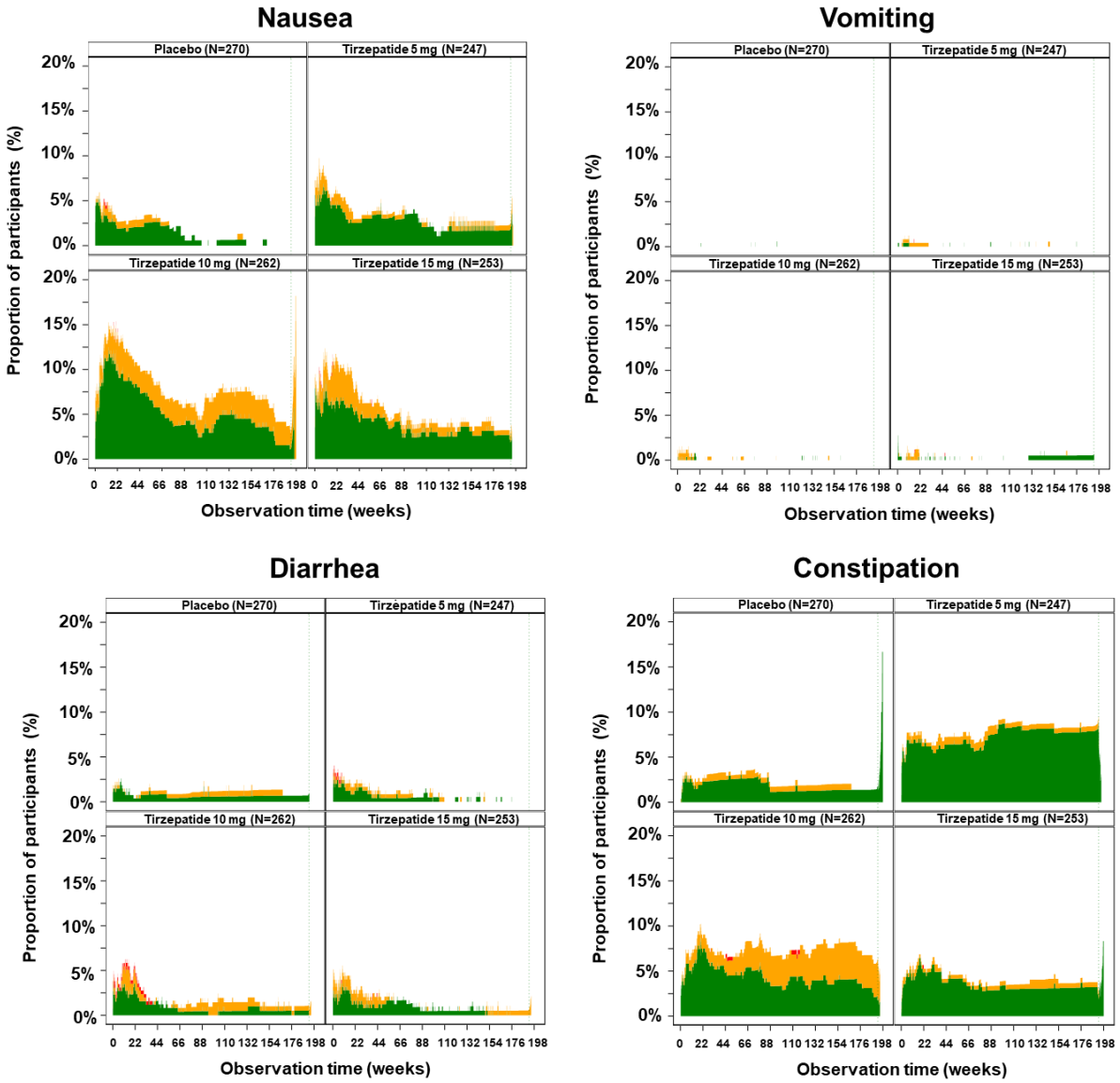
Prevalence of Gastrointestinal Adverse Events over Time

Severity:
- Mild
- Moderate
- Severe



Most of AEs of nausea, vomiting and diarrhea occurred primarily during the dose-escalation period and were mostly mild-to-moderate in severity.

Note: Proportions are based on number of participants at risk.

mITT population – participants with prediabetes at randomization (safety analysis set)

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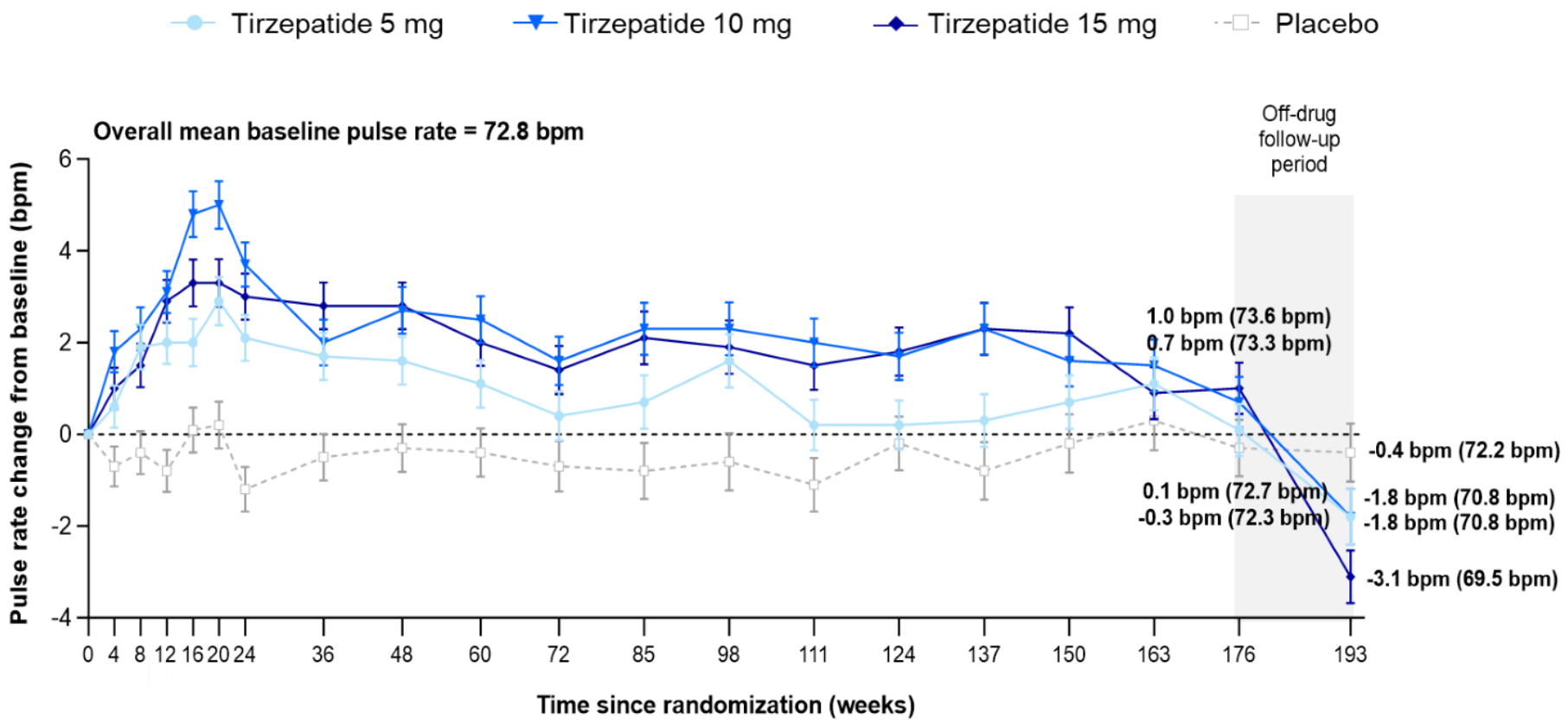
Change from Baseline in Pulse Rate Over Time



The magnitude of pulse rate increase with all tirzepatide doses was consistent with earlier observations with injectable, incretin-based therapies for obesity.

LSM change from baseline in pulse rate over time through safety follow-up from the mITT population in participants with prediabetes at randomization (safety analysis set). MMRM by treatment and visit from baseline to week 193.

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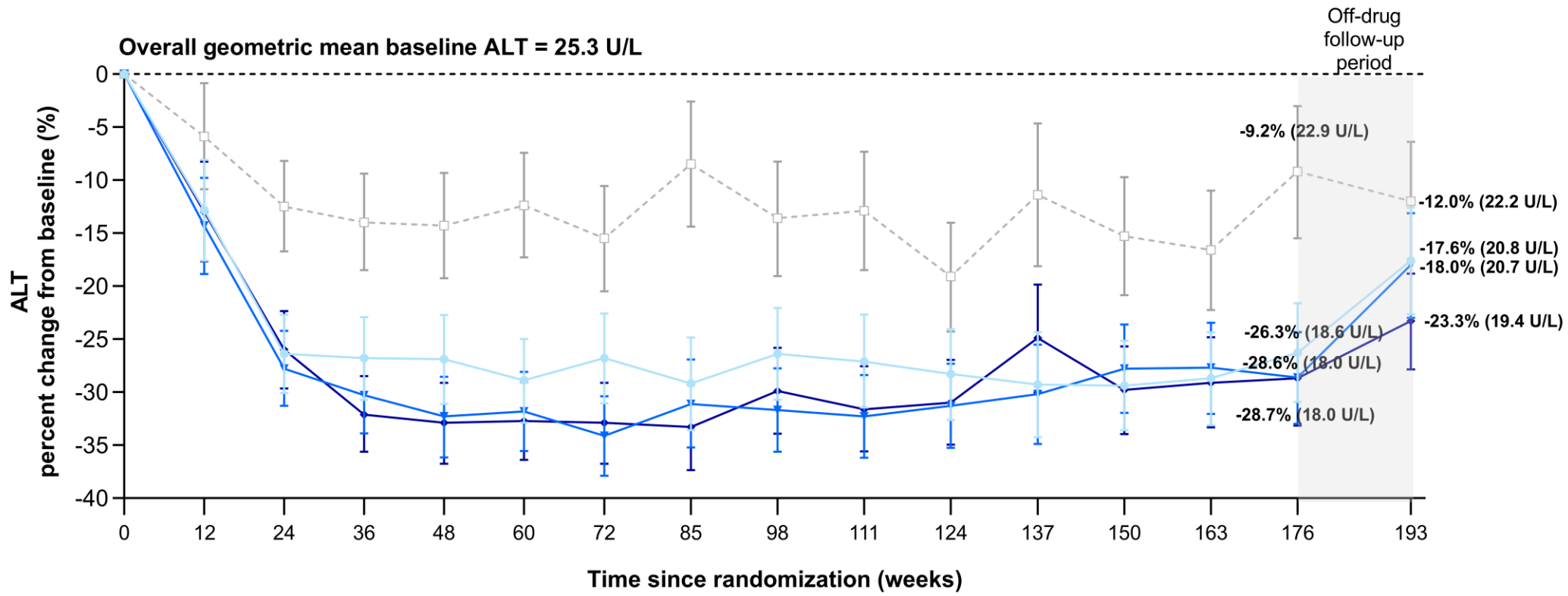
Change in Alanine Aminotransferase (ALT) Over Time



Mean ALT activity decreased with tirzepatide over the course of the treatment period.

MMRM analysis, mITT population – participants with prediabetes at randomization (safety analysis set).

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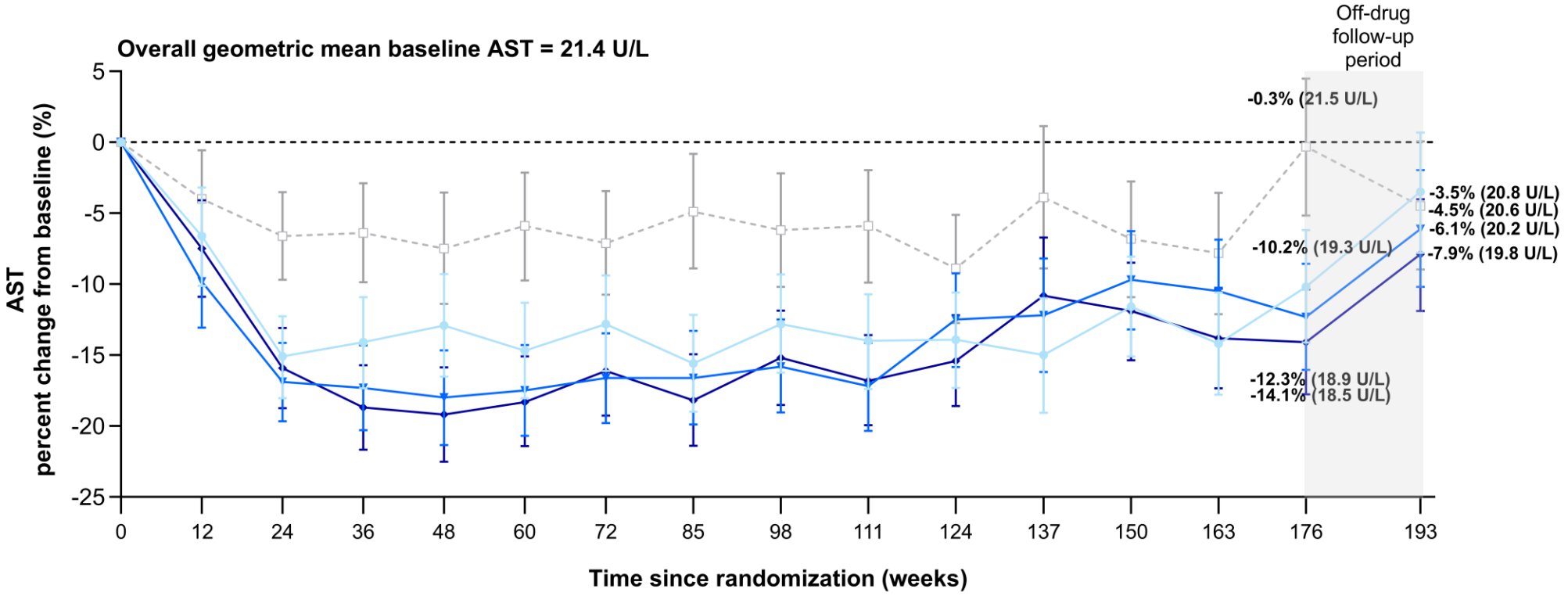
Change in Aspartate Aminotransferase (AST) Over Time



Mean AST activity decreased with tirzepatide over the course of the treatment period.

MMRM analysis, mITT population – participants with prediabetes at randomization (safety analysis set).

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Summary of Safety

The tolerability and safety profile of tirzepatide in this study of 3 years and 9 months duration was generally consistent with incretin-based therapies in people with obesity.

- The most common adverse events were gastrointestinal, generally mild to moderate in severity, occurring primarily during dose escalation.
- Among adverse events, the most common reasons for discontinuation of the medication were GI AEs.
- Gallbladder disease events were reported more frequently in participants from the tirzepatide 10 mg and 15 mg groups, compared to the placebo group.
  - The finding was mainly due to the increased incidence of cholelithiasis.

No new safety signals were observed in the 3-year SURMOUNT-1 study.

Thank You

We express our appreciation for the participants of this study, and the investigators and study coordinators, who cared for them, and the study sponsor, Eli Lilly.