

EASD
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The Landscape of Treatments for Obesity in Patients With Type 2 Diabetes

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Disclosures

CONSULTING FEES (PAID TO UNIVERSITY OF LIVERPOOL):

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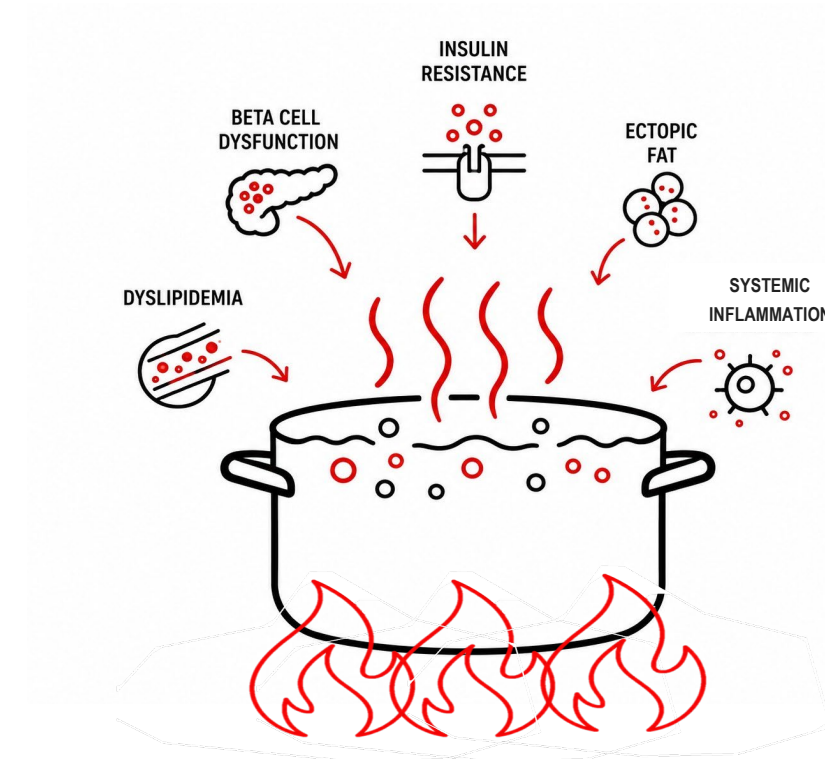
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RESEARCH SUPPORT (PAID TO UNIVERSITY OF LIVERPOOL / HOSPITAL TRUST):

- Amgen
- Eli Lilly
- Novo Nordisk
- Rhythm Pharmaceuticals

Type 2 Diabetes - Pathophysiology



Obesity/excess adiposity

Type 2 Diabetes

The '*Melting Pot*' of metabolic derangements that leads to vascular complications¹⁻⁶



MICROVASCULAR

- Retinopathy
- Nephropathy
- Neuropathy

MACROVASCULAR

- Coronary Artery Disease
- Stroke
- Peripheral Artery Disease

It's Time to Bring Obesity/Excess Adiposity Management Front and Center to Treatment Goals for Type 2 Diabetes...



Current Emphasis: Glucose Management¹

- Manage blood glucose
- Avoid metabolic derangements
- Reduce risk of downstream micro- and macrovascular complications
- Avoid/delay consequences of T2D

Proposed New Standard: Weight + Glucose Management^{2,3}

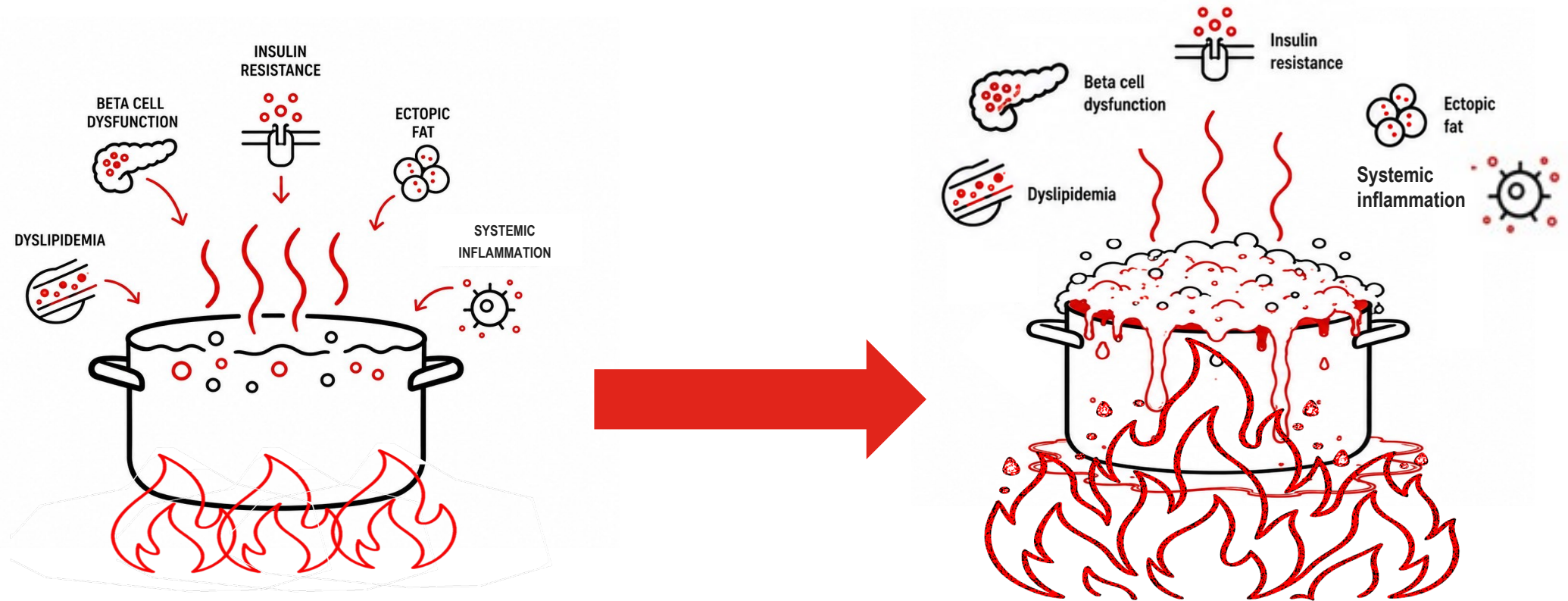
- Manage excess adiposity **first** to reduce risk of hyperglycemia and metabolic derangements **and**
- Delay or avoid vascular complications

Future Aim: Holistic Management of the Patient^{4,5,6}

- Weight + glucose management, prevent complications, **and**
- Improve overall HRQoL
- Manage other ORCs

Holy Grail
“Remission of T2D”

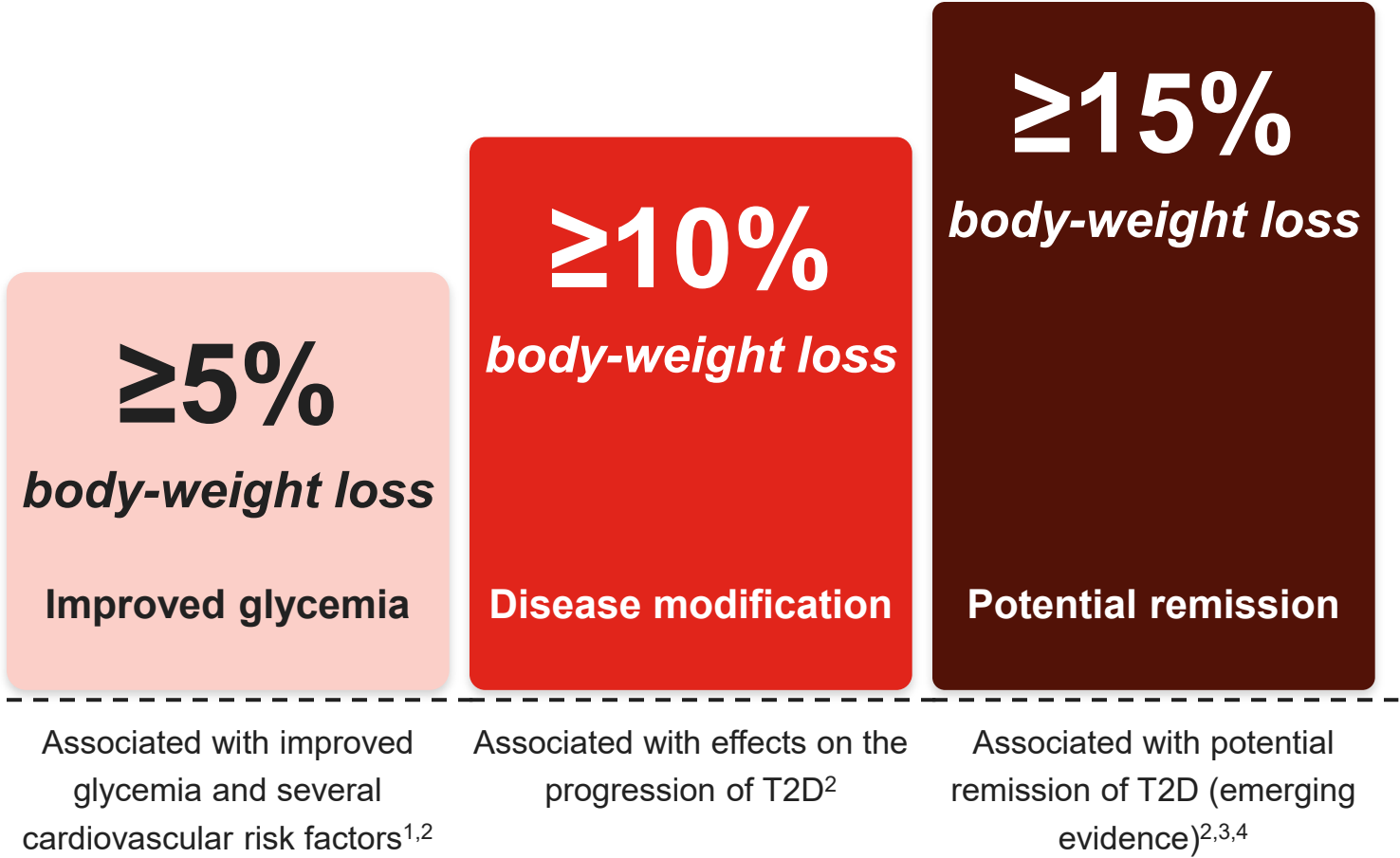
... Because if we Don't, Then...



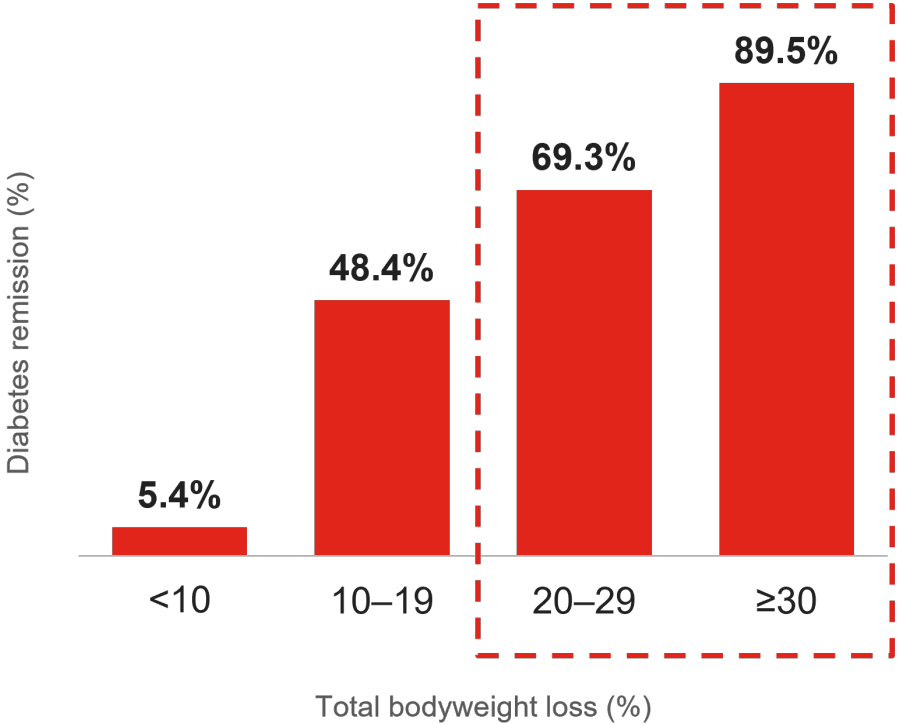
Obesity/Excess Adiposity

Will Continue to Fuel the Metabolic Derangement of Type 2 Diabetes¹⁻⁶

Greater Weight Loss in Type 2 Diabetes is Associated With Improved Metabolic Outcomes



T2D remission rises steeply with greater weight loss (Meta-regression analysis)^{a,5}



^aPartial remission defined as HbA1c <6.5% [48 mmol/mol] or FPG <126 mg/dL [7.0 mmol/L].
1. Ryan DH, et al. *Curr Obes Res.* 2017;6:187-194. 2. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care.* 2026;49(Suppl. 1):S166–S182. 3. Lean MEJ, et al. *Lancet.* 2018;391:541-551.
4. Lean MEJ, et al. *Lancet Diabetes Endocrinol.* 2019;7:344-355. 5. Kanbour S, et al. *Lancet Diabetes Endocrinol.* 2025. doi:10.1016/S2213-8587(24)00346-2.
T2D=type 2 diabetes.

Options for Weight Loss Management in Type 2 Diabetes

Three approaches to achieving weight loss in type 2 diabetes



Lifestyle Interventions^{1,2}

- Diet, physical activity, and behavioral support
- Can drive remission in early T2D
- Benefit fades without sustained weight loss



Bariatric Surgery^{4,5}

- Sleeve gastrectomy, or gastric bypass
- Largest, sustained weight reduction in T2D
- Invasive, not scalable



Pharmacological Interventions^{2,3}

- Incretin-based and other obesity management therapies
- Substantial, sustained weight loss and glycemic control
- Scalable, non-surgical option

1. Lean MEJ, et al. *Lancet*. 2018;391:541-551. 2. Wilding JPH, et al. *N Engl J Med*. 2021;384:989-1002. 3. Jastreboff AM, et al. *N Engl J Med*. 2022;387:205-216. 4. Schauer PR, et al. *N Engl J Med*. 2017;376:641-651. 5. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026; ;49(Suppl. 1):S166–S182.
T2D=type 2 diabetes.

Benefits and Challenges of Weight Management in Patients With T2D by *Lifestyle Intervention*



Benefits

- DiRECT trial: intensive weight management (≥ 15 kg loss) can drive remission in early T2D^{1,2}
 - **Year 1:** 46% achieved remission; 24% lost ≥ 15 kg
 - **Year 2:** 36% remission; 11% maintained ≥ 15 kg loss
- Improved blood pressure, lipids, and quality of life
- Remission durability depends on sustained weight loss

Challenges

- Long-term maintenance of weight loss is difficult
- Calorie restriction triggers lasting metabolic adaptation, including increased appetite and reduced EE (up to 12 months)³
- **DiRECT 5-year follow-up⁴:**
 - T2D remission fell to 13% in Year 5
 - HbA1c rose above baseline; blood pressure returned to baseline

T2D remission is possible with ≥ 15 kg weight loss, but sustaining the loss and its benefits long-term remains difficult with lifestyle intervention alone

Benefits and Challenges of Weight Management in Patients With T2D by *Bariatric Surgery*



Benefits

- Large, sustained weight loss improves glycemic control and long-term T2D outcomes
- Long-term (3–11 years) outcomes of bariatric surgery¹⁻³:
 - Up to 25% reduction in weight and BMI^{1,3}
 - Greater than 1.0% HbA1c reduction; ≥47% T2D remission^{b,1-2}
 - Improved lipid levels and blood pressure¹

Challenges

- Risk of peri-/post-operative events (obstruction, anastomosis issues, reflux, nutritional deficiencies, hypoglycemia)^{1,3}
- Requires high-volume centers with specialist surgical teams and lifelong follow-up^{2,4}
- Hard to scale; eligibility criteria vary⁴

Bariatric surgery offers the largest weight reduction, but is invasive and difficult to scale

^aMeta-analyses, long-term is between 3 and 11 years post-bariatric procedure (RYGB, GS, SG). ^bRemission defined as HbA1c <6.5% and not receiving any medications for diabetes; time post-procedure ≥1 year.

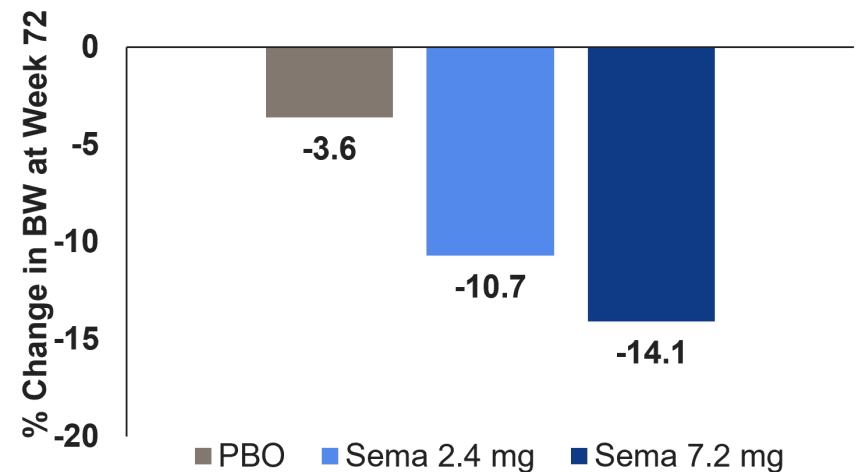
1. Kim JC, et al. *J Metab Bariatr Surg*. 2023;12:76-88. 2. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026; ;49(Suppl. 1):S166–S182. 3. Arterburn D, et al. *Ann Intern Med*. 2018;169:741-750. 4. Eisenberg D, et al. *Surg Obes Relat Dis* 2022; 18:1345-1356.

BMI=body mass index; HbA1c=glycated hemoglobin; T2D=type 2 diabetes.

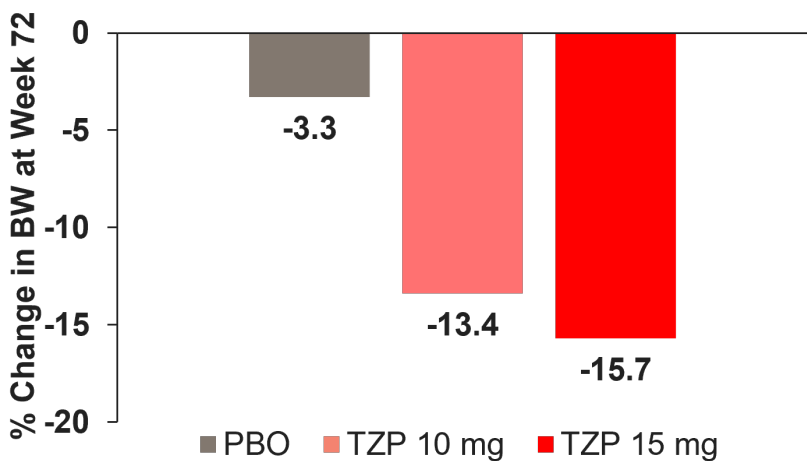
A Ceiling of ~15% Weight Reduction With Current Incretin-Based Therapies for Type 2 Diabetes at Highest Dose



GLP-1 RA¹
Semaglutide



GIP/GLP-1 RA²
Tirzepatide



Weight reduction threshold achieved, %	PBO	SEMA 2.4 mg	SEMA 7.2 mg
≥15%	8.3	30.4	43.2
≥20%	2.4	15.2	22.5

Weight reduction threshold achieved, %	PBO	TZP 10 mg	TZP 15 mg
≥15%	2.6	41.4	51.8
≥20%	1.0	23.0	34.0

1. Lingvay I, et al. *Lancet Diabetes Endocrinol.* 2025;13:935-948. 2. Garvey WT, et al. *Lancet.* 2023;402:613-626.
GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide 1; PBO=placebo; RA=receptor agonist; SEMA=semaglutide; TZP=tirzepatide.

Let's Dissect These Clinical Trials Data and Connect to Clinical Practice



These are Mean Values

Approximately **50%** of patients in these studies did NOT achieve the 15% weight loss^{1,2}

To get to 15% WL we Need Higher Doses

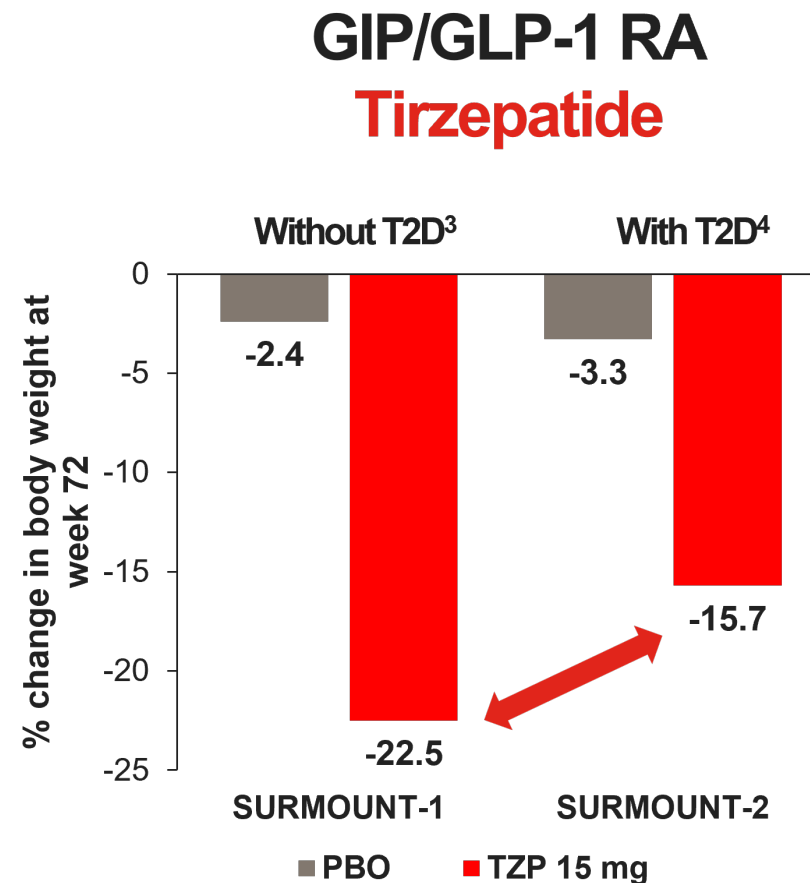
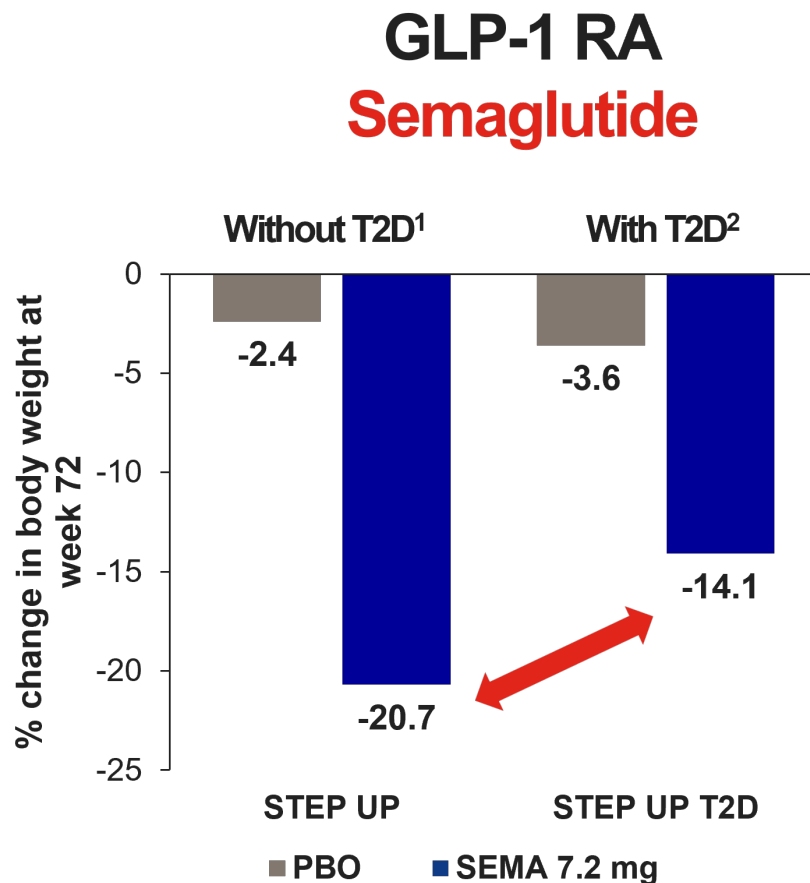
Optimal weight loss may only be achieved after a **prolonged, stepwise dose-escalation** period³

Clinical Trials vs. Practice

In practice **adherence and persistence can be suboptimal** and hence outcomes may be less favorable compared to clinical trials⁴

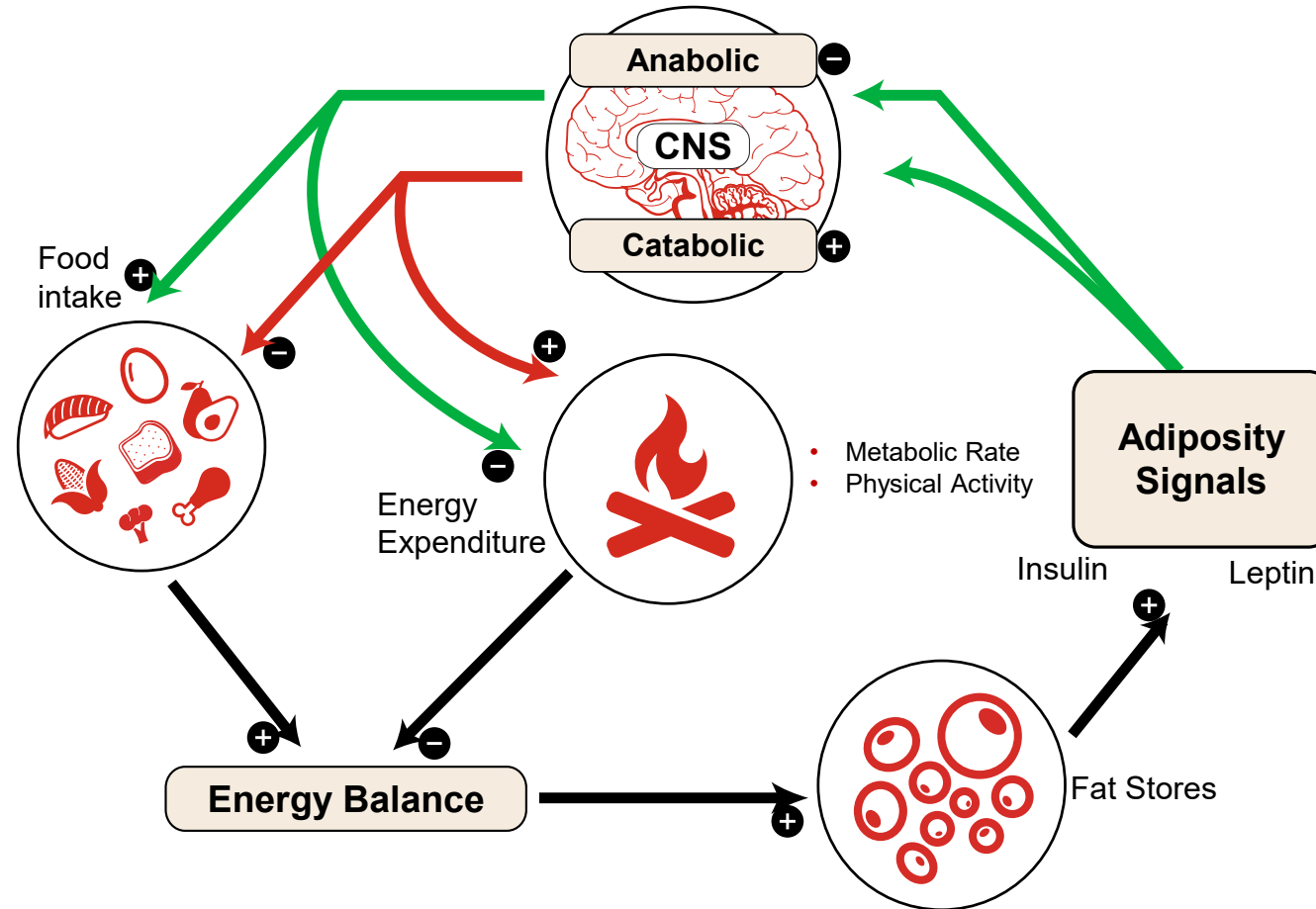
1. Lingvay I, et al. *Lancet Diabetes Endocrinol.* 2025;13:935-948. 2. Garvey WT, et al. *Lancet.* 2023;402:613-626. 3. Weiss T, et al. *Patient Prefer Adherence.* 2020;14:2337-2345.

A Clear Disparity in Weight Reduction With Current Incretin-Based Therapies in Participants With and Without Type 2 Diabetes



Approximately 30% lower weight loss is observed in patients with T2D compared to those without T2D

Obesity Biology is Complex and Targeting it May Require a Multi-Mechanism Approach Especially in Type 2 Diabetes



Multiple pathways contribute to energy balance and adiposity, providing rationale for therapies that engage several mechanisms^{1,2}

What are We Missing in Obesity Pharmacotherapy in Patients with Type 2 Diabetes?

1 Depth and Assurance of Treatment Response

- Allows more patients to break the **15% weight reduction ceiling in T2D**
- **Broad metabolic benefits** beyond weight loss
- **CVD risk reduction**
- Improvements in **QOL and other ORCs**

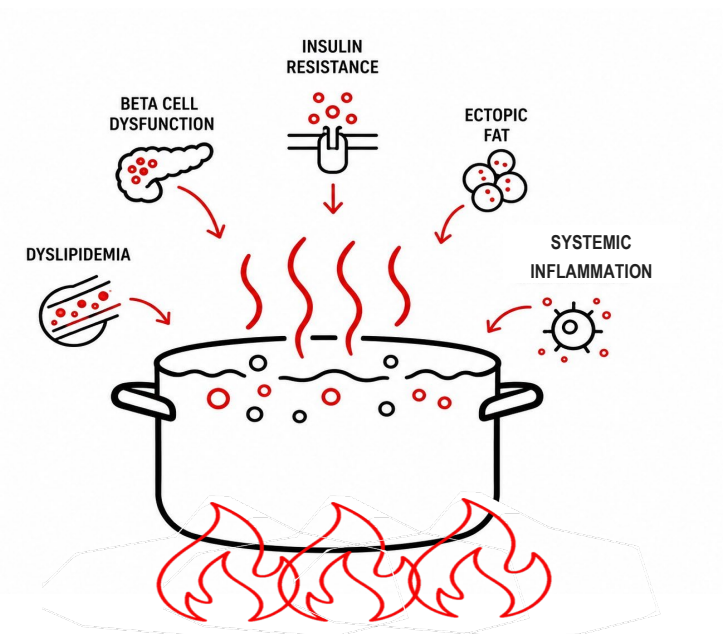
2 Simple Scalability

- **Efficacy at lower doses; no** long dose escalation
- May help **scaling of meaningful T2D weight reduction at busy primary care clinics**

3 Safety

- Well tolerated
- Well-characterized **safety profile**

A treatment that fundamentally targets Type 2 Diabetes at its core and cools the melting pot



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TRIUMPH-2: Study Design, Baseline Characteristics, and Efficacy Results

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Los Angeles, CA, USA

Juan Pablo Frías Disclosures

RESEARCH SUPPORT:

- AbbVie
- Eli Lilly
- Novo Nordisk
- Roche/Genentech
- Sparrow Pharmaceuticals

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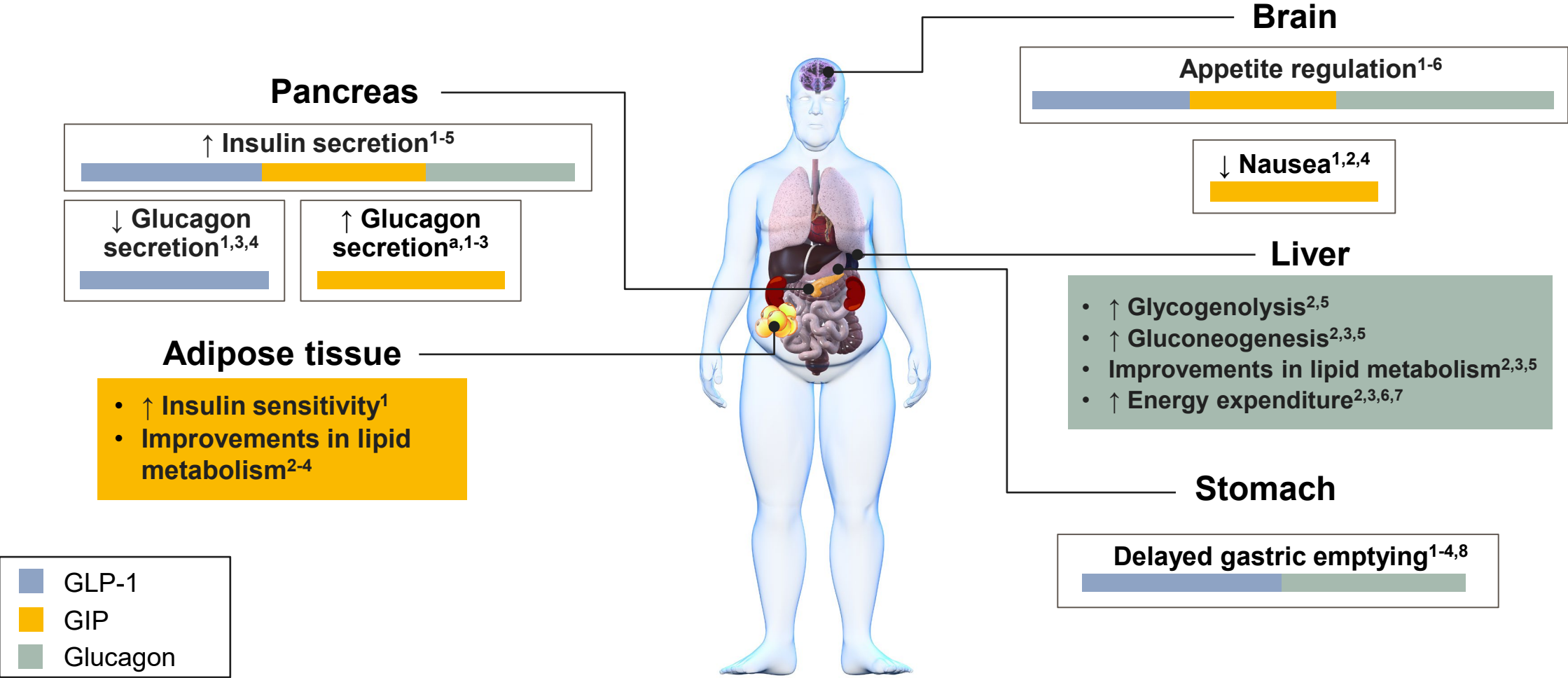
SPEAKER AND SPEAKERS BUREAU:

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- IONIS
- Madrigal

BOARD OF DIRECTORS:

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GLP-1, GIP, and Glucagon – Potential Roles in Obesity



^aGIP increases glucagon only in the hypoglycemic state; Indirect effect.
GIP=Glucose-Dependent Insulinotropic Polypeptide; GLP-1=Glucagon-Like Peptide-1.
1. Samms RJ, et al. *Trends Endocrinol Metab.* 2020;31(6):410-421. 2. Kusminski CM, et al. *Cell.* 2024;187(15):3829-3853. 3. Nogueiras R, et al. *Nat Metab.* 2023;5(6):933-944. 4. Hammoud R, Drucker DJ. *Nat Rev Endocrinol.* 2023;19(4):201-216. 5. Hædersdal S, et al. *Nat Rev Endocrinol.* 2023;19(6):321-335. 6. Novikoff A, Müller TD. *Peptides.* 2023;165:171003. 7. Klein T, et al. *Diabetes Res Clin Pract.* 2024;207:110779. 8. Urva S, et al. *Diabetes Obes Metab.* 2023;25(9):2784-2788.

Retatrutide: A Novel GIP, GLP-1, and Glucagon Receptor Agonist

Molecular Design¹

- Novel synthetic molecule
- C-20 fatty diacid moiety enables albumin binding and prolongs half-life

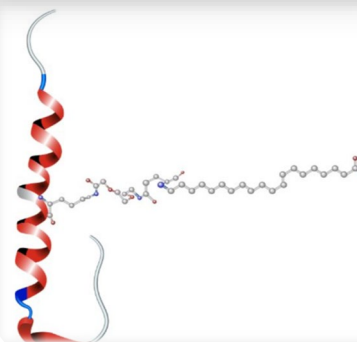
Pharmacokinetics^{1,2}

- Mean half-life: ~6 days
- Enables **weekly** SC dosing

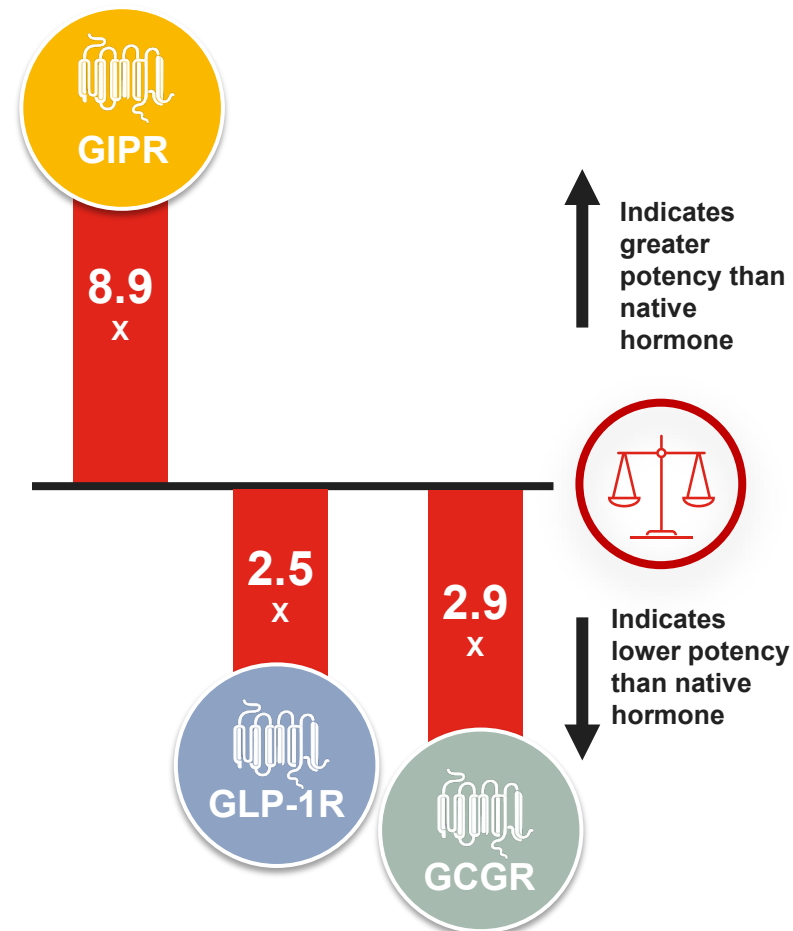
Mechanism of Action¹

- Agonist of **GIPR**, **GLP-1R**, and **GCGR**
 - Greater potency vs native GIP
 - Lower potency vs native GLP-1 and GCG

RETATRUTIDE¹



A Balanced Tri-Agonism by Design



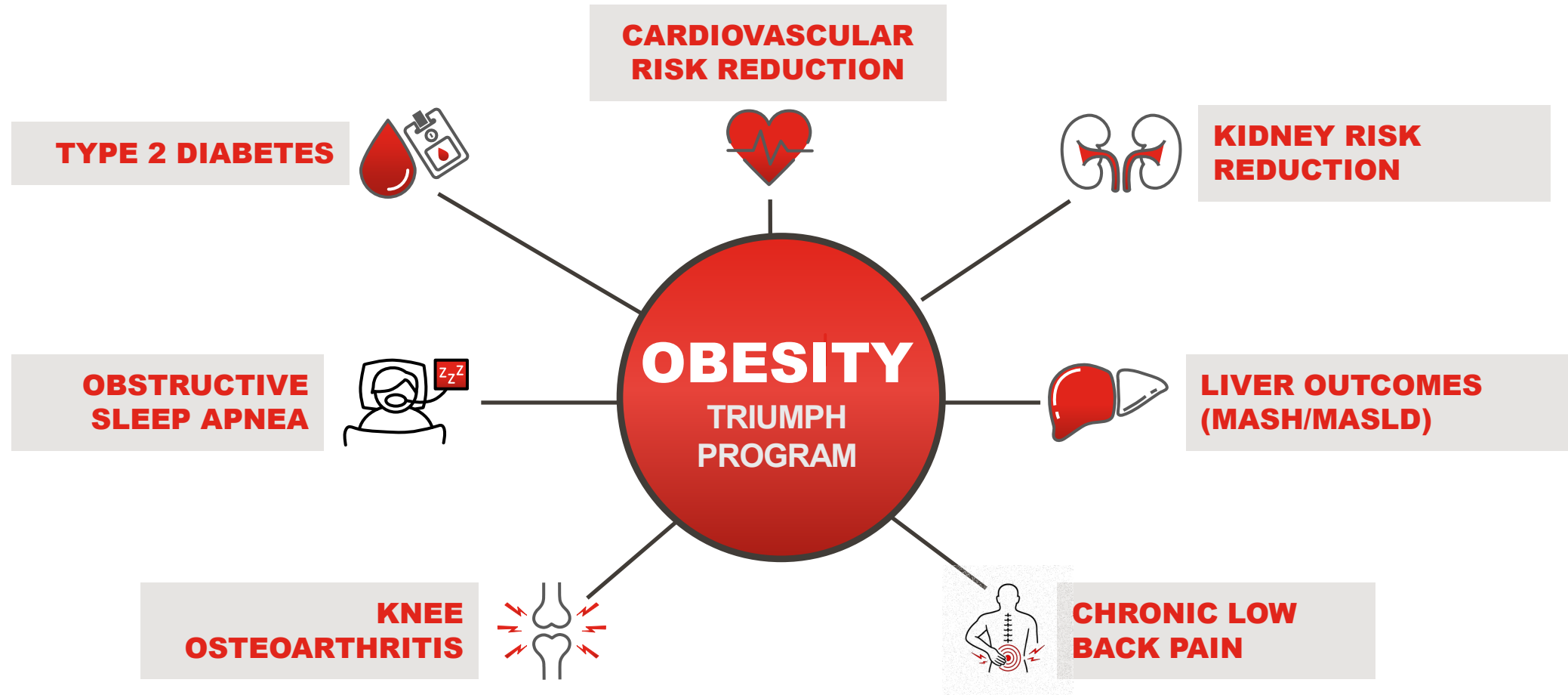
1. Coskun T, et al. *Cell Metab.* 2022;34:1234-1247.e9. 2. Urva S, et al. *Lancet.* 2022;400:1869-1881.

GCGR=glucagon receptor; GIP=glucose-dependent insulinotropic polypeptide; GIPR=GIP receptor; GLP-1R=glucagon-like peptide-1 receptor; SC=subcutaneous.

Retatrutide Phase 3 Program Across Obesity & Complications

~22,000 Participants Supporting 8 Potential Indications

TRIUMPH-2
OBESITY+T2D



TRIUMPH-2 is one of the 4 registrational trials supporting the obesity indication

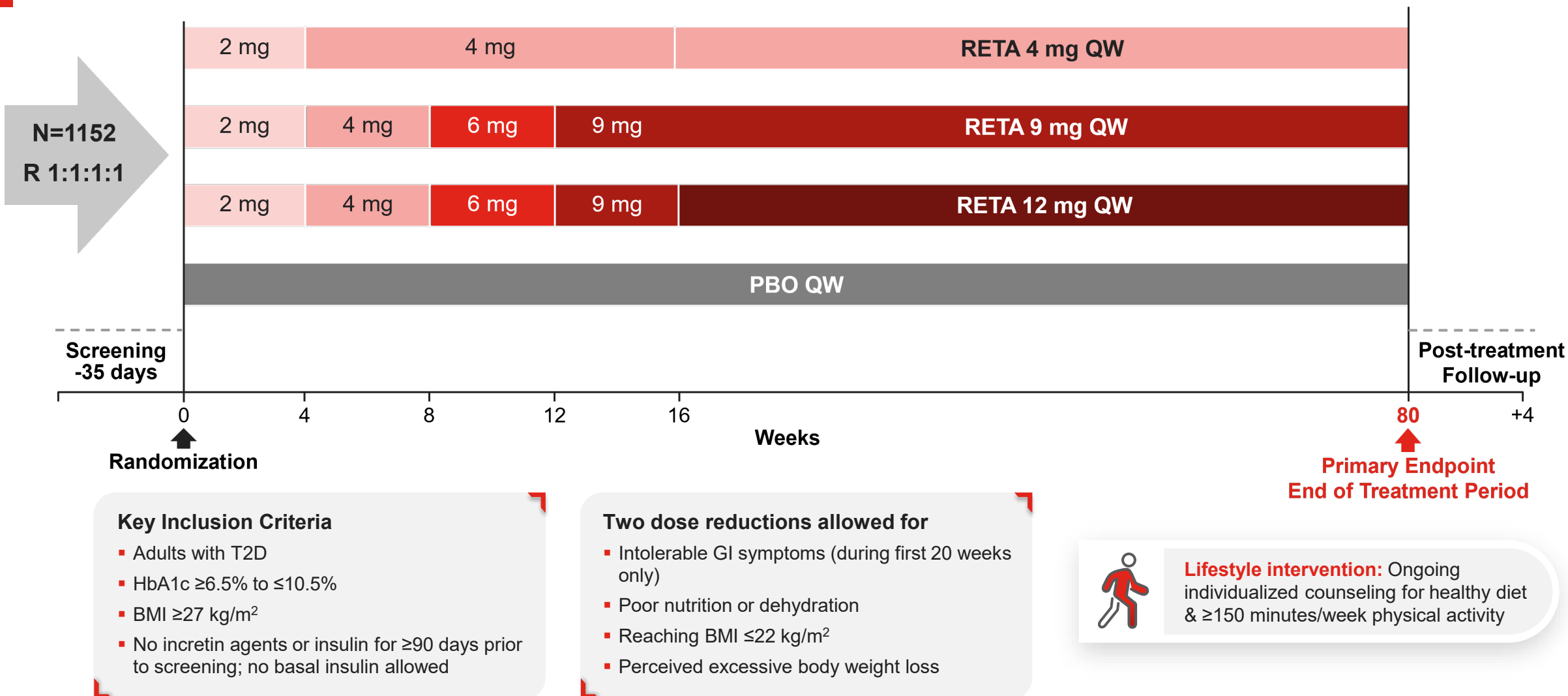
MASLD=metabolic dysfunction-associated steatotic liver disease; MASH=metabolic dysfunction-associated steatohepatitis; OA=osteoarthritis; OSA=obstructive sleep apnea; T2D=type 2 diabetes.

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Study Design and Baseline Characteristics

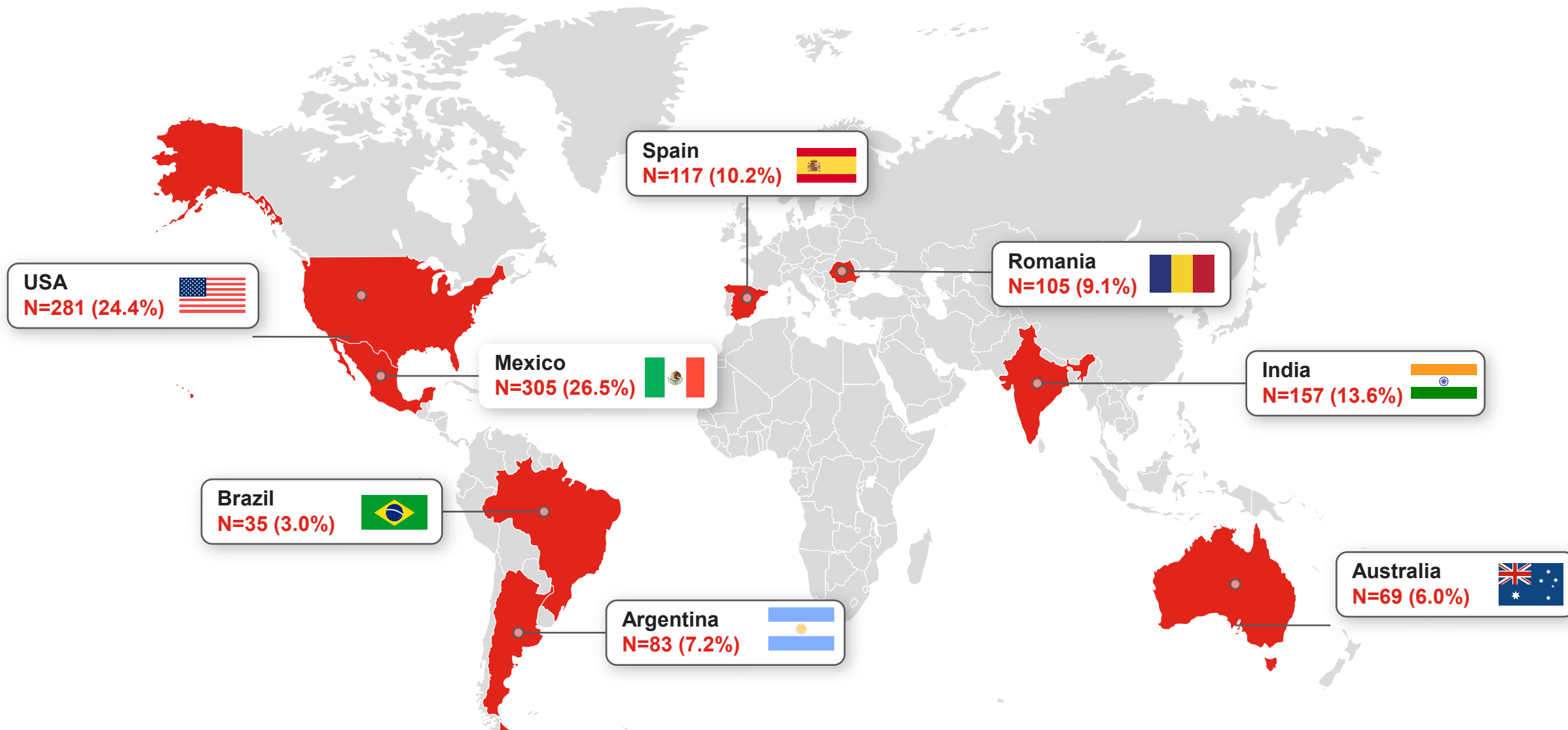
TRIUMPH-2 Study Design:

Phase 3 study in Participants with Overweight / Obesity and T2D

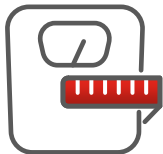


Multinational Trial:

N=1152 Participants Randomized at 92 Study Sites Across 8 Countries



Primary and Key Secondary Endpoints



Primary Endpoint

% change in body weight from baseline at Week 80 for RETA 9 mg and 12 mg



BODY WEIGHT AND OTHER ANTHROPOMETRIC ENDPOINTS

- % change in body weight from baseline for RETA 4 mg
- Proportion of participants achieving weight reduction of ≥5%, ≥10%, ≥15%, ≥20%, and ≥25%
- % change in body weight and achievement of weight reduction thresholds among participants with BMI ≥35 kg/m²
- Change in waist circumference

Key Secondary Endpoints^a



OTHER CV RISK FACTORS AND SYSTEMIC INFLAMMATION

- % change in TG, non-HDL-cholesterol, and hsCRP
- Change in SBP



GLYCEMIC MEASURES

- Change in HbA1c and fasting glucose
- Achievement of HbA1c ≤6.5%

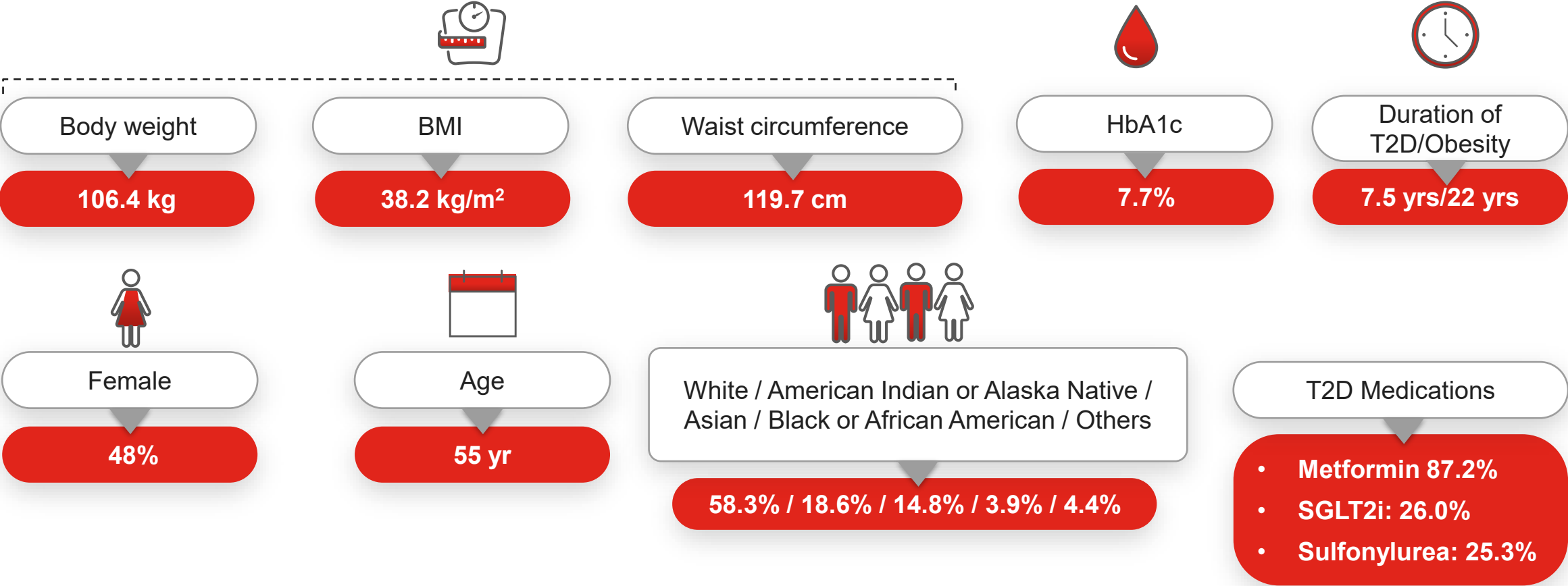


PATIENT-REPORTED OUTCOMES

- Change in IWQOL-Lite-CT Physical Function composite scores

^aChange from baseline at Week 80 for continuous endpoints, and status at Week 80 for categorical endpoints..
 BMI=body mass index; CV=cardiovascular; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; hsCRP=high-sensitivity C-reactive protein; IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version; QW=once weekly; RETA=retatrutide; SBP= systolic blood pressure; TG=triglycerides

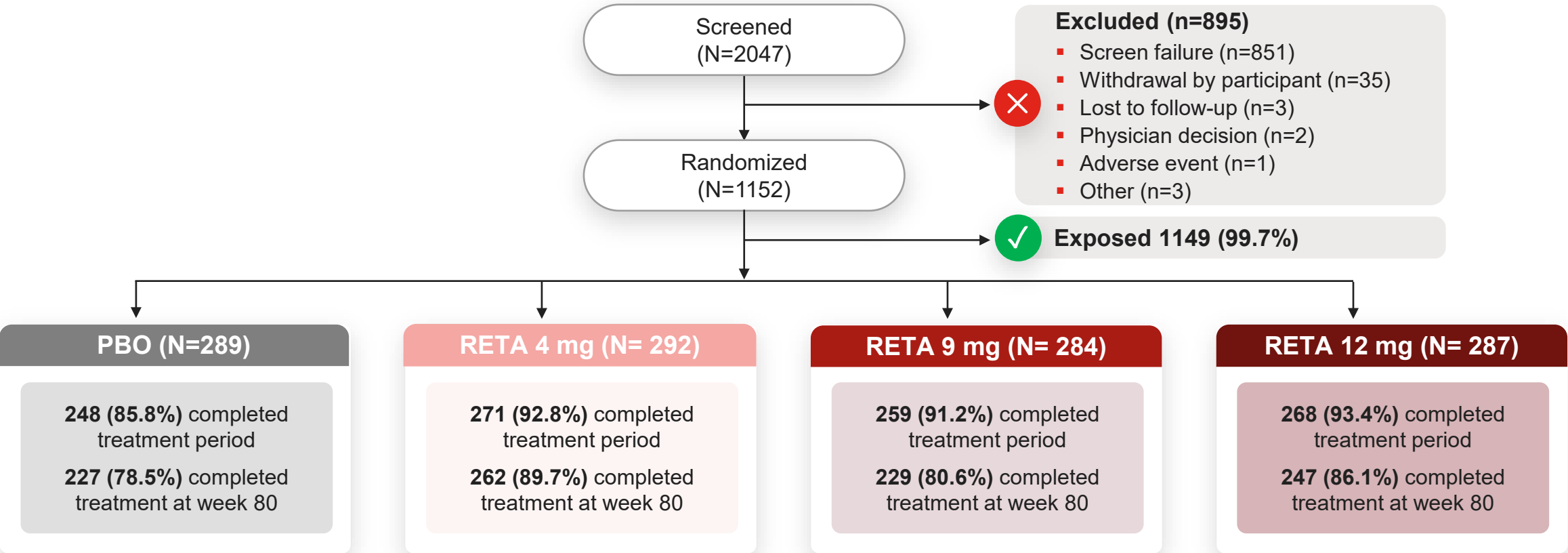
Key Demographics and Baseline Characteristics



Baseline Characteristics Were Well Balanced Across Treatment Arms

Note: all values are reported as mean values at baseline unless indicated otherwise.
 BMI=body mass index; HbA1c=glycated hemoglobin; SGLT2i=sodium glucose co-transporter-2 inhibitor; T2D=type 2 diabetes.

Participant Disposition

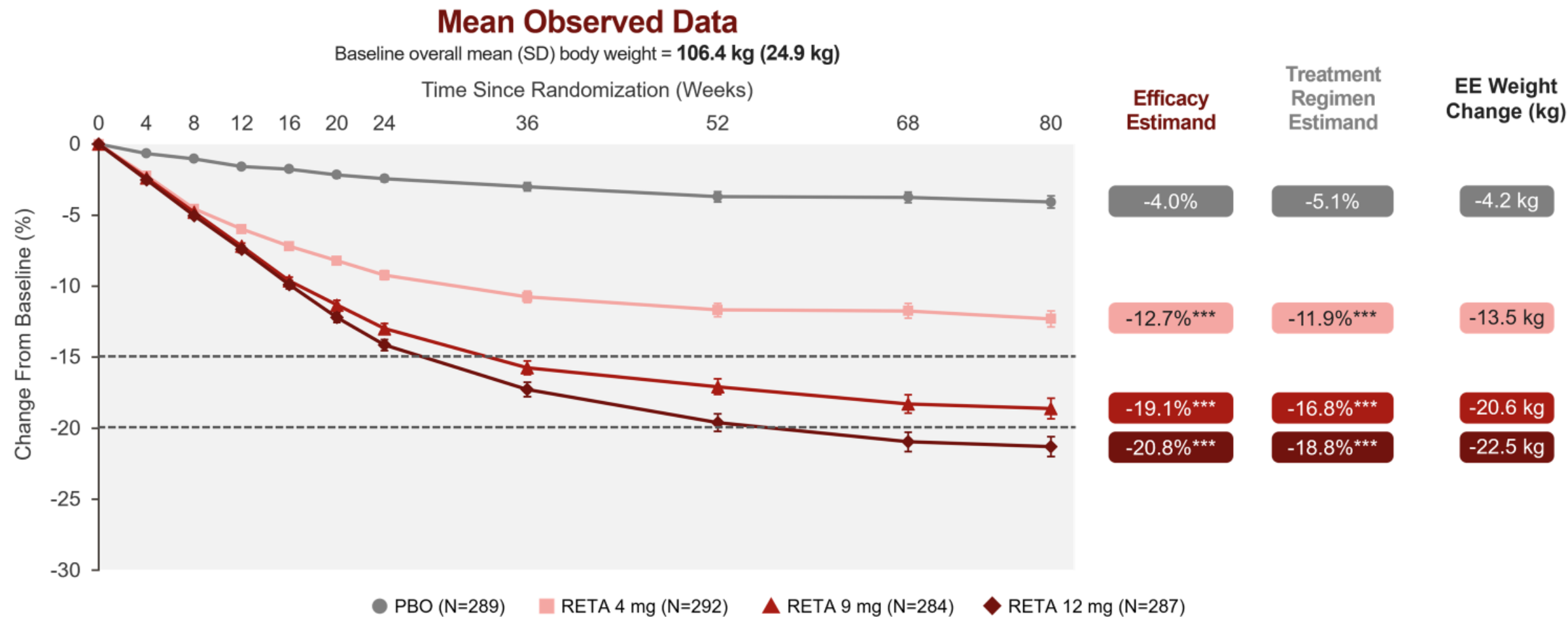


Across doses, 81% to 90% of retatrutide-treated participants remained on treatment through Week 80

N=all randomly assigned participants who took ≥1 dose of study drug; n=number of participants in the specified category/reason; PBO=placebo; RETA=retatrutide.

Body Weight and Other Anthropometric Measures

Percent Change in Body Weight Over 80 Weeks



With RETA 4 mg, which requires a single dose escalation, mean body weight decreased by 12.7%;
With RETA 12 mg, mean body weight decreased by 20.8%

RETA vs. PBO: ***p<0.001. p-values are for MBE change difference vs. PBO.

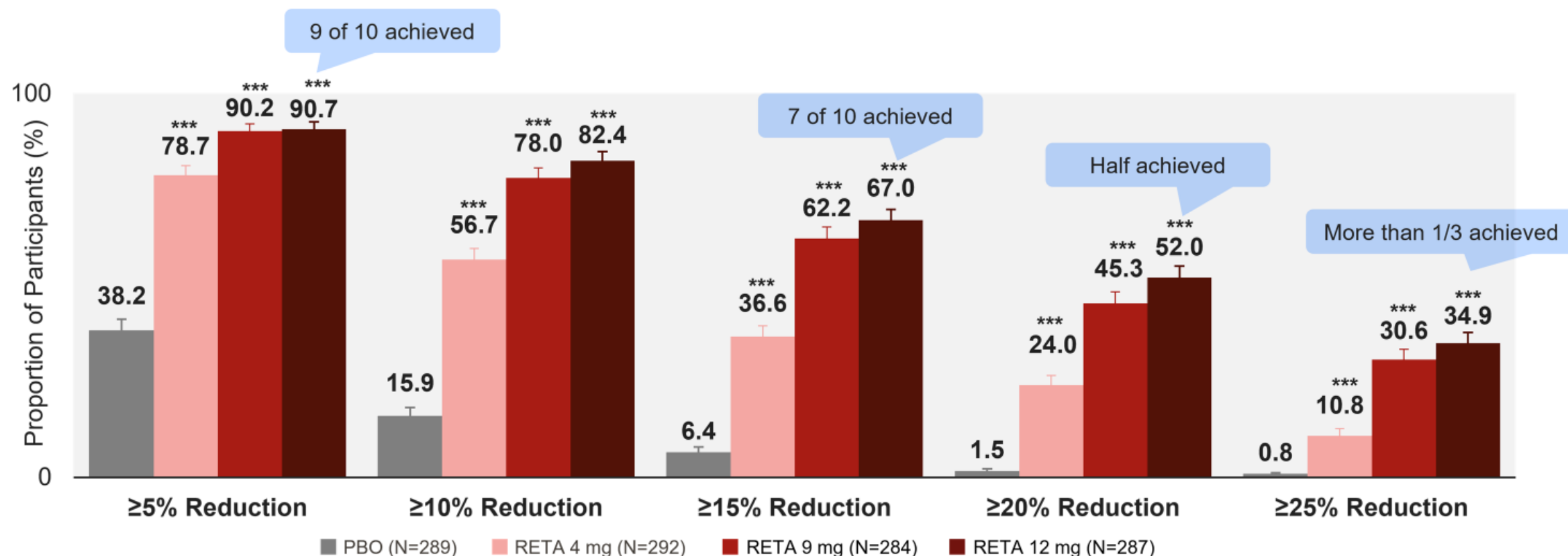
*Percent change in body weight from baseline to Week 80 is the primary endpoint for the comparison of RETA 9 mg and RETA 12 mg groups only vs. PBO (RETA 4 mg vs. PBO is a key secondary endpoint).

Notes: Data in time course plot are shown as mean (SE). Data for EE and TRE are MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. TRE analysis was conducted using ANCOVA. Data are from all randomized participants.

ANCOVA=analysis of covariance; EE=efficacy estimand; MBE=model-based estimate; MMRM=mixed model for repeated measures; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SD=standard deviation; SE=standard error; TRE=treatment regimen estimand.

Achievement of Body Weight Reduction Thresholds at 80 Weeks

Efficacy Estimand



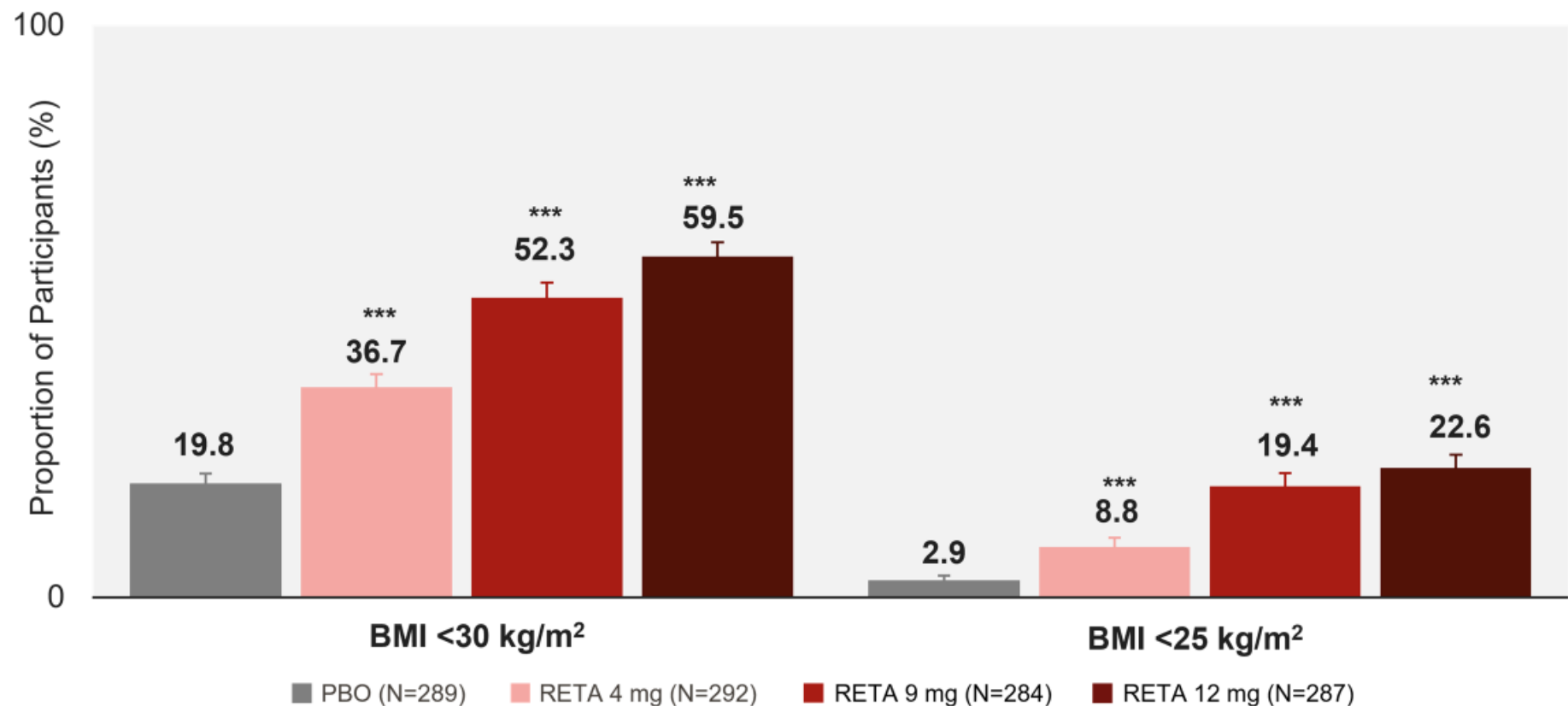
RETA vs. PBO: *p<0.05, **p<0.01, and ***p<0.001. p-values are for MBE (SE) risk difference vs. PBO.

Notes: Data are shown as MBE (SE) unless otherwise stated. EE analysis was conducted using logistic regression with multiple imputation. Data are from all randomized participants.

BW=body weight; EE=efficacy estimand; MBE=model-based estimate; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SE=standard error.

Proportion of Participants Achieving BMI Targets at Week 80

Efficacy Estimand



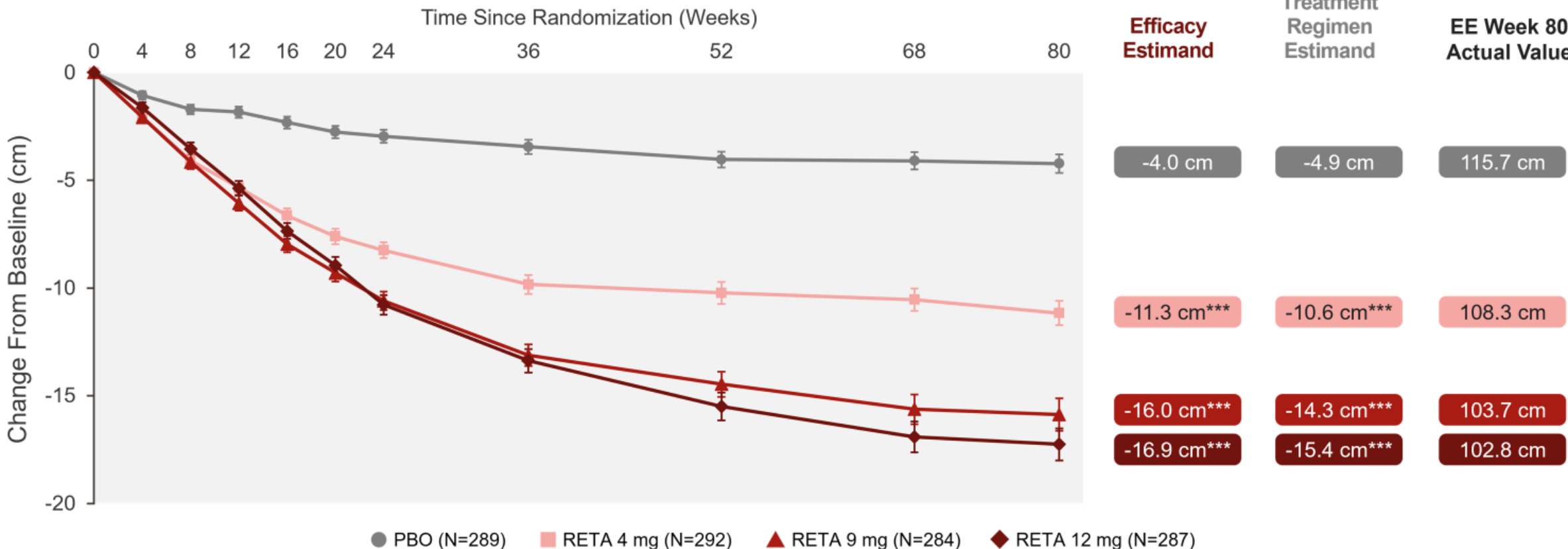
With RETA 9 mg and 12 mg, >50% of participants achieved a BMI <30 kg/m² and ~20% achieved a BMI <25 kg/m²

RETA vs. PBO: *p<0.05, **p<0.01, and ***p<0.001. p-values are for MBE risk difference vs. PBO.
 Note: Data are shown as MBE (SE) unless otherwise stated. EE analysis was conducted using logistic regression with multiple imputation. Data are from all randomized participants.
 BMI=body mass index; EE=efficacy estimand; MBE=model-based estimate; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SE=standard error.

Change in Waist Circumference From Baseline to Week 80

Mean Observed Data

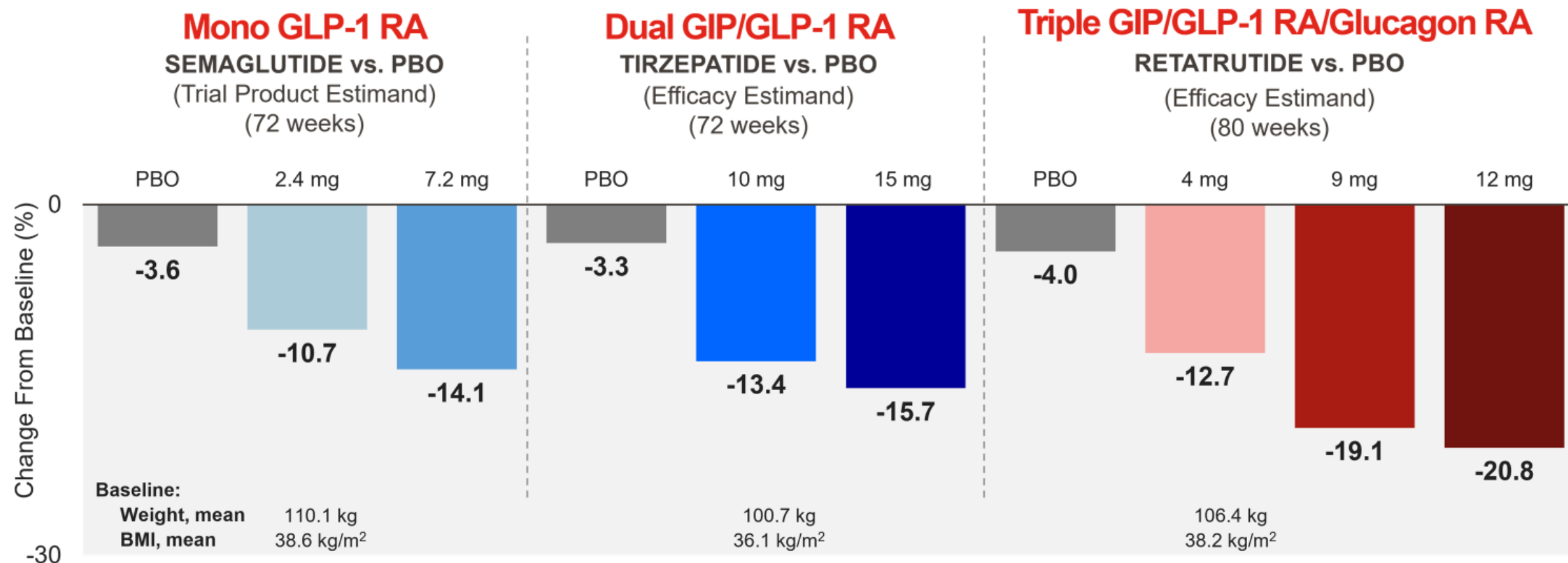
Baseline overall mean (SD) waist circumference = **119.7 cm (15.4 cm)**



Mean waist circumference decreased by up to 17 cm with RETA

RETA vs. PBO: ***p<0.001. p-values are for MBE change difference vs. PBO.
 Notes: Data in time course plot are shown as mean (SE). Data for EE and TRE are MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. TRE analysis was conducted using ANCOVA. Data are from all randomized participants.
 ANCOVA=analysis of covariance; EE=efficacy estimand; MBE=model-based estimate; MMRM=mixed model for repeated measures; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SD=standard deviation; SE=standard error; TRE=treatment regimen estimand.

Side-by-Side Indirect Comparison of Percent Change in Body Weight From Baseline vs. Similar Phase 3 Studies



RETA, a triple GIP/GLP-1/Glucagon RA crossed the ceiling of 20% average weight loss in participants with T2D

Note: Drawing conclusions based on the results of different studies is not appropriate.

1. Lingvay I, et al. *Lancet Diabetes Endocrinol.* 2025;13(11):935-948. 2. Garvey WT, et al. *Lancet.* 2023;402:613-626.

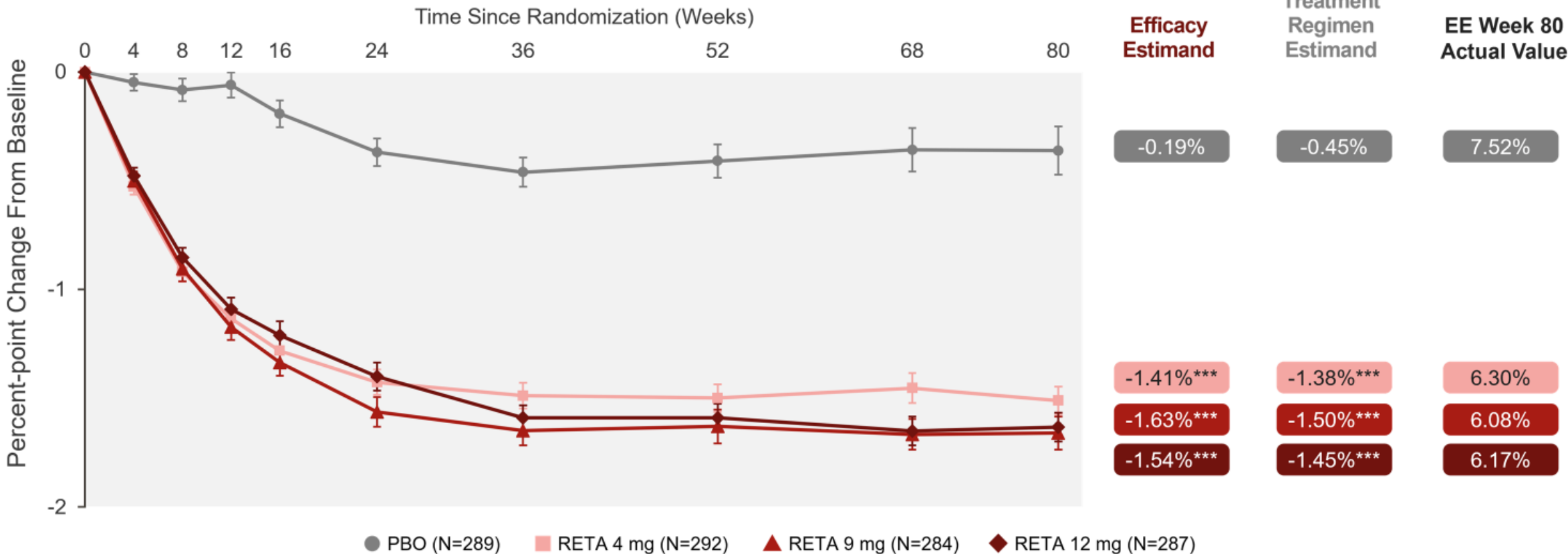
BMI=body mass index; PBO=placebo; RETA=retatrutide; SEMA=semaglutide; T2D=type 2 diabetes; TZP=tirzepatide.

Cardiometabolic Risk Parameters

Change in HbA1c from Baseline to Week 80

Percent-point Change From Baseline

Baseline overall mean (SD) HbA1c = 7.71% (1.07%)

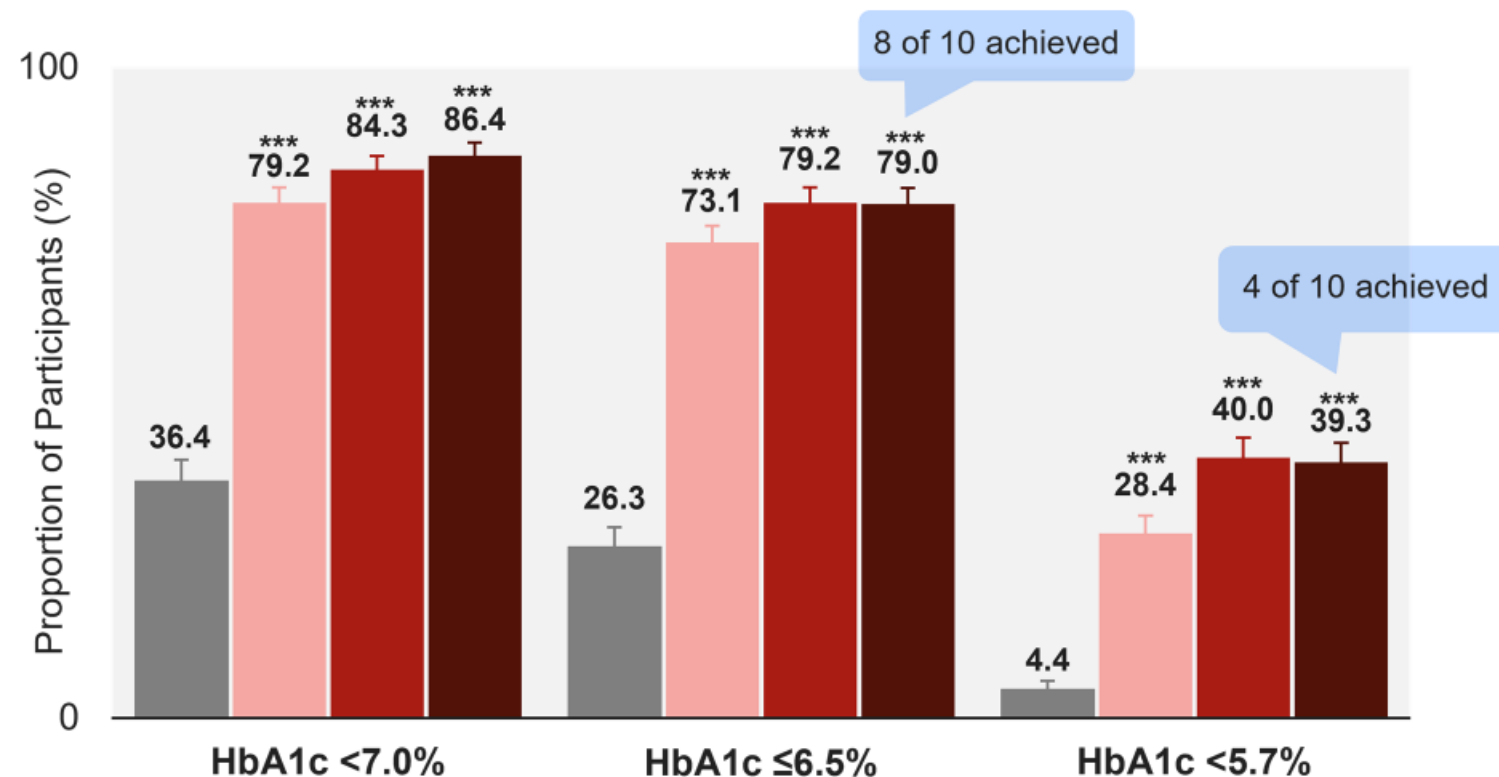


With RETA 12 mg participants reached a mean HbA1c of 6.17% at Week 80
Glycemic control was durable through 80 weeks

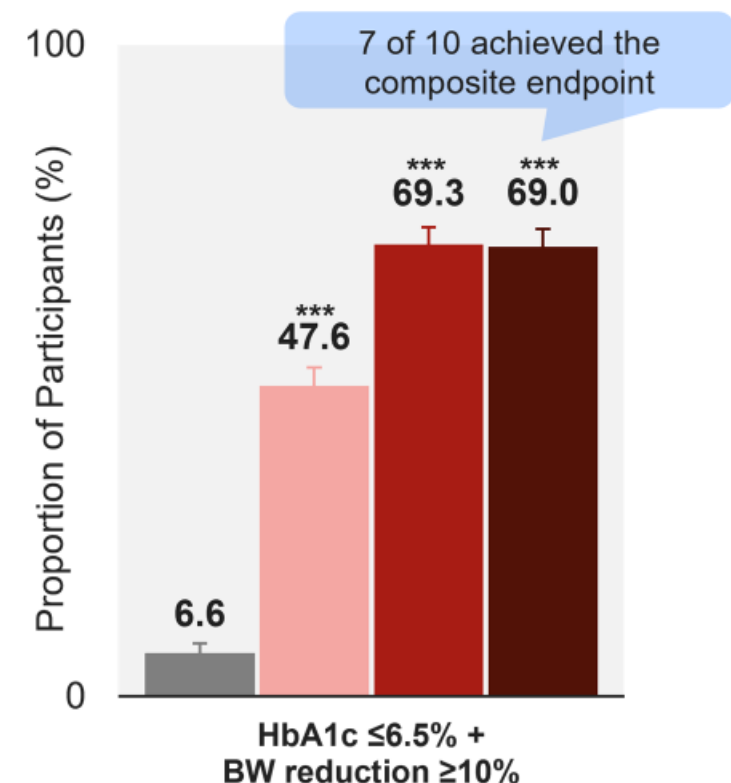
RETA vs. PBO: ***p<0.001. p-values are for MBE change difference vs. PBO.
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ANCOVA=analysis of covariance; EE=efficacy estimand; HbA1c=glycated hemoglobin; MBE=model-based estimate; MMRM=mixed model for repeated measures; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SD=standard deviation; SE=standard error; TRE=treatment regimen estimand.

Proportion of Participants Achieving HbA1c Targets at Week 80

Efficacy Estimand



Proportion of Participants Achieving HbA1c Targets



Proportion of Participants Achieving a Composite Target for HbA1c and Body Weight Reduction

■ PBO (N=289) ■ RETA 4 mg (N=292) ■ RETA 9 mg (N=284) ■ RETA 12 mg (N=287)

RETA vs. PBO: ***p<0.001. p-values are for MBE risk difference vs. PBO.

Note: Data are shown as MBE (SE) unless otherwise stated. EE analysis was conducted using logistic regression with multiple imputation. Data are from all randomized participants.

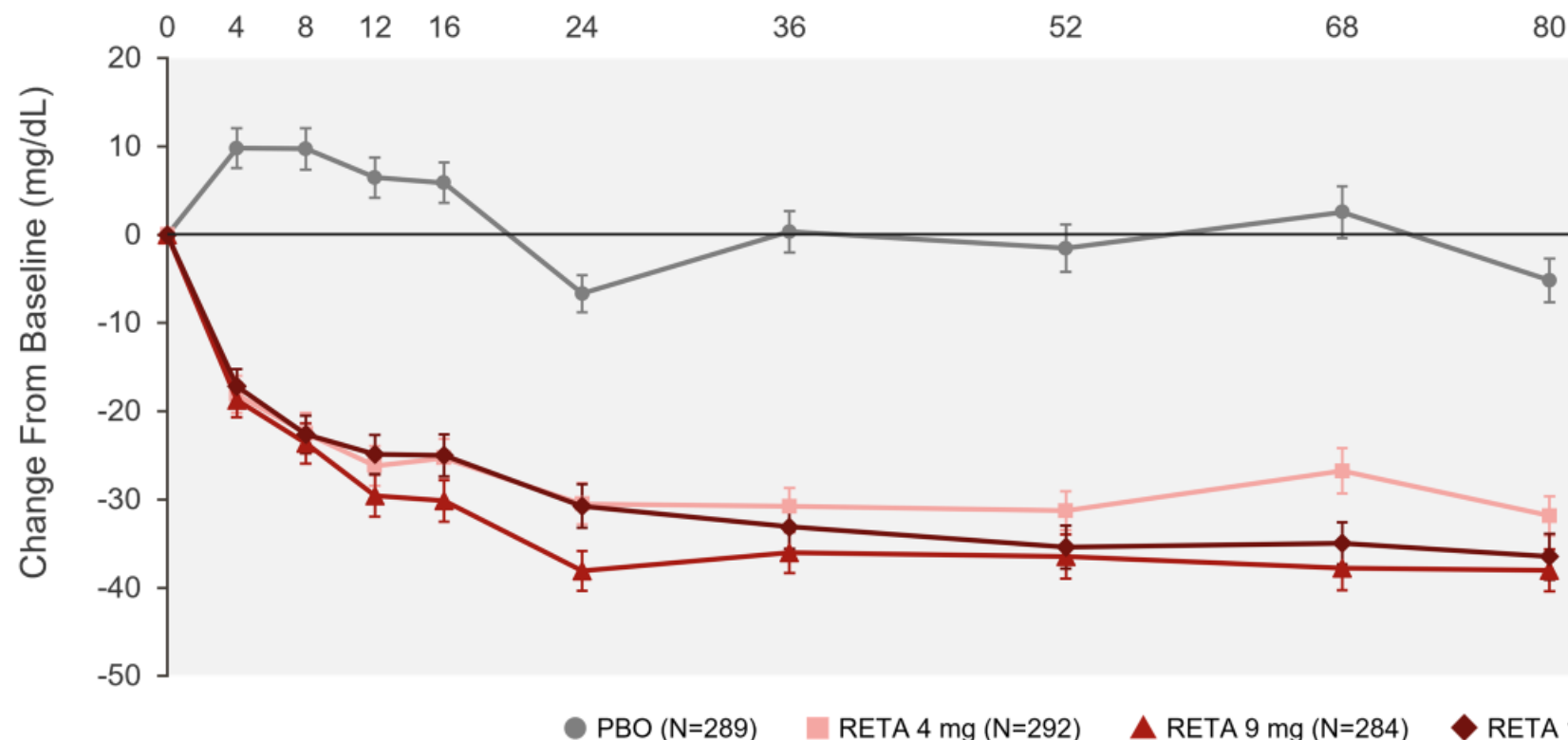
BW=body weight; HbA1c=glycated hemoglobin; MBE=model-based estimate; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SE=standard error.

Change in Fasting Glucose From Baseline to Week 80

Mean Observed Data

Baseline overall mean (SD) fasting glucose = **137.1 mg/dL (39.5 mg/dL)**

Time Since Randomization (Weeks)



**Efficacy
Estimand**

**Treatment
Regimen
Estimand**

**EE Week 80
Actual Value**

-4.3 mg/dL

-8.2 mg/dL

132.8 mg/dL

-30.9 mg/dL ***

-28.8 mg/dL ***

106.3 mg/dL

-36.8 mg/dL ***

-31.6 mg/dL ***

100.4 mg/dL

-35.7 mg/dL ***

-31.4 mg/dL ***

101.4 mg/dL

Mean fasting glucose concentrations at Week 80 were ~100 mg/dL (~5.6 mmol/L) for RETA 9 mg and 12 mg

RETA vs. PBO: ***p<0.001. p-values are for MBE change difference vs. PBO.

Notes: Data in time course plot are shown as mean (SE). Data for EE and TRE are MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. TRE analysis was conducted using ANCOVA. Data are from all randomized participants.

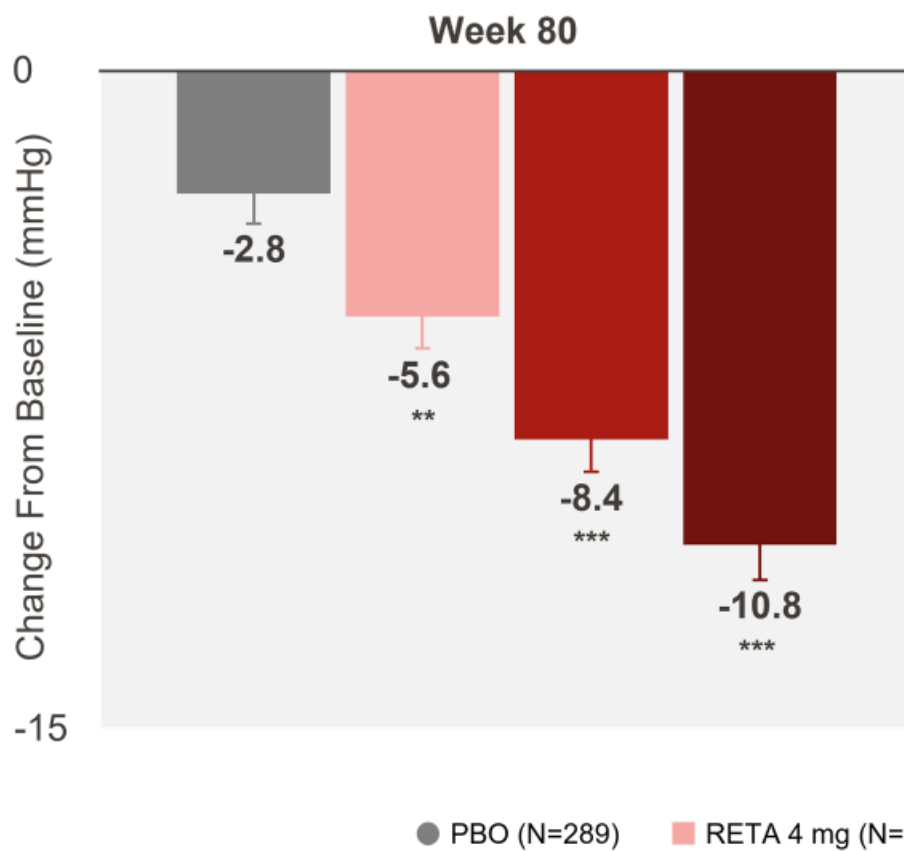
ANCOVA=analysis of covariance; EE=efficacy estimand; MBE=model-based estimate; MMRM=mixed model for repeated measures; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SD=standard deviation; TRE=treatment regimen estimand.

Change in Blood Pressure From Baseline to Week 80

Efficacy Estimand

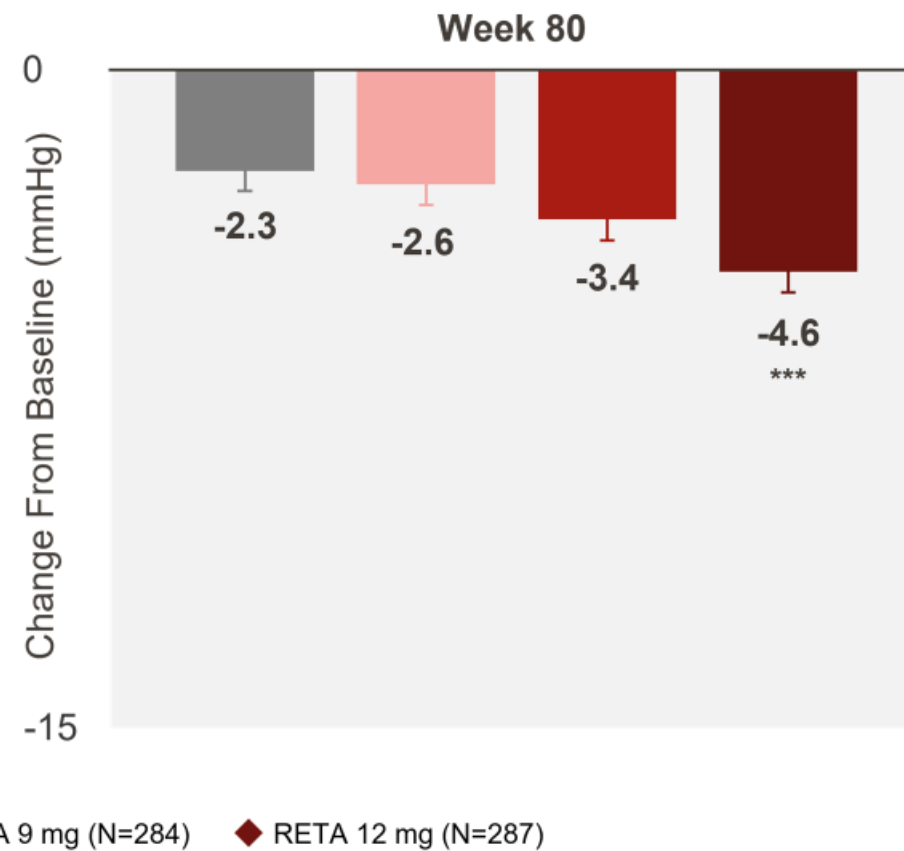
Systolic Blood Pressure

Baseline overall mean (SD) systolic blood pressure = **129.6 (13.7) mmHg**



Diastolic Blood Pressure

Baseline overall mean (SD) diastolic blood pressure = **80.4 (9.0) mmHg**



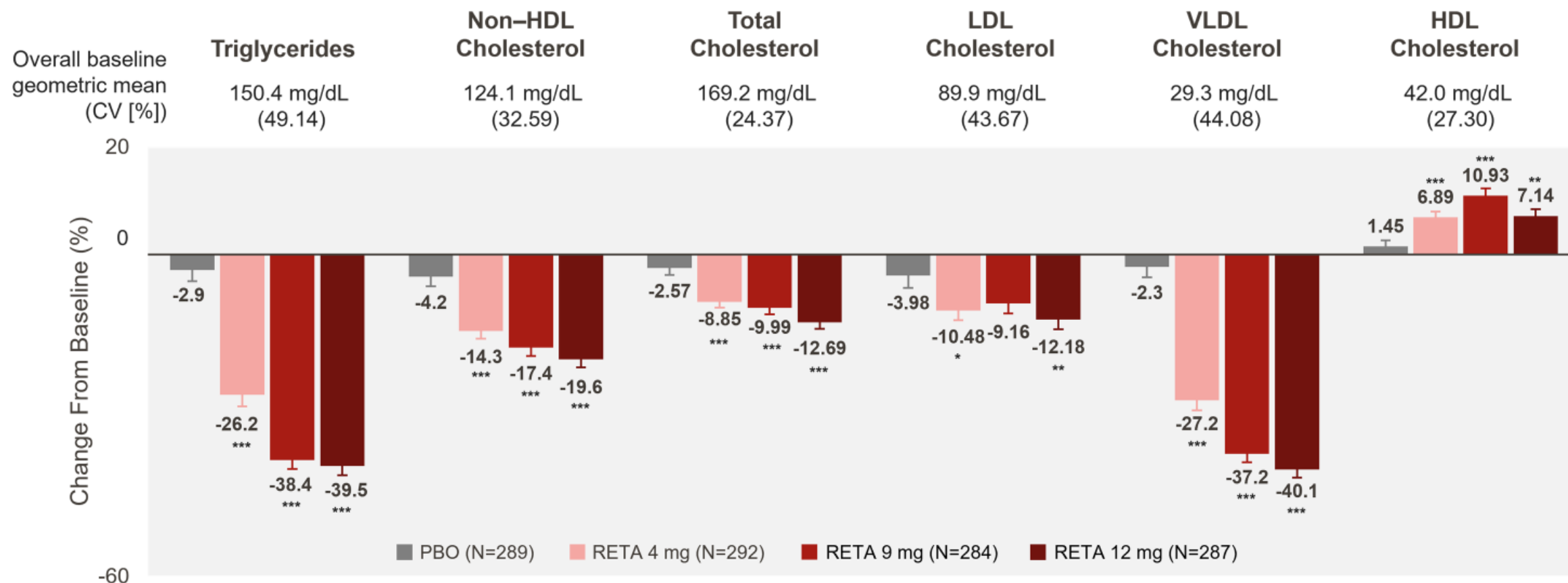
RETA vs. PBO: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. p-values are for MBE change difference vs. PBO.

Notes: Data in bar charts are shown as MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. Data are from all randomized participants.

ANCOVA=analysis of covariance; EE=efficacy estimand; MBE=model-based estimate; MMRM=mixed model for repeated measures; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SD=standard deviation; SE=standard error.

Percent Change in Lipid Parameters at Week 80

Efficacy Estimand



**At Week 80, RETA resulted in significant and clinically meaningful reductions in triglycerides and non-HDL cholesterol
LDL-C was reduced up to 12% with RETA**

RETA vs. PBO: *p<0.05, **p<0.01, and ***p<0.001. p-values are for MBE percent change difference vs. PBO.

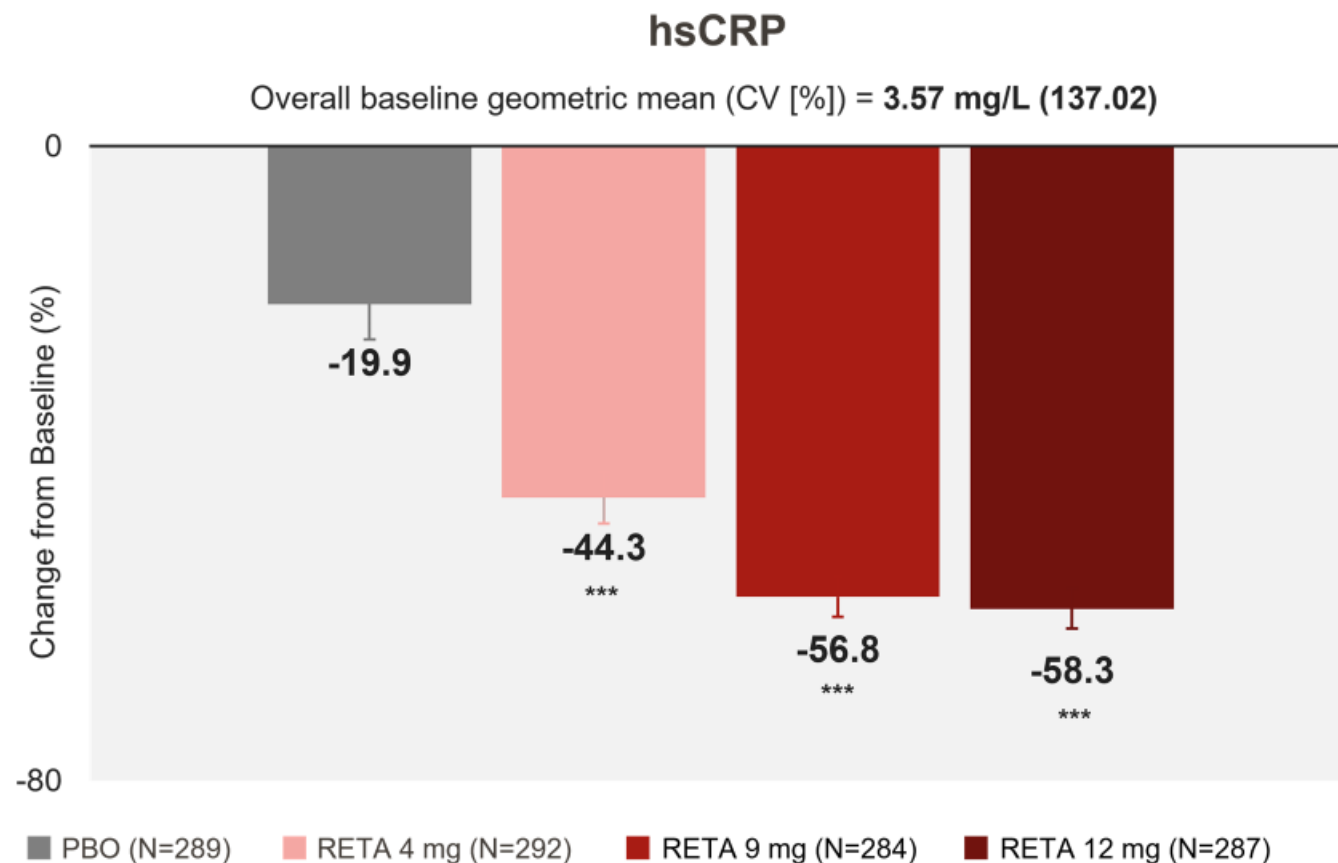
Note: Data are shown as MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. Data are from all randomized participants.

Only the comparisons between RETA 4mg, 9mg, and/or 12mg vs PBO with respect to the achievement of geometric mean percent change in triglycerides, and non-HDL cholesterol from baseline at week 80 are controlled for the type I error rate.

CV=coefficient of variation; EE=efficacy estimand; HDL=high-density lipoprotein; LDL=low-density lipoprotein; MBE=model-based estimate; MMRM, mixed model for repeated measures; N=number of participants in the population; non-HDL=non-high-density lipoprotein; PBO=placebo; RETA=retatrutide; SD=standard deviation; VLDL=very-low-density lipoprotein.

Percent Change in hsCRP at Week 80

Efficacy Estimand



Systemic inflammation, measured by hsCRP, was reduced by over 50% with RETA 9 mg and 12 mg

RETA vs. PBO: *p<0.05, **p<0.01, and ***p<0.001. p-values are for MBE percent change difference vs. PBO.

Note: Data are shown as MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. Data are from all randomized participants.

Only the comparisons between RETA 4mg, 9mg, and/or 12mg vs PBO with respect to the achievement of geometric mean percent change in hsCRP from baseline at week 80 are controlled for the type I error rate.

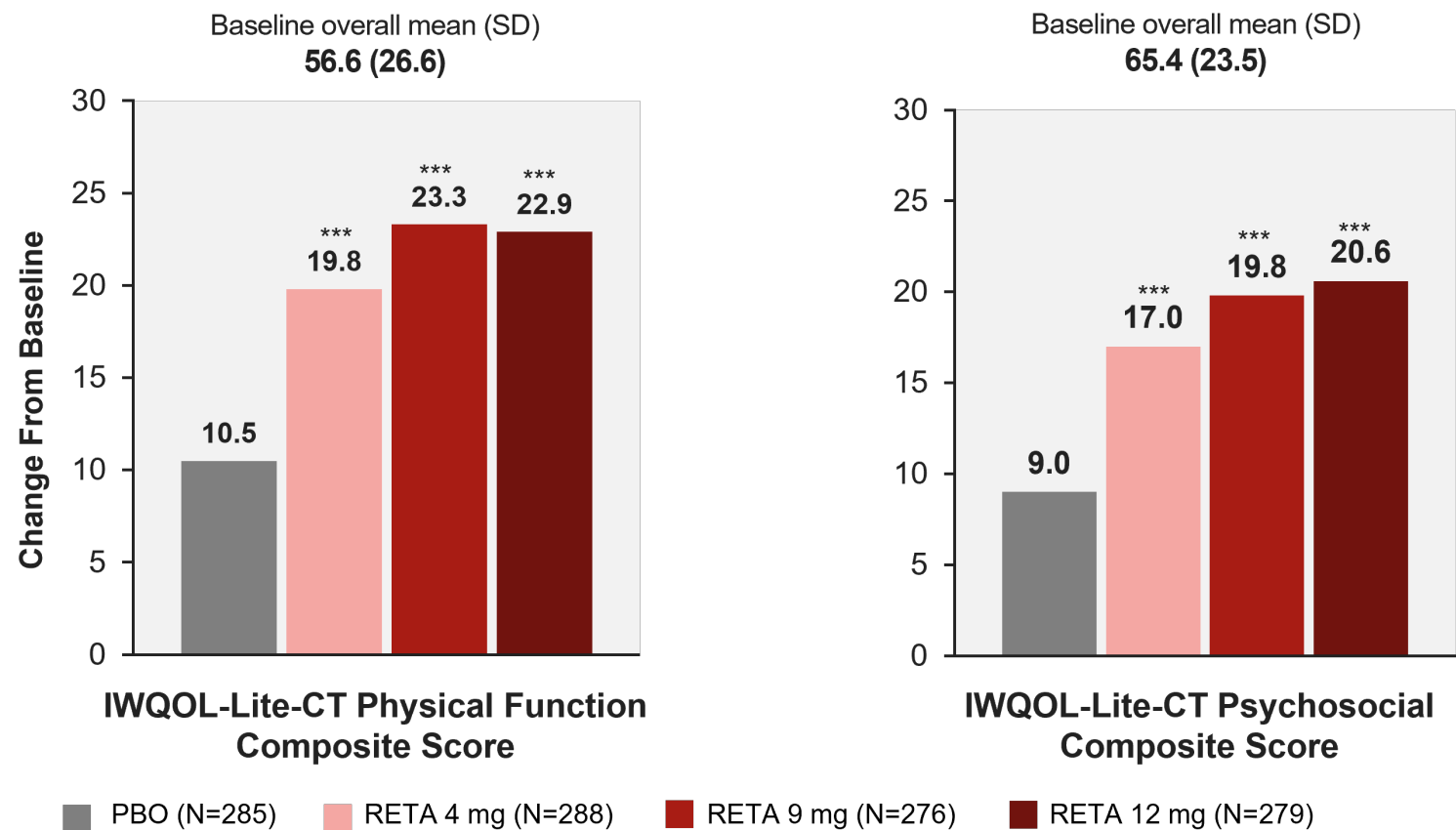
CV=coefficient of variation; EE=efficacy estimand; hsCRP=high-sensitivity C-reactive protein; MBE=model-based estimate; MMRM, mixed model for repeated measures; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SD=standard deviation.

Patient reported outcomes

IWQOL-Lite-CT: Physical Function and Psychosocial Composite Scores

Change in IWQOL-Lite-CT Scores From Baseline to Week 80

Efficacy Estimand



RETA at every dose level^a resulted in statistically significant and clinically meaningful reported improvements in physical function and psychosocial health

RETA vs. PBO: ***p<0.001. p-values are for MBE change difference vs. PBO.
^aIndividual dose levels were not controlled for multiplicity. IWQOL-Lite-CT Psychosocial Composite Score was not controlled for multiplicity.
 Notes: Data are shown as MBE unless otherwise stated. EE analysis was conducted using MMRM. Data are from all randomized participants..
 EE=efficacy estimand; IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials; MBE=model-based estimate; n=number of participants in the specified category;
 N=number of participants in the population; PBO=placebo; RETA=retatrutide; SF-36v2= Short Form 36-item Health Survey version 2; T2D=type 2 diabetes.

Summary of Efficacy Results

TRIUMPH-2

TRIUMPH-2: Summary of Retatrutide Efficacy at Week 80

BODY WEIGHT REDUCTION



-12.7%

with 4 mg

-20.8%

with 12 mg

Waist circumference decrease: up to 17 cm

WEIGHT REDUCTION THRESHOLDS



≥15%

67%
with 12 mg

≥20%

52%
with 12 mg

BMI THRESHOLDS



<30 kg/m²

60%
with 12 mg

<25 kg/m²

23%
with 12 mg

GLYCEMIC CONTROL

HbA1c

- Up to **79%** reached HbA1c ≤6.5%



FSG

- Mean FSG **~100 mg/dL** (~5.6 mmol/L) with 9 mg and 12 mg

LIPIDS



Triglycerides

- Up to **39.5%** reduction

Non-HDL-C LDL-C

- Up to **19.6%** reduction
- Up to **12.2%** reduction

BLOOD PRESSURE



SBP/DBP

- Up to **10.8 / 4.6 mmHg** reduction

SYSTEMIC INFLAMMATION



hsCRP

- Up to **58.3%** reduction

PHYSICAL FUNCTION



IWQOL-Lite-CT Score

- Up to **22.9** increase

RETA demonstrated a robust range of efficacy across doses (4 mg to 12 mg) for weight reduction, glycemic control, and cardiometabolic risk factor improvements in patients with Obesity/Overweight and T2D

Note: Data are efficacy estimands values; all data are model-based estimates for change from baseline at Week 80 unless otherwise stated. N=289 (PBO), 292 (RETA 4 mg), 284 (RETA 9 mg), 287 (RETA 12 mg).

BMI=body mass index; DBP=diastolic blood pressure; HbA1c=glycated hemoglobin; HDL-C=high-density lipoprotein cholesterol; hsCRP=high-sensitivity C-reactive protein; IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials; LDL-C=low-density lipoprotein cholesterol; PBO=placebo; RETA=retatrutide; SBP=systolic blood pressure; TG=triglycerides.

EASD
September 30, 2026

TRIUMPH-2: Safety Results and Conclusions

Professor Elif Ekinci, MBBS, FRACP, PhD

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Director, Australian Centre for Accelerating Diabetes Innovation (ACADI)

Co-chair, Australian Diabetes Clinical Trial Network

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Director, Centre for Research and Education in Diabetes and Obesity (CREDO), Austin Health

Co-chair, Heart Foundation Obesity and Cardiovascular Disease Guidelines

***RESEARCH SUPPORT (PAID TO AUSTIN HEALTH
OR TO THE UNIVERSITY OF MELBOURNE:***

- Abbott
- Amgen
- Arrowhead Pharmaceuticals
- Astra Zeneca
- Boehringer Ingelheim Pty Ltd
- Eli Lilly
- Endogenex
- NewAmsterdam
- Novartis
- Novo Nordisk
- Omnipod
- Versanis Bio

***CONSULTING FEES (PAID TO THE
UNIVERSITY OF MELBOURNE:***

- Boehringer Ingelheim
- Eli Lilly
- Novo Nordisk

TRIUMPH-2: Overview of Adverse Events

n (%)	PBO (N=287)	RETA 4 mg (N=292)	RETA 9 mg (N=284)	RETA 12 mg (N=286)
Participants with ≥1 TEAE	227 (79.1)	231 (79.1)	236 (83.1)	242 (84.6)
Participants with ≥1 serious AE	22 (7.7)	24 (8.2)	25 (8.8)	27 (9.4)
Discontinuation from study treatment due to AE	14 (4.9)	11 (3.8)	33 (11.6)	22 (7.7)
Discontinuation from study due to AE	6 (2.1)	5 (1.7)	6 (2.1)	7 (2.4)
Death ^a	1 (0.3)	2 (0.7)	3 (1.1)	1 (0.3)

Overall, RETA was generally well tolerated across all doses; compared with PBO, there were more treatment discontinuations due to AEs with RETA 9 and 12 mg doses, but fewer with the RETA 4 mg dose

^aDeaths are also included as serious AEs and discontinuations due to AEs.

Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of double-blind study intervention. MedDRA Version 29.0.

AE=adverse event; CV=cardiovascular; MedDRA=Medical Dictionary for Regulatory Activities; N=all randomly assigned participants who took ≥1 dose of study drug; n=number of participants in the specified category; PBO=placebo; RETA=retatrutide; TEAE=treatment-emergent adverse event.

AEs Leading to Treatment Discontinuation

n (%)	PBO N=287	RETA 4 mg N=292	RETA 9 mg N=284	RETA 12 mg N=286
Participants with AE leading to treatment discontinuation	14 (4.9)	11 (3.8)	33 (11.6)	22 (7.7)
Nausea	1 (0.3)	0	2 (0.7)	3 (1.0)
Lipase increased	0	0	3 (1.1)	1 (0.3)
Fatigue	0	0	3 (1.1)	1 (0.3)
Blood calcitonin increased	0	1 (0.3)	1 (0.4)	1 (0.3)
Atrial fibrillation	0	0	3 (1.1)	0

AEs leading to treatment discontinuation in at least 3 patients are reported.

Discontinuations of treatment due to an AE occurred in 3.8-11.6% of participants who received RETA and 4.9% for those who received placebo

Nausea, increased lipase, and fatigue were the most common reasons for treatment discontinuation

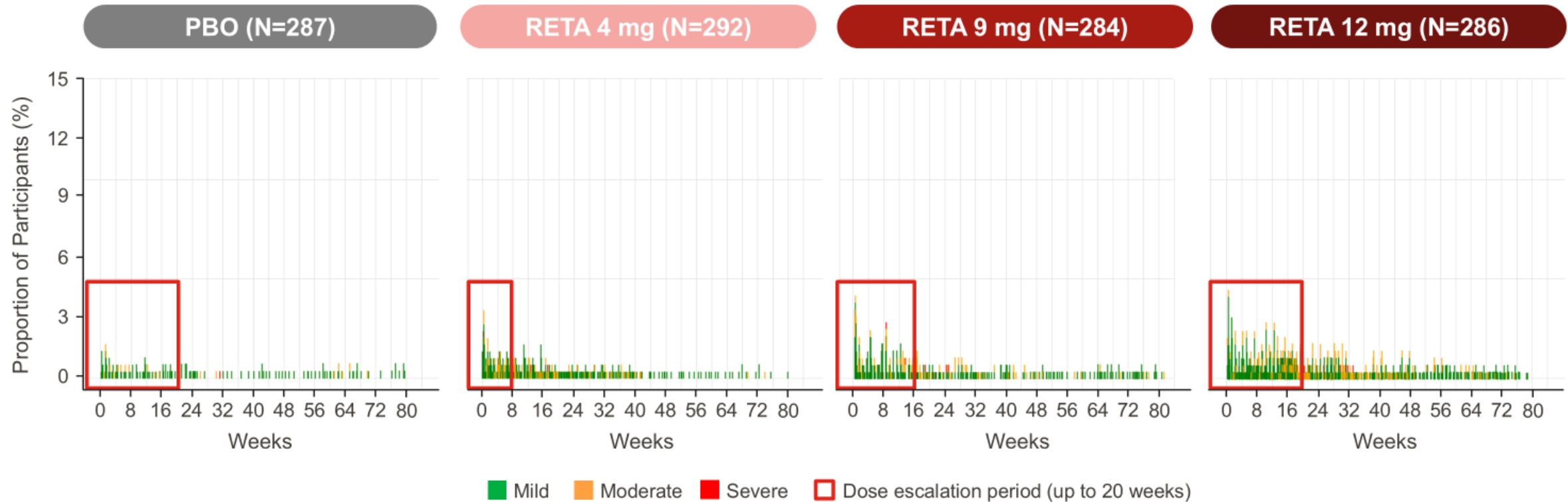
Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of double-blind study intervention. MedDRA Version 29.0.
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=all randomly assigned participants who took ≥1 dose of study drug; n=number of participants in the specified category; PBO=placebo; PT=Preferred Term; RETA=retatrutide

Treatment-Emergent Adverse Events

n (%)	PBO (N=287)	RETA 4 mg (N=292)	RETA 9 mg (N=284)	RETA 12 mg (N=286)
Participants with ≥1 TEAE	227 (79.1)	231 (79.1)	236 (83.1)	242 (84.6)
Diarrhea	38 (13.2)	80 (27.4)	95 (33.5)	96 (33.6)
Nausea	23 (8.0)	40 (13.7)	59 (20.8)	80 (28.0)
Constipation	27 (9.4)	41 (14.0)	46 (16.2)	48 (16.8)
Decreased appetite	13 (4.5)	17 (5.8)	35 (12.3)	49 (17.1)
Vomiting	12 (4.2)	16 (5.5)	29 (10.2)	45 (15.7)
Hyperglycemia	50 (17.4)	22 (7.5)	9 (3.2)	11 (3.8)
Dyspepsia	12 (4.2)	21 (7.2)	20 (7.0)	28 (9.8)
Nasopharyngitis	13 (4.5)	24 (8.2)	15 (5.3)	23 (8.0)
Abdominal distension	11 (3.8)	13 (4.5)	26 (9.2)	20 (7.0)
Urinary tract infection	19 (6.6)	10 (3.4)	15 (5.3)	23 (8.0)
Fatigue	8 (2.8)	13 (4.5)	19 (6.7)	22 (7.7)
Eructation	2 (0.7)	13 (4.5)	25 (8.8)	21 (7.3)
Arthralgia	15 (5.2)	11 (3.8)	17 (6.0)	18 (6.3)
Upper respiratory tract infection	17 (5.9)	17 (5.8)	12 (4.2)	14 (4.9)

TEAEs by PT occurring in ≥5% of overall participants.

Incidence and Severity of Nausea, Vomiting, and Diarrhea Over Time^a



Nausea, vomiting, and diarrhea occurred most frequently during dose escalation and generally decreased over time
The majority of events were mild to moderate in severity

^aNausea, vomiting, and diarrhea events combined.

Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥ 1 dose of study intervention. MedDRA Version 29.0.

MedDRA=Medical Dictionary for Regulatory Activities; N=all randomly assigned participants who took ≥ 1 dose of study drug; PBO=placebo; RETA=retatrutide.

Clinically Significant Hypoglycemia

TRIUMPH-2
OBESITY+T2D

n (%)	PBO (N=287)	RETA 4 mg (N=292)	RETA 9 mg (N=284)	RETA 12 mg (N=286)
Hypoglycemia <54 mg/dL (Level 2) or severe hypoglycemia (Level 3)^a				
All participants ^b	5 (1.7)	2 (0.7)	4 (1.4)	9 (3.1)
Participants on sulfonylurea only at baseline	1/74 (1.4)	0	1/71 (1.4)	4/76 (5.3)
Participants not on sulfonylurea at baseline	4/213 (1.9)	2/222 (0.9)	3/213 (1.4)	5/210 (2.4)
Severe hypoglycemia (Level 3)^a				
All participants	0	0	0	0

No cases of severe (Level 3) hypoglycemia were reported

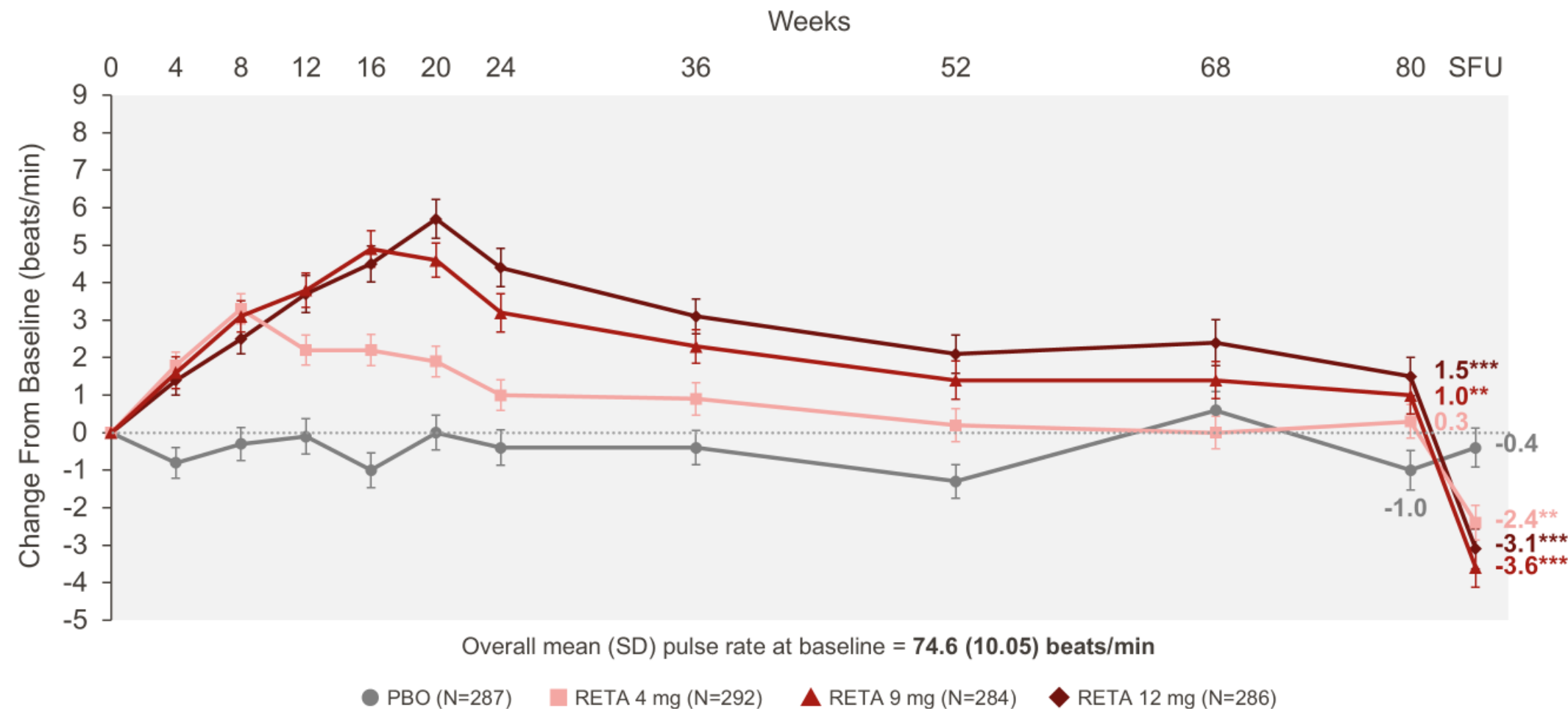
^aSevere hypoglycemia is characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. Numbers for hypoglycemia include events occurring post-baseline while on treatment and exclude hypoglycemic events occurring after initiation of any new anti-hyperglycemic therapy. ^bInsulin use prohibited except in certain cases as rescue therapy used for the shortest duration possible.

Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention. MedDRA Version 29.0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants with events meeting specified criteria;

N=number of participants in analysis population; PBO=placebo; RETA=retatrutide; T2D=type 2 diabetes.

Change in Pulse Rate From Baseline



A dose dependent increase in pulse rate was observed with RETA, which appeared to peak upon attainment of the maintenance dose, and gradually decreased thereafter

RETA vs. PBO: **p<0.01; ***p<0.001. p-values are for MBE change difference vs. PBO.

Notes: Data are shown as MBE (SE) unless stated otherwise. Data from safety participants.

MBE=model-based estimate; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SD=standard deviation; SE=standard error; SFU=safety follow-up.

Urinary Tract Infection

TEAE, n (%)	PBO N=287	RETA 4 mg N=292	RETA 9 mg N=284	RETA 12 mg N=286
UTI ^a	19 (6.6%)	11 (3.8%)	18 (6.3%)	23 (8.0%)

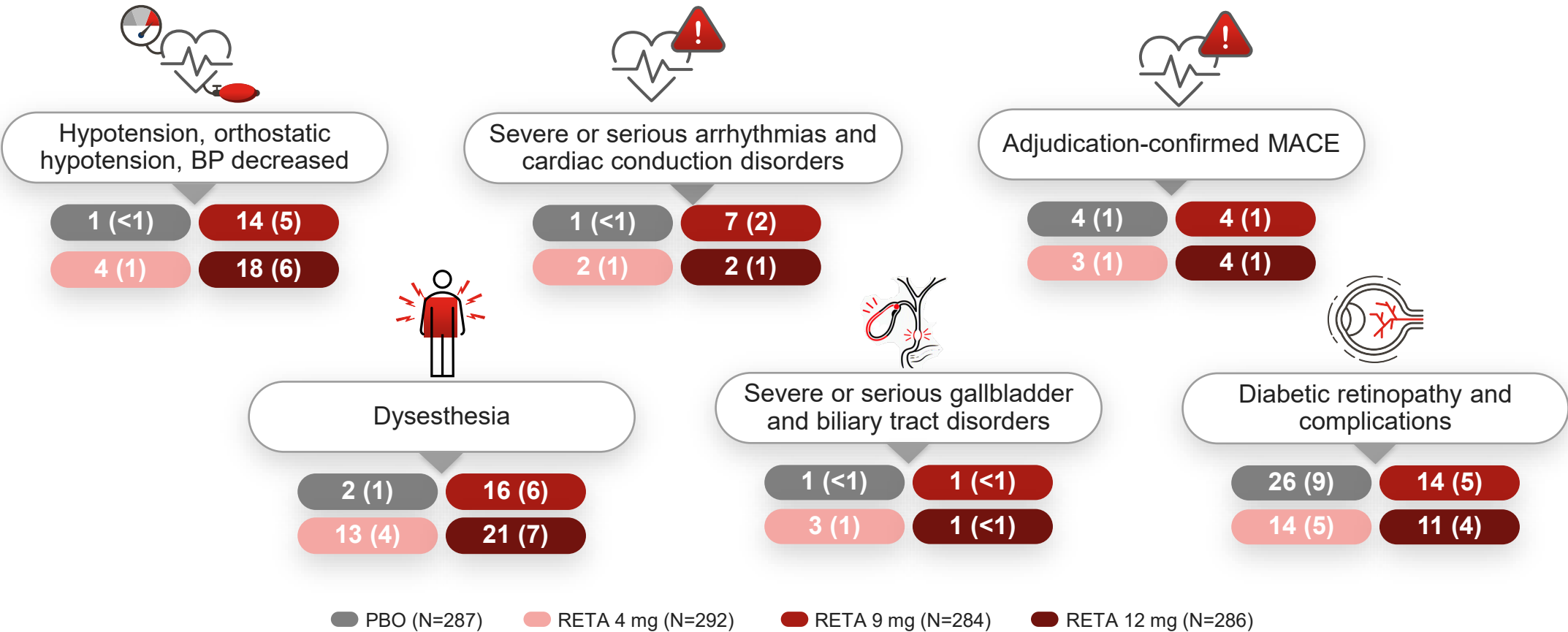
- **52** participants on RETA experienced **73** events of UTI
 - No severe event
 - No participant discontinued study drug
- **43/52 (82.7%)** participants with UTIs were female
- No difference in incidence of UTI observed in patients using / not using SGLT2i
- Events were scattered during both dose escalation period and maintenance period

**No imbalance was observed between RETA pooled doses and placebo;
events were mild to moderate with no study drug discontinuations**

^aHLT; high level term refers to a specific level in the Medical Dictionary for Regulatory Activities hierarchy used to group related preferred terms describing medical conditions in clinical trials.
AESI=adverse event of special interest; PBO=placebo; RETA=retatrutide; TEAE=treatment-emergent adverse event; UTI=urinary tract infection.

Other Key Adverse Events of Special Interest

n (%)



Incidence of key AESIs was generally consistent with other weekly incretin-based therapies¹

Notes: Data are reported for the safety data points set and presented as n (%). Safety population is all participants who were randomly assigned a study intervention and who received ≥1 dose of double-blind study intervention. MedDRA Version 29.0
 1. Jastreboff AM, et al. *N Engl J Med*. 2022;387:205-216.
 AE(SI)=adverse event (of special interest); MACE=major adverse cardiovascular events; MedDRA=Medical Dictionary for Regulatory Activities; N=all randomly assigned participants who took ≥1 dose of study drug; n=number of participants in the specified category; PBO=placebo; RETA=retatrutide.

Summary of Retatrutide Safety

TRIUMPH-2
OBESITY+T2D

TREATMENT DISCONTINUATION DUE TO AE



Up to 11.6%

- Rates were lower with 4 mg vs. PBO

SERIOUS ADVERSE EVENTS



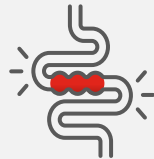
7.7%

PBO

9.4%

12 mg

GASTROINTESTINAL AEs



- Most common AEs
- Mostly mild to moderate
- Occurred mainly during dose escalation

HYPOGLYCEMIA



Level 2 (0.7% to 3.1%)

No reports of severe hypoglycemia

DYSESTHESIA



Up to 7.3%

- All events were mild or moderate
- 3 participants discontinued treatment

URINARY TRACT INFECTION



- Proportion similar between 4 mg, 9 mg, and 12 mg pooled and PBO
- All AEs were mild to moderate
- None required treatment discontinuation

Overall safety profile of RETA in TRIUMPH-2 was generally consistent with the safety profile of other incretin-based medications