Evidence for treatment targets from trials with obesity medications

Carel le Roux

University College Dublin

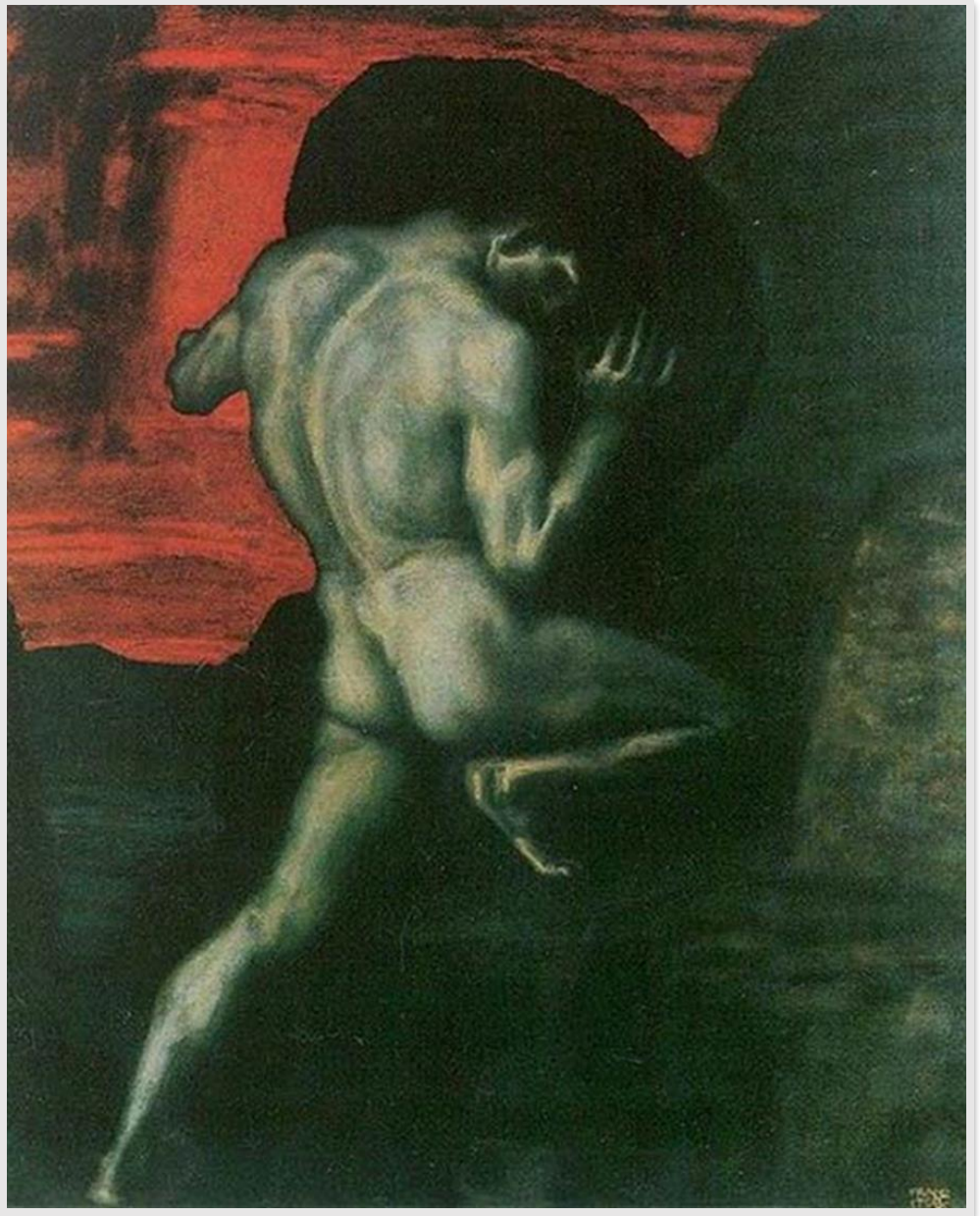
Ulster University

Scene of the plague in Florence in 1348
Described by Boccaccio
Painted by Baldassarre Calamai

Disclosures

- Consilient Health
- Novo Nordisk
- Herbalife
- Johnson & Johnson
- Covidien
- Fractyl Health
- GI Dynamics
- Olympus
- Lilly
- Boehringer Ingelheim
- Keyron

- AstraZeneca
- Roche
- Arrowhead Pharmaceuticals
- Amgen



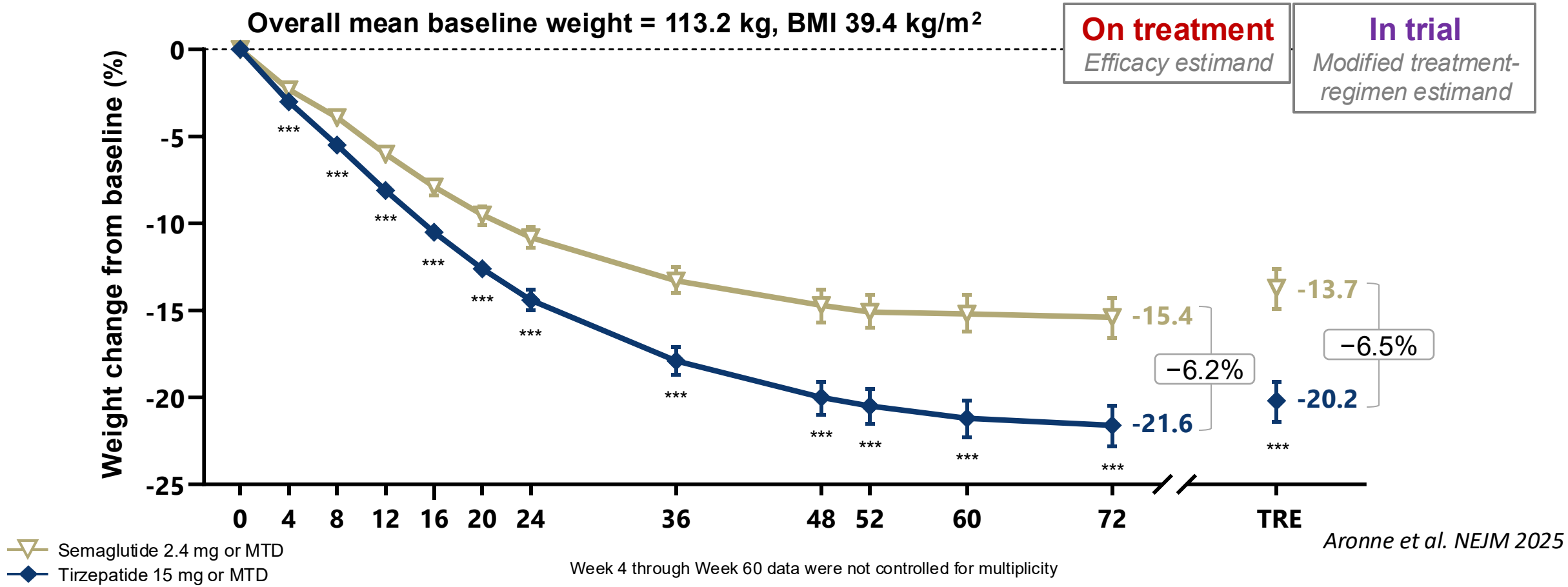
Sisyphus
Painted by Franz von Stuck, 1920

Validation of targets BMI <27 kg/m^2 and WHtR <0.53 in clinical trials

BMI, body mass index; WHtR, waist to height ratio.

Tirzepatide compared with semaglutide for the treatment of obesity: The SURMOUNT-5 trial

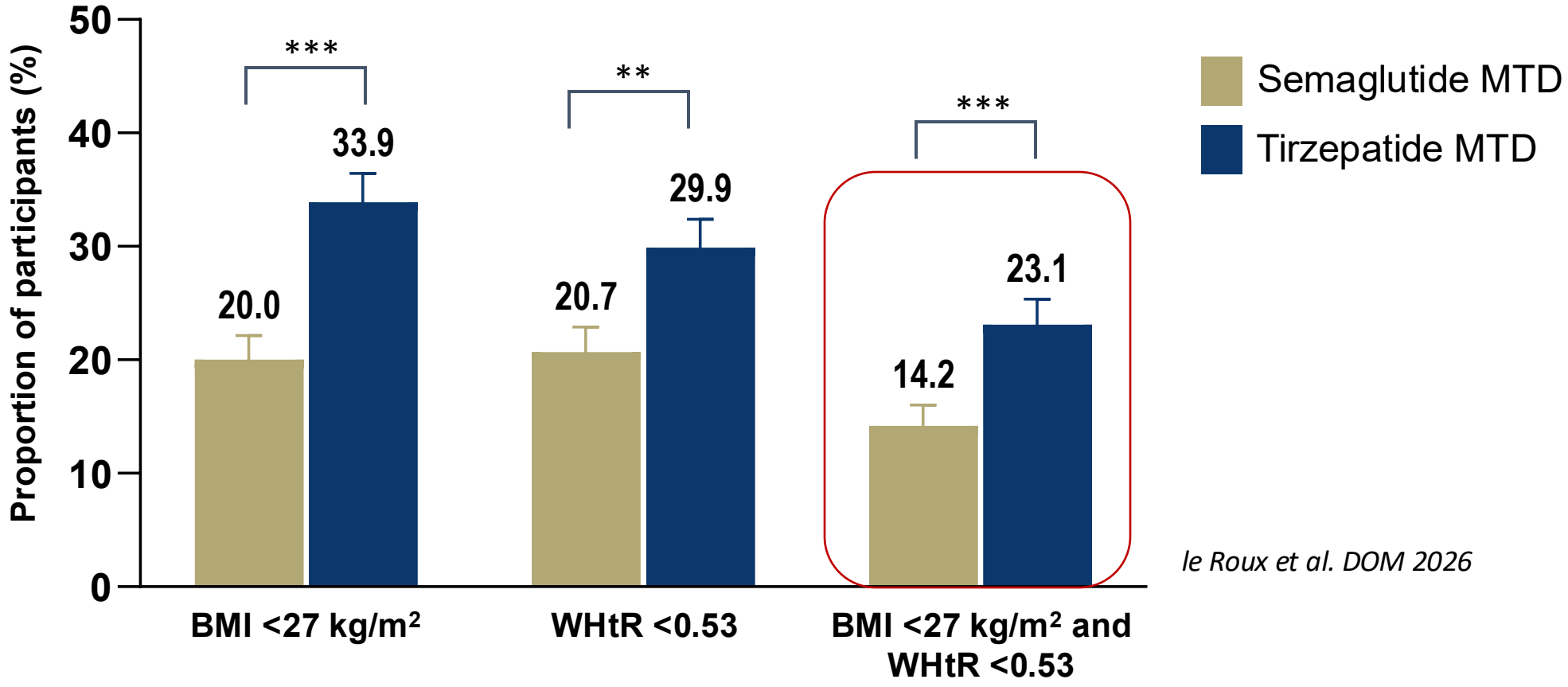
SURMOUNT-5: Percentage weight reduction from baseline to week 72, semaglutide vs tirzepatide



Aronne et al. NEJM 2025

***p<0.001 versus semaglutide. Data are LSM ± 95% CI.
BMI, body mass index; CI, confidence interval; LSM, least squares mean; MTD, maximum tolerated dose; TRE, treatment regimen estimand.
Aronne LJ et al. *N Engl J Med* 2025;393:26–36.

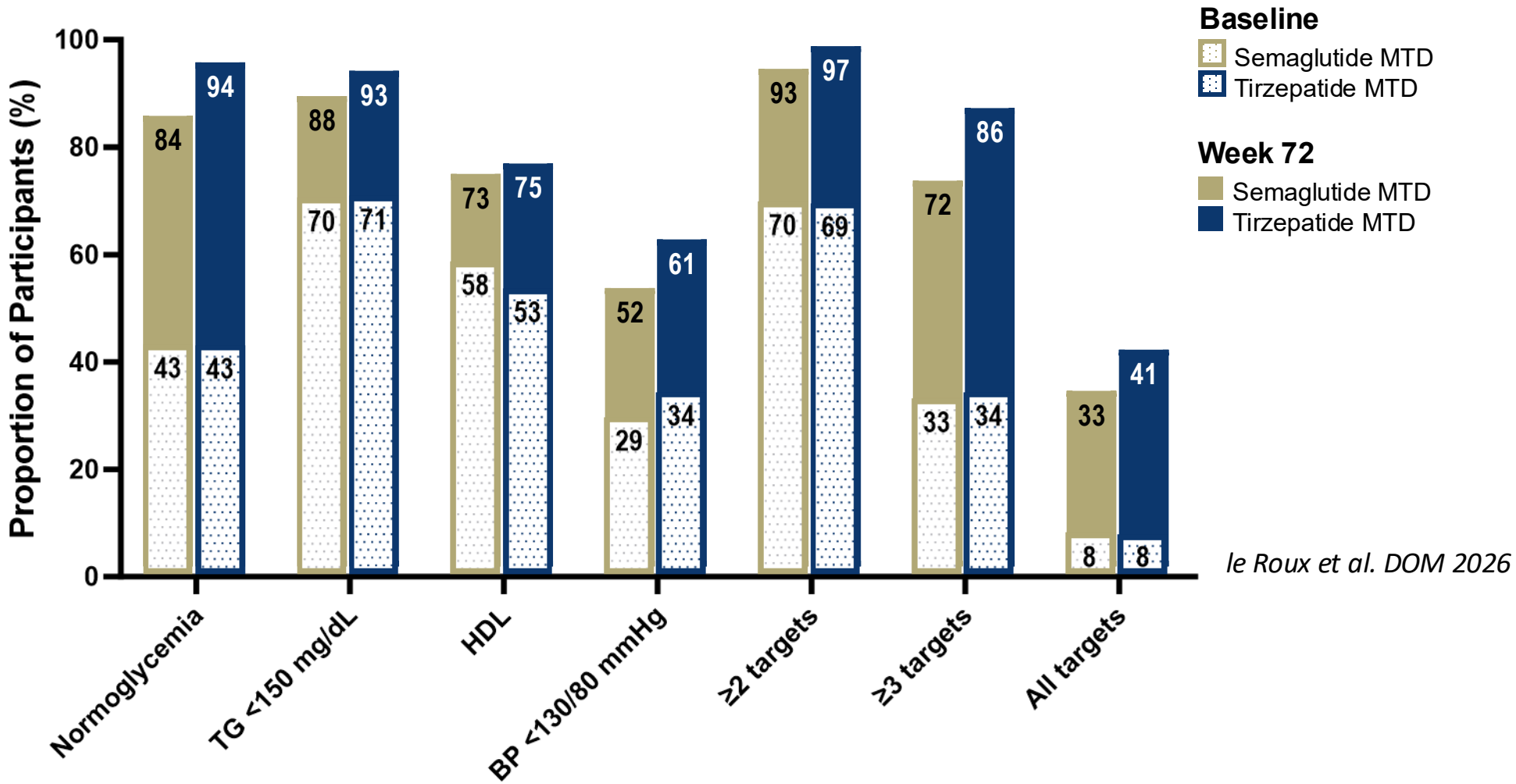
SURMOUNT-5: Proportion of participants reaching treat-to-target thresholds at week 72



le Roux et al. DOM 2026

Week 72 data in participants who discontinued study drug early was imputed by multiple imputation based on missing at random assumption using on-treatment data.
Error bars show 95% confidence intervals. Treatment comparisons were made via logistic regression with the aid of Rubin's rule. **p<0.01 versus semaglutide.
***p<0.001 versus semaglutide.
BMI, body mass index; MTD, maximum tolerated dose; WHtR, weight to height ratio.
le Roux CW et al. *Diabetes Obes Metab* 2026;28:3355–3366.

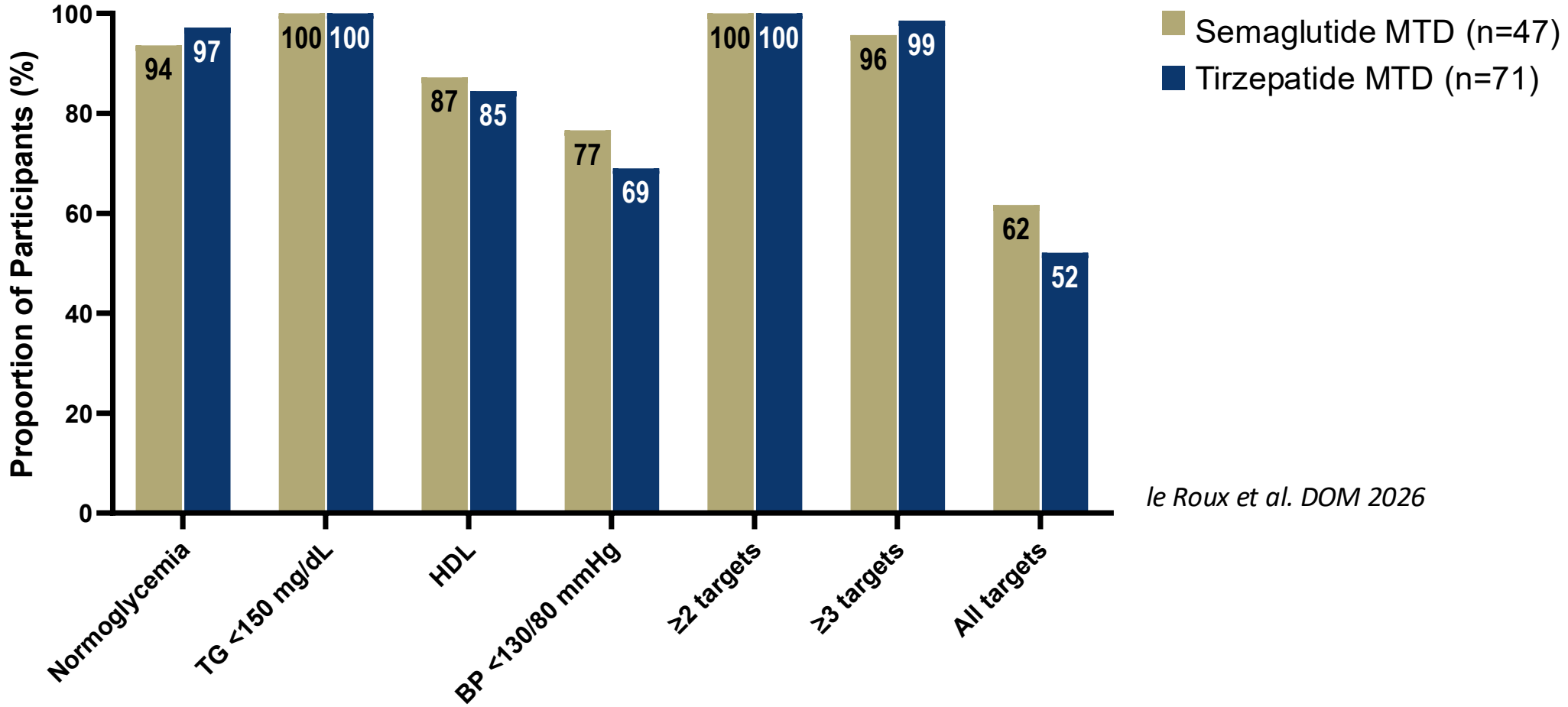
SURMOUNT-5: Proportion of participants with normalisation of cardiometabolic parameters



le Roux et al. DOM 2026

Normoglycemia (HbA_{1c} <5.7% and FSG <100 mg/dL). HDL cholesterol sex-specific goals (female ≥50 mg/dL, male ≥40 mg/dL). Data are mean based on observed data at Week 72 or LOCF for participants who completed treatment.
BP, blood pressure; FSG, fasting serum glucose; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; LOCF, last observation carried forward; MTD, maximum tolerated dose; TG, triglycerides.
le Roux CW et al. *Diabetes Obes Metab* 2026;28:3355–3366.

SURMOUNT-5: Normalisation of cardiometabolic parameters in participants reaching WHtR <0.53 and BMI <27 kg/m^2 at week 72

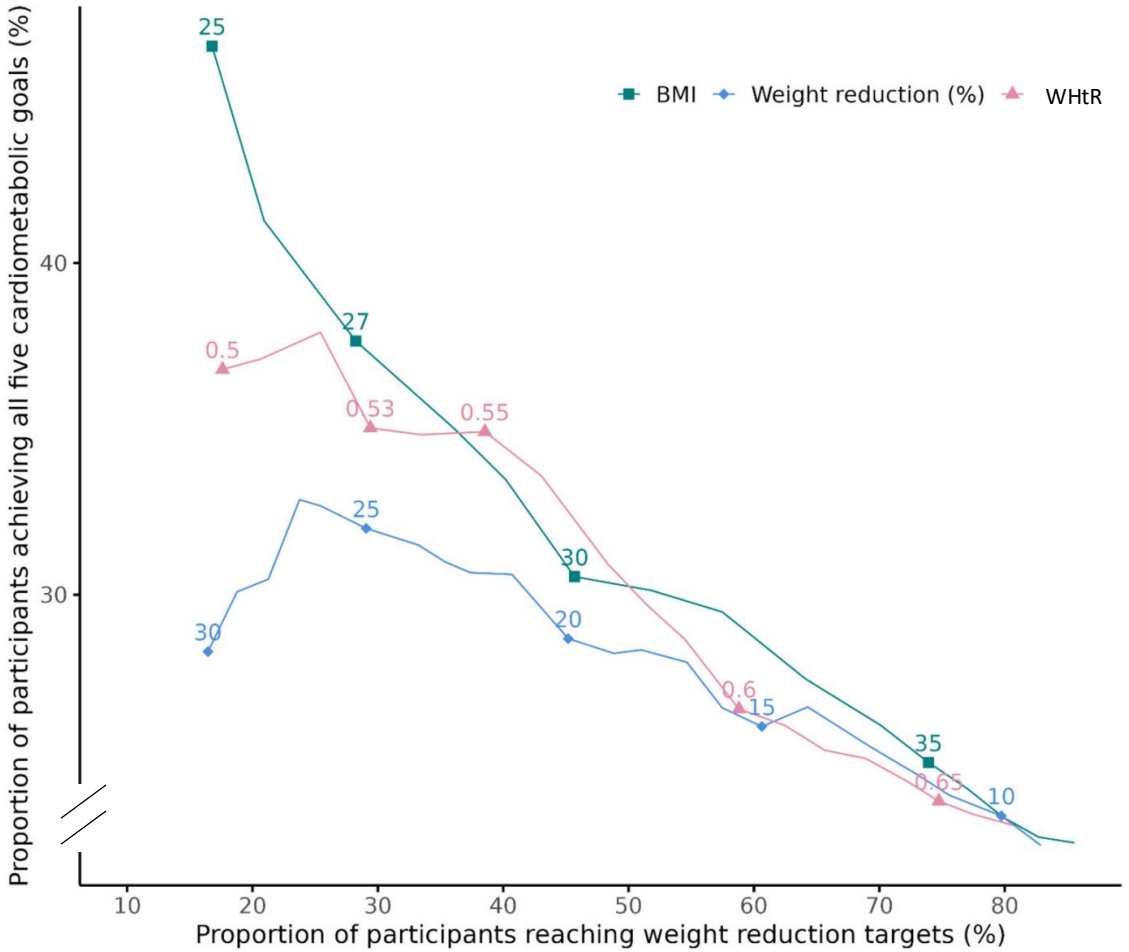


le Roux et al. DOM 2026

Normoglycemia (HbA_{1c} <5.7% and FSG <100 mg/dL). HDL cholesterol sex-specific goals (female ≥50 mg/dL, male ≥40 mg/dL). Data are mean based on observed data at Week 72 or LOCF for participants who completed treatment.
BMI, body mass index; BP, blood pressure; FSG, fasting serum glucose; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; LOCF, last observation carried forward; MTD, maximum tolerated dose; TG, triglycerides; WHtR, waist to height ratio.

le Roux CW et al. *Diabetes Obes Metab* 2026;28:3355–3366.

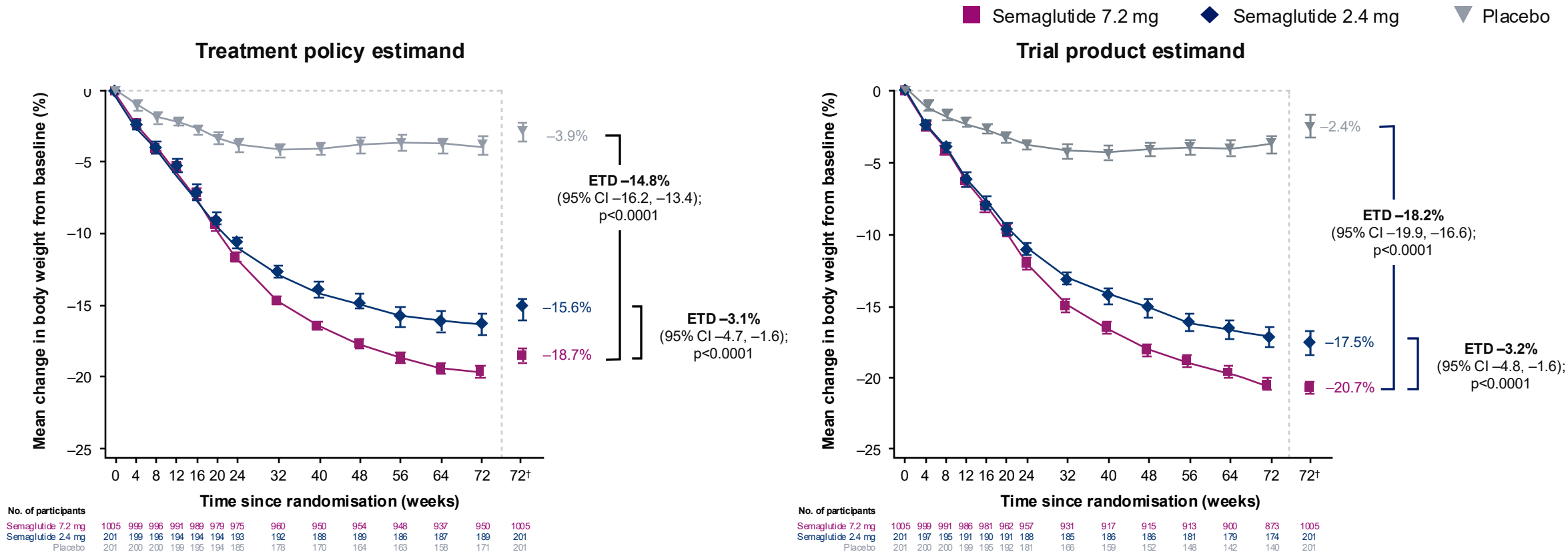
SURMOUNT-5: Treat-to-target outcomes



le Roux et al. DOM 2026

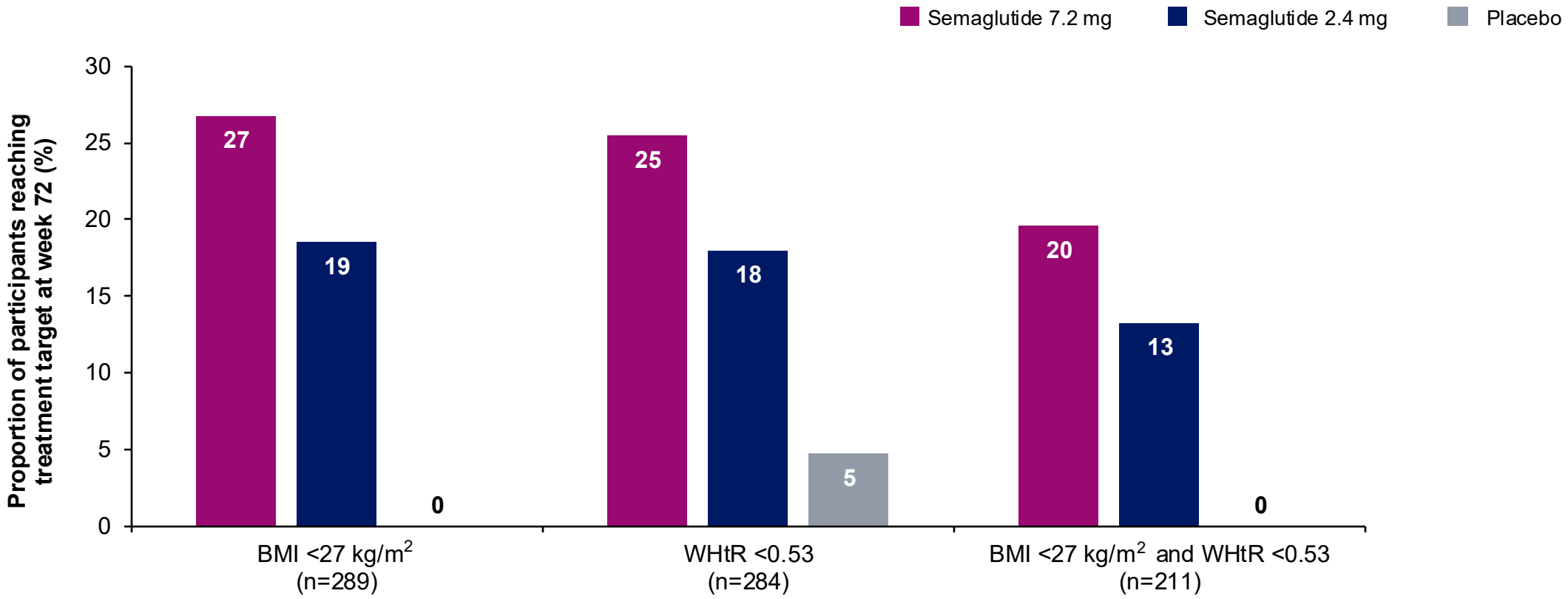
BMI, body mass index; WHtR, waist to height ratio.
le Roux CW et al. *Diabetes Obes Metab* 2026;28:3355–3366.

STEP UP: Semaglutide 2.4 mg versus 7.2 mg: Change in body weight (%) from baseline to week 72 in the overall STEP UP population[1,2]



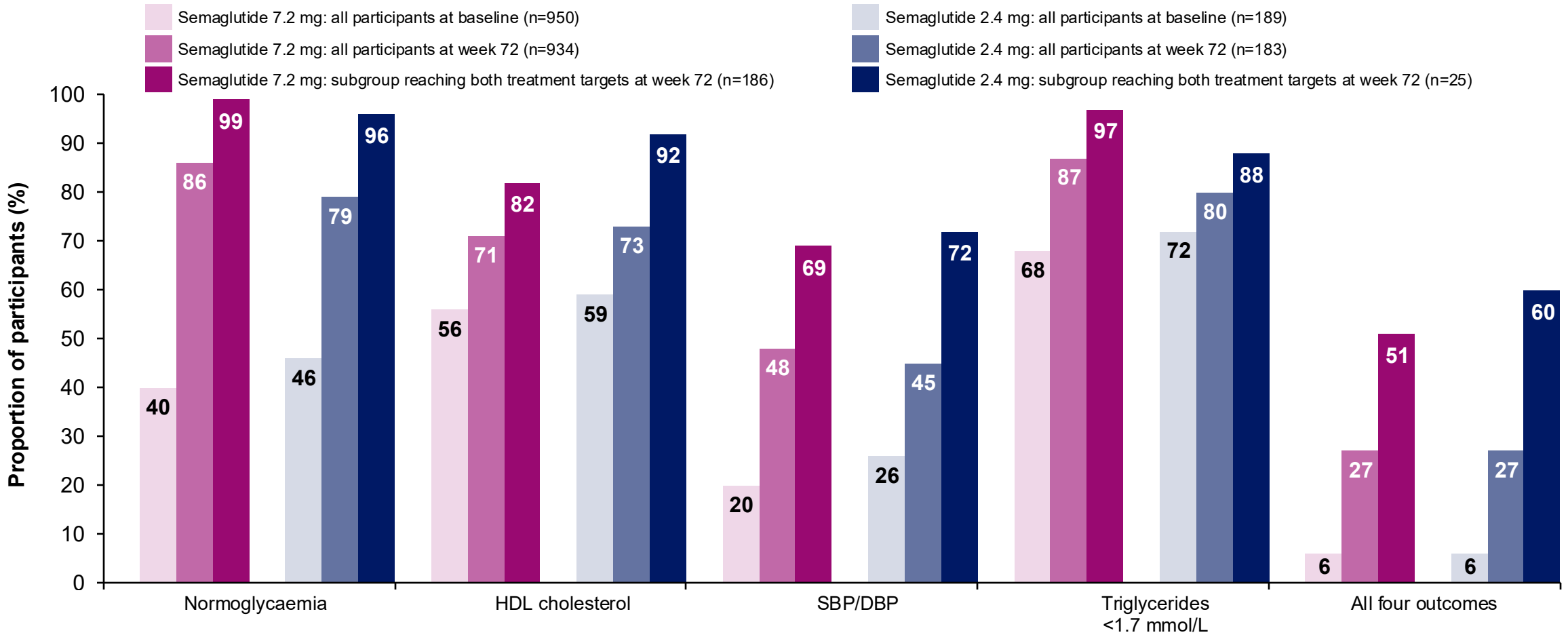
Sections of these figures have been reproduced from Wharton et al.[2] with permission from the American Diabetes Association.
Data are for the full analysis set, and observed data are from the in-trial observation period (left) and from the on-treatment observation period (right). Treatment comparisons were estimated with the treatment policy estimand (left), and the trial product estimand (right). Error bars are 95% CIs, and the numbers below the graphs are the number of participants contributing to the mean. †Estimated mean change at week 72.
CI, confidence interval; ETD, estimated treatment difference.
1. Wharton S et al. *Lancet Diabetes Endocrinol* 2025;13:949–963; 2. Wharton S et al. *Diabetes* 2025;74(Suppl 1):1966–LB.
le Roux C et al. Previously presented at the 43rd Annual Meeting of The Obesity Society held at ObesityWeek®, 4–7 November 2025, Atlanta, GA, USA.

STEP UP: Proportions of participants reaching treatment targets at week 72



Data are from the in-trial period for participants with observed data during weeks 0–72. Overall, 1310 participants had data available for all cardiometabolic outcomes at baseline and week 72.
BMI, body mass index; WHtR, waist to height ratio.
le Roux C et al. Previously presented at the 43rd Annual Meeting of The Obesity Society held at ObesityWeek®, 4–7 November 2025, Atlanta, GA, USA.

STEP UP: Normalisation of cardiometabolic parameters in participants reaching WHtR <0.53 and BMI <27 kg/m^2 at Week 72

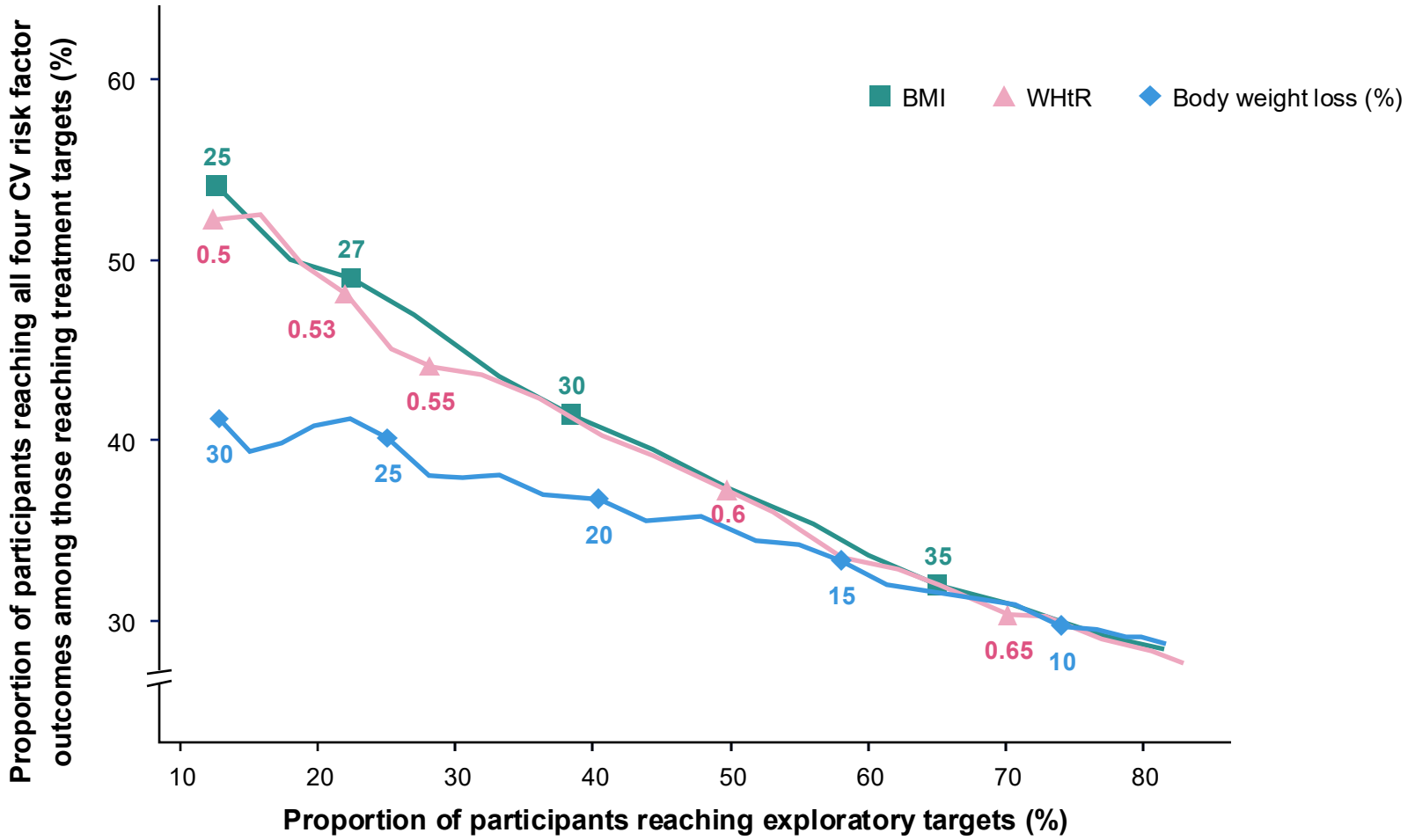


Data are from the in-trial period for participants with observed data during weeks 0–72. Overall, 1310 participants had data available for all cardiometabolic outcomes at baseline and week 72. Normoglycaemia is defined as HbA_{1c} <5.7% and FPG <5.6 mmol/L; HDL cholesterol ≥1.3 mmol/L (female) or ≥1.0 mmol/L (male); SBP/DBP <130/80 mmHg; triglycerides <1.7 mmol/L.

DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; SBP, systolic blood pressure.

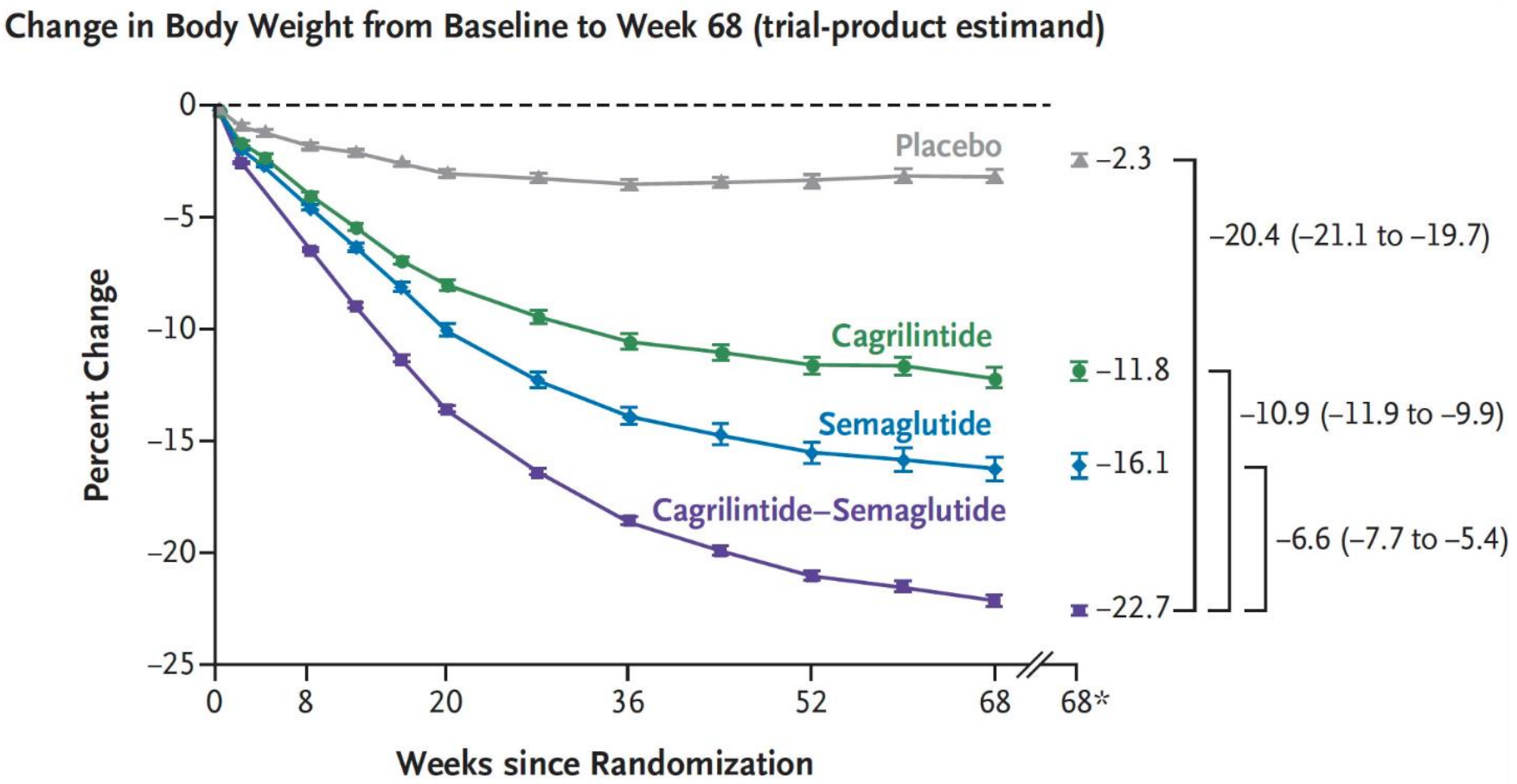
le Roux C et al. Previously presented at the 43rd Annual Meeting of The Obesity Society held at ObesityWeek®, 4–7 November 2025, Atlanta, GA, USA.

STEP UP: Treatment target performance comparison



Data are from the in-trial period for participants with observed data during weeks 0–72. Overall, 1310 participants had data available for all cardiometabolic outcomes at baseline and week 72.
Data from the semaglutide 2.4 mg and 7.2 mg treatment groups were pooled.
BMI, body mass index; CV, cardiovascular; WHtR, waist to height ratio.
le Roux C et al. Previously presented at the 43rd Annual Meeting of The Obesity Society held at ObesityWeek®, 4–7 November 2025, Atlanta, GA, USA.

REDEFINE 1: Change in body weight

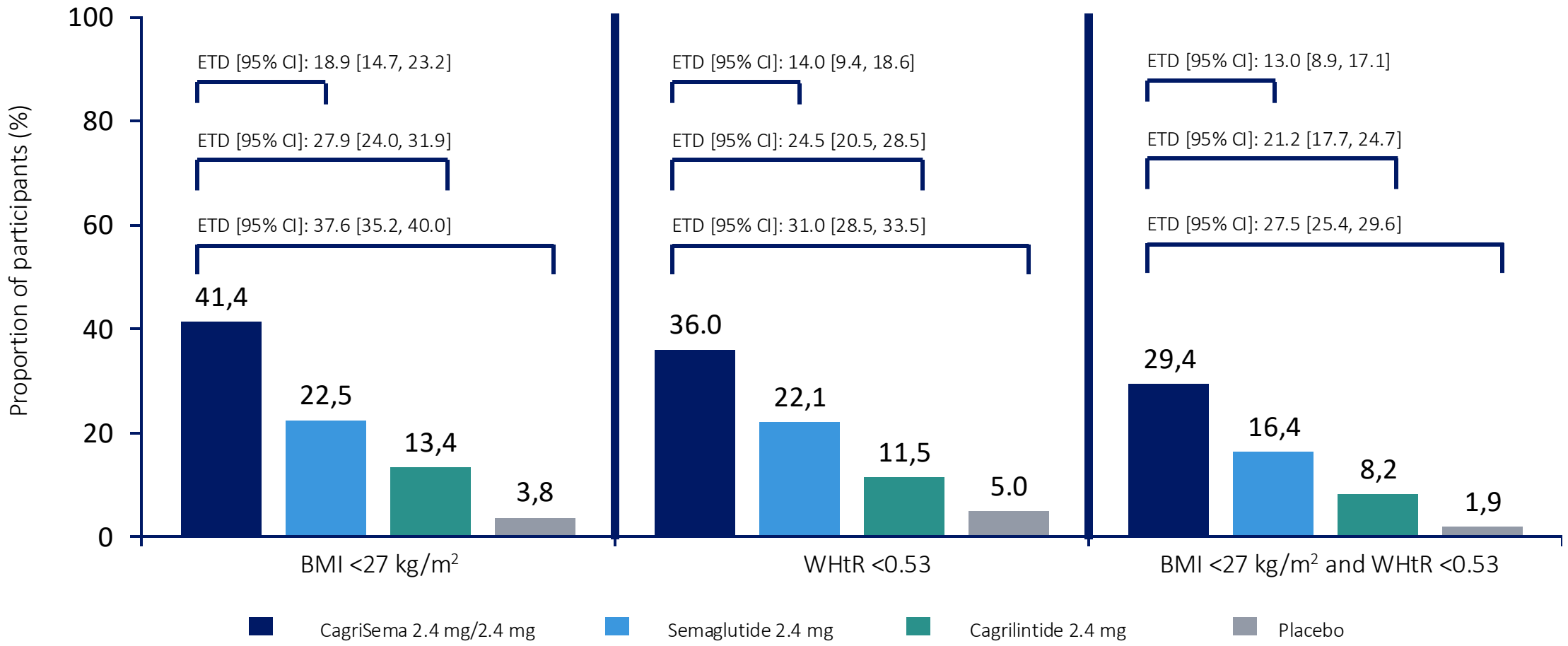


Estimated mean percent change in body weight and estimated differences among the groups with corresponding confidence intervals, as calculated on the basis of the trial-product estimand (analysis of the effects if the trial products were taken as intended). The values shown from week 0 to week 68 were observed during the on-treatment period, which was defined as the time from the first administration of an active drug or placebo to the first discontinuation (i.e., the date when no trial product had been administered for 14 days) without rescue intervention (i.e., other obesity medication or bariatric surgery). Bars indicate standard errors. The numbers at risk indicate participants with data that contributed to the mean. The asterisk indicates that data shown for this time point are the estimated means according to the trial product estimand.

Garvey WT et al. *N Engl J Med* 2025;393:635–647.

REDEFINE 1: The proportion of participants achieving anthropometric targets was higher with CagriSema 2.4 mg/2.4 mg versus monotherapies or placebo

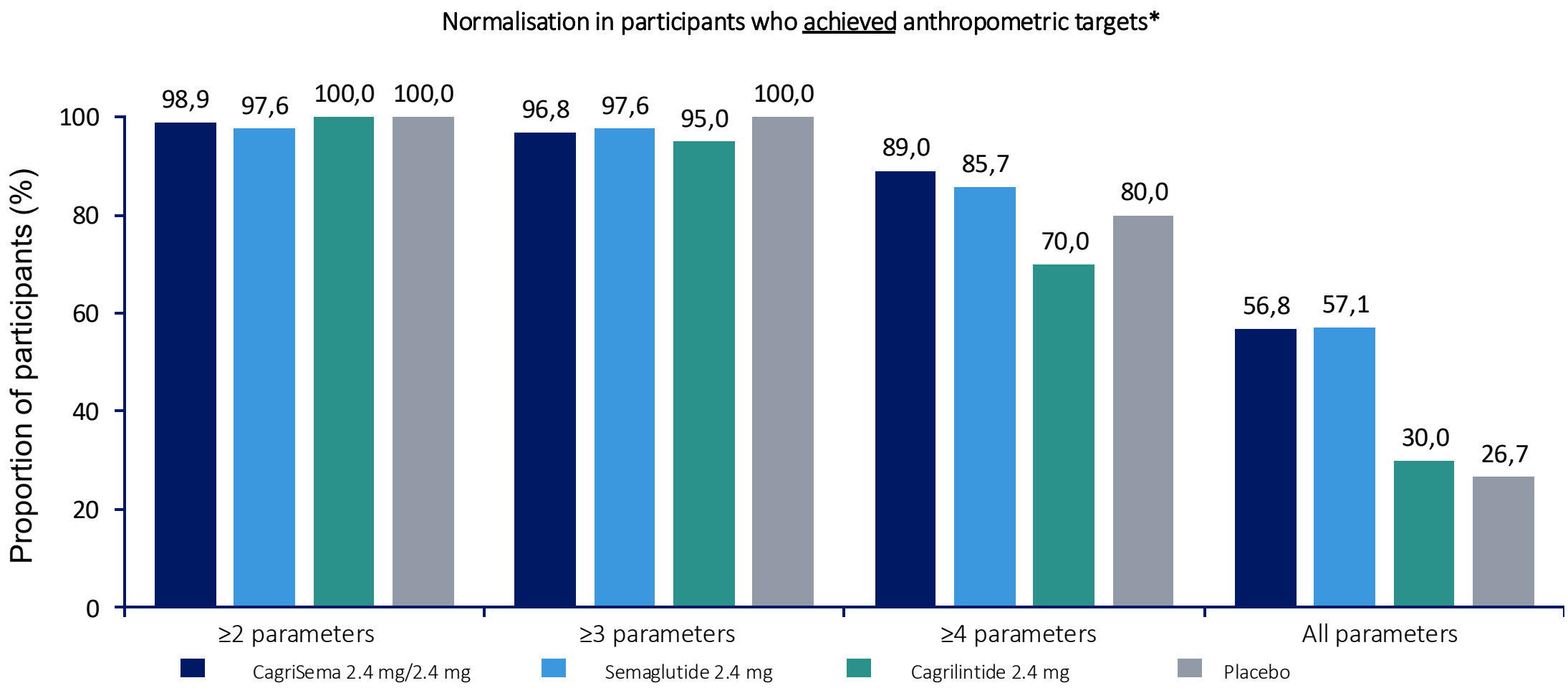
Oral presentation **AD04.03**



Data are for the trial product estimand, based on a marginal logistic regression model including data on treatment without rescue. Missing data and data off treatment are imputed assuming missing at random.
BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference; WHtR, waist to height ratio.
Busetto L et al. Presented at the 33rd European Congress on Obesity (ECO), 12–15 May 2026, Istanbul, Türkiye.

REDEFINE 1: In participants who achieved anthropometric targets, normalisation of multiple parameters was generally greatest in those receiving CagriSema and semaglutide

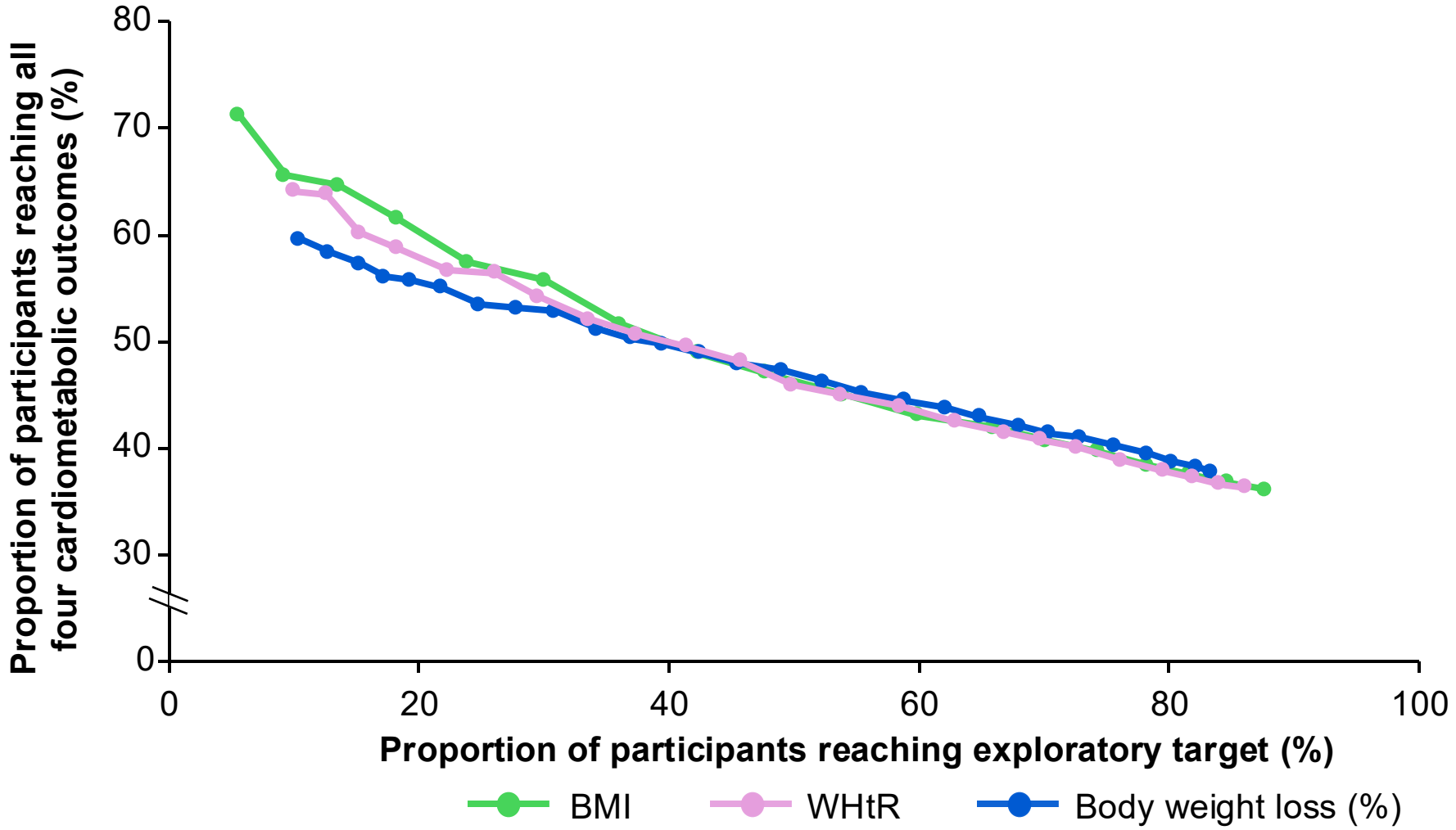
Oral presentation **AD04.03**



Data are observed data from the on-treatment period showing treatment completers only. *BMI <27 kg/m² and WHtR <0.53.
BMI, body mass index; WHtR, waist-to-height ratio.

Busetto L et al. Presented at the 33rd European Congress on Obesity (ECO), 12–15 May 2026, Istanbul, Türkiye.

REDEFINE 1: Treatment target performance comparison



BMI, body mass index; WHtR, waist to height ratio..

Summary

- Percentage weight loss less robust than the treatment targets of BMI <27 kg/m^2 or WHtR <0.53 for achieving a lower CV risk state
- Achieving the treat-to-target thresholds resulted in a lower CV risk state compared with those who did not reach target thresholds
- Future research with a treat-to-target approach should include outcomes meaningful to patients, with the proposed thresholds requiring further study before applied in clinical practice

Busetto L et al. *Obes Sci Pract* 2025;11:e70094.
BMI, body mass index; CV, cardiovascular; WHtR, waist to height ratio.