Indications, efficacy and safety of the new anti-obesity medications

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Conflict of Interest Disclosure

A/Prof Samantha L Hocking has received research grants from The Diabetes Australia Research Trust/Program and The National Health and Medical Research Council of Australia; received honoraria for lectures from Eli Lilly, Novo Nordisk, Inova, Sanofi Aventis, Astra Zeneca, Servier and Amgen and has been or is on advisory boards for Novo Nordisk, Eli Lilly, Inova, Seqirus and Pfizer; and has been an investigator for industry-sponsored clinical trials run by Novo Nordisk, Eli Lilly, Rhythm pharmaceuticals, Millendo, Spruce Biosciences and Amgen.

Overview

- Indications for new anti-obesity medications
- Efficacy of semaglutide 2.4 mg and tirzepatide for obesity
- Safety profiles of semaglutide and tirzepatide

Pharmacotherapy should be used when complications are present

	BMI 25–26.9 kg/m²	BMI 27–29.9 kg/m²	BMI 30–34.9 kg/m²	BMI 35–39.9 kg/m²	BMI ≥40 kg/m²
Surgery 			When optimal medical and behavioural management has been insufficient	With adiposity-related complications	+
Pharmacotherapy 		With adiposity-related complications	+	+	+
Behavioural modification 	+	+	+	+	+

- BMI, body mass index.

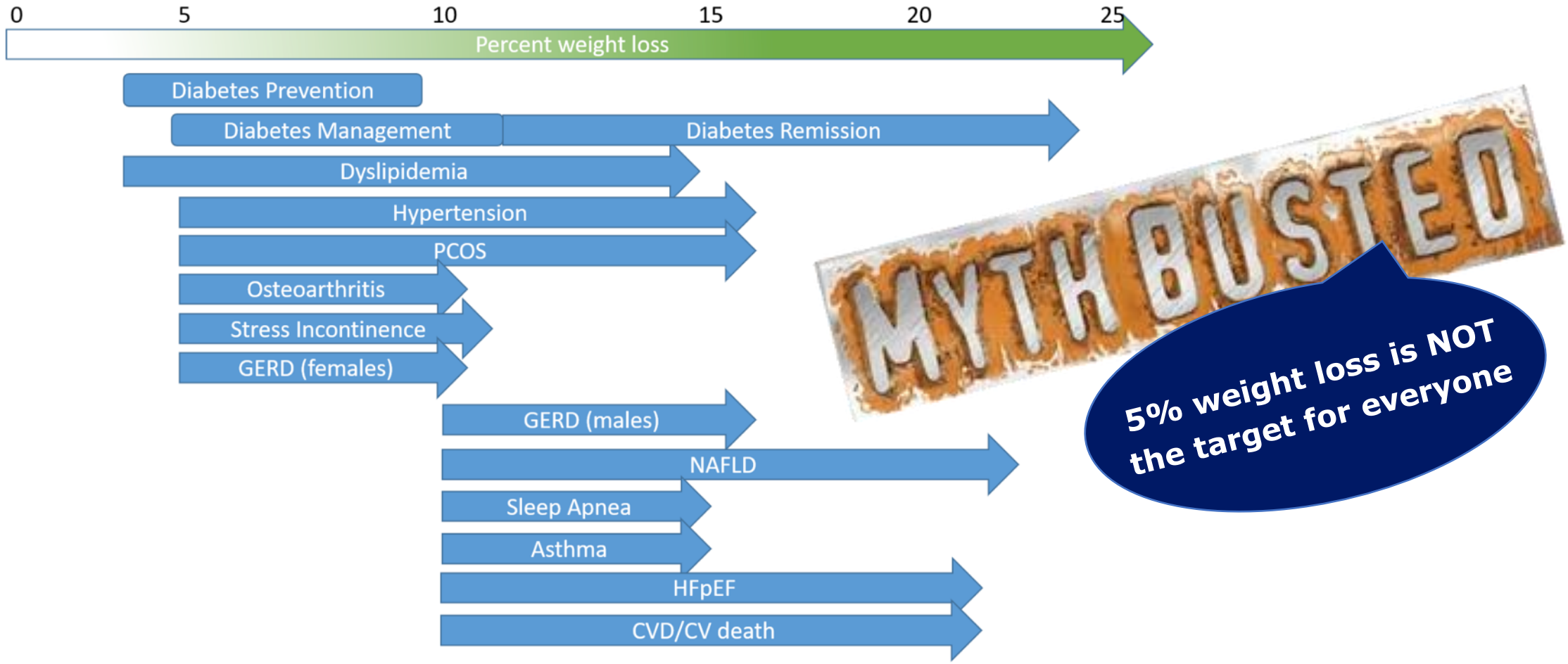
Wharton S et al. CMAJ 2020;192:E875–91.

Treating obesity to target for prevention and treatment of complications

	T2D	Hypertension	CVD	ABCD/obesity
Biomarker target	HbA_{1c}	Blood pressure	LDL cholesterol	% weight loss
Reason for target	Prevent complications			
Complications	CKD, retinopathy, neuropathy, CVD	CHF, stroke, CKD	MI, stroke, amputation	T2D, HTN, NAFLD/NASH, CVD risk, CKD, sleep apnea, osteoarthritis

References: Garvey et al, JCEM, 2022;107(4):e1339–e1347

‘dose-response’ relationships between weight loss and obesity-related complications



ORIGINAL ARTICLE

Once-Weekly Semaglutide in Adults with Overweight or Obesity

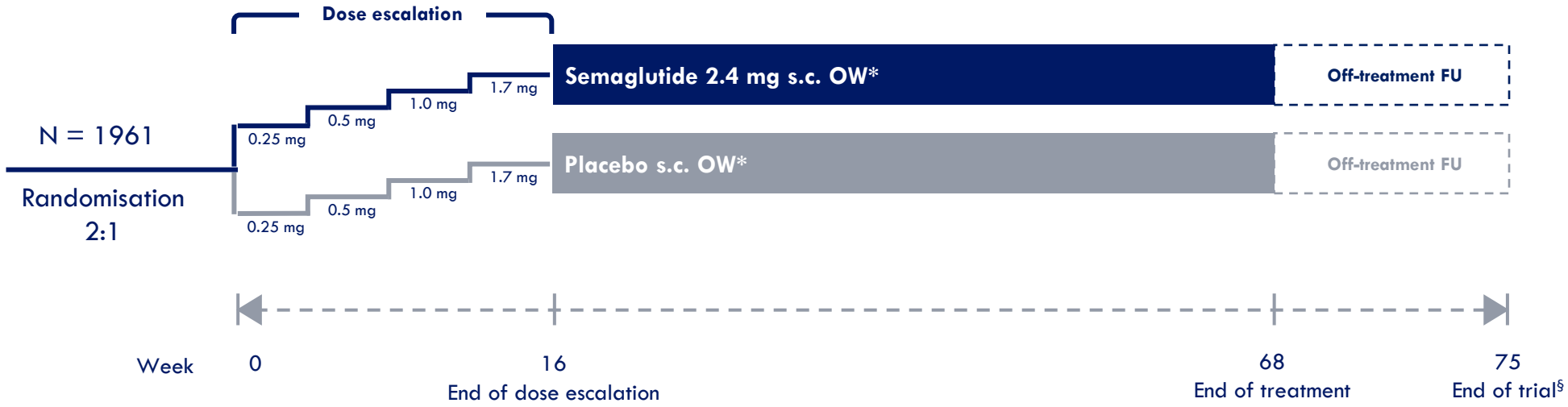
John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

Wilding JPH et al N Engl J Med 2021; 384:989-1002.

Study Design and Inclusion Criteria of Participants

Inclusion criteria

- Male or female
- ≥18 years
- BMI: ≥30 kg/m^2 or ≥27 kg/m^2 and ≥1 comorbidity
- HbA_{1c} ≤ 6.5%



*As an adjunct to lifestyle intervention (–500 kcal/day diet + 150 min/week physical activity). §End of trial for main phase.

Primary endpoints (Week 68)

- % weight loss from baseline
- ≥5% responders

Confirmatory secondary endpoints (Week 68)

- ≥10% and ≥15% responders
- Waist circumference, systolic blood pressure, SF-36 physical functioning, IWQOL-Lite-CT physical function

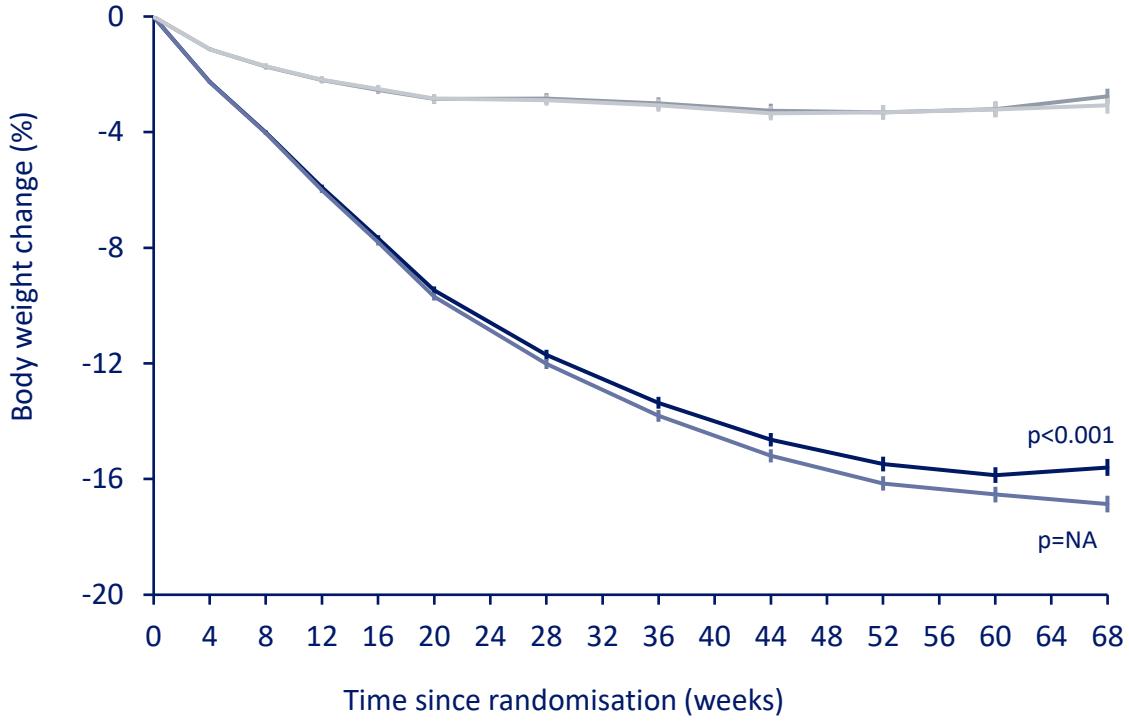
BMI: body mass index. **FU:** follow-up. **HbA_{1c}:** glycated haemoglobin. **IWQOL-Lite-CT:** Impact of Weight on Quality of Life–Lite Clinical Trials Version questionnaire. **OW:** once weekly. **s.c.:** subcutaneous. **SF-36:** Short-Form 36-item Health Survey.

Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

Semaglutide 2.4mg as an adjunct to lifestyle modification

Observed body weight change over time

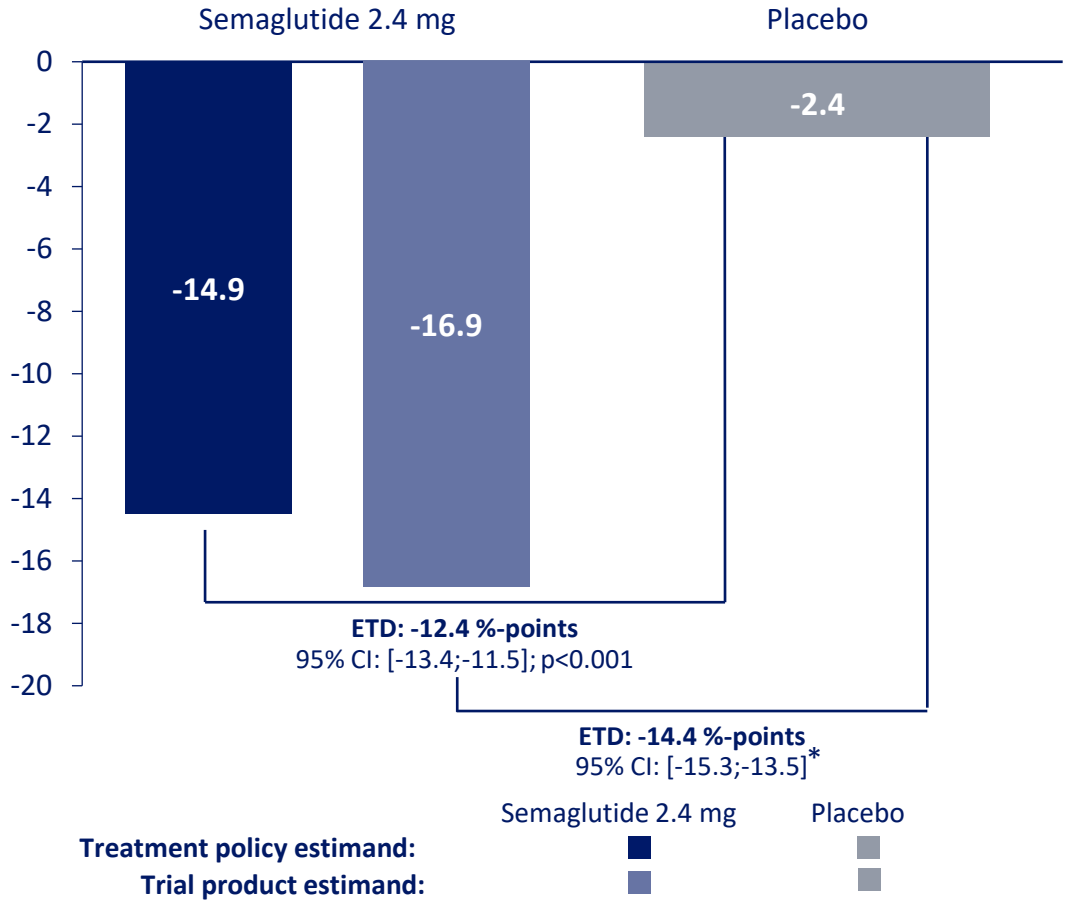
(Mean at baseline: 105.3 kg)



94.9% of participants randomised to semaglutide completed the STEP 1 study (n=1240/1306) and of these, 89.6% were receiving the 2.4 mg maintenance dose at Week 68.

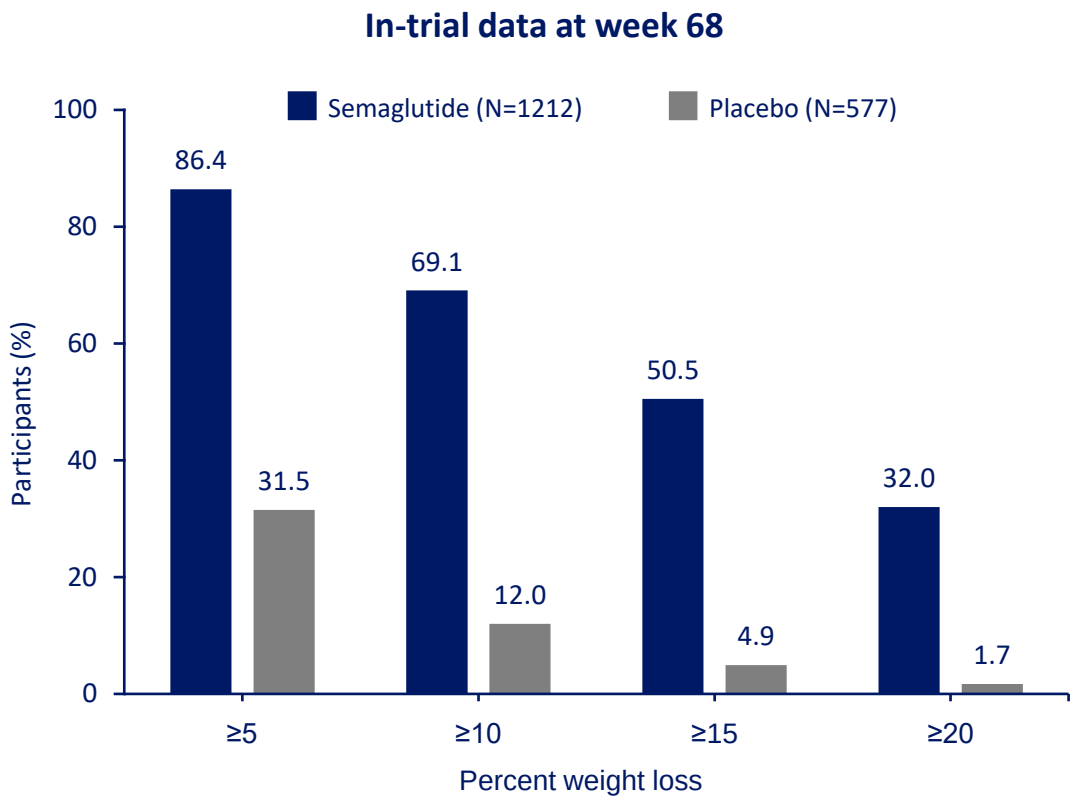
Estimated change from baseline to Week 68

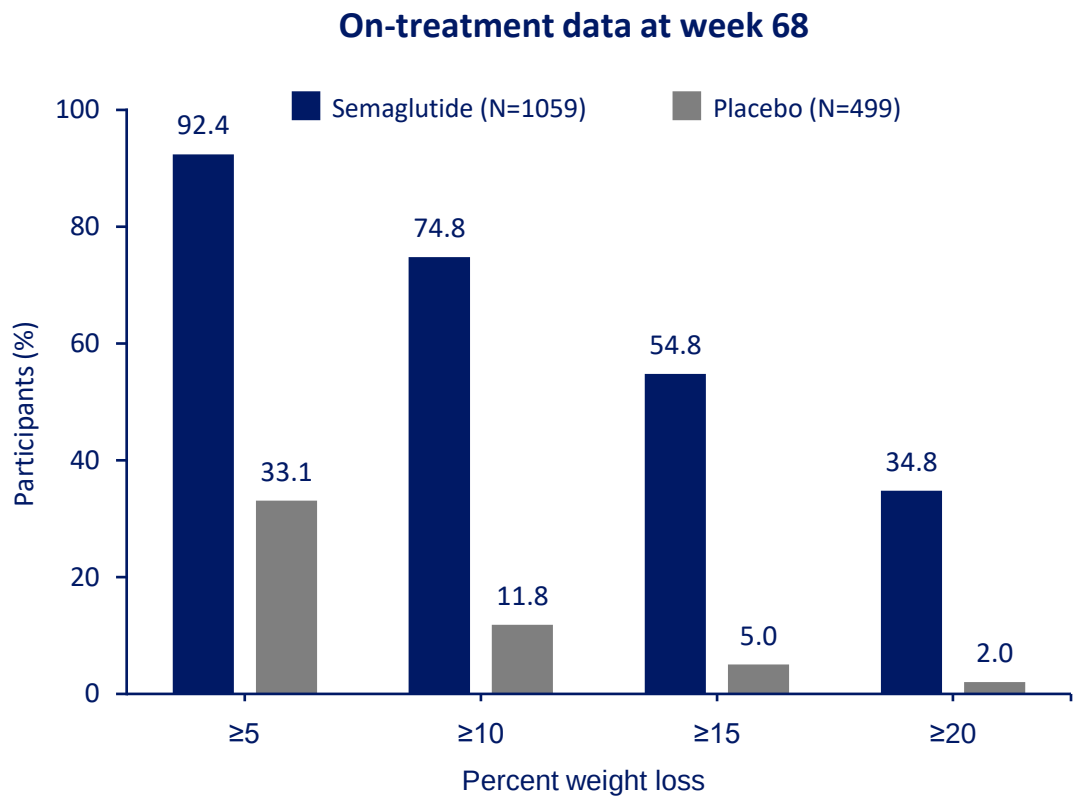
(Treatment policy and trial product estimands)



Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

Semaglutide 2.4 mg – Achievement of categorical body weight reductions at week 68





Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

Improvements in health parameters at Week 68

CONFIRMATORY SECONDARY ENDPOINTS

-13.5 cm
with semaglutide 2.4 mg vs -4.1 cm placebo, p<0.001
Waist circumference

-6.2 mmHg
with semaglutide 2.4 mg vs -1.1 mmHg placebo, p<0.001
Systolic blood pressure

+2.2
with semaglutide 2.4 mg vs +0.4 placebo, p<0.001
SF-36 physical function score

+14.7
with semaglutide 2.4 mg vs +5.3 placebo, p<0.001
IWQOL-Lite-CT physical function score

SUPPORTIVE SECONDARY ENDPOINTS

-0.45%
with semaglutide 2.4 mg vs -0.15% placebo, p=NA*
HbA_{1c}

-8.4 mg/dL
with semaglutide 2.4 mg vs -0.5 mg/dL placebo, p=NA*
Fasting plasma glucose

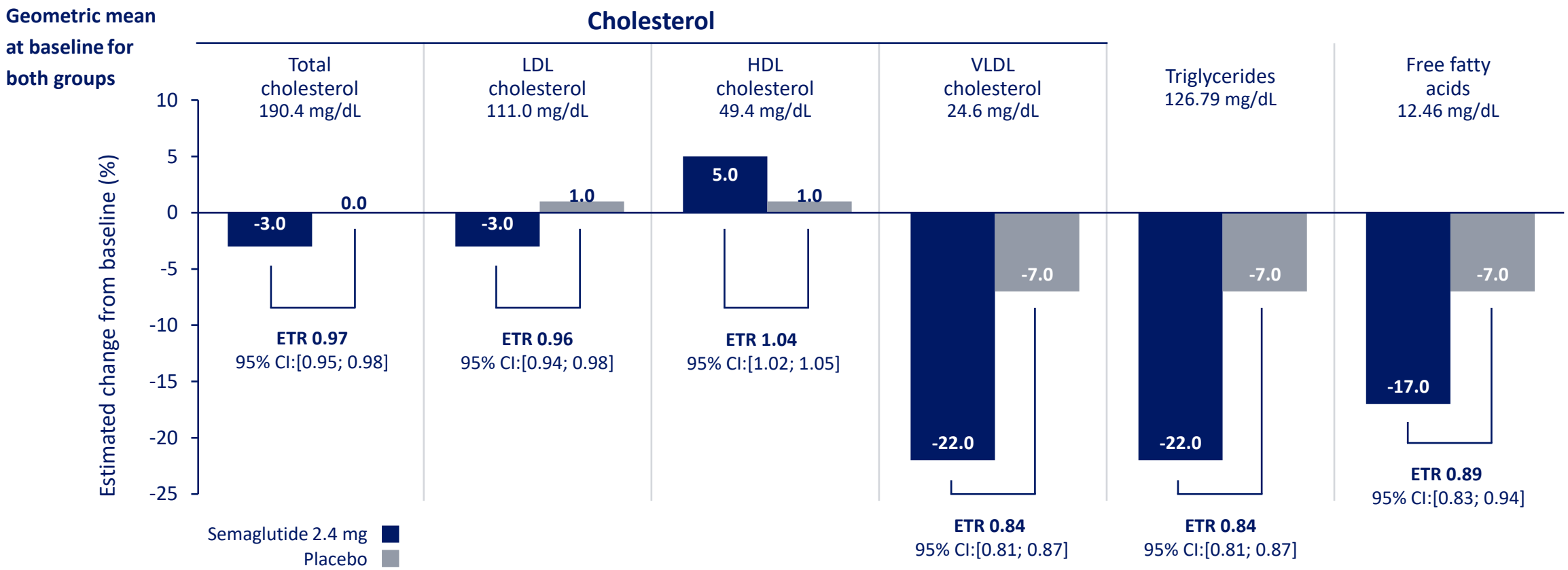
-2.8 mmHg
with semaglutide 2.4 mg vs -0.4 mmHg placebo, p=NA*
Diastolic blood pressure

-53.0%
with semaglutide 2.4 mg vs -15.0% placebo, p=NA*
C-reactive protein

***Not part of the statistical testing hierarchy; p-value not available (NA).**
All values are estimated for the treatment policy estimand.
HbA_{1c}: glycated haemoglobin. **IWQOL-Lite-CT:** Impact of Weight on Quality of Life–Lite Clinical Trials Version questionnaire. **SF-36:** Short-Form 36-item Health Survey.

Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

Changes in fasting lipids at Week 68*

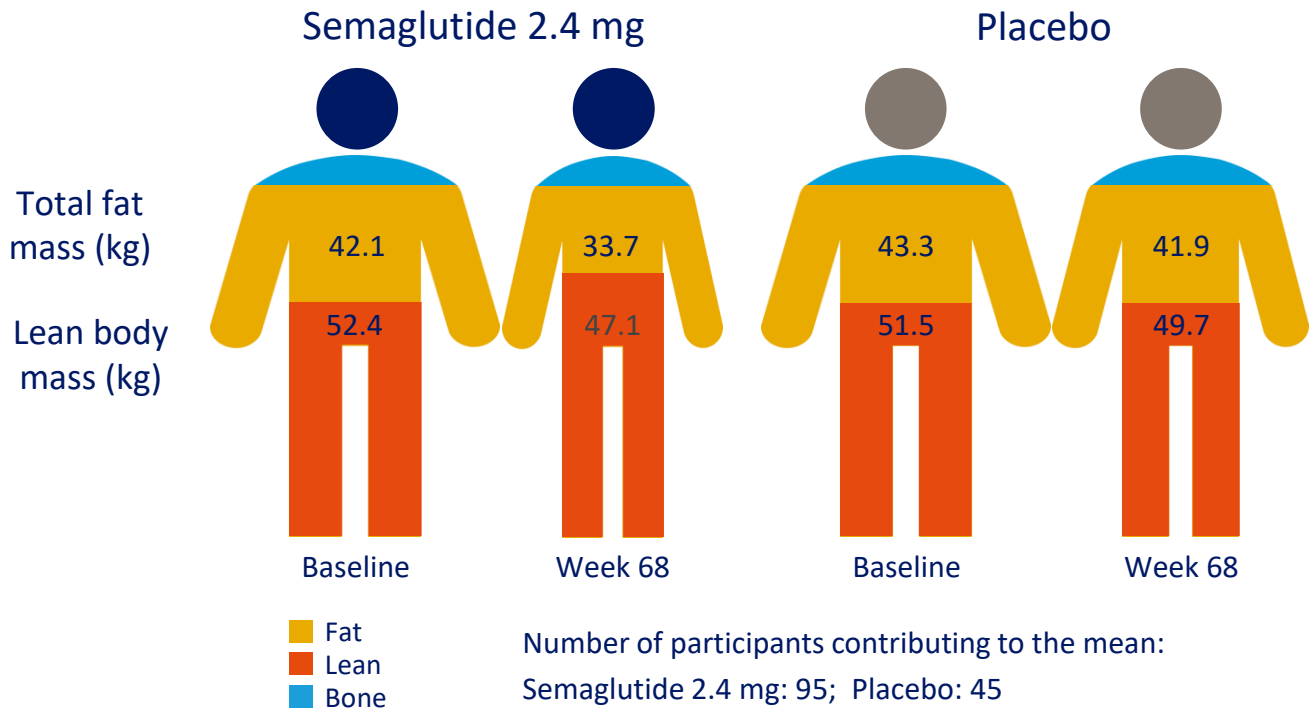


***Not part of the statistical testing hierarchy; p-value not available**.
All values are estimated for the treatment policy estimand.
CI: confidence interval. **ETR:** estimated treatment ratio. **HDL:** high-density lipoprotein. **LDL:** low-density lipoprotein. **VLDL:** very low-density lipoprotein.

Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

Changes in body composition at Week 68*

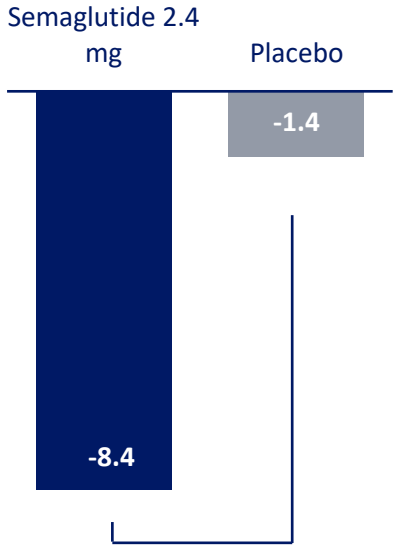
In-trial§



Number of participants contributing to the mean:
Semaglutide 2.4 mg: 95; Placebo: 45

Total fat mass (kg)#

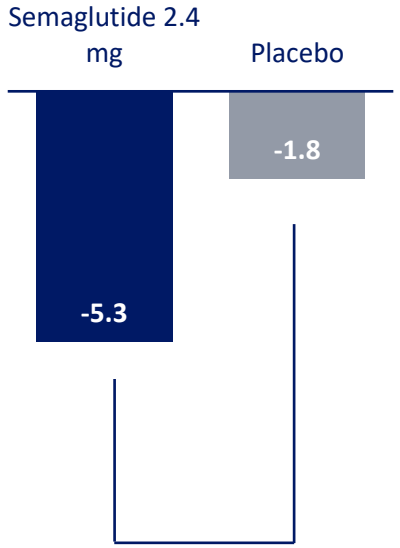
Mean baseline: 42.5 kg



ETD: -7.0 kg
95% CI: [-9.79;-4.19]

Lean body mass (kg)#

Mean baseline: 52.1 kg



ETD: -3.4 kg
95% CI: [-4.74;-2.13]

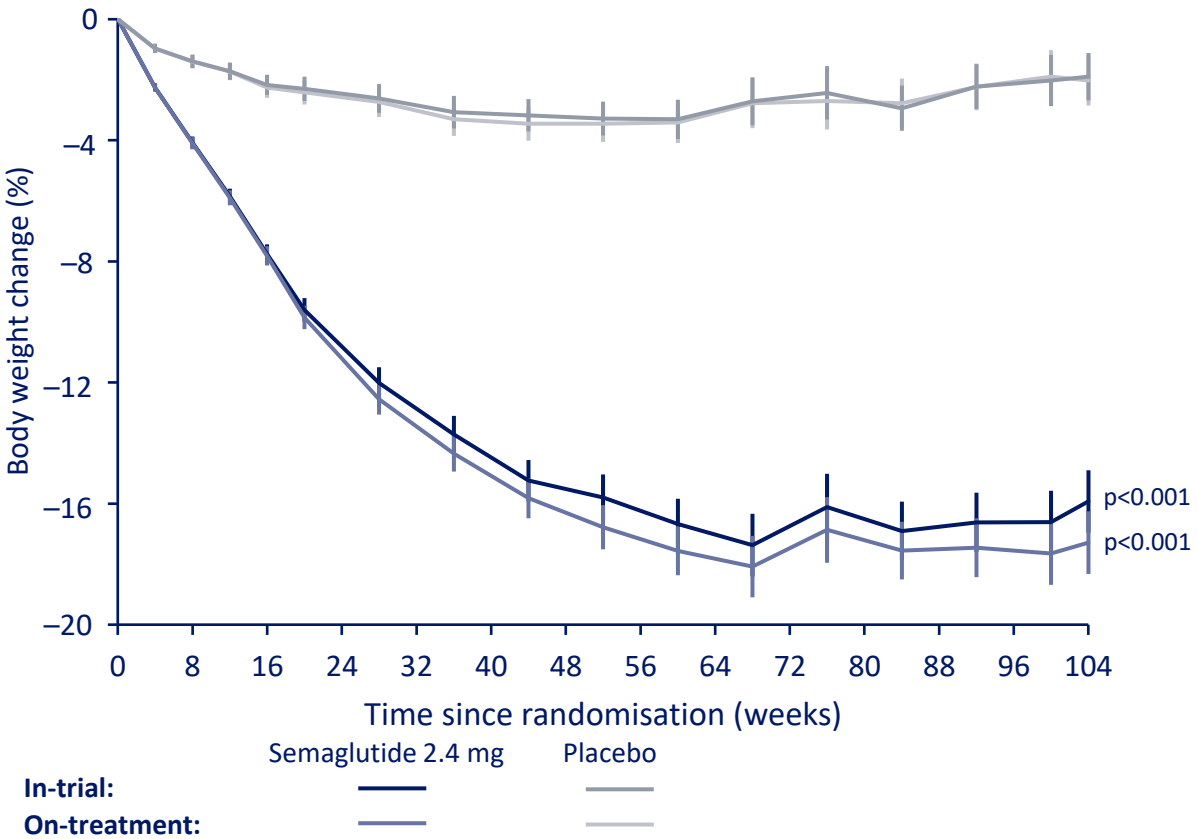
***Not part of the statistical testing hierarchy; p-value not available.**
§Observed data for the in-trial period; #Estimated data for the treatment policy estimand.
CI: confidence interval. **ETD:** estimated treatment difference.

Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

STEP 5: Change in body weight at Week 104

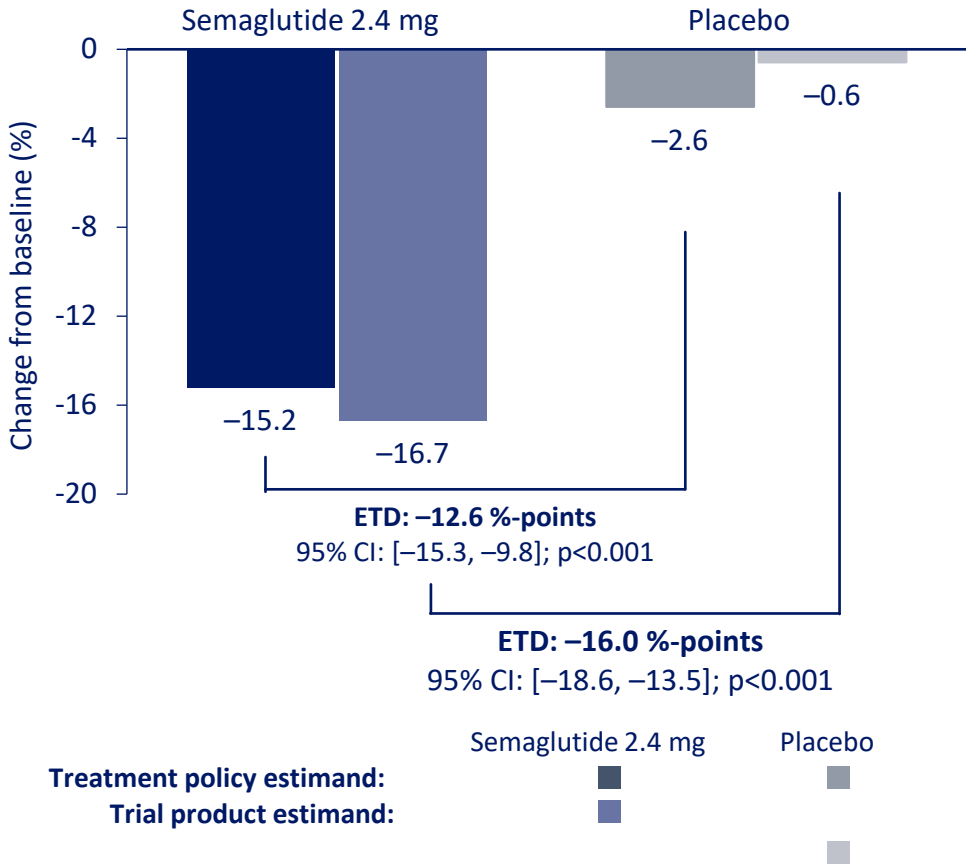
Observed body weight change over time

(Mean at baseline: 106.0 kg)



Estimated change from baseline to Week 104

(Treatment policy and trial product estimands)

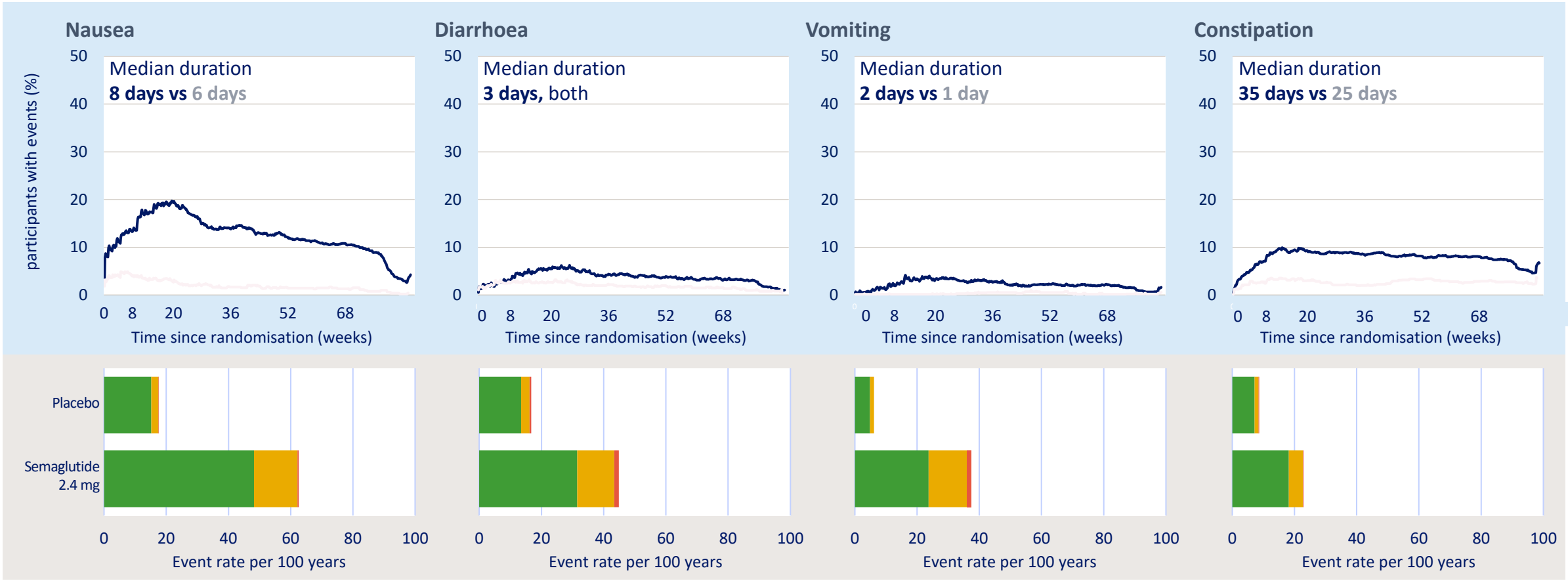


86.8% of participants randomised to semaglutide completed the STEP 5 study (n=132/152) and of these, 90.9% were receiving the 2.4 mg maintenance dose at Week 104.

Error bars are ± standard error of the mean. **CI:** confidence interval. **ETD:** estimated treatment difference.

Garvey WT, *et al. Nat Med.* 2022;28:2083–91.

Prevalence and severity of selected GI events (68 weeks)



Data are for the on-treatment observation period.

GI: gastrointestinal.

Wilding JPH, *et al. N Eng J Med.* 2021;384:989–1002

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*

Tirzepatide is not indicated for the treatment of obesity in Australia

Study Design and Inclusion Criteria of Participants

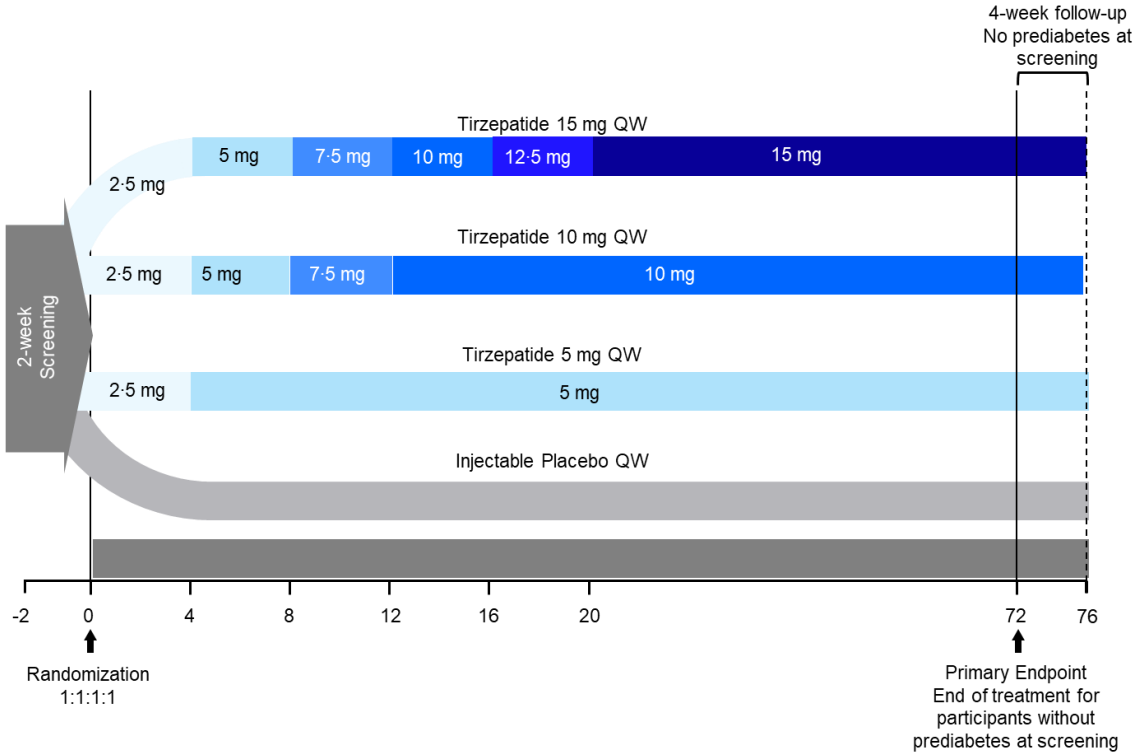
Phase 3, multicenter, randomized, double-blind, placebo-controlled trial at 118 sites in 9 countries (NCT04184622)

1 Key Inclusion Criteria

- Age ≥18 years
- BMI ≥30 kg/m^2 or ≥27 kg/m^2 and ≥1 weight-related comorbidities (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease)
- History of ≥1 self-reported unsuccessful dietary efforts to lose body weight

2 Key Exclusion Criteria

- Type 1 or Type 2 Diabetes mellitus
- Change in body weight >5 kg within 3 months prior to screening
- Obesity induced by other endocrinologic disorders or monogenetic or syndromic forms of obesity
- History of pancreatitis



Note: Tirzepatide was administered once weekly (QW) subcutaneously as an adjunct to a reduced-calorie diet and increased physical activity

Tirzepatide is not indicated for the treatment of obesity in Australia

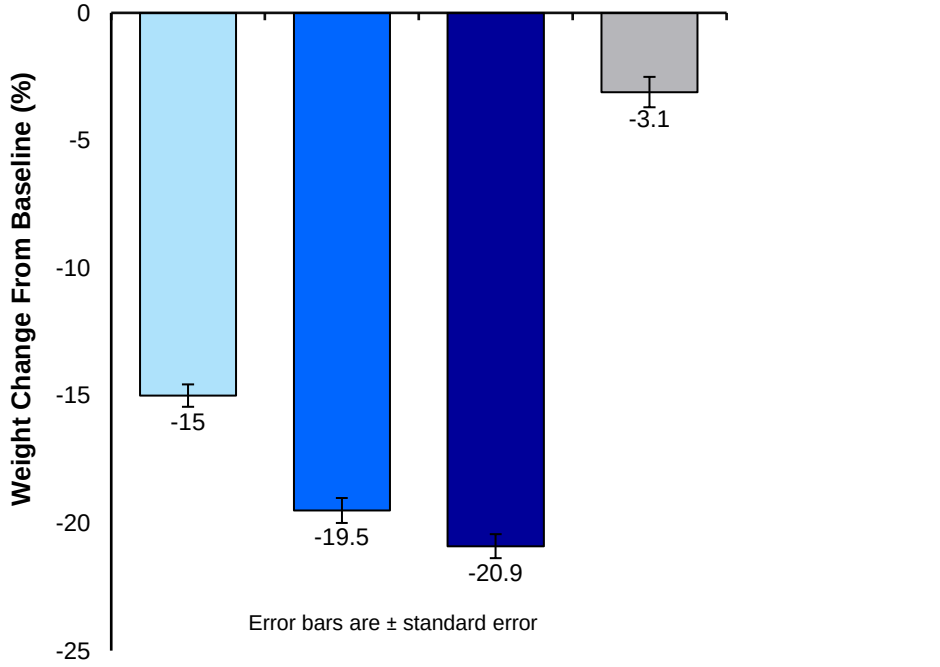
BMI = Body Mass Index; QW = Once Weekly.

Jastreboff AM, et al. N Engl J Med 2022;387:205-216

Change in Body Weight From Baseline to 72 Weeks

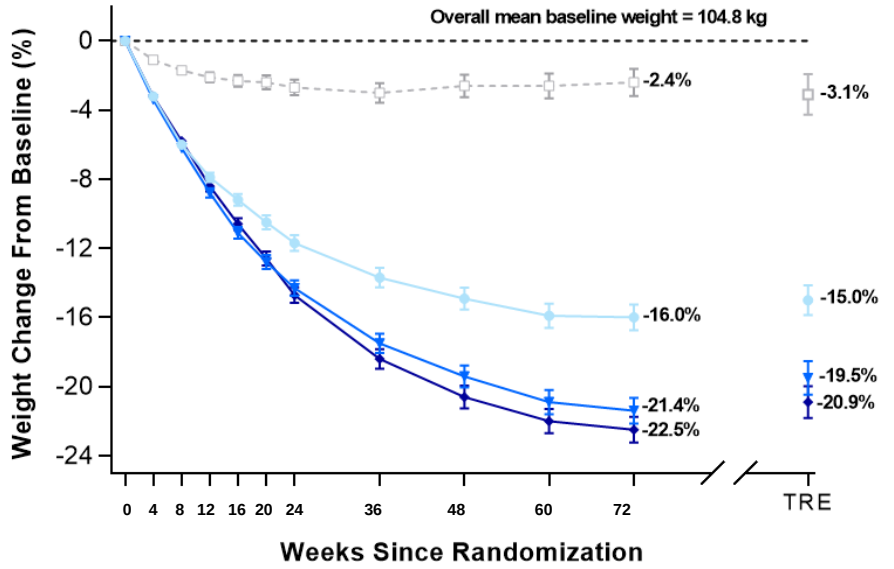
Tirzepatide 5 mg Tirzepatide 10 mg

	TZP 5 mg vs PBO	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	-11.9 (-13.4, -10.4)	-16.4 (-17.9, -14.8)	-17.8 (-19.3, -16.3)
P value		<.001	



Tirzepatide āa5 mg Placebo

	TZP 5 mg vs PBO	TZP 10 mg vs PBO	TZP 15 mg vs PBO
ETD (%) (95% CI)	−13.5 (−14.6 to −12.5)	−18.9 (−20.0, −17.8)	−20.1 (−21.2, −19.0)
P value		<.001	



Note: Data derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand; week 72 estimates for the treatment-regimen estimand are also shown
Error bars are ± standard error

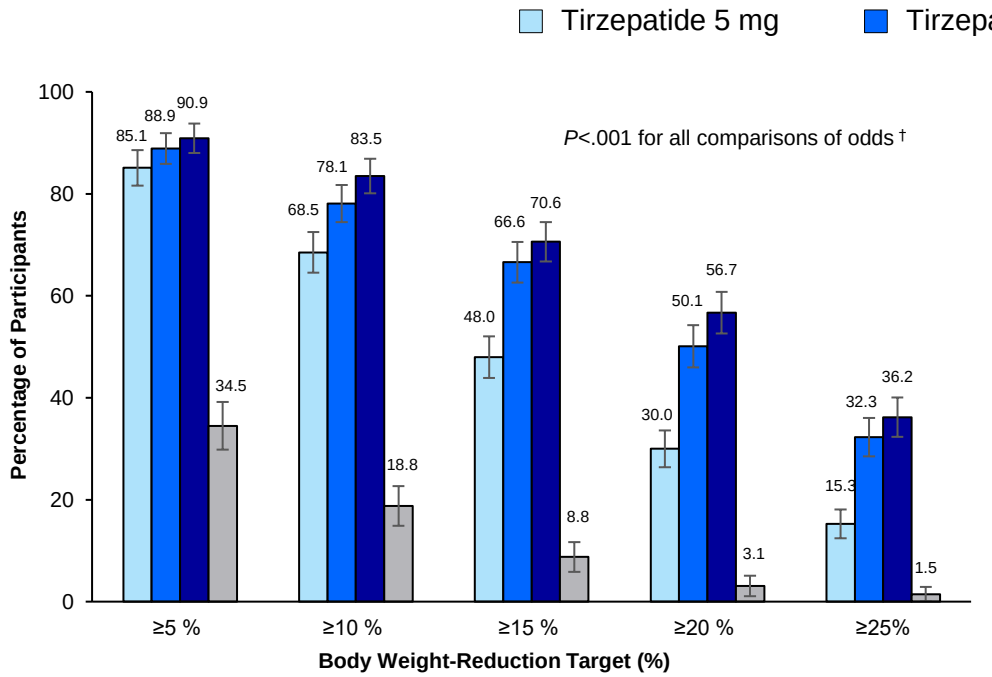
CI = Confidence Interval; ETD = Estimated Treatment Difference; TRE = Treatment Regimen Estimand; TZP = Tirzepatide; PBO = Placebo.

Tirzepatide is not indicated for the treatment of obesity in Australia

Jastreboff AM, et al. N Engl J Med 2022;387:205-216

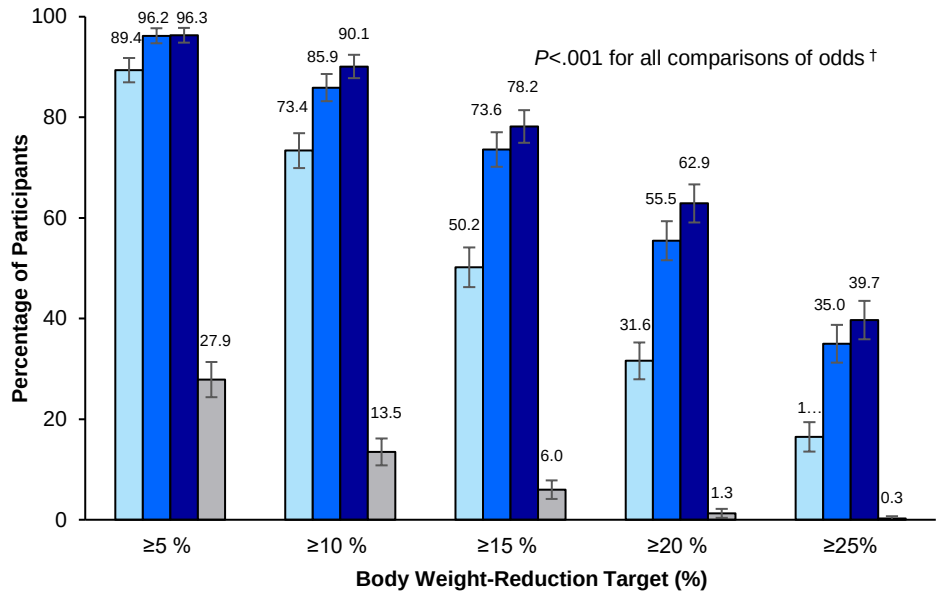
Percentage of Participants Achieving Body Weight Reductions Targets

Treatment Regimen Estimand*



Note: The percentage was calculated with the use of Rubin's rules by combining the percentages of patients who met the target in imputed data sets. Missing value at week 72 was imputed using MMRM if missing was solely due to COVID-19 and using multiple imputation if missing was not due to COVID-19

Efficacy Estimand*



Note: The percentage of participants achieving weight loss targets was obtained by dividing the number of participants reaching respective goals at week 72 by the number of participants with baseline value and at least one non-missing postbaseline value. Missing value at week 72 was predicted from MMRM analysis. Logistic regression analysis was used for all comparisons to placebo

*Least-squares means are presented, unless otherwise noted. Error bars indicate the 95% confidence interval

† Participants with weight reduction ≥25% is an exploratory endpoint and hence not controlled for type 1 error; therefore *P*-values are not shown

MMRM = Mixed-model or Repeated-measures..

Tirzepatide is not indicated for the treatment of obesity in Australia

Jastreboff AM, et al. N Engl J Med 2022;387:205-216

Improvements in health parameters

-18.5 cm
with tirzepatide 15 mg vs -4.0 cm placebo, p<0.001
Waist circumference

-42.9 mIU
with pooled tirzepatide vs -6.6 mIU placebo, p <0.001
Fasting insulin††

-7.2 mmHg
with with pooled tirzepatide vs -1.0 mmHg placebo, p<0.001
Systolic blood pressure

95.3%
with pooled tirzepatide vs 61.9% placebo, p=NA*
patients reverting to normoglycemia

+3.6
with pooled tirzepatide vs +0.4 placebo, p<0.001
SF-36 physical function score *†

-4.8 mmHg
with pooled tirzepatide vs -0.8 mmHg placebo, p=NA*
Diastolic blood pressure

-24.8 mg/dL
with pooled tirzepatide vs -5.6 placebo, p<0.001
Triglycerides††

8 mg/dL
with pooled tirzepatide vs – 0.7 mg/dL placebo, p <0.001
HDL cholesterol ††

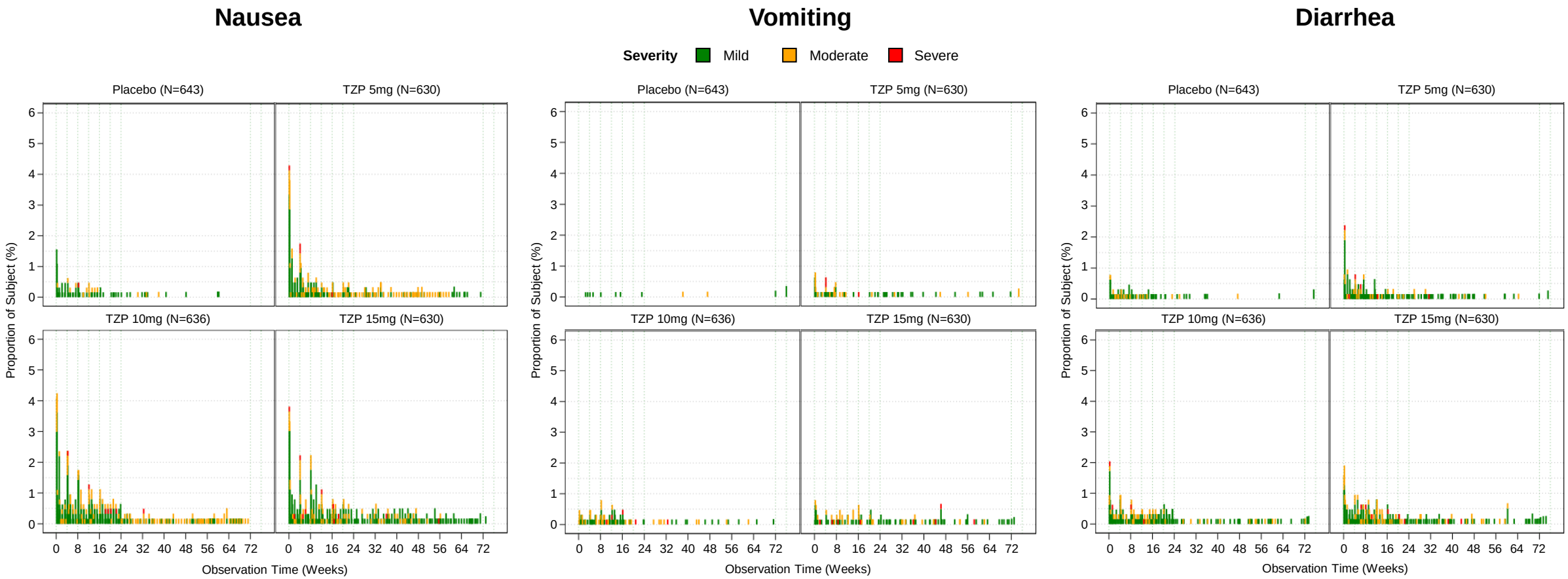
Note: Pooled tirzepatide refers to pooled tirzepatide 5 mg, 10 mg, and 15 mg groups, unless otherwise indicated ; *Data are for the pooled tirzepatide 10 mg and 15 mg groups †Change from baseline in SF-36 score was assessed using analysis of covariance model with terms for baseline SF-36 PF score, treatment, and stratification factors
††Lipid parameters and fasting insulin were analyzed using log-transformation. Data presented are model-based estimate ± SE Note: All changes are from baseline to week 72, unless otherwise stated

Tirzepatide is not indicated for the treatment of obesity in Australia

Jastreboff AM, et al. N Engl J Med 2022;387:205-216

Incidence of Nausea, Vomiting, and Diarrhoea Over Time

Most gastrointestinal events were transient, occurring primarily during the dose-escalation period, and were mostly mild to moderate in severity



Note: Percentages are based on number of participants at risk at specific observation time

Tirzepatide is not indicated for the treatment of obesity in Australia

Jastreboff AM, et al. N Engl J Med 2022;387:205-216

Key learning points

- Semaglutide and tirzepatide in people with obesity result in:
  - a significant and clinically meaningful reduction in body weight
  - improvement in cardiovascular risk factors
  - Improvements in quality of life

- The most common AEs with incretin therapy are gastrointestinal in nature, mostly mild or moderate in severity and occur early (during dose-escalation)

Tirzepatide is not indicated for the treatment of obesity in Australia