Once-weekly semaglutide 7·2 mg in adults with obesity (STEP UP): a randomised, controlled, phase 3b trial

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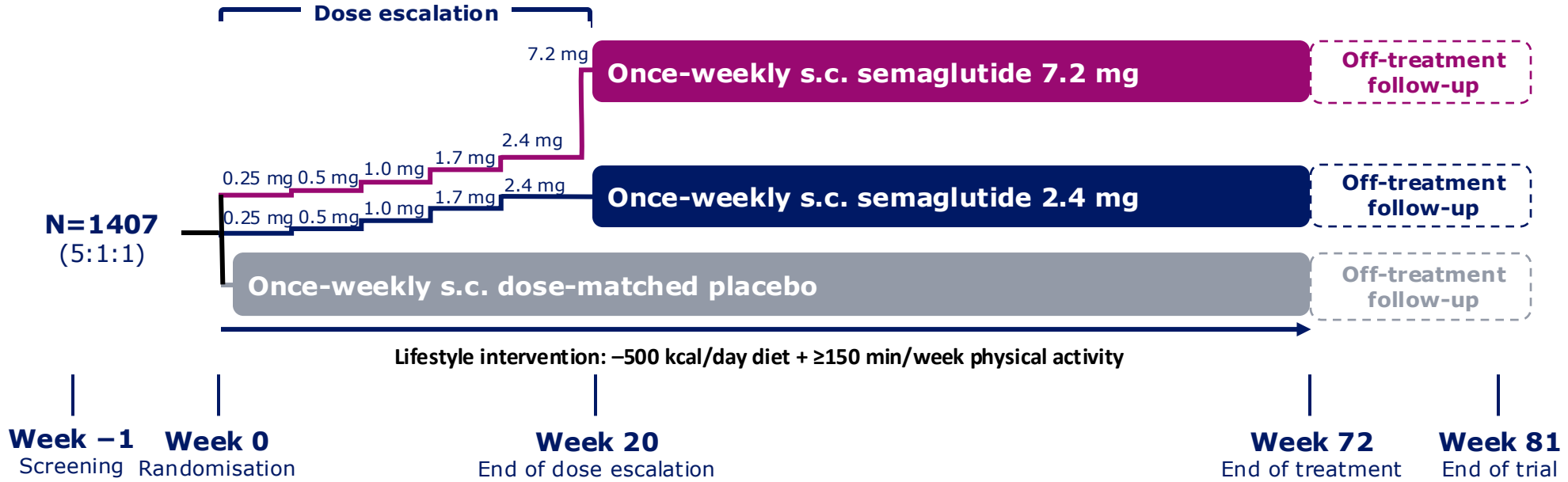
STEP UP trial design

72-week, randomised, double-blind, multicentre, placebo-controlled trial



Key inclusion criteria

- Adults with BMI ≥30 kg/m^2
- Without T2D (HbA$_{1c}$ <6.5%)

Co-primary endpoints*	• Change in body weight (%) • Proportion of participants achieving ≥5% WL
Confirmatory secondary endpoints	• Proportion of participants achieving ≥10%, ≥15%, ≥20%, and **≥25%** WL* • Change in waist circumference (cm)* • Change in body weight (%)† • Proportion of participants achieving ≥20% and ≥25% WL†

**Semaglutide 7.2 mg vs placebo; †Semaglutide 7.2 mg vs 2.4 mg. The trial was designed in a double-blind manner with respect to active versus placebo treatment and semaglutide dose, therefore, participants in all treatment arms underwent the same number of escalation steps.*

BMI, body mass index; HbA1c, glycated haemoglobin; N, number of participants; s.c., subcutaneous; T2D, type 2 diabetes; WL, weight loss.

Wharton S et al. Presented at the American Diabetes Association (ADA) 85th Scientific Sessions, June 20–23, 2025, Chicago, IL, USA: 6521-LB . Abstract 1966-LB - Efficacy and Safety of Semaglutide 7.2 mg in Obesity—STEP UP Trial .

Demographics and baseline characteristics

Male/Female

26.3% | 73.7%

Mean age

47 (12) years

Mean body weight

113.0 (24.1) kg

Mean BMI

39.9 (7.1) kg/m²

Mean waist circumference

118.7 (15.8) cm

Mean HbA_{1c}*

5.7 (0.3) %

Glycaemic status
Normoglycaemia/prediabetes

62.3% | 37.6%

Data are mean (standard deviation), unless otherwise stated.
BMI, body mass index; HbA_{1c}, glycated haemoglobin.
Wharton S et al. Presented at the American Diabetes Association (ADA) 85th Scientific Sessions, June 20–23, 2025, Chicago, IL, USA: 6521-LB Abstract 1966-LB - Efficacy and Safety of Semaglutide 7.2 mg in Obesity—STEP UP Trial .

Change in body weight (%)

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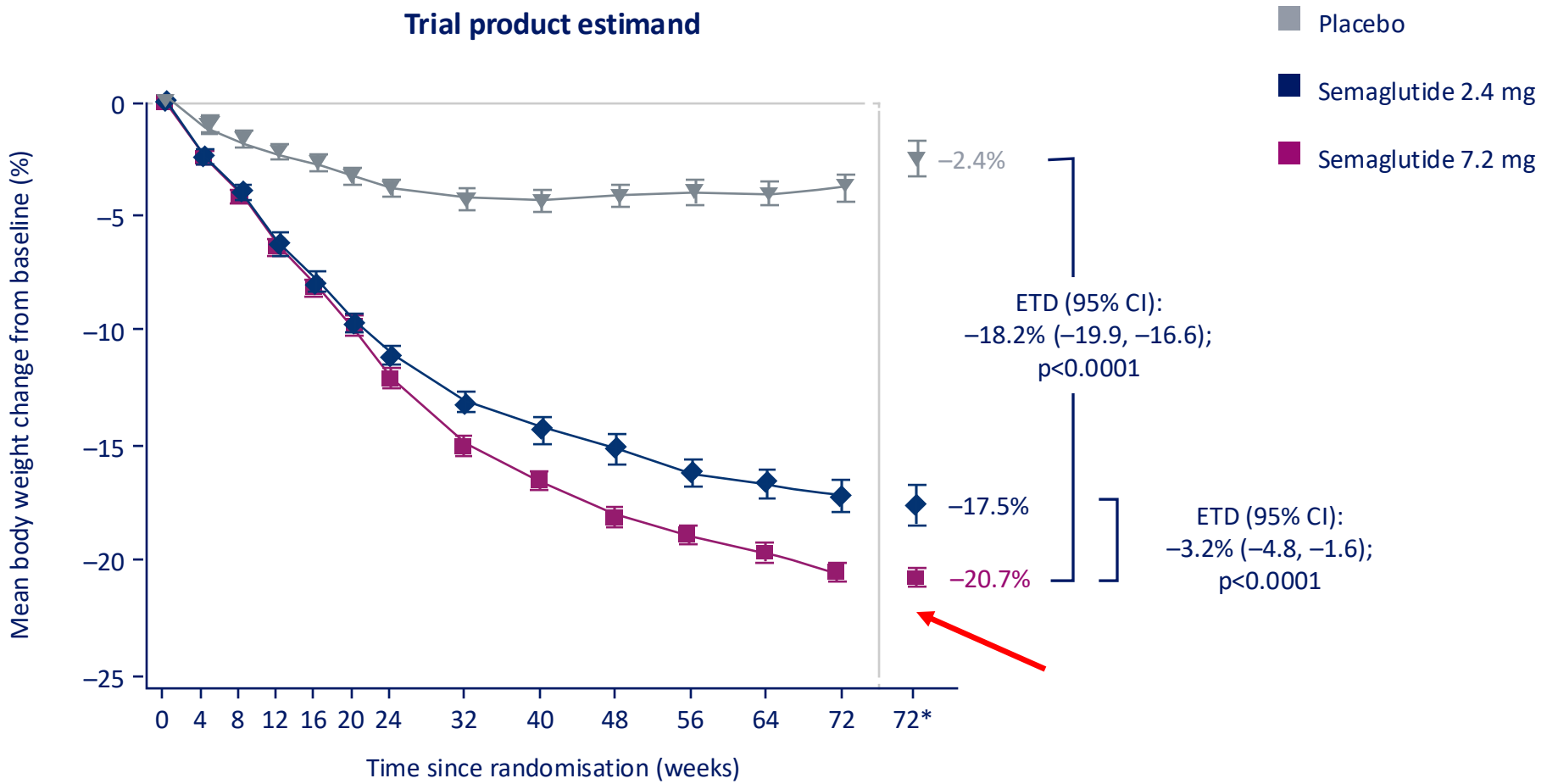

*Data are for the full analysis set, and observed data are from the on-treatment observation period. Treatment comparisons were estimated using the trial product estimand. Error bars are 95% CIs. *Estimated mean change at week 72. CI, confidence interval; ETD, estimated treatment difference.*

Wharton S et al. Lancet Diabetes Endocrinol 2025; DOI: 10.1016/S2213-8587(25)00226-8.

Wharton S, et al. *Lancet Diabetes Endocrinol* 2025; DOI: 10.1016/S2213-8587(25)00226-8.

Categorical body weight loss

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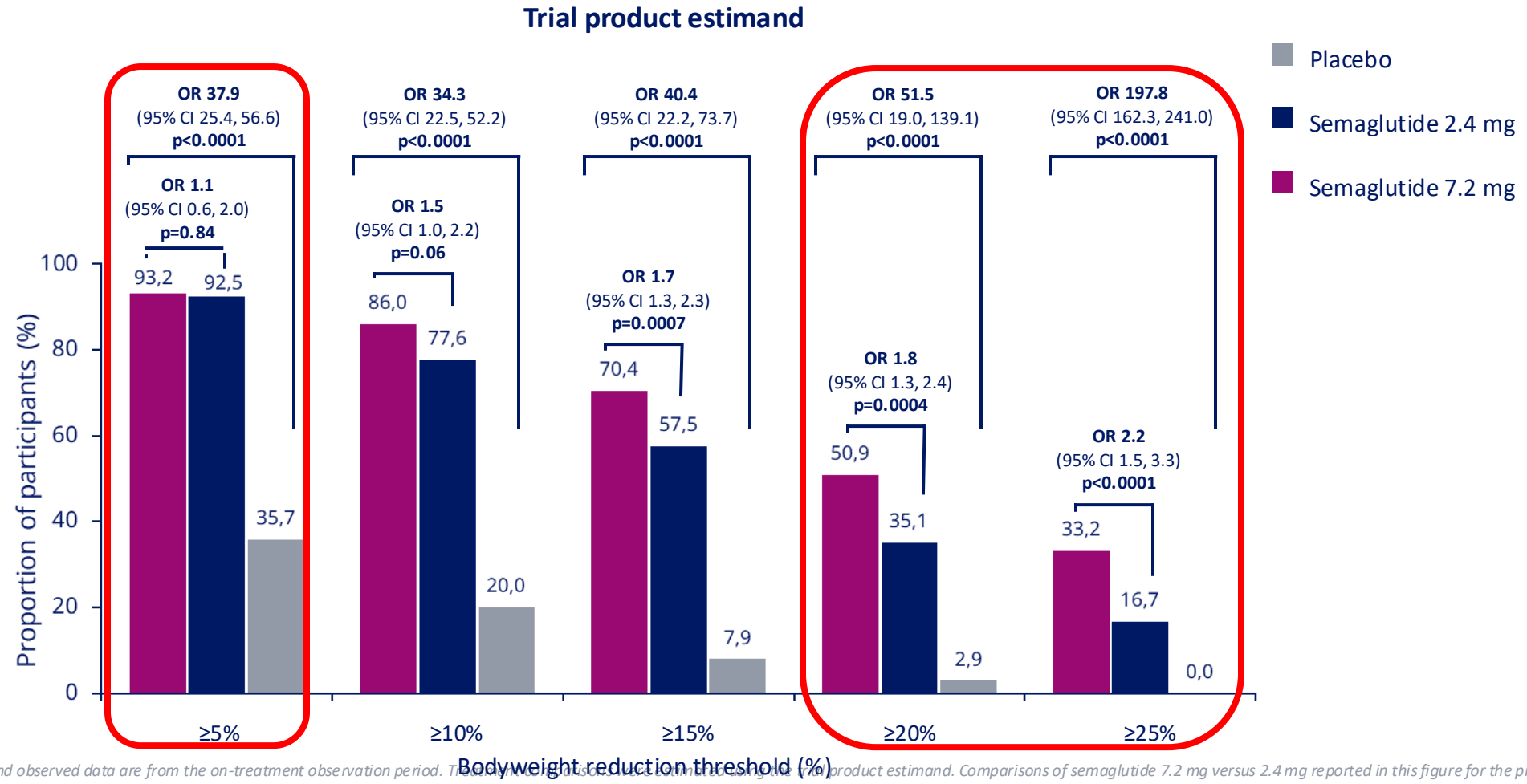

Data are for the full analysis set, and observed data are from the on-treatment observation period. The primary analysis was estimated using the trial product estimand. Comparisons of semaglutide 7.2 mg versus 2.4 mg reported in this figure for the proportion of participants with body weight reductions of 5% or greater, 10% or greater, and 15% or greater were conducted in a post-hoc manner. Post hoc analyses were not controlled for multiplicity, and findings for these endpoints should not be used to infer definitive treatment effects.

CI, confidence interval; OR, odds ratio.

Wharton S et al. Lancet Diabetes Endocrinol 2025; DOI: 10.1016/S2213-8587(25)00226-8.

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Change in BMI (kg/m^2)

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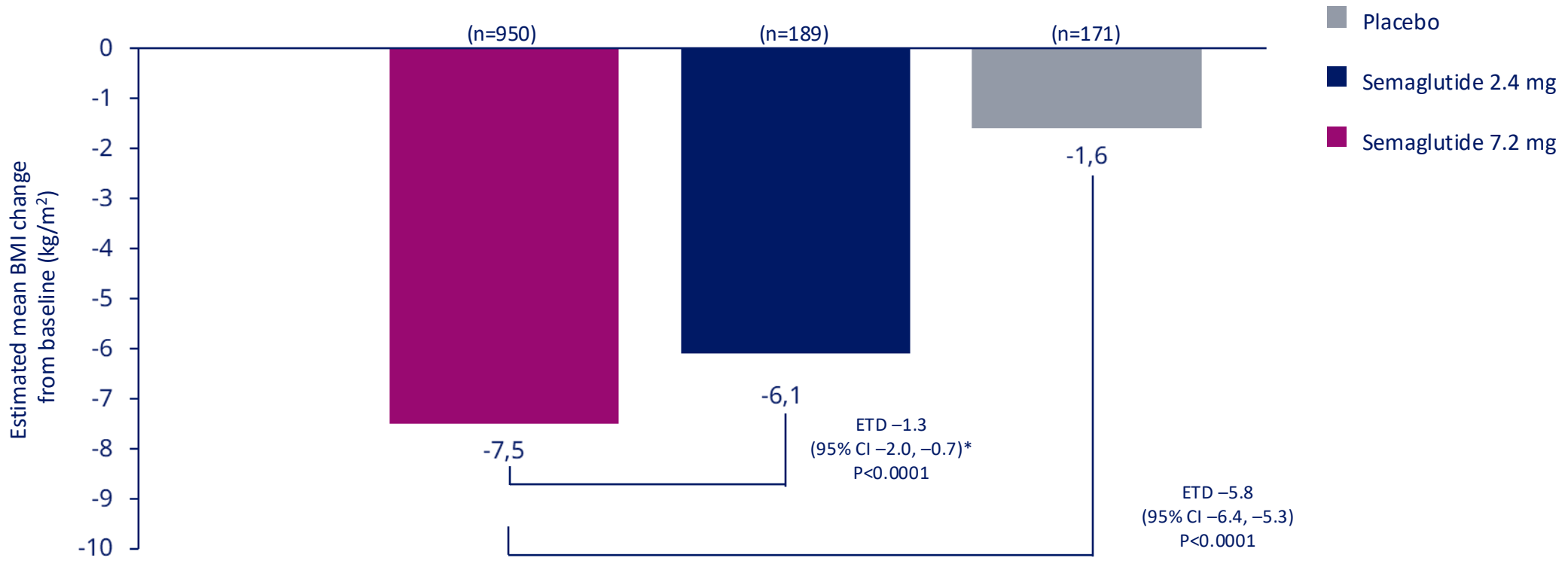

*Data are for the full analysis set and are from the in-trial observation period. Treatment comparisons were estimated with the treatment policy estimand. *Semaglutide 7.2 mg versus 2.4 mg comparisons reported were post hoc. Post hoc analyses were not controlled for multiplicity, and findings for these endpoints should not be used to infer definitive treatment effects.*

BMI, Body mass index; CI, confidence interval; ETD, estimated treatment difference.

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Change in HbA_{1c}

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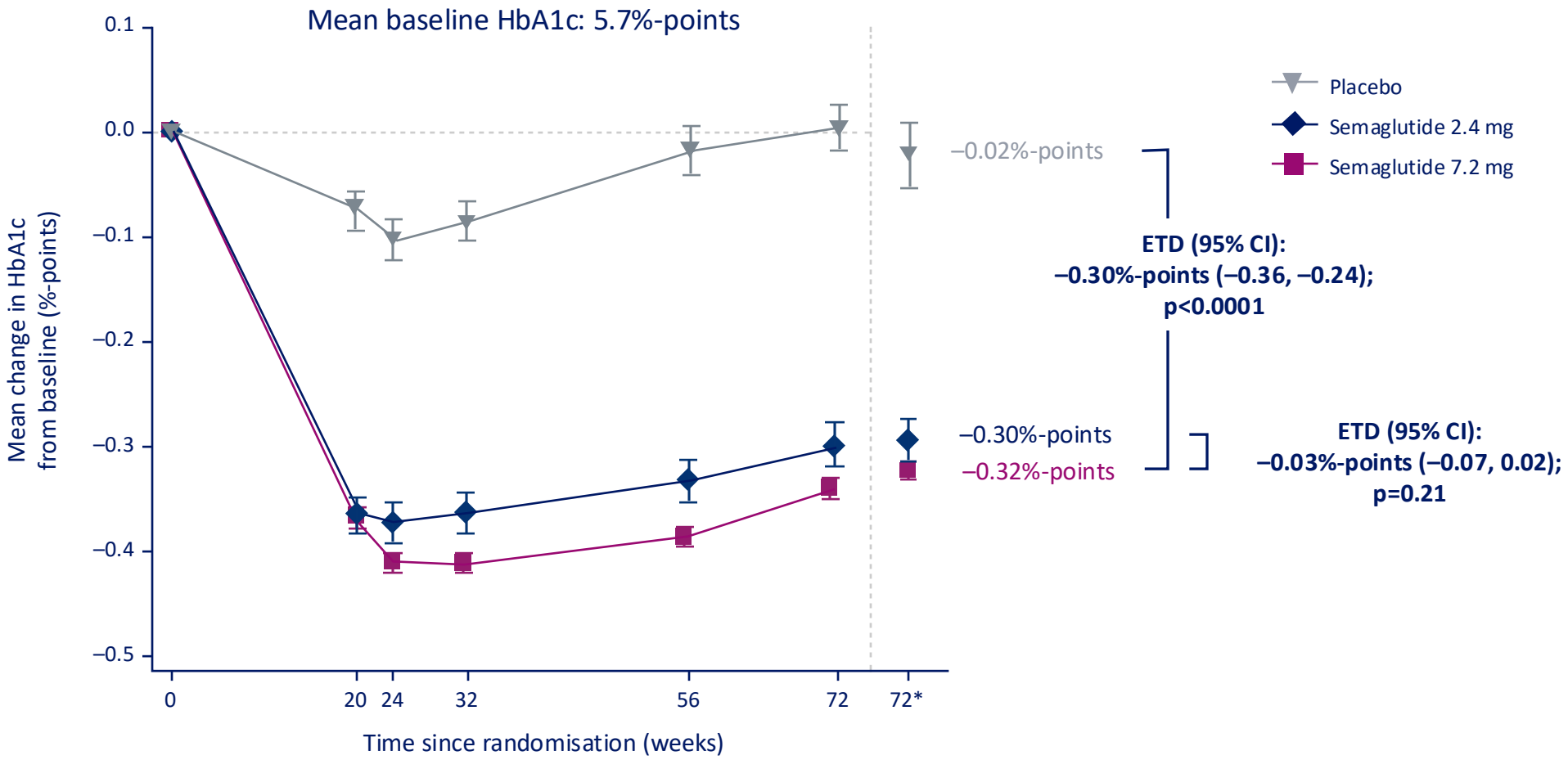
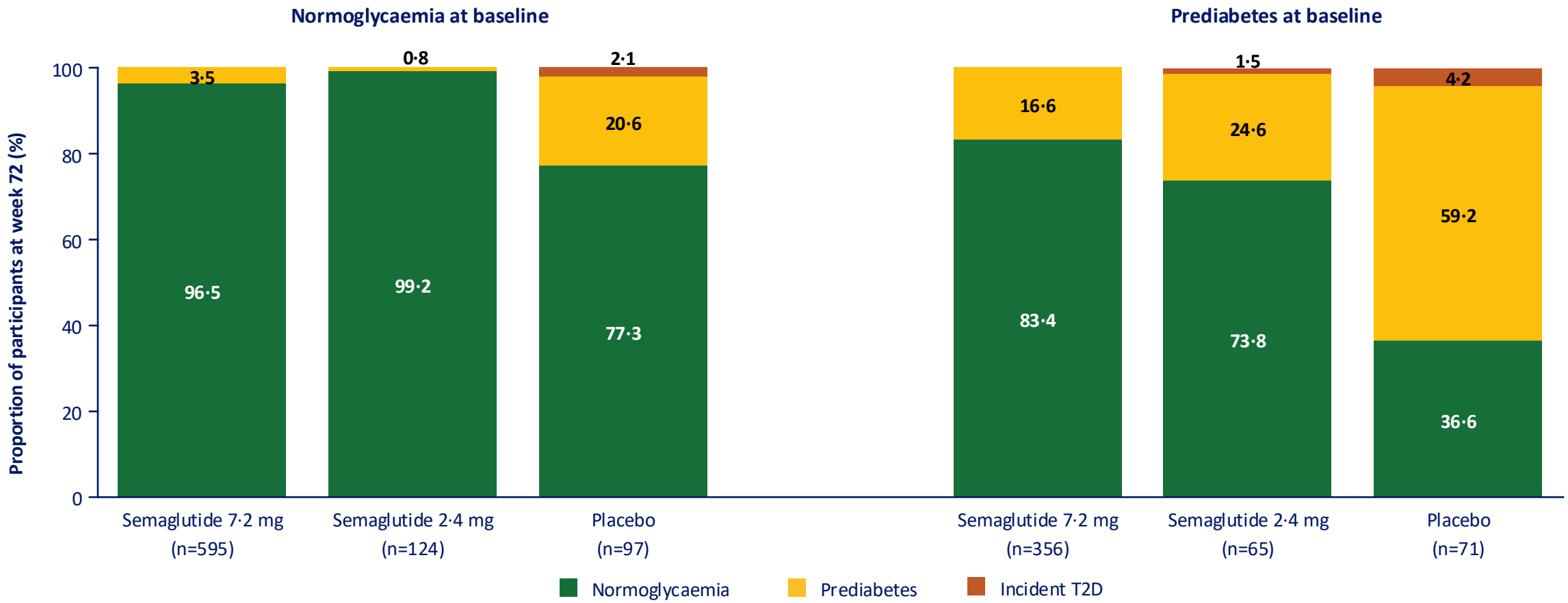


Treatment policy estimand data are from the in-trial observation period and for the full analysis set.
**Estimated mean change at week 72.*
CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin.
Wharton S et al. Lancet Diabetes Endocrinol 2025; DOI: 10.1016/S2213-8587(25)00226-8.

Change in glycaemic status



Data are from the in-trial observation period and for the full analysis set. Panel shows the shift in glycaemic control for each treatment group (i.e. the proportion of participants with normoglycaemia or prediabetes at baseline who had normoglycaemia, prediabetes, or incident T2D at week 72). The investigator evaluated glycaemic status periodically during the trial based on all available relevant information, including medical records, concomitant medication, blood glucose parameters (HbA_{1c} and fasting plasma glucose) and AEs. The participant's glycaemic status was categorised as normoglycaemia (HbA_{1c} <5·7%), prediabetes (≥5·7% to <6·5%), or T2D (≥6·5%) according to the American Diabetes Association definitions.

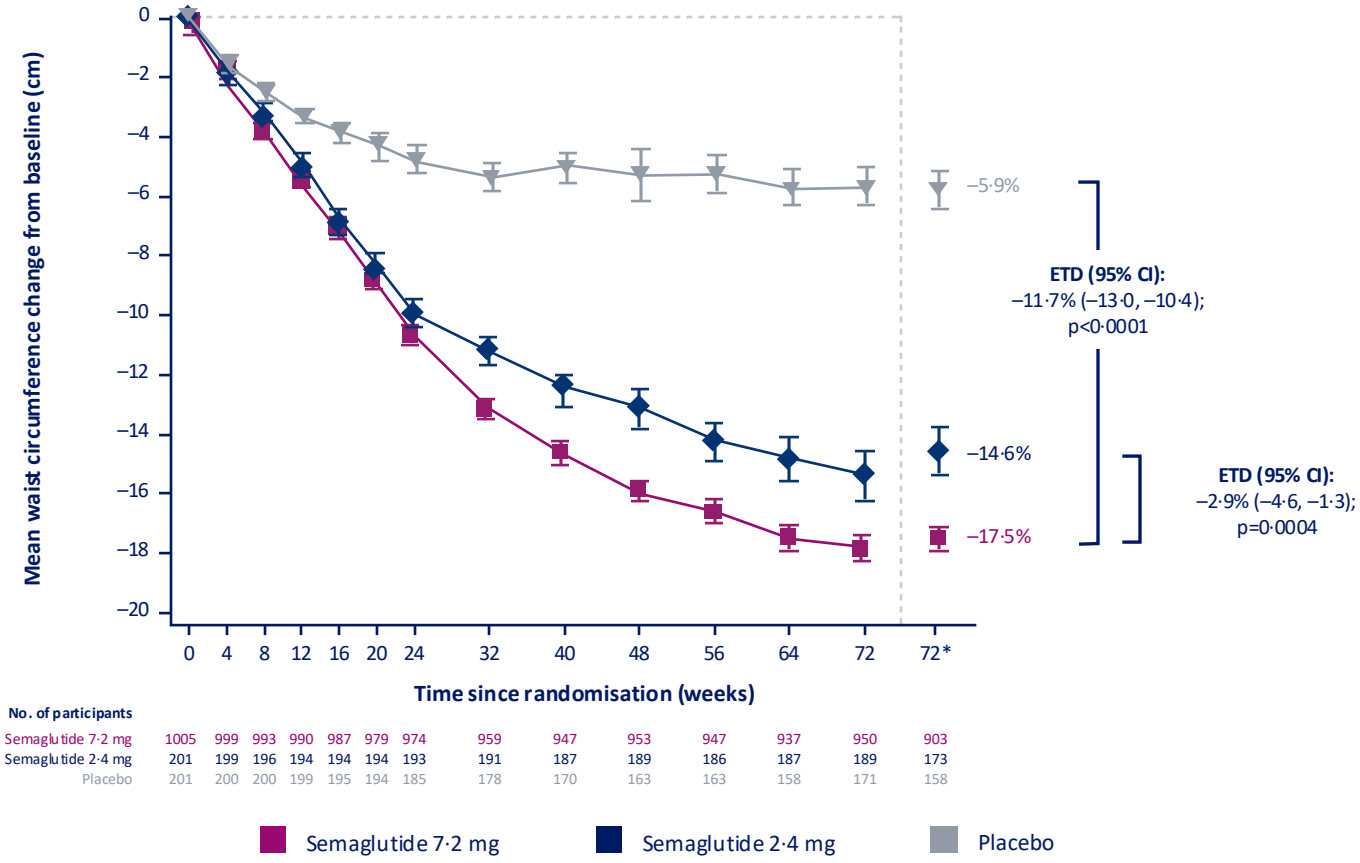
AE=adverse event. HbA_{1c}=glycated haemoglobin. T2D=type 2 diabetes.

Adapted from Figure 3. Change in waist circumference and glycaemia from baseline to week 72.

Wharton S, et al. *Lancet Diabetes Endocrinol* 2025; DOI: 10.1016/S2213-8587(25)00226-8.

Change in waist circumference

Treatment policy estimand



Data are from the in-trial observation period and for the full analysis set.
**Estimated mean change at week 72.*
Adapted from Figure 3. Change in waist circumference and glycaemia from baseline to week 72.

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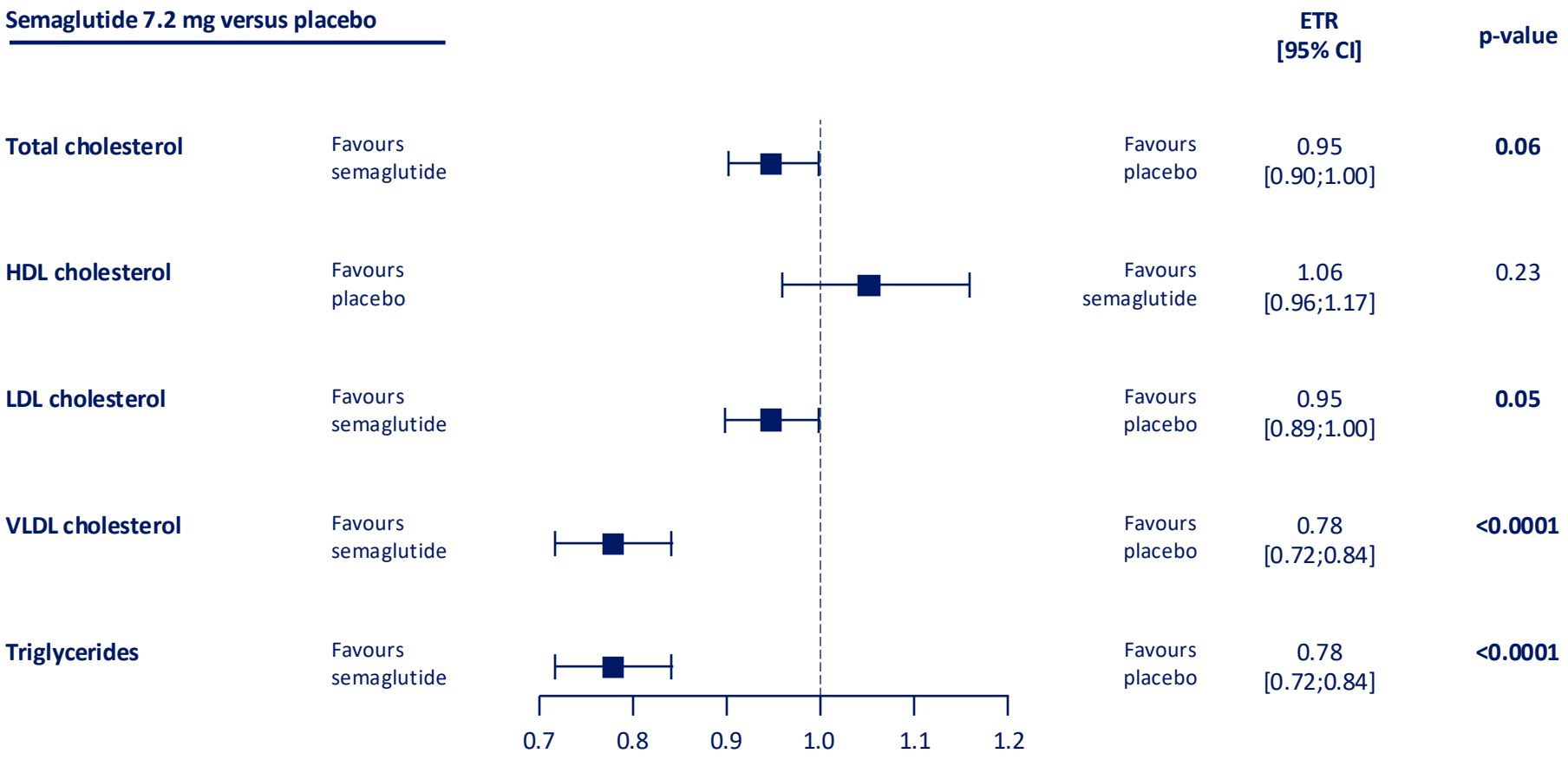
Change in lipid concentrations

STEP UP



Data are for the full analysis set and are from the in-trial observation period. Treatment comparisons were estimated with the treatment policy estimand.
CI, confidence interval; ETR, estimated treatment ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein
Wharton S et al. Lancet Diabetes Endocrinol 2025; DOI: 10.1016/S2213-8587(25)00226-8.

Change in systolic and diastolic blood pressure

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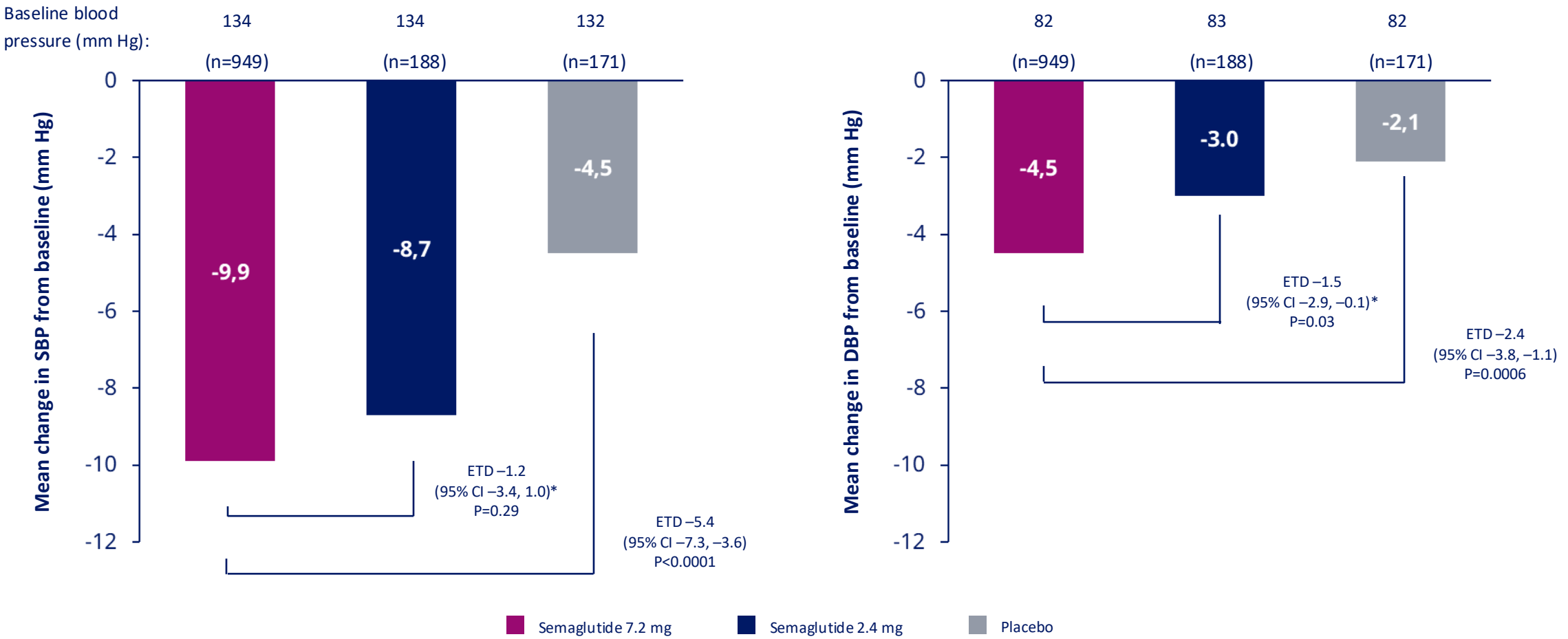

*Data are for the full analysis set and are from the in-trial observation period.. Treatment comparisons were estimated with the treatment policy estimand. *Semaglutide 7.2 mg versus 2.4 mg comparisons reported in this figure were post hoc. Post hoc analyses were not controlled for multiplicity, and findings for these endpoints should not be used to infer definitive treatment effects. DBP, diastolic blood pressure; ETD, estimated treatment difference; SBP, systolic blood pressure.*

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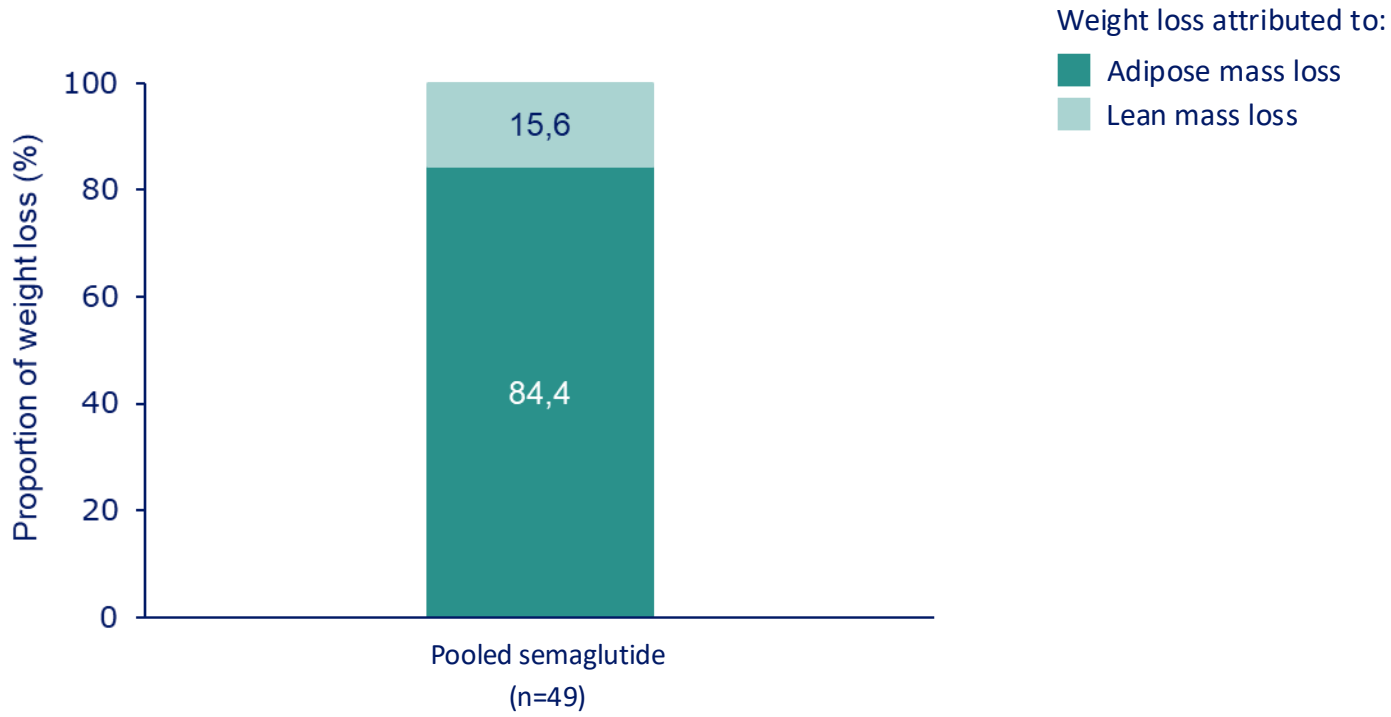
Proportion of weight loss from fat and lean mass

STEP UP secondary analysis



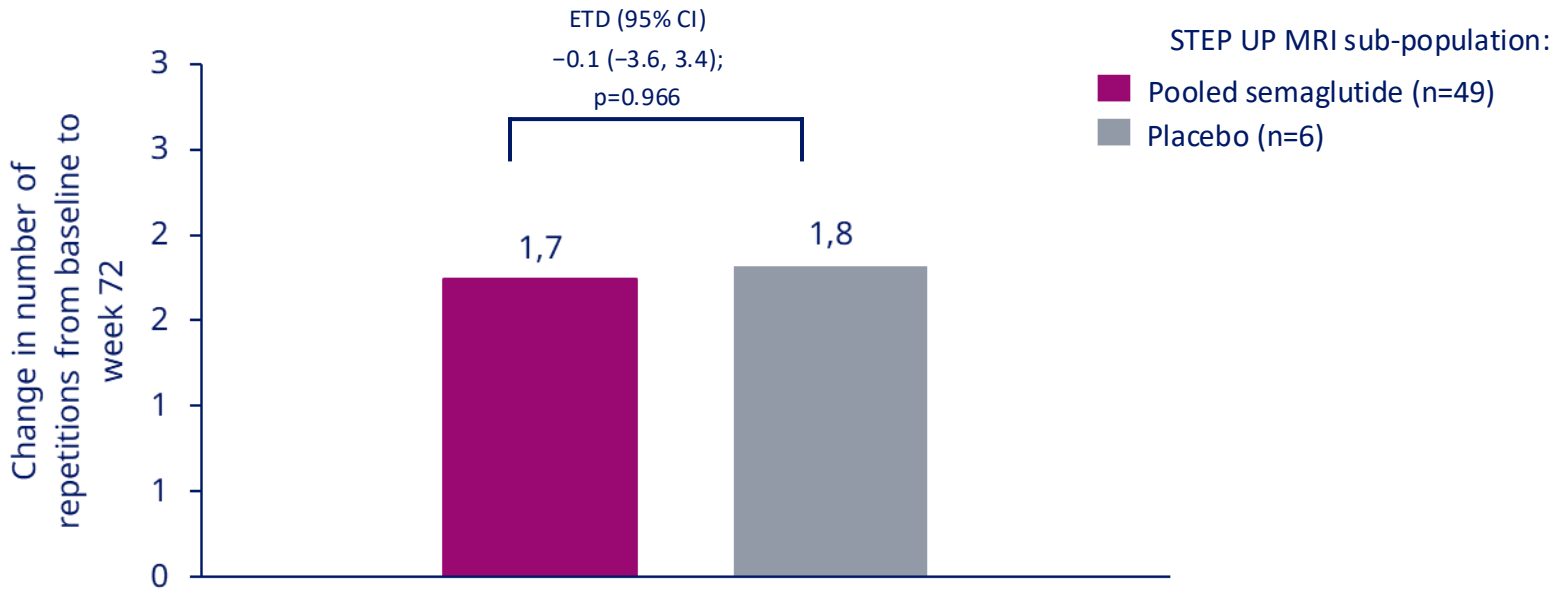
The change in adipose tissue mass as a proportion of mass reduction was calculated as: {[(absolute volume change [L] in adipose tissue × 0.92)/[(absolute volume change [L] in adipose tissue × 0.92) + (absolute volume change [L] in lean tissue × 1.1)]} × 100 = {(11.0 × 0.92)/[(11.0 × 0.92)+(1.7 × 1.1)]} × 100 = 84.4%. The change in lean tissue mass as a proportion of mass reduction was calculated as: {[(absolute volume change [L] in lean tissue × 1.1)/[(absolute volume change [L] in adipose tissue × 0.92) + (absolute volume change [L] in lean tissue × 1.1)]} × 100 = {(1.7 × 1.1)/[(11.0 × 0.92)+(1.7 × 1.1)]} × 100 = 15.6%.

Hjelmesæth J, et al. Presented at the European Association for the Study of Diabetes (EASD) 61st Annual Meeting, 15–19 September 2025, Vienna, Austria

Change in number of sit-to-stand repetitions

STEP UP secondary analysis

Number of sit-to-stand repetitions	Pooled semaglutide (n=49)	Placebo (n=6)
Baseline	13 (4)	13 (2)
Week 72	15 (4)	15 (1)

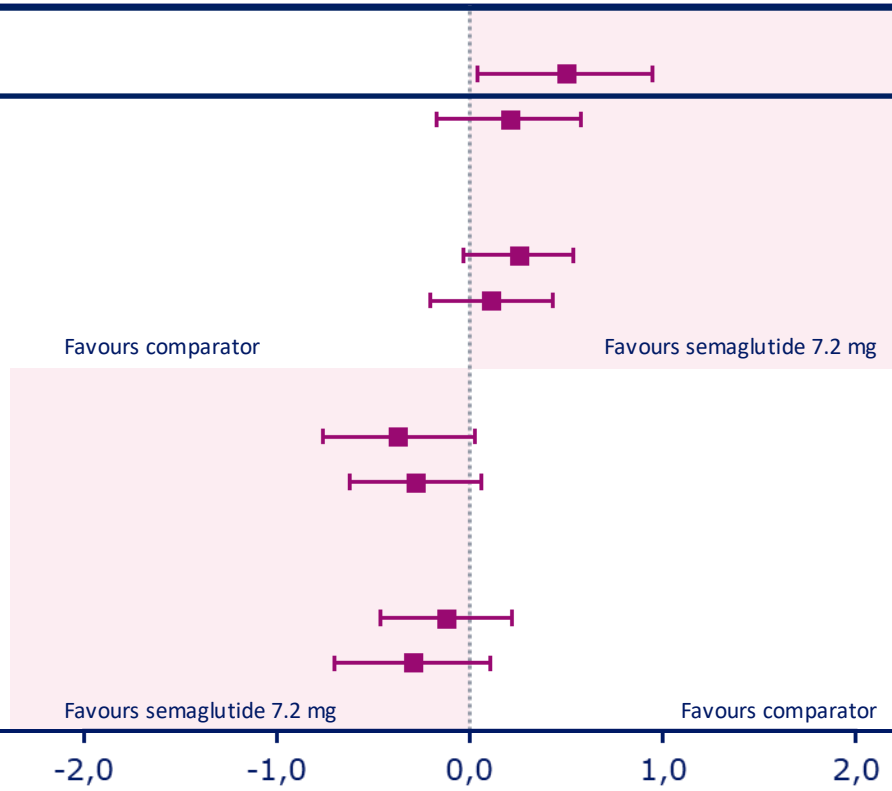


In the table, observed data are mean (standard deviation). In the figure, data are estimated for the in-trial period using the treatment policy estimand.
CI, confidence interval; ETD, estimated treatment difference; MRI, magnetic resonance imaging.
Hjelmesæth J, et al. Presented at the European Association for the Study of Diabetes (EASD) 61st Annual Meeting, 15–19 September 2025, Vienna, Austria

Change in CoEQ domain scores

STEP UP secondary analysis

Change in CoEQ domain score at week 72	ETD [95% CI]	p value
Craving control		
Semaglutide 7.2 mg vs placebo	0.50 [0.04, 0.95]	**0.03**
Semaglutide 7.2 mg vs semaglutide 2.4 mg	0.21 [−0.17, 0.58]	0.28
Positive mood		
Semaglutide 7.2 mg vs placebo	0.26 [−0.03, 0.54]	0.08
Semaglutide 7.2 mg vs semaglutide 2.4 mg	0.11 [−0.20, 0.43]	0.48
Craving for savoury		
Semaglutide 7.2 mg vs placebo	−0.37 [−0.76, 0.03]	0.07
Semaglutide 7.2 mg vs semaglutide 2.4 mg	−0.28 [−0.62, 0.06]	0.10
Craving for sweet		
Semaglutide 7.2 mg vs placebo	−0.12 [−0.46, 0.22]	0.49
Semaglutide 7.2 mg vs semaglutide 2.4 mg	−0.29 [−0.70, 0.11]	0.16

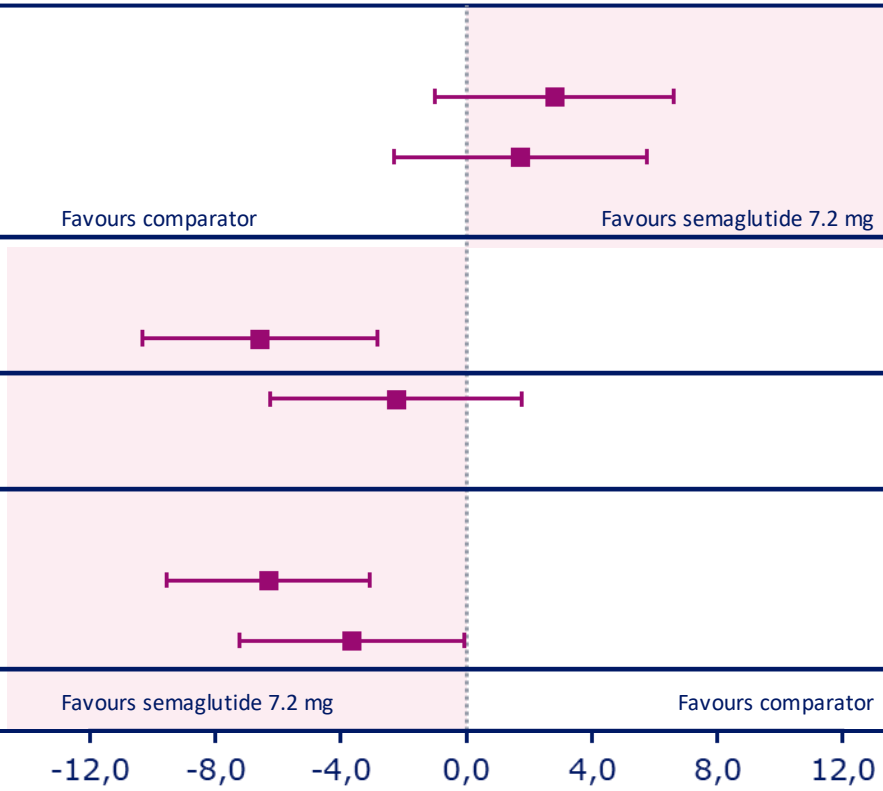


Data are ETDs for the treatment policy estimand (effect regardless of treatment discontinuation or rescue medication use). P values are not adjusted for multiplicity.
CI, confidence interval; CoEQ, Control of Eating Questionnaire; ETD, estimated treatment difference.
Wharton S, et al. Presented at the European Association for the Study of Diabetes (EASD) 61st Annual Meeting, 15–19 September 2025, Vienna, Austria.

Change in TFEQ-R18v2 scale scores

STEP UP secondary analysis

Change in TFEQ-R18v2 scale score at week 72	ETD [95% CI]	p value
Cognitive restraint		
Semaglutide 7.2 mg vs placebo	2.79 [−1.00, 6.59]	0.15
Semaglutide 7.2 mg vs semaglutide 2.4 mg	1.72 [−2.31, 5.76]	0.40
Emotional eating		
Semaglutide 7.2 mg vs placebo	−6.59 [−10.34, −2.84]	**0.0006**
Semaglutide 7.2 mg vs semaglutide 2.4 mg	−2.25 [−6.27, 1.78]	0.27
Uncontrolled eating		
Semaglutide 7.2 mg vs placebo	−6.31 [−9.54, −3.08]	**0.0001**
Semaglutide 7.2 mg vs semaglutide 2.4 mg	−3.66 [−7.24, −0.07]	**0.05**

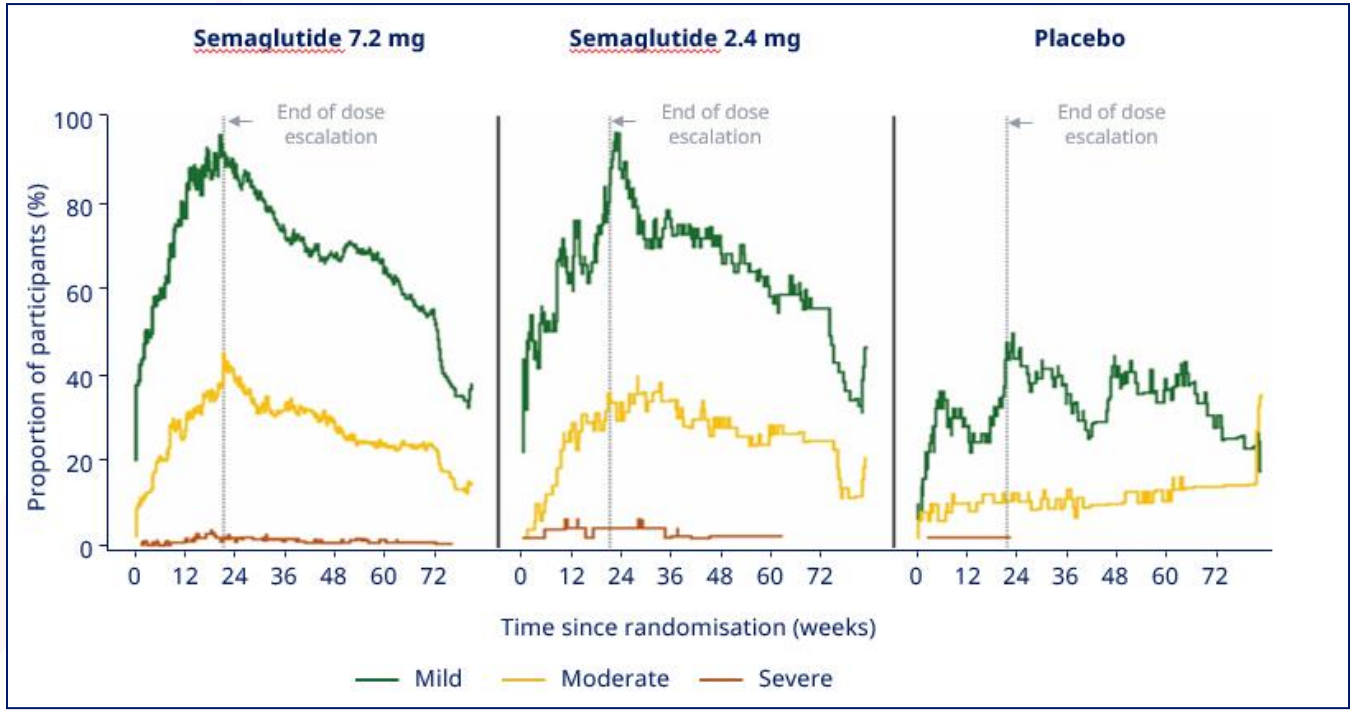


Data are ETDs for the treatment policy estimand (effect regardless of treatment discontinuation or rescue medication use). P values are not adjusted for multiplicity.
CI, confidence interval; ETD, estimated treatment difference; TFEQ-R18v2, Three-Factor-Eating Questionnaire revised 18-item version 2.
Wharton S, et al. Presented at the European Association for the Study of Diabetes (EASD) 61st Annual Meeting, 15–19 September 2025, Vienna, Austria.

Adverse event overview

AE, n (%)	Semaglutide 7.2 mg (n=1004)	Semaglutide 2.4 mg (n=201)	Placebo (n=201)
All AEs	**878 (87.5)**	**169 (84.1)**	**156 (77.6)**
Mild	**805 (80.2)**	**154 (76.6)**	**136 (67.7)**
Moderate	**506 (50.4)**	**97 (48.3)**	**73 (36.3)**
Severe	81 (8.1)	21 (10.4)	9 (4.5)
Serious AEs	68 (6.8)	22 (10.9)	11 (5.5)
AEs leading to dose reduction	186 (18.5)	25 (12.4)	1 (0.5)
AEs leading to permanent discontinuation	**54 (5.4)**	**8 (4.0)**	**2 (1.0)**
Fatal AEs (IT)	0	0	0
Hypoglycaemia events	3 (0.3)	2 (1.0)	0
Mild	3 (0.3)	2 (1.0)	0
Gastrointestinal AEs	**711 (70.8)**	**123 (61.2)**	**86 (42.8)**
Skin and subcutaneous tissue disorders	216 (21.5)	31 (15.4)	13 (6.5)
Nervous system disorders	309 (30.8)	39 (19.4)	28 (13.9)
Dysaesthesia*	230 (22.9)	12 (6.0)	1 (0.5)

Prevalence of gastrointestinal adverse events by severity



Data are for the safety analysis set and are from the on-treatment observation period, unless otherwise stated.
**Proportions are expressed in terms of participants who experienced dysaesthesia, except for "all events." Dysaesthesia AEs were identified by a pre-defined MedDRA search (version 27.1) and included AEs with preferred terms of allodynia, burning sensation, dysaesthesia, hyperaesthesia, hyperpathia, pain of skin, paraesthesia, sensitive skin, skin burning sensation, skin discomfort, and skin sensitisation.*
AE, adverse event; IT, in-trial; MedDRA, Medical Dictionary for Regulatory Activities.
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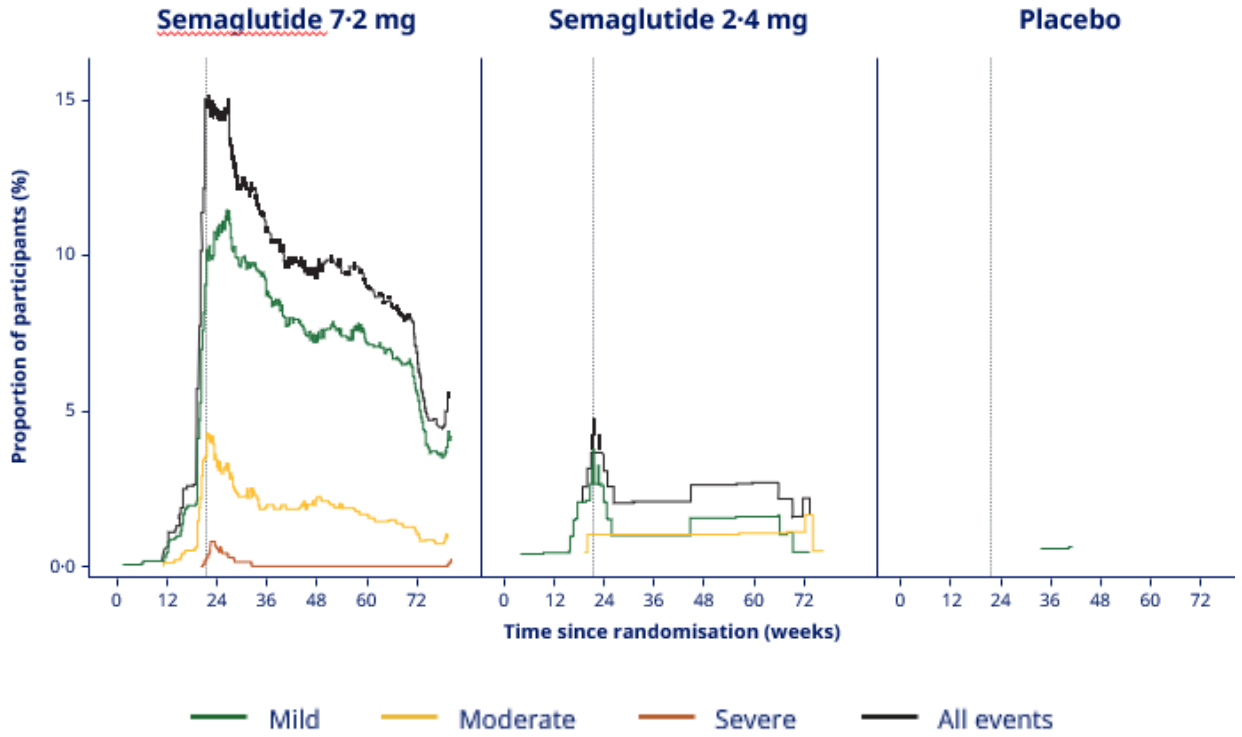
Dysaesthesia adverse events

STEP UP

participants were required to re-consent during the trial following an addition of dysaesthesia adverse events to the investigators brochure and informed consent forms, this could have introduced bias in all treatment groups.

Dysaesthesia AE, n (%)*	Semaglutide 7.2 mg (n=1004)	Semaglutide 2.4 mg (n=201)	Placebo (n=201)
All AEs	**230 (22.9)**	**12 (6.0)**	**1 (0.5)**
Mild	**177 (77.0)**	**9 (75.0)**	**1 (100)**
Moderate	**67 (29.1)**	**3 (25.0)**	**0**
Severe	8 (3.5)	0	0
Serious AEs	**0**	**0**	**0**
AEs leading to dose reduction	47 (20.4)	2 (16.7)	0
AEs leading to temporary discontinuation	17 (7.4)	0	0
AEs leading to permanent discontinuation	**4 (1.7)**	**0**	**0**
Recovered	197 (85.7)	10 (83.3)	1 (100)



Dysaesthesia AEs were identified by a pre-defined Medical Dictionary for Regulatory Activities version 27.1 search, and included AEs with preferred terms of allodynia, burning sensation, dysaesthesia, hyperaesthesia, hyperpathia, pain of skin, paraesthesia, sensitive skin, skin burning sensation, skin discomfort and skin sensitisation. **The most common dysaesthesia-associated adverse events were hyperaesthesia, dysaesthesia, and sensitive skin.**

The graph shows the cumulative incidence (time to first event) of events; the grey line at week 20 indicates the last stage of dose escalation for participants receiving semaglutide 7.2 mg. Data are for the safety analysis set (the full randomised population who were exposed to at least one dose of the trial product) and are from the on-treatment observation period. Participants could experience more than one AE.. AE, adverse event; R, events per 100 participant-years; SAE, serious adverse event.

Wharton S et al. Lancet Diabetes Endocrinol 2025; DOI: 10.1016/S2213-8587(25)00226-8.

Conclusions

Semaglutide 7·2 mg led to a mean weight loss of 21% with 33% of participants reaching ≥25% weight loss (trial product estimand

A **higher proportion of participants with prediabetes achieved normoglycaemia with semaglutide 7·2 mg versus semaglutide 2·4 mg and placebo**

Metabolic parameters and cardiometabolic risk factors were improved with semaglutide 7·2 mg compared with semaglutide 2·4 mg and placebo.
Overall, the **safety and tolerability** profiles of the semaglutide doses were **similar** to the GLP-1RA therapeutic class

Semaglutide improves body composition preserving muscle function and **significantly improves craving control, emotional eating and uncontrolled eating**

Results from STEP UP support a **favourable benefit–risk profile of semaglutide 7·2** mg for weight management in people with obesity, and **suggest that a higher dose of semaglutide up to 7·2 mg per week could be used to achieve greater clinical benefits**