Gastrointestinal tolerability of once-daily oral semaglutide 25 mg in adults with overweight or obesity, and the relationship with weight loss: a *post hoc* analysis of the OASIS 4 trial

Domenica Rubino[1], Oscar Birkhan[2], Agnieszka Klimek-Abercrombie[2], Chaithra Shaji[3], Minh Chau Tran[2], **Sean Wharton[4]**

[1]Washington Center for Weight Management and Research, Arlington, VA, USA; [2]Novo Nordisk A/S, Søborg, Denmark; [3]Novo Nordisk Global Business Services, Bengaluru, India; [4]University of Toronto, Toronto, Ontario, Canada

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

INCLUDED IN POSTER

Introduction

In OASIS 4, once-daily oral semaglutide 25 mg, a GLP-1RA, led to significantly greater body weight loss of 13.6% vs 2.2% with placebo ($p<0.001$, treatment policy estimand; trial product estimand: 16.6% vs 2.7%) after 64 weeks in people with overweight or obesity[1]

GI AEs, most commonly mild-to-moderate nausea, are a dose-dependent class effect of GLP-1RAs[2]

Weight loss induced by s.c. semaglutide 2.4 mg has been shown to be independent of GI AEs[3]

However, this has not previously been investigated with oral semaglutide

Physicians and patients may query whether GI AEs are, at least in part, responsible for the weight loss attained with these medications

This *post hoc* analysis of OASIS 4 investigated the relationship between GI AEs and weight loss for oral semaglutide 25 mg

AE, adverse event; GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; s.c., subcutaneous.

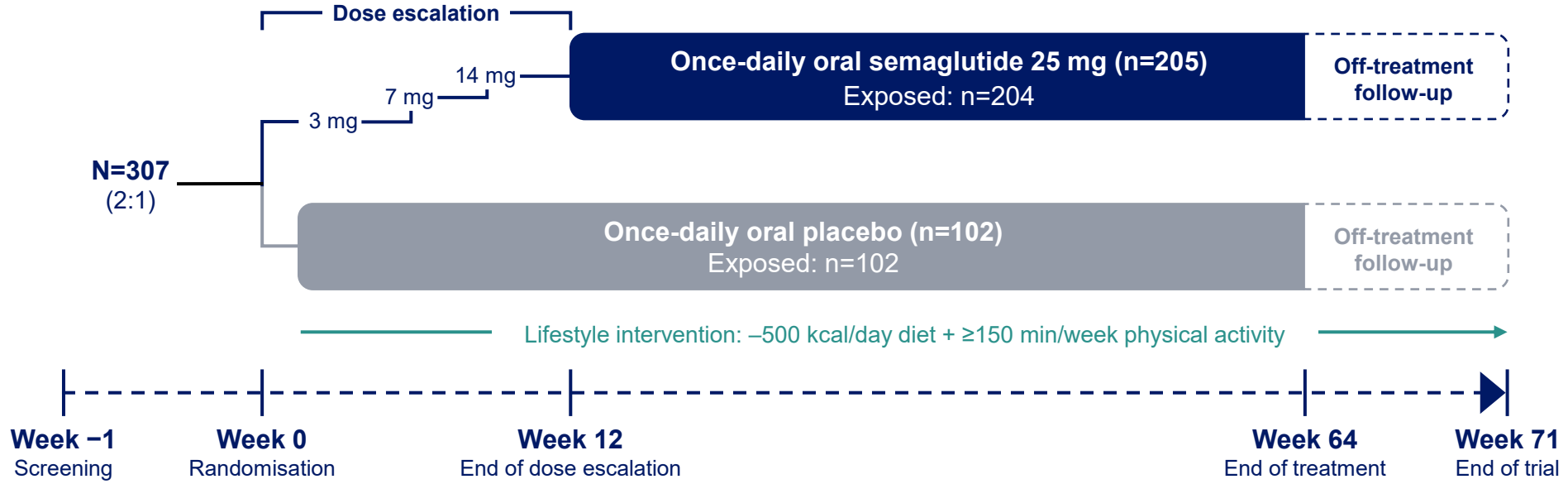
1. Wharton S et al. N Engl J Med 2025;393:1077–1087; 2. Bettge K et al. Diabetes Obes Metab 2017;19:336–347; 3. Wharton S et al. Diabetes Obes Metab 2022;24:94–105.

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

ADDITIONAL INFORMATION

OASIS 4 trial design

Phase 3b, randomised, double-blind, placebo-controlled multinational trial (NCT05564117)



Population

- Aged ≥18 years
- BMI ≥30 kg/m^2 (or ≥27 kg/m^2 with ≥1 obesity-related complication)
- ≥1 self-reported unsuccessful dietary effort to lose weight
- Without T2D (HbA_{1c} <6.5%)

Co-primary endpoints

- Percentage change in body weight (co-primary)
- Proportion of participants with a body weight reduction of ≥5% (co-primary)

Confirmatory secondary endpoints

- Proportion of participants with a body-weight reduction of ≥10%, ≥15% and ≥20%
- Change in IWQOL-Lite-CT Physical Function (5-items) score

The 3, 7 and 14 mg escalation doses are bioequivalent to 1.5, 4 and 9 mg.

BMI, body mass index; HbA_{1c}, glycated haemoglobin; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite Clinical Trials Version; T2D, type 2 diabetes.

Wharton S et al. N Engl J Med 2025;393:1077–1087.

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

INCLUDED IN POSTER

Study participants and endpoints

Outcomes

This *post hoc* analysis evaluated:

- Incidence and severity of GI AEs (of any type and of specific GI AEs of interest [nausea, vomiting and/or diarrhoea])
- Body weight loss attained at week 64 with and without GI AEs
- Degree of body weight loss mediated by GI AEs

AE information was collected using open-ended, non-leading verbal questions, with follow-up at each subsequent visit/contact

AEs were coded using the Medical Dictionary for Regulatory Activities (version 27.0)

Analysis

- Unless otherwise stated, analyses were descriptive and used data from the on-treatment period (time from trial product initiation to 3 days after last dose for body weight changes and 49 days after last dose for AEs) in all randomised participants
- The mediation analysis of body weight loss used a natural effects model based on mixed models for repeated measures for the trial product estimand (effect of taking the drug without discontinuation or use of rescue intervention)

AE, adverse event; GI, gastrointestinal.

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

INCLUDED IN POSTER

Baseline demographics and clinical characteristics

Characteristic	Oral semaglutide 25 mg (n=205)	Placebo (n=102)
Age, years	48 (13)	47 (13)
Female sex, n (%)	155 (75.6)	87 (85.3)
Body weight, kg	106.4 (23.5)	104.8 (19.7)
Ethnicity, n (%)		
Not Hispanic or Latino	188 (91.7)	95 (93.1)
Hispanic or Latino	17 (8.3)	7 (6.9)
Race, n (%)		
White	190 (92.7)	91 (89.2)
Black or African American	13 (6.3)	9 (8.8)
Asian	1 (0.5)	1 (1.0)
Other†	1 (0.5)	1 (1.0)
BMI, kg/m^2	37.5 (6.7)	37.8 (6.1)
Waist circumference, cm	114.0 (15.8)	113.6 (14.7)

Data are mean (SD) unless otherwise stated.

†Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other, or not reported.

BMI, body mass index; SD, standard deviation.

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

INCLUDED IN POSTER

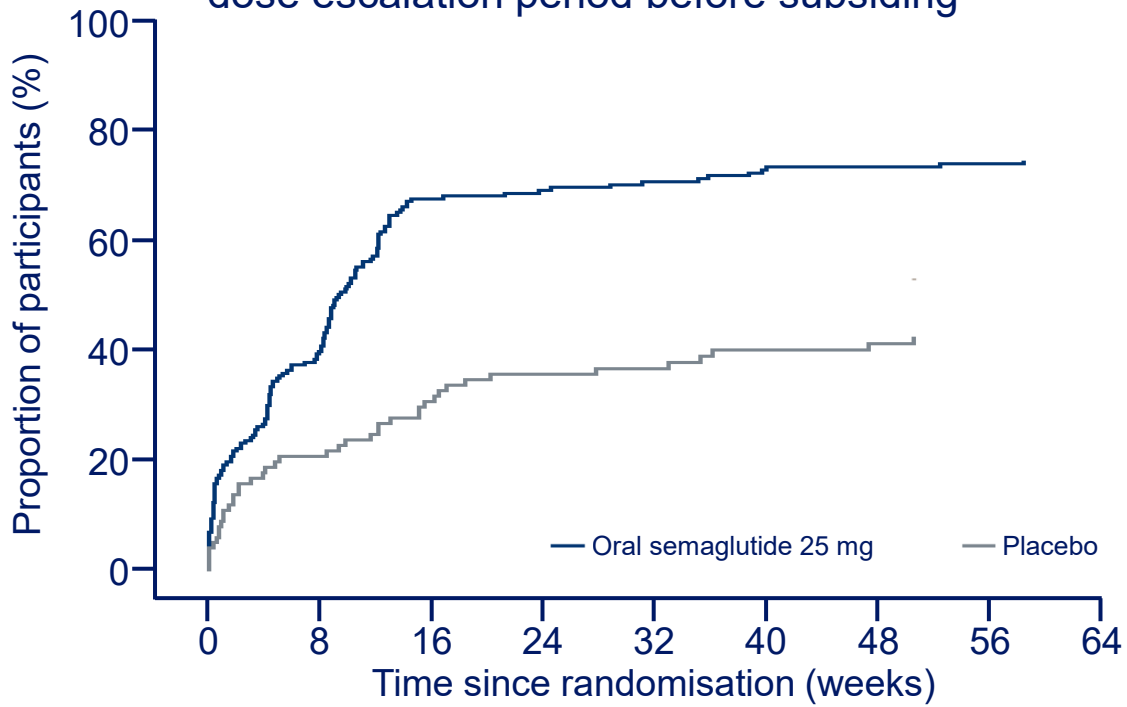
GI AEs were more common with oral semaglutide 25 mg than placebo

GI AEs
(oral semaglutide 25 mg vs placebo)

- **Any type: 74.0%** vs 42.2%
- **Nausea: 46.6%** vs 18.6%
- **Vomiting: 30.9%** vs 5.9%
- **Diarrhoea: 17.6%** vs 8.8%
- **Constipation: 20.1%** vs 9.8%

Time to onset of GI AEs

GI AEs with oral semaglutide 25 mg generally peaked during the dose escalation period before subsiding



Participants (n)									
Oral semaglutide 25 mg	204	124	64	60	56	51	50	49	47
Placebo	102	80	69	62	59	52	48	47	45

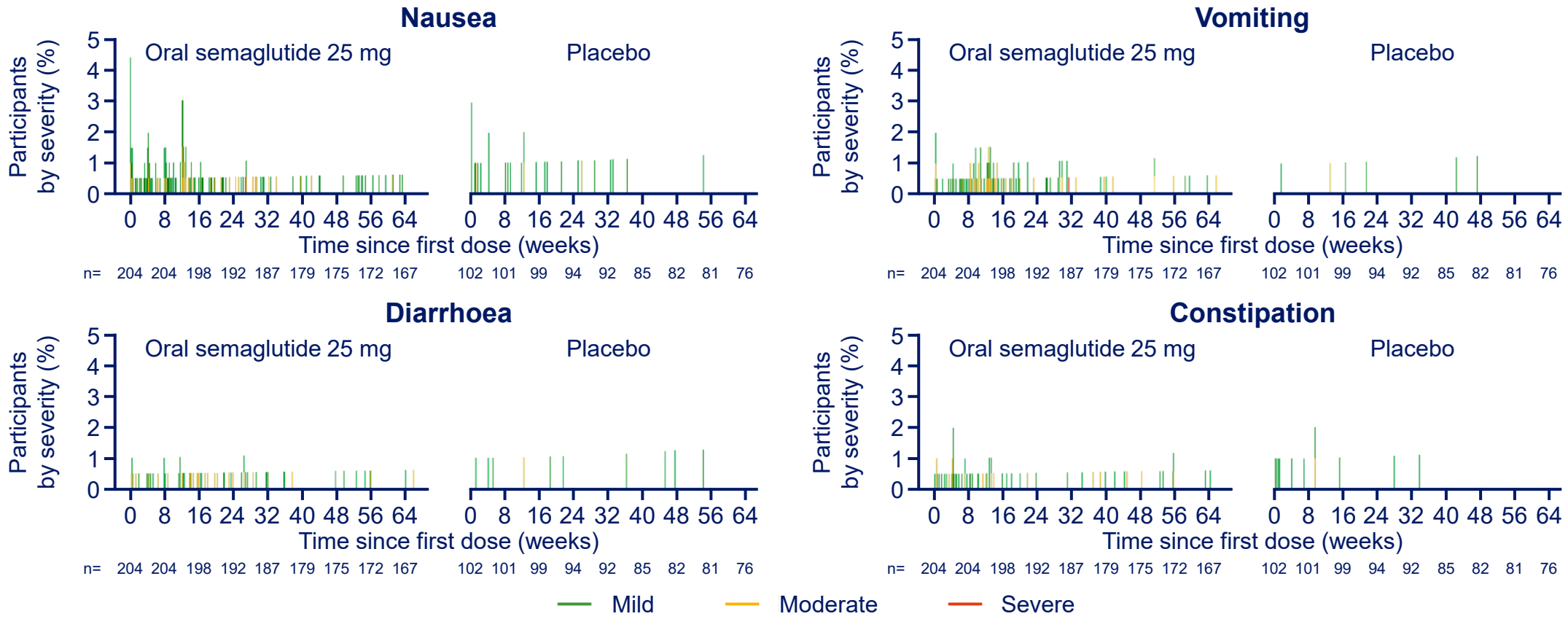
The graph shows observed data from the on-treatment period in all exposed participants. Numbers of participants remaining on treatment are shown below the graph.
AE, adverse event; GI, gastrointestinal.

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

ADDITIONAL INFORMATION

Most GI AEs with oral semaglutide 25 mg were of mild-to-moderate severity

Incidence of GI AEs by day and severity



Observed data are from the on-treatment period in all exposed participants. For participants with >1 event on a given day, the event of highest severity was included. Numbers of participants remaining on treatment are shown below each graph.
AE, adverse event; GI, gastrointestinal.

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

INCLUDED IN POSTER

Rates of serious GI AEs and permanent treatment discontinuations due to GI AEs were low

GI AEs leading to permanent treatment discontinuation

(oral semaglutide 25 mg vs placebo)

3.4% (n=7) vs **2.0% (n=2)**

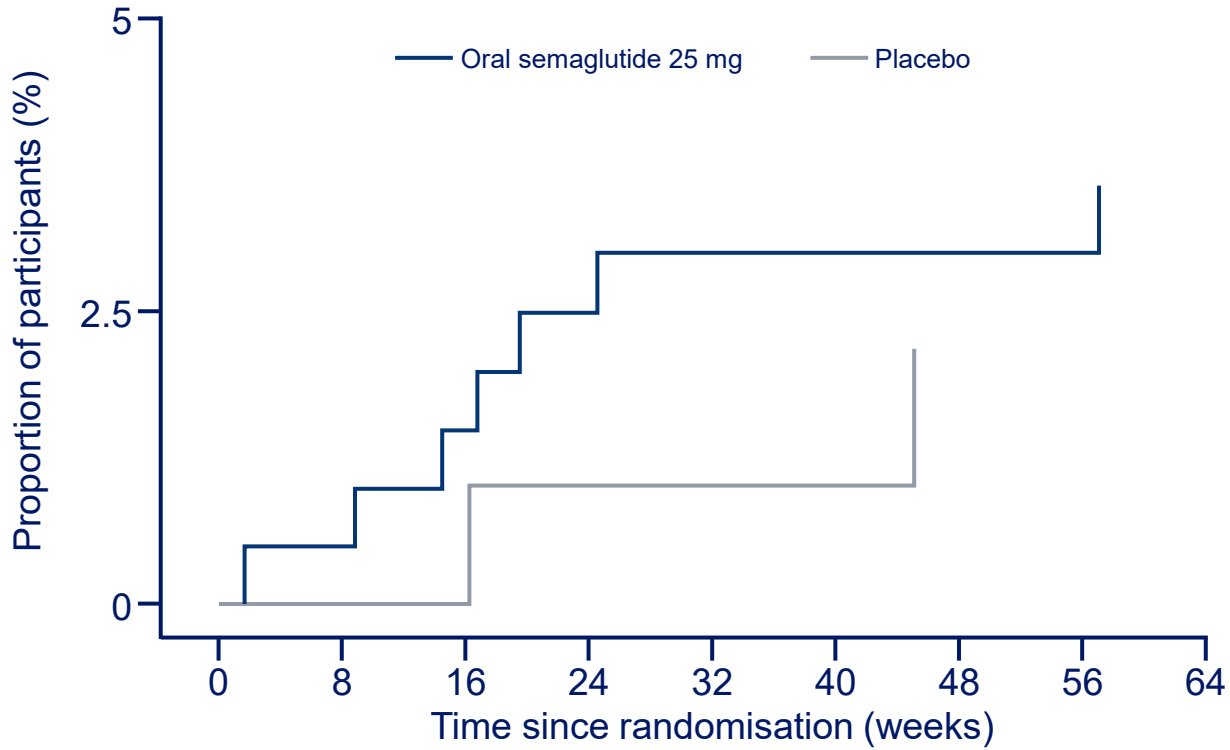
- All but one event occurred after week 12, during the maintenance phase (2.9% [n=6] vs 2.0% [n=2])
- For one participant on oral semaglutide 25 mg, the event occurred during dose escalation, but they did not discontinue until after week 12
- Four of these events were related to GI AEs of interest: nausea (n=3; 1.5%) and vomiting (n=1; 0.5%), all with oral semaglutide 25 mg

Serious GI AEs

(oral semaglutide 25 mg vs placebo)

0 vs **1.0% (n=1)** [acute pancreatitis]

Time to treatment discontinuation due to GI AEs



Participants (n)									
Oral semaglutide 25 mg	204	203	196	189	186	179	175	172	166
Placebo	102	101	99	94	92	85	81	80	76

Observed data are from the on-treatment period in all exposed participants. Numbers of participants remaining on treatment are shown below the graph.

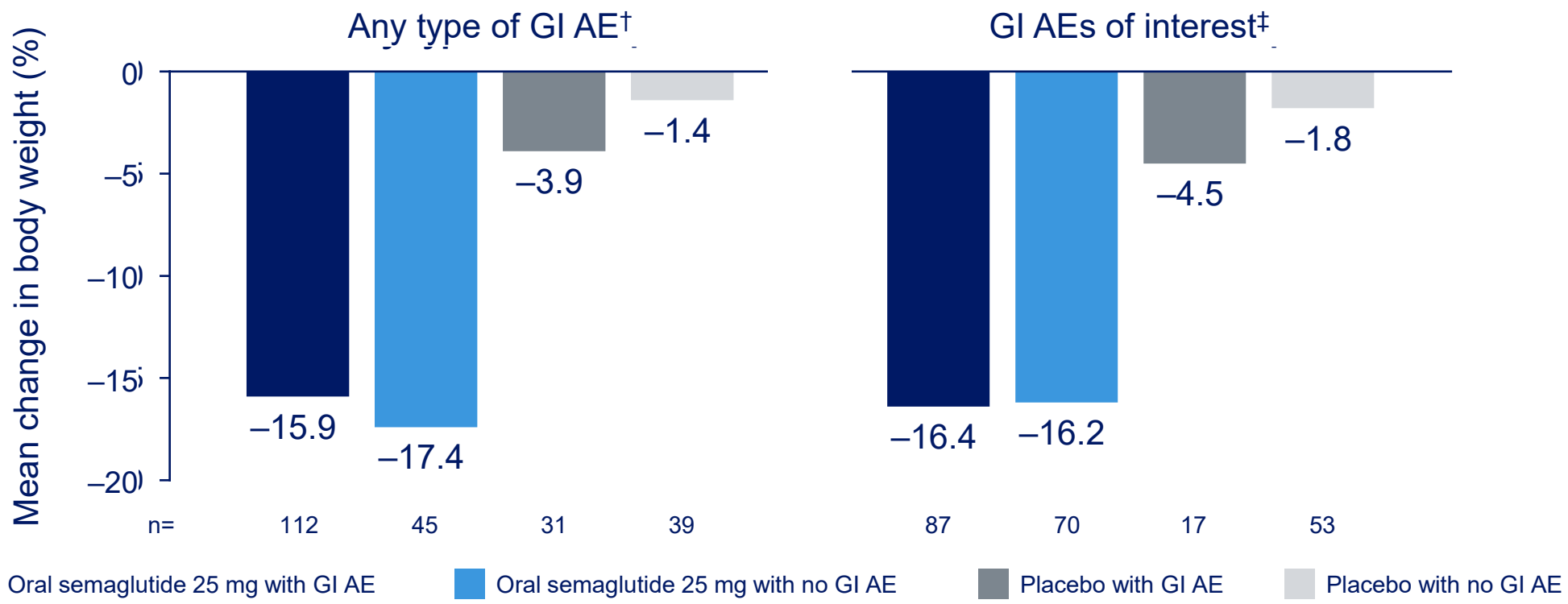
AE, adverse event; GI, gastrointestinal.

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

INCLUDED IN POSTER

Weight loss with oral semaglutide 25 mg was generally independent of GI AEs

Change from baseline in body weight at week 64 among participants with and without GI AEs



Observed data are from the on-treatment period in all randomised participants who had a week 64 body weight assessment. Numbers of participants contributing to the means are shown below the graph.

†Any type of GI-related AE, including but not limited to nausea, vomiting and diarrhoea. ‡Either nausea, vomiting or diarrhoea, or any combination thereof, only.

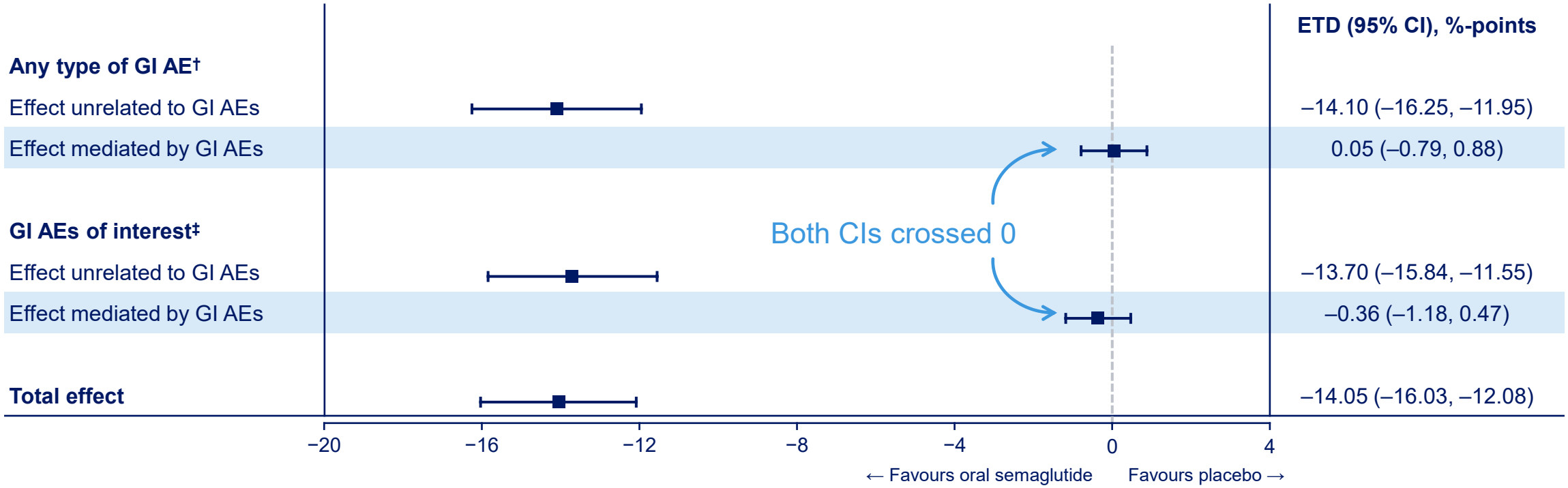
AE, adverse event; GI, gastrointestinal.

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

INCLUDED IN POSTER

GI AEs had no effect on the weight loss induced by oral semaglutide 25 mg

Mediation analysis of body weight changes mediated by or unrelated to GI AEs



ETD (95% CI) for the percentage change from baseline to week 64 in body weight (oral semaglutide 25 mg vs placebo)

Estimated data are for the trial product estimand (effect of taking the drug without discontinuation or use of rescue intervention), using data from the on-treatment period in all randomised participants. Changes in body weight were analysed using a mixed model for repeated measurements with randomised treatment as a factor and baseline body weight as a covariate, all nested within visit. Effects were estimated using natural effects models, with the interaction between treatment and any GI AEs or GI AEs of interest (as relevant) and baseline body weight as the main effect, assuming no interaction between the natural effects and the baseline variable. 95% CI were Wald CIs. †Any type of GI-related AE, including but not limited to nausea, vomiting and diarrhoea. ‡Either nausea, vomiting or diarrhoea, or any combination thereof, only.

AE, adverse event; CI, confidence interval; ETD, estimated treatment difference; GI, gastrointestinal.

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

INCLUDED IN POSTER

Conclusions

- GI AEs were more common with oral semaglutide 25 mg than placebo, but none of these events were serious
- With oral semaglutide 25 mg, GI AEs were typically transient and mild-to-moderate in severity
- Consistent with findings with subcutaneous semaglutide 2.4 mg, weight loss with oral semaglutide was generally independent of GI AEs
- These results indicate weight loss with semaglutide is attributable to treatment effects unrelated to GI AEs, regardless of the route of administration

AE, adverse event; GI, gastrointestinal.

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