Long-Term Efficacy and Safety of Once-Weekly Semaglutide for Weight Loss in Patients Without Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Semaglutide, a glucagon-like peptide-1 receptor agonist, has demonstrated clinically important weight loss effects in patients with type 2 diabetes. However, its effects on sustained weight loss in patients without diabetes remains unclear. Our objective was to examine the long-term efficacy and safety of semaglutide use for weight loss in patients with overweight/obesity and without diabetes. MEDLINE, EMBASE, and the Cochrane Libraries were systematically searched to identify randomized controlled trials that randomized participants with overweight/obesity and without diabetes to once-weekly 2.4 mg subcutaneous semaglutide versus placebo, with a follow-up of at least 68 weeks. The primary outcome was a change in relative body weight from baseline to the longest follow-up. Random-effects models with inverse variance weighting were used to estimate the weighted mean differences (WMDs) and relative risks (RRs) with 95% confidence intervals (CIs). A total of 4 randomized controlled trials (n = 3,087) were included. Of the 3 trials that provided body mass index by category (n = 2,783), 94.0% of the participants had a baseline body mass index ≥30 kg/m^2. Compared with placebo, the use of semaglutide was associated with substantial decreases in long-term relative (WMD −12.1%, 95% CI −13.5 to −10.7) and absolute body weight (WMD −12.3 kg, 95% CI −13.6 to −11.0). At the longest follow-up, 33.4% of participants randomized to semaglutide achieved ≥20% weight loss compared with 2.2% with placebo (RR 15.08, 95% CI 9.31 to 24.43). The risk of gastrointestinal adverse events was higher in participants who took semaglutide than placebo (RR 1:47, 95% CI 1.28 to 1.68); however, the majority of these events were transient and mild-to-moderate in severity and did not require treatment discontinuation. In conclusion, semaglutide is efficacious for sustained weight loss in patients with overweight/obesity and without diabetes. **(Am J Cardiol 2024;222:121−130)**

Keywords: semaglutide, GLP-1 receptor agonist, weight loss, obesity

Semaglutide is a glucagon-like peptide-1 receptor agonist that was previously used for the treatment of hyperglycemia in patients with type 2 diabetes. In addition to improving glycemic control, the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN) trials found that patients randomized to once-weekly subcutaneous semaglutide experienced clinically important weight loss.[1] In 2021, the US Food and Drug Administration approved semaglutide for the treatment of obesity in patients without diabetes.[2] Multiple randomized controlled trials (RCTs) have examined semaglutide for weight loss in patients with overweight/obesity without diabetes, finding that it is efficacious for weight loss in this population. However, previous meta-analyses in this area have not adequately assessed its long-term efficacy.[3−6] Therefore, we conducted a systematic review and meta-analysis of RCTs to examine the effects of once-weekly subcutaneous 2.4 mg semaglutide on long-term weight loss.

Methods

We developed and adhered to a prespecified study protocol to perform this systematic review and meta-analysis,

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See page 129 for Declaration of Competing Interest.

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publicly preregistered with the Open Science Framework Registries on May 29, 2023 (*http://osf.io/46vsj*). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 standards were followed in the reporting of this study.[7]

We systemically searched the MEDLINE (by way of PubMED), EMBASE (by way of Ovid), and Cochrane CENTRAL databases from their inception to June 29, 2023, to identify relevant trials. We also searched *ClinicalTrials.gov* for potentially eligible trials that our database search did not identify. Keywords (title/abstract), Medical Subject Headings, and EMTREE terms searched included those for semaglutide, overweight or obesity, and RCTs; the detailed search is listed in Supplementary Table 1. The Cochrane Handbook for Systematic Reviews of Interventions was used to apply a modified search hedge to limit the findings to RCTs in MEDLINE and EMBASE (by way of Ovid). No language restrictions were used in the search. Duplicates of publications identified by our search were removed after their import into EndNote (Clarivate).[8] The deduplicated search results were then imported into Covidence (Veritas Health Innovation Ltd), a systematic review management software.

Using predetermined inclusion and exclusion criteria, 2 authors (A.M. and K.P.) independently screened the titles and abstracts of identified publications to determine eligibility. A citation deemed potentially eligible by either reviewer was carried forward to full-text review, where discrepancies were addressed by consensus or by a third reviewer (J.Y.L.). The included studies were RCTs that randomized participants to once-weekly semaglutide versus placebo, in combination with lifestyle interventions. Once-weekly semaglutide was defined as an injectable subcutaneous 2.4 mg dose of semaglutide that is administered once a week. Pharmacokinetic modeling has suggested that this dose achieves maximum weight loss in adults with overweight/obesity.[9,10] The detailed inclusion and exclusion criteria is listed in Supplementary Appendix 2.

A total of 2 authors (A.M. and K.P.) independently extracted data, resolving any discrepancies by consensus or with a third reviewer (J.Y.L.). Intention-to-treat analysis data were extracted for all outcomes, where possible. All screening and data extraction were done using Covidence.

Our predetermined primary outcome was change in relative body weight from baseline to the longest available follow-up, by randomized treatment group. The predetermined secondary outcomes included reductions in body weight of 5%, 10%, 15%, or 20%, change in absolute body weight, change in body mass index (BMI), change in waist circumference, change in systolic blood pressure (SBP), and change in diastolic blood pressure (DBP)—all reported from baseline to the last follow-up. The safety outcomes included death, serious adverse events (SAEs), any adverse events (AEs), and AEs leading to trial product discontinuation as defined by the investigators at any time during the treatment period or follow-up.

A total of 2 reviewers (A.M. and K.P.) independently assessed the risk of bias in the included RCTs using version 2 of the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (RoB 2),[11] resolving any disagreements by consensus or with third reviewer (J.Y.L.). The RoB 2 tool provided an overall structured assessment of the quality of a randomized trial by dividing it into 5 domains (randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of reported result). Regardless of study quality, all eligible RCTs were included in our meta-analysis.

We used DerSimonian and Laird random-effects meta-analytic models with inverse variance weighting and the Jackson and modified Knapp−Hartung method extensions to pool continuous data across studies to estimate weighted mean differences (WMDs) and corresponding confidence intervals (CIs) or count data to estimate the risk ratios (RRs) and corresponding 95% CIs. Forest plots were used to visually display the results of individual studies and syntheses. Only outcomes reported by at least 3 sufficiently homogeneous and eligible trials were meta-analyzed to ensure meaningful interpretation.

The presence of statistical heterogeneity was assessed by using I^2 and Tau^2 statistics to estimate the amount of between-study variability. We conducted sensitivity analyses using a fixed-effects model with inverse variance weighting for the primary outcome and by restricting to studies at a low risk of bias. All analyses were performed using the *meta* and *metaphor* packages in R version 4.2.3.

Results

Of the 1,310 records screened, 24 were retrieved for full-text review of weight loss trials using semaglutide in patients without diabetes. Our systematic review and meta-analysis included 4 RCTs that met our inclusion criteria (Figure 1).

The included trials were all part of the Semaglutide Treatment Effect in People with Obesity (STEP) program, published between 2021 and 2022. A total of 9 STEP trials have been completed, with all but STEP-7 published. We included STEP-1, STEP-3, STEP-5, and STEP-8. STEP-2 was excluded because its trial population included participants with type 2 diabetes; STEP-4 was excluded because of a lack of placebo control for the first 20 weeks of treatment; STEP-6 was excluded because its trial population focused on East Asian participants; and STEP-TEENS was excluded because its trial population consisted of adolescents aged 12 to 17 years. There was no patient overlap in any of the STEP trials.[12]

All included trials had similar study designs (Table 1). A total of 3 of 4 trials had a treatment period of 68 weeks and a maximum follow-up of 75 weeks; STEP-5 had a treatment period of 104 weeks and follow-up of 111 weeks. In all trials, the once-weekly 2.4 mg semaglutide arm included a dose escalation period of 16 weeks. In addition, STEP-8 included an additional active arm of once-daily 3.0 mg liraglutide. All trials had a control arm of visually identical subcutaneous injectable placebo, including matching dose escalation. Participants in STEP-1 and STEP-3 were randomized 2:1 to receive weekly semaglutide or placebo injections, whereas participants in STEP-5 and STEP-8 were randomized 1:1 and 3:1, respectively. In all 4 trials, all arms received lifestyle interventions and counseling that consisted of a reduced-calorie diet, prescribed physical activity, and individual sessions with a registered dietitian or similarly qualified health care professional.

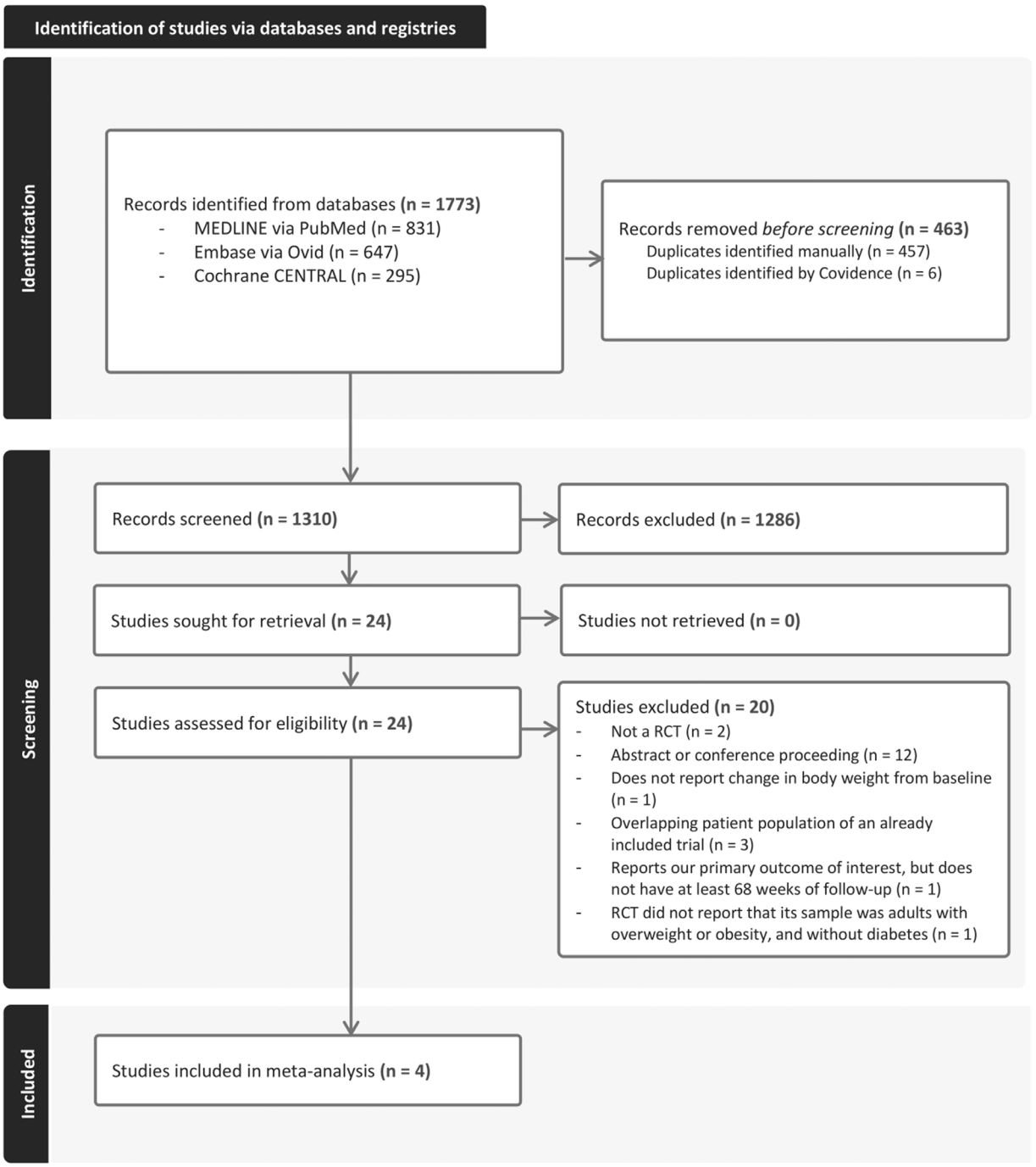

Figure 1. PRISMA Flow Diagram of study selection for randomized controlled trials of semaglutide use for weight loss in patients with overweight/obesity.

A total of 3,087 participants were included across the 4 trials, with 1,991 randomized to once-weekly semaglutide and 1,096 randomized to placebo (Table 2). All trials enrolled adults who reported at least 1 previous unsuccessful dietary effort to lose weight. Most participants were female (76.3%), and the mean age of each trial was between 46 and 51 years. The mean body weight of each trial was between 102.5 and 108.8 kg, and the mean BMI of each trial was between 37.0 and 38.8 kg/m^2. Excluding STEP-5, which did not report categorized BMI values, 6.0% of participants were overweight and 94.0% were obese. The mean waist circumference of each trial was between 111.8 and 115.7 cm. The mean SBPs and DBPs of each trial was between 123 and 126 and 79 and 81 mm Hg, respectively. The most common co-morbidities included dyslipidemia (36.9%), hypertension (36.4%), knee osteoarthritis (15.3%), and obstructive sleep apnea (13.0%) (Supplementary Table 3). Excluding STEP-5, which did not report the prevalence of co-morbidities, approximately 1/4 of participants (25.8%) had at least 1 co-morbidity, whereas 27.4% had at least 3 (Supplementary Table 4).

Table 1
Study design and characteristics of randomized controlled trials of once-weekly semaglutide versus placebo for weight loss

	STEP-1	STEP-3	STEP-5	STEP-8
Location	Argentina, Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, India, Japan, Mexico, Poland, Puerto Rico, Russia, Taiwan, United Kingdom, and United States	United States	Canada, Italy, Hungary, Spain, and United States	United States
Population	STEP Program Population*	STEP Program Population*	STEP Program Population*	STEP Program Population*
Sample Size	1961	611	304	338
Active Arm	Subcutaneous semaglutide 2.4 mg/week, lifestyle intervention and counseling	Subcutaneous semaglutide 2.4 mg/week, lifestyle intervention and counseling	Subcutaneous semaglutide 2.4 mg/week, lifestyle intervention and counseling	Subcutaneous semaglutide 2.4 mg/week, lifestyle intervention and counseling
Control	Matching subcutaneous placebo, lifestyle intervention and counseling	Matching subcutaneous placebo, lifestyle intervention and counseling	Matching subcutaneous placebo, lifestyle intervention and counseling	Matching subcutaneous placebo, lifestyle intervention and counseling
Extra Arm	-	-	-	Subcutaneous liraglutide 3.0 mg/day, lifestyle intervention, and counseling
Lifestyle Intervention	Reduced-calorie diet (500 kcal/day deficit) and physical activity (150 mins/week)	Diet: 1000-1200 kcal/day for first 8 weeks, 1200-1800 kcal/day for rest of treatment Physical activity: 100 mins/week increasing by 25 mins every 4 weeks to reach 200 min/week	Reduced-calorie diet (500 kcal/day deficit) and physical activity (150 mins/week)	Reduced-calorie diet (500 kcal/day deficit) and physical activity (150 mins/week)
Counselling Protocol	Every 4 weeks to help adhere to prescribed diet and physical activity	30 individual intensive behavioral therapy visits with a registered dietitian, instructing participants on diet, physical activity, and behavioral strategies	Every 4 weeks with a dietitian or similarly qualified healthcare professional via in-person visits or telephone on adherence to prescribed diet and physical activity	Every 4-6 weeks with a qualified healthcare professional via in-person visits or telephone to help adhere to diet and physical activity recommendations
Treatment Period	68 weeks	68 weeks	104 weeks	68 weeks
Primary Endpoint	Percentage change in body weight and weight loss of ≥5% from baseline at week 68	Percentage change in body weight and weight loss of ≥ 5% from baseline at week 68	Percentage change in body weight and weight loss of ≥ 5% from baseline at week 104	Percentage change in body weight from baseline at week 68
Other Endpoints	- Weight loss of ≥10%, ≥15% and ≥20% - Changes in body weight, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, 36-Item Short Form Survey physical functioning score, Impact of Weight on Quality of Life-Lite-Clinical physical function score, glycated hemoglobin, fasting plasma glucose, lipids and C-reactive protein	- Weight loss of ≥10%, ≥15% and ≥20% - Changes in body weight, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, SF-36 physical functioning score, glycated hemoglobin, fasting plasma glucose, fasting serum insulin, lipids and C-reactive protein	- Weight loss of ≥10%, ≥15% and ≥20% - Changes in body weight, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, glycated hemoglobin, fasting plasma glucose, fasting serum insulin, lipids, C-reactive protein, glycemic status, lipid-lowering medication use, and antihypertensive use	- Weight loss of ≥5%, ≥10%, ≥15% and ≥20% - Changes in body weight, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, glycated hemoglobin, fasting plasma glucose, fasting serum insulin, lipids, and C-reactive protein
Maximum Follow-Up	75 weeks	75 weeks	111 weeks	75 weeks

* ≥18 years of age with BMI≥27 kg/m^2 with ≥1 weight-related comorbidity or BMI≥30 kg/m^2, ≥1 self-reported unsuccessful dietary weight loss attempt, and without diabetes.

Table 2
Baseline demographic characteristics of participants enrolled in randomized controlled trials of semaglutide use for weight loss

	Sample Size	Age (mean)	Female (%)	Body Weight (kg, mean)	Body Mass Index (kg/m^2)*			Waist Circumference (cm, mean)	Blood Pressure (mmHg, mean)	
					Mean	<30 (%)	≥30 (%)		Systolic	Diastolic
STEP-1										
Semaglutide	1306	46	73.1	105.4	37.8	6.2	93.8	114.6	126	80
Placebo	655	47	76.0	105.2	38.0	5.5	94.5	114.8	127	80
STEP-3										
Semaglutide	407	46	77.4	106.9	38.1	5.7	94.3	113.6	124	80
Placebo	204	46	88.2	103.7	37.8	7.4	92.6	111.8	124	81
STEP-5										
Semaglutide	152	47.3	80.9	105.6	38.6	-	-	115.8	126	80
Placebo	152	47.4	74.3	106.5	38.5	-	-	115.7	125	80
STEP-8										
Semaglutide	126	48	81.0	102.5	37.0	7.1	92.9	111.8	125	81
Placebo†	85	51	77.6	108.8	38.8	4.7	95.3	115.4	123	79
TOTAL	3087	46.6	76.3	105.5	38.0	6.0†	94.0†	114.3	125.6	80.1

* Excluding Step-5.
† Placebo data for semaglutide and liraglutide groups were pooled.

A total of 3 trials had a low overall RoB 2–defined risk of bias and 1 (STEP-8, n = 211) had some concerns because of the domain of deviations from the intended intervention. This trial, which had an additional active arm, randomized participants (3:1:1:1) to receive once-weekly subcutaneous semaglutide or its matching placebo or once-daily subcutaneous liraglutide or its matching placebo. Randomization to semaglutide or liraglutide was not masked because of the differences in dosing; however, the active treatment groups were double-blinded against matching placebo group (once-weekly placebo injections for the semaglutide group versus once-daily placebo injections for the liraglutide group). To increase power for statistical analyses, both placebo groups were pooled in the results. However, there was no data provided on the outcomes of the individual placebo groups; therefore, the comparability of daily placebo versus weekly active intervention is unclear. A summary of the RoB 2 results stratified by risk domain is reported in Figure 2.

Compared with placebo, the long-term use of semaglutide was associated with decreases in relative (WMD −12.1%, 95% CI −13.5 to −10.7) (Figure 3) and absolute body weight (WMD −12.3 kg, 95% CI −13.6 to −11.0) (Figure 3). At the end of the treatment period, 85.8% of participants randomized to semaglutide achieved a ≥5% weight loss compared with 34.7% of participants randomized to placebo, and 33.4% of participants randomized to semaglutide achieved ≥20% weight loss compared with 2.2% of participants randomized to placebo (Supplementary Appendix 5, Table 3). Compared with participants randomized to placebo, participants randomized to semaglutide were more likely to achieve ≥5% (RR 2.37, 95% CI 1.67 to 3.36), ≥10% (RR 4.27, 95% CI 2.55 to 7.15), ≥15% (RR 7.12, 95% CI 3.66 to 13.85), and ≥20% weight loss (RR 15.08, 95% CI 9.31 to 24.43) (Supplementary Appendix 5, Table 3). Study-specific continuous and count data are listed in Supplementary Tables 6 and 7.

Compared with placebo, semaglutide was associated with decreased BMI (WMD −4.3 kg/m^2, 95% CI −4.9 to −3.7), waist circumference (WMD −9.2 cm, 95% CI −10.0 to −8.4), SBP (WMD −4.8 mm Hg, 95% CI −5.8 to −3.7), and DBP (WMD −2.5 mm Hg, 95% CI −3.2 to −1.8) (Supplementary Appendix 8, Table 3). STEP-8 was not pooled in the meta-analysis because it did not report data for BMI and was missing measures of variance for waist circumference, SBP, and DBP. However, STEP-8 reported similar numbers to the other 3 trials. The continuous trial data for waist circumference, SBP, and DBP are listed in Supplementary Table 6.

AEs were commonly reported in almost all participants in both groups (semaglutide 91.8%, placebo 89.3%, RR 1.02, 95% CI 0.97 to 1.08) (Supplementary Appendix 9, Table 4). The majority of these AEs were gastrointestinal (GI) disorders (namely nausea, constipation, diarrhea, and vomiting), which occurred more frequently in the semaglutide group (77.2%) than the placebo group (52.2%, RR 1:47, 95% CI 1.28 to 1.68). Most of the GI disorders were transient, mild-to-moderate in severity, and did not require treatment discontinuation.

The pooled incidence of SAEs during the treatment period was numerically higher in the semaglutide group (9.4%) than placebo (6.6%) (RR 1.36, 95% CI 0.51 to 3.60). Of the 6.5% of participants randomized to semaglutide and 3.3% of participants randomized to placebo that discontinued treatment because of any AE, 4.0% and 0.6% were GI-related, respectively (RR 5.36, 95 CI% 1.64 to 17.52). A total of 2 of the 4 studies included in the meta-analysis reported at least 1 death. In total, there were 2 deaths in the semaglutide group and 1 in the placebo group. The causes of death in the 2 participants who received semaglutide were sudden cardiac arrest and myocardial infarction. A total of 3 causes of death were reported in the participant in the placebo group: glioblastoma, aspiration pneumonia, and sepsis. All 3 participants had discontinued their assigned treatment, and none of the deaths were considered to be related to treatment with semaglutide or placebo. The study-specific count data for the safety outcome are listed in Supplementary Table 10.

The results of the prespecified sensitivity analyses are listed in Supplementary Appendices 11-12 and Tables 13-

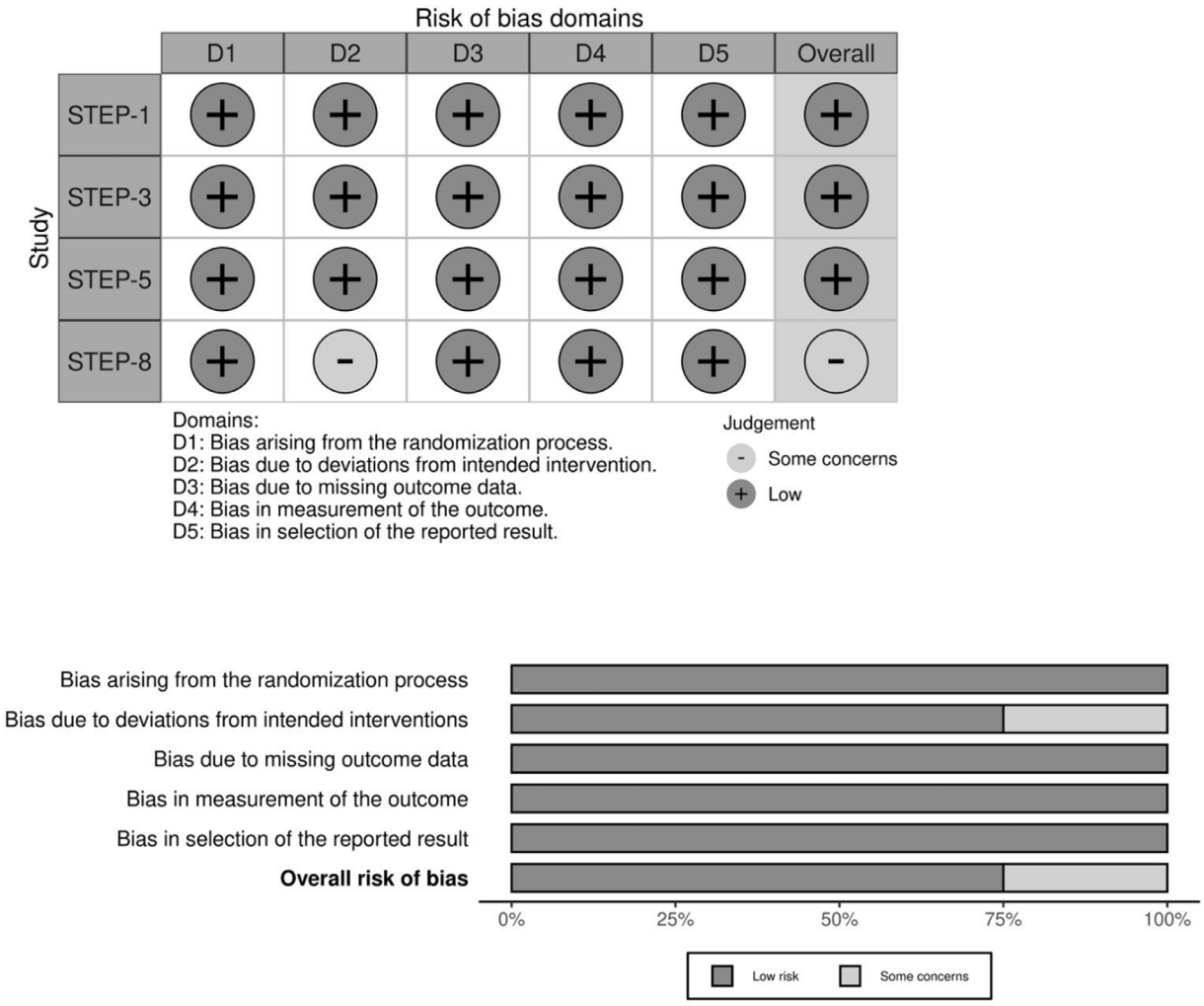

Figure 2. Summary of the Cochrane quality assessment risk of Bias 2 (RoB 2) results stratified by risk domains.

14. Overall, the use of a fixed-effects model with inverse variance weighting did not change the primary efficacy endpoints (change in relative and absolute body weight). In addition, the sensitivity analyses restricting to studies with a low risk of bias (excluding STEP-8) produced results that were consistent with our primary analyses. Funnel plots were not constructed and Egger test for small study effects was not performed because the number of included RCTs was <10.

Discussion

Our study was designed to assess the long-term efficacy and safety of once-weekly semaglutide versus placebo for sustained weight loss in adults with overweight/obesity and without diabetes. We found that the use of once-weekly 2.4 mg semaglutide, compared with placebo, was associated with a substantial increase in long-term relative (−12.1%) and absolute (−12.3 kg) weight loss. A third of participants randomized to semaglutide achieved at least a 20% reduction in body weight by the end of the treatment period compared with 2.2% of participants randomized to placebo. Semaglutide use also led to decreased BMI, waist circumference, SBP, and DBP. The rate of GI AEs was higher in the semaglutide group than in the placebo group; however, the majority of these events were transient and mild-to-moderate in severity and occurred primarily during and shortly after dose escalation. The rate of SAEs, AEs requiring treatment discontinuation, and death were low across all trials. Our results suggest that semaglutide is beneficial for promoting sustained weight loss in adults with overweight/obesity and without diabetes.

Older anti-obesity medications, including orlistat, phentermine-topiramate, lorcaserin, and naltrexone-bupropion, have not been as successful as semaglutide in achieving substantial weight reduction.[13] Previous systematic reviews and meta-analyses of RCTs have examined the efficacy and safety of semaglutide for weight loss in overweight/obesity without diabetes.[3–6] However, these studies included RCTs with different dosages and formulations of semaglutide (oral vs subcutaneous) and study durations ranging from 12 to 68 weeks, which added important heterogeneity to their results. Our meta-analysis, which included 4 of the 8 published STEP trials, sought to examine the long-term efficacy and safety of semaglutide with a standardized 2.4 mg once-weekly subcutaneous dose and a 68-week follow-up period.

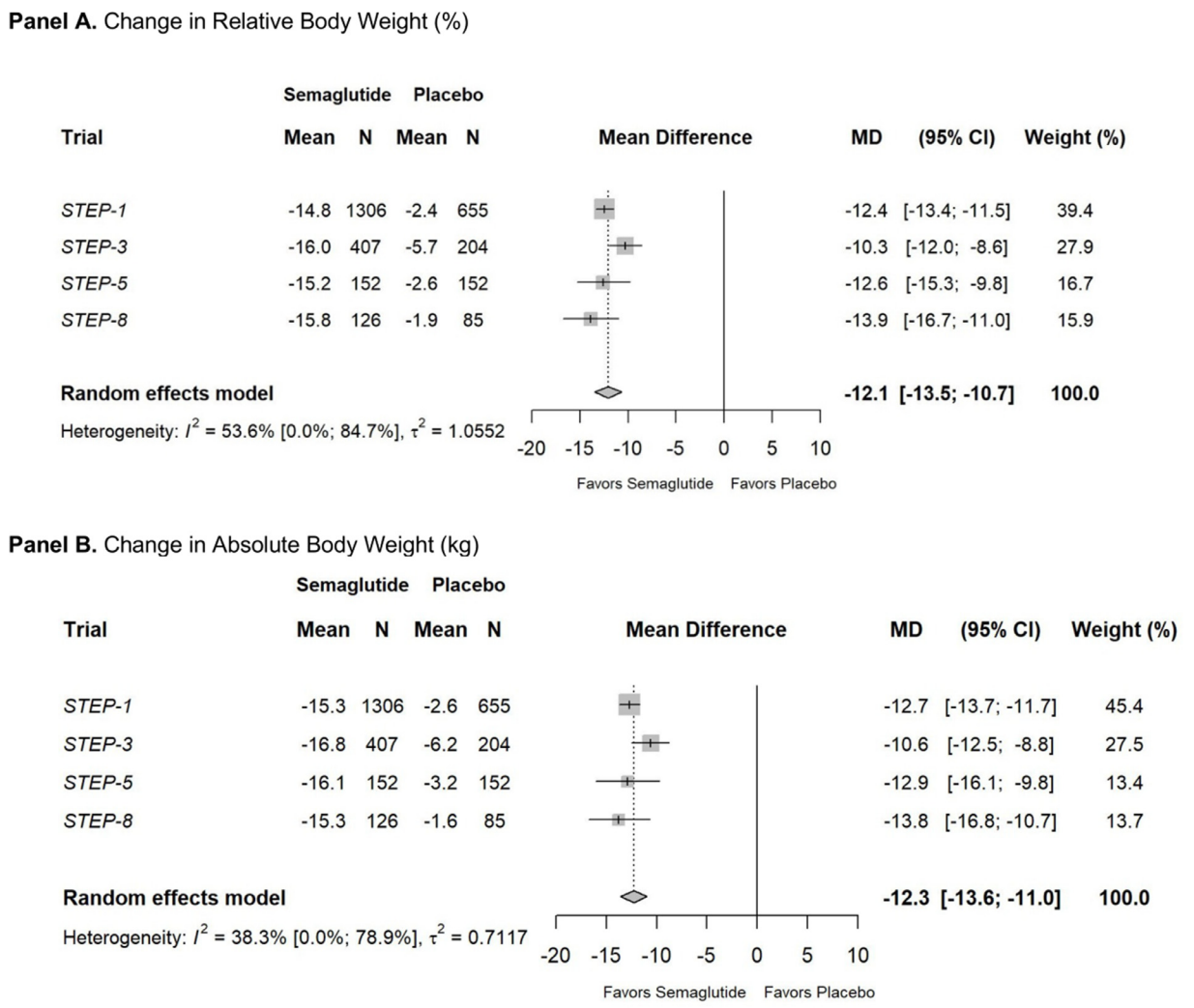

Figure 3. Forest plot of the mean differences in relative and absolute body weight changes in semaglutide versus placebo after 2 years of follow-up.

Table 3
Pooled weighted mean differences and relative risks of efficacy outcomes in participants enrolled in semaglutide use for weight loss

Outcome	Mean†		Weighted Mean Difference (95% Confidence Interval)	I^2
	Semaglutide	Placebo		
Change in Relative Body Weight (%)	-15.1	-3.0	-12.1 (-13.5, -10.7)	53.6%
Change in Absolute Body Weight (kg)	-15.7	-3.3	-12.3 (-13.6, -11.0)	38.3%
Change in Body Mass Index (kg/m^2)*	-5.6	-1.3	-4.3 (-4.9, -3.7)	59.7%
Change in Waist Circumference (cm)*	-13.8	-4.7	-9.2 (-10.0, -8.4)	0.0%
Change in Systolic Blood Pressure (mmHg)*	-6.0	-1.3	-4.8 (-5.8, -3.7)	0.0%
Change in Diastolic Blood Pressure (mmHg)*	-3.0	-0.5	-2.5 (-3.2, -1.8)	0.0%
Thresholds	Number of Participants (%)		Relative Risk (95% Confidence Interval)	I^2
	Semaglutide	Placebo		
Participants with ≥5% Weight Loss	1694/1974 (85.8%)	370/1065 (34.7%)	2.37 (1.67, 3.36)	85.1%
Participants with ≥10% Weight Loss	1381/1974 (70.0%)	163/1065 (15.3%)	4.27 (2.55, 7.15)	85.5%
Participants with ≥15% Weight Loss	1027/1974 (52.0%)	73/1065 (6.8%)	7.12 (3.66, 13.85)	76.6%
Participants with ≥20% Weight Loss	660/1974 (33.4%)	23/1065 (2.2%)	15.08 (9.31, 24.43)	0.0%

* Not including Step-8.
† Mean values are weighted, with the weight determined by sample size.

Table 4
Pooled relative risks of safety outcomes in participants enrolled in trials of semaglutide use for weight loss*

Outcome	Number of Participants (%)		Relative Risk (95% Confidence Interval)	I^2
	Semaglutide	Placebo		
Any Adverse Event During Treatment Period†	1827/1991 (91.8%)	979/1096 (89.3%)	1.02 (0.97, 1.08)	45.1%
Gastrointestinal Adverse Events During Treatment Period	1537/1991 (77.2%)	572/1096 (52.2%)	1.47 (1.28, 1.68)	47.0%
Any Adverse Events Leading to Trial Product Discontinuation During Treatment Period	129/1991 (6.5%)	36/1096 (3.3%)	1.94 (1.15, 3.28)	0.0%
Gastrointestinal Adverse Leading to Trial Product Discontinuation During Treatment Period	80/1991 (4.0%)	7/1096 (0.6%)	5.36 (1.64, 17.52)	0.0%
Serious Adverse Events During Treatment Period‡	187/1991 (9.4%)	72/1096 (6.6%)	1.36 (0.51, 3.60)	63.4%
Death at Maximum Follow-Up§	2/1991 (0.1%)¶	1/1096 (0.1%)#	1.05 (0.28, 3.93)	0.0%

* Included are all adverse events that occurred during the on-treatment period unless indicated otherwise. The safety population is the same as the full-analysis population since all participants received at least one dose of drug or placebo.

† The most common adverse events were nausea, diarrhea, vomiting, constipation, nasopharyngitis, headache, dyspepsia, abdominal pain, and upper respiratory tract infection.

‡ A serious adverse event was defined as an adverse event that fulfilled at least one of the following criteria: resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event.

§ Included are events which were observed during the in-trial period (time from random assignment to last contact with a trial site, regardless of treatment discontinuation or rescue intervention).

¶ In the semaglutide group, one death occurred due to acute myocardial infarction in a participant who was a previous smoker with a medical history of hypertension, obstructive sleep apnea and dyslipidemia. Another sudden cardiac death occurred in one participant with a medical history of hypertension and obstructive sleep apnea. Both participants had discontinued semaglutide.

In the placebo group, death due to glioblastoma, aspiration pneumonia, and severe sepsis occurred in one participant who had discontinued placebo.

In the STEP trials, an important majority of participants presented with at least 1 co-morbidity, and over 1/4 had at least 3. Dyslipidemia, hypertension, knee osteoarthritis, and obstructive sleep apnea were the most common co-morbidities, which are all recognized risk factors contributing to poor outcomes in cardiovascular disease, myocardial infarction, and stroke. In these participants, successful weight loss has shown great clinical benefits.[14] Previous research has indicated that a modest weight loss of 5% to 10% is associated with improvements in metabolic function, cardiovascular risk factors, and overall quality of life.[15] However, conventional lifestyle modifications focused on diet and physical activity alone often prove insufficient for sustained weight loss in cases of obesity.[16] The preliminary findings from the Semaglutide Effects on Heart Disease and Stroke (SELECT) trial are noteworthy. Compared with placebo, once-weekly subcutaneous 2.4 mg semaglutide showed a 20% reduction in major adverse cardiovascular events, alongside weight loss, when added to the standard of care in patients with established cardiovascular disease and overweight/obesity without diabetes.[17]

As with other weight loss drugs, there is evidence that participants using semaglutide may regain weight after treatment withdrawal. Per an off-treatment extension of the STEP-1 trial, participants who were randomized to semaglutide regained 67% of lost weight, whereas those randomized to placebo regained 95% after 1 year.[18] Cardiometabolic improvements seen at the end of treatment with semaglutide also reverted toward baseline at week 120 for most risk factors. The STEP-4 trial, which randomized all participants to a 20-week run-in period with semaglutide, showed that the mean weight change in participants who discontinued semaglutide treatment at week 20 was +6.9% at week 68, compared with −7.9% in those who completed treatment.[19] The results from these 2 studies suggest that continued treatment with semaglutide may be required to maintain improvements in weight and health. It is unknown whether other strategies can be used to sustain weight loss after treatment with semaglutide has been discontinued (e.g., titrating down to lower doses instead of completely stopping treatment).

In our meta-analysis, all trials administered semaglutide subcutaneously. Compared with once-daily oral administration, once-weekly subcutaneous semaglutide may have improved patient adherence by reducing the frequency of administration and simplifying the treatment regimen.[20] Nonetheless, the results from a study of 667 participants, which used a daily 50 mg dose of oral semaglutide suggested that the amount of weight loss achieved with oral semaglutide was similar to that achieved by subcutaneous semaglutide (−15.1% in oral compared with 2.4% in placebo vs −14.9% in subcutaneous compared with 2.4% in placebo).[21,22]

Several other glucagon-like peptide-1 receptor agonists, including tirzepatide, retratrutide, and orforglipron, are now being investigated for the treatment of obesity and have shown substantial weight reduction. In a phase 3 trial, subcutaneous tirzepatide demonstrated decreases in body weight ranging from 15% to 20% with weekly doses of 5 to 15 mg.[23] In phase 2 trials once-weekly subcutaneous 12 mg retratrutide was associated with a 24.2% decrease in body weight[24] and once-daily oral 45 mg orforglipron was associated with a 14.7% decrease in body weight.[25]

Our study has several potential limitations. First, because there were only 4 trials that met our inclusion criteria, we could not quantitatively assess the risk of publication bias. Second, all included studies were part of the STEP program and most of the participants were female. The treatment given in the context of an RCT may have

limited applicability to the general population. Third, although we assessed the longest available follow-up to examine longer-term outcomes, this follow-up duration remains relatively modest given that patients could use semaglutide for years in real-world settings. Nonetheless, our findings represent the efficacy of semaglutide for weight loss at the longest available follow-up duration (2 years). Finally, with limited follow-up posttreatment period, we could not assess whether participants maintained their achieved weight loss after treatment withdrawal.

In conclusion, our study was designed to compare the long-term efficacy and safety of semaglutide versus placebo in adults with overweight/obesity without diabetes. Once-weekly semaglutide was associated with reductions in relative and absolute body weight and had beneficial effects on cardiovascular risk factors, such as BMI, waist circumference, and blood pressure. Furthermore, the side effects related to semaglutide were mainly GI, transient, and mild-to-moderate in severity. Our results support the long-term use of semaglutide for the treatment of overweight/obesity in patients without diabetes.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Areesha Moiz: Writing − original draft, Data curation. **Jeremy Y. Levett:** Writing − review & editing, Conceptualization. **Kristian B. Filion:** Writing − review & editing, Supervision, Formal analysis, Conceptualization. **Katya Peri:** Writing − review & editing, Data curation. **Pauline Reynier:** Writing − review & editing, Formal analysis. **Mark J. Eisenberg:** Writing − review & editing, Supervision, Conceptualization.

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Authors Contributions

All authors had access to the data and a role in writing the manuscript.

Supplementary materials

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1. Aroda VR, Ahmann A, Cariou B, Chow F, Davies MJ, Jódar E, Mehta R, Woo V, Lingvay I. Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: insights from the SUSTAIN 1−7 trials. *Diabetes Metab* 2019;45:409–418.
2. United States Food and Drug Administration. FDA approves new drug treatment for chronic weight management, first since 2014. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014. Accessed on October 23, 2024.
3. Arastu N, Cummins O, Uribe W, Nemec EC. Efficacy of subcutaneous semaglutide compared to placebo for weight loss in obese, non-diabetic adults: a systematic review & meta-analysis. *Int J Clin Pharm* 2022;44:852–859.
4. Gao X, Hua X, Wang X, Xu W, Zhang Y, Shi C, Gu M. Efficacy and safety of semaglutide on weight loss in obese or overweight patients without diabetes: a systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol* 2022;13:935823.
5. Tan HC, Dampil OA, Marquez MM. Efficacy and safety of semaglutide for weight loss in obesity without diabetes: a systematic review and meta-analysis. *J ASEAN Fed Endocr Soc* 2022;37:65–72.
6. Zhong P, Zeng H, Huang M, Fu W, Chen Z. Efficacy and safety of once-weekly semaglutide in adults with overweight or obesity: a meta-analysis. *Endocrine* 2022;75:718–724.
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
8. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. *J Med Libr Assoc* 2016;104:240–243.
9. UpToDate. Obesity in adults: drug therapy. Available at: https://www.uptodate.com/contents/obesity-in-adults-drug-therapy. Accessed on May 25, 2023.
10. Shi Q, Wang Y, Hao Q, Vandvik PO, Guyatt G, Li J, Chen Z, Xu S, Shen Y, Ge L, Sun F, Li L, Yu J, Nong K, Zou X, Zhu S, Wang C, Zhang S, Qiao Z, Jian Z, Li Y, Zhang X, Chen K, Qu F, Wu Y, He Y, Tian H, Li S. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. *Lancet* 2022;399:259–269.
11. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
12. Kushner RF, Calanna S, Davies M, Dicker D, Garvey WT, Goldman B, Lingvay I, Thomsen M, Wadden TA, Wharton S, Wilding JPH, Rubino D. Semaglutide 2.4 mg for the Treatment of Obesity: key Elements of the STEP Trials 1 to 5. *Obesity (Silver Spring)* 2020;28:1050–1061.
13. Singh AK, Singh R. Pharmacotherapy in obesity: a systematic review and meta-analysis of randomized controlled trials of anti-obesity drugs. *Expert Rev Clin Pharmacol* 2020;13:53–64.
14. Wood GC, Bailey-Davis L, Benotti P, Cook A, Dove J, Mowery J, Ramasamy A, Iyer N, Smolarz BG, Kumar N, Still CD. Effects of sustained weight loss on outcomes associated with obesity comorbidities and healthcare resource utilization. *PLoS One* 2021;16:e0258545.
15. Ryan DH, Yockey SR. Weight loss and improvement in comorbidity: differences at 5%, 10%, 15%, and over. *Curr Obes Rep* 2017;6:187–194.
16. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. *Med Clin North Am* 2018;102:183–197.
17. Ryan DH, Lingvay I, Colhoun HM, Deanfield J, Emerson SS, Kahn SE, Kushner RF, Marso S, Plutzky J, Brown-Frandsen K, Gronning MOL, Hovingh GK, Holst AG, Ravn H, Lincoff AM. Semaglutide Effects on cardiovascular Outcomes in People with Overweight or Obesity (SELECT) rationale and design. *Am Heart J* 2020;229:61–69.
18. Wilding JPH, Batterham RL, Davies M, Van Gaal LF, Kandler K, Konakli K, Lingvay I, McGowan BM, Oral TK, Rosenstock J, Wadden TA, Wharton S, Yokote K, Kushner RF, STEP 1 Study Group. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab* 2022;24:1553–1564.
19. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, Lingvay I, Mosenzon O, Rosenstock J, Rubio MA, Rudofsky G, Tadayon S, Wadden TA, Dicker D, STEP 4 Investigators. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA* 2021;325:1414–1425.

20. Meier JJ. Efficacy of semaglutide in a subcutaneous and an oral formulation. *Front Endocrinol (Lausanne)* 2021;12:645617.
21. Knop FK, Aroda VR, do Vale RD, Holst-Hansen T, Laursen PN, Rosenstock J, Rubino DM, Garvey WT, OASIS 1 Investigators. Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2023;402:705–719.
22. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF, STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021;384:989–1002.
23. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A, SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;387:205–216.
24. Jastreboff AM, Kaplan LM, Frías JP, Wu Q, Du Y, Gurbuz S, Coskun T, Haupt A, Milicevic Z, Hartman ML, Retatrutide Phase 2 Obesity Trial Investigators. Triple-hormone-receptor agonist retatrutide for obesity - a phase 2 trial. *N Engl J Med* 2023;389:514–526.
25. Wharton S, Blevins T, Connery L, Rosenstock J, Raha S, Liu R, Ma X, Mather KJ, Haupt A, Robins D, Pratt E, Kazda C, Konig M, GZGI Investigators. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. *N Engl J Med* 2023;389:877–888.