

Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes

The STEP 8 Randomized Clinical Trial

Domenica M. Rubino, MD; Frank L. Greenway, MD; Usman Khalid, MD, PhD; Patrick M. O'Neil, PhD; Julio Rosenstock, MD; Rasmus Sørrig, MD, PhD; Thomas A. Wadden, PhD; Alicja Wizert, PhD; W. Timothy Garvey, MD; for the STEP 8 Investigators

IMPORTANCE Phase 3 trials have not compared semaglutide and liraglutide, glucagon-like peptide-1 analogues available for weight management.

OBJECTIVE To compare the efficacy and adverse event profiles of once-weekly subcutaneous semaglutide, 2.4 mg, vs once-daily subcutaneous liraglutide, 3.0 mg (both with diet and physical activity), in people with overweight or obesity.

DESIGN, SETTING, AND PARTICIPANTS Randomized, open-label, 68-week, phase 3b trial conducted at 19 US sites from September 2019 (enrollment: September 11–November 26) to May 2021 (end of follow-up: May 11) in adults with body mass index of 30 or greater or 27 or greater with 1 or more weight-related comorbidities, without diabetes (N = 338).

INTERVENTIONS Participants were randomized (3:1:3:1) to receive once-weekly subcutaneous semaglutide, 2.4 mg (16-week escalation; n = 126), or matching placebo, or once-daily subcutaneous liraglutide, 3.0 mg (4-week escalation; n = 127), or matching placebo, plus diet and physical activity. Participants unable to tolerate 2.4 mg of semaglutide could receive 1.7 mg; participants unable to tolerate 3.0 mg of liraglutide discontinued treatment and could restart the 4-week titration. Placebo groups were pooled (n = 85).

MAIN OUTCOMES AND MEASURES The primary end point was percentage change in body weight, and confirmatory secondary end points were achievement of 10% or more, 15% or more, and 20% or more weight loss, assessed for semaglutide vs liraglutide at week 68. Semaglutide vs liraglutide comparisons were open-label, with active treatment groups double-blinded against matched placebo groups. Comparisons of active treatments vs pooled placebo were supportive secondary end points.

RESULTS Of 338 randomized participants (mean [SD] age, 49 [13] years; 265 women [78.4%]; mean [SD] body weight, 104.5 [23.8] kg; mean [SD] body mass index, 37.5 [6.8]), 319 (94.4%) completed the trial, and 271 (80.2%) completed treatment. The mean weight change from baseline was -15.8% with semaglutide vs -6.4% with liraglutide (difference, -9.4 percentage points [95% CI, -12.0 to -6.8]; $P < .001$); weight change with pooled placebo was -1.9%. Participants had significantly greater odds of achieving 10% or more, 15% or more, and 20% or more weight loss with semaglutide vs liraglutide (70.9% of participants vs 25.6% [odds ratio, 6.3 {95% CI, 3.5 to 11.2}], 55.6% vs 12.0% [odds ratio, 7.9 {95% CI, 4.1 to 15.4}], and 38.5% vs 6.0% [odds ratio, 8.2 {95% CI, 3.5 to 19.1}], respectively; all $P < .001$). Proportions of participants discontinuing treatment for any reason were 13.5% with semaglutide and 27.6% with liraglutide. Gastrointestinal adverse events were reported by 84.1% with semaglutide and 82.7% with liraglutide.

CONCLUSIONS AND RELEVANCE Among adults with overweight or obesity without diabetes, once-weekly subcutaneous semaglutide compared with once-daily subcutaneous liraglutide, added to counseling for diet and physical activity, resulted in significantly greater weight loss at 68 weeks.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT04074161](https://clinicaltrials.gov/ct2/show/study/NCT04074161)

JAMA. 2022;327(2):138–150. doi:10.1001/jama.2021.23619

- [+ Visual Abstract](#)
- [+ Multimedia](#)
- [+ Supplemental content](#)

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A complete list of investigators for the Semaglutide Treatment Effect in People With Obesity (STEP) 8 Trial appears in Supplement 4.

Corresponding Author: Domenica M. Rubino, MD, Washington Center for Weight Management and Research, 2800 S Shirlington Rd, Ste 505, Arlington, VA 22206 (drubino@wtmgmt.com).

Once-weekly subcutaneous semaglutide, 2.4 mg, a glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA), is available for weight management in people with obesity (or overweight and ≥ 1 weight-related comorbidities).¹ It has demonstrated sustained, clinically meaningful reductions in body weight in people with overweight or obesity, with and without type 2 diabetes, in the ongoing global phase 3 Semaglutide Treatment Effect in People With Obesity (STEP) program.²⁻⁵ Semaglutide was the second GLP-1RA approved for weight management after once-daily subcutaneous liraglutide, 3.0 mg, which is available for chronic weight management in people with obesity (or overweight and ≥ 1 weight-related comorbidities).⁶

Semaglutide and liraglutide are modified, long-acting analogues of native GLP-1.⁷ Through addition of an albumin-binding C16 fatty acid side chain, liraglutide's half-life is 13 to 15 hours. Semaglutide's half-life is 165 hours, resulting from an amino acid replacement (preventing dipeptidyl peptidase 4 degradation) and a C18 fatty diacid addition.^{7,8}

In a phase 2 trial, once-daily subcutaneous semaglutide, 0.4 mg (equivalent to 2.8 mg once weekly), significantly increased weight loss vs liraglutide, 3.0 mg.⁹ The STEP 8 trial directly compared once-weekly semaglutide, 2.4 mg, vs once-daily liraglutide, 3.0 mg, for weight management in adults with overweight or obesity to rigorously assess differences in efficacy and adverse event (AE) profiles.

Methods

Trial Design and Oversight

See [Supplement 1](#) and [Supplement 2](#) for the trial protocol and statistical analysis plan, respectively.

This phase 3, 68-week, randomized, open-label trial was conducted at 19 US sites from September 2019 (enrollment: September 11–November 26) to May 2021 (end of follow-up: May 11; eFigure 1 in [Supplement 3](#)). It complied with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol and amendments were approved by the institutional review board or independent ethics committee at each site; all participants provided written informed consent.

Participants

Adults (≥ 18 years old) with 1 or more self-reported unsuccessful dietary weight loss efforts and a body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of 30 or greater or 27 or greater with 1 or more weight-related comorbidities (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease) were eligible (eAppendix 1 in [Supplement 3](#)). Key exclusion criteria included diabetes, hemoglobin A_{1c} (HbA_{1c}) level of 6.5% (48 mmol/mol) or greater, and self-reported body weight changes of more than 5 kg 90 days or less before screening. For regulatory requirements, race and ethnicity were recorded, determined by each participant according to fixed selection categories (including “other”).

Key Points

Question Among adults with overweight or obesity without diabetes, what is the effect of once-weekly subcutaneous semaglutide, 2.4 mg, vs once-daily subcutaneous liraglutide, 3.0 mg, on weight loss when each is added to counseling for diet and physical activity?

Findings In this randomized clinical trial that included 338 participants, mean body weight change from baseline to 68 weeks was -15.8% with semaglutide vs -6.4% with liraglutide, a statistically significant difference.

Meaning Among adults with overweight or obesity without diabetes, once-weekly subcutaneous semaglutide, compared with once-daily subcutaneous liraglutide, added to counseling for diet and physical activity resulted in significantly greater weight loss at 68 weeks.

Procedures

Participants were randomized (3:1:3:1) using a blocking schema (block size of 8) via an interactive web response system to receive once-weekly subcutaneous semaglutide, 2.4 mg, or matching placebo, or once-daily subcutaneous liraglutide, 3.0 mg, or matching placebo, for 68 weeks, with a 7-week follow-up.

Randomization to semaglutide or liraglutide was not masked (due to dosing differences), but active treatment groups were double-blinded against matching placebo groups to mitigate potential bias arising from open-label comparisons. The placebo groups also facilitated comparisons of semaglutide and liraglutide vs placebo (secondary trial objectives), allowing evaluation of trial results in the context of previous findings.

Semaglutide, initiated at 0.25 mg, was escalated to 2.4 mg (maintenance dose) over 16 weeks (eFigure 1 in [Supplement 3](#)). A 1.7-mg maintenance dose was permitted if 2.4 mg could not be tolerated; 1 or more attempts to reescalate was advised. Liraglutide was initiated at 0.6 mg and escalated to 3.0 mg over 4 weeks; escalation could be delayed by a week to aid tolerability. Commensurate with the prescribing information,⁶ treatment was discontinued if liraglutide, 3.0 mg, was not tolerated; treatment could be restarted, with reescalation over 4 weeks. Treatments were administered using a multidose pen injector; the semaglutide (and matched placebo) group switched to a single-dose pen injector for weeks 44 to 68.

All participants received counseling (from qualified health care professionals, every 4–6 weeks, via in-person visits or telephone) to adhere to diet (500-kcal/d deficit relative to baseline estimated energy expenditure) and physical activity recommendations (≥ 150 minutes/week).

Outcomes

The primary end point was percentage change from baseline in body weight at week 68. Confirmatory secondary end points (hierarchical testing order) were achievement of weight loss of 10% or more, 15% or more, and 20% or more by week 68. Primary and confirmatory secondary end points were assessed for semaglutide vs liraglutide; comparisons vs pooled placebo were supportive secondary end points. Other supportive secondary end points were changes from baseline in absolute body weight,

waist circumference, blood pressure, fasting lipid concentrations, C-reactive protein, HbA_{1c}, fasting plasma glucose, fasting serum insulin, and glycemic status, and permanent trial product discontinuations, all assessed to week 68 for semaglutide vs liraglutide (absolute body weight also assessed vs pooled placebo; eAppendix 2 in Supplement 3). Change in glycemic status data will be reported separately. Achievement of 5% or more weight loss was a prespecified exploratory end point. Separate placebo group body weight changes and changes in pulse were assessed post hoc. AEs were assessed at week 75.

Sample Size Calculation

The hypothesized superiority of semaglutide to liraglutide for the primary and confirmatory secondary end points was assessed using a predefined hierarchical gatekeeping approach (eTable 1 in Supplement 3),¹⁰ with a statistically superior result (2-sided at the 5% significance level) required for each end point before the next could be tested. Data from the 2 placebo groups were pooled to increase power for statistical analyses of active treatment vs placebo, while limiting the number of participants required.

The sample size calculations used a t test on the mean difference assuming equal variances for body weight changes, and a Pearson χ^2 test for 2 independent proportions for categorical weight loss. The calculation included assumed differences between active treatment groups of 5.5 percentage points in body weight change and ratios of 1.6, 2.2, and 4.5 for the proportions achieving 10% or more, 15% or more, and 20% or more weight loss (eTable 2 in Supplement 3). These assumptions were based on previous trials.^{9,11} The assumed difference in weight loss was greater than the US Food and Drug Administration-recommended 5% or greater difference threshold.¹² Under these assumptions, 126 participants in each active treatment group provided the desired power of more than 90%.

In the pooled placebo group, 84 participants (42 per separate group) gave more than 99% power for the semaglutide vs pooled placebo comparison, and 80% or more power for liraglutide vs pooled placebo, for the primary end point.

Statistical Analysis

Two estimands evaluated treatment efficacy from different perspectives and accounted for intercurrent events and missing data differently (eAppendix 3 in Supplement 3).¹³⁻¹⁵ Analyses in the statistical testing hierarchy addressed the treatment policy estimand (primary estimand) using data from all randomized participants from the in-trial period (time from randomization to last contact with trial site), regardless of treatment adherence or rescue intervention initiation (antiobesity medications or bariatric surgery).

Continuous end points were analyzed using analysis of covariance, with randomized treatment (semaglutide, liraglutide, or pooled placebo) as a factor and baseline value of the outcome measure of interest (eg, baseline body weight in kilograms for analysis of percentage change in body weight) as a covariate. Binary confirmatory secondary end points were analyzed using logistic regression, with the same factor, and baseline body weight as a covariate. Analyses included all randomized participants from all treatment groups.

A multiple imputation approach¹⁶ was used in which missing data were imputed by sampling from available measurements at week 68 from participants in the same treatment group and with the same treatment completion status. Imputation used a linear regression model with baseline value and last available observation of the outcome measure of interest from the on-treatment period as covariates. One thousand complete data sets were generated and analyzed, with results combined using Rubin's rules¹⁷ to obtain overall estimates.

Sensitivity analyses of the primary end point included prespecified tipping-point and jump-to-reference analyses (eAppendix 4 in Supplement 3), and a post hoc mixed-effects regression analysis with site as a random effect (to account for the multicenter design).

The secondary estimand (the trial product estimand) evaluated the effect of taking the drug as intended. Analyses addressing this estimand used data from all randomized participants from the on-treatment period (receipt of any dose of treatment within the previous 2 weeks [49 days for safety-related analyses]) until first discontinuation or rescue intervention initiation. The statistical models for assessing this estimand (including the post hoc analysis of change in pulse at week 68) are described in eAppendix 5 in Supplement 3.

Efficacy and AE-related end points were assessed for the full analysis set (all randomized participants) and the safety analysis set (all randomized participants exposed to ≥ 1 doses of randomized treatment), respectively.

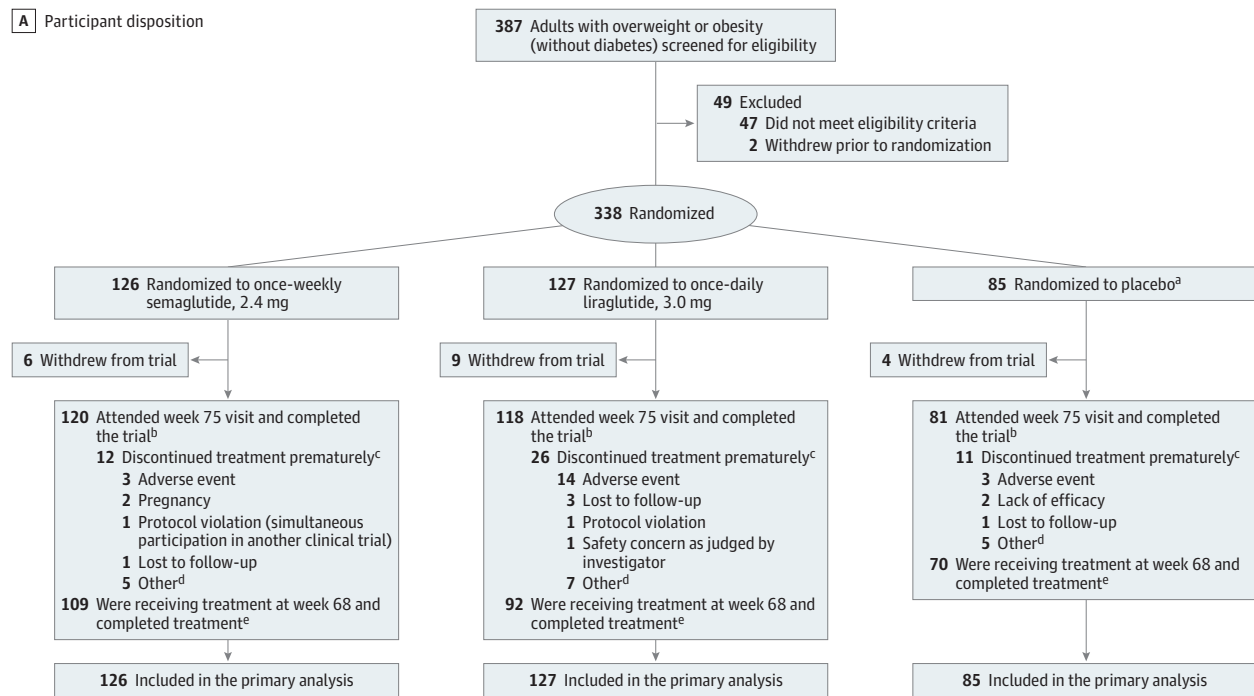
Only the primary and confirmatory secondary end points were controlled for multiplicity. Because of the potential for type I error due to multiple comparisons, findings for other secondary end points and analyses should be interpreted as exploratory. Two-sided 95% CIs and corresponding *P* values were calculated for all statistical analysis results. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc). Efficacy results are reported for the treatment policy estimand only (unless stated otherwise). Data for permanent treatment discontinuations, achievement of 5% or more weight loss, AEs, and change in pulse at week 75 were summarized by descriptive statistics only.

Results

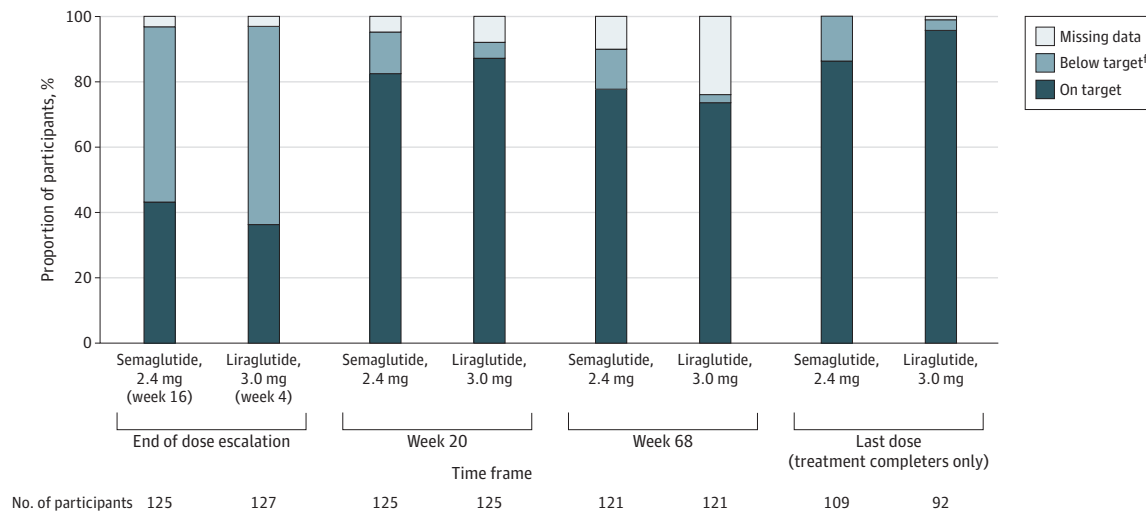
Participants

Overall, 387 participants were screened; 338 were enrolled and randomized to semaglutide (*n* = 126), liraglutide (*n* = 127), and placebo (*n* = 85) (Figure 1A). Demographics and baseline characteristics were similar between active treatment groups, whereas the placebo group had a slightly greater baseline body weight, greater proportions of participants in higher BMI groups, and a greater proportion of participants with 5 or more comorbidities (Table 1). Most participants were White (73.7%) and female (78.4%). Participants' mean age was 49 years, mean body weight was 104.5 kg, mean BMI was 37.5, mean waist circumference was 113.3 cm, and 36.1% had prediabetes, per American Diabetes Association criteria.¹⁸ Most had 0 to 2 comorbidities at screening, with dyslipidemia and hypertension being the most prevalent.

Figure 1. Participant Disposition and Dosing During the Trial



B Participants on or below the target dose during the trial (observed in-trial data)



A, Flow of participants during the Semaglutide Treatment Effect in People With Obesity Trial. B, The proportions of participants on or below the target dose at the end of the dose escalation period (week 16 for semaglutide, week 4 for liraglutide), at weeks 20 and 68, and for the last dose. Data presented are observed (ie, as-measured) proportions during the in-trial period (the time from randomization to last contact with trial site, irrespective of treatment discontinuation or rescue intervention), based on the numbers of participants remaining in the trial at each time point (except for the last dose, which is based on the number of treatment completers). *On target* indicates a dose of >0.0 to <2.4 mg for semaglutide and >0.0 to <3.0 mg for liraglutide; *below target*, a dose of >0.0 to <2.4 mg for semaglutide and >0.0 to <3.0 mg for liraglutide; *missing data*, no dosing information was provided at the visit; and *treatment completers*, participants who were receiving treatment at week 68. Data are only presented for the active treatment groups.

^b These participants were trial completers. Participants were considered trial completers if they attended the week 75 end-of-follow-up visit, regardless of whether they completed treatment.

^c These participants were trial completers who did not complete treatment.

^d Other reasons for premature treatment discontinuation are listed in eTable 6 in Supplement 3.

^e These participants were treatment completers: they were receiving treatment at week 68, regardless of whether they completed the trial. One participant in the semaglutide group completed treatment without completing the trial.

^f The numbers and proportions of participants who were below the target dose are shown in eTable 7 in Supplement 3 and are based on the total number of participants with dose data at each time point (ie, excluding those with missing data).

^a Pooled placebo data. Data from the 2 placebo groups were pooled to increase power for statistical analyses of active treatments vs placebo, while limiting the number of participants required.

Table 1. Baseline Demographics and Clinical Characteristics (Full Analysis Set)

Characteristic	No. (%)		
	Semaglutide, 2.4 mg (n = 126)	Liraglutide, 3.0 mg (n = 127)	Placebo (n = 85) ^a
Age, mean (SD), y	48 (14)	49 (13)	51 (12)
Sex			
Female	102 (81.0)	97 (76.4)	66 (77.6)
Male	24 (19.0)	30 (23.6)	19 (22.4)
Race ^b			
Asian	4 (3.2)	6 (4.7)	3 (3.5)
Black/African American	25 (19.8)	20 (15.7)	19 (22.4)
White	94 (74.6)	95 (74.8)	60 (70.6)
Other ^c	3 (2.4)	6 (4.7)	3 (3.5)
Hispanic/Latino ethnicity ^b	15 (11.9)	17 (13.4)	7 (8.2)
Body weight, mean (SD), kg	102.5 (25.3)	103.7 (22.5)	108.8 (23.1) ^d
BMI			
Mean (SD)	37.0 (7.4)	37.2 (6.4)	38.8 (6.5)
Distribution			
<30	9 (7.1)	11 (8.7)	4 (4.7)
≥30 to <35	51 (40.5)	42 (33.1)	20 (23.5)
≥35 to <40	37 (29.4)	38 (29.9)	31 (36.5)
≥40	29 (23.0)	36 (28.3)	30 (35.3)
Waist circumference, mean (SD), cm	111.8 (16.3)	113.5 (15.0)	115.4 (15.1)
Blood pressure, mean (SD), mm Hg			
Systolic	125 (14)	126 (16)	123 (14)
Diastolic	81 (9)	81 (10)	79 (9)
Pulse, mean (SD), bpm ^e	71 (9)	71 (10)	72 (10)
Fasting lipid profile, geometric mean (CV) [No. ^f], mg/dL			
Cholesterol level			
Total	184.9 (21.0) [125]	188.6 (20.8) [124]	182.2 (22.8) [84]
HDL	51.9 (24.1) [125]	53.7 (25.3) [124]	50.7 (27.7) [84]
LDL	106.4 (32.5) [125]	108.1 (30.4) [124]	105.2 (32.9) [84]
VLDL	21.4 (47.2) [125]	22.0 (48.1) [124]	21.1 (49.2) [84]
Free fatty acids	10.5 (72.0) [125]	11.8 (60.5) [121]	10.6 (56.5) [84]
Triglycerides	110.1 (49.1) [125]	113.1 (49.4) [124]	108.2 (49.2) [84]
CRP, geometric mean (CV) [No. ^f], mg/L	3.9 (124.1) [125]	3.9 (144.8) [124]	4.1 (187.1) [84]
HbA _{1c} level, mean (SD), %	5.5 (0.3)	5.5 (0.3)	5.6 (0.4)
Fasting plasma glucose, mean (SD) [No. ^f], mg/dL	96.1 (10.2) [125]	95.2 (8.5) [125]	97.6 (12.2) [84]
Fasting serum insulin, geometric mean (CV) [No. ^f], μIU/mL	12.4 (60.1) [125]	11.5 (51.2) [121]	12.1 (67.0) [84]
Prediabetes ^g	43 (34.1)	45 (35.4)	34 (40.0)
eGFR, geometric mean (CV), mL/min/1.73 m ^{2e,h}	96.1 (21.1)	95.3 (19.0)	92.4 (20.0)
Comorbidities at screening ^{e,i}			
Dyslipidemia	60 (47.6)	65 (51.2)	36 (42.4)
Hypertension	48 (38.1)	55 (43.3)	39 (45.9)
Knee osteoarthritis	23 (18.3)	17 (13.4)	22 (25.9)
Obstructive sleep apnea	24 (19.0)	18 (14.2)	19 (22.4)
Asthma/COPD	18 (14.3)	18 (14.2)	13 (15.3)
Nonalcoholic fatty liver disease	5 (4.0)	12 (9.4)	7 (8.2)
Polycystic ovary syndrome ^j	5 (4.9)	6 (6.2)	1 (1.5)
Coronary artery disease	4 (3.2)	3 (2.4)	4 (4.7)

(continued)

Table 1. Baseline Demographics and Clinical Characteristics (Full Analysis Set) (continued)

Characteristic	No. (%)		
	Semaglutide, 2.4 mg (n = 126)	Liraglutide, 3.0 mg (n = 127)	Placebo (n = 85) ^a
No. of comorbidities at screening ^{e,i}			
0	32 (25.4)	25 (19.7)	16 (18.8)
1	31 (24.6)	29 (22.8)	17 (20.0)
2	25 (19.8)	29 (22.8)	21 (24.7)
3	17 (13.5)	24 (18.9)	9 (10.6)
4	10 (7.9)	11 (8.7)	9 (10.6)
≥5	11 (8.7)	9 (7.1)	13 (15.3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); bpm, beats per minute; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CV, coefficient of variation (in percentage); eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

SI conversion factors: To convert HDL-C, LDL-C, and total cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; free fatty acids to mmol/L, multiply by 0.0355; glucose to mmol/L, multiply by 0.055; and insulin to pmol/L, multiply by 6.945.

^a Pooled placebo data.

^b To meet regulatory requirements, race and ethnicity were recorded in this study and were determined by the participant according to fixed selection categories (with the option of answering "other"). Percentages may not total 100 due to rounding.

^c Native American, Alaska Native, Native Hawaiian, Other Pacific Islander, or other.

^d The mean (SD) baseline body weight values for the separate placebo groups

were 110.4 (28.3) kg for the semaglutide-matched placebo group and 107.2 (16.4) kg for the liraglutide-matched placebo group.

^e Data are for the safety analysis set.

^f [No.] = number of participants analyzed (where different from the number in the full analysis set).

^g The presence of prediabetes was determined by investigators on the basis of available information (eg, medical records, concomitant medication, and blood glucose variables) and in accordance with American Diabetes Association criteria.¹⁸

^h Assessed at screening (week -1).

ⁱ Comorbidities were reported at screening based on medical history. Selected comorbidities are presented and included: dyslipidemia, hypertension, coronary artery disease, cerebrovascular disease, obstructive sleep apnea, impaired glucose metabolism, reproductive system disorders, liver disease, kidney disease, osteoarthritis, gout, and asthma/COPD. Percentages may not total 100 due to rounding.

^j Percentages are of female participants.

Of the randomized participants, 80.2% (n = 271) completed treatment (on-treatment at week 68) and 94.4% (n = 319) completed the trial (attended week 75 end-of-follow-up visit); see eTable 3 in Supplement 3 for completion rates by site. Among treatment completers, 86.2% received the 2.4-mg dose of semaglutide and 95.7% received the 3.0-mg dose of liraglutide (Figure 1B). Overall, 92.3% of participants (n = 312) had a week 68 body weight assessment; data were missing for 9 participants in the semaglutide group, 10 in the liraglutide group, and 7 in the placebo group. Six participants used rescue interventions: 1 had bariatric surgery (liraglutide) and 5 initiated other antiobesity medications, including GLP-1RAs used off-label (semaglutide: n = 1 [oral semaglutide]; liraglutide: n = 1 [semaglutide]; placebo: n = 3 [phentermine]).

Primary Outcome

At week 68, the estimated mean change in body weight was -15.8% with semaglutide and -6.4% with liraglutide (Table 2, Figure 2; see eFigure 2A in Supplement 3 for cumulative distribution plot). Weight loss with semaglutide was significantly greater vs with liraglutide (difference, -9.4 percentage points [95% CI, -12.0 to -6.8]; *P* < .001; Table 2). The prespecified and post hoc sensitivity analyses supported the robustness of the primary analysis (Table 2). The primary end point result could not be reversed in the tipping point analysis because of the small amount of missing data.

Results for the primary end point were similar for the trial product estimand (eTable 4 and eFigure 2B in Supplement 3).

Confirmatory Secondary Outcomes

The proportions of participants achieving 10% or more, 15% or more, and 20% or more weight loss were 70.9%, 55.6%, and 38.5% with semaglutide and 25.6%, 12.0%, and 6.0% with liraglutide, respectively (Table 2; eTable 4 and eFigure 3 in Supplement 3). The odds of achieving weight loss of 10% or more (odds ratio, 6.3 [95% CI, 3.5 to 11.2]), 15% or more (odds ratio, 7.9 [95% CI, 4.1 to 15.4]), and 20% or more (odds ratio, 8.2 [95% CI, 3.5 to 19.1]) were significantly greater with semaglutide vs with liraglutide (*P* < .001 for all).

Supportive Secondary Outcomes

Overall, 19.8% (n = 67) of participants permanently discontinued treatment (Figure 1); discontinuations were greatest with liraglutide (27.6%), followed by placebo (17.6%) and semaglutide (13.5%). Consistent with the shorter escalation period, time to first discontinuation and permanent discontinuation were shorter with liraglutide than semaglutide and placebo (eFigure 4 in Supplement 3).

At week 68, reductions in absolute body weight (difference, -8.5 kg [95% CI, -11.2 to -5.7]; see Figure 3 for changes in individual participants), waist circumference (-6.6 cm [95% CI, -9.1 to -4.2]), total cholesterol level (-7.0% [95% CI, -11.7% to -2.1%]), very low-density lipoprotein cholesterol level (-11.0% [95% CI, -18.5% to -2.7%]), triglyceride level (-11.0% [95% CI, -18.9% to -2.2%]), HbA_{1c} level (-0.2 percentage points [95% CI, -0.2 to -0.1]), fasting plasma glucose level (-3.9 mg/dL [95% CI, -7.2 to -0.7]), and C-reactive protein level

Table 2. Change in Efficacy Outcomes From Baseline to Week 68 (Treatment Policy Estimand; Full Analysis Set)^{a,b}

	Estimated mean change (95% CI) [No.]		Difference for semaglutide, 2.4 mg, vs liraglutide, 3.0 mg (95% CI) ^c	P value
	Semaglutide, 2.4 mg (n = 126)	Liraglutide, 3.0 mg (n = 127)		
Primary end point				
Body weight, % change	-15.8 (-17.6 to -13.9) [117]	-6.4 (-8.2 to -4.6) [117]	-9.4 (-12.0 to -6.8)	<.001
Confirmatory secondary end points				
Weight loss at week 68, No. (%) ^d				
Participants with ≥10%	83/117 (70.9)	30/117 (25.6)	Odds ratio: 6.3 (3.5 to 11.2)	<.001
Participants with ≥15%	65/117 (55.6)	14/117 (12.0)	Odds ratio: 7.9 (4.1 to 15.4)	<.001
Participants with ≥20%	45/117 (38.5)	7/117 (6.0)	Odds ratio: 8.2 (3.5 to 19.1)	<.001
Supportive secondary end points				
Body weight, kg	-15.3 (-17.3 to -13.4) [117]	-6.8 (-8.8 to -4.9) [117]	-8.5 (-11.2 to -5.7)	
Waist circumference, cm	-13.2 (-15.0 to -11.5) [114]	-6.6 (-8.3 to -4.9) [113]	-6.6 (-9.1 to -4.2)	
Blood pressure, mm Hg				
Systolic	-5.7 (-8.1 to -3.3) [114]	-2.9 (-5.3 to -0.5) [112]	-2.8 (-6.1 to 0.6)	
Diastolic	-5.0 (-7.0 to -3.1) [114]	-0.5 (-2.3 to 1.3) [112]	-4.5 (-7.1 to -1.9)	
Fasting lipid profile, % change ^e				
Cholesterol				
Total	-7.1 (-10.7 to -3.3) [113]	-0.1 (-3.3 to 3.2) [107]	-7.0 (-11.7 to -2.1)	
HDL	-0.3 (-3.6 to 3.0) [112]	1.9 (-1.0 to 5.0) [107]	-2.2 (-6.5 to 2.2)	
LDL	-6.5 (-12.4 to -0.1) [112]	0.9 (-4.4 to 6.5) [107]	-7.3 (-14.9 to 1.0)	
VLDL	-20.7 (-25.1 to -16.0) [112]	-10.9 (-16.7 to -4.8) [107]	-11.0 (-18.5 to -2.7)	
Free fatty acids	-12.6 (-22.1 to -2.0) [108]	-8.8 (-19.0 to 2.7) [110]	-4.2 (-18.8 to 13.1)	
Triglycerides	-20.7 (-25.6 to -15.6) [112]	-11.0 (-16.9 to -4.7) [107]	-11.0 (-18.9 to -2.2)	
CRP, % change ^e	-52.6 (-61.3 to -42.0) [113]	-24.5 (-36.1 to -10.9) [110]	-37.2 (-51.7 to -18.5)	
HbA _{1c} , %	-0.2 (-0.3 to -0.2) [113]	-0.1 (-0.1 to 0.0) [107]	-0.2 (-0.2 to -0.1)	
Fasting plasma glucose, mg/dL	-8.3 (-10.4 to -6.1) [112]	-4.3 (-6.7 to -1.9) [106]	-3.9 (-7.2 to -0.7)	
Fasting serum insulin, % change ^e	-27.8 (-36.5 to -17.9) [108]	-15.4 (-23.1 to -7.0) [110]	-14.6 (-27.3 to 0.3)	
Exploratory end point				
Participants with ≥5% weight loss at week 68, No./total (%) ^d	102/117 (87.2)	68/117 (58.1)	NA	
Prespecified sensitivity analysis (J2R)				
Body weight, % change ^f	-15.3 (-17.0 to -13.6) [117]	-6.0 (-7.7 to -4.3) [117]	-9.2 (-11.6 to -6.8)	
Post hoc sensitivity analysis				
Body weight, % change ^g	-15.8 (-17.7 to -13.8) [117]	-6.4 (-8.2 to -4.5) [117]	-9.4 (-12.0 to -6.7)	

Abbreviations: CRP, C-reactive protein; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; J2R, jump-to-reference; LDL, low-density lipoprotein; NA, not applicable; VLDL, very low-density lipoprotein.

^a Data are only presented for the active treatment groups. Data for the placebo groups are presented in eTable 5 in Supplement 3. Numbers of participants with an observation at week 68 are denoted by [No.] for each end point. The number of participants with imputed data can be calculated by subtracting No. from the number in the full analysis set, provided in the column headers.

^b The treatment policy estimand assessed the treatment effect at week 68, regardless of treatment discontinuation or rescue intervention use. The analyses were based on data from the in-trial observation period (the time from randomization to last contact with the trial site). Continuous end points were assessed using analysis of covariance, with randomized treatment as a factor and baseline value of the outcome measure of interest as a covariate, and a multiple imputation approach for missing data. Categorical end points were analyzed with logistic regression, with the same factor, and baseline body weight as a covariate. Analyses were not controlled for multiple comparisons, except for the primary and secondary confirmatory end points. Corresponding data for the trial product estimand (which assessed the treatment effect assuming participants continued taking randomized treatment for the planned study duration without rescue intervention) are shown in eTable 4 in Supplement 3.

^c Data are absolute differences between estimated mean changes unless stated

otherwise. The differences between mean percentage changes in body weight and mean changes in HbA_{1c} level are expressed in percentage points. P values are only shown for primary and confirmatory secondary end points.

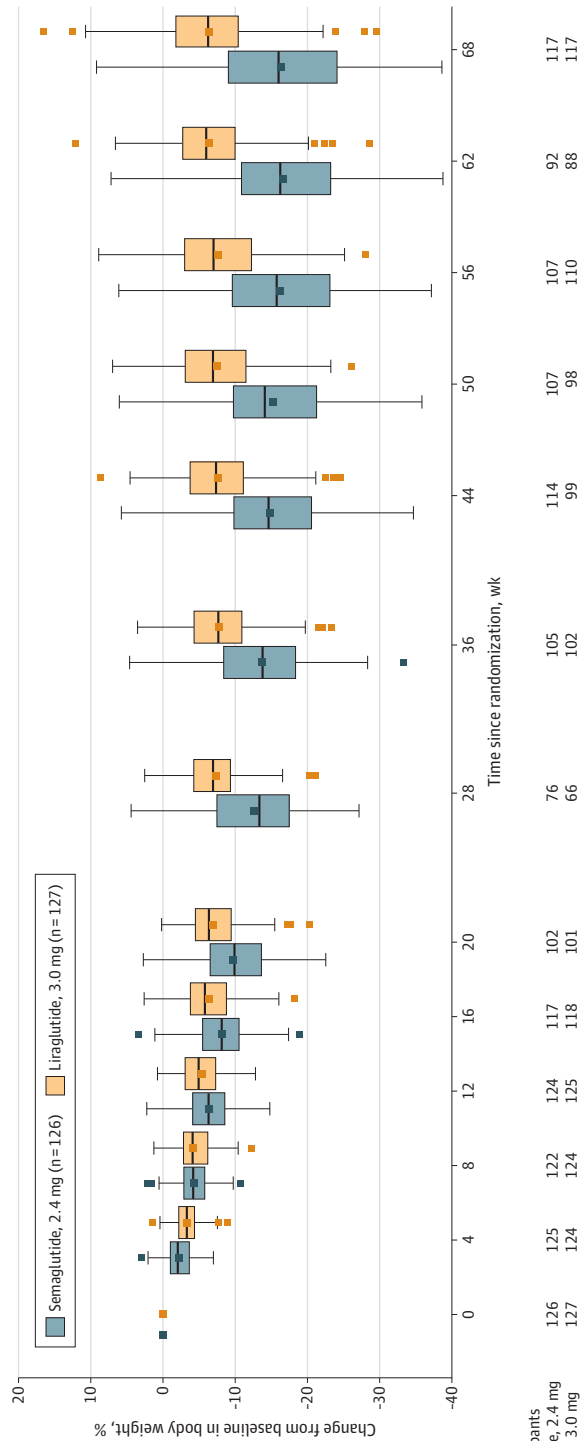
^d Data are observed (ie, as-measured) numbers and proportions of participants at week 68 from the in-trial period (the time from randomization to last contact with trial site, irrespective of treatment discontinuation or rescue intervention), and where applicable, estimated odds ratios for semaglutide vs liraglutide for the treatment policy estimand (achievement of ≥5% weight loss was an exploratory end point and not analyzed statistically).

^e These parameters were initially analyzed on a log scale as estimated ratio to baseline (within treatment groups) and estimated treatment ratios (between treatment groups). For interpretation, these data are expressed as relative percentage change and estimated relative percentage difference between groups, respectively, and were calculated using the formula: (estimated ratio - 1) × 100.

^f The sensitivity analysis was performed according to the primary analysis, but using jump-to-reference imputation (a technique in which missing data for participants in the active treatment groups were imputed by sampling from all available data [regardless of treatment completion status] from the pooled placebo group).

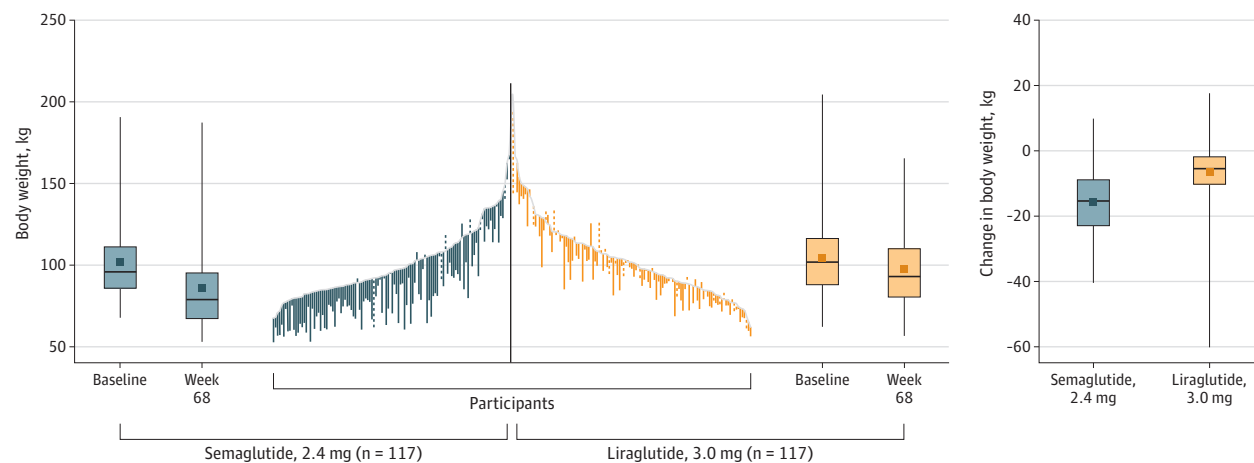
^g The post hoc analysis was performed using a mixed-effects regression analysis with study site as a random effect.

Figure 2. Percentage Change in Body Weight From Baseline to Week 68 (Observed In-Trial Data; Full Analysis Set)



Data presented are observed (ie, as-measured) changes during the in-trial period (the time from randomization to last contact with trial site, irrespective of treatment discontinuation or rescue intervention) for the full analysis set. Data for the on-treatment period are presented in Figure 5 in Supplement 3. The middle lines within each box represent the median observed changes from baseline; the symbols in the boxes represent the mean observed percentage change; the box tops and bottoms represent the interquartile range; the whiskers extend to the most extreme observed values with 1.5 times the IQR of the nearer quartile; and the symbols beyond these points represent the observed values outside that range. More negative values indicate greater reductions. Numbers shown below the graph are the number of participants with observed data at each time point. Participant numbers in the legend are for the full analysis set. Data are only presented for the active treatment groups.

Figure 3. Change in Absolute Body Weight From Baseline to Week 68 for Individual Participants (Observed In-Trial Data; Full Analysis Set)



Data presented are observed (ie, as-measured) changes during the in-trial period (the time from randomization to last contact with trial site, irrespective of treatment discontinuation or rescue intervention) for each individual participant in the full analysis set. Solid lines are for treatment completers (ie, participants who were receiving treatment at week 68), and dashed lines are for participants who prematurely discontinued treatment. A total of 117 participants in the semaglutide, 2.4 mg, group and 117 in the liraglutide,

3.0 mg, group had a week 68 assessment and so contribute to the data. Data are only presented for the active treatment groups. The middle lines within each box represent the median data; the symbols in the boxes represent the mean data; the box tops and bottoms represent the interquartile range; and the whiskers extend to the most extreme observed values with 1.5 times the IQR of the nearer quartile. The gray line indicates baseline.

(-37.2% [95% CI, -51.7% to -18.5%]) were significantly greater with semaglutide vs with liraglutide (Table 2; eTable 4 and eFigures 5, 6A, and 7 in Supplement 3). Changes in other end points were not significantly different (Table 2; eTable 4 and eFigures 6B and 7 in Supplement 3). The reduction in diastolic blood pressure was significantly greater with semaglutide vs liraglutide (-4.5 mm Hg [95% CI, -7.1 to -1.9]) at week 68, but changes at all other time points were comparable (Table 2; eFigure 6C in Supplement 3). Systolic blood pressure increased with placebo (eTable 5 in Supplement 3).

At week 68, the estimated mean change in body weight was -1.9% for pooled placebo (eTable 5 in Supplement 3). Weight loss with semaglutide and liraglutide were significantly greater vs placebo (difference, -13.9 percentage points [95% CI, -16.7 to -11.0] and -4.5 percentage points [95% CI, -7.3 to -1.7]). The proportions of participants achieving 10% or more, 15% or more, and 20% or more weight loss with placebo were 15.4%, 6.4%, and 2.6% (eTable 5 in Supplement 3). Changes in other end points for the placebo group are in eTable 5 in Supplement 3.

Exploratory Outcomes

The proportions of participants achieving 5% or more weight loss were 87.2% with semaglutide, 58.1% with liraglutide, and 29.5% with placebo (Table 2; eTables 4 and 5 and eFigure 3 in Supplement 3).

Post Hoc Outcomes

The estimated mean body weight changes at week 68 for the separate placebo groups were -0.5% (95% CI, -3.1% to 2.2%) for semaglutide-placebo and -3.2% (95% CI, -5.9% to -0.5%) for liraglutide-placebo (eTable 5 in Supplement 3).

Adverse Events

AEs were reported by 95.2% of participants with semaglutide, 96.1% with liraglutide, and 95.3% with placebo (Table 3). Gastrointestinal disorders were the most frequent AEs with semaglutide and liraglutide, reported by 84.1% and 82.7% of participants, respectively (placebo: 55.3%); more events occurred with semaglutide than with liraglutide. Most gastrointestinal events were mild to moderate in severity (severe gastrointestinal events were reported by 3.2% [n = 4], 2.4% [n = 3], and 3.5% [n = 3] with semaglutide, liraglutide, and placebo, respectively), transient, and resolved without permanent treatment discontinuation (Table 3; eFigure 8 in Supplement 3). Reports of gastrointestinal AEs were greatest during, and shortly after, dose escalation, with mild events persisting throughout the trial (eFigure 8 in Supplement 3).

Serious AEs were reported by 7.9% (n = 10) with semaglutide, 11.0% (n = 14) with liraglutide, and 7.1% (n = 6) with placebo (Table 3). Permanent treatment discontinuations because of AEs were more common with liraglutide (12.6% [n = 16]) vs semaglutide (3.2% [n = 4]) and placebo (3.5% [n = 3]); half of liraglutide discontinuations were gastrointestinal-related and tended to occur during dose escalation (Table 3; eFigure 9 in Supplement 3). There was no clustering of AEs leading to discontinuation by system organ class with semaglutide and placebo. No deaths occurred.

Gallbladder-related disorders (mostly cholelithiasis) were reported by 0.8% (n = 1) with semaglutide, 3.1% (n = 4) with liraglutide, and 1.2% (n = 1) with placebo. One participant (liraglutide group) reported subclinical pancreatitis that did not require treatment. Malignant neoplasms occurred in 2.4% with semaglutide (n = 3; basal cell carcinoma, clear cell renal cell carcinoma, and invasive ductal breast carcinoma), 2.4% with

Table 3. Adverse Event and Tolerability Profile (Safety Analysis Set)^a

	Semaglutide, 2.4 mg (n = 126)		Liraglutide, 3.0 mg (n = 127)		Placebo (n = 85) ^b	
	Participants, No. (%)	Events, No.	Participants, No. (%)	Events, No.	Participants, No. (%)	Events, No.
Fatal AEs ^c	0		0		0	
SAEs	10 (7.9)	14	14 (11.0)	18	6 (7.1)	9
AEs leading to trial product discontinuation	4 (3.2)	4	16 (12.6)	21	3 (3.5)	3
GI disorders	1 (0.8)	1	8 (6.3)	10	1 (1.2)	1
Any AEs	120 (95.2)	904	122 (96.1)	823	81 (95.3)	522
AEs in ≥10% of participants in any treatment group by MedDRA-preferred term						
Nausea	77 (61.1)	130	75 (59.1)	102	19 (22.4)	24
Constipation	49 (38.9)	80	40 (31.5)	52	20 (23.5)	24
Diarrhea	35 (27.8)	51	23 (18.1)	37	22 (25.9)	26
Vomiting	32 (25.4)	50	26 (20.5)	34	5 (5.9)	6
Headache	20 (15.9)	46	18 (14.2)	20	10 (11.8)	12
Eructation	17 (13.5)	20	5 (3.9)	5	4 (4.7)	4
Decreased appetite	15 (11.9)	15	16 (12.6)	18	3 (3.5)	3
Fatigue	12 (9.5)	12	14 (11.0)	17	4 (4.7)	4
Dyspepsia	11 (8.7)	14	15 (11.8)	16	5 (5.9)	7
Nasopharyngitis	10 (7.9)	10	11 (8.7)	13	9 (10.6)	11
Upper respiratory tract infection	9 (7.1)	11	19 (15.0)	26	18 (21.2)	23
Arthralgia	8 (6.3)	8	14 (11.0)	15	7 (8.2)	7
Sinusitis	8 (6.3)	9	8 (6.3)	8	13 (15.3)	14
Back pain	6 (4.8)	6	9 (7.1)	10	9 (10.6)	10
Influenza	5 (4.0)	5	14 (11.0)	14	6 (7.1)	6
Safety areas of interest ^d						
GI disorders	106 (84.1)	440	105 (82.7)	313	47 (55.3)	130
Cardiovascular disorders ^c	16 (12.7)	20	18 (14.2)	21	9 (10.6)	23
Allergic reactions	9 (7.1)	13	11 (8.7)	12	10 (11.8)	13
Psychiatric disorders	7 (5.6)	10	19 (15.0)	27	9 (10.6)	10
Injection site reactions	0		14 (11.0)	16	5 (5.9)	7
Malignant neoplasms ^c	3 (2.4)	3	3 (2.4)	3	1 (1.2)	1
Hepatic disorders	2 (1.6)	2	1 (0.8)	1	3 (3.5)	4
Gallbladder-related disorders	1 (0.8)	2	4 (3.1)	5	1 (1.2)	1
Cholelithiasis	1 (0.8)	1	2 (1.6)	2	1 (1.2)	1
Hypoglycemia	0		1 (0.8)	1	0	
Acute pancreatitis	0		1 (0.8)	1	0	
Acute kidney failure	1 (0.8)	1	0		1 (1.2)	1

Abbreviations: AE, adverse event; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

^a Data are for the on-treatment period (the time during which treatment with any dose of trial intervention was given within the previous 49 days [after excluding any temporary interruptions in taking trial intervention]) unless indicated otherwise.

^b Pooled placebo data.

^c Data are for the in-trial period (the time from randomization to last contact with trial site, irrespective of treatment discontinuation or rescue intervention).

^d Identified via MedDRA (version 23.1) searches.

liraglutide (n = 3; basal cell carcinoma, invasive ductal breast carcinoma, and invasive lobular breast carcinoma), and 1.2% with placebo (n = 1; invasive ductal breast carcinoma). More participants reported psychiatric-related AEs with liraglutide than semaglutide or placebo (Table 3), driven by differences in insomnia events (semaglutide: n = 3 [2.4%]; liraglutide: n = 7 [5.5%]; placebo: n = 2 [2.4%]). Other AEs are reported in Table 3.

At week 68, the estimated mean change in pulse (assessed post hoc for the trial product estimand) was 5.4 beats/min (95% CI, 3.7 to 7.1) with semaglutide, 4.3/min (95% CI, 2.5 to 6.0) with liraglutide, and 1.2/min (95% CI, -0.9 to 3.2) with

placebo. At week 75, observed mean (SD) changes from baseline were 2 (10)/min with semaglutide, 3 (9)/min with liraglutide, and 2 (10)/min with placebo.

Discussion

Among adults with overweight or obesity without diabetes, once-weekly subcutaneous semaglutide compared with once-daily subcutaneous liraglutide, added to counseling for diet and physical activity, resulted in significantly greater weight

loss at 68 weeks, accompanied by significantly greater improvements in several cardiometabolic risk factors.

Semaglutide and liraglutide induce weight loss by lowering energy intake.¹⁹⁻²² However, the reduction in caloric intake vs placebo appears to be larger with semaglutide (35%) than liraglutide (approximately 16%).^{19,20} Semaglutide has also been associated with reductions in food cravings, which is less evident with liraglutide, suggesting different mechanisms of energy intake regulation.²⁰⁻²² Further research is needed to investigate whether structural differences affect these mechanisms, for example, by allowing semaglutide to target a wider range of neuronal GLP-1 receptors than liraglutide.

Obesity is a chronic disease associated with multiple complications, including type 2 diabetes, nonalcoholic fatty liver disease, and cardiovascular disease, which place significant burdens on individuals and health care systems.²³⁻²⁶ Treatment guidelines recommend 5% to 15% weight loss to improve these conditions,²³⁻²⁵ with associated health care expenditure savings.²⁷ In this trial, the odds of achieving these clinically meaningful levels of weight loss were significantly greater with semaglutide vs liraglutide, accompanied by significant improvements in several cardiometabolic parameters. Whether semaglutide could be beneficial in preventing progression of cardiometabolic disease will be evaluated in the SELECT trial (NCT03574597).²⁸

The rates of AEs, which were mostly gastrointestinal-related, were similar with semaglutide and liraglutide in this trial, consistent with previous trials.^{2-5,9,11,29-32} More insomnia events occurred with liraglutide than semaglutide. Liraglutide has previously been found to slightly increase rates of insomnia and suicidal ideation/behavior when assessed post hoc, but is not associated with increased depression or suicidality indicators when assessed prospectively.³³

In contrast with previous trials,^{9,34} there were more discontinuations (AE-related and permanent discontinuations for any reason) with liraglutide than semaglutide in the present trial. There are several potential reasons for this. First, liraglutide has a shorter half-life (13-15 hours) than semaglutide (165 hours),^{1,6,8} potentially causing a more abrupt, and thus noticeable, return in hunger on pausing liraglutide vs semaglutide treatment. This could have negatively affected efficacy perceptions among the liraglutide group, leading some to permanently stop treatment. Second, the response to poor tolerance of the maintenance dose differed for semaglutide and liraglutide (see the Limitations subsection). Third, half of the AE-related discontinuations with liraglutide were gastrointestinal-related, potentially exacerbated by the weekly dose escalation schedule used, per the approved label.⁶ Fourth, liraglutide is dosed more frequently than semaglutide; dosing frequency is a key attribute for patients with type 2 diabetes when choosing a GLP-1RA treatment.³⁵ However, treatment satisfaction, including perceived efficacy, was not assessed and so the effect on the discontinuation rate remains unclear. No differences in treatment satisfaction have been identified between semaglutide and liraglutide in patients with type 2 diabetes, potentially because of the satisfactory glycemic control provided by liraglutide.³⁴ More research in the context of obesity is needed.

The results of this trial were generally consistent with previous semaglutide and liraglutide trials. The effect of semaglutide on body weight over liraglutide was similar to that in the phase 2 trial in obesity,⁹ while the placebo-adjusted weight loss and adverse effect profiles were similar to that in STEP 1 for semaglutide² and in SCALE Obesity and Prediabetes for liraglutide.^{6,11}

The COVID-19 pandemic occurred during this trial, with some visits conducted via telephone and not all planned body weight assessments obtained. However, 92% of participants in each treatment group had body weight assessments at week 68, suggesting no major effect on the efficacy findings.

This trial found weight loss with semaglutide was significantly greater than with liraglutide. However, the variability in treatment response means an individual's tolerance and sensitivity to a specific treatment is important for obesity management.^{23-25,36} Therefore, having multiple antiobesity medications proven to lower body weight through different mechanisms, with different adverse effect profiles and dosing regimens, can only benefit clinicians and patients.

Limitations

This trial has several limitations. First, the response to poor tolerance of the maintenance dose differed; semaglutide was administered at a lower dose, whereas liraglutide was discontinued and had to be reescalated if restarted. This difference ensured the liraglutide regimen was consistent with the approved prescribing information,⁶ but could have led to more participants permanently discontinuing liraglutide after an AE than semaglutide. Furthermore, weight loss achievable with liraglutide could have been affected as participants may have continued with treatment for a shorter period of time, thus deriving less benefit, and potentially introducing bias into the treatment comparisons. A crossover trial with a washout period could clarify the reasons for, and effects of, the greater discontinuation rate with liraglutide.

Second, dosing differences meant participants knew which active treatment they could potentially receive. The potential bias in the treatment comparisons was mitigated by the matched double-blind placebo controls, but this could have been further improved with a double-dummy approach. This, however, would have necessitated a greater number of injections for participants (8 per week) and so was not chosen for this trial.

Third, missing data were handled through multiple imputation, which can potentially introduce bias because there may be differences between the participants for whom data are imputed and those used for the imputation. However, retention in this trial was high, so the number of participants with missing data that needed to be imputed was low. Furthermore, the sensitivity analyses confirmed the primary analysis was robust.

Conclusions

Among adults with overweight or obesity without diabetes, once-weekly subcutaneous semaglutide, compared with once-daily subcutaneous liraglutide, added to counseling for diet and physical activity, resulted in significantly greater weight loss at 68 weeks.

ARTICLE INFORMATION

Accepted for Publication: December 12, 2021.

Author Affiliations: Washington Center for Weight Management and Research, Arlington, Virginia (Rubino); Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge (Greenway); Novo Nordisk A/S, Søborg, Denmark (Khalid, Sørrig, Wizert); Weight Management Center, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston (O'Neil); Dallas Diabetes Research Center at Medical City, Dallas, Texas (Rosenstock); Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Wadden); Department of Nutrition Sciences, University of Alabama at Birmingham (Garvey).

Author Contributions: Drs Rubino and Garvey had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Khalid, Sørrig, Wizert.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Rubino, Khalid, O'Neil, Sørrig, Wizert, Garvey.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Khalid, Wizert.

Administrative, technical, or material support: O'Neil.

Supervision: Rubino, Greenway, Rosenstock, Wadden, Garvey.

Conflict of Interest Disclosures: Dr Rubino reported being a clinical investigator for Boehringer Ingelheim, AstraZeneca, and Novo Nordisk; receiving honoraria from WebMD, speaker fees, consulting fees, scientific advisory fees, and honoraria from Novo Nordisk, grants from SARL, and personal fees from Medscape, PeerView, and the Endocrine Society; and being a shareholder in Novo Nordisk. Dr Greenway reported receiving grants from Novo Nordisk, Pennington Biomedical Research Center, and NuSirt to his institution during the conduct of the study and personal fees from Pfizer, NovMeta Pharma, Melior Discoveries, Jenny Craig, Basic Research, Gedeon Richter Pharma, Jazz Pharmaceuticals, General Nutrition Corp, Dr Reddy's Lab, and Regeneron and stock ownership in Academic Technology Ventures, Energesis, Ketogenic Health Systems, MetaSYn Therapeutics, Plensat, Slim Health Nutrition, UR Labs, and Rejuvenate Bio. In addition, Dr Greenway has a patent issued for orlistat and a patent pending for pramlintide/albuterol. Also, Dr Greenway served on the Novo Nordisk advisory board for the development of liraglutide that is now approved and was a comparator drug in the trial described in the present article. Dr Khalid reported being an employee of Novo Nordisk. Dr O'Neil reported receiving grants from Novo Nordisk during the conduct of the study and grants from WW International, Eli Lilly, and Epitome Medical and personal fees from Pfizer, Robard Corporation, Novo Nordisk, WebMD, and Gedeon Richter outside the submitted work. Dr Rosenstock reported receiving scientific advisory board fees, honoraria, consulting fees, and grants/research support from Novo Nordisk (during the conduct of the study and outside the submitted work), Applied Therapeutics, Boehringer Ingelheim, Eli Lilly, Intarcia, Oramed,

Hanmi, and Sanofi; honoraria or consulting fees from Zealand; and grants/research support from Genentech, Novartis, Pfizer, REMD Biotherapeutics, vTv Therapeutics, Metacrine, Merck, and Janssen outside the submitted work. Dr Sørrig reported being a full-time employee and shareholder of Novo Nordisk. Dr Wadden reported receiving grants from Novo Nordisk on behalf of the University of Pennsylvania and scientific advisory board fees from Novo Nordisk and WW (formerly Weight Watchers). Dr Wizert reported being a full-time employee and shareholder of Novo Nordisk. Dr Garvey reported receiving grants from Novo Nordisk; serving as site principal investigator for the clinical trial, which was sponsored by his university during the conduct of the study; receiving grants from Lexicon, Pfizer, Eli Lilly, and Epitome outside the submitted work; and serving as an ad hoc consultant on advisory committees for Jazz Pharmaceuticals, Boehringer Ingelheim, Novo Nordisk, and Pfizer. In each instance, he received no financial compensation, nor was there a financial relationship.

Funding/Support: This trial was funded by Novo Nordisk A/S.

Role of the Funders/Sponsor: Representatives of the sponsor (Novo Nordisk A/S) were involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript. Data were gathered by the site investigators, and the sponsor performed study site oversight, data collation, and analysis. A medical writer (Sophie Walton, MSc, of Axis, a division of Spirit Medical Communications Group Limited, funded by the sponsor) assisted with drafting the manuscript, under the direction of the authors. The sponsor did not have the right to veto publication or to control the decision regarding to which journal the manuscript was submitted. These decisions resided with the authors.

Group Information: A complete list of investigators for the Semaglutide Treatment Effect in People With Obesity (STEP) 8 trial appears in [Supplement 4](#).

Meeting Presentation: This study was presented at the 39th annual meeting of the Obesity Society; November 5, 2021; virtual meeting.

Data Sharing Statement: See [Supplement 5](#).

Additional Contributions: We thank all participants, investigators, trial staff, and research participants who were involved in the conduct of the trial. We also thank Søren Kruse Lilleøre, MSc, and Tobias Sydenal Grand, MSc, of Novo Nordisk A/S for reviewing the manuscript, for which they were compensated as part of their salaries as employees of Novo Nordisk.

REFERENCES

1. US Food and Drug Administration. Wegovy prescribing information. Accessed June 11, 2021. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=215256>
2. Wilding JPH, Batterham RL, Calanna S, et al; STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002. doi:10.1056/NEJMoa2032183

3. Davies M, Færch L, Jeppesen OK, et al; STEP 2 Study Group. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet*. 2021;397(10278):971-984. doi:10.1016/S0140-6736(21)00213-0
4. Wadden TA, Bailey TS, Billings LK, et al; STEP 3 Investigators. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA*. 2021;325(14):1403-1413. doi:10.1001/jama.2021.1831
5. Rubino D, Abrahamsson N, Davies M, et al; 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(14):1414-1425. doi:10.1001/jama.2021.3224
6. US Food and Drug Administration. Saxenda prescribing information. Accessed May 19, 2021. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=206321>
7. Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide. *Front Endocrinol (Lausanne)*. 2019;10:155. doi:10.3389/fendo.2019.00155
8. Lau J, Bloch P, Schäffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem*. 2015;58(18):7370-7380. doi:10.1021/acs.jmedchem.5b00726
9. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet*. 2018;392(10148):637-649. doi:10.1016/S0140-6736(18)31773-2
10. Yadav K, Lewis RJ. Gatekeeping strategies for avoiding false-positive results in clinical trials with many comparisons. *JAMA*. 2017;318(14):1385-1386. doi:10.1001/jama.2017.13276
11. Pi-Sunyer X, Astrup A, Fujioka K, et al; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373(1):11-22. doi:10.1056/NEJMoa1411892
12. US Food and Drug Administration. Guidance document: developing products for weight management, revision 1. Published February 2007. Accessed October 29, 2021. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-products-weight-management-revision-1>
13. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Efficacy guidelines: E9, statistical principles for clinical trials. Accessed May 19, 2021. <https://www.ich.org/page/efficacy-guidelines>
14. US Food and Drug Administration. E9(R1) Statistical principles for clinical trials: addendum: estimands and sensitivity analysis in clinical trials. Published May 2021. Accessed May 19, 2021. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical>

15. Wharton S, Astrup A, Endahl L, et al. Estimating and reporting treatment effects in clinical trials for weight management: using estimands to interpret effects of intercurrent events and missing data. *Int J Obes (Lond)*. 2021;45(5):923-933. doi:10.1038/s41366-020-00733-x
16. McEvoy BW. Missing data in clinical trials for weight management. *J Biopharm Stat*. 2016;26(1):30-36. doi:10.1080/10543406.2015.1094814
17. Little RJA, Rubin D B. *Statistical Analysis With Missing Data*. John Wiley & Sons; 1987.
18. American Diabetes Association. 2. Classification and diagnosis of diabetes. *Diabetes Care*. 2017;40 (suppl 1):S11-S24. doi:10.2337/dc17-S005
19. van Can J, Sloth B, Jensen CB, Flint A, Blaabk EE, Saris WH. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. *Int J Obes (Lond)*. 2014;38(6):784-793. doi:10.1038/ijo.2013.162
20. Friedrichsen M, Breitschaft A, Tadayon S, Wizert A, Skovgaard D. The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. *Diabetes Obes Metab*. 2021;23(3):754-762. doi:10.1111/dom.14280
21. Gabery S, Salinas CG, Paulsen SJ, et al. Semaglutide lowers body weight in rodents via distributed neural pathways. *JCI Insight*. 2020;5(6):e133429. doi:10.1172/jci.insight.133429
22. Chao AM, Wadden TA, Walsh OA, et al. Effects of liraglutide and behavioral weight loss on food cravings, eating behaviors, and eating disorder psychopathology. *Obesity (Silver Spring)*. 2019;27(12):2005-2010. doi:10.1002/oby.22653
23. Yumuk V, Tsigos C, Fried M, et al; Obesity Management Task Force of the European Association for the Study of Obesity. European guidelines for obesity management in adults. *Obes Facts*. 2015;8(6):402-424. doi:10.1159/000442721
24. Garvey WT, Mechanick JI, Brett EM, et al; Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(suppl 3):1-203. doi:10.4158/EP161365.GL
25. Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. *CMAJ*. 2020;192(31):E875-E891. doi:10.1503/cmaj.191707
26. Divino V, Ramasamy A, Anupindi VR, et al. Complication-specific direct medical costs by body mass index for 13 obesity-related complications: a retrospective database study. *J Manag Care Spec Pharm*. 2021;27(2):210-222. doi:10.18553/jmcp.2020.20272
27. Cawley J, Meyerhoefer C, Biener A, Hammer M, Wintfeld N. Savings in medical expenditures associated with reductions in body mass index among US adults with obesity, by diabetes status. *Pharmacoeconomics*. 2015;33(7):707-722. doi:10.1007/s40273-014-0230-2
28. Ryan DH, Lingvay I, Colhoun HM, et al. Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) rationale and design. *Am Heart J*. 2020;229:61-69. doi:10.1016/j.ahj.2020.07.008
29. Astrup A, Carraro R, Finer N, et al; NN8022-1807 Investigators. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond)*. 2012;36(6):843-854. doi:10.1038/ijo.2011.158
30. Wadden TA, Hollander P, Klein S, et al; NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond)*. 2013;37(11):1443-1451. doi:10.1038/ijo.2013.120
31. Davies MJ, Bergenstal R, Bode B, et al; NN8022-1922 Study Group. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes randomized clinical trial. *JAMA*. 2015;314(7):687-699. doi:10.1001/jama.2015.9676
32. Blackman A, Foster GD, Zammit G, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *Int J Obes (Lond)*. 2016;40(8):1310-1319. doi:10.1038/ijo.2016.52
33. O'Neil PM, Aroda VR, Astrup A, et al; Satiety and Clinical Adiposity—Liraglutide Evidence in individuals with and without diabetes (SCALE) study groups. Neuropsychiatric safety with liraglutide 3.0 mg for weight management: results from randomized controlled phase 2 and 3a trials. *Diabetes Obes Metab*. 2017;19(11):1529-1536. doi:10.1111/dom.12963
34. Capehorn MS, Catarig AM, Furberg JK, et al. Efficacy and safety of once-weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab*. 2020;46(2):100-109. doi:10.1016/j.diabet.2019.101117
35. Hauber AB, Nguyen H, Posner J, Kalsekar I, Ruggles J. A discrete-choice experiment to quantify patient preferences for frequency of glucagon-like peptide-1 receptor agonist injections in the treatment of type 2 diabetes. *Curr Med Res Opin*. 2016;32(2):251-262. doi:10.1185/03007995.2015.1117433
36. Pedersen SD, Manjoo P, Wharton S. Canadian adult obesity clinical practice guidelines: pharmacotherapy in obesity management. Accessed August 10, 2021. <https://obesitycanada.ca/guidelines/pharmacotherapy/>