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Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity
The STEP 4 Randomized Clinical Trial

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IMPORTANCE The effect of continuing vs withdrawing treatment with semaglutide, a glucagon-like peptide 1 receptor agonist, on weight loss maintenance in people with overweight or obesity is unknown.

OBJECTIVE To compare continued once-weekly treatment with subcutaneous semaglutide, 2.4 mg, with switch to placebo for weight maintenance (both with lifestyle intervention) in adults with overweight or obesity after a 20-week run-in with subcutaneous semaglutide titrated to 2.4 mg weekly.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, 68-week phase 3a withdrawal study conducted at 73 sites in 10 countries from June 2018 to March 2020 in adults with body mass index of at least 30 (or ≥27 with ≥1 weight-related comorbidity) and without diabetes.

INTERVENTIONS A total of 902 participants received once-weekly subcutaneous semaglutide during run-in. After 20 weeks (16 weeks of dose escalation; 4 weeks of maintenance dose), 803 participants (89.0%) who reached the 2.4-mg/wk semaglutide maintenance dose were randomized (2:1) to 48 weeks of continued subcutaneous semaglutide (n = 535) or switched to placebo (n = 268), plus lifestyle intervention in both groups.

MAIN OUTCOMES AND MEASURES The primary end point was percent change in body weight from week 20 to week 68; confirmatory secondary end points were changes in waist circumference, systolic blood pressure, and physical functioning (assessed using the Short Form 36 Version 2 Health Survey, Acute Version [SF-36]).

RESULTS Among 803 study participants who completed the 20-week run-in period (with a mean weight loss of 10.6%) and were randomized (mean age, 46 [SD, 12] years; 634 [79%] women; mean body weight, 107.2 kg [SD, 22.7 kg]), 787 participants (98.0%) completed the trial and 741 (92.3%) completed treatment. With continued semaglutide, mean body weight change from week 20 to week 68 was −7.9% vs +6.9% with the switch to placebo (difference, −14.8 [95% CI, −16.0 to −13.5] percentage points; $P < .001$). Waist circumference (−9.7 cm [95% CI, −10.9 to −8.5 cm]), systolic blood pressure (−3.9 mm Hg [95% CI, −5.8 to −2.0 mm Hg]), and SF-36 physical functioning score (2.5 [95% CI, 1.6-3.3]) also improved with continued subcutaneous semaglutide vs placebo (all $P < .001$). Gastrointestinal events were reported in 49.1% of participants who continued subcutaneous semaglutide vs 26.1% with placebo; similar proportions discontinued treatment because of adverse events with continued semaglutide (2.4%) and placebo (2.2%).

CONCLUSIONS AND RELEVANCE Among adults with overweight or obesity who completed a 20-week run-in period with subcutaneous semaglutide, 2.4 mg once weekly, maintaining treatment with semaglutide compared with switching to placebo resulted in continued weight loss over the following 48 weeks.

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Obesity is a chronic, relapsing disease with a substantial burden on individuals, society, and the economy.[1] Maintaining long-term weight loss is challenging because of metabolic adaptation[2] and the difficulty of adhering to lifestyle interventions,[3] with weight regain often following weight loss.[4]

Sustained weight loss of 5% to 15% is advised to improve many conditions associated with overweight/obesity, with adjunctive pharmacotherapy recommended to help achieve this goal.[5,6] However, approved antiobesity medications have only moderate efficacy (3%-8% body weight reduction beyond lifestyle intervention alone).[7-9] Short-term treatment (3-6 months) fails to produce long-term health benefits,[5] while several agents also have safety concerns.[7-9] Well-tolerated new therapies that can produce substantial, sustained weight loss, when used long term, are therefore needed.[7,10]

Subcutaneous semaglutide is a glucagon-like peptide 1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes at doses of 1.0 mg or less once weekly.[11] Weight loss with semaglutide is believed to stem from improved appetite control, and consequent reduced energy intake, via effects in the hypothalamus and area postrema of the brain.[12,13] Once-weekly subcutaneous semaglutide, 2.4 mg, is being investigated for the treatment of overweight/obesity in the global phase 3 Semaglutide Treatment Effect in People With Obesity (STEP) program.[10] This dose, which is greater than what is currently approved for type 2 diabetes, was chosen based on a phase 2 clinical trial, in which greater weight loss was seen with once-daily semaglutide, 0.4 mg (equal to 2.8 mg/wk), vs current approved medical therapy.[14] Proposed to be more clinically convenient, weekly administration was supported by a tolerability trial and pharmacokinetic modeling.[10,15]

The STEP 4 withdrawal trial was conducted to compare the effect of continuing once-weekly treatment with subcutaneous semaglutide, 2.4 mg, vs switching to placebo (both with lifestyle intervention) on body weight in participants with overweight/obesity who reached a semaglutide treatment dosage of 2.4 mg once weekly during an initial 20-week run-in.

Key Points

Question What effect does continued treatment with 2.4 mg of subcutaneous semaglutide have on the maintenance of body weight loss in adults with overweight or obesity without diabetes?

Findings In this randomized clinical trial of adults with overweight or obesity, 803 participants completed a 20-week run-in of weekly treatment with subcutaneous semaglutide, 2.4 mg, with a mean weight loss of 10.6%, and were randomized to continued treatment with subcutaneous semaglutide vs placebo for an additional 48 weeks. At the end of this time, mean weight change was −7.9% vs +6.9%, respectively, a difference that was statistically significant.

Meaning Among adults with overweight or obesity completing a 20-week run-in period, maintaining treatment with subcutaneous semaglutide compared with switching to placebo resulted in continued weight loss.

Methods

Trial Design and Oversight

This trial was a 68-week, randomized, double-blind, placebo-controlled withdrawal study conducted at 73 sites in 10 countries (eAppendix 1 in Supplement 1) from June 2018 to March 2020. The protocol and amendments (see trial protocol in Supplement 2 and statistical analysis plan in Supplement 3) were approved by an independent ethics committee or institutional review board at each site. The study was conducted according to the International Council for Harmonisation Good Clinical Practice Guideline and the Declaration of Helsinki[16]; all participants provided written informed consent.

Participants

Adults (≥18 years old) with at least 1 self-reported unsuccessful dietary effort to lose weight and with a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 30 or higher or a BMI of 27 or higher with at least 1 treated or untreated weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease; type 2 diabetes was excluded) were enrolled. Key exclusion criteria were a hemoglobin A_{1c} of 6.5% (48 mmol/mol) or greater and a self-reported change in body weight of more than 5 kg within 90 days of screening. Full eligibility criteria are shown in eAppendix 2 in Supplement 1. To meet regulatory requirements, race and ethnicity were recorded in this study and were determined by each participant according to fixed selection categories (with the option of answering "other," "not applicable," or "unknown"). Participants eligible for randomization at week 20 had to have attained the target maintenance dose of semaglutide (2.4 mg once weekly) by week 16 and have continued taking this dose until week 20.

Procedures

All participants initially received open-label once-weekly subcutaneous semaglutide, 0.25 mg, increased every 4 weeks to the maintenance dose of 2.4 mg once weekly by week 16, and continued to week 20 (run-in period; eFigure 1 in Supplement 1). Participants receiving semaglutide, 2.4 mg, at week 20 were randomized in a 2:1 ratio using a blocking schema (block size of 6) in a double-blind manner, via an interactive web-based response system, to continue this treatment or switch to matching placebo for 48 weeks (weeks 20-68; randomized period), with a 7-week follow-up. Participants unable to tolerate semaglutide, 2.4 mg/wk, during the randomized period were permitted to receive 1.7 mg/wk at the treating investigator's discretion and were recommended to make at least 1 attempt to reescalate.

All participants received a lifestyle intervention from week 0 to week 68, including monthly counseling by qualified health care professionals, in person or by telephone. Participants were prescribed a reduced-calorie diet (500-kcal/d deficit relative to estimated energy expenditure calculated at week 0) and increased physical activity (150 min/wk), recorded daily by participants (using paper diaries, apps, or other tools) and reviewed during counseling visits.

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Outcomes

The primary end point was percent change in body weight from randomization (week 20) to week 68. Confirmatory secondary end points (in hierarchical testing order) were change from week 20 to week 68 in waist circumference, systolic blood pressure, and physical functioning score on the Short Form 36 Version 2 Health Survey, Acute Version (SF-36; eAppendix 3 in Supplement 1). Supportive secondary end points were changes from week 20 to week 68 in absolute body weight (in kilograms), hemoglobin A_{1c}, fasting plasma glucose, fasting serum insulin, diastolic blood pressure, lipid levels, and the SF-36 physical and mental component summary scores (other than physical functioning, changes in domain scores are not reported); whether participants achieved the SF-36 physical functioning responder threshold (data not reported) and gained weight from week 20 to week 68; and total overall and categorical weight loss from week 0 to week 68. Exploratory end points included changes in antihypertensive and lipid-lowering medication use (see eAppendix 4 in Supplement 1 for a full list).

Adverse event assessments included the number of treatment-emergent and serious adverse events during run-in (weeks 0-20) and from randomization to trial end (weeks 20-75); adverse events were recorded for the randomized period if onset was after randomization. Additional safety-related end points are listed in eAppendix 4 in Supplement 1. Cardiovascular events, acute pancreatitis events, and deaths were reviewed by an independent external event adjudication committee.

Sample Size Calculation

A sample size of 750 randomized participants (assuming a 5% permanent discontinuation rate from week 20 to week 68 and available data for 60% of these participants at week 68) was calculated to provide 95% power for the primary and confirmatory secondary end points, tested in a predefined hierarchal order. The calculation included assumed differences between treatment groups of 8.7 percentage points in body weight change, 5.8 cm in waist circumference change, 4 mm Hg in systolic blood pressure change, and 3.9 points in SF-36 physical functioning score change, based on data from the phase 2 trial of semaglutide for obesity.[14] At least 900 participants were needed to start the trial intervention to ensure that at least 750 were randomized.

Statistical Analysis

Efficacy end points were analyzed using the full analysis set (ie, all participants randomly assigned to a treatment group regardless of whether they initiated treatment); assessments of adverse events and laboratory parameters used the safety analysis set (all participants exposed to ≥1 dose of study treatment). Observation periods included the in-trial period (time from week 0 to date of last contact with trial site) and the on-treatment period (administration of any dose of trial product within the prior 14 days [prior 49 days for adverse event evaluation]). All results from statistical analyses were accompanied by 2-sided 95% confidence intervals and corresponding *P* values (statistical significance defined as $P < .05$). Because of the potential for type I error due to multiple comparisons, findings for analyses of supportive secondary end points should be interpreted as exploratory. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

Two estimands (treatment policy estimand and trial product estimand) were used to evaluate treatment efficacy from different perspectives[10,17] and accounted for intercurrent events and missing data differently.[18-20] All analyses in the statistical hierarchy (eTable 1 in Supplement 1) were based on the treatment policy estimand (the primary estimand; similar to an intention-to-treat analysis), which quantified the average treatment effect regardless of adherence to treatment or initiation of rescue interventions (antiobesity medications or bariatric surgery) between week 20 and week 68. Continuous end points were analyzed using analysis of covariance, with randomized treatment as a factor and baseline (week 20) end point value as a covariate. Categorical end points were analyzed using logistic regression, with the same factor and covariate (baseline body weight in kilograms was used for the analysis of participants who gained weight).[10] A multiple imputation approach[21] was used in which missing data were imputed from week 68 measurements from participants in the same treatment group. One thousand complete data sets were generated and analyzed, and the results were combined using the Rubin formula[22] to obtain overall estimates. To account for the multicenter study design, a post hoc mixed-effects regression analysis of the primary end point was performed, with study site as a random effect.

The trial product estimand (the secondary estimand) quantified the average treatment effect modeled to assume participants continued taking randomized treatment for the planned study duration without medication discontinuation or rescue interventions between week 20 and week 68. Continuous end points were assessed using a mixed model for repeated measurements (MMRM), with randomized treatment as a factor and baseline (week 20) end point value as a covariate,[10] all nested within visit. An unstructured covariance matrix for measurements within the same participant was used. For the analysis of participants who gained weight, the MMRM (with baseline body weight in kilograms as the covariate) was used to classify participants according to whether they gained weight or not. This classification was then analyzed using logistic regression, with the same factor and covariate as the MMRM.

Two further estimands (the tertiary and quaternary estimands) addressing treatment effects between week 0 and week 68 were also included. The tertiary estimand was identical to the primary treatment policy estimand, and the quaternary estimand was identical to the secondary trial product estimand, except values at week 20 (baseline) were replaced by those at week 0 (start of run-in) in the respective analyses.

Results are reported for the treatment policy estimand unless stated otherwise. Exploratory data and data from the run-in period (weeks 0-20) are summarized by descriptive statistics only.

Results

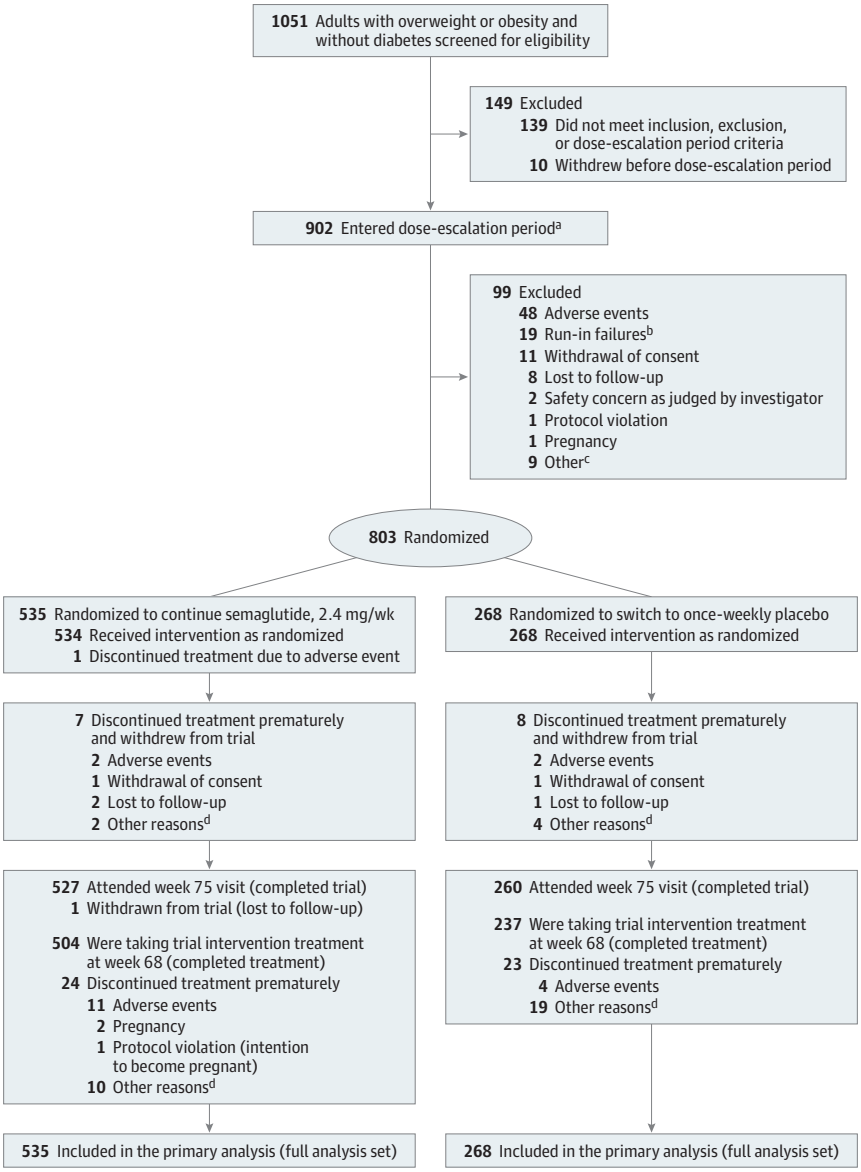
Study Participants

Overall, 1051 participants were screened and 902 entered the run-in. Of these, 803 (89.0%) were randomized at week 20

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Figure 1. Participant Flow in the Semaglutide Treatment Effect in People With Obesity (STEP) 4 Trial



[a] These participants received once-weekly semaglutide (safety analysis set).

[b] Run-in failures were defined as participants not meeting all 3 randomization criteria: attend the randomization visit, reach the semaglutide maintenance dose of 2.4 mg by week 16 (±3 days), and be receiving semaglutide, 2.4 mg, at week 20.

[c] Other reasons are listed in eTable 9 in Supplement 1.

[d] Other reasons are listed in eTable 10 in Supplement 1.

(continued semaglutide, n = 535; placebo, n = 268). Of the randomized participants, 787 (98.0%) completed the trial, 770 (95.9%) provided a body weight measurement at week 68, and 741 (92.3%) completed treatment (**Figure 1**). Of the 504 participants who continued semaglutide and completed treatment, 89.5% received 2.4 mg at week 68, 4.0% received 1.7 mg, and 2.8% received less than 1.7 mg; data were missing for 3.8%. One participant who switched to placebo received rescue intervention (liraglutide) during the randomized period. No participants had bariatric surgery.

Of the 803 randomized participants, most were female (79.0%) and White (83.7%), with a mean age of 46.0 years, a mean body weight of 107.2 kg, a mean BMI of 38.4, and a mean waist circumference of 115.3 cm at week 0 (**Table 1**; eTable 2 in Supplement 1). Most (64.8%) had 1 to 3 comorbidities, with dyslipidemia and hypertension most prevalent (Table 1).

Among those not randomized at week 20 (n = 99 [11%]; Figure 1), mean body weight at week 0 (103.6 kg) was lower than in the randomized population; other characteristics were similar (Table 1; eTable 4 in Supplement 1).

Changes During the Run-in Period

During the 20-week run-in, mean body weight declined by 10.6% to 96.1 kg (Table 1). This was accompanied by reductions in waist circumference, BMI, systolic and diastolic blood pressure, hemoglobin A_{1c}, and fasting plasma glucose and improvements in lipid profiles (Table 1; eTable 3 in Supplement 1). Participant characteristics at randomization (week 20) were comparable between treatment groups (Table 1; eTable 3).

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Table 1. Demographics and Clinical Characteristics at Week 0 and Week 20 (Full Analysis Set)

Characteristics	Week 0 (start of run-in period with semaglutide treatment) (n = 803)	Change during run-in period[a]	Week 20 (randomization)	
			Continued semaglutide, 2.4 mg/wk (n = 535)	Switched to placebo (n = 268)
Age, mean (SD), y	46 (12)		47 (12)	46 (12)
Sex, No. (%)				
Female	634 (79.0)		429 (80.2)	205 (76.5)
Male	169 (21.0)		106 (19.8)	63 (23.5)
Race, No. (%)[b]				
White	672 (83.7)		446 (83.4)	226 (84.3)
Black or African American	104 (13.0)		69 (12.9)	35 (13.1)
Asian	19 (2.4)		15 (2.8)	4 (1.5)
Other	8 (1.0)		5 (0.9)	3 (1.1)
Hispanic or Latino ethnicity, No. (%)	63 (7.8)		42 (7.9)	21 (7.8)
Body weight, mean (SD), kg	107.2 (22.7)	−11.1 (4.9)	96.5 (22.5)	95.4 (22.7)
Change, mean (SD), %		−10.6 (4.7)		
Body mass index[c]				
Mean (SD)	38.4 (6.9)	−4.0 (1.7)	34.5 (6.9)	34.1 (7.1)
No. (%)				
<25	0		7 (1.3)	9 (3.4)
≥25 to <30	22 (2.7)		153 (28.6)	69 (25.7)
≥30 to <35	274 (34.1)		166 (31.0)	97 (36.2)
≥35 to <40	249 (31.0)		116 (21.7)	52 (19.4)
≥40	258 (32.1)		93 (17.4)	41 (15.3)
Waist circumference, mean (SD), cm	115.3 (15.5)	−10.1 (6.2)	105.5 (15.9)	104.7 (16.9)
Blood pressure, mean (SD), mm Hg				
Systolic	127 (14)	−5.7 (13.6)	121 (13)	121 (13)
Diastolic	81 (10)	−3.0 (8.8)	78 (9)	78 (9)
Hemoglobin A_{1c}, mean (SD), %	5.7 (0.3)	−0.4 (0.2)[d]	5.4 (0.3)	5.4 (0.3)
Fasting plasma glucose, mean (SD), mg/dL	97.0 (10.7)	−9.5 (9.9)	87.9 (7.7)	86.9 (7.6)
Fasting lipids, median (IQR), mg/dL[e,f]				
Total cholesterol	194.6 (170.3-218.1) [n = 798]	0.9 (0.8-1.0)[g]	177.2 (152.9-201.9)	177.6 (156.0-198.8)
HDL-C	50.2 (42.1-59.1) [n = 798]	0.9 (0.8-1.0)[g]	44.4 (37.8-51.7)	44.0 (36.5-51.0)
LDL-C	116.6 (97.3-138.6) [n = 798]	1.0 (0.8-1.1)[g]	110.4 (91.1-130.9)	112.5 (93.6-130.9)
VLDL-C	22.8 (17.4-32.0) [n = 798]	0.8 (0.7-1.0)[g]	18.5 (14.3-24.7)	17.8 (13.5-24.7)
Free fatty acids	13.0 (9.0-17.8) [n = 789]	1.0 (0.7-1.4)[g]	12.5 (9.0-18.0) [n = 534]	12.5 (8.5-17.9)
Triglycerides	117.5 (88.1-164.7) [n = 798]	0.8 (0.7-1.0)[g]	95.2 (73.9-125.5)	90.8 (69.4-126.4)
SF-36 physical functioning score, mean (SD)[e,h]	51.7 (6.4) [n = 801]	2.2 (5.1)	53.8 (5.7) [n = 534]	54.1 (5.0)
Pulse, mean (SD), /min[i]	71 (10)	4.8 (9.3)	76 (9)	76 (9)
eGFR, median (IQR), mL/min/1.73 m^2[f,i,j]	100.5 (87.7-110.9)	1.0 (0.9-1.0)[g]	94.2 (81.3-106.6)	95.9 (83.5-108.1)
Comorbidities at screening, No. (%)				
Dyslipidemia	288 (35.9)		189 (35.3)	99 (36.9)
Hypertension	298 (37.1)		199 (37.2)	99 (36.9)
Knee osteoarthritis	99 (12.3)		72 (13.5)	27 (10.1)
Obstructive sleep apnea	94 (11.7)		61 (11.4)	33 (12.3)
Asthma/COPD	92 (11.5)		57 (10.7)	35 (13.1)
Nonalcoholic fatty liver disease	55 (6.8)		37 (6.9)	18 (6.7)
Polycystic ovary syndrome	25 (3.9)		15 (3.5)	10 (4.9)
Coronary artery disease	7 (0.9)		4 (0.7)	3 (1.1)

(continued)

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Table 1. Demographics and Clinical Characteristics at Week 0 and Week 20 (Full Analysis Set) (continued)

Characteristics	Week 0 (start of run-in period with semaglutide treatment) (n = 803)	Change during run-in period[a]	Week 20 (randomization)	
			Continued semaglutide, 2.4 mg/wk (n = 535)	Switched to placebo (n = 268)
Comorbidities at screening, No. (%)[i,k]				
0	214 (26.7)		144 (26.9)	70 (26.1)
1	238 (29.6)		160 (29.9)	78 (29.1)
2	171 (21.3)		103 (19.3)	68 (25.4)
3	111 (13.8)		77 (14.4)	34 (12.7)
4	53 (6.6)		38 (7.1)	15 (5.6)
≥5	16 (2.0)		13 (2.4)	3 (1.1)

Abbreviations: COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol.

SI conversions: To convert HDL-C, LDL-C, and total cholesterol to millimoles per liter, multiply by 0.0259. To convert glucose to millimoles per liter, multiply by 0.055. To convert triglycerides to millimoles per liter, multiply by 0.0113.

[a] Difference between values at week 0 and week 20 for individual participants in the total randomized population for selected parameters.

[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," "not applicable," or "unknown").

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Expressed as percentage points.

[e] Participant numbers are provided where the number analyzed differed from the number in the full analysis set.

[f] See eTable 3 in Supplement 1 for geometric mean (coefficient of variation) values for this parameter.

[g] Observed median (IQR) ratio to week 0.

[h] The Short Form 36 Version 2 Health Survey, Acute Version (SF-36) measures health-related quality of life and general health status. The SF-36 scores are norm-based scores, ie, scores transformed to a scale in which the 2009 US general population has a mean score of 50 and an SD of 10. The range of lowest to highest scores for the physical functioning domain is 19.03 to 57.60. An increase in score represents an improvement in health status. Further information on the SF-36 is provided in eAppendix 3 in Supplement 1.

[i] Data are for the safety analysis set.

[j] Assessed at screening (week −1).

[k] Comorbidities were reported at screening and are presented for all randomized participants (week 0) and by randomized treatment group (week 20 continued semaglutide and placebo). Selected comorbidities are presented based on a history of any of the following, as reported at screening: 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.

Changes During the Randomized Period

Primary End Point

Following randomization, the estimated mean weight change from week 20 to week 68 was −7.9% with continued semaglutide vs +6.9% in participants switched to placebo (difference, −14.8 [95% CI, −16.0 to −13.5] percentage points; $P < .001$) (**Table 2**; eFigure 2A, eFigure 2B [cumulative distribution plot], and eFigure 3 in Supplement 1). For the trial product estimand, corresponding changes were −8.8% vs +6.5%, respectively (difference, −15.3 [95% CI, −16.5 to −14.1] percentage points; $P < .001$) (eTable 5 and eFigure 4 in Supplement 1). Results were similar when analyzed post hoc with study site as a random effect, with an estimated mean weight change from week 20 to week 68 of −7.9% with continued semaglutide vs +6.9% with placebo (difference, −14.7 [95% CI, −16.1 to −13.4] percentage points; $P < .001$).

Confirmatory and Supportive Secondary End Points

Waist circumference (difference, −9.7 cm [95% CI, −10.9 to −8.5 cm]; $P < .001$) (**Figure 2**A; eFigure 3 in Supplement 1) and BMI (difference, −4.7 [95% CI, −5.2 to −4.3]) decreased from week 20 to week 68 with continued semaglutide and increased with placebo (Table 2; eTable 5 in Supplement 1).

From week 20 to week 68, systolic blood pressure remained stable with continued semaglutide and significantly increased with placebo (difference, −3.9 mm Hg [95% CI, −5.8 to −2.0 mm Hg]; $P < .001$) (Figure 2B; eFigure 3 in Supplement 1), with no change in diastolic blood pressure in either treatment group (Table 2; eTable 5 and eFigure 5 in Supplement 1).

During week 20 to week 68, continued semaglutide led to additional reductions in hemoglobin A_{1c} and fasting plasma glucose and improvements in lipid profile vs placebo (Table 2; eTable 5 in Supplement 1).

The SF-36 physical functioning scores significantly improved with continued semaglutide vs placebo from week 20 to week 68 ($P < .001$) (Table 2; eTable 5, eFigure 6, and eFigure 7 in Supplement 1). Improvements with continued semaglutide vs placebo were also seen in both the physical and mental component summary scores of the SF-36 (Table 2; eTable 5 and eFigure 7 in Supplement 1).

Further supportive secondary end point analyses, including absolute body weight changes, are reported in Table 2 and eTable 5 in Supplement 1.

Exploratory End Points

Among participants receiving antihypertensive medication at week 20 (continued semaglutide, n = 149; placebo, n = 67), greater proportions stopped or decreased use with continued semaglutide vs placebo (eTable 6 in Supplement 1). Corresponding data for lipid-lowering medications showed no noteworthy changes (eTable 7 in Supplement 1).

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Table 2. Changes in Efficacy End Points During the Randomized Period (Weeks 20-68; Treatment Policy Estimand; Full Analysis Set)[a]

End points	Estimated mean change (95% CI)		Difference (95% CI)[b]	*P* value
	Continued semaglutide, 2.4 mg/wk (n = 535)	Switched to placebo (n = 268)		
Primary end point				
Body weight, % change	−7.9 (−8.6 to −7.2)	6.9 (5.8 to 7.9)	−14.8 (−16.0 to −13.5)	<.001
Confirmatory secondary end points				
Waist circumference, cm	−6.4 (−7.1 to −5.7)	3.3 (2.3 to 4.3)	−9.7 (−10.9 to −8.5)	<.001
Systolic blood pressure, mm Hg	0.5 (−0.6 to 1.6)	4.4 (2.9 to 6.0)	−3.9 (−5.8 to −2.0)	<.001
SF-36 physical functioning score[c]	1.0 (0.6 to 1.4)	−1.5 (−2.2 to −0.7)	2.5 (1.6 to 3.3)	<.001
Supportive secondary end points				
Body weight, kg	−7.1 (−7.8 to −6.5)	6.1 (5.1 to 7.0)	−13.2 (−14.3 to −12.0)	<.001
Body mass index[d]	−2.6 (−2.8 to −2.4)	2.2 (1.8 to 2.5)	−4.7 (−5.2 to −4.3)	<.001
Diastolic blood pressure, mm Hg	0.3 (−0.4 to 1.1)	0.9 (−0.4 to 2.1)	−0.6 (−2.0 to 0.9)	.46
Hemoglobin A_{1c}, %	−0.1 (−0.2 to −0.1)	0.1 (0.1 to 0.1)	−0.2 (−0.3 to −0.2)	<.001
Fasting plasma glucose, mg/dL	−0.8 (−1.7 to 0.1)	6.7 (4.9 to 8.6)	−7.5 (−9.6 to −5.4)	<.001
Fasting serum insulin, % change[e]	−18 (−22 to −14)	0 (−10 to 11)	−18 (−27 to −8)	<.001
Fasting lipid profile, % change[e]				
Total cholesterol	5 (4 to 6)	11 (10 to 13)	−6 (−8 to −4)	<.001
HDL-C	18 (17 to 20)	18 (15 to 21)	0 (−2 to 3)	.83
LDL-C	1 (−1 to 3)	8 (5 to 10)	−6 (−9 to −3)	<.001
VLDL-C	−6 (−9 to −2)	15 (7 to 23)	−18 (−24 to −11)	<.001
Free fatty acids	−18 (−27 to −7)	−14 (−24 to −4)	−5 (−20 to 13)	.59
Triglycerides	−6 (−9 to −2)	15 (7 to 23)	−18 (−24 to −11)	<.001
SF-36 scores[c]				
Physical component summary	0.8 (0.3 to 1.3)	−0.9 (−1.8 to 0.0)	1.7 (0.6 to 2.7)	.002
Mental component summary	0.1 (−0.5 to 0.7)	−3.4 (−4.3 to −2.4)	3.4 (2.3 to 4.6)	<.001
Participants who gained weight, No. (%)[f]	79 (15.2)	206 (82.4)	0.0 (0.0 to 0.1)	<.001

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol.

SI conversions: To convert HDL-C, LDL-C, and total cholesterol to millimoles per liter, multiply by 0.0259. To convert glucose to millimoles per liter, multiply by 0.055. To convert triglycerides to millimoles per liter, multiply by 0.0113.

[a] The treatment policy estimand assessed the treatment effect regardless of treatment discontinuation or rescue intervention using analysis of covariance, with randomized treatment as a factor and baseline end point value as a covariate, and a multiple imputation approach for missing data.[10] Analyses were not controlled for multiple comparisons, except for changes in body weight (percent change), waist circumference, systolic blood pressure, and SF-36 physical functioning scores. eTable 5 in Supplement 1 shows 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).

[b] Data are absolute differences between estimated mean changes unless stated otherwise. The differences between mean percent changes in body weight, fasting serum insulin, and fasting lipid profile and mean changes in hemoglobin A_{1c} are expressed in percentage points.

[c] The Short Form 36 Version 2 Health Survey, Acute Version (SF-36) measures health-related quality of life and general health status. The SF-36 scores are norm-based scores, ie, scores transformed to a scale in which the 2009 US general population has a mean score of 50 and an SD of 10. The range of lowest to highest scores for the physical functioning domain is 19.03 to 57.60, for the physical component summary it is 6.11 to 79.67, and for the mental component summary it is −3.83 to 78.75. An increase in score represents an improvement in health status. Further information on the SF-36 is provided in eAppendix 3 in Supplement 1.

[d] Calculated as weight in kilograms divided by height in meters squared.

[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 percent change and estimated relative percent difference between groups, respectively, and were calculated using the formula (estimated ratio − 1) × 100.

[f] Data are observed proportions of participants who gained weight from week 20 to week 68, and estimated odds ratio (95% CI).

Changes Over the Entire Trial Period

For the treatment policy (tertiary) estimand, the estimated mean body weight change from week 0 to week 68 was −17.4% with continued semaglutide vs −5.0% with placebo (difference, −12.4 [95% CI, −13.7 to −11.0] percentage points) (Figure 2C; see eFigure 8 in Supplement 1 for cumulative distribution plot). For the trial product (quaternary) estimand, corresponding changes were −18.2% vs −5.2% (difference, −13.0 [95% CI, −14.3 to −11.7] percentage points).

The observed proportions of participants achieving 5% or more, 10% or more, 15% or more, and 20% or more body weight loss from week 0 to week 68 with continued semaglutide vs placebo were 88.7% vs 47.6%, 79.0% vs 20.4%, 63.7% vs 9.2%, and 39.6% vs 4.8%, respectively (Figure 2D; eFigure 9 in Supplement 1).

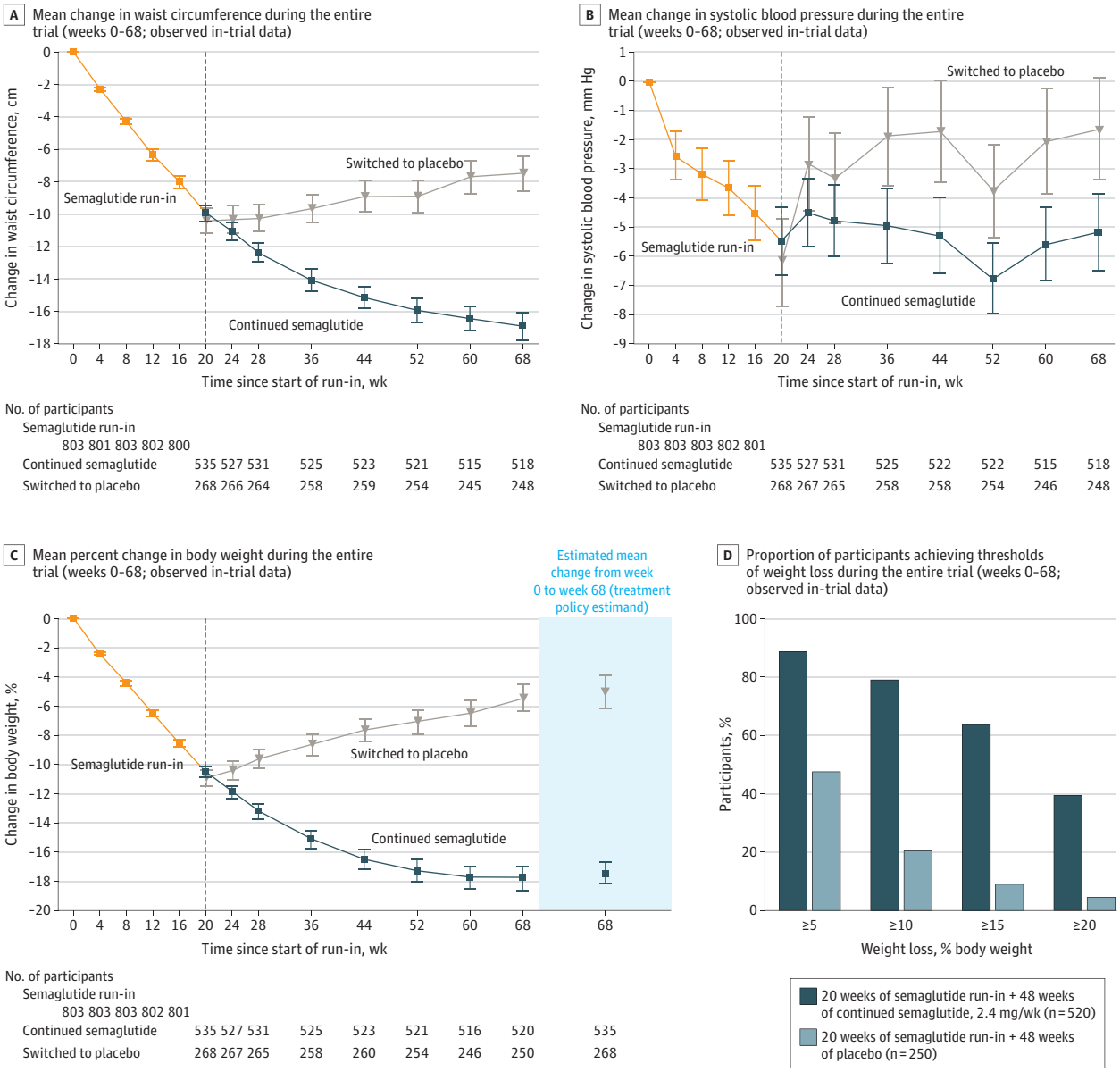
Adverse Events and Tolerability

During the run-in period, 84.3% of participants reported adverse events, with gastrointestinal tract disorders reported by 71.4% (eTable 8 in Supplement 1). In the randomized period, the proportions of those reporting new adverse events were 81.3% and 75.0% with continued semaglutide and placebo, respectively (**Table 3**). Gastrointestinal tract disorders were reported most frequently and in greater proportions with

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Figure 2. Effect of Semaglutide, 2.4 mg Once Weekly, Compared With Placebo on Efficacy Outcomes During the Entire Trial (Full Analysis Set)



Data presented in panels A, B, and C are observed data for the full analysis set from the in-trial period (the time from week 0 to the date of last contact with trial site). Error bars represent 95% confidence intervals for the mean. Participant numbers shown denote those contributing to the mean. The dashed vertical line at week 20 represents the randomization time point. Data in the shaded area on the right in panel C are estimated mean changes from week 0 to week 68 for the treatment policy estimand, analyzed using the full analysis set. (The treatment policy estimand assessed the treatment effect regardless of treatment discontinuation or rescue intervention using analysis of covariance, with randomized treatment as a factor and baseline end point value as a covariate, and a multiple imputation approach for missing data.[10]) Data in panel D are observed data among all randomized participants with a week 68 assessment from the in-trial period (the time from week 0 to the date of last contact with trial site).

continued semaglutide than placebo (41.9% vs 26.1%, respectively) (Table 3). Most gastrointestinal events were mild to moderate in severity, and the majority of participants recovered without treatment discontinuation.

Serious adverse events were reported in 2.3% of participants during the run-in period (eTable 8 in Supplement 1) and in 7.7% and 5.6% receiving continued semaglutide and placebo, respectively (Table 3). During the run-in, 5.3% of participants discontinued treatment because of adverse events, most of which were gastrointestinal tract disorders (eTable 8 in Supplement 1). In the randomized period, 2.4% and 2.2% of participants receiving continued semaglutide and placebo, respectively, discontinued treatment because of adverse events (Table 3). One death was reported in each treatment group during the randomized period, each considered unrelated to study treatment (Table 3). The death in the

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Table 3. Adverse Event and Tolerability Profile During the Randomized Period (Weeks 20-68; Safety Analysis Set)

	Continued semaglutide, 2.4 mg/wk (n = 535)			Switched to placebo (n = 268)		
Adverse events	No. (%) of participants	No. of events	Events per 100 patient-years[a]	No. (%) of participants	No. of events	Events per 100 patient-years[a]
Any adverse event	435 (81.3)	1885	346.3	201 (75.0)	779	292.8
Serious adverse events	41 (7.7)	51	9.4	15 (5.6)	19	7.1
Discontinuation of trial product due to adverse events[b]	13 (2.4)			6 (2.2)		
Fatal events[c,d]	1 (0.2)	1	0.2	1 (0.4)	2	0.7
Adverse events reported in ≥5% of participants[e]						
Diarrhea	77 (14.4)	114	20.9	19 (7.1)	26	9.8
Nausea	75 (14.0)	105	19.3	13 (4.9)	13	4.9
Constipation	62 (11.6)	75	13.8	17 (6.3)	19	7.1
Nasopharyngitis	58 (10.8)	77	14.1	39 (14.6)	54	20.3
Vomiting	55 (10.3)	88	16.2	8 (3.0)	13	4.9
Headache	41 (7.7)	48	8.8	10 (3.7)	10	3.8
Influenza	39 (7.3)	45	8.3	19 (7.1)	23	8.6
Abdominal pain	35 (6.5)	46	8.5	8 (3.0)	10	3.8
Back pain	28 (5.2)	32	5.9	18 (6.7)	19	7.1
Arthralgia	25 (4.7)	28	5.1	14 (5.2)	16	6.0
Safety areas of interest (MedDRA)[f]						
Gastrointestinal disorders	224 (41.9)	607	111.5	70 (26.1)	124	46.6
Psychiatric disorders	46 (8.6)	55	10.1	35 (13.1)	50	18.8
Cardiovascular disorders[c]	26 (4.9)	32	5.7	30 (11.2)	40	14.2
Allergic reactions	26 (4.9)	29	5.3	11 (4.1)	12	4.5
Gallbladder-related disorders	15 (2.8)	17	3.1	10 (3.7)	11	4.1
Injection site reactions	14 (2.6)	15	2.8	6 (2.2)	6	2.3
Hepatic disorders	11 (2.1)	12	2.2	4 (1.5)	4	1.5
Malignant neoplasms[c]	6 (1.1)	6	1.1	1 (0.4)	2	0.7
Hypoglycemia	3 (0.6)	3	0.6	3 (1.1)	3	1.1
Acute kidney failure	1 (0.2)	1	0.2	1 (0.4)	1	0.4
Acute pancreatitis	0			0		

[a] Events per 100 patient-years were calculated as (number of events/number of patient-years) × 100.

[b] Based on the number of participants from the full analysis set who stated that an adverse event was the reason for permanent trial intervention discontinuation on the end-of-treatment form.

[c] In-trial observation period data (time from randomization to last contact with trial site, irrespective of treatment discontinuation or rescue intervention).

[d] In the continued semaglutide group, there was 1 death in a participant with a history of chronic obstructive pulmonary disease, hypertension, and lower leg edema; the cause of death per the death certificate was "natural causes with underlying chronic obstructive pulmonary disease"; event adjudication outcome: undetermined cause. In the placebo group, there was 1 death due to malignant lung cancer and malignant pericardial effusion in a participant who had discontinued placebo.

[e] Most common adverse events by preferred term reported in 5% or more of participants in either treatment group.

[f] Identified via Medical Dictionary for Regulatory Activities (MedDRA) searches.

continued semaglutide group was attributed to natural causes with underlying chronic obstructive pulmonary disease on the death certificate; the death in the placebo group was due to metastatic lung cancer with pericardial effusion.

Gallbladder-related disorders (mostly cholelithiasis) were reported in 0.7% of participants during the run-in period and in 2.8% and 3.7% receiving continued semaglutide and placebo, respectively. Moderate acute pancreatitis was reported in 1 participant (during run-in), who recovered during the study. During the randomized period, malignant neoplasms occurred in 1.1% of participants taking continued semaglutide vs 0.4% taking placebo. Of the events in the continued semaglutide group, 3 were breast neoplasms (intraductal proliferative breast lesion, invasive breast cancer, and invasive ductal breast carcinoma), and the remaining 3 had no apparent clustering (endometrial adenocarcinoma, marginal zone lymphoma, and malignant melanoma). One event occurring in the placebo group was metastatic lung cancer. Other adverse events of special interest are described in Table 3 and in eTable 8 in Supplement 1.

Discussion

In this multicenter, randomized clinical trial, adults with obesity/overweight who continued once-weekly treatment with subcutaneous semaglutide, 2.4 mg, had ongoing and persistent weight loss vs participants who switched to placebo, who gained weight. Continued semaglutide also produced significantly better outcomes for waist circumference, systolic blood pressure, and SF-36 physical functioning scores vs placebo.

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In those who continued semaglutide after randomization, weight loss achieved during the run-in period not only was sustained but continued, reaching a plateau at week 60 to week 68 and ultimately resulting in an estimated reduction of 17.4% over the entire trial. In contrast, participants who switched to placebo at week 20 gradually regained weight. The benefits of continuing semaglutide treatment for 68 weeks, rather than switching to placebo after 20 weeks, are consistent with findings from other withdrawal trials of antiobesity medications.[23,24] These results emphasize the chronicity of obesity and the need for treatments that can maintain and maximize weight loss.

The significant and sustained weight loss demonstrated with continued semaglutide in this study was accompanied by sustained improvement in waist circumference, lipid profiles, and glucose metabolism, all of which are cardiometabolic risk factors. Sustained weight loss of a similar magnitude to that observed in this trial has been linked to improvements in obesity-related complications,[25-27] such as type 2 diabetes,[28] with treatment guidelines recommending sustained weight loss of 5% to 15% for people with these conditions.[5,6] The sustained effects of semaglutide on body weight and cardiometabolic risk factors, as well as participants' physical and mental functioning, indicate the potential for positive effects on such obesity-related complications.

The optimization and maintenance of weight loss are key goals of obesity management, but individuals can vary in their response to treatment[29]; it is therefore of clinical interest to examine the proportions of people achieving clinically relevant weight loss to support applicability in nonresearch clinical settings.[20] In the present study, 40% of participants who continued semaglutide lost an additional 10% of body weight during the randomized period, as shown by eFigure 2B in Supplement 1, supporting its use for long-term treatment of obesity. Furthermore, 64% of those who took semaglutide for 68 weeks lost at least 15% of their week 0 body weight, targets not achieved by currently approved pharmacotherapy. For example, with the GLP-1 receptor agonist liraglutide, at a 3.0-mg/d dosage, which is approved for weight management, weight losses of 10% or more and 15% or more were achieved by 33% and 14%, respectively, among people treated for 56 weeks.[30] Furthermore, weight loss with liraglutide in clinical trials was of lesser magnitude and appeared to plateau earlier (at 20 weeks[31] or 40 weeks[30]) than with semaglutide in the present trial (at 60-68 weeks). Given the modest efficacy of currently approved pharmacotherapies,[7-9] semaglutide may offer the potential to bridge the gap between behavioral and pharmacological options and bariatric surgery, which is currently considered the most effective and reliable intervention available for weight management.[6,27,32] For example, 40% of participants in this trial who took semaglutide for 68 weeks lost 20% or more of their initial body weight, approaching the level of weight loss seen with sleeve gastrectomy.[27,33]

Although a higher maintenance dosage of semaglutide (2.4 mg/wk) was used in this trial, the adverse event profile and tolerability were consistent with data from a phase 2 study in people with obesity[14] and semaglutide trials in patients with type 2 diabetes using lower maintenance dosages (up to 1.0 mg/wk),[34] as well as with that reported for other GLP-1 receptor agonists,[35] with no new concerns. Typical of this class, transient, mild to moderate gastrointestinal tract disorders were the most frequently reported adverse events. More of these events occurred during the run-in period, when semaglutide was escalated to the target dose, compared with the randomized period, despite the randomized period being twice as long. Over the entire trial, few participants in either group discontinued treatment because of adverse events, with the majority of participants who continued semaglutide and completed treatment receiving the 2.4-mg dose at week 68. These results indicate that most participants tolerated the strict up-titration schedule in the trial, and those who continued treatment at the 2.4-mg/wk dose beyond 20 weeks were unlikely to experience significant tolerability challenges thereafter.

The withdrawal design was a strength of the study, as participants receiving the experimental treatment continued to do so only if they achieved a desired target,[36] while also enabling study of the withdrawal effect in participants who switched to placebo. Additional strengths of the study include the large sample size, blinded design, and high rates of treatment regimen and trial completion. The high treatment and trial completion rates were likely a result of multiple factors, including a focus on participant retention, selection of a population who could tolerate semaglutide during run-in, and inclusion of participants who had previously attempted to lose weight and so were likely motivated to continue in the trial following weight loss in the run-in period.

Limitations

This study has several limitations. First, there was inflexibility in the run-in period, which limited assessment to only participants tolerating the strict dose titration schedule, unlike how the medication might be used in clinical practice, with some patients not tolerating the medication after it is prescribed. The run-in period, as well as the trial setting, likely resulted in a study population who was both more tolerant of semaglutide and more adherent to medication use than would be the case in a typical setting. Because of this, the average effect size in clinical use is likely to be less than was seen in this trial. Second, there was no assessment of adherence to lifestyle interventions. Third, while the withdrawal design is a strength, it can also result in selection bias and favorable carryover effects to the randomized period, potentially resulting in overestimation of weight loss with continued semaglutide compared with what would be expected in a typical individual. To lessen any potential effect of the long half-life of semaglutide on adverse event reporting, adverse events were counted only during the randomized period if onset was after randomization.

Conclusions

Among adults with overweight or obesity who completed a 20-week run-in period with subcutaneous semaglutide, 2.4 mg once weekly, maintaining treatment with semaglutide compared with switching to placebo resulted in continued weight loss over the following 48 weeks.

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Author Contributions: Drs Rubino and Dicker 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.
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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Rubino, Abrahamsson, Rubio, Tadayon, Wadden, Dicker.
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