ORIGINAL ARTICLE

Once-Weekly Semaglutide in Adolescents with Obesity

Daniel Weghuber, M.D., Timothy Barrett, Ph.D., Margarita Barrientos-Pérez, M.D., Inge Gies, Ph.D., Dan Hesse, Ph.D., Ole K. Jeppesen, M.Sc., Aaron S. Kelly, Ph.D., Lucy D. Mastrandrea, M.D., Rasmus Sørrig, Ph.D., and Silva Arslanian, M.D., for the STEP TEENS Investigators*

ABSTRACT

BACKGROUND

A once-weekly, 2.4-mg dose of subcutaneous semaglutide, a glucagon-like peptide-1 receptor agonist, is used to treat obesity in adults, but assessment of the drug in adolescents has been lacking.

METHODS

In this double-blind, parallel-group, randomized, placebo-controlled trial, we enrolled adolescents (12 to <18 years of age) with obesity (a body-mass index [BMI] in the 95th percentile or higher) or with overweight (a BMI in the 85th percentile or higher) and at least one weight-related coexisting condition. Participants were randomly assigned in a 2:1 ratio to receive once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo for 68 weeks, plus lifestyle intervention. The primary end point was the percentage change in BMI from baseline to week 68; the secondary confirmatory end point was weight loss of at least 5% at week 68.

RESULTS

A total of 201 participants underwent randomization, and 180 (90%) completed treatment. All but one of the participants had obesity. The mean change in BMI from baseline to week 68 was –16.1% with semaglutide and 0.6% with placebo (estimated difference, –16.7 percentage points; 95% confidence interval [CI], –20.3 to –13.2; P<0.001). At week 68, a total of 95 of 131 participants (73%) in the semaglutide group had weight loss of 5% or more, as compared with 11 of 62 participants (18%) in the placebo group (estimated odds ratio, 14.0; 95% CI, 6.3 to 31.0; P<0.001). Reductions in body weight and improvement with respect to cardiometabolic risk factors (waist circumference and levels of glycated hemoglobin, lipids [except high-density lipoprotein cholesterol], and alanine aminotransferase) were greater with semaglutide than with placebo. The incidence of gastrointestinal adverse events was greater with semaglutide than with placebo (62% vs. 42%). Five participants (4%) in the semaglutide group and no participants in the placebo group had cholelithiasis. Serious adverse events were reported in 15 of 133 participants (11%) in the semaglutide group and in 6 of 67 participants (9%) in the placebo group.

CONCLUSIONS

Among adolescents with obesity, once-weekly treatment with a 2.4-mg dose of semaglutide plus lifestyle intervention resulted in a greater reduction in BMI than lifestyle intervention alone. (Funded by Novo Nordisk; STEP TEENS ClinicalTrials.gov number, NCT04102189.)

From the Department of Pediatrics, Paracelsus Medical University, Salzburg, Austria (D.W.); the Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, United Kingdom (T.B.); the Division of Pediatric Endocrinology, Hospital Ángeles Puebla, Puebla City, Mexico (M.B.-P.); the Department of Pediatrics, Division of Pediatric Endocrinology, Universitair Ziekenhuis Brussel, Brussels (I.G.); Novo Nordisk, Søborg, Denmark (D.H., O.K.J., R.S.); the Department of Pediatrics and the Center for Pediatric Obesity Medicine, University of Minnesota Medical School, Minneapolis (A.S.K.); the Division of Pediatric Endocrinology and Diabetes, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY (L.D.M.); and the Center for Pediatric Research in Obesity and Metabolism, Division of Pediatric Endocrinology, Diabetes, and Metabolism, University of Pittsburgh School of Medicine, and UPMC Children's Hospital of Pittsburgh, Pittsburgh (S.A.). Dr. Weghuber can be contacted at d.weghuber@salk.at or at the Department of Pediatrics, Paracelsus Medical University, Müllner Hauptstrasse 48, 5020 Salzburg, Austria.

*A complete list of investigators in the STEP TEENS trial is provided in the Supplementary Appendix, available at NEJM.org.

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Among children and adolescents with obesity (a chronic, progressive disease), other conditions such as dysglycemia, hypertension, dyslipidemia, nonalcoholic fatty liver disease, and obstructive sleep apnea may develop, alongside impairment in mental health and quality of life.[1-3] It is predicted that more than 250 million children and adolescents will have obesity by 2030.[4]

For young people, obesity-management guidelines recommend multimodal lifestyle modification.[5-9] However, resulting reductions in body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) are generally modest, and long-term weight maintenance is challenging and rarely achieved.[7,10] Pharmacotherapy may be considered if lifestyle intervention alone is ineffective,[5,9] but options are limited.[9,11] The Food and Drug Administration has approved once-daily liraglutide (3.0 mg), orlistat (120 mg), and phentermine–topiramate (7.5 mg of phentermine with 46 mg of topiramate or 15 mg of phentermine with 92 mg of topiramate) for adolescents at least 12 years of age[12-14]; only liraglutide is approved by the European Medicines Agency.[15]

Semaglutide is a glucagon-like peptide-1 analogue that induces weight loss by decreasing appetite, thereby improving control of eating and reducing energy intake.[16] Among adults with overweight or obesity, once-weekly treatment with subcutaneous semaglutide at a dose of 2.4 mg plus lifestyle intervention elicited clinically meaningful weight loss and improvement with respect to cardiometabolic risk factors and participant-reported physical functioning.[17] Semaglutide at a dose of 2.4 mg is approved for long-term weight management as an adjunct to a reduced-calorie diet and increased physical activity for adults with obesity or for adults with overweight who have weight-related coexisting conditions.[18,19] The Semaglutide Treatment Effect in People with Obesity (STEP) TEENS trial assessed the efficacy and safety of once-weekly subcutaneous semaglutide plus lifestyle intervention among adolescents with obesity.

METHODS

TRIAL DESIGN AND OVERSIGHT

This multinational, double-blind, parallel-group, randomized, placebo-controlled, phase 3a clinical trial was conducted at 37 sites from October 2019 through March 2022. The trial was performed in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and all applicable laws and regulations. Institutional review boards and independent ethics committees at each site approved the protocol and amendments (available with the full text of this article at NEJM.org). Before the start of trial-related activities, written informed consent was obtained from the parents or legal guardians, and written or oral assent was obtained from the participants. An independent external data and safety monitoring committee (the members of which were aware of the trial-group assignments) monitored safety throughout the trial.

The sponsor (Novo Nordisk) designed the trial and oversaw its conduct. The investigators were responsible for collection of the data, and the sponsor performed site monitoring and collation and analysis of the data. The authors had full access to all trial data, participated in writing the first draft of the manuscript (with assistance from medical writers funded by the sponsor, who wrote the first draft under the direction of the authors), agreed to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PROCEDURES

After screening, participants entered a 12-week lifestyle intervention run-in phase according to regulatory guidelines.[20,21] At baseline (after the end of the run-in phase), eligible participants were randomly assigned, in a 2:1 ratio, to receive once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or matching placebo for 68 weeks; this treatment period was followed by a 7-week follow-up period during which the participants did not receive semaglutide or placebo (Fig. S1 in the Supplementary Appendix). Randomization was performed with the use of an interactive Web-response system, with stratification according to sex and pubertal status (Tanner stage 2 or 3 [early puberty] vs. Tanner stage 4 [late puberty] or 5 [adult-level maturity]). The dose of semaglutide was escalated over a period of 16 weeks from 0.25 mg to 2.4 mg or to the maximum dose that did not cause unacceptable adverse events. All the participants and parents or guardians

received behavioral lifestyle therapy (defined as counseling about healthy nutrition and physical activity for weight loss) throughout the trial. Participants who prematurely discontinued semaglutide or placebo were asked to attend the remaining trial visits. The dose-escalation schedule and details of the lifestyle intervention are provided in the Supplementary Appendix.

PARTICIPANTS

For the run-in phase, eligible participants were adolescents (12 to <18 years of age) with a BMI in the 95th percentile or higher (according to sex- and age-specific growth charts[22]); those with a BMI in the 85th percentile or higher who had at least one weight-related coexisting condition were also eligible. All the participants were required to have had at least one unsuccessful dietary weight-loss effort. These BMI criteria were also used to determine eligibility for randomization. Participants who completed the run-in phase but did not meet the BMI randomization criteria were considered to have been found ineligible at screening. In order to participate, persons with type 2 diabetes needed to be treated with diet and exercise alone or with metformin and to have a glycated hemoglobin level of 10.0% or less (≤86 mmol per mole).

Exclusion criteria were a weight change of more than 5 kg or use of a medication for obesity within 90 days before screening, previous bariatric surgery, uncontrolled thyroid disease, presence of secondary causes of obesity, major depressive disorder within 2 years before screening, diagnosis of severe psychiatric disorders or bulimia nervosa, and history of suicide attempt. Full eligibility criteria are provided in the Supplementary Appendix.

END POINTS AND ASSESSMENTS

A complete list of trial end points is provided in the Supplementary Appendix. Efficacy end points were assessed from baseline (the time of randomization [week 0]) to week 68, unless otherwise stated. The primary end point was the percentage change in BMI, and the secondary confirmatory end point was a reduction in body weight of at least 5%.

Selected secondary supportive efficacy end points not included in the statistical testing hierarchy were the changes in body weight (expressed as percentages and kilograms), BMI, BMI as a percentage of the 95th percentile (a measure of the exact percentage above the 95th percentile for a given age and sex) according to sex- and age-specific growth charts,[22] BMI standard-deviation score,[23] waist circumference, blood pressure, glycated hemoglobin level, lipid levels, and alanine aminotransferase (ALT) level; a BMI reduction of at least 5%; and a reduction in body weight of at least 10%, at least 15%, and at least 20%. Exploratory end points were the percentage change in BMI at week 75 and the change in the score on the Impact of Weight on Quality of Life–Kids (IWQOL-Kids) questionnaire (scores range from 0 to 100, with a score of 100 indicating the best possible quality of life).[24]

Secondary safety end points included changes from baseline to week 68 in the heart rate, amylase levels, lipase levels, and calcitonin levels and adverse events that occurred between baseline and week 75. An exploratory safety end point was mental health, assessed with the use of the Patient Health Questionnaire 9-item version (PHQ-9)[25] and the Columbia–Suicide Severity Rating Scale (C-SSRS).[26]

STATISTICAL ANALYSIS

The trial was designed to test the superiority of semaglutide to placebo with respect to the primary end point and secondary confirmatory end point with the use of a hierarchical testing strategy (Table S1). Superiority with respect to the primary end point (defined as a two-sided P value of <0.05) was required before the secondary confirmatory end point could be tested. A sample of 192 participants provided 90% power to detect superiority with respect to the primary end point and 72% power to detect superiority with respect to the secondary confirmatory end point.

Efficacy analyses were performed in the full analysis population (all participants who had undergone randomization) according to the intention-to-treat principle. Safety end points were assessed in the safety analysis population (all participants who had undergone randomization and were exposed to at least one dose of semaglutide or placebo). Observation periods included the in-trial period (the time from randomization to the last contact with a trial site, regardless of discontinuation of semaglutide or placebo or the use of rescue interventions [i.e., other medications for obesity or bariatric surgery]) and the on-treatment period (the time from the first dose of sema-

glutide or placebo to 14 days after the last dose for efficacy analyses, or the time from the first dose to 49 days after the last dose for the safety analyses, excluding any temporary interruptions).

For all estimated between-group differences, two-sided 95% confidence intervals were calculated; P values are reported only for the primary end point and secondary confirmatory end point. Analyses of secondary supportive end points and exploratory end points were not controlled for multiplicity, and findings for these end points should not be used to infer definitive treatment effects. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Semaglutide (N=134)	Placebo (N=67)	Total (N=201)
Sex — no. (%)			
Male	50 (37)	26 (39)	76 (38)
Female	84 (63)	41 (61)	125 (62)
Age — yr	15.5±1.5	15.3±1.6	15.4±1.6
Age group — no. (%)			
12 to <15	47 (35)	25 (37)	72 (36)
15 to <18	87 (65)	42 (63)	129 (64)
Race — no. (%)†			
Asian	3 (2)	1 (1)	4 (2)
Black	11 (8)	5 (7)	16 (8)
White	104 (78)	55 (82)	159 (79)
Other	16 (12)	6 (9)	22 (11)
Hispanic or Latino ethnic group — no. (%)†	14 (10)	8 (12)	22 (11)
Tanner stage — no. (%)‡			
2	3 (2)	5 (7)	8 (4)
3	11 (8)	3 (4)	14 (7)
4	40 (30)	14 (21)	54 (27)
5	80 (60)	45 (67)	125 (62)
Height — cm	170.1±9.4	168.8±10.6	169.7±9.8
Body weight — kg	109.9±25.2	102.6±22.3	107.5±24.5
BMI§			
Mean	37.7±6.7	35.7±5.4	37.0±6.4
Percentage of 95th percentile	133.8±22.7	127.8±17.6	131.8±21.2
Standard-deviation score	3.39±0.92	3.15±0.71	3.31±0.86
Waist circumference — cm	111.9±16.9	107.3±13.4	110.4±16.0
Glycated hemoglobin level — %	5.5±0.4	5.5±0.4	5.5±0.4
Blood pressure — mm Hg			
Systolic	120±11	120±12	120±11
Diastolic	73±9	73±9	73±9
Geometric mean lipid levels — mg/dl			
HDL cholesterol	43.7	43.3	43.5
Coefficient of variation	23.1	22.2	22.8
Triglycerides	111.3	108.1	110.2
Coefficient of variation	47.5	48.7	47.8

Table 1. (Continued.)

Characteristic	Semaglutide (N=134)	Placebo (N=67)	Total (N=201)
Geometric mean ALT level — U/liter	23	20	22
Coefficient of variation	69.9	70.8	70.7
IWQOL-Kids questionnaire total score¶	84.2±15.0	83.5±14.6	84.0±14.8

* Plus–minus values are means ±SD. For most variables, the last available and eligible observation made at or before the randomization visit (week 0) was selected for assessment, except for age, which was determined as the age on the date of informed consent. Data for blood pressure, lipid levels, alanine aminotransferase (ALT) levels, and the Impact of Weight on Quality of Life–Kids (IWQOL-Kids) questionnaire were obtained at week 0. To convert values for high-density lipoprotein (HDL) cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.01129. Coefficient of variation values are expressed as percentages. Percentages may not total 100 because of rounding.

† Race and ethnic group were reported by the participants. The category of "other" includes American Indian or Alaska Native, Native Hawaiian, or other Pacific Islander.

‡ Tanner stages 2 and 3 indicate early puberty, stage 4 indicates late puberty, and stage 5 indicates adult-level maturity.

§ Body-mass index (BMI) percentiles were assessed on the basis of sex- and age-specific growth charts.[22] The BMI as a percentage of the 95th percentile is a measure of the exact percentage above the 95th percentile for a given age and sex. The BMI standard-deviation scores were calculated with the use of growth reference data for children and adolescents (5 to 19 years of age) from the World Health Organization.[23]

¶ Total scores on the IWQOL-Kids questionnaire range from 0 to 100, with a score of 100 indicating the best possible quality of life.[24]

Treatment efficacy was assessed with the use of two estimands.[27] The treatment policy estimand (the primary estimand used in all statistical testing) was used to assess treatment efficacy in the full analysis population, regardless of adherence to the assigned regimen or the use of rescue interventions; analyses for the treatment policy estimand were conducted in accordance with the statistical analysis plan, with missing data imputed with the use of a multiple-imputation method.[28] The trial product estimand (secondary estimand) was used to assess treatment efficacy in the full analysis population under the assumption that the participants received the assigned regimen without the use of rescue interventions. Details regarding the analysis methods are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

Of the 229 participants who were screened from October 2019 through July 2020, a total of 201 underwent randomization: 134 participants were assigned to the semaglutide group, and 67 were assigned to the placebo group (Fig. S2). Three participants were randomly assigned in error but were included in the full analysis population (see the Supplementary Results section in the Supplementary Appendix). A total of 132 participants (99%) in the semaglutide group and 64 (96%) in the placebo group completed the trial; at week 68, treatment had been completed by 120 participants (90%) in the semaglutide group and 60 participants (90%) in the placebo group. One participant (in the semaglutide group) received phentermine after treatment discontinuation. Of the participants who completed treatment with semaglutide, 87% completed the trial at the 2.4-mg dose level (Fig. S3).

Baseline characteristics were similar in the two trial groups, except for body weight, BMI, and waist circumference, which were slightly greater in the semaglutide group than in the placebo group (Table 1 and Table S2). Most participants were girls (62%) and were White (79%); the mean age was 15.4 years, the mean body weight was 107.5 kg, and the mean BMI was 37.0. The representativeness of the trial population is described in Table S3. A minority of participants had hypertension (13%) or type 2 diabetes (4%) at baseline. Statements regarding adolescents with overweight are not possible, given that only one participant (in the semaglutide group) had overweight.

EFFICACY OUTCOMES

BMI and Body Weight

For the treatment policy estimand, the estimated mean percentage change in BMI from baseline to week 68 was –16.1% with semaglutide and 0.6%

with placebo (estimated difference, –16.7 percentage points; 95% confidence interval [CI], –20.3 to –13.2; P<0.001) (Table 2, Fig. 1, and Fig. S4). At week 75 (7 weeks after the end of the planned on-treatment period but during the time when participants were still receiving lifestyle intervention), the BMI remained below the baseline value in the semaglutide group and above the baseline value in the placebo group (change from baseline, –13.2% in the semaglutide group and 1.2% in the placebo group; estimated difference, –14.4 percentage points; 95% CI, –17.8 to –11.0). Participants were more likely to lose at least 5% of their baseline body weight with semaglutide than with placebo: 73% of the participants in the semaglutide group lost at least 5% of their

Table 2. End Points at Week 68 (Treatment Policy Estimand).*

End Point	Semaglutide (N=134)	Placebo (N=67)	Difference, Semaglutide vs. Placebo (95% CI)†	P Value
Primary end point				
Change in BMI — %	–16.1	0.6	–16.7 (–20.3 to –13.2)	<0.001
Secondary confirmatory end point				
≥5% reduction in body weight — no. of participants/total no. (%)‡	95/131 (73)	11/62 (18)	14.0 (6.3 to 31.0)	<0.001
Secondary supportive end points				
Change in BMI	–5.8	0.1	–6.0 (–7.3 to –4.6)	
Change in BMI as percentage of 95th percentile — percentage points§	–24.6	–4.2	–20.4 (–25.0 to –15.8)	
Change in BMI standard-deviation score¶	–1.1	–0.1	–1.0 (–1.3 to –0.8)	
BMI reduction of ≥5% — no. of participants/total no. (%)‡	99/131 (76)	14/62 (23)	13.8 (6.3 to 30.0)	
Change in body weight				
Absolute change — kg	–15.3	2.4	–17.7 (–21.8 to –13.7)	
Relative change — %	–14.7	2.7	–17.4 (–21.1 to –13.7)	
Reduction in body weight — no. of participants/total no. (%)‡				
≥10% reduction	81/131 (62)	5/62 (8)	23.0 (8.3 to 63.7)	
≥15% reduction	70/131 (53)	3/62 (5)	25.8 (7.6 to 88.0)	
≥20% reduction	49/131 (37)	2/62 (3)	20.0 (4.6 to 86.3)	
Change in waist circumference — cm	–12.7	–0.6	–12.1 (–15.6 to –8.7)	
Change in glycated hemoglobin level — percentage points				
Participants without type 2 diabetes‖	–0.4	–0.1	–0.2 (–0.3 to –0.1)	
All participants**	–0.4	–0.1	–0.3 (–0.3 to –0.2)	
Change in blood pressure — mm Hg				
Systolic	–2.7	–0.8	–1.9 (–5.0 to 1.1)	
Diastolic	–1.4	–0.8	–0.6 (–3.0 to 1.8)	
Percentage change in lipid levels††				
Total cholesterol	–8.3	–1.3	–7.1 (–10.5 to –3.5)	
HDL cholesterol	8.0	3.2	4.7 (–1.0 to 10.7)	
LDL cholesterol	–10.2	–3.4	–7.0 (–11.9 to –1.8)	
VLDL cholesterol	–28.4	1.6	–29.5 (–37.3 to –20.8)	
Triglycerides	–28.4	2.6	–30.2 (–38.0 to –21.5)	
Percentage change in ALT level††	–18.3	–4.9	–14.1 (–25.2 to –1.4)	

Table 2. (Continued.)

End Point	Semaglutide (N=134)	Placebo (N=67)	Difference, Semaglutide vs. Placebo (95% CI)†	P Value
Exploratory end points				
Change in IWQOL-Kids questionnaire scores — points				
Physical comfort domain	6.4	–0.3	6.6 (2.0 to 11.2)	
Body esteem domain	9.3	5.4	3.9 (–1.9 to 9.8)	
Social life domain	2.4	–0.7	3.1 (–1.8 to 7.9)	
Family relations domain	0.9	–2.6	3.4 (–0.3 to 7.1)	
Total score	5.3	1.0	4.3 (0.2 to 8.3)	

* Shown are estimated data for the full analysis population for the treatment policy estimand, which was used to assess treatment efficacy in all participants who had undergone randomization, regardless of adherence to the assigned regimen or the use of rescue interventions (i.e., other medications for obesity or bariatric surgery). The analyses were performed on the basis of data from the in-trial observation period (the time from randomization to the last contact with a trial site, regardless of discontinuation of the assigned regimen or the use of rescue interventions). Continuous end points were assessed with the use of analysis of covariance, with trial group and stratification group (sex and Tanner stage and the interactions of these terms) as factors and the baseline value of the end-point measure of interest as a covariate; categorical end points were analyzed with the use of logistic regression, with the same factors and covariate. A multiple-imputation approach was used for missing data. Analyses were not controlled for multiple comparisons, with the exception of analyses of the primary end point and the secondary confirmatory end point. Corresponding data for the trial product estimand (which was used to assess treatment efficacy under the assumption that participants received the assigned regimen for 68 weeks without the use of rescue interventions) are shown in Table S4 in the Supplementary Appendix. LDL denotes low-density lipoprotein and VLDL very-low-density lipoprotein.

† Data are the absolute differences between the estimated mean changes unless otherwise noted. The differences between mean percentage changes in BMI and body weight are expressed in percentage points.

‡ Data are the observed numbers and percentages of participants at week 68 for the in-trial period, and the difference is the estimated odds ratios for the treatment policy estimand.

§ BMI percentiles were assessed on the basis of sex- and age-specific growth charts.[22] The BMI as a percentage of the 95th percentile is a measure of the exact percentage above the 95th percentile for a given age and sex.

¶ BMI standard-deviation scores were calculated with the use of growth reference data for children and adolescents (5 to 19 years of age) from the World Health Organization.[23]

‖ Data are shown for the 129 participants in the semaglutide group and the 64 participants in the placebo group who did not have type 2 diabetes at baseline.

** Data are shown for all participants, regardless of type 2 diabetes status at baseline.

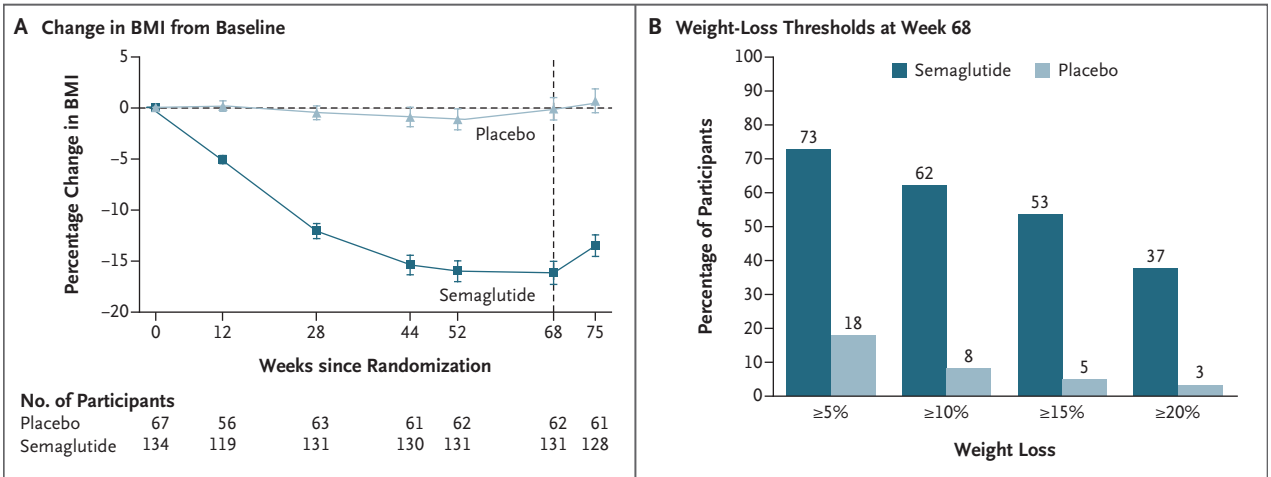
†† These measures were initially analyzed on a log scale as an estimated ratio to the baseline value (within trial groups) and estimated treatment ratios (between trial groups). For interpretation, the ratios to the baseline value are expressed as relative percentage changes and the treatment ratios are expressed as estimated relative percentage differences between groups and were calculated with the use of the following formula: (estimated ratio – 1) × 100.

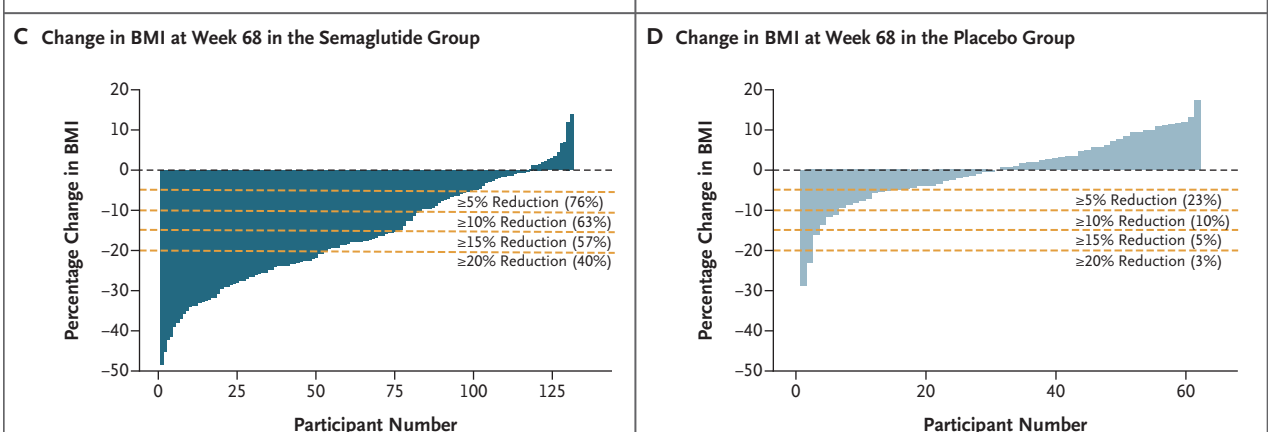
body weight, as compared with 18% of the participants in the placebo group (estimated odds ratio, 14.0; 95% CI, 6.3 to 31.0; P<0.001) (Table 2 and Fig. 1). Findings were similar for the trial product estimand (Table S4 and Fig. S5).

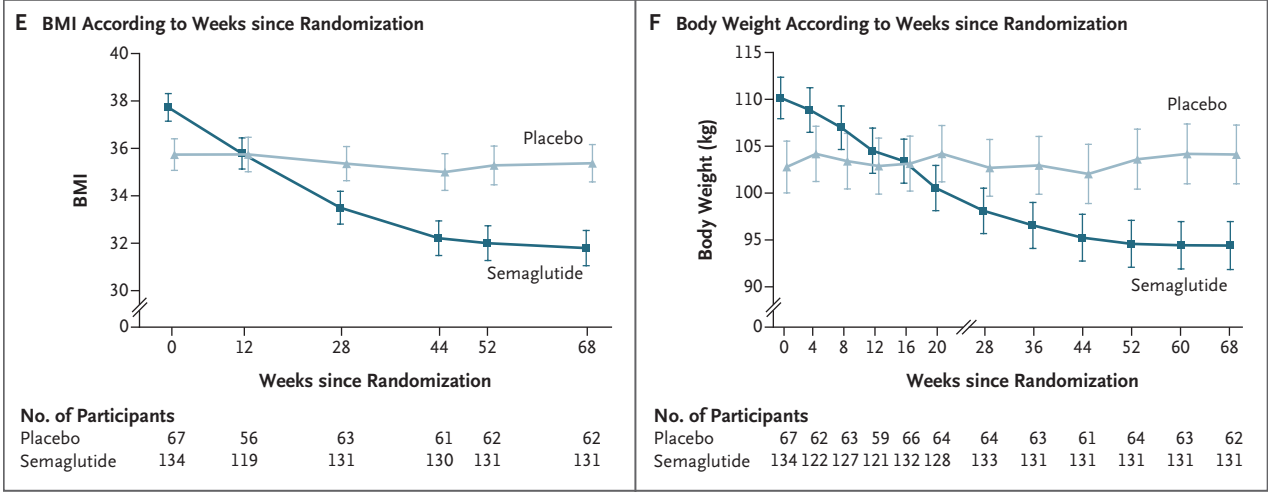
For the treatment policy estimand, semaglutide resulted in greater decreases than placebo in absolute BMI, in BMI as a percentage of the 95th percentile, in absolute body weight, and in percentage body weight at week 68 (Table 2 and Fig. 1). A reduction in BMI of at least 5% occurred in 76% of the participants in the semaglutide group and in 23% in the placebo group. A loss of body weight of at least 10% occurred in 62% of the participants in the semaglutide group and in 8% in the placebo group; a loss of at least 15% occurred in 53% and 5%, respectively; and a loss of at least 20% occurred in 37% and 3%, respectively (Table 2 and Fig. 1). Findings were similar for the trial product estimand.

Cardiometabolic Risk Factors

At week 68, waist circumference, glycated hemoglobin levels (among all participants with the exclusion of those with type 2 diabetes), total cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, triglycerides, and ALT levels were lower with semaglutide than with placebo. In the analysis for the treatment policy estimand, there were no significant between-group differences in changes in blood pressure or high-density lipoprotein cholesterol (Table 2). Findings were similar for the trial product estimand, with the exception that systolic blood







pressure was lower with semaglutide than with placebo.

Weight-Related Quality of Life

For the treatment policy estimand, semaglutide was associated with improvements in IWQOL-Kids total score and the physical comfort domain score at week 68 (Table 2). The improvement in the total score was driven mainly by the change in the physical comfort domain score. No differences between groups were observed for the other IWQOL-Kids domain scores for the treatment

Figure 1 (facing page). BMI and Body-Weight Measures in the Full Analysis Population.

The full analysis population included all participants who had undergone randomization. Data shown are the observed data from the in-trial observation period (the time from randomization to the last contact with a trial site, regardless of discontinuation of semaglutide or placebo or the use of rescue interventions [i.e., other medications for obesity or bariatric surgery]), unless otherwise indicated. Panel A shows the observed mean percentage change from baseline in body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) over time. The area to the right of the vertical dashed line represents the follow-up period, when participants were not receiving semaglutide or placebo. Panel B shows the observed percentages of participants who had body-weight reductions of at least 5%, at least 10%, at least 15%, and at least 20% from baseline to week 68. Panels C and D show waterfall plots of the observed mean percentage change in BMI from baseline to week 68 in the semaglutide group and the placebo group, respectively. Panels E and F show the observed mean BMI and body weight over time. The I bars in panels A, E, and F indicate the standard errors, and the numbers shown beneath the graphs are the participants contributing to the mean at each visit.

policy estimand or for any IWQOL-Kids domain scores for the trial product estimand (Table 2).

SAFETY

Adverse events were reported in 105 of 133 participants (79%) in the semaglutide group and in 55 of 67 (82%) in the placebo group; event rates were greater with semaglutide than with placebo (435.7 vs. 362.9 events per 100 person-years) (Table 3). Gastrointestinal disorders (primarily nausea, vomiting, and diarrhea) were the most frequent adverse events with semaglutide (occurring in 62% of participants, as compared with 42% in the placebo group) and were generally mild or moderate in severity and of short duration (median duration, 2 to 3 days for nausea, vomiting, and diarrhea in the semaglutide group) (Table 3 and Fig. S6). The prevalence of nausea, diarrhea, and vomiting with semaglutide peaked during or shortly after the 16-week dose-escalation period.

Serious adverse events were reported in 11% of the participants in the semaglutide group and in 9% in the placebo group (Table 3 and Table S5). No fatal adverse events were reported. The same percentage of participants in both groups (5%) discontinued semaglutide or placebo because of adverse events, with gastrointestinal events being the most common reason for discontinuation in the semaglutide group (Table 3).

Five participants (4%) in the semaglutide group had acute gallbladder disease (all five had cholelithiasis, one with concurrent cholecystitis); no participants in the placebo group had cholelithiasis (Table S6). An increase in amylase and lipase levels from baseline to week 68 was observed with semaglutide (Table S7), but no cases of pancreatitis were reported. No instances of acute renal failure, diabetic retinopathy, or severe hypoglycemia were reported. The heart rate increased by a mean of 1.2 beats per minute with semaglutide and decreased by a mean of 2.3 beats per minute with placebo. No other clinically relevant findings in biochemical, hematologic, or growth measures or pubertal development (Tanner stage) were noted.

PHQ-9[25] and C-SSRS[26] scores did not indicate differences in mental health between the two groups (Fig. S7). A smaller percentage of participants in the semaglutide group than in the placebo group reported psychiatric adverse events (7% vs. 15%).

DISCUSSION

In this phase 3a trial involving adolescents with obesity who were randomly assigned to receive semaglutide or placebo, each with lifestyle intervention, once-weekly subcutaneous semaglutide at a dose of 2.4 mg resulted in clinically relevant decreases in BMI and body weight, with substantially greater proportions of participants in the semaglutide group than in the placebo group reaching the 5 to 20% weight-loss thresholds. All other BMI-related and body weight–related measures were improved with semaglutide. Semaglutide was also associated with improvements with respect to cardiometabolic risk factors. In accordance with the relatively high treatment-completion rates, the results were generally similar for the two estimands. The safety of semaglutide in this adolescent population appeared to be consistent with findings among adults with overweight or obesity.[17]

The reductions in body weight and BMI observed with semaglutide were substantially greater than those reported among adolescents taking other glucagon-like peptide-1 receptor agonists and medications for obesity.[29-32] The placebo-subtracted change (i.e., the difference between

Table 3. Adverse Events.*

Event	Semaglutide (N=133)			Placebo (N=67)		
	no. of participants (%)	*no. of events*	*events/ 100 person-yr*	*no. of participants (%)*	*no. of events*	*events/ 100 person-yr*
Any adverse event	105 (79)	792	435.7	55 (82)	328	362.9
Serious adverse events	15 (11)	17	9.4	6 (9)	7	7.7
Adverse events leading to discontinuation of trial regimen	6 (5)	6	3.3	3 (4)	3	3.3
Gastrointestinal disorders	3 (2)	3	1.7	1 (1)	1	1.1
Fatal adverse events†	0	—	—	0	—	—
Adverse events reported in ≥5% of participants in either group‡						
Nausea	56 (42)	127	69.9	12 (18)	29	32.1
Vomiting	48 (36)	106	58.3	7 (10)	18	19.9
Diarrhea	29 (22)	54	29.7	13 (19)	19	21.0
Headache	22 (17)	52	28.6	11 (16)	20	22.1
Abdominal pain	20 (15)	32	17.6	4 (6)	4	4.4
Covid-19	16 (12)	17	9.4	10 (15)	10	11.1
Nasopharyngitis	16 (12)	21	11.6	7 (10)	12	13.3
Abdominal pain upper	11 (8)	19	10.5	9 (13)	12	13.3
Dizziness	10 (8)	13	7.2	2 (3)	3	3.3
Gastroenteritis	9 (7)	9	5.0	2 (3)	2	2.2
Constipation	8 (6)	8	4.4	1 (1)	1	1.1
Decreased appetite	8 (6)	8	4.4	3 (4)	4	4.4
Pyrexia	5 (4)	5	2.8	5 (7)	5	5.5
Acne	4 (3)	4	2.2	4 (6)	4	4.4
Cough	4 (3)	5	2.8	4 (6)	4	4.4
Fatigue	4 (3)	4	2.2	5 (7)	5	5.5
Contusion	2 (2)	2	1.1	5 (7)	5	5.5
Dysmenorrhea	2 (2)	3	1.7	4 (6)	7	7.7
Blood creatinine phosphokinase increased	1 (1)	1	0.6	4 (6)	4	4.4

* Safety was assessed in all participants who underwent randomization and were exposed to at least one dose of semaglutide or placebo. Shown are the observed data in the safety analysis population during the on-treatment period (the time from the first dose of semaglutide or placebo to 49 days after the last dose, excluding any temporary interruptions), unless otherwise indicated. Covid-19 denotes coronavirus disease 2019.

† Data are the observed data in the safety population from the in-trial period (the time from randomization to the last contact with a trial site, regardless of discontinuation of semaglutide or placebo or the use of rescue interventions).

‡ Adverse events are listed according to the preferred term in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 24.1.

the active drug and placebo) in BMI was −16.7 percentage points at week 68 with semaglutide, as compared with −4.6 percentage points at week 56 in the phase 3 trial of once-daily liraglutide in adolescents.[29] In addition, the placebo-subtracted change in the BMI standard-deviation score with semaglutide was −1.0 at week 68, substantially greater than the −0.2 reported at week 56 for liraglutide[29] and the −0.1 reported at week 24 for once-weekly exenatide in a small trial in adolescents.[30] Beyond glucagon-like peptide-1 receptor agonists, trials of orlistat (360 mg) in adolescents have shown relatively small placebo-subtracted changes in absolute BMI (−0.5 to

–0.9),[31] as compared with the placebo-subtracted change of –6.0 with semaglutide in this trial. In a trial of phentermine and extended-release topiramate in adolescents with obesity, the placebo-subtracted BMI reduction with the 15-mg dose of phentermine and the 92-mg dose of topiramate at week 56 (10.4 percentage points) was lower than that with semaglutide.[32] However, when considering these findings, it should be noted that these are not head-to-head comparisons, and therefore they need to be interpreted cautiously owing to differences in participant populations and durations of treatment periods as well as secular trends, such as the coronavirus disease 2019 pandemic.

The placebo-subtracted change in body weight of –17.4 percentage points with semaglutide in our trial was greater than that reported in the STEP 1 trial involving adults (–12.4 percentage points).[17] In both trials, weight loss occurred over a similar time frame, reaching a nadir at approximately 60 weeks.[17] It cannot be ruled out that the higher treatment-completion rates in this trial than in the STEP 1 trial contributed to this difference; nevertheless, the apparent difference was also observed for the trial product estimand, for which it was assumed that all participants took semaglutide or placebo as intended. The reason for this finding is currently unclear and will require further research.

Semaglutide was also associated with improvement with respect to cardiometabolic end points. These findings are clinically relevant, given that BMI, triglycerides, and total cholesterol levels have all been established as childhood risk factors associated with subsequent cardiovascular events in adulthood.[33] Furthermore, we observed an improvement in weight-related quality of life, mostly due to an improved IWQOL-Kids physical comfort domain score, which was not observed in previous trials of phentermine–topiramate or liraglutide in adolescents with obesity.[29,32]

The safety profile of semaglutide among adolescents with obesity in our trial was consistent with that observed among adults[17] and with that of the glucagon-like peptide-1 receptor agonist drug class in general.[34] No new safety concerns were identified. As expected, gastrointestinal adverse events were the most common adverse events reported in the semaglutide group and occurred more frequently than in the placebo group. However, permanent discontinuations because of gastrointestinal disorders were very low. Furthermore, semaglutide did not appear to affect growth or pubertal development during the trial period.

Strengths of the trial include the double-blind, multinational design as well as the high percentages of participants in the semaglutide group who completed the trial (99%) and completed treatment (90%), which compare favorably with shorter trials involving adolescents with obesity that assessed liraglutide (79% trial completion and 81% treatment completion)[29] and phentermine–topiramate (75% trial completion and 65% treatment completion; 70% of participants completed treatment with the 7.5-mg dose of phentermine and 46-mg dose of topiramate and 61% completed treatment with the 15-mg dose of phentermine and 92-mg dose of topiramate).[32] As compared with other trials, the focus in this trial on participant retention by the sites and the sponsor, as well as aspects of the trial design, such as flexibility in dose escalation in order to limit unacceptable adverse effects, may have facilitated adherence. Furthermore, the inclusion of a 12-week lifestyle intervention run-in phase before randomization reflects clinical practice recommendations to implement lifestyle modifications for weight loss before initiating pharmacotherapy in adolescents.[5,9] The inclusion of parents or guardians in the lifestyle intervention provided throughout the trial may also have contributed to the high completion rates, since the inclusion of parents or guardians in lifestyle counseling is known to improve weight-loss outcomes among young people.[35]

This trial had certain limitations. A longer treatment period would have provided insight into the durability of the effect of semaglutide; in adults, the effect of semaglutide persists over 2 years of treatment.[36] A longer follow-up period would have enabled the effect of treatment cessation to be monitored, considering the small BMI regain between weeks 68 and 75. Weight regain after treatment discontinuation has also been observed with liraglutide in adolescents[29] and with semaglutide in adults.[37,38] In addition, the enrolled trial population may limit the generalizability of the results, in light of the greater number of female than male participants, the relatively small proportions of some racial and ethnic groups, and the inclusion of only eight

participants with type 2 diabetes and only one with overweight. Our sample may therefore not be fully representative of the adolescent population with obesity in all countries; for example, in the United States, the prevalence of obesity among male and female adolescents is generally equal and is greater among Hispanic and Black adolescents than among White adolescents.[39] It is possible that adolescents of the racial and ethnic groups that were underrepresented in this trial may have different responses to semaglutide, and future studies should address this issue.

In adolescents with obesity, once-weekly treatment with subcutaneous semaglutide at a dose of 2.4 mg in addition to lifestyle intervention resulted in a substantial reduction in BMI as compared with lifestyle intervention alone.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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