ORIGINAL ARTICLE

Liraglutide for Children 6 to <12 Years of Age with Obesity — A Randomized Trial

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ABSTRACT

BACKGROUND

No medications are currently approved for the treatment of nonmonogenic, nonsyndromic obesity in children younger than 12 years of age. Although the use of liraglutide has been shown to induce weight loss in adults and adolescents with obesity, its safety and efficacy have not been established in children.

METHODS

In this phase 3a trial, which consisted of a 56-week treatment period and a 26-week follow-up period, we randomly assigned children (6 to <12 years of age) with obesity, in a 2:1 ratio, to receive either once-daily subcutaneous liraglutide at a dose of 3.0 mg (or the maximum tolerated dose) or placebo, plus lifestyle interventions. The primary end point was the percentage change in the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters). The confirmatory secondary end points were the percentage change in body weight and a reduction in BMI of at least 5%.

RESULTS

A total of 82 participants underwent randomization; 56 were assigned to the liraglutide group and 26 to the placebo group. At week 56, the mean percentage change from baseline in BMI was −5.8% with liraglutide and 1.6% with placebo, representing an estimated difference of −7.4 percentage points (95% confidence interval [CI], −11.6 to −3.2; P<0.001). The mean percentage change in body weight was 1.6% with liraglutide and 10.0% with placebo, representing an estimated difference of −8.4 percentage points (95% CI, −13.4 to −3.3; P=0.001), and a reduction in BMI of at least 5% occurred in 46% of participants in the liraglutide group and in 9% of participants in the placebo group (adjusted odds ratio, 6.3 [95% CI, 1.4 to 28.8]; P=0.02). Adverse events occurred in 89% and 88% of participants in the liraglutide and placebo groups, respectively. Gastrointestinal adverse events were more common in the liraglutide group (80% vs. 54%); serious adverse events were reported in 12% and 8% of participants in the liraglutide and placebo groups, respectively.

CONCLUSIONS

Among children (6 to <12 years of age) with obesity, treatment with liraglutide for 56 weeks plus lifestyle interventions resulted in a greater reduction in BMI than placebo plus lifestyle interventions. (Funded by Novo Nordisk; SCALE Kids ClinicalTrials.gov number, NCT04775082.)

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This article was published on September 10, 2024, at NEJM.org.

DOI: 10.1056/NEJMoa2407379

Obesity is a chronic, relapsing, and progressive disease that necessitates appropriate management strategies endorsed by multiple guidelines.[1-5] Childhood obesity, which is a predictor of adolescent obesity and often persists into adulthood, is associated with serious, lifelong complications, including type 2 diabetes, metabolic dysfunction–associated steatohepatitis, many cancers, and an increased risk of death from cardiovascular disease in adulthood.[6-11] Lifestyle interventions that support a healthy diet and regular physical activity are the cornerstones of treatment of obesity in children and adolescents; however, the sustained effect of these interventions on the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) is modest, and they require intensive delivery (≥26 contact hours recommended in the relevant studies).[4,9,12,13] Thus, adjuncts to lifestyle interventions, including medications, may be needed to treat obesity effectively in children.

The glucagon-like peptide-1 (GLP-1) analogues liraglutide and semaglutide are approved by the Food and Drug Administration and the European Medicines Agency for long-term weight management in adolescents 12 years of age or older with obesity, as adjunct treatments to lifestyle interventions.[14-19] These medications act centrally to increase satiety signaling, reduce appetite and energy intake, and decrease food reward; these medications also increase postprandial insulin levels, reduce glucagon secretion, and delay gastric emptying.[20-22] No medications are currently approved for the treatment of nonmonogenic, nonsyndromic obesity in children younger than 12 years of age.[5,23,24]

The SCALE Kids trial, the results of which are presented here, assessed the efficacy and safety of liraglutide, as compared with placebo, as an adjunct treatment to lifestyle interventions, for the treatment of obesity in children 6 to younger than 12 years of age.

Methods

Trial Design and Oversight

We conducted this phase 3a, double-blind, randomized, placebo-controlled trial at 23 sites in nine countries. The trial was initiated in March 2021; the main phase, which is reported here, was completed in January 2024 and comprised a 2-week screening period, a 12-week run-in period, and a 56-week treatment period, followed by a 26-week follow-up period (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). An open-label extension phase is ongoing, with anticipated completion in January 2027. The trial was conducted in accordance with the principles of the Declaration of Helsinki,[25] the Good Clinical Practice guidelines of the International Council for Harmonisation,[26] and all applicable laws and regulations. The trial protocol and amendments (available, along with the statistical analysis plan, at NEJM.org), participant information sheet, and consent form were approved by an independent ethics committee or institutional review board at each site. Before initiation of trial-related procedures, written informed consent was obtained from all parents or legal guardians, and informed assent was obtained from all participants.

The trial was designed and overseen by the sponsor (Novo Nordisk) and an independent data monitoring committee, with input from the investigators, who gathered the data. The sponsor performed the data analyses. The manuscript was written with medical writing support, funded by the sponsor, under the guidance of the authors. All the authors had access to the data, vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, agreed to data confidentiality during the trial and manuscript preparation, and agreed to submit the manuscript for publication.

Participants

Eligible participants were children (6 to <12 years of age) with obesity, which was defined as an age-adjusted and sex-adjusted BMI in the 95th percentile or higher, according to the Centers for Disease Control and Prevention clinical growth charts,[27] and a pubertal development of Tanner stage 1 through 5, without type 1 diabetes or secondary causes of obesity. Full eligibility criteria are listed in Table S1.

Procedures

After the 2-week screening period, participants completed a 12-week run-in period, after which eligible participants were randomly assigned in a 2:1 ratio to once-daily subcutaneous liraglutide,

at a dose of 3.0 mg, or matching placebo. Participants received lifestyle interventions from the run-in period until after the end of the trial. Lifestyle interventions consisted of individualized counseling at every visit by a qualified health care professional to encourage adherence to a healthy diet and a goal of 60 minutes per day of moderate-to-high-intensity physical activity, with an optional activity tracker provided. Randomization was performed with the use of an interactive Web response system, stratified according to sex and Tanner stage. Subcutaneous liraglutide was initiated at a dose of 0.6 mg per day for 1 week for participants with a body weight at randomization of at least 45 kg (0.3 mg per day for 1 week for those with a body weight at randomization of <45 kg). Dosing was increased in increments of 0.6 mg per week, over a maximum of 8 weeks (for participants with a body weight of ≥45 kg) or 10 weeks (for those with a body weight <45 kg) until a once-daily dose of 3.0 mg or the maximum tolerated dose was reached.

END POINTS AND ASSESSMENTS

All primary and confirmatory end points were assessed from baseline (the time of randomization [week 0]) to the end of the treatment period (week 56). The primary end point was the percentage change in BMI. The confirmatory secondary end points were the percentage change in body weight and a reduction in BMI of at least 5%. Supportive secondary end points included a BMI reduction of at least 10%; change in 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 age-adjusted and sex-adjusted growth charts[27]; and change in BMI standard-deviation score, body weight, waist circumference, blood pressure, and glycated hemoglobin level. Key exploratory efficacy data are also presented for the follow-up period (weeks 56 through 82). Safety assessments included adverse events and serious adverse events reported during the treatment period (defined as the time from administration of the first dose of liraglutide or placebo to 14 days after the last dose). A complete list of end points is provided in Table S2.

STATISTICAL ANALYSIS

For the primary end point of the percentage change in BMI, we determined that a sample size of 78 participants randomly assigned in a ratio of 2:1 would provide the trial with at least 80% power to detect an estimated difference between the liraglutide group and placebo group of −5.0 percentage points, with a standard deviation of 5.5 percentage points. Efficacy end points were analyzed in the full analysis set, which included all the participants who underwent randomization, according to the group to which they were assigned. Safety was assessed in the safety analysis set, which included all the participants who received at least one dose of liraglutide or placebo. Analyses were conducted with the use of the treatment policy estimand, which assessed treatment effect regardless of discontinuation of liraglutide or placebo or initiation of rescue interventions, and the trial product estimand, which assumed that all the participants adhered to the assigned regimen as intended (see the Statistical Analysis section in the Supplementary Appendix). Estimated differences between liraglutide and placebo are reported with two-sided 95% confidence intervals and corresponding P values (with superiority defined as $P<0.05$). If superiority was confirmed for the primary end point, testing of the confirmatory secondary end points was performed in a prespecified hierarchical order at a 5% significance level. Testing of the supportive secondary end points was not included in the statistical testing hierarchy. Safety data and exploratory end points were summarized descriptively. Statistical analyses were performed with the use of SAS software, version 8.4.

We used an analysis-of-covariance model to analyze continuous end points for the treatment policy estimand. This assumed unequal variances between the two groups, with the randomly assigned regimen and the stratification group (sex and Tanner stage and their interaction) as factors and the baseline level of the respective end point as a covariate. A logistic-regression method was used to assess the proportion of participants with a BMI reduction of at least 5% and at least 10%, with the randomly assigned regimen, the stratification groups (sex and Tanner stage at baseline), and the interaction between the stratification groups as factors and the baseline BMI as a covariate. A mixed model for repeated measurements was used for the trial product estimand. A multiple imputation method was used for missing values. Additional details regarding the

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Liraglutide (N=56)	Placebo (N=26)	Total (N=82)
Sex — no. (%)			
Male	30 (54)	14 (54)	44 (54)
Female	26 (46)	12 (46)	38 (46)
Age — yr	10±2	10±2	10±2
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	1 (2)	0	1 (1)
Asian	6 (11)	2 (8)	8 (10)
Black	4 (7)	2 (8)	6 (7)
White	37 (66)	22 (85)	59 (72)
Other	8 (14)	0	8 (10)
Tanner stage — no. (%)‡			
1	24 (43)	10 (38)	34 (41)
2 or 3	22 (39)	13 (50)	35 (43)
4 or 5	10 (18)	3 (12)	13 (16)
Obesity class — no. (%)§			
1	10 (18)	10 (38)	20 (24)
2	26 (46)	4 (15)	30 (37)
3	20 (36)	12 (46)	32 (39)
BMI			
Mean	30.9±4.7	31.3±7.0	31.0±5.5
Standard-deviation score	3.65±0.81	3.87±1.35	3.72±1.01
Percentage of the 95th percentile	135.5±17.9	138.7±28.5	136.5±21.7
Body weight — kg	69.8±17.7	71.0±23.2	70.2±19.5
Height — cm	149.2±10.4	148.8±11.5	149.0±10.7
Height standard-deviation score	1.5±1.2	1.6±1.3	1.5±1.2
Waist circumference — cm	94.4±13.1	97.4±17.2	95.3±14.5
Obesity-related complications at screening — no. (%)¶			
0	26 (46)	11 (42)	37 (45)
1	13 (23)	8 (31)	21 (26)
2	10 (18)	4 (15)	14 (17)
≥3	7 (12)	3 (12)	10 (12)
Insulin resistance	14 (25)	2 (8)	16 (20)
Asthma	7 (12)	7 (27)	14 (17)
Impaired glucose tolerance	6 (11)	4 (15)	10 (12)
Precocious puberty‖	7 (12)	3 (12)	10 (12)
Type 2 diabetes	0	0	0
Blood pressure — mm Hg			
Systolic	113±9	115±12	113±10
Diastolic	67±9	71±12	68±10

Table 1. (Continued.)

Characteristic	Liraglutide (N=56)	Placebo (N=26)	Total (N=82)
Pulse — beats per minute	85±13	91±13	87±13
Glycated hemoglobin — %	5.4±0.3	5.4±0.4	5.4±0.3

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the participant.
‡ Tanner stages were defined according to breast development and pubic hair development for girls and genital development and pubic hair development for boys. Tanner stages range from 1 to 5, with higher stages indicating more advanced pubertal development.
§ Obesity class was defined according to the Centers for Disease Control and Prevention (CDC). Obesity class 1 is defined by a body-mass index (BMI is the weight in kilograms divided by the square of the height in meters) of ≥95% to <120% of the 95th percentile, obesity class 2 by a BMI of ≥120% to <140% of the 95th percentile, and obesity class 3 by a BMI of ≥140% of the 95th percentile. No participants were classified as having overweight according to the CDC definition.
¶ The presence of obesity-related complications at screening was determined by the investigators. Complications included asthma, dyslipidemia, gastroesophageal reflux disease, impaired glucose tolerance, hepatic steatosis, hypertension, impaired fasting glucose, insulin resistance, sleep apnea syndrome, and precocious puberty.
‖ Precocious puberty was defined by the investigator as premature thelarche, accelerated adrenarche, premature adrenarche, and advanced puberty.

statistical analyses are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

Of the 92 participants who were screened, 82 underwent randomization; 56 participants received at least one dose of liraglutide (3.0 mg or the maximum tolerated dose) and 26 received placebo. Of the 82 participants who underwent randomization, 74 (90%) completed the main phase of the trial (Fig. S2), and 66 (80%) received all the assigned doses of liraglutide or placebo, including 44 of 56 participants (79%) in the liraglutide group and 22 of 26 (85%) in the placebo group. Overall, 50 of 56 participants (89%) in the liraglutide group received the maximum dose of 3.0 mg; 84% and 86% of participants in the liraglutide and placebo groups, respectively, completed the assigned regimen at the maximum dose. Data on treatment completion for other doses are shown in Table S3. Baseline characteristics were generally similar in the two groups (Table 1). The participants enrolled in this trial included slightly more boys than girls (54% vs. 46%), most participants had obesity that was defined as either class 2 (37%) or class 3 (39%), and most participants were White (72%) (Table 1). Baseline characteristics according to sex are shown in Table S4.

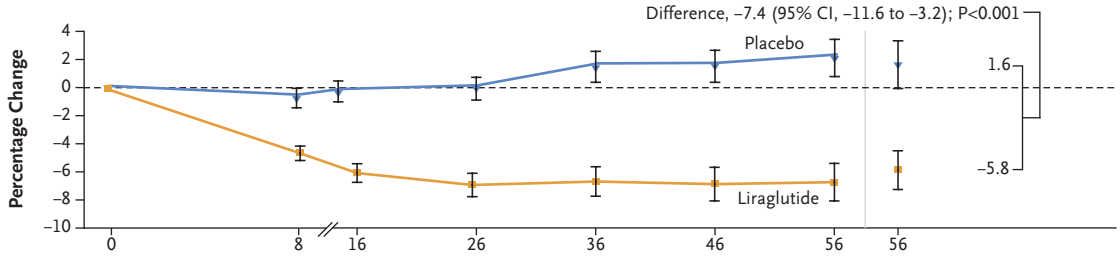
EFFICACY

BMI and Body Weight

On the basis of the treatment policy estimand, at week 56, the estimated mean percentage change from baseline in BMI (the primary end point) was –5.8% with liraglutide and 1.6% with placebo, representing an estimated difference of –7.4 percentage points (95% confidence interval [CI], –11.6 to –3.2; P<0.001) (Fig. 1A and Table 2). The estimated mean percentage change in body weight (confirmatory secondary end point) was 1.6% with liraglutide and 10.0% with placebo, representing an estimated difference of –8.4 percentage points (95% CI, –13.4 to –3.3; P=0.001) (Fig. 1B and Table 2). A reduction in BMI of at least 5% occurred in 24 of 52 participants (46%) in the liraglutide group and in 2 of 23 participants (9%) in the placebo group (Fig. 1C and 1D). The odds of a BMI reduction of at least 5% (confirmatory secondary end point) were significantly greater with liraglutide than with placebo (adjusted odds ratio, 6.3 [95% CI, 1.4 to 28.8]; P=0.02) (Table 2). Findings were similar for the trial product estimand (Table S5).

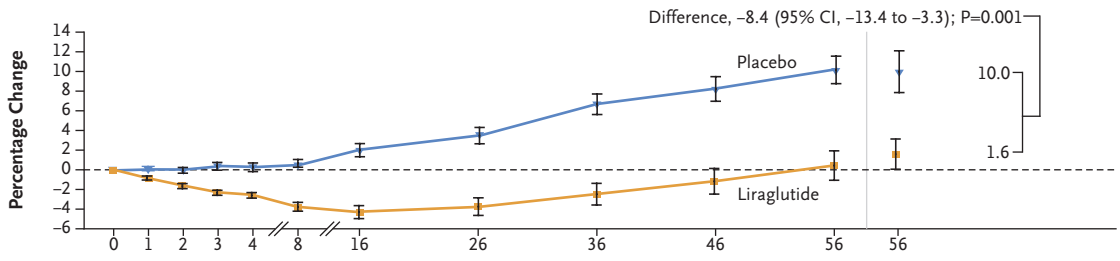
During the follow-up period, BMI and body weight increased in both groups. At week 56, the observed mean change from baseline in BMI was –6.7% with liraglutide and 2.1% with placebo; at week 82, the change in BMI was –0.8% and 6.7%, respectively. At week 56, the observed mean

A Change in BMI from Baseline



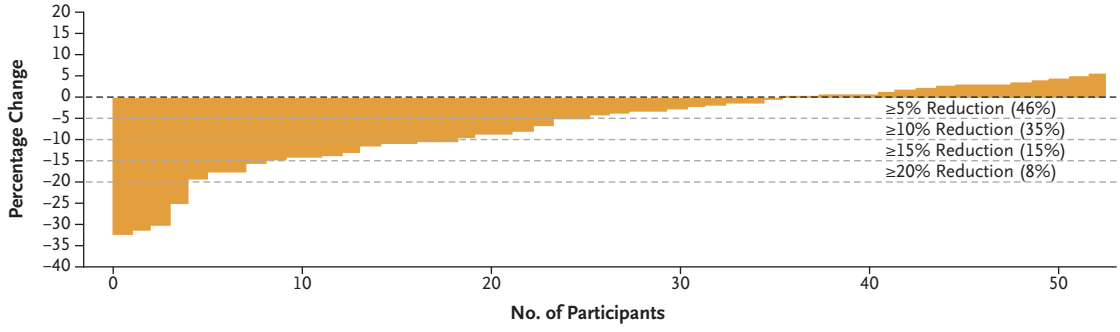
No. of Participants								
Placebo	26	24	24	24	24	23	23	26
Liraglutide	56	53	51	53	52	51	52	56

B Change in Body Weight from Baseline



No. of Participants											
Placebo	26	26	25	26	26	24	24	24	24	23	23	26
Liraglutide	56	52	53	52	54	53	51	53	52	51	52	56

C Change in BMI from Baseline in the Liraglutide Group



D Change in BMI from Baseline in the Placebo Group

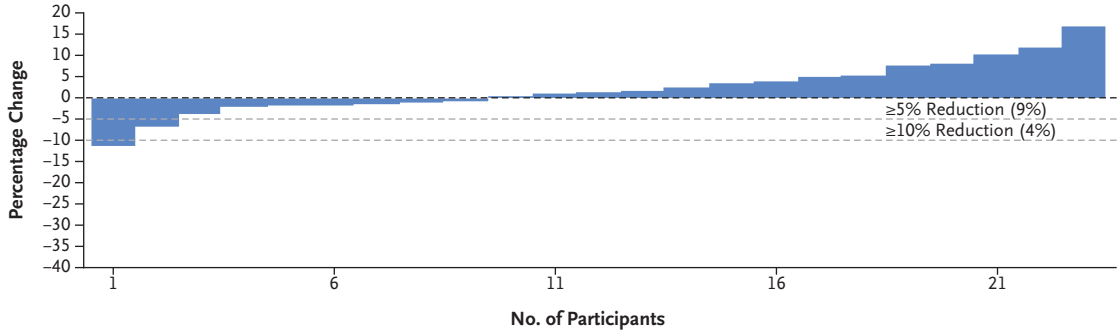


Figure 1 (facing page). BMI and Body-Weight Measures.
The data shown here are the observed values from the in-trial period, for the full analysis set. Panel A shows the mean percentage change from baseline in body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) over time, and Panel B the mean percentage change from baseline in body weight over time. Also shown is the estimated difference between the groups at week 56 for the treatment policy estimand, which assessed effect regardless of discontinuation of liraglutide or placebo or initiation of rescue interventions. The I bars indicate standard errors. The numbers shown below the graphs are the participants contributing to the mean. Panels C and D show the mean percentage change from baseline in BMI at week 56 in the liraglutide group and the placebo group, respectively.

change from baseline in body weight was 0.8% with liraglutide and 10.2% with placebo; at week 82, these had increased to 10.7% and 19.0%, respectively (Fig. S3). Data for the absolute BMI from the run-in period to week 82 are shown in Figure S4.

For the treatment policy estimand, results for all supportive secondary end points related to body weight also favored liraglutide at week 56, except the change in mean waist circumference. The absolute body weight increased from baseline by a mean of 1.1 kg with liraglutide and 7.1 kg with placebo, representing an estimated difference of −6.0 kg (95% CI, −9.3 to −2.7) (Table 2). A reduction in BMI of at least 10% from baseline was observed in 35% of participants in the liraglutide group and in 4% in the placebo group (Fig. 1C and 1D). Changes in BMI as a percentage of the 95th percentile and the BMI standard-deviation score also favored liraglutide over placebo (Fig. 2A and 2B and Table 2). The observed mean percentage of the 95th percentile for BMI was 119.8% with liraglutide and 136.9% with placebo at week 56, and 124.9% and 140.1% at week 82. The observed mean BMI standard-deviation score was 2.9 with liraglutide and 3.6 with placebo at week 56 and 3.0 and 3.7 at week 82 (Fig. S5). Data for the trial product estimand are reported in Table S5.

Cardiometabolic Risk Factors

The changes observed in diastolic blood pressure and glycated hemoglobin level favored liraglutide over placebo for the treatment policy estimand and the trial product estimand (Table 2, Table S5, and Fig. S6). The estimated difference in systolic blood pressure between the liraglutide group and placebo group was −3.4 mm Hg (95% CI, −8.9 to 2.0).

SAFETY

Adverse events were reported in 50 of 56 participants (89%) in the liraglutide group and in 23 of 26 participants (89%) in the placebo group during the treatment period (Table 3). Most were mild or moderate in severity and resolved without apparent sequelae. The most common adverse events were gastrointestinal disorders, which were reported in 45 of 56 participants (80%) in the liraglutide group and in 14 of 26 participants (54%) in the placebo group (Table 3 and Table S6). The difference between the groups primarily reflected a greater incidence of mild-to-moderate nausea and vomiting with liraglutide than with placebo, which occurred mainly during the dose-escalation period (Table 3 and Fig. S7). Gastrointestinal events were treated with antiemetic agents or antinausea medications (in 10 participants [18%] receiving liraglutide and 1 participant [4%] receiving placebo) and proton-pump inhibitors (in 2 participants [4%] receiving liraglutide) and by means of liraglutide dose reduction (15 participants [27%]) or temporary interruption of treatment with liraglutide (3 participants [5%]).

Serious adverse events were reported in 7 participants receiving liraglutide (12%) and in 2 participants receiving placebo (8%) during the treatment period (Table 3). Three serious adverse events that were considered by the investigators to be possibly or probably related to treatment with liraglutide included two cases of vomiting and one of colitis. A total of 6 participants (11%) discontinued treatment with liraglutide because of adverse events, including 3 participants who discontinued because of gastrointestinal disorders (Table 3). No discontinuations due to adverse events occurred in the placebo group.

Changes in height, height standard-deviation score, bone age, and pubertal status (Tanner stage 1, 2 or 3, and 4 or 5) from baseline were similar in the two groups at week 56 (Table S7). Although the levels of amylase and lipase increased with the use of liraglutide, they did not exceed the upper limit of the normal range (Table S7). The pro-

Table 2. End Points at Week 56 (Treatment Policy Estimand).*

End Point	Liraglutide (N=56)	Placebo (N=26)	Difference (95% CI)	P value
Primary end point				
Percentage change in BMI	−5.8	1.6	−7.4 (−11.6 to −3.2)	<0.001
Confirmatory secondary end points				
Percentage change in body weight	1.6	10.0	−8.4 (−13.4 to −3.3)	0.001
BMI reduction of ≥5% — % of participants	46	9	6.3 (1.4 to 28.8)†	0.02
Supportive secondary end points				
Change in body weight — kg	1.1	7.1	−6.0 (−9.3 to −2.7)	
Change in BMI percentage of 95th percentile — percentage points‡	−14.0	−4.0	−10.0 (−15.1 to −4.8)	
Change in BMI standard-deviation score	−0.7	−0.3	−0.4 (−0.6 to −0.2)	
BMI reduction of ≥10% — % of participants	35	4	8.2 (1.0 to 65.3)†	
Change in waist circumference — cm	−2.0	1.3	−3.4 (−9.4 to 2.7)	
Change in blood pressure — mm Hg				
Systolic	−1.7	1.7	−3.4 (−8.9 to 2.0)	
Diastolic	−1.2	3.0	−4.2 (−8.4 to 0.0)	
Change in glycated hemoglobin level — %	−0.2	−0.1	−0.1 (−0.2 to 0.0)	

* Data are mean changes from baseline unless indicated otherwise. Observed data are from the in-trial period (defined as the time from randomization until last site contact) for the full analysis set, which included all the participants who underwent randomization; estimated differences and adjusted odds ratios are for the treatment policy estimand, which assessed effect regardless of discontinuation of liraglutide or placebo or initiation of rescue interventions.
† This value is the adjusted odds ratio (rather than the absolute difference), with placebo as the reference and with the assigned regimen, stratification groups (sex and Tanner stage at baseline), and the interaction between stratification groups as factors and the baseline BMI as a covariate.
‡ The BMI percentage of the 95th percentile is defined by the CDC as a measure of the exact percentage above the 95th percentile for a given age and sex.

portion of female participants who had had menarche was similar in the groups at weeks 0, 56, and 82 (Table S8). The weight-to-BMI ratio and height-to-BMI ratio stratified according to Tanner stage are shown in Table S9. At week 56, the mean (±SD) change from baseline in pulse was 0±14 beats per minute and −4±12 beats per minute in the liraglutide and placebo groups, respectively.

DISCUSSION

This phase 3a trial examined the use of the GLP-1 analogue liraglutide (at a dose of 3.0 mg or the maximum tolerated dose) for long-term weight management in children 6 to younger than 12 years of age with nonmonogenic, nonsyndromic obesity. In this trial, liraglutide was superior to placebo with regard to the percentage change from baseline in BMI and body weight. At week 56, the difference between the liraglutide and placebo groups was −7.4 percentage points for the change from baseline in BMI and −8.4 percentage points for the change from baseline in body weight. The proportions of participants with a reduction in BMI from baseline of at least 5% or at least 10%, as well as the changes in BMI standard-deviation score and BMI as a percentage of the 95th percentile, were greater with liraglutide than with placebo, with the latter measures showing a treatment benefit with liraglutide that was still present after adjustment for age and sex.

A large trial evaluating BMI among a German population-based sample of 51,505 children showed that almost 90% of children with obesity at 3 years of age had overweight or obesity in adolescence; the investigators concluded that among adolescents with obesity, the most rapid weight gain had occurred between 2 and 6 years of age.[28] Therefore, clinical management of obesity should

consider the most appropriate timing for treatment initiation and continue throughout life.[5]

In the present trial, the treatment difference in the BMI standard-deviation score relative to placebo was −0.40, which is almost double that observed in the SCALE Teens trial, which compared the use of liraglutide with placebo in adolescents.[29] The proportion of participants who had a reduction in BMI with liraglutide was slightly higher among children than among adolescents.[29] Although caution is required when comparing studies that were not performed head-to-head, particularly studies in different age groups, the larger treatment difference that was observed in children than in adolescents may imply advantages to treating obesity at younger ages. Our findings are consistent with evidence suggesting that lifestyle interventions may be more effective in younger children than in adolescents; however, the supporting evidence is not consistent.[13,30] Among children and adolescents,[29] an increase in BMI occurred after discontinuation of pharmacotherapy, which supports the evidence that obesity is a chronic, relapsing disease. The goal of obesity treatment in children is not necessarily absolute weight loss but reduction in the BMI percentile, and thus prevention of obesity and its adverse consequences.[31] BMI as a percentage of the 95th percentile continued to be lower in the liraglutide group than in the placebo group during the follow-up period, which points to a sustained treatment benefit with liraglutide. Nonetheless, the percentage of the 95th percentile was still greater than 120% at the end of the treatment period in the liraglutide group, which highlights the continued need for prioritizing research for effective treatments.

In our trial, improvements were also observed in diastolic blood pressure and the glycated hemoglobin level; the data for systolic blood pressure showed a trend in the same direction, although the trial was not powered to detect small-size effects on systolic blood pressure. No notable changes in pulse were reported.

The most common adverse events reported in the liraglutide group were gastrointestinal in nature, including nausea, vomiting, and diarrhea. Three cases of vomiting in the liraglutide group were considered by investigators to be serious (each required emergency care); however, none of the events required hospitalization and all resolved without sequelae. Gastrointestinal events were managed with the use of antiemetic agents, antinausea medications, and proton-pump inhibitors and by means of liraglutide dose reduction or interruption. Completion of the treatment period, with the maximum dose of 3.0 mg, was high in both groups, despite the protocol allowing for high flexibility in dosing. The similarity of the changes in height, height standard-deviation score, bone age, and Tanner stages (1, 2 or 3, and 4 or 5) in the two groups suggests that liraglutide had no apparent adverse effects on growth and development when evaluated after

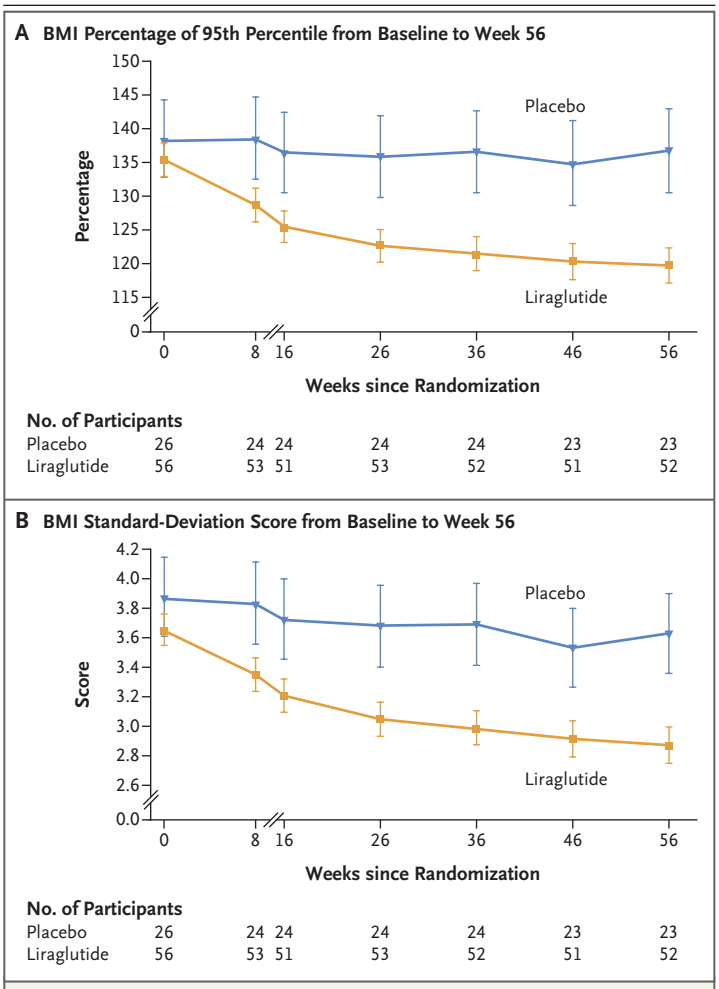


Figure 2. Supportive Secondary End Points Related to Body Weight.
The data shown here are observed values for the in-trial period, for the full analysis set. Panel A shows BMI as a percentage of the 95th percentile from baseline to week 56. The 95th percentile is measured on age-adjusted and sex-adjusted growth charts from the Centers for Disease Control and Prevention. Panel B shows the BMI standard-deviation score from baseline to week 56. I bars indicate the standard errors. The numbers shown beneath the graphs are the numbers of participants contributing to the mean.

Table 3. Adverse Events.*

Event	Liraglutide (N=56)			Placebo (N=26)		
	%	*no. of events*	*events/100 person-yr*	%	*no. of events*	*events/100 person-yr*
Adverse event						
Any	89	50	801.1	88	23	582.7
Gastrointestinal	80	45	428.1	54	14	156.9
Serious adverse event						
Any	12	7	22.0	8	2	7.5
Gastrointestinal	7	4	9.2	0	0	0
Adverse event leading to treatment discontinuation†						
Any	11	6	11.0	0	0	0
Gastrointestinal	5	3	5.5	0	0	0
Fatal adverse event	0	0	0	0	0	0

* Observed data are from the treatment period for the safety analysis set. The treatment period was defined as the time from administration of the first dose of liraglutide or placebo to 14 days after the last dose. The safety analysis set included all the participants who underwent randomization and received at least one dose of liraglutide or placebo.
† One participant (excluded from this table) in the liraglutide group had "drug withdrawn" marked as an action for an adverse event in the associated case-report form. This participant resumed treatment before week 56 and completed treatment; however, the patient was captured as having permanently discontinued the trial product.

56 weeks of treatment. During the follow-up period, BMI as a percentage of the 95th percentile and BMI standard-deviation score were relatively unchanged, which shows relative stability in BMI adjusted for age and sex.

This phase 3a trial adds to the base of evidence for the management of pediatric obesity. The superiority of liraglutide over placebo was shown with respect to the primary end point. Although the trial was not powered to test superiority of secondary end points, liraglutide appeared to be superior to placebo with respect to changes in BMI and body weight.

The trial had a number of limitations. An important limitation is the lack of an international consensus on the definition of clinically meaningful BMI reduction in children. Since obesity-related complications were reported to investigators by the participants, they may have been underestimated. Participants were not screened or monitored for eating disorders as part of the trial; however, medical history was captured, and participants with a confirmed diagnosis of bulimia nervosa disorder were not eligible for enrollment. Data on bone mineral density during treatment were not collected and should be included in future studies. Although the trial enrolled participants from nine countries, approximately 70% of the participants were White, which limits the generalizability of the data (Table S10). Long-term studies evaluating the efficacy and safety of liraglutide in children and any potential effects on growth patterns are needed, as is postmarketing surveillance.

The ongoing open-label extension phase of the present trial, with anticipated completion in January 2027, will add data on longer-term outcomes of treatment with liraglutide in children 6 to younger than 12 years of age. Given the evidence that supports the safety and efficacy of obesity medications such as liraglutide for use in adolescents, the American Academy of Pediatrics Clinical Practice Guideline recommends offering obesity medications to adolescents at least 12 years of age with obesity, as adjuncts to lifestyle interventions, according to medication indications, risks, and benefits.[5] Such guidelines may change over time, as the evidence base for obesity medications in children increases.

This trial showed that among children 6 to younger than 12 years of age with obesity, liraglutide at a dose of 3.0 mg plus lifestyle interventions resulted in a greater reduction in BMI than placebo plus lifestyle interventions.

Supported by Novo Nordisk.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

We thank the trial participants, their parents and caregivers; the investigators, and the trial site staff who conducted the trial; the data monitoring committee; Anne Sophie Hoff Hagelskjær, Christine Frithioff-Bøjsøe, and Paula Hale (all of Novo Nordisk) for assistance with trial conduct and scientific input; and Dinesh Chauhan (Novo Nordisk) for assistance with interpretation of the safety data; and Louisa Lyon (who wrote the first draft of the manuscript) and Silvia Pregnolato of Apollo, a division of OPEN Health Communications, for medical writing support, funded by Novo Nordisk, in accordance with Good Publication Practice guidelines.

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