ORIGINAL ARTICLE

A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity

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ABSTRACT

BACKGROUND

Obesity is a chronic disease with limited treatment options in pediatric patients. Liraglutide may be useful for weight management in adolescents with obesity.

METHODS

In this randomized, double-blind trial, which consisted of a 56-week treatment period and a 26-week follow-up period, we enrolled adolescents (12 to <18 years of age) with obesity and a poor response to lifestyle therapy alone. Participants were randomly assigned (1:1) to receive either liraglutide (3.0 mg) or placebo subcutaneously once daily, in addition to lifestyle therapy. The primary end point was the change from baseline in the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) standard-deviation score at week 56.

RESULTS

A total of 125 participants were assigned to the liraglutide group and 126 to the placebo group. Liraglutide was superior to placebo with regard to the change from baseline in the BMI standard-deviation score at week 56 (estimated difference, −0.22; 95% confidence interval [CI], −0.37 to −0.08; P=0.002). A reduction in BMI of at least 5% was observed in 51 of 113 participants in the liraglutide group and in 20 of 105 participants in the placebo group (estimated percentage, 43.3% vs. 18.7%), and a reduction in BMI of at least 10% was observed in 33 and 9, respectively (estimated percentage, 26.1% vs. 8.1%). A greater reduction was observed with liraglutide than with placebo for BMI (estimated difference, −4.64 percentage points) and for body weight (estimated difference, −4.50 kg [for absolute change] and −5.01 percentage points [for relative change]). After discontinuation, a greater increase in the BMI standard-deviation score was observed with liraglutide than with placebo (estimated difference, 0.15; 95% CI, 0.07 to 0.23). More participants in the liraglutide group than in the placebo group had gastrointestinal adverse events (81 of 125 [64.8%] vs. 46 of 126 [36.5%]) and adverse events that led to discontinuation of the trial treatment (13 [10.4%] vs. 0). Few participants in either group had serious adverse events (3 [2.4%] vs. 5 [4.0%]). One suicide, which occurred in the liraglutide group, was assessed by the investigator as unlikely to be related to the trial treatment.

CONCLUSIONS

In adolescents with obesity, the use of liraglutide (3.0 mg) plus lifestyle therapy led to a significantly greater reduction in the BMI standard-deviation score than placebo plus lifestyle therapy. (Funded by Novo Nordisk; NN8022-4180 ClinicalTrials.gov number, NCT02918279.)

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OBESITY IS A CHRONIC AND PROGRESsive disease[1-3] that affects approximately 107.7 million children and adolescents worldwide[4] and is associated with multiple coexisting conditions and complications.[5] More than 70% of persons who have obesity before puberty will also have obesity as adults, which underscores the need for effective and durable interventions with adequate safety profiles early in life.[5-7] In pediatric patients, first-line treatment for obesity is typically lifestyle therapy, which often yields poor responses.[5,8,9]

Orlistat and phentermine are the only Food and Drug Administration (FDA)–approved pharmacotherapies for the treatment of obesity in pediatric patients, and they can be used only in persons 12 years of age or older and in persons older than 16 years of age, respectively.[10] The European Medicines Agency (EMA) has not approved any pharmacotherapeutic agents for obesity in pediatric patients.[11] Bariatric surgery is offered to adolescents only when they have severe obesity, and it is performed infrequently.[12,13] Thus, pharmacologic treatment options that can be used as adjuncts to lifestyle therapy in adolescents with obesity are of interest.

Liraglutide, a glucagon-like peptide 1 (GLP-1) analogue, increases the postprandial insulin level in a glucose-dependent manner, reduces glucagon secretion, delays gastric emptying, and induces weight loss through reductions in appetite and energy intake.[14,15] Liraglutide (3.0 mg) has been approved by the FDA and the EMA as an adjunct to lifestyle therapy for weight management in adults with obesity or overweight who have at least one weight-related coexisting condition.[16,17] In a previous study that involved adults with obesity or overweight who had either hypertension or dyslipidemia, liraglutide (3.0 mg) resulted in clinically meaningful weight loss and improvements in cardiometabolic markers and health-related quality of life.[18] The present trial evaluated the efficacy and safety of subcutaneous liraglutide (3.0 mg) as an adjunct to lifestyle therapy for weight management in adolescents with obesity.

METHODS

TRIAL OVERSIGHT

We conducted this randomized, double-blind, placebo-controlled, phase 3 trial from September 29, 2016, through August 8, 2019, at 32 sites in five countries (Belgium, Mexico, Russia, Sweden, and the United States). The trial had a 12-week run-in period, a 56-week treatment period (including dose escalation over a period of 4 to 8 weeks), and a 26-week follow-up period without treatment (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial protocol with the statistical analysis plan is available at NEJM.org. The trial was designed and overseen by representatives of the trial sponsor (Novo Nordisk) with input from selected site investigators. The site investigators gathered the data, and the sponsor performed the data analyses. All the authors had full access to the data, directed and supervised the data analyses, interpreted the data, and vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol. The first author wrote the first draft of the manuscript with assistance from an independent medical writer funded by the sponsor. The manuscript was subsequently revised and approved by all the authors, who agreed to submit the manuscript for publication.

The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.[19] An independent ethics committee or institutional review board at each site approved the trial protocol and any subsequent amendments. Safety of the participants and evaluation of the benefit–risk balance were overseen by an independent external data monitoring committee. Written informed consent was obtained from all parents or legally acceptable representatives; informed assent was obtained from all participants before the initiation of any trial-related procedures.

PARTICIPANTS

Pubertal adolescents (12 to <18 years of age) were eligible for inclusion in the trial if they met the following criteria: obesity, defined as a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) that corresponded to an adult value of 30 or more, in accordance with international cutoff points,[20] and was in the 95th or higher percentile for age and sex[5]; stable body weight, defined as a self-reported weight change of less than 5 kg during the 90 days before screening; and a poor response to lifestyle therapy alone, based on the judgment of the site investigator and documented in the participant's medical records. Adolescents with type 2 diabetes

were eligible, but adolescents with type 1 diabetes were excluded. Complete lists of inclusion, exclusion, and randomization criteria are provided in the Supplementary Appendix.

TRIAL PROCEDURES AND END POINTS

During the 12-week run-in period, all participants received lifestyle therapy, defined as counseling about healthy nutrition and physical activity for weight loss (further information is provided in the Supplementary Appendix). Participants who fulfilled the randomization criteria were randomly assigned, in a 1:1 ratio, to receive liraglutide (3.0 mg) or volume-matched placebo administered subcutaneously once daily for 56 weeks, followed by 26 weeks of follow-up without treatment. Treatment was initiated at a dose of 0.6 mg daily for 1 week, and then the dose was increased weekly until the maximum tolerated dose or the 3.0-mg dose (highest dose allowed) was reached (Fig. S1). Randomization was stratified according to pubertal status (Tanner stage 2 or 3 vs. Tanner stage 4 or 5) and glycemic status (normoglycemia vs. prediabetes or type 2 diabetes) and was performed with the use of an interactive Web response system, in permuted blocks, with block sizes of 4. Lifestyle therapy continued from the start of the trial to week 82.

The primary end point was the change from baseline in the BMI standard-deviation score at week 56. The BMI standard-deviation score is a measure of the number of standard deviations from the population mean BMI, matched for age and sex. Key secondary efficacy end points included the change in the BMI standard-deviation score from week 56 to week 82, the percentage of participants who had a reduction in BMI of at least 5% and of at least 10% at week 56, and the change from baseline in BMI, body weight, waist circumference, waist:hip ratio, glucose metabolism, blood pressure, and quality of life (assessed with the Impact of Weight on Quality of Life–Kids questionnaire) at week 56.

Key safety end points included adverse events that were reported during the treatment period (from week 0 to week 56), hypoglycemic episodes, and the change from baseline in bone age, Tanner stage, height standard-deviation score, hormone levels, and heart rate at week 56 and week 82. Mental health was repeatedly assessed with the use of validated questionnaires (the Columbia–Suicide Severity Rating Scale and the Patient Health Questionnaire–9), which were completed at the time of screening and at every visit from randomization to the end of the trial. Safety was monitored from screening to week 82. A complete list of end points is provided in the protocol.

STATISTICAL ANALYSIS

We hypothesized that liraglutide would show superiority to placebo with regard to weight reduction in adolescents. For the primary end point of the change from baseline in the BMI standard-deviation score at week 56, we calculated that a sample of 228 participants would provide the trial with 90% power to show a significant treatment effect, with a standard deviation in the liraglutide group of 0.35 and an estimated treatment difference (i.e., difference between the liraglutide group and the placebo group) of −0.26. Primary and secondary efficacy end points were analyzed according to the intention-to-treat principle, with analyses including all participants who had undergone randomization with imputations for participants who were lost to follow-up. All missing data were handled with the multiple-imputation method under the assumption that participants who were withdrawn from the trial responded as though they had been treated with placebo for the entire trial. For weight-related end points, an additional analysis was performed with the use of a mixed model for repeated measurements to estimate the treatment effect if all participants had adhered to the assigned treatment throughout the trial. The primary and continuous secondary efficacy end points were assessed with an analysis-of-covariance model. The categorical secondary efficacy end points were evaluated with a logistic-regression model. Safety end points were analyzed in the safety population, which included all the participants who had undergone randomization and had been exposed to at least one dose of the randomly assigned treatment, as described in the Supplementary Appendix. The statistical analysis plan did not include a provision of correction for multiplicity. Results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects. Additional details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

TRIAL PARTICIPANTS

Of 299 participants who were screened, 251 underwent randomization; 125 were assigned to the liraglutide group and 126 were assigned to the placebo group (Fig. S2). At week 56, treatment was completed by 101 participants (80.8%) in the liraglutide group and 100 participants (79.4%) in the placebo group. Among those who discontinued treatment, 12 of 24 in the liraglutide group and 5 of 26 in the placebo group underwent height and weight assessments at week 56. Baseline characteristics were similar in the two groups (Table 1).

TREATMENT

Escalation to the 3.0-mg dose was reached by 103 participants (82.4%) in the liraglutide group and 124 participants (98.4%) in the placebo group (Table S1). For pharmacokinetic analysis of liraglutide, sparse samples were obtained on six different occasions (646 samples from 121 participants); the median measured liraglutide concentration was initially 110 μg per liter (29.4 nmol per liter) (Fig. S3).

BMI AND WEIGHT-RELATED END POINTS

Liraglutide was superior to placebo with regard to the change from baseline in the BMI standard-deviation score at week 56 (Fig. 1A), with an estimated treatment difference of −0.22 (95% confidence interval [CI], −0.37 to −0.08; P=0.002) (Table 2). In contrast to the intention-to-treat analysis, an analysis performed with the use of a mixed model for repeated measurements resulted in an estimated treatment difference of −0.26 (95% CI, −0.39 to −0.13) (Fig. S4 and Table S2). The use of liraglutide led to a greater relative change in BMI than placebo (Fig. 1B), with an estimated treatment difference of −4.64 percentage points (95% CI, −7.14 to −2.14) in an intention-to-treat analysis (Table 2) and −5.31 percentage points (95% CI, −7.61 to −3.00) as assessed with a mixed model for repeated measurements. At week 56, a reduction in BMI of at least 5% was observed in 51 of 113 participants in the liraglutide group and in 20 of 105 participants in the placebo group (estimated percentage, 43.3% vs. 18.7%), and a reduction in BMI of at least 10% was observed in 33 and 9, respectively

(estimated percentage, 26.1% vs. 8.1%) (Fig. 1C and 1D and Figs. S5 and S6). At week 56, a greater reduction was observed with liraglutide than with placebo for the following end points: BMI reported as a percentage of the 95th percentile (estimated treatment difference, −6.24 percentage points), body weight (estimated treatment difference, −4.50 kg [for absolute change] and −5.01 percentage points [for relative change]) (Fig. 1E and 1F), and waist circumference (Table 2).

After treatment discontinuation (from week 56 to week 82), a greater increase in the BMI standard-deviation score was observed with liraglutide than with placebo (0.22 vs. 0.07; estimated treatment difference, 0.15; 95% CI, 0.07 to 0.23). Results for additional weight-related end points are shown in Figures S7 and S8.

GLYCEMIC AND CARDIOMETABOLIC RESULTS AND HEALTH-RELATED QUALITY OF LIFE

At week 56, there was no substantial difference between treatment groups in the change in glycemic and cardiometabolic variables or in overall weight-related quality of life (Table 2 and Fig. S9).

SAFETY

Overall, the percentage of participants who reported adverse events during the treatment period (from week 0 to week 56) was similar in the liraglutide group and the placebo group (111 participants [88.8%] and 107 participants [84.9%], respectively) (Table 3). Most adverse events were mild or moderate in severity and were deemed by the individual site investigator as unlikely to be related to the trial treatment. Gastrointestinal events — including nausea, vomiting, and diarrhea — were the events most frequently reported with liraglutide; these events were more common with liraglutide than with placebo (occurring in 81 participants [64.8%] vs. 46 participants [36.5%], P<0.001) (Table 3 and Fig. S10), and they occurred primarily within the initial 4 to 8 weeks of the treatment period, during liraglutide dose escalation (Figs. S11, S12, and S13). Adverse events that led to discontinuation of the trial treatment occurred in 13 participants in the liraglutide group and none in the placebo group (P<0.001); in 10 participants, discontinuation was due to gastrointestinal events (Table 3 and Table S3).

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Liraglutide (N = 125)	Placebo (N = 126)
Female sex — no. (%)	71 (56.8)	78 (61.9)
Age — yr	14.6±1.6	14.5±1.6
Race or ethnic group — no. (%)†		
White	105 (84.0)	115 (91.3)
Black	14 (11.2)	6 (4.8)
Asian	2 (1.6)	0
American Indian or Alaska Native	0	1 (0.8)
Other	4 (3.2)	4 (3.2)
Hispanic ethnic group — no. (%)†	32 (25.6)	24 (19.0)
Tanner stage — no. (%)‡		
2	6 (4.8)	8 (6.3)
3	16 (12.8)	13 (10.3)
4	38 (30.4)	40 (31.7)
5	65 (52.0)	65 (51.6)
Height — m	1.7±0.1	1.7±0.1
Body weight — kg	99.3±19.7	102.2±21.6
BMI§	35.3±5.1	35.8±5.7
BMI standard-deviation score¶	3.14±0.65	3.20±0.77
BMI as percentage of the 95th percentile — %	137.7±18.0	139.6±21.4
Waist circumference — cm	104.87±12.67	106.99±13.57
Waist:hip ratio	0.908±0.079	0.915±0.080
Glycated hemoglobin — %	5.3±0.4	5.3±0.4
Fasting plasma glucose — mg/dl	94.1±7.6	94.5±11.1
Dysglycemia — no. (%)‖	32 (25.6)	33 (26.2)
Blood pressure — mm Hg		
Systolic	116±10	117±12
Diastolic	72±8	73±8
Cholesterol — mg/dl		
Total	156.4±27.0	154.9±29.6
High-density lipoprotein	43.8±10.0	43.8±10.3
Low-density lipoprotein	88.6±24.0	86.6±25.2
Triglycerides — mg/dl	121.0±59.4	124.5±62.5
Free fatty acids — mg/dl	13.1±5.4	14.3±5.5
Total score on IWQOL–Kids questionnaire**	84.5±12.4	82.4±14.5

* Plus–minus values are observed means ±SD. For variables that were not measured at baseline, data obtained at screening are shown. Data for glycated hemoglobin and fasting plasma glucose were obtained at screening, and data for low-density–lipoprotein cholesterol and triglycerides were obtained at week 0. To convert values for cholesterol to millimoles per liter, multiply by 0.02586; for fasting plasma glucose, multiply by 0.05551; for triglycerides, multiply by 0.01129; and for free fatty acids, multiply by 0.0355. Percentages may not total 100 because of rounding.

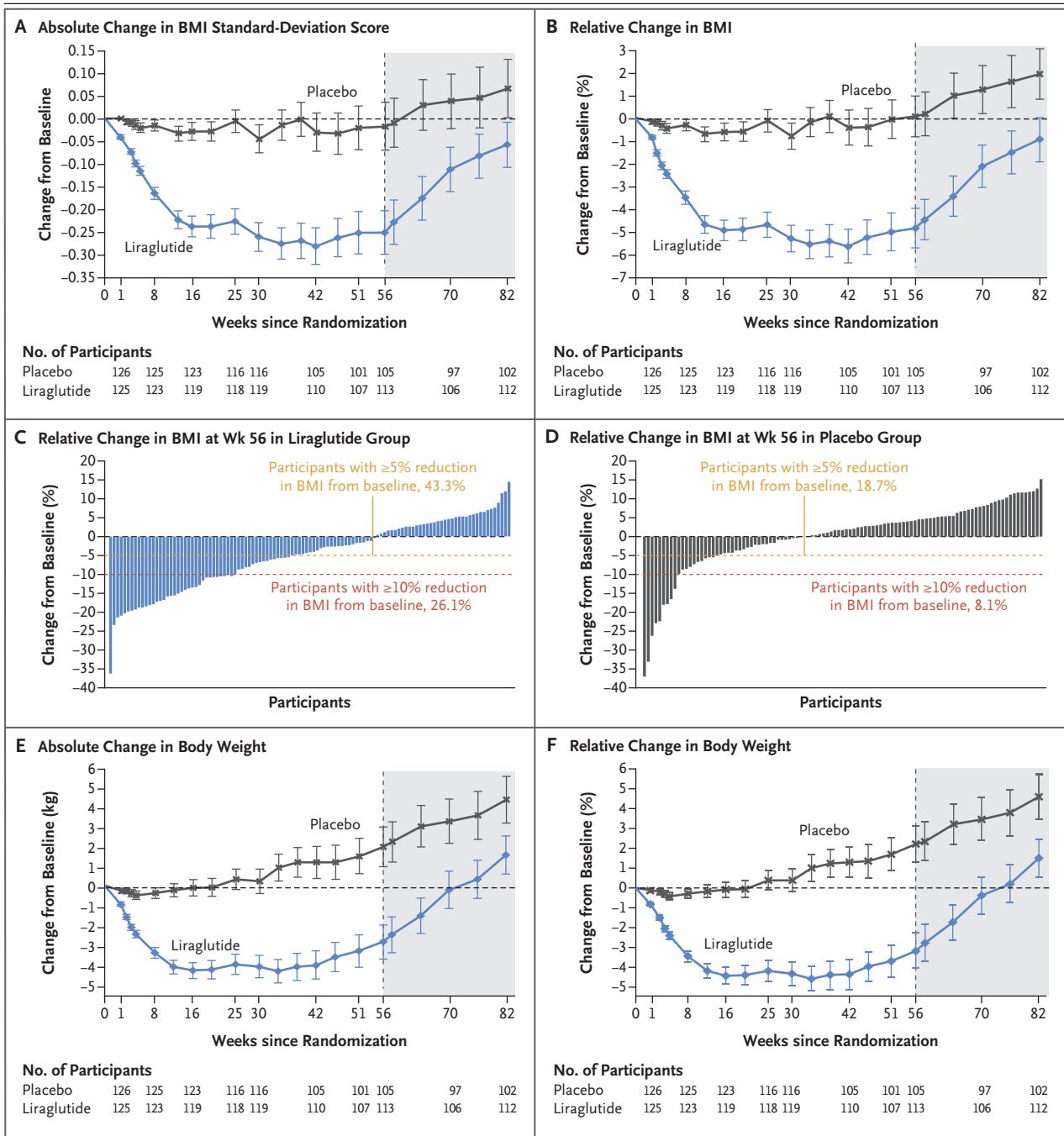† Race and ethnic group were reported by the participant.

‡ For each participant, the overall Tanner stage was the maximum Tanner stage, which was calculated by combining the results for all categorical questions at the visit. Tanner stage 2 indicates early pubertal development, and stage 5 full maturity.

§ Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

¶ The BMI standard-deviation score is a measure of the number of standard deviations from the population mean BMI.

‖ Dysglycemia is defined as type 2 diabetes or prediabetes with a fasting plasma glucose level of at least 100 mg per deciliter (≥5.6 mmol per liter), a glycated hemoglobin level of at least 5.7%, or both.

** Scores on the Impact of Weight on Quality of Life–Kids (IWQOL–Kids) questionnaire range from 0 to 100, with a score of 100 indicating the best possible quality of life.

A Absolute Change in BMI Standard-Deviation Score

B Relative Change in BMI

C Relative Change in BMI at Wk 56 in Liraglutide Group

D Relative Change in BMI at Wk 56 in Placebo Group

E Absolute Change in Body Weight

F Relative Change in Body Weight

Serious adverse events were reported by 3 participants receiving liraglutide (three events) and 5 participants receiving placebo (six events) during the 56-week treatment period (Table 3 and Table S4). During the 26-week follow-up period, additional serious adverse events occurred in 1 participant who had received liraglutide (one event) and 4 participants who had received placebo (five events) (Table S5). There was no clustering of serious adverse events.

Events related to psychiatric disorders occurred in 13 participants (10.4%) in the liraglutide group and in 18 participants (14.3%) in the placebo group during the treatment period (Ta-

Figure 1 (facing page). Efficacy and Weight-Related End Points.

Panel A shows the observed absolute change from baseline in the standard-deviation score for the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) over time; the observed mean (±SD) absolute change was –0.25±0.51 in the liraglutide group (113 participants) and –0.02±0.54 in the placebo group (105 participants) at week 56 and was –0.06±0.53 in the liraglutide group (112 participants) and 0.07±0.66 in the placebo group (102 participants) at week 82. Panel B shows the observed relative change from baseline in BMI over time. Panels C and D show waterfall plots of the observed relative change from baseline in BMI at week 56 in the liraglutide group (113 participants) and the placebo group (105 participants), respectively. The percentages of participants with a reduction from baseline in BMI of at least 5% and of at least 10% were estimated with the use of a logistic-regression multiple-imputation approach. Panel E shows the observed absolute change from baseline in body weight over time; the observed mean absolute change was –2.7±9.1 kg in the liraglutide group (113 participants) and 2.1±10.2 kg in the placebo group (105 participants) at week 56 and was 1.7±10.1 kg in the liraglutide group (112 participants) and 4.4±11.7 kg in the placebo group (102 participants) at week 82. Panel F shows the observed relative change from baseline in body weight over time; the observed mean relative change was –3.2±9.4% in the liraglutide group (113 participants) and 2.2±9.5% in the placebo group (105 participants) at week 56 and was 1.5±10.5% in the liraglutide group (112 participants) and 4.6±11.5% in the placebo group (102 participants) at week 82. In Panels A, B, E, and F, the shaded area indicates the 26-week follow-up period, and I bars indicate the standard error.

ble S6). There were no clinically relevant differences between treatment groups with respect to results on mental health questionnaires (Fig. S14). However, 1 participant in the liraglutide group committed suicide approximately 340 days after the initiation of treatment, and 2 participants (1 per treatment group) reported a suicide attempt during the 26-week follow-up period (Tables S7 and S8). The site investigators and sponsor deemed these three events as unlikely to be related to the trial treatment. The data monitoring committee reviewed suicide-related events during the trial and recommended that the trial continue in accordance with the protocol.

One participant in the placebo group had acute cholecystitis and cholelithiasis during the treatment period. One participant in the liraglutide group had a single episode of pancreatitis, which was moderate in severity, and recovered without treatment. More hypoglycemic episodes occurred with liraglutide than with placebo (26 vs. 18). No instance of hypoglycemia in either group was deemed severe according to the American Diabetes Association–International Society for Pediatric and Adolescent Diabetes classifications (Table S9).

There were no apparent differences between treatment groups in growth or pubertal development (Tables S10 and S11). The change in the mean bone age at week 56 was similar in the liraglutide group and the placebo group (1.40 years and 1.37 years, respectively). Adverse events reported during the run-in period and the entire trial period (from week 0 to week 82) are shown in Tables S12 and S13.

DISCUSSION

In this trial involving adolescents with obesity, the use of liraglutide (3.0 mg or the maximum tolerated dose) plus lifestyle therapy led to a significantly greater reduction in the BMI standard-deviation score (primary end point) than placebo plus lifestyle therapy. It is well established that a weight loss of 3 to 5% significantly improves some health-related outcomes in adults. Although evidence in children is limited, a change in the BMI standard-deviation score of at least 0.20 has been suggested to be clinically meaningful.[8,9,21] The estimated treatment difference in the mean reduction in the BMI standard-deviation score that we observed in our trial of liraglutide (–0.22) was greater than differences observed in trials of lifestyle therapy conducted by the U.S. Preventive Services Task Force (–0.17)[8] and in an overview of six Cochrane reviews (–0.13).[9]

The primary analysis in our trial was performed according to the intention-to-treat principle, which is used to estimate the treatment effect regardless of discontinuation of the trial treatment and provides a perspective of the treatment effect in the entire population.[22] An analysis performed with the use of a mixed model for repeated measurements yielded an estimated treatment difference of –0.26 for the reduction in the BMI standard-deviation score; this approach provided a different perspective, since it estimated the treatment effect if all participants had adhered to the assigned treatment throughout the

Table 2. Estimated Mean Change from Baseline in Primary and Supportive Secondary Efficacy End Points at Week 56.*

End Point	Change from Baseline		Liraglutide vs. Placebo (95% CI)
	Liraglutide (N=125)	Placebo (N=126)	
BMI standard-deviation score			
Absolute change	−0.23±0.05	−0.00±0.05	−0.22 (−0.37 to −0.08)
Relative change — %	−8.32±1.68	−0.68±1.74	−7.64 (−12.41 to −2.87)
BMI			
Absolute change	−1.39±0.31	0.19±0.33	−1.58 (−2.47 to −0.69)
Relative change — %	−4.29±0.88	0.35±0.91	−4.64 (−7.14 to −2.14)
BMI as percentage of the 95th percentile — percentage points	−5.47±1.22	0.77±1.27	−6.24 (−9.70 to −2.79)
Body weight			
Absolute change — kg	−2.26±0.94	2.25±0.98	−4.50 (−7.17 to −1.84)
Relative change — %	−2.65±0.93	2.37±0.95	−5.01 (−7.63 to −2.39)
Waist circumference — cm	−4.35±0.85	−1.42±0.88	−2.93 (−5.24 to −0.63)
Waist:hip ratio	−0.02±0.005	−0.02±0.005	0.00 (−0.02 to 0.01)
Glycated hemoglobin — percentage points	−0.10±0.03	−0.03±0.03	−0.06 (−0.14 to 0.01)
Fasting plasma glucose — mg/dl	−1.98±0.85	−0.16±0.86	−1.82 (−4.14 to 0.51)
Blood pressure — mm Hg			
Systolic	−1.21±0.90	0.84±0.90	−2.05 (−4.53 to 0.43)
Diastolic	0.77±0.69	−0.46±0.69	1.24 (−0.66 to 3.14)
Heart rate — beats/min	1.87±0.91	−0.14±0.95	2.01 (−0.50 to 4.52)
Cholesterol†			
Total	1.00±0.01	0.99±0.01	1.01 (0.97 to 1.04)
High-density lipoprotein	1.04±0.02	1.01±0.02	1.02 (0.97 to 1.07)
Low-density lipoprotein	1.00±0.02	1.00±0.02	1.00 (0.94 to 1.05)
Non–high-density lipoprotein	0.98±0.02	0.98±0.02	1.00 (0.95 to 1.05)
Very-low-density lipoprotein	0.92±0.04	0.93±0.04	0.98 (0.89 to 1.08)
Triglycerides†	0.92±0.04	0.93±0.04	0.98 (0.89 to 1.08)
Free fatty acids†	0.97±0.04	0.97±0.04	1.00 (0.90 to 1.10)
Fasting insulin†	1.03±0.06	1.14±0.06	0.91 (0.77 to 1.06)
Fasting C-peptide†	0.97±0.04	1.01±0.04	0.96 (0.86 to 1.06)
β-cell function on HOMA†	1.11±0.05	1.14±0.05	0.97 (0.85 to 1.12)
Insulin resistance on HOMA†	1.01±0.06	1.11±0.06	0.91 (0.77 to 1.08)
High-sensitivity C-reactive protein†	0.81±0.08	0.93±0.08	0.87 (0.70 to 1.09)
Total score on IWQOL–Kids questionnaire	7.88±1.04	6.57±1.06	1.31 (−1.57 to 4.20)

* Plus–minus values are estimated means ±SE with corresponding estimated treatment differences, except where noted. Confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. Statistical analyses were performed with the use of analysis of covariance for continuous end points and logistic regression for categorical end points. End points were analyzed according to the intention-to-treat principle. HOMA denotes homeostatic model assessment.
† Plus–minus values are geometric mean ratios ±CV (coefficient of variation) relative to baseline with corresponding estimated treatment ratios. Because these values are ratios, units are not provided.

Table 3. Adverse Events during the Treatment Period.*

Event	Liraglutide (N = 125)			Placebo (N = 126)			P Value
	no. of participants (%)	no. of events	events/1000 exposure-yr	no. of participants (%)	no. of events	events/1000 exposure-yr	
Any adverse events	111 (88.8)	777	6187.8	107 (84.9)	627	5018.5	0.07†
Gastrointestinal adverse events	81 (64.8)	319	2540.4	46 (36.5)	121	968.5	0.001†
Serious adverse events‡	3 (2.4)	3	23.9	5 (4.0)	6	48.0	0.72§
Adverse events that led to treatment discontinuation	13 (10.4)	19	151.3	0	0	0	<0.001§
Adverse events that occurred in ≥5% of participants							
Nasopharyngitis	34 (27.2)	68	541.5	38 (30.2)	80	640.3	0.60¶
Nausea	53 (42.4)	101	804.3	18 (14.3)	25	200.1	<0.001¶
Headache	29 (23.2)	43	342.4	35 (27.8)	53	424.2	0.41¶
Vomiting	43 (34.4)	85	676.9	5 (4.0)	8	64.0	<0.001¶
Diarrhea	28 (22.4)	44	350.4	18 (14.3)	29	232.1	0.10¶
Upper abdominal pain	17 (13.6)	25	199.1	17 (13.5)	23	184.1	0.98¶
Oropharyngeal pain	11 (8.8)	11	87.6	15 (11.9)	18	144.1	0.42¶
Influenza	11 (8.8)	11	87.6	12 (9.5)	12	96.0	0.84¶
Gastroenteritis	16 (12.8)	22	175.2	6 (4.8)	9	72.0	0.02¶
Upper respiratory tract infection	11 (8.8)	14	111.5	11 (8.7)	16	128.1	0.98¶
Abdominal pain	10 (8.0)	15	119.5	11 (8.7)	15	120.1	0.83¶
Pyrexia	10 (8.0)	11	87.6	9 (7.1)	11	88.0	0.80¶
Dizziness	13 (10.4)	15	119.5	4 (3.2)	5	40.0	0.02¶
Dysmenorrhea	4 (3.2)	5	39.8	8 (6.3)	16	128.1	0.38§
Arthralgia	3 (2.4)	3	23.9	8 (6.3)	8	64.0	0.22§
Pharyngitis	4 (3.2)	5	39.8	7 (5.6)	7	56.0	0.54§

* Adverse events and serious adverse events that occurred from week 0 through week 56 among adolescents in the safety population are included in the table and presented with their preferred terms. Events were included if the date of onset was between the first day the trial drug was administered and 14 days after the last day the trial drug was administered, at the follow-up visit, or at the last trial visit.
† The P value was calculated with a negative binomial model. The number of events was analyzed with a negative binomial model with log-link function and the logarithm of the exposure time (1000 years) for which an adverse event is considered to be reported during the treatment period as an offset. The model included treatment, sex, region, baseline glycemic category, stratification factor for Tanner stage, and interaction between baseline glycemic category and stratification factor for Tanner stage as fixed effects.
‡ The following serious adverse events were reported in one participant each: postprocedural hemorrhage, myositis, and completed suicide in the liraglutide group; and appendicitis, pneumonia, acute cholecystitis, cholelithiasis, and thrombophlebitis in the placebo group.
§ The P value was calculated by means of Fisher's exact test on the basis of the number of participants.
¶ The P value was calculated by means of Pearson's chi-square test on the basis of the number of participants.

trial, thereby providing information on the anticipated effect of the medication.[22]

The primary efficacy end point of the change in the BMI standard-deviation score was required by the EMA and deemed acceptable by the FDA.[23] Limitations of applying this measure in a pediatric population with severe obesity have been described previously.[24,25] BMI standard-deviation scores can vary substantially from empirical estimates in the context of severe obesity.[24,25] Therefore, we obtained other relevant BMI-related metrics, all of which showed greater reductions with liraglutide than with placebo. When we apply these metrics to gauge the degree of efficacy

of liraglutide in relation to pediatric weight-management programs in the United States and to orlistat, it appears that liraglutide compared favorably in terms of BMI reduction.[8,26] In addition, the estimated treatment difference of –5.01 percentage points for change in body weight observed in our trial was similar to the treatment effect observed in the corresponding trial of liraglutide in adults (estimated treatment difference, –5.4 percentage points), despite differences in the weight-loss trajectory.[18] In line with observations from placebo-controlled trials of liraglutide (3.0 mg) in adults, weight regain was seen in the 26-week follow-up period, reinforcing the concept that obesity is a chronic disease that requires continued treatment.[2,18,27] Some studies indicate that even temporary weight loss may have long-term benefits,[28] but the extent to which this applies in adolescents and the extent to which long-term adherence to pharmacotherapy can be expected are unknown.

Adherence was relatively high in our trial (>80%), as compared with many previous trials involving adolescents with obesity (approximately 70%).[9,29] However, the proportion of samples obtained for pharmacokinetic analysis that had liraglutide concentrations below the lower limit of quantification increased toward the end of the treatment period (7 of 112 samples at week 8 vs. 29 of 98 samples at week 56) (Fig. S3), a finding that suggests decreasing adherence to the medication.

In contrast to trials involving adults and to an observational trial involving adolescents, our trial showed no substantial differences between the liraglutide group and the placebo group in cardiometabolic markers or results on quality-of-life assessments.[18,27,30] These results could be due to the fact that most participants had baseline variables within the normal range or could reflect the limited sample size, which was selected on the basis of power calculations relevant to the BMI standard-deviation score. However, the U.S. Preventive Services Task Force determined that comprehensive intensive lifestyle therapy, which consisted of 26 to 51 contact hours over a year, led to a greater reduction in the mean BMI standard-deviation score than the control regimen (difference, –0.17), with no associated improvements in cardiometabolic markers.[8] In contrast, in a 26-week randomized, controlled trial, weekly exenatide led to a modestly greater reduction in the BMI standard-deviation score (difference, –0.09) and greater improvements in glucose and cholesterol levels than placebo.[31] As in our trial, a heterogenous treatment response was observed in terms of change in BMI. Such findings highlight the need, in the future, to characterize predictors of treatment response to identify patients who would benefit the most from treatment.[32]

Overall, the safety profile of liraglutide was consistent with reports from a phase 1 trial involving adolescents[33] and phase 3 trials involving adults.[18,27,34] The most commonly reported adverse events were gastrointestinal events, including nausea, vomiting, and diarrhea, and more of these events were reported with liraglutide than with placebo. Gastrointestinal events are a known class effect of GLP-1 receptor agonists,[35] and they mostly occurred during dose escalation and then became less frequent. However, there was a clear imbalance between groups in the frequency of adverse events that led to discontinuation of the trial treatment (occurring in 13 participants who were treated with liraglutide and none who were treated with placebo), which was primarily due to gastrointestinal side effects, a finding that suggests liraglutide may not be suitable for all patients. Liraglutide had no apparent effect on growth and development during the trial. Suicide-related events were reported in 3 participants in the two groups, highlighting that adolescents are a vulnerable group that should be monitored carefully. The participant who completed suicide, who was in the liraglutide group, had a history of attention deficit–hyperactivity disorder; the 2 participants who attempted suicide during the 26-week follow-up period had received a diagnosis of depression.[36,37]

Although the sample in this trial involving adolescents was smaller than samples in similar phase 3 trials involving adults,[18] strengths of our trial included the randomized and placebo-controlled trial design, the multinational and diverse population, and the relatively high retention rate, as compared with rates previously reported in trials evaluating obesity in pediatric patients.[8,9] Limitations included the lack of measurements of body composition and of other potentially relevant cardiometabolic variables, as well as the limited power to detect significant differences

with regard to secondary outcomes of cardio-metabolic markers and results on quality-of-life assessments.

In adolescents with obesity, the use of liraglutide (3.0 mg) as an adjunct to lifestyle therapy led to a greater reduction in the BMI standard-deviation score than placebo. The higher frequency of gastrointestinal adverse events observed with liraglutide suggests that this treatment may not be suitable for all patients.

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