ORIGINAL ARTICLE

Liraglutide in Children and Adolescents with Type 2 Diabetes

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ABSTRACT

BACKGROUND

Metformin is the regulatory-approved treatment of choice for most youth with type 2 diabetes early in the disease. However, early loss of glycemic control has been observed with metformin monotherapy. Whether liraglutide added to metformin (with or without basal insulin treatment) is safe and effective in youth with type 2 diabetes is unknown.

METHODS

Patients who were 10 to less than 17 years of age were randomly assigned, in a 1:1 ratio, to receive subcutaneous liraglutide (up to 1.8 mg per day) or placebo for a 26-week double-blind period, followed by a 26-week open-label extension period. Inclusion criteria were a body-mass index greater than the 85th percentile and a glycated hemoglobin level between 7.0 and 11.0% if the patients were being treated with diet and exercise alone or between 6.5 and 11.0% if they were being treated with metformin (with or without insulin). All the patients received metformin during the trial. The primary end point was the change from baseline in the glycated hemoglobin level after 26 weeks. Secondary end points included the change in fasting plasma glucose level. Safety was assessed throughout the course of the trial.

RESULTS

Of 135 patients who underwent randomization, 134 received at least one dose of liraglutide (66 patients) or placebo (68 patients). Demographic characteristics were similar in the two groups (mean age, 14.6 years). At the 26-week analysis of the primary efficacy end point, the mean glycated hemoglobin level had decreased by 0.64 percentage points with liraglutide and increased by 0.42 percentage points with placebo, for an estimated treatment difference of –1.06 percentage points ($P<0.001$); the difference increased to –1.30 percentage points by 52 weeks. The fasting plasma glucose level had decreased at both time points in the liraglutide group but had increased in the placebo group. The number of patients who reported adverse events was similar in the two groups (56 [84.8%] with liraglutide and 55 [80.9%] with placebo), but the overall rates of adverse events and gastrointestinal adverse events were higher with liraglutide.

CONCLUSIONS

In children and adolescents with type 2 diabetes, liraglutide, at a dose of up to 1.8 mg per day (added to metformin, with or without basal insulin), was efficacious in improving glycemic control over 52 weeks. This efficacy came at the cost of an increased frequency of gastrointestinal adverse events. (Funded by Novo Nordisk; Ellipse ClinicalTrials.gov number, NCT01541215.)

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The incidence of type 2 diabetes in children and adolescents is increasing, with the increase driven by childhood obesity, and type 2 diabetes disproportionately affects disadvantaged minorities.[1-3] Metformin is the regulatory-approved treatment of choice for most youth with type 2 diabetes early in the disease.[4,5] However, rapid decline in β-cell function combined with severe insulin resistance contributes to early loss of glycemic control with metformin monotherapy.[2,4,6] Insulin is the only drug class approved for use in youth who do not have an adequate response to metformin monotherapy,[4,5] whereas a large number of oral and injectable agents of different classes are approved for adults.[7] This discrepancy in available treatments for youth as compared with adults persists because of a lack of successfully completed trials needed for approval of new drugs for the treatment of type 2 diabetes in children since a trial of metformin was completed in 1999.[8]

Regulatory agencies mandate that new drugs that have been approved for use in adults with type 2 diabetes undergo efficacy and safety trials in youth with the disease.[9,10] A phase 2 study of the glucagon-like peptide-1 analogue liraglutide showed that approved adult dose ranges were also appropriate for children with type 2 diabetes.[11,12] The Evaluation of Liraglutide in Pediatrics with Diabetes (Ellipse) phase 3 trial of liraglutide was launched in 2012, enrolled patients for a period of 4 years and 4 months, and was successfully completed in 2018. Here we report the efficacy and safety outcomes of this trial.

Methods

Trial Design and Oversight

We aimed to confirm the superiority of liraglutide to placebo in controlling glycemia in children and adolescents when added to treatment with metformin with or without insulin. We conducted a randomized, parallel-group, placebo-controlled trial with a 26-week double-blind period followed by a 26-week open-label extension period at 84 sites in 25 countries. Written informed consent was obtained from a legally acceptable representative of all participants, and assent from all child participants was obtained except in Israel, where the assent form was not applicable.

The trial protocol and statistical analysis plan (available with the full text of this article at NEJM.org) were designed by the sponsor (Novo Nordisk). The protocol (without the statistical analysis plan) was developed in accordance with local regulations and was reviewed and approved by an independent ethics committee or institutional review board at each site. An independent data monitoring committee had access to all unblinded data for the purpose of ensuring patient safety. Amendments to the protocol are listed in the Supplementary Appendix, available at NEJM.org. Site investigators gathered the data, and the sponsor performed site monitoring, collected the data, and performed the analyses.

All the authors had access to the trial results and vouch for the fidelity of the trial to the protocol. The first author wrote the first draft of the manuscript, and the manuscript was subsequently revised and approved by all the authors, who agreed to submit the manuscript for publication. The first author also vouches for the accuracy and completeness of the data. An independent medical writer, funded by the sponsor, provided editorial support, with guidance from the authors.

Patients

Eligible patients were 10 to less than 17 years of age at the time of randomization, had type 2 diabetes, had glycated hemoglobin levels between 7.0 and 11.0% if they were being treated with diet and exercise alone or between 6.5 and 11.0% if they were being treated with metformin (with or without insulin), and had a body-mass index (BMI) greater than the 85th percentile (with an age- and sex-matched population as reference).

Patients were excluded if they had type 1 diabetes, maturity-onset diabetes of the young, a fasting C-peptide level of less than 0.6 ng per milliliter, or antibodies against insulinoma-associated 2 or glutamic acid decarboxylase. Other exclusion criteria were the use of any antidiabetic agent other than metformin or basal insulin within 90 days before screening; a history of pancreatitis; serum calcitonin levels of 50 ng or more per liter; a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2; an alanine aminotransferase level 2.5 times the upper limit of the normal range or higher; serum creatinine levels greater than the upper limit of the normal range for age; a recent history of heart disease, proliferative retinopathy or maculopathy; and recurrent severe hypoglycemia or hypoglycemic unawareness. Complete inclusion and exclusion criteria are listed in the Supplementary Appendix.

TRIAL PROCEDURES

All screening variables to determine eligibility were assessed within a 2-week period. Eligible patients entered an 11-to-12-week run-in period (3 to 4 weeks during which metformin was increased to the maximum tolerated dose between 1000 mg and 2000 mg per day, followed by 8 weeks of maintenance). Eligibility criteria included a fasting plasma glucose level between 126 mg and 220 mg per deciliter (between 7.0 mmol and 12.2 mmol per liter) and a stable metformin dose (in most patients, 1000 mg to 2000 mg per day) for at least 8 weeks. Patients who were receiving metformin at a dose of more than 2000 mg when they entered the trial continued receiving that dose. Patients who were being treated with basal insulin had to have been on a stable dose for at least 8 weeks. Diet and exercise counseling was provided, according to local standards, at several visits.

Eligible patients were randomly assigned, in a 1:1 ratio, to receive subcutaneous liraglutide or placebo for 26 weeks, in combination with metformin, with or without basal insulin, on a background of a diet and exercise regimen. An interactive voice-response or Web-based response system randomly assigned the patients and maintained blinding until the end of week 26. Randomization was stratified by sex and by age at the end of treatment (≤14 years or >14 years).

After randomization, administration of liraglutide or placebo by subcutaneous injection (with visually identical prefilled pen injectors) was initiated at a dose of 0.6 mg per day, and the dose was escalated in both groups in increments of approximately 0.6 mg each week over the course of 2 to 3 weeks. Dose adjustment was based on side effects and the efficacy of the lower dose. Doses were not increased if the average of three fasting plasma glucose measurements during 3 consecutive days preceding the dose-escalation visit was 110 mg per deciliter (6.1 mmol per liter) or less. If the average fasting plasma glucose was more than 110 mg per deciliter, the dose was increased in 0.6-mg increments to a maximum dose of 1.8 mg per day. After the 3-week dose-escalation period, patients maintained a stable dose of liraglutide or placebo. Patients who were being treated with basal insulin reduced their insulin doses by 20% at the time of randomization, but after completion of the dose-escalation period of liraglutide or placebo, the basal insulin dose could be increased — but to no more than the baseline dose.

The treatment assignment (liraglutide or placebo) was unblinded after the 26-week visit, but the trial continued for an additional 26-week open-label period. During the open-label period, patients assigned to liraglutide continued their treatment unchanged, whereas those assigned to placebo discontinued the placebo but continued metformin (with or without basal insulin).

Prespecified criteria for rescue treatment with insulin that were based on fasting plasma glucose levels were applied to ensure acceptable glycemic control in both treatment groups. Rescue treatment, which was administered in addition to the trial product, was prescribed at the investigators' discretion (see the Supplementary Appendix). Basal insulin, either alone or in combination with rapid-acting insulin, was permitted.

END POINTS

The primary efficacy end point was the change from baseline in glycated hemoglobin level at week 26. Confirmatory secondary efficacy end points were the change in fasting plasma glucose levels from baseline, the percentage of patients who reached a glycated hemoglobin level of less than 7.0%, and the change from baseline in the BMI z score (the z score represents the number of standard deviations by which the BMI differs from the mean in a reference sex- and age-matched population), all at week 26 (also measured at week 52). Additional secondary end points included the changes from baseline in body weight, fasting lipid levels, and systolic and diastolic blood pressure.

Adverse events, serious adverse events, and medical events of special interest were assessed throughout the trial (definitions are provided in the Supplementary Appendix). Hypoglycemic episodes were classified according to the Novo Nordisk and American Diabetes Association definitions (see the Supplementary Appendix). Lipase, amylase, and calcitonin levels at baseline and during the trial were evaluated with standard laboratory tests.

STATISTICAL ANALYSES

The sample size was calculated for the primary glycated hemoglobin end point alone; we determined that a sample size of 47 patients in each treatment group would give the study 80% power, assuming a mean (±SD) difference of 0.9±1.2 percentage points between the liraglutide group and the placebo group (a difference of 0.7 percent-

age points after adjustment for a 22% withdrawal rate). According to regulatory requirements, at least 30% of patients who underwent randomization were to be 10 to 14 years of age, at least 40% were to be female, and at least 30% were to be from the European Union or from countries with lifestyle and diabetes care similar to those in European Union countries. The full analysis set (patients as randomly assigned) and the safety analysis set (patients as treated) included all patients who received at least one dose of liraglutide or placebo.

For the primary statistical analysis, we used a pattern-mixture model, which allowed estimation of the treatment difference for all patients in the full analysis set, regardless of whether they received rescue treatment with insulin. Missing data at week 26 were imputed with the use of a regression model that was based on data from patients in the placebo group who completed week 26, with missing data for patients in the placebo group imputed from data throughout the trial and missing data for patients in the liraglutide group imputed from baseline data.

Missing data at week 26 were imputed 10,000 times, and for each of the 10,000 imputed data sets, the change in glycated hemoglobin level from baseline to week 26 was assessed with an analysis of covariance, with treatment and stratification groups (sex and age group) as categorical fixed effects and baseline glycated hemoglobin level as a covariate. The results obtained from analyzing the data sets were combined with the use of Rubin's rule to draw inference.[13]

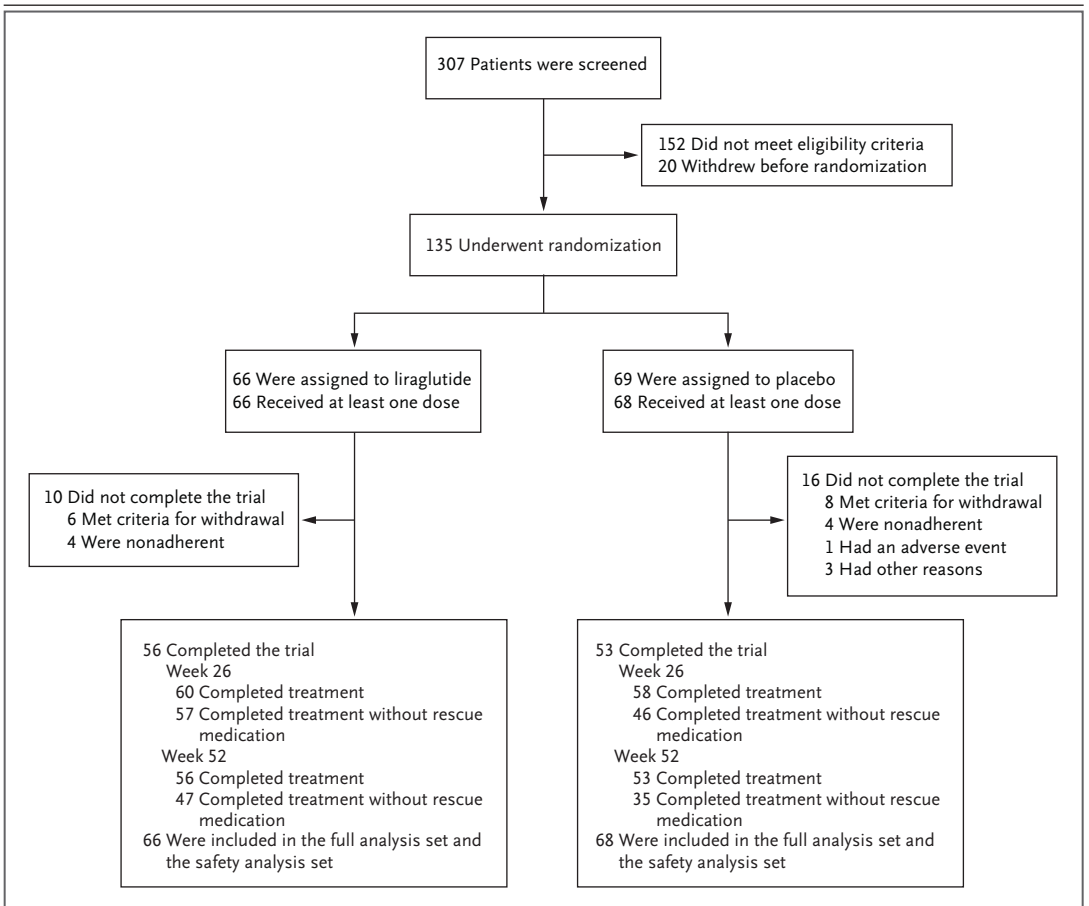


Figure 1. Screening, Randomization, and Follow-up.

The number of patients who were screened (307) and the number who were randomly assigned to a group (135) were higher than anticipated owing to the time that regulatory authorities needed to review and approve a protocol amendment. Once the amendment was approved, all screening of patients was stopped. One patient in the placebo group who underwent randomization in error did not receive the assigned placebo.

Primary and confirmatory secondary end points were analyzed in the order of the hierarchy to maintain a family-wise type I error rate of 5% in tests of the superiority of liraglutide to placebo with respect to the change from baseline in fasting plasma glucose level, glycated hemoglobin level of less than 7.0%, and BMI z score after 26 weeks of treatment. To be able to claim superiority for the listed end points, we first needed to show superiority with respect to the primary end point. A sensitivity analysis (mixed model of repeated measurements) in which data after initiation of rescue treatment were excluded was completed for all end points. Details of the other sensitivity analyses are provided in the Supplementary Appendix. Post hoc analyses of

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Liraglutide (N=66)	Placebo (N=68)	Total (N=134)
Age — yr	14.6±1.7	14.6±1.7	14.6±1.7
Female sex — %	62.1	61.8	61.9
Age of 10 to 14 yr at end of trial — no. (%)	21 (31.8)	19 (27.9)	40 (29.9)
Region — no. (%)			
Asia	6 (9.1)	6 (8.8)	12 (9.0)
Europe	24 (36.4)	21 (30.9)	45 (33.6)
North America	28 (42.4)	35 (51.5)	63 (47.0)
Rest of the world	8 (12.1)	6 (8.8)	14 (10.4)
Race or ethnic group — no. (%)†			
White	42 (63.6)	45 (66.2)	87 (64.9)
Black	9 (13.6)	7 (10.3)	16 (11.9)
Asian	10 (15.2)	8 (11.8)	18 (13.4)
American Indian or Alaska Native	2 (3.0)	1 (1.5)	3 (2.2)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	3 (4.5)	7 (10.3)	10 (7.5)
Hispanic or Latino ethnic group — no. (%)†			
Yes	16 (24.2)	23 (33.8)	39 (29.1)
No	50 (75.8)	45 (66.2)	95 (70.9)
Duration of diabetes — yr	1.9±1.7	1.9±1.3	1.9±1.5
Body weight — kg	93.3±31.0	89.8±22.1	91.5±26.8
BMI‡	34.55±10.87	33.27±7.36	33.90±9.25
BMI z score	3.03±1.47	2.86±1.11	2.94±1.30
Glycated hemoglobin — %	7.87±1.35	7.69±1.34	7.78±1.34
Fasting plasma glucose — mg/dl	156.8±52.2	146.8±38.3	151.7±45.8
Blood pressure — mm Hg			
Systolic	118.4±11.4	115.3±12.0	116.8±11.8
Diastolic	73.2±8.5	71.2±7.6	72.2±8.1
Metformin dose at baseline — mg	1912±286	1877±384	1894±339
Basal insulin use at baseline			
No. (%) of patients	15 (22.7)	10 (14.7)	25 (18.7)
Mean dose — U	29.6±19.5	29.6±17.7	29.6±18.4

* There were no significant differences between the groups in the characteristics listed. Percentages may not total 100 because of rounding. To convert the values for plasma glucose to millimoles per liter, multiply by 0.05551.
† Race and ethnic group were reported by the patient or the patient's guardian.
‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

the primary end point and two of the confirmatory secondary end points were performed with data stratified by sex and age group.

Proportions of patients who attained specified glycated hemoglobin levels were analyzed with the use of logistic regression (with missing data imputed as in the primary analysis). We analyzed additional secondary end points using a pattern-mixture model with multiple imputations (as for primary analysis). Safety end points were summarized with descriptive statistics.

Testing of the supportive secondary end points (all secondary end points other than the end points in the hierarchy) and post hoc subgroup analyses were not adjusted for multiplicity. Results are reported as point estimates with 95% confidence intervals, and widths of these confidence intervals should not be used to infer definitive treatment effects.

Figure 2 (facing page). Change from Baseline during the 52-Week Trial Period in the Primary and Two Secondary End Points.

Shown are the changes from baseline in the mean glycated hemoglobin level (the primary end point; Panel A), fasting plasma glucose level (Panel B), and BMI z score (Panel C) in the liraglutide group and the placebo group. Means are estimated from a mixed model of repeated measurements (MMRM) that included treatment, sex, and age group as fixed effects and baseline value as a covariate, all nested as interactions according to patient visits. Results from a pattern-mixture model (PMM) are shown at weeks 26 and 52. In the MMRM, data collected after initiation of rescue medication were handled as missing data. Liraglutide data included data from all patients who received liraglutide at any dose. I bars indicate standard errors. ETD denotes estimated treatment difference.

RESULTS

PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Enrollment began in November 2012 and was completed in May 2018. Of 307 patients screened, 135 were randomly assigned to a trial group, of whom 134 received at least one dose of either liraglutide (66 patients) or placebo (68 patients; 1 patient in this group did not received any dose) (Fig. 1, and Table S1 in the Supplementary Appendix). These 134 patients made up the full and safety analysis sets. Among all patients who underwent randomization, 118 patients (87.4%) — 60 (90.9%) in the liraglutide group and 58 (84.1%) in the placebo group — completed 26 weeks of treatment. Subsequently, 109 patients (80.7%) completed 52 weeks of treatment — 56 (84.8%) in the liraglutide group and 53 (76.8%) in the placebo group. A total of 86.4% of the patients in the liraglutide group and 66.7% in the placebo group completed the assigned regimen until week 26 without rescue medication, and 71.2% and 50.7%, respectively, completed the assigned regimen until week 52 without rescue medication. The baseline characteristics were balanced between the two groups (Table 1).

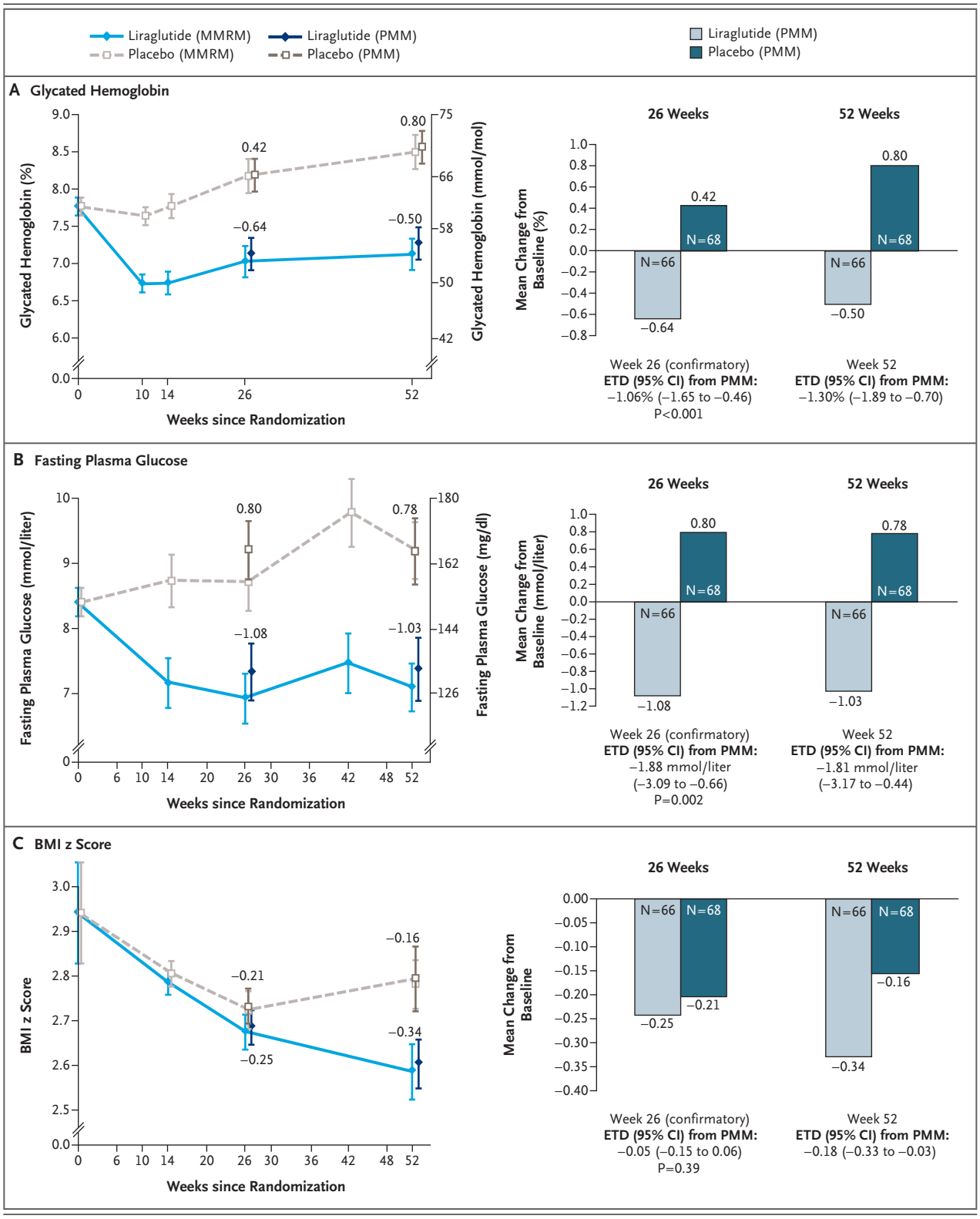
DOSE ESCALATION PERIOD

At the end of week 3, a total of 55.6% of the patients in the liraglutide group and 72.7% in the placebo group reached the 1.8-mg dose (Fig. S1 in the Supplementary Appendix). Throughout the remainder of the trial, doses in both groups remained relatively stable. Most patients did not receive the maximum dose of liraglutide or placebo because fasting plasma glucose levels of 110 mg or less per deciliter were achieved with the lower dose. Only six patients who received liraglutide and four who received placebo were unable to increase the dose, owing to unacceptable side effects.

EFFICACY OUTCOMES

Mean glycated hemoglobin levels at week 26 (the primary efficacy end point) were reduced from baseline by 0.64 percentage points in the liraglutide group, whereas the levels increased by 0.42 percentage points in the placebo group (estimated treatment difference, –1.06 percentage points; 95% confidence interval [CI], –1.65 to –0.46; P<0.001). This finding showed the superiority of liraglutide to placebo. The estimated treatment difference increased at week 52 (–1.30 percentage points; 95% CI, –1.89 to –0.70) (Fig. 2A). All six sensitivity analyses showed treatment differences consistent with the primary analysis, and there were no indications of effect by sex or age group (Fig. S2 and Table S2 in the Supplementary Appendix).

The superiority of liraglutide to placebo in reducing fasting plasma glucose levels by 26 weeks and by 52 weeks was also shown (Fig. 2B). Moreover, 63.7% of the patients in the liraglutide group, as compared with 36.5% in the pla-



cebo group, attained glycated hemoglobin levels of less than 7.0% (P<0.001) (Fig. S3 in the Supplementary Appendix). In contrast, the statistical superiority of liraglutide to placebo in lowering the BMI z score was not shown; the estimated treatment difference at week 26 was −0.05 (95% CI, −0.15 to 0.06), which subsequently increased at week 52 to −0.18 (95% CI, −0.33 to −0.03) (Fig. 2C). Similarly, mean body weight decreased in both groups at week 26 (–2.3 kg with liraglutide and −0.99 kg with placebo) but was maintained only with liraglutide at week 52 (–1.91 kg with liraglutide vs. 0.87 kg with placebo).

Very-low-density lipoprotein cholesterol levels were decreased more with liraglutide than with placebo at week 26 (ratio of change between liraglutide and placebo, 0.82; 95% CI, 0.72 to 0.94), as were triglyceride levels (ratio of change, 0.83; 95% CI, 0.72 to 0.95), but no differences were apparent at week 52. No between-group differences were seen in systolic and diastolic blood pressure at either time point (Tables S3 and S4 in the Supplementary Appendix).

SAFETY OUTCOMES

The percentage of patients with adverse events with an onset (or increase in severity) on or after the first day of exposure to the trial drug and no later than 7 days after the last day of receipt of the trial drug was similar in the liraglutide and placebo groups (Table 2, and Table S5 in the Supplementary Appendix). However, the rate of adverse events per 1 patient-year of exposure was higher with liraglutide than with placebo (Table 2), primarily owing to a higher incidence of gastrointestinal adverse events, especially during the initial 8 weeks. Nausea was the most frequently reported adverse event (Table 2), and the majority of all adverse events were mild in severity, resolved, and were considered by the investigators to be unrelated to liraglutide or placebo.

A higher percentage of patients in the liraglutide group than in the placebo group had serious adverse events and medical events of special interest (Table 2). There was no clustering of serious adverse events (Table S6 in the Supplementary Appendix). No deaths were reported.

The percentage of patients who had hypoglycemic episodes and the incidence of hypoglycemia were higher with liraglutide than with placebo (Table 2). There were no severe hypoglycemic episodes with liraglutide, and there was one severe episode in the placebo group in an insulin-treated patient.

The majority of patients in both treatment groups had normal lipase and amylase values, and all had normal calcitonin levels overall during the 52 weeks (Fig. S4 in the Supplementary Appendix). However, lipase levels were higher with liraglutide than with placebo at week 26 (treatment ratio 1.20; 95% CI, 1.08 to 1.32) and at week 52 (treatment ratio, 1.11; 95% CI, 1.01 to 1.23), whereas amylase levels were similar in the two treatment groups at week 26 and week 52.

DISCUSSION

Results from this double-blind, randomized, phase 3 trial showed the superiority of liraglutide to placebo in improving glycemic control at 26 weeks in youth with type 2 diabetes who had not had an adequate response to metformin, with or without insulin. Liraglutide also lowered fasting plasma glucose more than placebo, and almost twice as many patients in the liraglutide group than in the placebo group reached glycated hemoglobin levels less than 7.0%. Moreover, over the course of 52 weeks, a decrease of 0.50 percentage points in mean glycated hemoglobin levels was observed with liraglutide, whereas an increase of 0.80 percentage points was observed with placebo — an increase similar to previously reported changes in glycated hemoglobin levels observed over 12 months in youth with type 2 diabetes treated with metformin with or without insulin.[14,15]

An unexpected finding of this trial was the lack of difference between the groups in BMI z score or body weight at week 26, a finding that differs from the results of trials in adults.[16,17] Although the mean difference in weight loss between these treatment groups was similar to that in trials involving adults,[16,17] the relatively small number of patients in the current study and the fact that some children were probably still growing may explain the findings. Another explanation may be the fact that only approximately 50% of the liraglutide group received the full dose of 1.8 mg per day during the trial.

As was the case in studies involving adults with type 2 diabetes,[16,17] mild gastrointestinal complaints were the main cause of increased rates of adverse events with liraglutide. The observed incidence of hypoglycemia in the liraglu-

Table 2. Adverse Events and Hypoglycemic Episodes That Occurred during the 52-Week Trial Period.*

Event	Liraglutide (N=66)			Placebo(N=68)			Relative Risk (95% CI)
	no. of patients (%)	*no. of events*	*rate/1 pt-yr of exposure*	*no. of patients (%)*	*no. of events*	*rate/1 pt-yr of exposure*	
All events	56 (84.8)	426	7.144	55 (80.9)	321	5.425	1.05 (0.90–1.22)
Serious adverse events	9 (13.6)	10	0.168	4 (5.9)	5	0.085	2.32 (0.75–7.16)
Medical events of special interest	6 (9.1)	10	0.168	3 (4.4)	3	0.051	2.06 (0.54–7.90)
Adverse events leading to discontinuation	1 (1.5)†	1	0.017	1 (1.5)	2	0.034	1.03 (0.07–16.13)
Adverse events in at least 5% of patients‡							
Nausea	19 (28.8)	25	0.419	9 (13.2)	12	0.203	2.18 (1.06–4.46)
Vomiting	17 (25.8)	46	0.771	6 (8.8)	8	0.135	2.92 (1.23–6.95)
Diarrhea	15 (22.7)	22	0.369	11 (16.2)	13	0.220	1.40 (0.70–2.83)
Headache	14 (21.2)	27	0.453	13 (19.1)	39	0.659	1.11 (0.57–2.18)
Abdominal pain	12 (18.2)	23	0.386	5 (7.4)	6	0.101	2.47 (0.92–6.63)
Nasopharyngitis	11 (16.7)	16	0.268	19 (27.9)	28	0.473	0.60 (0.31–1.16)
Dizziness	8 (12.1)	10	0.168	2 (2.9)	4	0.068	4.12 (0.91–18.69)
Gastroenteritis	7 (10.6)	8	0.134	2 (2.9)	2	0.034	3.61 (0.78–16.73)
Upper respiratory tract infection	6 (9.1)	10	0.168	5 (7.4)	8	0.135	1.24 (0.40–3.86)
Dyspepsia	5 (7.6)	6	0.101	1 (1.5)	1	0.017	5.15 (0.62–42.92)
Rash	4 (6.1)	5	0.084	1 (1.5)	1	0.017	4.12 (0.47–35.91)
Pyrexia	4 (6.1)	5	0.084	5 (7.4)	5	0.085	0.82 (0.23–2.94)
Decreased appetite	4 (6.1)	4	0.067	3 (4.4)	3	0.051	1.37 (0.32–5.90)
Constipation	4 (6.1)	4	0.067	1 (1.5)	1	0.017	4.12 (0.47–35.91)
Dysmenorrhea	3 (4.5)	10	0.168	6 (8.8)	11	0.186	0.52 (0.13–1.98)
Upper abdominal pain	2 (3.0)	3	0.050	8 (11.8)	9	0.152	0.26 (0.06–1.17)
Increase in alanine aminotransferase	0	0	0	4 (5.9)	5	0.085	—
Hypoglycemia							
Minor§	16 (24.2)	23	0.386	7 (10.3)	13	0.220	2.35 (1.04–5.35)
ADA classification for all events¶	30 (45.5)	160	2.683	17 (25.0)	63	1.065	1.82 (1.11–2.97)
Severe	0	—	—	1 (1.5)	1	0.017	—
Documented symptomatic	19 (28.8)	55	0.922	6 (8.8)	26	0.439	3.26 (1.39–7.66)
Asymptomatic	21 (31.8)	75	1.258	12 (17.6)	23	0.389	1.80 (0.97–3.36)

* Data on liraglutide include data from all doses (0.6, 1.2, and 1.8 mg). Events include those that occurred from the time the first dose of liraglutide or placebo was administered to 7 days after the last date of administration at week 52.

† One patient in the liraglutide group who had an adverse event of hyperglycemia leading to treatment discontinuation was withdrawn owing to nonadherence to the drug.

‡ Selected adverse events are reported here; all adverse events that occurred in at least 5% of the patients, including hyperglycemia, pharyngitis, oropharyngeal pain, influenza, cough, and rhinorrhea, are listed in Table S5 in the Supplementary Appendix.

§ Minor hypoglycemia was defined by a symptomatic or asymptomatic hypoglycemic episode in a patient who had a plasma glucose of less than 55.8 mg per deciliter (3.1 mmol per liter).

¶ Not all American Diabetes Association (ADA) classifications are listed here; data on the classifications of probable symptomatic, relative, and ADA unclassifiable are provided in Table S5 in the Supplementary Appendix.

tide group was low as compared with the previously reported incidence of clinically important hypoglycemia in youth with type 1 diabetes,[18,19] and many of the reported hypoglycemic episodes were due to low plasma glucose levels, without any symptoms.

A potential limitation of this trial is the dose-escalation schedule that we used, including the possibility that the escalation may have been too quick, since only approximately 50% of the patients received the highest dose of liraglutide. The fact that approximately half the patients did not receive the highest dose may have limited data collection related to the safety profile of liraglutide. The trial was also limited by the long recruitment period (owing to problems inherent in clinical trials of youth with type 2 diabetes[2]), which necessitated some protocol amendments. In addition, because of the somewhat limited diversity of the trial population, the results may not be generalizable to all other populations.

In summary, the current study showed the superiority of liraglutide to placebo, when added to metformin, with or without basal insulin, with respect to glycemic control in children and adolescents. Gastrointestinal adverse events were more common in the liraglutide group.

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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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