Once-Weekly Exenatide in Youth With Type 2 Diabetes

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OBJECTIVE

Approved treatments for type 2 diabetes in pediatric patients include metformin, liraglutide, and insulin. However, approximately one-half of the youth fail metformin monotherapy within 1 year, insulin therapy is associated with challenges, and liraglutide requires daily injections. Consequently, the efficacy and safety of once-weekly injections of exenatide for the treatment of youth with type 2 diabetes was evaluated.

RESEARCH DESIGN AND METHODS

Participants (aged 10 to <18 years) were randomized (5:2) to once-weekly exenatide 2 mg or placebo, respectively. The primary efficacy end point was change in glycated hemoglobin from baseline to week 24. Secondary efficacy end points were also evaluated, and the frequency of adverse events (AEs) was assessed.

RESULTS

A total of 83 participants were randomized (exenatide, 59; placebo, 24) and 72 completed 24-week treatment (exenatide, 49; placebo, 23). At 24 weeks, the least squares mean change in glycated hemoglobin was −0.36% for the exenatide and +0.49% for the placebo groups (between-group difference, −0.85%; 95% CI −1.51, −0.19; *P* = 0.012). Nonsignificant least squares mean differences from baseline to 24 weeks favoring exenatide were observed: fasting glucose −21.6 mg/dL (−49.0, 5.7; *P* = 0.119), systolic blood pressure −2.8 mmHg (−8.0, 2.4; *P* = 0.284), and body weight −1.22 kg (−3.59, 1.15; *P* = 0.307). AEs occurred in 36 (61.0%) and 17 (73.9%) participants in the exenatide and placebo groups, respectively.

CONCLUSIONS

In youth with type 2 diabetes suboptimally controlled with current treatments, once-weekly exenatide reduced glycated hemoglobin at 24 weeks and was well tolerated.

The global epidemic of childhood obesity has been accompanied by an increase in the incidence and prevalence of type 2 diabetes in children and adolescents, especially among minority racial and ethnic groups (1–5). Type 2 diabetes is typically more aggressive in youth than in adults (6); data from the Pediatric Diabetes Consortium T2D Registry show that it is not uncommon for glycated hemoglobin levels to increase by almost 1% over a year in youth with glycated hemoglobin levels <6.5% (48 mmol/mol) on enrollment in the registry (7). Until recently, the only approved treatments for type 2 diabetes in pediatric patients were metformin and insulin (3). While both these agents have been shown to be effective during the initial treatment of new-onset type 2 diabetes (8,9), results of the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study demonstrated that ~50% of youth with type 2 diabetes fail metformin monotherapy within 11.5

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months of treatment initiation (10). Moreover, rescue therapy with exogenous insulin in these age groups is associated with numerous challenges, including risks of hypoglycemia, excessive weight gain, and poor adherence (1,11).

Liraglutide, a once-daily injectable antihyperglycemic drug, was approved by the U.S. Food and Drug Administration and European Medicines Agency as an add-on therapy for pediatric patients with type 2 diabetes aged ≥10 years who have been receiving metformin with or without basal insulin (12,13). Liraglutide was studied in the double-blind, randomized Ellipse trial, the results of which demonstrated that liraglutide, when added to metformin with or without basal insulin, was superior to placebo in children and adolescents with type 2 diabetes in reducing glycated hemoglobin levels at 26 weeks (mean treatment difference −1.06% [$P < 0.001$]) (12). Exenatide, a glucagon-like peptide 1 receptor agonist, was the first agent approved in adults with type 2 diabetes that can be administered on a once-weekly basis (14,15). A major difference between the current study and the Ellipse trial is that liraglutide was administered as a daily injection, whereas in the current study exenatide was administered as a once-weekly injection (12). This study was undertaken to evaluate the efficacy and safety of once-weekly injection of exenatide for the treatment of children and adolescents with type 2 diabetes, which recently led to its approval by the U.S. Food and Drug Administration as an adjunct to diet and exercise in pediatric patients aged 10 to <18 years with type 2 diabetes (15).

RESEARCH DESIGN AND METHODS

Study Design

This was an international, multicenter, randomized, parallel-group, phase III study in youth aged 10 to <18 years with type 2 diabetes. Eligible participants were treated with diet and exercise alone or in combination with a stable dose of an oral glucose-lowering drug (metformin and/or a sulfonylurea) and/or insulin for at least 2 months prior to enrollment. The study—conducted at 27 sites in six countries (Supplementary Material)—included a 24-week, double-blind, placebo-controlled assessment period followed by a 28-week open-label extension period during which there was a single-arm crossover of participants from the placebo group to treatment with once-weekly exenatide (Supplementary Fig. 1).

Written informed consent was obtained from all participants as well as their caregivers. The trial protocol was approved by the ethics committee or institutional review board at each trial site (Supplementary Material). The study was performed in accordance with the ethics principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

Participants

Eligible participants had type 2 diabetes, were aged 10 to <18 years at enrollment, and had a glycated hemoglobin level of 6.5% (48 mmol/mol) to 11% (97 mmol/mol) for participants not taking insulin or a sulfonylurea and 6.5% (48 mmol/mol) to 12.0% (108 mmol/mol) for participants taking insulin or a sulfonylurea. Major exclusion criteria included C-peptide levels ≤0.6 ng/mL and renal disease or serum creatinine >1.5 mg/dL (132.6 μmol/L) in males or >1.4 mg/dL (123.8 μmol/L) in females. The full inclusion and exclusion criteria are available in Supplementary Material.

Study Procedures

Participants were randomized in a 5:2 ratio to receive once-weekly exenatide 2 mg or matching placebo. Randomization was stratified according to the glycated hemoglobin at screening (<9.0% or ≥9.0%). No titration was performed in starting the 2-mg once-weekly dose of exenatide, and dosing adjustments during the trial were prohibited. Rescue treatment was mandated for participants with a loss of glycemic control, defined as either an increase from baseline in glycated hemoglobin levels by ≥1.0% at two consecutive clinic visits that were at least 1 month apart or fasting plasma glucose level ≥250 mg/dL (13.9 mmol/L) or random blood glucose level >300 mg/dL (16.7 mmol/L) for 4 days during a 7-day period. Blood samples for fasting glucose were to be collected at weeks 0, 4, 8, 12, and 24.

Participants who required rescue therapy received antihyperglycemic therapy (e.g., insulin) administered by the investigator or were referred to their treating physician to seek conventional antihyperglycemic intervention. Participants receiving rescue therapy remained in the study and continued receiving the study medication at the investigator's discretion. Temporary use of insulin to treat acute decompensation due to an intercurrent illness was permitted for up to 2 weeks and was not considered rescue treatment.

Efficacy and Safety End Points From Baseline to Week 24

The primary efficacy end point was the change in glycated hemoglobin levels from baseline to week 24 in the exenatide and placebo groups. Secondary efficacy end points included changes in fasting plasma glucose levels, body weight, systolic blood pressure, and fasting insulin levels. Additional secondary end points included lipid profiles; proportion of participants with glycated hemoglobin <7% (53 mmol/mol), ≤6.5% (48 mmol/mol), and <6.5% at week 24; and proportion of participants requiring rescue treatment. Safety and tolerability end points included incidence of adverse events (AEs) and hypoglycemic events, laboratory parameters (insulin and lipid profiles), heart rate, and Tanner stage during the 24-week randomized treatment period.

Single-Arm Crossover During the 28-Week Extension Period

To limit the number and duration of placebo injections and to enhance recruitment, we switched participants in the placebo group from weekly injections of placebo to weekly injections of exenatide 2 mg during the 28-week extension period. Consequently, between-group efficacy and safety comparisons were limited to the initial 24-week randomization period.

Statistical Analyses

Assuming a true treatment difference of −0.7% between once-weekly exenatide and placebo in changes from baseline in glycated hemoglobin, an estimated dropout rate of 10%, a power of 74%, SD of 1.0%, and a two-sided significance level of 0.05, a sample size of 77 randomized participants was estimated.

The intention-to-treat population comprised all randomized participants who had received at least one dose of the randomized study medication. The evaluable population comprised all intention-to-treat participants who had received at least one dose of the study medication and had at least one baseline and postbaseline glycated hemoglobin assessment. Safety analyses were performed for the intention-to-treat population based on the actual treatment taken.

In general, the primary and secondary continuous efficacy variables for which multiple postbaseline measurements were collected were analyzed with a mixed model with a repeated-measures approach. Analyses of the categorical variables were conducted with a stratified Cochran-Mantel-Haenszel test, and data collected at the early termination visit were included in the analyses. Intercurrent events that may have occurred during the study were defined as receipt of rescue therapy, study medication discontinuation, and study withdrawal. Efficacy data collected after the initiation of rescue medication or following discontinuation of the study medication were excluded from the analyses.

The primary efficacy analysis model included change in glycated hemoglobin as the dependent variable and treatment group, visit, interaction between visit and treatment, region, baseline glycated hemoglobin, and interaction between visit and baseline glycated hemoglobin as the fixed effects. A fixed-sequence procedure hierarchical testing strategy was followed for the primary and secondary end points to account for the family-wise error rate, such that if superiority for the primary end point was established at the two-sided significance level of α = 0.05, the same superiority test was performed for selected secondary end points in the following prespecified order: glycated hemoglobin, fasting plasma glucose, body weight, and fasting insulin. These end points were based on the efficacy estimand, with exclusion of data after intercurrent events of rescue medication use and treatment discontinuation.

All safety and tolerability variables, including examination of AEs, clinical laboratory measurements, physical examination findings, and vital signs, were summarized descriptively by visit up to week 24. Observations after rescue medication use were included for safety analyses. AEs were summarized according to the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0. For hypoglycemic events, participants were asked to record and report any hypoglycemia symptoms and the blood glucose values associated with these symptoms. If the investigator determined these symptoms to be consistent with hypoglycemia, data were entered in an electronic case report form (eCRF) designed for collection of information on hypoglycemic events, with grading according to intensity. Based on data entered in the eCRF, hypoglycemia was programmatically classified as major, minor, or other hypoglycemia. Major hypoglycemia events were defined as events that resulted in loss of consciousness, seizure, or coma (or other mental status changes consistent with neuroglycopenia as judged by the investigator) that resolved after administration of glucagon or glucose or events that required third-party assistance to resolve because of severe impairment in consciousness or behavior (regardless of whether symptoms of hypoglycemia were detected by the participant) and were associated with plasma or capillary glucose level $<$3 mmol/L (54 mg/dL). Minor hypoglycemia was defined as nonmajor hypoglycemia with symptoms consistent with hypoglycemia and glucose level $<$3 mmol/L (54 mg/dL) prior to treatment for the hypoglycemic episode. Other hypoglycemia was defined as hypoglycemia events that did not meet the criteria for a major or minor event. During the study, new American Diabetes Association (ADA) hypoglycemia criteria were released (16,17). In these, hypoglycemia was defined as level 1, glucose level $\leq$3.9 mmol/L (70 mg/dL); level 2, glucose level $<$3.0 mmol/L (54 mg/dL); and level 3, severe hypoglycemia (severe cognitive impairment requiring external assistance for recovery). Hypoglycemia according to the ADA definitions was also programmatically derived based on the available original hypoglycemia eCRF data; the results are given in Supplementary Material.

RESULTS

Participant Demographics and Clinical Characteristics

The first participant was enrolled on 12 May 2016, and the last visit of the last participant was on 6 May 2020. Of 159 participants enrolled and screened at the 36 centers, 83 were randomized (once-weekly exenatide, 59; placebo, 24) from 27 centers and entered the double-blind controlled assessment period; of these, 72 (86.7%) completed 24 weeks of treatment (Supplementary Fig. 2). One participant who was randomized to once-weekly exenatide did not receive any study medication due to an AE of vomiting, which led to study discontinuation before the first exenatide dose; this participant was not counted as completing or discontinuing treatment. Baseline characteristics were generally balanced between the two groups (Table 1), although severe obesity was slightly more common in the once-weekly exenatide group. All participants were aged 10 to $<$18 years. Overall, 59% of participants were female and 42.7% were White, 30.5% Black or African American, 6.1% American Indian or Alaska Native, and 44% Hispanic or Latino. At baseline, 12% of participants were treatment naive and 38% were treated with both insulin and metformin.

Most participants (95.1%) used 80% to $<$120% of dispensed study medication: 57 participants (96.6%) in the once-weekly exenatide group and 21 participants (91.3%) in the placebo group.

Efficacy Outcomes During the 24-Week Controlled Assessment Period

At 24 weeks, the least squares mean change in glycated hemoglobin, which was the primary end point, was $-$0.36% for the once-weekly exenatide group and 0.49% for the placebo group, with a between-group difference of $-$0.85% (95% CI $-$1.51, $-$0.19; P = 0.012), demonstrating the superiority of exenatide to placebo (Fig. 1).

Nonsignificant numerical differences, favoring exenatide, were observed in changes in the secondary end points from baseline to 24 weeks (Fig. 2). These included changes in fasting plasma glucose (least squares mean difference $-$21.6 mg/dL; 95% CI $-$49.0, 5.7), systolic blood pressure ($-$2.8 mmHg; $-$8.0, 2.4), and body weight ($-$1.22 kg; $-$3.59, 1.15). Conversely, fasting insulin levels increased in the exenatide group compared with the placebo group ($+$94.9 pmol/L; $-$95.6, 285.5). Furthermore, mean changes from baseline in triglyceride levels were $-$0.12 mmol/L for exenatide vs. 0.09

Table 1—Baseline participant characteristics (intention-to-treat analysis set)

	Exenatide (*N* = 58)	Placebo (*N* = 24)	Total (*N* = 82)
Age, years, mean ± SD (min, max)	15 ± 1.9 (11, 17)	16 ± 1.7 (12, 17)	15 ± 1.8 (11, 17)
Female sex	31 (53.4)	17 (70.8)	48 (58.5)
Region			
Europe	8 (13.8)	4 (16.7)	12 (14.6)
Middle East	2 (3.4)	1 (4.2)	3 (3.7)
North America	35 (60.3)	17 (70.8)	52 (63.4)
South America	13 (22.4)	2 (8.3)	15 (18.3)
Race			
White	23 (39.7)	12 (50.0)	35 (42.7)
Black or African American	17 (29.3)	8 (33.3)	25 (30.5)
Asian	2 (3.4)	1 (4.2)	3 (3.7)
Native Hawaiian or other Pacific Islander	0	0	0
American Indian or Alaska Native	4 (6.9)	1 (4.2)	5 (6.1)
Other	12 (20.7)	2 (8.3)	14 (17.1)
Hispanic or Latino ethnic group			
Yes	25 (46.3)	8 (38.1)	33 (44.0)
No	29 (53.7)	13 (61.9)	42 (56.0)
Duration of diabetes, years, mean ± SD	2 ± 2	3 ± 2	2 ± 2
Body weight, kg, mean ± SD	102.2 ± 30.1	96.7 ± 22.7	100.6 ± 28.1
BMI, kg/m^2, mean ± SD	36.86 ± 9.28	35.14 ± 6.58	36.36 ± 8.57
Glycated hemoglobin, %, mean ± SD (mmol/mol)	8.1 ± 1.2 (65.0)	8.3 ± 1.5 (67.2)	8.2 ± 1.3 (66.1)
Fasting plasma glucose, mg/dL, mean ± SD	165.0 ± 59.3	170.5 ± 60.4	166.6 ± 59.3
Prior antihyperglycemia treatment naive	8 (13.8)	2 (8.3)	10 (12.2)
Prior antihyperglycemia drug use			
Metformin only	22 (37.9)	11 (45.8)	33 (40.2)
Insulin only	6 (10.3)	1 (4.2)	7 (8.5)
Insulin and metformin	21 (36.2)	10 (41.7)	31 (37.8)
Metformin and a sulfonylurea	1 (1.7)	0	1 (1.2)

Data are *n* (%) unless otherwise indicated. Baseline was defined as the last nonmissing assessment (scheduled or unscheduled) on or prior to the first dose of the randomized study medication. Percentages were calculated from the number of participants in the analysis set with nonmissing data, by treatment group and in total. max, maximum; min, minimum.

mmol/L for placebo. Only marginal changes were observed in total cholesterol and LDL or HDL cholesterol (Supplementary Table 1).

Among participants treated with insulin at baseline (mean daily insulin dose 42.2 IU/day), a mean decrease from baseline of 3.1 IU/day was observed in the exenatide group compared with a mean increase from baseline to week 24 of 3.2 IU/day in the placebo group. Moreover, during the 24-week study period, one participant in the exenatide group and no participants in the placebo group received rescue medication.

Supplementary Fig. 3 shows the proportions of participants achieving glycated hemoglobin levels of $<$7% (53 mmol/mol) and $\leq$6.5% (48 mmol/mol) at week 24. Similar results were obtained for participants achieving glycated hemoglobin levels of $<$6.5% at week 24 (data not shown).

Safety Outcomes During the 24-Week Controlled Assessment Period

A total of 36 participants (61.0%) in the once-weekly exenatide group vs. 17 participants (73.9%) in the placebo group had at least one AE. In addition, serious AEs were reported by two participants (3.4%) in the exenatide group compared with one participant (4.3%) in the placebo group. No deaths were reported in either group. Overall, gastrointestinal disorder–related AEs were reported slightly less frequently in the exenatide group (22.0%) than in the placebo group (26.1%) (Table 2). Conversely, upper abdominal pain, abdominal distension, diarrhea, dyspepsia, nausea, and vomiting were more frequent in participants treated with exenatide versus those treated with placebo. However, none of the gastrointestinal disorder–related AEs in the exenatide group led to study drug discontinuation by the investigator and most were mild or moderate in intensity and resolved during the study period. In general, the most common AEs were upper respiratory tract infections (10.2%) in the exenatide group (vs. 0% in the placebo group) and abdominal pain (13%) in the placebo group (vs. 3.4% in the exenatide group).

There were no major hypoglycemia events in either treatment group. Minor hypoglycemia occurred in one participant in each group, both of whom were receiving insulin. Other hypoglycemia events were reported in eight participants in the exenatide group (six of whom were receiving insulin treatment at baseline) (Table 2). Supplementary Table 2 shows the incidence of hypoglycemia as defined by the newer ADA guidelines (16,17). One participant in the exenatide group experienced a level 3 hypoglycemic event, described further in Supplementary Table 2. Supplementary Table 3 shows the

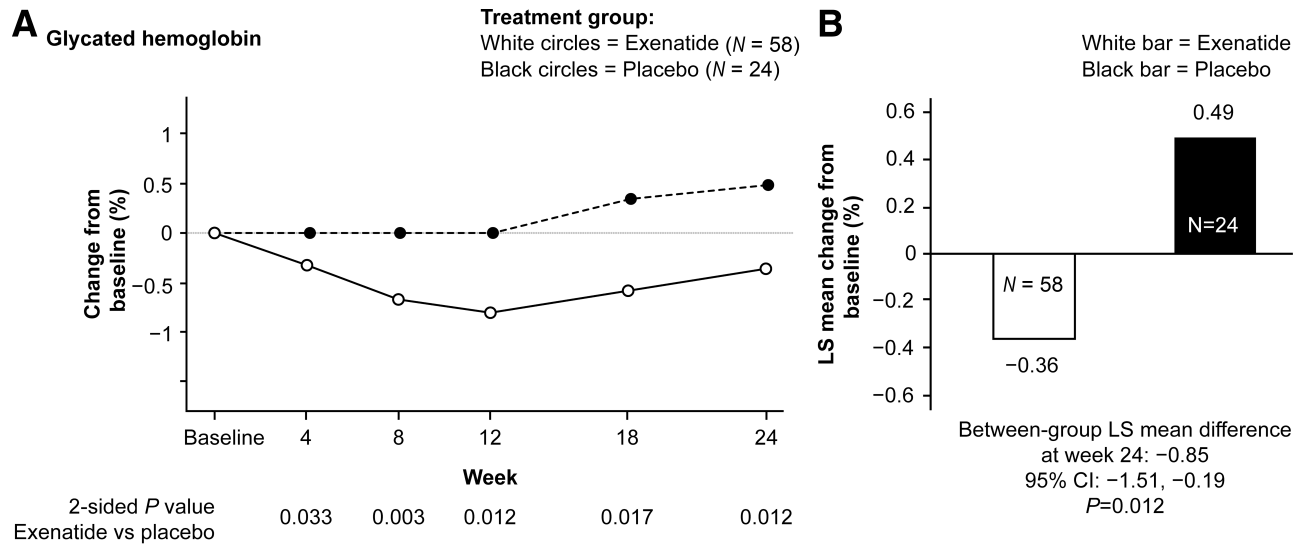

Figure 1—Change in glycated hemoglobin (%) from baseline to each visit between baseline and week 24 with a mixed model with repeated-measures analysis (*A*) and change in least squares (LS) mean at week 24 (evaluable analysis set) (*B*). Adjusted LS means at each visit were modeled with use of a mixed model with repeated measures including treatment group, region, visit, treatment group–by–visit interaction, baseline glycated hemoglobin level (continuous), and baseline glycated hemoglobin–by–visit interaction as fixed effects, with an unstructured covariance matrix. Baseline was defined as the last nonmissing assessment (scheduled or unscheduled) on or prior to the first dose of the randomized study medication. Data collected after the initiation of rescue medication or after premature discontinuation of the study medication were excluded.

incidence of hypoglycemia in participants using insulin and/or a sulfonylurea at baseline.

A small increase in heart rate was observed from baseline to week 24 in both the exenatide (mean +5.0 bpm) and placebo (+8.5 bpm) groups. No participants reported hypotension during the study. There were no clinically meaningful trends or notable differences in laboratory parameters or growth and development indices as assessed with Tanner staging.

Single-Arm Crossover of Placebo Group Participants During the 28-Week Extension

A total of 23 participants from the placebo group crossed over to treatment with exenatide during the entire 28-week extension period. For these participants, mean glycated hemoglobin was 8.75% (72.1 mmol/mol) at week 24, which decreased to 8.41% (68.4 mmol/mol) at the end of the 28-week extension period.

CONCLUSIONS

The results of the current study demonstrated the efficacy of a once-weekly injection of exenatide, a glucagon-like peptide 1 receptor agonist, in children and adolescents with type 2 diabetes aged 10 to <18 years at study entry. Specifically, add-on therapy with once-weekly exenatide was superior to placebo in participants who did not have effective treatment for their type 2 diabetes with a lifestyle intervention with or without metformin and with or without insulin. In addition, once-weekly exenatide allowed a greater proportion of participants to achieve strict glycemic targets after 24 weeks of treatment. Improved glucose control was observed in conjunction with trends toward increased endogenous insulin secretion and reduced body weight. Moreover, a consistent response to once-weekly exenatide with regard to lowering of glycated hemoglobin levels was evident in participants in the placebo group who crossed over to treatment with exenatide during the 28-week extension period of the study.

Although the effect size for reduction in glycated hemoglobin levels was smaller than that found in adult studies (18), a possible reason is that type 2 diabetes is more aggressive in youth than in adults, as illustrated by the faster increase in glycated hemoglobin levels (6) and more rapid deterioration of β-cell function in youth than in adults (19–21). The aggressive nature of type 2 diabetes in youth can also explain the observation that the estimated change from baseline in glycated hemoglobin levels for participants in the exenatide group was not that large. However, there was a dramatic increase in glycated hemoglobin levels in participants in the placebo group. Since the effect size is the difference versus placebo, not the difference versus baseline, we consider the −0.85% difference between groups in glycated hemoglobin levels to be clinically relevant. With a disease that is so relentlessly progressive in this population, large treatment effects are needed to maintain glycated hemoglobin levels or to show even modest improvements in comparison with the glycated hemoglobin levels prior to starting treatment. The modest change from baseline in glycated hemoglobin levels for participants in the exenatide group is therefore a reminder of the aggressive nature of youth-onset type 2 diabetes and the treatment challenges this population presents.

Although differences between the two treatment groups in secondary end points consistently favored exenatide over placebo in terms of changes in fasting plasma glucose, body weight, and systolic blood pressure, these secondary outcomes failed to achieve statistical significance.

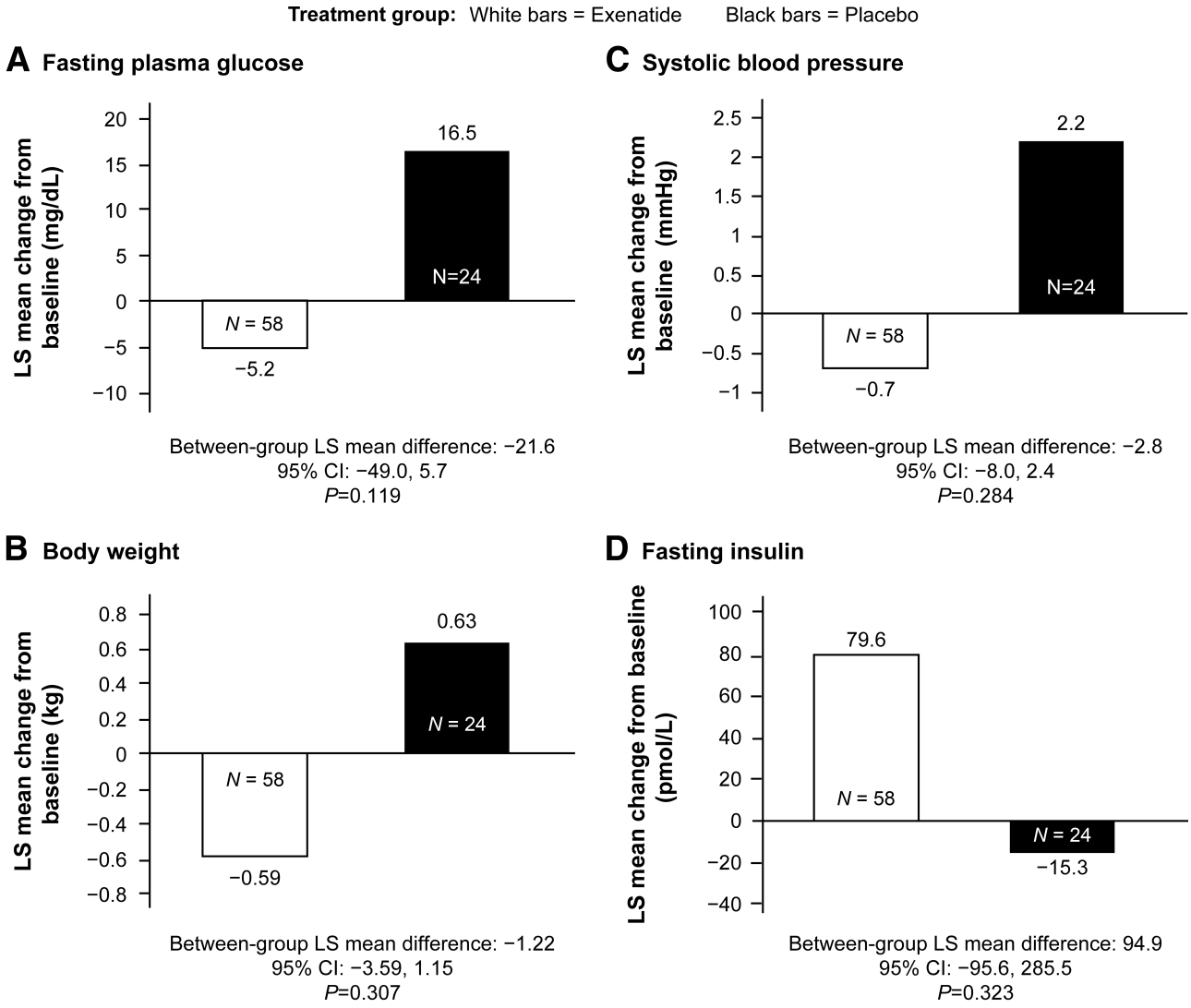

Figure 2—Changes in fasting plasma glucose (*A*), body weight (*B*), systolic blood pressure (*C*), and fasting insulin (*D*) from baseline to week 24 with use of a mixed model with repeated measures analysis (least squares [LS] mean). Adjusted LS mean and treatment group difference in the change from baseline at week 24 were modeled with use of a mixed model with repeated measures including treatment group, region, screening glycated hemoglobin category, visit, treatment group–by–visit interaction, baseline level, and baseline level–by–visit interaction as fixed effects, with an unstructured covariance matrix. Baseline was defined as the last nonmissing assessment (scheduled or unscheduled) on or prior to the first dose of the randomized study medication. Data collected after the initiation of rescue medication or after premature discontinuation of the study medication were excluded. *N*, number of participants in the evaluable analysis set within the treatment group.

The finding that once-weekly exenatide was safe and well tolerated by our participants with type 2 diabetes is as important as its demonstrated efficacy. There were no events of major hypoglycemia in either treatment group, based on definitions of hypoglycemia as originally specified in the protocol when the study was designed. The definition of "major" hypoglycemia that was applied in the study is distinct from the current ADA definition (16,17) of "severe" hypoglycemia that was programmatically derived after the study had been completed. The result of this reevaluation indicated one severe event of unclear significance in the exenatide group, as described in Supplementary Material. Safety factors of particular importance in this study included the low rates of hypoglycemia despite insulin use and comparatively good gastrointestinal tolerability reflective of the slow buildup of exenatide when treatment starts due to the microsphere technology. It is also noteworthy that the safety profile of exenatide was consistent with the known safety profile in adults (14). In adults with type 2 diabetes, the most frequently reported AEs associated with treatment with once-weekly exenatide are gastrointestinal AEs (nausea, diarrhea, vomiting) and injection site reactions (pruritus, erythema, nodules) (14). Thus, the decreased patient burden and greater patient and provider acceptability of a once-weekly injectable medication might offer benefits in the treatment of youth with type 2 diabetes.

Some limitations of the study should be noted. One of the major reasons why very few drugs have been approved for use in pediatric type 2 diabetes is the well-described difficulty in recruiting patients in this age range for pivotal

Table 2—Summary of adverse events for participants on treatment during the controlled assessment period (safety analysis set)*

Event	Exenatide (*N* = 59)	Placebo (*N* = 23)	Total (*N* = 82)
Any AE	36 (61.0)	17 (73.9)	53 (64.6)
Any AE with outcome of death	0	0	0
Any SAE including those with outcome of death	2 (3.4)	1 (4.3)	3 (3.7)
Any AE related to treatment†	15 (25.4)	5 (21.7)	20 (24.4)
Gastrointestinal disorders‡	13 (22.0)	6 (26.1)	19 (23.2)
Abdominal distension	1 (1.7)	0	1 (1.2)
Abdominal pain	2 (3.4)	3 (13.0)	5 (6.1)
Abdominal pain upper	3 (5.1)	0	3 (3.7)
Diarrhea	5 (8.5)	1 (4.3)	6 (7.3)
Dyspepsia	1 (1.7)	0	1 (1.2)
Gastrointestinal pain	0	1 (4.3)	1 (1.2)
Gastroesophageal reflux disease	0	1 (4.3)	1 (1.2)
Gingival pain	1 (1.7)	0	1 (1.2)
Irritable bowel syndrome	0	1 (4.3)	1 (1.2)
Nausea	4 (6.8)	1 (4.3)	5 (6.1)
Salivary gland mucocele	0	1 (4.3)	1 (1.2)
Vomiting	3 (5.1)	0	3 (3.7)
Hypoglycemia	8 (13.6)	1 (4.3)	9 (11.0)
Major§	0	0	0
Minor‖	1 (1.7)	1 (4.3)	2 (2.4)
Other¶	8 (13.6)	1 (4.3)	9 (11.0)

Data are *n* (%). A controlled assessment period AE was defined as an AE starting on or after the day of the first dose of the study medication up to but not including week 24 for participants entering the extension period. For participants not entering the extension period, the period was defined up to and including the last dose of the study medication +7 days (+90 days for SAEs and other clinically significant or related AEs). Events were captured for the controlled assessment period whose length depended on whether participants entered the extension period as described above. Percentages were calculated from the number of participants in the analysis set for the study period by treatment group and in total. AEs were coded with MedDRA, version 23.0. SAE, serious AE. *Participants with multiple events in the same category were counted only once in that category. Participants with events in more than one category were counted once in each of those categories. †Included causally related AEs as judged by the investigator. ‡Number (%) of participants were sorted in international order for system organ class and alphabetical order for preferred term. §An event that resulted in loss of consciousness, seizure, or coma (or other mental status changes consistent with neuroglycopenia as judged by an investigator or physician) and that resolved after at least 1 item of intervention recorded in the hypoglycemic event eCRF or an event that required third-party assistance and was associated with a plasma or capillary glucose level of <3 mmol/L (54 mg/dL). ‖Nonmajor hypoglycemia event with symptoms consistent with hypoglycemia and a glucose level of <3 mmol/L (54 mg/dL) prior to treating the episode. ¶Hypoglycemia events that did not meet the criteria for a major or minor event.

studies (7,22–24). Some of these challenges include restrictive inclusion/exclusion criteria, the small patient pool from which to recruit, and socioeconomic factors that make it difficult for families to participate (23). Thus, it is not surprising that a limitation of this study includes its small sample size. Due to the limited size of the study, it was not possible to evaluate the results for each of the several classes of background antihyperglycemic medications used by the trial population. Given that the participants came from around the globe, unaccounted for differences in access to health care and other resources pertinent to diabetes management could have impacted the results. Although many confounding factors could have contributed to the results, differences in glycated hemoglobin levels between the two treatment groups were significant during the 24-week efficacy study.

In conclusion, the once-weekly glucagon-like peptide 1 receptor agonist exenatide demonstrated superiority in improving glycemic control versus placebo in youth with type 2 diabetes not optimally controlled with current treatments. Of significance, once-weekly exenatide was well tolerated, with a safety profile similar to that of adults. The results support once-weekly exenatide as a new treatment option for children and adolescents and highlight the challenges of treating youth-onset type 2 diabetes.

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work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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