Lixisenatide Therapy in Older Patients With Type 2 Diabetes Inadequately Controlled on Their Current Antidiabetic Treatment: The GetGoal-O Randomized Trial

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OBJECTIVE

To evaluate the efficacy and safety of lixisenatide versus placebo on glycemic control in older patients with type 2 diabetes uncontrolled on their current antidiabetic treatment.

RESEARCH DESIGN AND METHODS

In this phase III, double-blind, randomized, placebo-controlled, two-arm, parallel-group, multicenter trial, patients aged ≥70 years were randomized to receive once-daily lixisenatide 20 μg or placebo before breakfast concomitantly with their existing antidiabetic therapy (including insulin) for 24 weeks. Patients at risk for malnutrition or with moderate to severe cognitive impairment were excluded. The primary end point was absolute change in HbA_{1c} from baseline to week 24. Secondary end points included change from baseline to week 24 in 2-h postprandial plasma glucose (PPG) and body weight.

RESULTS

A total of 350 patients were randomized. HbA_{1c} decreased substantially with lixisenatide (−0.57% [6.2 mmol/mol]) compared with placebo (+0.06% [0.7 mmol/mol]) from baseline to week 24 ($P < 0.0001$). Mean reduction in 2-h PPG was significantly greater with lixisenatide (−5.12 mmol/L) than with placebo (−0.07 mmol/L; $P < 0.0001$). A greater decrease in body weight was observed with lixisenatide (−1.47 kg) versus placebo (−0.16 kg; $P < 0.0001$). The safety profile of lixisenatide in this older population, including rates of nausea and vomiting, was consistent with that observed in other lixisenatide studies. Hypoglycemia was reported in 17.6% of patients with lixisenatide versus 10.3% with placebo.

CONCLUSIONS

In nonfrail older patients uncontrolled on their current antidiabetic treatment, lixisenatide was superior to placebo in HbA_{1c} reduction and in targeting postprandial hyperglycemia, with no unexpected safety findings.

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**A complete list of the GetGoal-O Trial principal investigators can be found in the Supplementary Data online.*

See accompanying articles, pp. 440, 444, 453, 461, 468, 476, 494, 502, 509, 518, and 526.

Type 2 diabetes is a common condition in elderly people, with the highest prevalence in those aged between 70 and 79 years (1). Older patients with diabetes frequently have well-established complications of the disease and, as such, diabetes is a major contributing factor to mortality in this population (2,3).

Differences in the control of blood glucose exist between older and younger patients. In older patients, postprandial plasma glucose (PPG) appears to be affected more than fasting plasma glucose (FPG) (4,5), although this may be more a function of diabetes duration than age itself. Therefore, agents that preferentially lower PPG may be effective in achieving glycemic goals in this older population.

Hypoglycemia is a frequent adverse event (AE) of diabetes treatment and is common in older patients with type 2 diabetes (2,6), who are particularly prone to hypoglycemia owing to an impaired glucose counterregulation response to hypoglycemic conditions compared with younger patients (7). Hypoglycemia is a major treatment-limiting factor in older patients, and the risk of developing more severe symptoms associated with hypoglycemia increases with aging. In addition, the use of insulin and some sulfonylureas in older patients has been linked to an increased risk of hypoglycemia (8–10).

Few studies specifically in older adults with type 2 diabetes exist, limiting the applicability of the evidence to older, complex patients (11–16). In recognition of the particular pathophysiologic features of older patients with diabetes, the International Diabetes Federation (IDF) and the American Diabetes Association (ADA) developed guidelines specifically for the older population. The IDF 2013 global guideline for managing older patients with type 2 diabetes and the ADA, in alignment with American Geriatric Society guidelines (2004), recommend that functionally independent older patients who are active, have good cognitive function, and have a significant life expectancy should be treated with the standard goals used for younger adult patients with diabetes. For dependent patients with advanced diabetic complications, life-limiting comorbid illness, or substantial cognitive or functional impairment, less-intensive glycemic target goals are recommended because these patients are more likely to experience serious adverse effects from hypoglycemia (3,17).

Agents that can preferentially lower PPG without increasing the risk of hypoglycemia may be particularly useful in the treatment of geriatric patients with diabetes. The feature that most distinguishes short-acting glucagon-like peptide 1 receptor agonists (GLP-1RAs) from other oral antidiabetic drug (OAD) treatments is the ability to target and decrease PPG with a low risk of hypoglycemia, making this class of compound an attractive treatment option for achieving glycemic control in this patient group.

Lixisenatide (Lyxumia [European Union trade name]; Adlyxin [U.S. trade name]; Sanofi, Paris, France) is a selective GLP-1RA approved in >60 countries worldwide for use with oral glucose-lowering agents and/or basal insulin for the treatment of adults with type 2 diabetes when the use of these agents with diet and exercise has provided inadequate glycemic control (18,19). Lixisenatide enhances glycemic control, with a pronounced effect on PPG that is partly due to a delay in gastric emptying (20).

In two separate meta-analyses of five randomized controlled trials from the GetGoal phase III clinical trial program, lixisenatide plus OADs showed improved glycemic control in older patients inadequately controlled with OADs compared with placebo plus OADs and was effective and well tolerated in older (≥65 years) and very old (≥75 years) patients with type 2 diabetes (21,22).

The GetGoal-O trial investigated the efficacy and safety of lixisenatide in nonfrail patients aged ≥70 years with type 2 diabetes and with characteristics typical of the geriatric population encountered in clinical practice, including long-standing diabetes, use of a combination of antidiabetic therapies (basal insulin or sulfonylurea), renal impairment, polypharmacy, hypoglycemia symptoms typical in older patients, and hypoglycemia unawareness. Although this study excluded patients with moderate to severe cognitive impairment and those at risk for malnutrition, it is the first to our knowledge of a GLP-1RA that specifically focuses on older patients who may have had comorbidities and were inadequately controlled on their current antidiabetic treatment.

RESEARCH DESIGN AND METHODS

Trial Design

GetGoal-O was a phase III, double-blind, randomized, placebo-controlled, two-arm, parallel-group, multinational, multicenter study. The trial was double blinded with regard to active and placebo treatments.

Patients were stratified at randomization by HbA_{1c} (<8%, ≥8% [<64 mmol/mol, ≥64 mmol/mol]), basal insulin use (yes, no), and estimated glomerular filtration rate (eGFR) (≥60 mL/min/1.73 m^2, ≥30 to <60 mL/min/1.73 m^2). The trial comprised a screening period of up to 7 weeks, which included a screening phase of up to 3 weeks followed by a 4-week run-in phase. During the run-in phase, patients underwent training for self-monitoring of blood glucose, AE reporting, and hypoglycemia awareness and management of typical symptoms in older patients (i.e., nonspecific neurologic signs, including psychiatric or visual disorder, confusion, difficulty speaking, sensient sensory or motor defect). Patients were also required to report concomitant treatments daily. During the last week of the run-in phase, patients performed daily placebo self-injections as training. After the screening period, eligible patients entered a 24-week treatment phase (Supplementary Fig. 1). A 3-day safety follow-up period followed permanent study treatment discontinuation.

The protocol, protocol amendments, consent form, and written patient information were reviewed and approved by local independent ethics committees and/or institutional review boards before study initiation. The trial was conducted in accordance with the recommendations of the Declaration of Helsinki and Good Clinical Practice. All patients provided written consent before study participation.

Trial Population

Key inclusion criteria included diagnosis of type 2 diabetes inadequately controlled with a current antidiabetic treatment regimen, age ≥70 years at the time of signing the informed consent, at least 3 months on the current antidiabetic treatment regimen, and the ability to be compliant and to complete study procedures, including self-injection. Permitted antidiabetic therapies were metformin, sulfonylurea (except glibenclamide >10 mg and gliclazide >160 mg), meglitinide (except

repaglinide >6 mg), pioglitazone, and basal insulin. Patients taking basal insulin in combination with a sulfonylurea or meglitinide were not included.

Key exclusion criteria included HbA_{1c} ≤7% (≤53 mmol/mol) and >10% (>86 mmol/mol); however, because the threshold of 7% (53 mmol/mol) may not be appropriate for all older patients (23), inclusion was also based on the investigator's assessment of the individual patient, FPG >13.9 mmol/L at screening, basal insulin therapy combined with either a sulfonylurea or meglitinide, severe renal impairment (eGFR <30 mL/min/1.73 m^2) at visit 6 (week −1), amylase and/or lipase >3 times the upper limit of normal at visit 6 (week −1), and a history of severe hypoglycemia associated with unawareness of symptoms or leading to unconsciousness, coma, or seizure ≤6 months before screening. Patients at risk for malnutrition as defined by a score of <12 on the Mini-Nutritional Assessment-Short Form (MNA-SF) (24) or with moderate to severe cognitive impairment as defined by a score of <24 on the Mini Mental State Examination (25) were excluded also.

Randomization

After the run-in placebo phase, patients whose HbA_{1c} was >7% (>53 mmol/mol) and ≤10% (≤86 mmol/mol) at week −1 and who were able to self-manage (according to study procedure) were eligible for the 24-week, double-blind randomized treatment period. Eligible patients were randomized (1:1) to receive lixisenatide or placebo once daily (in the morning). An interactive voice/Web response system generated patient randomization.

Interventions

Lixisenatide or placebo was self-administered once daily by subcutaneous injection 30–60 min before breakfast. Lixisenatide treatment was initiated at the starting dose of 10 μg once daily for 2 weeks and then increased to the maintenance dose of 20 μg, which was continued until the end of the treatment period. If the target maintenance dose was not tolerated, the lixisenatide dose could be reduced to 10 μg during the first 8 weeks of treatment. Thereafter, the maintenance dose was kept stable. In patients who were receiving basal insulin at the start of the study and whose HbA_{1c} was 7.0–8.0% (53–64 mmol/mol) inclusive, the basal insulin dose was reduced by 20% when lixisenatide was initiated to avoid hypoglycemia. Between study weeks 4 and 12, the insulin dose was titrated according to self-monitored plasma glucose (SMPG) values, and the dose was permitted to be increased to the baseline value in the absence of hypoglycemia. Patients with HbA_{1c} between 7.0% (53 mmol/mol) and 8.5% (69 mmol/mol) who were receiving a sulfonylurea at baseline were required to reduce the sulfonylurea dose by 25% for the first 4 weeks of lixisenatide therapy. Similarly, the sulfonylurea dose could be titrated back to the baseline dose by week 12, provided that no hypoglycemia occurred. Patients whose HbA_{1c} was greater than the upper limits of the ranges described above did not have a mandated dose reduction of insulin or sulfonylurea at the time of lixisenatide initiation, but doses could be reduced in the case of two or more symptomatic or one severe symptomatic hypoglycemic episode.

The study included a standardized 400-mL liquid meal test, which was administered as breakfast during week −1 and again during week 24. The standardized meal was administered while patients had been in a fasting state for at least 8 h, and the lixisenatide injection was given 30 min before the meal. The liquid meal was composed of 53.8% carbohydrate, 16.7% protein, and 29.5% fat and contained 600 kcal energy.

A requirement for rescue therapy was defined as a period of 3 consecutive days during which a patient's fasting blood glucose value exceeded predefined thresholds: 270 mg/dL (15.0 mmol/L) from study week 0 to week 8, 240 mg/dL (13.3 mmol/L) from week 8 to week 12, and 200 mg/dL (11.1 mmol/L) or HbA_{1c} >9% from week 12 to week 24.

Study End Points

The primary end point was the absolute change in HbA_{1c} from baseline to week 24. Secondary efficacy end points were changes from baseline to week 24 in 2-h PPG and plasma glucose excursions during the standardized liquid breakfast meal test, 7-point SMPG profile, body weight, FPG, and total daily basal insulin dose for patients receiving basal insulin. Another secondary end point was the percentage of patients requiring rescue therapy during the 24-week, double-blind treatment period. A composite end point included the percentage of patients achieving a >0.5% (>5.5 mmol/mol) reduction in HbA_{1c} levels at week 24 without documented symptomatic hypoglycemia (<3.3 mmol/L). Other exploratory end points were nutritional and frailty status (MNA-SF), percentage of patients with an MNA-SF score of <12 at week 23, and quality-of-life assessment (Short Form 12-Item survey, 1-week recall) (26).

Safety end points were incidence of AEs (in particular, hypoglycemia and gastrointestinal side effects), other AEs and serious AEs, clinical laboratory parameters, and vital signs. Any hypoglycemic event, as reported by the investigator, included symptomatic (with specific symptoms for older patients) or asymptomatic (plasma glucose ≤3.9 mmol/L without symptoms) hypoglycemia. Symptomatic hypoglycemia as defined per protocol was an event with clinical symptoms considered to result from a hypoglycemic episode with an accompanying plasma glucose concentration <3.3 mmol/L or associated with prompt recovery after oral glucose or carbohydrate that contained glucose, intravenous glucose, or glucagon administration if no plasma glucose measurement was available. Documented symptomatic hypoglycemia was defined as an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of <3.3 mmol/L.

Statistical Analyses

The sample size calculations were based on the primary end point. A sample size of 340 randomized patients (170 per group) was to provide at least 90% power to detect a difference of 0.4% in the change in HbA_{1c} from baseline to week 24 between lixisenatide and placebo, assuming a common SD of 1.1% with a two-sided test at the 5% significance level.

Absolute change in HbA_{1c} from baseline to week 24 was analyzed by ANCOVA, with treatment (lixisenatide, placebo), HbA_{1c} (<8%, ≥8% [<64 mmol/mol, ≥64 mmol/mol]) at visit 6 (week −1), basal insulin use at screening (yes, no), eGFR (≥60 mL/min/1.73 m^2, ≥30 to <60 mL/min/1.73 m^2) at visit 6 (week −1), and country as fixed effects and baseline HbA_{1c} as a covariate. Comparisons of lixisenatide and placebo groups for all continuous secondary efficacy variables at week 24 were also analyzed by ANCOVA. Missing data were imputed by last observation carried forward (LOCF). All categorical efficacy parameters were analyzed by using the Cochran-Mantel-Haenszel

method stratified by the randomization strata mentioned above. AEs were summarized with descriptive statistics. Secondary efficacy end points were subject to multiple comparisons. To control for type I error, a step-down testing procedure was applied (testing order: 2-h PPG, 7-point SMPG, body weight, FPG, and percentage of patients requiring rescue therapy).

Efficacy analyses were performed for the modified intention-to-treat population, which was defined as all randomized patients who received at least one dose of study drug and had both a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy variables irrespective of compliance with the study protocol and procedures. Efficacy assessments were obtained during the on-treatment period (before medication was taken in the event of rescue therapy), unless otherwise specified. The effect size was calculated by comparing mean changes from baseline to end of treatment between treatment groups by using the Cohen classification for interpretation of change (27).

RESULTS

Overall, 350 patients were randomized in 73 centers in 13 countries. A total of 176 patients in the lixisenatide group and 174 patients in the placebo group were exposed to the treatment and included in the safety analyses. Twenty-one patients from each group discontinued treatment. In both groups, the main reason for treatment discontinuation was an AE (15 and 10 patients in the lixisenatide and placebo groups, respectively) (Supplementary Fig. 2). Baseline characteristics were similar across treatment groups, including duration of diabetes, age at onset of diabetes, HbA_{1c}, and BMI (Table 1). Overall, 37% of the patients were aged ≥75 years (11% were >80 years), and 28% had moderate renal impairment. A high proportion (93.1%) of patients had a history of cardiovascular/cerebrovascular disorders, although this was mainly driven by high rates of hypertension and dyslipidemia. In terms of background antidiabetic treatments, approximately one-third of patients were treated with basal insulin with or without OADs; one-third with a combination of OADs, including sulfonylureas; and one-third with a combination of OADs, excluding sulfonylureas (Table 1). At the end of the on-treatment period, 35 (20%) patients were receiving a maintenance dose of 10 μg lixisenatide, and 141 (80%) were receiving the target dose of 20 μg.

Primary Efficacy End Point

In the lixisenatide group, mean HbA_{1c} decreased steadily from baseline over the 24-week treatment period, although it remained stable in the placebo group (Fig. 1*A*). At week 24, mean HbA_{1c} levels were 7.36% (57 mmol/mol) and 8.01% (64 mmol/mol) for the lixisenatide and placebo groups, respectively. Superiority of lixisenatide compared with placebo was demonstrated for HbA_{1c} change from baseline to week 24 (least squares mean [LSM] difference 0.64%; $P < 0.0001$) (Table 2). The effect of lixisenatide on HbA_{1c} reduction was consistent regardless of patient age, renal function, and background antidiabetic therapy (Supplementary Fig. 3).

Secondary Efficacy and Exploratory End Points

The decrease from baseline to week 24 in 2-h PPG was significantly greater for lixisenatide than for placebo (LSM difference −5.05 mmol/L; $P < 0.0001$) (Table 2). The LSM difference in glucose excursion for lixisenatide versus placebo was −4.46 mmol/L (95% CI −5.231, −3.688 mmol/L). The daily average of the 7-point SMPG decreased significantly more from baseline to week 24 in the lixisenatide group than in the placebo group ($P < 0.0001$) (Fig. 1*B*). At week 24, the maximum difference between lixisenatide and placebo in the 7-point SMPG was seen after breakfast, and a sustained effect was observed before lunch, after lunch, and up to dinner time.

The decrease in body weight in the lixisenatide group was significantly greater than that in the placebo group (LSM difference −1.32 kg; $P < 0.0001$) (Table 2) but had no impact on nutritional status. A slight decrease in MNA-SF screening score was seen in both groups (−0.61 and −0.44 in the lixisenatide and placebo groups, respectively) (Table 2). The LSM difference between the two groups was −0.17 (95% CI −0.422, 0.088). Patients with an MNA-SF (6 items) screening score of <12 at week 23 were evaluated further to confirm the risk of malnutrition by completing the full MNA questionnaire (18 items) for additional information on factors that could affect nutritional status (28). The total score for the full questionnaire was 24.13 in the lixisenatide group (16 patients) and 24.45 in the placebo group (10 patients). In this population, greater weight loss in the lixisenatide group was reported in responses to specific questions on the MNA. On the other hand, responses to other questions demonstrated lower psychologic stress or acute disease with lixisenatide than with placebo. Therefore, although the overall MNA scores were largely unchanged, some changes to individual elements balanced one another and thus were not revealed in the total scores.

A subgroup analysis was performed to examine the change from baseline in body weight for both treatment groups and in subgroups determined by baseline BMI (<27 kg/m^2 [n = 48] and ≥27 kg/m^2 [n = 125]). The LSM (SE) difference in weight change from baseline to week 24 between lixisenatide- and placebo-treated patients was –1.26 (0.56) in patients with a BMI <27 kg/m^2 and –1.30 (0.32) in patients with a BMI ≥27 kg/m^2. This finding demonstrates the relatively low variability in weight loss according to baseline BMI and the absence of excessive weight change in either subgroup.

FPG in both groups decreased slightly from baseline, but no significant difference was observed between the two groups (Table 2). The percentage of patients requiring rescue therapy during the 24-week treatment period was lower in the lixisenatide group (5 [2.9%] patients) than in the placebo group (18 [10.4%] patients), with a proportion difference of −7.8% for lixisenatide versus placebo (95% CI −13.12%, −2.41%) (Table 2). The basal insulin requirement fell in both groups from baseline to week 24; the reduction in dose was 1.67 units greater with lixisenatide than with placebo (95% CI –4.282, 1.049 units). The number of patients with a decrease in HbA_{1c} >0.5% (5.5 mmol/mol) and no documented symptomatic hypoglycemia at the end of the study was close to three times higher in the lixisenatide group than in the placebo group (Table 2).

The Short Form 12-Item quality-of-life questionnaire showed a higher increase in physical health composite score from baseline to week 23 in the lixisenatide group than in the placebo group (2.12 and 0.39, respectively), with an LSM difference of 1.73 (95% CI 0.011, 3.456), which corresponds to an effect size of 0.21 (Cohen classification), indicating a

Table 1—Baseline demographics and disease characteristics of the randomized population

Characteristic	Placebo (*n* = 174)	Lixisenatide (*n* = 176)	All (*N* = 350)
Age (years)	74.4 (3.8)	74.0 (4.0)	74.2 (3.9)
Age ≥75 years, *n* (%)	69 (39.7)	62 (35.2)	131 (37.4)
Male, *n* (%)	90 (51.7)	92 (52.3)	182 (52.0)
White, *n* (%)	122 (70.1)	128 (72.7)	250 (71.4)
BMI (kg/m^2)	30.1 (4.5)	29.9 (3.7)	30.0 (4.1)
Body weight (kg)	80.1 (16.8)	80.8 (14.5)	80.5 (15.7)
eGFR, *n* (%)			
≥30 to <60 mL/min/1.73 m^2	47 (27.0)	50 (28.4)	97 (27.7)
≥60 mL/min/1.73 m^2	127 (73.0)	126 (71.6)	253 (72.3)
FPG (mmol/L)	8.9 (2.3)	8.8 (2.4)	8.9 (2.3)
HbA_{1c} at week −1 (%)	8.1 (0.7)	8.1 (0.7)	8.1 (0.7)
HbA_{1c} at week −1 (mmol/mol)	65 (1.1)	65 (1.1)	65 (1.1)
Duration of diabetes (years)	14.6 (7.9)	13.6 (7.3)	14.1 (7.6)
Age at onset of type 2 diabetes (years)	59.7 (8.4)	60.4 (8.2)	60.1 (8.3)
Diabetic sensory or motor neuropathy, *n* (%)	51 (29.3)	58 (33.0)	109 (31.1)
Diabetic retinopathy, *n* (%)	21 (12.1)	28 (15.9)	49 (14.0)
History of cardiovascular/cerebrovascular disorder, *n* (%)	162 (93.1)	164 (93.2)	326 (93.1)
Hypertension	142 (81.6)	146 (83.0)	288 (82.3)
Dyslipidemia	116 (66.7)	122 (69.3)	238 (68.0)
Background therapy by regimen, *n* (%)			
Basal insulin ± OADs	55 (31.6)	54 (30.7)	109 (31.1)
Met ± OADs (except SU)	57 (32.8)	52 (29.5)	109 (31.1)
SU + Met ± OADs	51 (29.3)	59 (33.5)	110 (31.4)
SU ± OADs (except Met)	8 (4.6)	11 (6.3)	19 (5.4)
OADs (except Met and SU)	1 (0.6)	0	1 (0.3)
No OAD*	2 (1.1)	0	2 (0.6)
Concomitant nondiabetic medications, *n* (%)			
Renin-angiotensin system agents	128 (73.6)	130 (73.9)	258 (73.7)
Analgesics	112 (64.4)	114 (64.8)	226 (64.6)
Lipid-modifying agents	108 (62.1)	110 (62.5)	218 (62.3)
Topical products for joint and muscular pain	104 (59.8)	98 (55.7)	202 (57.7)
Antithrombotic agents	103 (59.2)	94 (53.4)	197 (56.3)

Data are mean (SD) unless otherwise indicated. Met, metformin; SU, sulfonylurea. *Protocol deviation.

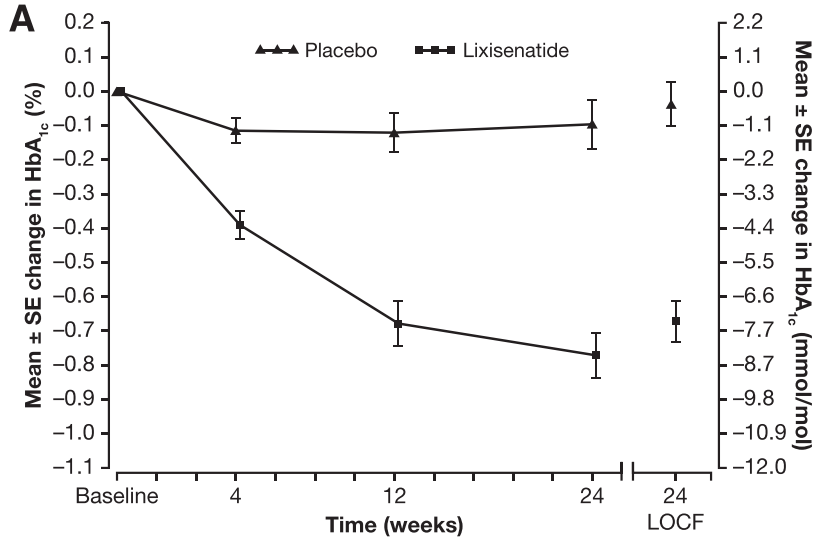
small but clinically meaningful difference between groups (27). The change in mental health composite score from baseline to week 23 was 0.05 in the lixisenatide group and −0.28 in the placebo group, with an LSM difference of 0.33 (95% CI −1.573, 2.229) between groups.

Hypoglycemia

Hypoglycemia (symptomatic or asymptomatic) was reported more frequently in the lixisenatide versus placebo group (31 [17.6%] vs. 18 [10.3%] patients, respectively) (Supplementary Table 1). The incidence of symptomatic hypoglycemia as defined per protocol was slightly higher in the lixisenatide group (13 [7.4%] patients) than in the placebo group (10 [5.7%] patients) (Supplementary Table 1). This difference may be due to patients receiving the combination of lixisenatide plus sulfonylurea. In patients receiving a sulfonylurea as background therapy, symptomatic hypoglycemia was reported in 7 (11.9%) patients in the lixisenatide group versus 2 (3.9%) patients in the placebo group. In those receiving basal insulin as background therapy, symptomatic hypoglycemia occurred in 3 (5.6%) patients in the lixisenatide group versus 7 (12.7%) patients in the placebo group. In patients receiving metformin with OADs (other than a sulfonylurea) as background therapy, one patient in each group reported symptomatic hypoglycemia (1.9% in the lixisenatide group vs. 1.8% in the placebo group) (Table 3). The incidence of hypoglycemia on the basis of the current ADA definition (<70 mg/dL [<3.9 mmol/L]) is shown in Supplementary Table 2. One severe hypoglycemia event per protocol definition was reported in one patient in the lixisenatide group. This 72-year-old female who was treated concomitantly with lixisenatide, metformin, and glimepiride experienced an episode of hypoglycemic unconsciousness after skipping a meal. Lixisenatide was temporarily discontinued, and the patient recovered from the event without sequelae.

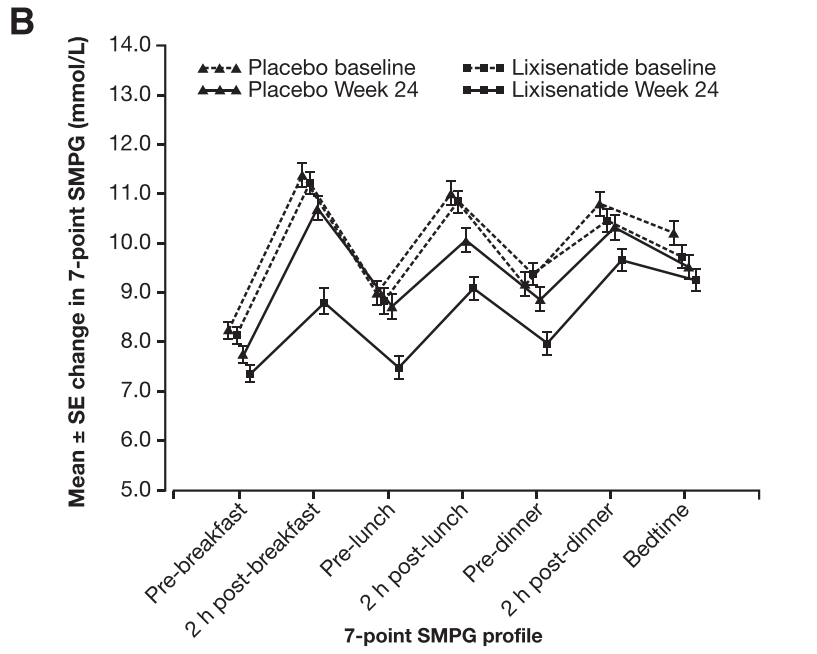
Other AEs

Safety and tolerability data are presented in Supplementary Table 1 and were consistent with the established safety profile of lixisenatide. Similar proportions of patients in the lixisenatide and placebo groups reported treatment-emergent AEs. Nausea and vomiting were reported more frequently in patients in the lixisenatide group than in the placebo group (46 [26.1%] and 13 [7.5%] patients, respectively). Discontinuation as a result of nausea and vomiting was reported in 8 (4.5%) patients and 1 (0.6%) patient, respectively, in the lixisenatide group and none in the placebo group. All events were mild to moderate in severity, occurring generally within the first 4–5 weeks of



Number of patients

Placebo	173	167	160	135	172
Lixisenatide	175	169	159	150	172



Number of patients

Placebo baseline	162	161	159	160	160	157	159
Lixisenatide baseline	170	165	169	168	167	165	162
Placebo week 24	132	131	131	129	128	131	132
Lixisenatide week 24	140	139	138	140	141	141	138

Figure 1—*A*: Mean change in HbA_{1c} from baseline to week 24. *B*: Mean 7-point SMPG at baseline and week 24.

treatment (Supplementary Fig. 4). No severe vomiting, nausea, or dehydration were observed in the study (Table 3). Four patients in the placebo group and one in the lixisenatide group experienced falls. No deaths were reported in the lixisenatide group; one death (aortic aneurysm) was reported in the placebo group. The cause of death in this patient was septic shock, respiratory failure, and renal failure as a result of surgical complications, and the investigator considered the event unrelated to the study treatment. One case of acute pancreatitis was reported in the placebo group. No confirmed isolated increase in lipase and/or amylase was reported in any patient during the on-treatment period.

CONCLUSIONS

To our knowledge, this study is the first to evaluate the efficacy and safety/tolerability of a GLP-1RA in older patients with diabetes and significant comorbidities. Lixisenatide showed superior efficacy versus placebo in older nonfrail patients (≥70 years) with type 2 diabetes inadequately controlled with their current antidiabetic treatments. A significantly greater reduction in HbA_{1c} was observed at week 24 with lixisenatide than with placebo, which was mainly driven by a strong postprandial effect, which was maximal after breakfast and persisted up to dinner. Overall, a low risk of hypoglycemia and no unexpected safety concerns were revealed.

Lixisenatide demonstrated clinical efficacy with a favorable tolerability profile both as monotherapy and in combination with OADs and/or basal insulin in the phase III GetGoal clinical trial program (29–34). The relative contribution of PPG is higher than FPG in older patients; thus, agents such as lixisenatide that preferentially lower postprandial hypoglycemia may be more effective in achieving glycemic goals without increasing the risk of hypoglycemia in these patients (3). In the current study, the reduction in 2-h PPG was greater than that seen in the 2-h postbreakfast SMPG curve. The reason for this finding may be that PPG was measured during the standardized liquid breakfast test, whereas SMPG was the average of values taken after patients' regular breakfast meals; the difference in apparent change may reflect differences in the composition of the standardized and regular breakfasts. PPG is recognized as a better predictor of cardiovascular disease and all-cause mortality than FPG (5,35,36) and was demonstrated in a post hoc analysis of the HEART2D (Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus) trial, which showed lower cardiovascular risk in older patients, targeting postprandial versus fasting/premeal glycemia (37).

GLP-1RAs have been reported to induce weight loss (38), which often is advantageous in mitigating the weight-gain effect of insulin therapy. Thus, the weight benefits of this class of compounds make it suitable for diabetes treatment. In this

study, approximately half of the patients were obese (BMI >30 kg/m^2), and a greater decrease in body weight was observed in the lixisenatide group than in the placebo group after 24 weeks of treatment, with a slight improvement in physical function as perceived by patients. It should be noted, however, that weight loss can be detrimental in the frail, underweight older patient, so a careful, individualized approach to treatment of these patients should be taken. In this trial, which excluded frail and malnourished patients, no impact on nutritional status was observed in the study population, and the subgroup analysis of weight change revealed no excessive weight loss in patients with lower-than-average baseline BMI.

Symptomatic hypoglycemia was observed in a higher proportion of patients in the lixisenatide versus placebo group possibly because of a higher incidence of hypoglycemia in patients receiving lixisenatide plus a sulfonylurea. These results

Table 2—Response to treatment at week 24 (modified intention-to-treat population)

Efficacy end point	Placebo (*n* = 173)	Lixisenatide (*n* = 175)
HbA_{1c} (%/mmol/mol)		
Baseline	8.05/64 (0.70)	8.03/64 (0.72)
Week 24	8.01/64 (0.96)	7.36/57 (1.00)
LSM (SE) change from baseline to week 24, LOCF	0.06 (0.072)	−0.57 (0.075)
LSM (SE) difference vs. placebo	—	−0.64 (0.088)
95% CI	—	−0.810, −0.464
P value	—	<0.0001
2-h PPG (mmol/L)		
Baseline	14.85 (3.73)	15.00 (3.70)
Week 24	14.72 (3.83)	9.74 (4.46)
LSM (SE) change from baseline to week 24, LOCF	−0.07 (0.393)	−5.12 (0.392)
LSM (SE) difference vs. placebo	—	−5.05 (0.464)
95% CI	—	−5.960, −4.132
P value	—	<0.0001
FPG (mmol/L)		
Baseline	8.85 (2.28)	8.83 (2.40)
Week 24	8.70 (2.09)	8.35 (2.81)
LSM (SE) change from baseline to week 24, LOCF	0.01 (0.218)	−0.30 (0.224)
LSM (SE) difference vs. placebo	—	−0.31 (0.262)
95% CI	—	−0.828, 0.204
P value	—	0.2347
Body weight (kg)		
Baseline	80.24 (16.67)	80.76 (14.48)
Week 24	79.99 (16.90)	79.13 (14.51)
LSM (SE) change from baseline to week 24, LOCF	−0.16 (0.228)	−1.47 (0.241)
LSM (SE) difference vs. placebo	—	−1.32 (0.278)
95% CI	—	−1.862, −0.769
P value	—	<0.0001
Patients requiring rescue therapy during the 24-week treatment period, *n* (%)	18 (10.4)	5 (2.9)
Difference vs. placebo (%)	—	−7.8
95% CI	—	−13.12, −2.41
P value	—	—*
Basal insulin daily dose (units)		
n	55	54
Baseline	38.53 (22.64)	37.64 (21.65)
Week 24	37.93 (23.52)	35.17 (21.44)
LSM (SE) change from baseline to week 24, LOCF	−1.30 (1.076)	−2.97 (1.145)
LSM (SE) difference vs. placebo	—	−1.67 (1.368)
95% CI	—	−4.382, 1.049
P value	—	—
Patients with HbA_{1c} reduction >0.5% (5.5 mmol/mol) and no symptomatic hypoglycemia, *n* (%)	37 (21.5)	99 (57.6)
Response rate difference vs. placebo (%)	—	35.8
95% CI	—	26.71, 44.97
MNA-SF score		
Baseline	13.44 (0.89)	13.68 (0.63)
Week 23, LOCF	13.24 (1.05)	13.12 (1.19)
LSM (SE) difference vs. placebo	—	−0.17 (0.130)
95% CI	—	−0.422, 0.088

Data are mean (SD) unless otherwise indicated. *A hierarchical testing procedure was performed to test the secondary efficacy variables in the following prioritized order: 2-h PPG, 7-point SMPG, body weight, FPG, and percentage of patients requiring rescue therapy. Testing stopped when an end point was found not to be statistically significant.

Table 3—Symptomatic hypoglycemia by background therapy during the on-treatment period (safety population)

	Basal insulin + OADs		Met + OADs (except SU)		SU + Met + other OADs	
	Placebo (*n* = 55)	Lixi (*n* = 54)	Placebo (*n* = 57)	Lixi (*n* = 52)	Placebo (*n* = 51)	Lixi (*n* = 59)
Symptomatic hypoglycemia						
Patients with events	7 (12.7)	3 (5.6)	1 (1.8)	1 (1.9)	2 (3.9)	7 (11.9)
Patients with events per 100 patient-years*	29.3	12.2	3.7	4.5	8.8	26.7
Events	9	7	1	1	2	18
Events per 100 patient-years†	37.7	28.6	3.7	4.5	8.8	68.7
Documented symptomatic hypoglycemia <3.3 mmol/L‡						
Patients with events	7 (12.7)	3 (5.6)	1 (1.8)	1 (1.9)	2 (3.9)	6 (10.2)
Patients with events per 100 patient-years*	29.3	12.2	3.7	4.5	8.8	22.9
Events	9	7	1	1	2	15
Events per 100 patient-years†	37.7	28.6	3.7	4.5	8.8	57.2

Data are *n* or *n* (%). Lixi, lixisenatide; Met, metformin; SU, sulfonylurea. *Calculated as number of patients with events × 100/total exposure + 3 days in patient-years. †Calculated as number of events × 100/total exposure + 3 days in patient-years. ‡Three patients receiving lixisenatide and SU + Met + other OADs had no blood glucose reported.

are in line with the overall phase III data in younger patients. A reduction of the dose of sulfonylurea may be considered to reduce the risk of hypoglycemia (18,19). Consistent with the known safety profile of lixisenatide and the GLP-1RA class, gastrointestinal AEs, especially mild to moderate nausea and vomiting, were reported more frequently with lixisenatide than with placebo. Although these AEs were mild to moderate, they can be harmful to frail older patients (3), a population excluded from the current study. The rate of discontinuation for nausea and vomiting in the lixisenatide group was consistent with the rate in the overall population included in the phase III program, and 88% of patients completed the 24-week treatment period. The percentage of patients with serious treatment-emergent AEs was low and similar between the two treatment groups. Another important safety consideration for older patients is the number of falls, which is a common clinical problem in this population that causes substantial mortality and morbidity (39). In the current study, fewer patients in the lixisenatide group experienced falls than in the placebo group despite higher rates of hypoglycemia and nausea.

Patient age and characteristics make these results highly relevant to clinical practice, providing valuable evidence for the treatment of older, complex patients with type 2 diabetes. Another strength of this study was the use of a frailty assessment, which often is overlooked but has been identified by the IDF as an important factor when selecting the appropriate treatment for older patients with diabetes. In addition, the screening period makes the trial design unique, allowing for further stabilization of the patient on the background therapy and evaluation of background therapy compliance as well as for injection training, self-monitoring of glucose, and reporting of AEs. The opportunity also presented itself to educate patients to recognize, report, and manage potential hypoglycemia.

This trial had some limitations. Numerous subtypes of the older population were excluded from this study, including those who were frail and those with cognitive impairments. Patients may also have underreported hypoglycemia. Although 7-point SMPG values were measured, some hypoglycemia may have been missed owing to inaccurate self-reporting. In future studies, continuous 24-h glucose monitoring may eliminate the uncertainty that can result from self-reporting. As with most studies of glucose-lowering drugs, this trial was short (24 weeks); therefore, it did not evaluate long-term clinical outcomes.

In conclusion, lixisenatide showed superiority over placebo in HbA_{1c} reduction and PPG control in patients with diabetes aged ≥70 years who were inadequately controlled with other antihyperglycemic therapy. No unexpected safety findings are reported. Therefore, lixisenatide can be considered a valuable option for treating older, nonfrail patients with type 2 diabetes with uncontrolled glycemia on their current antidiabetic treatment.

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