Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in Type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S)☆,☆☆

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ABSTRACT

Aims: To assess efficacy and safety of lixisenatide once-daily versus placebo in Type 2 diabetes mellitus (T2DM) patients inadequately controlled on sulfonylurea (SU) ± metformin.
Methods: In this randomized, double-blind, two-arm, parallel-group, multicenter study, patients received lixisenatide 20 μg once-daily or placebo for 24 weeks in a stepwise dose increase on top of SUs ± metformin. Primary outcome was change in HbA_{1c} from baseline to Week 24.
Results: Lixisenatide provided a significant reduction in HbA_{1c} at Week 24 versus placebo (LS mean: −0.85% vs. −0.10%; $p < 0.0001$) and more patients achieved $HbA_{1c} < 7.0\%$ (36.4% vs. 13.5%; $p < 0.0001$). Lixisenatide significantly lowered FPG and body weight versus placebo. In breakfast meal test patients, lixisenatide reduced 2-hour PPG versus placebo (LS mean: −111.48 vs. −3.80 mg/dL [−6.19 vs. −0.21 mmol/L]; $p < 0.0001$) and glucose excursion (−94.11 vs. +6.24 mg/dL [−5.22 vs. +0.35 mmol/L]), and reduced 2-hour glucagon, insulin, proinsulin, and C-peptide. The percentage of AEs was 68.3% for lixisenatide and 61.1% for placebo; and for SAEs: 3.5% versus 5.6%, respectively. Lixisenatide did not significantly increase symptomatic hypoglycemia versus placebo (15.3% vs. 12.3%, respectively); one severe episode of hypoglycemia was reported with lixisenatide.
Conclusions: Once-daily lixisenatide significantly improved glycemic control, with a pronounced postprandial effect, without significant increase in symptomatic/severe hypoglycemia risk and with weight loss over 24 weeks.

1. Introduction

Metformin remains the most widely used first-line treatment for Type 2 diabetes mellitus (T2DM), although treatment to maintain glycemic control typically progresses to the use of multiple oral antidiabetic drugs (OADs) and/or insulin (Inzucchi, Bergenstal, & Buse, 2012). In this instance, combining a sulfonylurea (SU) with metformin is a common treatment strategy that is driven mainly by its low cost (Inzucchi et al., 2012). However, as a class of drugs, SUs are often associated with weight gain and hypoglycemia — factors that need to be considered when subsequent add-on therapies are required (IDF, 2005; Rodbard, Jellinger, & Davidson, 2009). The development of glucagon-like peptide-1 (GLP-1) receptor agonists represents an attractive strategy to improve metabolic control in patients with T2DM; these agents achieve a physiological blood glucose–insulin response with a low risk of hypoglycemia as a result of their glucose-dependent action (Nauck, Heimesaat, & Behle, 2002) and are associated with beneficial effects on weight and appetite reduction (Drucker, 2006), making them good candidates for combination with OADs, including SUs.

Lixisenatide is a once-daily prandial GLP-1 receptor agonist for the treatment of T2DM. It is a 44-amino-acid peptide that is amidated at the C-terminal amino acid and shares structural elements with exendin-4, the primary difference being the addition of six lysine residues at the C terminus (Werner, Haschke, & Herling, 2010). In a 13-week, randomized, double-blind, placebo-controlled, dose-ranging study, lixisenatide 20 μg once-daily significantly improved glycated hemoglobin (HbA_{1c}) compared with placebo in patients with T2DM inadequately controlled with metformin, and this dose provided the best efficacy–tolerability ratio compared with 5, 10, and 30 μg once-daily and 5, 10, 20, and 30 μg twice-daily (Ratner et al., 2010). Lixisenatide 20 μg once-daily has subsequently been shown to significantly improve glycemic control, with low rates of hypoglycemia and beneficial effects on weight, when administered as monotherapy (Fonseca et al., 2012), as add-on therapy to OADs (Ahrén et al., 2013; Bolli et al., 2013; Pinget et al., 2013; Rosenstock et al., 2013), and in combination with basal insulin with or without oral antidiabetic therapy (Riddle et al., 2013a; Riddle et al., 2013b; Seino et al., 2012).

In the present study, we report the 24-week results from a Phase III, placebo-controlled study (GetGoal-S; NCT00713830) that investigated the efficacy and safety of lixisenatide once-daily as add-on therapy in patients with T2DM inadequately controlled on SU therapy, with or without concomitant metformin. Of note is that this study included a large subgroup of patients who underwent a meal challenge test, allowing the rigorous assessment of postprandial metabolic parameters.

2. Methods

2.1. Study design

This was a Phase III, randomized, double-blind, placebo-controlled, two-arm, parallel-group, multicenter, multinational study consisting of up to 2 weeks screening and a 1-week single-blind run-in period, followed by a 24-week main treatment period plus a controlled extension period of variable duration of at least 52 weeks mainly for safety purposes (not reported here). The study was conducted in 136 centers in 16 countries (Bulgaria, Czech Republic, Egypt, Germany, India, Israel, Japan, Korea, The Netherlands, Romania, Russia, Taiwan, Thailand, Tunisia, Turkey, and the United States). The study was approved by the local institutional review boards or ethics committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent to participate in the study.

2.2. Participants

Male and female participants aged 20–79 years with T2DM currently receiving a SU with or without metformin and with an HbA_{1c} level of 7–10%, inclusive, were included in the present study. The main exclusion criteria were: Use of oral or injectable glucose-lowering agents other than a SU or metformin within 3 months prior to the time of screening; fasting plasma glucose (FPG) at screening >250.0 mg/dL (>13.9 mmol/L); history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, or inflammatory bowel disease; history of gastrointestinal disease with prolonged nausea and vomiting in the 6 months prior to study initiation; history of metabolic acidosis, including diabetic ketoacidosis, within 1 year prior to screening; history of myocardial infarction, stroke, or heart failure requiring hospitalization within the previous 6 months; uncontrolled/inadequately controlled hypertension at the time of screening, with a resting systolic blood pressure of >180 mmHg or diastolic blood pressure >95 mmHg; amylase and/or lipase >3 times or aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase >2 times the upper limit of the normal laboratory range; and end-stage renal disease (defined by serum creatinine clearance of <15 mL/min) and/or dialysis. In the case of treatment with metformin, patients with renal impairment (defined by creatinine of >1.4 mg/dL in women and >1.5 mg/dL in men) were excluded.

2.3. Rescue policy

Routine fasting self-monitored plasma glucose (SMPG) and central laboratory alerts on FPG (and HbA_{1c} after Week 12) were set up to ensure that glycemic parameters remained under predefined threshold values. If one fasting SMPG value exceeded the specific glycemic limit on one day, the patient was instructed to check it again on the following two days. If all the values in the three consecutive days exceeded the specific limit, the patient was instructed to contact the investigator and a central laboratory FPG measurement (and HbA_{1c} after Week 12) was performed. Patients were censored for modified intent-to-treat (mITT) at the time that rescue medication was initiated.

2.4. Randomization

Eligible patients were randomized in a 2:1 ratio to receive either lixisenatide once-daily or matching placebo in a 2-step dose-increase regimen (10 μg once-daily for 1 week, 15 μg once-daily for 1 week, then 20 μg once-daily). Randomization was stratified by HbA_{1c} at screening (<8%, ≥8%) and metformin use at screening (yes/no). Lixisenatide and placebo were administered subcutaneously within 1 hour before the morning meal.

During the dose-increase period, and depending on how well the patient tolerated the titration, the investigator could maintain the achieved dose level for an additional week before attempting a dose increase, reduce the dose (back to 15 μg once-daily and then, if necessary, to 10 μg once-daily), or discontinue treatment. If the dose was not increased as initially planned, another attempt had to be made within the subsequent 4 weeks. If the patient could not reach or tolerate the target dose of 20 μg once-daily, the 15 μg or 10 μg daily dose was maintained. Patients continued on their established doses of SU and, when appropriate, of metformin. Only in the case of a screening that resulted in HbA_{1c} <8% was the SU dose decreased by 25–50% at the randomization visit to prevent hypoglycemia. The SU dose was then gradually increased to the dose received at screening between Weeks 4 and 12, according to fasting SMPG measurements. Both treatment groups received lifestyle and dietary counseling at screening and then every 3 months thereafter.

2.5. Efficacy and safety outcomes

The primary efficacy endpoint was the absolute change in HbA_{1c} from baseline to Week 24 for the mITT population, which consisted of all randomized patients who received at least one dose of double-blind investigational product and had both a baseline and at least one post-baseline assessment of any primary or secondary efficacy parameter. Measurement of HbA_{1c} was performed at a National Glycohemoglobin Standardization Program Level 1 certified central laboratory, using a high-performance liquid chromatography method. The secondary efficacy measures included the percentage of patients reaching HbA_{1c} <7.0% or ≤6.5% at Week 24, changes in FPG and body weight from baseline to Week 24, and the percentage of patients requiring rescue medication during the 24-week treatment period. In addition, in all sites in selected countries (Israel, Japan, Republic of Korea, Russia, and the United States), all randomized patients were selected to undergo a standardized 600 kcal liquid breakfast meal challenge test (400 mL of Ensure Plus®, Abbott Nutrition, Columbus, OH, USA; composed of 53.8% carbohydrate, 16.7% protein, and 29.5% fat) 30 minutes after drug administration at baseline and Week 24 for assessment of the secondary efficacy measure of 2-hour postprandial plasma glucose (PPG). The 2-hour glucose excursion (an exploratory endpoint) was calculated as 2-hour PPG minus plasma glucose levels 30 minutes prior to the meal test before study drug administration. Changes in glucagon, plasma insulin, proinsulin, proinsulin-to-insulin ratio, and C-peptide under fasting conditions and 2 hours after the standardized breakfast from baseline to Week 24 were also assessed.

The safety population comprised all randomized patients exposed to at least one dose of double-blind investigational product. Safety and tolerability were assessed by review of adverse events (AEs), occurrence of symptomatic and severe hypoglycemia, and clinical laboratory data. Possible allergic reaction events were blindly reviewed and adjudicated by the Allergic Reaction Assessment Committee (ARAC). Symptomatic hypoglycemia was defined as symptoms consistent with hypoglycemia, with accompanying blood glucose <60 mg/dL (3.3 mmol/L) or, if no plasma glucose measurement was available, a prompt recovery with carbohydrate, intravenous glucose, or glucagon administration. Severe symptomatic hypoglycemia was defined as symptomatic hypoglycemia requiring the assistance of another person, because the patient could not treat him/herself due to acute neurological impairment, and which was associated either with a plasma glucose level <36 mg/dL (2.0 mmol/L) or, if no plasma glucose measurement was available, a prompt recovery with carbohydrate, intravenous glucose, or glucagon administration. Laboratory tests were performed for hematology, creatinine, microalbuminuria, pregnancy (in females of childbearing potential), and serum chemistry, including lipoproteins, amylase and lipase, and calcitonin.

2.6. Statistical analyses

The primary efficacy endpoint was analyzed using an analysis of covariance (ANCOVA) model, with treatment group, randomization strata and country as fixed factors, and baseline HbA_{1c} as a covariate. Continuous secondary efficacy variables were also analyzed by ANCOVA; categorical secondary efficacy variables were analyzed using a Cochran–Mantel–Haenszel method stratified on randomization strata. Differences between lixisenatide and placebo and two-sided 95% confidence intervals (CIs), as well as p-values, were estimated within the framework of ANCOVA.

A sample size of 855 participants (570 in the lixisenatide group and 285 in the placebo group) was calculated as sufficient to detect a difference of 0.4% in the absolute change from baseline in HbA_{1c} to Week 24 between lixisenatide and placebo, with a power of 98%. This assumed a common standard deviation (SD) of 1.3% with a 2-sided test at a 5% significance level. The last observation carried forward

(LOCF) procedure was used to handle missing assessments or early discontinuation during the double-blind treatment period.

3. Results

3.1. Demographic and baseline characteristics

A total of 1438 patients were screened and 859 eligible patients were randomized to receive either lixisenatide once-daily (n = 573) or matching placebo (n = 286). Patient disposition is shown in Supplementary Fig. 1. The most common reason for screening failure was an HbA_{1c} value out of the defined protocol range at the screening visit. All randomized patients were exposed to the study treatment and included in the safety population. At selected sites, all randomized patients (n = 468 [54% of the total population]; 313 lixisenatide, 155 placebo) underwent the standardized breakfast meal challenge test and 467 (155 in the placebo group and 312 in the lixisenatide group) were included in the mITT population.

Approximately 84% of patients were receiving metformin in addition to their SU therapy at baseline; the remaining patients were on SU monotherapy. The majority of patients (87% lixisenatide, 89% placebo) completed the 24-week main treatment period (Supplementary Fig. 1). The rate of treatment discontinuation was 12.9% (n = 74) in the lixisenatide group and 10.8% (n = 31) in the placebo group. The rate of discontinuation due to AEs was 8.4% (n = 48) with lixisenatide and 3.8% (n = 11) with placebo. Approximately 89% of patients reached and stayed on the lixisenatide maintenance dose of 20 μg once-daily at Week 24.

Demographic and baseline characteristics were well matched between the two study groups (Table 1). Overall, 52.2% (n = 448) of patients were Caucasian and 44.8% (n = 385) were Asian. At baseline, 44.5% (n = 382) of patients were obese, with a mean body mass index (BMI) of 30.2 kg/m^2. The mean duration of known diabetes was approximately 9.4 years.

3.2. Efficacy

3.2.1. HbA_{1c}

Lixisenatide resulted in a significant reduction in HbA_{1c} at Week 24 versus placebo (Fig. 1). Mean (± SD) HbA_{1c} decreased from 8.3% (0.9) to 7.4% (1.0) with lixisenatide and from 8.2% (0.8) to 8.1% (1.1) with placebo. The least squares (LS) mean (standard error [SE]) HbA_{1c} reduction at Week 24 (LOCF) was −0.85% (0.06) for lixisenatide versus −0.10% (0.07) for placebo (LS mean difference vs. placebo: −0.74%; 95% CI [−0.867, −0.621]; p < 0.0001). The HbA_{1c} targets of <7.0% and ≤6.5% were both achieved by significantly more patients in
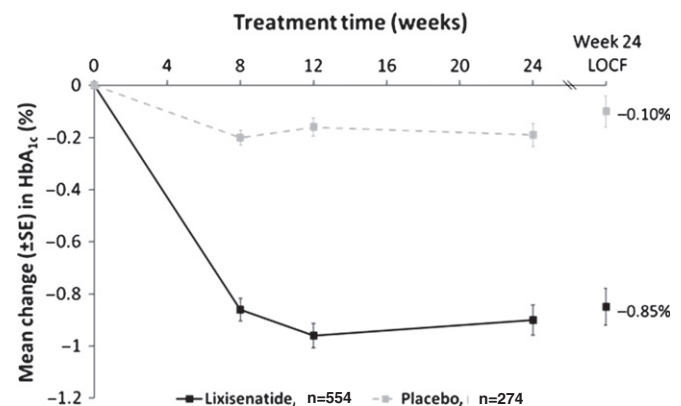
Fig. 1. Mean change in HbA_{1c} from baseline to Week 24 by visit. Week 24 LOCF data represent the LS mean change. HbA_{1c} = glycated hemoglobin; LOCF = last observation carried forward; SE = standard error.

Table 1
Demographic and baseline characteristics (safety population).

Variable	Lixisenatide (n = 574)*	Placebo (n = 285)*
Male, n (%)	284 (49.5)	150 (52.6)
Race, n (%)		
Caucasian	297 (51.7)	151 (53.0)
Black	17 (3.0)	9 (3.2)
Asian	260 (45.3)	125 (43.9)
Mean age, years (SD)	57.0 (9.8)	57.8 (10.1)
Duration of diabetes, years (SD)	9.1 (6.0)	9.8 (6.2)
Weight, kg (SD)	82.6 (21.9)	84.5 (22.8)
BMI, kg/m² (SD)	30.1 (6.6)	30.4 (6.6)
HbA$_{1c}$, % (SD)	8.3 (0.9)	8.2 (0.8)
FPG, mg/dL (SD)	174.2 (39.6)	167.4 (43.2)
FPG, mmol/L (SD)	9.67 (2.2)	9.29 (2.4)
2-hour PPG, mg/dL (SD)†	299.3 (73.9)	298.2 (66.7)
2-hour PPG, mmol/L (SD)†	16.6 (4.1)	16.6 (3.7)
2-hour glucose excursion, mg/dL (SD)†	124.9 (72.1)	126.8 (59.5)
2-hour glucose excursion, mmol/L (SD)†	6.9 (3.8)	7.0 (4.0)
SU therapy (Glim/Glyb/Glic/Glip/Other), %	41/33/18/8/<1	45/32/13/9/<1
Duration of SU treatment, years (SD)	5.2 (4.4)	5.3 (4.2)
Metformin use (yes/no), %	85/15	84/16

BMI = body mass index; FPG = fasting plasma glucose; Glyb = glyburide (any formulation); Glic = gliclazide (any formulation); Glim = glimepiride; Glip = glipizide (any formulation); HbA$_{1c}$ = glycated hemoglobin; PPG = postprandial plasma glucose; SD = standard deviation; SU = sulfonylurea.

  * One patient who was randomized to placebo received lixisenatide during the study (543 out of 561 days) due to a site dispensing error and was, therefore, considered a placebo patient in the modified intent-to-treat population (for efficacy analysis), but a lixisenatide-treated patient in the safety population (for safety analysis).

  † Based on 463 patients undergoing a standardized breakfast meal challenge test at selected sites.

the lixisenatide group compared with the placebo group: 36.4% versus 13.5% of patients, respectively, for the target of <7.0%; 19.3% and 4.7%, respectively, for the target of ≤6.5% (p < 0.0001 for both).

3.2.2. Fasting plasma glucose

Lixisenatide provided a significant reduction in FPG from baseline to Week 24 compared with placebo (Fig. 2A). Mean (±SD) FPG decreased from 174.2 (40.3) to 157.5 (41.8) mg/dL (9.7 [2.2] to 8.7 [2.3] mmol/L) with lixisenatide and from 167.4 (42.7) to 165.6 (42.0) mg/dL (9.3 [2.4] to 9.2 [2.3] mmol/L) with placebo (LS mean difference vs. placebo: −11.4 mg/dL, 95% CI [−16.6, −6.2]; −0.6 mmol/L, 95% CI [−0.9, −0.3]; p < 0.0001).

3.2.3. Body weight

Lixisenatide provided a significantly greater reduction in body weight compared with placebo (Supplementary Fig. 2). Mean (±SD) body weight decreased from 82.6 (21.9) kg to 80.9 (21.4) kg with lixisenatide and from 84.5 (22.8) kg to 83.6 (23.0) kg with placebo. The LS mean (SE) body weight reduction at Week 24 (LOCF) was −1.76 ± 0.20 kg for lixisenatide versus −0.93 ± 0.23 kg for placebo (LS mean change difference: −0.84 kg, 95% CI [−1.250, −0.421]; p < 0.0001). Overall, 14.4% of lixisenatide-treated patients and 7.2% of placebo-treated patients had ≥5% weight loss from baseline to Week 24 (LOCF).

3.2.4. Rescue medication

A significantly lower percentage of patients in the lixisenatide group (n = 23 [4.0%]) versus the placebo group (n = 36 [12.6%]) required rescue therapy during the 24-week main treatment period (p < 0.0001).

3.3. Meal test analysis

In the subset of patients undergoing the standardized breakfast meal test, lixisenatide provided a significant reduction in 2-hour PPG from baseline to Week 24 compared with placebo (Table 2).

Mean (±SD) 2-hour PPG decreased from 299.3 (73.6) to 191.2 (85.2) mg/dL (16.6 [4.1] to 10.6 [4.7] mmol/L) with lixisenatide, but increased marginally from 298.2 (67.5) to 300.3 (70.2) mg/dL (16.6 [3.7] to 16.7 [3.9] mmol/L) with placebo (LS mean difference vs. placebo: −107.7 mg/dL, 95% CI [−124.5, −90.8]; −6.0 mmol/L, 95% CI [−6.9, −5.0]; p < 0.0001) (Fig. 2B).

When looking specifically at the 2-hour glucose excursion, mean (±SD) values decreased from 124.8 (68.3) to 34.9 (75.4) mg/dL (6.9 [3.8] to 1.9 [4.2] mmol/L) with lixisenatide and increased slightly from 126.9 (72.2) to 137.2 (59.4) mg/dL (7.0 [4.0] to 7.6 [3.3] mmol/L) with placebo (LS difference vs. placebo: −100.4 mg/dL, 95% CI [−115.2, −85.5]; −5.6 mmol/L, 95% CI [−6.4, −4.7]) (Fig. 2B).

The 2-hour post-meal glucagon, insulin, proinsulin, and C-peptide levels were significantly reduced with lixisenatide relative to placebo (Table 2). In patients treated with lixisenatide, decreases from baseline to Week 24 in fasting levels of glucagon, insulin, proinsulin, and C-peptide levels were also observed.

### 3.4. Safety and tolerability

During the 24-week treatment period, the percentage of patients with AEs was 68.3% (n = 392) in the lixisenatide group and 61.1% (n = 174) in the placebo group. The percentage of patients with serious AEs was 3.5% (n = 20) and 5.6% (n = 16), respectively (Table 3). The most common AEs in the lixisenatide group were gastrointestinal in nature, mostly nausea (Table 3). Events of nausea in the lixisenatide treatment group mainly occurred in the first month of treatment; few patients experienced nausea after Week 5. Similarly, the frequency of vomiting events was reduced after Week 4 compared with the first month of treatment. A higher percentage of patients in the lixisenatide group discontinued treatment due to an AE compared with the placebo group (Table 3). The most frequently reported AE leading to treatment discontinuation in the lixisenatide group was nausea (22 patients [3.8%] vs. no patients in the placebo group). One death was reported during the 24-week treatment period (a case of sudden cardiac death after 17 days of exposure to lixisenatide), but it was considered not related to study treatment.

During the 24-week treatment period, injection-site reactions were reported in 4.5% (n = 26) lixisenatide-treated and 1.8% (n = 5) placebo-treated patients. Three patients discontinued treatment due to an injection-site reaction, two of which were reported as being of moderate intensity. A total of six patients (1.0%) in the lixisenatide group reported an event adjudicated as an allergic reaction by the ARAC. However, only one of them (0.2%) was considered possibly related to study drug (an unspecified increasingly large local reaction). Other events (angioedema, generalized pruritus, urticaria, and two events of allergic rhinitis) were all considered by the ARAC not to be related to the study drug.

The percentage of patients with symptomatic hypoglycemia was not significantly greater in the lixisenatide group compared with the placebo group (15.3% [n = 88.0] vs. 12.3% [n = 35.0], respectively; NS; Table 3). Among patients reporting at least one hypoglycemic episode, the average number of hypoglycemic episodes per patient was similar in the lixisenatide and placebo groups. Only one patient (in the lixisenatide group) experienced a severe hypoglycemic event.

A slight decrease in blood pressure (both systolic and diastolic blood pressure) from baseline to Week 24 was observed in both treatment groups. There were minimal changes in heart rate from baseline to Week 24 in both treatment groups (mean changes [±SD]: −0.1 [8.7] bpm in the lixisenatide group and 0.1 [9.2] bpm in the placebo group). There was no relevant change in lipid levels in the lixisenatide group compared with the placebo group.

There were two patients (0.7%) with increased blood calcitonin (calcitonin levels ≥20 ng/L) in the placebo group and four patients (0.7%) with increased blood calcitonin in the lixisenatide group.

A

B

(i)

(ii)
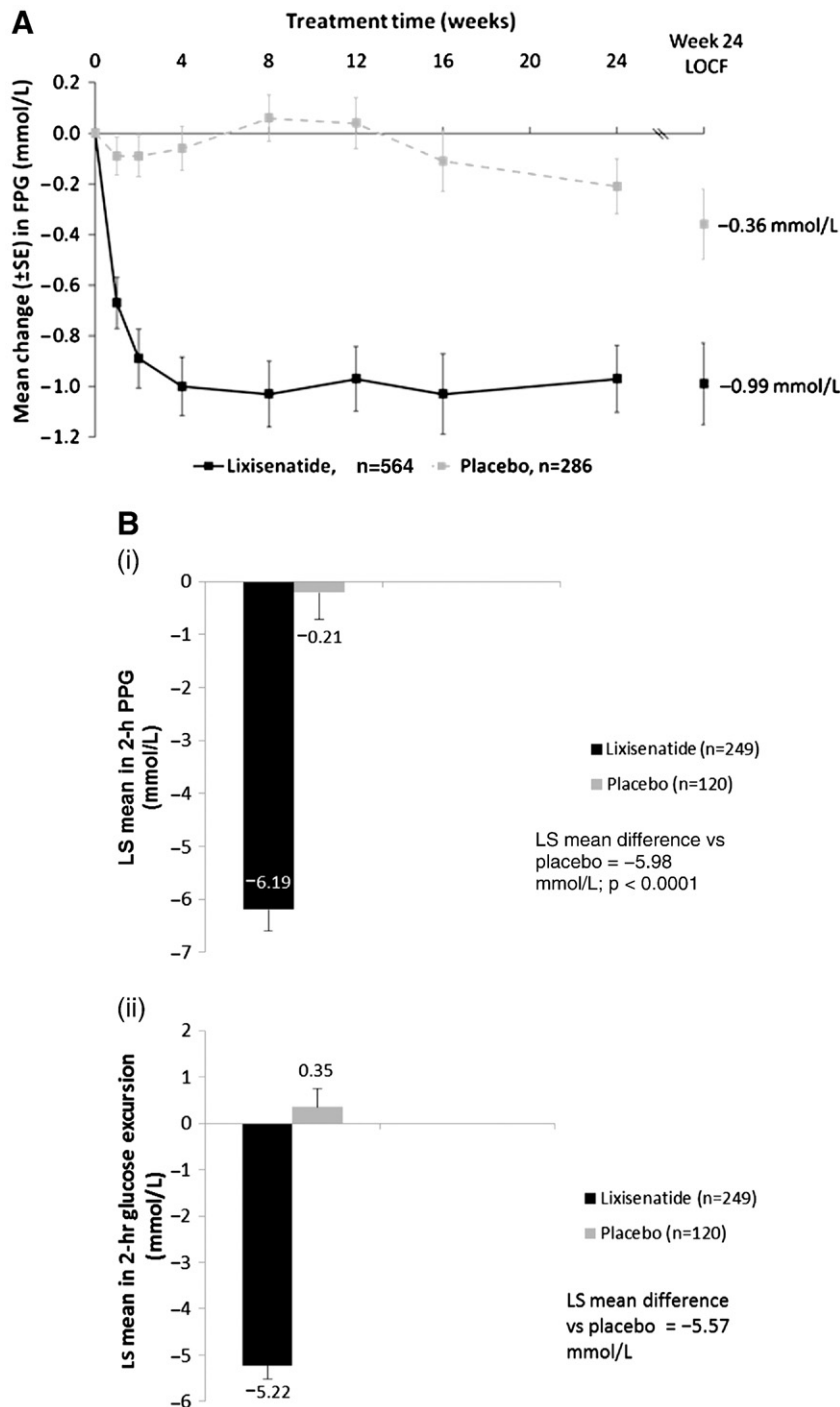
Fig. 2. A. Mean changes from baseline in fasting plasma glucose (mmol/L) by visit. Week 24 LOCF data represent the LS mean change. FPG = fasting plasma glucose; LS = least squares, LOCF = last observation carried forward; SE = standard error. B. 2-hour postprandial plasma glucose (i) and glucose excursion (ii) changes from baseline to Week 24 (LOCF) (mmol/L). LOCF = last observation carried forward; LS = least squares, PPG = postprandial plasma glucose.

4. Discussion

In this placebo-controlled trial, the GLP-1 receptor agonist lixisenatide administered at a dose of 20 μg once-daily provided a significant improvement in glycemic control in patients inadequately controlled on SU therapy, including 84% of those receiving both SU and metformin. Lixisenatide significantly reduced HbA_{1c} at Week 24 versus placebo (−0.85% vs. −0.10%) and allowed considerably more patients to achieve the HbA_{1c} targets of <7.0% and ≤6.5%. Maximum HbA_{1c} reduction was observed at Week 12 and the effect was sustained up to

the study end (Fig. 1). In addition, there were significant reductions in FPG and body weight compared with placebo. Notably, these improvements in glycemic control with lixisenatide were mainly at the expense of robust postprandial reductions during a meal test and occurred without imparting any significant increase in the proportion of patients experiencing symptomatic hypoglycemia versus placebo (15.3% vs. 12.3%, respectively).

The magnitude of the HbA_{1c} reduction reported here in patients receiving lixisenatide and SU therapy (and metformin for the majority) is similar to that reported with exenatide 10 μg twice-

Table 2
24-week changes in 2-hour postprandial parameters in the subset of patients undergoing the standardized breakfast meal test (mITT population).

Parameter		Lixisenatide	Placebo	LS mean difference [95% CI]
2-hour postprandial plasma glucose (mmol/L) [mg/dL]	N	249	120	
	Baseline (SD)	16.6 (4.1)	16.6 (3.7)	
		[299.3 (73.6)]	[298.2 (67.5)]	
	Week 24 (SD)	10.6 (4.7)	16.7 (3.9)	
		[191.2 (85.2)]	[300.3 (70.2)]	
	LS mean change ± SE	−6.2 (0.4)	−0.2 (0.5)	−5.98 [−6.91, −5.04]*
		[−111.5 (7.3)]	[−3.8 (8.8)]	
Glucose excursion (mmol/L) [mg/dL]	N	249	120	
	Baseline (SD)	6.9 (3.8)	7.0 (4.0)	
		[124.8 (68.3)]	[126.8 (72.2)]	
	Week 24 (SD)	1.9 (4.2)	7.6 (3.3)	
		[34.9 (75.4)]	[137.2 (59.4)]	
	LS mean change (SE)	−5.2 (0.4)	+0.4 (0.4)	−5.57 [−6.40, −4.74]
		[−93.7 (7.2)]	[7.2 (7.2)]	
Glucagon (ng/L)	N	234	114	
	Baseline (SD)	97.4 (31.7)	100.3 (39.0)	
	Week 24 (SD)	77.6 (30.1)	100.0 (38.8)	
	LS mean change (SE)	−23.3 (2.5)	−1.2 (3.0)	−22.14 [−27.91,−16.37]
Insulin (pmol/L)	N	244	120	
	Baseline (SD)	256.6 (176.8)	279.8 (241.1)	
	Week 24 (SD)	195.1 (180.9)	270.2 (232.9)	
	LS mean change (SE)	−67.7 (15.9)	−2.22 (18.8)	−65.5 [−100.2, −30.7]
Proinsulin (pmol/L)	N	193	93	
	Baseline (SD)	62.1 (44.6)	60.1 (45.9)	
	Week 24 (SD)	55.2 (49.3)	61.0 (44.3)	
	LS mean change (SE)	−4.2 (3.6)	+3.6 (4.2)	−7.75 [−15.13, −0.37]
C-peptide (nmol/L)	N	248	119	
	Baseline (SD)	2.0 (0.9)	2.1 (1.0)	
	Week 24 (SD)	1.7 (0.9)	1.9 (1.0)	
	LS mean change (SE)	−0.4 (0.1)	−0.1 (0.1)	−0.23 [−0.40,–0.07]

Glucose excursion = 2-hour PPG minus plasma glucose 30 minutes prior to the meal test before study drug administration.
CI = confidence interval; LS = least squares; mITT = modified intent-to-treat; PPG = postprandial plasma glucose; SD = standard deviation; SE = standard error.
 * p < 0.0001 (p values not available for other measures, as they were exploratory endpoints).

daily over 30 weeks in patients on a SU plus metformin (−0.8% [from 8.5% to 7.7%]), but this occurred alongside a 2.2-fold increase in the incidence of overall hypoglycemia with exenatide (27.8% vs. 12.6% of patients on placebo; no severe cases) (Kendall, Riddle, & Rosenstock, 2005). Exenatide 10 μg twice-daily over 30 weeks also provided a similar improvement in glycemia control in patients on SU mono-therapy (−0.9% [from 8.6% to 7.7%]), but markedly increased the incidence of overall hypoglycemia by 11-fold (35.7% vs. 3.3% on placebo; no severe cases) (Buse, Henry, & Han, 2004).

In the LEAD-1 study involving patients on glimepiride mono-therapy, add-on liraglutide 1.2 mg and 1.8 mg once-daily provided reductions in HbA$_{1c}$ of − 1.1% for both doses (Marre, Shaw, & Brandle, 2009). In absolute terms, hypoglycemia rates were lower than in GetGoal-S, possibly due to a lower threshold in defining events (minor episodes [FPG <3.1 mmol/L]: 9.1% [1.2 mg], and 8.2% [1.8 mg]; one

major episode with 1.8 mg). However, this represented a greater than 3-fold increase relative to placebo (2.6%) in LEAD-1 compared to a marginal difference versus placebo in our study (Marre et al., 2009).

As mentioned above, the most notable result from the present study was the pronounced postprandial effect observed with lixisenatide during the breakfast meal challenge, with significant placebo-subtracted reductions (>100 mg/L [>5.56 mmol/L]) for both 2-hour PPG and glucose excursion. This represents an approximately 80% reduction in 2-hour glucose excursion compared with placebo. This result is from 369 patients analyzed (including 249 patients on lixisenatide) and represents one of the most comprehensive meal challenge assessments for any GLP-1 receptor agonist. In the present study, lixisenatide also reduced postprandial glucagon, insulin, and proinsulin levels during the meal test. This comprehensive postpran-dial effect observed with lixisenatide is associated with its effect on

Table 3
Adverse events (AEs) during the 24-week, double-blind treatment period – safety population.

Type of adverse event	Lixisenatide (n = 574)	Placebo (n = 285)
Any AE, n (%)	392 (68.3)	174 (61.1)
Any serious AE, n (%)	20 (3.5)	16 (5.6)
Death, n (%)	1 (0.2)*	0
Discontinuation due to AE, n (%)	56 (9.8)	14 (4.9)
Gastrointestinal disorders (any), n (%)	235 (40.9)	57 (20.0)
Nausea, n (%)	145 (25.3)	20 (7.0)
Vomiting, n (%)	50 (8.7)	10 (3.5)
Diarrhea, n (%)	51 (8.9)	19 (6.7)
Symptomatic hypoglycemia[†], n (%)	88 (15.3)	35 (12.3)
Severe hypoglycemia[‡], n (%)	1 (0.2)	0

AE = adverse event.
 * Sudden cardiac death after 17 days of exposure.
 [†] Symptomatic hypoglycemia = episode with clinical symptoms with either plasma glucose <60 mg/dL (3.3 mmol/L) or prompt recovery after oral carbohydrate administration (if no plasma glucose measurement was available).
 [‡] Severe hypoglycemia = symptomatic hypoglycemia in which the patient required the assistance of another person, and which was associated either with a plasma glucose level <36 mg/dL (2.0 mmol/L) or, if no plasma glucose measurement was available, prompt recovery with carbohydrate.

delaying gastric emptying. Indeed, a recent 28-day, randomized, double-blind, placebo-controlled, parallel-group study reported that lixisenatide 20 μg once-daily reduced postprandial glycemic excursions in patients with T2DM, together with a sustained slowing of gastric emptying (Lorenz et al., 2013).

Moreover, results from a 4-week, randomized, open-label, repeated-dose study in patients with T2DM inadequately controlled on metformin demonstrated that lixisenatide 20 μg once-daily has a significantly greater PPG-lowering effect than liraglutide 1.8 mg once-daily. Overall, lixisenatide provided a significantly greater reduction in PPG (glucose $AUC_{0:30–4:30h}$) compared with liraglutide (p < 0.0001). Furthermore, lixisenatide provided significantly greater reductions in maximum PPG excursion compared with liraglutide (-70.5 mg/dL [-3.91 mmol/L] with lixisenatide vs. -24.9 mg/dL [-1.38 mmol/L] with liraglutide; p < 0.0001). A greater proportion of lixisenatide-treated patients (69%) also achieved 2-hour PPG levels <140 mg/dL (<7.8 mmol/L) at Day 28 compared with liraglutide-treated patients (29%) (Kapitza, Forst, & Coester, 2013). This is probably related to a greater effect on slowing gastric emptying as longer-acting GLP-1 receptor agonists, such as liraglutide, have little to no effect on gastric emptying due to tachyphylaxis (Meier, 2012).

As expected, the most frequent AEs associated with lixisenatide were gastrointestinal. The majority of these events were mild or moderate nausea and vomiting that were transient, occurring mostly during the first 4 weeks. The nausea incidence of 25% over 24 weeks is generally comparable to studies with other GLP-1 receptor agonists, which range widely from 13% to 51% with exenatide 10 μg twice-daily and from 5% to 29% with liraglutide 1.2 and 1.8 mg once-daily (Aroda & Ratner, 2011; Montanya & Sesti, 2009). Furthermore, the incidence of nausea in this study is virtually identical to that from another 24-week, randomized trial in which fewer patients reported nausea with lixisenatide 20 μg once-daily compared with exenatide 10 μg twice-daily (24.5% vs. 35.1%, respectively; p < 0.05) (Rosenstock et al., 2013).

It should be noted that 84% of the patients were inadequately controlled on the combination of a SU with metformin at study end. As such, this represented a population with relatively advanced disease. Such patients would typically be candidates for basal insulin therapy as the next step in their treatment intensification (IDF, 2005; Nathan et al., 2009; Rodbard et al., 2009). The postprandial characteristic makes lixisenatide an attractive option for use in combination with agents that mainly target FPG, including SU or basal insulin.

In conclusion, in patients with T2DM uncontrolled on a SU with or without metformin, add-on treatment with lixisenatide 20 μg once-daily provided significant improvements in glycemic control – including a pronounced postprandial effect – with weight loss and without increasing symptomatic or severe hypoglycemia risk over 24 weeks. Reduction of the dose of the SU may be considered to further reduce the risk of hypoglycemia. Beneficial effects on weight and no increased risk of hypoglycemia in spite of improved glycemic control are particularly desirable characteristics for an add-on therapy in patients receiving a SU. The results demonstrated the efficacy–tolerability profile of lixisenatide once-daily in the context of SU-based oral agent failure and highlighted its potential as a valuable option for the treatment of T2DM.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jdiacomp.2014.01.012.

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