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Research Paper

Efficacy and safety of the glucagon-like peptide-1 receptor agonist lixisenatide versus the dipeptidyl peptidase-4 inhibitor sitagliptin in young (<50 years) obese patients with type 2 diabetes mellitus☆

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ABSTRACT

Objective: To compare the efficacy and safety of the once-daily prandial glucagon-like peptide-1 receptor agonist lixisenatide with the dipeptidyl peptidase-4 inhibitor sitagliptin in patients aged <50 years affected by obesity and type 2 diabetes mellitus (T2DM).
Materials and methods: This was a 24-week, double-blind, randomized, parallel-group study. Obese patients with T2DM inadequately controlled on metformin were randomized to lixisenatide 20 μg once-daily injection ($n = 158$) or once-daily oral sitagliptin 100 mg ($n = 161$). The primary endpoint was the proportion of patients with a glycated hemoglobin (HbA_{1c}) <7% and ≥5% weight loss at 24 weeks.
Results: The proportion of patients that achieved the primary endpoint was 12.0% for lixisenatide versus 7.5% for sitagliptin; weighted average of proportion difference: 4.6%, $p = 0.1696$). A total of 40.7% of patients achieved HbA_{1c} <7% with lixisenatide versus 40.0% with sitagliptin. Lixisenatide produced greater reductions in body weight (LS mean difference: −1.3 kg, $p = 0.0006$) and postprandial plasma glucose after a standardized meal test (LS mean difference: −34.4 mg/dL [−1.9 mmol/L], $p = 0.0001$) versus sitagliptin. There was a similar incidence of treatment-emergent adverse events (63.9% vs. 60.9%) and serious treatment-emergent adverse events (1.9% vs. 1.9%), with low rates of symptomatic hypoglycemia (0.6% vs. 1.9%) for lixisenatide and sitagliptin, respectively, and no cases of severe hypoglycemia.
Conclusion: In obese patients aged <50 years with T2DM, the proportion of patients with an HbA_{1c} <7% with weight loss ≥5% was similar between groups. Lixisenatide, however, resulted in significantly greater reductions in body weight and postprandial plasma glucose excursions than sitagliptin. Tolerability was similar between groups.

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) has increased to epidemic proportions worldwide [1]. The rapid increase in new cases of T2DM in people aged 30–39 years, and in children and adolescents, is of particular concern [1]. In the USA, for example, the prevalence of T2DM is expected to rise in people aged 30–39 years, from 3.7% in 2001 to 5.2% in 2031 [2].

Obesity complicates the management of diabetes by increasing insulin resistance and blood glucose concentrations [3]. Obesity is also an independent risk factor for dyslipidemia, hypertension and cardiovascular disease [4–6]. There may be a relationship between body mass index (BMI) and age at diagnosis of T2DM, with the risk of a T2DM diagnosis rising continuously with increasing BMI [7]. The control of body weight can be an important aspect of diabetes management and it has been shown that moderate weight loss can improve insulin sensitivity, decrease fasting plasma glucose (FPG) concentrations, and reduce the need for diabetes medications [8,9]. However, weight loss may not improve glycemic control in all obese patients with T2DM [10,11] and a substantial proportion of patients who lose weight may not have any reduction in plasma glucose levels [10].

Abbreviations: AE, adverse event; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin; LOCF, last observation carried forward; LS, least squares; PPG, postprandial plasma glucose; T2DM, type 2 diabetes mellitus; TEAE, treatment-emergent adverse event.

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Glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors are relatively recent additions to the drugs available for the management of T2DM [12,13]. GLP-1 receptor agonists work by mimicking the action of the endogenous incretin GLP-1, which acts to control glycemia via several pathways, including stimulation of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying and induction of satiety [12]. DPP-4 inhibitors work by inhibiting the DPP-4 enzyme that breaks down GLP-1, thus prolonging the half-life of endogenous GLP-1; DPP-4 inhibitors also augment gastric inhibitory polypeptide (GIP) signaling, which like GLP-1 signaling, stimulates insulin release in the presence of elevated glucose levels [12]. GLP-1 receptor agonists and DPP-4 inhibitors have been demonstrated to reduce glycated hemoglobin (HbA_{1c}). GLP-1 receptor agonists are generally associated with weight reduction and DPP-4 inhibitors are usually weight neutral [13].

Lixisenatide is a once-daily prandial GLP-1 receptor agonist for the treatment of T2DM. In a series of Phase III clinical trials known as the GetGoal programme, lixisenatide produced reductions in HbA_{1c}, with a limited risk of hypoglycemia and beneficial effects on body weight as monotherapy, in combination with oral antidiabetic drugs, and as add-on to basal insulin [14–20]. Lixisenatide was approved by the European Medicines Agency in February 2013 for the treatment of adults with T2DM in combination with oral antidiabetic drugs and/or basal insulin when diet and exercise are not adequate. Sitagliptin is the first registered representative of the new class of DPP-4 inhibitors for the treatment of patients with T2DM. The current study evaluated the safety and efficacy of lixisenatide compared with sitagliptin in a young (<50 years of age), obese population with T2DM.

Methods

Study design

This study used a 24-week, double-blind, double-dummy, randomized, active-controlled, two-arm, parallel-group trial design to compare the efficacy of lixisenatide with sitagliptin in obese (BMI $\geq$ 30 kg/m^2) patients with T2DM < 50 years of age, inadequately controlled on metformin. Patients were randomized to lixisenatide 20 μg once-daily injection or oral sitagliptin 100 mg once daily. All subjects provided written informed consent to participate in the study.

Participants

Inclusion criteria included obese (BMI $\geq$ 30 kg/m^2) patients with T2DM, diagnosed at least 1 year before the screening visit, insufficiently controlled with metformin at a stable dose of at least 1.5 g/day for at least 3 months prior to screening, and who were aged $\geq$18 to <50 years, with HbA_{1c} $\geq$7.0% and $\leq$10% at screening. Exclusion criteria included FPG at screening >250 mg/dL (>13.9 mmol/L); history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, inflammatory bowel disease; history of metabolic acidosis, including diabetic ketoacidosis within 1 year prior to screening; history of myocardial infarction, stroke, or heart failure requiring hospitalization within 6 months prior to screening; and amylase and/or lipase values of more than three times the normal laboratory range.

Efficacy and safety endpoints

The primary endpoint was a composite of the proportion of patients achieving HbA_{1c} <7.0% and a body weight loss of at least 5% of baseline body weight at Week 24. Secondary efficacy assessments included: change in HbA_{1c}; the proportion of patients achieving HbA_{1c} <7.0%; change in body weight; FPG; change in 2-h postprandial plasma glucose (PPG), glucose excursion, insulin, proinsulin, C-peptide, and glucagon after a standardized test meal; and change in insulin resistance (assessed by homeostatic model assessment [HOMA]-IR) and beta cell function (assessed by HOMA-β). A *post-hoc* analysis based on the primary endpoint and the duration of diabetes was undertaken to investigate the effect of the natural history phase of diabetes on the effectiveness of the study drugs.

The standardized meal was a 400 mL 600 kcal drink (Ensure Plus® Drink, Abbott Laboratories, Berkshire, UK) composed of 53.8% carbohydrate, 16.7% protein and 29.5% fat. A central laboratory (Bio Analytical Research Corporation) performed all clinical laboratory assessments except for HbA_{1c}, which was measured by a certified level I National Glycohemoglobin Standardization Program central laboratory. Reference range upper and lower limits for HbA_{1c} were 4.0% and 6.0% and for FPG were 70 and 110 mg/dL (3.89 and 6.11 mmol/L), respectively. HbA_{1c} was assessed via ion exchange high-performance liquid chromatography (HPLC) measured using the Tosoh G7 (Tessenderlo, Belgium) HPLC analyzer in the USA and the Menarini (Firenze, Italy) 8160 chromatogram in the EU. Glucose levels were measured using a hexokinase UV endpoint method on the Roche Diagnostics (Indianapolis, IN, USA) Modular-P analyzer. Proinsulin levels were assessed via Mercodia (Uppsala, Sweden) enzyme-linked immunosorbent assay. Insulin and C-peptide were measured using the Siemens (Erlangen, Germany) Immulite® 2000 chemiluminescence assay system. Glucagon was assessed using the DPC (Los Angeles, CA, USA) Coat-A-Count® radioimmunoassay.

Safety assessment included adverse events (AEs), treatment-emergent AEs (TEAEs) and occurrence of symptomatic severe hypoglycemia.

Statistical analysis

The safety population comprised all randomized patients who were exposed to at least one dose of treatment. The efficacy analyses were performed on the modified intent-to-treat (mITT) population. The primary analysis of the efficacy variables at Week 24 was performed based on measurements obtained during the 24-week on-treatment period (before the rescue medication in the event of rescue therapy), with last observation carried forward (LOCF) for missing Week 24 values. The primary efficacy endpoint was analyzed using a Cochran–Mantel–Haenszel method stratified on randomization strata (screening HbA_{1c} [<8.0%, $\geq$8.0%] and screening BMI [<35 kg/m^2, $\geq$35 kg/m^2]). Data for all continuous secondary efficacy endpoints were analyzed by analysis of covariance with treatment group, randomization strata (screening HbA_{1c} and screening BMI) and country as fixed effects and the corresponding baseline value as a covariate. Sample size was determined based on the primary efficacy endpoint. A sample size of 300 (150 in each group) had 90% power to demonstrate superiority of lixisenatide over sitagliptin with a 2-sided test at 5% significance level, assuming the percentage of patients defined as responders on HbA_{1c} (<7%) and weight (at least 5% loss) was 25% with lixisenatide (based on a 13-week dose-ranging study of lixisenatide [21]) and 10% with sitagliptin.

Diabetes duration tertiles were based on a complete diabetes duration dataset with equal patient distribution: <2.2 years (1st tertile), $\geq$2.2 to <4.8 years (2nd tertile), and $\geq$4.8 years (3rd tertile). Tertiles were used to assess percent of patients who had both HbA_{1c} <7% and body weight loss $\geq$5% at the end of treatment.

Results

Patients

A total of 620 patients were screened and 319 patients were randomized to one of the two treatment groups (n = 158 for

Table 1
Baseline characteristics (safety population)

Mean values	Lixisenatide $n = 158$	Sitagliptin $n = 161$
Male, %	34.8	45.3
Race, %		
Caucasian	83.5	78.9
Black	5.1	6.8
Asian	0.6	0.6
Other	10.8	13.7
Age, years (SD)	42.7 (5.2)	43.4 (4.7)
Diabetes duration, years		
Mean (SD)	4.4 (3.9)	4.4 (3.6)
Median (min, max)	3.2 (1.0, 29.6)	3.4 (1.0, 19.6)
MET, daily dose, mg (SD)	1985 (414)	1937 (405)
HbA_{1c}, % (SD)	8.16 (0.89)	8.1 (1.0)
HbA_{1c} by diabetes duration, % (SD)[a]		
<2 years	8.02 (0.71)	8.02 (0.87)
≥2.2 to <4.8 years	8.24 (0.70)	8.23 (0.79)
≥4.8 years	8.56 (0.91)	8.48 (0.87)
2-h PPG		
mg/dL (SD)	247.9 (68.0)	250.6 (71.8)
mmol/L (SD)	13.8 (3.8)	13.9 (4.0)
Glucose excursion		
mg/dL (SD)	78.7 (47.5)	80.6 (46.6)
mmol/L (SD)	4.4 (2.6)	4.5 (2.6)
FPG		
mg/dL (SD)	163.6 (46.8)	161.3 (46.6)
mmol/L (SD)	9.1 (2.6)	9.0 (2.6)
BMI, kg/m^2 (SD)	36.8 (7.3)	36.8 (6.3)
Body weight, kg (SD)	98.5 (23.5)	100.6 (23.8)

SD = standard deviation; MET = metformin; HbA_{1c} = glycated hemoglobin; PPG = postprandial plasma glucose; FPG = fasting plasma glucose; BMI = body mass index.
[a] Intention-to-treat population with baseline $HbA_{1c} \leq 7\%$.

lixisenatide, $n = 161$ for sitagliptin). Each of the 319 randomized patients were exposed to the study treatment and included in the analyses. During the 24-week treatment period, 8.5% of patients ($n = 27/319$) discontinued from the study (10.1% [$n = 16/158$] in the lixisenatide group and 6.8% [$n = 11/161$] in the sitagliptin group), primarily due to nonspecific causes listed by investigators as 'other reasons' (4.4% in the lixisenatide group vs. 3.1% in the sitagliptin group).

Patient demographics and clinical characteristics were generally similar between the two groups (Table 1), although the lixisenatide group had a lower proportion of male patients (35% vs. 45% with sitagliptin).

Glycated hemoglobin and body weight

A greater proportion of patients met the criteria for the primary endpoint of HbA_{1c} <7% with weight loss of ≥5% in the lixisenatide group than in the sitagliptin group (12.0% vs. 7.5%, respectively) with a weighted average of proportion difference for lixisenatide versus sitagliptin (95% confidence interval [CI]) of 4.6% (−1.8, 11.0), $p = 0.1696$ (Figure 1).

A similar proportion of patients in each treatment group achieved HbA_{1c} <7% (40.7% for lixisenatide vs. 40.0% for sitagliptin; weighted average of proportion difference for lixisenatide vs. sitagliptin [95% CI]: 0.8% [−9.7, 11.3]; $p = 0.884$) (Figure 2A).

Least squares (LS) mean change from baseline in HbA_{1c} was similar for lixisenatide and sitagliptin (LS mean change ± standard error [SE]: −0.7% ± 0.1 vs. −0.7% ± 0.1, respectively; LS mean difference vs. sitagliptin [95% CI]: 0.1% [−0.2, 0.3]; $p = 0.6042$).

Lixisenatide therapy was associated with greater reductions in body weight versus sitagliptin over the 24-week study period (LS mean change: −2.5 kg for lixisenatide vs. −1.2 kg for sitagliptin; LS mean difference vs. sitagliptin at Week 24 [95% CI]: −1.3 kg [−2.1, −0.6], $p = 0.0006$) (Figure 2B).

Postprandial plasma glucose

Lixisenatide-treated subjects also showed significantly greater reductions in 2-h PPG. LS mean change from baseline ± SE: −60.3 ± 6.8 mg/dL (−3.4 ± 0.4 mmol/L) and −25.9 ± 6.9 mg/dL (−1.4 ± 0.4 mmol/L) for lixisenatide and sitagliptin, respectively (LS mean difference: −34.4 mg/dL; 95% CI −51.8, −17.0 mg/dL [−1.9 mmol/L; 95% CI −2.9, −0.9 mmol/L]; $p = 0.0001$; Figure 3A), and glucose excursion. LS mean change from baseline ± SE: −45.9 ± 4.9 mg/dL (−2.6 ± 0.3 mmol/L) and −7.6 ± 5.0 mg/dL (−0.4 ± 0.3 mmol/L) for lixisenatide and sitagliptin, respectively (LS mean difference: −38.3 mg/dL; 95% CI −50.8, −25.8 mg/dL [−2.1 mmol/L; 95% CI −2.8, −1.4 mmol/L]; $p < 0.0001$; Figure 3B), after a standardized meal test versus sitagliptin.

Fasting plasma glucose

There were no significant differences in changes in FPG between groups (LS mean change ± SE: −8.1 ± 3.5 mg/dL [−0.5 ± 0.2 mmol/L] for lixisenatide vs. −12.54 ± 3.6 mg/dL [−0.7 ± 0.2 mmol/L] for sitagliptin; LS mean difference ± SE vs. sitagliptin: 4.4 ± 4.6 mg/dL; 95% CI −4.6, 13.4 mg/dL [0.3 ± 0.3 mmol/L; 95% CI −0.3, 0.7 mmol/L]; $p = 0.3342$).

Insulin, pro-insulin, C-peptide and glucagon

There were no significant differences between the two groups in changes in fasting plasma insulin (LS mean difference for lixisenatide vs. sitagliptin: −0.1 μU/mL), pro-insulin (0.4 μU/mL), C-peptide (0.03 ng/mL) or glucagon (−1.63 pg/mL).

Insulin resistance and beta cell function

No significant differences were observed between lixisenatide and sitagliptin in terms of their effect on insulin resistance or beta-cell function. Week 24 LS mean ± SE change from baseline in HOMA-IR was −0.52 ± 0.37 and −0.57 ± 0.38 with lixisenatide and sitagliptin, respectively (LS mean difference 0.05; 95% CI −0.82, 0.92). Week 24 LS mean ± SE change from baseline in HOMA-β was

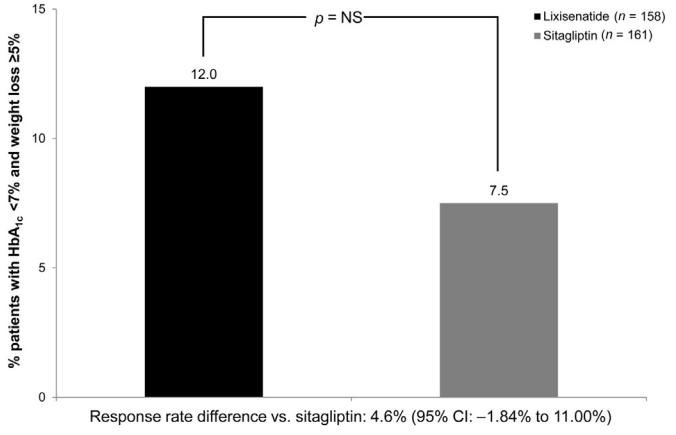

Figure 1. HbA_{1c} <7% and weight loss of ≥5% (mITT population). The proportion of patients achieving the primary endpoint of HbA_{1c} <7% and weight loss of ≥5% of baseline body weight at Week 24. HbA_{1c} = glycated hemoglobin; mITT = modified intent-to-treat; NS = not significant; CI = confidence interval.

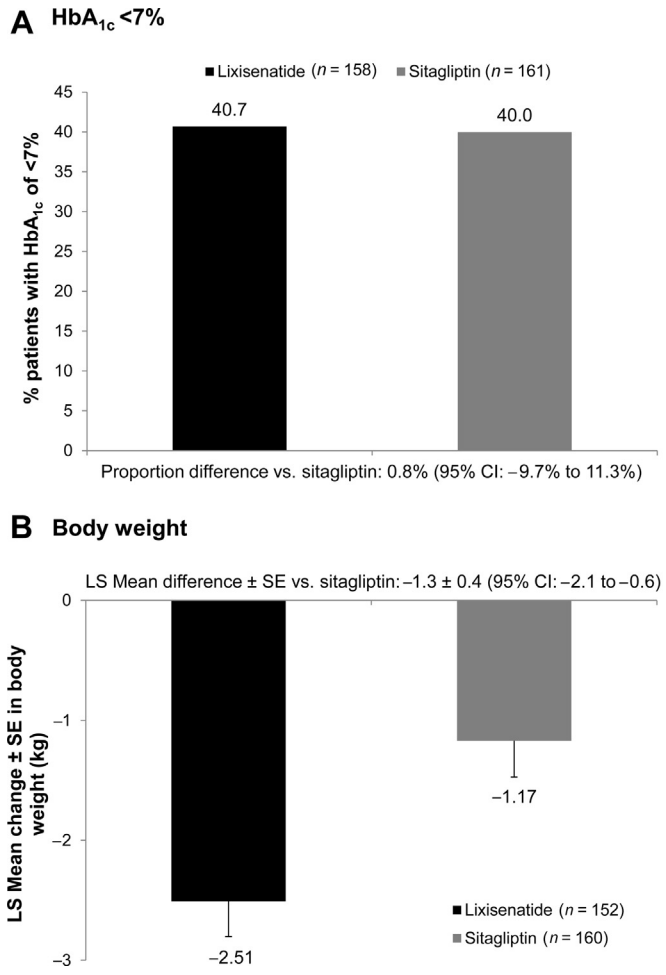

Figure 2. HbA_{1c} <7% and body weight (mITT population). (A) The proportion of patients achieving a target HbA_{1c} <7% at Week 24; (B) LS mean change from baseline in body weight (kg) ± SE at Week 24. HbA_{1c} = glycated hemoglobin; mITT = modified intent-to-treat; LS = least squares; CI = confidence interval; SE = standard error.

17.7 ± 9.7 and 17.8 ± 10.0 with lixisenatide and sitagliptin, respectively (LS mean difference −0.13; 95% CI −23.1, 22.8).

Safety

There was a similar incidence of TEAEs and serious TEAEs for lixisenatide and sitagliptin (Table 2). The percentage of patients with TEAEs leading to treatment discontinuation was low and was similar between the groups (2.5% for lixisenatide and 3.1% for sitagliptin). Gastrointestinal (GI) disorders were slightly more frequent for lixisenatide than sitagliptin, with nausea being the most frequently reported GI event in the lixisenatide group. Only one patient discontinued treatment due to nausea, vomiting, diarrhea and abdominal pain. There was a low rate of symptomatic hypoglycemia in both groups, 0.6% for lixisenatide and 1.9% for sitagliptin, and no cases of severe hypoglycemia. No cases of confirmed pancreatitis were observed and one case of calcitonin increase was seen in the sitagliptin arm (Table 2).

Post-hoc *analyses*

A tertile *post-hoc* analysis was conducted to investigate the effect of the natural history of diabetes. The findings showed that a similar percentage of patients treated with lixisenatide achieved the composite primary endpoint of HbA_{1c} <7% and weight loss ≥5% across all tertiles of diabetes duration (10.9%, 14.4% and 11.1% at <2.2 years, 2.2–4.8 years and ≥4.8 years, respectively). In contrast, sitagliptin appeared to be more effective in patients with a duration of diabetes <2.2 years (12.7%, 5.5% and 3.9% across the respective diabetes duration tertiles) (Figure 4).

Discussion

With the rising prevalence of T2DM in younger people [1,2], the evaluation of new antidiabetic drugs in younger populations is increasingly important. In this study, both a GLP-1 receptor agonist, namely lixisenatide, and a DPP-4 inhibitor, sitagliptin, demonstrated efficacy in leading patients to an HbA_{1c} of <7.0% with a concomitant reduction in body weight of at least 5% at the end of the study. Results from the *post-hoc* analyses, however, suggest that lixisenatide treatment may be more beneficial than sitagliptin treatment in patients with a relatively longer diabetes duration.

Lixisenatide treatment resulted in greater reductions in body weight compared with sitagliptin. These results are in line with previous reports that DPP-4 inhibitors are body weight neutral while treatment with GLP-1 RAs confers body weight benefits [13], and are consistent with previous trials of lixisenatide in combination with metformin [15,17]. Differing body weight changes with these medications are due to their distinct mechanisms of action. GLP-1 RAs augment the incretin hormone GLP-1, which has a role in

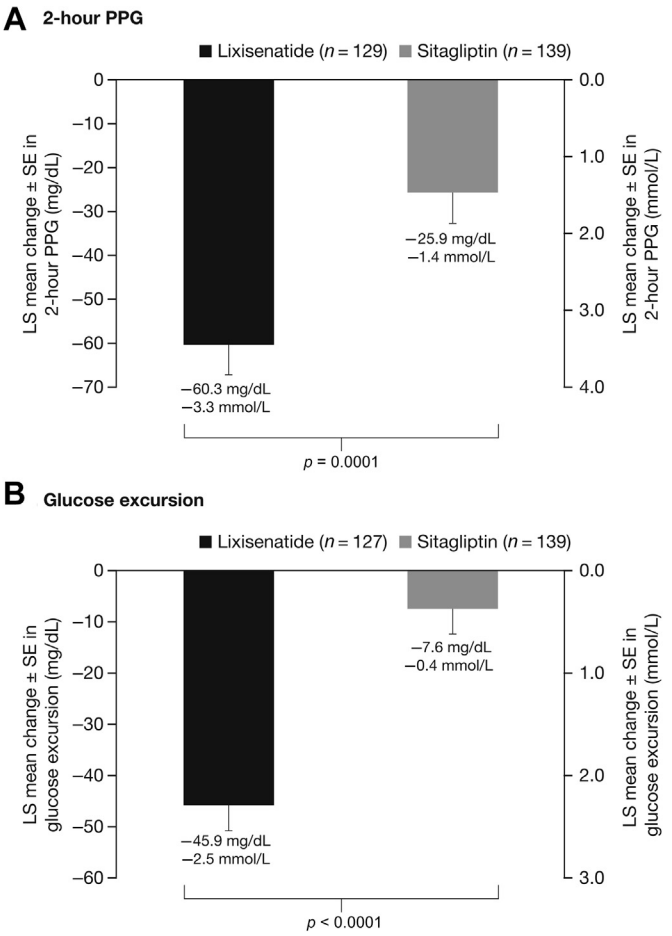

Figure 3. PPG and glucose excursion (mITT population). LS mean change ± SE from baseline in (A) 2-h PPG and (B) glucose excursion after a standardized meal test at Week 24. PPG = postprandial plasma glucose; mITT = modified intent-to-treat; LS = least squares; SE = standard error.

Table 2
Adverse events (safety population)

Adverse event, *n* (%)	Lixisenatide *n* = 158	Sitagliptin *n* = 161
Any TEAE	101 (63.9)	98 (60.9)
Any serious TEAE	3 (1.9)	3 (1.9)
Death	0	0
Discontinuation due to TEAE	4 (2.5)	5 (3.1)
Discontinuation due to nausea and vomiting	1 (0.6)	0
Treatment-emergent GI disorders	48 (30.4)	34 (21.1)
Most common TEAEs		
Nausea	28 (17.7)	11 (6.8)
Headache	20 (12.7)	15 (9.3)
Diarrhea	14 (8.9)	12 (7.5)
Vomiting	7 (4.4)	0
Confirmed diagnosis of pancreatitis	0	0
Calcitonin increase	0	1 (0.6)
Treatment-emergent symptomatic hypoglycemia[a]	1 (0.6)	3 (1.9)
Blood glucose <60 mg/dL (<3.3 mmol/L)	1 (0.6)	1 (0.6)
Severe symptomatic hypoglycemia[b]	0	0
Blood glucose <36 mg/dL (<2.0 mmol/L)	0	0

TEAE = treatment-emergent adverse event; GI = gastrointestinal.
[a] Event with clinical symptoms with either plasma glucose <60 mg/dL (<3.3 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration if no plasma glucose value was available.
[b] Symptomatic hypoglycemia in which the patient required the assistance of another person and one of the following: plasma glucose <36 mg/dL (<2.0 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration if no plasma glucose value was available.

inducing satiety, reducing food intake, and slowing of gastric emptying. Like GLP-1 RAs, DPP-4 inhibitors also augment GLP-1; however, in contrast with GLP-1 RAs, DPP-4 inhibitors also augment GIP signaling. GIP does not reduce food intake and also facilitates gastric emptying, which shortens the duration of satiety. Therefore co-augmentation of these two incretin hormones by DPP-4 inhibitors may cancel out their effects on body weight, resulting in weight neutrality [22]. Nevertheless, weight loss has important additional health benefits in patients with diabetes as it improves risk factors for cardiovascular disease by decreasing blood pressure, improving serum lipid concentrations and reducing serum markers of inflammation, and shows a positive association with incretin-induced glucose lowering [23,24]; consequently, weight loss is recommended for all overweight or obese adults with T2DM [24,25]. Significant body weight benefits with lixisenatide in the absence of significant differences compared with sitagliptin in terms of C-peptide and fasting plasma glucose appear to be counterintuitive. However, the insulin-independent effects of lixisenatide (i.e. slowed gastric emptying) and the differing incretin hormone augmentation profiles of the two medications provide some explanation for this apparent paradox. In addition, weight loss may not consistently improve glycemic control in obese patients with T2DM [10,11].

Lixisenatide demonstrated a significantly greater reduction in PPG after a standardized meal test compared with sitagliptin: these results are consistent with previous lixisenatide studies that demonstrate robust PPG reduction with lixisenatide treatment across the various stages of the natural history of the disease [14,16–20]. Postprandial hyperglycemia may be an independent risk factor for cardiovascular events, and glycemic variability may have a more deleterious effect than sustained hyperglycemia in the development of diabetic complications [26,27]. Furthermore, the postprandial contribution to hyperglycemia has been described as pivotal to achievement of optimal glycemic control both when HbA_{1c} approaches target levels [28] and when fasting plasma glucose has already reached acceptable control [29]. As a result, PPG is now recognized as a key therapeutic target for improving glycemic control in patients with T2DM.

One limitation of the present study is the patient population, which was limited to patients affected by T2DM and obesity and a relatively young age (<50 years). Participants had a mean age, BMI and median diabetes duration of 43 years, 36.8 kg/m^2 and 3.2–3.3 years, respectively, which could be considered a proxy for a relatively early stage of the disease. In this population, beta-cell function may still be relatively normal [30]. Interestingly, lixisenatide

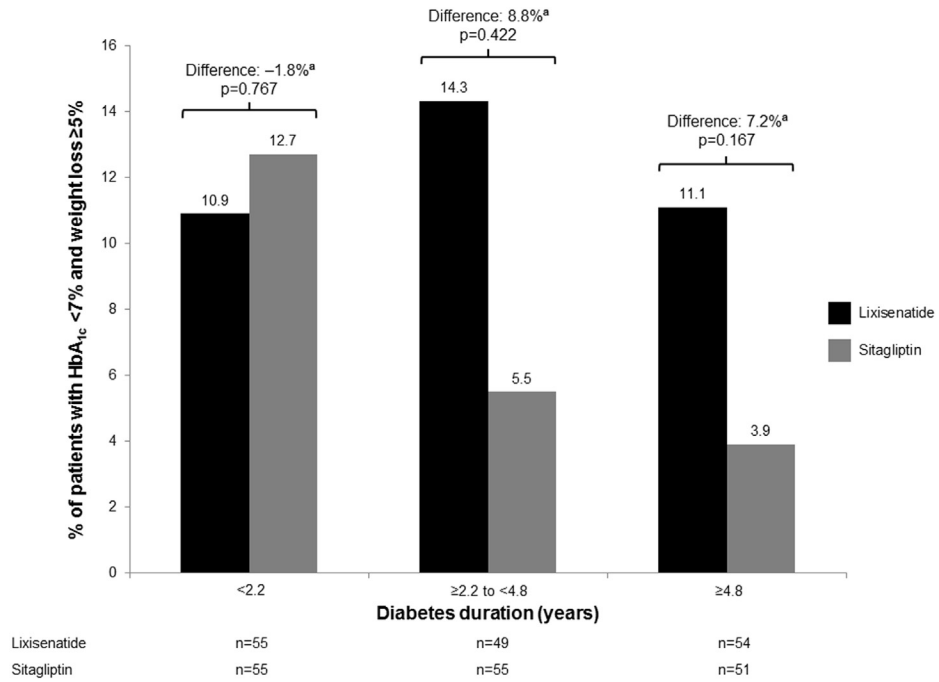

Figure 4. A *post-hoc* analysis of HbA_{1c} <7% and weight loss ≥5% according to baseline diabetes duration (mITT population). HbA_{1c} = glycated hemoglobin; mITT = modified intent-to-treat; NS = not significant. [a]Response rate differences versus sitagliptin at Week 24. Analysis was carried out on crude rates using a chi-square test of difference in rates.

has been demonstrated to be effective also in patients with low beta-cell function [31], and in special populations such as elderly patients [32]. In contrast to long-acting, non-prandial GLP-1 receptor agonists, which predominantly reduce FPG levels by stimulating insulin secretion from pancreatic beta-cells [33], short-acting, or prandial, agents such as lixisenatide primarily lower PPG via deceleration of gastric emptying [33,34]. As a result, lixisenatide may be beneficial in patients with relatively low beta-cell function, such as older patients and/or those with a longer duration of diabetes. In the dose-ranging study [21] used to estimate the lixisenatide primary endpoint responder rate for the power calculation in the present study, patients were older (55–57 years) and had longer mean duration of disease (6–7 years), with >60% of patients achieving HbA_{1c} <7% with lixisenatide 20 μg once daily. As stated above, lixisenatide may be more beneficial than sitagliptin in patients with longer disease duration. It is possible, therefore, that the patient characteristics (relatively young with earlier disease) in the current study were partly responsible for the overestimation of lixisenatide efficacy; if the patient population had been older with more advanced disease, response rates with lixisenatide may have been closer to those observed in the dose ranging study.

In this study, lixisenatide and sitagliptin demonstrated similar tolerability profiles with similar rates of overall AEs and discontinuations due to AEs. In general, DPP-4 inhibitors demonstrate slightly better tolerability profiles than GLP-1 receptor agonists, particularly in terms of GI disorders. In our study, however, GI disorders were only slightly more frequent with lixisenatide than with sitagliptin.

In conclusion, this study demonstrated that the GLP-1 receptor agonist lixisenatide had a favorable safety profile and was well tolerated in obese adults aged <50 years with T2DM. Lixisenatide was as effective in reducing HbA_{1c} as the DPP-4 inhibitor sitagliptin, with the additional advantage of greater reductions in body weight and PPG excursions after a test meal, accompanied by a similar incidence of AEs (and consequent discontinuation) as well as symptomatic hypoglycemia.

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Author contributions: Luc Van Gaal contributed to the protocol development, involved in the clinical conduct of the study, analysis of the data, and led the writing of the manuscript. Elisabeth Souhami designed and wrote the protocol, medical supervision of the study, data review and preparation of the manuscript. Tianyue Zhou contributed to the statistical analyses and reporting of results. Ronnie Aronson and other external authors were involved in the clinical conduct of the study and preparation of the manuscript.

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