Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)

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Summary

Background: Unlike most antihyperglycaemic drugs, glucagon-like peptide-1 (GLP-1) receptor agonists have a glucose-dependent action and promote weight loss. We compared the efficacy and safety of liraglutide, a human GLP-1 analogue, with exenatide, an exendin-based GLP-1 receptor agonist.

Methods: Adults with inadequately controlled type 2 diabetes on maximally tolerated doses of metformin, sulphonylurea, or both, were stratified by previous oral antidiabetic therapy and randomly assigned to receive additional liraglutide 1.8 mg once a day (n=233) or exenatide 10 ug twice a day (n=231) in a 26-week open-label, parallel-group, multinational (15 countries) study. The primary outcome was change in glycosylated haemoglobin (HbA1c). Efficacy analyses were by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00518882.

Findings: Mean baseline HbA1c for the study population was 8.2%. Liraglutide reduced mean HbA1c significantly more than did exenatide (-1.12% [SE 0.08] vs -0.79% [0.08]; estimated treatment difference -0.33; 95% CI -0.47 to -0.18; p<0.0001) and more patients achieved a HbA1c value of less than 7% (54% vs 43%, respectively; odds ratio 2.02; 95% CI 1.31 to 3.11; p=0.0015). Liraglutide reduced mean fasting plasma glucose more than did exenatide (-1.61 mmol/L [SE 0.20] vs -0.60 mmol/L [0.20]; estimated treatment difference -1.01 mmol/L: 95% CI -1.37 to -0.65; p<0.0001) but postprandial glucose control was less effective after breakfast and dinner. Both drugs promoted similar weight losses (liraglutide -3.24 kg vs exenatide -2.87 kg). Both drugs were well tolerated, but nausea was less persistent (estimated treatment rate ratio 0.448, p<0.0001) and minor hypoglycaemia less frequent with liraglutide than with exenatide (1.93 vs 2.60 events per patient per year; rate ratio 0.55; 95% CI 0.34 to 0.88; p=0.0131; 25.5% vs 33.6% had minor hypoglycaemia). Two patients taking both exenatide and a sulphonylurea had a major hypoglycaernic episode.

Interpretation: Liraglutide {Victoza} once a day provided significantly greater improvements in glycaemic control than did exenatide {Byetta} twice a day, and was generally better tolerated. The results suggest that liraglutide might be a treatment option for type 2 diabetes, especially when weight loss and risk of hypo glycaemia are major considerations.

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Introduction

Type 2 diabetes is an increasingly common chronic disease. Although diagnosed on the basis of hyperglycaemia, it is associated with broad metabolic abnormalities that contribute to microvascular and macrovascular complications. Importantly, unmet pharmacological needs remain despite great advances in diabetes care and treatment, and availability of ten different antihyperglycaemic medication classes.

To reach glycaemic targets, various antihyperglycaemic drugs—alone or in combination—are commonly required in addition to lifestyle interventions. Some agents are eventually combined with insulin in complex regimens that need daily titration based on glucose monitoring. Careful selection of therapies and follow-up is crucial to achieve glycaemic control while avoiding other substantial problems, particularly weight gain and hypoglycaemia.[1]

Glucagon-like peptide-1 (GLP-1) is secreted by intestinal L-cells, mainly in response to food intake. It has broad physiological effects, including stimulation of insulin secretion and reduction of glucagon secretion, both in a glucose-dependent manner, and resulting in reduced hepatic glucose production. Furthermore, GLP-1 slows gastrointestinal motility and increases satiety with reduced food intake. In animal models, it promotes β-cell proliferation and probably neogenesis, while reducing apoptosis.[2-4] Because GLP-l is rapidly degraded by dipeptidyl peptidase-4.[5] GLP-1 receptor agonists based on exendin or human analogues resistant to dipeptidyl peptidase-4 have been developed.

The current consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) about the medical management of hyperglycaemia in type 2 diabetes suggests that comprehensive lifestyle management combined with metformin should be initiated at diagnosis, except in cases of severely uncontrolled hyperglycaernia.[1] Subsequently, treatment should be intensified promptly if glycosylated haemoglobin (HbA1c) values exceed the ADA target of less than 7%. Recently, the consensus panel added GLP-1 receptor agonists as options when weight loss or risk of hypoglycaemia are major considerations. This decision was based on clinical data for the exendin-based GLP-1 receptor agonist exenatide, a molecule with 53% amino acid identity with human GLP-l. Exenatide causes a decrease in HbA1c values of 0.5-1. 0%, and treatment is associated with weight loss[1] and with frequent gastrointestinal side-effects that tend to subside over time but can lead to treatment discontinuation. With elimination by glomerular filtration and a half-life of 2.4 h, administration of exenatide twice a day 0-60 min before meals is recommended.[6] The drug's predominant effect is the reduction of postprandial glucose concentration, especially after breakfast and dinner.[7]

Liraglutide is a human GLP-1 analogue with one amino acid substitution (Arg34Lys) and a C-16 palmitic acid side chain attached via a glutamyl spacer. These modifications result in slower absorption from subcutaneous tissue, reversible albumin binding, and resistance to GLP-1 inactivation by dipeptidyl peptidase-4. Unlike exenatide, liraglutide is 99% bound to albumin, with free liraglutide degraded by endogenous peptidases, and not via renal

elimination.[8] Liraglutide injection produces maximal concentrations within 10-14 h after administration, with a half-life of 13 h.[9] Liraglutide has been developed as a once-a-day treatment for type 2 diabetes, as an adjunct to lifestyle therapy and in combination with oral antidiabetic drugs.[7]

Because the molecular structure, amino acid sequence identity shared with human GLP-1, metabolism, and pharmacokinetics of exenatide and liraglutide differ, we designed the liraglutide effect and action in our diabetes (LEAD-6) study to compare their efficacy and safety. We report the results of the 26-week randomised comparator trial.

Methods

Participants

Participants aged 18-80 years with type 2 diabetes were eligible if their HbA1c value was 7-11% and if they had a body-mass index (BMI) of 45.0 kg/m2 or less on stable treatment with maximally tolerated doses of metformin, sulphonylurea, or both, for 3 months or more. Exclusion criteria included previous insulin treatment (except short-term treatment for intercurrent illness), previous exposure to exenatide or liraglutide, impaired liver or renal function, clinically significant cardiovascular disease, retinopathy or maculopathy requiring acute treatment, uncontrolled hypertension (≥180/100 mm Hg), or cancer.

All participants provided written consent before any procedure. The trial was done in accordance with the Declaration of Helsinki[10] and Good Clinical Practice guidelines.[11] Before trial initiation, the protocol, its amendments, consent form, and patient information sheets were approved by independent local ethics committees. The study is registered with ClinicalTrials.gov, number NCT00518882.

Trial design and interventions

This study was a 26-week randomised, open-label, active-comparator, parallel-group, multinational (132 office-based sites across 15 countries) trial. Participants were screened for eligibility and enrolled by investigators. They were randomly assigned (1:1) to subcutaneous liraglutide 1.8 mg once a day (Novo Nordisk A/S, Bagsvaerd, Denmark) or subcutaneous exenatide 10 ug twice a day (Byetta, Amylin Pharmaceuticals Inc, San Diego, CA, USA), and were stratified by previous oral antidiabetic drug treatment. Randomisation was done with telephone-based or web-based systems. Participants were randomly assigned by investigators to the lowest available number from the range of numbers allocated to the site. The study began on Aug 24, 2007, and was completed on April 9, 2008.

After randomisation, participants underwent a 2-week liraglutide dose-escalation period (during which the initial dose of 0. 6 mg was increased by 0.6 mg a week to a maximum dose of l.8 mg once a day) or 4-week exenatide dose-escalation period (during which 5 ug twice a day was increased to 10 ug twice a day after 4 weeks).[6] This was followed by a 22-24-week maintenance period when no dose reduction of liraglutide or exenatide was allowed. Intolerance to these doses required study discontinuation. Background oral antidiabetic drugs were maintained at pre study doses unless unacceptable hypoglycaemia occurred, in which case sulphonylurea doses could be reduced to no less than 50% of the starting dose.

Both liraglutide and exenatide were injected in the upper arm, abdomen, or thigh with a pre-filled pen. Participants were encouraged to take liraglutide at the same time each day. Exenatide was administered 0-60 min before breakfast and dinner (or before each of the two main daily meals, about 6 h or more apart). Participants completing this study could enroll in a 52-week liraglutide 1.8-mg extension phase.

Assessments and endpoints

The primary efficacy outcome was change in HbA1c values from baseline to week 26. Secondary efficacy endpoints included proportion of patients reaching HbA1c targets (<7.0% and ≤6.5%), changes in fasting plasma glucose, self-measured 7-point plasma glucose profiles,

bodyweight, β-cell function, glucagon, blood pressure, and lipid profiles. Assays were done by central laboratories (MDS Pharma Services in Canada, France, Germany, Switzerland, and USA). Participants used Precision Xceed or Precision Xtra glucose meters (Abbott Diagnostics Inc, Abbott Park, IL, USA) to measure plasma glucose, and values were recorded in diaries. Overall treatment satisfaction was assessed with the Diabetes Treatment Satisfaction Questionnaire in a subgroup of participants.[12] Overall treatment satisfaction was based on six of the eight items in the questionnaire (each item was scored on a scale from +3 [better] to , -3 [worse]).

Safety variables included adverse events, vital signs, electrocardiogram, biochemical and haematological measures, and patient-reported hypoglycaemic episodes. A serious adverse event was defined as an adverse event that resulted in death, hospitalisation, disability, a birth defect, was life-threatening, or that required medical or surgical intervention to prevent one of the other outcomes. A severe adverse event was defined as an adverse event causing unacceptable and considerable interference with the patient's daily activities. Major hypoglycaemic episodes were defined as requiring third-party assistance with food only, glucagon, or intravenous glucose. Minor episodes were defined as those that the participant could self-treat and for which the plasma glucose concentration was less than 3.1 mmol/L, At glucose concentrations of 3.1 mmol/L or more, or in the absence of glucose measurements, episodes were regarded as symptoms only. Because of the nature of the antibody assay, analysis of emergent antibodies against liraglutide cannot be completed until participants have been through a washing-out period from therapy. Antibody data are not reported here and will be analysed once the liraglutide exension phase is completed.

Statistical analysis

The primary endpoint was the difference between treatment groups in HbA1c values from baseline to week 26. 163 individuals in each group were needed for 85% power to detect a difference of 0.4% between groups (assuming a SD of 1.2%), a clinically meaningful margin for non-inferiority. Assuming a 25% drop-out rate, 431 participants (217 per group) were needed at randomisation.

Analyses of efficacy outcomes were based on the intention-to-treat population. The primary endpoint was also analysed for the per-protocol population. We analysed most endpoints with the analysis of covariance (ANCOVA) with treatment, country, and current antidiabetic drug as explanatory variables, and baseline HbA1c values as covariate. We imputed missing values by carrying the last observation forward. We did hierarchical tests for non-inferiority and superiority of liraglutide and back-ground oral antidiabetic drugs versus exenatide and background oral antidiabetic drugs. We first established non-inferiority and then tested superiority, each at 2.5% significance level. We assumed non-inferiority if the uppe1limit of the two-sided 95% CI for treatment difference was less than 0.4%, and superiority if the upper limit was less than 0. We compared the proportions of patents achieving HbA1c target values using logistic regression with treatment, country, and background oral antidiabetic drug as explanatory variables, and baseline HbA1c values as covariate. We developed estimates of overall \treatment satisfaction from an ANCOVA model with treatment, country, and background oral antidiabetic drug as fixed effects, and baseline Diabetes Treatment Satisfaction Questionnaire summary score as covariate. Missing data were not imputed.

We analysed hypoglycaemic episodes using a generalised linear model with treatment, background oral antidiabetic drug, and country as fixed effects. We compared other safety data with descriptive statistics. Significance level was set at $p < 0.05$, and data are expressed as least square means (SE) unless stated otherwise.

Role of the funding source

The sponsor was involved in study design, data collection, data review, and data analysis. All authors had full access to the data and had final responsibility for the content of the manuscript;

JBB had final decision to submit for publication.

Results

464 participants were randomly assigned to treatment (figure 1). Three participants received treatment without randomisation (2 in the liraglutide group, 1 in exenatide group), and they were included in the safety but not intention-to-treat populations. 33 of 235 participants withdrew from liraglutide and 45 of 232 from exenatide treatment; withdrawal rates were not significantly different between groups. Adverse events were the most common reason for withdrawal in both groups. The characteristics of the study population were typical for participants with type 2 diabetes. and baseline characteristics were well matched between treatment groups (table 1).

HbA1c values decreased more in the group treated with liraglutide 1.8 mg once a day than in that treated with exenatide 10 ug twice a day over 26 weeks (figure 2A). The mean change from baseline to week 26 was significantly greater in the group treated with liraglutide than in that treated with exenatide (-1.12% [0.08] vs -0.79% [0.08]; estimated treatment difference [ETD] -0.33; 95% CI -0.47 to -0.18; figure 2B). Reduction of HbA1c values with liraglutide was statistically superior to that seen with exenatide. Differences in HbA1c values between treatment groups did not depend on baseline therapy, BMI. country, sex, ethnic origin. or age because the interaction effects were not significant (p>0.05). The significance of treatment-by-race interaction (p=0.0256) might be due to the small number of non-white participants (table 1). Data in the intention-to-treat population were similar to those in the per-protocol population (change from baseline to week 26 HbA1c; liraglutide -1.16% [0.09] vs exenatide -0.87% [0.09]; ETD -0.29%; 95% CI -0.45 to -0.13; p<0.0001). We confirmed robustness of the ETD using last-observation carried-forward data with repeated-measures analysis and multiple imputation methods (data not shown). Mean reductions in HbA1c values were generally greater for the liraglutide group than for the exenatide group across the spectrum of HbA1c values. However, the difference was greatest for patients with baseline HbA1c of 10% or more (liraglutide -2.4% [SE 0.21] vs exenatide -1. 2% [0. 37]).

The proportion of participants achieving HbA1c targets was significantly higher in the liraglutide than in the exenatide group (target of <7%: 54% vs 43%; odds ratio [OR] 2.02; 95% CI 1.31 to 3.11; target of ≤6.5%: 35% vs 21%; OR2. 73; 95% CI 1.68 to 4.43; figure 2C). Liraglutide also reduced fasting plasma glucose from baseline significantly more than did exenatide (-1.61 mmol/L [0.20] vs -0.60 mmol/L [0.20]; ETD -1.01 mmol/L; 95% CI -1.37to -0.65; p<0.0001; figure 2D). In contrast, exenatide reduced postprandial plasma glucose increment more than did liraglutide (self-measured with 7-point plasma glucose profiles; figure 2E) after breakfast and dinner (breakfast: ETD 1.33 mmol/L: 95% CI 0.80 to 1.86; p<0.0001; dinner: ETD 1.01 mmol/L: 95% CI o .44to 1. 57; p=0.0005); treatment differences after lunch were not significant.

Liraglutide and exenatide were associated with similar weight losses (liraglutide -3.24 kg [0.33] vs exenatide -2.87 kg [0.33]; ETD -0.38 kg; 95% CI -0.99 to 0.23; p=0.2235; figure 2F) and similar proportions of participants who lost weight (liraglutide 78% [182 of 233] vs exenatide 76% [176 of 231]). Mean reductions in HbA1c values were clinically meaningful irrespective of whether participants lost weight (weight loss: liraglutide -1.3% vs exenatide -0.9%; no weight loss: liraglutide -1. 0% vs exenatide -0.5%).

Table 2 shows changes in islet function, blood pressure, and lipids. Increases in fasting insulin and the associated homoeostasis model assessment index of β-cell function (HOMA-B) were significantly greater for the liraglutide than for the exenatide group. Treatment differences for fasting C-peptide or proinsulin-to-insulin ratio were not significant. Fasting glucagon and blood pressure decreased with both treatments, and differences between treatments were not significant for fasting glucagon or either systolic or diastolic blood pressures. Reductions of triglycerides and free fatty acid values were significantly greater in the liraglutide group than in the exenatide group, and increases in very low-

density lipoprotein cholesterol were smaller in the liraglutide group than in the exenatide group.

Overall treatment satisfaction was significantly better in the liraglutide group (n=161) than in the exenatide group (n=143) (15.18 [0.58] vs 13.30 [0.58]; ETD 1.89; 95% CI 0.85 to 2.92; p=0.0004).

Despite an overall lower reporting of adverse events in the liraglutide group than in the exenatide group (74.9% vs 78. 9%), the liraglutide group had more serious and severe adverse events (serious: 5 .1% vs 2.6%; severe: 7.2% vs 4. 7%; table 3). Serious adverse events showed no consistent pattern for system organ class and only one event (severe hypoglycaemia requiring medical attention in the exenatide group) was judged probably related to study medication by the investigator. The most frequent severe adverse events were dyspepsia in the liraglutide group (n=3) and nausea in the exenatide group (n=4). The distribution of most adverse events was similar between groups (table 3). Although the incidence of nausea was similar initially, it was less persistent with liraglutide (estimated treatment rate ratio 0 .448 for liraglutide vs exenatide; proportion of participants with nausea at week 26, 5 of 202 [3%] vs 16 of186 [9%]; figure 3).

One episode of mild pancreatitis, which the investigator regarded as chronic and unlikely to be related to study drug, was diagnosed after 88 days of liraglutide therapy in a 69-year-old man with a history of abdominal distension and hypercholesterolaemia. No data for pancreatic enzyme concentrations were reported. Liraglutide was continued for another 10 weeks until the patient was withdrawn because of lung adenocarcinoma (unlikely to be related to treatment). No episodes of acute pancreatitis were reported with either agent.

No major hypoglycaemia occurred with liraglutide but there were two episodes in patients receiving exenatide and a sulphonylurea. The proportion of patients who had minor hypoglycaemia (26% [60 out of 235] with liraglutide vs 34% [78 out of 232] with exenatide) and event rate for minor hypoglycaemia (1.932 vs 2.600 events per participant per year; rate ratio

0.55, 95% CI 0.34 to 0.88; p=0.0131) were lower with liraglutide than with exenatide, with greater differences between treatments during the evening (figure 4). The proportion of patients who had episodes of minor hypo glycaemia was lower in the subgroups using metformin as background therapy (6% [4 out of 64] and 11% [7 out of 63] for liraglutide and exenatide groups, respectively) than in those taking a sulphonylurea with or without metformin (33% [56 out of 171] and 42% [71 out of 169], respectively). However, most patients could continue sulphonylurea treatment at the dose used in the period before enrollment (liraglutide 89% [150 of 169] and exenatide 85% [142 of 168]).

Calcitonin concentrations were monitored in all participants to assess any effect of GLP-l receptor agonists on C-cell function. At baseline, mean calcitonin concentrations were less than 1 ng/L, below the upper normal reference range for both women (5.0 ng/L) and men (8.4 ng/L), Small decreases in calcitonin occurred during the trial in both treatment groups, without significant difference between groups at any timepoint. Heart rates increased slightly in both treatment groups (liraglutide 3.28 [0.83] beats per minute; exenatide 0.69 [0.84] beats per minute) but the increase was significantly greater for liraglutide (ETD: 2.58; 95% CI 1.03 to 4.13; p=0.0012).

Discussion

This trial provides a direct comparison of efficacy and safety between liraglutide and exenatide, both of which interact with the GLP-l receptor but differ in aminoacid identity with human GLP-l, frequency and timing of administration, clearance, and especially pharmacokinetics. The results show that liraglutide provides superior overall glycaemic control on the basis of HbA1c data.

We show HbA1c reductions that are consistent with those from other studies with liraglutide and exenatide. Liraglutide 1.8 mg once a day reduced HbA1c values by 1.12% in the present study compared with 1.14% in the LEAD-3 monotherapy study.[13] and 1.00-1.48% in LEAD studies in which it was administered together with oral antidiabetic drugs.[14-17]

Exenatide 10 ug twice a day reduced HbA1c values by 0.79%, which is consistent with reductions of 0.78-0.89% reported elsewhere.[18-21] Greater mean reductions were shown in a recent study (-1.5%), but these were significantly less than those achieved with exenatide once a week (-1.9%).[22] Although liraglutide has been compared with glimepiride,[13] rosiglitazone,[14] and insulin glargine,[17] showing superiority in lowering HbA1c values, exenatide twice a day has been compared with insulin glargine[23] and premixed analogue insulin,[24] showing non-inferiority in lowering HbA1c values.

The greater reduction of HbA1c values with liraglutide than that with exenatide is likely to be related to greater reduction of fasting plasma glucose. In fact, postprandial glucose increments were reduced slightly more by exenatide than by liraglutide after breakfast and dinner, the meals before which exenatide is usually administered. Liraglutide also increased the HOMA index of β-cell function more than did exenatide. Glucagon concentrations were modestly reduced by both drugs and treatment differences were not significant. Changes in C-peptide and the proinsulin-to-insulin ratio were small and similar between treatments. Although assessment of β-cell function with fasting measures is challenging and the clinical significance is uncertain, the results are consistent and likely to indicate more-sustained GLP-1 receptor activation with liraglutide than with exenatide.

Weight losses (~3 kg) were similar for both treatments. Treatment differences for the various lipid parameters were not significant except for greater reductions in triglycerides and free fatty acids, and a smaller increase in very low-density lipoprotein cholesterol, with liraglutide than with exenatide. Other studies have reported similar results for these parameters for both agents.[13,15,18,21]

Treatments were well tolerated, with most adverse events being mild or moderate in severity and serious adverse events mainly judged unlikely to be related to treatment. Gastrointestinal adverse events are of special interest for this class of drugs. Nausea was the most frequent adverse event but, although the proportion of patients affected was initially similar in the two groups, nausea resolved more quickly in patients treated with liraglutide than in those treated with exenatide. By week 6, the proportion of participants having nausea in the liraglutide group had fallen below 10% (8.1% vs 15.8% for exenatide), whereas the exenatide group reached this value after 22 weeks. At week 26, only 2.5% of the liraglutide group had nausea compared with 8.6% of the exenatide group. Similar patterns are apparent in other studies.[13-15,18,19]

Only two major hypoglycaemic episodes occurred (both in the exenatide group). Minor hypoglycaemia was less frequent with liraglutide than with exenatide despite greater reductions in fasting glucose and HbA1c. As expected from the glucose dependence of insulin secretion with GLP-1 receptor agonists, hypoglycaemia with both agents occurred mainly in patients on sulpfonylureas. However, most patients could continue their sulphonylurea medication throughout the trial at an unchanged prestudy dose.

Acute pancreatitis—including severe and fatal episodes—has been spontaneously reported in patients taking exenatide, raising concerns about a potential association with GLP-1 receptor agonists. However, obesity, hypertriglyceridaemia, and gallstones are all known risk factors for acute pancreatitis, and are all associated with type 2 diabetes. In fact, acute pancreatitis seems to be about three times more common in type 2 diabetes patients than in the general population.[25] Although the single case of mild pancreatitis treated with liraglutide in this study has not been well characterised and the diagnosis was based solely on clinical symptoms, the patient continued liraglutide therapy without substantial incident. It is uncertain whether GLP-1 receptor agonists cause pancreatitis; if a correlation exists, it is distinct from the usual course of drug-induced pancreatitis.[26]

This study shows that members of the GLP-1 receptor agonist class can be useful as new agents for the effective treatment of type 2 diabetes. Exenatide has generated substantial interest because it improves glycaemic control in patients who are suboptimally controlled with

multiple oral antidiabetic drugs, and causes modest weight loss with possible improved cardiovascular risk markers and benefits for progressive β-cell failure, which defines the pathophysiological status of type 2 diabetes. In this study, liraglutide once a day caused greater HbA1c reduction, less nausea, and greater improvements in treatment satisfaction than did exenatide twice a day. Furthermore, liraglutide was associated with less frequent therapy discontinuation and hypoglycaemia. The current consensus from ADA and EASD indicates that a GLP-1 receptor agonist is an option for the treatment of patients with type 2 diabetes, which should be taken into consideration when initial therapy fails and hypoglycaemia or weight loss are major considerations.[1]

Although in this trial some markers of β-cell function improved, the ability of GLP-1 receptor agonists to reduce or reverse the progressive loss of β-cell mass remains unclear. GLP-1 receptor agonists increase β-cell mass in rodents over some weeks,[2,4,27] but islet-cell turnover in humans is significantly longer than that in rodents,[28] and it is unclear how long it would take before an effect on human β-cell mass is detectable. In studies of liraglutide, mean HbA1c values decrease to about 7%,[13,15,16] which is in agreement with ADA recommendations for HbA1c control. In most studies lasting up to 12 months, HbA1c values are sustained at the nadir.[13,15,16] Our results are consistent with previous studies: despite a small increase in HbA1c values between weeks 12 and 26, mean values at week 26 were 7.0% in the liraglutide group and 7.3% in the exenatide group. Longer-term studies, especially in patients at earlier stages of progression of type 2 diabetes, are thus needed.

In this large, randomised, controlled, multinational trial, findings are consistent with other randomised studies of liraglutide and exenatide. Nonetheless, the open-label design might have affected outcomes. Moreover, the population was heterogeneous for background therapy with oral antidiabetic drugs, and patients were mainly white, with a mixture of European and American people who are likely to have different BMIs. Although these issues are not unusual in trials for type 2 diabetes, they affect extrapolation to other populations. Our study was also not appropriately powered to assess differences between treatments for rare clinical safety adverse events, and additional data are needed to investigate long-term clinical benefits of liraglutide.

In this study, liraglutide once a day was more effective than exenatide twice a day for overall glycaemic control, causing less hypoglycaemia and less persistent nausea. GLP-1 receptor agonists are options for treatment intensification for type 2 diabetes, especially when hypoglycaemia and weight loss are major considerations.[1] The positive results obtained with liraglutide suggest that, subject to regulatory approvals, liraglutide should be considered as a treatment option under these circumstances.

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Conflicts of interest

Acknowledgments

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