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 μg 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 (HbA_{1c}). Efficacy analyses were by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00518882.

Findings Mean baseline HbA_{1c} for the study population was 8·2%. Liraglutide reduced mean HbA_{1c} 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 HbA_{1c} 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 hypoglycaemic episode.

Interpretation Liraglutide once a day provided significantly greater improvements in glycaemic control than did exenatide 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 hypoglycaemia 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 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-1 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 hyperglycaemia.[1]

glycosylated haemoglobin (HbA_{1c}) 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% aminoacid identity with human GLP-1. Exenatide causes a decrease in HbA_{1c} 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 aminoacid 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, aminoacid 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 HbA_{1c} 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 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 µg 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 1·8 mg once a day) or 4-week exenatide dose-escalation period (during which 5 µg twice a day was increased to 10 µg 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 prestudy 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 enrol in a 52-week liraglutide 1·8-mg extension phase.

Assessments and endpoints

The primary efficacy outcome was change in HbA_{1c} values from baseline to week 26. Secondary efficacy endpoints included proportion of patients reaching HbA_{1c} 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

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 extension phase is completed.

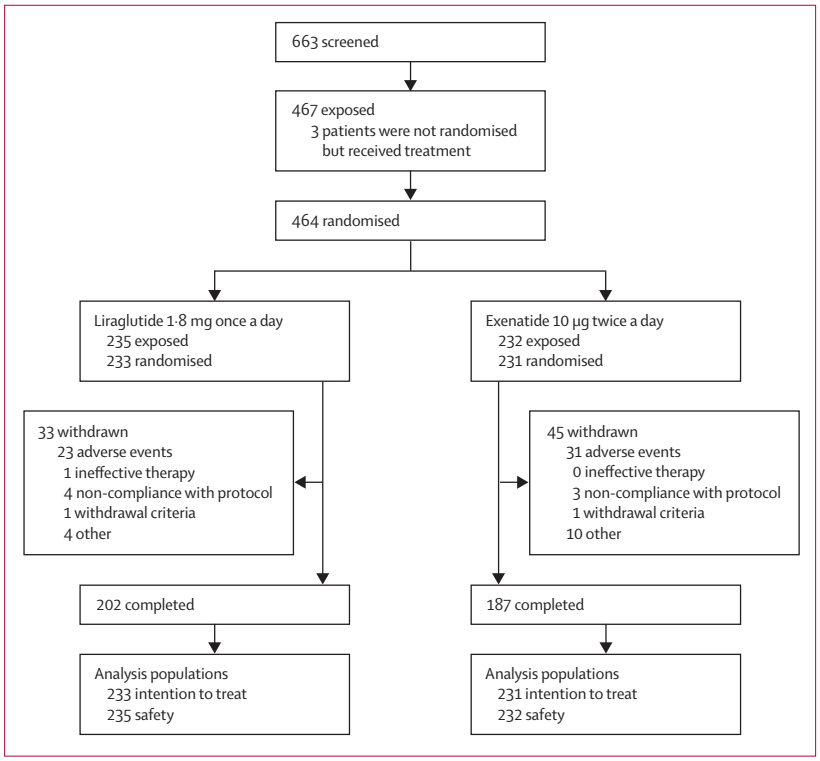

Figure 1: **Trial profile**
Of the adverse events leading to withdrawal, nausea was the most common (14 patients in the liraglutide group and 16 in the exenatide group). Participants were exposed to treatment if they had received at least one dose of study medication.

Statistical analysis

The primary endpoint was the difference between treatment groups in HbA_{1c} 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, 434 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 HbA_{1c} 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 background 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 upper limit 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 patients achieving HbA_{1c} target values using logistic regression with treatment, country, and background oral antidiabetic drug as explanatory variables, and baseline HbA_{1c} values as covariate. We developed estimates of 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

	Liraglutide 1·8 mg once a day (n=233)	Exenatide 10 µg twice a day (n=231)
Men	114 (49%)	127 (55%)
Age (years)	56·3 (9·8)	57·1 (10·8)
Race		
White	216 (93%)	210 (91%)
Asian/Pacific Islander	1 (<1%)	5 (2%)
Black*	13 (6%)	12 (5%)
Other	3 (1%)	4 (2%)
Hispanic or Latin American ethnic origin	32 (14%)	25 (11%)
Weight (kg)	93·1 (20·1)	93·0 (19·5)
Body-mass index (kg/m²)	32·9 (5·5)	32·9 (5·7)
Duration of diabetes (years)	8·5 (6·2)	7·9 (5·9)
Fasting C-peptide (nmol/L)	1·25 (0·56)	1·26 (0·58)
Prestudy antidiabetic treatment		
Metformin and SU combination	145 (62%)	147 (64%)
SU alone	24 (10%)	21 (9%)
Metformin alone	64 (27%)	63 (27%)
HbA_{1c}	8·2% (1·0%)	8·1% (1·0%)
Fasting plasma glucose (mmol/L)	9·8 (2·5)	9·5 (2·4)
Systolic blood pressure (mm Hg)	132 (16·2)	134 (17·0)
Diastolic blood pressure (mm Hg)	79·6 (8·4)	78·9 (8·9)

Data are mean (SD) or number (%). HbA_{1c}=glycosylated haemoglobin. SU=sulphonylurea. *Includes African-American.

Table 1: **Baseline demographic and disease characteristics**

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).

HbA_{1c} values decreased more in the group treated with liraglutide 1·8 mg once a day than in that treated with exenatide 10 µg 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 HbA_{1c} values with liraglutide was statistically superior to that seen with exenatide. Differences in HbA_{1c} 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 HbA_{1c}: 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 methods (data not shown). Mean reductions in HbA_{1c} values were generally greater for the liraglutide group than for the exenatide group across the spectrum of HbA_{1c} values. However, the difference was greatest for patients with baseline HbA_{1c} of 10% or more (liraglutide –2·4% [SE 0·21] *vs* exenatide –1·2% [0·37]).

The proportion of participants achieving HbA_{1c} 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%; OR 2·73; 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 –1·37 to –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 0·44 to 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 HbA_{1c} 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

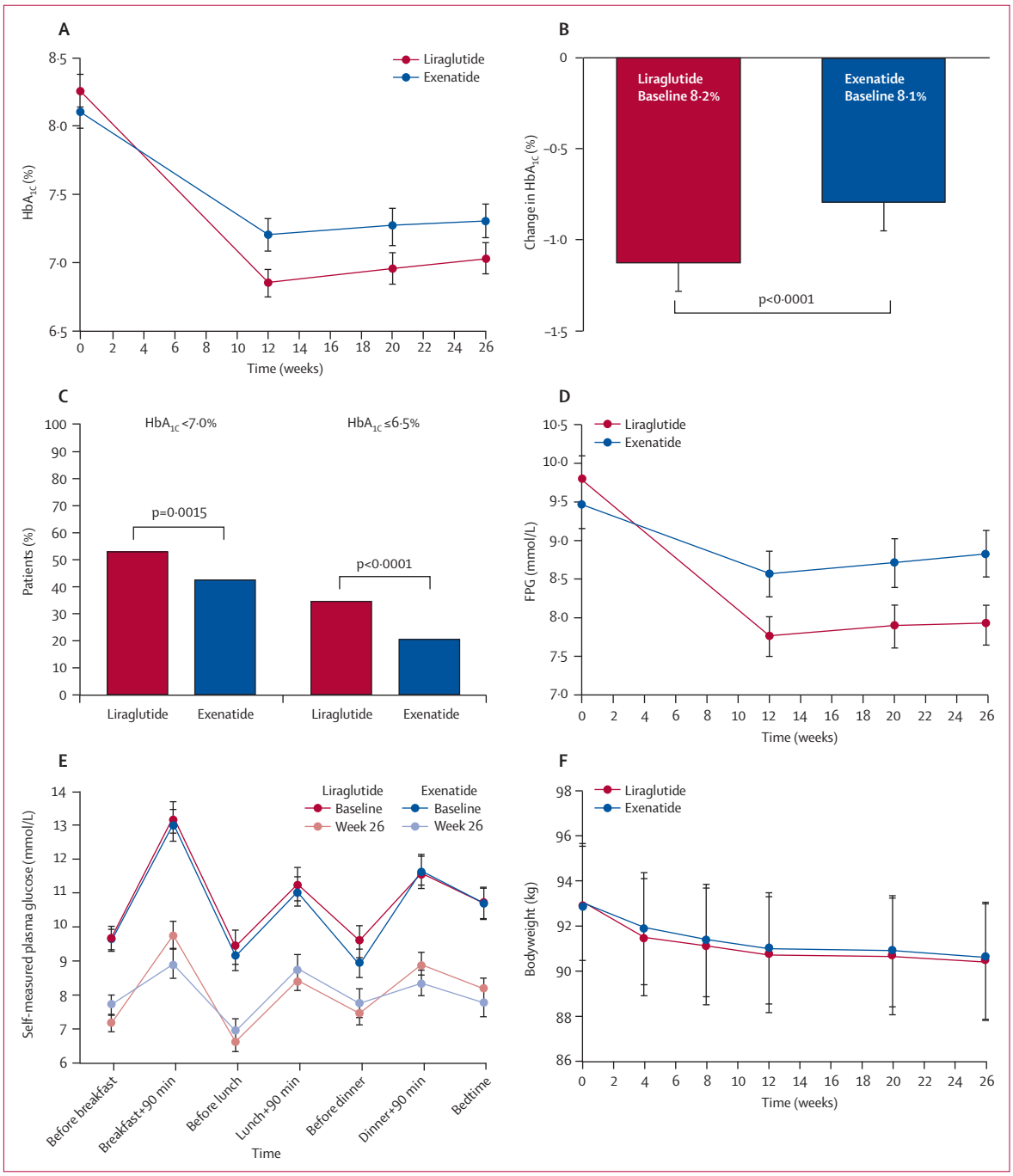

Figure 2: **Efficacy of treatment with liraglutide 1·8 mg once a day or exenatide 10 µg twice a day**
(A) Glycosylated haemoglobin (HbA_{1c}) values from baseline to week 26. (B) Change in HbA_{1c} values from baseline to week 26. (C) Percentage of patients achieving HbA_{1c} target values. (D) Fasting plasma glucose (FPG) concentrations from baseline to week 26. (E) 7-point self-measured plasma glucose profiles. (F) Bodyweight from baseline to week 26. Data are mean (1·96 SE) unless stated otherwise, with last observation carried forward (except for panel E, observed case).

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 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*

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