Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study

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Summary

Background **Exenatide is an incretin mimetic that shares glucoregulatory properties with glucagon-like peptide 1 (GLP-1), and improves glycaemic control, with progressive bodyweight reductions, when administered twice a day in patients with type 2 diabetes. We compared the efficacy of a once-weekly formulation of exenatide to that of a twice daily dose.**

Methods **A 30-week, randomised, non-inferiority study compared a long-acting release formulation of exenatide 2 mg administered once weekly to 10 µg exenatide administered twice a day, in 295 patients with type 2 diabetes (haemoglobin A_{1c} [HbA_{1c}] 8·3% [SD 1·0], mean fasting plasma glucose 9 [SD 2] mmol/L, weight 102 [SD 20] kg, diabetes duration 6·7 [SD 5·0] years). The patients were naive to drug therapy, or on one or more oral antidiabetic agents. The primary endpoint was the change in HbA_{1c} at 30 weeks. This study is registered with ClinicalTrials.gov, number NCT00308139.**

Findings **At 30 weeks, the patients given exenatide once a week had significantly greater changes in HbA_{1c} than those given exenatide twice a day (–1·9 [SE 0·1%] *vs* –1·5 [0·1%], 95% CI –0·54% to –0·12%; p=0·0023). A significantly greater proportion of patients receiving treatment once a week versus twice a day achieved target HbA_{1c} levels of 7·0% or less (77% *vs* 61% of evaluable patients, p=0·0039).**

Interpretation **Exenatide once weekly resulted in significantly greater improvements in glycaemic control than exenatide given twice a day, with no increased risk of hypoglycaemia and similar reductions in bodyweight.**

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Introduction

Type 2 diabetes is an increasingly common, complex metabolic disorder, characterised by progressive hyperglycaemia and a high risk of microvascular and macrovascular complications.[1–4] Maintenance of strict glycaemic control, which is crucial for prevention of complications, frequently requires treatment with more than one drug.[1,5–8] However, despite the introduction of several new classes of drugs, many patients do not achieve recommended glycaemic targets.[9,10] In view of the complex and chronic nature of type 2 diabetes and its increasing prevalence, a need exists for well tolerated and effective agents that provide additional options for optimising glycaemic control.

Two new classes of antidiabetic agents based on potentiation of incretin action have been approved for the treatment of type 2 diabetes: glucagon-like peptide-1 receptor (GLP-1R) agonists or incretin mimetics, and dipeptidyl peptidase-4 (DPP-4) inhibitors or incretin enhancers.[11,12] Exenatide, the first incretin mimetic approved by the Food and Drug Administration and the European Medicines Agency for the treatment of type 2 diabetes, has multiple glucoregulatory effects, including enhancement of glucose-dependent insulin secretion, reduction of glucagon secretion, reduction of food intake, and slowing of gastric emptying.[13] In placebo-controlled clinical trials, exenatide administered twice a day significantly improved glycaemic control in patients with type 2 diabetes suboptimally controlled on one or more commonly used oral therapies, including metformin, sulphonylureas, and thiazolidinediones.[14–17] Mean haemoglobin A_{1c} (HbA_{1c}) reductions with exenatide in placebo-controlled trials were roughly 1% from baseline values of 7·9% to 8·4%, whereas open-label comparator studies showed HbA_{1c} reductions of 1·1–1·4% from baseline values of 8·2–9·0%.[14–20]

Exenatide lowers fasting and postprandial plasma blood glucose concentrations, and reduces bodyweight in a substantial proportion of treated patients.[14–17] However, its current delivery method requires twice daily subcutaneous injection, and does not provide continuous GLP-1R activation. Furthermore, some evidence exists that the rate of nausea, a transient but commonly reported side-effect of therapy with GLP-1R agonists, could be reduced with long-acting GLP-1R agonists, that achieve peak drug concentrations more slowly over a longer time.

Although GLP-1 is mostly secreted postprandially, several lines of evidence support a role for basal concentrations of GLP-1 in the control of fasting glucose.[18,19] Indeed, blockade of endogenous GLP-1 action increases fasting plasma glucose.[20] Moreover, infusion of GLP-1 over 24 h provides better glucose control than a 16 h infusion.[18] These

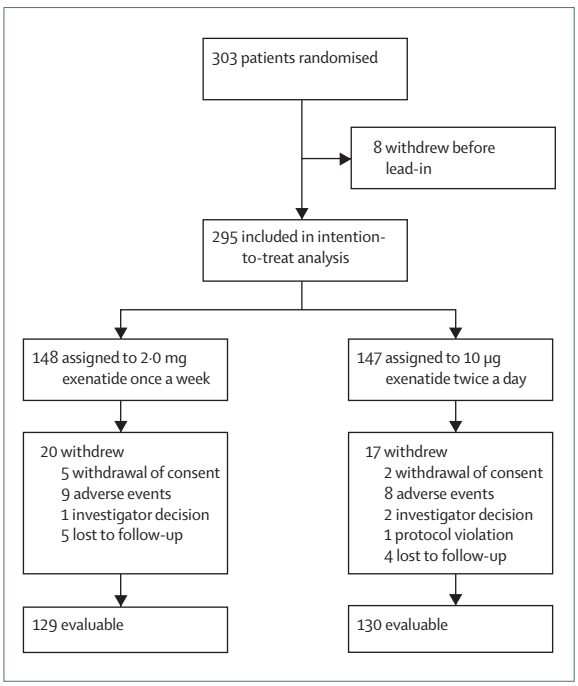

Figure 1: **Trial profile**
Patients who completed study procedures to at least week 26 without protocol violations were considered evaluable. Of the 258 30-week completers, 255 patients were evaluable. Of the 35 patients who withdrew before week 30, four completed 26 weeks of treatment and were considered evaluable, resulting in 129 patients allocated exenatide once a week and 130 twice a day.

observations provide a rationale for exploration of GLP-1R agonists with prolonged pharmacokinetic profiles.

A long-acting release form of exenatide has been developed for use as a once-weekly injection.[21] This sustained-release formulation consists of injectable microspheres of exenatide and poly (D,L lactic-co-glycolic acid), a common biodegradable medical polymer with established use in absorbable sutures and extended-release pharmaceuticals, that allows gradual drug delivery at a controlled rate.[22] A small pilot study of exenatide once a week over 15 weeks resulted in significant reductions in HbA_{1c}, fasting plasma glucose, postprandial plasma glucose, and bodyweight.[21] In the current study, we compared the safety and efficacy of exenatide once a week to that of exenatide given twice daily, over 30 weeks, in patients with type 2 diabetes.

Methods

Patients

303 patients were enrolled. Study participants were at least 16 years of age, with type 2 diabetes treated for at least 2 months before screening. Entry criteria included a baseline HbA_{1c} of 7·1–11·0%, fasting plasma glucose of less than 16 mmol/L, body-mass index of 25–45 kg/m², and therapy with diet modification and exercise, or pharmacological treatment with metformin, a sulphonylurea, a thiazolidinedione, or any combination of two of these agents.

Eligible patients were weight-stable—their weight did not vary more than 10% for 6 months before screening—and had no abnormal results of clinical significance on blood testing. Exclusion criteria included use of meglitinides, α-glucosidase inhibitors, insulin therapy, weight-loss drugs, corticosteroids, drugs known to affect gastrointestinal motility, or any investigational drug; any previous exposure to exenatide or a GLP-1 analogue; or evidence of clinically significant medical conditions that might preclude safe participation in the study.

A common clinical protocol was approved for each site by Institutional Review Boards. All patients provided written informed consent before participation and the study was done in accordance with the principles described in the Declaration of Helsinki, including all amendments up to and including the 1996 South Africa revision.[23]

Study design

The study was a randomised, comparator-controlled, open-label assessment of the efficacy, safety, and tolerability of exenatide once a week, compared with twice a day (figure 1). For this non-inferiority study, treatment duration was consistent with that in the pivotal trials of twice a day exenatide.[14–16] Patients were randomised, underwent a 3-day lead-in with 5 µg exenatide twice a day, and then began the assigned treatment with subcutaneous injections of 2·0 mg exenatide once a week, or 5 µg twice a day for the first 28 days, then 10 µg twice a day for the remainder of the 30-week assessment period. Randomisation was stratified according to concomitant sulphonylurea use at screening and HbA_{1c} strata (<9·0% *vs* ≥9·0%). In keeping with the current recommendations for use of exenatide twice a day, and to mitigate the risk of hypoglycaemia in patients treated with sulphonylurea, a decrease in sulphonylurea dosage to the minimum labelled dose was required in both treatment groups until week 10, at which point steady state concentrations of exenatide would be anticipated in those receiving treatment once a week. Subsequently, the sulphonylurea dose was up-titrated, based on daily glucose measurements, to reach the target goal of fasting plasma glucose of 6 mmol/L or less. Patients self-administered exenatide during the trial after being trained by study site personnel. In accordance with its open-label design, the investigators, sponsor, patients, and all personnel involved with the study were not blinded to the identity of study medication. However, blinding to the HbA_{1c} and fasting plasma glucose results were maintained by sponsor personnel throughout the 30-week assessment period, such that individual patient data were anonymised through scrambling before review.

In a subset of patients, rates of gastric emptying were assessed at baseline and at week 14 by determining plasma paracetamol concentrations over 5 h after a single oral dose (1000 mg; 2×500 mg tablets). After an overnight fast, patients ingested paracetamol immediately before

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receiving a standardised breakfast (55% carbohydrates, 15% protein, 30% fat). Patients who received exenatide twice daily had a dose before breakfast; those who received it once a week took it after completion of the paracetamol absorption test. 7-point self-monitored blood glucose profiles (15 min before each meal, 1·5–2 h after each meal, and an additional glucose measurement at 0300 h) were obtained on 3 separate days before baseline, and at week 30. Patients did not receive additional instruction on nutrition or caloric restriction during the course of the study.

Study endpoints

The study was designed to test the hypothesis that the change in HbA_{1c} from baseline achieved with exenatide once a week is non-inferior to that of exenatide twice a day by 0·4% at the end of 30 weeks of treatment. The primary endpoint in this study was the change in HbA_{1c} at 30 weeks. Secondary endpoints included examining safety and tolerability, and analysis of fasting and postprandial plasma glucose concentrations, bodyweight, fasting glucagon, fasting lipids, blood pressure, exenatide pharmacokinetics, and paracetamol absorption. We also recorded the proportion of patients achieving target HbA_{1c} concentrations of 7·0% or less, 6·5% or less, and 6·0% or less, overall and by baseline HbA_{1c} strata; HbA_{1c} by antibody titre; and bodyweight, in the presence and absence of nausea.

Laboratory values

Blood tests, including HbA_{1c}, were done by Quintiles Laboratories (Smyrna, GA, USA) using standard methods. HbA_{1c} was measured by high performance liquid chromatography.[24] Plasma exenatide and anti-exenatide antibodies were measured by enzyme-linked immunosorbent assay (ELISA), as previously described.[25] Antibody titres less than 1/625 were classified as low, and 1/625 or more classified as high.

Statistical analysis

Baseline demographic data were presented as mean (SD) for continuous variables (age, duration of diabetes, body-mass index, weight, and HbA_{1c}) and tallied for categorical variables (sex and race). Exenatide pharmacokinetics after weekly injection were analysed by standard non-compartmental methods, and summarised descriptively from day 1 to week 30.

Exenatide once a week was regarded as non-inferior to treatment twice a day if, after 30 weeks of treatment, the upper limit of the two-sided 95% CI for the difference in HbA_{1c} change was less than 0·4%. By protocol, a sample size of 300 patients was estimated to provide 90% power to test the hypothesis that exenatide once a week was non-inferior to treatment twice a day, assuming a greater reduction (0·1%) in HbA_{1c} from baseline to week 30 for exenatide once a week versus twice a day, a 20% early discontinuation rate, and an expected interpatient SD of 1·2%. A CI with an upper limit lying entirely below zero was deemed significant evidence that treatment once a week was better than twice a day. The CI for the difference in the change of HbA_{1c} between treatment groups was generated from an analysis of variance model (ANOVA) including treatment, concomitant use of sulphonylurea at screening, and baseline HbA_{1c} strata.

	2·0 mg exenatide once a week	10 µg exenatide twice a day
Sex (%)		
Men	82 (55%)	75 (51%)
Women	66 (45%)	72 (49%)
Race (%)		
White	123 (83%)	107 (73%)
Black	9 (6%)	19 (13%)
Hispanic	16 (11%)	20 (14%)
Asian	0 (0%)	1 (1%)
Age, years	55 (10)	55 (10)
Weight, kg	102 (19)	102 (21)
Body-mass index (kg/m²)	35 (5)	35 (5)
HbA_{1c} (%)	8·3 (1·0)	8·3 (1·0)
Fasting plasma glucose (mmol/L)	9·6 (2·4)	9·2 (2·3)
Duration of diabetes, years	7 (6)	6 (5)
Diabetes management at screening		
Diet/exercise	21 (14%)	23 (16%)
Metformin only	56 (38%)	50 (34%)
Sulphonylurea only	6 (4%)	10 (7%)
Thiazolidinedione only	2 (1%)	7 (5%)
Metformin+sulphonylurea	43 (29%)	39 (27%)
Metformin+thiazolidinedione	14 (10%)	13 (9%)
All* metformin	114 (77%)	102 (69%)
All* sulphonylurea	55 (37%)	54 (37%)
All* thiazolidinedione	22 (15%)	25 (17%)

Data are n (%) or mean (SD). *Includes specified agent alone or in combination.

Table 1: **Baseline characteristics**

The analysis of bodyweight, fasting plasma glucose, and postprandial plasma glucose at 2 h was based on an analysis of covariance (ANCOVA): baseline values of bodyweight and plasma glucose, treatment, concomitant use of sulphonylurea at screening, and baseline HbA_{1c} strata (above and below 9%) were included in the model. For triglyceride data, ratios were derived from a general linear model including treatment, baseline HbA_{1c} strata, concomitant sulphonylurea use at screening, and baseline value of triglycerides after the natural logarithmic transformation of the data. For the meal tolerance assessments comparing baseline and week 14, the ratios of the area under the curve (AUC) for paracetamol, and the $AUC_{(0–120\,min)}$ ratios of insulin to glucose, were calculated, and CIs were determined.

The intention-to-treat population consisted of all randomised patients who received at least one injection of exenatide, whereas the evaluable population consisted

of patients from the intention-to-treat population who completed the study procedures to at least week 26, in compliance with the protocol. Descriptive statistics on demographics, analysis of primary glycaemic endpoints, and bodyweight were provided for the intention-to-treat population (N=295). Results on the proportion of patients achieving HbA_{1c} levels of 7·0% or less, 6·5% or less, and 6·0% or less, and 7-point self-monitored blood glucose measurements are reported for the evaluable population (N=259). Treatment groups were compared with respect to the proportion of patients achieving HbA_{1c} levels of 7·0% or less, 6·5% or less, and 6·0% or less by use of a Cochran-Mantel-Haenszel test, after adjusting for baseline HbA_{1c} strata and concomitant sulphonylurea use at screening. Missing data were imputed by the last observation carried forward method. Of the total number of HbA_{1c}, fasting plasma glucose, and bodyweight measures that were scheduled to be collected, the percentage of missing values for each of these parameters was less than 10% (once a week: 9·3% for HbA_{1c}, 9·2% for fasting plasma glucose, 7·5% for weight; twice a day: 8·6% for HbA_{1c}, 9·8% for fasting plasma glucose, 8·0% for weight). Pharmacokinetic data for plasma exenatide concentrations are expressed as geometric mean (Q1–Q3 interquartile range). Efficacy data on mean changes from baseline in HbA_{1c}, bodyweight, fasting glucose, and fasting glucagon are expressed as least square means (SE).

All safety analyses were done in the intention-to-treat population. Treatment-emergent adverse events were defined as those occurring on or after receiving the first injection of study medication. Patients who had a loss of glucose control, predefined as a 1·5% increase from baseline in HbA_{1c} value or an HbA_{1c} of 11·5% or higher at or after week 14, were withdrawn from the study. Hypoglycaemic episodes were classified as major or

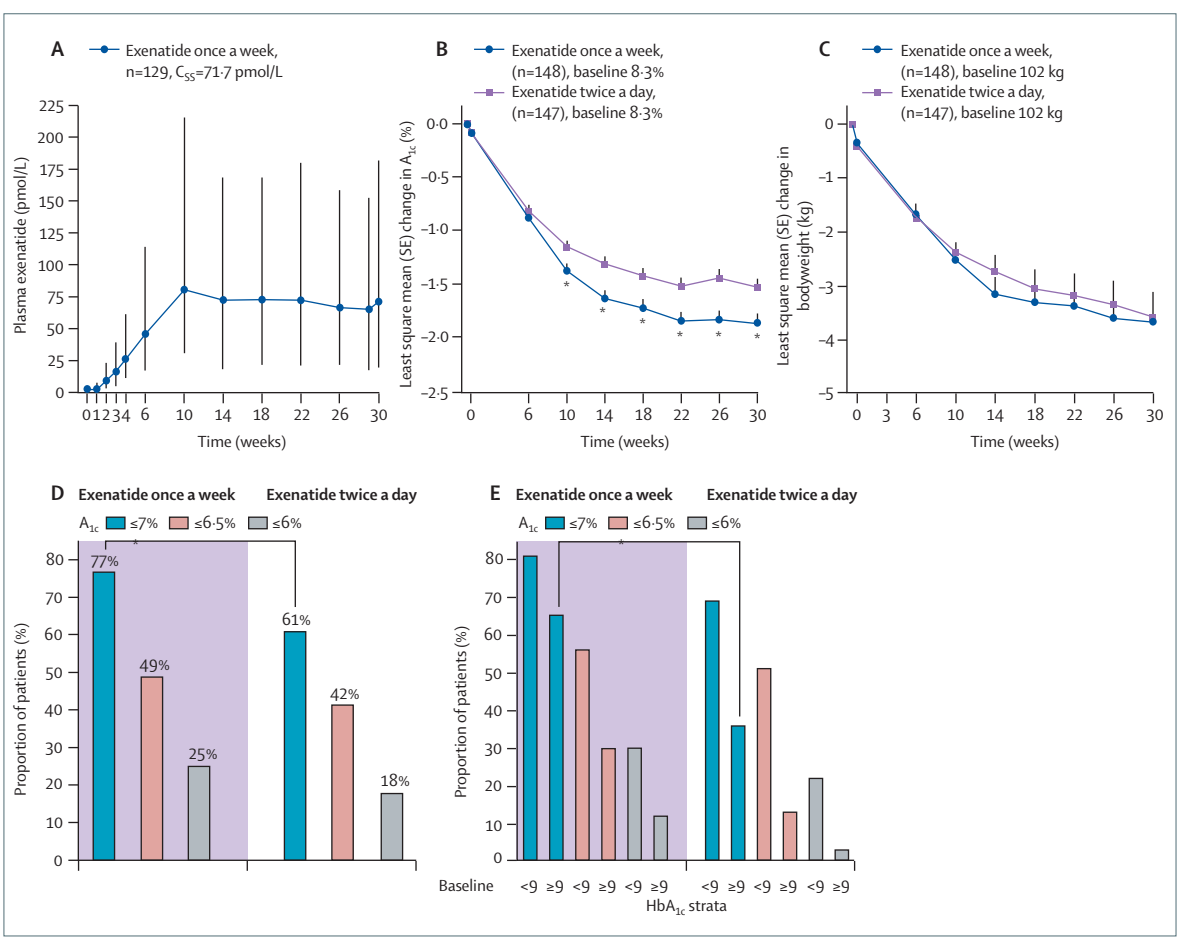

***Figure 2*: Pharmacokinetics and efficacy of exenatide once weekly versus twice daily**

*p<0·05. (A) Pharmacokinetic profile of plasma exenatide (geometric mean [interquartile (Q1–Q3) range]). Plasma levels were in therapeutic range by week 2. (B) Change in HbA_{1c} from baseline over 30 weeks (least square mean [SE], intention-to-treat population, N=295). Baseline HbA_{1c} values were 8·3% (SD 1·0) for both exenatide arms. Greater reductions in HbA_{1c} with exenatide once a week versus exenatide twice a day were significant from week 10 (p<0·01); HbA_{1c} changes at endpoint were –1·9% (0·08) and –1·5% (0·08; p=0·0023). (C) Change in bodyweight from baseline over 30 weeks (least square mean [SE], intention-to-treat population, N=295). Similar reductions in bodyweight were shown with exenatide once a week (3·7 [0·5] kg) and twice a day (3·6 [0·5] kg). (D) Percentage of evaluable patients (N=259) achieving HbA_{1c} ≤7%, ≤6·5% and ≤6·0% at week 30. (E) Percentage of evaluable patients (N=259) by baseline HbA_{1c} strata of <9·0% and ≥9·0% achieving HbA_{1c} ≤7%, ≤6·5% and ≤6·0% at week 30. Shaded area indicates exenatide once a week.

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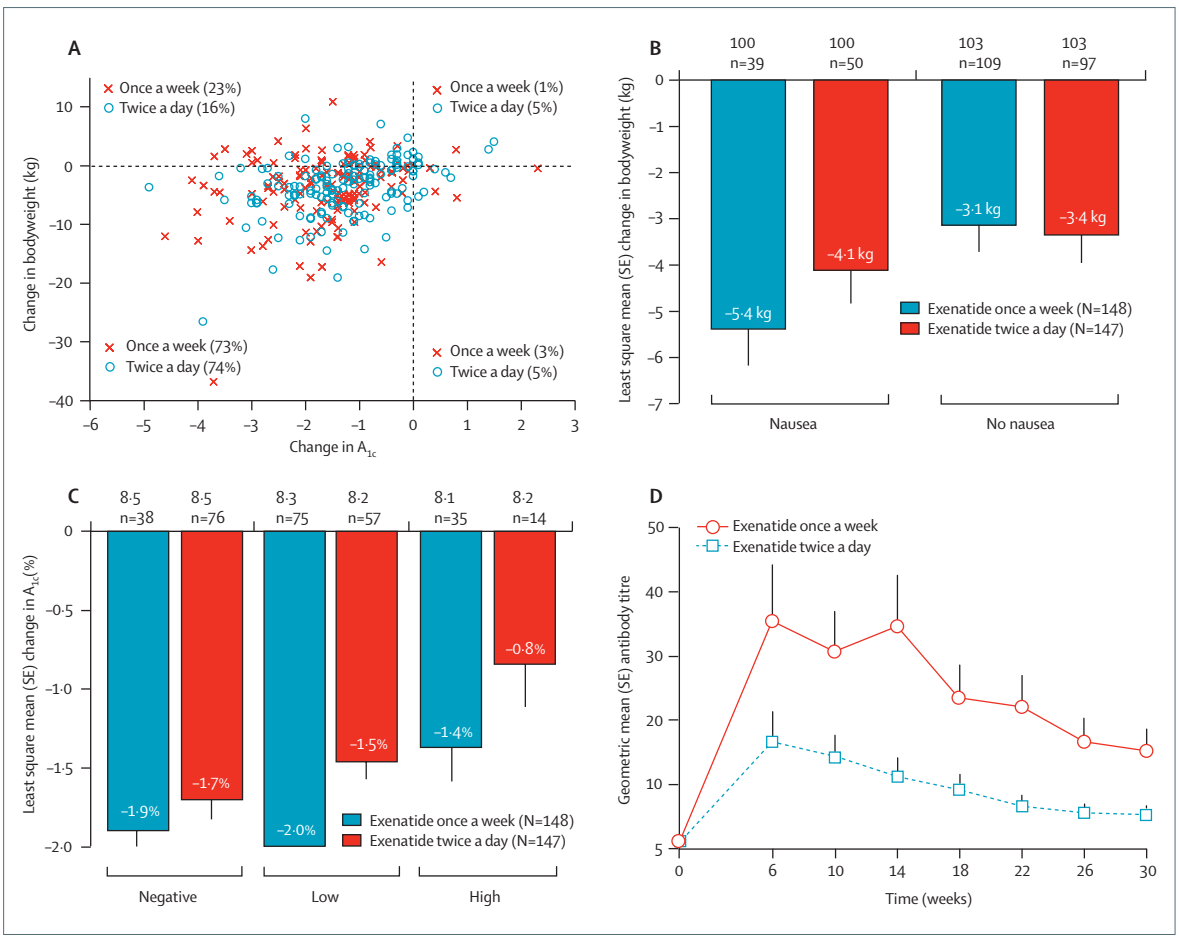

***Figure 3*: Bodyweight, glycaemic control, and antibody titres in patients treated with exenatide**
(A) Individual patient data on treatment responses for HbA_{1c} and bodyweight with once a week (x) and twice a day (o). Pearson partial correlation coefficient between the change in HbA_{1c} and change in bodyweight after adjusting for baseline HbA_{1c} strata and concomitant sulphonylurea use at screening was calculated; R=0·34 (p<0·0001) for exenatide once a week and 0·45 (p<0·0001) for twice a day. (B) Intention-to-treat subanalysis (N=295) of effects on bodyweight based on whether patients had at least one episode of nausea, or no nausea at all. (C) Intention-to-treat subanalysis (N=295) of change in HbA_{1c} (least square mean (SE) by antibody status: Negative=antibodies were not detectable in repeated analyses throughout the 30 weeks; low titre ≤1/625 at any point during the 30 weeks; and high titre=titres ≥1/625 at any point during the 30 weeks; HbA_{1c} reductions of −1·4% were observed in patients treated once a week in the high titre group. (D) Geometric mean of anti-exenatide antibody titres over time; antibody titres gradually diminished over 30 weeks in both exenatide groups (intention to treat, N=295).

minor. Minor hypoglycaemia was defined as patients reporting symptoms consistent with hypoglycaemia, and a plasma glucose concentration of less than 3 mmol/L. Major hypoglycaemia was defined as loss of consciousness, seizure, or coma which resolved after administration of glucagon or glucose, or required third-party assistance to resolve, and a glucose concentration of less than 3 mmol/L.

Role of the funding source

This study was sponsored by Amylin Pharmaceuticals and Eli Lilly and Company. Sponsors were involved in the study design, protocol development, and the collection, review, and analysis of the data. DJD and JBB had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Results

Demographics, baseline characteristics, and disposition by treatment are shown in table 1. Baseline characteristics in the current study were similar to those reported for the 30-week placebo-controlled trials with exenatide twice a day, particularly with respect to age (55 years), sex (42% women), body-mass index (34 kg/m²), and baseline HbA_{1c} (8·4%).[14–17] 258 (88%) of the 295 patients randomised in the intention-to-treat population completed 30 weeks of treatment (128 [87%] exenatide once a week, 130 [88%] exenatide twice a day). Withdrawal rates during the 30-week assessment were equally distributed across treatment groups. No significant differences were seen in baseline demographics between groups. Patient distribution with respect to specific background therapy was also similar across groups.

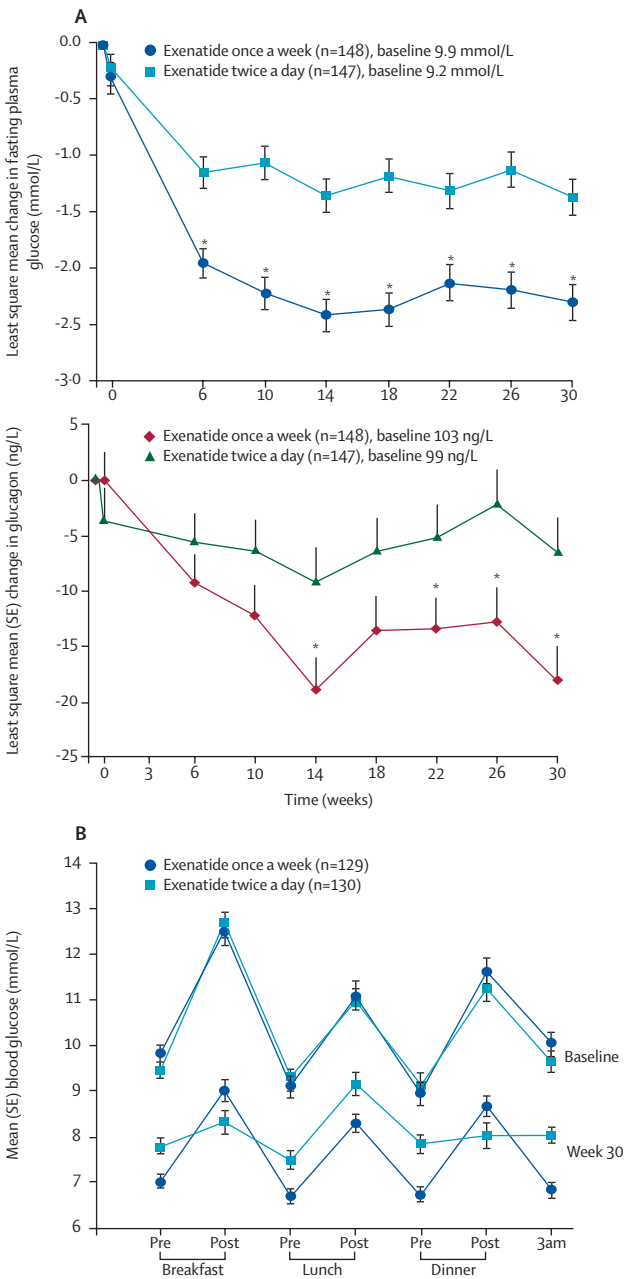

Figure 4: **Fasting plasma glucose, glucagon, and postprandial glucose in patients treated with exenatide**
(A) Change in fasting plasma glucose from baseline over 30 weeks (least square mean (SE, intention-to-treat population, N=295). *p≤0·0001. Change in fasting plasma glucagon from baseline over 30 weeks (least square mean [SE], intention-to-treat population, N=295). *p<0·05 for suppression of glucagon with exenatide once a week versus exenatide twice a day. Glucagon change from baseline at endpoint was –18·0 (2·9) ng/L and –6·4 (2·9) ng/L from baseline values of 103 (3·1) ng/L for exenatide once a week and 99·0 [3·0] ng/L for exenatide twice a day. (B) 7-point self-monitored blood glucose profiles at baseline and week 30 for exenatide once a week versus twice a day showing reductions in both fasting and postprandial plasma glucose excursions. 1 mg/dL glucose=0·05551 mmol/L, 1 pg/mL glucagon=1 ng/L.

Patients treated with exenatide once a week achieved plasma exenatide concentrations in the known therapeutic range as early as 2 weeks after initiation of therapy (figure 2A). The mean plasma exenatide concentration increased progressively, until plateau concentrations were reached at between 6 and 10 weeks. The geometric mean plasma exenatide concentration at steady state with exenatide once a week was 71·7 pmol/L.

Patients in both treatment groups had significant reductions in HbA_{1c} from baseline by week 6 of treatment (figure 2B). The mean reduction in HbA_{1c} was significantly greater with exenatide once a week by 10 weeks, and this difference persisted through the remainder of the study period. At 30 weeks, the mean difference in HbA_{1c} change at endpoint was –0·33 (SE 0·1)%; 95% CI –0·54 to –0·12) with reductions from baseline of 1·9 (0·1%) for exenatide once a week *vs* 1·5 (0·1%) for twice a day (intention to treat, p=0·0023). HbA_{1c} reductions were consistent across all treatment background therapies, for patients in both treatment groups. Reductions in HbA_{1c} did not vary notably with sex or age (>65 years *vs* <65 years).

Exenatide once a week resulted in a greater proportion of patients achieving an HbA_{1c} of 7% or less (77% for once a week *vs* 61% twice a day, p=0·0039; figure 2D) than did treatment twice a day. 49% of patients achieved HbA_{1c} values of 6·5% or less, and 25% achieved HbA_{1c} values of 6·0% or less, on treatment once a week, after 30 weeks (figure 2D). In patients with baseline HbA_{1c} values of 9·0% or more, significantly more patients (65% *vs* 35%, p=0·02) achieved an HbA_{1c} of 7·0% or less after 30 weeks of exenatide once a week *vs* exenatide twice a day. 29% of patients treated with exenatide once a week achieved an HbA_{1c} of 6·5% or less; 12% achieved an HbA_{1c} of 6·0% or less (figure 2E).

There were no substantial changes in sulphonylurea dose from randomisation to 30 weeks. The mean screening sulphonylurea dose for patients receiving exenatide once a week was 57% of maximum labelled daily dose; at 30 weeks, the mean dose was reduced to 52%. For exenatide twice a day, mean screening sulphonylurea dose was 49%, and at 30 weeks was 64% of maximum labelled daily dose.

Bodyweight decreased progressively in both groups during the 30-week treatment period (changes from baseline of –3·7 [SE 0·5] kg with exenatide once a week and –3·6 [0·5] kg with exenatide twice a day; 95% CI –1·3 to 1·1, intention to treat, p=0·89, figure 2C). In evaluable patients, reductions in bodyweight of 4·0 (0·5) kg were recorded with exenatide once a week and 3·8 (0·5) kg for exenatide twice a day. At week 30, the mean percentage of weight loss from baseline was 3·6% with exenatide once a week, and 3·7% with treatment twice a day (p>0·05).The distribution of individual patients, and their changes in HbA_{1c} and bodyweight, are shown in figure 3A. 96% of patients treated with exenatide once a week, and 90% treated twice a day, had a reduction in HbA_{1c} from baseline at study endpoint. Significant reductions in HbA_{1c} were observed with both regimens, independent of concomitant weight loss. In patients that did not lose

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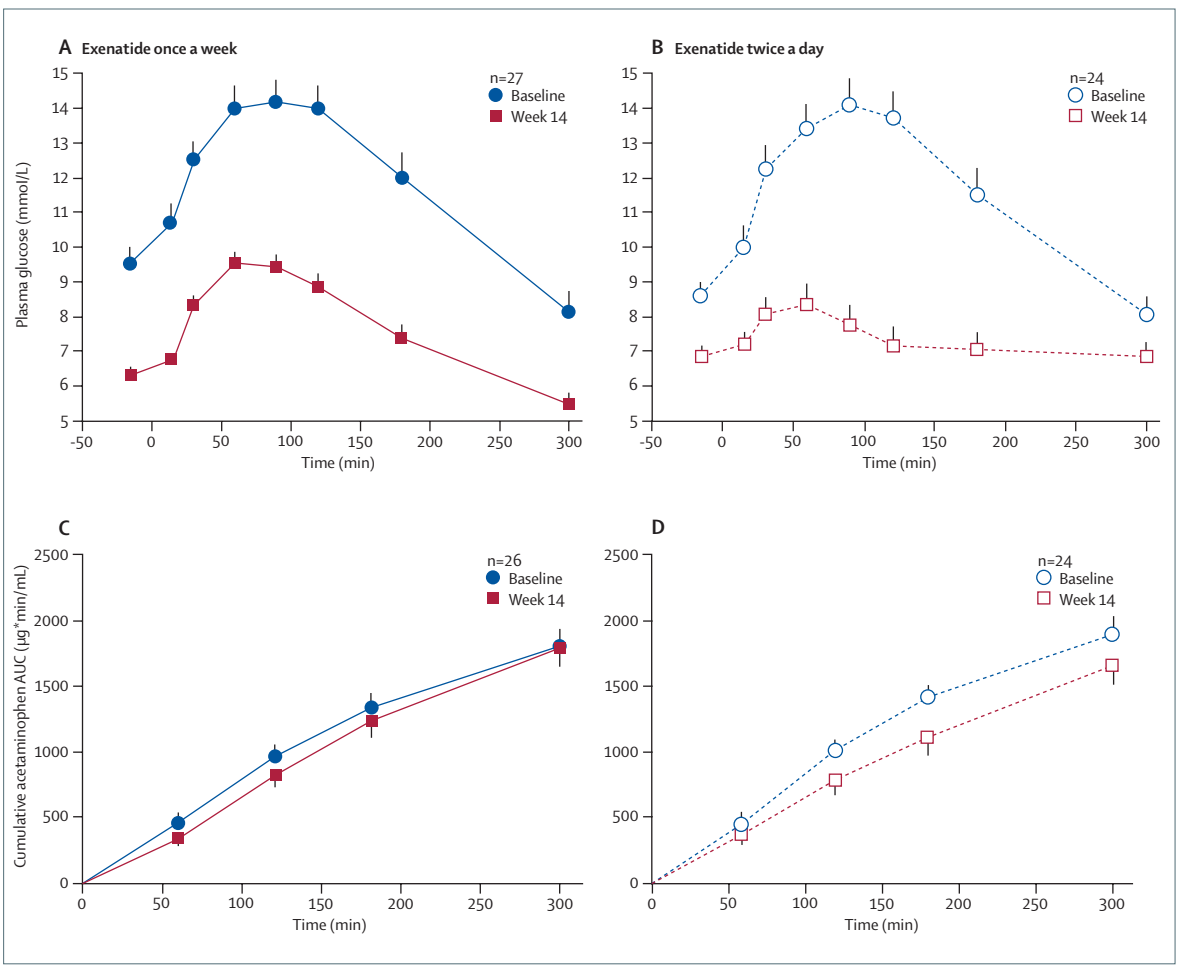

Figure 5: **Time profiles of postprandial plasma glucose concentrations and cumulative paracetamol area**
(A, B) Time profiles of postprandial plasma glucose concentrations (mean [SE]) and (C, D) cumulative paracetamol area under the curve (AUC) after a standardised meal at baseline and week 14 comparing exenatide once a week (left panels) versus exenatide twice a day (right panels; evaluable subgroup, N=51). Gastric emptying was assessed by absorption of paracetamol in patients receiving an oral dose (1000 mg) before a standardised meal test.

weight, a reduction in HbA_{1c} of 1·7% was seen with exenatide once a week (N=36), whereas those treated twice a day (N=31) had a 0·8% reduction in HbA_{1c} (webfigure). More than 75% of treated patients in both groups lost weight (76% for once a week *vs* 79% for twice a day, figure 3A), and most patients had reductions in both HbA_{1c} and bodyweight (73% for exenatide once a week, and 74% for exenatide twice a day; figure 3A). See Online for webfigure

	Exenatide once a week (N=148)			Exenatide twice a day (N=147)		
	Baseline (SE)	Change from baseline (SE)	95% CI	Baseline (SE)	Change from baseline (SE)	95% CI
Triglycerides (mmol/L) or (%)	1·88 (0·10)	−15% (0·03)	−20 to −9	1·78 (0·09)	−11% (0·03)	−16 to −4
Total cholesterol (mmol/L)	4·49 (0·09)	−0·31 (0·06)	−0·42 to −0·19	4·72 (0·10)	−0·10 (0·06)	−0·22 to 0·02
HDL-C (mmol/L)	1·14 (0·02)	−0·02 (0·01)	−0·05 to +0·01	1·20 (0·02)	−0·03 (0·01)	−0·06 to −0·01
LDL-C (mmol/L)	2·37 (0·07)	−0·13 (0·05)	−0·23 to −0·03	2·6 (0·08)	+0·03 (0·05)	−0·07 to 0·13
Systolic blood pressure (mm Hg)	127·8 (1·1)	−4·7 (1·1)	−6·9 to −2·6	129·5 (1·2)	−3·4 (1·1)	−5·5 to 1·3
Diastolic blood pressure (mm Hg)	77·7 (0·7)	−1·7 (0·7)	−3·1 to −0·3	79·6 (0·6)	−1·7 (0·7)	−3·1 to −0·3

Least square mean % change (SE) is presented for triglycerides. Least square mean change (SE) for all other data.

Table 2: **Comparative changes in cardiovascular parameters with exenatide once a week versus exenatide twice a day treatment over 30 weeks in the intention-to-treat population**

	2·0 mg exenatide once a week (N=148) n (%)	10 µg exenatide twice a day (N=145) n (%)
Nausea	39 (26·4)	50 (34·5)
Vomiting	16 (10·8)	27 (18·6)
Injection site pruritus	26 (17·6)	2 (1·4)
Upper respiratory tract infection	12 (8·1)	25 (17·2)
Diarrhoea	20 (13·5)	19 (13·1)
Constipation	16 (10·8)	9 (6·2)
Injection site bruising	7 (4·7)	15 (10·3)
Urinary tract infection	15 (10·1)	12 (8·3)
Adverse events leading to withdrawal during 30-week assessment period (n)		
All, n	9	7
Abdominal pain	0	1
Anorexia	0	1
Blood potassium increased	1	0
Impaired gastric emptying	1	0
Injection site nodule	1	0
Malaise	1	0
Myocardial infarction	1	0
Nausea	1	2
Paraesthaesia	1	0
Regurgitation of food	0	1
Vomiting	1	2
Weight decreased	1	0

Frequent treatment-emergent adverse events ≥10% incidence.

Table 3: **Overall incidence of treatment-emergent adverse events occurring in 10% or more of patients who received one or more doses of study drug**

	Non-sulphonylurea background		Sulphonylurea background	
	Exenatide once a week N=93	Exenatide twice a day N=93	Exenatide once a week N=55	Exenatide twice a day N=54
Major	0	0	0	0
Minor	0	1 (1·1)	8 (14·5)	8 (15·4)

Data are n (%).

Table 4: **Percentage of patients with at least one episode of hypoglycaemia, by treatment and concomitant sulphonylurea use**

Weight loss was observed in patients who reported no episodes of nausea throughout the trial (70%) in both groups, with modestly greater weight loss in the subset of patients reporting at least one episode of nausea (figure 3B).

As previously reported in studies with exenatide twice a day,[26] anti-exenatide antibodies also developed in subsets of patients treated with exenatide once a week. Anti-exenatide antibody levels were higher with exenatide once a week (p=0·0002 *vs* exenatide twice a day); however, most antibodies were either not detectable or of low (<1/625) titre (figure 3C). There were significant reductions in mean HbA_{1c} over 30 weeks in patients with negative, low titre (1/25 to 1/125), and high titre (>1/625) antibodies (figure 3C). The geometric mean of antibody titres remained fairly constant over 6–14 weeks, and declined progressively thereafter for both treatment groups (figure 3D). At study endpoint, four patients (1·4% of the total study cohort; three taking exenatide once a week and one taking exenatide twice a day) had antibody titres of 1/3125. In these individuals, one had a reduction in HbA_{1c} from baseline, two had an increase in HbA_{1c}, and one had no change in HbA_{1c}; one had a reduction in weight, two had an increase in weight, and one had no change in weight.

Both treatment regimens resulted in significant reductions in fasting and postprandial glucose (figures 4A and 4B). The change in fasting plasma glucose was significantly greater with treatment once a week after 30 weeks (–2·3 [SE 0·2] mmol/L for exenatide once a week *vs* –1·4 [0·2] mmol/L for exenatide twice a day; 95% CI –1·3 to –0·52, intention to treat, p<0·0001, figure 4A). Analysis across all background treatments revealed similar improvements in fasting plasma glucose (mmol/L) of –2·6 (0·4) with diet and exercise, –2·0 (0·3) with sulphonylureas, –2·3 (0·2) with metformin, and –2·3 (0·4) with thialzolidinediones in patients treated with exenatide once weekly. Consistent with the reductions in fasting glucose, plasma glucagon levels were significantly lower with exenatide once a week (figure 4B). Both exenatide once a week and exenatide twice a day resulted in significant improvements in 7-point self-monitored blood glucose profiles (figure 4B).

Meal tolerance tests were done in a subset of patients (N=51; figure 5); results showed that exenatide once a week (figure 5A, 5C) and exenatide twice a day (figure 5B, 5D) both significantly lowered fasting and postprandial blood glucose values. Consistent with the known increase in β-cell sensitivity caused by GLP-1R agonists, ratios of insulin $AUC_{(0–120min)}$ to glucose $AUC_{(0–120min)}$ were increased in both exenatide groups, with significant improvements from baseline shown with exenatide once a week, but no significant difference between exenatide groups (ΔI/ΔG [µIU/mg]: 8·8 [SE 3·6] exenatide once a week *vs* 3·2 [3·1] exenatide twice a day, p=0·234). Change from baseline in 2-h postprandial plasma glucose concentration was significantly greater in patients treated with exenatide twice a day (–6·9 [0·5] mmol/L) than those treated once a week (–5·3 [0·5] mmol/L; 95% CI 0·4–2·9, evaluable meal tolerance tests N=51, p=0·0124). Consistent with these observations, assessment of gastric emptying during the meal tolerance tests showed a significant slowing of paracetamol appearance in plasma for exenatide twice a day (biphasic daily exenatide exposure, figure 5D), whereas this effect was less pronounced with exenatide once a week (figure 5C).

Significantly greater reductions from baseline in mean total and LDL-cholesterol were observed in intention-to-treat patients treated once a week than those treated twice a day (table 4). Fasting triglyceride concentrations were reduced in both treatment groups (–15% for once a

week and –11% for twice a day). Patients in both groups had similar, significant improvements in systolic and diastolic blood pressure (table 2, webtable). During the 30-week assessment period, doses of lipid-lowering or antihypertensive agents remained stable in most patients in both treatment groups.

The adverse events reported in more than 10% of treated patients are detailed in table 3. The most common adverse events reported with exenatide once a week were nausea (26·4%) and injection site pruritus (17·6%). Gastrointestinal complaints including nausea (34·5%) and vomiting (18·6%) were the most frequent adverse events reported for patients treated twice a day, consistent with previous reported studies.[14–17] Treatment-related nausea was reported in significantly fewer patients treated once a week than twice a day. The nausea reported in both groups was predominantly mild in intensity and no severe nausea was reported in patients treated with exenatide once a week. Injection site pruritus, an effect more commonly reported with injectable sustained release formulations that undergo in-vivo-degradation,[27,28] was typically mild in intensity, and resolved with continued exenatide treatment. There were no episodes of major hypoglycaemia for either exenatide regimen, irrespective of background sulphonylurea use, and the incidence of minor hypoglycaemia was low (table 4), with most cases of minor hypoglycaemia limited to patients using concomitant sulphonylurea therapy. Withdrawals due to adverse events during the 30-week assessment period were 6·1% for exenatide once a week and 4·8% for twice a day. No patients were withdrawn due to the predefined loss of glucose control criteria. Treatment compliance (injections received/injections planned) was 98% with both exenatide regimens during the 30-week assessment period. In response to Diabetes Treatment Satisfaction Questionnaires, patients treated with exenatide once a week reported significant increases in treatment satisfaction from baseline.

No clinically significant abnormalities in vital signs, ECG reports, or haematological, chemistry, or urinalysis values were reported during the study. The incidence of serious adverse events was low for both groups (5·4% for once a week and 3·4% for twice a day). Events were not clustered around any specific diagnosis or organ system; none were considered by the investigators to be related to exenatide treatment. No cases of pancreatitis were reported with either treatment regimen.

Discussion

Although both exenatide once a week and twice a day resulted in significant reductions in HbA_{1c} and bodyweight from baseline after 30 weeks of treatment, our results show that exenatide once a week produces better glycaemic control than exenatide twice a day: the mean difference in reduction of HbA_{1c} between the two groups was 0·33% (95% CI 0·54% to 0·12%). 77% of patients treated with exenatide once a week achieved HbA_{1c} levels of 7% or less at study endpoint, from an mean baseline HbA_{1c} of more than 8%. Additionally, in those patients who entered the study with a baseline HbA_{1c} of more than 9%, nearly two-thirds achieved HbA_{1c} levels of 7% or less.

See Online for webtable

A previous 15-week study of exenatide once a week, using doses of 0·8 or 2·0 mg in 31 patients with type 2 diabetes, reported effects on glycaemic variables, weight, and adverse events similar to those reported in the current study.[21] These observations support the reproducibility of the pharmacokinetic profile and pharmacodynamic responses obtained with exenatide treatment once a week.[21] The results of the current study extend previous findings by allowing comparison with exenatide twice a day, and by providing additional information on safety, tolerability, and mechanism of action.

The magnitude of both the HbA_{1c} reduction and weight loss observed with exenatide twice a day in the current study is slightly greater than that seen in previous placebo-controlled and open-label studies with this compound. Previous randomised, placebo-controlled trials with exenatide twice a day have shown HbA_{1c} reductions averaging around 1%, with weight loss of 1·6–2·8 kg, in patients on either metformin, sulphonylurea, or metformin and sulphonylurea in studies ranging from 16 to 30 weeks.[14–17] In previous open-label, active comparator trials comparing exenatide twice a day with starter insulins, mean HbA_{1c} reductions with exenatide ranged from 1·0% to 1·4%, whereas weight reduction averaged 2–3 kg.[29–31]

The significantly greater reduction in HbA_{1c} observed with treatment once a week (1·9%) than with treatment twice a day is likely due in part to the continuous exposure to exenatide resulting in a greater suppression of fasting glucagon, and a corresponding reduction in fasting glucose levels. Although pharmacological levels of GLP-1R agonists have been shown to suppress postprandial glucose excursions, the current study indicates that a 24-h profile of exenatide more potently reduces levels of fasting glucagon, fasting plasma glucose and HbA_{1c} than that observed with exenatide given twice a day. Conversely, although both therapies reduced postprandial glycaemic excursion, the absolute reduction in postprandial glucose excursion (during meal tolerance testing), and the relative inhibition of gastric emptying as assessed using paracetamol, were greater with exenatide twice a day than with once a week. These observations suggest that repeated acute exposure to GLP-1R agonists might produce greater inhibition of gastric emptying than that seen with continuous GLP-1R activation.

Although the current study shows the significantly greater reduction in HbA_{1c} achievable with once weekly therapy, and shows similar results for safety and tolerability for the two regimens, several potential

limitations warrant mention. First, the lack of active comparator treatment groups with other modalities such as insulin limit conclusions about the relative efficacy of different therapies. Further studies directly comparing exenatide once weekly with other available classes of antidiabetic drugs are needed to assess the potential differences in these therapeutic approaches. Moreover, open-label studies could inject bias and affect patient expectations and adherence to therapy, although such bias can potentially affect both forms of treatment. Nevertheless, in our study, treatment once a week achieved HbA_{1c} reductions of nearly 2%, similar to those reported in another double-blind placebo controlled study of exenatide once a week where a 2·1% placebo-corrected HbA_{1c} reduction was reported.[21]

Both treatment regimens were generally well-tolerated during this study, as shown by withdrawal rates related to adverse events (around 5%) that were less than that observed in previous placebo-controlled studies with exenatide and comparable with other diabetes therapies.[32–35] Nearly 90% of patients treated with exenatide once a week completed the 30-week study. Although patients in both treatment groups developed anti-exenatide antibodies, the presence of antibodies did not correlate with rates of reported adverse events. Although antibody titres were higher in those treated once a week, the mean A_{1c} reduction was significantly lower after 30 weeks of therapy with exenatide once a week, and most patients with measurable antibodies at the end of the study had significant reductions in HbA_{1c} (figure 3C).

In view of the complexity of current diabetes treatment options requiring once or twice daily administration of therapeutic agents, the significant improvement in HbA_{1c} in association with weight loss observed with a once-weekly formulation of exenatide suggests that continuous GLP-1R activation offers a promising treatment option for the management of type 2 diabetes.

Contributors

DJD and JBB had full access to the primary data and led decisions on content and publication submission. All authors contributed to data analysis and interpretation, and writing and editing of the manuscript.

Conflict of interest statement

DJD has served as an adviser or consultant within the past 12 months to Amylin Pharmaceuticals, Arisaph Pharmaceuticals, Conjuchem, Eli Lilly, Emisphere Technologies, GlaxoSmithKline, Glenmark Pharmaceuticals, Isis Pharmaceuticals, Merck Research Laboratories, Novartis Pharmaceuticals, Novo Nordisk, Phenomix, Roche, Takeda, and Transition Pharmaceuticals, and does not hold stock directly or indirectly in any of these companies. DJD has prepared a slide kit on GLP-1 action for Amylin in the past 12 months. JBB has received Grant or Research support from Amylin, Eli Lilly, and Novo Nordisk, has been a Consultant for and received lecture honoraria from Amylin, Eli Lilly, and Novo Nordisk. MT is employed by and holds stock in Eli Lilly and Company, which manufactures and markets pharmaceuticals related to the treatment of diabetes. KT, DZ, DK, and LP, are employed by and hold stocks in Amylin Pharmaceuticals, which manufactures and markets pharmaceuticals related to the treatment of diabetes.

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Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study

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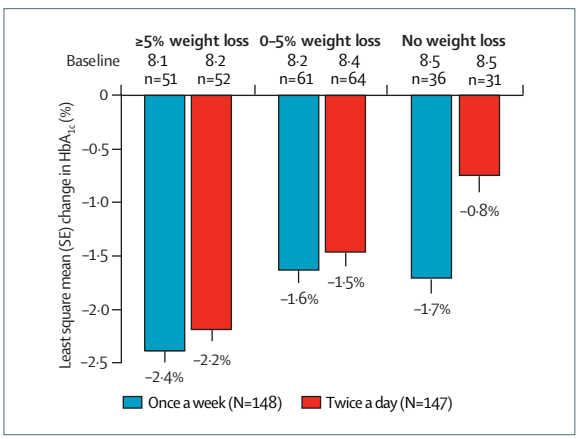

Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study

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	Exenatide once a week			Exenatide twice a day		
	No weight change N=67	<5% weight loss N=125	≥5% weight loss N=103	No weight change N=67	<5% weight loss N=125	≥5% weight loss N=103
Triglycerides (mmol/L)	–0·59 (0·29)	–0·31 (0·15)	–0·56 (0·13)	+0·05 (0·17)	–0·16 (0·12)	–0·45 (0·23)
Total cholesterol (mmol/L)	–0·08 (0·16)	–0·10 (0·09)	–0·21 (0·11)	–0·20 (0·11)	–0·21 (0·11)	–0·40 (0·9)
HDL-C (mmol/L)	–0·04 (0·03)	–0·03 (0·02)	+0·02 (0·02)	–0·05 (0·02)	–0·05 (0·02)	–0·002 (0·03)
LDL-C (mmol/L)	+0·03 (0·1)	–0·08 (0·09)	–0·22 (0·08)	–0·03 (0·12)	+0·01 (0·09)	–0·03 (0·08)
Systolic blood pressure (mm Hg)	–1·6 (2·1)	–4·4 (1·9)	–6·2 (1·4)	–0·6 (2·8)	–3·1 (1·9)	–6·2 (2·2)
Diastolic blood pressure (mm Hg)	–0·1 (1·2)	–2·5 (1·2)	–0·1 (1·4)	+0·2 (2·1)	–2·8 (1·2)	–2·8 (1·3)

Data are mean change from baseline (SE)

Webtable: **Plasma lipids and blood pressure in patients treated with exenatide**