Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial

Baptist Gallwitz, Juan Guzman, Francesco Dotta, Bruno Guerci, Rafael Simó, Bruce R Basson, Andreas Festa, Jacek Kiljański, Hélène Sapin, Michael Trautmann, Guntram Schernthaner

Lancet 2012; 379: 2270–78

Published Online June 9, 2012 DOI:10.1016/S0140-6736(12)60479-6

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Department of Medicine IV, Eberhard-Karls-University Tübingen, Tübingen, Germany, (Prof B Gallwitz MD); **Celaya Centre for Specialist Medicine, Guanajuato, Mexico** (J Guzman MD); **Department of Internal Medicine, Endocrine and Metabolic Sciences, Policlinico Le Scotte, Sienna, Italy** (F Dotta MD); **Hospital Brabois and Centres d'Investigation Clinique Inserm, CHU de Nancy, Vandoeuvre-Lès-Nancy, France** (B Guerci MD); **Vall d'Hebron Research Institute and Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, Carlos III Health Institute, Barcelona, Spain** (R Simó MD); **Eli Lilly and Company, St Cyr au Mont D'Or, France** (B R Basson MSc); **Eli Lilly and Company, Vienna, Austria** (A Festa MD); **Eli Lilly Polska, Warsaw, Poland** (J Kiljański MD); **Eli Lilly and Company, Suresnes, France** (H Sapin MSc); **Lilly Deutschland, Hamburg, Germany** (M Trautmann MD); **and Department of Medicine I, Rudolfstiftung Hospital, Vienna, Austria** (Prof G Schernthaner MD)

Correspondence to: Prof Baptist Gallwitz, Medizinische Klink IV, Universitätklinikum Tübingen, 72076 Tübingen, Germany **baptist.gallwitz@med.uni-tuebingen.de**

Summary

Background Glycaemic control deteriorates progressively over time in patients with type 2 diabetes. Options for treatment escalation remain controversial after failure of first-line treatment with metformin. We compared add-on exenatide with glimepiride for durability of glycaemic control in patients with type 2 diabetes inadequately controlled by metformin alone.

Methods We did an open-label, randomised controlled trial at 128 centres in 14 countries between Sept 5, 2006, and March 29, 2011. Patients aged 18–85 years with type 2 diabetes inadequately treated by metformin were randomly assigned via a computer-generated randomisation sequence to receive exenatide twice daily or glimepiride once daily as add-on to metformin. Randomisation was stratified by predetermined categories of glycated haemoglobin (HbA_{1c}) concentration. The primary outcome was time to inadequate glycaemic control and need for alternative treatment, defined as an HbA_{1c} concentration of more than 9% after the first 3 months of treatment, or more than 7% at two consecutive visits after the first 6 months. Analysis was by intention to treat. This trial is registered with EudraCT, number 2005-005448-21, and ClinicalTrials.gov, number NCT00359762.

Findings We randomly assigned 515 patients to the exenatide group and 514 to the glimepiride group, of whom 490 versus 487 were the intention-to-treat population. 203 (41%) patients had treatment failure in the exenatide group compared with 262 (54%) in the glimepiride group (risk difference 12·4 [95% CI 6·2–18·6], hazard ratio 0·748 [0·623–0·899]; p=0·002). 218 (44%) of 490 patients in the exenatide group, and 150 (31%) of 487 in the glimepiride group achieved an HbA_{1c} concentration of less than 7% (p<0·0001), and 140 (29%) versus 87 (18%) achieved concentrations of 6·5% and less (p=0·0001). We noted a significantly greater decrease in bodyweight in patients given exenatide than in those given glimepiride (p<0·0001). Five patients in each treatment group died from causes unrelated to treatment. Significantly fewer patients in the exenatide group than in the glimepiride group reported documented symptomatic (p<0·0001), nocturnal (p=0·007), and non-nocturnal (p<0·0001) hypoglycaemia. Discontinuation because of adverse events (mainly gastrointestinal) was significantly higher (p=0·0005) in the exenatide group than in the glimepiride group in the first 6 months of treatment, but not thereafter.

Interpretation These findings provide evidence for the benefits of exenatide versus glimepiride for control of glycaemic deterioration in patients with type-2 diabetes inadequately controlled by metformin alone.

Funding Eli Lilly and Company; Amylin Pharmaceuticals.

Introduction

Metformin is widely used as a first-line glucose-lowering drug;[1,2] however, selection of the most appropriate treatment after metformin failure is poorly established. Sulphonylureas are commonly chosen as add-on treatment because of their rapid effect and low cost.[1,3,4] Although these drugs can improve the short-term function of β cells, glycaemic control subsequently deteriorates; furthermore, because effects are not glucose-dependent, risk of hypoglycaemia might be increased, which can restrict doses used in clinical practice.[5]

Glucagon-like peptide (GLP)-1 receptor agonists have become established as treatments for type 2 diabetes.[6,7] They improve glycaemic control, with glucose-dependent stimulation of insulin secretion and no increased risk of hypoglycaemia, and have been associated with weight loss and improvements in biomarkers of cardiovascular risk.[8-11] These drugs have shown protective action in β cells, and findings from clinical trials have noted improved β-cell function,[12–14] thus raising expectations that GLP-1 receptor agonists might delay disease progression.[15,16]

We aimed to assess durability of glycaemic control achieved with GLP-1 receptor agonist exenatide twice a day and sulphonylurea glimepiride in patients with type 2 diabetes inadequately controlled by metformin alone.

Methods

Study design and participants

We undertook this open-label, randomised controlled European Exenatide (EUREXA) trial at 128 centres in 14 countries (Austria, Czech Republic, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Mexico, Poland, Spain, Switzerland, and the UK) between Sept 5, 2006, and March 29, 2011. The rationale and baseline characteristics of the EUREXA phase 3, multinational study have been described previously.[17] Eligible participants had type 2 diabetes; were overweight to obese (body-mass index [BMI] ≥25 kg/m² to <40 kg/m²); aged 18–85 years; had been on stable, maximum tolerated doses of metformin; and had developed suboptimum glycaemic control, defined by a glycated haemoglobin (HbA_{1c}) concentration of 6·5% and more or 9·0% and less.

Exclusion criteria were contraindications for metformin or glimepiride, according to the product-specific label; active or untreated malignancy or remission for less than 5 years; evidence of renal or liver disease or dysfunction; haemoglobinopathy or clinically significant chronic anaemia; active proliferative retinopathy or macular oedema; or severe gastrointestinal disease. Excluded drugs were those affecting gastrointestinal motility, chronic systemic glucocorticoids, prescription drugs to promote weight loss in the past 3 months, and treatment for more than 2 weeks in the past 3 months with insulin, thiazolidinediones, α-glucosidase inhibitors, sulphonylureas, or meglitinides.

The study protocol was approved by appropriate institutional review boards, in accordance with country-specific regulations. We did the study in compliance with Good Clinical Practice and the Declaration of Helsinki, and obtained signed informed consent from all patients.

Randomisation and masking

We used a computer-generated randomisation sequence to randomly assign patients, in a 1:1 ratio, to receive either exenatide or glimepiride. Randomisation was stratified by HbA_{1c} categories of 7·3% and less, more than 7·3% to 8·2% and less, and more than 8·2%. Before database lock the study team were masked to group assignment and statistical anlyses were planned with no knowledge of groups.

Procedures

Exenatide was injected subcutaneously within 60 min before breakfast and evening meals, starting at 5 µg twice daily for 4 weeks, followed by 10 µg twice daily for the remaining study period. If patients had daily episodes of nausea for more than 1 week, the 10 µg dose was reduced to 5 µg twice daily and could be increased again after nausea subsided. The recommended starting dose for patients in the glimepiride group was 1 mg per day, given once daily immediately before breakfast. Attending physicians established the glimepiride dose as per their

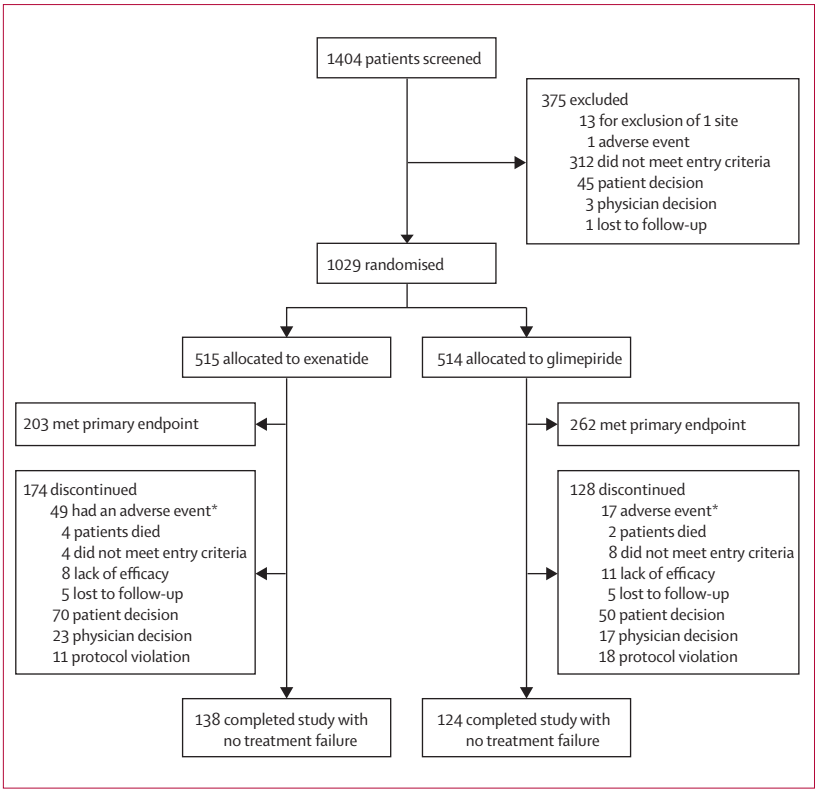

Figure 1: **Trial profile**

The intention-to-treat population consisted of 490 patients randomised to exenatide (five did not receive the study drug and 20 did not have at least one baseline or post-baseline HbA_{1c} measurement) and 487 randomised to glimepiride (six did not receive the study drug and 21 did not have at least one baseline or post-baseline HbA_{1c} measurement). *p=0·001 for difference between groups.

	Exenatide (n=490)	Glimepiride (n=487)
Age (years)	56 (10·0)	56 (9·1)
Age ≥65 years	102 (21%)	98 (20%)
Sex		
Male	272 (56%)	252 (52%)
Female	218 (44%)	235 (48%)
Race		
White	450 (92%)	444 (91%)
Hispanic	36 (7%)	35 (7%)
African or Asian	4 (<1%)	8 (2%)
Bodyweight (kg)	92·8 (16·7)	91·1 (14·8)
Body-mass index (kg/m²)	32·6 (4·2)	32·3 (3·9)
Systolic blood pressure (mm Hg)	132·8 (15·7)	133·4 (15·1)
Diastolic blood pressure (mm Hg)	80·4 (9·4)	79·8 (9·9)
Heart rate (beats per min)	74·1 (9·3)	74·0 (10·1)
Diabetes duration (years)	5·8 (4·8)	5·5 (4·3)
Metformin dose (mg per day)	1956 (596)	1989 (634)
HbA_{1c} concentration (%)	7·5% (0·7)	7·4% (0·7)
Fasting plasma glucose (mmol/L)	8·9 (2·3)	8·6 (1·9)
Taking antihypertensive drugs	340 (69%)	367 (75%)

Data are mean (SD) or n (%). Data are for the intention-to-treat population. HbA_{1c}=glycated haemaglobin A_{1c}.

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

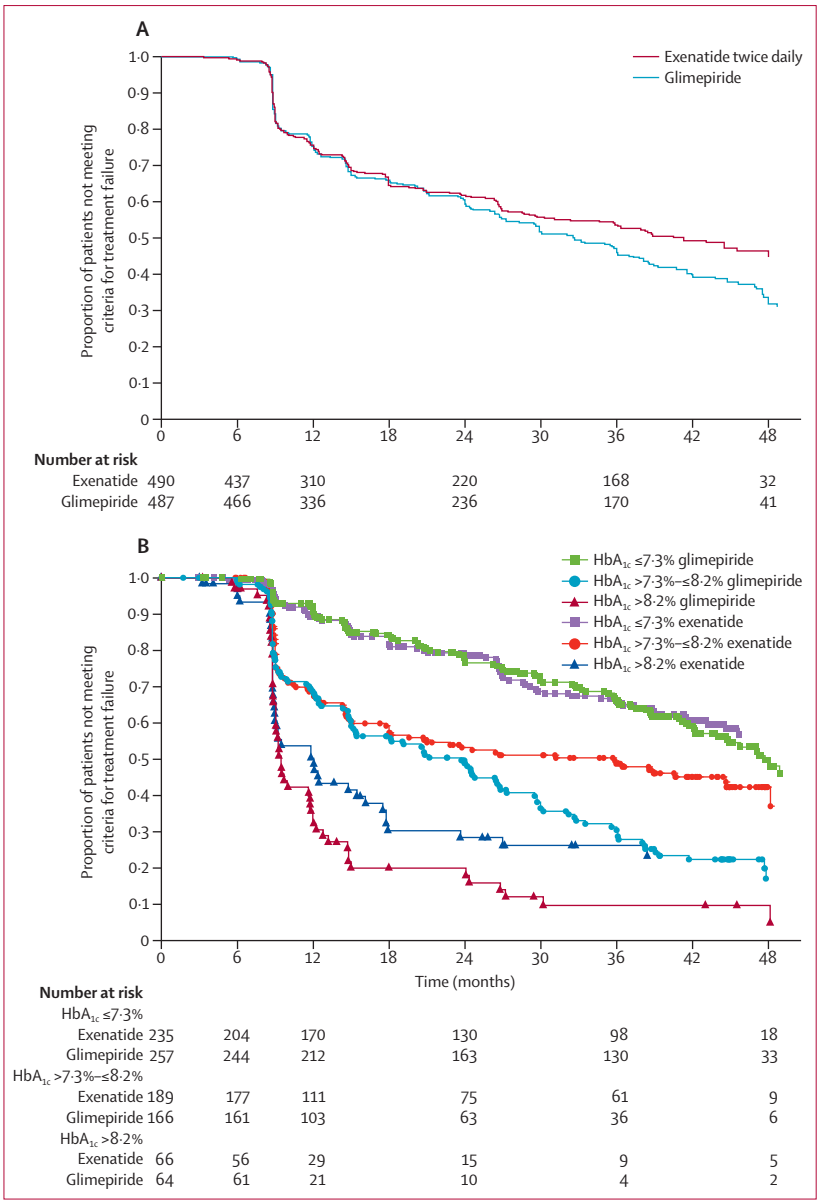

Figure 2: **Time-to-event curves for patients meeting criteria for treatment failure (A) and for those meeting treatment failure criteria according to baseline HbA_{1c} categories (B)**
Event rates in figure 2A are Kaplan-Meier estimates. The sharp drop at 9 months corresponds to when patients could first meet the criterion of HbA_{1c} concentration >7·0% at two consecutive visits after the first 6 months of treatment. HbA_{1c}=glycated haemaglobin A_{1c}.

For the **HOMA calculator** see http://www.dtu.ox.ac.uk/homacalculator/index.php

usual practice, and investigators were instructed to adjust the dose every 4 weeks, according to tolerability, up to the maximum tolerated dose in accordance with the country-specific summary of product characteristics. Concomitant metformin was continued throughout the study for all patients, in the same form and at the same dose as used at study entry.

Study outcomes

The primary outcome was time to inadequate glycaemic control, defined as an HbA_{1c} concentration of more than 9% after the first 3 months of treatment, or more than 7% at two consecutive visits 3 months apart after the first 6 months. We defined treatment failure in line with recommendations of diabetes associations and the known timecourse of changes in HbA_{1c} concentration, and allowed quick identification of patients with poor glycaemic control who needed alternative treatment.[1] Because the primary outcome was a time-to-event measure, we regarded a study period of 2–3 years as appropriate. Patients who had treatment failure were discontinued, but could enrol in an extension study to examine further treatment options; findings from this study will be described elsewhere. Secondary outcomes were markers of β-cell function, bodyweight, hypoglycaemia, and surrogate markers of cardiovascular risk (blood pressure and heart rate).

Laboratory measurements were done at a central laboratory (Interlab GmbH, Munich, Germany). Plasma glucose was measured with an automated hexokinase method (Cobas Gluco-quant, Roche Diagnostics GmbH, Mannheim, Germany), HbA_{1c} with automated high-performance liquid chromatography (Tosoh Bioscience Inc, San Francisco, CA, USA), and insulin with a two-site chemiluminescent immunometric assay (Immulite 2000, Siemens Diagnostics, Tarrytown, NY, USA). All patients underwent oral glucose-tolerance tests, starting in a fasted state and before the morning doses of metformin and study drug. Homoeostatic model assessment (HOMA)-B and HOMA-IR were calculated with standard formulas and programs. We established insulinogenic index from changes in glucose and insulin at 30 min and adjusted the index for HOMA-IR for the disposition index.[15] Additionally, patients self-monitored blood glucose before and 2 h after meals for 2 consecutive days before study visits.

We classified hypoglycaemic episodes as recommended by the American Diabetes Association Workgroup on Hypoglycemia.[18] Blood pressure and heart rate were measured at all study visits. We recorded and classified adverse events according to the Medical Dictionary for Regulatory Activities.

Statistical analysis

We declared non-inferiority of exenatide to glimepiride if the 97·5% CI for the hazard ratio (HR), with a Cox proportional hazards model with baseline HbA_{1c} as covariate, excluded 1·25, thus rejecting the hypothesis that risk of treatment failure with exenatide was more than 25% greater than that with glimepiride. If non-inferiority was shown, we tested superiority with 95% CI (excluding 1).[19] Kaplan-Meier curves were calculated for patients with inadequate HbA_{1c} criteria. We calculated sample size on the basis of the non-inferiority test of exenatide versus glimepiride, an expected mean baseline HbA_{1c} concentration of 8·2%, a 1 year patient accrual, maximum follow-up of 3 years, drop-out rate of 15% per year (for reasons other than treatment failure), and a 58%

event rate in each group after 1 year. With these assumptions, 527 patients per study group would provide about a 90% power to conclude non-inferiority of exenatide.

Analyses were by intention to treat with the caveat that only randomly assigned patients receiving at least one dose of study treatment, and with baseline and at least one post-baseline HbA_{1c} measurement were included. We analysed the as-treated population according to treatment actually received and included only patients with at least 6 months' follow-up for HbA_{1c}. For all measures except primary endpoint, tests were two-sided (α=0·05). We did sensitivity analysis to examine the effect of discontinuations as a possible competing risk before the primary endpoint was met. Furthermore, we did a post-hoc analysis to examine proportions of patients meeting each of the two definitions of inadequate HbA_{1c} control.

We used a mixed model repeated measures analysis for continuous variables, with terms for visit, treatment, and interaction, and included the baseline value as a covariate. We included only visits with more than 25% of originally enrolled patients and made no imputations for missing data. Least-squares means with 95% CI were derived from the model for 1, 2, and 3 years (visits eight, 12, and 16). Analyses of covariance (ANCOVA), including terms for treatment, baseline HbA_{1c} stratum, and baseline values were done for changes from baseline to treatment failure or other endpoint. For secondary outcomes not identified at each study visit, we used last observation carried forward to account for missing values.

We based safety analyses on all patients who received study drug. Percentages of patients with adverse events after treatment, and those who had hypoglycaemia, were compared between treatment groups with Pearson's χ^2 test. This trial is registered with EudraCT, number 2005-005448-21, and ClinicalTrials.gov, number NCT00359762.

Role of the funding source

The sponsor took part in study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to the data and responsibility for the content of the report. BGa and GS had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. We randomly assigned 1029 of 1404 screened patients to receive either exenatide or glimepiride as add-on treatment to metformin. The intention-to-treat population consisted of 490 patients in the exenatide group and 487 in the glimepiride group; conclusions from the as-treated population were not different from those from the intention-to-treat analysis and are therefore not presented. Of patients who met the primary endpoint, five of those in the exenatide group and seven in the glimepiride group had an HbA_{1c} concentration of more than 9%, and 198 versus 255 had concentrations of more than 7% at two visits. One patient

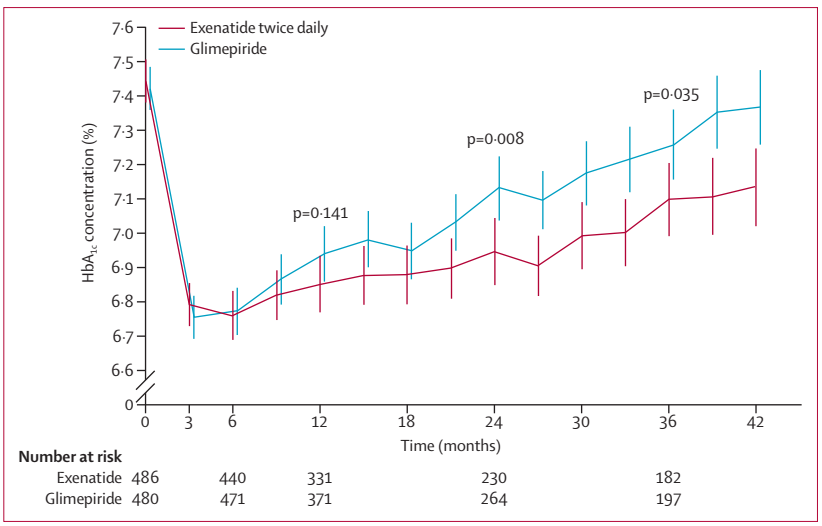

Figure 3: **Changes in HbA_{1c} concentration during treatment with exenatide or glimepiride**
Values show least-squares means with 95% CI from mixed model repeated measures model analysis, including terms for baseline HbA_{1c}, visit, and treatment by visit interaction, with an unstructured covariance matrix. We included only visits with >25% of originally enrolled patients remaining. p values for treatment difference are shown are at years 1, 2, and 3. HbA_{1c}=glycated haemaglobin A_{1c}.

in the glimepiride group had an HbA_{1c} concentration of more than 9% after the first 6 months of treatment and 113 and 164 patients in the exenatide and glimepiride groups, respectively, had concentrations of more than 7% at two visits after the first 9 months of treatment. The most common reason for study discontinuation was patient decision (figure 1).

Table 1 shows baseline demographic and diabetes characteristics of the intention-to-treat population. The mean HbA_{1c} concentration of enrolled patients was lower than originally assumed, and history of type 2 diabetes was fairly short. Consistent with inclusion criteria, patients were taking metformin at close to the recommended maximum dose, with a median dose of 2000 mg per day (IQR 1700–2550). Average treatment time was about 2 years (exenatide group, mean 101·9 weeks [SD 73·8]; glimepiride group, 113·1 weeks [70·9]). Mean exenatide dose was 17·35 (4·07) µg per day and mean glimepiride dose was 2·01 (1·02) mg per day.

Treatment failure diverged for each group with time (figure 2). 203 (41%) of 490 patients in the exenatide group had treatment failure compared with 262 (54%) of 487 in the glimepiride group (risk difference 12·4%, 95% CI 6·2–18·6), despite more patients from the exenatide group discontinuing treatment (figure 1). The HR for inadequate glycaemic control with exenatide compared with glimepiride was 0·748. The upper one-sided CI of the Cox proportional hazard analysis was 0·899, which was less than the predefined non-inferiority value of 1·25. According to the two-sided 95% CI, exenatide was more effective than glimepiride as add-on treatment for patients with metformin failure (95% CI 0·623–0·899; p=0·002). Median time to inadequate HbA_{1c} control was 180 weeks (IQR 52·3 [upper values not

	Exenatide (n=490)	Glimepiride (n=487)	Exenatide LS mean (95% CI; n)	Glimepiride LS mean (95% CI; n)	Difference LS mean (95% CI)	p value
Ratio of change in glucose and insulin at 30 min						
Baseline	17·9 (10·4–30·1)	16·9 (10·4–29·8)	..	..	..	..
1 year	25·1 (14·0–43·6)	22·7 (14·1–33·3)	35·3 (29·9–40·7; 279)	27·4 (22·4–32·4; 320)	7·9 (0·5–15·2)	0·036
2 years	22·5 (15·0–38·8)	12·4 (13·0–33·9)	31·2 (16·0–46·4; 182)	16·4 (2·4–30·3; 216)	14·9 (–5·8 to 35·5)	0·157
3 years	23·4 (13·0–41·3)	19·8 (11·6–31·4)	25·8 (19·3–32·3; 130)	26·4 (20·4–32·3; 156)	–0·6 (–9·4 to 8·3)	0·900
HOMA-IR						
Baseline	4·87 (3·06–7·48)	4·66 (2·97–7·22)	..	..	..	..
1 year	3·13 (1·83–5·10)	4·16 (2·67–6·78)	4·50 (4·00–5·00; 299)	5·30 (4·83–5·77; 336)	–0·80 (–1·48 to –0·12)	0·022
2 years	2·84 (1·65–5·08)	4·24 (2·43–7·05)	4·15 (3·66–4·65; 197)	5·05 (4·59–5·51; 230)	–0·89 (–1·57 to –0·21)	0·010
3 years	2·54 (1·35–4·75)	3·76 (2·12–6·42)	3·51 (2·98–4·03; 149)	4·83 (4·34–5·33; 166)	–1·33 (–2·05 to –0·60)	0·0003
Disposition index						
Baseline	3·84 (2·16–6·62)	3·90 (2·15–6·46)	..	..	..	..
1 year	7·89 (4·11–14·83)	5·24 (3·26–8·42)	12·43 (10·78–14·07; 279)	7·37 (5·83–8·91; 320)	5·06 (2·81–7·31)	<0·0001
2 years	7·90 (4·25–15·43)	5·39 (3·00–9·41)	13·79 (6·20–21·38; 182)	3·36 (–3·61 to 10·33; 216)	10·43 (0·13–20·73)	0·047
3 years	8·75 (4·55–18·37)	5·31 (3·21–9·30)	12·56 (10·25–14·88; 130)	7·89 (5·78–10·01; 156)	4·67 (1·53–7·81)	0·004
Proinsulin to insulin ratio						
Baseline	0·12 (0·07–0·20)	0·12 (0·07–0·20)	..	..	..	..
1 year	0·14 (0·08–0·22)	0·15 (0·10–0·25)	0·19 (0·16–0·21; 292)	0·20 (0·19–0·22; 338)	–0·02 (–0·05 to 0·01)	0·163
2 years	0·15 (0·08–0·24)	0·16 (0·10–0·27)	0·21 (0·18–0·24; 200)	0·24 (0·21–0·26; 228)	–0·03 (–0·07 to 0·01)	0·134
3 years	0·14 (0·06–0·23)	0·14 (0·08–0·28)	0·22 (0·18–0·27; 152)	0·23 (0·18–0·27; 170)	–0·00 (–0·07 to 0·06)	0·904

Data are unadjusted median (IQR), unless otherwise indicated. LS=least-squares. HOMA=homoeostatic model assessment.

Table 2: **Variables from oral glucose tolerance tests at baseline and after treatment with exenatide or glimepiride**

reached because of inadequate control in less than 75% of patients in each group]) with exenatide versus 142·1 weeks (52·3) with glimepiride (p=0·032). Risk of treatment failure was significantly affected by baseline HbA_{1c} concentration (HR 2·417, 95% CI 2·127–2·745; p<0·0001). Risk of treatment failure was greatest for patients with high baseline HbA_{1c}, and the reduction in risk with exenatide compared with glimepiride was greater for those with higher baseline HbA_{1c} concentrations (figure 2). We noted no significant interactions of treatment with country, age or sex (data not shown).

Mean HbA_{1c} concentration fell from baseline to treatment failure or other endpoint in the exenatide group from 7·45% (SD 0·69) to 7·08% (0·89), and in the glimepiride group from 7·42% (0·71) to 7·22% (0·79). Least-squares mean change in HbA_{1c} from baseline to treatment failure differed significantly (p=0·002) in patients in the exenatide group (–0·36%; 95% CI –0·43 to –0·30) compared with those in the glimepiride group (–0·21%; –0·28 to –0·14). Figure 3 shows mean HbA_{1c} concentration over time for each treatment group. We noted an overall treatment effect in favour of the exenatide group, and the difference between groups in least-squares mean HbA_{1c} concentration was significant at years 2 (p=0·008) and 3 (p=0·035); however, the difference in HbA_{1c} change from baseline was significant at years 1 (p=0·043), 2 (p=0·001), and 3 (p=0·013). Significantly more patients attained an HbA_{1c} concentration of less than 7% in the exenatide group than in the glimepiride group (218 [45%] of 490 *vs* 150 [31%] of 487; p<0·0001), and a target HbA_{1c} concentration of 6·5% and less (140 [29%] *vs* 87 [18%]; p=0·0001).

Fasting plasma glucose concentration was significantly lower in the exenatide group after years 1 (p=0·048),

	Exenatide (n=511)	Glimepiride (n=508)
Serious adverse events*	73 (14%)	68 (13%)
Treatment-emergent adverse events†		
Nausea	147 (29%)	11 (2%)
Nasopharyngitis	96 (19%)	93 (18%)
Diarrhoea	62 (12%)	33 (7%)
Headache	56 (11%)	48 (9%)
Influenza	55 (11%)	35 (7%)
Back pain	52 (10%)	54 (11%)
Vomiting	44 (9%)	12 (2%)
Bronchitis	34 (7%)	31 (6%)
Arthralgia	21 (4%)	42 (8%)
Pharyngitis	26 (5%)	21 (4%)
Dyspepsia	26 (5%)	21 (4%)

Data are n (%). Hypoglycaemia was reported separately and not included in adverse events. *Most frequent (>0·5% of patients) adverse events in the exenatide group were cases of fall (n=3), breast cancer (3), and nephrolithiasis (3); and in the glimepiride group were osteoarthritis (7), coronary artery disease (4), meniscus lesion (4), goitre (3), and tendon rupture (3). †Reported by >5% of either group.

Table 3: **Treatment-emergent adverse events**

2 (p=0·004), and 3 (p<0·0001) of treatment (appendix). Plasma glucose concentration at 0·5 h of the oral glucose tolerance test fell in both treatment groups, with no statistical difference between groups at any time (data not shown). The decrease from baseline to endpoint in plasma glucose at 2 h of the tolerance test was greater in patients in the exenatide group (p<0·0001) than in those in the glimepiride group, and mean value was significantly lower at 1, 2, and 3 years of treatment (p<0·0001 at all times). Plasma insulin at fasting and 0·5 h of the oral glucose tolerance test did not differ between treatments at any timepoint. Insulin at 2·0 h in the test was significantly greater in patients in the exenatide group at years 2 (p=0·008) and 3 (p=0·022).

Mean insulinogenic index—ie, changes in glucose and insulin at 30 min—differed between groups only at 1 year (table 2). The decrease from baseline to treatment failure with HOMA-IR was significantly greater in the exenatide group than in the glimepiride group (least-squares mean difference between groups –0·99, 95% CI –1·86 to –0·11; p=0·027), and mean HOMA-IR was significantly lower in the exenatide group than the glimepiride group at all 3 years (table 2). The increase in disposition index was significantly greater in patients in the exenatide group than in those in the glimepiride group (least-squares mean difference 6·16, 0·40–11·91; p=0·036), and mean disposition index was significantly higher in the exenatide group at all 3 years (table 2). We noted no significant differences between treatments in proinsulin to insulin ratio (table 2), or in HOMA-B mean values or changes from baseline (data not shown). Self-monitored excursions of blood glucose after meals were significantly lower in the exenatide group than in the glimepiride group after breakfast (least-squares mean excursion from ANCOVA: exenatide 0·30 mmol/L [95% CI 0·13–0·47] *vs* glimepiride 0·90 mmol/L [0·73–1·07]; p<0·0001), lunch (1·09 mmol/L [0·91–1·27] *vs* 1·70 mmol/L [1·52–1·89]; p<0·0001), and dinner (0·63 mmol/L [0·44–0·82] *vs* 1·60 mmol/L [1·41–1·79]; p<0·0001).

Five patients in each treatment group died; death was given as the reason for discontinuation for six patients, with other reasons given for discontinuation for four patients (figure 1). All deaths were from causes regarded by investigators as unrelated to study treatment. Significantly more patients discontinued in the exenatide group than in the glimepiride group because of adverse events (49 *vs* 17; p=0·001). However, discontinuations due to adverse events were only significantly different between treatments in the first 6 months of study (32 patients in the exenatide and six in the glimepiride group; p=0·0005), and not thereafter. Consistent with the known tolerability profile of exenatide, adverse events leading to discontinuations in the exenatide group were mainly gastrointestinal, and included nausea (22 [4%] patients in the exenatide group *vs* 0 in the glimepiride group) and diarrhoea (13 [3%] *vs* 0). Table 3 summarises the most frequent adverse events occurring after treatment. One patient in each study group had pancreatitis and one in the glimepiride group had thyroid cancer.

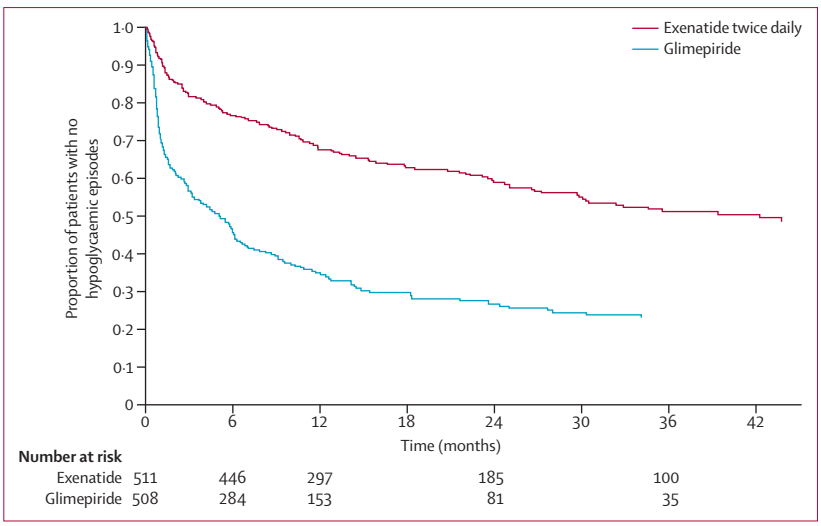

Figure 4: **Incidence of hypoglycaemia**
Kaplan-Meier survival curves for patients reporting any hypoglycaemic episodes; median time to first hypoglycaemic episode was 42·3 months (IQR 7·5 [upper values not reached because <75% of patients had a hypoglycaemic episode]) in the exenatide group *vs* 5·0 months [IQR 0·8–27·8]) in the glimepiride group. p<0·0001 for treatment difference.

	Exenatide (n=511)	Glimepiride (n=508)	p value
Documented symptomatic*	102 (20%)	240 (47%)	<0·0001
Documented symptomatic†	34 (7%)	63 (12%)	0·002
At least one hypoglycaemic episode reported	186 (36%)	338 (67%)	<0·0001
Nocturnal hypoglycaemia	53 (10%)	82 (16%)	0·007
Non-nocturnal hypoglycaemia	178 (35%)	333 (66%)	<0·0001
Severe hypoglycaemia	1 (<1%)	0 (0%)	0·319

Data are n (%). *Blood glucose <3·9 mmol/L. †Blood glucose <2·8 mmol/l.

Table 4: **Patients reporting hypoglycaemia at any time during the study**

See Online for appendix

Systolic blood pressure decreased in patients in the exenatide group (change to endpoint –1·9 mm Hg; p=0·006), but not in the glimepiride group (1·1 mm Hg; p=0·096), resulting in a significant difference between groups from year 1 (–3·1 mm Hg, 95% CI –5·0 to –1·2; p=0·001) to year 3 (–5·2 mm Hg, –7·6 to –2·8; p<0·0001). Heart rate increased at endpoint in patients given exenatide (1·2 beats per min [bpm]; p=0·024), but not in those given glimepiride (0·6 bpm; p=0·282), with no difference between groups at any time.

Bodyweight fell from baseline to endpoint in the exenatide group (–3·32 kg [SD 5·45]) and rose in the glimepiride group (1·15 kg [4·18]); difference in change from baseline between groups was significant after 4 weeks and at each time thereafter (p<0·0001). Consequently, BMI was significantly lower in the exenatide group than the glimepiride group from

1 month (least-squares mean difference –0·39 kg/m² [95% CI –0·46 to –0·32]; p<0·0001) to 3 years (–1·88 kg/m² [–2·20 to –1·57; p<0·0001). Proportion of patients reporting hypoglycaemia was lower in patients in the exenatide group than in those in the glimepiride group (p<0·0001; figure 4). Occurrences of symptomatic documented hypoglycaemia and nocturnal and non-nocturnal hypoglycaemia were significantly lower for patients in the exenatide group than for those in the glimepiride group (table 4). Although one patient reported severe hypoglycaemia within the first month after randomisation to exenatide, blood glucose was not measured for confirmation. For hypoglycaemia of any type during the study, the least-squares mean rate estimated from a negative binomial model was 1·52 (95% CI 1·26–1·82) episodes per year in the exenatide group compared with 5·32 (4·47–6·34) episodes per year in the glimepiride group, with an exenatide to glimepiride ratio for rate of hypoglycaemia of 0·29 (95% CI 0·22–0·37; p<0·0001). In patients on glimepiride, the dose at which any type of hypoglycaemia was reported was 1 mg per day for 49·3% of episodes, 2 mg per day for 37%, 3 mg per day for 5·6%, 4 mg per day for 6·5%, 5 mg per day for 0·3%, and 6 mg per day for 0·7%.

Discussion

Our findings show that exenatide twice daily as add-on to metformin reduced worsening of glycaemic control and rate of hypoglycaemia compared with add-on glimepiride in patients with type 2 diabetes inadequately controlled by metformin alone. Furthermore, exenatide was more effective than glimepiride for fasting glucose, glucose excursions after meals, and HbA_{1c} concentration. Overall, safety and tolerability of both drugs was consistent with the known safety profiles. The most frequently reported adverse events with exenatide were gastrointestinal; these events resulted in more frequent study discontinuations at the start of the study, but not after the first 6 months of treatment.

Randomised controlled head-to-head studies are important to guide clinical decisions, especially for new treatments different from the standard of care, which, according to our findings, would be a sulphonylurea. Up to now, EUREXA is the longest study undertaken with a GLP-1 receptor agonist, and could contribute substantially to decisions in clinical practice. We chose treatment failure needing alternative treatment as the primary endpoint to assess the clinical effect of two different second-line treatments on disease progression; therefore, our analyses represent real-life medical practice with early and late treatment failure (panel). This endpoint is similar to that of the ADOPT study[5] in previously untreated patients. ADOPT showed a reduction in treatment failure for rosiglitazone compared with metformin or glyburide as monotherapy, with the effect subsequently shown to correspond with improved β-cell function and insulin sensitivity.[24] Although our findings did not show a significant difference in HOMA-B, HOMA-IR and disposition index were significantly improved in patients in the exenatide group, which might be related to the improvements in bodyweight and glycaemia.

When our study started, treatment options in the event of metformin failure were scarce.[1] Add-on options were insulin[25] or a thiazolidinedione;[26] however, these drugs are associated with increased risks of hypoglycaemia, weight gain, oedema, congestive heart failure, and bone fractures.[27,28] Dipeptidyl peptidase-4 inhibitors are now also used as add-on drugs,[7,9,29,30] but were not available at the start of this study, and their effectiveness might not be higher than that of sulphonylureas.[31]

Improvements in fasting glucose, glucose excursions after meals, and HbA_{1c} concentration in patients in the exenatide group were associated with initially enhanced insulinogenic index, increased disposition index, and decreased HOMA-IR. Improvements from baseline in such factors were similar to those reported in previous studies with exenatide,[12,13] and our findings were consistent with the decreased risk of hypoglycaemia and decreased bodyweight associated with exenatide treatment. Improved glycaemic control and β-cell function with reduced hypoglycaemia noted with exenatide use are achieved through glucose-dependent stimulation of

Panel: Research in context

Systematic review

Common practice for patients with type 2 diabetes inadequately controlled by metformin has been to add a sulphonylurea to the treatment regimen.[1,4] GLP-1 receptor agonists can be used as add-on to metformin as an alternative treatment option.[6–8] We searched PubMed from 1970 to 2012 for "randomised clinical trials", "GLP-1 receptor agonists" and "sulphonylureas", with no restriction on language. This search identified 22 studies, of which six compared a GLP-1 receptor agonist with a sulphonylurea; three[11,14,20] with treatments as add-on to metformin for up to 1 year, and three as monotherapies for up to 2 years.[21–23] None of the reported studies continued beyond 2 years.

Interpretation

This is the longest randomised controlled study of a GLP-1 receptor agonist reported so far. With comparative treatment for up to 4·5 years, our findings show that glycaemic control in terms of HbA_{1c} concentration was maintained for longer and in a higher proportion of patients given exenatide than for those given glimepiride as add-on to metformin. Furthermore, those in the exenatide group had maintained weight loss and reduced rates of hypoglycaemia. Exenatide twice a day is therefore a more effective treatment option than is glimepiride for patients with type 2 diabetes with metformin failure.

insulin secretion, by contrast with glimepiride, which increases insulin secretion via non-glucose dependent pathways. The effectiveness of both treatments could have been affected by the lower than anticipated baseline concentration of HbA_{1c}. However, exenatide was better than glimepiride for prevention of inadequate glycaemic control in patients with raised HbA_{1c} at baseline, and inclusion of patients with decreased control would not change the benefits of exenatide.

The population enrolled was not ethnically diverse, which limits applicability of our study findings mainly to white patients. Furthermore, the glimepiride dose used was fairly low, despite titration to the maximum tolerated dose recommended by the protocol. However, the highest dose given to individual patients was identified by the attending physicians, and high incidence of hypoglycaemia could have prevented investigators from increasing the sulphonylurea dose. For use of an increased dose of glimepiride, findings from two previous studies did not show improved effectiveness. In the GUIDE study,[32] although glimepiride was titrated from 1 mg to 6 mg daily, HbA_{1c} reduction was not improved. When glimepiride was compared with vildagliptin,[33] the increased glimepiride dosage of 4·5 mg per day decreased HbA_{1c} by only 0·53%, from 7·3% at baseline; these values are almost identical to our findings at 12 months with a glimepiride dosage of 2 mg, when HbA_{1c} was decreased by 0·5%, from 7·4% at baseline.

In conclusion, our findings provide evidence for a beneficial effect of exenatide twice daily versus usual care with glimepiride, for deterioration of glycaemia in patients with type 2 diabetes.

Contributors

BGa and GS designed, submitted, and drafted the report. All authors analysed and interpreted data, and revised the text.

Conflicts of interest

BGa has been a consultant for, and received honoraria from, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, Merck, Roche, Sanofi-Aventis, and Takeda. BGu has been a consultant for GlaxoSmithKline, Eli Lilly, Merck, AstraZeneca, Bristol-Myers Squibb, Pfizer, Novo Nordisk, Novartis, Abbott, Lifescan, Medtronic, and Menarini. RS has been a consultant for, and received honoraria from, Novo Nordisk, Eli Lilly, and Abbott. GS has been a consultant for, and received honoraria, from Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Poxel, Roche, Sanofi-Aventis, Novo Nordisk, Servier, and Takeda. BRB, AF, JK, MT and HS are employees of Eli Lilly and Company, and BRB, AF, JK, and MT hold stocks in Eli Lilly and Company.

Acknowledgments

We thank the EUREXA investigators and clinical teams; the study participants; Ludger Rose (Münster, Germany) for his helpful advice; Christof Kazda (Lilly Research Center) for his involvement in study design and implementation; and Peter Bates (Cambridge Medical Writing Services, UK) for writing support and assistance with manuscript preparation.

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