Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial

*Richard M Bergenstal, Carol Wysham, Leigh MacConell, Jaret Malloy, Brandon Walsh, Ping Yan, Ken Wilhelm, Jim Malone, Lisa E Porter, for the DURATION-2 Study Group**

Summary

Background Most patients with type 2 diabetes begin pharmacotherapy with metformin, but eventually need additional treatment. We assessed the safety and efficacy of once weekly exenatide, a glucagon-like peptide 1 receptor agonist, versus maximum approved doses of the dipeptidyl peptidase-4 inhibitor, sitagliptin, or the thiazolidinedione, pioglitazone, in patients treated with metformin.

Methods In this 26-week randomised, double-blind, double-dummy, superiority trial, patients with type 2 diabetes who had been treated with metformin, and at baseline had mean glycosylated haemoglobin (HbA_{1c}) of 8·5% (SD 1·1), fasting plasma glucose of 9·1 mmol/L (2·6), and weight of 88·0 kg (20·1), were enrolled and treated at 72 sites in the USA, India, and Mexico. Patients were randomly assigned to receive: 2 mg injected exenatide once weekly plus oral placebo once daily; 100 mg oral sitagliptin once daily plus injected placebo once weekly; or 45 mg oral pioglitazone once daily plus injected placebo once weekly. Primary endpoint was change in HbA_{1c} between baseline and week 26. Analysis was by intention to treat, for all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT00637273.

Findings 170 patients were assigned to receive once weekly exenatide, 172 to receive sitagliptin, and 172 to receive pioglitazone. 491 patients received at least one dose of study drug and were included in the intention-to-treat analysis (160 on exenatide, 166 on sitagliptin, and 165 on pioglitazone). Treatment with exenatide reduced HbA_{1c} (least square mean –1·5%, 95% CI –1·7 to –1·4) significantly more than did sitagliptin (–0·9%, –1·1 to –0·7) or pioglitazone (–1·2%, –1·4 to –1·0). Treatment differences were –0·6% (95% CI –0·9 to –0·4, p<0·0001) for exenatide versus sitagliptin, and –0·3% (–0·6 to –0·1, p=0·0165) for exenatide versus pioglitazone. Weight loss with exenatide (–2·3 kg, 95% CI–2·9 to –1·7) was significantly greater than with sitagliptin (difference –1·5 kg, 95% CI –2·4 to –0·7, p=0·0002) or pioglitazone (difference –5·1 kg, –5·9 to –4·3, p<0·0001). No episodes of major hypoglycaemia occurred. The most frequent adverse events with exenatide and sitagliptin were nausea (n=38, 24%, and n=16, 10%, respectively) and diarrhoea (n=29, 18%, and n=16, 10%, respectively); upper-respiratory-tract infection (n=17, 10%) and peripheral oedema (n=13, 8%) were the most frequent events with pioglitazone.

Interpretation The goal of many clinicians who manage diabetes is to achieve optimum glucose control alongside weight loss and a minimum number of hypoglycaemic episodes. Addition of exenatide once weekly to metformin achieved this goal more often than did addition of maximum daily doses of either sitagliptin or pioglitazone.

Funding Amylin Pharmaceuticals and Eli Lilly.

Lancet 2010; 376: 431–39

Published Online June 26, 2010 DOI:10.1016/S0140-6736(10)60590-9

See Comment page 393

*Members listed at end of paper

International Diabetes Center at Park Nicollet, Minneapolis, MN, USA (R M Bergenstal MD); **Rockwood Clinic, Spokane WA, USA** (C Wysham MD); **Amylin Pharmaceuticals, San Diego, CA, USA** (L MacConell PhD, J Malloy PhD, B Walsh PhD, P Yan PhD, K Wilhelm MD, L E Porter MD); **and Eli Lilly, Indianapolis, IN, USA** (J Malone MD)

Correspondence to: Dr Richard M Bergenstal, International Diabetes Center at Park Nicollet, 3800 Park Nicollet Blvd, Minneapolis, MN 55416, USA **richard.bergenstal@parknicollet.com**

Introduction

In the original American Diabetes Association and the European Association for the Study of Diabetes treatment algorithm for type 2 diabetes, Nathan and colleagues[1] introduced the concept of starting all patients on metformin, if not contraindicated, and adding basal insulin, sulphonylurea, or thiazolidinedione therapy if needed. A revised version of this algorithm,[2] and the American Association of Clinical Endocrinologists and American College of Endocrinology's most recent treatment algorithm for type 2 diabetes ,[3] place metformin as the cornerstone of combination therapy, but also include new classes of drugs to consider after metformin, with an emphasis on keeping hypoglycaemia and weight gain to a minimum. These new treatments, which include glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, not only improve glycaemic control, but could also positively affect some of the metabolic abnormalities associated with type 2 diabetes,[3] including obesity, hypertension, and dyslipidaemia. Such effects are of particular importance because excess bodyweight and drug-associated hypoglycaemia are continuing concerns for many patients with type 2 diabetes, and, in the USA, only one in eight patients treated for type 2 diabetes simultaneously reaches the often-referenced targets for glycosylated haemoglobin (HbA_{1c}), blood pressure, and LDL cholesterol.[4]

For patients already taking metformin, selection of the most appropriate subsequent treatment is complicated by a paucity of data directly comparing the safety and

	Exenatide once weekly (n=160)	Sitagliptin once daily (n=166)	Pioglitazone once daily (n=165)
Sex			
Men	89 (56%)	86 (52%)	79 (48%)
Women	71 (44%)	80 (48%)	86 (52%)
Race			
White	53 (33%)	50 (30%)	65 (39%)
Black	19 (12%)	20 (12%)	13 (8%)
Hispanic	50 (31%)	49 (30%)	44 (27%)
Asian	37 (23%)	42 (25%)	40 (24%)
Native American	0	3 (2%)	0
Other	1 (1%)	2 (1%)	3 (2%)
Age (years)	52 (10)	52 (11)	53 (10)
Bodyweight (kg)	89 (20)	87 (20)	88 (20)
Body-mass index (kg/m²)	32 (5)	32 (5)	32 (6)
HbA_{1c}	8·6% (1·2)	8·5% (1·2)	8·5% (1·1)
Fasting plasma glucose (mmol/L)	9·2 (2·9)	9·1 (2·5)	9·1 (2·4)
Duration of diabetes (years)	6 (5)	5 (4)	6 (5)
Daily metformin dose (mg)	1504 (586)	1583 (510)	1480 (559)
Systolic blood pressure (mm Hg)	126 (14)	126 (14)	127 (14)
Blood lipid profile (mmol/L)			
Total cholesterol	4·5 (1·0)	4·6 (1·1)	4·9 (1·1)
LDL cholesterol	2·7 (0·8)	2·7 (0·9)	2·9 (1·0)
HDL cholesterol	1·1 (0·2)	1·1 (0·3)	1·1 (0·3)
Triglyceridees	1·9 (1·1)	1·9 (1·3)	2·2 (1·3)

Data are number (%) or mean (SD). HbA_{1c}=glycosylated haemoglobin.

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

efficacy of drugs,[5–7] particularly new classes. In this randomised superiority trial DURATION-2 (Diabetes therapy Utilization: Researching changes in A1c, weight and other factors Through Intervention with exenatide ONce weekly), we directly compared the efficacy, safety, and tolerability of three recommended therapies for patients not sufficiently controlled on metformin:[2,3] exenatide once weekly (GLP-1 receptor agonist), and maximum approved doses of sitagliptin (DPP-4 inhibitor) and pioglitazone (thiazolidinedione).

Methods

Patients

Patients were recruited between Jan 22, 2008, and Aug 6, 2008, and received treatment in 72 hospitals and clinics in the USA, India, and Mexico. Eligible patients were aged 18 years or older, had type 2 diabetes but were otherwise healthy, and had been treated with a stable metformin regimen for at least 2 months before screening. Women who were pregnant were excluded. Additional inclusion criteria were HbA_{1c} of 7·1–11·0% and a body-mass index of 25–45 kg/m²; further details are supplied in webappendix p 1.

See Online for webappendix

A common clinical protocol was approved for each site by the appropriate ethical review board. Patients provided written informed consent before enrolment. The study was done in accordance with the Declaration of Helsinki, including all amendments through the South Africa revision.[8]

Randomisation and masking

Randomisation was done centrally by UBC Clinical Technologies (San Francisco, CA, USA) via an interactive voice response system to conceal allocation, and was independent of the sponsor, investigators, study-site staff, and patients. The randomisation sequence was computer-generated. In this double-blind, double-dummy study, patients were randomly allocated in a 1:1:1 ratio to receive: 2 mg exenatide as a once weekly injection plus oral placebo once daily; 100 mg oral sitagliptin once daily plus placebo as a once weekly injection; or 45 mg oral pioglitazone once daily plus placebo as a once weekly injection. Oral capsules and injected liquids with identical appearance were used to mask treatment allocation. All injections were subcutaneous. The first injection was administered by study staff, and thereafter by the patient or a caregiver. Randomisation was stratified by country and by HbA_{1c} at screening (<9·0% *vs* ≥9·0%). All patients, study-site staff, investigators, and the sponsor were masked to treatment allocation during the double-blind treatment period. After finalisation of the statistical analysis plan and subsequent database lock, the sponsor was unmasked to treatment allocation.

Procedures

Patients received treatment for 26 weeks. Stable doses of metformin were received throughout the study. The primary endpoint was change in HbA_{1c} from baseline to week 26. Prespecified endpoints recorded from baseline to week 26 were: proportion of patients achieving the HbA_{1c} target of 6·5% or lower, or 7·0% or lower; fasting plasma glucose (target ≤7 mmol/L); six-point self-monitored blood glucose profile; bodyweight; fasting lipid profile; fasting insulin profile; systolic and diastolic blood pressures; cardiovascular risk markers (urinary albumin-to-creatinine ratio, serum adiponectin, B-type natriuretic peptide, high-sensitivity C-reactive protein, and plasminogen activator inhibitor-1); patient-reported outcomes from the Impact of Weight on Quality of Life Questionnaire-Lite (IWQOL),[9] Psychological General Well-being (PGWB) index,[10] the Diabetes Treatment Satisfaction Questionnaire (DTSQ),[11] and EuroQol-5 dimensions (EQ-5D);[12] safety; and tolerability. An additional secondary endpoint, proportion of patients achieving HbA_{1c} targets of lower than 7·0%, was not prespecified.

Plasma and urine analytes and HbA_{1c} were quantitated by standard methods. Further descriptions of methods used to measure primary and secondary outcomes are available in webappendix p 2. Plasma antibodies to exenatide were measured as previously described.[13,14] Treatment-emergent antibodies to exenatide were defined as a positive titre reported after a negative or missing titre at baseline, or a positive titre that had increased by at least three dilutions from a detectable baseline titre.

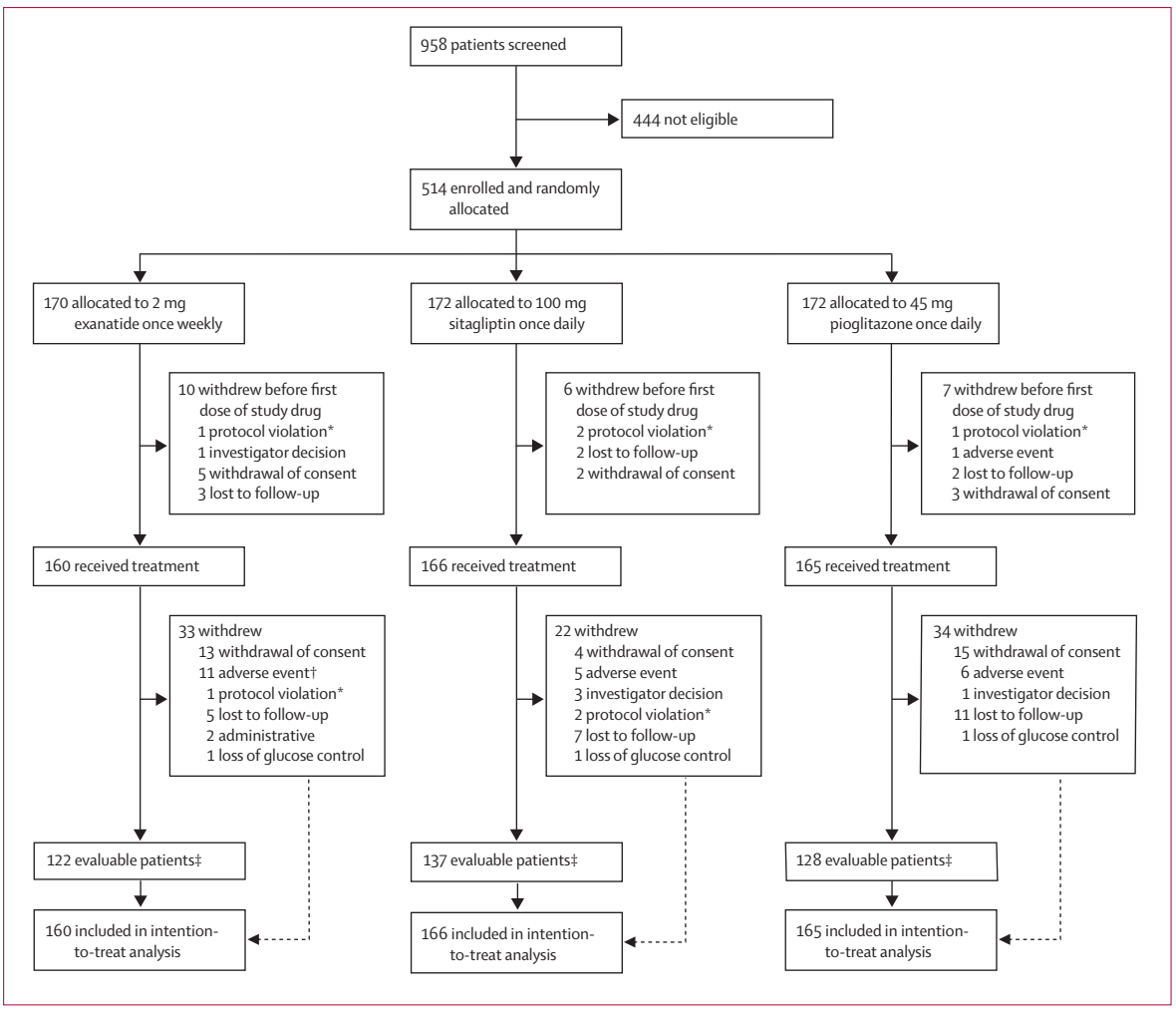

Figure 1: **Trial profile**

*All protocol violations after randomisation were due to non-compliance with study visits or treatment, or both. †One adverse event was not treatment-emergent. ‡Patients completed study procedures through week 22 in compliance with the protocol and received adequate exposure to the study drug during the treatment period.

Treatment-emergent adverse events were defined as those occurring or worsening during or after the first dose of study drug. Hypoglycaemia was categorised as major or minor. Major hypoglycaemia was defined as loss of consciousness, seizure, or coma that resolved after treatment with glucagon or glucose, or severe impairment that required third-party assistance to resolve the episode and a blood glucose concentration of lower than 3 mmol/L. Minor hypoglycaemia was defined as a report of symptoms consistent with hypoglycaemia and glucose of lower than 3 mmol/L before treatment of the episode.

Statistical analysis

We estimated that 500 patients would provide at least 90% power to detect a statistically significant difference (α=0·05, two-sided test) between exenatide once weekly and sitagliptin or pioglitazone with Hochberg's multiple test procedure,[15] and assumptions of a difference of 0·5% between groups, a common SD of 1·2%, and an early withdrawal rate of 10%. Multiplicity for the comparisons of exenatide versus sitagliptin or pioglitazone were adjusted by use of the Hochberg procedure[15] to control the overall type 1 error rate at 5% for HbA_{1c}, fasting plasma glucose, bodyweight, fasting lipid profile, and blood pressure. Unless specified otherwise, descriptive statistics for demographic indicators and analyses are for the intention-to-treat population, comprising all randomised patients who received at least one dose of study drug. The evaluable population consisted of all intention-to-treat participants who completed study procedures up to week 22, in compliance with the protocol and received dequate exposure.

Analyses of change in HbA_{1c} at each visit were based on a general linear model including treatment, country, and baseline HbA_{1c} strata (<9·0% *vs* ≥9·0%). Additionally, interaction between treatment and baseline HbA_{1c} strata

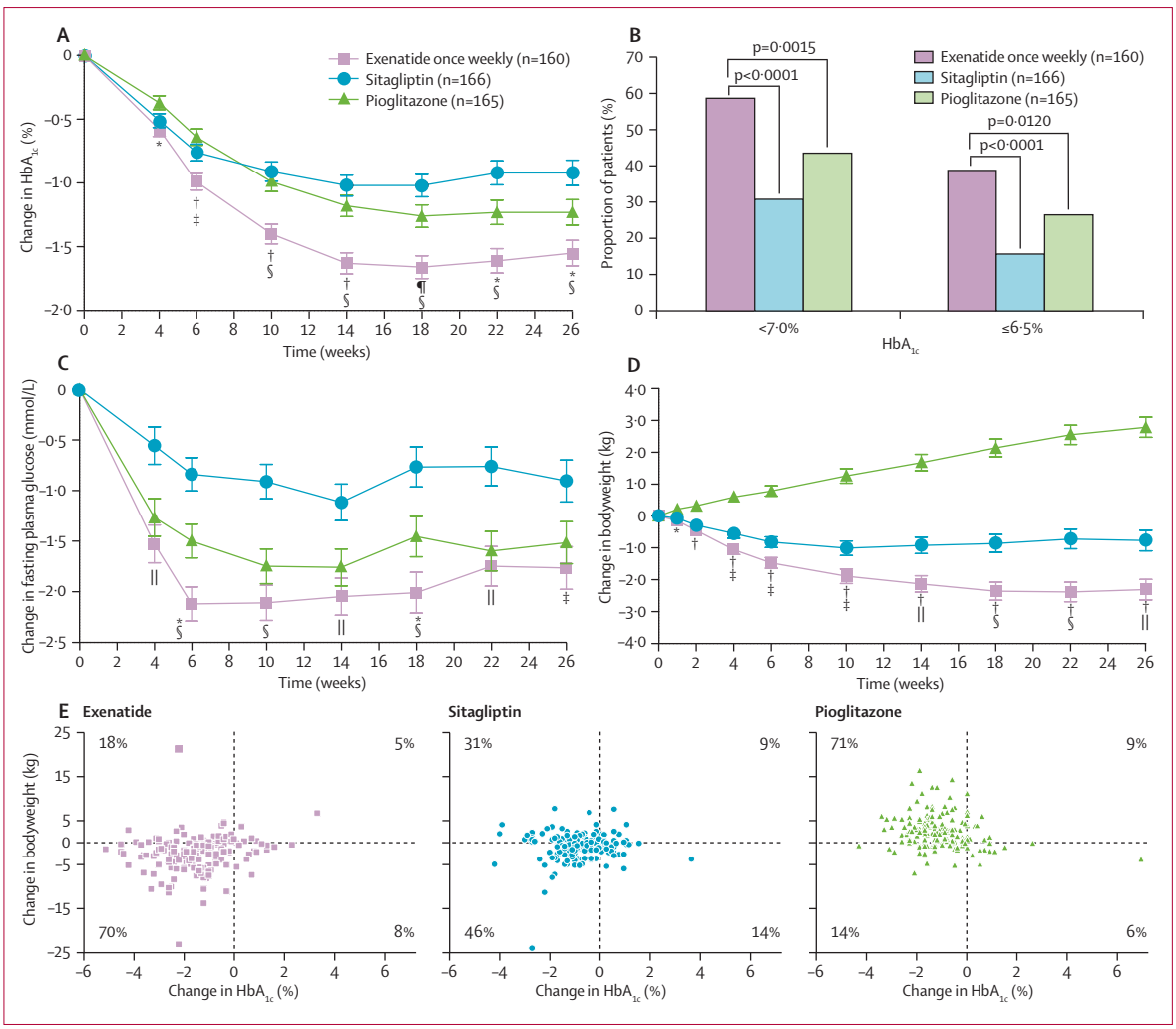

Figure 2: **Change in glycaemic control and bodyweight between baseline and week 26**
(A) Change in glycosylated haemoglobin (HbA_{1c}) over 26 weeks. (B) Proportion of patients achieving HbA_{1c} target values at week 26. (C) Change in fasting plasma glucose over 26 weeks. (D) Change in bodyweight over 26 weeks. (E) Scatterplot of change in HbA_{1c} versus change in bodyweight at week 26. In A, C, and D data are least squares mean, and error bars are SEs. All p values are adjusted according to the Hochberg method.[15] *p<0·05 for exenatide versus pioglitazone. †p<0·0001 for exenatide versus pioglitazone. ‡p<0·05 for exenatide versus sitagliptin. §p<0·0001 for exenatide versus sitagliptin. ¶p<0·001 for exenatide versus pioglitazone. ||p<0·001 for exenatide versus sitagliptin.

was assessed. Analyses of change in other parameters at each visit were based on a general linear model including treatment, country, and baseline HbA_{1c} strata, with the corresponding baseline value of the parameter as a covariate. Log-transformation was applied to triglycerides and cardiovascular risk markers before fitting the model. Values of high-sensitivity C-reactive protein of more than 10 mg/L were excluded from the comparison because highly raised high-sensitivity C-reactive protein indicates non-cardiovascular causes of inflammation.[16] Comparison of treatment groups for proportions of patients achieving targets for HbA_{1c} and fasting plasma glucose was done with a Cochran-Mantel-Haenszel test, stratified by baseline HbA_{1c} stratum and country. Differences in the proportions of patients completing the study between treatment groups were assessed with a Fisher's exact test. Missing data were imputed by last observation carried forward. Changes from baseline to week 26 for efficacy endpoints were expressed as least square means. A post-hoc analysis for between-group differences for all three treatments was also done. Statistical analyses were done with SAS (version 8.2).

This trial is registered with ClinicalTrials.gov, number NCT00637273.

Role of the funding source

Amylin Pharmaceuticals and Eli Lilly paticipated in the study design, study conduct, and data collection, and assisted the authors in data analysis and interpretation and preparation and review of the report. RMB and CW had full access to all the data in the study, take responsibility for the integrity of the data and the accuracy

	HbA_{1c} <9·0%			HbA_{1c} ≥9·0%		
	Exenatide once weekly (n=102)	Sitagliptin (n=106)	Pioglitazone (n=109)	Exenatide once weekly (n=58)	Sitagliptin (n=60)	Pioglitazone (n=56)
Baseline HbA_{1c}	7·8% (0·1)	7·7% (0·1)	7·8% (0·1)	9·9% (0·1)	9·8% (0·1)	9·7% (0·1)
Change in HbA_{1c}	−1·1% (−1·3 to −0·9)	−0·5% (−0·8 to −0·3)	−0·9% (−1·1 to −0·7)	−2·0% (−2·4 to −1·6)	−1·3% (−1·7 to −0·9)	−1·5% (−1·9 to −1·1)
Treatment difference *vs* exenatide	NA	0·5% (0·3 to 0·8), p=0·0005	0·2% (−0·1 to 0·5), p=0·1926	NA	0·8% (0·3 to 1·3), p=0·0071	0·5% (0·0 to 1·1), p=0·0436

For baseline glycosylated haemoglobin (HbA_{1c}), data are mean (SE); and for change in HbA_{1c}, and for treatment difference, data are least square mean (95% CI). p values were adjusted with the Hochberg method[15] within each stratum. NA=not applicable.

Table 2: **Change in HbA_{1c} from baseline to week 26, stratified by baseline HbA_{1c}**

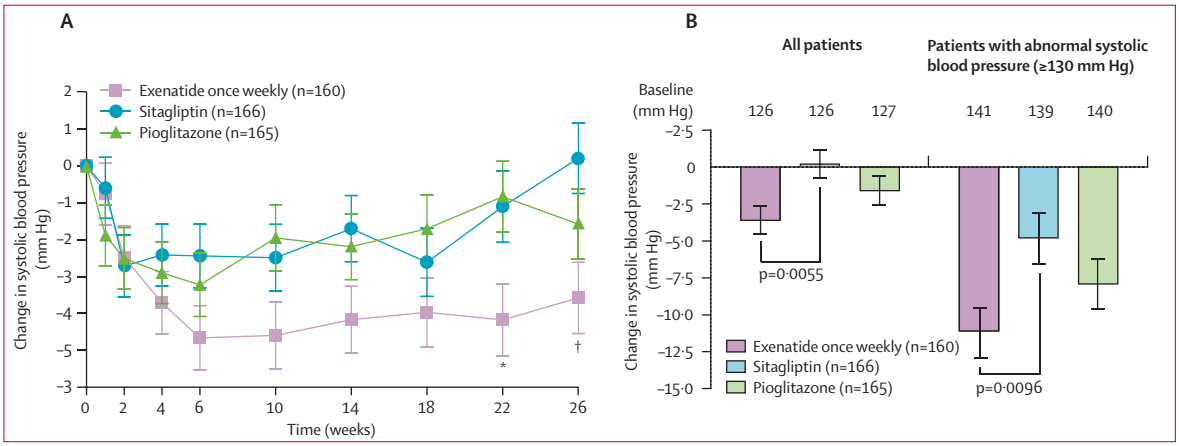

Figure 3: **Change in systolic blood pressure between baseline and week 26**

(A) Change in systolic blood pressure over 26 weeks. (B) Change in systolic blood pressure at week 26 in all patients and in a subgroup of patients with abnormal systolic blood pressure (≥130 mm Hg) at baseline. Data are least squares mean, and error bars are SEs. All p values are adjusted according to the Hochberg method.[15] *p=0·0162 for exenatide versus sitagliptin and for exenatide versus pioglitazone at week 22. †p=0·0055 for exenatide versus sitagliptin at week 26.

of the data analysis, and had final responsibility for the decision to submit for publication.

Results

Demographic and clinical characteristics were well balanced between treatment groups (table 1). Fewer patients withdrew from treatment with sitagliptin (13%) than did those receiving exenatide once weekly (21%, p=0·0784) or pioglitazone (21%), which was mainly due to greater proportions of patients withdrawing consent on exenatide (8%) and pioglitazone (9%) than on sitagliptin (2%; figure 1).

Treatment with once weekly exenatide resulted in a significantly greater reduction in HbA_{1c} than did pioglitazone by week 4, or sitagliptin by week 6; statistical significance was maintained throughout the remainder of the study (figure 2A). After 26 weeks' treatment, mean HbA_{1c} was 7·2% (SE 0·1) for exenatide, 7·7% (0·1) for sitagliptin, and 7·4% (0·1) for pioglitazone. Between baseline and week 26, reduction in HbA_{1c} with exenatide (−1·5%, 95% CI −1·7 to −1·4) was significantly greater than with sitagliptin (−0·9%, −1·1 to −0·7) or pioglitazone (−1·2%, −1·4 to −1·0). Treatment differences were −0·6% (95% CI −0·9 to −0·4, adjusted p<0·0001) for exenatide versus sitagliptin, and −0·3% (−0·6 to −0·1, adjusted p=0·0165) for exenatide versus pioglitazone. Similar reductions were recorded for the evaluable patient group (webappendix p 3). When data were stratified by baseline HbA_{1c}, exenatide once weekly was associated with a significantly greater reduction in HbA_{1c} than was sitagliptin in all patients, but for exenatide versus pioglitazone, the difference was significant only in patients with baseline HbA_{1c} of 9% or higher (table 2). Interaction between baseline HbA_{1c} stratum and treatment was not significant (p=0·4054). Significantly more patients achieved HbA_{1c} targets of less than 7·0% and 6·5% or lower with exenatide than with sitagliptin or pioglitazone (figure 2B).

All treatments improved fasting plasma glucose; exenatide once weekly resulted in a significantly greater reduction (−1·8 mmol/L, 95% CI −2·2 to −1·3) than did sitagliptin (−0·9 mmol/L, −1·3 to −0·5), but not pioglitazone (−1·5 mmol/L, −1·9 to −1·1; figure 2C; webappendix p 3). Treatment differences were −0·9 mmol/L (95% CI −0·3 to −1·4, adjusted p=0·0038) for exenatide versus sitagliptin, and −0·2 mmol/L (−0·8 to 0·3, adjusted p=0·3729) for exenatide versus pioglitazone. The percentage of patients who achieved the target of 7 mmol/L or less with exenatide (60%, n=96 patients) was significantly greater than with sitagliptin (35%, n=58, adjusted p<0·0001), and was similar to pioglitazone (52%, n=86, adjusted p=0·1024).

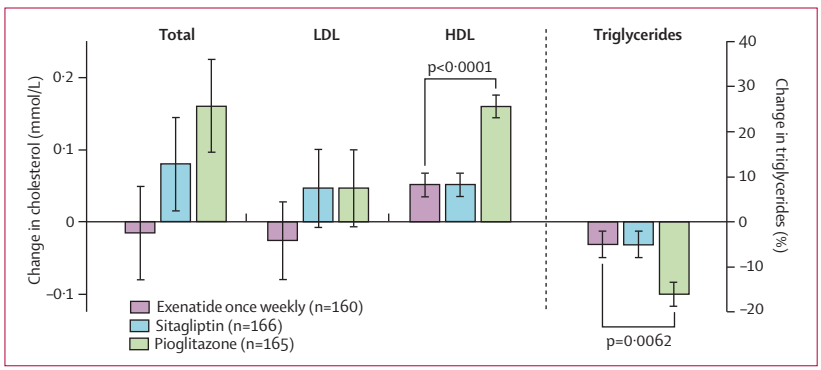

Figure 4: **Change in blood lipid profiles between baseline and week 26**
Data are least squares mean, and error bars are SEs. Statistical analysis for triglycerides was done on log-transformed data. All p values are adjusted according to the Hochberg method.[15]

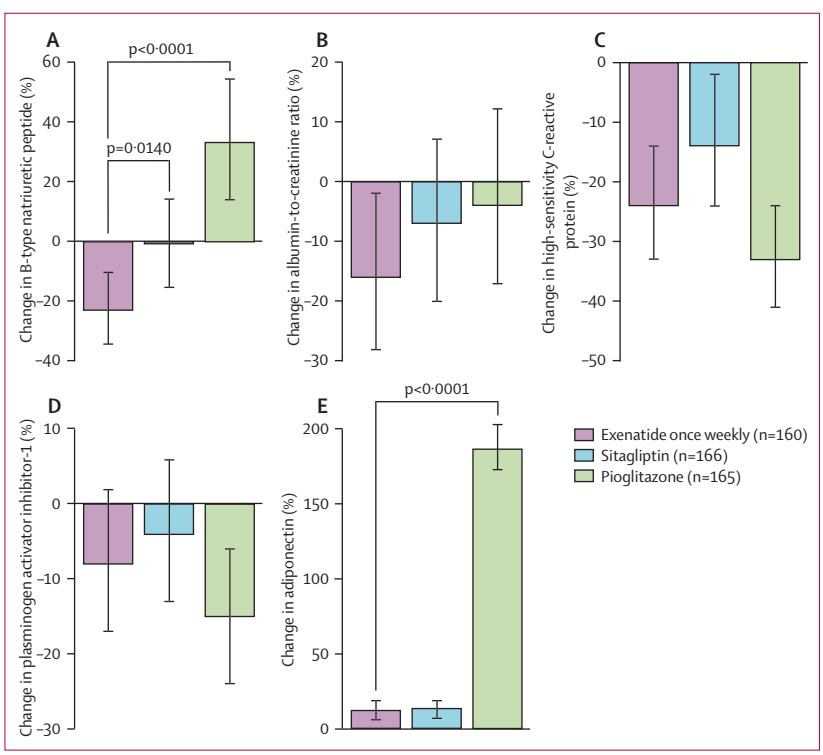

Figure 5: **Changes in markers of cardiovascular risk between baseline and week 26**
Data are least squares mean change (95% CI). (A) B-type natriuretic peptide. (B) Albumin-to-creatinine ratio. (C) High-sensitivity C-reactive protein. (D) Plasminogen activator inhibitor-1. (E) Adiponectin. Statistical analysis was done on log-transformed data.

Fasting insulin was significantly increased at week 26 with exenatide once weekly (3·6 μIU/mL, 95% CI 1·6 to 5·6) compared with sitagliptin (0·4 μIU/mL, –1·6 to 2·3) and pioglitazone (–3·9 μIU/mL, –5·9 to –2·0). Treatment differences were 3·2 μIU/mL (95% CI 0·6 to 5·8, p=0·0161) for exenatide versus sitagliptin, and 7·5 μIU/mL (4·9 to 10·1, p<0·0001) for exenatide versus pioglitazone. In all measurements of the six-point self-monitored blood glucose profile, reductions at week 26 were significantly greater with exenatide than with sitagliptin, but not pioglitazone (webappendix p 4).

Exenatide once weekly resulted in a significantly greater reduction in bodyweight than did pioglitazone by week 1 and sitagliptin by week 4 (figure 2D). At week 26, weight loss with exenatide (–2·3 kg, 95% CI –2·9 to –1·7) was significantly greater than with sitagliptin (–0·8 kg, –1·4 to –0·1) or pioglitazone (2·8 kg, 2·2 to 3·4). Treatment differences were –1·5 kg (95% CI –2·4 to –0·7, adjusted p=0·0002) for exenatide versus sitagliptin, and –5·1 kg (–5·9 to –4·3, adjusted p<0·0001) for exenatide versus pioglitazone. Similar changes were recorded in evaluable patients (webappendix p 3). More than 75% (n=123) of patients on once weekly exenatide lost bodyweight, compared with 61% (n=101) of those on sitagliptin and 21% (n=35) of those on pioglitazone. 28% (n=45) of patients receiving exenatide had weight loss of 5% or more, compared with 10% (n=16) of those on sitagliptin and 2% (n=3) of those on pioglitazone. Change in bodyweight was similar between patients with baseline body-mass index of less than 30 kg/m² or of 30 kg/m² or more (data not shown). More patients on exenatide had reductions in both HbA_{1c} and bodyweight than did those on sitagliptin or pioglitazone (figure 2E).

Improvements in systolic blood pressure were recorded within a few weeks of starting all treatments (figure 3A). After 26 weeks' treatment, the reduction in systolic blood pressure was significantly greater with exenatide once weekly than with sitagliptin in all patients (difference –4 mm Hg, 95% CI –6 to –1) and in those with abnormal systolic blood pressure at baseline (–6 mm Hg, –11 to –2); the difference between exenatide and pioglitazone was not significant in either patient group (figure 3B). Change in diastolic blood pressure at week 26 did not differ significantly between groups. Changes in concomitant antihypertensive drugs were allowed only if they were deemed to be necessary by the investigator. Of the 237 patients who used an antihypertensive agent at screening and completed the 26-week assessment period, 210 (89%; similar between treatment groups) did not change dose.

Significant improvement in HDL cholesterol was recorded with all treatments, and improvement was significantly greater with pioglitazone than with exenatide once weekly (difference 0·11 mmol/L, 95% CI 0·07 to 0·15; figure 4). Pioglitazone was the only treatment associated with a significant reduction in triglycerides (–16%, 95% CI –21 to –11) and increase in total cholesterol (0·16 mmol/L, 95% CI 0·04 to 0·28), the former of which was significantly different from changes with exenatide (–5%, 95% CI –11 to 0). Changes to lipid-lowering drug regimens were not allowed unless the investigator directed the change. Of the 166 patients who had used a lipid-lowering agent at screening and completed the 26-week assessment period, 151 (91%; similar between treatment groups) did not change dose.

A post-hoc analysis of change in HbA_{1c}, fasting plasma glucose, bodyweight, blood pressure, and blood lipid profile between all three treatment groups showed

significantly greater improvement in HbA_{1c}, diastolic blood pressure, HDL cholesterol, and triglycerides with pioglitazone than with sitagliptin, whereas sitagliptin resulted in significantly greater weight loss than did pioglitazone (webappendix p 5).

All treatments were associated with significant improvements in high-sensitivity C-reactive protein and adiponectin (figure 5). Exenatide once weekly was the only treatment associated with significantly improved B-type natriuretic peptide and ratio of albumin to creatinine; B-type natriuretic peptide was also significantly greater than on sitagliptin or pioglitazone. Pioglitazone was associated with a significantly greater increase in adiponectin than was exenatide, and was the only treatment associated with significantly improved plasminogen activator inhibitor-1 and significant worsening of B-type natriuretic peptide.

All five domains of weight-related QOL and IWQOL total score were significantly improved with exenatide once weekly (IWQOL total score 5·15, 95% CI 3·11 to 7·19) and sitagliptin (4·56, 2·56 to 6·57), but not pioglitazone (1·20, –0·87 to 3·28), which improved only on self-esteem. Significantly greater improvements in IWQOL total score were recorded for exenatide than for pioglitazone (difference 3·94, 95% CI 1·28 to 6·61, p=0·0038), consistent with differences in bodyweight change. All groups showed significant improvements in all domains of the PGWB and the DTSQ total score; greater improvement in overall treatment satisfaction was recorded with exenatide (3·96, 95% CI 2·78 to 5·15) than with sitagliptin (2·35, 1·19 to 3·51; difference 1·61, 95% CI 0·07 to 3·16, p=0·0406).

For patients on exenatide once weekly and sitagliptin, the most common treatment-emergent adverse events were nausea and diarrhoea, whereas upper-respiratory-tract infection and peripheral oedema were most common in those on pioglitazone (table 3). Vomiting was more common with exenatide once weekly than with sitagliptin or pioglitazone. Treatment-emergent adverse events leading to withdrawal from the study drug occurred in ten patients on exenatide, five on sitagliptin, and six on pioglitazone. The only event leading to withdrawal in more than one patient per treatment group was diarrhoea, which caused withdrawal of two patients on each of exenatide and sitagliptin. During the 26-week study, 19 patients had 26 treatment-emergent serious adverse events (table 3). One serious adverse event was fatal (uncontrolled hypertension on sitagliptin), but all other events resolved. Two serious adverse events led to withdrawal (cryptogenic organising pneumonia on exenatide and necrotising pancreatitis on pioglitazone).

There were no episodes of major hypoglycaemia. The frequency of minor hypoglycaemic events was low and similar between treatment groups: two events (n=2 patients, 1%) on exenatide once weekly; nine events (n=5, 3%) on sitagliptin; and one event (n=1, 1%) on pioglitazone. Few events related to the injection site occurred on exenatide (n=16, 10%; 28 events), and the frequency was similar to that with placebo microsphere injection in the sitagliptin and pioglitazone groups (n=22, 7%; 42 events). Most patients on exenatide had either low (<1/625; n=74, 48%) or not detectable (n=61, 40%) titres of treatment-emergent antibodies to exenatide during their final study visit (153 samples were available for assay of antibody status). Similar to previous reports,[14] antibody status was not predictive of safety or individual change in HbA_{1c}.

	Exenatide once weekly (n=160)		Sitagliptin (n=166)		Pioglitazone (n=165)	
	Patients	Events	Patients	Events	Patients	Events
Serious adverse events						
Overall	4 (3%)	4	5 (3%)	6	10 (6%)	16
Non-cardiac chest pain	0	0	1 (1%)	1	1 (1%)	1
Coronary artery occlusion	0	0	0	0	2 (1%)	2
Cerebrovascular accident	0	0	1 (1%)	1	1 (1%)	1
Pancreatitis	0	0	0	0	2 (1%)	2
Unstable angina	0	0	0	0	1 (1%)	1
Bile-duct obstruction	0	0	0	0	1 (1%)	1
Cholelithiasis	0	0	0	0	1 (1%)	1
Clostridial infection	0	0	0	0	1 (1%)	1
Dengue fever	0	0	0	0	1 (1%)	1
Pancreatic abscess	0	0	0	0	1 (1%)	1
Sepsis	0	0	0	0	1 (1%)	1
Viral infection	0	0	0	0	1 (1%)	1
Staphylococcal wound infection	0	0	0	0	1 (1%)	1
Acute renal failure	0	0	0	0	1 (1%)	1
Bacterial pyelonephritis	0	0	1 (1%)	1	0	0
Escherichia bacteraemia	0	0	1 (1%)	1	0	0
Papillary thyroid cancer	0	0	1 (1%)	1	0	0
Hypertension	0	0	1 (1%)	1	0	0
Viral pericarditis	1 (1%)	1	0	0	0	0
Postoperative wound complication	1 (1%)	1	0	0	0	0
Nephrolithiasis	1 (1%)	1	0	0	0	0
Cryptogenic organising pneumonia	1 (1%)	1	0	0	0	0
Frequent treatment-emergent adverse events						
Nausea	38 (24%)	62	16 (10%)	22	8 (5%)	9
Diarrhoea	29 (18%)	39	16 (10%)	21	12 (7%)	13
Upper-respiratory-tract infection	6 (4%)	7	15 (9%)	16	17 (10%)	20
Headache	15 (9%)	16	15 (9%)	19	7 (4%)	9
Vomiting	18 (11%)	29	4 (2%)	4	5 (3%)	7
Urinary-tract infection	10 (6%)	10	9 (5%)	10	6 (4%)	7
Peripheral oedema	2 (1%)	3	5 (3%)	5	13 (8%)	14
Injection-site pruritus	8 (5%)	8	8 (5%)	13	2 (1%)	2
Sinusitis	5 (3%)	5	2 (1%)	2	11 (7%)	12
Fatigue	9 (6%)	10	0	0	5 (3%)	9
Constipation	9 (6%)	9	3 (2%)	4	2 (1%)	2

Data are number of patients (%) or number of events.

Table 3: **Serious adverse events in any treatment group and treatment-emergent adverse events occurring in 5% or more of patients**

Discussion

Treatment of type 2 diabetes is a specialty in which comparative data are needed to better inform treatment decisions because of the heterogeneity of patients and the availability of several treatment options. Our double-blind, double-dummy trial directly compared the safety and efficacy of three antihyperglycaemic drugs that might be appropriate adjunctive medication in patients with insufficient glycaemic control on metformin. Once weekly treatment with exenatide elicited significantly greater improvements in HbA_{1c} than did maximum approved doses of sitagliptin and pioglitazone. The improvements in HbA_{1c} with maximum doses of sitagliptin and pioglitazone were consistent with their respective drug product labels for the treatment of type 2 diabetes on metformin background.[17,18] Thus, these data suggest that exenatide once weekly offers clinically important improvements in patients not achieving adequate glycaemic control on metformin alone. Although HbA_{1c} reduction during the first 26 weeks of treatment is not predictive of the durability of glycaemic improvements, all three drugs have shown sustained improvements in glycaemic control up to 2 years.[19–21]

To achieve optimum treatment of type 2 diabetes, clinicians should also consider the effects of treatment on weight and intermediate cardiovascular measures, such as blood pressure and lipids. Exenatide once weekly was associated with significantly greater weight loss and weight loss in more patients than were sitagliptin or pioglitazone. The reduction in systolic blood pressure recorded with exenatide once weekly was similar to previous reports with exenatide twice daily,[22,23] and significantly greater than was that recorded with sitagliptin. Improvement in lipids and markers of cardiovascular risk were noted to varying degrees with all treatments. In agreement with the established effects of pioglitazone on blood lipids,[24] pioglitazone was associated with the greatest improvement in HDL cholesterol and triglycerides, and was the only drug associated with an increase in total cholesterol. Exenatide once weekly was the only treatment associated with favourable mean changes in all lipid parameters. Consistent with the reduction in systolic blood pressure, exenatide significantly decreased the ratio of albumin to creatinine. All treatments were associated with improved high-sensitivity C-reactive protein and adiponectin, although the absence of a placebo comparator restricts the conclusions that can be drawn with respect to treatment-related changes from baseline.[25] Further studies are warranted to establish whether the changes in cardiovascular markers reported in our trial will translate into a reduction in cardiovascular outcomes. However, our report of the effects of these drugs on bodyweight, blood pressure, lipids, and markers of cardiovascular risk could be important considerations for some patients.

Adverse events were generally mild to moderate and consistent with previous reports. Notably, this double-blind, double-dummy trial did not show a difference in the overall safety profile between the three treatment groups. All three drugs, on a background of metformin, had low frequency of hypoglycaemia and no cases of severe hypoglycaemia. Thus, each of these drugs could be considered when risk of hypoglycaemia is a concern.[2] As in previous trials with exenatide, mild-to-moderate gastrointestinal events, including nausea, diarrhoea, and vomiting were the main adverse events associated with treatment, and should be taken into account when assessing exenatide as a potential treatment.[14,26–29] These events occurred less frequently with sitagliptin and pioglitazone, and did not significantly affect participation.

Our study is limited by the fact that we did not study all classes of potential adjunctive drugs, particularly basal insulin and sulphonylureas. A direct comparison is also warranted with 1·8 mg liraglutide, which is a modified version of GLP-1 that is taken once daily. In combination with metformin in patients predominantly on metformin background, 26 weeks' treatment with 1·8 mg liraglutide resulted in a greater reduction in HbA_{1c} (–1·3%) than did metformin alone (–0·4%), with similar weight loss and occurrence of nausea as we recorded with exenatide.[30] Assessment of intermediate outcome markers (eg, HbA_{1c}, bodyweight, blood pressure, fasting lipid profile) rather than long-term outcomes, such as mortality and cardiovascular disease, is also a limitation. Although long-term outcome studies of GLP-1-related therapies are needed, our study provides one of the most comprehensive direct comparisons of key intermediate outcome markers with adjunctive treatments to metformin. The improvements in HbA_{1c} and bodyweight with once weekly exenatide suggest that this drug should be considered as an adjunct to metformin in patients needing improvements in glucose control and bodyweight, and in whom the risk of hypoglycaemia needs to be kept to a minimium.

Contributors

LM, JMall, and LEP contributed to the study concept and design. RMB and CW collected data; and RMB, CW, JMall, PY, and LEP supervised the study. All authors analysed and interpreted data, and PY did the statistical analysis. RMB, JMall, BW, and PY drafted the report, and all authors critically revised the report.

DURATION-2 Study Group

Anna Chang, Lisa Cohen, Waymon Drummond, Raymond Fink, Ronald Graf, Richard Guthrie, Stephen Ong, Ronald Stegemoller, Richard Beasley, Thomas Blevins, Joseph Cleaver, Munni R Selagamsetty, James Snyder, Jesse Wallace, Bruce Berwald, David Kayne, Leonard Chuck, Dean Kereiakes, Thomas Moretto, Kenneth Sall, Ruben Pipek, Steven Yarows, Bruce Rankin, Michelle Welch, Eric Klein, Sherwyn Schwartz, Lane Handke, John Pullman, Ernesto Fuentes, Stephen Aronoff, Louise Taber, Michael Guice, Thomas Littlejohn, Elmer Stout, Richard Bergenstal, Edward Horton, Frank Schwartz, Jeffrey L Miller, Franklin Zieve, Rajat Bhushan, Linda Gaudiani, Peter Weissman, Kenneth Hershon, Guillermo Gonzalez-Galvez, Melchor Alpizar Salazar, Leobardo Sauque Reyna, Enrique Rafael Granados Reyes, Angela Cabeza Gomez, Hiromi Rodriguez Pattzi, Mala Dharmalingam, Shailaja Kale, Sunil M Jain, Sanjay Kalra, Sathyanarayana Srikanta, Sanjiv Shah, Nadeem Rais, K M Prasanna Kumar, Michael Sanson, Sashi Makam, William Cefalu, Pedro Velasquez-Mieyer, Pedro Garcia Hernandez, Lawrence S Phillips, Carol Wysham, John Buse, Daniel Donovan, Vanita Aroda, Jeffrey B Rosen, Christian F Breton, Nashwa W Gabra, Miguel Sosa-Padilla, William Reid Litchfield.

Conflicts of interest

RMB's institution has received consultancy fees or research grant support, or both, with receipt of travel and accommodation expenses in some cases, from Abbott Diabetes Care, Amylin, Bayer, Eli Lilly, Intuity Medical, Hygieia Medical, LifeScan, Mannkind, Medtronic-Minimed, National Institutes of Health, Novo Nordisk, ResMed, Roche, Sanofi-Aventis, United Health Group, and Valeritas; all research activity, and advisory or consultancy services were done under contract with the non-profit International Diabetes Center at Park Nicollet. RMB owns stock in Merck. CW is a member of the scientific advisory board for Amylin Pharmaceuticals; is a consultant for Amylin Pharmaceuticals, Eli Lilly, and AstraZeneca; is on the speakers' bureaux of Amylin Pharmaceuticals, Eli Lilly, Merck, Novo Nordisk, and Sanofi-Aventis; and has received travel and accommodation expenses from Amylin Pharmaceuticals. LM, JMall, BW, PY, KW, and LEP are employees and stockholders of Amylin Pharmaceuticals. JMalo is an employee and stockholder of Eli Lilly.

Acknowledgments

We thank the DURATION-2 Study Group and their staff for their excellent work in the conduct, reporting, and quality control of the study; the study patients for their participation; Kristin Taylor and Larry Shen (employees of Amylin Pharmaceuticals) for assistance with study design and data interpretation; and Alkermes for the development and manufacture of the longacting release formulation of exenatide. This study was supported by Amylin Pharmaceuticals and Eli Lilly.

References

1 Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2006; **29:** 1963–72.

2 Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; **32:** 193–203.

3 Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract* 2009; **15:** 540–59.

4 Cheung BM, Ong KL, Cherny SS, Sham PC, Tso AW, Lam KS. Diabetes prevalence and therapeutic target achievement in the United States, 1999 to 2006. *Am J Med* 2009; **122:** 443–53.

5 Alexander GC, Stafford RS. Does comparative effectiveness have a comparative edge? *JAMA* 2009; **301:** 2488–90.

6 Conway PH, Clancy C. Comparative-effectiveness research—implications of the Federal Coordinating Council's report. *N Engl J Med* 2009; **361:** 328–30.

7 Stafford RS, Wagner TH, Lavori PW. New, but not improved? Incorporating comparative-effectiveness information into FDA labeling. *N Engl J Med* 2009; **361:** 1230–33.

8 World Medical Association. World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 1997; **277:** 925–26.

9 Kolotkin RL, Crosby RD, Williams GR. Assessing weight-related quality of life in obese persons with type 2 diabetes. *Diabetes Res Clin Pract* 2003; **61:** 125–32.

10 Dupuy HJ. The psychological general well-being (PGWB) index. In: Wenger NK, ed. Assessment of quality of life in clinical trials of cardiovascular therapies. New York, NY, USA: LeJacq Publications, 1984: 170–83.

11 Bradley C. The diabetes treatment satisfaction questionnaire: DTSQ. In: Chur BC, ed. Handbook of psychology and diabetes: a guide to psychological measurement in diabetes research and practice. Switzerland: Harwood Academic Publishers, 1994: 111–32.

12 Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). *Med Decis Making* 2002; **22:** 340–49.

13 Fineman MS, Bicsak TA, Shen LZ, et al. Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care* 2003; **26:** 2370–77.

14 Drucker DJ, Buse JB, Taylor K, et al, for the DURATION-1 Study Group. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* 2008; **372:** 1240–50.

15 Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 1988; **75:** 800–02.

16 Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; **107:** 499–511.

17 Takeda Pharmaceuticals America. Actos (pioglitazone hydrochloride) tablets (prescribing information). Deerfield, Illinois: Takeda Pharmaceuticals America, 2009.

18 Merck. Januvia (sitagliptin) tablets (prescribing information). Whitehouse Station, New Jersey: Merck, 2009.

19 Kim T, Taylor K, Wilhelm W, Trautmann M, Zhuang D, Porter L. Exenatide once weekly treatment elicits sustained glycemic control and weight loss over 2 years. *Diabetes* 2009; **58** (suppl 1)**:** A42, abstr 159-OR.

20 Tan MH, Baksi A, Krahulec B, et al. Comparison of pioglitazone and gliclazide in sustaining glycemic control over 2 years in patients with type 2 diabetes. *Diabetes Care* 2005; **28:** 544–50.

21 Williams-Herman DE, Seck TL, Golm G, et al. Long-term efficacy with sitagliptin as monotherapy or add-on therapy to metformin: improvements in glycemic control over 2 years in patients with type 2 diabetes. *Diabetes* 2009; **58** (suppl 1)**:** A144, abstr 560-P.

22 Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin* 2008; **24:** 275–86.

23 Ratner RE, Maggs D, Nielsen LL, et al. Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2006; **8:** 419–28.

24 Goldberg RB, Kendall DM, Deeg MA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005; **28:** 1547–54.

25 Pradhan AD, Everett BM, Cook NR, Rifai N, Ridker PM. Effects of initiating insulin and metformin on glycemic control and inflammatory biomarkers among patients with type 2 diabetes: the LANCET randomized trial. *JAMA* 2009; **302**: 1186–94.

26 Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 2004; **27:** 2628–35.

27 DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; **28:** 1092–100.

28 Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 2005; **28:** 1083–91.

29 Zinman B, Hoogwerf BJ, Duran Garcia S, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2007; **146:** 477–85.

30 Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care* 2009; **32**: 84–90.