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ORIGINAL ARTICLE

Exenatide versus insulin glargine in patients with type 2 diabetes in the UK: a model of long-term clinical and cost outcomes

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ABSTRACT

Objectives: The aim of this study was to evaluate the long-term clinical and economic outcomes associated with exenatide or insulin glargine, added to oral therapy in individuals with type 2 diabetes inadequately controlled with combination oral agents in the UK setting.

Methods: A published and validated computer simulation model of diabetes was used to project long-term complications, life expectancy, quality-adjusted life expectancy and direct medical costs. Probabilities of diabetes-related complications were derived from published sources. Treatment effects and patient characteristics were extracted from a recent randomised controlled trial comparing exenatide with insulin glargine. Simulations incorporated published quality of life utilities and UK-specific costs from 2004. Pharmacy costs for exenatide were based on 20, 40, 60, 80 and 100% of the US value (as no price for the UK was available at the time of analysis). Future costs and clinical benefits were discounted at 3.5% annually. Sensitivity analyses were performed.

Results: In the base–case analysis exenatide was associated with improvements in life expectancy of 0.057 years and in quality-adjusted life expectancy of 0.442 quality-adjusted life years (QALYs) versus insulin glargine. Long-term projections demonstrated that exenatide was associated with a lower cumulative incidence of most cardiovascular disease (CVD) complications and CVD-related death than insulin glargine. Using the range of cost values, evaluation results showed that exenatide is likely to fall in a range between dominant (cost and life saving) at 20% of the US price and cost-effective (with an ICER of £22 420 per QALY gained) at 100% of the US price, versus insulin glargine.

Conclusions: Based on the findings of a recent clinical trial, long-term projections indicated that exenatide is likely to be associated with improvement in life expectancy and quality-adjusted life expectancy compared to insulin glargine. The results from this modelling analysis suggest that that exenatide is likely to represent good value for money by generally accepted standards in the UK setting in individuals with type 2 diabetes inadequately controlled on oral therapy.

Introduction

The strict control of hyperglycaemia is the cornerstone of successful diabetes management. Pancreatic β-cell dysfunction and insulin resistance contribute to the hyperglycaemia characteristic of type 2 diabetes and the landmark UK Prospective Diabetes Study (UKPDS) demonstrated that improved patient outcomes are directly related to improved glycaemic control[1]. However, the UKPDS also showed that, due to the progressive nature of type 2 diabetes, glycaemic control deteriorates with time as the insulin-secreting capacity of the pancreas is further reduced[2]. Therefore individuals with type 2 diabetes often progress from adequate glycaemic control with only diet and exercise, to a need for oral antidiabetic agents (OADs) initially administered as monotherapy, then in combination, and finally as β-cell function continues to deteriorate, individuals develop an increasing dependence on the administration of exogenous insulin[3].

Although use of exogenous insulin in addition to or as a replacement for, OADs can improve glycaemic control, landmark studies have shown it does not maintain glycaemic control over time and is associated with a number of drawbacks (both real and perceived) that limit its clinical use, patient acceptance and ability to maintain glycaemic control[1,2,4,5]. Reluctance to use insulin is partly due to the complexity of insulin therapy. For example, patients are required to adjust the timing and content of their meals to suit their insulin injection regimen[6]. In addition to these complexities, there is a need to monitor blood glucose levels on a regular basis to allow for titration of insulin dose. Perhaps the greatest barrier to uptake of insulin therapy is the increased risk of hypoglycaemia[7]. However the use of newer, long-acting insulins such as insulin glargine has been shown to reduce the incidence of hypoglycaemia, specifically nocturnal hypoglycaemia, compared to previously used insulin preparations[4]. Use of insulin (including newer analogues) is often associated with weight gain that further exacerbates the diabetic condition via its impact on blood pressure, dyslipidaemia and insulin resistance[8]. As a consequence of the reluctance to use insulin, many patients with long-standing type 2 diabetes remain poorly controlled and therefore at increased risk of diabetes-related complications.

A novel anti-diabetic drug has recently been approved in the US for use in patients inadequately controlled with oral agents. Exenatide acts directly on the β cell to restore first-phase insulin secretion and enhance glucose-dependent insulin secretion. It can be administered by twice daily injection with a fixed dose regimen and thus reduces the need for dose adjustments and associated blood glucose monitoring. Further, exenatide treatment is associated with significant weight loss, as opposed to the weight gain typically linked to insulin, with no increased risk of hypoglycaemia when used with metformin[8–11]. The relevance of this attribute becomes apparent when one considers that recent estimates suggest that 52% of type 2 diabetes patients in the UK are obese and a further 28% are overweight[12].

Whilst the short-term benefits associated with use of exenatide have been demonstrated (up to 2 years), the long-term clinical and economic implications of this therapy option have not been examined[13]. In the present study we sought to determine the long-term clinical and cost outcomes associated with the use of exenatide in the UK setting as an alternative to insulin glargine in patients inadequately controlled with oral agents alone. Based on results of a recently reported randomised trial of exenatide versus insulin glargine[14], we have used the previously published CORE Diabetes Model to project the long-term clinical and economic outcomes that can be expected with use of exenatide in patients inadequately controlled with oral agents alone.

Methods

Overview

For the analysis, data on patient characteristics at baseline and treatment effects associated with exenatide and insulin glargine were extracted from a previously published 26-week trial in 549 type 2 diabetes patients failing to achieve adequate glycaemic control with a maximally tolerated dose of metformin and sulfonylurea therapy[14]. Subjects in the trial were randomly allocated to receive either exenatide *bis in diem* (BID) (before morning and evening meals) or insulin glargine *que diem* (once daily at bedtime) in addition to their current oral regimen (metformin and sulfonylurea) for the duration of the trial. The study showed that both treatments were associated with an improvement in HbA_{1c} levels, but that exenatide treatment led to a reduction in body weight compared to an increase in body weight observed in glargine arm. Rates of hypoglycaemic events were comparable in both treatment arms. However, nausea was reported more commonly by subjects in the exenatide group than in the insulin glargine treatment arm. Based on these findings, a previously published and validated computer simulation model of diabetes was used to project the long-term outcomes of life expectancy, quality-adjusted life expectancy, complication rates and associated costs for this patient cohort. In addition to the clinical input data for the base–case analysis from the published 26-week trial, data from a 2-year open-label extensions study was used in some of the sensitivity analyses reported in this manuscript[13].

Model

The CORE Diabetes Model has been previously published in considerable detail but a brief description of the model is provided here for the interested reader[15]. Briefly, the model is an interactive computer simulation model of diabetes, developed to determine the long-term health outcomes and economic consequences of interventions in type 1 or type 2 diabetes. Comprising 15 inter-dependant sub-models, the model simulates the diabetic complications of angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation and non-specific mortality. Each sub-model is a Markov model using time-, state-, and diabetes type dependant probabilities derived from published sources, and they are interconnected using tracker variables. Patient cohorts can be defined in terms of age, gender, baseline risk factors and pre-existing complications, whilst disease management components are able to be altered in the disease management module to reflect country specific patterns of care. A validation analysis of the CORE Diabetes Model in which the model was used to recreate outcomes from published clinical trials in 66 separate comparisons has also been published, indicating that the model is capable of reliably reproducing 'real-life' data[16].

Simulation cohorts

A cohort was generated based upon the combined baseline demographics, complications and treatments of the two treatment groups included in the intention to treat cohort of the clinical trial[14] (Table 1). Subjects were predominately Caucasian, with a mean baseline age of 58.9 years and a duration of diagnosed diabetes of 10 years. Important criteria for study entry were inadequate glycaemic control (i.e. $HbA_{1c} > 7.0\%$ and $\leq 10.0\%$) and treatment with metformin and sulfonylurea therapy. Patients were assumed to continue to receive their pre-study dose of combined OAD throughout the simulation.

Intervention effects

Intervention effects (unadjusted) were extracted from the same randomised controlled trial (RCT) upon which the simulation cohort was based[14] and, where necessary, was supplemented with additional, unpublished data from the same study (Table 2). Treatment with exenatide was associated with an unadjusted 0.99%-point reduction in HbA_{1c} from baseline versus a decrease of 1.07%-points with insulin glargine (non-significant difference). Exenatide was associated with numerically greater improvements in BMI, systolic blood pressure (SBP), total cholesterol and low density lipoprotein-cholesterol (LDL) compared to insulin glargine. Treatment with exenatide was also associated with a significantly greater incidence of nausea compared to insulin glargine. The proportion of patient who experienced nausea was approximately 57% in the exenatide group compared to only 9% in the glargine group. The majority of the nausea episodes in the exenatide group were reported during the first 8 weeks of the trial. The difference in overall hypoglycaemia rates was not statistically significant. Clinically, exenatide added to metformin and sulfonylurea, led to slightly higher rates of daytime mild and moderate hypoglycaemia with lower rates of nocturnal hypoglycaemia compared to insulin glargine[14]. In the simulations, following the application of the intervention effects described above, risk factors such as HbA_{1c}, SBP and serum lipid levels were assumed to follow a natural progression over patient lifetimes as observed in the UKPDS and the Framingham study[1,17,18].

Costs

UK-specific costs for the year 2004 were derived from published sources and are summarised in Table 3. Where cost data for the year 2004 were not available, values were inflated using the composite UK National Health Service (NHS) price inflation index[19]. Pharmacy costs were based upon the dose of interventions administered in the controlled trial[14] and were provided by the sponsor (Table 3). Exenatide is not currently approved for use in the UK and therefore no wholesale or public price was available for the analysis. For the base–case simulations, costs for exenatide were based upon the current wholesale price for 10 μg exenatide in the USA, converted to UK pounds sterling (£), as well as values corresponding to 80%, 60%, 40% and 20% of the US wholesale price. It was assumed that, as diabetes medication costs in the UK are typically lower than those in the US, this range of costs would capture the likely UK cost of exenatide. Patients administered exenatide were assumed to receive 10 μg twice daily until death in the simulation. Patients treated with insulin glargine were assumed to receive 25 IU per day in the first year of treatment and 40 IU per day in each subsequent year. The current per unit price of insulin glargine in the UK was used.

Health state utilities

For type 2 diabetes and its complications, health state utilities for the model were derived wherever possible from the UKPDS[20] with supplementation from the

Table 1. *Baseline demographics, complications, relevant concomitant medications and management of patients in the simulated cohort*

	Mean	SD
Demographics		
Sex (% male)	55.7	–
Ethnic origin, (%)		–
Caucasian	82.3	–
Black	0.9	–
Hispanic	15.3	–
Other	1.5	–
Mean age (years)	58.9	9.18
BMI (kg/m^2)	31.33	4.52
Mean duration of diabetes (years)	10	5.84
Risk factors		
Glycolated haemoglobin (HbA_{1c}) (%-points)	8.21	0.97
Systolic blood pressure (mmHg)	137.25	17.28
Total cholesterol (mg/dL)	188.03	38.7
High density lipoprotein-cholesterol (mg/dL)	46.63	10.449
Low density lipoprotein-cholesterol (mg/dL)	106.94	33.282
Triglycerides (mg/dL)	199.12	150.44
Pre-existing complications		
Myocardial infarction (%)	5.1	
Stroke (%)	0.2	
Microalbuminuria (%)	0.4	
Background retinopathy (%)	5.5	
Macular oedema (%)	0.5	
Neuropathy (%)	12.8	
Management		
Taking ACE-I/ARB (%)	39.3	
Taking statins (%)	34.4	
Taking aspirin (%)	11.1	
Screened for retinopathy (assumed treated with laser if detected) (%)	63.2	
Screened for renal disease (assumed treated with ACE or ARB if detected) (%)	60.0	

LVH = left ventricular hypertension; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index

Australian Institute of Health and Welfare 'Burden of Illness in Australia' report[21] and Tengs *et al.*[22]. Health-state utilities associated with BMI and nausea were also included in the analysis and were derived from a study designed to determine utility and disutility values relevant to medication related variables and are based upon standard gamble interviews conducted with 129 type 2 diabetes patients throughout the UK[23]. The utility/disutility values from this study were applied for weight loss/gain and nausea in the first 2 years of the simulation and subsequently, the impact of BMI on patients' quality of life was captured by applying utility scores from CODE-2 in the simulation[24]. This approach was used, as the Matza *et al.* values capture the disutility associated with nausea in the early stages of exenatide treatment as well as body weight change (as opposed to BMI level utility scores as given by CODE-2) in the early years of treatment. These utilities were applied for the first 2 years of the simulation as this is the period over which patients have been shown to lose weight in clinical studies[13]. Utility values applied in the first 2 years of simulation were within the range –0.044 to –0.065 for body weight increases and +0.020 and +0.032 for weight decreases, depending on

Table 2. *Treatment effects derived from the Heine et al.[14] clinical trial and applied in the simulations*

Risk factor	Exenatide		Insulin glargine	
	Mean	95% CI	Mean	95%CI
Change in HbA_{1c} (%-points)	–0.99	–1.11 to –0.87	–1.07	–1.19 to –0.96
Change in SBP (mmHg)	–4.15	–6.24 to –2.06	–0.57	–2.49 to 1.36
Change in total cholesterol (mg/dL)	–3.47	–6.97 to 0.0	–0.39	–4.26 to 3.87
Change in LDL (mg/dL)	–1.54	–4.64 to 1.55	5.80	2.32 to 9.28
Change in HDL (mg/dL)	1.54	0.77 to 2.32	1.54	0.77 to 2.32
Change in triglycerides (mg/dL)	–15.04	–28.34 to –1.77	–30.08	–46.06 to –13.29
Change in BMI (kg/m^2)	–0.80	–0.93 to –0.66	0.55	0.42 to 0.68
Proportion with nausea	57.1%		8.6%	
All hypoglycaemia*	693.94		584.37	

Treatment effects were taken from clinical trial data and reflect changes from baseline to 26 weeks
*Events per 100 patient years; SBP = systolic blood pressure; LDL = low density li poprotein; HDL = high density lipoprotein

magnitude of change and presence/absence of nausea (additional detail are provided in the publication[23]). In subsequent years, a utility score of –0.061 for each unit of BMI over 25 kg/m^2 was applied in line with the time trade-off (TTO model) analysis from the CODE-2 study derived from the EQ5D index[24]. Utilities were applied in the simulations according to the following assumptions (based on data from the clinical trial of Heine *et al.*[14], 2-year open-label extension studies of exenatide[13] and from the literature on insulin weight gain[8–25]), with weight change referred to as a percentage change from baseline:

- In the clinical trial, incidence was defined as any report of nausea over the 26-week period. For the model, first year of exenatide treatment was associated with 3% weight loss, and 57.1% of patients experienced nausea for the first 6-month period as observed in trial. In the second 6-month period, no nausea disutility was applied.
- Subsequent years of exenatide treatment were associated with a weight loss of 5% and no nausea.
- First year of insulin glargine treatment was associated with a 3% increase in weight, and 8.6% of patients experienced nausea for a 6-month period. In the second 6-month period, no nausea disutility was applied.
- Subsequent years of insulin glargine treatment were associated with a 5% weight gain and no nausea.

Discounting, time horizon and perspective

Life expectancy, quality-adjusted life expectancy and future costs were discounted at the recommended rate of 3.5% annually[26]. A time horizon of 35 years was used in the base–case analysis to capture all relevant long-term complications, their associated costs and impact on life expectancy. This approach is in line with published good practice guidelines for cost-effectiveness analyses in healthcare and medicine[27]. The study was conducted from the perspective of a third-party healthcare payer (NHS) in the UK setting.

Sensitivity analyses

Sensitivity analysis was performed on key assumptions used in the base–case analysis: time horizon, discount rate, insulin dose, sustainability of HbA_{1c} effect and (dis)utility value for weight loss (gain) and nausea. All sensitivity analyses reported in this paper were performed assuming a UK price for exenatide equivalent to 100% of the US wholesale price. Changes in HbA_{1c} were analysed by varying the change in HbA_{1c} from the mean value observed in the RCT of exenatide versus insulin glargine to the corresponding upper and lower limits of the 95% confidence interval of this mean. With respect to insulin it was assumed in the base-case that patients received 25 IU in the first year and 40 IU thereafter delineated as the typical daily dose of insulin by the World Health Organization, in the sensitivity analysis the impact of this was assessed by assuming patients continued on 25 IU throughout. The impact of including test strip costs for the monitoring of blood glucose levels was investigated, which was estimated to be £24.16 per month on exenatide and £38.48 per month on glargine, based on the results of a recent study of predicted test strip usage in the UK[28]. The impact of time horizon on cost and clinical benefits was assessed by varying the time horizon between 0 and 35 years (for purposes of brevity we report only values at 5, 10 and 15 years in this paper). Similarly, the impact of applied discount rates was assessed by varying the rates between 0 and 6%.

Table 3. *Cost per event or state used in the analysis*

Description of event or state	Annual costs (£)	Reference
Myocardial infarction, year of event	4598	55
Myocardial infarction, each subsequent year	757	55
Angina, year of onset	2385	55
Angina, each subsequent year	788	55
Congestive heart failure, year of onset	2659	55
Congestive heart failure, each subsequent year	932	55
Stroke, fatal	3548	55
Stroke, year of event	2813	55
Stroke, each subsequent year	532	55
Peripheral vascular disease, onset	2450	56*
Haemodialysis	26 073	57
Peritoneal dialysis	19 577	57
Kidney transplant, first year	20 500	58
Kidney transplant, each subsequent year	6749	58
Retinal photocoagulation	707	57
Severe vision loss/blindness, year of onset	914	55
Severe vision loss/blindness, each subsequent year	295	55
Cataract extraction	1629	55
Cataract annual follow-up	110	55
Neuropathy, onset	997	56*
Uninfected ulcer	1312	59
Infected ulcer	1345	59
Gangrene	2160	59
Amputation, year of event	9201	55
Amputation, prosthesis	585	55
Major hypoglycaemic event	391	60
Ketoacidosis	852	61
Annual cost of aspirin	65	MIMS (75 mg Angettes t.d.s.)
Annual cost of statins	386	MIMS (20 mg Crestor o.d.)
Annual costs of ACE-I	235	MIMS (25 mg Captopril t.d.s.)
Annual costs of exenatide (100% US cost)	660.67	Eli Lilly
Annual costs of insulin glargine at 25 IU/day	361.76	Eli Lilly
Annual costs of insulin glargine at 40 IU/day	484.62	Eli Lilly
Costs of screening for retinopathy	28	62
Costs of screening for nephropathy	33	63
Costs non-standard ulcer treatment	18	MIMS (Regranex 12 g per year)

*Assuming one hospital admission at onset for investigation of symptoms; ACE-I, angiotensin converting enzyme inhibitor; MIMS, MIM Monthly Index of Medical Specialties. Costs are expressed in pounds sterling (£), 2004 values

One attribute of exenatide that has been demonstrated in animal models is the stimulation of pancreatic cell generation, which in diabetes patients could potentially result in stabilisation of diabetes or delayed progression due to increased insulin synthesis[29]. This hypothesis is supported by 2-year follow-up data that shows stabilisation of HbA_{1c} levels in patients receiving exenatide[13]. To assess the potential impact of this on simulation outcomes, sensitivity analysis was performed assuming a 2-year delay in progression of HbA_{1c}, such that with exenatide treatment, patient HbA_{1c} was stable for 2 years before following the progressive increase observed in the UKPDS trial. This was further investigated by stabilising HbA_{1c}, i.e. no increase over time, for the remainder of the patient's life in the exenatide arm.

The impact of the base–case assumptions relating to disutilities as applied to changes in body weight with and without nausea was assessed by applying the disutilities reported by the CODE-2 study (TTO model) throughout the entire simulation period. The impact of assumptions made with respect to change in body weight were tested in two ways; firstly by projecting outcomes using the corresponding upper and lower limits of the 95% confidence interval of the reported mean weight loss, and secondly by assuming no changes in SBP and lipid levels with exenatide since these changes appear to be associated with weight loss and impact directly on diabetes complication event rates in the CORE Diabetes Model.

Statistical methodology

The analysis was performed using a non-parametric bootstrapping approach in which the progression of diabetes was simulated in 1000 patients and run through the model 1000 times to calculate the mean and standard deviation of life expectancy, quality-adjusted life expectancy and costs using second order Monte Carlo simulation[30]. The mean values of incremental cost and incremental effectiveness from the 1000 simulations were plotted on the cost–effectiveness plane, and these data were used to generate acceptability curves by calculating the proportion of points below a range of willingness to pay thresholds.

Results

Long-term clinical outcomes

In the base–case analysis, treatment with exenatide was associated with improvements in life expectancy and quality-adjusted life expectancy compared to insulin glargine (Table 4). Undiscounted life expectancy was improved by 0.105 (0.356) years and discounted (by 3.5% per annum) life expectancy by 0.057 (0.213) years with exenatide versus glargine (mean (standard deviation)). Taking quality of life into account, exenatide was associated with an improvement of 0.442 (0.146) quality-adjusted life years (QALYs) compared to insulin glargine. Quality-adjusted life expectancy was projected to be 7.39 (0.11) QALYs and 6.95 (0.10) QALYs in the exenatide and glargine arms respectively (discounted values). The difference between incremental life expectancy and quality-adjusted life expectancy was largely attributable to the difference in body weight changes between the two treatments and the impact that body weight has on quality of life.

Evaluation of the cumulative incidence of diabetes-related complications over patients' lifetimes indicated that treatment with exenatide was associated with a lower cumulative incidence of most cardiovascular disease complications and cardiovascular disease-related death than treatment with glargine (Table 5). In contrast, the cumulative incidence of renal disease and diabetic foot complication was greater with exenatide than with insulin glargine, due to the marginal benefit in terms of glycaemic control associated with the latter.

Long-term direct medical costs

As no wholesale or public price for exenatide in the UK was available at the time of analysis, lifetime direct cost estimates were created based on the current (2005) US wholesale price for exenatide (converted to pounds sterling), as well as prices based on 80%, 60%, 40% and 20% of this value (as diabetes pharmaceutical prices are typically lower in the UK than in the USA). Calculation of lifetime direct medical costs (pharmacy plus complication costs) based on these values produced lifetime cost estimates in the exenatide arm of £29 401 (100% of US value), £26 704 (80%), £24 006 (60%), £21 308 (40%) and £18 611 (20%) compared to a value of £19 489 in the glargine arm (Table 6). Evaluation of incremental cost values showed that exenatide treatment was more expensive than glargine in the 100% (£9912), 80% (£7215), 60% (£4517) and 40% (£1820) of US costs scenarios but was cost saving by approximately £878 in the 20% scenario.

Long-term cost-effectiveness

Calculation of incremental cost-effectiveness ratios (ICERs) for exenatide versus glargine demonstrated

Table 4. *Summary of base–case results: exenatide versus insulin glargine using 100% of US cost for exenatide*

Outcome	Exenatide	Insulin glargine	Difference
Undiscounted life expectancy (years)	14.62 (0.16)	14.51 (0.15)	0.105 (0.356)
Discounted life expectancy (years)	10.66 (0.16)	10.61 (0.15)	0.057 (0.213)
Quality-adjusted life expectancy (QALYs)	7.39 (0.11)	6.95 (0.10)	0.442 (0.146)
Direct medical costs (£)	29 401 (676)	19 489 (636)	9 912 (891)
ICER	£22 420 per QALY gained		

QALY = quality-adjusted life years; ICER = incremental cost-effectiveness ratio. Values shown are means with standard deviation in parentheses. Values are expressed as means from 1000 cohorts each of 1000 patients

Table 5. *Cumulative incidence of diabetes-related complications and cardiovascular-related mortality in the base–case simulation*

Complication	Cumulative incidence diabetic complications (%)*		
	Exenatide	Insulin glargine	Difference
Proliferative diabetic retinopathy	2.41 (0.47)	2.33 (0.46)	0.08
Severe vision loss	8.82 (0.92)	8.89 (0.91)	0.14
Microalbuminuria	37.96 (1.48)	37.91 (1.55)	0.05
Gross proteinuria	13.47 (1.04)	13.31 (1.11)	0.17
End-stage renal disease	4.35 (0.65)	4.27 (0.63)	0.08
First foot ulcer	27.17 (1.42)	27.20 (1.39)	–0.03
First amputation due to an ulcer	6.62 (0.87)	6.75 (0.86)	–0.13
Congestive heart failure	33.28 (1.46)	33.81 (1.58)	–0.53
Myocardial infarction	31.35 (1.53)	31.96 (1.44)	–0.61
Stroke	14.52 (1.11)	15.10 (1.15)	–0.57
Congestive heart failure, death	18.49 (1.23)	18.74 (1.27)	–0.25
Myocardial infarction, death	22.57 (1.46)	22.89 (1.23)	–0.32
Stroke, death	5.13 (0.66)	5.25 (0.74)	–0.12

*Cumulative incidence of complications over patient lifetimes expressed as a mean percentage from 1000 cohorts each of 1000 patients. Apparent discrepancies in arithmetic are due to rounding.

Table 6. *Lifetime direct medical costs and cost-effectiveness of exenatide versus insulin glargine in the UK setting using different prices for exenatide*

Cost of exenatide as a percentage of US cost	Lifetime direct medical costs – exenatide	ICER Cost (£) per QALY gained
100%	29 401 (676)	22 420
80%	26 704 (653)	16 318
60%	24 006 (632)	10 217
40%	21 308 (613)	4116
20%	18 611 (594)	DOMINANT

that, in all five of these cost scenarios, exenatide would be considered to represent good value for money by commonly accepted standards in the UK (Figure 1). Using the range of exenatide cost values, evaluation of cost-effectiveness showed that exenatide is likely to fall in a range between dominant (cost and life saving at 20% of the US price) and highly cost-effective with an ICER of £22 420 per QALY gained (100% of US price) versus glargine. Using this price range approach, it was possible to ascertain that treatment with exenatide would become dominant to glargine at UK below approximately 27% of the 2005 US wholesale price. When the ICER was calculated based on life expectancy (as opposed to quality-adjusted life expectancy), the value was £173 936 per life year gained for exenatide versus glargine at 100% of the US price.

The data from the 100% cost scenario were used to create an acceptability curve to assess the likelihood of exenatide being cost-effective over a range of willingness to pay values in the UK setting. This analysis indicated that, with a willingness to pay of £30 000 per QALY gained (which is commonly quoted as the threshold representing good value for money in the UK setting), there was an 80% likelihood that exenatide would be considered cost-effective (with costs equal to 100% of the US price); i.e. 80% of the 1000 iterations (each in a cohort of 1000 patients) indicated that exenatide would be associated with an ICER below this threshold (Figure 2). When this approach was repeated using only life expectancy values (i.e. not taking into account patients' quality of life), only 8% of values were below the £30 000 per life year gained threshold at 100% of the US price.

Sensitivity analyses

Sensitivity analyses, based on the 100% of US price scenario, demonstrated that ICERs were most sensitive to variation in the disutility values applied for weight change and nausea (Table 7). Variations in key assump-

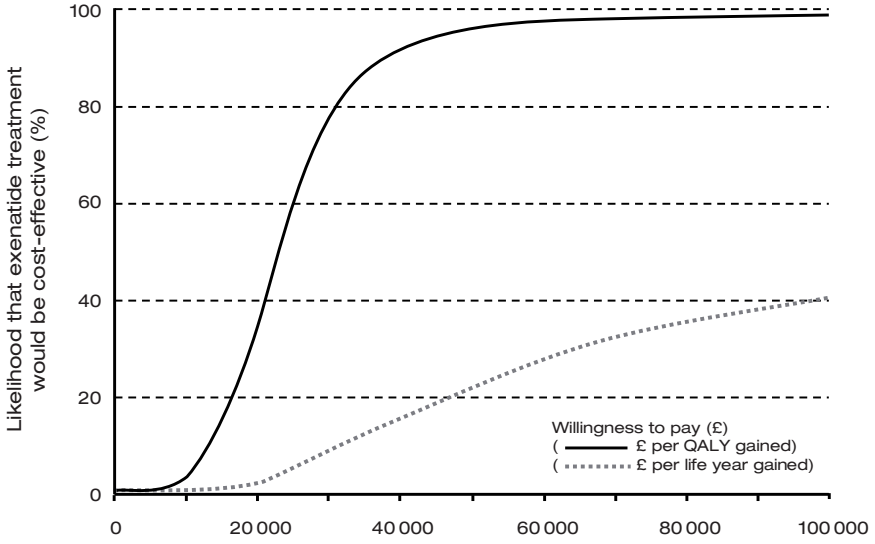

Figure 1. *Cost-effectiveness of exenatide versus insulin glargine at various prices for exenatide based upon a percentage of US wholesale cost*

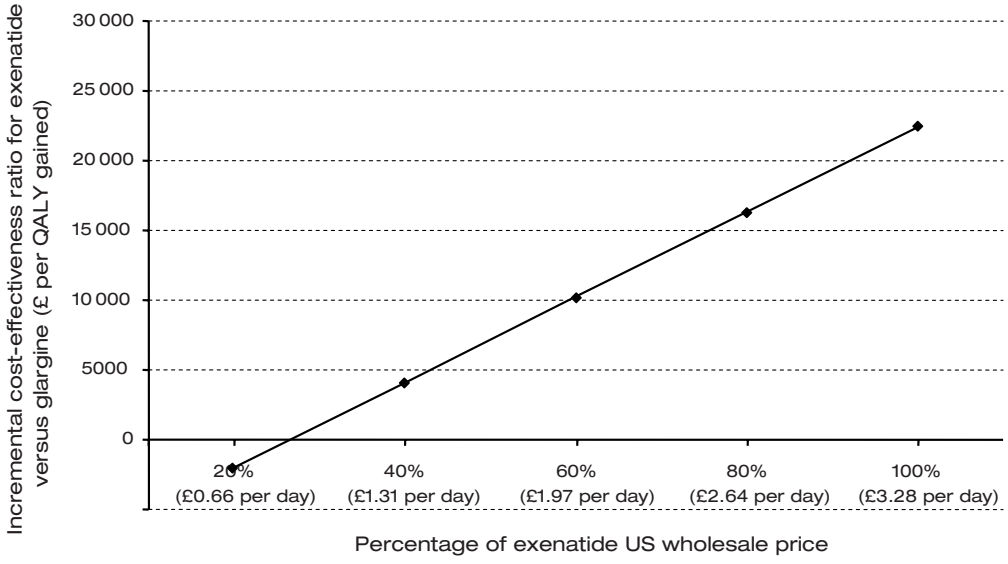

Figure 2. *Acceptability curve for exenatide versus insulin glargine in the base–case scenario at 100% of US cost for exenatide*

tions including change in HbA_{1c}, body weight, long-term HbA_{1c} stabilisation, daily dose of insulin glargine and discount rates had little impact on the relative results. Shorter time horizon failed to capture many of the long-term benefits associated with exenatide treatment (most notably CVD events avoided), and therefore smaller improvements were observed in terms of quality-adjusted life expectancy. However, patients accumulated less medication costs at the shorter time horizons investigated and, as a result, ICERs at 5-, 10- and 15-year time horizons were comparable to those reported in the base-case. When the disutility values for weight change were substituted with those reported from the CODE-2 study, which were smaller but do not make any adjustments for nausea, the ICER for exenatide versus insulin glargine increased to £39 763 per QALY gained for exenatide versus insulin glargine (100% of the US price) (compared to £22 420 per QALY gained in the base-case). In the 80%, 60% and 40% exenatide cost scenarios, ICERs with use of CODE-2 TTO utilities were in the range £7000 to £28 000 per QALY gained.

Discussion

We have used the previously published CORE Diabetes Model to analyse long-term economic and clinical outcomes that can be expected with the uptake of exenatide versus insulin glargine in patients failing to achieve adequate control with OADs in the UK setting. Because of between-country differences in terms

Table 7. *Summary results of the sensitivity analyses of exenatide versus insulin glargine*

Assumption	Quality-adjusted life expectancy (QALYs)			Lifetime direct medical costs (£)			Outcome/ICER (£ per QALY gained)
	Exenatide	Insulin glargine	Difference	Exenatide	Insulin glargine	Difference	
Base-case, 100% US price	7.395 (0.110)	6.953 (0.099)	0.442	29 401 (676)	19 489 (636)	9912	22 420
Upper limit in HbA_{1c} change	7.462 (0.113)	6.953 (0.099)	0.509	29 270 (695)	19 489 (636)	9781	19 226
Lower limit in HbA_{1c} change	7.368 (0.105)	6.953 (0.099)	0.415	29 582 (738)	19 489 (636)	10 093	24 309
Patient taking 25 IU insulin throughout	7.395 (0.110)	6.953 (0.099)	0.442	29 401 (676)	18 596 (629)	10 805	24 439
5-year time horizon	3.115 (0.024)	2.937 (0.023)	0.178	8183 (164)	4298 (155)	3884	21 773
10-year time horizon	5.226 (0.051)	4.953 (0.051)	0.273	15 613 (316)	9006 (306)	6606	24 224
15-year time horizon	6.471 (0.071)	6.133 (0.075)	0.338	21 558 (452)	13 201 (447)	8358	24 745
Discount rate 0%	9.781 (0.170)	9.415 (0.162)	0.366	44 560 (1 266)	30 804 (1 148)	13 756	37 586
Discount rate 6%	6.253 (0.085)	5.773 (0.074)	0.479	22 889 (475)	14 748 (475)	8141	16 980
HbA_{1c} creep after 2 years	7.456 (0.107)	6.953 (0.099)	0.504	29 199 (701)	19 489 (636)	9701	19 283
No HbA_{1c} creep	7.732 (0.120)	6.953 (0.099)	0.779	27 394 (610)	19 489 (636)	7905	10 147
CODE-2 TTO utilities for weight	7.305 (0.106)	7.054 (0.096)	0.251	29 401 (676)	19 489 (636)	9912	39 763
Including test strip costs for blood glucose monitoring	7.395 (0.110)	6.953 (0.099)	0.442	30 512 (685)	21 249 (649)	9263	20 950
Upper limit in body weight change	7.395 (0.110)	6.953 (0.099)	0.442	29 415 (676)	19 489 (636)	9926	22 437
Lower limit in body weight change	7.396 (0.111)	6.953 (0.099)	0.443	29 385 (703)	19 489 (636)	9896	22 346
No change in SBP with exenatide	7.339 (0.104)	6.953 (0.099)	0.386	29 590 (741)	19 489 (636)	10 101	26 144
No change in lipids with exenatide	7.363 (0.105)	6.953 (0.099)	0.410	29 332 (648)	19 489 (636)	9843	23 996

of patient management and treatment costs, where possible, we have used UK specific data to generate the most realistic evaluation. In the absence of exenatide prices for the UK and based on the assumption that diabetes pharmaceutical prices are typically lower in the UK than in the US, we used a range of exenatide cost scenarios in the base-case between 20% and 100% of the US wholesale price. It was anticipated that any future UK price for exenatide would fall within this range and would be captured in the present analysis. Compared to long-acting insulin glargine, the model projections indicate that use of exenatide is associated with improvements in life expectancy, quality-adjusted life expectancy and cumulative incidence of diabetes-related cardiovascular complications. The increased direct costs associated with use of exenatide over patient lifetimes amount to between £9912 and £1820 based on a cost for exenatide between 100% and 40% of the current US price, whilst at 20% of US price exenatide is associated with cost savings of £878 compared to insulin glargine. Taking into account the improvement in quality-adjusted life expectancy associated with exenatide, resulted in ICER values of between £22 420 and £4116 per QALY gained and corresponding to exenatide prices between 100% and 40% of current US price. In the 20% scenario, treatment with exenatide was dominant to glargine. These data suggest that treatment with exenatide would represent good value for money versus insulin glargine in patients with type 2 diabetes, by generally accepted standards in the UK setting.

A potential limitation of the analysis presented here is that the pharmacy costs for exenatide were based on the US wholesale price. However, pricing (and indeed approval) for exenatide in the UK has as yet not been announced, and the aim of this report was to provide a timely and realistic indication as to the cost-effectiveness of exenatide in the UK setting and hence the appropriateness of prescribing this therapy option in the future. Further analyses should be performed if/when a UK wholesale or public price for exenatide becomes available. In the assessment of quality-adjusted life expectancy in the present study, we used a combination approach involving recently published disutilities associated with body weight and nausea from the UK setting for the first 2 years of the simulation when patients were experiencing changes in body weight and possible nausea. Although other sources of body weight or BMI utility values exist, the values used in the present analysis from the study by Matza *et al.*, using the standard gamble method, are the most appropriate for the present analysis as they are from the UK and use the specific percentage of weight loss and weight gain from the exenatide and insulin glargine clinical trial data. Moreover, the disutility of nausea was accounted for in the Matza *et al.* study[23]. Further, given that changes in body weight and nausea were commonly seen with both exenatide and insulin glargine, it would appear appropriate that these utilities be included in any projected outcome encompassing quality of life. Sensitivity analysis investigating utilities associated with BMI showed that using the utility scores from CODE-2 for the entire duration of the simulation produced an ICER of approximately £39 763 per QALY gained for exenatide versus glargine. However, it is noteworthy that the CODE-2 BMI utility value refers to set levels of BMI rather than changes in body weight, and may therefore be less suitable than the values from Matza *et al.* in terms of capturing the impact of changes in body weight on quality of life during the first 2 years on treatment. Moreover, selecting the BMI utility score from the TTO model from CODE-2 was a much more conservative approach than the alternative visual analogue scale (VAS) model score reported in the same publication[24]. Indeed, the utility scores reported by Matza *et al.* appear relatively conservative compared with the VAS score from CODE-2 (–0.29 per unit of BMI over 25).

A number of recent studies have provided evidence that there is an inverse relationship between body weight and quality of life utility[24,31–43]. This could potentially have important implications for modelling studies in diabetes, where a number of interventions are associated with weight gain, particularly in cases where the interventions being compared have different effects on body weight. However, the studies published to date span a wide range of methodologies and reported utility values, and it may well be that more research is required to identify the most appropriate values for individual patient populations before incorporating body weight changes/levels into the assessment of quality-adjusted life expectancy becomes commonplace. In addition to directly influencing patients' quality of life, BMI was modelled as an independent risk factor for the development of congestive heart failure in the simulations as part of the regression function described by Kannel *et al.*[44]. None of the other risk formulae used to assess cardiovascular risk in the model (as described previously by Palmer *et al.*[15]) incorporated BMI as an independent risk factor.

A possible criticism of this modelling analysis is that it was based on the results of single clinical trial of exenatide versus glargine. A number of large clinical trials have been completed with exenatide in addition to the insulin glargine comparator study described in the current report[9–11,45–47]. These trials range in duration from 16 to 52 weeks, and were conducted in type 2 diabetes patients adjunctive to existing therapy with metformin, sulfonylurea, thiazolidinediones, or their combinations. In general, the effects that were seen in the exenatide–

insulin glargine comparator study were very representative of the effects observed in these other trials. Of particular note with respect to the present analysis, is the fact that in general exenatide was associated with modest effects on cholesterol, triglycerides and blood pressure that trend toward clinically significant improvements in these cardiovascular risk factors in all of the trials. In open label extensions of the pivotal phase III clinical trials for exenatide (these are the same extension studies from which the 2-year data in the manuscript are derived), patients receiving 82 weeks of exenatide treatment exhibited statistically and clinically significant reductions in triglycerides, systolic and diastolic blood pressure, and increases in HDL-cholesterol[48]. One possible interpretation of these observations is that, in the controlled clinical trials, follow-up was not of sufficient duration to demonstrate the statistically significant effects seen in the long-term extension studies. Consistent with this interpretation, in the longest controlled clinical trial cited above, exenatide treated patients demonstrated statistically significant increases in HDL cholesterol, statistically significant reductions in systolic and diastolic blood pressure, and favourable changes in lipoprotein particle size at 52 weeks.

Another potential drawback of the present analysis is that it was based on a trial in which a simplified insulin titration schedule was used, and this may have contributed to lower insulin doses at study end, when compared to other published large-scale randomised clinical trials of insulin glargine[4,49–52]. Interestingly, the mean reduction in HbA_{1c} in the exenatide comparator trial (–1.1%) was at the high end of the range of reductions observed in previous insulin glargine trials with comparable study designs (ranging from –0.4 to –1.0% for 28–52 weeks)[49–52], with the exception of the Treat-to-Target trial (–1.65% at 24 weeks)[4]. In the Treat-to-Target report, Riddle *et al.* described a number of factors to explain the magnitude of the HbA_{1c} decrease observed, including an ambitious titration target combined with a protocol for encouraging patient adherence. Although problematic to compare across trials, the Treat-to-Target trial also reported a higher incidence of symptomatic (13.9 events per year) and nocturnal hypoglycaemia (4.0 events per year) and slightly greater weight gain (+3.0 kg) than observed in the present trial. Moreover, patients in the Treat-to-Target trial started from a significantly higher baseline HbA_{1c}, but the mean HbA_{1c} achieved at week 26 in the Treat-to-Target trial (6.9%) was not greatly different from the mean value achieved in the exenatide comparator study (7.1%). Importantly, a meta-analysis of phase III/IIIb controlled trials comparing insulin glargine to NPH insulin in 1142 adults with type 2 diabetes, including the Treat-to-Target study, reported an average HbA_{1c} change associated with insulin glargine from a baseline of 8.8 ± 1.1% to 7.8 ± 1.3% (mean ± SD, trial end points ranged from 24–28 weeks)[53]. The different titration schedule employed in some of the other published treat to target studies is an important consideration; however, in general, based on previously published data described above, one might not expect huge HbA_{1c} gains to be achieved, but might predict more substantial weight gain and hypoglycaemia to develop, with a more aggressive titration schedule.

It is perhaps noteworthy that the modelling analysis did not capture the differential drop-out rates from the clinical trial. During the trial, of the 551 patients who participated, 19.4% of those receiving exenatide and 9.7% of those receiving insulin glargine withdrew[54]. For the purposes of clarity and because the aim of the modelling analysis was to directly compare the cost-effectiveness of treatment with exenatide versus insulin glargine, we did not model patients switching treatment after withdrawal. However, working on the assumption that patients withdrawing from the exenatide arm would start treatment with insulin glargine and therefore experience the clinical effects and accumulate the costs of that treatment (as opposed to the costs and effects of exenatide), it is unlikely that accommodating withdrawals in the modelling analysis would substantially change the outcomes or conclusions of the study.

Due to the rapidly increasing number of individuals with type 2 diabetes world-wide, realistic and country specific assessments of the long-term economic and clinical implications of new treatments need to be considered if optimal treatment is to be provided to all patients. We have used the CORE Diabetes Model to project the long-term outcomes associated with the use of exenatide versus insulin glargine amongst type 2 diabetes patients sub-optimally controlled with combination oral therapy. As with all modelling analyses, there is a degree of uncertainty surrounding long-term extrapolation, albeit based on the best available published data sources, of short-term clinical trial results, and this should be noted when interpreting the conclusion of any long-term modelling analysis. In the present study, based on the findings of a recent clinical trial published by Heine *et al.*[14], use of exenatide was projected to yield improvements in life expectancy and quality-adjusted life expectancy when compared to insulin glargine. Additionally, in this model simulation, the use of exenatide was also associated with reduced cumulative incidence of cardiovascular-related complications and is likely to represent a clinically and economically attractive treatment option in the UK setting.

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