

# Estimating the Long-Term Cost-Effectiveness of Exenatide in the United States: An Adjunctive Treatment for Type 2 Diabetes Mellitus

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## ABSTRACT

**Objectives:** This analysis provides an early estimate of the cost-effectiveness of adjunctive exenatide in treating type 2 diabetes mellitus in the United States. Data from pivotal phase III 30-week clinical trials and 52 weeks of their subsequent open-label extension studies (i.e., 82 weeks total) were used to project the effects of 30 years of adjunctive exenatide treatment.

**Methods:** This analysis utilized a published and validated Markov model incorporating Monte Carlo simulation with tracker variables to estimate the clinical and cost outcomes of adding exenatide to a background of metformin and/or sulfonylurea treatment, with the effects of 30 years of adjunctive exenatide treatment (projected from data from 82 weeks of exenatide treatment) compared with no additional treatment beyond metformin and/or a sulfonylurea. Sensitivity analyses were performed on key clinical assumptions, discount rates, and shorter time horizons.

**Results:** The base-case scenario (30 years of exenatide) yielded an incremental cost-effectiveness ratio (ICER) of \$35,571. We found that shortening the time horizons and removing the lipid effects of exenatide had the greatest negative impact on ICERs when performing sensitivity analysis.

**Conclusions:** Our analysis demonstrated that exenatide used for 20 or 30 years compared with no additional treatment beyond metformin and/or a sulfonylurea is cost-effective in the adjunctive treatment of type 2 diabetes with an ICER less than \$50,000 per life-year gained. Sensitivity analyses suggest that, in addition to sustained reduction in HbA<sub>1c</sub>, the added clinical effects of improved lipid values, systolic blood pressure, and reduced body mass index all positively contributed to the cost-effectiveness of exenatide.

**Keywords:** BYETTA, cost-effectiveness, exenatide, modeling, type 2 diabetes.

## Introduction

Type 2 diabetes is a chronic disease characterized by hyperglycemia caused by progressive failure of the pancreatic  $\beta$  cells and insulin resistance [1,2]. One of the earliest manifestations of  $\beta$ -cell dysfunction is a loss of glucose responsiveness, which occurs many years before the diagnosis of diabetes. It is estimated that approximately 50% of  $\beta$ -cell function remains at the time of diagnosis, with a further loss of approximately 5% annually thereafter [3]. No existing therapy has conclusively been shown to halt this progressive decline in  $\beta$ -cell function. In addition to declining  $\beta$ -cell function, weight can also contribute to the pathogenesis of type 2 diabetes, with the risk of developing type 2 diabetes increasing exponentially with body-mass index (BMI) [4,5]. In contrast, losing even modest amounts of weight has been shown to delay the

progression from glucose intolerance to overt diabetes [6]. For those diagnosed with diabetes, 80% to 90% are overweight, more than 90% exhibit insulin resistance, and, by definition, 100% have  $\beta$ -cell dysfunction [2,5,7]. Given these key associations, weight control is a cornerstone of diabetes management, and progressive  $\beta$ -cell dysfunction is a key target for new therapies.

Current clinical treatment recommendations for type 2 diabetes generally involve a stepwise approach. Education centers on exercise and medical nutritional therapy. If these measures are ineffective, patients are often started on single oral antidiabetic agents, commonly metformin or sulfonylurea [8,9]. These pharmacologic therapies are often initially effective, but frequently become less so over time [9]. Often, additional oral agents are added, and, when these fail, increasing doses of exogenous insulin are required in an attempt to maintain glycemic control [8,9].

Cardiovascular disease accounts for greater than 65% of mortality and morbidity in individuals with diabetes [10,11]. Accordingly, the clinical focus for

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treating diabetes is to address cardiovascular risk factors, such as central obesity, hyperglycemia, dyslipidemia, and hypertension [12,13]. In addition to the beneficial effects of managing cardiovascular risk factors, sustained weight loss and glycemic management may lessen the burden of depression, which is nearly three times as prevalent in people with diabetes as in the general population [14]. Any weight reduction may offer other health benefits, because obesity is associated with many other diseases, including cancer, osteoarthritis, and gall bladder disease [5,12].

The increasing incidence of diabetes mellitus represents one of the most serious health challenges facing the United States. Diabetes and its complications have been estimated to cost over \$130 billion each year, approximately 10% of total medical care costs in the United States [15]. Targeting diabetes care resources to medical interventions that address the core pathophysiologic defects in a cost-effective manner is crucial for optimizing the use of health-care dollars and for managing this epidemic both now and in the future.

The Academy of Managed Care Pharmacy has recommended guidelines that call for the economic evaluation of new pharmaceutical compounds to aid managed care organizations in determining formulary placement [16]. Although long-term comparative data with standard of care treatments are the most desirable analyses from a formulary decision-making standpoint, the available data regarding new pharmaceutical compounds are usually limited to placebo-controlled clinical trials of relatively short duration, which are then used to support new drug applications. Economic models can be a useful tool for health-care decision-makers by utilizing clinical trial data to estimate the long-term clinical and economic impacts of a specific medical intervention.

Exenatide (exendin-4) (BYETTA, Amylin Pharmaceuticals, Inc., San Diego, CA), which is administered subcutaneously twice daily b.i.d. before the morning and evening meals, is the first in a class of antidiabetic

therapies called incretin mimetics (approved by the United States Food and Drug Administration on April 28, 2005). Exenatide is a peptide that exhibits several of the glucoregulatory properties observed with the naturally occurring incretin, glucagon-like peptide-1 (GLP-1). Circulating concentrations of GLP-1 are decreased in people with type 2 diabetes [17]. The glucoregulatory properties of exenatide are multiple and result in direct restoration of acute  $\beta$ -cell function (restoration of first-phase insulin secretion and enhancement of glucose-dependent insulin secretion) and a decreased glucose load presented to the failing  $\beta$  cell (suppression of inappropriately elevated glucagon secretion, slowing of gastric emptying, and reduction of food intake). The direct  $\beta$ -cell effects of immediately restoring first-phase insulin secretion and improving markers of  $\beta$ -cell function (proinsulin:insulin ratio) over the longer term indicate that this therapy targets a core defect of diabetes:  $\beta$ -cell dysfunction [17,18]. Of note, the enhancement of insulin secretion mimics natural physiology, because it is glucose-dependent. That is, insulin secretion is only enhanced when glucose concentrations are elevated. Importantly, in addition to its  $\beta$ -cell effects, exenatide also causes a reduction in food intake [19]. These combined effects position exenatide as the first therapy in diabetes to offer improved glycemic control and significant weight reductions over the longer term.

In three phase III clinical trials of exenatide in patients with type 2 diabetes who did not achieve HbA<sub>1c</sub> less than or equal to 7% with metformin and/or sulfonylureas, 30 weeks of treatment with 10  $\mu$ g exenatide b.i.d. resulted in a mean HbA<sub>1c</sub> reduction of approximately 1.0%, along with a mean weight reduction of approximately 2 kg (Table 1) [18,20,21]. No significant treatment differences were observed for subgroups categorized by age, sex, or race [22]. The most frequent adverse event was mild to moderate nausea, which occurred predominantly at the initiation of therapy and was ameliorated by initiating therapy at 5  $\mu$ g exenatide b.i.d. before titrating to 10  $\mu$ g

**Table 1** Summary of HbA<sub>1c</sub> and weight changes in the exenatide 30-week pivotal placebo-controlled trials in patients treated on background therapies of metformin (MET) and/or sulfonylureas (SFU)

Parameter	Population	N	Placebo	5 $\mu$ g b.i.d.	10 $\mu$ g b.i.d.	Reference
$\Delta$ HbA <sub>1c</sub> by concomitant treatment	MET	336	+0.1%	-0.4%	-0.8%	[18]
	SFU	377	+0.1%	-0.5%	-0.9%	[20]
	MET + SFU	733	+0.2%	-0.6%	-0.8%	[21]
$\Delta$ HbA <sub>1c</sub> for baseline HbA <sub>1c</sub> <9%	SFU	239	+0.1%	-0.4%	-0.7%	[20]
	MET + SFU	513	+0.3%	-0.4%	-0.5%	[21]
$\Delta$ HbA <sub>1c</sub> for baseline HbA <sub>1c</sub> $\geq$ 9%	SFU	138	+0.1%	-0.6%	-1.2%	[20]
	MET + SFU	220	0.0%	-0.9%	-1.4%	[21]
$\Delta$ Weight by concomitant treatment	MET	336	-0.3 kg	-1.6 kg	-2.8 kg	[18]
	SFU	377	-0.6 kg	-0.9 kg	-1.6 kg	[20]
	MET + SFU	733	-0.9 kg	-1.6 kg	-1.6 kg	[21]
$\Delta$ Weight for baseline BMI <30 kg/m <sup>2</sup>	MET	89	+0.4 kg	-0.5 kg	-2.4 kg	[18]
$\Delta$ Weight for baseline BMI $\geq$ 30 kg/m <sup>2</sup>	MET	247	-0.5 kg	-2.1 kg	-3.0 kg	[18]

BMI, body mass index.

exenatide b.i.d. [18,20,21]. There was also an increased risk of hypoglycemia when exenatide was used in conjunction with a sulfonylurea, but not with metformin. The prescribing information for exenatide thus recommends that when exenatide is added to a sulfonylurea, a reduction in the dose of sulfonylurea may be considered to reduce the risk of hypoglycemia [22]. Another important consideration is that exenatide is not a substitute for insulin in patients who require insulin. Furthermore, there is currently no evidence to support the use of exenatide with insulin.

Patients who continued in optional, open-label extension studies for a total of 82 weeks of exenatide had a sustained mean HbA<sub>1c</sub> reduction (−1.1%) and a progressive mean body weight reduction (−4.4 kg), as well as significant improvements in triglycerides, high-density lipoprotein cholesterol (HDL-C), and diastolic blood pressure [23,24]. These results from 82 weeks of exenatide treatment were used in the present analysis to project the effects of 10, 20, and 30 years of exenatide treatment on background therapy of metformin and/or sulfonylureas. These interim data represent the longest exposure to exenatide treatment to date. Specifically, we determined whether adjunctive exenatide treatment would result in an additional year of life gained for an expenditure of \$50,000 or less. We use this \$50,000 figure for life-year gained (LYG) because that is the threshold that is generally considered cost-effective for medical interventions [25].

## Methods

### Center for Outcomes Research (CORE)

#### Diabetes Model

The CORE Diabetes Model (CDM) has been described and validated in two separate publications in a peer-reviewed journal supplement and is consistent with recently published American Diabetes Association modeling guidelines and principles [26–28]. The CDM is designed to predict the development and progression of type 1 or type 2 diabetes (through separate and distinct modules of the model) over long time horizons ( $\geq 5$  years) using the best available published clinical and epidemiological data. The model has a standard Markov structure, combined with Monte Carlo simulation and tracker variables, which allows for the development and progression of multiple complications within an individual patient, while at the same time overcoming the memory-free properties of basic Markov models. For example, traditional Markov models cannot adjust for changes in risk factors that affect transition probabilities when a patient with diabetes has a myocardial infarction (MI), because the risk of a future MI event is different if the patient survives. Once deceased, patients are not included in the subsequent incidence periods. The transition prob-

abilities for the CDM come from the epidemiological and clinical studies from the published literature, including such landmark studies as the United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT) studies [29,30]. The process of deciding which transition probabilities and risk adjustments to incorporate into the CDM were taken from published resources by a team of health economists and clinicians, as fully described in Palmer et al. 2004 [27].

The CDM design includes 15 submodels that simulate diabetes-related complications (angina, cataract, congestive heart failure, foot ulcer and amputation, hypoglycemia, ketoacidosis, lactic acidosis, macular edema, myocardial infarct (MI), nephropathy, neuropathy, peripheral vascular disease, retinopathy, and stroke) and nonspecific mortality [27]. During a simulation, all submodels run in parallel to allow patients to develop complications concomitantly (where appropriate and documented in peer-reviewed clinical and epidemiological literature). Where published data indicate that the presence of one complication increased the probability of another complication occurring, that increased probability for the second complication was incorporated into the model as time progresses through the simulation exercise.

#### CDM Substantiation

The CDM was validated through 66 separate analyses, which covered the published epidemiological and clinical studies used to create the model (second-order), along with published epidemiological and clinical studies not used to create the model (third-order) [28]. The published clinical and epidemiological studies used to validate the model were selected based on the availability of appropriate outcome data, the quality of the study design, and the availability of appropriate baseline population risk factors, including HbA<sub>1c</sub>, systolic blood pressure, total cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C), triglycerides, and BMI [28]. Secondly, studies were chosen that described a range of type 2 diabetic populations, treatments, product delivery settings, and resulting outcomes [28]. Lastly, published studies were chosen based on the breadth of coverage for specific diabetic complications (e.g., Wisconsin Epidemiological Study of Diabetic Retinopathy for retinopathy outcomes) and time periods (from 1960 to 2003) [28].

#### Exenatide

This economic-modeling study uses data from those 314 patients who completed 82 weeks of treatment with exenatide to project the effects of 30 years of exenatide treatment. The primary objective of the extension phase of the trials was to examine the long-term effects of exenatide (10  $\mu$ g b.i.d.) on glycemic

control (HbA<sub>1c</sub>), safety, and tolerability. Safety end points included adverse events occurring upon or after receiving the first exenatide dose during the placebo-controlled trials through the 82-week period, as well as clinical laboratory tests, physical examination, 12-lead ECG, and vital signs. Change in body weight and fasting lipids were secondary end points.

### Simulation Cohort

The theoretical population of 1000 patients used in this exercise 1000 times was based on patients with type 2 diabetes who did not achieve adequate glycemic control with metformin and/or sulfonylureas and who were subsequently treated with exenatide in addition to their pre-existing oral antidiabetic regimen. Specific demographic characteristics, such as age, sex, race, duration of diabetes, baseline HbA<sub>1c</sub>, and baseline BMI were taken from the same group of patients with type 2 diabetes who completed 82 weeks of treatment in the exenatide open-label extension studies (N = 314) (Table 2). Other characteristics taken from this group of patients included baseline values for cardiovascular risk factors, such as systolic blood pressure, total cholesterol, HDL-C, LDL-C, and triglycerides. There were, however, some characteristics, such as baseline prevalence of diabetes-related diseases and proportion of patients receiving specific treatments relevant to diabetes, which were not available for this exenatide-treated population. Therefore, we used published data for general type 2 diabetes populations for the following characteristics: prevalence of cardiovascular disease, renal disease and retinopathy; proportion of patients treated with angiotension converting enzyme inhibitors, statins, and aspirin; and proportion of patients screened for retinopathy, renal disease, and foot disease.

### Treatment Effects

The clinical effects of exenatide over 82 weeks, including changes in HbA<sub>1c</sub>, lipid parameters, BMI, and systolic blood pressure used in the modeling to project the effects of 30 years of exenatide treatment, are detailed in Table 3. Exenatide showed consistent and sustained reductions over the 82-week treatment period in HbA<sub>1c</sub>, BMI, and triglycerides, coupled with an increase in HDL-C [23,24]. After the initial 82-week exenatide extension phase study data set, long-term changes in HbA<sub>1c</sub> were assumed to follow the UKPDS trend, which demonstrated an annual increase of 0.15%/year [30]. This approach likely underestimates the cost-effectiveness of exenatide, because further clinical data suggest that the reduction in HbA<sub>1c</sub> observed with exenatide over 82 weeks is sustained for at least 2 years [31]. Other parameters, such as systolic blood pressure, BMI and cholesterol, were assumed to not change after week 82. Again, this 82-week data was used to project the effects of 30 years of exenatide treatment. Because

**Table 2** Characteristics of a type 2 diabetes population used in constructing the simulation cohort (based on the 82-week exenatide cohort and published descriptions of type 2 diabetes populations) (N = 314)

Characteristic	Baseline value ± SD	Reference
<b>Patient demographics</b>		
Mean age (years)	56 ± 10	[23]
Duration of diabetes (years)	7 ± 6	[23]
Proportion male	63%	[23]
<b>Risk factors</b>		
HbA <sub>1c</sub> (%)	8.3 ± 1.0	[23]
Systolic blood pressure (mm Hg)	128.6 ± 13.7	[23]
Body mass index (kg/m <sup>2</sup> )	34 ± 6	[23]
Total cholesterol (mg/dL)	185.9 ± 39.3	[23]
High-density lipoprotein cholesterol (mg/dL)	38 ± 9.1	[23]
Low-density lipoprotein cholesterol (mg/dL)	115.1 ± 35.7	[23]
Triglycerides (mg/dL)	239 ± 181.6	[23]
<b>Ethnic group (%)</b>		
White	78	[23]
African American	11	[23]
Hispanic	9	[23]
Asian	1	[23]
Other	1	[23]
<b>Cardiovascular disease (%)</b>		
Stroke	8.4	[41]
Angina pectoris	11.2	[41]
Myocardial infarction	15.0	[41]
Congestive heart failure	11.8	[42]
Atrial fibrillation	0.75	[43]
Left ventricular hypertrophy detected by ECG	4.2	[44]
Peripheral vascular disease	14	[45]
<b>Renal disease (%)</b>		
Microalbuminuria	28.2	[46]
Gross proteinuria	7.6	[46]
End-stage renal disease	0.4	[46]
<b>Retinopathy (%)</b>		
Background diabetic retinopathy	39.0	[41]
Proliferative diabetic retinopathy	3.0	[41]
<b>Other complications (%)</b>		
Peripheral neuropathy	40.0	[47]
Foot ulcer	10.5	[48]
Amputation	2.6	[48]
Cataract	14.0	[41]
Macular edema	4.0	[41]
Severe vision loss	2.2	[41]
<b>Patient management of type 2 diabetes (%)</b>		
Taking angiotension-converting enzyme-inhibitor (ACE-I)/angiotension receptor blocker (ARB)	50.0	[49]
Taking statins	45.0	[50]
Taking aspirin	45.6	[51]
Screened for retinopathy (assumed to be treated with laser if detected)	74.0	[45]
Screened for renal disease (assumed to be treated with ACE-I or ARB if detected)	55.0	[45]
Screened for foot disease	87.0	[45]

the exenatide open-label extension study did not contain a placebo arm, we compared exenatide with a group that received no additional treatment beyond metformin and/or a sulfonylurea and that assumed continued disease progression with no cost and no clinical effect of therapy.

**Table 3** Treatment effects for exenatide: 82-week data summary (used to project effects of 30 years of exenatide treatment)

Intermediate clinical outcome	Change in baseline value $\pm$ SD	Reference
HbA <sub>1c</sub> (%)	-1.1 $\pm$ 1.3	[24]
Systolic blood pressure (mm Hg)	-1.3 $\pm$ 16.4	[24]
Body mass index (kg/m <sup>2</sup> )	-1.5 $\pm$ 2.0	Data on File, Amylin Pharmaceuticals, Inc.
Total cholesterol (mg/dL)	-2.4 $\pm$ 35.1	[24]
High-density lipoprotein cholesterol (mg/dL)	4.6 $\pm$ 7.8	[24]
Low-density lipoprotein cholesterol (mg/dL)	-1.6 $\pm$ 31.9	[24]
Triglycerides (mg/dL)	-39 $\pm$ 153	[24]

### Costs and Perspective

A third-party (Medicare) payer perspective was used for this analysis. Descriptions of the event, state, and other direct medical costs used in this modeling exercise were based on data previously published by Palmer et al. [27]. The costs for treating diabetes-related complications were inflated to 2005 \$US using the consumer price index for the health-care sector [32] and were taken from published resources (Table 4). The cost of exenatide (\$US5.75 per day of therapy, annual cost of \$2099 assuming 365 days of therapy) was the initial published wholesale average cost price from May 2005, while the cost for no addi-

tional treatment beyond metformin and/or a sulfonylurea was assumed to be zero.

### Type 2 Utility Values

Cost-effectiveness was also determined for quality-adjusted life-year (QALY) gained. Utility values to calculate QALY were based on data from patients with type 2 diabetes in the Cost of Diabetes in Europe—Type II diabetes (CODE-2) study, one of the few studies in type 2 diabetes assessing utility values. Specifically, while the entire study evaluated more than 7000 patients with type 2 diabetes in eight European countries, a subset of these patients, 4641 from five

**Table 4** Event, state, and other costs used in the Center for Outcomes Research Diabetes Model expressed in \$US, inflated to 2005 values for the United States

Description of event or state	Cost per event or state (\$)	Reference
Myocardial infarction, year of event	35,065	[52]
Myocardial infarction, each subsequent year	1,938	[52]
Angina, year of onset	6,956	[52]
Angina, each subsequent year	1,797	[52]
Congestive heart failure, year of onset	3,012	[52]
Congestive heart failure, each subsequent year	3,012	[52]
Stroke, year of event	46,434	[52]
Stroke, each subsequent year	15,497	[52]
Peripheral vascular disease, onset	4,410	[53]
End-stage renal disease	42,763	[52]
Retinal photocoagulation	781	[52]
Severe vision loss/blindness, year of onset	3,784	[52]
Severe vision loss/blindness, subsequent years	3,784	[52]
Cataract extraction	2,488	[53]
Neuropathy, onset	382	[52]
Uninfected ulcer	1,658	[54]
Infected ulcer	2,997	[54]
Gangrene	5,847	[54]
Amputation, year of event	31,162	[52]
Amputation, years 2+ after event	1,120	[52]
Ketoacidosis event	12,560	[52]
Major hypoglycemic event	257	[52]
Annual cost aspirin	22	[55]
Annual cost statins (assume simvastatin 10 mg @\$238/100 tablets, inflated to \$US 2005)	888	[55]
Annual costs angiotensin converting enzyme inhibitor (based on 25 mg Captopril <i>Tris In Diem</i> )	399	[56]
Annual costs for exenatide (\$5.75/day of therapy, published wholesale average cost price for Exenatide, published in May, 2005)	2,099	—
No additional treatment comparator cost	0	—
Costs of screening for retinopathy	77	[52]
Costs of screening for microalbuminuria	17	[52]
Costs of screening for gross proteinuria	26	[52]
Costs (monthly) nonstandard ulcer treatment (Regranex)	157	[57]

Capoten (captopril), Bristol Myers Squibb, Princeton, NJ; Regranex gel (beclaplermin), Ortho-McNeil Pharmaceutical, Raritan, NJ; Zocor (simvastatin), Merck and Co., Whitehouse Station, NJ.

countries, responded to the EuroQol EQ-5D questionnaire [33,34]. The questionnaire responses provided a large set of relevant patient data, which were then used to model health-related utility values from both visual analog scale and time trade-off index scores. The CODE-2 analyses reported in this article used said utility values. Of note, these utility values do not account for effects related to weight reductions, and so may not capture the full effects of exenatide on quality of life.

### Time Horizon and Discounting

The simulation was run over a 30-year period, consistent with current guidelines, which recommend that the time horizon be sufficient to capture the development of long-range disease complications [35]. Costs and clinical outcomes were both discounted at 3% per annum, also in accordance with published US recommendations [35]. This discounting adjusts for estimated inflation of health-care costs.

### Sensitivity Analyses

Exploratory simulations were run on shorter time horizons of 10 and 20 years. Annual discount rates of 0% and 6% were also examined. Additional sensitivity analyses were performed on the following clinical parameters: varying the observed HbA<sub>1c</sub> change ( $\pm 20\%$ ), removing the BMI effects, removing the lipid effects, and removing the blood pressure effects. Analyses were also performed with the HbA<sub>1c</sub> changes observed for those patients with baseline HbA<sub>1c</sub> less than 9% as compared with patients with baseline HbA<sub>1c</sub> greater than or equal to 9%. Lastly, the analysis was performed using the week 30 data for the 82-week cohort.

### Probabilistic Sensitivity Analysis

The range of clinical values used in the probabilistic sensitivity analysis was derived from the 82-week exenatide data for the base-case analysis (Table 3). We evaluated the individual contributions of each clinical element of exenatide treatment by removing each of the effects individually, then comparing the resulting incremental cost-effectiveness ratio (ICER) with the base-case ICER. This provides an indication of the relative contribution of each clinical variable to the overall ICER. For example, we removed the BMI

effect (i.e., reductions in body weight) and calculated the ICER without this clinical effect. We then compared this ICER with the base-case ICER. We did the same for changes in lipids (total cholesterol, HDL-C, LDL-C, and triglycerides), as well as for systolic blood pressure, to examine the role of each of these variables in the overall ICER value. In essence, the probabilistic sensitivity analysis was used to value each part of the exenatide profile individually to allow payers to evaluate the relative contribution of each clinical element to the entire product profile.

### Bootstrapping

A nonparametric bootstrapping technique was used to explore uncertainty in clinical and cost outcomes for the CDM simulations [36]. In summary, each transition probability used in the CDM was simulated by applying first-order Monte Carlo simulation techniques to characterize sampling uncertainty [27]. The bootstrap analysis was then performed by simulating costs and outcomes for 1000 theoretical patients, with each patient proceeding through the model 1000 times. The mean costs and outcomes were then calculated from these simulations. This simulation was performed for the base case and repeated for all sensitivity analyses.

## Results

### Base-Case Analysis

The 30-year base-case analysis showed that 30 years of adjunctive exenatide treatment (based on the projected effects from data from 82 weeks of exenatide treatment) in patients with type 2 diabetes not achieving adequate glycemic control with metformin and/or sulfonylureas, compared with a hypothetical no additional treatment arm (i.e., nothing in addition to metformin and/or a sulfonylurea), demonstrated improved clinical outcomes at a higher cost per patient (Table 5). Exenatide demonstrated a mean discounted life expectancy of 9.63 years and mean total costs of \$86,281 per patient, compared with 9.10 years and mean total costs of \$67,531 per patient if no additional treatment were added. The resulting ICER for 30 years of exenatide treatment was \$35,571/LYG (Table 6). When this analysis was repeated for QALY using CODE-2 utility values, the mean discounted life

**Table 5** Summary results for the base-case analysis

30-year time horizon	Exenatide	No additional treatment beyond MET and/or SFU
Total costs as mean (SD) per patient, discounted at 3% annually (\$US)	86,281 (2,401)	67,531 (2,438)
Life expectancy mean (SD) (years)	9.63 (0.18)	9.10 (0.17)
Quality-adjusted life expectancy (34) (years)	6.33 (0.12)	5.81 (0.11)

MET, metformin; SFU, sulfonylurea.

**Table 6** Summary results at 10-, 20- and 30-year time horizons (exenatide compared with no additional treatment)

Time horizon	$\Delta$ Life expectancy (years)	$\Delta$ Quality-adjusted life expectancy (years)	$\Delta$ Costs (\$)	ICER (life expectancy) (\$/year or QALY)	ICER (quality-adjusted life expectancy) (\$/year or QALY)
10-year	0.124	0.193	12,429	100,633	64,538
20-year	0.394	0.429	16,843	42,732	39,219
30-year	0.527	0.519	18,750	35,571	36,133

ICER, incremental cost-effectiveness ratio.

expectancy for exenatide was 6.33 QALY, compared with 5.81 QALY for no additional treatment. The resulting CODE-2 ICER for 30 years of exenatide treatment was \$36,133/QALY (Table 6). A shorter time horizon of 10 years demonstrated a larger ICER and CODE-2 ICER of \$100,633/LYG and \$64,538/QALY, respectively, while a 20-year horizon resulted in an intermediate ICER and CODE-2 ICER of \$42,732/LYG and \$39,219/QALY, respectively.

The cumulative incidence of diabetes complications is described for the 10-, 20-, and 30-year time horizons for both groups to demonstrate which diabetes complications account for greater differences in clinical outcomes over the three simulation periods (Table 7). These data suggest that 30 years of adjunctive exenatide treatment, in addition to metformin and/or sulfonylurea treatment, compared with no additional therapy, may have a meaningful impact on reducing the incidence of MI, eye disease, renal disease, and neuropathy complications over time.

The incremental cost-effectiveness scatter plot displays the difference in mean costs plotted against

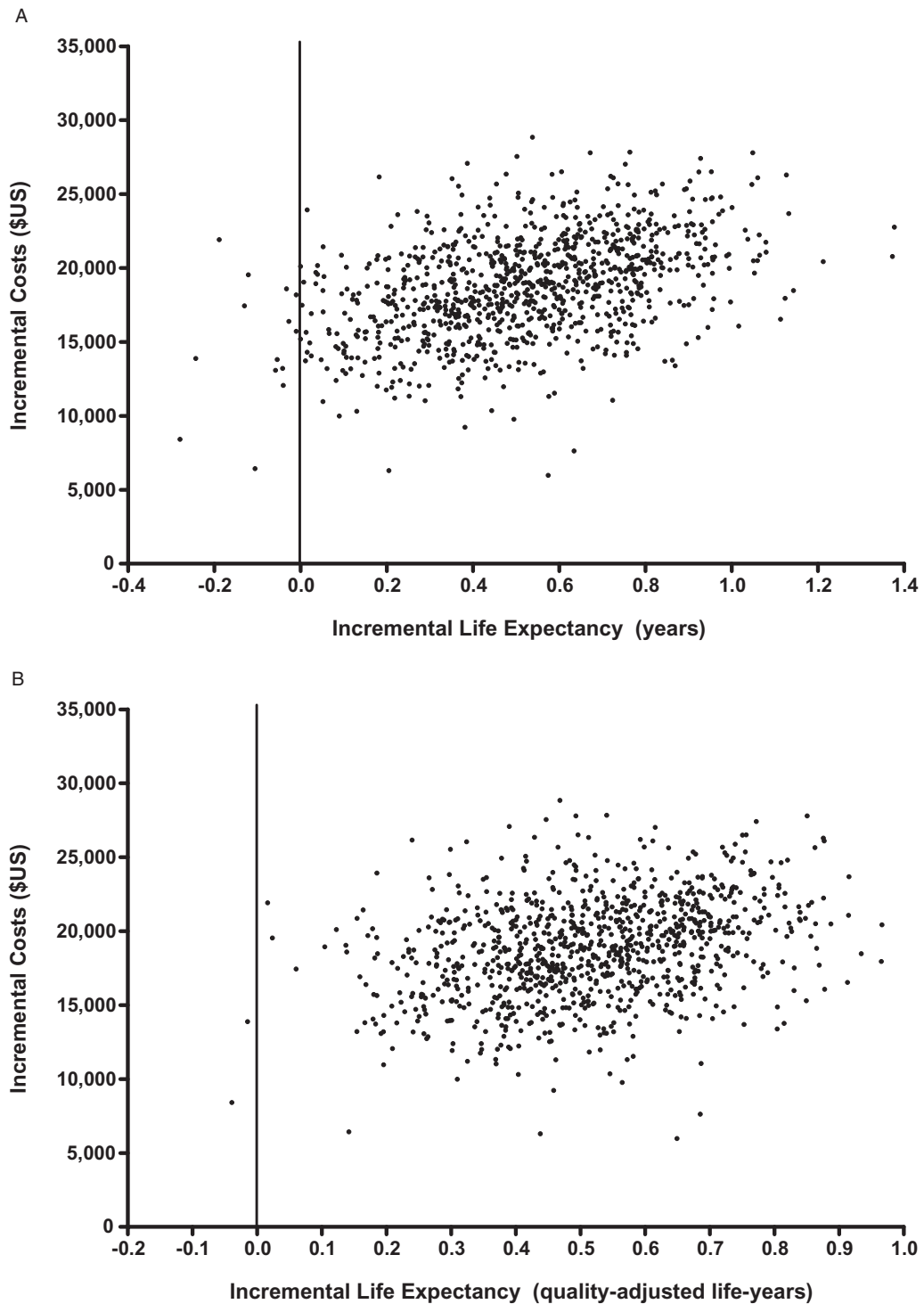
the difference in mean life expectancy between the exenatide and comparison group for 1000 patients both for the base-case situation (Fig. 1A) and for QALY (Fig. 1B). The majority of points in both scatter plots are in the upper right quadrant, indicating that exenatide was both more costly and more effective than adding no additional therapy. When the scatter plots were converted into a cost-effectiveness probability curve (Fig. 2), the probability that the treatment cost to obtain an additional year of life with exenatide would be \$50,000 or less was 74% for the base case and 81% for QALY. These were in comparison with the theoretical no additional treatment option.

#### Sensitivity Analysis

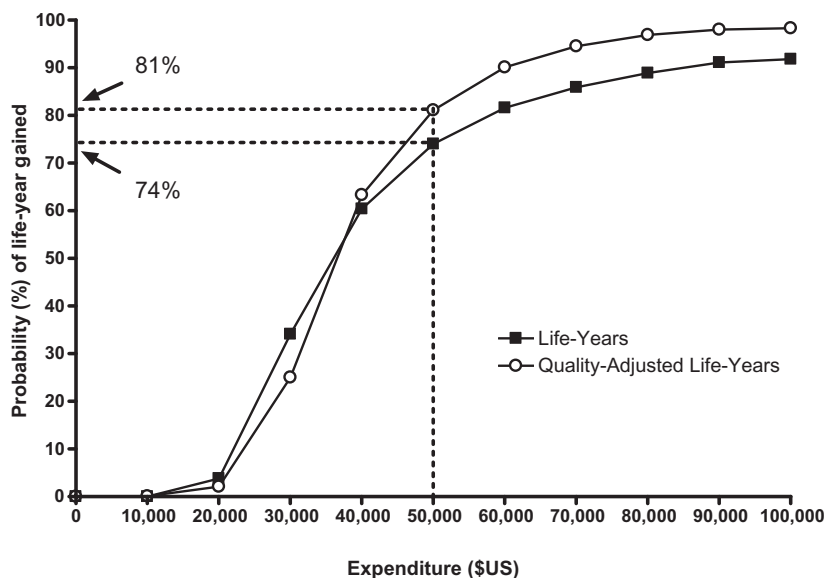
Reducing the HbA<sub>1c</sub> effectiveness of exenatide by a theoretical 20% (i.e., from -1.1% to -0.88%) likewise increased the ICER from \$35,571/LYG in the base case to \$ 42,875/LYG, and the CODE-2 ICER from \$36,133/QALY to \$41,917/QALY. Assuming no impact of exenatide on BMI (changing from -1.5 kg/m<sup>2</sup> in the base case to 0 kg/m<sup>2</sup>) or systolic

**Table 7** Cumulative incidence of complications over time in the theoretical cohort of 1000 patients with type 2 diabetes over 10-, 20- and 30-year time horizons (in addition to baseline prevalence)

System	Complication	Incidence $\pm$ SD (%)					
		10 years		20 years		30 years	
		Exenatide	No additional treatment	Exenatide	No additional treatment	Exenatide	No additional treatment
Vision	Background diabetic retinopathy	8.79 $\pm$ 1.22	13.61 $\pm$ 1.42	17.20 $\pm$ 1.67	23.02 $\pm$ 1.74	20.63 $\pm$ 1.66	25.57 $\pm$ 1.76
	Proliferative diabetic retinopathy	0.81 $\pm$ 0.30	1.34 $\pm$ 0.34	1.77 $\pm$ 0.44	2.65 $\pm$ 0.52	2.39 $\pm$ 0.50	3.32 $\pm$ 0.56
	Cataract	4.49 $\pm$ 0.67	5.38 $\pm$ 0.76	7.25 $\pm$ 0.84	8.22 $\pm$ 0.93	8.09 $\pm$ 0.96	8.95 $\pm$ 1.01
	Macular edema	6.62 $\pm$ 0.79	10.40 $\pm$ 0.99	13.40 $\pm$ 1.18	18.40 $\pm$ 1.25	16.45 $\pm$ 1.17	20.94 $\pm$ 1.41
	Severe vision loss	3.69 $\pm$ 0.63	4.73 $\pm$ 0.67	7.60 $\pm$ 0.89	9.52 $\pm$ 0.97	9.58 $\pm$ 0.97	11.19 $\pm$ 0.98
Renal	Microalbuminuria	13.24 $\pm$ 1.33	19.62 $\pm$ 1.53	24.22 $\pm$ 1.69	31.01 $\pm$ 1.90	28.49 $\pm$ 1.79	34.56 $\pm$ 1.82
	Gross proteinuria	3.97 $\pm$ 0.64	6.83 $\pm$ 0.83	10.13 $\pm$ 0.97	15.14 $\pm$ 1.20	14.03 $\pm$ 1.18	18.62 $\pm$ 1.28
	End-stage renal disease	0.89 $\pm$ 0.29	1.67 $\pm$ 0.43	2.80 $\pm$ 0.51	4.99 $\pm$ 0.72	4.96 $\pm$ 0.71	7.39 $\pm$ 0.81
	Nephropathy death	0.62 $\pm$ 0.25	1.00 $\pm$ 0.32	1.80 $\pm$ 0.42	3.16 $\pm$ 0.57	3.33 $\pm$ 0.59	5.05 $\pm$ 0.71
Cardiovascular	Myocardial infarction	8.62 $\pm$ 0.85	12.13 $\pm$ 1.03	17.58 $\pm$ 1.23	23.08 $\pm$ 1.33	21.92 $\pm$ 1.31	27.11 $\pm$ 1.44
	Myocardial infarction death	12.12 $\pm$ 1.04	14.04 $\pm$ 1.12	20.63 $\pm$ 1.33	23.85 $\pm$ 1.37	24.29 $\pm$ 1.40	27.40 $\pm$ 1.41
	Stroke event	3.97 $\pm$ 0.60	4.13 $\pm$ 0.65	8.43 $\pm$ 0.88	8.24 $\pm$ 0.87	11.42 $\pm$ 0.99	10.58 $\pm$ 0.95
	Stroke death	2.90 $\pm$ 0.52	2.84 $\pm$ 0.51	5.11 $\pm$ 0.72	4.96 $\pm$ 0.66	6.41 $\pm$ 0.76	5.98 $\pm$ 0.75
	Congestive heart failure	15.73 $\pm$ 1.23	18.95 $\pm$ 1.33	29.78 $\pm$ 1.50	34.19 $\pm$ 1.63	36.41 $\pm$ 1.55	39.33 $\pm$ 1.57
	Congestive heart failure death	7.85 $\pm$ 0.87	8.57 $\pm$ 0.91	16.69 $\pm$ 1.19	18.05 $\pm$ 1.23	22.15 $\pm$ 1.26	22.45 $\pm$ 1.24
	Peripheral vascular disease	4.00 $\pm$ 0.65	6.29 $\pm$ 0.83	10.31 $\pm$ 1.01	14.68 $\pm$ 1.18	14.71 $\pm$ 1.23	18.69 $\pm$ 1.33
Angina	6.20 $\pm$ 0.83	7.67 $\pm$ 0.88	10.93 $\pm$ 1.06	12.97 $\pm$ 1.17	12.99 $\pm$ 1.09	14.68 $\pm$ 1.23	
Extremities	Peripheral neuropathy	25.52 $\pm$ 1.81	34.64 $\pm$ 1.93	42.17 $\pm$ 2.05	50.80 $\pm$ 2.22	46.17 $\pm$ 2.09	52.48 $\pm$ 2.08
	Foot ulcer	14.60 $\pm$ 1.11	15.36 $\pm$ 1.12	23.10 $\pm$ 1.32	24.32 $\pm$ 1.39	26.39 $\pm$ 1.44	26.93 $\pm$ 1.45
	Recurring foot ulcer	20.56 $\pm$ 1.96	20.45 $\pm$ 1.99	35.78 $\pm$ 2.99	35.56 $\pm$ 3.01	41.69 $\pm$ 3.33	40.58 $\pm$ 3.32
	Amputation from foot ulcer	5.23 $\pm$ 0.79	5.36 $\pm$ 0.76	8.47 $\pm$ 1.03	8.60 $\pm$ 1.05	9.67 $\pm$ 1.02	9.4 $\pm$ 1.05
	Amputation from recurring foot ulcer	1.69 $\pm$ 0.49	1.64 $\pm$ 0.45	3.19 $\pm$ 0.72	3.12 $\pm$ 0.66	3.83 $\pm$ 0.75	3.57 $\pm$ 0.75



**Figure 1** Scatter plots of 1,000 samples of mean incremental costs plotted against mean incremental life-expectancy (life-years gained or quality-adjusted life-years gained). The scatter plots were generated for the mean incremental costs of 1,000 patients comparing exenatide with a theoretical no additional treatment option (metformin and/or a sulfonylurea only) for incremental life expectancy under the base-case scenario for life-year gained (A) or quality-adjusted life-year gained (B). For both plots, the majority of the points lie in the upper right-hand quadrant, indicating higher costs and improved effectiveness for exenatide compared with a theoretical no additional treatment option.



**Figure 2** Probability of life-year gained or quality-adjusted life-year gained with exenatide plotted against expenditure. The curves were generated for probability life-year gained or quality-adjusted life-year gained compared with expenditure from 1,000 samples for 1,000 patients treated with exenatide compared with a theoretical no additional treatment option (metformin and/or sulfonylurea only). The curve shows how likely (y-axis) it will be that exenatide is cost-effective for any particular expenditure (x-axis). The probability that the treatment cost to obtain an additional year of life with exenatide would be \$50,000 or less was 74% for life-year gained and 81% for quality-adjusted life-year gained, as compared with a theoretical no additional treatment option.

blood pressure (from  $-1.3$  mm Hg to 0 mm Hg) had little impact on the ICERs. Lastly, removal of the lipid effects (total cholesterol from  $-2.4$  mg/dL to 0 mg/dL; LDL-C from  $-1.6$  mg/dL to 0 mg/dL; HDL-C from 4.6 mg/dL to 0 mg/dL; and triglycerides from  $-39$  mg/dL to 0 mg/dL) had the largest impact on the base-case ICER, increasing it by approximately 26% to \$44,950/LYG. The CODE-2 ICER increased to a lesser degree, by 16% to \$41,738/QALY. Decreasing the discount rate from 3% to 0% decreased the ICER approximately 17% to \$29,397/LYG, and CODE-2 ICER by 7% to \$33,751/QALY. Increasing the discount rate from 3% to 6% increased the ICER approximately 22% to \$43,267/LYG, and CODE-2 ICER by 5% to \$38,114/QALY.

Patients with baseline HbA<sub>1c</sub> less than 9% had HbA<sub>1c</sub> changes of  $-0.8\%$ , as compared with  $-2.0\%$  for those with baseline HbA<sub>1c</sub> greater than or equal to 9%. The corresponding ICERs for the two baseline HbA<sub>1c</sub> subgroups were \$48,284/LYG and \$18,243/LYG, respectively. The CODE-2 ICERs for these two subgroups were \$45,971/QALY and \$20,548/QALY. Analysis of week 30 data (from the 82-week cohort) resulted in an ICER of \$51,354/LYG, while the CODE-2 ICER was \$47,981/QALY.

## Discussion

Our early modeling study suggests that sustained glycemic control and progressive weight reduction leading to positive clinical effects on lipids, BMI, and systolic blood pressure all contribute to the projected long-term cost-effectiveness of adjunctive exenatide treatment for patients with type 2 diabetes not achieving adequate glycemic control with metformin and/or a sulfonylurea, as compared with adding no additional

therapy to metformin and/or a sulfonylurea when measured for either a 20-year or a 30-year time horizon. Use of a 10-year time horizon with diabetes is somewhat difficult to interpret, because many of the complications associated with diabetes develop over the course of decades, not years. Therefore, it would be unlikely that any diabetes treatment would show cost-effectiveness for this time horizon. The cost-effectiveness of exenatide is in large part due to beneficial effects on lipids, which thus reduce the risk of cardiovascular disease. Not surprisingly, given this projected relationship with cardiovascular disease, exenatide treatment was not cost-effective when examined for a 10-year time horizon. As the incidence of complications rise with longer time horizons, the benefits of exenatide in reducing their incidence become more evident. The difference in results with the different time horizons highlights the benefit of using longer-term time horizons, which capture these chronic conditions. These longer time horizons are consistent with various guidelines that maintain that any economic modeling analysis in diabetes must be carried on long enough to capture all of the relevant outcomes of interest [35,37].

The positive clinical effects of exenatide could translate into reduced incidence of long-term diabetic complications, reduce long-term treatment costs, and improve life expectancy for patients with type 2 diabetes in the United States. The conclusions of this early modeling study suggest that the study results were also robust over a wide range of clinical and economic assumptions, including discount rates and clinical effects. The ICERs for the base case and most sensitivity analyses fell below \$50,000/LYG or QALY, a threshold that is considered cost-effective in the United States [25,38].

The chief limitation of our economic analysis of exenatide is the lack of clinical data directly comparing exenatide with other type 2 diabetes treatments. Although some of these studies are underway, the current paucity of data and the lack of a true placebo comparator arm (beyond the initial 30 weeks of treatment) required us to pursue a preliminary comparison of exenatide with a theoretical no additional treatment beyond metformin and/or a sulfonylurea option, with no added costs and no clinical effects. This is clearly a drawback of our analysis. Nevertheless, this lack of long-term or comparative data is common when a new product is introduced, because most registration trials are placebo-controlled for a relatively short duration. With this in mind, we provided a preliminary analysis on the cost-effectiveness of exenatide with the full realization that our clinical and comparative data are limited. We used the exenatide 82-week data to project the effects of 30 years of exenatide treatment, because these data represent the longest-term and most robust source of data at this time. Longer-term data (2 years from the same study and 2.5 years from an open-label study) demonstrate that with continued exenatide treatment glycemic control is sustained and weight reduction is progressive, with further beneficial changes in lipid concentrations [31,39]. These data indicate that, if anything, the current analysis underestimates the cost-effectiveness of exenatide.

Other limitations of our analysis include the assumption that the difference in HbA<sub>1c</sub> between exenatide and the theoretical no additional treatment arm would be maintained over the entire analysis time horizon. This assumption is common practice in health economic modeling analyses in diabetes, especially when clinical experience with a new treatment is limited. Nonmedical costs, such as lost productivity and transportation costs, are excluded and could lead to an underestimation of costs from a broader perspective. Also, this model utilizes data from credible sources to calculate epidemiological risk functions. As such, this may diminish the potential contribution of risk factors for which available data are currently sparse. Postprandial control, for example, is increasingly being recognized as a potentially important risk factor that independently contributes to the development of macrovascular complications [40]. The model does not factor in the potential impact of postprandial glycemia effects because the current evidence base is not sufficient to inform the model with any degree of scientific certainty. Of note, exenatide has been shown to significantly reduce postprandial glucose excursions. In addition, the clinical benefit of reduced BMI, independent of the known effects on improved cardiovascular disease markers, is not fully known. As more clinical research is performed in the area of weight reduction, it may become apparent

that this model does not fully capture the range of clinical benefits associated with weight reduction. On a related note, the CODE-2 study, which formed the basis for the utility values used in the quality of life analysis, did not account for utility associated with weight reduction. Additional studies in patients with type 2 diabetes are needed to determine to what extent weight reductions impact quality of life, and thus cost-effectiveness.

Further research should focus on increasing the amount of long-term clinical data with exenatide, including comparative data with other clinical treatments for type 2 diabetes, and on accounting for other positive clinical effects of exenatide, such as postprandial glucose control and weight reduction.

## Conclusions

Our analysis demonstrated that using 30-year base-case assumptions and data from 82 weeks to project the effects of 30 years of exenatide treatment, exenatide provides good value for money in the treatment of patients with type 2 diabetes not achieving adequate glycemic control with metformin and/or sulfonylureas, with an ICER of \$35,571/LYG and \$36,133/QALY, compared with no additional treatment beyond metformin and/or a sulfonylurea. When assumptions were varied (for HbA<sub>1c</sub>, BMI, lipid, and blood pressure effects), the ICERs remained less than \$50,000/LYG in most sensitivity analyses. Specifically, the largest effects were observed when varying the time horizon, HbA<sub>1c</sub> effect, and lipid changes (in that order). Varying the BMI and blood pressure effects, however, did not significantly affect the cost-effectiveness.

This early economic modeling analysis can provide managed care formularies and other health-care payers with important information on the economic value of another option to treat type 2 diabetes in the United States. Our analysis is the first step in documenting the cost-effectiveness of exenatide in type 2 diabetes and informing future health-care decision-making in the United States.

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