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ORIGINAL ARTICLE

Cost-utility of albiglutide versus insulin lispro, insulin glargine, and sitagliptin for the treatment of type 2 diabetes in the US

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ABSTRACT

Objective To compare the cost-utility of the glucagon-like peptide-1 receptor agonist albiglutide with those of insulin lispro (both in combination with insulin glargine), insulin glargine, and the dipeptidyl peptidase-4 inhibitor sitagliptin, representing treatments along the type 2 diabetes treatment continuum.

Methods The Centre for Outcomes Research and Effectiveness (CORE) Diabetes Model was used for the cost-utility analysis. Data from three Phase 3 clinical trials (HARMONY 6, HARMONY 4, and HARMONY 3) evaluating albiglutide for the treatment of patients with type 2 diabetes were used for the baseline characteristics and treatment effects. Utilities and costs were derived from published sources.

Results Albiglutide treatment was associated with an improvement in mean quality-adjusted life expectancy of 0.099, 0.033, and 0.101 years when compared with insulin lispro, insulin glargine, and sitagliptin, respectively. Over the 50-year time horizon, mean total costs in the albiglutide arm were $4332, $2597, and $2223 more than in the other respective treatments. These costs resulted in an incremental cost-utility ratio of $43,541, $79,166, and $22,094 per quality-adjusted life-year (QALY) gained for albiglutide vs insulin lispro, insulin glargine, and sitagliptin, respectively. At a willingness-to-pay threshold of $50,000 per QALY gained, there was a 53.0%, 41.5%, and 67.5% probability of albiglutide being cost-effective compared with the other respective treatments.

Limitations This analysis was an extrapolation over a 50-year time horizon based on relatively short-term data obtained during clinical trials. It does not take into account potential differences between the respective treatments in adherence and persistence that can influence both effects and costs.

Conclusions Albiglutide represents a reasonable treatment option for patients with type 2 diabetes based on its cost-utility, relative to insulin lispro, insulin glargine, and sitagliptin.

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Introduction

Diabetes in the US represents a significant economic burden, with estimated total costs of $245 billion in 2012, including $176 billion in direct medical costs[1]. The largest components of these medical costs were hospital inpatient care (43%), prescription medications to treat complications of the disease (18%), and antidiabetic agents and diabetes supplies (12%)[1].

Because type 2 diabetes is a chronic, progressive disease, it is associated with increasing treatment intensity and long-term complications that result in a significant financial burden for the patient[2,3]. Lifetime direct medical costs for treating type 2 diabetes for patients diagnosed at the ages of 45–54 years are estimated to be $106,200 for men and $110,400 for women[3]. These costs encompass those for treating type 2 diabetes-associated complications, such as coronary heart disease and nephropathy; and diabetes management, including medications, physician visits and self-monitoring of blood glucose. Additionally, treatment of hypoglycemia, a potential risk associated with medications for type 2 diabetes, particularly insulin, also represents a significant cost burden[2,4].

Although there are a number of approved agents available for the treatment of type 2 diabetes, patients continue to have trouble reaching and maintaining targets for glycemic control[2,5]. Since 2006, incretin-based therapies, such as the injectable glucagon-like peptide-1 receptor agonists (GLP-1RAs) and oral dipeptidyl peptidase-4 inhibitors, have been introduced[2,5]. Currently, three GLP-1RAs are approved in the US for once-weekly (QW) administration: albiglutide (Tanzeum†), exenatide extended-release (Bydureon‡), and dulaglutide (Trulicity§)[6–8].

The GLP-1RA class is the most expensive diabetes class of medications in terms of annual costs[9,10]. From 2008–2012, the total (payer and patient) average annual cost per person for GLP-1RAs rose 75% from $1224 to $2143[9]. In comparison, the average annual cost of providing pharmaceutical care for diabetes increased from $667 to $741 (11%) in the same period[9]. In 2014, annual Wholesale Acquisition Costs of QW GLP-1RAs

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‡Bydureon is a registered trade name of Bristol-Myers Squibb, Princeton, NJ.
§Trulicity is a registered trade name of Eli Lilly and Company, Indianapolis, IN.

ranged from ~$4200 for albiglutide to $6300 for dulaglutide[10]. The consequence of this high cost is that some payers question the value of GLP-1RAs and are denying coverage for some agents of this class[11]. Given these high costs and concerns expressed by managed care organizations, the cost-utility of new GLP-1RAs relative to other agents warrants investigation. Furthermore, managed care organizations typically look at the short-term perspective, whereas in diabetes, treatment is given to prevent negative outcomes that occur later in the patient's life. Therefore, a long-term perspective is needed to assess the value of diabetes treatment.

Presented is a cost-utility analysis comparing albiglutide to relevant comparators at different stages of type 2 diabetes disease: failure of first-line oral therapy, type 2 diabetes requiring basal insulin, and type 2 diabetes requiring prandial as well as basal insulin. Data from 3 Phase 3 studies[12–14] that were designed to reflect real-world practice patterns as far as possible showed that albiglutide treatment was non-inferior to insulin lispro (both in combination with insulin glargine) treatment ($p < 0.0001$) and insulin glargine treatment ($p = 0.0086$), and superior to sitagliptin treatment ($p < 0.0001$) in terms of lowering HbA_{1c}, whereas body mass index (BMI) and hypoglycemic events were reduced with albiglutide treatment relative to either insulin treatment.

Research design and methods

Model methodology

The Centre for Outcomes Research (CORE) Diabetes Model, developed by Palmer *et al.*[15], was used for the cost-utility analyses. This model is a validated, interactive Markov-based computer model designed to evaluate the long-term health outcomes and economic consequences of interventions in patients with type 1 or type 2 diabetes[15,16].

The model is composed of 16 sub-models that simulate non-specific mortality and the major complications of diabetes, including cardiovascular disease, stroke, neuropathy, eye disease, nephropathy and end-stage renal disease, lactic acidosis, ketoacidosis, hypoglycemia, foot ulcer, and amputation. Each sub-model has a semi-Markov structure that uses transition probabilities derived from published sources and indexed by time, state, time-in-state, and diabetes type (all type 2 diabetes in the present analysis). Monte Carlo simulation using tracker variables is employed to overcome the memory-less properties of the standard Markov model and allows interconnectivity and interaction between individual complication sub-models.

The progression of diabetes over the 50-year time horizon was individually simulated for a cohort of 1000 hypothetical patients. This was then repeated for 1000 cohorts (first-order Monte Carlo simulation) to produce a joint distribution of incremental costs and effectiveness, which were plotted and from which cost-acceptability curves were derived by calculating the likelihood of albiglutide being cost-effective over a range of willingness-to-pay thresholds. Long-term outcomes evaluated for each analysis using the CORE Diabetes Model[15,16] were life expectancy, quality-adjusted life expectancy, cumulative incidence of diabetes-related complications, time to onset of diabetes-related complications, and direct medical costs.

Simulation cohorts

This study evaluated the cost-utility of albiglutide relative to a comparator treatment from latest to earliest stage of the treatment paradigm; insulin lispro (Humalog†), in combination with insulin glargine; insulin glargine (Lantus‡); and the dipeptidyl peptidase-4 inhibitor sitagliptin (Januvia§), for the treatment of patients with type 2 diabetes in the US. These three agents were selected for comparison because they are not available as generic medications and are included in treatment guidelines at similar stages of therapy as GLP-1RAs[2,5]. Separate ethical approval for this study was not required as modeling was based on results from primary studies conducted with institutional review board approval.

For each comparison, a simulated cohort of patients was defined using the baseline characteristics from three Phase 3 studies of albiglutide in patients with type 2 diabetes: HARMONY 6[12], HARMONY 4[13], and HARMONY 3[14] (Table 1). HARMONY 6 (NCT00976391) was a 52-week, randomized open-label study with a 26-week primary end-point that compared the safety and efficacy of albiglutide to insulin lispro, both in combination with insulin glargine, in patients whose disease was inadequately controlled with intermediate- or long-acting insulin[12]. HARMONY 4 (NCT00838916) was a 3-year, randomized open-label study with a 52-week primary end-point that compared the safety and efficacy of albiglutide with that of insulin glargine in patients whose disease was inadequately controlled on metformin with or without sulfonylurea[13]. HARMONY 3 (NCT00838903) was a 3-year, randomized double-blind, parallel-group study with a 104-week primary end-point that compared the efficacy and safety of albiglutide to sitagliptin, glimepiride and placebo in patients whose disease was inadequately controlled with metformin[14]. In HARMONY 6 and 4, patients in the insulin lispro and insulin glargine treatment groups had their respective insulin treatment initiated as per standard of care at the study site[12,13]. Adjustments were made for the respective insulin treatment based on the average of the 2 previous days' home blood glucose monitoring results[12,13].

Baseline characteristics for smoking and alcohol consumption were based on data from the US Centers for Disease Control and Prevention and the National Institute on Alcohol Abuse and Alcoholism, respectively[17,18].

Treatment effects, safety, and summary of modifiable inputs

Treatment effects and adverse event rates were obtained using pre-rescue, intent-to-treat data from the respective clinical trials (Table 2)[12–14]. For the HARMONY 6, 4 and 3 analyses, data were used from the primary end-point (reduction in

†Humalog is a registered trade name of Eli Lilly and Company, Indianapolis, IN.
‡Lantus is a registered trade name of Sanofi, Bridgewater, NJ.
§Januvia is a registered trade name of Merck & Co., Inc. Whitehouse Station, NJ.

Table 1. Baseline cohort characteristics* [12–14,17,18].

Treatment	Albiglutide vs insulin lispro (both + insulin glargine)	Albiglutide vs insulin glargine	Albiglutide vs sitagliptin
n	566	745	604
Age, years	55.6 (9.0)	55.5 (9.5)	54.5 (10.0)
Male, %	47.3	56.0	47.6
Race, %			
Caucasian	34.7	52.0	37.5
Hispanic	25.6	16.0	34.5
African American	12.9	26.0	14.8
Native American	8.7	0.5	7.2
Asian or Pacific Islander	18.1	5.5	6.0
Duration of diabetes, years	11.1 (6.4)	8.8 (6.3)	6.0 (4.9)
Metabolic characteristics			
HbA_{1c}, %	8.5 (0.9)	8.3 (0.9)	8.1 (0.8)
HbA_{1c}, mmol/mol	69.0	67.0	65.0
Total cholesterol, mg/dL	175.2 (41.5)	179.1 (41.1)	185.3 (41.2)
HDL cholesterol, mg/dL	46.6 (11.4)	44.5 (10.9)	46.1 (11.3)
LDL cholesterol, mg/dL	95.5 (36.3)	96.6 (34.7)	99.5 (34.1)
Triglycerides, mg/dL	171.4 (105.1)	198.4 (129.6)	204.0 (118.5)
BMI, kg/m^2	33.0 (5.9)	33.1 (5.5)	32.6 (5.5)
Clinical characteristics			
SBP, mm Hg	103.2 (13.4)	130.7 (14.0)	127.9 (13.9)
Smoking and alcohol use			
Smokers, %	19.3	19.3	19.3
Cigarettes per day	15.1	15.1	15.1
Alcohol consumption (fl oz/week)	5.6	5.6	5.6

*Mean (SD), unless noted.
SBP, systolic blood pressure; SD, standard deviation.

Table 2. Treatment effects associated with albiglutide and comparators*† [12–14].

	Albiglutide + insulin glargine‡	Insulin lispro + insulin glargine§	Albiglutide‡	Insulin glargine§	Albiglutide|	Sitagliptin|	Albiglutide Year 2|	Sitagliptin Year 2|
HbA_{1c}, %	−0.82 (0.97)	−0.66 (0.97)	−0.67 (0.98)	−0.79 (0.99)	−0.73 (0.91)	−0.43 (1.10)	0.10 (0.00)	0.15 (0.00)
SBP, mm Hg	−2.50 (13.12)	−0.30 (13.22)	−1.40 (14.40)	0.30 (13.71)	0.50 (12.34)	−0.20 (12.34)	−1.20 (0.00)	0.20 (0.00)
Total cholesterol, mg/dL	−6.40 (36.30)	−2.20 (30.14)	−2.10 (27.82)	−2.50 (31.66)	−3.90 (36.81)	−1.90 (26.47)	1.30 (0.00)	−1.70 (0.00)
HDL cholesterol, mg/dL	0.10 (8.02)	0.40 (7.17)	2.10 (6.36)	1.90 (6.51)	1.80 (7.37)	1.40 (6.88)	−0.10 (0.00)	−0.40 (0.00)
LDL cholesterol, mg/dL	−4.10 (30.63)	1.20 (25.27)	−1.80 (22.64)	−0.30 (27.25)	−2.50 (29.41)	−1.00 (22.04)	1.40 (0.00)	−0.90 (0.00)
Triglycerides, mg/dL	−14.60 (78.70)	−5.10 (90.55)	−17.30 (102.45)	−20.70 (83.76)	−23.40 (105.90)	−10.90 (90.88)	5.80 (0.00)	−2.50 (0.00)
BMI, kg/m^2	−0.26 (1.17)	0.29 (1.17)	−0.37 (1.33)	0.55 (1.33)	−0.43 (1.48)	−0.31 (1.47)	0.00	0.00
Major hypoglycemic event rate (events per 100 patient years), mean	0.00	1.26	0.43	0.89	0.00	0.00	0.00	0.00
Minor hypoglycemic event rate (events per 100 patient years), mean	85.62	205.60	61.37	108.75	2.68	2.95	2.68	2.95

*Mean change from baseline (SD), unless indicated.
†Year 1, unless indicated.
‡Based on the pre-rescue, intent-to-treat, 26-week (primary endpoint) data.
§Taken from the pre-rescue, intent-to-treat, 52-week (primary endpoint) data.
|Taken from (year 1) or based on (year 2) the pre-rescue, intent-to-treat, 104-week (primary endpoint) data.
SBP, systolic blood pressure; SD, standard deviation.

HbA_{1c}) times of 26, 52, and 104 weeks, respectively[12–14]. The base-case time horizon was 50 years in all comparisons.

Treatment strategies and time between treatment switches and intensifications were based on previous published studies for albiglutide[12–14] along with clinician guidance and assumptions derived from prior diabetes health economic modeling work[19–21]. Following application of the initial treatment effects, patients were ultimately switched to a basal-bolus insulin treatment for the remainder of the simulation. In the comparison with insulin lispro, patients in the albiglutide/insulin glargine arm were assumed to take albiglutide 30 mg QW (uptitrated to albiglutide 50 mg QW) plus insulin glargine 53.2 IU once daily (QD) for 3 years and then switched to a basal-bolus insulin treatment of insulin glargine 50.6 IU QD plus insulin lispro 30.6 IU QD for the remainder of the 50-year time horizon. Patients in the comparator arm were assumed to take insulin glargine 50.6 IU QD plus insulin lispro 30.6 IU QD for the duration of the 50-year time horizon with no treatment switching at any stage of the analysis.

In the comparison with insulin glargine, patients in the albiglutide arm were assumed to take albiglutide 30 mg QW (with a majority selecting the option to uptitrate to 50 mg QW) for 3 years followed by insulin glargine 35.1 IU QD for 1 year, before switching to basal-bolus therapy. Patients in the comparator arm were assumed to take insulin glargine 35.1 IU QD for 4 years before switching to basal-bolus insulin.

In the comparison with sitagliptin, patients in the albiglutide arm were assumed to take albiglutide 30 mg QW (with a majority selecting the option to uptitrate to 50 mg QW) for 2 years; and patients in the comparison arm were assumed to

Table 3. Health status utilities used in the modeling analysis[15,25–28].

Complication	Utility
Diabetes, no complications	0.814
MI, year of event	−0.129
MI, years 2+	0.736
Angina	0.682
CHF	0.633
Stroke, year of event	−0.181
Stroke, years 2+	0.545
PVD	0.570
Microalbuminuria	0.814
Gross proteinuria	0.814
Hemodialysis	0.490
Peritoneal dialysis	0.560
Kidney transplant	0.762
Background diabetic retinopathy	0.814
Background diabetic retinopathy, incorrectly treated	0.814
Proliferative diabetic retinopathy	0.794
Proliferative diabetic retinopathy, no laser	0.794
Macular edema	0.794
Severe vision loss	0.734
Cataract	0.794
Neuropathy	0.624
Healed ulcer	0.814
Active ulcer	−0.600
Amputation, year of event	−0.109
Amputation, years 2+	0.680
Major hypoglycemia	−0.012
Minor hypoglycemia	−0.004
Each unit of BMI over 25	−0.006

CHF, congestive heart failure; MI, myocardial infarction; PVD, peripheral vascular disease.

take sitagliptin 100 mg QD for 2 years. In both study arms, it was assumed that the study medication was replaced by insulin glargine 35.1 IU QD in year 3 of treatment and then basal-bolus insulin in year 4 of the analysis.

Long-term modeling used commonly accepted approaches[15,22,23]. HbA_{1c} and systolic blood pressure (SBP) progressions in all analyses followed the UK Prospective Diabetes Study panel regression models, whereas serum lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) followed the CORE Diabetes Model default progressions based on the Framingham Heart Study[15,22,23]. BMI progression in all analyses assumed the albiglutide arm to converge to the comparator arm at the point when both arms were on similar treatments (at the start of year 4 in the comparisons with insulin lispro and with insulin glargine and at the start of year 3 in the comparison with sitagliptin) and remain level thereafter. Mortality data were obtained from the Global Health Observatory Data Repository of the World Health Organization[24].

Utilities and costs

Health state utilities used in the modeling analysis were derived from previously published studies (Table 3)[15,25–28]. Costs of study medication and concomitant oral antidiabetic medications were calculated based on doses and medications used in the respective clinical studies[12–14], whereas blood glucose monitoring costs were based on previous reports[29]. Dosages used were as follows: albiglutide 30 and 50 mg QW; insulin glargine 35.1 IU QD and 50.6 IU QD (in combination with insulin lispro) or 53.2 IU QD (in combination with albiglutide); insulin lispro 30.6 IU QD; metformin 1000 mg QD; sitagliptin 100 mg QD. All costs of diabetes-related complications (Table 4), except for laser treatment[30] and prosthesis following amputation[31], were based on the study by Yeaw *et al.*[32]. When necessary, costs were inflated to 2014 values using the Consumer Price Index from the Bureau of Labor Statistics[33].

Table 4. Cost input associated with diabetes-related complications and medications used in the base-case analysis* [32].

Complication	2014 cost ($)	
	Year of event/onset	≥2 years following event/onset
Cardiovascular		
MI	13,396	1507
Angina	2823	453
CHF	9920	4925
Stroke	5782	803
Stroke, death within 30 days†	0	n/a
PVD	4167	1520
Renal and hypoglycemia		
Hemodialysis	14,872	10,752
Peritoneal dialysis	22,761	11,735
Kidney transplant	5625	3782
Major hypoglycemia	253	n/a
Retinal		
Laser treatment[30]	847	n/a
Cataract operation	399	n/a
Cost following cataract operation	103	n/a
Blindness	890	231
Other		
Neuropathy	1586	523
Amputation, procedure	5355	n/a
Amputation, prosthesis[31]	1548	n/a
Gangrene treatment	9702	n/a
Cost after healed ulcer	2311	n/a
Infected foot ulcer	4940	n/a
Uninfected foot ulcer	0	n/a
Cost after healed ulcer (history of amputation)	2311	n/a
Medications	**Annual per patient cost ($)‡**	
HARMONY 6 cohort		
Albiglutide cohort	9309	
Insulin lispro cohort	7977	
HARMONY 4		
Albiglutide cohort	4590	
Insulin glargine cohort	3677	
HARMONY 3		
Albiglutide cohort	4509	
Sitagliptin cohort	3920	

*Except for the cost of laser treatment and prosthesis after amputation[30,31], all costs were based on the study by Yeaw *et al.*[32]. Costs were inflated to 2014 values when necessary, using the consumer price index from the Bureau of Labor Statistics[33].
†Assumption of CORE diabetes model.
‡Medication costs include study medication, concomitant oral antidiabetic medications, and blood glucose monitoring costs.
CHF, congestive heart failure; MI, myocardial infarction; n/a, not applicable; PVD, peripheral vascular disease; $, United States dollars.

Sensitivity analyses

Because of the uncertainty associated with extrapolating clinical results by modeling long-term consequences, one-way sensitivity analyses were performed on key parameters to assess the robustness of the base-case findings. Alternative assumptions were investigated for time horizon (5, 10, and 20 years), discount rates (0% and 6%), cost of complications

Table 5. Modeled long-term clinical outcomes and costs associated with albiglutide vs comparators* †.

	Albiglutide + insulin glargine	Insulin lispro + insulin glargine	Difference	Albiglutide	Insulin glargine	Difference	Albiglutide	Sitagliptin	Difference
Life expectancy, years	13.345 (0.178)	13.247 (0.172)	0.099	13.795 (0.200)	13.778 (0.191)	0.017	14.335 (0.180)	14.225 (0.190)	0.110
Quality-adjusted life expectancy, QALYs	8.707 (0.119)	8.608 (0.117)	0.099	9.141 (0.133)	9.108 (0.127)	0.033	9.618 (0.125)	9.517 (0.130)	0.101
Total costs, $	151,940 (1972)	147,608 (1916)	4332	136,902 (2199)	134,305 (2071)	2597	140,806 (1948)	138,583 (2071)	2223
Treatment	114,811	110,334	4477	102,403	99,721	2682	106,380	103,870	2510
Management	13,292	13,165	127	13,687	13,655	32	14,188	14,081	107
Complications	23,839	24,109	−270	20,812	20,929	−117	20,238	20,632	−394
ICER (Cost per QALY gained), $			43,541			79,166			22,094

*Mean (SD), unless noted.
†Discrepancies in summations and differences due to number rounding.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SD, standard deviation.

(10% increase or decrease), ethnicity (based on 2012 data from the US Census Bureau[34]), and drivers of clinical benefit (albiglutide treatment effect on HbA_{1c}, SBP, serum lipids, and BMI set to equivalence with the comparator). Sensitivity analysis was also performed around the disutility (negative impact on health-related quality-of-life) associated with minor hypoglycemia: in the base-case analyses, a disutility decrement of −0.0035 per minor event was used[27], whereas the sensitivity analyses used data derived from Marrett *et al.*[35], in which the adjusted EuroQol-5D (EQ-5D) score decrement over a 6-month period for a single mild hypoglycemic event was −0.01.

Probabilistic sensitivity analyses were conducted around the base case, with sampling from distributions defined by the standard deviations (SD) of baseline cohort characteristics and treatment effects in Tables 1 and 2, respectively.

Results

Albiglutide vs insulin lispro (both combined with insulin glargine)

Base-case analysis

Over the 50-year time horizon, albiglutide plus insulin glargine treatment resulted in an improvement in mean life expectancy of 0.099 years compared with insulin lispro plus insulin glargine (13.345 years; SD = 0.178 vs 13.247 years; SD = 0.172), mean quality-adjusted life expectancy by 0.099 years (8.707 years; SD = 0.119 vs 8.608 years; SD = 0.117), and diabetes-related complications (Tables 5 and 6). During the 50-year time horizon, mean total cost in the albiglutide plus insulin glargine arm was $4332 more than in the insulin lispro plus insulin glargine arm, with an incremental cost-effectiveness ratio (ICER) of $43,541 per quality-adjusted life-year (QALY) gained (Table 5 and Figure 1).

Sensitivity analysis

For patients in the albiglutide plus insulin glargine arm, at a willingness-to-pay threshold of $50 000 per QALY gained, there was a 53.0% probability of cost-utility compared with insulin lispro plus insulin glargine (Figure 2). The probability increased to 65.0% at a threshold of $100,000 per QALY gained.

In the one-way analysis, a noteworthy impact on ICER relative to the base-case analysis was seen when the time horizon decreased from 50 years (in the base-case) to 5 years, with the ICER increasing to $133 234 per QALY gained (Table 7). Additionally, a substantial decrease in ICER to $8777 per QALY gained was observed when a greater hypoglycemia disutility decrement value was used in the analysis.

Albiglutide vs insulin glargine

Base-case analysis

Albiglutide treatment was associated with a modest improvement in mean life expectancy of 0.017 years compared with insulin glargine (13.795 years; SD = 0.200 vs 13.778 years; SD = 0.191), a mean quality-adjusted life expectancy increase of 0.033 years (9.141 years; SD = 0.133 vs 9.108 years; SD = 0.127) and reduced diabetes-related cardiovascular complications (Tables 5 and 6). During the 50-year time horizon, mean total cost in the albiglutide arm was $2597 more than in the insulin glargine arm, with an ICER of $79 166 per QALY gained (Table 5 and Figure 1).

Sensitivity analysis

Based on the acceptability curves (Figure 2), at a willingness-to-pay threshold of $50,000 per QALY gained, there was a 41.5% probability of albiglutide being cost-effective vs insulin glargine. The probability increased to 49.9% when the willingness-to-pay threshold was increased to $100,000 per QALY gained.

One-way analysis found that the lower BMI associated with albiglutide treatment compared to insulin glargine treatment was the key driver of cost-effectiveness. In the long-term modeling analysis, in years 1–3 BMI was 32.75 kg/m^2 for the albiglutide treatment group compared to 33.67 kg/m^2 for the insulin glargine treatment group (Figure 3). Abolishing this difference resulted in an ICER of $470,788 per QALY gained (Table 7). Additionally, a noteworthy decrease in ICER to $13,454 per QALY gained was observed when an increased disutility decrement value associated with a mild hypoglycemic event was used, based on data from Marrett *et al.*[35].

Albiglutide vs sitagliptin

Base-case analysis

An improvement in mean life expectancy of 0.110 years was seen with albiglutide vs sitagliptin treatment (14.335 years;

Table 6. Cumulative modeled incidence of diabetes-related complications with albiglutide and comparators.

	Albiglutide + insulin glargine	Insulin lispro + insulin glargine	Difference	Albiglutide	Insulin glargine	Difference	Albiglutide	Sitagliptin	Difference
CVD (%)									
CHF death	9.218 (0.888)	9.373 (0.908)	−0.155	9.134 (0.912)	9.595 (0.987)	−0.461	9.860 (0.880)	9.849 (0.923)	0.011
CHF event	12.911 (1.087)	13.223 (1.066)	−0.312	12.728 (1.043)	13.449 (1.113)	−0.721	13.462 (0.992)	13.525 (1.078)	−0.063
PVD onset	13.697 (1.139)	14.005 (1.139)	−0.308	14.418 (1.159)	14.534 (1.207)	−0.116	14.114 (1.093)	14.477 (1.206)	−0.363
Angina	9.529 (0.996)	9.705 (0.955)	−0.176	10.582 (1.041)	10.585 (0.992)	−0.003	10.582 (0.993)	11.042 (0.993)	−0.460
Stoke death	2.538 (0.526)	2.541 (0.481)	−0.003	1.759 (0.420)	1.758 (0.414)	0.001	2.817 (0.534)	2.795 (0.510)	0.022
Stroke event	3.604 (0.589)	3.772 (0.598)	−0.168	4.521 (0.610)	4.562 (0.656)	−0.041	4.796 (0.669)	4.826 (0.686)	−0.030
MI death	7.391 (0.846)	7.622 (0.864)	−0.231	7.413 (0.810)	7.459 (0.784)	−0.046	8.044 (0.922)	8.241 (0.889)	−0.197
MI event	10.583 (1.053)	10.947 (1.012)	−0.364	11.613 (1.040)	11.680 (0.975)	−0.067	12.939 (1.141)	13.286 (1.138)	−0.347
Renal disease (%)									
Microalbuminuria	47.567 (1.664)	47.837 (1.70)	−0.270	44.90 (1.628)	44.810 (1.591)	0.090	47.202 (1.573)	47.652 (1.630)	−0.450
Gross proteinuria	24.225 (1.431)	24.319 (1.320)	−0.094	18.947 (1.270)	18.858 (1.344)	0.089	21.695 (1.347)	22.025 (1.325)	−0.330
End-stage renal disease	13.664 (1.024)	13.671 (1.004)	−0.007	9.032 (0.950)	8.993 (0.897)	0.039	10.047 (0.966)	10.216 (0.931)	−0.169
Eye disease (%)									
Background diabetic retinopathy	31.334 (1.615)	31.651 (1.571)	−0.317	32.374 (1.397)	32.173 (1.561)	0.201	31.328 (1.519)	31.803 (1.523)	−0.475
Proliferative diabetic retinopathy	4.176 (0.643)	4.182 (0.658)	−0.006	3.292 (0.570)	3.302 (0.577)	−0.010	3.099 (0.518)	3.056 (0.550)	0.043
Macular edema	24.520 (1.314)	24.997 (1.332)	−0.477	25.156 (1.360)	24.838 (1.395)	0.318	23.862 (1.381)	24.145 (1.330)	−0.283
Severe vision loss	12.937 (1.076)	13.085 (1.058)	−0.148	12.678 (1.055)	12.421 (1.043)	0.257	12.058 (1.061)	12.299 (1.049)	−0.241
Cataract	11.840 (0.977)	11.760 (0.998)	0.080	12.308 (1.003)	12.112 (1.046)	0.196	12.270 (1.002)	12.293 (1.068)	−0.023
Neuropathic and diabetic foot complications (%)									
Neuropathy	72.288 (1.658)	72.643 (1.590)	−0.355	74.473 (1.567)	74.285 (1.511)	0.188	71.952 (1.525)	72.535 (1.585)	−0.583
Ulcer	49.711 (1.574)	50.083 (1.566)	−0.372	50.558 (1.539)	50.508 (1.554)	0.050	47.495 (1.484)	48.080 (1.592)	−0.585
Recurring ulcer	77.301 (4.483)	77.707 (4.880)	−0.406	75.394 (4.346)	75.447 (4.296)	−0.053	69.325 (4.323)	70.331 (4.487)	−1.006
Amputation following ulcer	17.554 (1.442)	17.531 (1.427)	0.023	17.185 (1.338)	17.197 (1.381)	−0.012	15.818 (1.361)	15.842 (1.354)	−0.024
Amputation following recurring ulcer	9.594 (1.445)	9.491 (1.349)	0.103	9.177 (1.340)	9.188 (1.325)	−0.011	8.449 (1.344)	8.480 (1.322)	−0.031

CHF, congestive heart failure; MI, myocardial infarction; PVD, peripheral vascular disease.

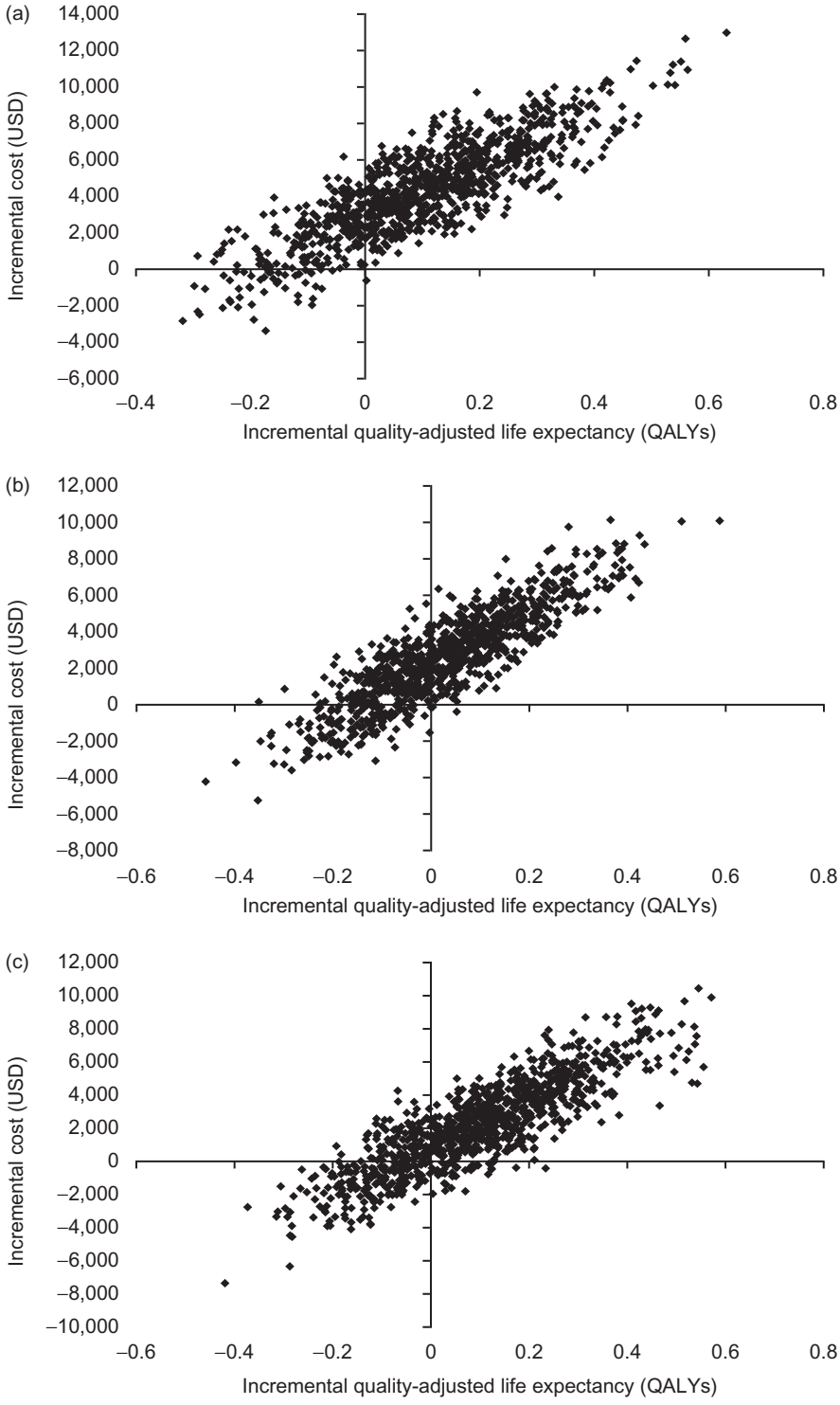

Figure 1. Scatter plots of incremental cost vs incremental effectiveness for albiglutide vs comparator. (a) Albiglutide plus insulin glargine vs insulin lispro plus insulin glargine; (b) albiglutide vs insulin glargine; (c) albiglutide vs sitagliptin. QALY, quality-adjusted life-year; USD, US dollars.

SD = 0.180 vs 14.225 years; SD = 0.190), with mean quality-adjusted life expectancy increasing by 0.101 years (9.618 years; SD = 0.125 vs 9.517 years; SD = 0.130) and fewer diabetes-related complications (Tables 5 and 6). After 1 year, HbA_{1c} decreased by 0.73% with albiglutide and 0.43% with sitagliptin (Table 2, Figure 3)[14]. Over the 50-year time horizon, mean total cost in the albiglutide arm was $2223 more than in the sitagliptin arm, and the ICER was $22,094 per QALY gained (Table 5 and Figure 1).

Sensitivity analysis

There was a 67.5% probability of albiglutide being cost-effective vs sitagliptin at a willingness-to-pay threshold of $50,000 per QALY gained. It increased to 69.8% when the threshold was increased to $100,000 per QALY gained (Figure 2).

The largest effect on the ICER compared with the base-case analysis was observed when the time horizon decreased from 50 years to 5 years, with the ICER increasing to $148,893 per QALY gained (Table 7). Abolishing the HbA_{1c} difference

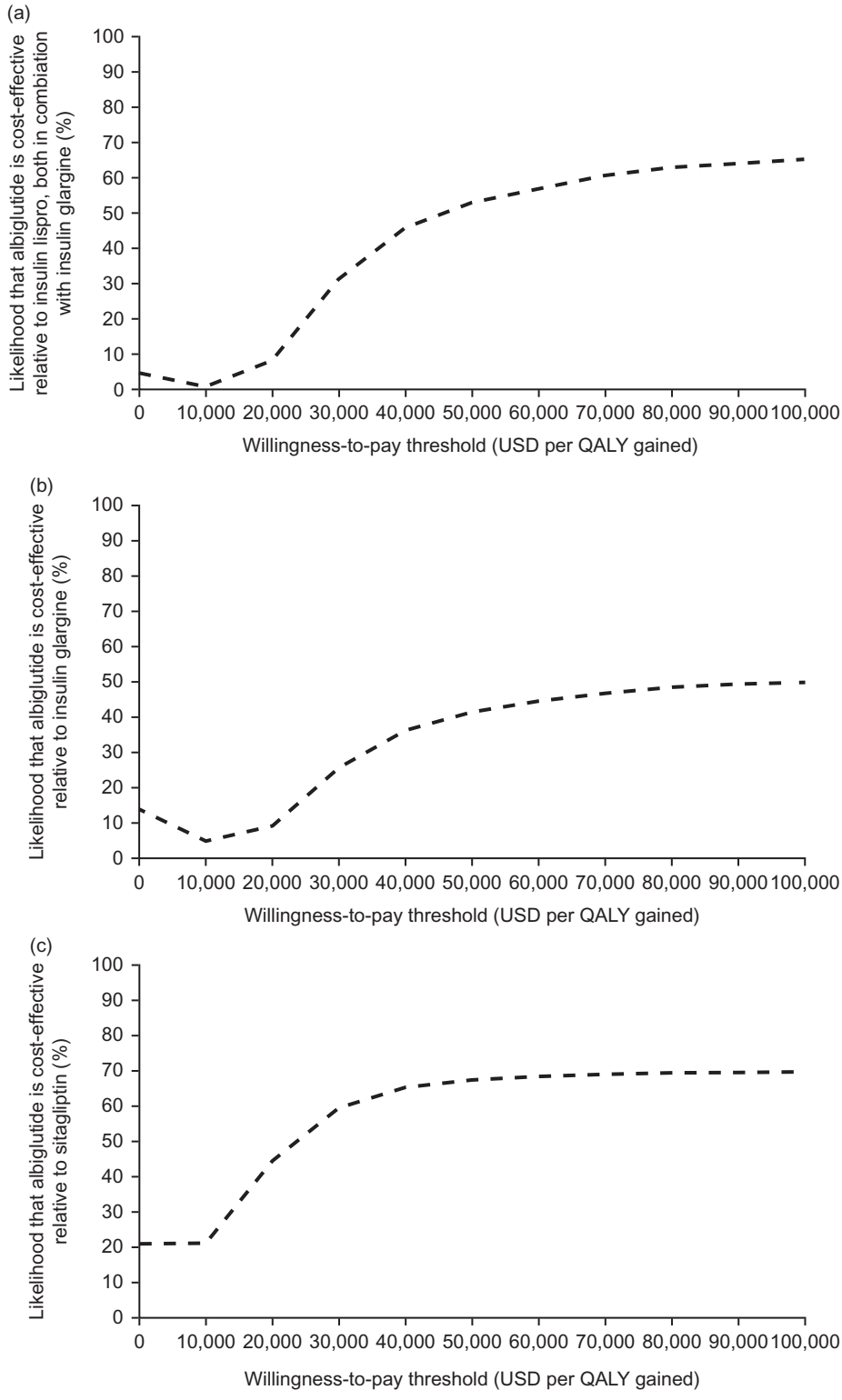

Figure 2. Cost-utility acceptability curves for albiglutide vs comparators. (a) Albiglutide plus insulin glargine vs insulin lispro plus insulin glargine; (b) albiglutide vs insulin glargine; (c) albiglutide vs sitagliptin. QALY, quality-adjusted life-year; USD, United States dollars.

also had a substantial effect, with ICER increasing to $66,714 per QALY gained, indicating that this property was the main driver of incremental benefit for albiglutide vs sitagliptin.

Discussion

This study evaluated the cost-utility of albiglutide treatment in patients with type 2 diabetes compared with other agents for diabetes, based on a US third-party payer perspective. Although the high upfront costs of GLP-1RA, such as albiglutide, may cause physicians to prescribe other medications to treat this disease, without a long-term cost analysis, such decisions may be premature. Furthermore, long-term economic evaluation may bridge the gap between use of surrogate markers in clinical trials with hard outcomes that drive the disease burden in the long-term.

Table 7. Results of sensitivity analysis for albiglutide vs comparators*.

	Albiglutide + insulin glargine vs insulin lispro + insulin glargine			Albiglutide vs insulin glargine			Albiglutide vs sitagliptin		
	Quality-adjusted life expectancy difference, QALY	Direct costs difference, $	ICER (Cost per QALY gained), $	Quality-adjusted life expectancy difference, QALY	Direct costs difference, $	ICER (Cost per QALY gained), $	Quality-adjusted life expectancy difference, QALY	Direct costs difference, $	ICER (Cost per QALY gained), $
Base case	0.100	4332	43,541	0.033	2597	79,166	0.101	2223	22,094
5-year time horizon	0.027	3637	133,234	0.022	2556	117,230	0.010	1548	148,893
10-year time horizon	0.037	3554	96,318	0.021	2549	123,721	0.031	1478	47,840
20-year time horizon	0.070	3740	53,502	0.025	2616	103,007	0.070	1680	23,823
0% discount rate	0.152	5199	34,297	0.044	2852	64,820	0.173	3181	18,390
6% discount rate	0.071	3822	53,902	0.027	2418	90,217	0.064	1771	27,894
Complication costs +10%	0.100	4306	43,276	0.033	2585	78,817	0.101	2183	21,701
Complication costs -10%	0.100	4359	43,805	0.033	2608	79,515	0.101	2262	22,486
US ethnic breakdown	0.084	3930	47,009	0.016	2545	161,069	0.073	1665	22,777
HbA_{1c} difference between treatment groups eliminated	0.091	4371	48,033	0.074	2820	37,951	0.028	1868	66,714
SBP benefit difference between treatment groups eliminated	0.081	4154	51,027	0.018	2667	152,400	0.086	2042	23,797
Lipid benefit difference between treatment groups eliminated	0.089	4193	47,057	0.030	2558	85,851	0.091	2065	22,646
BMI benefit difference between treatment groups eliminated	0.087	4320	49,823	0.005	2542	470,788	0.097	2170	22,443
Marrett hypoglycemia disutility	0.494	4332	8777	0.193	2597	13,454	0.072	2.223	30,913

*Mean (SD), unless noted.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SBP, systolic blood pressure; US, United States.

For type 2 diabetes management decisions, both short-term and long-term costs are important. The American Managed Care Pharmacy (AMCP) internationally recognized guidelines recommend the use in models of both short- and long-term time horizons for chronic diseases[36,37]. Furthermore, surrogate markers of long-term outcomes are evaluated in clinical trials. The CORE Diabetes Model used in this analysis leverages the value of these surrogate markers for predicting long-term outcomes using the United Kingdom Prospective Diabetes Study risk equations[15,16].

In this analysis, albiglutide was associated with a modest improvement in quality-adjusted life expectancy relative to insulin glargine, insulin lispro (both in combination with insulin glargine), and sitagliptin. This improvement was largely driven by mean differences in HbA_{1c} (the primary end-point in the HARMONY studies) and/or by improvements in BMI[12–14]. The projected improvements in life expectancy and quality-adjusted life expectancy were accompanied by an increase in total costs, primarily due to the greater acquisition costs for albiglutide vs the comparator agents. These increases in total costs were partially offset by a reduction in expenditure as a result of a reduction in diabetes-related complications and self-monitoring of blood glucose (compared with those observed with insulin lispro).

At a willingness-to-pay threshold of $100,000 per QALY gained, albiglutide was cost-effective vs all comparators; whereas, at a threshold of $50,000 per QALY gained, albiglutide was cost-effective vs sitagliptin and insulin lispro. A value of $50,000 to $100,000 per QALY gained is commonly cited as a threshold for cost-utility[38], although thresholds greater than $100,000 per QALY gained have been suggested by Braithwaite *et al.*[39] to account for inflation and the perspective of patients, society, and payers.

In sensitivity analyses, shortening the time horizon relative to the base-case analyses consistently resulted in higher ICERs. These increases were likely driven by the up-front costs of albiglutide not being fully balanced by the reduced risk of diabetes complications, which typically emerge over longer periods.

Another aspect that was captured in the sensitivity analysis was the notable relationship between the cost-utility of albiglutide and its ability to improve several drivers of clinical benefit relative to its comparators. For example, eliminating the BMI benefit in the analysis with insulin glargine resulted in an increase in ICER from $79,166 to $470,788, whereas eliminating the HbA_{1c} benefit in the analysis with sitagliptin raised the ICER from $22,094 to $66,714. For BMI, this benefit was seen in years 1–3, while, for HbA_{1c}, the benefit was primarily through years 1–7; thus, the BMI benefit was less affected by discounting. In sensitivity analysis, eliminating differences in individual drivers of clinical benefit resulted in only modest differences in the ICER for albiglutide vs insulin lispro, indicating that the combined effect of all treatment effects produced the overall result, rather than any one difference between treatments.

Additionally, the sensitivity analyses captured the relevance of hypoglycemia in ICER differences between albiglutide and insulin treatment. When a greater hypoglycemia disutility decrement value was used, ICERs substantially

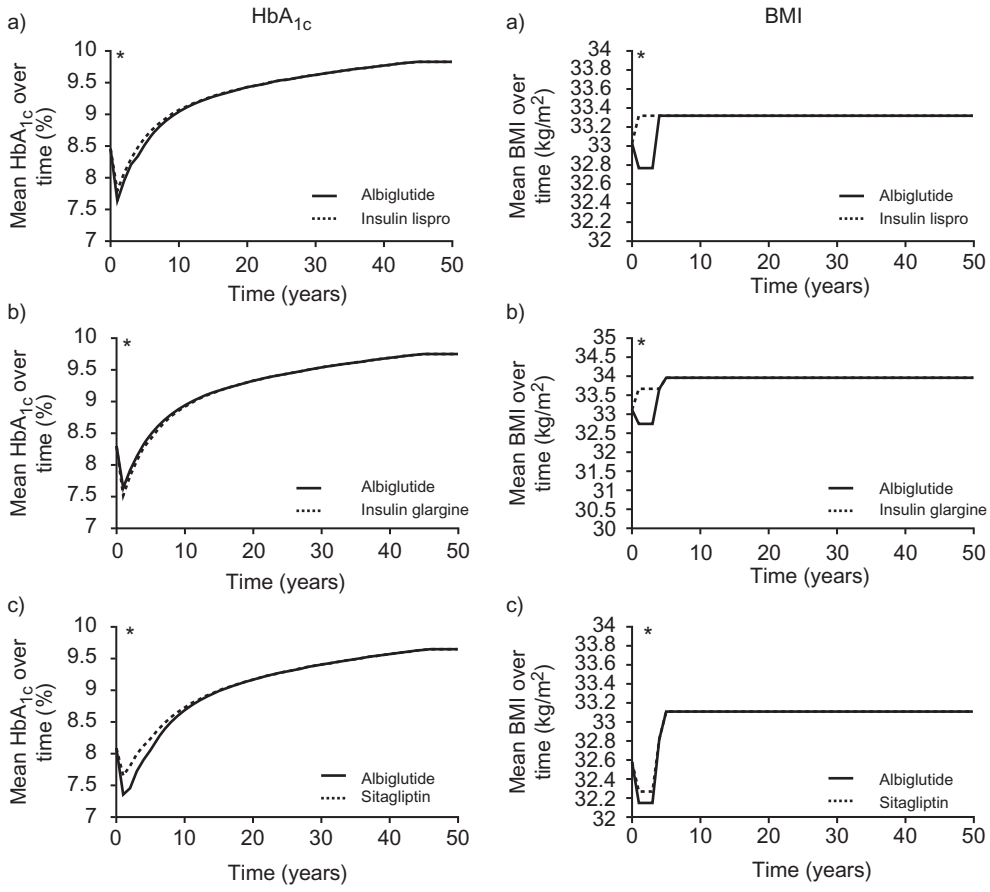

Figure 3. HbA_{1c} and BMI progression. (a) Albiglutide plus insulin glargine vs insulin lispro plus insulin glargine; (b) albiglutide vs insulin glargine; (c) albiglutide vs sitagliptin. * Denotes where plots are initially based on CORE model-derived data. Prior to this, plots based on clinical data: (a) 26-week; (b) 52-week; (c) 104 week.

decreased in the comparisons of albiglutide to insulin lispro (both in combination with insulin glargine) or insulin glargine.

These results are consistent with published analyses of the cost-utility of the GLP-1RA exenatide QW vs insulin glargine and sitagliptin[20,21]. However, direct comparisons between the albiglutide and exenatide QW cost-effectiveness studies cannot be made because of fundamental differences in the study designs and assumptions, such as length of time on study drug and assumptions on persistence of differential effects on HbA_{1c} and BMI after the study drug was stopped.

One limitation of this analysis was that it was an extrapolation over a patient's lifetime (50 years in the base-case analysis) of relatively short-term data obtained during clinical trials. However, the model used has been extensively validated against real-life data and is consistent with published guidance on modeling diabetes[15,16,40]. Because long-term clinical data are not yet available, health economic modeling remains one of the best available options for informed decision-making. Nevertheless, although such models may perform reasonably well in estimating relative risk, they are limited in their ability to predict absolute risk[41].

Another limitation of this study is that the modeling does not take into account potential differences in adherence and persistence between the respective treatments that can influence both effects and costs, particularly those associated with the complications of diabetes. A number of treatment-specific factors have been shown to affect adherence and persistence, including adverse events, cost of medication, and convenience[2,4,42,43]. For example, hypoglycemia and its accompanying anxiety, which can be associated with insulin use[2], can influence healthcare costs and adherence[4,42]. The frequent monitoring of blood glucose levels, which is recommended by the American Diabetes Association for patients taking insulin, can affect adherence because of its effect on quality-of-life and its financial burden[3,43]. The need for frequent injections, which was not included in the methods for this analysis, is also a factor associated with adherence to injectables[43].

The effect of nausea and vomiting on cost utility was not evaluated, although the incidence of this adverse event is greater in patients administered albiglutide compared with insulin lispro[12]. However, because of the transient nature of nausea and vomiting and the low proportion of patients (1.4%) who withdrew owing to this adverse event[12], nausea and vomiting would be anticipated to have a negligible effect on QALY.

Conclusions

In summary, this analysis indicates that albiglutide would modestly increase quality-adjusted life expectancy, partly as a result of increased life expectancy, relative to the combination of insulin lispro and insulin glargine, insulin glargine, or sitagliptin in patients with type 2 diabetes. Albiglutide represents a cost-effective choice compared with other treatments, owing to its reduction in HbA_{1c} and BMI and lower

hypoglycemic events. These results support albiglutide as a reasonable second-line treatment option for patients with type 2 diabetes.

Transparency

Declaration of funding

This study was sponsored by GlaxoSmithKline.

Declaration of financial/other relationships

AM and DB are employees of and own stock in GlaxoSmithKline. RT is an employee of GlaxoSmithKline. RP and BH are full-time employees of Ossian Health Economics and Communications GmbH, which received consulting fees from GlaxoSmithKline to conduct the cost-utility analyses. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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