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Original article

Evaluation of the long-term cost-effectiveness of liraglutide therapy for patients with type 2 diabetes in France

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Abstract**Objectives:**

The present study aimed to compare the projected long-term clinical and cost implications associated with liraglutide, sitagliptin and glimepiride in patients with type 2 diabetes mellitus failing to achieve glycemic control on metformin monotherapy in France.

Methods:

Clinical input data for the modeling analysis were taken from two randomized, controlled trials (LIRA-DPP4 and LEAD-2). Long-term (patient lifetime) projections of clinical outcomes and direct costs (2013 Euros; €) were made using a validated computer simulation model of type 2 diabetes. Costs were taken from published France-specific sources. Future costs and clinical benefits were discounted at 3% annually. Sensitivity analyses were performed.

Results:

Liraglutide was associated with an increase in quality-adjusted life expectancy of 0.25 quality-adjusted life years (QALYs) and an increase in mean direct healthcare costs of €2558 per patient compared with sitagliptin. In the comparison with glimepiride, liraglutide was associated with an increase in quality-adjusted life expectancy of 0.23 QALYs and an increase in direct costs of €4695. Based on these estimates, liraglutide was associated with an incremental cost-effectiveness ratio (ICER) of €10,275 per QALY gained vs sitagliptin and €20,709 per QALY gained vs glimepiride in France.

Conclusion:

Calculated ICERs for both comparisons fell below the commonly quoted willingness-to-pay threshold of €30,000 per QALY gained. Therefore, liraglutide is likely to be cost-effective vs sitagliptin and glimepiride from a healthcare payer perspective in France.

Introduction

Diabetes mellitus (both type 1 and type 2) represents a significant challenge for healthcare providers in France with the prevalence in 2013 estimated at 7.5% and predicted to increase to 8.2% by 2035¹. The disease is associated with a large clinical burden, with 22,953 deaths attributable to diabetes in 2013 in France¹. As well as the clinical burden, diabetes is associated with an economic burden estimated to be between United States dollars (\$) 17–32 billion in 2010, with this predicted to rise to between \$21–40 billion in 2030². The main driver of this expenditure, that accounts for 10% of national healthcare expenditures in France, is treatment of diabetes-related complications². Long-term clinical trials have shown there is potential to reduce this burden by optimizing therapy³.

Traditionally, maintaining glycemic control has formed the cornerstone of diabetes treatment, but evidence suggests that controlling other risk factors is also important in reducing the long-term risk of complications. This includes blood pressure, body weight and serum lipid levels. The benefits of multifactorial intervention have been demonstrated in a number of studies (both clinical trials and cost-effectiveness analyses), including the Steno-2 study, which compared conventional treatment for multiple risk factors vs intensive multifactorial treatment^{4–8}. Intensive treatment was associated with reduced risk of all-cause mortality, cardiovascular events, end-stage renal disease, retinopathy, and neuropathy, over 13 years of follow-up. Most long-established diabetes interventions have been shown to improve glycemic control, but do little to address other risk factors (such as weight gain, hypoglycemia, and systolic blood pressure), and meet the multifaceted needs of modern patients with type 2 diabetes⁹.

Clinical development programs have targeted the modulation of incretin activity to identify new therapeutic options that better meet the need for a multi-factorial intervention in diabetes¹⁰. This has led to the development of two new classes of anti-diabetic agents: degradation-resistant glucagon-like peptide-1 (GLP-1) receptor agonists (that mimic the action of GLP-1), such as liraglutide, and inhibitors of dipeptidyl peptidase-4 (DPP-4, the protease that rapidly degrades GLP-1), such as sitagliptin.

Whilst the interventions that target the incretin axis may provide a more complete approach to treatment of type 2 diabetes than traditional second-line interventions, such as sulfonylurea, they also come at an increased acquisition cost in the short-term, although this can be partially offset by the avoidance of treatment of diabetes-related complications as a result of better control. In a healthcare system with limited funds, the aim is to maximize health outcomes across the population with the finite resources available. Healthcare payers must make decisions on how best to allocate scarce resources to maximize health outcomes across the population. Economic evaluations of alternative treatment strategies (e.g., new and existing medications) are playing an increasingly important role in informing these decisions^{11,12}. The majority of economic evaluations are based on modeling techniques which allow projections of long-term costs and clinical outcomes, allowing healthcare payers to make decisions before long-term clinical trials evaluating these drugs are available. This is particularly relevant to the French setting, where the Haute Autorité de Santé (HAS) has recently released revised guidelines on the conduct of health economic evaluation (including type of analysis, perspective, population, interventions, time horizon, discounting, calculation of cost-effectiveness, and modeling methods)¹³. This, along with the changing legislation around approval of pharmaceuticals in France, has led to

an increased interest in health technology assessment in the French setting over recent years.

Cost-effectiveness analyses of liraglutide have been published for the other settings, but, to date, no such analysis has been conducted for France^{14,15}. The aim of the present analysis was to assess the cost-effectiveness of liraglutide 1.2 mg vs sitagliptin, and vs glimepiride, as an add-on to metformin in patients with type 2 diabetes mellitus failing to achieve glycemic control on metformin monotherapy in France.

Methods

Clinical data sources

Two cost-effectiveness analyses were performed based on the LIRA-DPP4 trial (liraglutide vs sitagliptin) and the LEAD-2 study (liraglutide vs glimepiride)^{16–18}. The LIRA-DPP4 trial study enrolled patients with type 2 diabetes mellitus who had inadequate glycemic control (HbA1c 7.5–10.0%) on metformin in Europe and North America. Patients were randomly allocated to receive 1.2 mg liraglutide ($n = 225$), 1.8 mg liraglutide ($n = 221$), or 100 mg sitagliptin ($n = 219$) with metformin treatment continued. The LEAD-2 study enrolled patients with HbA1c between 7–11% (if previously treated with oral hypoglycemic agent monotherapy for at least 3 months) or HbA1c 7–10% (if previously treated with oral hypoglycemic agent combination therapy for at least 3 months). Patients were randomly allocated to receive 0.6 mg liraglutide ($n = 242$), 1.2 mg liraglutide ($n = 240$), 1.8 mg liraglutide ($n = 242$), 4 mg glimepiride ($n = 242$), or placebo ($n = 121$), all plus metformin. However, only the subgroup of patients in which liraglutide or glimepiride was added to ongoing metformin monotherapy (~30% of the total trial population) was included in the present analyses, as this was considered to be more reflective of clinical practice and brings the analysis into line with the sitagliptin comparison.

Model description

The cost-effectiveness analysis was performed using the IMS CORE Diabetes Model (IMS Health, Basel, Switzerland), the architecture, assumptions, features, and capabilities of which have been previously published¹⁹. The model is a validated, non-product specific diabetes policy analysis tool and is based on a series of inter-dependent sub-models that simulate the complications of diabetes (angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular edema, cataract, hypoglycemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer and amputation, and non-specific mortality)^{20,21}. Each sub-model has a

semi-Markov structure and uses time, state, time-in-state and diabetes type-dependent probabilities derived from published sources. Monte Carlo simulation using tracker variables overcomes the memory-less properties of the standard Markov model, and allows interconnectivity and interaction between individual complication sub-models. Long-term outcomes projected by the model have been validated against real life data in 2004 and more recently in 2014^{20,21}.

The model was used to project life expectancy, quality-adjusted life expectancy, cumulative incidence of diabetes-related complications, time to onset of diabetes-related complications and direct medical costs based on the outcomes of the LIRA-DPP4 and LEAD-2 studies. Future costs and clinical benefits were discounted symmetrically by 3% *per annum* in line with published health economic guidance for France¹³. The time horizon was set to patient lifetimes in the base case to capture all relevant long-term complications, associated costs, and to assess their impact on life expectancy and quality-adjusted life expectancy.

Simulated cohort and treatment effects

The baseline cohort characteristics were taken from the LIRA-DPP4 trial and the LEAD-2 trial sub-group (Table 1). In the analysis of liraglutide vs sitagliptin, treatment effects applied in the first year of the modeling analysis were taken from the 52-week end-point of the trial (Table 2), as using the longest-duration data available from the trial was considered the most appropriate approach to inform long-term modeling. In the comparison of liraglutide and glimepiride, treatment effect data were based on the 26-week trial data (Table 2). Assumptions regarding progression of risk factors in the following years of the simulation were aligned with the cost-effectiveness analysis of liraglutide in the Spanish

Table 1. Baseline characteristics of the simulated cohorts.

Characteristic	LIRA-DPP4 ¹⁶ (mean (SD))	LEAD-2 ¹⁸ (mean (SD))
Age (years)	55.3 (9.2)	55.8 (9.0)
Duration of diabetes (years)	6.0 (4.5)	6.0 (4.7)
Males (%)	52.9	54.2
HbA1c (%)	8.4 (0.8)	8.3 (1.1)
SBP (mmHg)	132.2 (14.6)	130.6 (14.0)
Total cholesterol (mg/dL)	185.1 (44.1)	188.6 (43.3)
HDL cholesterol (mg/dL)	44.6 (12.1)	49.7 (12.6)
LDL cholesterol (mg/dL)	102.3 (31.6)	119.9 (34.4)
Triglycerides (mg/dL)	210.5 (196.3)	194.1 (146–9)
Body mass index (kg/m ²)	32.8 (5.2)	31.0 (4.7)

HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein SBP, systolic blood pressure; SD, standard deviation. In the LEAD-2 analysis only patients in which liraglutide or glimepiride was added to ongoing metformin monotherapy (~30% of the total trial population) were included, as this was considered to be more reflective of clinical practice and brings the analysis into line with the LIRA-DPP4 comparison.

Table 2. Treatment effects applied in the first year of the analysis.

Physiological parameter	Liraglutide vs sitagliptin ¹⁷			Liraglutide vs glimepiride ¹⁸		
	Liraglutide 1.2 mg (mean (SD))	Sitagliptin 100 mg (mean (SD))	Difference	Liraglutide 1.2 mg (mean (SD))	Glimepiride 4 mg (mean (SD))	Difference
Change in HbA1c (%)	-1.29 (1.05)	-0.88 (1.04)	-0.41	-1.25 (1.02)	-1.16 (0.97)	-0.10
Change in SBP (mmHg)	-0.37 (13.95)	-1.03 (13.76)	+0.66	-3.33 (12.90)	+2.26 (12.65)	-5.59
Change in total cholesterol (mg/dL)	-0.39 (34.80)	1.16 (34.34)	-1.55	-0.77 (21.72)	+3.31 (30.88)	-4.07
Change in HDL cholesterol (mg/dL)	0.39 (5.80)	0.39 (5.72)	0.00	+0.79 (8.02)	-0.82 (7.84)	+1.62
Change in LDL cholesterol (mg/dL)	3.48 (29.00)	6.57 (28.61)	-3.09	+5.73 (26.42)	+8.49 (25.71)	-2.76
Change in triglycerides (mg/dL)	-8.86 (132.86)	-20.37 (131.07)	+11.51	-39.27 (114.28)	-0.82 (7.84)	-17.43
Change in body mass index (kg/m ²)	-0.93 (—)	-0.33 (—)	-0.57	-0.64 (0.95)	+0.48 (3.69)	-1.12
Major hypoglycemic events (per 100 patient years)	0.60	0.00	+0.60	0.00	0.00	0.00
Minor hypoglycemic events (per 100 patient years)	14.30	13.70	+0.60	4.90	217.20	-212.30

HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein SBP, systolic blood pressure; SD, standard deviation. In the LEAD-2 analysis only patients in which liraglutide or glimepiride was added to ongoing metformin monotherapy (~30% of the total trial population) were included, as this was considered to be more reflective of clinical practice and brings the analysis into line with the LIRA-DPP4 comparison.

setting¹⁵. HbA1c was assumed to remain unchanged for the duration of the analysis. As such, the treatment-specific HbA1c reduction was applied at year 1 of the analysis and maintained for the rest of the simulation. A relatively constant HbA1c level may be a plausible assumption under adequate monitoring and timely treatment intensification, as demonstrated in the Action in Diabetes and Vascular disease (ADVANCE) trial²². With this assumption, it was also possible to capture the legacy effect, whereby early benefits in glycemic control are maintained, even after the HbA1c reduction no longer persists, as this is not otherwise explicitly captured in the model²³. Systolic blood pressure increased based on the UKPDS progression equation, whilst serum lipids followed the Framingham progression equations¹⁹. Patients were assumed to receive liraglutide, sitagliptin, or glimepiride for 5 years, before intensifying treatment to basal insulin (previous therapy withdrawn). Alternative assumptions around timing of treatment switching were evaluated in sensitivity analyses. On treatment intensification, BMI differences between the treatment arms were abolished and hypoglycemic event rates were assumed to be the same in both arms, but no other treatment effects were applied. Treatment costs were considered to be equivalent in all arms when patients were receiving basal insulin (based on the defined daily dose of insulin glargine), as this is likely to be a conservative assumption.

Estimation of direct costs and health state utilities

In the base case analyses, costs were accounted from a healthcare payer perspective in France. The costs of diabetes medications, self-monitoring of blood glucose, concomitant medications (statins, aspirin, and angiotensin-converting enzyme inhibitors), and diabetes-related complications were captured (supplementary information). Costs were identified through a literature search of the Medline database, with searches carried out in October 2013. Articles published in both French and English were included. Where necessary, costs were inflated to 2013 values, using the consumer prices index²⁴. Health state utilities used in the analysis were as per previously published cost-effectiveness analyses of liraglutide^{14,15}.

Sensitivity analysis

A series of sensitivity analyses were conducted to identify key drivers of outcomes and assess the robustness of results of the two analyses. The influence of time horizon on the outcomes projected by the model was investigated by running analyses over 5, 10, and 20 years. Similarly, the effect of alternative discount rates on calculated outcomes was investigated in analyses in which they were set to 0% and 5% *per annum*. Analyses with indirect costs included were

conducted, to capture the impact of lost workplace productivity. Literature review only identified French-specific days off work estimates following a major hypoglycemic event, and, therefore, estimates for other complications came from other settings^{25,26}. The impact of using an alternative source for the cost of complications was assessed using values identified in an alternative literature review (all values differed from the base case analysis)²⁷. The importance of changes in physiological parameters were investigated in five sensitivity analysis for each comparison, with differences in HbA1c, systolic blood pressure, blood lipids, BMI, and hypoglycemic event rates individually abolished between the liraglutide and comparator arms. A further analysis in which only statistically significant differences between treatments were applied was performed for each comparison. For each comparison, two analyses were conducted using alternative assumptions around long-term progression of HbA1c. In the first, the HbA1c values in the two treatment arms became equal on intensification, while in the second HbA1c was assumed to progress according to the UKPDS progression curve for the duration of the analysis. The effect of the timing of treatment switching was examined by varying the treatment switch to 7 and 3 years in both arms of the analyses. Analyses in which patients switched from liraglutide 1.2 mg to liraglutide 1.8 mg after 2 years of treatment were conducted. Only costs were altered in these analyses, with clinical outcomes remaining unchanged as data to inform these changes were not available (it is likely that this is a conservative assumption). A scenario was evaluated in which the baseline cohort was based on the patients enrolled in the EVIDENCE study, an observational study of liraglutide in the French setting, representing a typical cohort of patients with type 2 diabetes receiving liraglutide in France²⁸. A probabilistic sensitivity analysis was performed, with sampling around all model variables based on default distributions defined by the IMS CORE Diabetes Model.

Results

Liraglutide vs sitagliptin: base case

Treatment with liraglutide was associated with increases in discounted life expectancy and quality-adjusted life expectancy of 0.19 years (95% confidence interval [CI] = 0.17–0.21) and 0.25 quality-adjusted life years (QALYs, 95% CI = 0.24–0.26) in comparison with treatment with sitagliptin (Table 3). The clinical benefits in the liraglutide arm were primarily driven by improved glycemic control with liraglutide over sitagliptin, resulting in a reduction in the incidence of all diabetes-related complications. The mean time to onset of diabetes-related complications was also increased with liraglutide, with

Table 3. Cost-effectiveness outcomes of the base case analyses.

Liraglutide vs sitagliptin	Liraglutide 1.2 mg (mean (SD))	Sitagliptin 100 mg (mean (SD))	Difference
Undiscounted life expectancy (years)	23.46 (0.37)	23.05 (0.37)	+0.41
Discounted life expectancy (years)	15.62 (0.20)	15.43 (0.20)	+0.19
Discounted quality-adjusted life expectancy (QALYs)	10.09 (0.13)	9.84 (0.13)	+0.25
Discounted direct costs (EUR)	43,031 (1532)	40,472 (1513)	+2558
ICER (EUR per QALY gained)			10,275

Liraglutide vs glimepiride	Liraglutide 1.2 mg (mean (SD))	Glimepiride (mean (SD))	Difference
Undiscounted life expectancy (years)	23.48 (0.39)	23.16 (0.36)	+0.32
Discounted life expectancy (years)	15.63 (0.21)	15.47 (0.19)	+0.16
Discounted quality-adjusted life expectancy (QALYs)	10.25 (0.14)	10.02 (0.13)	+0.23
Discounted direct costs (EUR)	41,481 (1339)	36,786 (1229)	+4695
ICER (EUR per QALY gained)			20,709

EUR, 2013 Euros; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

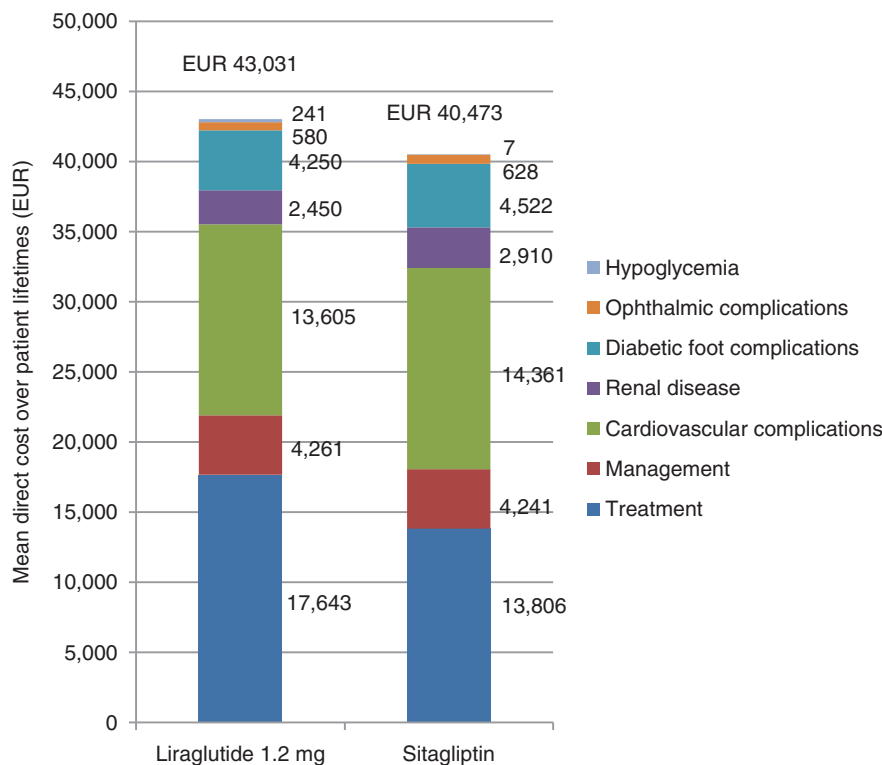


Figure 1. Mean direct costs associated with liraglutide 1.2 mg and sitagliptin over patient lifetimes. EUR, 2013 Euros.

the mean time free from all complications increased from 6.8 years with sitagliptin to 7.7 years with liraglutide.

Liraglutide was associated with higher mean direct costs vs sitagliptin by €2558 per patient (95% CI = €2427–€2689). This increase was driven by the increased acquisition costs of liraglutide over sitagliptin in the first 5 years of the simulation (Figure 1). However, the higher pharmacy costs were partially offset by the reduced costs of treating diabetes-related complications. The most notable savings were made as a result of cardiovascular complications avoided, where treatment with liraglutide was

associated with cost savings of €756 per patient. Based on these estimates, liraglutide was associated with an incremental cost-effectiveness ratio (ICER) of €10,275 per QALY gained vs sitagliptin in France.

Liraglutide vs sitagliptin: sensitivity analyses

Sensitivity analyses (shown in full in Table 4) found that the cost-effectiveness outcomes were most sensitive to changes in the time horizon of the modeling analysis. As the time horizon was reduced, the ICER increased, with a

Table 4. Liraglutide vs sitagliptin: Results of the sensitivity analyses.

Analysis	Quality-adjusted life expectancy (QALYs)			Costs (EUR)		ICER (EUR per QALY gained)
	Liraglutide	Sitagliptin	Difference (95% CI)	Liraglutide	Sitagliptin	
Base case	10.09	9.84	0.25 (0.24–0.26)	43,031	40,473	10,275
Indirect costs included	10.09	9.84	0.25 (0.24–0.26)	50,747	48,458	9197
20-year time horizon	8.33	8.17	0.15 (0.15–0.16)	32,005	28,636	22,028
10-year time horizon	5.39	5.33	0.06 (0.06–0.06)	19,258	15,598	61,634
5-year time horizon	3.09	3.05	0.03 (0.03–0.04)	11,626	7776	114,401
0% discount rate	14.86	14.40	0.46 (0.44–0.48)	68,274	66,268	4372
5% discount rate	8.15	7.98	0.17 (0.17–0.18)	33,538	30,829	15,606
Alternative costs of complications	10.09	9.85	0.25 (0.24–0.26)	40,156	37,825	9457
No HbA1c difference	9.89	9.84	0.05 (0.03–0.05)	44,304	40,473	81,511
No SBP difference	10.10	9.84	0.26 (0.25–0.27)	43,062	40,473	10,113
No lipid difference	10.10	9.84	0.26 (0.24–0.27)	43,227	40,473	10,511
No BMI difference	10.05	9.84	0.21 (0.19–0.21)	43,189	40,473	12,933
No hypoglycemia difference	10.10	9.84	0.26 (0.24–0.26)	42,932	40,473	9643
Statistically significant differences only	10.10	9.84	0.26 (0.24–0.26)	43,132	40,473	10,387
HbA1c difference abolished on treatment switching	9.98	9.84	0.14 (0.12–0.14)	44,067	40,473	25,856
UKPDS creep	9.38	9.28	0.10 (0.09–0.11)	49,350	45,541	38,090
Treatment switch after 7 years	10.13	9.87	0.26 (0.25–0.27)	44,327	40,239	15,641
Treatment switch after 3 years	10.07	9.84	0.23 (0.22–0.24)	42,189	40,825	5951
Switch to liraglutide 1.8 mg after 2 years	10.07	9.84	0.25 (0.24–0.26)	44,723	40,473	17,071
France-specific cohort	9.05	8.81	0.24 (0.23–0.26)	47,065	44,377	10,994
Probabilistic sensitivity analysis	9.80	9.56	0.24 (0.23–0.25)	44,837	42,038	11,777

BMI, body mass index; CI, confidence interval; EUR, 2013 Euros; HbA1c; glycated hemoglobin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SBP, systolic blood pressure; UKPDS, United Kingdom Prospective Diabetes Study.

5-year time horizon producing an ICER of €114,401 per QALY gained. This was primarily due to the improvements in physiological parameters associated with liraglutide reducing the risk of long-term complications, as these benefits are not fully realized over shorter time horizons. Changing the discount rate also reflected the long-term benefits associated with liraglutide, with the ICER increasing when a discount rate of 5% was applied, and falling when a discount rate of 0% was applied.

Abolishing each of the treatment effects in turn identified that the key driver of improved health outcomes with liraglutide was the improvement in HbA1c. When this difference was abolished (i.e., the change was assumed to be the same as in the sitagliptin arm), the incremental quality-adjusted life expectancy benefit fell from 0.25 QALYs to 0.05 QALYs, and the ICER increased to €81,511 per QALY gained. Removing other treatment differences and applying only statistically significant differences had a smaller impact on the outcomes relative to the base case. Using alternative assumptions (either assuming that HbA1c was equal following treatment intensification or using the UKPDS progression curve) around the long-term progression of HbA1c resulted in changes in the cost-effectiveness outcomes, with ICERs increased when the alternative approaches were used.

Changing the timing of treatment switching led to changes in the ICER. It was found to increase when patients received incretin therapy for 7 years, due to the increased acquisition costs of liraglutide, and fell when treatment switching was brought forward. Switching

patients receiving liraglutide from 1.2 mg to 1.8 mg after 2 years led to an increased ICER of €17,071 per QALY gained, due to the increased acquisition cost of the higher liraglutide dose.

Taking into account indirect as well as direct costs reduced the cost increase associated with liraglutide and consequently the ICER decreased by ~€1000 per QALY gained (from €10,275 to €9197 per QALY gained).

Liraglutide vs sitagliptin: PSA

PSA with sampling around cohort characteristics, treatment effects, complication costs, and utilities showed similar mean results to the base case, but increased measures of variance around the mean outcomes. The mean incremental improvement in quality-adjusted life expectancy with liraglutide was 0.24 QALYs at an increased cost of €2799 vs sitagliptin. This produced an ICER of €11,777 per QALY gained. The incremental cost-effectiveness scatterplot presents the incremental costs vs incremental effectiveness (QALYs gained) for liraglutide vs sitagliptin (Figure 2), and shows 1000 mean values, each from a cohort of 1000 patients run through the model with sampling from distributions around model input parameters. The majority (80.1%) of points fell in the upper right quadrant, with both increased effectiveness (i.e., incremental quality-adjusted life expectancy) and increased total costs for liraglutide compared with sitagliptin. The data from the scatterplot were used to generate a cost-effectiveness acceptability curve (CEAC, Figure 3).

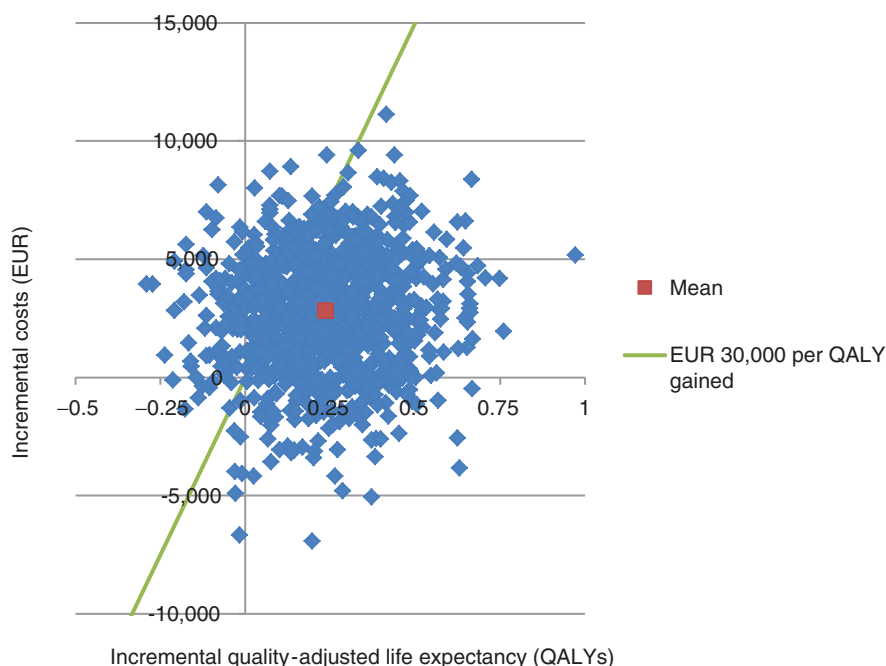


Figure 2. Liraglutide vs sitagliptin: Cost-effectiveness scatterplot for the probabilistic sensitivity analyses. EUR, 2013 Euros, QALY, quality-adjusted life year.

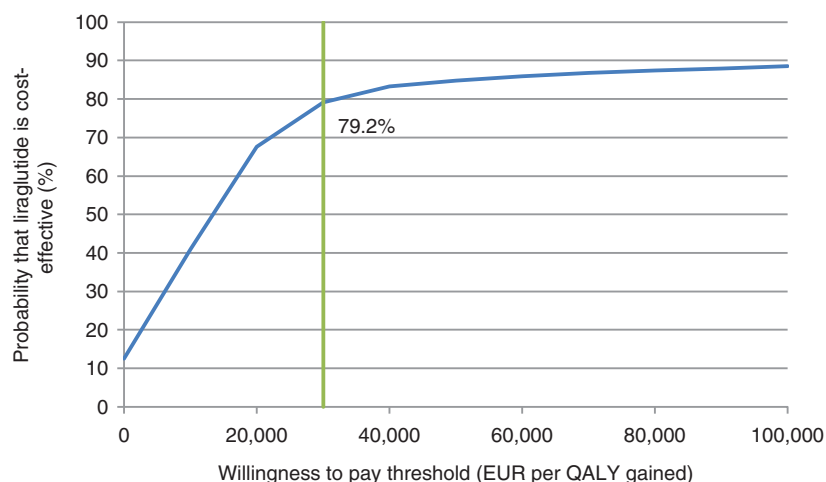


Figure 3. Liraglutide vs sitagliptin: Cost-effectiveness acceptability curve for the probabilistic sensitivity analysis. EUR, 2013 Euros; QALY, quality-adjusted life year.

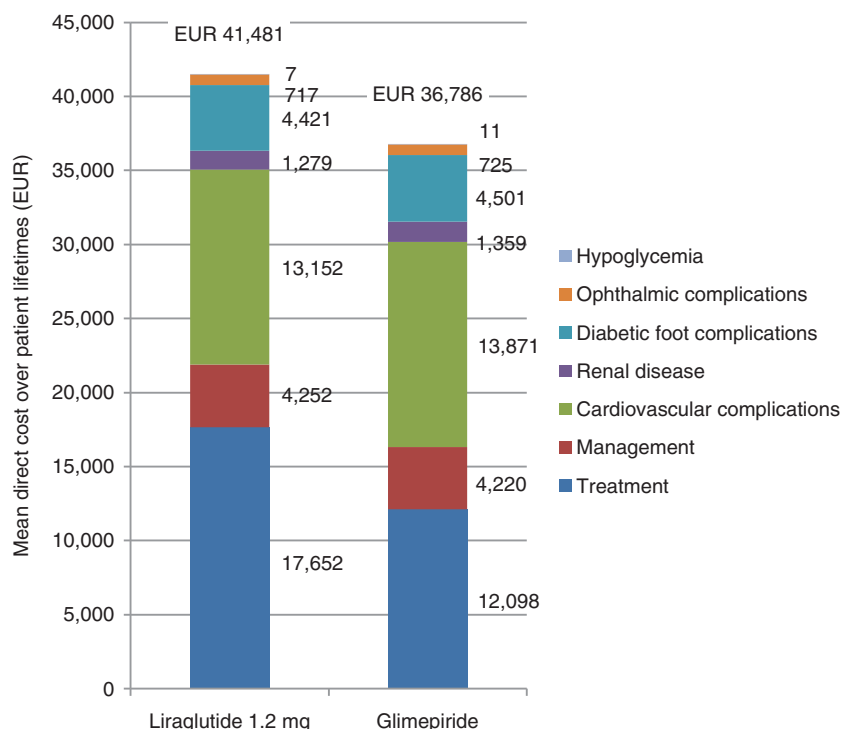


Figure 4. Mean direct costs associated with liraglutide 1.2 mg and glimepiride over patient lifetimes EUR, 2013 Euros; QALYs, quality-adjusted life years.

Based on this analysis, assuming a willingness-to-pay threshold of €30,000 per QALY gained, the modeling analysis indicated that there was a 79.2% probability that liraglutide would be cost-effective vs sitagliptin.

Liraglutide vs glimepiride: base case

Liraglutide therapy was associated with increased discounted life expectancy by 0.16 years (95% CI = 0.14–0.18 years) and increased discounted quality-adjusted life

expectancy by 0.23 QALYs (95% CI = 0.22–0.24) compared with glimepiride (Table 3). The clinical benefits in the liraglutide arm were primarily driven by a reduction in BMI with liraglutide over glimepiride. The mean time to onset of diabetes-related complications was increased with liraglutide, with the mean time free from all complications increased from 6.3 years with glimepiride to 6.6 years with liraglutide.

Liraglutide was associated with increased mean direct costs by €4695 (95% CI = €4582–€4807), vs glimepiride

(Figure 4). This increase in costs was driven by the increased acquisition cost of liraglutide over glimepiride during the first 5 years of the simulation. However, this was partially offset by the reduced costs of treating diabetes-related complications; most notably cardiovascular complications where liraglutide was associated with mean savings of €719. These projections of cost and clinical outcomes produced an ICER of €20,709 per QALY gained.

Liraglutide vs glimepiride: sensitivity analyses

As in the comparison with sitagliptin, sensitivity analyses for the liraglutide vs glimepiride comparison (Table 5) found that outcomes were most sensitive to changes in time horizon. At a time horizon of 5 years the ICER increased to €57,285 per QALY gained. As in the analysis vs sitagliptin, this was as a result of the long-term benefits of liraglutide therapy not being fully captured at shorter time horizons. Applying alternative discount rates also showed the long-term benefits associated with liraglutide. Removing differences between the treatment arms identified that the key driver of cost-effectiveness was the reduction in BMI with liraglutide, as opposed to a BMI increase with glimepiride. In the scenario with no difference in BMI, the ICER was €27,675 per QALY gained. Applying only the statistically significant differences (of BMI and systolic blood pressure) resulted in an ICER of €35,884 per QALY gained. Using alternative assumptions (either assuming that HbA1c was equal following treatment intensification or using the UKPDS progression curve) around the long-term progression of HbA1c resulted in changes in the cost-effectiveness outcomes, with ICERs increased when the alternative approaches were used, but these remained below €30,000 per QALY gained.

Changing the timing of treatment switching led to changes in the ICER. ICERs increased when patients received liraglutide or glimepiride for 7 years, and fell when treatment switching was brought forward. Switching patients receiving liraglutide from 1.2 mg to 1.8 mg after 2 years led to an increased ICER of €28,533 per QALY gained, due to the increased acquisition cost of the higher liraglutide dose.

Taking into account indirect as well as direct costs reduced the cost increase associated with liraglutide and consequently the ICER decreased by ~€1200 per QALY gained.

Liraglutide vs glimepiride: PSA

PSA with sampling around cohort characteristics, treatment effects, complication costs, and utilities showed similar mean results to the base case, but increased measures

of variance around the mean outcomes. The mean incremental improvement in quality-adjusted life expectancy with liraglutide was 0.23 QALYs at an increased cost of €4495 vs glimepiride. This resulted in an ICER of €19,803 per QALY gained. The incremental cost-effectiveness scatterplot presents the incremental costs vs incremental effectiveness (QALYs gained) for liraglutide vs glimepiride (Figure 5), and shows 1000 mean values, each from a cohort of 1000 patients run through the model with sampling from distributions around model input parameters. The majority (86.6%) of points fell in the upper right quadrant with both increased effectiveness (i.e. incremental quality-adjusted life expectancy) and increased total costs for liraglutide compared with glimepiride. The data from the scatterplot were used to generate a cost-effectiveness acceptability curve (Figure 6). Based on this analysis, assuming a willingness-to-pay threshold of €30,000 per QALY gained, the modeling analysis indicated that there was a 65.0% probability that liraglutide would be cost-effective vs glimepiride.

Discussion

The present long-term cost-effectiveness analyses have demonstrated that liraglutide 1.2 mg is associated with improved life expectancy and quality-adjusted life expectancy compared with sitagliptin and glimepiride. Clinical improvements in both comparisons resulted from a reduced incidence and increased time to onset of diabetes-related complications. The gains in quality-adjusted life expectancy with liraglutide over alternative treatments are likely to be considered significant by a health-care payer. Liraglutide was associated with an increase in direct medical costs over patient lifetimes in both comparisons. This was due to increased pharmacy costs with liraglutide over the short-term, but was partially offset by reduced costs of treating diabetes-related complications over the long-term. Based on the projected outcomes, liraglutide was associated with ICERs of €10,436 and €20,709 per QALY gained vs sitagliptin and glimepiride, respectively, in the French setting for patients with type 2 diabetes not achieving glycemic targets on metformin monotherapy. These ICERs fall below the commonly quoted willingness-to-pay threshold of €30,000 per QALY gained, and, therefore, liraglutide is likely to be considered cost-effective. As interest in economic evaluation of new health technologies in France increases, the results of studies such as the present analysis are likely to become increasingly important for healthcare decision-making.

Metformin remains the first-line therapy for patient with type 2 diabetes, but modulation of incretin activity, through addition of a GLP-1 receptor agonist or a DPP-4 inhibitor, represents a potential therapy option

Table 5. Liraglutide vs glimepiride: Results of the sensitivity analyses.

Analysis	Quality-adjusted life expectancy (QALYs)			Costs (EUR)		ICER (EUR per QALY gained)
	Liraglutide	Glimepiride	Difference (95% CI)	Liraglutide	Glimepiride	
Base case	10.25	10.02	+0.23 (0.22–0.24)	41,481	36,786	+4695 (4582–4807)
Indirect costs included	10.25	10.02	+0.23 (0.22–0.24)	49,466	45,050	+4417 (4299–4534)
20-year time horizon	8.42	8.27	+0.16 (0.15–0.17)	30,586	25,764	+4822 (4736–4908)
10-year time horizon	5.44	5.33	+0.11 (0.11–0.11)	18,095	13,038	+5057 (4999–5114)
5-year time horizon	3.12	3.03	+0.09 (0.09–0.09)	10,665	5401	+5265 (5232–5298)
0% discount rate	15.14	14.77	+0.37 (0.34–0.39)	66,167	61,470	+4697 (4499–4896)
5% discount rate	8.27	8.09	+0.18 (0.17–0.19)	32,149	27,641	+4507 (4423–4592)
Alternative costs of complications	10.25	10.02	+0.23 (0.22–0.24)	39,565	34,703	+4952 (4830–5075)
No HbA1c difference	10.21	10.02	+0.19 (0.18–0.20)	41,783	36,786	+4997 (4892–5103)
No SBP difference	10.21	10.02	+0.19 (0.18–0.20)	41,772	36,786	+4986 (4798–5013)
No lipid difference	10.21	10.02	+0.19 (0.17–0.20)	41,740	36,786	+4954 (4850–5058)
No BMI difference	10.19	10.02	+0.17 (0.16–0.18)	41,463	36,786	+4677 (4570–4783)
No hypoglycemia difference	10.22	10.02	+0.20 (0.18–0.21)	41,501	36,786	+4715 (4523–4748)
Statistically significant differences only	10.17	10.02	+0.15 (0.13–0.16)	42,061	36,786	+5275 (5099–5291)
HbA1c difference abolished on treatment switching	10.24	10.02	+0.22 (0.20–0.23)	41,693	36,786	+4907 (4720–4934)
UKPDS creep	9.55	9.36	+0.19 (0.18–0.20)	47,068	42,338	+4730 (4591–4869)
Treatment switch after 7 years	10.29	10.02	+0.26 (0.25–0.27)	42,529	35,941	+6588 (6473–6703)
Treatment switch after 3 years	10.23	10.03	+0.20 (0.19–0.21)	40,463	37,868	+2595 (2486–2705)
Switch to liraglutide 1.8 mg after 2 years	10.25	10.02	+0.23 (0.22–0.24)	43,263	36,786	+6477 (6364–6589)
France-specific cohort	9.25	9.01	+0.24 (0.23–0.25)	46,590	42,119	+4471 (4305–4638)
Probabilistic sensitivity analysis	9.90	9.68	+0.23 (0.22–0.24)	42,697	38,201	+4495 (4370–4620)

BMI, body mass index; CI, confidence interval; EUR, 2013 Euros; HbA1c; glycated hemoglobin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SBP, systolic blood pressure; UKPDS, United Kingdom Prospective Diabetes Study.

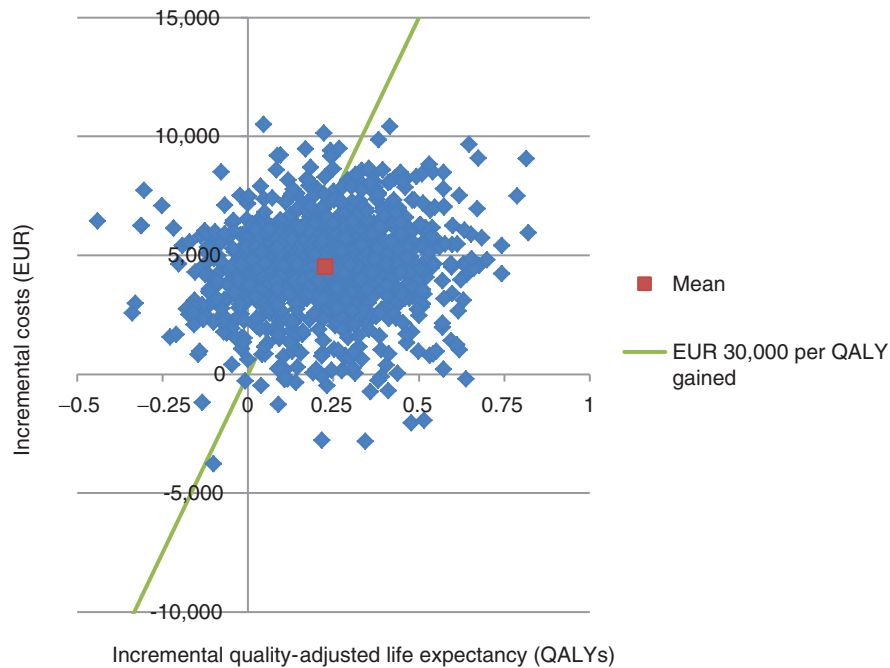


Figure 5. Liraglutide vs glimepiride: Cost-effectiveness scatterplot for the probabilistic sensitivity analyses. EUR, 2013 Euros, QALY, quality-adjusted life year.

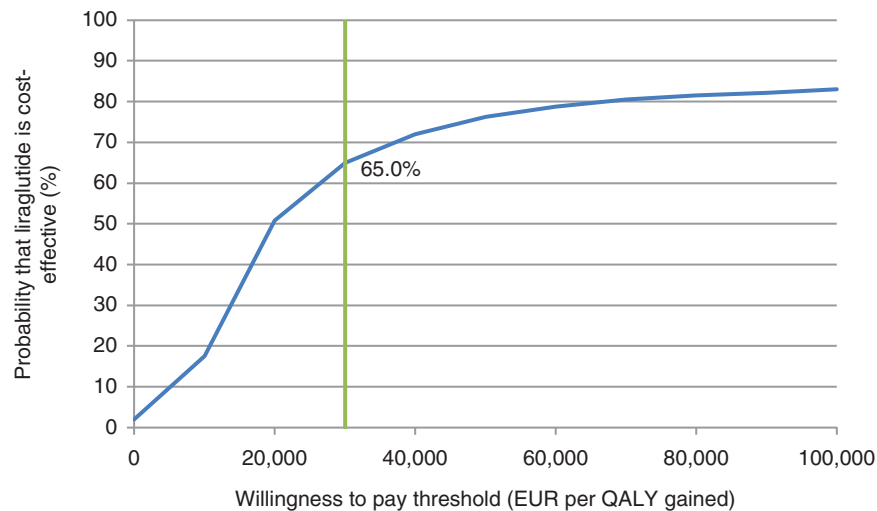


Figure 6. Liraglutide vs glimepiride: Cost-effectiveness acceptability curve for the probabilistic sensitivity analysis. EUR, 2013 Euros; QALY, quality-adjusted life year.

for patients failing to achieve glycemic control. The GLP-1 receptor agonists and DPP-4 inhibitors offer alternatives to long-standing second-line treatment options, such as sulfonylureas (associated with increased risk of hypoglycemic events and modest weight gain)²⁹. Modern treatment of type 2 diabetes is based around maintaining glycemic control, but also addressing the comorbidities associated with diabetes, specifically

obesity, hypertension, and dyslipidemia, and the trial data suggest that incretin therapy may be useful in terms of managing a variety of risk factors^{16–18}. Through maintaining this multi-factorial control, the risk of long-term diabetes-related complications can be reduced. The present analysis also suggests that these approaches may be cost-effective from a health-care payer perspective in France.

A systematic review by Zueger *et al.*³⁰ identified two previous studies comparing the cost-effectiveness of liraglutide and sitagliptin, one comparing liraglutide and glimepiride, and one comparing liraglutide with both sitagliptin and glimepiride. These studies evaluated cost-effectiveness in the UK, Spain, the US, and China^{14,15,31,32}. The results of the comparison with sitagliptin in the present analysis are in agreement with previous analyses, with liraglutide associated with increased effectiveness and increased costs. In all three settings, ICERs fell below commonly quoted country-specific willingness-to-pay thresholds. Results for the comparison with glimepiride vary across the two previously published analyses. In the UK, 1.2 mg liraglutide was found to be cost-effective, agreeing with the results of the present analysis. However, in the analysis in the Chinese setting, 0.6 mg liraglutide and 1.2 mg liraglutide were found to be dominated by glimepiride (associated with worse clinical outcomes at a higher cost), while 1.8 mg liraglutide was found to improve clinical outcomes but was not considered cost-effective. The results of the analysis in the Chinese setting are likely to differ from the present analysis and the UK analysis due to the clinical trial on which the analyses were based. The present analysis and the UK analysis used the same data to inform the comparison (LEAD 2, a multi-national study carried out in 21 countries), whereas the analysis in the Chinese setting used an alternative trial carried out in Asia. Use of alternative models (CORE Diabetes Model and UKPDS Outcomes Model) may also have affected the agreement of the modeling analysis.

One potential shortcoming of the present analysis is that the health-state utilities used were not specific to the French setting. There is evidence that suggests that the same health state may be valued differently in alternative settings, with a number of country-specific EQ-5D value sets now available³³. Recently a French-specific valuation set for the EQ-5D has been published³⁴. The present study investigated the possibility of using this valuation set to modify the utility values used, but this was not possible as the required patient-level data was not accessible. As the France-specific EQ-5D valuation set becomes more widely used, the opportunity to use France-specific values in economic evaluation should be taken up, increasing the relevance of analyses to the French setting and healthcare payers.

A potential limitation of the comparison with sitagliptin is that all parts of the LIRA-DPP4 trial used to inform the analysis were open label (the LEAD-2 study was double-blinded). This may have led to patients having different expectations of the effects of liraglutide or sitagliptin, which may have influenced adherence to lifestyle recommendations, although the extent of any such effect is difficult to assess. The impact of this potential effect on the present study has been minimized by only using trial end-

points measured through objective tests (such as HbA1c and systolic blood pressure). Moreover, the findings of the trial reported in the LIRA-DPP4 study are similar to other head-to-head trials comparing GLP-1 receptor agonists with DPP-4 inhibitors^{35,36}.

In real-world clinical practice, the impact of adherence to the diabetes medications evaluated may also need to be considered. Whilst adherence to alternative GLP-1 receptor agonists has been assessed, currently there is no evidence to suggest that injectable GLP-1 receptor agonists are associated with lower adherence rates than oral DPP-4 inhibitors or glimepiride^{37,38}. Moreover, the impact of adherence on cost-effectiveness is difficult to assess, as both clinical outcomes and costs will be affected by adherence rates and insufficient data is currently available. To date, the impact of adherence on an economic evaluation has only been assessed in theoretical examples, due to the large number of assumptions around both costs and effects that this entails³⁹.

The present analysis relies on short-term clinical data to make long-term predictions of outcomes over long-term time horizons using risk equations based on surrogate outcomes. This approach has been criticized in two recent reviews^{40,41}. However, this is a limitation inherent to most cost-effectiveness modeling studies, and studies of this type represent one of the best available options for making estimates of long-term clinical and economic outcomes in the absence of long-term clinical data. Moreover, the use of long-term time horizons for diabetes modeling is supported by published guidance⁴². The generalizability of the risk equations used in modeling analyses must also be considered, with data (such as that from the UKPDS) now historic and perhaps not representative of modern diabetes treatment in France. There is likely to be considerable uncertainty around risk equations (used to calculate incidence of complications) and progression equations (used to calculate long-term changes in surrogate outcomes) over long-term time horizons, and these may not reflect the population evaluated in the present analysis due to insufficient calibration. As a result there is unavoidable uncertainty around how well the modeling analysis represents the real world. The present study aims to minimize this limitation, through use of a recently validated model to conduct the analysis, and basing changes in physiological parameters on data collected in two randomized controlled trials^{22,23}. Furthermore, extensive sensitivity analysis has been conducted to investigate uncertainty and the impact of alternative model inputs.

Conclusions

Long-term projections based on two recent clinical trials provided evidence that liraglutide is cost-effective vs

sitagliptin and glimepiride in patients with type 2 diabetes failing metformin monotherapy in France.

Transparency

Declaration of funding

The study was supported by funding from Novo Nordisk.

Declaration of financial/other relationships

RR has served as an advisor or consultant for AstraZeneca, Lilly; Boehringer Ingelheim; Janssen; MSD; Novo Nordisk; Sanofi; Abbvie; Novartis; Roche. LM has served as an advisor or consultant for Amgen Inc.; AstraZeneca Pharmaceuticals LP; GlaxoSmithKline; Ipsen; Lilly; Mayoly Spindler; Menarini; Novo Nordisk; Pfizer Inc; Abbvie; Novartis; Roche. BH and WV are employees of Ossian Health Economics and Communications, which received a consulting fee from Novo Nordisk to support the study. TV, HD, PE, and MG are employees of Novo Nordisk.

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