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Cost-effectiveness of second-line empagliflozin versus liraglutide for type 2 diabetes in the United States

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Abstract

Aim: To estimate the cost-effectiveness of sequential use of the sodium-glucose co-transporter-2 inhibitor empagliflozin and glucagon-like peptide-1 receptor agonist liraglutide after metformin in patients with type 2 diabetes (T2D) from the US payer perspective.

Materials and Methods: An economic simulation model with a lifetime horizon was developed to estimate T2D-related complications (including cardiovascular [CV] death, myocardial infarction, stroke, and renal outcomes) using EMPA-REG OUTCOME data or UK Prospective Diabetes Study risk equations, in patients with or without a history of cardiovascular disease (CVD), respectively. Evidence synthesis methods were used to provide effectiveness inputs for empagliflozin and liraglutide. Population characteristics, adverse event rates, treatment escalation, costs ($2019), and utilities (both discounted 3%/year) were taken from US sources.

Results: Compared with second-line liraglutide in the overall T2D population, second-line empagliflozin was dominant as it was associated with lower total lifetime cost ($11 244/patient less) and resulted in a quality-adjusted life-year (QALY) gain (0.32/patient). Second-line empagliflozin was associated with reductions in CV death (by 5%) and lower cumulative complication rates in patients with CVD (by 2%), relative to second-line liraglutide. These findings were consistent among patients with co-morbid CVD, with gains in incremental QALYs (0.43/patient) and lower lifetime cost (by $10 175/patient) relative to second-line liraglutide. Scenario analyses consistently showed dominance for second-line empagliflozin.

Conclusion: For patients with T2D, use of second-line empagliflozin combined with metformin was a dominant strategy for US payers, associated with extended survival, improved QALYs, and lower costs compared with second-line liraglutide.

KEYWORDS

cardiovascular disease, cost-effectiveness, empagliflozin, GLP-1, liraglutide, SGLT-2 inhibitor

1 | INTRODUCTION

Type 2 diabetes (T2D) is a leading cause of premature morbidity and mortality in the adult population within the United States (US).[1] Alone, or combined with risk factors (e.g. high blood glucose, overweight/obesity, and high blood pressure), patients with T2D are at a high risk of microvascular and macrovascular complications, including cardiovascular disease (CVD), kidney disease, blindness, and lower-limb amputation.[1]

Recent trials showing the clinical benefits of sodium-glucose co-transporter-2 inhibitor (SGLT-2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) treatments have shifted the landscape of cardiovascular (CV) risk management in patients with T2D, with treatment guidelines by the American Diabetes Association (ADA)[2] and the American College of Cardiology[3] recommending an SGLT-2i or GLP-1RA in T2D patients with CVD or at a high risk of CVD who are inadequately controlled on metformin. Empagliflozin, an SGLT-2i, showed a significant CV benefit in patients with T2D with established CVD in the EMPA-REG OUTCOME CV outcomes trial (CVOT),[4] leading to an indication to reduce CV death in this population. In the LEADER CVOT,[5] the GLP-1RA liraglutide significantly reduced the risks of major adverse CV events (MACE) in patients with T2D and high CV risk, leading to an indication for MACE reduction. With this evidence, treatment pathways for patients with T2D are expected to increasingly consider empagliflozin and/or liraglutide as treatment options following metformin.

Clinical trials do not capture the potential sequences of therapies that physicians could recommend in real-world practice, and there is a lack of published data documenting the economic implications of sequential use of these therapies to ensure healthcare decision-makers recommend therapies that bring value to patients, healthcare systems, and payers. This analysis estimated the cost-effectiveness of adding empagliflozin as a second-line agent followed by liraglutide as third line compared with liraglutide as a second-line agent followed by empagliflozin as third line, in patients with T2D from the US payer perspective. A counterfactual comparison of projected lifetime health outcomes and costs of these two treatment pathways was performed, where the main difference was the drug added as second-line therapy, to understand the costs and benefits of initiating empagliflozin earlier in the treatment pathway rather than later. By combining clinical trial data and economic modelling methods, this study contributes a novel analysis of two alternative treatment escalation pathways in T2D that have not been directly compared in clinical research, focusing on long-term patient outcomes and direct medical costs for US payers. This study was conducted using a previously published model for the United States that assessed sequential treatment with second-line empagliflozin versus sitagliptin, with appropriate modifications to reflect clinical efficacy, drug adverse events (AEs), health-related quality of life (QoL), and costs with liraglutide.[6]

2 | MATERIALS AND METHODS

2.1 | Model overview

An economic model was developed in Microsoft Excel using the discretely integrated condition event platform.[7] The starting population included patients with T2D initiating second-line therapy combined with metformin. Two pathways were simulated for each patient, one with second-line empagliflozin and the other with second-line liraglutide prior to third-line therapy (liraglutide or empagliflozin, respectively) followed by fourth-line insulin (Figure 1).

The model simulated individual patients with T2D over a lifetime horizon, considering treatment efficacy, T2D-related complications, drug AEs, and associated costs and utilities. Fourteen T2D-related complications were considered in the model: myocardial infarction (MI), stroke, heart failure (HF), renal failure, and CV death in patients with or without CVD; ischaemic heart disease (IHD), blindness, ulcer, and amputation in simulated patients without CVD; and unstable angina (UA), transient ischaemic attack (TIA), revascularization, macroalbuminuria, and renal injury in patients with CVD.

The simulation was performed for each individual patient until the end of the time horizon or the patient's death. After each simulated patient exited the model, the model recorded the patient's lifetime cost, life years (LYs), quality-adjusted life-years (QALYs), and clinical event history, using a 3% annual discount rate for costs and QALYs as recommended for US cost-effectiveness analysis.[8] The

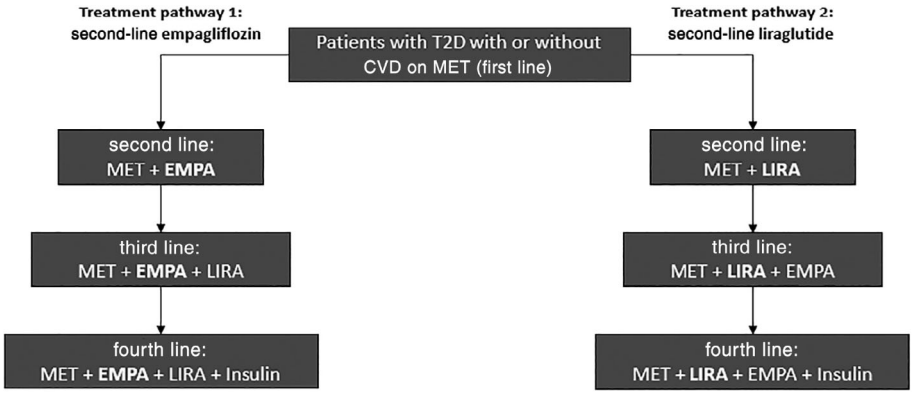

FIGURE 1 Modelled treatment pathways. CVD, cardiovascular disease; EMPA, empagliflozin; LIRA, liraglutide; MET, metformin; T2D, type 2 diabetes

model averaged each outcome over the simulated population to estimate aggregate model results. Aggregated outcomes of treatment with second-line empagliflozin and liraglutide were compared to estimate the incremental cost-effectiveness ratio (ICER).

2.2 | Patient population

The model generated a hypothetical population of 2000 individuals representative of US patients with T2D inadequately controlled on metformin eligible to receive an SGLT-2i or GLP-1RA (Appendix S1). Each individual entered the model with a profile of CV risk factors and other characteristics to predict T2D-related complications. Patients were duplicated to form two identical populations to run through each modelled treatment pathway. The model tracked CVD status (i.e. patients with established CVD, patients without prior CVD at high risk for CVD) at baseline and over time as patients accumulated a history of T2D-related complications.

2.3 | Treatment initiation

Treatment initiation was based on a mean rate of initiations for third-line (12.6 initiations per 100 person-years) and fourth-line (3.1 initiations per 100 person-years) treatment in US adults with T2D from 2005 to 2016 published by Montvida et al.[9] The authors conducted analyses using data on antidiabetes drug use, including start/stop dates and information on treatment changes, from the US Centricity Electronic Medical Records database.[9] Simulated patients were assumed to receive their optimally titrated dosage of insulin. Patients remained on treatment until the end of the time horizon or their death.

2.4 | Clinical and treatment efficacy inputs

The occurrence of T2D-related complications in patients without CVD was determined by published UK Prospective Diabetes Study (UKPDS) Outcomes Model 2 (UKPDS-OM2)[10] risk equations using individual-level state transitions with annual probability of events based on patient demographics, evolving risk factors (e.g. age, HbA1c, systolic blood pressure [SBP], smoking status, diabetes duration), and history of T2D-related complications. These equations estimate first events of MI, stroke, HF, IHD, blindness, ulcer, amputation, and renal failure, and an equation to predict a second amputation event was available. Definitions of these complications have been previously published by Hayes et al.[10] Four equations were available to predict death, based on history of complications, and which complications occurred in the current annual cycle.[10] During each annual cycle, one or more complications or death could occur. Simulated patients who experienced non-fatal MI, non-fatal stroke, or IHD were assumed to develop CVD (Figure SA1).

Risk of complications for patients without CVD was impacted by the efficacy of empagliflozin and liraglutide, represented by changes in HbA1c levels, body weight, and SBP associated with 12 to 40 weeks of treatment as add-on therapy to metformin in patients with T2D (-Table SM2). These parameters were derived from an indirect treatment comparison (ITC) performed in a network meta-analysis, in which the relative clinical efficacy of treatment was compared with placebo in adult patients with T2D who were inadequately controlled with metformin (Appendix S1). The model considered treatment effects during the first year of treatment and assumed that patients progressed subsequently according to the UKPDS Outcomes Model 1 (UKPDS-OM1)[11] equations for evolving risk factors. The efficacy of these treatments as third-line therapy was assumed to be the same as for second-line therapy.

In patients with CVD, published event-free survival (EFS) curves developed from EMPA-REG OUTCOME CVOT data were applied to estimate the time to non-fatal MI, non-fatal stroke, HF, UA, TIA, revascularization, macroalbuminuria, renal injury, renal failure, and CV death using baseline (i.e. at the time CVD is established) and time-dependent covariates.[12] These complications were defined as reported by Kansal et al.[12] The shape of the EFS curves were assumed to implicitly capture HbA1c and other evolving risk factors that contribute to changing rates of complications and disease progression over time. Thus, the treatment benefit of glycaemic control was not directly modelled in patients with CVD. The equations were supplemented with non-CV death according to US age- and sex-adjusted life table data.[13]

Time to each T2D-related complication was estimated with empagliflozin treatment as a covariate to capture efficacy shown in the EMPA-REG OUTCOME CVOT. The relative clinical efficacy of liraglutide was taken from an ITC,[14] in which liraglutide was compared with empagliflozin in treating adult patients with T2D and established CVD based on EMPA-REG OUTCOME and published LEADER CVOT data. A hazard ratio (HR) for liraglutide versus empagliflozin on each complication except UA, TIA, and revascularization was obtained (Table SA1).[14] Data on these complications were not available from the LEADER CVOT publication,[5] therefore risks were assumed to be similar to the placebo arm of the EMPA-REG OUTCOME CVOT. The HRs were applied to the EFS functions for empagliflozin to estimate outcomes among simulated patients treated with liraglutide.

Risks of treatment-related AEs for empagliflozin and liraglutide were based on US prescribing labels; AEs with 5% or more incidence or key adverse reactions were selected, specifically urinary tract infection, genital mycotic infection, nausea, hypoglycaemia, and injection site reaction.[15,16] AE occurrence was assumed to be mutually exclusive and not impact treatment use.

2.5 | Utility inputs

Utility scores that captured the QoL of modelled patients with different health status were used to adjust survival and estimate QALYs (-Table SA2). Utility values were sourced from published literature and the algorithm developed by Sullivan and Ghushchyan[17] was used (Appendix S1). The same study reported US-specific values for patient utility at baseline and disutilities for most clinical events.[17] Other

TABLE 1 Base case model results

Outcome	Second-line empagliflozin	Second-line liraglutide	Incremental versus second-line liraglutide
Overall survival (LYs; undiscounted), per patient	15.55	15.40	0.15
CVD-free survival, per patient	11.62	11.62	0.00
QALY (discounted)[a], per patient	8.39	8.07	0.32
Cumulative T2D-related events, per 100 PY	32.18	32.72	−0.54
T2D-related events, patients without CVD			
Myocardial infarction	1.23	1.23	0.00
Stroke	0.81	0.81	0.00
Heart failure	0.55	0.54	0.01
Ischaemic heart disease	0.39	0.38	0.01
Blindness	0.20	0.20	0.00
Ulcer	0.16	0.16	0.00
Amputation	0.23	0.21	0.02
Renal failure	0.31	0.31	0.00
CV death	2.64	2.64	0.00
Non-CV death	1.83	1.84	−0.01
Total T2D-related events, patients without CVD	8.34	8.31	0.03
T2D-related events, patients with CVD			
Myocardial infarction	2.15	2.14	0.01
Stroke	1.68	1.55	0.13
Heart failure	1.79	1.99	−0.20
Unstable angina	1.49	1.51	−0.02
Transient ischaemic attack	0.60	0.66	−0.06
Revascularization	2.83	2.87	−0.04
Macroalbuminuria	4.88	4.98	−0.10
Renal injury	0.67	0.75	−0.08
Renal failure	0.12	0.17	−0.05
CV death	4.02	4.22	−0.20
Non-CV death	3.62	3.58	0.04
Total T2D-related events, patients with CVD	23.84	24.41	−0.57
AEs			
Urinary tract infection	5.19	3.60	1.59
Genital mycotic infection	5.10	3.54	1.56
Nausea	4.43	5.72	−1.29
Hypoglycaemia	5.72	5.45	0.27
Injection site reaction	1.34	2.00	−0.66
Total AEs	21.78	20.33	1.45
Cost (discounted)[a], USD, per patient			
Drug cost	$79 096	$90 423	−$11 327
T2D-related management cost	$33 142	$33 295	−$153
Patients without CVD	$14 951	$14 899	$52
Patients with CVD	$18 191	$18 396	−$205
AE management cost	$752	$516	$236
Total cost	$112 990	$124 234	−$11 244
QALY ICER, USD			Dominates

Abbreviations: AE, adverse event; CV, cardiovascular; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; LYs, life years; PY, person-years; QALY, quality-adjusted life year; T2D, type 2 diabetes; USD, United States dollar.
[a]Discounted at an annual rate of 3.0%.

published studies provided disutilities for renal failure,[18] revascularization,[19] nausea,[20] hypoglycaemia,[21] and injection site reaction[22] (the last based on daily frequency of injectable medication). For T2D-related complications, the same disutility was applied permanently in subsequent years following the event. For transient AEs, disutilities were applied short-term.

An important difference exists between the administration of empagliflozin (oral) and liraglutide (subcutaneous injection) that may affect QoL. Boye et al.[22] have shown injectable T2D therapies, such as liraglutide, to be associated with a QoL impairment. Based on this study, a permanent disutility associated with a daily injection flexible dosing regimen was applied for liraglutide.[22] No additional disutility was applied for insulin, as both arms would be similarly impacted and therefore not affect the incremental comparison.

2.6 | Cost inputs

All costs were expressed in 2019 US dollars (USD) inflated using the medical component of the Consumer Price Index,[23] as needed. Only costs related to direct reimbursable medical care were considered, including drug acquisition, acute care of T2D-related complications, and acute care of AEs. Unit wholesale acquisition costs of pharmaceuticals were obtained from Red Book (Table SA3),[24] and adjusted for a manufacturer discount (assumed to be 51%) and co-payment ($35)[25] to provide an estimate of the payer's expected cost. Patients receiving care for T2D-related complications were assigned inpatient costs reported in the Healthcare Cost and Utilization Project (HCUP) (Tables SA4 and SA5).[26] A primary care physician visit cost from Centers for Medicare & Medicaid Services[27] or InHealth[28] or inpatient hospitalization cost from HCUP

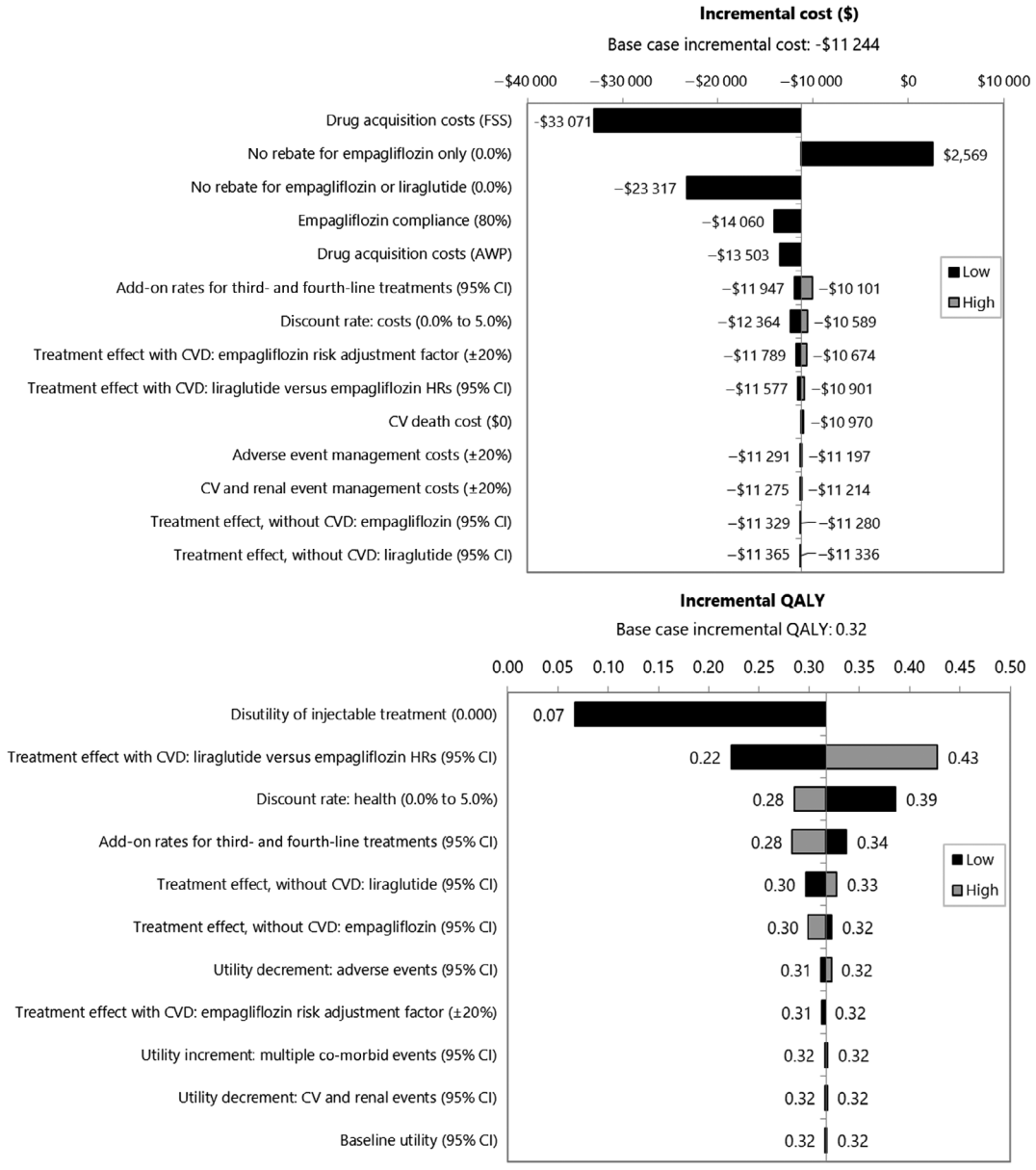

FIGURE 2 Deterministic sensitivity analysis tornado diagrams illustrating the impact of variation in key model parameters. AWP, average wholesale price; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; FSS, Federal Supply Schedule; HR, hazard ratio

NIS data[26] was assigned for AE management (Tables SA6 and SA7). Costs for the overall population were estimated by weighting costs for a commercially-insured (55% <65 years of age) and Medicare (45% ≥65 years of age) payer. Refer to Appendix S1 for additional details.

2.7 | Sensitivity analysis inputs

Deterministic sensitivity analyses (DSA) assessed the impact of model inputs and assumptions on the results. Scenarios included variation in treatment effects, add-on rates for third- and fourth-line treatment, drug manufacturer rebates, costs, utilities, and discount rates. A probabilistic sensitivity analysis (PSA) evaluated the impact of varying cost, utility, and treatment effect parameters simultaneously on the results. Parameters varied in DSA and PSA are shown in Tables SA1, SA2, SA5, and SA7.

2.8 | Model validation and verification

Model validation and verification included evaluation of face validity, technical validity, and predictive validity. The validation approach and results are provided in Tables SA8 and SA9; Appendix S1.

3 | RESULTS

3.1 | Population characteristics

Baseline characteristics of the simulated population have been previously reported.[6] The mean age was 61.4 ± 13.3 years, 50% were female, mean body mass index was 31.0 ± 7.0 kg/m^2, mean HbA1c was 9.4% ± 3.5% (79 ± 15 mmol/mol), and mean SBP was 144.8 ± 27.1 mmHg. At baseline, 20% of patients had CVD.

3.2 | Base case results

Base case results are shown in Table 1. Patients using second-line empagliflozin compared with liraglutide were predicted to experience 2% fewer T2D-related complications over a lifetime horizon, but additional AEs occurred (7%). The lower cumulative rate of T2D-related complications predicted for second-line empagliflozin versus liraglutide was driven by fewer events in patients with CVD, including fewer CV deaths (−0.20 events per 100 patient-years). The survival gain meant a prolonged time at risk of expensive T2D-related complications, with drug costs and LYs (translating to QALYs) accruing over a longer duration. The predicted gain in LYs was 0.15 and QALYs was 0.32. CVD-free LYs (incremental, 0.004) were similar across treatment pathways. Despite the longer survival, empagliflozin was associated with lower drug costs (−$11 327/patient) and a modest incremental event management cost ($83/patient) versus liraglutide, yielding a net lifetime cost savings of −$11 244/patient. The cost-effectiveness analysis showed that second-line empagliflozin dominated second-line liraglutide, being associated with lower costs and longer quality-adjusted survival.

3.3 | Sensitivity analyses results

In DSA, all scenarios showed that second-line empagliflozin provides QALY improvement with cost savings compared with second-line liraglutide (Figure 2). Empagliflozin also provides survival benefits at

TABLE 2 Scenario analyses results

Scenario	Incremental outcomes			QALY ICER, USD
	Costs, USD[a]	QALY[a]	LY[b]	
Subpopulation with CVD	−$10 175	0.43	0.37	Dominant[c]
Subpopulation without CVD	−$12 344	0.28	0.04	Dominant[c]
Commercial payer	−$12 941	0.34	0.15	Dominant[c]
Medicare payer	−$9773	0.27	0.11	Dominant[c]
All patients, 1-y horizon	−$2221	0.05	0.00	Dominant[c]
All patients, 3-y horizon	−$5712	0.12	0.01	Dominant[c]
All patients, 5-y horizon	−$7882	0.17	0.01	Dominant[c]
All patients, 10-y horizon	−$10 810	0.25	0.05	Dominant[c]
CVD subpopulation, 1-y horizon	−$2378	0.05	0.00	Dominant[c]
CVD subpopulation, 3-y horizon	−$6068	0.13	0.02	Dominant[c]
CVD subpopulation, 5-y horizon	−$8486	0.20	0.04	Dominant[c]
CVD subpopulation, 10-y horizon	−$10 769	0.32	0.15	Dominant[c]

Abbreviations: CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; USD, United States dollar.

[a]Discounted at an annual rate of 3.0%.

[b]Undiscounted.

[c]Second-line empagliflozin is less expensive and more effective than second-line liraglutide.

time horizons of 5 years or longer; at time horizons of 1 year and 3 years, survival was similar to liraglutide. Cost results were most sensitive to parameters related to drug costs (i.e. manufacturer discounts for empagliflozin and liraglutide, compliance). QALY results were most sensitive to the disutility of injectable treatment and HRs for liraglutide versus empagliflozin on complications in patients with CVD.

The PSA substantiated the robustness of results. Considering sampling from distributions to account for variation in parameter inputs simultaneously, second-line empagliflozin yielded higher QALYs and was less expensive than second-line liraglutide in all iterations (Figure S2A).

3.4 | Scenario analyses results

The results of scenario analyses are shown in Table 2. A subpopulation of T2D patients with co-morbid CVD and another subpopulation with no CVD at baseline both benefitted from second-line empagliflozin, showing dominance over second-line liraglutide. Second-line empagliflozin remained the economically dominant strategy versus liraglutide considering average payment rates by US commercial and Medicare payers. Scenarios that tested short time horizons (1, 3, 5, and 10 years) for the overall T2D population and subpopulation with CVD at baseline consistently showed dominance for second-line empagliflozin versus liraglutide.

4 | DISCUSSION

For patients with T2D, the use of empagliflozin compared with liraglutide on background metformin was a dominant strategy from a US-managed care perspective. The analysis suggested that using empagliflozin followed by metformin in patients with T2D results in reduced costs to payers and lower mortality and morbidity for patients, as well as higher QoL. Improvements in life expectancy associated with second-line empagliflozin were driven by a decreased risk of CV death in patients with CVD who began receiving empagliflozin earlier in the treatment pathway. By delaying liraglutide initiation until third line, second-line empagliflozin also reduced cumulative treatment costs and the QoL burden associated with injectable treatment. Results were consistent in patients with T2D and co-morbid diagnosis. DSA showed that the model was sensitive to drug costs (such as price discounting and compliance), injectable treatment disutility, and HRs for complications in patients with CVD. In every iteration of the PSA, second-line empagliflozin dominated second-line liraglutide.

Results of this analysis build on the available evidence showing that empagliflozin has economic benefits in various settings compared with different antidiabetic agents, and in a broader T2D population and in patients with T2D and established CVD.[6,12,29-35] Notably, other economic evaluations have identified empagliflozin as a dominant strategy versus liraglutide for the treatment of patients with T2D.[36,37] Using the IQVIA Core Diabetes Model, empagliflozin has been compared with liraglutide, both in addition to background standard of care therapies, in patients with T2D with established CVD in the UK and Denmark based on data from the EMPA-REG OUTCOME and LEADER CVOTs.[35,36] Treatment sequences were not considered, other than switch to insulin, and patients without CVD were not assessed. An evaluation by the US Institute for Clinical and Economic Review, reporting total QALYs and costs (USD) for several treatments plus background therapy in a T2D population with inadequate glycaemic control, suggests that empagliflozin is dominant compared with liraglutide.[37]

Despite these publications, there is a lack of analyses evaluating alternative treatment sequences of empagliflozin and liraglutide to assess the value to patients and payers of beginning treatment at an earlier point in patients' treatment pathways. Our model also simulates health economic outcomes in patients treated with empagliflozin or liraglutide before CVD develops, following current guidance from the ADA advising early use of SGLT-2is and GLP-1RAs with the goal of improving cardiorenal outcomes in patients with T2D.[2] The finding that empagliflozin is dominant versus liraglutide aligns with previous studies, indicating that this key result is robust to different modelling methodologies and assumptions.

The strengths of the model include that outcomes in patients with CVD were based on hard endpoint data from CVOTs to more accurately capture observed CV event rates. Furthermore, analyses were based on US-specific inputs for the population, non-CV death rates, treatment escalation rates, utilities, and costs.

The model included several assumptions. The occurrence of diabetes-related complications estimated from the UKPDS data was assumed to reflect rates observed in T2D patients without CVD in the United States. As the UKPDS-OM2 equations have been broadly used in diverse T2D populations worldwide, the applicability of these equations to a US population without CVD is reasonable.[38] Next, the treatment effect of liraglutide on revascularization, UA, and TIA in patients with CVD was assumed to be similar to the placebo arm in the EMPA-REG OUTCOME CVOT, because the LEADER CVOT publication did not report treatment benefit on these outcomes. This was challenged in sensitivity analyses by assuming: (a) liraglutide had the same effect as empagliflozin on these outcomes; and (b) the effect of UA and revascularization to be the same as MI, and the effect of TIA to be the same as stroke. Results were insensitive to this assumption. Additionally, because of a lack of clinical evidence on the effects of empagliflozin and liraglutide combination therapy, these drugs were assumed to have additive benefits when combined. This assumption is supported by a retrospective study by Goncalves and Bell that looked at the effects of a combined therapeutic regimen consisting of a SGLT-2i and GLP-1RA on lowering HbA1c, SBP, body weight, and cardiac risk to synergistically reduce CV events and slow renal dysfunction.[39] Furthermore, treatment escalation was not directly linked to an HbA1c threshold, but instead based on published literature that considered HbA1c levels indirectly. Moreover, simulated patients were assumed to receive antidiabetic medications for life. This assumption was considered conservative, as it limits cost offsets because of empagliflozin's

survival benefit. Testing the adherence of treatment (80%) through a reduction in drug costs showed that second-line empagliflozin remained the dominant therapy versus liraglutide. Last, outpatient costs of disease management were not considered in the model, although in practice patients would probably experience outpatient visits to manage their disease. These costs were assumed to be similar between treatment pathways, and thus it is unlikely that the incremental model results and conclusions would change.

Some limitations should be considered in interpreting the results. To simplify the model, only four lines of T2D therapy were considered. In clinical practice, patients may receive multiple lines of therapy after fourth line. Patients in both pathways had the same assumptions, therefore the incremental results are not expected to be materially affected. Next, evidence synthesis methods were used to provide efficacy data for empagliflozin and liraglutide. Although this is a standard approach to estimate the relative efficacy of compared interventions, the parameters are subject to more bias than if direct-comparison clinical trial data were used. Also, because evidence about the effectiveness of specific treatment sequences is lacking, the model applied individual efficacy estimates for each treatment independent of the position in the sequence. The influence of efficacy variables was tested in sensitivity analyses, which showed no difference in the base case results. Next, the model relied on surrogate measures (e.g. HbA1c) to predict the occurrence of T2D-related complications in patients without CVD. The association between surrogate measures and event risk is neither straightforward nor concretely established. Furthermore, the model used short-term clinical data to estimate long-term health outcomes assuming that intervention effects are constant, as is common in cost-effectiveness analyses. Nonetheless, simulation modelling offers an efficient way to synthesize evidence from multiple sources when long-term clinical follow-up data are not available, and our results are consistent with other models of long-term cost-effectiveness that have identified cost savings and improved QoL for empagliflozin versus liraglutide. Moreover, the analysis did not include some AEs that were expected to have a marginal impact on results. Diabetic ketoacidosis, an infrequent but recognized AE of empagliflozin, was not modelled. Insulin-related hypoglycaemia and metformin-induced AEs were not captured. Adding these AEs would have limited impact on the incremental results for the compared treatment pathways and not impact cost-effectiveness conclusions. Last, the results reflect current US practice and are not easily transferrable to other settings with country-specific treatment guidelines and healthcare-financing systems.

For patients with T2D, the use of second-line empagliflozin versus liraglutide in addition to background metformin was associated with extended survival (LYs), improved QALYs, and lower costs. This analysis showed that empagliflozin as second-line treatment in the overall T2D population, as well as the T2D and CVD population, is a dominant strategy (i.e. more effective and less expensive) over second-line liraglutide from the perspective of the US healthcare system.

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CONFLICT OF INTEREST

PP and SS are employees of Boehringer Ingelheim Pharmaceuticals Inc. OSR and SB are salaried employees of Evidera, a research and consulting firm in the biopharmaceutical field. During the conduct of this study, EBW was employed by Evidera. As such, they work with a variety of companies and are/were explicitly precluded from accepting any payment or honoraria directly from them for services rendered. Evidera received funding from Boehringer Ingelheim Pharmaceuticals Inc. for collaboration on this project and article. Boehringer Ingelheim Pharmaceuticals Inc. was given the opportunity to review the manuscript for medical and scientific accuracy, as well as intellectual property considerations. NRD works under contract with the Centers for Medicare and Medicaid Services to develop and maintain performance measures used for public reporting and pay for performance programmes. He reports research grants and consulting for Amgen, AstraZeneca, Boehringer Ingelheim, Cytokinetics, MyoKardia, Relypsa, Novartis, and SCPharmaceuticals.

AUTHOR CONTRIBUTIONS

OSR and SB contributed to the model development, identification of data sources, conduct of analyses, and implementation of the design. EBW facilitated the network meta-analysis and indirect treatment comparison. PP, NRD, and SS reviewed the final model design, data sources, and results. All authors contributed to the interpretation of data and reviewed/edited the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14625.

DATA AVAILABILITY STATEMENT

Our study data (which is based on de-identified data from a clinical trial) is not in a repository, but is available upon reasonable request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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