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A Long-term Cost-Effectiveness Analysis of Treatments for Type 2 Diabetes in Portugal: Once-Weekly Semaglutide 1 mg Versus Once-Daily Empagliflozin 25 mg

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A B S T R A C T

Introduction: Management of type 2 diabetes includes aiming to maintain glycemic control, reduce cardiovascular events, with a low risk of hypoglycemic events and avoidance of weight gain. The present analysis assessed the long-term cost-effectiveness of once-weekly semaglutide 1 mg versus once-daily empagliflozin 25 mg for the treatment of patients with type 2 diabetes mellitus with inadequate glycemic control on metformin monotherapy from a healthcare payer perspective in Portugal.
Methods: Long-term clinical and economic outcomes with once-weekly semaglutide 1 mg and once-daily empagliflozin 25 mg were projected using the IQVIA CORE Diabetes Model. Clinical inputs in terms of patient characteristics and the impact of treatments on risk factors were based on an indirect comparison conducted using patient-level data from four randomized controlled trials as, to date, there is no head-to-head clinical trial comparing the two interventions. In the modeling analysis, both treatments were added to metformin and continued until glycated hemoglobin exceeded a threshold of 7.5%, at which point patients switched therapy to basal insulin. Pharmacy and complication costs, expressed in 2019 Euros (EUR), and utilities were applied. Future outcomes were discounted at 4% per annum.
Results: Over simulated patient lifetimes, once-weekly semaglutide 1 mg was associated with increased life expectancy (12.80 *vs* 12.70 years) and quality-adjusted life expectancy (7.18 vs 6.98 quality-adjusted life years [QALYs]) compared with once-daily empagliflozin 25 mg. The benefits resulted from a reduced incidence and delayed onset of projected diabetes-related complications. Increased pharmacy costs with once-weekly semaglutide were partially offset by cost savings resulting from avoided diabetes-related complications, most notably cardiovascular disease and renal disease, with mean per patient cost savings of EUR 110 and EUR 88, respectively. This led to an overall cost increase of EUR 2 804 per patient with once-weekly semaglutide (EUR 24 845 *vs* EUR 22 041). Once-weekly semaglutide was associated with an incremental cost-effectiveness ratio of EUR 14 114 per QALY gained versus once-daily empagliflozin.
Conclusion: Compared with once-daily empagliflozin 25 mg, once-weekly semaglutide 1 mg was projected to be a cost-effective treatment from a healthcare payer perspective for patients with type 2 diabetes in Portugal.

Palavras-chave:
Análise Custo-Benefício;
Diabetes Mellitus/tratamento farmacológico;
Hipoglicemiantes.

Análise Custo-Efetividade a Longo Prazo de Tratamentos para a Diabetes tipo 2 em Portugal: Semaglutido 1 mg Semanal Versus Empagliflozina 25 mg Diário

R E S U M O

Introdução: A gestão da diabetes tipo 2 inclui a manutenção do controlo glicémico reduzindo eventos cardiovasculares, com risco diminuído de hipoglicemias ou aumento do peso corporal. A presente análise avaliou a relação custo-efetividade a longo prazo de semaglutido 1 mg semanal *versus* empagliflozina 25 mg diário, na diabetes *mellitus* tipo 2 inadequadamente controlada com

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metformina, em monoterapia, na perspetiva do Serviço Nacional de Saúde (SNS) em Portugal.
Métodos:Os resultados clínicos e económicos do tratamento com semaglutido 1 mg semanal e empagliflozina 25 mg diário foram projetados utilizando o *IQVIA CORE Diabetes Model*. Pela ausência de ensaios clínicos comparativos diretos, as características dos doentes e o impacto dos tratamentos nos fatores de risco basearam-se numa comparação indireta utilizando dados individualizados dos participantes de quatro ensaios clínicos aleatorizados incluídos. Na análise modelada, os tratamentos adicionados à metformina foram mantidos até que a hemoglobina glicada ultrapassasse o limiar 7,5%, momento em que os doentes transitaram para insulina basal. Foram considerados custos das complicações e da medicação, em Euros (2019), e aplicadas as utilidades geradas através da qualidade de vida relacionada com saúde. Aos custos projetados aplicou-se um desconto 4% ao ano.
Resultados: O semaglutido 1 mg foi associado a um aumento da esperança de vida (12.80 *vs* 12.70 anos) e da esperança de vida ajustada pela qualidade de vida (7.18 *vs* 6.98 anos de vida ajustados pela qualidade de vida [QALYs]) comparativamente a empagliflozina 25 mg. Estes benefícios resultam da menor incidência e do atraso no aparecimento das complicações da diabetes. Os custos adicionais com a medicação associados a semaglutido foram parcialmente compensados pela redução dos custos das complicações evitadas, especialmente doença cardiovascular e renal, em média de 110 EUR e 88 EUR, respetivamente, por doente. Isto conduziu a um balanço final de 2 804 EUR por doente (EUR 24 845 vs EUR 22 041). O semaglutido foi associado a um rácio custo-efetividade incremental de 14 114 por QALY ganho *versus* empagliflozina.
Conclusão: Quando comparado com empagliflozina 25 mg diário, o semaglutido 1 mg semanal é um tratamento custo-efetivo no tratamento da diabetes tipo 2, conforme projeções a longo prazo, na perspetiva do SNS em Portugal.

Introduction

The International Diabetes Federation estimates that in 2019 the prevalence of diabetes in Portugal was 9.8%, with type 2 diabetes making-up 90% of cases.[1,2] The prevalence is expected to rise to 11.2% by 2030 and to 12% by 2045.[1] Diabetes results in significant mortality in Portugal, with an estimated 5 796 deaths attributable to diabetes annually.[1] The Portuguese National Diabetes Observatory (Observatório Nacional da Diabetes) last estimated the cost of diabetes in 2015, finding that the condition was associated with costs between EUR 1 300 and EUR 1 550 million, equating to 0.7 to 0.9% of gross domestic product and 8% to 10% of total healthcare expenditure.[2] The most significant costs of diabetes were as a result of hospitalization to treat diabetes-related complications.[2] Improving glycemic control, lowering blood pressure, and reducing body weight have been shown to reduce the risk of developing diabetes-related complications.[3-6] Therefore improvements in outcomes for patients and reduced costs for the National Health Service (NHS) in Portugal can be achieved by improving treatment. Choosing therapies that are both effective and cost-effective is increasingly important in order to deliver high quality healthcare within constrained resources, as healthcare budgets come under increasing pressure.

The European Association for the Study of Diabetes (EASD) has released guidelines that recommend the use of GLP-1 receptor agonists or SGLT-2 inhibitors with proven cardiovascular benefits for patients with or at high risk of atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease as second-line therapies (following metformin).[7,8] These therapies are also recommended for patients with a need to minimize the risk of hypoglycemia and those with a need to minimize weight gain or promote weight loss. Once-weekly semaglutide and once-daily empagliflozin have both been shown to be associated with a cardiovascular benefit.[7,8] Data on the relative effectiveness and cost-effectiveness of once-weekly semaglutide and once-daily empagliflozin is important, as physicians may be required to make decisions between which of these treatment options to prescribe.

There is currently no head-to-head clinical trial that allows a direct comparison of once-weekly semaglutide 1 mg with once-daily empagliflozin 25 mg. However, a meta-analysis has been conducted using individual patient data to compare the efficacy of the two interventions for the treatment of patients with type 2 diabetes previously receiving metformin monotherapy.[9] The meta-analysis was conducted in line with guidance on the conduct of indirect comparisons from the NICE Decision Support Unit.[10] The use of individual patient data, rather than aggregated clinical trial data, allows potential prognostic factors and effect modifiers to be adjusted for at an individual patient level, resulting in a potentially better isolation of the effect of a single treatment on outcomes of interest than when aggregated (i.e. clinical trial) data are used. The analysis captured data from four randomized controlled trials: SUSTAIN 2 (once-weekly semaglutide versus sitagliptin), SUSTAIN 3 (once-weekly semaglutide versus once-weekly exenatide), SUSTAIN 8 (once-weekly semaglutide versus canagliflozin) and PIONEER 2 (once-daily oral semaglutide versus once-daily empagliflozin). The primary regression analysis included all four trials, which had durations of 52 or 56 weeks, with a complementary analysis conducted using only the 52-week trials (SUSTAIN 8 and PIONEER 2). Outcomes were assessed for change from baseline in HbA1c, body weight, body mass index (BMI), waist circumference, systolic and diastolic blood pressure, lipid parameters, and estimated glomerular filtration rate.

The present analysis aimed to assess the long-term cost-effectiveness of once-weekly semaglutide 1 mg versus once-daily empagliflozin 25 mg for the treatment of patients with type 2 diabetes mellitus with inadequate glycemic control on metformin monotherapy from a healthcare payer perspective in Portugal, based on the results from previously published meta-analysis using patient-level data.

Methods

Modeling approach and overview

To assess the cost-effectiveness of once-weekly semaglutide 1 mg versus once-daily empagliflozin 25 mg, an analysis was performed over patient lifetimes using version 9.0 of the IQVIA CORE Diabetes Model. The features and capabilities of the model have been previously published.[11] The model reflects the natural course of diabetes, with risk factors developing over time and patients at risk of experiencing diabetes-related complications. Model outputs include time to onset and cumulative incidence of complications, life expectancy, quality-adjusted life expectancy

(expressed in quality-adjusted life years [QALYs]), direct costs and, incremental cost-effectiveness ratios (ICERs). Long-term outcomes projected by the model have been validated against real-life data in 2004 and more recently in 2014.[12,13]

The present analysis conducted for Portugal was aligned with previously published cost-effectiveness analyses of once-weekly semaglutide and oral semaglutide in the UK setting.[14,15] Outcomes were projected over patient lifetimes in order to capture all differences in long-term complications (and their impact on costs and quality of life) and mortality with once-weekly semaglutide 1 mg and once-daily empagliflozin 25 mg, as recommended in the methodological guidelines for economic evaluation of health technologies in Portugal.[16] Projected cost and clinical outcomes were discounted at 4% annually, in line with modelling guidelines for Portugal.[16] Base case and sensitivity analyses were performed using a second-order Monte Carlo approach, with baseline cohort characteristics, treatment effects, costs of complications, utilities and transition probabilities relating to myocardial infarction, stroke, congestive heart failure and angina sampled in each model iteration. This aimed to capture the uncertainty around model inputs and their impact on the development of diabetes-related complications.

Clinical data

The analysis used baseline characteristics taken from the pooled data from the studies that informed the meta-analysis: SUSTAIN 2, SUSTAIN 3, SUSTAIN 8 and PIONEER 2. The mean (standard deviation [SD]) age of the cohort was 56 (10.3) years, with mean duration of diabetes of 7 (5.9) years, mean HbA1c of 8.2 (1.0) %, and mean BMI of 32.8 (6.7) kg/m^2. Alcohol and tobacco consumption data were not collected in the clinical trials and therefore were assumed to be the same as the general Portuguese population.[17,18] Treatment effects associated with initiation of once-weekly semaglutide 1 mg and once-daily empagliflozin 25 mg were based on the outcomes calculated in the meta-regression based on individual patient data (Table 1).[9] Once-weekly semaglutide 1 mg was associated with significantly greater improvements in HbA1c, total cholesterol, LDL cholesterol, triglycerides and BMI compared with once-daily empagliflozin 25 mg, while once-daily empagliflozin 25 mg was associated with significantly greater improvements in diastolic blood pressure and HDL cholesterol.

Treatment effects from the meta-analysis were applied in the first year of the analysis, after which HbA1c was assumed to increase based on the UKPDS progression equation in both arms. This resulted in HbA1c increasing over time, with the difference between the treatment arms gradually diminished. When HbA1c exceeded 7.5% (a commonly used threshold for treatment intensification) patients discontinued once-weekly semaglutide 1 mg or once-daily empagliflozin 25 mg and initiated treatment with basal insulin (assumed to be biosimilar glargine [insulin Abasaglar]). Initiation of basal insulin was assumed to result in a reduction in HbA1c, with this calculated using the "Core" multivariate equations for an insulin-naïve population estimated by Willis *et al*.[19] Both once-weekly semaglutide 1 mg and once-daily empagliflozin 25 mg were associated with reductions in BMI, and these were assumed to persist while patients received initial treatments. BMI was assumed to return to baseline when basal insulin was initiated (thereby abolishing the difference between the treatment arms). In both arms, changes in blood pressure and serum lipids were based on the natural progression algorithms built into the IQVIA CORE Diabetes Model, based on the UKPDS and Framingham data, respectively.

Costs

Costs captured all costs falling within the NHS budget, in line with modeling guidelines for Portugal.[16] Direct costs captured included pharmacy costs, costs associated with diabetes-related complications and patient management costs. All costs were expressed in 2019 Euros (EUR). Unit costs of diabetes medications were based on the pharmacy selling price (PSP) including value added tax (VAT) and captured the appropriate reimbursement levels. Once-weekly semaglutide is supplied with needles included in the pack and therefore do not need to be purchased separately, once-daily empagliflozin is delivered orally and therefore needles are not required, and basal insulin (following treatment switching) was associated with the use of one needle per day. It was assumed that patients receiving once-weekly semaglutide and

Table 1. Treatment effects associated with once-weekly semaglutide 1 mg and once-daily empagliflozin

Parameter	Mean (standard error)		Estimated treatment difference (Mean [95% confidence interval])	*p*-value
	Once-weekly semaglutide 1 mg	Once-daily empagliflozin 25 mg		
HbA_{1c} (%)	−1.44 (0.03)	−0.83 (0.05)	−0.61 (−0.72 to −0.49)	<0.0001
HbA_{1c} (mmol/mol)	−15.7 (0.3)	−9.1 (0.5)	−6.7 (−7.9 to −5.4)	<0.0001
Systolic blood pressure (mmHg)	−4.11 (0.36)	−4.48 (0.56)	0.37 (−0.95 to 1.68)	0.5842
Diastolic blood pressure (mmHg)	−1.27 (0.23)	−2.39 (0.37)	1.12 (0.27 to 1.97)	0.0103
Total cholesterol (mg/dL)	−6.15 (0.90)	4.14 (1.39)	−10.28 (−13.56 to −7.01)	<0.0001
HDL cholesterol (mg/dL)	1.53 (0.22)	2.63 (0.34)	−1.10 (−1.89 to −0.30)	0.0073
LDL cholesterol (mg/dL)	−2.48 (0.77)	4.18 (1.19)	−6.66 (−9.44 to −3.87)	<0.0001
Triglycerides (mg/dL)	−31.16 (3.36)	−15.13 (5.17)	−16.03 (−28.17 to −3.90)	0.0097
BMI (kg/m^2)	−1.92 (0.06)	−1.32 (0.09)	−0.60 (−0.81 to −0.39)	<0.0001
Estimated glomerular filtration rate (ml/min/1.73 m^2)	0.15 (0.23)	−0.06 (0.37)	0.21 (−0.65 to 1.07)	0.6304

BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

once-daily empagliflozin did not use any self-monitoring of blood glucose (SMBG) testing due to the low rates of hypoglycemic events, but that patients receiving basal insulin used one SMBG test per day. Annual costs of treatment were calculated from an NHS perspective with once-weekly semaglutide 1 mg, once-daily empagliflozin 25 mg, and basal insulin (assumed to be 40 IU daily based on the defined daily dose).[20] Costs of complications and patient management were taken from NHS tariffs where possible, in line with guidance for Portugal, with peer-reviewed publications and expert advice used to fill data gaps.[16]

Utilities

The analysis captured the impact of diabetes-related complications on quality of life by applying disutilities in the year of the event and in subsequent years. Utilities associated with each diabetes-related complication were taken from a 2014 review by Beaudet et al, with hypoglycemia disutilities coming from Evans *et al* 2013 (published after the literature searches by Beaudet *et al* had been completed).[21,22] Beaudet et al preferentially chose utilities elicited using the EQ-5D, which is aligned with guidance on economic evaluation in the Portuguese setting.[16]

Sensitivity analysis

The projection of outcomes over patient lifetimes using a health-economic model is associated with uncertainty, and therefore a series of sensitivity analyses with alternative model inputs were performed to assess the robustness of the model results. The base case analysis used a 50-year time horizon, and the impact of shortening the time horizon of the analysis was examined by running analyses over 20- and 10-year time horizons. Annual discount rates of 4% were applied to future clinical and cost outcomes in the base case, and a sensitivity analysis was conducted with 0% discount rates applied. The base case analysis applied all treatment effects irrespective of statistical significance, and a sensitivity analysis was prepared with only the statistically significant differences between the treatments applied.

In the base case analysis, a disutility per BMI unit above 25 kg/m^2 of −0.0061 was applied, as used in previous analyses conducted by the National Institute for Health and Care Excellence.[23] In a sensitivity analysis an alternative value of −0.01 per BMI unit above 25 kg/m^2 was used, with this larger disutility gives greater impact to weight changes compared with the conservative disutility used in the base case analysis.[24] The base case analysis applied hypoglycemic event disutilities based on Evans *et al*, and a sensitivity analysis examined the impact of applying alternative disutilities for severe and non-severe hypoglycemic events as reported by Currie *et al*.[25]

The UKPDS 64 risk equations were used to predict the incidence of first cardiovascular events in the base case analysis, with the UKPDS 82 risk equations incorporated into the IQVIA CORE Diabetes model in 2014 applied in a sensitivity analysis. Whilst a validation study of the revised model has been published, the model owners suggest that the update is used in a sensitivity analysis, with the previous version used in the base case.[13]

HbA1c increased based on the UKPDS progression equation for the duration of the analysis in both arms of the base case analysis, and an alternative modeling approach was explored, with HbA1c increasing by 0.14% per year in both arms of the analysis while patients received once-weekly semaglutide 1 mg or once-daily empagliflozin 25 mg, based on the metformin arm of the ADOPT study.[26] When patients initiated basal insulin, HbA1c followed the UKPDS equation, as in the base case. In the base case analysis, BMI returned to baseline when treatment switching to basal insulin occurred, and an alternative was explored with BMI returning to baseline followed by a further increase based on the Willis *et al* equations.[19]

In order to maintain simplicity and transparency only one treatment switch was included in the base case analysis, and a sensitivity analysis was conducted with a second switch to basal bolus insulin when HbA1c exceeded 7.5% for the second time. A reduction in HbA1c and an increase in BMI were applied, based on the Willis *et al*. equations for insulin experienced patients.[19]

In the base case analysis, insulin Abasaglar (the most commonly used biosimilar insulin glargine analogue) was used as the basal insulin, and a sensitivity analysis was performed with the cost of insulin NPH applied. The base case analysis was performed using a second-order Monte Carlo approach, with sampling around inputs to capture both first and second order uncertainty. A sensitivity analysis was performed using a first-order Monte Carlo approach, with no sampling around baseline characteristics, treatment effects, costs of complications utilities or transition probabilities.

Results

Base case analysis

Long-term projections found that once-weekly semaglutide was associated with improved discounted life expectancy by 0.10 years and improved discounted quality-adjusted life expectancy of 0.20 QALYs per patient compared with once-daily empagliflozin 25 mg over patient lifetimes (Table 2). The greater reductions in HbA1c and BMI identified in the indirect comparison with once-weekly semaglutide 1 mg compared with once-daily empagliflozin 25 mg drove a reduced cumulative incidence and delayed time to onset of diabetes-related complications. This led to improved duration and quality of life with once-weekly semaglutide 1 mg compared with once-daily empagliflozin 25 mg. Furthermore, the improved glycemic control with once-weekly

Table 2. Long-term cost-effectiveness outcomes in the base case analysis

Outcomes	Once-weekly semaglutide 1 mg	Once-daily empagliflozin 25 mg	Difference
Discounted life expectancy (years)	12.80 (12.65 to 12.96)	12.70 (12.55 to 12.86)	0.10 (0.09 to 0.12)
Discounted quality-adjusted life expectancy (QALYs)	7.18 (7.10 to 7.27)	6.98 (6.90 to 7.07)	0.20 (0.19 to 0.21)
Discounted direct costs (EUR)	24 845 (24 556 to 25 134)	22 041 (21 747 to 22 334)	2,804 (2,695 to 2,914)
ICER	EUR 14 114 per QALY gained		

Values are means (95% confidence intervals). EUR, euros; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

semaglutide 1 mg led to delayed switching to insulin compared with once-daily empagliflozin 25 mg. This resulted in a delay of the weight gain and hypoglycemic events associated with insulin therapy, driving further improvements in life expectancy and quality-adjusted life expectancy.

Projections suggest that once-weekly semaglutide 1 mg was associated with mean costs of EUR 24 845 compared with EUR 22 041 with once-daily empagliflozin 25 mg over patient lifetimes (Fig. 1). The higher acquisition cost of once-weekly semaglutide 1 mg compared with once-daily empagliflozin 25 mg and the increased duration of treatment due to improved glycemic control drove this increase in costs. However, once-weekly semaglutide 1 mg was associated with cost savings due to avoided diabetes-related complications, and this partially offset the increased treatment costs. Cost savings were identified in all categories of complications modelled but the most significant contributions were as a result of avoided cardiovascular disease and renal disease, with mean per patient cost savings of EUR 110 and EUR 88, respectively.

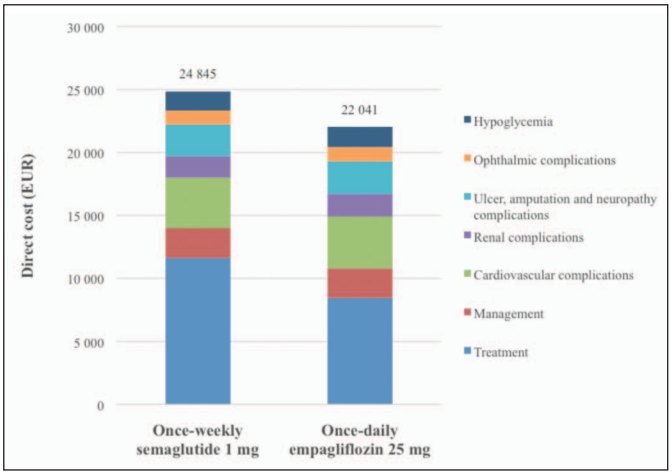

Figure 1. Direct costs over patient lifetimes

EUR, euros; QALY, quality-adjusted life year. Treatment costs captured the costs of diabetes medications and consumables; management costs included the costs of concomitant non-diabetes medications and screening; costs of cardiovascular complications included the costs of myocardial infarction, angina, congestive heart failure, stroke and peripheral vascular disease; costs of renal complications included the costs of dialysis and transplant, costs of ulcer, amputation and neuropathy complications included the costs of ulcer, gangrene, amputation, prosthesis, and neuropathy; costs of ophthalmic complications captured the costs of laser treatment, cataract surgery and blindness; costs of hypoglycemia included the costs of severe and non-severe hypoglycemic events.

Combination of cost and clinical outcomes to assess cost-effectiveness found that once once-weekly semaglutide 1 mg was associated with an ICER of EUR 14 114 per QALY gained versus once-daily empagliflozin 25 mg over patient lifetimes. This ICER falls below the willingness to pay threshold of EUR 30 000 per QALY gained where an intervention is considered cost-effective, with this threshold used as a benchmark when comparing with other health technologies.[16] In 90.6% of model iterations once-weekly semaglutide 1 mg was associated with improved outcomes and increased costs compared with once-daily empagliflozin 25 mg, and in a further 2.6% of model iterations once-weekly semaglutide 1 mg was associated with improved outcomes and cost savings (Fig. 2). At a willingness to pay threshold of EUR 30 000 per QALY gained there was a 77.6% probability that once-weekly semaglutide 1 mg was considered cost-effective (Fig. 3).

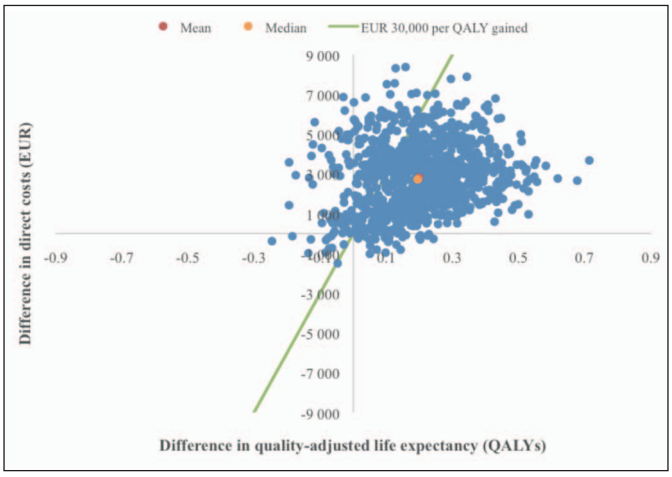

Figure 2. Cost-effectiveness scatterplot

EUR, euros; QALY, quality-adjusted life year.

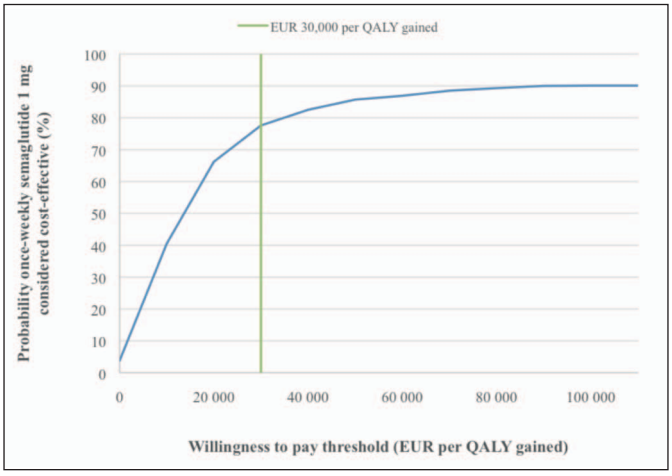

Figure 2. Cost-effectiveness acceptability curve

EUR, euros; QALY, quality-adjusted life year.

Sensitivity analysis results

Application of alternative model inputs and assumptions in sensitivity analyses did not change the conclusions of the analysis, with all calculated ICERs remaining below a willingness to pay threshold of EUR 30 000 per QALY gained (Table 3). Evaluating outcomes over shorter time horizons led to higher ICERs for once-weekly semaglutide 1 mg versus once-daily empagliflozin 25 mg as the long-term benefits of once-weekly semaglutide 1 mg in terms of avoiding diabetes-related complications were not fully captured. When discount rates of 0% were applied, once-weekly semaglutide 1 mg was found to be more cost-effective than in the base case analysis, further reflecting the long-term benefits. When only treatment effects that were significantly different between the treatment arms applied, results remained similar to the base case.

When the impact of weight loss on quality of life was increased, the ICER was reduced compared with the base case analysis, as the greater reduction in BMI with once-weekly semaglutide 1 mg had a greater impact. In the analysis with the impact of hypoglycemic events on quality of life reduced, quality-adjusted life expectancy increased in both treatment arms, with a small reduction in the clinical benefits associated with once-weekly semaglutide 1 mg as the increased frequency of hypoglycemia in the

Table 3. Sensitivity analysis results

Analysis	Discounted quality-adjusted life expectancy (QALYs)			Discounted direct costs (EUR)			ICER (EUR per QALY gained)
	Once-weekly semaglutide 1 mg	Once-daily empagliflozin 25 mg	Difference	Once-weekly semaglutide 1 mg	Once-daily empagliflozin 25 mg	Difference	
Base case	7.18	6.98	0.20	24 845	22 041	2 804	14 114
20-year time horizon	6.36	6.18	0.19	19 632	16 873	2 760	14 821
10-year time horizon	4.55	4.40	0.15	12 737	9 863	2 874	19 046
Statistically significant different treatment effects only	11.19	10.90	0.29	44 344	41 239	3 106	10 683
0% discount rates	7.18	6.98	0.20	24 845	22 041	2 804	13 937
Alternative BMI disutility	6.80	6.59	0.21	24 845	22 041	2 804	13 580
Alternative hypoglycemia disutilities	7.64	7.47	0.17	24 845	22 041	2 804	16 429
UKPDS 82 risk equations applied	7.45	7.26	0.19	25 936	23 095	2 841	15 338
Linear annual HbA1c increase while patients receive initial therapies	7.71	7.24	0.47	26 468	21 500	4 969	10 631
BMI returned to baseline and then a further increase on treatment switching	7.13	6.93	0.20	24 830	22 034	2 796	13 755
Second treatment switch to basal-bolus insulin when HbA1c exceeded 7.5% during basal insulin treatment	6.24	5.95	0.28	36 499	34 606	1 893	6 664
Insulin NPH used as basal insulin	7.18	6.98	0.20	23 348	20 452	2 896	14 575
First-order Monte Carlo simulation	7.43	7.21	0.23	25 078	22 559	2 519	11 101

BMI, body mass index; EUR, euros; HbA1c, glycated hemoglobin; ICER, incremental cost-effectiveness ratio; NPH; Neutral Protamine Hagedorn; QALY, quality-adjusted life-year; UKPDS, United Kingdom Prospective Diabetes Study.

once-daily empagliflozin 25 mg arm (due to earlier switching to basal insulin) had a smaller impact on quality of life.

Use of alternative risk equations to estimate the incidence of cardiovascular events resulted in greater quality-adjusted life expectancy and costs in both arms. However, differences between the arms remained similar to the base case analysis, as did the ICER. When it was assumed that HbA1c increased by 0.14% in both arms (rather than using the UKPDS progression equation), differences in HbA1c were maintained for longer than in the base case, resulting in a greater improvement in quality-adjusted life expectancy with once-weekly semaglutide 1 mg versus once-daily empagliflozin 25 mg. This resulted in a lower ICER than in the base case analysis. When it was assumed that BMI increased to above baseline levels on treatment switching, quality-adjusted life expectancy was reduced in both arms, but incremental outcomes and the calculated ICERs showed only small changes. When a second treatment switch to basal-bolus insulin was included in the modelling analysis, quality-adjusted life expectancy was reduced and costs increased in both arms. As well as delaying initiation of basal insulin, once-weekly semaglutide 1 mg also delayed switching to basal-bolus insulin, and this resulted in greater clinical benefits, a smaller increase in costs, and a lower ICER than in the base case. Use of a less costly basal insulin formulation (NPH) had only a small impact on cost outcomes, with the ICER remaining similar to the base case analysis. Similarly, projected outcomes remained comparable to the base case analysis when sampling of patient characteristics and treatment effects was turned off.

Discussion

Greater improvements in HbA1c and BMI with once-weekly semaglutide 1 mg *versus* once-daily empagliflozin 25 mg as described in a previously published meta-analysis were projected to result in reduced cumulative incidence and delayed time to onset of diabetes-related complications, increased life expectancy, and increased quality-adjusted life expectancy over patient lifetimes. Increased costs of treatment with once-weekly semaglutide 1 mg were partially offset by reduced costs of diabetes related complications. The projected ICER of EUR 14 114 per QALY falls below the willingness to pay threshold of EUR 30 000 per QALY gained where an intervention is considered cost-effective, with this threshold used as a benchmark when comparing with other health technologies in Portugal.[16] Compared with once-daily empagliflozin 25 mg, once-weekly semaglutide 1 mg was projected to be a cost-effective treatment from a healthcare payer perspective for patients with type 2 diabetes with inadequate glycemic control on metformin monotherapy in Portugal.

The present analysis was based on clinical data from a meta-analysis, and the strengths and weaknesses of this data source must be considered to provide context. The meta-regression was conducted using individual patient data, allowing for a better isolation of the effect of a treatment on each outcome of interest than when trial-level data are used. Additionally, the analysis was able to capture a wider range of outcomes (such as lipid parameters) than is possible based on published trial-level data, giving a more accurate reflection of the differences in risk factors for diabetes-related complications. There was limited heterogeneity between the included clinical trials, with all having a similar design and inclusion/exclusion criteria. However, there were some differences in trial designs, such as blinding and the study duration ranging from 52 to 56 weeks. To assess the importance of study duration on outcomes the authors conducted an analysis using only the 52-week trials, and this confirmed that study duration did not significantly impact the results. One potential downside of the approach is that no common comparator was included as an anchor. Unanchored indirect comparisons assume that all potential prognostic factors and effect modifiers are identified, and this is difficult to confirm for this (or any other) meta-analysis. It should also be

noted that data from randomized controlled trials were used to assess the cost-effectiveness of interventions in the real world, and therefore there is an implicit assumption that efficacy is similar in randomized controlled trials and routine clinical practice.

A previously published network meta-analysis (NMA) has compared the efficacy of once-weekly semaglutide 0.5 mg and 1 mg with SGLT-2 inhibitors, including once-daily empagliflozin 25 mg using trial-level data.[27] The clinical trials included showed some overlap with the analysis based on patient-level data, capturing SUSTAIN 2, SUSTAIN 7, and EMPA-REG MET. This NMA found that the estimated treatment difference in change from baseline in HbA1c for once-weekly semaglutide 1 mg versus once-daily empagliflozin 25 mg was −0.80% (95% confidence interval [CI] −1.04 to −0.58%). The estimated treatment difference in change from baseline in weight was −2.05 kg (95% CI −2.94 to −1.15 kg), and the estimated treatment difference in change from baseline in systolic blood pressure: −2.47 mmHg (95% CI −5.79 to 0.83 mmHg). These results are similar to those calculated in the meta-regression based on individual patient data, with both showing significantly greater reductions in HbA1c and weight. Due to the similarities between the results, conducting a scenario analysis using the NMA data was not considered necessary.

The present analysis is the first to assess the cost-effectiveness of once-weekly semaglutide in Portugal, and therefore provides new information for healthcare payers. To date, only one published analysis has compared once-weekly semaglutide with once-daily empagliflozin.[28] This was based on the NMA conducted using trial-level data, and assessed cost-effectiveness from a healthcare payer perspective in Spain.[27,28] The analysis projected that once-weekly semaglutide 0.5 mg and 1 mg were associated with incremental cost-effectiveness ratios of EUR 3 090 and EUR 625 per QALY gained, respectively, versus once-daily empagliflozin 25 mg. These results concur with the present analysis, suggesting that once-weekly semaglutide is likely to be cost-effective versus once-daily empagliflozin.

The present analysis aimed to reflect clinical practice, with glycemic control declining over time and subsequent use of insulin therapy, and a consequent reduction in HbA1c accompanied by an increase in BMI and risk of hypoglycemia. This approach is also in line with previously published cost-effectiveness analyses, both in the peer-reviewed literature and in the NICE multiple technology appraisal of SGLT-2 inhibitors.[14,15,29] Using a clinically realistic approach aimed to ensure that the present analysis can be useful to healthcare decision makers. However, the present analysis captured only one treatment pathway, with switching from GLP-1 receptor agonists or SGLT-2 inhibitors to basal insulin. In clinical practice, alternative treatment pathways may be used, such as addition of an SGLT-2 inhibitor to a GLP-1 receptor agonist, addition of a GLP-1 receptor agonist to an SGLT-2 inhibitor, or continuation of previous therapies alongside basal insulin. There is currently a lack of clinical data to allow modelling of more these complex treatment pathways, and this is an area for future study.

Both once-weekly semaglutide and once-daily empagliflozin have been shown to reduce the risk of major adverse cardiovascular events compared with standard care in the SUSTAIN 6 and EMPA-REG OUTCOME trials, respectively.[30,31] However, data from these cardiovascular outcomes trials (CVOTs) were not incorporated in the present analysis. To date, no risk equations for projecting long-term outcomes in people with type 2 diabetes that include data from CVOTs have been published. Such an approach is challenging, as CVOTs generally enroll participants at high risk of experiencing cardiovascular events, and it is currently unknown whether these benefits would also be observed in lower risk populations. Furthermore, diabetes medications impact conventional cardiovascular risk factors, and the separation of the impact of these changes from the impact associated with the treatments themselves is difficult. Early analyses suggest that capturing cardiovascular risk can have an important impact on the results of long-term analyses, and therefore including this in revised risk equations represents a key goal for modelling analyses in the future.[32]

The present analysis projected outcomes over patient lifetimes based on short-term data, and this is associated with inherent uncertainty, particularly around how risk factors change over time and how well risk equations based on historic data predict outcomes for modern patients. However, projection of long-term outcomes remains the best available option to inform decision making in the absence of long-term clinical trial data, and is recommended in health-economic guidelines. The impact of uncertainty on the present analysis has been mitigated as far as possible by using a model that has been extensively published and validated and by conducting extensive sensitivity analyses.[12,13]

Conclusion

Compared with once-daily empagliflozin 25 mg, once-weekly semaglutide 1 mg was projected to be a cost-effective treatment from a healthcare payer perspective for patients with type 2 diabetes with inadequate glycemic control on metformin monotherapy in Portugal, based on a willingness to pay threshold of EUR 30 000 per QALY gained.

Responsabilidades Éticas

Conflitos de Interesse: Davide Carvalho recebeu honorários de consultoria e como palestrante e foi membro dos conselhos consultivos da AstraZeneca, Bial, Boehringer Ingelheim, Lilly, Merck Serono, MSD, Novartis, Novo Nordisk, Sanofi e Servier. Catarina Costa é funcionária da Novo Nordisk, Lda. Nino Hallén e James Baker-Knight são funcionários da Novo Nordisk A/S. Barnaby Hunt recebeu honorários de consultoria da Novo Nordisk A/S.
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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia de 2013 da Associação Médica Mundial.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of interest: Davide Carvalho has received honoraria for speaking and consulting and has served as a member of advisory boards for AstraZeneca, Bial, Boehringer Ingelheim, Lilly, Merck Serono, MSD, Novartis, Novo Nordisk, Sanofi and Servier. Catarina Costa is an employee of Novo Nordisk, Lda. Nino Hallén and James Baker-Knight are employees of Novo Nordisk A/S. Barnaby

Hunt is an employee of Ossian Health Economics and Communications, which received consulting fees from Novo Nordisk A/S.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

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