ORIGINAL PAPER

The long-term cost-effectiveness of once-weekly semaglutide 1 mg vs. dulaglutide 3 mg and 4.5 mg in the UK

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Abstract

Aims Once-weekly semaglutide and dulaglutide represent two highly efficacious treatment options for type 2 diabetes. A recent indirect treatment comparison (ITC) has associated semaglutide 1 mg with similar and greater improvements in glycated haemoglobin (HbA1c) and body weight, respectively, vs. dulaglutide 3 mg and 4.5 mg. The present study aimed to evaluate the long-term cost-effectiveness of semaglutide 1 mg vs. dulaglutide 3 mg and 4.5 mg in the UK.

Materials and methods The IQVIA CORE Diabetes Model (v9.0) was used to project outcomes over patients' lifetimes. Baseline cohort characteristics were sourced from SUSTAIN 7, with changes in HbA1c and body mass index applied as per the ITC. Modelled patients received semaglutide or dulaglutide for 3 years, after which treatment was intensified to basal insulin. Costs (expressed in 2020 pounds sterling [GBP]) were accounted from a healthcare payer perspective.

Results Semaglutide 1 mg was associated with improvements in quality-adjusted life expectancy of 0.05 and 0.04 quality-adjusted life years (QALYs) vs. dulaglutide 3 mg and 4.5 mg, respectively, due to a reduced incidence of diabetes-related complications with semaglutide. Direct costs were estimated to be GBP 76 lower and GBP 8 higher in the comparisons with dulaglutide 3 mg and 4.5 mg, respectively. Overall outcomes were similar, but favoured semaglutide, and based on modelled mean outcomes it was considered dominant vs. dulaglutide 3 mg and associated with an incremental cost-effectiveness ratio of GBP 228 per QALY gained vs. dulaglutide 4.5 mg.

Conclusions Semaglutide 1 mg represents a cost-effective treatment vs. dulaglutide 3 mg and 4.5 mg for type 2 diabetes from a healthcare payer perspective in the UK.

Introduction

Reducing the incidence of long-term complications attributable to type 2 diabetes is vital to minimising the high and increasing expenditure associated with the disease. Total diabetes-related expenditure in the UK was estimated to be more than GBP 17 billion in 2021, with projections indicating that the prevalence of diabetes is expected to increase from 6.3% in 2021 to 7.5% by 2045 [1]. Improving glycaemic control remains a key target of care based on landmark studies, including the United Kingdom Prospective Diabetes Study (UKPDS), which associated improvements in glycated haemoglobin (HbA1c) with a reduced incidence of long-term diabetes-related complications [2–6]. However, modern clinical practice has moved towards a more holistic approach to diabetes care, with evidence indicating that reductions in blood pressure, serum lipids and body weight are also associated with a reduced risk of diabetes-related complications [7–10]. Guidelines published by the National Institute for Health and Care Excellence (NICE) therefore recommend an HbA1c target of 6.5% (48 mmol/mol) for people with type 2 diabetes managed with lifestyle modifications and

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one anti-diabetic agent, and a target of 7.0% (53 mmol/mol) for people with type 2 diabetes not adequately controlled by a single glucose-lowering drug, as well as a weight loss target of 5–10% of body weight [11]. Interventions that can provide reductions in blood glucose levels and body weight for people with type 2 diabetes, while providing value for money over the long term, are therefore highly relevant for the National Health Service (NHS) in the UK, where healthcare resources are coming under ever-increasing strain.

Modern therapies for type 2 diabetes, such as glucagon-like peptide-1 (GLP-1) receptor agonists, combine clinically important reductions in blood glucose levels with weight loss and a low risk of hypoglycaemia [12]. Several GLP-1 receptor agonists are approved for use in the UK, including once-weekly injectable treatments semaglutide and dulaglutide. Once-weekly semaglutide 0.5 mg and 1 mg were compared with dulaglutide 0.75 mg and 1.5 mg, respectively, in the SUSTAIN 7 clinical trial, and were associated with greater reductions in HbA1c and body weight in people with type 2 diabetes with inadequate glycaemic control on metformin, with a subsequent long-term cost-effectiveness analysis in the UK demonstrating that these clinical benefits translated to improved life expectancy, quality of life and cost savings over patients' lifetimes [13, 14].

Since the publication of SUSTAIN 7, further studies have been designed to evaluate higher doses of GLP-1 receptor agonists, to elucidate if further efficacy can be gained without sacrificing safety. The published AWARD-11 trial, also conducted in patients with inadequate glycaemic control on metformin, demonstrated that escalation from dulaglutide 1.5 mg to 3 mg or 4.5 mg provided a similar safety profile while offering clinically relevant, dose-related reductions in HbA1c and body weight [15]. Similarly, the SUSTAIN FORTE trial demonstrated superior reductions in HbA1c and body weight with once-weekly semaglutide 2 mg compared with once-weekly semaglutide 1 mg alongside a similar safety profile [16]. However, as yet, no clinical trial has assessed these newly approved high doses of one GLP-1 receptor agonist vs. any dose of another GLP-1 receptor agonist.

A recent indirect treatment comparison (ITC) has evaluated once-weekly semaglutide 1 mg vs. dulaglutide 3 mg and 4.5 mg, based on the results of SUSTAIN 7 and AWARD-11 [17]. The ITC was performed using the Bucher method, which accounts for cross-trial differences by measuring treatment effects relative to a common comparator arm (in this case, dulaglutide 1.5 mg) and requires only the availability of summary-level data for each trial [18]. This method is considered appropriate if the relative treatment effect can be assumed to be the same across the two trial populations, which was deemed to hold in the populations of SUSTAIN 7 and AWARD-11 (both conducted in people with type 2 diabetes with inadequate glycaemic control on metformin). Results from the ITC indicated that once-weekly semaglutide 1 mg was associated with significantly greater reductions in HbA1c and body weight vs. dulaglutide 3 mg, and similar reductions in HbA1c and significantly greater reductions in body weight vs. dulaglutide 4.5 mg, in people with inadequate glycaemic control on metformin.

Previous long-term analyses have assessed the cost-effectiveness of once-weekly semaglutide in the UK. These include comparisons vs. the lower 0.75 mg and 1.5 mg doses of dulaglutide, once-daily GLP-1 receptor agonist liraglutide 1.2 mg, and sodium-glucose cotransporter-2 (SGLT-2) inhibitor empagliflozin 25 mg [14, 19, 20]. However, to date, no study has evaluated the cost-effectiveness of once-weekly semaglutide 1 mg vs. the higher 3 mg and 4.5 mg doses of dulaglutide, treatments that people with type 2 diabetes in the UK are expected to receive during the course of their disease. The present study was, therefore, designed to answer a pertinent research question for physicians, healthcare payers and people with type 2 diabetes in the UK and to elucidate the relative cost-effectiveness of several highly efficacious GLP-1 receptor agonist therapies.

Based on the results from the ITC, the aim of the present study was to evaluate the long-term cost-effectiveness of once-weekly semaglutide 1 mg vs. dulaglutide 3 mg and 4.5 mg for the treatment of people with type 2 diabetes not achieving glycaemic control on metformin in the UK.

Methods

Modelling approach

The IQVIA CORE Diabetes Model (version 9.0) was used to project clinical and cost outcomes over patients' lifetimes (50 years), in line with guidance on the cost-effectiveness of interventions for diabetes [21]. The structure, assumptions, features and capabilities of the model, as well as two validation studies, have been previously described [22–24]. Relevant model outputs include life expectancy (measured in years), quality-adjusted life expectancy (measured in quality-adjusted life years [QALYs]), direct costs, incremental cost-effectiveness ratios (ICERs), cumulative incidence and time to onset of diabetes-related complications, and cost-effectiveness scatterplots and acceptability curves.

Base case and sensitivity analyses were performed using a first-order Monte Carlo approach, with second-order uncertainty captured in the probabilistic sensitivity analysis (PSA). In line with recommendations from the model proprietors, the UKPDS 68 risk equations were used to predict outcomes in the base case analysis [24]. Future clinical and

cost outcomes were discounted at 3.5% *per annum*, in line with guidance published by NICE [25]. Background mortality was captured based on UK-specific life tables published by the World Health Organisation (WHO) [26].

Baseline cohort characteristics and treatment effects

Baseline cohort characteristics were sourced from the full population in the SUSTAIN 7 clinical trial, as this was used to inform the once-weekly semaglutide arm of the ITC (Table S1) [13, 17]. These cohort characteristics were used in a previously published cost-effectiveness analysis of once-weekly semaglutide in the UK [14]. The mean (standard deviation) age of the cohort was 56 (10.6) years, with a mean duration of diabetes of 7.4 (5.7) years, mean HbA1c of 8.2 (0.9)% [66.1 (10.1) mmol/mol], and mean body mass index (BMI) of 33.5 (6.8) kg/m^2. Alcohol and tobacco consumption were not collected in the SUSTAIN 7 study and these were therefore assumed to be the same as the general UK population [27, 28].

Treatment effects were taken from the ITC, and comprised changes in HbA1c and BMI (calculated from changes in body weight from the ITC using the mean height from SUSTAIN 7; Table S2) [17]. Once-weekly semaglutide was associated with mean changes in HbA1c and BMI of − 1.78 (standard error 0.06)% and − 2.33 (0.10) kg/m^2, respectively, while dulaglutide 3 mg was associated with corresponding changes of − 1.54 (0.10)% and − 1.44 (0.16) kg/m^2. Dulaglutide 4.5 mg was associated with mean changes in HbA1c and BMI of − 1.71 (0.10)% and − 1.67 (0.16) kg/m^2, respectively. Once-weekly semaglutide 1 mg was associated with statistically significant reductions in HbA1c and BMI vs. dulaglutide 3 mg, and in BMI vs. dulaglutide 4.5 mg. Changes in all other physiological parameters and adverse event rates included in the IQVIA CORE Diabetes Model, including blood pressure, serum lipids and hypoglycaemic event rates, were set to zero in all treatment arms to ensure that assumptions in these parameters did not drive cost-effectiveness outcomes.

Treatment switching and long-term parameter progression

In the base case analysis, a simple treatment algorithm was employed to evaluate cost-effectiveness, aiming to limit the impact of modelling assumptions on the overall conclusions of the analysis. Modelled patients were assumed to receive once-weekly semaglutide or dulaglutide for 3 years, in line with previously published analyses of GLP-1 receptor agonists and data from general practice in Europe, which reported a mean duration of treatment

with GLP-1 receptor agonists of 29.35 months (rounded to 3 years, as treatment switching in the IQVIA CORE Diabetes Model can only occur at the end of an annual cycle) [14, 29–31]. After 3 years, treatment with once-weekly semaglutide and dulaglutide was discontinued and patients were assumed to intensify to basal insulin therapy with insulin Abasaglar® (the most common biosimilar insulin glargine in the UK). Patients remained on basal insulin for the remainder of their lifetimes. Alternative approaches to treatment switching were explored in sensitivity analyses, while different treatment algorithms were explored in pathway scenario analyses.

After the application of changes in HbA1c and BMI in the first year of the analysis, values in each arm were assumed to remain constant while patients received semaglutide or dulaglutide treatment. On intensification to basal insulin, differences were abolished by bringing HbA1c in all arms to 7.0% and returning BMI to baseline. This ensured a balanced cost-effectiveness analysis, with differences in physiological parameters only maintained while there was a difference in the medications received. On treatment intensification, non-severe and severe hypoglycaemic event rates of 408 and 10 events per 100 person-years, respectively, were applied, based on data from the UK Hypoglycaemia Study Group [32].

Costs and utilities

Costs were accounted from a healthcare payer perspective in the UK and expressed in 2020 pounds sterling (GBP). Captured costs included pharmacy and management costs, based on list prices published on the Monthly Index of Medical Specialities (MIMS) database, and the costs of treating diabetes-related complications, which were based on a published literature review (Table S3) [33, 34]. Costs from the literature review were updated by sourcing up-to-date costs from the most recent publications of annually updated sources, and inflated were necessary to 2020 GBP using the Health and Community Health Services Index published by the Personal Social Services Research Unit (PSSRU) [33, 35–42].

Annual treatment costs were calculated based on resource use from SUSTAIN 7, with 100% of patients receiving concomitant metformin for the duration of the analysis (Table S4). No needle or self-monitoring of blood glucose (SMBG) use was assumed for patients receiving semaglutide or dulaglutide, with one needle and one SMBG test per day assumed to be required once patients intensified to basal insulin.

Utilities were taken from a 2014 review by Beaudet et al. with hypoglycaemia disutilities coming from Evans et al. 2013 (published after the literature searches by

Beaudet et al. had been completed; Table S5) [43, 44]. Beaudet et al. reviewed the methods of the identified publications to ensure that they met the criteria of the NICE reference case.

Key drivers of clinical benefits

A series of analyses were performed to evaluate the key drivers of clinical outcomes. Separate analyses applied the differences in HbA1c and BMI in the once-weekly semaglutide arm in turn, with the other parameter set to the value observed in the respective dulaglutide arm.

Sensitivity analyses

The extrapolation of clinical results by modelling the long-term consequences is inherently associated with uncertainty. Sensitivity analyses were, therefore, performed to assess the robustness of the base case findings. These included: shortening the time horizon to 35, 20, 10, 5 and 3 years; applying clinical and cost discount rates of 0% and 6% in separate analyses; maintaining the treatment effects on BMI for patient lifetimes; applying the upper and lower 95% confidence interval bounds of the estimated treatment differences in HbA1c and BMI in separate analyses; assuming treatment switching after 5 years; applying the UKPDS progression equation for HbA1c and assuming treatment switching when HbA1c exceeded 7.5%; applying the cost of insulin Semglee® on intensification; increasing and decreasing the direct costs of treating diabetes-related complications by 10%; applying the UKPDS 82 risk equations to predict model outcomes; applying an alternative BMI disutility, giving greater weight to changes in BMI; and PSA [45].

Pathway scenario analyses

Further, more hypothetical analyses were performed to evaluate the impact of modelling different treatment algorithms on cost-effectiveness outcomes. These aimed to capture more clinically realistic treatment intensification patterns, as per NICE guidelines, but were associated with significant uncertainty regarding changes in risk factors at each intensification step [11]. These analyses included two different pathways:

- Patients were modelled to receive once-weekly semaglutide or dulaglutide for 3 years, at which point a sodium-glucose cotransporter-2 (SGLT-2) inhibitor was added to all treatment arms, and patients continued with both GLP-1 receptor agonist and SGLT-2 inhibitor therapy. After a further 3 years, basal insulin was added to all treatment arms, and patients again continued GLP-1 receptor agonist and SGLT-2 inhibitor therapy. Following

a further 3 years, patients discontinued GLP-1 receptor agonist and SGLT-2 inhibitor therapy and were assumed to receive basal-bolus insulin for the remainder of their lifetimes.

- Patients were modelled to receive once-weekly semaglutide or dulaglutide for 3 years, at which point basal insulin was added to all treatment arms, and patients continued with GLP-1 receptor agonist therapy. After a further 3 years, patients discontinued GLP-1 receptor agonist therapy and were assumed to receive basal-bolus insulin for the remainder of their lifetimes.

In these analyses, following the addition of an SGLT-2 inhibitor, HbA1c and BMI were assumed to remain constant (at the levels observed following application of the initial treatment effects with semaglutide and dulaglutide), based on the rationale that additional treatments would be required to maintain glycaemic control, while on the addition of basal insulin, HbA1c was brought to 7.0% and BMI was returned to baseline. On initiation of bolus insulin, no changes in HbA1c were applied, while an increase in BMI was applied based on the 'insulin-experienced' multivariate prediction equations published by Willis et al. [46]. Non-severe and severe hypoglycaemic event rates were increased to 1,020 and 70 events per 100 person-years, respectively, based on data from the UK Hypoglycaemia Study Group [32].

Compliance with ethics guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Results

Base case analysis

Long-term projections in patients with inadequate glycaemic control on metformin indicated that once-weekly semaglutide 1 mg was associated with improvements in discounted life expectancy of 0.05 and 0.04 years, and discounted quality-adjusted life expectancy of 0.05 and 0.04 QALYs, vs. dulaglutide 3 mg and 4.5 mg, respectively (Table 1). Clinical benefits with once-weekly semaglutide were a result of a reduced cumulative incidence and delayed time to onset of diabetes-related complications over the long term, with improvements observed in both micro- and macrovascular complications (Fig. 1).

Direct costs were estimated to be GBP 76 lower with once-weekly semaglutide 1 mg vs. dulaglutide 3 mg, and GBP 8 higher with once-weekly semaglutide 1 mg vs. dulaglutide 4.5 mg (Fig. 2). Once-weekly semaglutide was

Table 1 Base case analysis results

Health outcomes	Once-weekly semaglutide 1 mg	Dulaglutide 3 mg	Difference
Discounted life expectancy, years	14.28 (14.27–14.29)	14.23 (14.22–14.25)	+0.05 (0.03–0.06)
Discounted quality-adjusted life expectancy, QALYs	9.41 (9.40–9.42)	9.36 (9.35–9.37)	+0.05 (0.05–0.06)
Discounted direct costs, GBP	24,146 (24,105–24,186)	24,222 (24,182–24,261)	−76 (−128–−24)
ICER	Once-weekly semaglutide dominant		
Health outcomes	**Once-weekly semaglutide 1 mg**	**Dulaglutide 4.5 mg**	**Difference**
Discounted life expectancy, years	14.28 (14.27–14.29)	14.25 (14.24–14.26)	+0.04 (0.02–0.05)
Discounted quality-adjusted life expectancy, QALYs	9.41 (9.40–9.42)	9.38 (9.37–9.38)	+0.04 (0.03–0.05)
Discounted direct costs, GBP	24,146 (24,105–24,186)	24,138 (24,098–24,177)	+8 (−38–55)
ICER	GBP 228 per QALY gained		

GBP 2020 pounds sterling, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year

associated with increased treatment costs in both comparisons despite identical acquisition costs, due to increased survival and further treatment of patients over the long term. In the comparison with dulaglutide 3 mg, increased treatment costs were entirely offset by cost savings from avoidance of diabetes-related complications (most notably cardiovascular complications, with mean cost savings of GBP 62 per patient), while in the comparison with dulaglutide 4.5 mg, increased treatment costs were partially offset by the avoidance of complications (most notably by ophthalmic complications, with mean cost savings of GBP 27 per patient).

Projections of long-term outcomes indicated that both life expectancy and quality-adjusted life expectancy were improved with once-weekly semaglutide 1 mg compared with dulaglutide 3 mg and 4.5 mg, at reduced and increased costs, respectively, from a healthcare payer perspective (Table 1). Overall clinical and cost outcomes were similar, but significantly favoured semaglutide at a 95% confidence level, and it was therefore considered dominant vs. dulaglutide 3 mg and associated with an ICER of GBP 228 per QALY gained vs. dulaglutide 4.5 mg based on modelled mean outcomes for the treatment of type 2 diabetes in the UK.

Key drivers of clinical benefits

Testing for the key drivers of clinical benefits by applying the differences in HbA1c and BMI in turn showed that reductions in both HbA1c and BMI were equally important in driving improved quality-adjusted life expectancy for once-weekly semaglutide 1 mg vs. dulaglutide 3 mg, with improvements of 0.02 QALYs when each of these differences was applied sequentially. In the comparison with dulaglutide 4.5 mg, greater reductions in BMI were identified as the key driver of benefits, with improvements in quality-adjusted life expectancy of 0.03 QALYs with once-weekly semaglutide 1 mg when only this difference between the treatment arms was applied.

Sensitivity analyses

Wide-ranging sensitivity analyses showed that the results of the base case analysis were robust to changes in the input parameters and assumptions used (Table 2). In the comparison with dulaglutide 3 mg, once-weekly semaglutide 1 mg remained associated with small but significant clinical benefits and cost savings in all-but-one analysis. When HbA1c
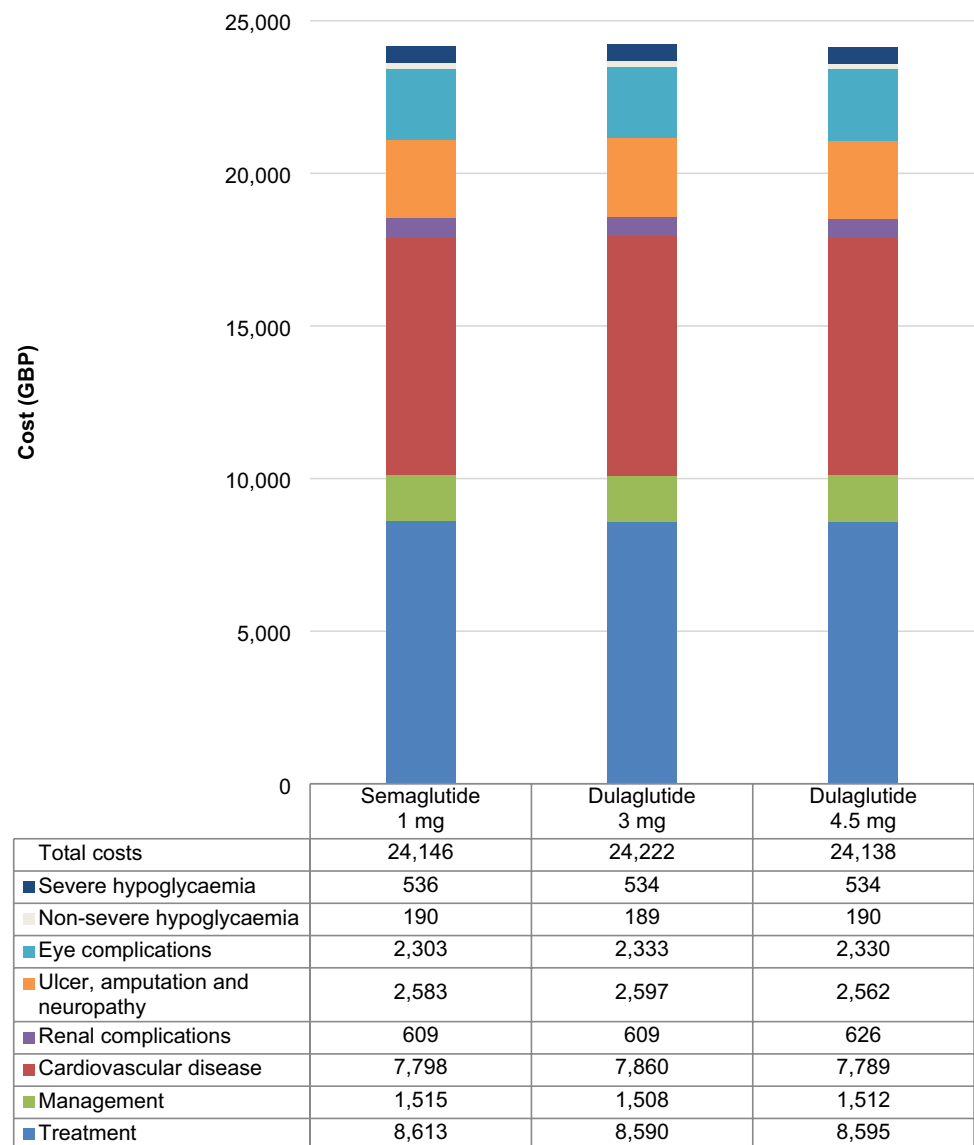
Fig. 1 Time to onset of diabetes-related complications over patients' lifetimes
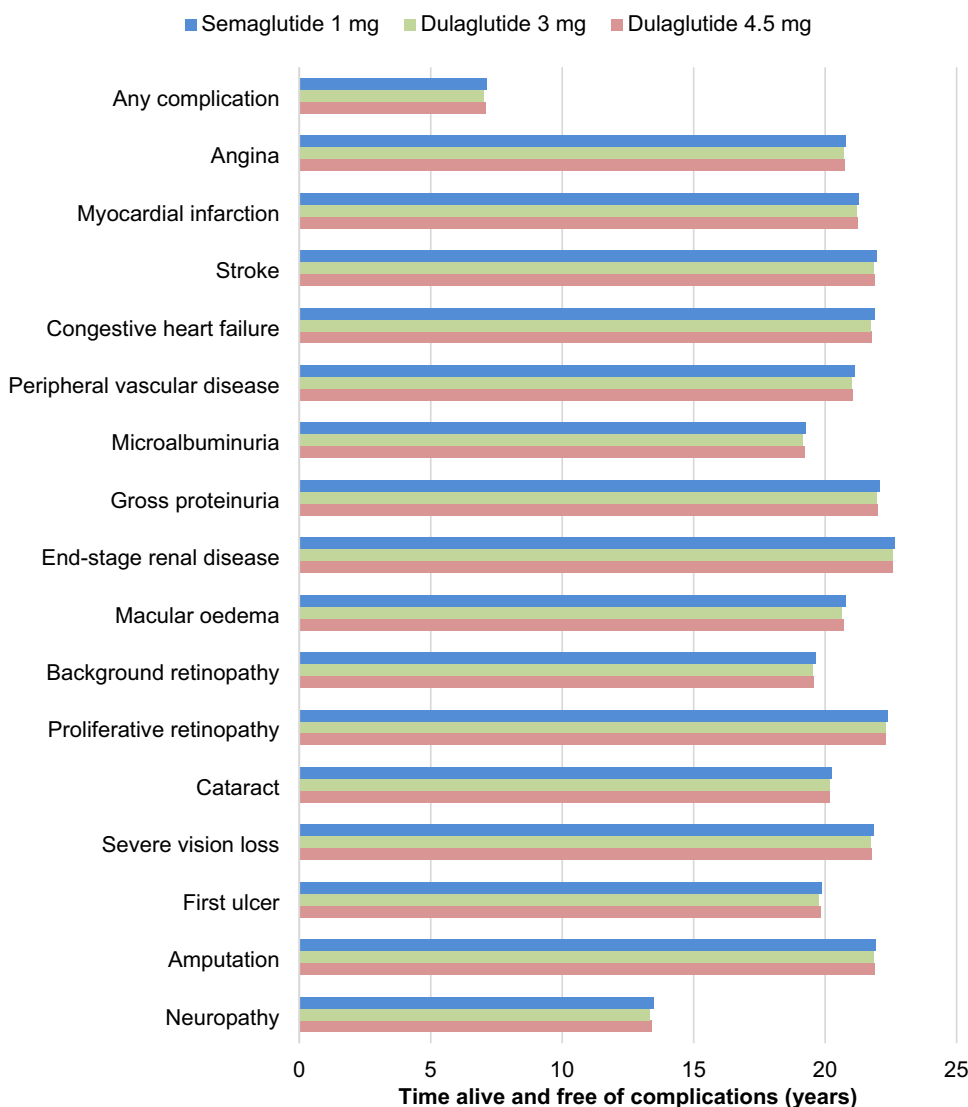
was assumed to follow the UKPDS progression equation and treatment switching occurred at a 7.5% HbA1c threshold, once-weekly semaglutide was associated with an ICER of GBP 2,603 per QALY gained. In this analysis, once-weekly semaglutide was associated with increased costs, due to different times of treatment switching in the two arms (with patients receiving once-weekly semaglutide 1 mg for 4 years and dulaglutide 3 mg for 3 years). Patients, therefore, accrued higher treatment costs in the once-weekly semaglutide arm, due to one further year of treatment with GLP-1 receptor agonist therapy.

In the comparison with dulaglutide 4.5 mg, once-weekly semaglutide 1 mg remained associated with low ICERs in the majority of analyses. The largest deviation in the ICER occurred when applying the lower 95% confidence interval of the estimated treatment difference in HbA1c between the treatment arms, yielding an ICER of GBP 4,976 per QALY gained for once-weekly semaglutide.

PSA showed similar mean results to the base case analysis, but increased measures of variance around the mean outcomes (Fig. 3). Once-weekly semaglutide 1 mg was associated with mean improvements in quality-adjusted life expectancy of 0.05 QALYs vs. dulaglutide 3 mg and 0.03 QALYs vs. dulaglutide 4.5 mg, with direct costs estimated to be GBP 82 and GBP 13 lower, respectively. While these differences were small, they were statistically significant at a 95% confidence level, and once-weekly semaglutide 1 mg was, therefore, considered dominant vs. both doses of dulaglutide in the PSA based on mean outcomes. Based on this analysis, and assuming a willingness-to-pay threshold of GBP 20,000 per QALY gained, the probabilities of once-weekly semaglutide 1 mg being cost-effective vs. dulaglutide 3 mg and 4.5 mg were 62.9% and 56.9%, respectively (Fig. 4).

Fig. 2 Direct costs over patients' lifetimes

	Semaglutide 1 mg	Dulaglutide 3 mg	Dulaglutide 4.5 mg
Total costs	24,146	24,222	24,138
■ Severe hypoglycaemia	536	534	534
▫ Non-severe hypoglycaemia	190	189	190
■ Eye complications	2,303	2,333	2,330
■ Ulcer, amputation and neuropathy	2,583	2,597	2,562
■ Renal complications	609	609	626
■ Cardiovascular disease	7,798	7,860	7,789
■ Management	1,515	1,508	1,512
■ Treatment	8,613	8,590	8,595

GBP, 2020 pounds sterling.

Pathway scenario analyses

Hypothetical analyses evaluating different treatment pathways showed that addition of other anti-diabetic agents to GLP-1 receptor agonist therapy did not change the conclusions of the base case analysis (Table 2).

The addition of an SGLT-2 inhibitor followed by the addition of basal insulin and eventual intensification to basal-bolus therapy led to poorer outcomes and increased costs in all treatment arms, due to the further increase in BMI applied on intensification to bolus insulin (following the return of BMI to baseline on initiation of basal insulin) and the increased number of anti-diabetic agents, respectively. Small but statistically significant clinical benefits and cost savings were maintained with once-weekly semaglutide 1 mg vs. dulaglutide 3 mg, and it was associated with an ICER of GBP 556 per QALY gained vs. dulaglutide 4.5 mg.

The addition of basal insulin followed by intensification to basal-bolus therapy led to further reduced life expectancy and quality-adjusted life expectancy in all treatment arms, as the initiation of bolus insulin (and corresponding increase in BMI) was earlier in the analysis. Costs were also increased in comparison with the base case analysis, but reduced in comparison with the addition of an SGLT-2 inhibitor pathway analysis. Once-weekly semaglutide was associated with increased costs in both comparisons, due to increased survival and further treatment of patients over the long term, and was therefore associated with ICERs of GBP 618 and GBP 4,412 per QALY gained vs. dulaglutide 3 mg and 4.5 mg, respectively.

Table 2 Sensitivity and pathway scenario analyses results

Analysis	Once-weekly semaglutide 1 mg versus dulaglutide 3 mg			Once-weekly semaglutide 1 mg versus dulaglutide 4.5 mg		
	Difference in discounted quality-adjusted life expectancy, QALYs	Difference in discounted direct costs, GBP	ICER, GBP per QALY gained	Difference in discounted quality-adjusted life expectancy, QALYs	Difference in discounted direct costs, GBP	ICER, GBP per QALY gained
Base case	+0.05	−76	Semaglutide dominant	+0.04	+8	228
Sensitivity analyses						
35-year time horizon	+0.06	−98	Semaglutide dominant	+0.03	−51	Semaglutide dominant
20-year time horizon	+0.05	−76	Semaglutide dominant	+0.02	−15	Semaglutide dominant
10-year time horizon	+0.02	−75	Semaglutide dominant	+0.02	−3	Semaglutide dominant
5-year time horizon	+0.02	−21	Semaglutide dominant	+0.01	−8	Semaglutide dominant
3-year time horizon	+0.02	−11	Semaglutide dominant	+0.01	−2	Semaglutide dominant
0% discount rates	+0.09	−50	Semaglutide dominant	+0.06	+59	1,013
6% discount rates	+0.04	−70	Semaglutide dominant	+0.03	−5	Semaglutide dominant
BMI difference maintained for patient lifetimes	+0.13	−115	Semaglutide dominant	+0.09	−22	Semaglutide dominant
Upper 95% CI of HbA1c estimated treatment difference	+0.08	−159	Semaglutide dominant	+0.06	−75	Semaglutide dominant
Lower 95% CI of HbA1c estimated treatment difference	+0.03	−27	Semaglutide dominant	+0.01	+57	4,976
Upper 95% CI of BMI estimated treatment difference	+0.07	−70	Semaglutide dominant	+0.05	+13	263
Lower 95% CI of BMI estimated treatment difference	+0.05	−108	Semaglutide dominant	+0.03	−24	Semaglutide dominant
Treatment switching at 5 years	+0.07	−103	Semaglutide dominant	+0.04	−31	Semaglutide dominant
Treatment switching at 7.5% (58 mmol/mol) HbA1c threshold (using UKPDS progression)	+0.08	+220	2,603	+0.04	−53	Semaglutide dominant
Semglee cost applied on treatment intensification	+0.05	−78	Semaglutide dominant	+0.04	+6	180
Cost of complications +10%	+0.05	−85	Semaglutide dominant	+0.04	+7	202
Cost of complications −10%	+0.05	−66	Semaglutide dominant	+0.04	+9	253
UKPDS 82 risk equations applied	+0.02	−101	Semaglutide dominant	+0.02	+1	42
Lee *et al.* BMI disutility applied	+0.06	−76	Semaglutide dominant	+0.04	+8	196
Pathway scenario analyses						
Addition of SGLT-2 inhibitor and basal insulin, then basal-bolus	+0.08	−43	Semaglutide dominant	+0.03	+18	566
Addition of basal insulin, then basal-bolus	+0.06	+38	618	+0.03	+121	4,412

BMI body mass index, *CI* confidence interval, *GBP* 2020 pounds sterling, *HbA1c* glycated haemoglobin, *QALY* quality-adjusted life year. Quality-adjusted life expectancy outcomes are rounded to 2 decimal places

Fig. 3 Cost-effectiveness scatterplot from the probabilistic analyses
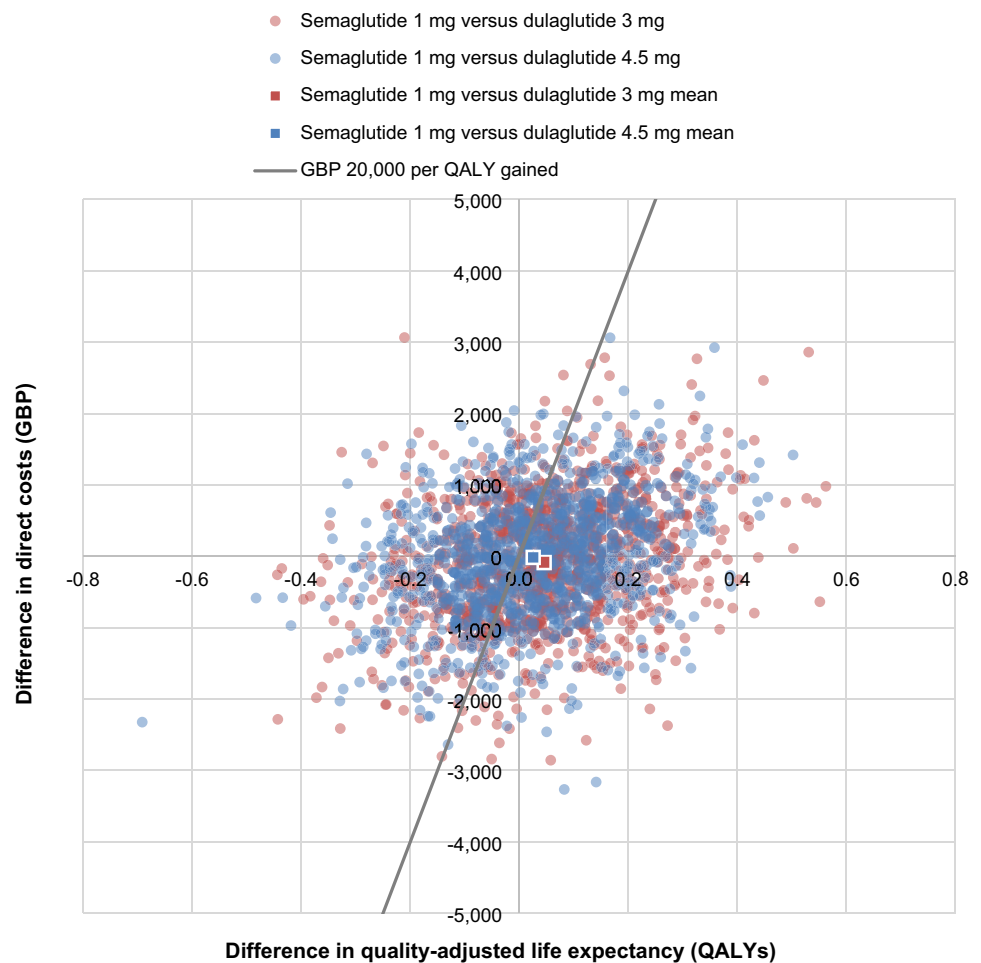
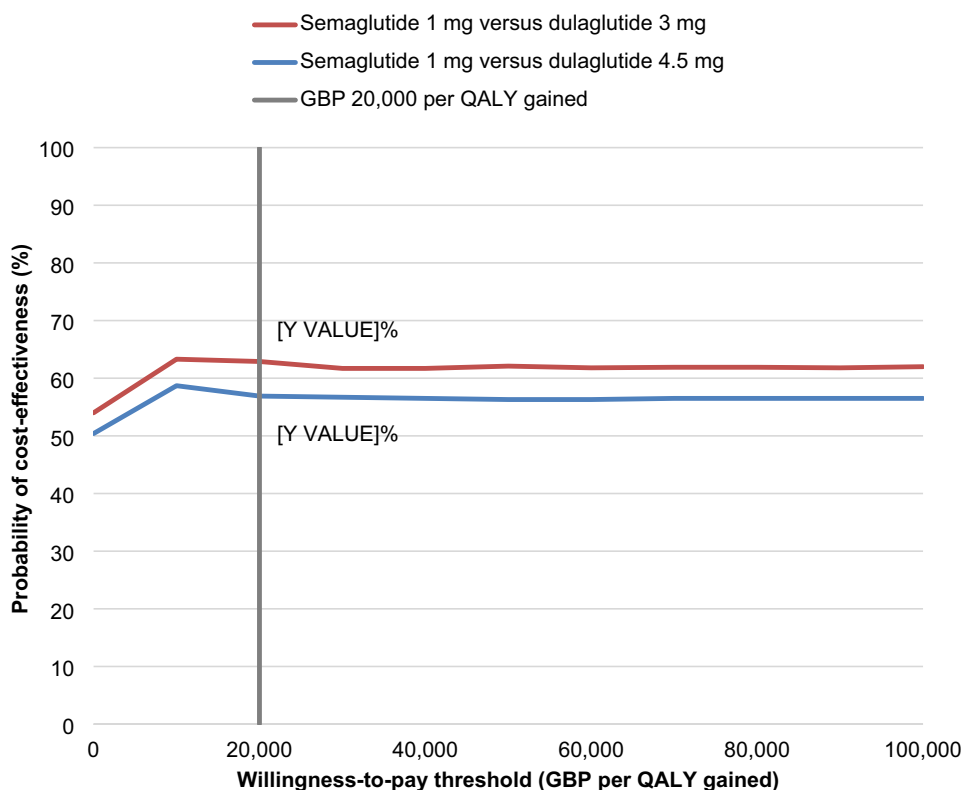GBP, 2020 pounds sterling; QALY, quality-adjusted life year.

Discussion

The present analysis has shown that, based on the results of a recent ITC, once-weekly semaglutide 1 mg is likely to represent a cost-effective treatment option vs. dulaglutide 3 mg and 4.5 mg for the treatment of people with type 2 diabetes in the UK. Greater reductions in HbA1c and BMI were shown to result in a reduced incidence of long-term diabetes-related complications, and thereby improved life expectancy and quality of life. These results should inform healthcare payers, physicians and patients in the UK when evaluating potential treatment options for type 2 diabetes.

Once-weekly semaglutide and dulaglutide have been shown to be efficacious in populations with inadequate glycaemic control when treated with metformin in the SUSTAIN 7 and AWARD-11 clinical trials, respectively, and in the ITC [13, 15, 17]. However, the populations evaluated in these clinical studies and in the present analysis did not align with the recommended population for GLP-1 receptor agonists in the current NICE guidelines, which indicate GLP-1 receptor agonists as part of triple therapy for people with type 2 diabetes with a BMI over 35 kg/m^2, for those whom insulin therapy would have significant occupational implications, or where weight loss would benefit other obesity-related comorbidities [11]. That acknowledged, the joint guidelines released by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend GLP-1 receptor agonists as a preferred second-line treatment option in patients with established cardiovascular disease or high cardiovascular risk, and as a potential second-line therapy in populations with a compelling need to minimise hypoglycaemia or weight gain or promote weight loss [12]. Previously published cost-effectiveness analyses have also evaluated once-weekly semaglutide vs. other second-line treatment options, including SGLT-2 inhibitor empagliflozin in the UK, insulin glargine U100 in the Netherlands, and dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin in Spain, as well as the lower 0.75 mg and 1.5 mg doses of dulaglutide in people with inadequate glycaemic control on metformin in the UK [14, 19, 30, 47].

Fig. 4 Cost-effectiveness acceptability curve from the probabilistic analyses

GBP, 2020 pounds sterling; QALY, quality-adjusted life year.

In line with results from the present study, once-weekly semaglutide was found to be cost-effective throughout all these comparisons, even with differences in country-specific parameters such as healthcare systems, costs, and mortality. Results from the present study can also add to the current evidence base of cost-effectiveness analyses of once-weekly semaglutide, as described in a systematic literature review published in 2021 [48]. Additionally, sub-group analyses based on baseline HbA1c and BMI have shown that once-weekly semaglutide is consistently more efficacious than other treatment options included in the SUSTAIN trial programme in all sub-groups, rather than just those with a high BMI at baseline [49–51]. Based on this evidence, and the results generated in the present study, once-weekly sema-glutide would likely represent an effective treatment while providing value for money if used as second-line therapy in the general population with type 2 diabetes in the UK.

The pathway scenario analyses performed in the present study represent a key strength. While the approach used in the base case analysis, with patients receiving semaglutide or dulaglutide for 3 years before intensification to basal insulin, allowed a fair and direct comparison of two interventions, this approach can be accused of oversimplifying clinical reality, where multiple agents are often required throughout patients' lifetimes to maintain glycaemic control. These additional pathway analyses thereby compliment the

base case analysis by offering further evidence of cost-effectiveness in scenarios that can be considered more clinically relevant. However, the assumptions used to inform these analyses must be considered when interpreting the results. HbA1c and BMI benefits from the ITC were assumed to persist when patients initiated SGLT-2 inhibitor therapy, and HbA1c and BMI were brought to 7.0% and reverted to baseline, respectively, on initiation of basal insulin. These assumptions were used *in lieu* of clinical data informing changes in HbA1c and BMI on initiation of SGLT-2 inhibitor or basal insulin therapy in populations previously receiving metformin and GLP-1 receptor agonist therapy, and this remains the key limitation in modelling more complex treatment algorithms for type 2 diabetes. While the impact of the addition of a GLP-1 receptor agonist to an SGLT-2 inhibitor has been tested in SUSTAIN 9, the impact of adding an SGLT-2 inhibitor in those already receiving a GLP-1 receptor agonist has not been tested [52]. Future studies evaluating changes in physiological parameters on initiation of different treatment classes, stratified by background medication, would therefore provide pertinent information in the diabetes modelling area and allow more clinically relevant treatment algorithms to be accurately assessed.

The present analysis did not include any outcomes from the cardiovascular outcomes trials (CVOTs) of once-weekly semaglutide (SUSTAIN 6) or dulaglutide (REWIND), and

this could be seen as a limitation [53, 54]. Indeed, recent guidelines published by the EASD have indicated GLP-1 receptor agonists and SGLT-2 inhibitors as treatments for patients with high cardiovascular risk [12]. However, the incorporation of results from CVOTs into current modelling approaches for type 2 diabetes is a challenge. Based on the currently available data, it is unclear whether changes in known risk factors (such as HbA1c and body weight or BMI) are the primary cause of outcomes observed in CVOTs, or whether there are as-yet-unknown mechanisms of action that wholly or partially influence these outcomes [55, 56]. The present study utilised a model primarily based on UKPDS data, with changes in known biomarkers associated with significant reductions in the incidence of microvascular complications and non-significant reductions in the incidence of macrovascular complications, and the application of further risk reductions in the outcomes evaluated in CVOTs, therefore, risked double counting of benefits. Differences in populations must also be considered, with SUSTAIN 6 and REWIND enrolling patients with a higher cardiovascular risk than those recruited for SUSTAIN 7 and AWARD-11, and outcomes may therefore not be generalisable across studies. Ideally, novel risk equations should be developed incorporating data from CVOTs, and this should be the focus of future research in the area. Calibration of existing models for type 2 diabetes could also offer a stop-gap solution that would allow these data to be utilised in health economic evaluations based on individual CVOTs [56].

A limitation of the analysis, inherent to all long-term modelling studies, was the projection of long-term outcomes from short-term data. However, this is an essential tenet of long-term diabetes modelling, and, given the progressive nature of the disease, arguably represents the best option for informing decision making in absence of long-term clinical trial data. Indeed, projecting outcomes over patients' lifetimes is recommended in the computer modelling guidance for diabetes interventions [21]. Moreover, every effort was made to minimise clinical doubt, by using a model of diabetes that has been extensively published and validated and by performing a series of wide-ranging sensitivity analyses that were conducted around numerous aspects of the modelling analysis, including the time horizon, treatment switching approaches, and applied reductions in HbA1c and BMI, and these did not change the conclusions of the analysis.

Conclusions

Once-weekly semaglutide 1 mg is likely to represent a cost-effective treatment option vs. dulaglutide 3 mg and 4.5 mg for the treatment of people with type 2 diabetes with inadequate glycaemic control on metformin from a healthcare payer perspective in the UK.

Declarations

Ethical approval 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.

References

1. International Diabetes Federation (IDF). Diabetes Atlas—10th Edition. 2021. https://diabetesatlas.org/data/en/country/209/gb.html. Accessed 10 Dec 2021.
2. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet **352**, 837–853 (1998)
3. Patel, A., MacMahon, S., Chalmers, J., Neal, B., Billot, L., Woodward, M., Marre, M., Cooper, M., Glasziou, P., Grobbee, D., Hamet, P., Harrap, S., Heller, S., Liu, L., Mancia, G., Mogensen, C.E., Pan, C., Poulter, N., Rodgers, A., Williams, B., Bompoint, S., de Galan, B.E., Joshi, R., Travert, F., ADVANCE Collaborative Group: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N. Engl. J. Med. **358**, 2560–2572 (2008)
4. Holman, R.R., Paul, S.K., Bethel, M.A., Matthews, D.R., Neil, H.A.: 10-year follow-up of intensive glucose control in type 2 diabetes. N. Engl. J. Med. **359**, 1577–1589 (2008)
5. Stettler, C., Allemann, S., Jüni, P., Cull, C.A., Holman, R.R., Egger, M., Krähenbühl, S., Diem, P.: Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials. Am. Heart J. **152**(1), 27–38 (2006)
6. Ismail-Beigi, F., Craven, T., Banerji, M.A., Basile, J., Calles, J., Cohen, R.M., Cuddihy, R., Cushman, W.C., Genuth, S., Grimm, R.H., Jr., Hamilton, B.P., Hoogwerf, B., Karl, D., Katz, L., Krikorian, A., O'Connor, P., Pop-Busui, R., Schubart, U., Simmons, D., Taylor, H., Thomas, A., Weiss, D., Hramiak, I., ACCORD trial group: Effect of intensive treatment of

hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet **376**, 419–430 (2010)

7. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ **317**(7160), 703–713 (1998)

8. Kearney, P.M., Blackwell, L., Collins, R., Keech, A., Simes, J., Peto, R., Armitage, J., Baigent, C., Cholesterol Treatment Trialists' (CTT) Collaborators: Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet **371**(9607), 117–125 (2008)

9. Gaede, P., Lund-Andersen, H., Parving, H.H., Pedersen, O.: Effect of a multifactorial intervention on mortality in type 2 diabetes. N. Engl. J. Med. **358**, 580–591 (2008)

10. Griffin, S.J., Borch-Johnsen, K., Davies, M.J., Khunti, K., Rutten, G.E., Sandbæk, A., Sharp, S.J., Simmons, R.K., van den Donk, M., Wareham, N.J., Lauritzen, T.: Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet **378**(9786), 156–167 (2011)

11. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management (NG28). 2015. https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-pdf-1837338615493. Accessed 12 Dec 2017.

12. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2019; dci190066.

13. Pratley, R.E., Aroda, V.R., Lingvay, I., Lüdemann, J., Andreassen, C., Navarria, A., Viljoen, A., SUSTAIN 7 investigators: Semaglutide vs. dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol. **6**(4), 275–286 (2018)

14. Viljoen, A., Hoxer, C.S., Johansen, P., Malkin, S., Hunt, B., Bain, S.C.: Evaluation of the long-term cost-effectiveness of once-weekly semaglutide vs. dulaglutide for the treatment of type 2 diabetes mellitus in the UK. Diabetes Obes. Metab. **21**(3), 611–621 (2019)

15. Frias, J.P., Bonora, E., Nevarez Ruiz, L., et al.: Efficacy and safety of Dulaglutide 3.0 mg and 4.5 mg vs. Dulaglutide 1.5 mg in metformin-treated patients with type 2 diabetes in a randomized controlled trial (AWARD-11). Diabetes Care **44**(3), 765–773 (2021)

16. Frías, J.P., Auerbach, P., Bajaj, H.S., et al.: Efficacy and safety of once-weekly semaglutide 2·0 mg vs. 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial. Lancet Diabetes Endocrinol. **9**(9), 563–574 (2021)

17. Pratley, R.E., Catarig, A.-M., Lingvay, I., et al.: An indirect treatment comparison of the efficacy of semaglutide 1.0 mg vs. dulaglutide 3.0 and 4.5 mg. Diabetes Obes. Metab. **23**(11), 2513–2520 (2021)

18. Bucher, H.C., Guyatt, G.H., Griffith, L.E., Walter, S.D.: The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J. Clin. Epidemiol. **50**(6), 683–691 (1997)

19. Capehorn, M., Hallén, N., Baker-Knight, J., Glah, D., Hunt, B.: Evaluating the cost-effectiveness of once-weekly semaglutide 1 mg vs. empagliflozin 25 mg for treatment of patients with type 2 diabetes in the UK setting. Diabetes Ther. **12**(2), 537–555 (2021)

20. Johansen, P., Chubb, B., Hunt, B., Malkin, S.J.P., Sandberg, A., Capehorn, M.: Evaluating the long-term cost-effectiveness of once-weekly semaglutide vs. once-daily liraglutide for the treatment of type 2 diabetes in the UK. Adv Ther. **37**(5), 2427–2441 (2020)

21. American Diabetes Association Consensus Panel: Guidelines for computer modeling of diabetes and its complications. Diabetes Care **27**, 2262–2265 (2004)

22. Palmer, A.J., Roze, S., Valentine, W.J., Minshall, M.E., Foos, V., Lurati, F.M., et al.: The CORE diabetes model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Curr. Med. Res. Opin. **20**(Suppl 1), S5-26 (2004)

23. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, Let al. Validation of the CORE Diabetes Model against epidemiological and clinical studies. Curr .Med. Res. Opin. 2004;20(Suppl 1):S27–40.

24. McEwan, P., Foos, V., Palmer, J.L., Lamotte, M., Lloyd, A., Grant, D.: Validation of the IMS CORE diabetes model. Value Health **17**, 714–724 (2014)

25. National Institute for Health and Care Excellence. The guidelines manual: Process and methods (PMG6). https://www.nice.org.uk/process/pmg6/resources/the-guidelines-manual-pdf-2007970804933. Accessed 10 Dec 2021.

26. World Health Organisation. *Global Health Observatory data repository: Life tables by country (United Kingdom)*. 2020. https://apps.who.int/gho/data/view.main.LT62260?lang=en. Accessed 10 Dec 2021.

27. Office for National Statistics. Adult Smoking Habits in Great Britain. 2019. https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/healthandsocialcare/drugusealcoholandsmoking/datasets/adultsmokinghabitsingreatbritain/2019/adultsmokinghabitsingreatbritain2019final.xls. Accessed 10 Dec 2021.

28. World Health Organisation. Global Alcohol Report. 2014. http://www.who.int/substance_abuse/publications/global_alcohol_report/profiles/gbr.pdf. Accessed 10 Dec 2021.

29. Hunt, B., Vega-Hernandez, G., Valentine, W.J., Kragh, N.: Evaluation of the long-term cost-effectiveness of liraglutide vs. lixisenatide for treatment of type 2 diabetes mellitus in the UK setting. Diabetes Obes. Metab. **19**(6), 842–849 (2017)

30. Hunt, B., Malkin, S.J.P., Moes, R.G.J., Huisman, E.L., Vandebrouck, T., Wolffenbuttel, B.: Once-weekly semaglutide for patients with type 2 diabetes: a cost-effectiveness analysis in the Netherlands. BMJ Open Diabetes Res. Care. **7**, e000705 (2019)

31. Heap G. Decision Resources Group Report: Current Treatment Type 2 Diabetes Detailed, Expanded Analysis (EU5). https://decisionresourcesgroup.com/report/499707-biopharma-type-2-diabetes-current-treatment-detailed/. Accessed 12 Mar 2018.

32. UK Hypoglycaemia Study Group: Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia **50**(6), 1140–1147 (2007)

33. Monthly Index of Medical Specialities. https://www.mims.co.uk/. Accessed 10 Dec 2021.

34. Rtveladze, K., Hoxer, C.S.: Cost of type 2 diabetes management and associated complications in the United Kingdom. Value Health. **20**(9), A477 (2017)

35. NHS England. National Tariff Payment System 2020/21. 2021. Available at: https://www.england.nhs.uk/publication/national-tariff-payment-system-documents-annexes-and-supporting-documents/. Accessed 10 Dec 2021.

36. Alva, M.L., Gray, A., Mihaylova, B., Leal, J., Holman, R.R.: The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diabet. Med. **32**(4), 459–466 (2015)

37. Danese, M., Gleeson, M., Kutikova, L., Griffiths, R., Azough, A., Khunti, K., et al.: Costs of cardiovascular (CV) events in the United Kingdom (UK) using real-world data. Value Health. **18**, A335–A766 (2015)

38. Kent, S., Schlackow, I., Lozano-Kuhne, J., Reith, C., Emberson, J., Haynes, R., Gray, A., Cass, A., Baigent, C., Landray, M.J.,

Herrington, W., Mihaylova, B., SHARP Collaborative Group: What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? BMC Nephrol. **16**, 65 (2015)

39. Chubb, B., Tikkanen, C.: The cost of non-severe hypoglycaemia in Europe. Value Health. **18**(7), A611 (2015)

40. Hammer, M., Lammert, M., Mejias, S.M., Kern, W., Frier, B.M.: Costs of managing severe hypoglycaemia in three European countries. J. Med. Econ. **12**(4), 281–290 (2009)

41. Ghatnekar, O., Willis, M., Persson, U.: Cost-effectiveness of treating deep diabetic foot ulcers with Promogran in four European countries. J. Wound Care. **11**(2), 70–74 (2002)

42. Curtis L, Burns A. *Unit Costs of Health and Social Care 2020*. Personal Social Services Research Unit, University of Kent, Canterbury. 2020. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/. Accessed 10 Dec 2021.

43. Beaudet, A., Clegg, J., Thuresson, P.O., Lloyd, A., McEwan, P.: Review of utility values for economic modeling in type 2 diabetes. Value Health. **17**(4), 462–470 (2014)

44. Evans, M., Khunti, K., Mamdani, M., Galbo-Jorgensen, C.B., Gundgaard, J., Bogelund, M., Harris, S.: Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. Health Qual. Life Outcomes. **11**(1), 90 (2013)

45. Lee, A.J., Morgan, C.L., Morrissey, M., Wittrup-Jensen, K.U., Kennedy-Martin, T., Currie, C.J.: Evaluation of the association between the EQ-5D (health-related utility) and body mass index (obesity) in hospital-treated people with Type 1 diabetes, Type 2 diabetes and with no diagnosed diabetes. Diabet. Med. **22**(11), 1482–1486 (2005)

46. Willis, M., Asseburg, C., Nilsson, A., Johnsson, K., Kartman, B.: Multivariate prediction equations for HbA1c lowering, weight change, and hypoglycemic events associated with insulin rescue medication in type 2 diabetes mellitus: Informing economic modeling. Value Health **20**, 357–371 (2017)

47. Martín, V., Vidal, J., Malkin, S.J.P., Hallén, N., Hunt, B.: Evaluation of the long-term cost-effectiveness of once-weekly semaglutide vs. dulaglutide and sitagliptin in the spanish setting. Adv. Ther. **37**(10), 4427–4445 (2020)

48. Ruan, Z., Yang, L., Shi, H., Yue, X., Wang, Y., Liang, M., Hu, H.: The cost-effectiveness of once-weekly semaglutide compared with other GLP-1 receptor agonists in type 2 Diabetes: a systematic literature review. Expert. Rev. Pharmacoecon. Outcomes Res. **21**(2), 221–233 (2021)

49. Viljoen, A., Blüher, M., Chow, F., le Roux, C., Rosenstock, J., Lausvig, N.L., Yildirim, E., Lingvay, I.: Semaglutide reduces body weight vs. dulaglutide across baseline BMI Subgroups in SUSTAIN 7. Diabetes (2018). https://doi.org/10.2337/db18-1083-P

50. Bain, S., Araki, E., Desouza, C., Garg, S., Rose, L., Tsoukas, G., Bergan, E.Q., Derving Karsbøl, J., Devries, J.H.: Semaglutide reduces HbA1c across baseline HbA1c subgroups across SUSTAIN 1–5 clinical trials. Diabetes (2017). https://doi.org/10.1002/central/CN-01919984/

51. Leiter, L.A., Charpentier, G., Chaykin, L., Garvey, W.T., Warren, M.L., Karsbøl, J.D., Thielke, D., Masmiquel, L.: Semaglutide reduces body weight across baseline BMI subgroups across SUSTAIN 1–5. Diabetes (2017). https://doi.org/10.1016/j.jcjd.2017.08.020

52. Zinman, B., Bhosekar, V., Busch, R., et al.: Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. **7**(5), 356–367 (2019)

53. Marso, S.P., Bain, S.C., Consoli, A., SUSTAIN-6 Investigators, et al.: Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N. Engl. J Med. **375**(19), 1834–1844 (2016)

54. Gerstein, H.C., Colhoun, H.M., Dagenais, G.R., REWIND Investigators, et al.: Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet **394**(10193), 121–130 (2019)

55. Si, L., Willis, M.S., Asseburg, C., et al.: Evaluating the ability of economic models of diabetes to simulate new cardiovascular outcomes trials: a report on the ninth mount hood diabetes challenge. Value Health. **23**(9), 1163–1170 (2020)

56. Willis, M., Asseburg, C., Nilsson, A., Neslusan, C.: Challenges and opportunities associated with incorporating new evidence of drug-mediated cardioprotection in the economic modeling of type 2 diabetes: a literature review. Diabetes Ther. **10**, 1753–1769 (2019)