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ORIGINAL ARTICLE

Evaluation of the long-term cost-effectiveness of once-weekly semaglutide versus dulaglutide for treatment of type 2 diabetes mellitus in the UK

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Aims: Glucagon-like peptide-1 (GLP-1) receptor agonists are appealing as glucose-lowering therapy for individuals with type 2 diabetes mellitus (T2DM) as they also reduce body weight and are associated with low rates of hypoglycaemia. This analysis assessed the long-term cost-effectiveness of semaglutide 0.5 and 1 mg vs dulaglutide 1.5 mg (two once-weekly GLP-1 receptor agonists) from a UK healthcare payer perspective, based on the head-to-head SUSTAIN 7 trial, to inform healthcare decision making.

Materials and Methods: Long-term outcomes were projected using the IQVIA CORE Diabetes Model (version 9.0). Baseline cohort characteristics, changes in physiological parameters and adverse event rates were derived from the 40-week SUSTAIN 7 trial. Costs to a healthcare payer were assessed, and these captured pharmacy costs and costs of complications. Utilities were taken from published sources.

Results: Once-weekly semaglutide 0.5 and 1 mg were associated with improvements in quality-adjusted life expectancy of 0.04 and 0.10 quality-adjusted life years, respectively, compared with dulaglutide 1.5 mg. Clinical benefits were achieved at reduced costs, with lifetime cost savings of GBP 35 with once-weekly semaglutide 0.5 mg and GBP 106 with the once-weekly semaglutide 1 mg, resulting from fewer diabetes-related complications due to better glycaemic control. Therefore, both doses of once-weekly semaglutide were considered dominant vs dulaglutide 1.5 mg (improving outcomes and reducing costs).

Conclusions: Compared with treatment with dulaglutide, once-weekly semaglutide represents a cost-effective option for treating individuals in the UK with T2DM who are not achieving glycaemic control with metformin, projected to both improve clinical outcomes and reduce costs.

KEYWORDS

antidiabetic drug, cost-effectiveness, GLP-1 analogue, incretin therapy

1 | INTRODUCTION

Improving glycaemic control remains a key focus of care for individuals with type 2 diabetes mellitus (T2DM), and landmark studies show that good glycaemic control can reduce the incidence of diabetes-related complications.^{1–5} Guidelines from the National Institute for Health and Care Excellence (NICE) recommend a glycated haemoglobin

(HbA1c) target of 6.5% (48 mmol/mol) for individuals with T2DM who are managed with lifestyle modifications and a single drug, and a target of 7% (53 mmol/mol) for individuals with T2DM who are not adequately controlled by a single glucose-lowering drug.⁶ In addition, there is substantial evidence that multifactorial care, targeting not only glycaemic control but also blood pressure, serum lipids, body weight and hypoglycaemia risk, is associated with a reduced risk of

complications.^{7–10} Consequently, NICE guidelines recommend a weight loss target of 5% to 10% of body weight and a blood pressure target of below 140/80 mmHg, in conjunction with glycaemic control targets.⁶

A significant number of individuals with T2DM in the UK are not reaching recommended targets. Data from the National Diabetes Audit show that during 2016–2017, one third of the individuals with T2DM in England and Wales had an HbA1c value above 7.5% (58 mmol/mol), and one quarter had blood pressure above 140/80 mmHg.¹¹ In Scotland, over 40% of the individuals with T2DM had an HbA1c value above 7.5% (58 mmol/mol) and one quarter had systolic blood pressure greater than 140 mmHg in 2016.¹² Therefore, there is a significant need to improve care for individuals with T2DM in the UK. Bringing a greater proportion of individuals with T2DM to glycaemic control and multifactorial treatment targets can improve long-term outcomes for patients and reduce the costs of treating diabetes-related complications for healthcare providers and UK society as a whole. This is key in optimizing the use of the limited resources within the National Health Service (NHS).

In addition to its impact on glycaemic control, glucagon-like peptide 1 (GLP-1) receptor agonist therapy is associated with weight loss, as opposed to other treatment options, such as sulfonylurea and thiazolidinediones which are associated with weight gain, or dipeptidyl peptidase-4 (DPP-4) inhibitors which are weight neutral.¹³ Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are the only other second-line treatment option associated with weight loss, but these are less efficacious than GLP-1 receptor agonists in terms of glucose-lowering.^{14,15} Once-weekly semaglutide, a novel GLP-1 receptor analogue, has been approved for use in Europe.¹⁶ Other GLP-1 receptor agonists that are approved for once-weekly administration include dulaglutide and exenatide extended-release.^{17,18} The SUSTAIN clinical trial programme found that once-weekly semaglutide was more efficacious in terms of both HbA1c and weight reduction than exenatide extended-release and dulaglutide, with a similar side-effect profile, in head-to-head studies.^{19,20} Additionally, a network meta-analysis (NMA) has shown that once-weekly semaglutide is more efficacious than other GLP-1 receptor agonists.²¹

The SUSTAIN 7 clinical trial assessed the efficacy and safety of once-weekly semaglutide vs dulaglutide.²⁰ The SUSTAIN 7 trial was a 40-week, randomized, open-label trial comparing once-weekly semaglutide 0.5 mg with dulaglutide 0.75 mg, and comparing once-weekly semaglutide 1 mg with dulaglutide 1.5 mg. The study included individuals with T2DM who were not achieving glycaemic control, defined as HbA1c 7.0% to 10.5% (53–91 mmol/mol) with metformin. Pre-specified statistical analyses indicated that once-weekly semaglutide 1 mg was associated with significantly greater reductions in HbA1c (–1.8% vs –1.4% [–19.4 vs –14.9 mmol/mol]; $P < 0.001$) and body weight (–6.5 kg vs –3.0 kg; $P < 0.001$) vs dulaglutide 1.5 mg.²⁰ *Post-hoc* analysis has shown that both once-weekly semaglutide and dulaglutide were associated with greater weight reduction in patients with a higher body mass index (BMI) at baseline, and once-weekly semaglutide was associated with greater reductions than dulaglutide across all baseline BMI sub-groups.²² As dulaglutide 0.75 mg is not considered a maintenance dose in dual therapy by the European Medicines Agency (EMA), it is not included in the present analysis.¹⁷

The aim of the present study was to assess the long-term cost-effectiveness of both doses of once-weekly semaglutide vs dulaglutide 1.5 mg for treatment of individuals with T2DM who are not achieving glycaemic control with metformin, based on SUSTAIN 7 clinical trial data from the perspective of a UK healthcare payer.

2 | MATERIALS AND METHODS

2.1 | IQVIA CORE Diabetes Model

A cost-effectiveness analysis was performed using the IQVIA CORE Diabetes Model (CDM), the architecture and capabilities of which have been previously published.²³ Projected long-term outcomes have been validated against real-life data in 2004 and more recently in 2014.^{24,25} Model outputs include complication rates and time to onset of complications, life expectancy, quality-adjusted life expectancy expressed in quality-adjusted life years (QALYs), direct costs and incremental cost-effectiveness ratios (ICERs), as well as cost-effectiveness scatterplots and acceptability curves. Version 9.0 is the most recent release of the CDM and was used for all analyses, with the UKPDS 68 risk equations applied for prediction of risk of cardiovascular complications.²⁶ Base case and sensitivity analyses were performed using a first-order Monte Carlo approach, with probabilistic sensitivity analysis (PSA) performed separately using a second-order Monte Carlo approach. Clinical and cost outcomes were discounted at 3.5% per annum, as per NICE guidelines.²⁷ Outcomes were projected over patient lifetimes, in line with guidance on the assessment of cost-effectiveness of interventions for diabetes.^{27,28} The model takes into account mortality as a result of diabetes-related complications and background mortality based on UK-specific life tables.²⁹

2.2 | Baseline cohort characteristics and initial treatment effects

Baseline cohort characteristics for the modelling analysis were taken from the SUSTAIN 7 study.²⁰ The mean (standard deviation [SD]) age of the cohort was 56 (10.6) years, with a mean duration of T2DM of 7.4 (5.7) years, mean HbA1c of 8.2 (0.9)% (66.1 [10.1] mmol/mol), and mean BMI of 33.5 (6.8) kg/m². Alcohol and tobacco consumption were assumed to be the same as that of the general UK population, as these data were not collected in the SUSTAIN 7 study.^{30,31} Changes in physiological parameters with once-weekly semaglutide and dulaglutide were based on mean changes from baseline at 40 weeks in the SUSTAIN 7 study, with hypoglycaemic events assessed across the duration of the trial (Table 1).²⁰ Both statistically and non-statistically significant differences between the treatment arms were included. Pre-specified statistical analyses assessed the statistical significance of differences in treatment effects between once-weekly semaglutide 1 mg and dulaglutide 1.5 mg, but *post-hoc* analyses were required to determine the statistical significance of differences in treatment effects between once-weekly semaglutide 0.5 mg and dulaglutide 1.5 mg. Data were taken from pre-specified endpoints wherever possible, but in order to fulfil all data requirements for an analysis using the CDM, a number of analyses of *post-hoc* endpoints were required,

TABLE 1 Treatment effects and adverse event rates

Parameter	Mean (standard error)		
	Once-weekly semaglutide 0.5 mg	Once-weekly semaglutide 1 mg	Dulaglutide 1.5 mg
<i>Physiological parameters (applied in the first year of the analysis)</i>			
HbA1c (%)	-1.5 (0.06)	-1.8 (0.06)*	-1.4 (0.06)
HbA1c (mmol/mol)	-16.5 (0.6)	-19.4 (0.6)*	-14.9 (0.6)
Systolic blood pressure (mmHg)	-2.4 (0.8)	-4.9 (0.8)	-2.9 (0.8)
Diastolic blood pressure (mmHg)	-0.6 (0.5)	-2.0 (0.5)*	0.0 (0.5)
Total cholesterol (mg/dL)	-7.0 (1.7)	-5.2 (1.8)	-2.6 (1.8)
HDL cholesterol (mg/dL)	-0.5 (0.3)*	0.7 (0.4)	0.8 (0.4)
LDL cholesterol (mg/dL)	-3.1 (1.5)	-0.2 (1.6)	0.7 (1.5)
Triglycerides (mg/dL)	-14.3 (3.1)	-21.8 (2.9)	-16.5 (3.0)
BMI (kg/m ²)	-1.6 (0.1)*	-2.3 (0.1)*	-1.1 (0.1)
Estimated glomerular filtration rate (mL/min/1.73 m ²)	-2.5 (0.6)	-2.7 (0.6)	-3.8 (0.5)
<i>Adverse event rates (applied in the first 3 years of the analysis)</i>			
Non-severe hypoglycaemia event rate (events per 100 patient years)	1.3	2.6	1.3
Severe hypoglycaemia event rate (events per 100 patient years)	0.00	0.4	0.8
Proportion of non-severe hypoglycaemic events that are nocturnal	0.00	0.00	0.00
Proportion of severe hypoglycaemic events that are nocturnal	0.00	0.00	0.00

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

*Statistically significant difference at 95% confidence level vs dulaglutide 1.5 mg. Lipid values are presented in mg/dL, as these are required by the IQVIA CORE Diabetes Model. Total cholesterol, HDL cholesterol and LDL cholesterol values can be converted from mg/dL to mmol/L by multiplying by 38.67. Triglyceride values can be converted from mg/dL to mmol/L by multiplying by 88.5.

including serum lipids and hypoglycaemic events, to ensure that definitions met those used in the IQVIA CORE Diabetes Model.

2.3 | Treatment switching and long-term parameter progression

A simple treatment algorithm which assumed that patients received once-weekly semaglutide or dulaglutide for 3 years was employed, as per previous long-term cost-effectiveness analyses of GLP-1 receptor agonists submitted to NICE and published in peer-reviewed journals.^{32–35} This is also supported by data from general practice in the European Union big five markets, which reported a mean duration of treatment with GLP-1 receptor agonists of 29.35 months, rounded to 3 years, as treatment switching can occur only at the end of an annual cycle in the CDM.³⁶ After 3 years, treatment with once-weekly semaglutide or dulaglutide was discontinued and patients were assumed to intensify to basal insulin therapy with the most commonly used basal insulin analogue available in the UK, insulin glargine, with the cost of the least expensive, biosimilar version of insulin glargine applied (Abasaglar). Patients continued this treatment for the remainder of their lifetimes. It should be noted that further treatment switching, such as switching to basal-bolus insulin, would not have affected the differences in clinical outcomes and the costs between treatment arms, provided that it occurred at the same time point. Hypoglycaemic events following intensification were modelled based on the UK Hypoglycaemia Study Group and were equal in all treatment arms.³⁷

After applying the treatment effects in the first year of the analysis, benefits in terms of HbA1c and BMI were assumed to persist for the 3 years during which patients received GLP-1 receptor agonist

treatment, with differences abolished upon treatment intensification. Upon intensification, HbA1c was brought to 7% (53 mmol/mol) in all treatment arms, based on guidelines released by NICE (although a patient-centred approach may result in modification of this goal).⁶ HbA1c remained equal in all treatment arms for the remainder of the analysis. BMI returned to baseline following intensification. Therefore, no differences in HbA1c and BMI were seen following treatment intensification and, while clinical practice may vary among patients in the UK, this resulted in a balanced cost-effectiveness analysis, with differences maintained only while there were differences in costs. Alternative treatment-switching and parameter-progression assumptions were explored in sensitivity analyses.

2.4 | Costs and utilities

Costs were accounted from the perspective of a UK healthcare payer, with all costs expressed in 2016 pounds sterling (GBP). Unit costs of T2DM medications were taken from the Monthly Index of Medical Specialities (MIMS) database and were used to calculate annual treatment costs, with resource use based on the SUSTAIN 7 trial.^{20,38} Annual costs of treatment with once-weekly semaglutide and dulaglutide were equivalent. Following intensification after 3 years, patients were assumed to receive 40 IU of basal insulin, based on the defined daily dose.

Costs associated with treatment of diabetes-related complications were sourced from a systematic literature review, conducted in 2017, which identified UK-specific costs from published sources.^{39–50} Costs were inflated to 2016 values where necessary, using the Health and Community Health Services Index (Appendix S1).⁵¹

Utilities were taken from a 2014 review by Beaudet et al, with the cost of hypoglycaemia disutilities coming from Evans et al 2013, published after the literature searches by Beaudet et al had been completed.^{52,53} Beaudet et al reviewed the methods of identified publications to ensure that they met the criteria of the NICE reference case. Values used in the present analysis are shown in Appendix S1. Quality-adjusted life expectancy was assessed using the CORE Default Method, which involves taking the lowest state utility associated with existing complications and adding event disutilities for any events that occur during that year to create annual utility scores for each simulated patient.

2.5 | Identifying key drivers of clinical outcomes

To identify the key drivers of outcomes with once-weekly semaglutide 0.5 and 1 mg compared with dulaglutide 1.5 mg, a series of five simulations were run for each comparison. In each analysis, only the difference in one of the following was applied in the once-weekly semaglutide arm: HbA1c, blood pressure (systolic and diastolic), serum lipids, BMI and hypoglycaemic event rates. All other parameters were equal to the dulaglutide 1.5 mg arm, allowing assessment of the relative impact of each aspect on long-term outcomes.

2.6 | Sensitivity analyses

A series of sensitivity analyses were performed to assess the robustness of the base case findings. An analysis was performed with only the statistically significant differences in treatment effects applied in the once-weekly semaglutide arms: high-density lipoprotein (HDL) cholesterol and BMI in the once-weekly semaglutide 0.5 mg comparison, HbA1c, diastolic blood pressure and BMI in the once-weekly semaglutide 1 mg comparison (Table 1). Simulations were run with time horizons of 10, 25 and 35 years. It should be noted that a time horizon of 50 years was required for all modelled patients to have died; therefore, shorter time horizons do not capture all complications and costs. Simulations were performed with discount rates of 0% and 6%. Treatment effects were applied in an alternative cohort, with baseline data taken from the NICE THIN cohort (Appendix S1), chosen, as in the development of the NICE T2DM treatment guidelines (NG28), to reflect a typical cohort of individuals with T2DM in the UK.⁵⁴

Alternative parameter progressions and treatment effects were assessed in a series of analyses. Base case analyses assumed that the BMI benefit associated with once-weekly semaglutide was abolished upon treatment switching so an alternative was explored, with BMI differences maintained for the duration of the simulation. In a separate analysis, the UKPDS HbA1c progression equation was applied in all arms from initiation of the simulation, resulting in an increase in HbA1c over time, with the differences between arms gradually reduced. Simulations were also performed, applying the upper and lower limits of the 95% confidence intervals of the estimated treatment differences in HbA1c and BMI.

Simulations were performed with the year of treatment switching brought forward to the end of year 2 and pushed back to the end of year 5. An additional scenario was prepared, applying the UKPDS

HbA1c progression equation and with treatment switching occurring when HbA1c exceeded 7.5% (58 mmol/mol), the threshold for treatment intensification according to the NICE guidelines.⁶ The impact of alternative insulin costs following intensification was explored by applying the cost of neutral protamine Hagedorn (NPH) insulin. The effect of over- or underestimating the direct cost of treating diabetes-related complications was investigated in two scenarios, with costs increased and decreased by 10%.

An update to the CDM, incorporating data from the UKPDS 82, has been released and an analysis using these risk equations to predict cardiovascular events was run. Whilst a validation study of the revised model has been published, the proprietors of the model suggest that the update is used in a sensitivity analysis, with the previous version being used in the base case.²⁵ Alternative utilities relating to BMI and hypoglycaemic events were applied to two scenarios, applying a BMI disutility from Lee et al and disutilities relating to hypoglycaemic events from Currie et al (Appendix S1).⁵⁵

PSA was performed using the predefined function in the CDM. Cohort characteristics, treatment effects, and complication costs and utilities were sampled from distributions and the simulation was carried out using a second-order Monte Carlo approach. Sampling around model inputs allows the uncertainty around these inputs to be captured and the confidence in the model outputs to be assessed.

3 | RESULTS

3.1 | Base case analysis

Projections of long-term clinical outcomes in individuals with T2DM in the UK who were not achieving glycaemic control with metformin indicated that once-weekly semaglutide 0.5 and 1 mg were associated with improvements in discounted life expectancy of 0.04 and 0.10 years, respectively, and discounted quality-adjusted life expectancy of 0.04 and 0.10 QALYs, respectively, compared with dulaglutide 1.5 mg, with all differences found to be statistically significant (Table 2). Improved clinical outcomes were the result of reduced cumulative incidence and delayed time to onset of diabetes-related complications over patient lifetimes, with benefits observed across all micro- and macrovascular complications included in the analysis (Appendix S1).

Once-weekly semaglutide 0.5 and 1 mg were associated with overall cost savings of GBP 35 (not statistically significant) and GBP 106 (statistically significant), respectively, vs dulaglutide 1.5 mg over a patient's lifetime (Table 2). Differences between the treatment arms are relatively small, as differences in HbA1c and BMI were assumed to be maintained for only 3 years in the modelling analysis. Both doses of once-weekly semaglutide were associated with small increases in treatment costs because of increased survival, despite equivalent treatment costs with once-weekly semaglutide and dulaglutide. However, this was entirely offset by the reduced costs associated with diabetes-related complications, most notably, ophthalmic and cardiovascular complications, with once-weekly semaglutide 0.5 mg (both resulting in cost savings of GBP 17) and avoided cardiovascular

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

Health outcomes	Once-weekly semaglutide 0.5 mg	Dulaglutide 1.5 mg	Difference
Discounted life expectancy (years)	13.64 (0.18)	13.60 (0.18)	+0.04 (+0.02 to +0.05)
Discounted quality-adjusted life expectancy (QALYs)	9.00 (0.12)	8.96 (0.12)	+0.04 (+0.03 to +0.05)
Discounted direct costs (GBP)	21 659 (562)	21 693 (538)	-35 (-81 to +12)
ICER (GBP per QALY gained)	Once-weekly semaglutide dominant		
Health outcomes	Once-weekly semaglutide 1 mg	Dulaglutide 1.5 mg	Difference
Discounted life expectancy (years)	13.70 (0.19)	13.60 (0.18)	+0.10 (+0.08 to +0.11)
Discounted quality-adjusted life expectancy (QALYs)	9.06 (0.13)	8.96 (0.12)	+0.10 (+0.09 to +0.11)
Discounted direct costs (GBP)	21 588 (557)	21 693 (538)	-106 (-151 to -60)
ICER (GBP per QALY gained)	Once-weekly semaglutide dominant		

Abbreviations: GBP, 2016 pounds sterling; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. Values are means (standard deviation) for outcomes in each arm and mean (95% confidence interval) for differences. Life expectancy and quality-adjusted life expectancy outcomes are rounded to two decimal places.

complications with once-weekly 1 mg (resulting in cost savings of GBP 96).

Projection of long-term outcomes indicated that both life expectancy and quality-adjusted life expectancy were improved with once-weekly semaglutide 0.5 and 1 mg treatment compared with dulaglutide 1.5 mg, at a reduced cost from a healthcare payer perspective. Therefore, once-weekly semaglutide 0.5 and 1 mg were considered dominant vs dulaglutide 1.5 mg for treatment of individuals with T2DM in the UK who were not achieving glycaemic control with metformin.

3.2 | Key drivers of clinical outcomes

Testing for the key drivers of quality-adjusted life expectancy benefits showed differences between the two once-weekly semaglutide doses (Table 3). With once-weekly semaglutide 0.5 mg, the greater HbA1c reduction vs dulaglutide (-1.5% vs -1.4% [16.5 vs 14.9 mmol/mol]) was the biggest contributor to improved clinical outcomes. In the comparison of once-weekly semaglutide 1 mg vs dulaglutide, the greater BMI reduction (-2.33 kg/m² vs -1.08 kg/m²) was the biggest contributor to improved clinical outcomes, followed by the greater reductions in HbA1c (-1.8% vs -1.4% [19.4 vs 14.9 mmol/mol]) and blood pressure (systolic blood pressure, -4.9 mm Hg vs -2.9 mm Hg and diastolic blood pressure, -2.1 mm Hg vs 0.0 mmHg).

TABLE 3 Key drivers of clinical differences between once-weekly semaglutide and dulaglutide

Analysis	Difference in quality-adjusted life expectancy (QALYs)	
	Once-weekly semaglutide 0.5 mg versus dulaglutide 1.5 mg	Once-weekly semaglutide 1 mg versus dulaglutide 1.5 mg
Base case analysis	+0.04	+0.10
HbA1c difference only	+0.02	+0.02
Blood pressure difference only	0.00	+0.02
Lipid difference only	0.00	0.00
BMI difference only	+0.01	+0.03
Hypoglycaemia difference only	0.00	0.00

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; QALY, quality-adjusted life year. Quality-adjusted life expectancy outcomes are rounded to two decimal places.

3.3 | Sensitivity analyses

Sensitivity analyses showed that the base case results were robust to changes in the input parameters and assumptions used, with both doses of once-weekly semaglutide remaining dominant in all except one scenario each (Table 4). Including only the statistically significant differences between semaglutide 0.5 mg and dulaglutide 1.5 mg led to decreased clinical benefits and increased incremental costs, yielding an ICER of GBP 18446 per QALY gained. The only differences between treatment arms in this scenario were in BMI and HDL cholesterol; as such, the greater reduction in HbA1c with once-weekly semaglutide 0.5 mg, the key driver of improved clinical outcomes, was no longer applied.

When the UKPDS HbA1c progression equation was applied with treatment switching when HbA1c exceeded 7.5% (58 mmol/mol), once-weekly semaglutide 1 mg was associated with greater clinical benefits but increased costs vs dulaglutide 1.5 mg, resulting in an ICER of GBP 1135 per QALY gained. This was the result of asymmetric timing of treatment switching in the two treatment arms. Patients received once-weekly semaglutide 1 mg for 4 years, while patients received dulaglutide 1.5 mg for only 3 years and received the less costly insulin abasaglar during the fourth year of analysis.

While the magnitude of clinical benefits and cost savings varied, once-weekly semaglutide 0.5 and 1 mg were considered dominant vs dulaglutide 1.5 mg in all other analyses.

PSA showed mean results similar to those of the base case, but increased measures of variance around the mean outcomes, with both doses of once-weekly semaglutide remaining dominant. Based on this analysis, assuming a willingness-to-pay threshold of GBP 20 000 per QALY gained, the probabilities of once-weekly semaglutide 0.5 and 1 mg being cost-effective vs dulaglutide 1.5 mg were 57.2% and 77.8%, respectively. A cost-effectiveness acceptability curve is shown in Figure 1, and the cost-effectiveness scatterplot is shown in Appendix S1.

TABLE 4 Sensitivity analysis results

Analysis	Discounted quality-adjusted life expectancy (QALYs)			Discounted direct costs (GBP)			ICER (GBP per QALY gained)
	Once-weekly semaglutide 1 mg	Dulaglutide 1.5 mg	Difference	Once-weekly semaglutide 1 mg	Dulaglutide 1.5 mg	Difference	
Base case	9.06	8.96	+0.10	21 588	21 693	−106	Once-weekly semaglutide dominant
Statistically significant differences only	9.03	8.96	+0.07	21 642	21 693	−52	Once-weekly semaglutide dominant
35-year time horizon	9.01	8.92	+0.08	21 266	21 467	−201	Once-weekly semaglutide dominant
20-year time horizon	7.81	7.74	+0.07	16 957	17 136	−179	Once-weekly semaglutide dominant
10-year time horizon	5.17	5.13	+0.04	10 167	10 287	−120	Once-weekly semaglutide dominant
0% discount rates	13.69	13.53	+0.16	35 436	35 564	−128	Once-weekly semaglutide dominant
6% discount rates	7.13	7.05	+0.08	16 238	16 329	−90	Once-weekly semaglutide dominant
NICE (THIN) baseline cohort data	8.86	8.78	+0.08	19 261	19 471	−210	Once-weekly semaglutide dominant
BMI difference maintained for patient lifetimes	9.15	8.96	+0.19	21 586	21 693	−107	Once-weekly semaglutide dominant
UKPDS HbA1c creep for duration of the analysis (no change upon treatment intensification)	8.57	8.47	+0.11	24 517	24 722	−205	Once-weekly semaglutide dominant
Upper 95% CI of HbA1c estimated treatment difference	9.06	8.96	+0.10	21 498	21 693	−196	Once-weekly semaglutide dominant
Lower 95% CI of HbA1c estimated treatment difference	9.03	8.96	+0.07	21 614	21 693	−79	Once-weekly semaglutide dominant
Upper 95% CI of BMI estimated treatment difference	9.06	8.96	+0.10	21 537	21 693	−156	Once-weekly semaglutide dominant
Lower 95% CI of BMI estimated treatment difference	9.05	8.96	+0.09	21 604	21 693	−89	Once-weekly semaglutide dominant
Treatment switching at 2 years	8.99	8.93	+0.06	21 220	21 360	−140	Once-weekly semaglutide dominant
Treatment switching at 5 years	9.14	9.02	+0.12	22 112	22 377	−265	Once-weekly semaglutide dominant
Treatment switching at 7.5% (58 mmol/mol) HbA1c threshold (using UKPDS progression)	8.60	8.47	+0.13	24 874	24 722	+152	1135
NPH basal insulin cost upon treatment intensification	9.06	8.96	+0.10	20 205	20 322	−117	Once-weekly semaglutide dominant
Cost of complications +10%	9.06	8.96	+0.10	22 761	22 883	−122	Once-weekly semaglutide dominant
Cost of complications −10%	9.06	8.96	+0.10	20 408	20 497	−89	Once-weekly semaglutide dominant

TABLE 4 (Continued)

Analysis	Discounted quality-adjusted life expectancy (QALYs)			Discounted direct costs (GBP)			ICER (GBP per QALY gained)
	Once-weekly semaglutide 1 mg	Dulaglutide 1.5 mg	Difference	Once-weekly semaglutide 1 mg	Dulaglutide 1.5 mg	Difference	
UKPDS 82 risk equations applied	9.35	9.31	+0.04	22 160	22 338	-178	Once-weekly semaglutide dominant
Lee et al BMI disutility applied	8.61	8.50	+0.11	21 588	21 693	-106	Once-weekly semaglutide dominant
Currie et al hypoglycaemia disutilities	9.18	9.09	+0.10	21 588	21 693	-106	Once-weekly semaglutide dominant
Analysis	Discounted quality-adjusted life expectancy (QALYs)			Discounted direct costs (GBP)			ICER (GBP per QALY gained)
	Once-weekly semaglutide 0.5 mg	Dulaglutide 1.5 mg	Difference	Once-weekly semaglutide 0.5 mg	Dulaglutide 1.5 mg	Difference	
Base case	9.00	8.96	+0.04	21 659	21 693	-35	Once-weekly semaglutide dominant
Statistically significant differences only	8.97	8.96	+0.01	21 824	21 693	+131	18 446
35-year time horizon	8.94	8.92	+0.01	21 384	21 467	-83	Once-weekly semaglutide dominant
20-year time horizon	7.76	7.74	+0.01	17 052	17 136	-84	Once-weekly semaglutide dominant
10-year time horizon	5.15	5.13	+0.02	10 235	10 287	-51	Once-weekly semaglutide dominant
0% discount rates	13.58	13.53	+0.06	35 512	35 564	-52	Once-weekly semaglutide dominant
6% discount rates	7.08	7.05	+0.03	16 301	16 329	-28	Once-weekly semaglutide dominant
NICE (THIN) baseline cohort data	8.81	8.78	+0.02	19 463	19 471	-8	Once-weekly semaglutide dominant
BMI difference maintained for patient lifetimes	9.03	8.96	+0.07	21 671	21 693	-23	Once-weekly semaglutide dominant
UKPDS HbA1c creep for duration of the analysis (no change upon treatment intensification)	8.50	8.47	+0.03	24 643	24 722	-78	Once-weekly semaglutide dominant
Upper 95% CI of HbA1c estimated treatment difference	9.00	8.96	+0.04	21 599	21 693	-94	Once-weekly semaglutide dominant
Lower 95% CI of HbA1c estimated treatment difference	8.97	8.96	+0.01	21 671	21 693	-23	Once-weekly semaglutide dominant
Upper 95% CI of BMI estimated treatment difference	9.00	8.96	+0.04	21 683	21 693	-10	Once-weekly semaglutide dominant
Lower 95% CI of BMI estimated treatment difference	8.98	8.96	+0.02	21 679	21 693	-14	Once-weekly semaglutide dominant
Treatment switching at 2 years	8.94	8.93	+0.01	21 324	21 360	-36	Once-weekly semaglutide dominant

TABLE 4 (Continued)

Analysis	Discounted quality-adjusted life expectancy (QALYs)			Discounted direct costs (GBP)			ICER (GBP per QALY gained)
	Once-weekly semaglutide 0.5 mg	Dulaglutide 1.5 mg	Difference	Once-weekly semaglutide 0.5 mg	Dulaglutide 1.5 mg	Difference	
Treatment switching at 5 years	9.04	9.02	+0.02	22 212	22 377	-165	Once-weekly semaglutide dominant
Treatment switching at 7.5% (58 mmol/mol) HbA1c threshold (using UKPDS progression)	8.50	8.47	+0.03	24 643	24 722	-78	Once-weekly semaglutide dominant
NPH basal insulin cost upon treatment intensification	9.00	8.96	+0.04	20 283	20 322	-39	Once-weekly semaglutide dominant
Cost of complications +10%	9.00	8.96	+0.04	22 843	22 883	-41	Once-weekly semaglutide dominant
Cost of complications -10%	9.00	8.96	+0.04	20 468	20 497	-29	Once-weekly semaglutide dominant
UKPDS 82 risk equations applied	9.33	9.31	+0.02	22 252	22 338	-86	Once-weekly semaglutide dominant
Lee et al BMI disutility applied	8.55	8.50	+0.04	21 659	21 693	-35	Once-weekly semaglutide dominant
Currie et al hypoglycaemia disutilities	9.12	9.09	+0.04	21 659	21 693	-35	Once-weekly semaglutide dominant

Abbreviations: BMI, body mass index; CI, confidence interval; GBP, 2016 pounds sterling; HbA1c, glycated haemoglobin; NPH, neutral protamine Hagedorn; QALY, quality-adjusted life year. Quality-adjusted life expectancy outcomes are rounded to two decimal places.

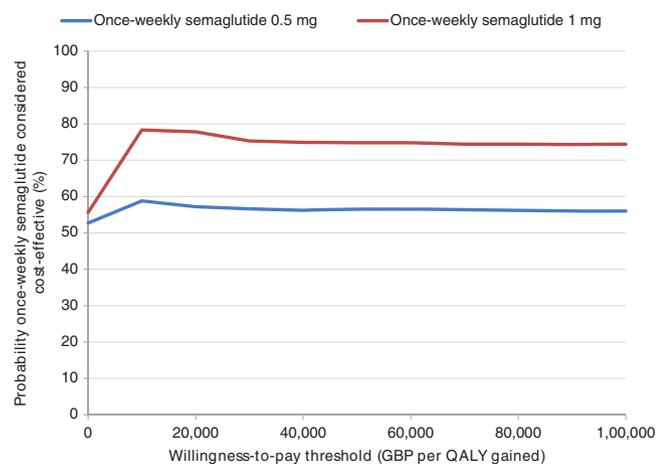


FIGURE 1 Cost-effectiveness acceptability curve from the probabilistic sensitivity analysis. Abbreviations: GBP, 2016 pounds sterling; QALY, quality-adjusted life year

4 | DISCUSSION

Once-weekly semaglutide 0.5 and 1 mg were found to be dominant over dulaglutide 1.5 mg based on the SUSTAIN 7 trial, improving clinical outcomes and reducing direct costs in individuals with T2DM. Greater reductions in HbA1c and BMI were the key drivers of improved long-term outcomes. Once-weekly semaglutide was associated with increased treatment costs compared with dulaglutide,

despite equal acquisition costs, because of the increase in survival resulting from improved outcomes. However, cost savings resulting from the avoided diabetes-related complications entirely offset this increase. While overall cost savings per patient were small, these were found to be statistically significant for the higher dose of once-weekly semaglutide. These small cost savings at a per patient level would translate to a substantially larger amount when extrapolated over a national patient population with type 2 diabetes using once-weekly GLP-1 receptor agonist therapy.

Achievement of treatment goals and tolerability can affect adherence, which may impact cost-effectiveness. In the SUSTAIN 7 clinical trial, once-weekly semaglutide 0.5 mg was associated with proportions of patients achieving glycaemic control targets similar to those associated with dulaglutide 1.5 mg, while once-weekly semaglutide was associated with a significantly greater proportion of patients achieving HbA1c targets.²⁰ Discontinuation rates were slightly higher with once-weekly semaglutide 0.5 mg (16%) and 1 mg (17%) compared with dulaglutide 1.5 mg (12%).²⁰ The percentages of patients experiencing adverse events, adverse events that led to premature treatment discontinuation, and gastrointestinal adverse events were similar with once-weekly semaglutide 0.5 mg, once-weekly semaglutide 1 mg and dulaglutide 1.5 mg. Further studies are required to determine how the outcomes identified in randomized, controlled trials translate to clinical practice.

There is increasing interest in the impact of medications for T2DM on cardiovascular risk, in addition to their impact on

conventional risk factors for cardiovascular events. Once-weekly semaglutide demonstrated cardiovascular benefits in the SUSTAIN 6 trial (NCT01720446). Once-weekly semaglutide was associated with a significantly lower risk of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke compared with placebo plus standard of care.⁵⁶ The REWIND study (NCT01394952) to assess the impact of dulaglutide on cardiovascular risk has not yet been reported. Until data from the REWIND study are available, it is not possible to include further information concerning differential impact on cardiovascular risk with once-weekly semaglutide and dulaglutide.

NICE guidelines currently recommend GLP-1 receptor agonists as part of triple therapy for individuals with T2DM and a BMI over 35 kg/m², those for whom insulin therapy would have significant occupational implications and those for whom weight loss would benefit other significant obesity-related comorbidities.⁶ This is not in agreement with the present analysis in which dual therapy following metformin failure was considered. However, the joint guidelines released by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend the use of GLP-1 receptor agonists as a second-line treatment option. The draft update to ADA/EASD consensus guidelines states that GLP-1 receptor agonists are a preferred second-line treatment if weight gain is a concern, and that interventions with a proven cardiovascular benefit are preferred (new guidelines are due to be released following the 54th EASD Annual Meeting 2018 in Berlin, Germany).^{13,57} Other second-line options for individuals with T2DM include DPP-4 inhibitors, SGLT-2 inhibitors and basal insulin.⁶ In the SUSTAIN 2 trial, both doses of once-weekly semaglutide were associated with significantly larger reductions in HbA1c, systolic blood pressure and BMI vs the DPP-4 inhibitor sitagliptin.⁵⁸ There are currently no head-to-head clinical trials comparing once-weekly semaglutide with SGLT-2 inhibitors, but an NMA suggests that both doses of once-weekly semaglutide are associated with greater reductions in HbA1c, that once-weekly semaglutide 1 mg is associated with greater reductions in body weight, and that once-weekly semaglutide 0.5 mg is associated with weight loss similar to that with SGLT-2 inhibitors.¹⁴ The SUSTAIN 8 trial (NCT03136484) will provide a head-to-head comparison of once-weekly semaglutide with SGLT-2 inhibitors (canagliflozin 300 mg). As well as in the SUSTAIN 7 trial (NCT02648204), once-weekly semaglutide was compared with other GLP-1 receptor agonists in the SUSTAIN 3 trial (exenatide extended-release, NCT01885208) and in an NMA (liraglutide, dulaglutide, exenatide twice-daily, exenatide extended-release, lixisenatide and albiglutide) in which once-weekly semaglutide was associated with greater reductions in HbA1c and body weight in all comparisons.^{19,21} Once-weekly semaglutide was compared with basal insulin in the SUSTAIN 4 trial (NCT02128932) and was associated with significant improvements in HbA1c and body weight.⁵⁹ 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 simply in groups with a high BMI at baseline.^{22,60,61} As once-weekly semaglutide has been shown to be more efficacious than a number of treatment options for individuals with T2DM, further analyses are required

to assess its cost-effectiveness at each stage of the T2DM treatment algorithm, to elucidate the optimal place for once-weekly semaglutide and to maximize value for money within the NHS.

A limitation of this study was the reliance on short-term clinical trial data to make long-term projections. However, this remains one of the essential tenets of health economic modelling and it is arguably one of the best available options to inform decision making in the absence of long-term data. Moreover, projecting outcomes over patient lifetimes is recommended in guidelines for economic evaluation of interventions for T2DM.²⁸ Whilst there is always an element of clinical doubt concerning the accuracy of such an approach, every effort was made in the present analysis to minimize this doubt, primarily by using a model of diabetes that has been extensively published and validated, in addition to extensive sensitivity analyses.^{24,25} The aim of health economic analyses, such as the present study, is to inform and to reduce uncertainty concerning decision making when long-term data are lacking.

A further limitation of the present analysis is that the model does not reflect personalization of treatment. EASD and ADA guidelines indicate that patients should be routinely assessed and their therapy should be modified and their treatment goals revised accordingly.^{13,58} The 3-year treatment switch presented in this analysis could therefore be subject to criticism. The modelling analysis also did not include addition of basal insulin with continuation of GLP-1 receptor agonists. This approach is recommended in treatment guidelines, but all studies have assessed addition of a GLP-1 receptor agonist to a basal insulin regimen rather than addition of basal insulin to a GLP-1 receptor agonist regime.^{13,58} Therefore, changes in risk factors upon addition of basal insulin to once-weekly semaglutide and dulaglutide would be associated with significant uncertainty. Despite these limitations, the present study offers a clear and simple direct comparison of the two interventions, aiming to assess the cost-effectiveness of once-weekly semaglutide and dulaglutide in the UK.

In conclusion, once-weekly semaglutide represents a cost-effective option for treating individuals with T2DM in the UK who are not achieving glycaemic control with metformin and it is projected to both improve quality-adjusted life expectancy and reduce costs compared with treatment with dulaglutide.

CONFLICTS OF INTEREST

A. V. has conducted clinical trials funded by and has received lecture and advisory board fees from Astra Zeneca, Boehringer-Ingelheim, Ely Lilly, Merck Sharpe Dohme, Napp, Novo Nordisk, Takeda and Sanofi. C. S. H. is an employee of Novo Nordisk Ltd and owns shares in Novo Nordisk A/S. P. J. is an employee of Novo Nordisk A/S. S. M. and B. H. are employees of Ossian Health Economics and Communications, which received consulting fees from Novo Nordisk A/S to support preparation of the analysis. S. C. B. has received honoraria, teaching and research sponsorship/grants from Astra-Zeneca, Boehringer Ingelheim, BMS, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novo Nordisk, Pfizer, Sanofi and Takeda. S. C. B. owns a share of Glycosmedia.

Author contributions

The study was designed by all authors. B. H. and S. M. conducted the study. All authors contributed to analysis of the results. S. M. and B. H. drafted the manuscript and A. V., S. C. B., C. S. H and P. J. critically reviewed the manuscript and revised it for important intellectual content. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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