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Oral Semaglutide Versus Empagliflozin, Sitagliptin and Liraglutide in the UK: Long-Term Cost-Effectiveness Analyses Based on the Pioneer Clinical Trial Programme

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ABSTRACT

Introduction: The PIONEER trial program has shown that, after 52 weeks, the novel oral glucagon-like peptide-1 (GLP-1) analogue semaglutide 14 mg was associated with significantly greater reductions in glycated haemoglobin (HbA1c) versus a sodium-glucose cotransporter-2 inhibitor (empagliflozin 25 mg), a dipeptidyl peptidase-4 inhibitor (sitagliptin 100 mg) and an injectable GLP-1 analogue (liraglutide 1.8 mg). The aim of the present analysis was to assess the long-term cost-effectiveness of oral semaglutide 14 mg versus these comparators in the UK setting.

Methods: Analyses were performed from a healthcare payer perspective using the IQVIA CORE Diabetes Model, projecting outcomes over patient lifetimes (50 years). Baseline cohort characteristics and treatment effects were based on 52-week data from the PIONEER 2, 3 and 4 randomised controlled trials, comparing oral semaglutide with empagliflozin, sitagliptin and liraglutide, respectively. Treatment switching occurred when HbA1c exceeded 7.5% (58 mmol/mol). Utilities, treatment costs and costs of diabetes-related complications (in pounds sterling [GBP]) were taken from published sources. The acquisition cost of oral semaglutide was assumed to match once-weekly semaglutide.

Results: Oral semaglutide was associated with improvements in quality-adjusted life expectancy of 0.09 quality-adjusted life years (QALYs) versus empagliflozin, 0.20 QALYs versus sitagliptin and 0.07 QALYs versus liraglutide. Direct costs over a patient's lifetime were GBP 971 and GBP 963 higher with oral semaglutide versus empagliflozin and sitagliptin, respectively, but GBP 1,551 lower versus liraglutide. Oral semaglutide was associated with a reduced incidence of diabetes-related complications versus all comparators. Therefore, oral semaglutide 14 mg was associated with incremental cost-effectiveness ratios of GBP 11,006 and 4,930 per QALY gained versus empagliflozin 25 mg and sitagliptin 100 mg, respectively, and was more effective and less costly (dominant) versus liraglutide 1.8 mg.

Conclusion: Oral semaglutide was cost-effective versus empagliflozin and sitagliptin, and dominant versus liraglutide, for the treatment of type 2 diabetes in the UK.

Keywords: Costs and cost analysis; Cost-effectiveness; Diabetes mellitus; Empagliflozin; GLP-1 receptor agonist; Liraglutide; Oral semaglutide; Sitagliptin; United Kingdom

Key Summary Points

Why carry out this study?

- Type 2 diabetes is associated with a substantial and increasing clinical and economic burden in the UK, meaning cost-effective therapies that improve patient outcomes while minimising costs for the healthcare payer are crucial.
- The recent PIONEER clinical trial programme has shown that oral semaglutide, the first oral medication in its class, was associated with improved glycaemic control and reductions in body weight versus empagliflozin, sitagliptin and liraglutide, factors that have been associated with a reduced risk of long-term diabetes-related complications.
- The present analysis used a clinically-relevant treatment approach to assess the long-term cost-effectiveness of oral semaglutide 14 mg versus empagliflozin 25 mg, sitagliptin 100 mg and liraglutide 1.8 mg for the treatment of patients with type 2 diabetes from a healthcare payer perspective in the UK.

What was learned from the study?

- Oral semaglutide 14 mg was projected to improve both life expectancy and quality-adjusted life expectancy versus empagliflozin 25 mg, sitagliptin 100 mg and liraglutide 1.8 mg.
- Direct costs over patient lifetimes were estimated to be higher with oral semaglutide versus empagliflozin and sitagliptin, but lower versus liraglutide, with costs associated with the treatment of diabetes-related complications lower with oral semaglutide in all comparisons.
- Oral semaglutide 14 mg was therefore considered a cost-effective treatment option versus empagliflozin 25 mg, sitagliptin 100 mg and liraglutide 1.8 mg for the treatment of type 2 diabetes in the UK.

INTRODUCTION

Diabetes accounts for a substantial health and economic burden in the UK, with over 4.7 million people living with the disease and over 12.3 million people at an increased risk of developing the disease in 2018 [1]. Diabetes-related healthcare expenditure (expressed in pounds sterling [GBP]) was estimated to be over GBP 10 billion in 2018, accounting for 10% of the entire National Health Service (NHS) budget [1]. An estimated 80% of diabetes-related expenditure in the UK is associated with the treatment of long-term complications, with a more than two-fold increase in risk of myocardial infarction, heart failure and stroke in people with type 2 diabetes versus those without the disease [1]. Interventions that are cost-effective, offering clinical benefits while providing value for money, are becoming vital as healthcare payers' budgets come under increasing pressure.

Improvements in glycated haemoglobin (HbA1c) and blood pressure have long been associated with reductions in long-term diabetes-related complications, demonstrated in the landmark United Kingdom Prospective Diabetes Study (UKPDS), and more recent evidence has suggested that reductions in other parameters, such as body weight, can provide further benefits [2,3,4,5]. Clinical guidelines published by the National Institute for Health and Care Excellence (NICE) in the UK recommend an individualised approach for the treatment of each patient, incorporating personal preferences and comorbidities [6]. Moreover, the most recent guidelines released by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) recommend a more holistic approach to diabetes treatment, rather than a sole focus on glycaemic control [7]. In particular, updated recommendations for people with type 2 diabetes with established cardiovascular disease, or those who are overweight or obese or have a high risk of hypoglycaemia, now consider the effects of therapies on cardiovascular disease, body weight and hypoglycaemia risk alongside reductions in HbA1c [7].

Glucagon-like peptide-1 (GLP-1) receptor agonists represent a highly efficacious class of interventions for type 2 diabetes, with injectable GLP-1 analogue once-weekly semaglutide

shown to be both efficacious and cost-effective versus a variety of therapies [8,9,10,11]. However, up to now, GLP-1 receptor agonists were previously only available in injectable formulations, which could have proved a barrier for patient use compared with other modern treatment options such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors, which are administered orally. Indeed, in the UK, injectable GLP-1 receptor agonists are only recommended as an intensification step for patients with inadequate glycaemic control following a triple therapy combination of metformin plus a DPP-4 inhibitor, a sulfonylurea, pioglitazone or an SGLT2 inhibitor, for whom insulin therapy would have significant occupational implications, or weight loss would benefit other obesity-related comorbidities [6]. Given the efficacy benefits GLP-1 receptor agonists appear to offer, earlier intensification to such medications could overcome the documented and substantial therapeutic inertia in people with type 2 diabetes [8,9,10,11,12].

Oral semaglutide is a novel formulation of the GLP-1 analogue semaglutide developed for once-daily oral administration, using the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate to facilitate absorption across the gastric mucosa. The efficacy and safety of oral semaglutide has been assessed in the PIONEER clinical trial programme, with once-daily oral semaglutide 14 mg compared with once-daily SGLT2 inhibitor empagliflozin 25 mg in PIONEER 2, once-daily DPP-4 inhibitor sitagliptin 100 mg in PIONEER 3 and once-daily injectable GLP-1 receptor agonist liraglutide 1.8 mg in PIONEER 4 [13,14,15].

The aim of the present analysis was to assess the long-term cost-effectiveness of oral semaglutide 14 mg versus empagliflozin 25 mg, sitagliptin 100 mg and liraglutide 1.8 mg in the UK setting, based on the results of the PIONEER 2, 3 and 4 studies, respectively.

METHODS

Modelling Approach

Long-term projections of clinical and cost outcomes were performed from a healthcare payer perspective using the IQVIA CORE Diabetes Model (version 9.0), a proprietary, validated, internet-based, interactive computer model developed to determine the long-term health outcomes and economic consequences of implementing interventions in the treatment of type 1 and type 2 diabetes mellitus (accessible at www.core-diabetes.com) [16,17]. The architecture, assumptions, features and capabilities of the model have been previously published [16]. Validation studies of the model have been published both in 2004 and more recently in 2014 [17,18].

Model outputs include time to onset and cumulative incidence of complications, life expectancy, quality-adjusted life expectancy (expressed in quality-adjusted life years [QALYs]), direct costs and, where required, incremental cost-effectiveness ratios (ICERs), which describe the cost per additional unit of effectiveness gained for the intervention versus the comparator. In comparisons where an intervention is associated with cost savings while providing greater clinical benefits, no calculation of an ICER is required and it is considered dominant versus the comparator.

Analyses were performed over patient lifetimes (up to 50 years), as recommended in the guidelines for the cost-effectiveness assessment of interventions for type 2 diabetes, to ensure all relevant diabetes-related complications, and their impact on clinical and cost outcomes, were captured [19]. The UKPDS 68 risk equations were applied to predict model outcomes. Background mortality was captured based on UK-specific life tables published by the World Health Organisation (Supplementary Material, Table S1).²⁰ Health-state utilities and event disutilities were based on published sources (Supplementary Material, Table S2) [21,22,23,24,25,26,27]. 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.

Clinical Data

Baseline cohort characteristics and treatment effects were sourced from the PIONEER 2, 3 and 4 trials for comparisons of oral semaglutide 14 mg with empagliflozin 25 mg, sitagliptin 100 mg and liraglutide 1.8 mg, respectively (Supplementary Material, Table S3 and Table 1). PIONEER 2 enrolled people with type 2 diabetes with an HbA1c level between 7.0–10.5% (53–91 mmol/mol) receiving metformin, while PIONEER 3 enrolled people with type 2 diabetes with an HbA1c level between 7.0–10.5% receiving metformin with or without a sulfonylurea. PIONEER 4 enrolled people with type 2 diabetes with HbA1c values between 7.0–9.5% (53–80 mmol/mol) receiving metformin with or without an SGLT2 inhibitor. Two estimands, the treatment policy estimand and the trial product estimand, were used in the PIONEER trial programme to address two different efficacy questions. The treatment policy estimand reflected the intention-to-treat principle by including all study participants randomly assigned to each treatment, using data regardless of discontinuation of study medications and/or use of additional anti-diabetic medications during the trial [28,29]. In contrast, the trial product estimand assessed treatment effects under the assumption that patients received the study drug for the duration of the trial and did not receive any additional anti-diabetic medications, aiming to reflect the effects of the study medications without the confounding effects of rescue medication or any other changes in glucose-lowering medication [28]. To match the annual cycle length of the model, and to avoid the confounding impact of additional anti-diabetic medications on clinical and cost outcomes, the analyses were performed using the 52-week data evaluated by the trial product estimand. The impact of using data evaluated by the treatment policy estimand was explored in a sensitivity analysis.

Treatment Switching and Long-Term Parameter Progression

Following application of the treatment effects in the first year of the analysis, HbA1c was modelled to follow the UKPDS progression equation, and patients were assumed to receive oral semaglutide or comparator treatment until HbA1c exceeded 7.5% (58 mmol/mol), the

threshold for treatment intensification defined in NICE guidelines [6]. At this stage, treatment with oral semaglutide or the comparator was discontinued and patients were assumed to intensify to basal insulin, with a reduction in HbA1c based on an insulin-naïve population derived from the “Core” multivariate equations estimated by Willis *et al.* [30]. HbA1c was subsequently modelled to follow the UKPDS progression equation for the remainder of patient lifetimes. This approach was chosen to mirror the HbA1c progression used by NICE for evaluating SGLT2 inhibitors as monotherapy in the UK, and to reflect common clinical practice, where, due to the progressive nature of type 2 diabetes, glycaemic control cannot be maintained indefinitely by the addition of one medication [7,31]. Variations in treatment switching thresholds, as well as further treatment intensification to basal-bolus insulin, were explored in sensitivity analyses.

Body mass index (BMI) benefits were assumed to persist while patients received either oral semaglutide or comparator treatment, before reverting to baseline following intensification to basal insulin therapy. Therefore, no difference in BMI was seen between the patient arms following treatment intensification with basal insulin.

Changes in blood pressure and serum lipids were assumed to follow the natural progression algorithms built into the IQVIA CORE Diabetes Model in all arms, based on the UKPDS or Framingham data (as described by Palmer *et al.*), following application of the treatment effects in the first year of the analysis [16]. Hypoglycaemia rates following treatment intensification were based on published data, with non-severe and severe hypoglycaemic events projected to increase to 4.08 and 0.10 events per patient per year, respectively [32].

Cost Data

Costs were accounted from a UK healthcare payer perspective. Direct costs captured included pharmacy costs, costs associated with diabetes-related complications and patient management costs (Supplementary Material, Tables S4 and S5). The annual acquisition cost of oral semaglutide was assumed to be the same as once-weekly semaglutide, based on the

similar level of pricing seen between the GLP-1 analogues in the US market. Costs of other included medications and consumables were based on published list prices (sourced in July 2019), while costs of diabetes-related complications were identified through a 2017 literature review and updated or inflated where necessary to the most recent costs available (2018 GBP) using published NHS diagnosis-related groups and the healthcare inflation index published by the Personal Social Services Research Unit [33,34,35,36,37,38,39,40,41,42]. No self-monitoring of blood glucose (SMBG) testing costs were associated with oral semaglutide, empagliflozin, sitagliptin or liraglutide, as all these interventions are associated with low rates of hypoglycaemia, meaning little to no SMBG testing would be required. No needles were required for administration of oral semaglutide, empagliflozin or sitagliptin, as these medications are administered orally, but one needle per day was required for liraglutide administration. Following intensification to basal insulin therapy (assumed to be insulin Abasaglar, the most widely used biosimilar of insulin glargine in the UK), patients were assumed to require one SMBG test per day and use one needle per day for administration.

Sensitivity Analyses

The extrapolation of clinical results by modelling the long-term consequences is associated with uncertainty. Sensitivity analyses were therefore performed on key parameters in the modelling analysis to assess the robustness of the base case findings. Sensitivity analyses conducted for all comparisons included: applying only statistically significant differences between the treatment arms; shortening the time horizon of the analyses to 35, 20 and 10 years (for which it should be noted that some patients were still alive at the end of the modelling period, and therefore not all costs and consequences were captured); applying discount rates of 0% and 6% in separate analyses; applying the upper and lower limits of the 95% confidence intervals for the estimated treatment differences in HbA1c and BMI in separate analyses; maintaining BMI treatment effects for patient lifetimes; altering the HbA1c threshold for treatment intensification to 7.0% (53 mmol/mol) and 8.0% (64 mmol/mol); applying a second treatment intensification step to basal-bolus insulin at an HbA1c threshold

of 7.5% (58 mmol/mol); exploring the effect of applying alternative basal insulin costs (insulin neutral protamine Hagedorn, Semglee and Lantus®) following treatment intensification; increasing and decreasing the annual acquisition cost of oral semaglutide by 5% in separate analyses; application of the liraglutide 1.2 mg price in the liraglutide arm of PIONEER 4; increasing and decreasing the costs of complications by 10% in separate analyses; applying an alternative cost of stroke in the year of event and subsequent years, based on a publication by Patel *et al.* [43]; applying the UKPDS 82 risk equations to predict model outcomes; application of alternative disutilities for increases in BMI (based on a publication by Lee *et al.* [26]) and hypoglycaemic events (based on publications by Currie *et al.* [44] and Lauridsen *et al.* [45]); application of the 26-week clinical data; and application of data evaluated by the treatment policy estimand from the PIONEER 2, 3 and 4 clinical trials [13,14,15].

Probabilistic sensitivity analyses (PSA) were also performed using a second-order Monte Carlo approach. Cohort characteristics, treatment effects and complication costs and utilities were sampled from distributions, with cohorts of 1,000 patients run through the model 1,000 times.

RESULTS

Base Case Analysis

Long-term projections of clinical outcomes indicated that oral semaglutide 14 mg was associated with improvements in discounted life expectancy of 0.06, 0.17 and 0.07 years and improvements in discounted quality-adjusted life expectancy of 0.09, 0.20 and 0.07 QALYs versus empagliflozin 25 mg, sitagliptin 100 mg and liraglutide 1.8 mg, respectively (Table 2). Clinical benefits arose from a reduced incidence of diabetes-related complications with oral semaglutide in all comparisons. The mean times to any diabetes-related complication in the analyses were lengthened with oral semaglutide 14 mg treatment by 0.2 years versus empagliflozin 25 mg and sitagliptin 100 mg, and 0.1 years versus liraglutide 1.8 mg.

Oral semaglutide was associated with direct cost increases of GBP 971 and GBP 963 versus empagliflozin 25 mg and sitagliptin 100 mg, respectively, over patient lifetimes, driven by the assumed higher acquisition cost of oral semaglutide and the differential times to treatment intensification, with patients receiving oral semaglutide for one additional year in the comparison with empagliflozin and two additional years in the comparison with sitagliptin (Figure 1). However, higher treatment costs were partially offset by cost savings due to avoidance of diabetes-related complications, most notably avoided cardiovascular complications (mean cost savings of GBP 99 per patient compared with empagliflozin 25 mg and GBP 146 per patient compared with sitagliptin 100 mg). In the analyses based on PIONEER 4, oral semaglutide 14 mg was associated with estimated cost savings of GBP 1,551 versus liraglutide 1.8 mg over patient lifetimes, driven by the lower acquisition cost of oral semaglutide. Further cost savings were achieved through reduced needle use (with none required for oral semaglutide versus one per day for liraglutide) and avoidance of diabetes-related complications with oral semaglutide, most notably avoided cardiovascular complications (mean cost savings of GBP 101 per patient).

In the analyses based on PIONEER 2 and 3, oral semaglutide 14 mg was associated with improved clinical outcomes and increased costs from a healthcare payer perspective, yielding ICERs of GBP 11,006 and GBP 4,930 per QALY gained versus empagliflozin 25 mg and sitagliptin 100 mg, respectively. Based on the commonly-quoted willingness-to-pay threshold of GBP 20,000 per QALY gained in the UK, oral semaglutide 14 mg represents a cost-effective treatment option versus empagliflozin 25 mg and sitagliptin 100 mg. In the analyses based on PIONEER 4, oral semaglutide 14 mg was associated with improved clinical outcomes and reduced costs versus liraglutide 1.8 mg, and it was therefore considered dominant.

Deterministic Sensitivity Analyses

Sensitivity analyses showed that the results of the of the cost-effectiveness analyses comparing oral semaglutide 14 mg with empagliflozin 25 mg, sitagliptin 100 mg and

liraglutide 1.8 mg were robust to changes in the input parameters and assumptions used (Table 3).

Oral Semaglutide Versus Empagliflozin (PIONEER 2)

For the analyses based on PIONEER 2, the biggest change in the ICER from the base case analysis was seen when applying a 10-year time horizon. Clinical benefits with oral semaglutide 14 mg were reduced and incremental costs were increased, yielding an ICER of GBP 21,821 per QALY gained versus empagliflozin 25 mg. However, this was due to the shorter time horizon of the analysis not capturing all of the long-term diabetes-related complications patients may experience, and their subsequent impact on clinical and cost outcomes. The largest reduction in the ICER was observed when applying a second treatment intensification step to basal-bolus insulin at 7.5% (58 mmol/mol), which resulted in increased clinical benefits and reduced incremental costs with oral semaglutide and an ICER of GBP 4,316 per QALY gained.

Lowering the HbA1c treatment switching threshold to 7.0% (53 mmol/mol) also greatly influenced cost-effectiveness outcomes, reducing the incremental costs associated with oral semaglutide while increasing the incremental clinical benefits. This resulted in an ICER of GBP 5,232 per QALY gained versus empagliflozin. Conversely, application of an 8.0% (64 mmol/mol) treatment switching threshold yielded increased incremental costs, and an ICER of GBP 17,545 per QALY gained for oral semaglutide versus empagliflozin.

All other sensitivity analyses yielded similar ICERs to the base case analysis.

Oral Semaglutide Versus Sitagliptin (PIONEER 3)

For the analyses based on PIONEER 3, the largest change in the ICER was also observed when applying a 10-year time horizon. Clinical benefits with oral semaglutide 14 mg were greatly reduced, while incremental costs were increased, resulting in an ICER of GBP 11,232 per QALY gained versus sitagliptin 100 mg. Performing a second treatment intensification to

basal-bolus insulin at 7.5% (58 mmol/mol) led to greatly increased clinical benefits and reduced incremental costs, and an ICER of GBP 779 per QALY gained.

Using a lower 7.0% (53 mmol/mol) HbA1c threshold for treatment switching lowered the clinical benefits associated with oral semaglutide but also reduced incremental costs, yielding an ICER of GBP 1,514 per QALY gained. Applying a higher 8.0% (64 mmol/mol) HbA1c threshold also led to lowered clinical benefits but with increased incremental costs, and oral semaglutide was associated with an ICER of GBP 6,977 per QALY gained versus sitagliptin. Maintaining the treatment effects of BMI for patient lifetimes resulted in increased clinical benefits with oral semaglutide, and incremental costs similar to the base case analysis, yielding an ICER of GBP 3,817 per QALY gained versus sitagliptin.

ICERs in all other sensitivity analyses remained similar to the base case analysis.

Oral Semaglutide Versus Liraglutide (PIONEER 4)

For the analyses based on PIONEER 4, the base case conclusion that oral semaglutide was dominant versus liraglutide did not change. Application of shorter time horizons lowered the clinical benefits observed with oral semaglutide, while application of a 7.0% (53 mmol/mol) HbA1c threshold for treatment switching and the liraglutide 1.2 mg price in the liraglutide 1.8 mg arm yielded lower cost savings with oral semaglutide, but clinical and cost benefits remained consistently in favour of oral semaglutide 14 mg throughout all analyses, and it remained dominant versus liraglutide 1.8 mg.

Probabilistic Sensitivity Analysis

PSA with sampling around cohort characteristics, treatment effects, complication costs and utilities showed similar mean results to the base case analyses, but increased measures of variance around the mean outcomes (Figure 2). The mean incremental improvements in quality-adjusted life expectancy with oral semaglutide 14 mg were 0.09, 0.18 and 0.07 QALYs versus empagliflozin 25 mg, sitagliptin 100 mg and liraglutide 1.8 mg, respectively. Mean

costs estimated to be GBP 1,021 and GBP 817 higher with oral semaglutide versus empagliflozin and sitagliptin, respectively, but GBP 1,177 lower versus liraglutide. This resulted in ICERs of GBP 11,580 and GBP 4,620 per QALY gained for oral semaglutide 14 mg versus empagliflozin 25 mg and sitagliptin 100 mg, respectively, while it was considered dominant versus liraglutide 1.8 mg. At a willingness-to-pay threshold of GBP 20,000 per QALY gained, the probabilities of oral semaglutide 14 mg being cost-effective versus empagliflozin 25 mg, sitagliptin 100 mg and liraglutide 1.8 mg were 59.9%, 77.6% and 79.5%, respectively, while at a willingness-to-pay threshold of GBP 30,000 per QALY gained, these probabilities were estimated to be 64.3%, 80.2% and 74.7%, respectively (Figure 3).

DISCUSSION

Based on long-term projections of clinical and cost outcomes, oral semaglutide 14 mg offers a cost-effective treatment option versus other modern treatments for type 2 diabetes, including empagliflozin 25 mg, sitagliptin 100 mg, and liraglutide 1.8 mg. Clinical benefits were a result of a reduced incidence and delayed time to onset of long-term diabetes-related complications with oral semaglutide. Fewer diabetes-related complications also yielded cost savings with oral semaglutide, which partially offset higher treatment costs versus empagliflozin and sitagliptin. Oral semaglutide was associated with lower treatment costs versus liraglutide, with further cost savings achieved through a reduced incidence of diabetes-related complications. Oral semaglutide 14 mg was therefore associated with ICERs of GBP 11,006 and GBP 4,930 per QALY gained versus empagliflozin 25 mg and sitagliptin 100 mg, and was considered cost-effective based on a willingness-to-pay threshold of GBP 20,000 per QALY gained. With improved clinical outcomes and reduced costs, oral semaglutide 14 mg was considered dominant versus liraglutide 1.8 mg.

Oral semaglutide is the first GLP-1 receptor agonist available for oral administration. Offering patients the benefits of a GLP-1 receptor agonist in a once-daily tablet could overcome some of the obstacles that lead to therapeutic inertia, as evidence suggests that patient

concerns over potential side effects of therapies, including hypoglycaemia and weight gain, as well as fear of injections, often lead to delayed intensification of treatment, despite poor glycaemic control [12,46,47,48]. The PIONEER clinical trial programme enrolled patients receiving differing background therapies, with PIONEER 2 enrolling patients with inadequate glycaemic control on metformin, PIONEER 3 enrolling patients with inadequate glycaemic control on metformin with or without a sulfonylurea, and PIONEER 4 enrolling patients with inadequate glycaemic control on metformin with or without an SGLT2 inhibitor [13,14,15]. As shown in the present study, oral semaglutide represents a cost-effective treatment option in all of these patient populations. Moreover, while the lower 1.2 mg dose of liraglutide is commonly recommended in the UK for the majority of patients, the present study has demonstrated that oral semaglutide remains more effective and less costly versus the more efficacious 1.8 mg dose of liraglutide when the lower 1.2 mg price is applied.

The present analysis used a clinically-relevant approach for HbA1c progression and treatment intensification, in line with recent publications and cost-effectiveness assessments of GLP-1 receptor agonists and SGLT2 inhibitors [10,31]. This is representative of clinical practice in a real-world population with type 2 diabetes, where patients continue treatments while they remain within their glycaemic target, and intensification is necessary as the disease progresses and glycaemic control becomes increasingly challenging over the long term. Indeed, the latest EASD/ADA guidelines recommend that patients are evaluated every 3–6 months to ensure treatments are performing effectively, and treatment intensification at a 7.5% (58 mmol/mol) HbA1c threshold is recommended in clinical guidelines published by NICE in the UK [6,7]. The use of multivariate equations published by Willis *et al.*, estimating changes in HbA1c on initiation of basal insulin therapy, also represents a key strength of the present analysis [30]. These equations are informed by a variety of sources captured in a literature review, allowing the analyses to avoid the use of specific treatment effects designed to artificially improve model outcomes. Therefore, the present study offers a highly relevant approach to real-world practice, where glycaemic control cannot be maintained indefinitely with one medication. However, a potential limitation of

this approach is the use of the UKPDS equations for HbA1c progression, as these are based on data from 20 years ago, which may no longer be as applicable in modern clinical practice. Nonetheless, there are no readily available long-term type 2 diabetes studies equivalent in length to the UKPDS to test this.

When evaluating the clinical and cost outcomes associated with the interventions included in the present analysis, it is important to consider the impact of differential treatment switching occurring due to the 7.5% (58 mmol/mol) HbA1c threshold. In the long-term projections based on PIONEER 2, patients received empagliflozin 25 mg for 2 years and oral semaglutide 14 mg for 3 years, while in the projections based on PIONEER 3, patients received sitagliptin 100 mg for 1 year and oral semaglutide 14 mg for 3 years. This improved glycaemic control resulted in initial treatment costs being maintained for one additional year in the analyses based on PIONEER 2 and two additional years in the analyses based on PIONEER 3. However, alternative HbA1c thresholds were tested, including adding a further treatment intensification step to basal-bolus insulin, and these analyses did not change the conclusion that oral semaglutide is cost-effective.

A limitation inherent in all long-term health economic analyses is the reliance on short-term clinical trial data to project outcomes over patient lifetimes. However, this is an essential tenet of all long-term diabetes modelling, and arguably represents the best source of evidence for decision-making in the absence of long-term clinical trial data. The use of 52-week data from the PIONEER trials, matching the annual cycle length of the model, also represents a strength of the analysis. Moreover, the variety of sensitivity analyses performed with different treatment switching assumptions and time horizons did not change the conclusion that oral semaglutide is cost-effective.

CONCLUSIONS

Oral semaglutide 14 mg was projected to be a cost-effective treatment option versus empagliflozin 25 mg, sitagliptin 100 mg and liraglutide 1.8 mg for the treatment of patients with type 2 diabetes in the UK.

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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.

Data Availability

All data generated or analysed during this study are included in this published article/as supplementary information files.

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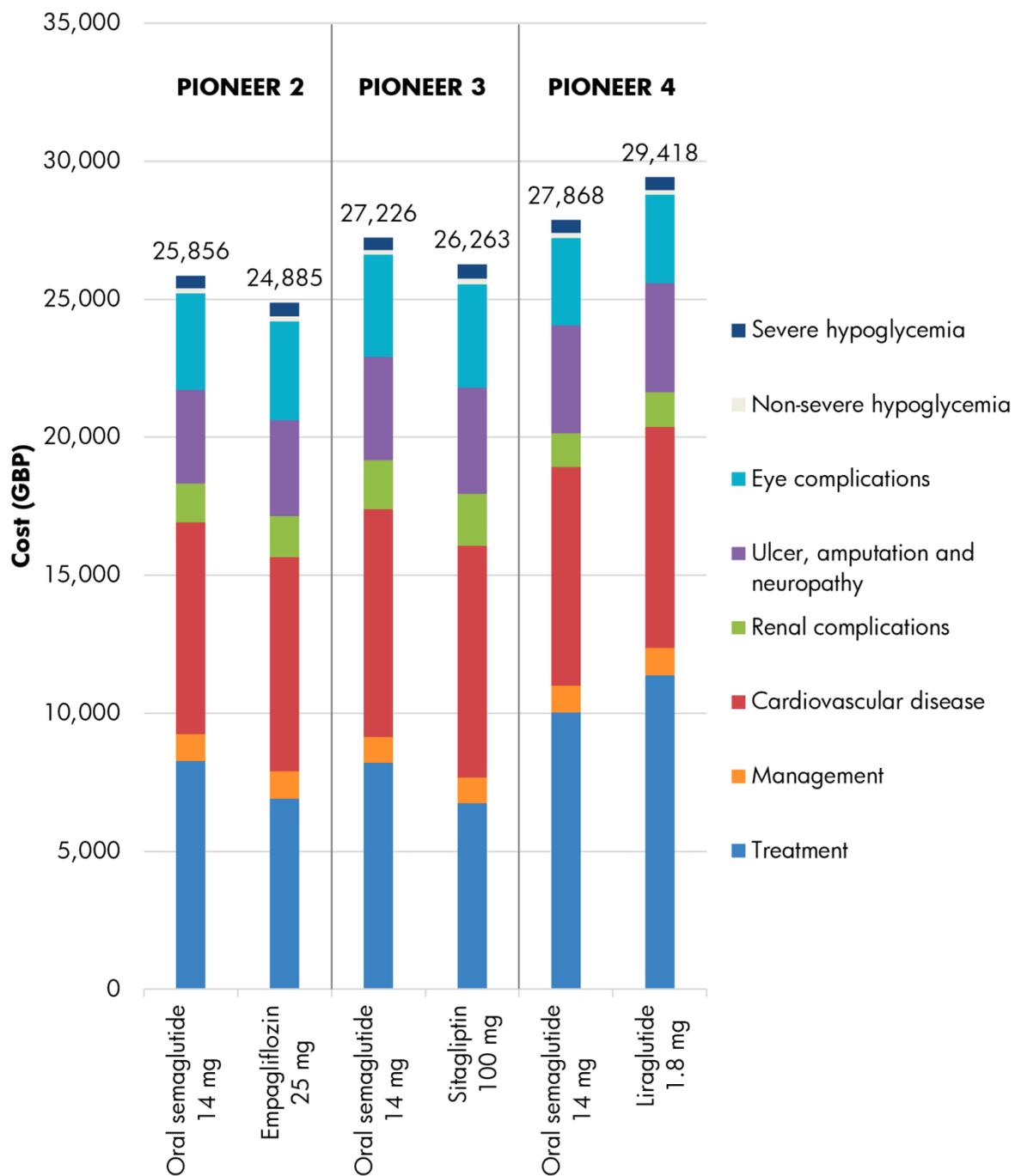


Figure 1 Direct cost outcomes over patient lifetimes

GBP, pounds sterling.

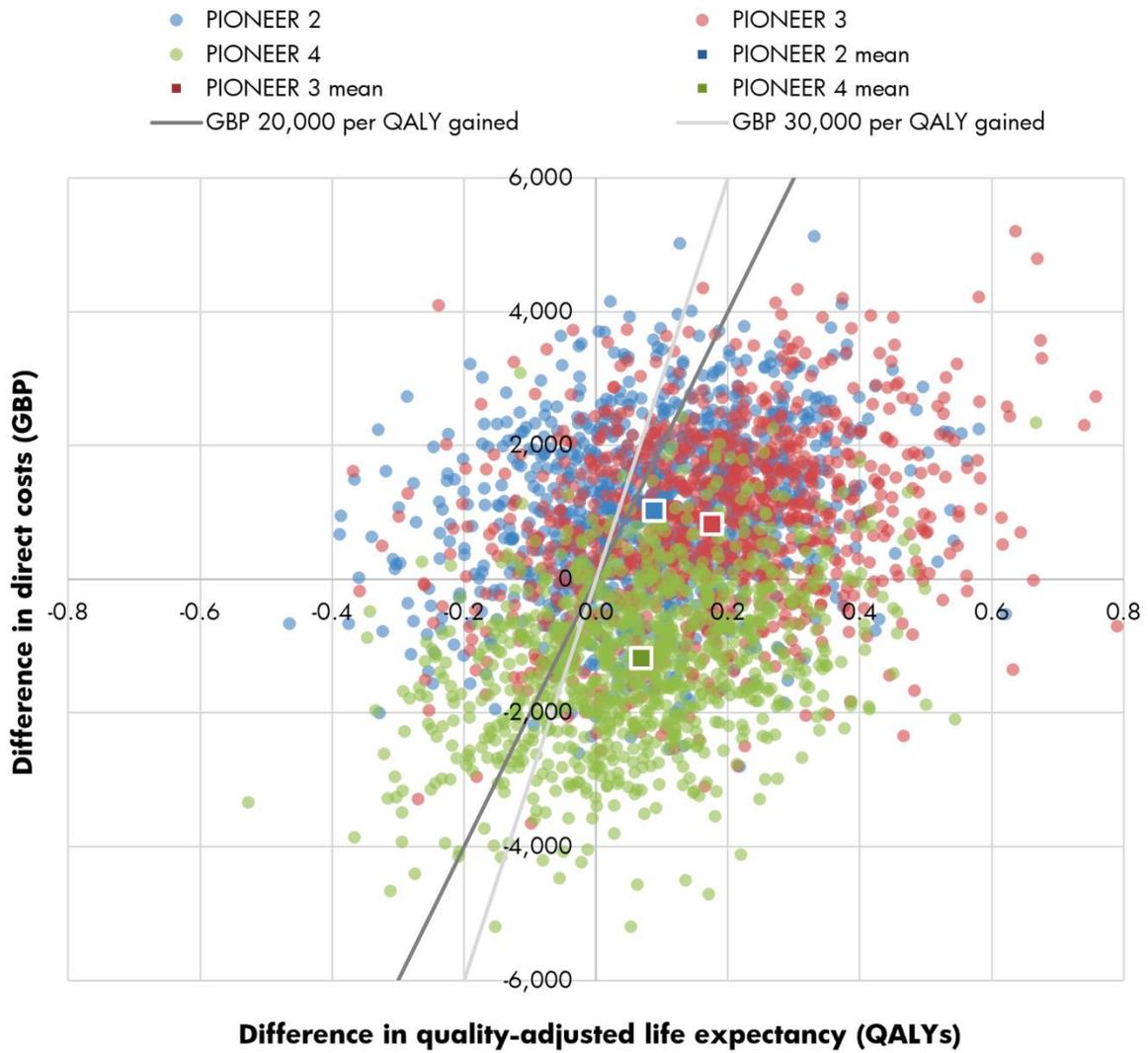


Figure 2 Cost-effectiveness scatterplot based on the PSAs

GBP, pounds sterling; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

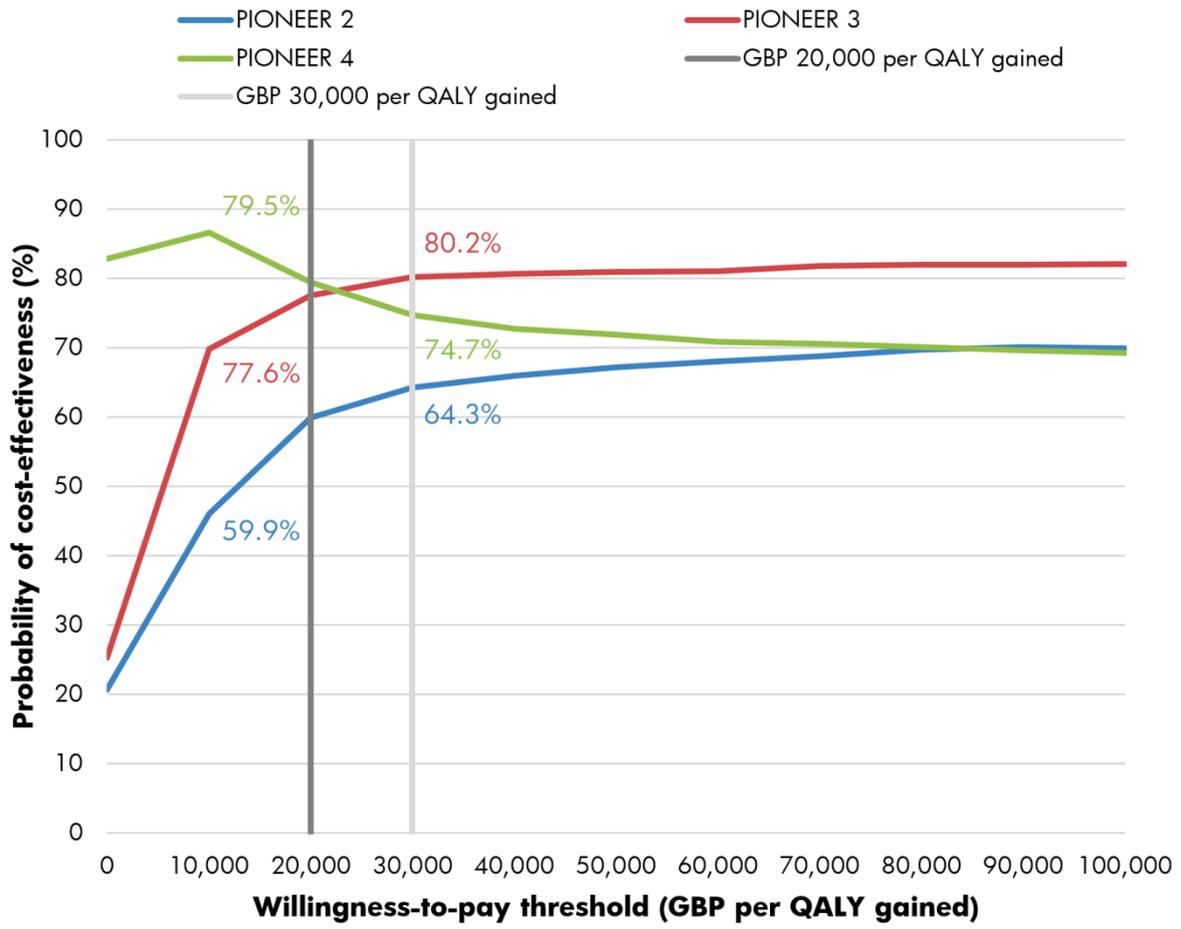


Figure 3 Cost-effectiveness acceptability curves based on the PSAs

GBP, pounds sterling; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Table 1 Treatment effects and adverse event rates applied in the analyses

Parameter	PIONEER 2		PIONEER 3		PIONEER 4	
	Oral semaglutide 14 mg	Empagliflozin 25 mg	Oral semaglutide 14 mg	Sitagliptin 100 mg	Oral semaglutide 14 mg	Liraglutide 1.8 mg
Physiological parameters applied in the first year of the analysis, mean (SE)						
HbA1c (%)	-1.30 (0.05)*	-0.79 (0.05)	-1.25 (0.05)*	-0.52 (0.05)	-1.19 (0.06)*	-0.92 (0.06)
Systolic blood pressure (mmHg)	-4.85 (0.65)	-4.34 (0.63)	-3.13 (0.63)*	-0.82 (0.61)	-3.36 (0.75)	-2.86 (0.74)
Diastolic blood pressure (mmHg)	-2.27 (0.45)	-2.67 (0.44)	-1.07 (0.39)	-0.92 (0.38)	-1.10 (0.45)	-1.05 (0.44)
Total cholesterol (mg/dL) ^a	-5.08 (1.62)*	4.74 (1.57)	-3.66 (1.50)*	1.02 (0.57)	-5.47 (2.07)	-5.36 (2.05)
HDL cholesterol (mg/dL) ^a	0.73 (0.35)*	3.11 (0.34)	0.54 (0.34)	0.20 (0.35)	1.17 (0.41)	0.23 (0.41)
BMI (kg/m ²)	-1.73 (0.10)*	-1.37 (0.09)	-1.36 (0.07)*	-0.32 (0.07)	-1.82 (0.11)*	-1.11 (0.11)
Hypoglycaemic event rates applied while patients received treatment						
Non-severe hypoglycaemic event rate (events per 100 patient years) ^b	2.25	1.90	12.12	11.99	0.71	3.16
Severe hypoglycaemic event rate (events per 100 patient years) ^b	0.25	0.24	0.24	0.90	0.00	0.00
Proportion of non-severe hypoglycaemic events that are nocturnal ^b	0.11	0.13	0.14	0.13	0.00	0.11

Parameter	PIONEER 2		PIONEER 3		PIONEER 4	
	Oral semaglutide 14 mg	Empagliflozin 25 mg	Oral semaglutide 14 mg	Sitagliptin 100 mg	Oral semaglutide 14 mg	Liraglutide 1.8 mg
Proportion of severe hypoglycaemic events that are nocturnal ^b	0.00	0.00	0.00	0.00	0.00	0.00

*Statistically significant difference at the 95% confidence level.

^a Estimated with an arithmetic mean. ^b Data on file (not previously published).

Hypoglycaemic events were assessed as safety endpoints at 57 weeks in PIONEER 2 and 4 and 52 weeks in PIONEER 3.^{13,14,15} All data, unless otherwise indicated, were evaluated by the trial product estimand at 52 weeks.^{13,14,15}

BMI, body mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; SE, standard error.

Table 2 Long-term cost-effectiveness outcomes

Health outcomes	PIONEER 2		
	Oral semaglutide 14 mg	Empagliflozin 25 mg	Difference
Discounted life expectancy (years)	13.19	13.13	+0.06
Discounted quality-adjusted life expectancy (QALYs)	8.58	8.49	+0.09
Discounted direct costs (GBP)	25,856	24,885	+971
ICER	GBP 11,006 per QALY gained		
Health outcomes	PIONEER 3		
	Oral semaglutide 14 mg	Sitagliptin 100 mg	Difference
Discounted life expectancy (years)	12.74	12.57	+0.17
Discounted quality-adjusted life expectancy (QALYs)	8.20	8.00	+0.20
Discounted direct costs (GBP)	27,226	26,263	+963
ICER	GBP 4,930 per QALY gained		
Health outcomes	PIONEER 4		
	Oral semaglutide 14 mg	Liraglutide 1.8 mg	Difference
Discounted life expectancy (years)	13.28	13.21	+0.07
Discounted quality-adjusted life expectancy (QALYs)	8.53	8.46	+0.07
Discounted direct costs (GBP)	27,868	29,418	-1,551
ICER	Oral semaglutide dominant		

Values are means (standard deviation).

GBP, pounds sterling; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 3 Sensitivity analyses results

Analysis	Oral semaglutide 14 mg versus empagliflozin 25 mg (PIONEER 2)			Oral semaglutide 14 mg versus sitagliptin 100 mg (PIONEER 3)			Oral semaglutide 14 mg versus liraglutide 1.8 mg (PIONEER 4)		
	Δ discounted QALE (QALYs)	Δ discounted direct costs (GBP)	ICER (GBP per QALY gained)	Δ discounted QALE (QALYs)	Δ discounted direct costs (GBP)	ICER (GBP per QALY gained)	Δ discounted QALE (QALYs)	Δ discounted direct costs (GBP)	ICER (GBP per QALY gained)
Base case	+0.09	+971	11,006	+0.20	+963	4,930	+0.07	-1,551	Oral semaglutide dominant
Statistically significant differences only	+0.08	+973	11,605	+0.19	+960	5,048	+0.06	-1,572	Oral semaglutide dominant
35-year time horizon	+0.09	+1,074	11,572	+0.19	+855	4,532	+0.07	-1,473	Oral semaglutide dominant
20-year time horizon	+0.08	+999	12,924	+0.15	+811	5,438	+0.03	-1,492	Oral semaglutide dominant
0% discount rates	+0.14	+906	6,693	+0.32	+1,049	3,333	+0.12	-1,646	Oral semaglutide dominant
6% discount rates	+0.07	+988	14,182	+0.15	+954	6,315	+0.05	-1,467	Oral semaglutide dominant
Upper 95% CI of HbA1c ETD	+0.11	+828	7,615	+0.14	+667	4,840	+0.06	-1,452	Oral semaglutide dominant

Analysis	Oral semaglutide 14 mg versus empagliflozin 25 mg (PIONEER 2)			Oral semaglutide 14 mg versus sitagliptin 100 mg (PIONEER 3)			Oral semaglutide 14 mg versus liraglutide 1.8 mg (PIONEER 4)		
	Δ discounted QALE (QALYs)	Δ discounted direct costs (GBP)	ICER (GBP per QALY gained)	Δ discounted QALE (QALYs)	Δ discounted direct costs (GBP)	ICER (GBP per QALY gained)	Δ discounted QALE (QALYs)	Δ discounted direct costs (GBP)	ICER (GBP per QALY gained)
Lower 95% CI of HbA1c ETD	+0.08	+1,098	13,211	+0.20	+880	4,307	+0.13	-1,227	Oral semaglutide dominant
Upper 95% CI of BMI ETD	+0.10	+976	9,371	+0.18	+961	5,278	+0.06	-1,564	Oral semaglutide dominant
Lower 95% CI of BMI ETD	+0.07	+942	13,752	+0.20	+985	4,846	+0.08	-1,529	Oral semaglutide dominant
BMI difference maintained for patient lifetimes	+0.12	+978	8,257	+0.25	+971	3,817	+0.07	-1,562	Oral semaglutide dominant
Treatment switching at 7.0%	+0.11	+557	5,232	+0.11	+168	1,514	+0.09	-305	Oral semaglutide dominant
Treatment switching at 8.0%	+0.10	+1,726	17,545	+0.19	+1,333	6,977	+0.07	-2,387	Oral semaglutide dominant
Second treatment intensification at 7.5% to basal-bolus	+0.15	+654	4,316	+0.27	+210	779	+0.07	-1,420	Oral semaglutide dominant

Analysis	Oral semaglutide 14 mg versus empagliflozin 25 mg (PIONEER 2)			Oral semaglutide 14 mg versus sitagliptin 100 mg (PIONEER 3)			Oral semaglutide 14 mg versus liraglutide 1.8 mg (PIONEER 4)		
	Δ discounted QALE (QALYs)	Δ discounted direct costs (GBP)	ICER (GBP per QALY gained)	Δ discounted QALE (QALYs)	Δ discounted direct costs (GBP)	ICER (GBP per QALY gained)	Δ discounted QALE (QALYs)	Δ discounted direct costs (GBP)	ICER (GBP per QALY gained)
NPH basal insulin cost applied	+0.09	+1,111	12,600	+0.20	+1,237	6,334	+0.07	-1,562	Oral semaglutide dominant
Lantus cost applied	+0.09	+1,082	12,267	+0.20	+1,054	5,397	+0.07	-1,418	Oral semaglutide dominant
Semglee cost applied	+0.09	+1,013	11,480	+0.20	+1,044	5,348	+0.07	-1,554	Oral semaglutide dominant
Oral semaglutide price +5%	+0.09	+1,102	12,490	+0.20	+1,093	5,594	+0.07	-1,420	Oral semaglutide dominant
Oral semaglutide price -5%	+0.09	+840	9,522	+0.20	+833	4,266	+0.07	-1,681	Oral semaglutide dominant
Liraglutide 1.2 mg price applied	—	—	—	—	—	—	+0.07	-246	Oral semaglutide dominant
Cost of complications +10%	+0.09	+933	10,583	+0.20	+915	4,687	+0.07	-1,570	Oral semaglutide dominant
Cost of complications -10%	+0.09	+1,011	11,467	+0.20	+1,017	5,206	+0.07	-1,531	Oral semaglutide dominant

Analysis	Oral semaglutide 14 mg versus empagliflozin 25 mg (PIONEER 2)			Oral semaglutide 14 mg versus sitagliptin 100 mg (PIONEER 3)			Oral semaglutide 14 mg versus liraglutide 1.8 mg (PIONEER 4)		
	Δ discounted QALE (QALYs)	Δ discounted direct costs (GBP)	ICER (GBP per QALY gained)	Δ discounted QALE (QALYs)	Δ discounted direct costs (GBP)	ICER (GBP per QALY gained)	Δ discounted QALE (QALYs)	Δ discounted direct costs (GBP)	ICER (GBP per QALY gained)
Alternative costs of stroke applied	+0.09	+968	10,973	+0.20	+946	4,846	+0.07	-1,551	Oral semaglutide dominant
UKPDS 82 risk equations applied	+0.07	+1,026	14,041	+0.14	+806	5,671	+0.03	-1,520	Oral semaglutide dominant
Lee <i>et al.</i> BMI disutility applied	+0.10	+971	10,219	+0.20	+963	4,729	+0.07	-1,551	Oral semaglutide dominant
Diminishing hypoglycaemia disutility model	+0.09	+971	10,920	+0.20	+963	4,922	+0.07	-1,551	Oral semaglutide dominant
Currie <i>et al.</i> hypoglycaemia disutilities	+0.08	+971	12,195	+0.18	+963	5,409	+0.07	-1,551	Oral semaglutide dominant
26-week treatment effects applied	+0.07	+1,079	15,413	+0.15	+872	5,874	+0.08	-1,108	Oral semaglutide dominant
Treatment policy estimand	+0.06	+722	12,274	+0.12	+584	4,704	+0.05	-1,356	Oral semaglutide dominant

Δ , difference in; BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference; GBP, pounds sterling; HbA1c, glycated haemoglobin; ICER, incremental cost-effectiveness ratio; NPH, neutral protamine Hagedorn; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life year; UKPDS, United Kingdom Prospective Diabetes Study.

