Early use of oral semaglutide in the UK: A cost-effectiveness analysis versus continuing metformin and SGLT-2 inhibitor therapy

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Aim

- The aim of the present analysis was to evaluate the long-term cost-effectiveness of immediate oral semaglutide treatment versus continuing metformin plus sodium-glucose cotransporter-2 (SGLT-2) inhibitor therapy in the UK.

Introduction

- Diabetes affects more than 4.9 million people in the UK, with type 2 diabetes accounting for around 90% of cases, and more than GBP 19 billion spent on treating the disease and its complications in 2021.[1,2]
- Guidelines published by the National Institute for Health and Care Excellence (NICE) in the UK aim to control glycated haemoglobin (HbA1c) and other risk factors to reduce the incidence of costly long-term diabetes-related complications, and recommend metformin as a first-line pharmacologic therapy followed by addition of other oral agents as second- and third-line therapies.
- A number of people with type 2 diabetes experience clinical inertia, remaining in poor glycaemic control on oral antidiabetic medications such as metformin and SGLT-2 inhibitors rather than treatment-intensifying with a glucagon-like peptide-1 (GLP-1) receptor agonist, despite an efficacious, orally administered option, oral semaglutide, being available.
- Oral semaglutide 14 mg has demonstrated improvements in HbA1c and body mass index (BMI) versus continuation of metformin and an SGLT-2 inhibitor in a sub-group of the PIONEER 4 clinical trial, data that could translate to improved clinical outcomes over the long term.

Methods

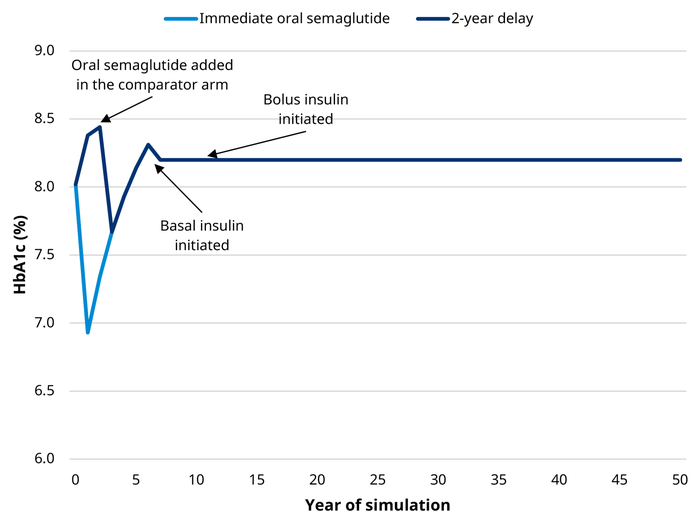
- Clinical and cost outcomes were projected over patients' lifetimes using the IQVIA CORE Diabetes Model (v9.0), symmetrically discounted at 3.5% annually.
- Baseline cohort characteristics and treatment effects were taken from the oral semaglutide and placebo arms of the patient subgroup receiving metformin plus an SGLT-2 inhibitor in PIONEER 4 (Table 1).
- Modelled patients received oral semaglutide immediately or after a 2-year delay to reflect clinical inertia, after which physiological parameters were brought to the values observed in the immediate therapy arm.[3]
- HbA1c followed the UKPDS 68 progression equation, with patients assumed to receive oral semaglutide until HbA1c exceeded 8.2% (based on data from The Health Improvement Network), after which patients treatment-intensified with the addition of basal insulin, with HbA1c brought to and held at 8.2% for the remainder of the analysis (Figure 1).[4]
- After 4 years of oral semaglutide plus basal insulin therapy, patients discontinued oral semaglutide and intensifed to basal-bolus insulin therapy, which they received for the remainder of their lifetimes.[5]
- BMI remained constant following application of first-year treatment effects, reverted to baseline on initiation of basal insulin, and increased on initiation of bolus insulin based on the 'insulin-experienced' multivariate prediction equations published by Willis *et al.*[6]
- Costs were expressed in 2021 pounds sterling (GBP) and accounted from a healthcare payer perspective in the UK.

Table 1: Treatment effects from the PIONEER 4 sub-group receiving metformin plus an SGLT-2 inhibitor

Parameter	Immediate oral semaglutide 14 mg	Continuing metformin plus an SGLT-2 inhibitor (placebo)
HbA1c, %	–1.1 (0.1)*	0.4 (0.2)
SBP, mmHg	–2.4 (1.3)	1.7 (1.8)
Total cholesterol, mg/dL	–2.0 (4.4)	4.1 (6.9)
HDL cholesterol, mg/dL	0.8 (0.9)	–0.6 (1.4)
BMI, kg/m^2	–1.8 (0.2)*	–0.3 (0.3)
Non-severe hypoglycaemia, events per 100 patient years	1.4	2.7
Severe hypoglycaemia, events per 100 patient years	0.0	0.0

BMI, body mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; SBP, systolic blood pressure. *Statistically significant at a 95% confidence level. Values are means (standard errors).

Figure 1: HbA1c progression and treatment intensification in the base case analysis



HbA1c, glycated haemoglobin.

Results

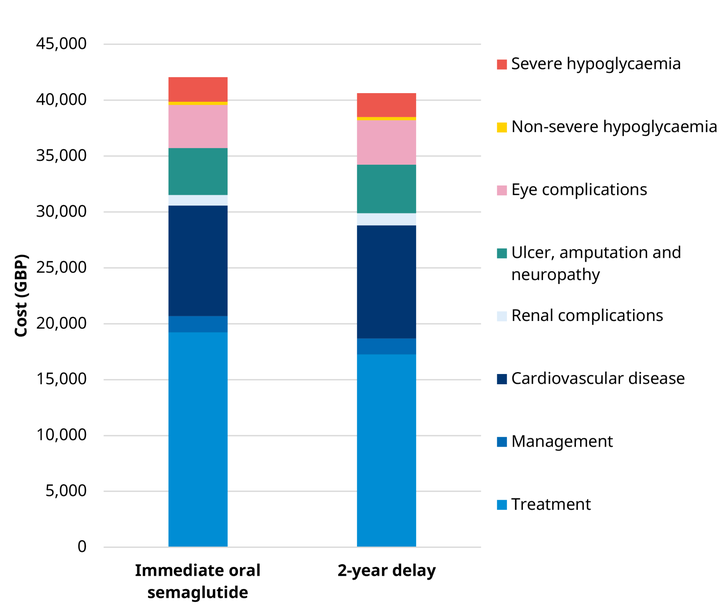
- Long-term projections indicated that immediate oral semaglutide therapy was associated with improvements in life expectancy of 0.17 years, and quality-adjusted life expectancy of 0.15 quality-adjusted life years (QALYs), versus a 2-year delay.
- Benefits were due to a reduced incidence and delayed time to onset of diabetes-related complications with immediate oral semaglutide.
- Direct costs were estimated to be GBP 1,423 higher with immediate oral semaglutide versus a 2-year delay, with higher costs due to an extra 2 years of oral semaglutide treatment in the immediate use arm compared with the 2-year delay arm (Figure 2).
- However, higher treatment costs were partially offset by cost savings from avoidance of diabetes-related complications with immediate oral semaglutide use, most notably avoided cardiovascular complications (mean cost savings of GBP 258 per patient).
- With improved clinical outcomes and increased costs, immediate oral semaglutide therapy was associated with an incremental cost-effectiveness ratio of GBP 9,404 per QALY gained versus continuing metformin plus an SGLT-2 inhibitor for a further 2 years for the treatment of type 2 diabetes in the UK.

Table 2: Base case analysis results

Health outcomes	Immediate oral semaglutide	2-year delay	Difference
Discounted life expectancy, years	13.61 (0.19)	13.43 (0.18)	+0.17
Discounted quality-adjusted life expectancy, QALYs	8.29 (0.11)	8.14 (0.11)	+0.15
Discounted direct costs, GBP	42,064 (848)	40,641 (923)	+1,423
ICER	GBP 9,404 per QALY gained		

GBP, 2021 pounds sterling; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. Values are means (standard deviations).

Figure 2: Direct costs over patients' lifetimes



GBP, 2021 pounds sterling.

Figure 3: Cost-effectiveness scatterplot from the PSA

GBP, 2021 pounds sterling; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

- Probabilistic sensitivity analysis (PSA) showed showed similar mean results to the base case, but increased measures of variance around the mean outcomes (Figure 3).
- Immediate oral semaglutide treatment was associated with mean improvements in quality-adjusted life expectancy of 0.15 QALYs versus continuing metformin plus an SGLT-2 inhibitor for 2 years, with direct costs estimated to be GBP 1,469 higher.
- Immediate oral semaglutide therapy was therefore associated with an ICER of GBP 10,076 per QALY gained in the PSA.
- Based on this analysis, and assuming a willingness-to-pay threshold of GBP 20,000 per QALY gained, the probability of immediate oral semaglutide therapy being cost-effective versus a 2-year delay was 68.5% (Figure 3).

Discussion

- The present study aimed to evaluate a novel research question for the cost-effectiveness of diabetes interventions, specifically whether immediate oral semaglutide initiation could improve health outcomes for people with type 2 diabetes while providing value for money for the National Health Service in the UK.
- Based on a willingness-to-pay threshold of GBP 20,000 per QALY gained, long-term projections indicated that immediate oral semaglutide is likely to be cost-effective versus continuing metformin plus an SGLT-2 inhibitor for a further 2 years and remaining in poor glycaemic control.
- Projected clinical benefits with immediate oral semaglutide were due to greater short-term improvements in HbA1c and BMI translating to a reduced cumulative incidence and delayed time to onset of diabetes-related complications over the long term.
- These findings should help to drive policy recommendations by NICE, and help guide treatment decisions made by physicians for people with type 2 diabetes in the UK.
- There is growing clinical interest in modelling more realistic treatment algorithms for type 2 diabetes, and use of this approach required novel modification of key modelling, which could be seen as a limitation.
- However, all assumptions were informed by published data in lieu of long-term studies evaluating changes in surrogate physiological parameters (or even direct health outcome measures) with modern diabetes interventions, which are currently lacking.[3,4,5,6]
- These aspects of the analysis were also chosen to adequately represent real-world clinical practice whilst preserving modelling fairness, with differences in clinical and cost parameters only maintained while there was a difference in received treatments.
- Future clinical (and subsequent cost-effectiveness) studies should focus on elucidating the effects of initiating oral semaglutide versus continuing dipeptidyl peptidase-4 (DPP-4) inhibitor therapy, as these data are currently lacking.

Conclusion

- Based on clinical trial data, immediate treatment with oral semaglutide is likely to represent a cost-effective treatment option for people with type 2 diabetes with inadequate glycaemic control on metformin plus an SGLT-2 inhibitor in the UK, compared with remaining on their current therapies and delaying oral semaglutide initiation for 2 years.

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Presented at ISPOR Europe 2022, 6–9 November, Vienna, Austria.

References:

(**1**) Diabetes UK. Diabetes statistics. 2022 [online]; (**2**) IDF. Diabetes Atlas – 10th Edition. 2021 [online]; (**3**) Boye *et al.* Drugs R D 2019;19(2):213–25; (**4**) NICE. NG28. Appendix F: Full Health Economics Report. 2015 [online]; (**5**) Khunti *et al.* Diabetes Obes Metab 2016;18(4):401–9; (**6**) Willis *et al.* Value Health 2017;20:357–71