Once-Weekly Subcutaneous Semaglutide 2.4 mg Injection is Cost-Effective for Weight Management in the United Kingdom

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ABSTRACT

Objectives: The objective of the current pre-liminary study was to present the cost-effectiveness analyses submitted to the National Institute for Health and Care Excellence (NICE) (TA10765) that deemed semaglutide 2.4 mg subcutaneous (s.c.) injection a cost-effective option for weight management in the United Kingdom (UK) alongside diet and exercise (D&E).
Methods: The study was conducted from the National Health Service (NHS) and Personal Social Services perspective and based on the NICE reference case. The clinical safety and efficacy of semaglutide 2.4 mg s.c. injection were obtained from the Semaglutide Treatment Effect in People with Obesity (STEP) 1 trial. The previously published and validated Core Obesity Model was used to project lifetime occurrence of obesity complications, their costs and quality of life consequences over 40 years. The base case cohort had a mean starting age of 48 years and BMI of 38.7 kg/m². The confidential NHS price for semaglutide 2.4 mg s.c. injection was provided by Novo Nordisk. The incremental cost-effectiveness ratios (ICERs) were expressed as cost/quality-adjusted life-year (QALY). Uncertainty was assessed through sensitivity analyses, including a scenario analysis using clinical data from the STEP 2 trial and a previously published and validated Core Diabetes Model to investigate a cohort with type 2 diabetes at baseline.
Results: Semaglutide 2.4 mg s.c. injection showed higher total costs and health benefits compared with D&E, with an ICER of £14,827/QALY gained. The probabilistic sensitivity analysis showed that semaglutide 2.4 mg s.c. injection was cost-effective in 90% of cases at a willingness-to-pay threshold of £20,000/QALY. The ICER from the scenario analysis for the diabetic population was £16,613/QALY gained, using the Core Diabetes Model.
Conclusion: Semaglutide 2.4 mg s.c. injection is a cost-effective therapy compared to D&E alone for patients with obesity and weight-

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related comorbidities in the UK. Sensitivity and scenario analyses confirm the robustness of the analyses.

Keywords: Cost-effectiveness analysis; Core obesity model; Obesity; Semaglutide 2.4 mg; United Kingdom

Two-year treatment with semaglutide 2.4 mg s.c. injection as adjunct to D&E is a cost-effective therapy in the UK setting with low associated uncertainty for patients with obesity and weight-related comorbidities.

Key Summary Points

Obesity is a chronic health condition with an increased risk of morbidity and mortality and its treatment is crucial to reduce the immense burden on patients as well as the healthcare system in the United Kingdom (UK).

Semaglutide 2.4 mg subcutaneous (s.c.) injection (Wegovy®, Novo Nordisk) is indicated in the UK as a weight management therapy in conjunction with a reduced-calorie diet and increased physical activity among adults with obesity or overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and having ≥ 1 weight-related comorbidity.

The current preliminary study describes the cost-effectiveness analyses (CEAs) of semaglutide 2.4 mg s.c. injection as adjunct to diet and exercise (D&E) compared with D&E alone, that were presented to the National Institute for Health and Care Excellence for a population with a BMI ≥ 30 kg/m^2 and ≥ 1 weight-related comorbidity.

The base case CEA was conducted using a UK adaptation of the Core Obesity Model, and clinical, safety and efficacy data were used from the STEP 1 study.

When compared with D&E alone, semaglutide 2.4 mg s.c. injection showed higher total costs and health benefits with an incremental cost-effectiveness ratio of £14,827/quality-adjusted life-year (QALY) gained, and a probabilistic sensitivity analysis indicating its cost-effectiveness in 90% of cases at a willingness-to-pay (WTP) threshold of £20,000 per QALY.

INTRODUCTION

Obesity is a chronic health condition defined by a body mass index (BMI) of ≥ 30 kg/m^2 for White, Hispanic, and Black individuals and > 25 kg/m^2 for Asians [1]. It is associated with an increased risk of morbidity and mortality due to the accompanying comorbidities, such as type 2 diabetes (T2D), obstructive sleep apnoea (OSA), cardiovascular disease (CVD), osteoarthritis, and some cancers [2]. In England, about 27% of men and 29% of women were reported to be living with obesity in 2019 [3]. By 2035, an estimated 37% of adult men and women in the United Kingdom (UK) will have obesity (BMI ≥ 30 kg/m^2) [4]. In the UK, the overall cost of obesity to the wider society is estimated to be £27 billion, and is estimated to increase to approximately £50 billion in 2050 if obesity rates continue to rise [5]. Thus, obesity treatment is crucial to reduce the burden on patients as well as the healthcare system in the UK.

The human glucagon-like peptide-1 (GLP-1) analogue, semaglutide [2.4 mg subcutaneous (s.c.) injection, Wegovy®, Novo Nordisk), is indicated in the UK for weight management as an adjunct to a reduced-calorie diet and increased physical activity among adults with obesity (≥ 30 kg/m^2) or overweight (≥ 27 kg/m^2 to < 30 kg/m^2) with at least one weight-related comorbidity [6]. Its approval was based on four of the randomised, double-blind, placebo-controlled phase III trials from the Semaglutide Treatment Effect in People with Obesity (STEP) programme conducted among approximately 5000 patients [7–10].

The objective of the current preliminary study was to present the cost-effectiveness analyses submitted to the National Institute for

Health and Care Excellence (NICE) (TA10765) that deemed semaglutide 2.4 mg s.c. injection a cost-effective option for weight management in the UK alongside diet and exercise (D&E) [11].

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

METHODS

Perspective

The analysis was conducted from the perspective of the National Health Service (NHS) and Personal Social Services (PSS), following the NICE reference case [12].

Population

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The target population were adults with a BMI $\geq$ 30 kg/m^2 having $\geq$ 1 weight-related comorbidity. The baseline characteristics for the base case population were sourced from a post hoc subgroup analysis of the STEP 1 trial [7]. The base case population starting mean age was 48 years, and had an initial BMI of 38.7 kg/m^2 which is reflective of the UK NHS specialist weight management services (SWMS) [11]. A scenario analysis using the STEP 2 trial was conducted to investigate a cohort with BMI $\geq$ 30 kg/m^2 and T2D at baseline [8]. Detailed baseline characteristics for both scenarios are reported in Table S1. The comparator of interest for the target population was D&E, which is the standard management in NHS SWMS [13].

Clinical Efficacy and Safety

The clinical data were provided by the STEP 1 trial, which showed the benefit of treatment with semaglutide 2.4 mg s.c. injection through outcomes, including changes in BMI and glycaemic status [7]. The full analysis set (all

patients) for the STEP 1 trial, from the trial product estimand, a modified intention to treat (mITT) population, were used to reflect the efficacy of the target population who stayed on treatment [7]. The Medicines and Healthcare products Regulatory Agency licence states, "if patients have been unable to lose at least 5% of their initial body weight after 6 months on treatment, a decision is required on whether to continue treatment". Therefore, a stopping rule was applied to 'non-responders' of semaglutide 2.4 mg s.c. injection treatment. Consequently, semaglutide 2.4 mg s.c. injection responder efficacy was utilised from STEP 1 for patients continuing treatment. The scenario analysis for the diabetic population used clinical data from the STEP 2 trial [8]. Detailed treatment efficacy inputs for both scenarios are reported in Table S2. Safety input clinical data were also sourced from STEP 1 [7]. This included severe and non-severe hypoglycaemic adverse events (AEs), as these were most relevant for clinical practice, and severe gastrointestinal AEs, as these were the most common AEs with semaglutide 2.4 mg s.c. injection (Table S3).

Modelling Approach

The treatment effects on surrogate outcomes, including percentage weight change, systolic blood pressure (SBP), total cholesterol, high-density lipoprotein (HDL) cholesterol as well as reversal of non-diabetic hyperglycaemia to normal glucose tolerance, predicted the incidence of diseases and events. This was modelled over a time horizon of 40 years using an adaptation of the Core Obesity Model (COM) for the UK [14–16] (Fig. 1). This adaptation included restricting the model health states to those with strong evidence of association with obesity as reported by the WHO consultation on obesity [17]. The features of the model are described in Table 1. The COM focuses on the value of weight loss rather than the clinical pathways of T2D patients. Consequently, the model may underestimate in the treatment benefit from glycaemic control. Therefore, a scenario analysis was also conducted using the Core Diabetes Model (CDM) for the diabetic population to test
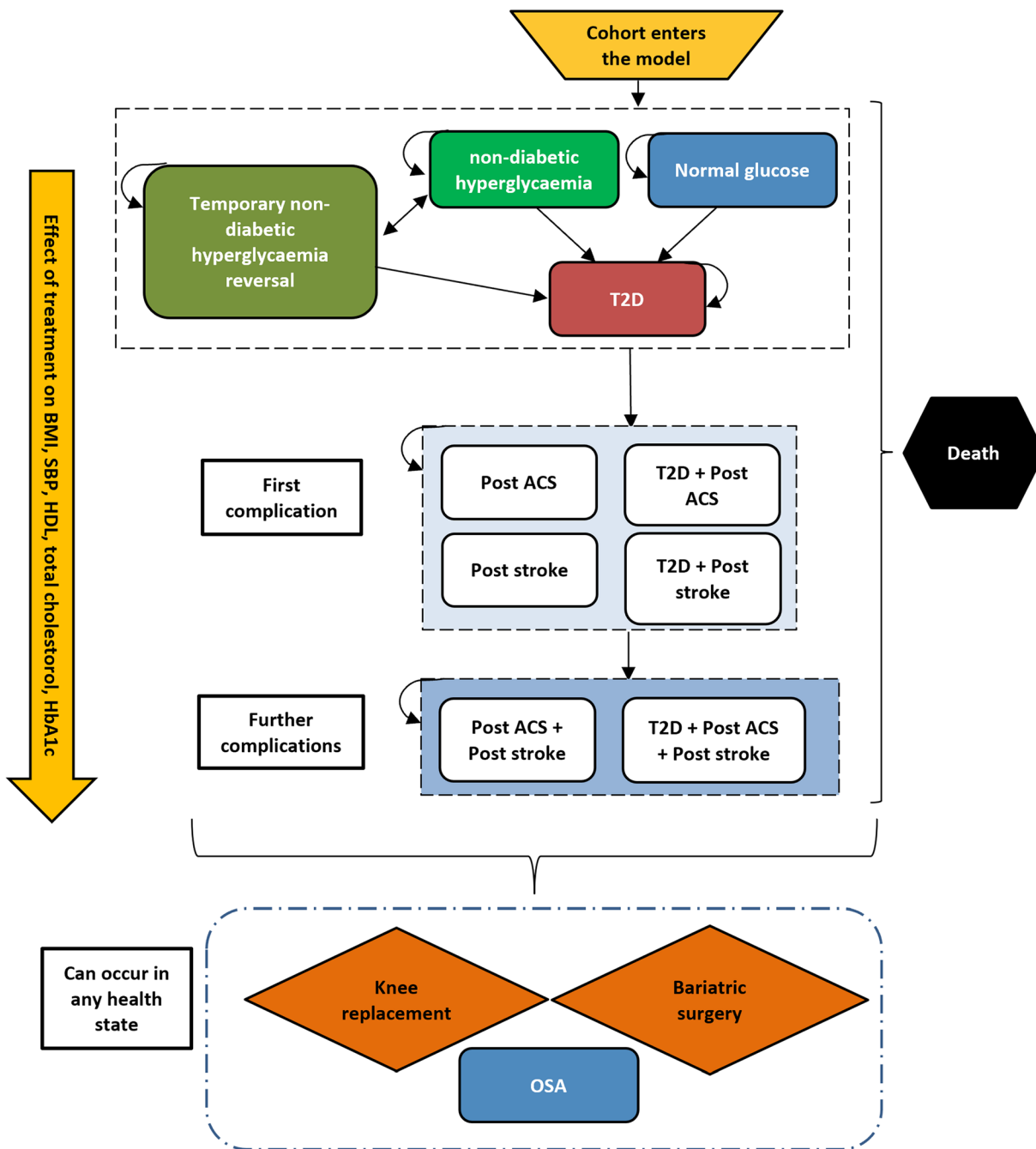
Fig. 1 Core obesity model UK adaptation structure; reproduced/adapted from Lopes et al. [15] with permission from Wiley. *ACS* acute coronary syndrome, *BMI* body mass index, *HbA₁c* haemoglobin A₁c, *HDL* high-density lipoprotein, *SBP* systolic blood pressure, *T2D* type 2 diabetes, *OSA* obstructive sleep apnoea

this hypothesis [18]. Inputs for the CDM scenario analysis are provided in Tables S4–S9.

Transition Probabilities and Risk Equations

The COM was adapted to the UK perspective by utilising the available risk equations relevant to this population. These adaptations are

Table 1 Core obesity model UK adaptations and settings

Model aspect	Model setting
Cycle length	3-month cycles for the first year to account for treatment discontinuation and then annual cycles were used thereafter
Treatment duration	Treatment with semaglutide 2.4 mg and D&E was applied for a maximum of 2 years
Semaglutide 2.4 mg treatment efficacy	Semaglutide 2.4 mg efficacy from the mITT population was used until cycle 2 and responder efficacy is applied from cycle 3 until end of treatment in cycle 5 (year 2)
D&E treatment efficacy	D&E efficacy from the mITT population was used until end of treatment in cycle 5 (year 2)
Waning of treatment effect following treatment cessation	The effects on the surrogate outcomes and glycaemic status are assumed to diminish linearly within 3 years (catch-up period) at rates of 33%, 67% and 100%, respectively [23]
Natural progression of disease following catch up period	BMI was assumed to increase naturally at a rate of 0.1447 kg/m^2 (males) and 0.1747 kg/m^2 (females) per year, while SBP and lipids were assumed to remain at their baseline values [23]
Transition probabilities and risk equations	Patients with NGT or prediabetes:
	Incidence of first cardiovascular event = QRisk3 [26]
	Incidence of T2D = QDiabetes [27]
	Patients with T2D:
	Incidence of first and recurrent cardiovascular events = UKPDS 82 risk model [28]
Mortality	Mortality was applied in the following ways:
	General population mortality, defined as age- and gender-specific all-cause mortality [29] was adjusted to exclude mortality attributable to causes accounted for in the model, using mortality statistics, and by underlying cause of death [30]
	Disease-specific mortality was applied to obesity complications (T2D, post-acute coronary syndrome and post-stroke)
	Event fatality was also applied to CV events, knee replacement surgery and bariatric surgery
	Mortality was adjusted with a BMI-specific hazard ratio to account for the increased mortality at higher levels of BMI [16]
Discount rate	3.5% per year for costs and outcomes

BMI body mass index, *D&E* diet and exercise, *mITT* modified intention-to-treat, *NGT* normal glucose tolerance, *T2D* type 2 diabetes, *UKPDS* United Kingdom Prospective Diabetes Study

described in Table 1, while detailed information on the other risk equations and transition probabilities used in the model have been provided in earlier publications [14–16].

Mortality
Mortality was applied in the model as described in Table 1. The mortality data were sourced from the UK where available and are shown in Table S10.

Costs
Costing perspectives from the NHS and PSS were considered in the model. Obesity monitoring costs, health state costs, bariatric surgery costs, acute event costs, and AE treatment costs were all factored into the model. These were sourced from the literature, and NHS reference costs have been provided as supplementary data (Table S11). The confidential price of semaglutide 2.4 mg s.c. injection for NHS England was provided by Novo Nordisk. All costs have been reported in 2021 British pounds sterling (GBP), inflated, if necessary, using the NHS cost inflation index [19].

Utilities
The COM applies BMI-related disutilities based on the paper of Soltoft et al. ,which relates change in utility based on the starting BMI (Table S12) [20]. Baseline utility values were adjusted for quality-of-life (QoL) decrements associated with weight-related comorbidities. In addition to acute decrements in baseline utility, long-term absolute QoL decrements associated with each chronic complication were considered in the model (Table S13). Such QoL decrements are derived from the literature, and are subtracted from age-, gender-, and BMI-dependent baseline utility values at each cycle to derive health state utility values.

Analysis

A cost-effectiveness analysis (CEA) was conducted on the target population using the STEP 1 trial. Scenario and sensitivity analyses were performed around key assumptions and inputs.

The scenario analyses included using the STEP 2 trial and the CDM for the diabetic population.

RESULTS

The base-case analysis using the STEP 1 trial showed that treatment with semaglutide 2.4 mg s.c. injection was associated with higher total costs and health benefits compared to D&E, with an incremental cost-effectiveness ratio (ICER) of £14,827/QALY gained. The probabilistic sensitivity analysis showed that semaglutide 2.4 mg s.c. injection was cost-effective in 90% of cases at a willingness-to-pay (WTP) threshold of £20,000/QALY (Fig. S1). The scenario analysis for the diabetic population provided an ICER of £21,277/QALY gained, using the COM, and £16,613/QALY gained using the CDM. The extensive scenario analyses performed, indicated low uncertainty with results (Table S14).

DISCUSSION

The results indicate that treatment with semaglutide 2.4 mg s.c. injection is cost-effective in the UK setting with low associated uncertainty. Semaglutide 2.4 mg s.c. injection is provided in SWMS where the patients either have a BMI of ≥ 35 kg/m^2 or a BMI between 30–34.9 kg/m^2 with ≥ 1 comorbidity, hence cost-effectiveness analyses were restricted to the target population of a BMI ≥ 30 kg/m^2 with ≥ 1 weight-related comorbidity [11].

Patients who have both obesity and T2D are also referred to SWMS. The STEP 2 trial showed clinical benefit can be achieved for this population. However, the scenario results show that the COM underestimated the cost-effectiveness in the diabetic population when compared to the CDM. Since the focus of the COM is weight management and BMI, it does not reflect the glycaemic heterogeneity of patients within STEP 2 data on the progressive nature of T2D, or provide granularity on the cost of glucose-lowering medication, and did not model individual health states for microvascular complications. The CDM, which addresses these shortcomings

and focuses on the clinical pathway of T2D patients, showed that semaglutide 2.4 mg s.c. injection is likely to be cost-effective. During the NICE appraisal (TA10765), the NICE committee concluded that, while there was some uncertainty, once-weekly semaglutide 2.4 mg s.c. injection is a cost-effective treatment option for patients with obesity and T2D in the UK.

In TA10765, the Evidence Review Group (ERG) base case analysis was cost-effective, with an ICER of £16,337/QALY gained. The ERG preferred to assume that patients with non-diabetic hyperglycaemia do not automatically develop T2D after a CVD event. This assumption had a minimal effect on the ICER, and the validation in Lopes et al. (2020) showed that the COM does not overestimate the incidence of T2D [14]. Other ERG assumptions included a natural weight increase of 0.30 kg per year compared to 0.46 kg, weight no longer increased after age 66 compared to age 68, natural weight decreased by 0.30 kg after age 66 compared to remaining constant, and the annual cost of sleep apnoea was £274 compared to £1081. The NICE committee found that either assumption was reasonable, and that, individually, none had a major effect on the ICER.

This analysis presented D&E as a comparator against semaglutide 2.4 mg s.c. injection. However, NICE mentions, in addition to D&E, liraglutide 3.0 mg (for patients with BMI ≥ 35 mg/kg^2 with non-diabetic hyperglycaemia and high CVD risk) as a suitable comparator against semaglutide 2.4 mg s.c. injection [11]. For simplicity, liraglutide 3.0 mg was not presented as a comparator, since the analyses from TA10765 showed that, in its reimbursed population, treatment with semaglutide 2.4 mg s.c. injection projected lower costs and higher effectiveness when compared with liraglutide 3.0 mg. The improved efficacy of semaglutide 2.4 mg s.c. injection over liraglutide 3.0 mg was also confirmed in the STEP 8 trial [21] which directly compared both treatments. Orlistat was not considered a suitable comparator, as it is no longer widely used in clinical practice due to undesirable side effects. Therefore, the inclusion of D&E as the only comparator in this study was considered appropriate.

NICE decided that semaglutide 2.4 mg s.c. injection should be used for a maximum of 2 years. The 2-year efficacy in the model was informed by the week 68 results of the STEP 1 trial. This assumption was confirmed by the STEP 5 trial (long-term weight management), which showed that the efficacy of semaglutide 2.4 mg s.c. injection was maintained from 68 weeks to 2 years [22]. However, we also note that limiting treatment to 2 years may not be ideal for treating a long-term chronic condition. Currently, in the absence of any published clinical data, it is unclear whether patients would receive a single course of pharmacotherapy with semaglutide 2.4 mg s.c. injection, continue indefinitely or if (and when) it could be repeated. The assumptions for weight regain and reversal of glycaemic status following treatment cessation were considered uncertain in TA10765. The base case used a catch-up rate of 3 years, based on Ara et al., but a more conservative scenario of 2 years was within a cost-effective range [23]. At the time of the appraisal there were no additional data to inform the consequences of discontinuing treatment; however, the extension phase of the STEP 1 trial has subsequently reported the results of discontinuing treatment, which warrant future research [24].

Clinical efficacy data for this analysis were sourced from large, phase III, randomised, double-blind, placebo-controlled studies involving 1961 patients in STEP 1 and 1210 patients in STEP 2. The scenario analyses conducted in TA10765 showed the cost-effectiveness conclusions were robust [11]. A recently published analysis conducted from a US third-party payer perspective also supported the results [25].

Finally, we note a few limitations regarding modelling. Although obesity is associated with many health issues, it was not possible to include all of them in the model. Furthermore, weight-related comorbidities defined in STEP 1, such as kidney disease, gout, and asthma, have not been captured in the model. Weight loss may have other benefits that have not been captured, such as a decreased risk of AEs

associated with respiratory infections, a reduction in social isolation and improvements in fertility. To this end, the analyses conducted here may provide a conservative estimate of the relevant costs and benefits of weight-loss management in terms of its impact on the reversal and/or delay of weight-related comorbidities. To reduce the number of health states and to minimise model complexity, only the most economically significant comorbidities have been included.

CONCLUSIONS

The current CEA showed that a once-weekly s.c. injection of semaglutide 2.4 mg is a cost-effective option for obesity management in the UK versus D&E alone at a WTP of £20,000 per QALY gained. Sensitivity and scenario analyses confirm the robustness of the analyses.

ACKNOWLEDGEMENTS

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