NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Semaglutide for managing overweight and obesity [ID3850]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Semaglutide for managing overweight and obesity [ID3850]

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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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Document B

Company evidence submission

20 July 2021

File name	Version	Contains confidential information	Date
ID3850_Semaglutide 2.4mg NICE Document B_Final_redacted	1.0	Yes	20 July 2021

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List of abbreviations

ACS	Acute coronary syndrome
ADA	American Diabetes Association
AE	Adverse event
BMI	Body mass index
BOMSS	British Obesity & Metabolic Surgery Society
CEAC	Cost-effectiveness acceptability curve
CV	Cardiovascular
CVD	Cardiovascular disease
DEXA	Dual-energy x-ray absorptiometry
DMC	Data monitoring committee
EAC	Event adjudication committee
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ETD	Estimated treatment difference
FAS	Full analysis set
FDA	US Food and Drug Administration
FPG	Fasting plasma glucose
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
GPRD	General Practice Research Datalink
HbA1c	Haemoglobin A1c
HDL	High density lipoprotein
HRQoL	Health-related quality of life
IBT	Intensive behavioural therapy
ICER	Incremental cost-effectiveness ratio
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IHD	Ischaemic heart disease
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trials Version
LYG	Life years gained
MCS	Mental component summary
MDT	Multidisciplinary team
MI	Myocardial infarction
NASH	Non-alcoholic steatohepatitis
NAFLD	Non-alcoholic fatty liver disease
NGT	Normal glucose tolerance
NHS	National Health Service
OGTT	2-hour post-challenge
OSA	Obstructive sleep apnoea
PCS	Physical component summary
PYE	Patient years of exposure

PYO	Patient years of observation
QALY	Quality-adjusted life year
SBP	Systolic blood pressure
SD	Standard deviation
SF-36	Short Form-36
SLR	Systematic literature review
SmPC	Summary of product characteristics
SWMS	Specialist weight management services
T2D	Type 2 diabetes
TEAE	Treatment-emergent adverse event
UK	United Kingdom
WAMC	Weight assessment and management clinic
WHO	World Health Organization

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

Table 1 presents the decision problem for the submission. The population defined in the final scope is consistent with the anticipated marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) for semaglutide 2.4 mg ([redacted]).

Semaglutide 2.4 mg is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management (weight loss and weight maintenance) in adult patients with an initial body mass index (BMI) of:

- ≥ 30 kg/m^2 (obesity), or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity

Note, that as part of the MHRA licence, a stopping rule may be applied to 'non-responders' of semaglutide 2.4 mg; however, discussions with the Medicines and Healthcare products Regulatory Agency (MHRA) are still ongoing. The rule states that if patients have not lost at least 5% of their initial body weight after 6 months on the 2.4 mg/day maintenance dose of semaglutide 2.4 mg, a decision is required on whether to continue treatment, taking into account the benefit-to-risk profile in the individual patient.[1]

This submission focuses on adult patients with a BMI of ≥ 30 mg/kg^2 in the presence of at least one weight-related comorbidity.

As per NICE quality standards, QS127, these patients are eligible for treatment within specialist weight management services (SWMS; defined as a weight management service led by a specialist multidisciplinary team e.g. Tier 3 or integrated Tier 3 and Tier 4 services where pharmacotherapy is provided [see Section B.1.3.4.1 for tier definitions]) in the UK.[2] This population is narrower than the technology's anticipated marketing authorisation because patients with obesity who have comorbidities are anticipated to benefit most from pharmacological treatment

within SWMS in National Health Service (NHS) England clinical practice. The comorbidities recorded at baseline in the key clinical trial for this submission (STEP 1) were considered by clinicians to be highly representative of the weight-related comorbidities typically seen in SWMS in UK clinical practice. This submission will also address the patient population eligible to receive liraglutide 3.0 mg (Saxenda®), which is available within SWMS for patients with a BMI ≥ 35 mg/kg^2 with non-diabetic hyperglycaemia and high cardiovascular (CV) risk.

Obesity is a serious chronic disease associated with significant morbidity and mortality.[3] Obesity is also associated with a substantial number of weight-related comorbidities that have significant detrimental impact on patients and healthcare systems (see Section B.1.3.3).[4-15] Therefore, treating obesity is paramount to reducing the burden on patients and the healthcare system.

Indeed, studies have shown that as little as 5% weight loss in patients with obesity can lead to significant improvements in patient health.[16] Furthermore, weight loss of ≥ 10%, and in particular, weight loss of 15%, is associated with substantial benefits to patients with obesity who have comorbidities (see Section B.1.3.3.1). Weight loss of 10–15% can reduce in the burden of existing comorbidities, reduce the risk of developing further weight-related comorbidities and improve patient quality of life.[16-22] This view is supported by the clinical community, who have also advised that weight loss of 10–15% is considered highly significant and seldom achieved with standard care, suggesting that there are a substantial number of comorbidities that can be meaningfully alleviated with weight loss of this magnitude.[23]

Despite the benefits of treating obesity with pharmacotherapy, there are currently very few efficacious pharmacological treatment options for patients with obesity who are seeking SWMS. Orlistat was the mainstay of treatment but is rarely used today and is associated with undesirable side effects, insufficient weight loss and poor adherence (discussed further in Section B.1.3.4.2).[24-26] More recently, NICE approved liraglutide 3.0 mg for use within SWMS for patients with a BMI ≥ 35 mg/kg^2 with non-diabetic hyperglycaemia and high CV risk (TA664).[27] However, there remains a substantial unmet clinical need for patients with obesity and comorbidities who can access SWMS but do not meet the criteria for liraglutide 3.0 mg, meaning these patients may be deprived of benefitting from clinically meaningful weight loss.

This view is shared by the clinical community, who have expressed a desire to use pharmacotherapy to treat a broader population of patients in SWMS, rather than just those eligible for liraglutide 3.0 mg.[23]

The need for additional treatment options for obesity is also apparent when considering the increasing prevalence of the disease[28], which will result in more patients requiring SWMS. If additional pharmacotherapy treatment options are not made available within SWMS, an increasing number of patients will be at risk of developing additional weight-related comorbidities or dying from obesity-related complications such as COVID-19.[22, 29, 30] Furthermore, there is a substantial burden on the healthcare system due to increasing numbers of obesity-related hospitalisations and comorbidities that require treatment[31, 32]; this burden could be alleviated with the introduction of new, efficacious therapies.

Semaglutide 2.4 mg has the potential to address this unmet clinical need by providing a treatment option for those patients with obesity and comorbidities who are referred to a SWMS. The weight loss observed with semaglutide 2.4 mg (~15% weight loss observed across the entire STEP trial programme) is a significant advancement for obesity treatment with more than double the weight loss observed over existing pharmacotherapy options (patients typically achieve between 5–7% weight loss in SWMS[23]), representing a substantial step change in treatment.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults who have a BMI of: • ≥ 30 kg/m^2 (obese) or • ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity	Adults who have a BMI of ≥ 30 kg/m^2 (obese) in the presence of at least one weight-related comorbidity	Patients with BMI ≥ 30 kg/m^2 in the presence of at least one weight-related comorbidity are anticipated to benefit most from pharmacological treatment within SWMS in NHS England clinical practice. Per the NICE obesity clinical management policy (QS127), patients with a BMI ≥ 30 kg/m^2 for whom Tier 2 interventions have been unsuccessful can access Tier 3 services (see Section B.1.3.4.1 for Tier definitions)[2]; however, there are limited treatment options for these patients and many do not meet the criteria for effective pharmacotherapy (i.e. liraglutide 3.0 mg). This is problematic as patients with obesity and comorbidities can benefit greatly from weight loss of 10–15%. Therefore, there is a clinical unmet need for these patients that could be met with semaglutide 2.4 mg.
Intervention	Semaglutide	Semaglutide 2.4 mg	Semaglutide is approved for use at a dose of 0.25 mg, 0.5 mg and 1 mg (solutions for injection) for the treatment of adults with insufficiently controlled

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			type 2 diabetes mellitus as an adjunct to diet and exercise. Semaglutide 2.4 mg is the specific maintenance dose for obesity treatment.
Comparator(s)	• Standard management without semaglutide (including a reduced calorie diet and increased physical activity) • Liraglutide (for the population for whom liraglutide is recommended in TA664: patients with a BMI ≥ 35 mg/kg^2 with prediabetes and high CV risk) • Orlistat (prescription dose)	• Standard management without semaglutide (including a reduced calorie diet and increased physical activity) • Liraglutide 3.0 mg (for the population for whom liraglutide is recommended in TA664: patients with a BMI ≥ 35 mg/kg^2 with prediabetes and high CV risk)	Orlistat (prescription dose) is not a relevant comparator for semaglutide 2.4 mg. In Section 3.2 of the final appraisal determination for TA494, orlistat was not considered to be widely used by the clinical experts in clinical practice due to undesirable side effects leading to poor adherence and outcomes. These sentiments were again reflected in the recent appraisal of liraglutide for managing overweight and obesity [TA664] and were discussed at length during consultation. Section 3.4 of the final appraisal determination stated that many people decide not to have orlistat or stop taking it because of undesirable, and socially unacceptable side effects. These issues are reflected by the decreasing use of orlistat over the past decade, with a long-term downward trend on the prescription of orlistat in the UK.[26] For these reasons, and in line with the clear determination made in TA494 and TA664, orlistat should not be considered a relevant comparator.
Outcomes	• BMI	• BMI	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Weight loss • Waist circumference • Incidence of type 2 diabetes • Glycaemic status • Cardiovascular events • Mortality • Adverse effects of treatment • Health-related quality of life	• Weight loss • Waist circumference • Incidence of type 2 diabetes • Glycaemic status • Cardiovascular events • Mortality • Adverse effects of treatment • Health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the	Same as NICE scope.	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	intervention will be taken into account.		
Subgroups to be considered	None.	The submission will also address the subset of patients who are eligible to receive treatment with liraglutide 3.0 mg (patients with a BMI ≥ 35 mg/kg^2 with prediabetes and high CV risk) following its approval in TA664.	NA (specified in final scope under comparators)

Key: BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SWMS, specialist weight management services.
Notes: [a], defined as haemoglobin A1c (HbA1c) levels in the range 6.0–6.4%, or fasting plasma glucose (FPG) levels in the range 5.5–6.9 mmol/L; [b], including polycystic ovary syndrome, irregular intermenstrual bleeding, and infertility.

B.1.2. Description of the technology being appraised

Table 2 presents a description of semaglutide 2.4 mg. The draft summary of product characteristics (SmPC) is presented in Appendix C. The European Public Assessment Report (EPAR) is expected to be available in 2022. The publication date of the Public assessment report (PAR) of the MHRA is still to be confirmed.

Table 2: Technology being appraised

UK approved name and brand name	Semaglutide 2.4 mg [redacted])
Mechanism of action	Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological regulator of appetite and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. Semaglutide has direct effects on areas in the brain involved in homeostatic regulation of food intake in the hypothalamus and the brainstem, and direct and indirect effects on areas involved in hedonic regulation of food intake, including the septum, thalamus and amygdala. Semaglutide reduces blood glucose in a glucose dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.
Marketing authorisation/CE mark status	An application for an accelerated assessment procedure was submitted to the MHRA on 5 January 2021 and a decision is expected in September 2021.The application for the marketing authorisation with the EMA was submitted 18 December 2020 and a positive opinion from the Committee for Medicinal Products for Human Use is expected on 22 January 2022.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Semaglutide 2.4 mg is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial BMI of ≥ 30 kg/m^2 (obesity), or a BMI between ≥ 27 mg/kg^2 and < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity.

Method of administration and dosage	Semaglutide 2.4 mg is administered once-weekly via subcutaneous injection at any time of the day, with or without meals. The maintenance dose of semaglutide is 2.4 mg. The maintenance dose is reached by starting with a dose of 0.25 mg and gradually titrating up through the following dosage escalation every four weeks: 0.5 mg, 1.0 mg and 1.7 mg, before reaching the 2.4 mg maintenance dose after 16 weeks.
Additional tests or investigations	No additional tests or investigations are required.
List price and average cost of a course of treatment	<u>Maintenance</u> 2.4mg presentation: £[redacted] per pack. Each pack contains 4 pre-filled pens containing 2.4 mg of semaglutide in 0.75 mL. <u>Titration</u> 1.7mg presentation: £[redacted] per pack (4 prefilled pens) 1.0mg presentation: £73.25 per pack (4 pre-filled pens) 0.5mg presentation: £73.25 per pack (4 pre-filled pens) 0.25mg presentation: £73.25 per pack (4 pre-filled pens) **Average cost of a course of treatment (list price)**: The cost of treatment for a duration of 2 years is £[redacted]
Patient access scheme (if applicable)	The company is in ongoing discussions with NHS England regarding a confidential arrangement for semaglutide 2.4mg.

Key: BMI, body mass index; EMA, European Medicines Agency GLP-1, glucagon-like peptide 1; MHRA, Medicines and Healthcare products Regulatory Agency.
Source: Novo Nordisk (semaglutide SmPC), 2021.
Note: The treatment costs listed above do not include VAT and treatment discontinuation.

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease background

Obesity is a serious chronic disease and is considered one of the greatest long-term health challenges facing the United Kingdom (UK).[3, 30] According to the World Health Organization (WHO), obesity is defined as abnormal or excessive fat accumulation

that may impair health, and is characterised by a BMI of ≥ 30 kg/m^2. Patients with obesity can be further classified into one of the following BMI categories:[33]

- Obesity Class I: BMI of ≥ 30 – < 35 kg/m^2
- Obesity Class II: BMI of ≥ 35 – < 40 kg/m^2
- Obesity Class III: BMI of ≥ 40 kg/m^2

Obesity is a complex and multifactorial disease driven by imbalances in energy intake and expenditure, leading to weight gain.[34] A number of causative mechanisms for obesity have been observed, including appetite dysregulation and abnormal hormone signalling, as well as a range of genetic factors (e.g. genes associated with excess weight gain), psychological factors (e.g. depression and food addiction) and environmental factors (e.g. poor socioeconomic conditions, and certain diseases or medications).[34-38]

Regarding the hormonal mechanism of the disease, a gastrointestinal (GI)-derived hormone known as glucagon-like peptide 1 (GLP-1) integrates in the hypothalamus where it regulates feelings of appetite and satiety.[39] More specifically, GLP-1 is released in response to food intake and regulates blood glucose by enhancing insulin secretion and inhibiting glucagon secretion from the pancreas.[39, 40] Activation of GLP-1 receptors in the brain also regulates appetite by increasing satiety and reducing hunger, a process modulated by several other hormones and gut peptides, including leptin and ghrelin.[41-43] In addition, GLP-1 is known to reduce energy intake in humans.[41, 42, 44]

B.1.3.2 Epidemiology

As of 2019, the majority of adults in England were overweight or obese (68% of men and 60% of women); this included 27% of men and 29% of women who were obese.[45] These numbers reflect a sharp rise in the prevalence of obesity in England over recent decades, increasing from 13% of men and 16% of women in 1993.[45] The prevalence of obesity in England increases with age, from 13% of adults aged between 16 and 24 years, to 36% of those aged 65 to 74 years; although it was lower among adults aged ≥ 75 years (26%).[45] Among all adults, the prevalence of obesity was highest in the North East and West Midlands (34% of adults) and was

lowest in the South East (24%) and London (23%), suggesting a socioeconomic trend (further discussed in B.1.4).

By 2035, an estimated 37% of adult men and women in the UK will be obese (BMI ≥30)[28], highlighting the importance of tackling obesity now.

B.1.3.2.1 Mortality and life-expectancy

Obesity is associated with significant morbidity and mortality. Public Health England estimates that obesity is responsible for more than 30,000 deaths each year.[32] In 2018/2019, 11,117 hospital admissions were directly attributable to obesity and it was a factor in 876,000 hospital admissions, an increase of 4% and 23% on the previous year, respectively.[31]

Obesity in adulthood is associated with a decrease in life expectancy of approximately 6–13 years.[46-48] A systematic review and meta-analysis of 97 studies including more than 2.88 million individuals and 270,000 deaths found patients with obesity had an 18% increase in all-cause mortality compared with individuals with a normal BMI.[49] Similarly, a population-based cohort study of 3.6 million adults in the UK using data from the Clinical Practice Research Datalink (CPRD) found that in patients with obesity aged ≥ 40 years, life expectancy was 4.2 years shorter in men and 3.5 years shorter in women compared with individuals of healthy weight (BMI: 18.5–24.9 kg/m^2).[50] These results are unsurprising given that patients who are overweight or obese are at increased risk of developing weight-related comorbidities than individuals with a normal BMI.[51]

B.1.3.3 Burden of disease

B.1.3.3.1 Weight-related complications and the impact of weight loss

Patients with a BMI of ≥ 30 kg/m^2 have a significant risk of developing weight-related comorbidities[4], of which a large number are reported throughout the literature. Perhaps the most pertinent given recent events is the strong relationship between obesity and COVID-19.[29, 52] Patients with obesity are at an increased risk of hospitalisation, severe symptoms, advanced treatment requirements (e.g. a need for mechanical ventilation or admission to intensive care units) or dying from COVID-19.[29, 30] Furthermore, the higher a patient's BMI, the more likely they are to die from

the disease. Public Health England estimated that having a BMI of 35–40 mg/kg^2 could increase a person's risk of dying from COVID-19 by 40%, while a BMI > 40 mg/kg^2 could increase the risk by 90%.[53]

Other commonly reported weight-related complications include: pre-diabetes, type 2 diabetes (T2D), cardiovascular disease (CVD, e.g. coronary heart disease, dyslipidaemia and hypertension), knee osteoarthritis, liver disease (e.g. NASH or NAFLD), reproductive system disorders (e.g. infertility), kidney disease, gout, asthma and obstructive sleep apnoea.[4-14] Note that this list is not comprehensive and that the number of different weight-related complications observed in UK clinical practice, and their burden on the healthcare system, is vast.

The benefits of weight loss in patients with obesity who have comorbidities are well documented. Indeed, as little as 5% weight loss can lead to significant improvements in glycaemic status, blood pressure, triglycerides, and high density lipoprotein (HDL) cholesterol.[16] Weight loss of 5−10% is associated with a reduction of intrahepatocellular lipids in NAFLD; reduction in triglycerides, increase in HDL cholesterol and reduction in non-HDL cholesterol; improvements in ovulation and regularisation of menstrual cycles; and prevention of T2D and various cancers.[54] Furthermore, the Look AHEAD study, which examined the impact of short-term weight loss on the incidence of cardiovascular disease in 4,384 patients with obesity with T2D, found that patients who achieved 10% weight loss in the first year after treatment had a 20% reduction in the risk of cardiovascular events.[17] Weight loss ≥ 10% has also been shown to improve symptomatology and increase physical function in people with osteoarthritis, gastroesophageal reflux disease, and obstructive sleep apnoea; reduce inflammation and fibrosis in NASH; and reduce the frequency of incontinence.[18]

Substantial health benefits have been observed with weight loss of 15% or greater. For instance, weight loss of ≥ 15% has also been shown to greatly reduce blood pressure in patients with hypertension, much more so than seen with 5% weight loss.[54] Similarly, although patients with dyslipidaemia (i.e. elevation of plasma cholesterol or triglycerides) and hyperglycaemia (elevated haemoglobin A1C [HbA1C]) benefit from as little as 3% weight loss, triglycerides and HbA1C are further

reduced with ≥ 15% weight loss.[54] Furthermore, weight loss > 15% has been shown to reduce the risk of heart failure and cardiovascular mortality.[20, 21]

Besides reducing the impact of current weight-related comorbidities, weight loss also reduces the chance of developing additional weight-related comorbidities. A UK study of 571,961 patients from the CPRD GOLD database found that a median weight loss of 13% was associated with risk reductions in developing T2D (41%), sleep apnoea (40%), hypertension (22%), dyslipidaemia (19%), asthma (18%), chronic kidney disease (15%), hip or knee osteoarthritis (13%) and heart failure (8%).[22]

B.1.3.3.2 Patient health-related quality of life and the impact of weight loss

People who are obese typically have poorer health-related quality of life (HRQoL) than individuals with normal weight.[55] Individuals living with being obese internalise feelings of being stigmatised and often feel shame or distress about their size and habits; this can contribute to low self-esteem, impaired work and social life, and diminished overall psychological well-being.[56]

Perhaps the most prominent impact obesity has on patient HRQoL is its effect on physical functioning.[57, 58] A cross-sectional study involving approximately 9,000 individuals in the UK reported statistically significant differences in the Short Form 36 Health Survey Questionnaire (SF-36) physical functioning subscale scores between overweight (BMI: 25.0−29.9 kg/m^2), moderately obese (BMI: 30.0−39.9 kg/m^2), and morbidly obese (BMI: ≥ 40.0 kg/m^2) patients, with scores worsening as BMI increased.[57] The authors noted that physical well-being deteriorated markedly with increasing weight.[57] Similarly, a systematic review based on 43,086 patients found that adults who were obese had significantly reduced physical component scores of the SF-36 questionnaire compared with individuals of healthy weight (weighted mean difference referent to normal weight: –2.54 points for Class I obesity; –3.91 for Class II obesity; –9.72 for Class III obesity; all $p < 0.001$).[59]

Improvements in physical functioning have been observed among patients achieving weight loss.[60, 61] More specifically, weight loss of 5−10% is associated with improvements in certain aspects of HRQoL (e.g. mental functioning), with the most notable improvements observed in physical functioning scores for both SF-36 and

the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) domains.[57, 62] Pertaining to this, a study of overweight and obese individuals (mean BMI, 32.5 kg/m^2) who underwent a 6 month clinical weight loss programme showed increases in scores on the SF-36 physical functioning subscale.[60] This finding echoes results of an earlier study which found a statistically significant improvement in physical functioning subscale scores among obese individuals (n = 38) following a weight loss treatment programme.[61] Overall, these results demonstrate that weight loss leads to substantial improvements in patient HRQoL, particularly with regards to physical functioning.

B.1.3.3.3 Socioeconomic burden

Obesity incurs a significant financial burden through both increased total direct healthcare costs and indirect costs.[63, 64] 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.[32] The total cost to the NHS specifically was estimated to be £6.1 billion in 2014/15 and is projected to reach £9.7 billion by 2050.[32]

A significant portion of the economic burden of obesity is driven by the associated comorbidities, which impose substantial medical costs from their treatment. In a UK study of 250,046 patients, healthcare costs were greater as the BMI category increased, reaching a maximum mean annual cost per person of £456.[15] However, after adjusting for BMI, the presence of a comorbidity was the single largest predictor of healthcare costs, with an additional £1,366 mean increase in annual patient costs if a comorbidity was present. The second greatest predictor was depression, at £1,044 per patient per year.[15]

Studies investigating the indirect costs of obesity in the UK are scarce, and the value is hard to quantify given the large number of weight-related complications.[65] As such, any estimate of indirect cost is likely to be an underestimate as calculations cannot include all diseases associated with obesity and because differing societal variables are used in different studies.[65] In 1998, the indirect costs of obesity were estimated to be greater than the direct costs (£2.1 billion versus £500 million, respectively).[63] Some examples of the indirect costs associated with obesity include absenteeism

from work, the cost of time spent in travel and waiting by the patient and by caregivers, as well as the time spent in actually receiving treatment.[63, 66]

Taken together, this abundance of literature supports the notion that substantial weight loss is associated with significant and far-reaching downstream benefits, both in terms of clinical outcomes for the patients and their quality of life, and ultimately the cost-savings associated with reducing the burden and incidence of weight-related comorbidities.

B.1.3.4 Clinical care pathway and proposed positioning of the technology

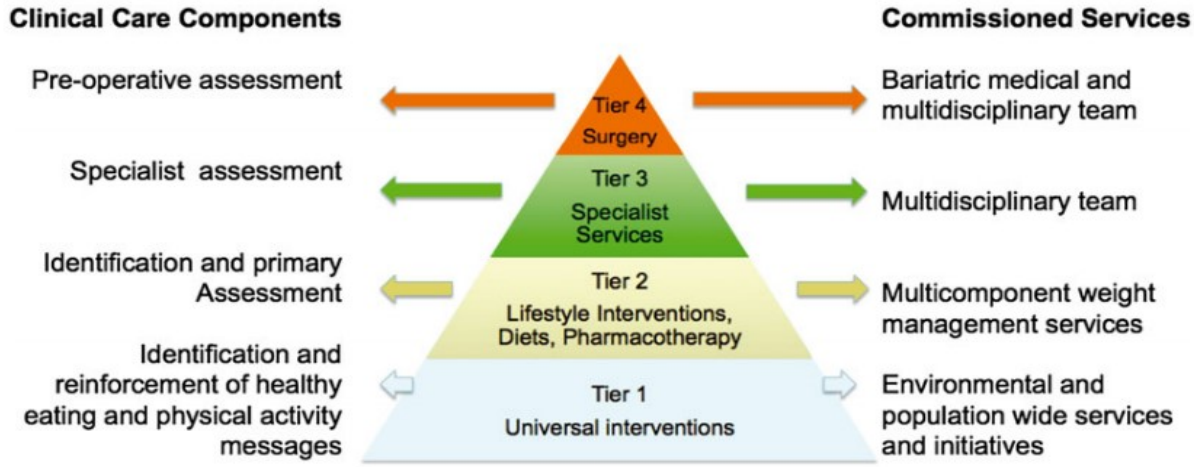
Semaglutide 2.4 mg should be administered as an adjunct to a reduced-calorie diet and increased physical activity to patients with a BMI ≥ 30 mg/kg^2 and at least one weight-related comorbidity (listed in Section B.1.3.4.3) within a SWMS [defined below in Section B.1.3.4.1]). It should be noted that as part of NICE quality standards, QS127, these patients are eligible for SWMS in UK clinical practice (also further discussed in Section B.1.3.4.1).[2]

The following sections provide an overview of the UK clinical guidelines for managing obesity in the UK, the current treatment options and unmet need, and justification for proposed use of semaglutide 2.4 mg in SWMS.

B.1.3.4.1 UK clinical guidelines

Within the NHS in England, obesity management is currently delivered through a tiered system.[67] In 2014, the Department of Health Working Group report on the joined up clinical pathways for obesity described the four weight management tiers; these are depicted in Figure 1.

Figure 1: Tiered model of obesity services



Source: Welbourn et al. 2018.[68]

The different tiers of weight management services cover different activities; however, it should be noted that definitions of weight management tiers are intended as a guide and local definitions vary.[69, 70] Tier 1 is a universal intervention aimed at prevention and re-enforcement of healthy lifestyle principles[71], and Tier 1 forms the basis of all future treatment. Tier 2 covers lifestyle interventions that aim to reduce a person's energy intake and help them to be more physically active by changing their lifestyle behaviour; interventions may also include pharmacotherapy in appropriate clinical circumstances.[72] Broadly, Tier 3 and Tier 4 comprise multidisciplinary team (MDT) weight assessment and management clinics (WAMCs) located in primary or secondary care that provide advice for patients[68]; at a minimum, MDTs must include a clinician, specialist dietician, physician and clinical psychologist.[69, 73] In this submission, these settings will be referred to as SWMS to reflect settings where pharmacotherapy can be offered under the guidance of a specialist MDT. The primary aim of Tier 3 is to achieve clinically meaningful weight loss (defined by NICE as weight loss of 5–10%)[74] in patients with weight-related comorbidities who are not considering bariatric surgical intervention (i.e. Tier 4).[71] Another important remit of Tier 3 is to prepare appropriately selected patients for bariatric surgery.[70, 71, 73]

NICE has issued guidance on the management of obesity (CG189), which states that the referral of patients to Tier 3 services should be considered if:[70]

- The underlying causes of living with overweight or obesity need to be assessed

- The person has complex disease states or needs that cannot be managed adequately in Tier 2 (for example, the additional support needs of people with learning disabilities)
- Conventional treatment has been unsuccessful
- Drug treatment is being considered for a person with a BMI > 50 kg/m^2
- Specialist interventions (such as a very-low-calorie diet) may be needed; or
- Bariatric surgery is being considered

Following commissioning guidance from NHS England in 2016[75], NICE is currently updating CG189 to align with published guidance from The Royal College of Surgeons of England and The British Obesity & Metabolic Surgery Society (BOMSS), which recommends referral to Tier 3 settings for patients with severe and complex obesity (i.e. patients with a BMI > 40 kg/m^2 or a BMI ≥ 35 kg/m^2 with comorbidities; these patients are currently recommended for Tier 4 as part of CG189.[76, 77] However, it should also be noted that as part of the accompanying quality standards for the CG189 guidelines (QS127), NICE states that adults with a BMI ≥ 30 kg/m^2 for whom Tier 2 interventions have been unsuccessful should discuss their choice of alternative interventions for weight management, including referral to a SWMS.[2]

B.1.3.4.2 Current treatment options and relevant comparators for semaglutide 2.4 mg

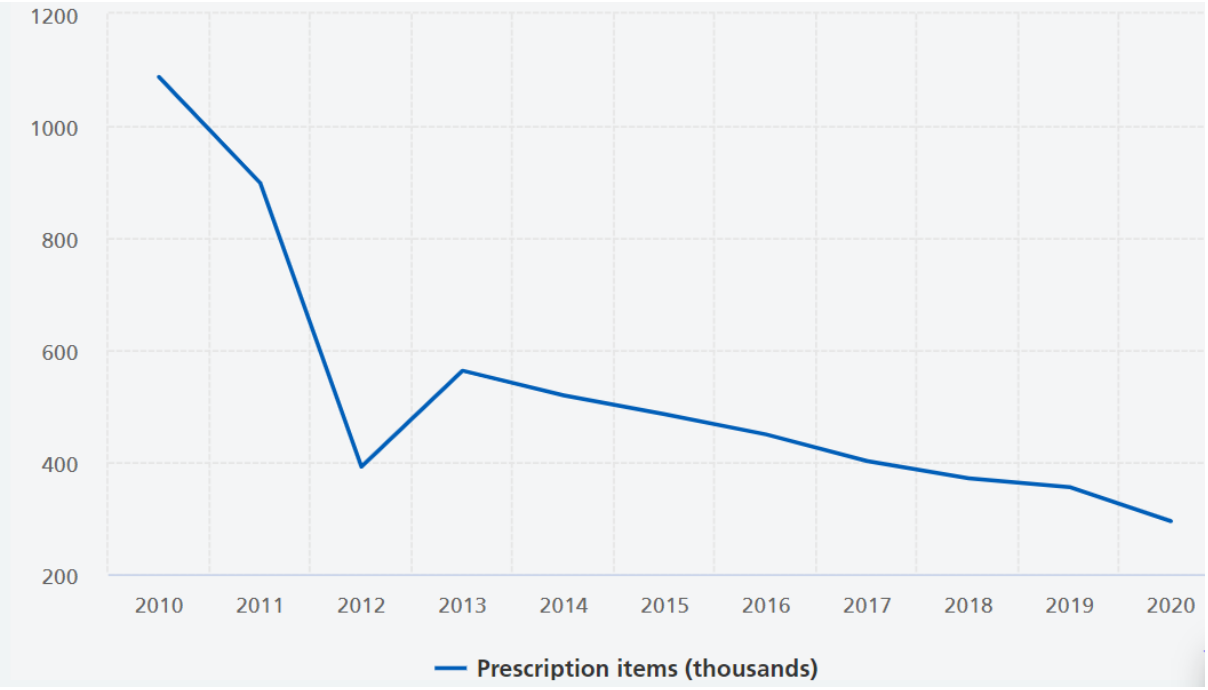
Interventions for managing obesity include lifestyle interventions (such as diet and exercise); pharmacotherapy, namely orlistat and liraglutide 3.0 mg; and bariatric surgery.

Lifestyle intervention in the form of diet and exercise counselling is essential in treating obesity and forms the basis of all treatment programmes. However, evidence suggests that lifestyle interventions alone are not enough to help patients lose weight and maintain weight loss. In the UK, it was reported that only 20% of individuals in the general population successfully lose 10% of their body weight and maintain that weight loss for 1 year.[78] Given that in clinical practice, lifestyle intervention is prescribed for all patients who are obese, lifestyle intervention without

pharmacotherapy is considered a relevant comparator to semaglutide 2.4 mg for the purpose of this submission.

Regarding pharmacotherapy, orlistat is currently recommended for managing obesity in adults who have a BMI ≥ 28 kg/m^2 with associated risk factors such as T2D, hypertension, or hypercholesterolaemia; or a BMI ≥ 30 kg/m^2. However, as part of the NICE technology appraisal for naltrexone–bupropion (TA494), clinical experts and consultees reported that orlistat is not commonly prescribed in clinical practice due to efficacy and tolerability issues.[25] These sentiments were reflected in the appraisal of liraglutide 3.0 mg (TA664), where clinicians stated that many people decide not to have orlistat or stop taking it because of undesirable, and socially unacceptable side effects.[27] Orlistat also appears to be much less effective in general practice than in randomised clinical trials, leading to undesirable side effects, poor adherence and insufficient weight loss outcomes.[24, 25] Pertaining to this, data from NHSE highlight a long-term downward trend on the prescription of orlistat in the UK , as depicted in Figure 2.

Figure 2: Number of items (orlistat) prescribed for the treatment of obesity



Notes: y-axis = number of items prescribed in thousands.
Source: National Health Service England, 2021.[26]

For these reasons, orlistat is not considered a relevant comparator to semaglutide 2.4 mg for this submission. Conversely, liraglutide 3.0 mg is considered a relevant comparator to semaglutide 2.4 mg for this submission for those patients with a BMI ≥ 35 mg/kg^2 with non-diabetic hyperglycaemia and high CV risk. Liraglutide 3.0 mg is recommended by NICE for use in a restricted population of adult patients with obesity, only if:[27]

- They have a BMI ≥ 35 kg/m^2 and non-diabetic hyperglycaemia (defined as a HbA1c level of 42–47 mmol/mol or a fasting plasma glucose level of 5.5–6.9 mmol/litre
- They have a high risk of cardiovascular disease based on risk factors such as hypertension and dyslipidaemia
- It is prescribed in secondary care by a specialist multidisciplinary Tier 3 weight management service

In the UK, bariatric surgery is only available for patients with a high BMI (a BMI ≥ 40 kg/m^2, or between 35–40 kg/m^2 and other significant disease) and is rarely used in clinical practice (between 0.002–0.1% of eligible patients).[25, 71] Hence, bariatric surgery was not included in the scope and is not considered a relevant comparator to semaglutide 2.4 mg for the purpose of this submission.

B.1.3.4.3 The unmet clinical need and proposed use of semaglutide 2.4 mg

Currently, there are limited efficacious pharmacological treatment options for patients with obesity who are seeking SWMS. Orlistat was the mainstay of treatment but is rarely used today and is associated with undesirable side effects, insufficient weight loss and poor adherence (as discussed in Section B.1.3.4.2).[24-26] More recently, NICE approved liraglutide 3.0 mg for use within SWMS for patients with a BMI ≥ 35 mg/kg^2 with non-diabetic hyperglycaemia and high CV risk (TA664).[27] However, there remains a substantial unmet clinical need for patients with obesity and comorbidities who can access SWMS but fall outside of the criteria for liraglutide 3.0 mg treatment; these patients may be deprived of benefitting from clinically meaningful weight loss.

Indeed, studies have shown that patients with a BMI below 35 mg/kg^2 (and even below 30 mg/kg^2) can benefit from weight loss.[71] Furthermore, clinicians explained that weight loss of 10–15% is considered highly significant and not something routinely possible with standard care, and that there are a significant number of weight-related comorbidities that can be meaningfully alleviated from a weight loss of this magnitude.[23] Patients with a BMI ≥ 35 mg/kg^2 may also benefit from additional pharmacotherapy options, and NICE acknowledges that weight loss > 10% may be needed for patients with a BMI ≥ 35 mg/kg^2.[74] However, in SWMS currently, clinicians advised that patients typically achieve between 5–7% weight loss[23], and the most recent data indicates that only between 20–25% are currently achieving ≥ 10% weight loss with the current pharmacotherapy options.[71]

The need for additional treatment options for obesity is also apparent when considering the increasing prevalence of the disease[28], which will result in more patients requiring SWMS. Those patients with a BMI ≥ 30 kg/m^2 with comorbidities who do not meet the criteria for liraglutide 3.0 mg in SWMS will be left without an effective pharmacotherapy treatment option, which may deprive them of benefitting from clinically meaningful weight loss and cause their disease to worsen. This can put patients at risk of developing additional weight-related comorbidities or dying from obesity-related complications such as COVID-19.[22, 29, 30] Furthermore, there is a substantial burden on the healthcare system due to increasing numbers of obesity-related hospitalisations and comorbidities that require treatment[31, 32]; this burden could be alleviated with the introduction of new, efficacious pharmacotherapies. As such, there is a clear need for additional pharmacotherapy options for patients being treated in SWMS. This view is shared by the clinical community, who have expressed a desire to use pharmacotherapy to treat a broader population of patients in SWMS, rather than just those eligible for liraglutide 3.0 mg.[23]

Taken together, there is a clear need for a more widely accessible and effective pharmacotherapy option within SWMS for treating patients with obesity, particularly for those patients who have comorbidities that can be meaningfully alleviated with weight loss. As such, the proposed target population for semaglutide 2.4 mg is patients with a BMI ≥ 30 mg/kg^2 (obese) and at least one weight-related comorbidity.

These patients represent a population that has the potential to experience substantial clinical benefits from weight loss with semaglutide 2.4 mg.

B.1.4. Equality considerations

Several equality considerations are relevant to this submission:

- **BMI variations between different ethnicities** – NICE has issued public health guidance (PH46) in line with advice from WHO, which states that members of black, Asian (South Asian and Chinese) and other minority ethnic groups are at an increased risk of chronic health conditions at a lower BMI than the white population (BMI < 25 kg/m^2).[79] NICE recommends using lower BMI thresholds (23 kg/m^2 to indicate increased risk and 27.5 kg/m^2 to indicate high risk) for BMI to trigger action to prevent T2D among Asian populations (compared to 25 kg/m^2 and 30 kg/m^2 for the white population, respectively)[79]
- **Access inequalities** – There are often hurdles to overcome to gain access to treatment
  - According to a report by the Royal College of Surgeons, 31% of Clinical Commissioning Groups have at least one mandatory policy on BMI level and weight management.[80] This means patients who require rapid weight loss to get another procedure (e.g. a hip/knee operation) may end up waiting for prolonged periods of time to access services and may or may not achieve the target weight loss to allow their procedure to be performed
- **Socioeconomic inequalities** – A higher prevalence of obesity has been found in people of lower socioeconomic status, as highlighted by data published by the House of Commons Library:
  - In the most deprived areas in England, the prevalence of excess weight is 9% higher than the least deprived areas.[81] This difference was particularly pronounced for women, where 39% of women in the most deprived areas were obese, compared with 22% in the least deprived areas.[45] The most recent available data covers surveys from 2018/19, and shows that levels of excess weight are estimated to be highest in the West Midlands, the North East, and Yorkshire & the Humber[81]
  - Among people with disabilities, excess weight is 10% higher than among those without disabilities[81]

- Compared with all other ethnic groups, black people have the highest rates of excess weight, followed by white British people[81]
- Among people with no qualifications, rates of excess weight are 12% higher than among people with Level 4 qualifications or higher (i.e. a degree)[81]

- **COVID-19 inequalities** – People with obesity are at an increased risk of hospitalisation, severe symptoms, advanced treatment requirements or dying from COVID-19. [29, 30]

If semaglutide 2.4 mg is recommended for use within SWMS, a greater number of patients with obesity would have access to effective pharmacotherapy, which could help to mitigate some of these inequalities.

B.2. Clinical effectiveness

Semaglutide 2.4 mg is currently being investigated in a series of clinical trials known as the STEP programme. The STEP programme is a comprehensive examination of semaglutide 2.4 mg for weight management in a variety of populations and treatment settings. In total, the programme consists of 17 individual studies: eight global Phase IIIa studies, two regional Phase IIIa studies, six Phase IIIb studies and one Phase IV study. An overview of the STEP programme is presented in Section B.2.11.

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify randomised controlled trial (RCT) evidence for this submission from the current treatment landscape for patients who are overweight or obese.[82] Full details of the process and methods used to identify and select the relevant clinical evidence are in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

The clinical SLR identified two potentially relevant RCTs from the STEP programme: STEP 1 and STEP 3. A full overview of the STEP clinical trial programme, including rationale for inclusion or exclusion of the trials from the submission, is provided in Section B.2.11.

STEP 3 was a Phase IIIa randomised, double-blind, multicentre, placebo-controlled trial of 611 adults who were obese (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2)

with at least one weight-related comorbidity and without diabetes or HbA1c ≥ 6.5%. During the study, semaglutide 2.4 mg was administered in conjunction with intensive behavioural therapy (IBT), which consisted of combined behavioural counselling, reduced-calorie diet, and increased physical activity. However, as discussed in TA664, IBT is not standard clinical practice in the UK. Therefore STEP 3 is not considered relevant for this submission.

The Phase III STEP 1 trial is the pivotal RCT providing evidence of the clinical benefits of semaglutide 2.4 mg for treating patients with a BMI ≥ 30 mg/kg^2 and at least one weight-related comorbidity. The trial is summarised in Table 3.

Table 3: Clinical effectiveness evidence

Study title	STEP 1				
Trial number	NCT03548935				
Study design	Phase III, randomised, double-blind, placebo-controlled study				
Population	1,961 adults with obesity (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least one weight-related comorbidity, and without diabetes or HbA1c ≥ 6.5%				
Intervention	Semaglutide 2.4 mg as an adjunct to lifestyle intervention (counselling and a reduced calorie diet [500 kcal/day deficit relative to estimated total energy expenditure at Week 0], together with 150 minutes/week of physical activity)				
Comparator	Placebo as an adjunct to lifestyle intervention (counselling and a reduced calorie diet [500 kcal/day deficit relative to estimated total energy expenditure at Week 0], together with 150 minutes/week of physical activity)				
Indicate if trial supports application for marketing authorisation	Yes	**X**	**Indicate if trial used in the economic model**	Yes	**X**
	No			No	
Rationale for use/non-use in the model	Pivotal trial supporting this indication				

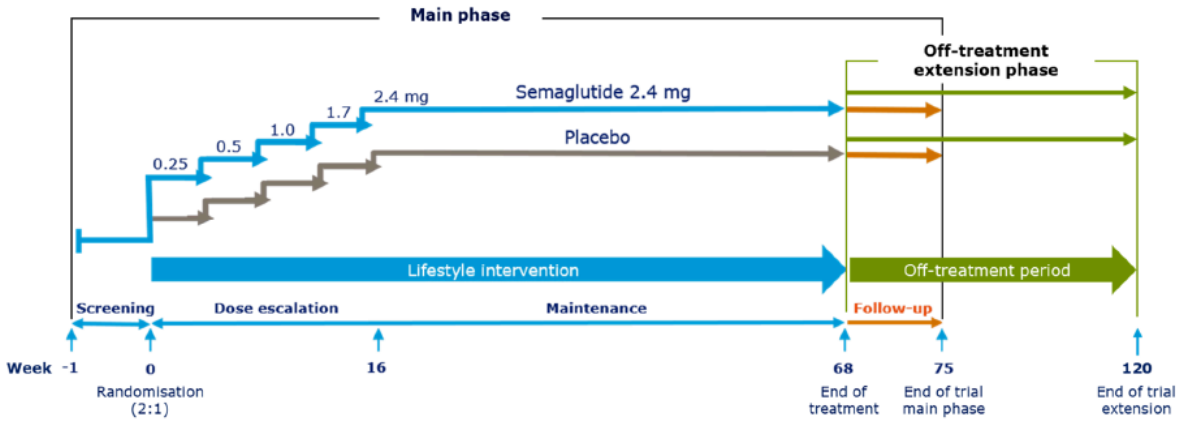
Reported outcomes specified in the decision problem	• BMI • **Weight loss** • Incidence of type 2 diabetes • Waist circumference • **Glycaemic status** • Cardiovascular events • Mortality • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	• Change in HbA1c from baseline • **Change in systolic blood pressure form baseline** • **Change in fasting lipid profile from baseline (specifically, HDL and total cholesterol)**
Key: BMI, body mass index; HbA1C, haemoglobin A1C; HDL, high density lipoprotein. **Notes:** Outcomes in bold are those directly used in the economic modelling.	

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Study design

STEP 1 was a Phase III, randomised, double-blind, placebo-controlled study in 1,961 adults who were obese (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least one weight-related comorbidity, and without diabetes or HbA1c ≥ 6.5%.[83] The study was conducted across 129 sites in 16 countries, including 10 sites in the UK (of which nine where in England). Figure 3 presents a study design schematic for the STEP 1 study.[83, 84] The primary objective of the study was to compare the effect on body weight of semaglutide 2.4 mg once weekly versus placebo as an adjunct to lifestyle intervention in patients who were overweight or obese.[83]

Figure 3: STEP 1 study design schematic



Source: Novo Nordisk (STEP 1 clinical study report), 2020.[85]

In the main phase, 1,961 patients who were overweight or obese were randomised 2:1 to receive either semaglutide 2.4 mg once weekly or placebo once weekly as an adjunct to lifestyle intervention (counselling, a reduced calorie diet [500 kcal/day deficit relative to estimated total energy expenditure at Week 0] together with 150 minutes/week of physical activity).[83] The study included an initial 16-week dose-escalation period during which the dose of semaglutide was gradually increased to the maintenance dose of 2.4 mg once weekly. Treatment was continued for an additional 52 weeks until Week 68 (end of treatment).[85] The study also included a further 52-week off treatment extension phase, during which a subset of patients who had completed the main phase on the maintenance dose of semaglutide 2.4 mg

once weekly or placebo discontinued both treatment and structured lifestyle intervention.

Table 4: Summary of STEP 1 study methodology

Trial name	**STEP 1**
Location	129 sites in 16 countries, including Argentina, Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, India, Japan, Mexico, Poland, Puerto Rico, Russia, Taiwan, the UK and the US.
Trial design	Phase III, randomised, double-blind, placebo-controlled study in 1,961 adults with obesity (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least one weight-related comorbidity, and without diabetes or HbA1c ≥ 6.5%.
Key eligibility criteria for patients	**Inclusion criteria** • Males or females aged ≥ 18 years at the time of signing informed consent • BMI ≥ 30.0 kg/m^2 or ≥ 27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease • History of at least one self-reported unsuccessful dietary effort to lose body weight **Exclusion criteria** • HbA1c ≥ 48 mmol/mol (6.5%) as measured by the central laboratory at screening • A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records **Randomisation criteria** Patients who fulfilled all inclusion criteria and did not meet any exclusion criteria were eligible to be randomised in the trial if: • They kept a food diary with at least one entry per day between screening and randomisation (missed entries for a maximum of two days were allowed) • They had a PHQ-9 score of < 15 at randomisation • They had no suicidal behaviour in the period between screening and randomisation, or suicidal ideation corresponding to Type 4 or Type 5 on the C-SSRS in the period between screening and randomisation **Randomisation criteria applicable only for the DEXA sub-population** • Patients must have a BMI ≤ 40.0 kg/m^2 at screening • Evaluation of the quality of the baseline DEXA scan must be performed and found acceptable by the

	imaging laboratory before randomisation to the body composition sub-study
Settings and locations where the data were collected	• Novo Nordisk established an internal semaglutide subcutaneous safety committee to perform ongoing safety surveillance during trial conduct • An independent external EAC performed ongoing blinded adjudication of selected AE types • An independent DMC was set up to provide oversight of patient safety • Data were collected locally by fully trained investigators. Site monitoring and pre-specified data validation checks were regularly conducted to ensure data quality
Trial drugs	Semaglutide 2.4 mg given once weekly via subcutaneous injection. Semaglutide included an initial 16-week dose-escalation period during which the dose of semaglutide was gradually increased to the maintenance dose of 2.4 mg once weekly. Treatment was continued for an additional 52 weeks until Week 68
Permitted and disallowed concomitant medication	Concomitant medication relevant for the trial population included[a]: • Agents acting on the renin-angiotensin system (23.6%) • Lipid modifying agents (18.5%) with statins being the most frequent (14.3%) • Diuretics (11.1%) with thiazides being the most frequent (6.8%) • Beta blocking agents (10.6%) • Antithrombotic agents (8.5%) • Calcium channel blockers (8.3%) with dihydropyridine derivatives being the most frequent (7.8%)
Primary outcomes (including scoring methods and timings of assessments)	• Percentage change in body weight from baseline to 68 weeks • Proportion of patients achieving baseline body weight loss ≥ 5% at 68 weeks Body weight was measured without shoes, on an empty bladder and in light clothing. Measurements were to be recorded on a digital scale in kilograms or pounds (one decimal) using the same scale throughout the trial, calibrated yearly as a minimum. Height was measured without shoes in centimetres or inches (one decimal). BMI was automatically calculated by the eCRF.

Other outcomes used in the economic model/specified in the scope	Change from baseline to Week 68 in: • BMI • Incidence of type 2 diabetes • Waist circumference • Glycaemic status • Cardiovascular events • Mortality • Adverse effects of treatment • Health-related quality of life • Change in fasting lipid profile from baseline (specifically, HDL and total cholesterol)
Pre-planned subgroups	A subgroup of 140 patients with a BMI ≤ 40 mg/kg^2 underwent DEXA to assess body composition.
Key: AE, adverse event; BMI, body mass index; DEXA, dual-energy x-ray absorptiometry; DMC, data monitoring committee; EAC, event adjudication committee; eCRF, electronic case report form; HbA1C, haemoglobin A1C; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite Clinical Trials Version; SF-36, Short Form-36.**Notes:** [a], the full list of permitted and disallowed concomitant medication is available in the STEP 1 clinical study report. **Source:** Novo Nordisk (STEP 1 clinical study report), 2020[85]; Wilding et al. 2021.[83]	

B.2.3.2 Patient baseline demographics, disease characteristics and comorbidities

Table 5 presents the baseline demographics and disease characteristics for patients in the full analysis set (FAS, see Section B.2.4.1 for a definition) and the BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity subgroup from the STEP 1 study. Patient disposition data for STEP 1 is presented in Appendix D2, alongside a Consolidated Standards of Reporting Trials (CONSORT) diagram of patient flow.

Overall, across both the FAS and the BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity subgroup (hereby referred to as the target population), baseline demographics and disease characteristics were well balanced between the semaglutide 2.4 mg and placebo treatment arms.[83, 86]

Baseline demographics and disease characteristics were also very similar across the FAS and the target population. As expected given the exclusion of the lower BMI patients, some of the disease characteristics were slightly higher in the target population, such as lipid levels, waist circumference and blood pressure (Table 5).

Note that ethnicity and BMI category were not reported for the target population; however, in line with the other baseline characteristics, the proportion of patients in each group is expected to be similar to the FAS.

Table 6 presents the baseline comorbidities for patients in the FAS and the target population from the STEP 1 study. As with the baseline demographics and disease characteristics, the distribution was similar between the semaglutide 2.4 mg and placebo treatment arms in both the FAS and target population. Furthermore, the baseline comorbidities were similar between the FAS and the target population.

Clinicians considered the baseline demographics, disease characteristics and comorbidities observed in the STEP 1 study to reflect the UK obesity patient population, including those patients commonly referred to SWMS.[23]

Table 5: Patient baseline demographics and disease characteristics, STEP 1

	BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity (n = 1,470)		Full analysis set (n = 1,961)	
	Semaglutide 2.4 mg (n = 974)	**Placebo (n = 496)**	**Semaglutide 2.4 mg (n = 1,306)**	**Placebo (n = 655)**
Mean age, years (range)	[redacted]	[redacted]	46 (18–86)	47 (18–82)
Female, n (%)	696 (71.5)	375 (75.6)	955 (73.1)	498 (76.0)
Race, n (%)				
White	NR	NR	973 (74.5)	499 (76.2)
Asian	NR	NR	181 (13.9)	80 (12.2)
Black or African American	NR	NR	72 (5.5)	39 (6.0)
Other*	NR	NR	80 (6.1)	37 (5.6)
Hispanic or Latino ethnic group, n (%)	NR	NR	150 (11.5)	86 (13.1)
BMI				
Mean BMI, kg/m^2 (SD)	[redacted]	[redacted]	37.8 (6.7)	38.0 (6.5)
< 30 kg/m^2, n (%)	0	0	81 (6.2)	36 (5.5)
≥ 30 – < 35 kg/m^2, n (%)	NR	NR	436 (33.4)	207 (31.6)
≥ 35 – < 40 kg/m^2, n (%)	NR	NR	406 (31.1)	208 (31.8)
≥ 40 kg/m^2, n (%)	NR	NR	383 (29.3)	204 (31.1)
Mean waist circumference, cm (SD)	116.8 (14.5)	116.9 (13.9)	114.6 (14.8)	114.8 (14.4)
Mean HbA1c (%)	5.8 (0.3)	5.8 (0.3)	5.7 (0.3)	5.7 (0.3)
Mean systolic blood pressure, mmHg (SD)	[redacted]	[redacted]	126.3 (14)	126.8 (14)
Mean fasting plasma glucose, mmol/L (SD)	5.4 (0.6)	5.3 (0.6)	5.3 (0.6)	5.3 (0.6)
Lipid levels, geometric mean, mg/dL (CV)				
Total cholesterol	[redacted]	[redacted]	189.6 (20.5)	192.1 (19.4)

	BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity (n = 1,470)		Full analysis set (n = 1,961)	
	Semaglutide 2.4 mg (n = 974)	**Placebo (n = 496)**	**Semaglutide 2.4 mg (n = 1,306)**	**Placebo (n = 655)**
HDL cholesterol	[redacted]	[redacted]	49.4 (25.6)	49.5 (25.0)
Triglycerides	145.6 (84.4)	147.6 (95.7)	126.2 (47.4)	127.9 (49.0)
Smoker status, n (%)				
Current smoker	123 (12.6)	49 (9.9)	160 (12.2)	68 (10.4)
Previous smoker	261 (26.8)	145 (29.2)	318 (24.3)	178 (27.2)
Never smoked	590 (60.6)	302 (60.9)	828 (63.4)	409 (62.4)
On anti-hypertensive medication, n (%)				
Yes	282 (29.0)	141 (28.4)	311 (23.8)	152 (23.2)
No	692 (71.0)	355 (71.6)	995 (76.2)	503 (76.8)
On lipid-lowering medication, n (%)				
Yes	223 (22.9)	102 (20.6)	249 (19.1)	114 (17.4)
No	751 (77.1)	394 (79.4)	1057 (80.9)	541 (82.3)

Key: BMI, body mass index; CV, coefficient of variation; NR, not reported; SD, standard deviation.
Source: Novo Nordisk (data on file), 2021[86]; Wilding et al. 2021.[83]

Table 6: Baseline comorbidities, STEP 1

Comorbidity	BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity (n = 1,470)		Full analysis set (n = 1,961)	
	Semaglutide 2.4 mg (n = 974)	Placebo (n = 496)	Semaglutide 2.4 mg (n = 1,306)	Placebo (n = 655)
Patients with at least one comorbidity, n (%)	974 (100)	496 (100)	1048 (80.2)	532 (81.2)
Non-diabetic hyperglycaemia[a]	518 (53.2)	253 (51.0)	550 (42.1)	271 (41.4)
Dyslipidaemia	445 (45.7)	206 (41.5)	499 (38.2)	226 (34.5)
Hypertension	425 (43.6)	215 (43.3)	472 (36.1)	234 (35.7)
Hip or knee osteoarthritis	189 (19.4)	113 (22.8)	194 (14.9)	117 (17.9)
Coronary artery disease	30 (3.1)	15 (3.0)	32 (2.5)	17 (2.6)
Asthma	140 (14.4)	78 (15.7)	147 (11.3)	80 (12.2)
Liver disease (NASH or NAFLD)	94 (9.7)	54 (10.9)	105 (8.0)	63 (9.6)
Cerebrovascular disease	11 (1.1)	6 (1.2)	13 (1.0)	6 (0.9)
Obstructive sleep apnoea	156 (16.0)	67 (13.5)	159 (12.2)	71 (10.8)
Disorder of reproductive system (PCOS, irregular intermenstrual bleeding, infertility)	164 (16.8)	85 (17.1)	167 (12.8)	87 (13.3)
Kidney disease	25 (2.6)	12 (2.4)	26 (2.0)	14 (2.1)
Gout (including hyperuricaemia)	73 (7.5)	25 (5.0)	89 (6.8)	27 (4.1)

Key: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
Notes: [a], defined as haemoglobin A1c (HbA1c) levels in the range 6.0–6.4%, or fasting plasma glucose (FPG) levels in the range 5.5–6.9 mmol/L.
Source: Novo Nordisk (data on file), 2021[87]; Wilding et al. 2021.[83]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Table 7 presents the hypothesis and associated statistical analysis methods adopted in the STEP 1 study.

Table 7: Summary of statistical analyses in STEP 1

Objectives	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Primary To compare the effect on body weight of semaglutide 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in patients who are overweight or obese. **Secondary** To compare the effect of semaglutide 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in patients who are overweight or obese on: • Cardiovascular risk factors • Clinical outcome assessments • Glucose metabolism • Other factors related to body weight To compare the safety and tolerability of	**Planned analysis** The primary endpoint of the 68-week assessment of the trial was a linear regression (ANCOVA) of percentage weight change with randomised treatment as a factor and baseline body weight (kg) as covariate. The analysis model for the 5% responder endpoint was a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate. **Post-hoc analysis** Mean changes from baseline in continuous endpoints were recorded for each visit and estimated using an analysis of covariance model with treatment as factor and baseline value as covariate. For HDL and total cholesterol, mean change form baseline values are	The sample size and thereby the power of the trial was primarily defined to support safety. However, no formal statistical inference was planned based on the number of adverse events. The sample size of 1,300 patients assigned to receive semaglutide 2.4 mg and 650 patients assigned to receive placebo was estimated to provide more than 99% power to detect a between group difference for the first seven endpoints* in the hierarchical testing procedure efficacy endpoints of the main 68 week trial. The power was calculated using a two-sided t-test on the mean difference assuming equal variances was used. The significance level was 5% and the randomisation ratio was 2:1 for	**Primary analysis** The last available and eligible observation at or before randomisation was used as the baseline value. If no assessments are available, the mean value at randomisation across all patients was used as the baseline value. Missing observations were multiple (x1000), imputed from retrieved patients of the same randomised treatment arm (done for patients on treatment at landmark visit). **Post-hoc analysis** Missing observations were multiple (x1000), imputed from retrieved patients of the same randomised treatment arm (done for patients on

Objectives	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
semaglutide 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in patients with overweight or obesity.	presented as log-scale values. Glycaemic status was also summarised for each visit.	semaglutide 2.4 mg vs placebo.	treatment at landmark visit). Values were imputed based on extrapolation by linear regression based on change estimates from off treatment periods (done for patients off treatment at landmark visit).
Key: HDL, high density lipoprotein. **Notes**: * = % weight change; 5%, 10% and 15% responders; waist circumference; systolic blood pressure; SF-36 physical functioning score; and IWQOL-Lite-CL physical function score. **Source**: Novo Nordisk (STEP 1 clinical trial protocol), 2019.[88]			

B.2.4.1 Analyses sets and evaluations

- The FAS included all randomised patients according to the intention-to-treat principle.
  - The efficacy evaluation for the STEP 1 study was based on the FAS
- The safety analysis set (SAS) included all randomised patients exposed to at least one dose of randomised treatment (semaglutide 2.4 mg or placebo)
  - The safety evaluation for the study was based on the SAS
- The dual energy X-ray absorptiometry (DEXA) analysis set included a subgroup of patients with a BMI ≤ 40 mg/kg^2 at screening and a DEXA scan performed at baseline considered to be of acceptable quality by the imaging laboratory
  - The body composition subgroup study was performed on the DEXA analysis set

B.2.4.2 Post-hoc subgroup analyses

The subgroups analysed post-hoc were as follows:

- Patients with a BMI ≥ 30 mg/kg^2 who have at least one weight-related comorbidity (i.e. the target population for this submission)
- Patients with a BMI ≥ 35 kg/m^2 who have non-diabetic hyperglycaemia and high CV risk (i.e. the TA664 population)

The efficacy evaluation conducted for the FAS was also conducted for these two subgroups. Note that no safety analyses were conducted for the subgroups.

B.2.4.3 Observation periods

Two observation periods were defined for the efficacy and safety evaluations[85]:

- **The in-trial period** – defined as the uninterrupted time interval from randomisation to last contact with trial site; used for:
  - Efficacy: observed values
  - Safety: death and events with potential long latency to diagnosis
- **The on-treatment period** – defined as the interval from first to last trial product administration plus 2 or 7 weeks of follow-up and excluding any period of temporary treatment interruption defined as > 2 or > 7 consecutive missed doses (corresponding to > 2 or > 7 weeks off treatment).
  - The on-treatment period (+2 weeks) was used for:
    - Efficacy: observed values
    - Safety: ECG, laboratory assessments, physical examination and pulse
  - The on-treatment period (+7 weeks) was used for:
    - Safety: adverse events (AEs) and adjudicated events

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.[85]

B.2.4.4 Trial estimands

An estimand is a detailed description of the treatment effect estimated to address a scientific question of interest; more than one estimand can be defined for the same endpoint.[89] The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 (R1) draft addendum on estimands and sensitivity analysis in clinical trials sets out five estimand strategies for estimating the treatment effect (note that this is used by both the EMA and US Food and Drug Administration [FDA]).[90, 91]

According to the guidance, an estimand is defined by four inter-related attributes: the population of interest, the variable (endpoint) of interest, the way intercurrent events

are handled and the population level summary.[90, 91] Different estimands are employed to handle intercurrent events that occur during a trial. In the case of STEP 1, the intercurrent events were the initiation of other anti-obesity therapies (weight management drugs or bariatric surgery) and premature discontinuation of the trial product.

For STEP 1, two estimand strategies were applied to the efficacy analyses to address two different aspects of the treatment effect of semaglutide 2.4 mg:

- **The treatment policy estimand** (primary estimand used in the trial analyses) – estimated the treatment effect of semaglutide 2.4 mg relative to placebo for all randomised patients regardless of premature discontinuation of trial product or initiation of other anti-obesity therapies (weight management drugs or bariatric surgery)
  - The treatment policy estimand estimates the population level treatment effect of semaglutide 2.4 mg regardless of treatment adherence and/or other anti-obesity therapies, and therefore the overall treatment impact of semaglutide 2.4 mg for the indicated patient population. Therefore, these results are presented throughout Sections B.2.6 and B.2.7 (note that these results were also used in regulatory approval)
- **The hypothetical (trial product) estimand** (secondary estimand used in the trial analyses) – estimated the treatment effect of semaglutide 2.4 mg relative to placebo for all randomised patients, assuming they remained on their randomised treatment for the entire planned duration of the trial and had not initiated other anti-obesity therapies
  - The trial product estimand excludes the effects of any other anti-obesity therapies and any effects after first treatment discontinuation, and provides a clinically relevant estimate of the average treatment effect of semaglutide 2.4 mg. These results are used to inform the economic model (Section B.3.3.1.1), which captures the effects of alternative anti-obesity therapy use based on published literature; the results are presented in Appendix E2

B.2.4.5 Prediabetes definition used in the analyses

For the analyses presented in this submission, pre-diabetes was defined according the NICE preferred definition (as used in TA664), that is non-diabetic hyperglycaemia, defined as a HbA1c level of 42–47 mmol/mol (6.0–6.4%) or a FPG level of 5.5–mmol/L.[27, 92] Note that this is different to the definition used in the primary analyses, which used the American Diabetes Association (ADA) definition: HbA1c 5.7−6.4% both inclusive; or FPG ≥ 5.6 mmol/L and ≤ 6.9 mmol/L; or 2-hour post-challenge (OGTT) PG ≥ 7.8 mmol/L and ≤ 11.0 mmol/L.[93]

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

A summary of the quality assessment for the STEP 1 trial is presented in Appendix D3.

STEP 1 was conducted in accordance with Good Clinical Practice (GCP) as defined by the International Council on Harmonisation (ICH), and in accordance with the ethical principles underlying the Declaration of Helsinki.[85] For each study site, the adequacy of the research facility to execute the protocol requirements was confirmed by the local trial management in the country, before study initiation. The study was conducted by qualified investigators, in accordance with a single protocol to promote consistency across sites and measures taken to minimise bias. The study was also monitored by the sponsor by means of central and off-site monitoring, on-site visits, telephone calls, and regular inspection of the electronic case report form (eCRF) with sufficient frequency to verify the study conduct. In addition, all patients provided written consent before study initiation.[85]

Several committees were involved, including the Novo Nordisk safety committee, which performed safety surveillance during the study.[85] An independent external event adjudication committee (EAC) performed ongoing blinded adjudication of selected event types, using definitions and guidelines pre-specified in the EAC Charter. All protocol amendments and patient-informed consent forms received approval by the Institutional Review Board/Independent Ethics Committee at each site, before study initiation.[85]

Baseline demographics and disease characteristics for patients in the STEP 1 study were generally well-balanced between treatment arms (see Section B.2.3.2), and according to clinical expert opinion, the overall population was representative of the general UK obesity patient population.[23]

As a consequence of the COVID-19 pandemic, it was decided as of 23 March 2020 to stop source data validation of remaining data, as monitors were not able to visit the sites and remote validation was not possible. However, all data were entered into the eCRF and checked for completeness, and data cleaning and casebook sign-off

were ensured. The decision was in alignment with ICH GCP and regulatory guidance regarding COVID-19.[85]

B.2.6. Clinical effectiveness results of the relevant trials

This section presents the efficacy results of the STEP 1 trial. The results of the in-trial efficacy analysis for the FAS (n = 1,961), evaluated using the treatment policy estimand (see Section B.2.4.3 for definitions), are presented in the following sections. The results of the in-trial efficacy analysis for the FAS using the trial product estimand is presented in Appendix E2. The results of the in-trial efficacy analysis for the BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity subgroup (i.e. the target population) and the BMI ≥ 35 mg/kg^2 plus non-diabetic hyperglycaemia plus high CV risk subgroup using the treatment policy estimand is summarised in Section B.2.7; the corresponding results of the in-trial efficacy analysis using the trial product estimand are presented in Appendix E2.

The results of the FAS are the primary focus of the submission and are subsequently used in the model to demonstrate the effectiveness of semaglutide 2.4 mg. The results of the FAS, and not the target population (BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity; summarised in Section B.2.7), were selected as the primary data source given NICE's preference not to use post-hoc trial data for economic modelling. However, as discussed in the subsequent sections, the results of the FAS and the BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity subgroup are consistent with ~75% of the FAS population having a BMI ≥ 30 and at least 1 weight-related comorbidity (presented in Appendix E2). As such, the FAS can be considered a reasonable proxy for the target population for this submission.

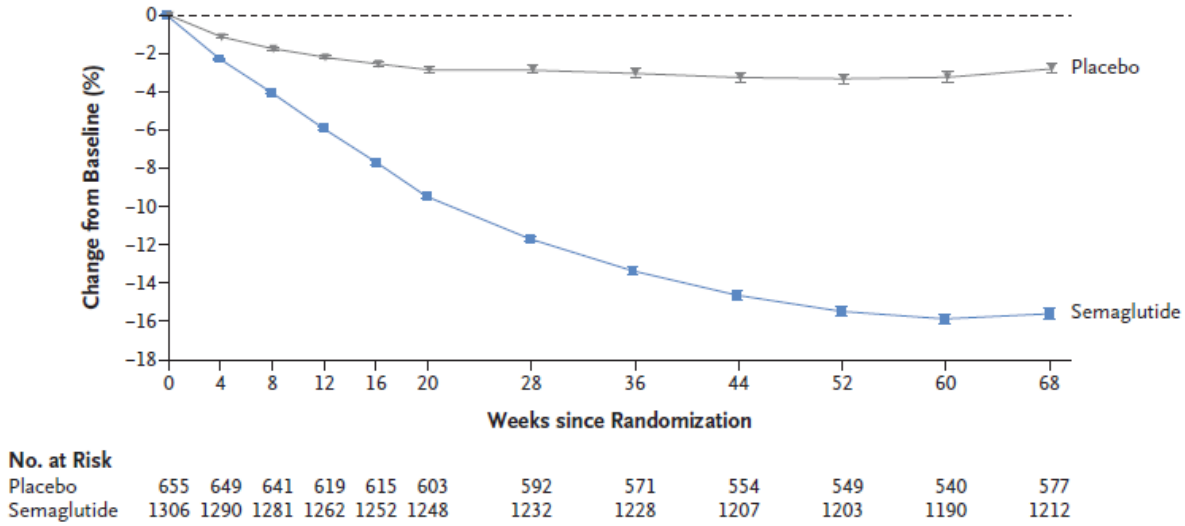
B.2.6.1 Co-primary endpoint: percentage weight change

In the semaglutide 2.4 mg treatment arm, weight loss was observed from the first post-randomisation assessment (4 weeks) onward, reaching a nadir at 60 weeks (Figure 4).[83] In the placebo arm, weight loss decreased less and a plateau was reached after approximately 20 weeks of treatment. The estimated mean weight change at 68 weeks (based on observed data) was −14.9% with semaglutide 2.4 mg, compared to −2.4% with placebo (estimated treatment difference [ETD]: −12%; 95% CI: −13.4, −11.5; p < 0.001).[83] Overall, approximately 95% of patients receiving

semaglutide 2.4 mg experienced weight loss, compared with 65% of patients receiving placebo.[85]

The mean change in body weight (based on observed data) from baseline to 68 weeks was −15.3 kg in the semaglutide 2.4 mg treatment arm compared with −2.6 kg in the placebo treatment arm (ETD: −12.7 kg; 95% CI: −13.7, −11.7).[83]

Figure 4: Mean (%) change in body weight from baseline by week, observed data

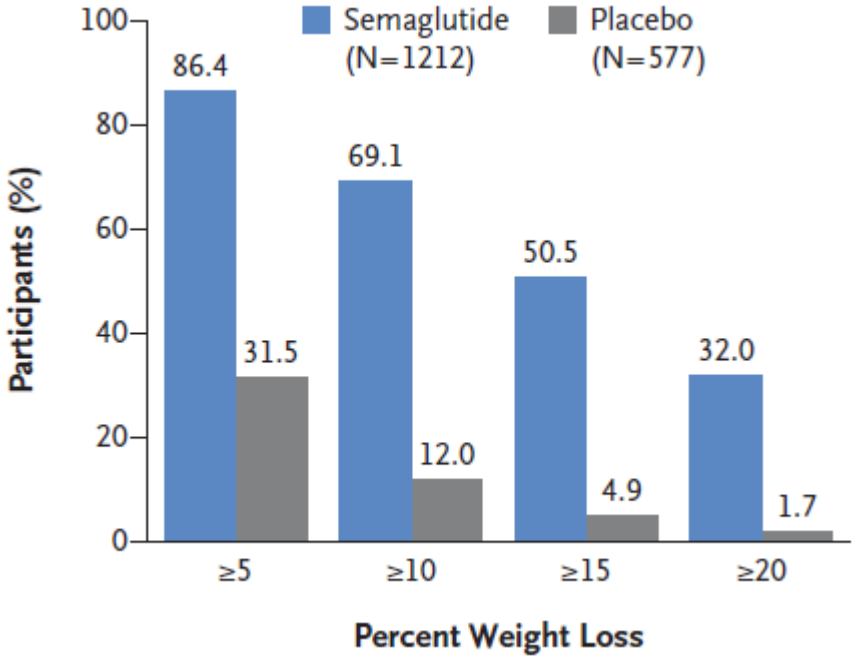


Source: Wilding et al. 2021.[83]

B.2.6.2 Co-primary and secondary endpoints: categorical weight change

Patients in the semaglutide 2.4 mg treatment arm were more likely to lose ≥ 5% (i.e. co-primary endpoint), ≥ 10%, ≥ 15% and ≥ 20% (i.e. secondary endpoints) of their baseline body weight at Week 68 compared with those who received placebo (Figure 5); the difference was significant ($p < 0.001$) for the ≥ 5%, ≥ 10% and ≥ 15% thresholds (the 20% threshold was not part of the statistical testing hierarchy).[83] Note that at 68 weeks, categorical weight loss results were available for 1212 patients in the semaglutide 2.4 mg treatment arm and 577 patients in the placebo treatment arm (Figure 5).

Figure 5: Proportion of patients achieving ≥ 5%, ≥ 10%, ≥ 15% and ≥ 20% weight loss at 68 weeks

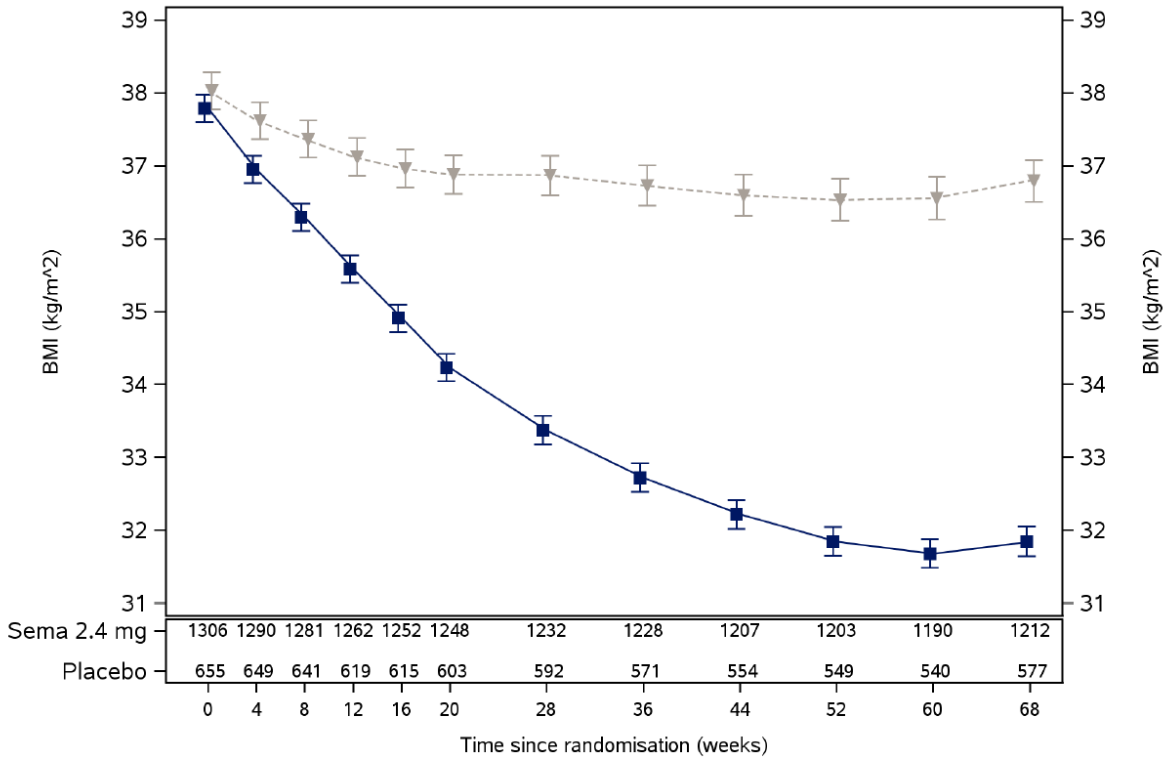


Source: Wilding et al. 2021.[83]

B.2.6.3 Secondary endpoint: change in BMI

At baseline, mean BMI was similar in the semaglutide 2.4 mg and placebo treatment arms (37.8 mg/kg^2 versus 38.0 mg/kg^2, respectively). Figure 6 presents the mean change in BMI by week for patients in the semaglutide 2.4 mg and placebo treatment arms. After 68 weeks, semaglutide 2.4 mg was associated with greater reductions from baseline than placebo in average BMI (-5.54 versus -0.92, respectively; ETD [95%CI]: -4.61 [-4.96, -4.27]).[83]

Figure 6: Mean (%) change in body mass index from baseline by week



Source: Novo Nordisk (STEP 1 clinical study report), 2020.

B.2.6.4 Secondary endpoint: change in systolic blood pressure

Full details of the waist circumference analysis are presented in Appendix R1. Overall, treatment with semaglutide 2.4 mg resulted in greater reductions from baseline in systolic blood pressure (SBP) compared with placebo (−6.16 mmHg versus −1.06 mmHg; ETD: –5.1; 95% CI: –6.3, –3.9).[83]

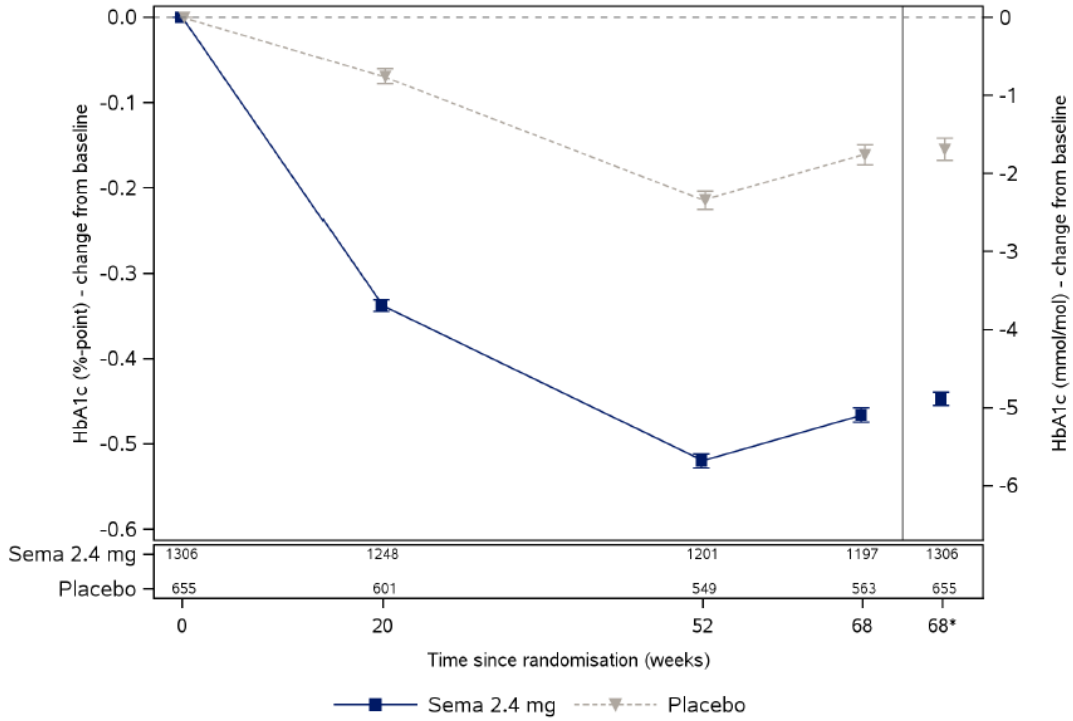
B.2.6.5 Fasting lipid profile

Full details of the fasting lipid profile analysis are presented in Appendix R2. Regarding total cholesterol levels, the mean (standard deviation [SD]) change from baseline to 68 weeks in the semaglutide 2.4 mg and placebo treatment arms was -0.04 (0.14) and 0.00 (0.13), respectively.[94] For HDL levels, the mean (SD) change from baseline to 68 weeks in the semaglutide 2.4 mg and placebo treatment arms was 0.04 (0.14) and 0.01 (0.14), respectively.[94] Note that these results are on the log-scale.

B.2.6.6 Change in HbA1c from baseline

Semaglutide 2.4 mg was associated with greater reductions from baseline in HbA1c than placebo at 68 weeks (mean reduction of −0.5% versus −0.2%, respectively; ETD: −0.29%; 95% CI: −0.32, −0.26), as presented in Figure 7.[85] The mean HbA1c decreased from baseline through to Week 52 in both treatment arms, but to a larger extent in the semaglutide 2.4 mg arm (Figure 7).[85]

Figure 7: Mean change in HbA1c by week



Key: HbA1C, haemoglobin A1C.
Source: Novo Nordisk (STEP 1 clinical study report), 2020.[85]

B.2.6.7 Secondary endpoint: change in waist circumference

Full details of the waist circumference analysis are presented in Appendix R3. Overall, semaglutide 2.4 mg was associated with greater reductions from baseline in waist circumference than placebo (mean reduction of –13.54 cm versus –4.13 cm, respectively; ETD: –9.42 cm; 95% CI: –10.30¸–8.53).[83]

B.2.6.8 Secondary endpoint: change in glycaemic status

Glycaemic status (normo-glycaemia, prediabetes [non-diabetic hyperglycaemia] and T2D [per NICE preferred definitions]) was assessed at baseline and 68 weeks. At

these time points, data were available for 1,306 patients in the semaglutide 2.4 mg arm and 655 patients in the placebo arm.[95] Table 8 presents the glycaemic status at baseline for patients in the semaglutide 2.4 mg and placebo treatment arms. Note that the proportion of patients in each category was similar between treatment arms.

Table 8: Glycaemic status at baseline during STEP 1

Glycaemic category at baseline	Semaglutide 2.4 mg (n = 1,306)	Placebo (n = 655)
Number of patients, n (%)		
Normo-glycaemia	738 (56.5)	367 (56.0)
Non-diabetic hyperglycaemia	550 (42.1)	271 (41.4)
Type 2 diabetes	18 (1.4)	17 (2.6)
Source: Novo Nordisk (STEP 1 data on file).[95]		

Of those patients who had non-diabetic hyperglycaemia at baseline, a greater proportion of patients treated with semaglutide 2.4 mg shifted to normo-glycaemic at 68 weeks than with placebo (79.8% versus 39.1%, respectively).[95] Similarly, of those patients who had either T2D or normo-glycaemia at baseline, a greater proportion of those treated with semaglutide 2.4 mg shifted to or remained normo-glycaemic at 68 weeks than with placebo (61.1% versus 23.5%, and 95.3% versus 83.4% respectively).[95]

B.2.6.9 Secondary endpoint: health-related quality of life

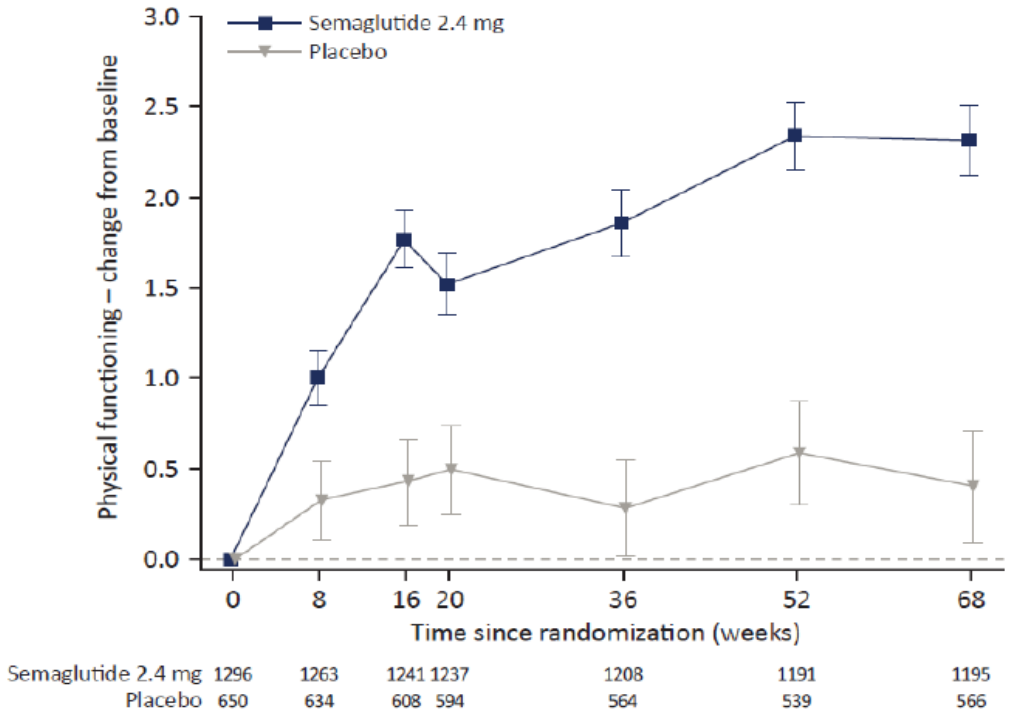
This section presents the results of the HRQoL analyses using the 36-Item Short Form Survey (SF-36) and the short form of Impact of Weight on Quality of Life-Lite for Clinical Trials (IWQOL-Lite-CT). The two measures are the most commonly used to assess the effect of weight loss in patient functioning and HRQoL.[57] The focus of this section is the impact of semaglutide 2.4 mg on patient physical functioning relative to placebo given the prominence of this factor on HRQoL in patients with obesity (as discussed in Section B.1.3.3.2)[57, 58]; the overall results are presented in Appendix R4. Information about the instruments used in the analyses is also provided in Appendix R4.

B.2.6.9.1 SF-36

At baseline, mean SF-36 scores (all domains) were similar between the semaglutide 2.4 mg and placebo treatment arms.[85] After 68 weeks, semaglutide 2.4 mg was associated with improvements in patients' physical and mental functioning, as measured using SF-36. SF-36 scores are norm-based scores (NBS). NBS are scores transformed to a scale where the 2009 US general population has a mean of 50 and a standard deviation of 10.

Figure 8 presents the mean change in SF-36 physical functioning score from baseline to 68 weeks. The estimated mean change in physical functioning score was significantly greater ($p < 0.001$) for semaglutide 2.4 mg compared with placebo (2.21 versus 0.41, respectively; ETD: 1.8; 95% CI: 1.2, 2.4).[83] Note also that a higher proportion of patients achieved a clinically meaningful within-patient change (i.e. an increase of at least 3.7 points) with semaglutide 2.4 mg compared with placebo (40% versus 27%; OR [95% CI]: 2.08 [1.60, 2.70]).[83]

Figure 8: Change in SF-36 physical functioning score by week



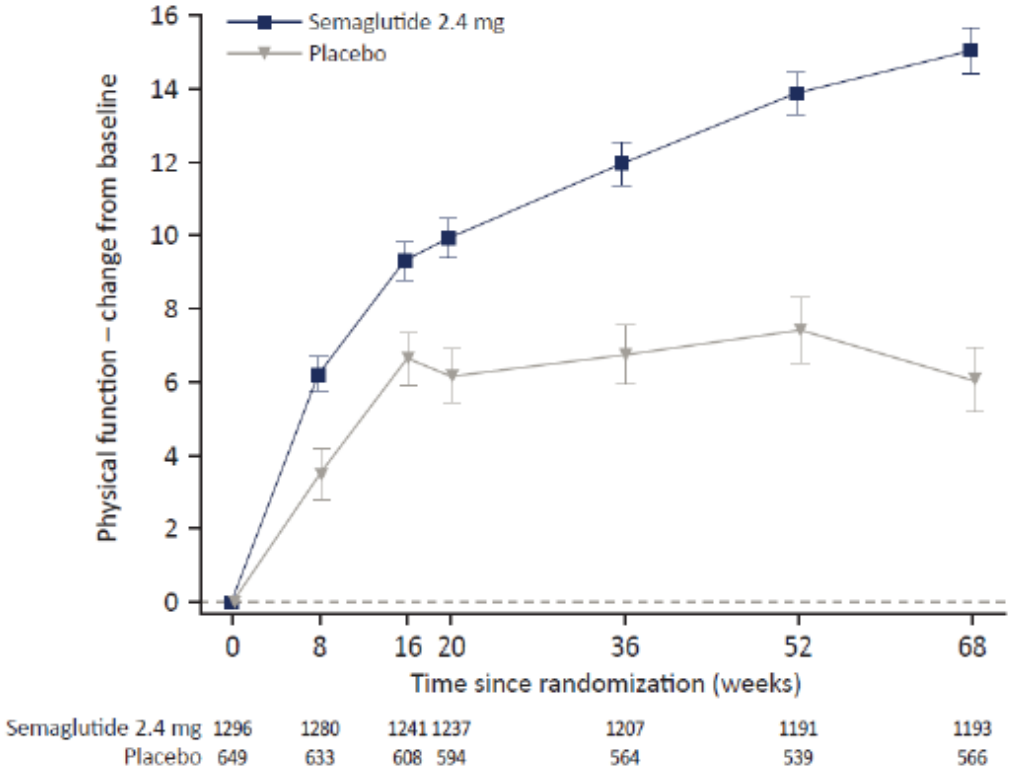
Notes: SF-36 scores are norm-based scores (NBS). NBS are scores transformed to a scale where the 2009 US general population has a mean of 50 and a standard deviation of 10.
Source: Wilding et al. 2021.[83]

B.2.6.9.2 IWQOL-Lite-CT scores

At baseline, mean IWQOL-Lite-CT scores (all domains) were similar between the semaglutide 2.4 mg and placebo treatment arms.[85]

Figure 9 presents the mean change in IWQOL-Lite-CT physical functioning score from baseline to 68 weeks. The estimated mean change in physical function score was significantly greater ($p < 0.001$) for semaglutide 2.4 mg compared with placebo (14.67 versus 5.25, respectively; ETD: 9.43; 95% CI: 7.5, 11.35).[83] Again, a higher proportion of patients achieved a clinically meaningful within-patient change (i.e. an increase of at least 14.6 points) with semaglutide 2.4 mg compared with placebo (51% versus 33%; OR [95% CI]: 2.72 [2.14, 3.47]).[83]

Figure 9: Change in IWQOL-Lite physical function score by week



Key: IWQOL-Lite-CT, short form of Impact of Weight on Quality of Life-Lite for Clinical Trials.
Source: Wilding et al. 2021.[83]

B.2.7. Subgroup analysis

This section presents the post-hoc subgroup analyses for the STEP 1 trial. The in-trial efficacy results evaluated using the treatment policy estimand are presented for

the target population (i.e. patients with a BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity), which represented 75.0% of the FAS, and the BMI ≥ 35 mg/kg^2 plus non-diabetic hyperglycaemia plus high CV risk subgroup, which represented 21.5% of the FAS (presented in Sections B.2.7.1 and B.2.7.2, respectively). The corresponding results of the efficacy analysis for these subgroups using the trial product estimand are presented in Appendix E2. Note that the results of the pre-specified analysis for the DEXA subgroup are provided in Appendix E3.

Overall, semaglutide 2.4 mg performed consistently well across all subgroups analysed.

B.2.7.1 Patients with a BMI ≥ 30 mg/kg^2 with at least one comorbidity

Table 9 presents the results of the efficacy analyses for the target population relative to the efficacy results of the FAS analyses. Overall, the results of the efficacy analyses conducted for the target population were consistent with those of the FAS.[83, 96]

Table 9: Co-primary, confirmatory and selective supportive secondary endpoints for the BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity subgroup

	BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity (n = 1,470)		**Full analysis set (n = 1,961)**	
	Semaglutide 2.4 mg (n = 974)	**Placebo (n = 496)**	**Semaglutide 2.4 mg (n = 1306)**	**Placebo (n = 655)**
Coprimary end point: change from baseline to Week 68				
Mean body weight, % (SD)	-14.8 (8.8)	-2.6 (8.8)	-14.9 (9.1)	-2.5 (9.1)
Confirmatory secondary end points: change from baseline to Week 68				
Mean waist circumference, cm (SD)	-13.6 (8.8)	-4.3 (8.8)	-13.5 (8.8)	-4.2 (8.8)
Mean systolic blood pressure, mm Hg (SD)	-6.4 (12.1)	-1.0 (12.1)	-6.1 (11.9)	-1.0 (11.9)
Supportive secondary end points: change from baseline to Week 68				
Mean HbA1C, % (SD)	-0.5 (0.3)	-0.1 (0.3)	-0.4 (0.3)	-0.1 (0.3)
Mean HDL cholesterol[a], mg/dL (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
Mean total cholesterol[a], mg/dL (SD)	-0.0 (0.1)	0.0 (0.1)	-0.0 (0.1)	0.0 (0.1)
Glycaemic shift from baseline to Week 68				

Number of patients with non-diabetic hyperglycaemia at baseline	518	253	550	271
Proportion of patients shifting from non-diabetic hyperglycaemia to normo-glycaemic, n (%)	410 (79.2)	99 (20.0)	439 (79.8)	106 (39.1)

Key: BMI, Body Mass Index; HbA1C, haemoglobin A1C; HDL, high density lipoprotein; SD, standard deviation.
Notes: Data presented as ratio to baseline and estimated treatment ratio (ratios to baseline and corresponding baseline values were log-transformed prior to analysis).
The estimation of slopes used for single imputation of missing off-treatment results has been updated to ensure a more optimal use of data. The referenced STEP 1 subgroup data provide the updated analysis, but this table lists the previous results since the update happened very close to the submission date. Previously, linear regression was done on means for each visit week, but now linear regression is done using the individual assessments for all participants. This impacts the estimated slopes, but due to the small amount of missing data, the change in slopes has minor effect on the estimates for the different endpoints.
Source: Novo Nordisk (STEP 1 subgroup data – change from baseline)[96] Novo Nordisk (STEP 1 data on file)[95]; Wilding et al. 2021.[83]

B.2.7.2 Patients with a BMI ≥ 35 mg/kg^2 plus non-diabetic hyperglycaemia plus high cardiovascular risk

Table 10 presents the results of the efficacy analyses for the BMI ≥ 35 mg/kg^2 plus non-diabetic hyperglycaemia plus high CV-risk subgroup relative to the efficacy results of the FAS analyses. Overall, the results of the efficacy analyses conducted for the BMI ≥ 35 mg/kg^2 plus non-diabetic hyperglycaemia plus high CV risk subgroup were similar to those of the FAS.[83, 96]

Table 10: Co-primary, confirmatory and selective supportive secondary endpoints for the BMI ≥ 35 mg/kg^2 plus non-diabetic hyperglycaemia plus high CV-risk subgroup

	BMI ≥ 35 mg/kg^2 plus non-diabetic hyperglycaemia plus high CV-risk (n = 421)		**Full analysis set (n = 1,961)**	
	Semaglutide 2.4 mg (n = 273)	**Placebo (n = 148)**	**Semaglutide 2.4 mg (n = 1306)**	**Placebo (n = 655)**
Coprimary end point: change from baseline to Week 68				
Mean body weight, % (SD)	-14.2 (8.9)	-2.8 (8.8)	-14.9 (9.1)	-2.5 (9.1)
Confirmatory secondary end points: change from baseline to Week 68				
Mean waist circumference, cm (SD)	-13.1 (9.1)	-5.4 (9.1)	-13.5 (8.8)	-4.2 (8.8)

Mean systolic blood pressure, mm Hg (SD)	-7.7 (12.3)	-1.6 (12.3)	-6.1 (11.9)	-1.0 (11.9)
Supportive secondary end points: change from baseline to Week 68				
Mean HbA1C, % (SD)	-0.5 (0.3)	-0.2 (0.3)	-0.4 (0.3)	-0.1 (0.3)
Mean HDL cholesterol[a], mg/dL (SD)	0.1 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
Mean total cholesterol[a], mg/dL (SD)	-0.0 (0.1)	-0.0 (0.1)	-0.0 (0.1)	0.0 (0.1)
Glycaemic shift from baseline to Week 68				
Number of patients with non-diabetic hyperglycaemia at baseline	273	148	550	271
Proportion of patients shifting from non-diabetic hyperglycaemia to normo-glycaemic, n (%)	214 (78.4)	54 (36.5)	439 (79.8)	106 (39.1)

Key: BMI, Body Mass Index; CV, cardiovascular; HbA1C, haemoglobin A1C; HDL, high density lipoprotein; SD, standard deviation.
Notes: Data presented as ratio to baseline and estimated treatment ratio (ratios to baseline and corresponding baseline values were log-transformed prior to analysis).
The estimation of slopes used for single imputation of missing off-treatment results has been updated to ensure a more optimal use of data. The referenced STEP 1 subgroup data provide the updated analysis, but this table lists the previous results since the update happened very close to the submission date. Previously, linear regression was done on means for each visit week, but now linear regression is done using the individual assessments for all participants. This impacts the estimated slopes, but due to the small amount of missing data, the change in slopes has minor effect on the estimates for the different endpoints.
Source: Novo Nordisk (STEP 1 subgroup data – change from baseline)[96]; Novo Nordisk (STEP 1 data on file)[95]; Wilding et al. 2021.[83]

B.2.8. Meta-analysis

All efficacy data supporting the use of semaglutide 2.4 mg for the treatment of adult patients with a BMI ≥ 30 kg/m^2 and at least one weight-related comorbidity were provided by the STEP 1 trial; therefore, a meta-analysis was not required.

B.2.9. Indirect and mixed treatment comparisons

The STEP 1 trial provides head-to-head data for semaglutide 2.4 mg as an adjunct to lifestyle intervention (counselling, a reduced calorie diet [500 kcal/day deficit relative to estimated total energy expenditure at Week 0] together with 150 minutes/week of physical activity) versus lifestyle intervention without pharmacotherapy. In the absence of STEP 8, a head to head trial of semaglutide 2.4mg vs liraglutide 3.0mg, which will report in Q4 2021, an indirect treatment comparison (ITC) was conducted between semaglutide 2.4 mg and liraglutide 3.0 mg using individual patient data (IPD).An SLR was conducted to identify relevant studies

for inclusion in the indirect comparisons of semaglutide 2.4 mg versus liraglutide 3.0 mg; details of the SLR and a summary of the included studies is presented in Appendix D. The ITCs included data from two trials: STEP 1, providing patient data for semaglutide 2.4 mg; and SCALE obesity and pre-diabetes (SCALE 1839), providing patient data for liraglutide 3.0 mg. A summary of the methodology and outcomes of the STEP 1 trial is presented in Sections B.2.3-B.2.10. A summary of the methodology and outcomes of the STEP 1 trial is presented in Appendix D.1.3.1.

The main patient population of interest consisted of sub-populations of patients from these trials, those with a BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high CV risk.[97] Table 11 presents the baseline characteristics of patients with a BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high CV risk in the STEP 1 and SCALE 1839 trials. Note that only those characteristics identified as potential effect modifiers are presented (the effect modifiers are discussed further in Section B.2.9.1.1). Overall, the baseline characteristics for patients with a BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high CV risk were similar between the STEP 1 and SCALE 1839 trial.

Table 11: Baseline characteristics of patients in the STEP 1 and SCALE 1839 trials: patients with a BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high CV risk

Variable	SCALE 1839 (n = 3731)	STEP 1 (n = 1,961)
Age, years, mean (SD)	48.2 (11.24)	48.1 (12.06)
BMI, kg/m^2, mean (SD)	41.7 (5.35)	42.1 (6.28)
HbA_{1c}, %, mean (SD)*	5.8 (0.34)	5.9 (0.28)
Weight, kg, mean (SD)*	115.9 (19.76)	117.2 (21.91)
CVD, n/N (%)	88/800 (11.0)	36/421 (8.6)
Dyslipidaemia, n/N (%)	272/800 (34.0)	164/421 (39.0)
Hypertension, n/N (%)	389/800 (48.6)	190/421 (45.1)
Female, n/N (%)*	606/800 (75.8)	314/421 (74.6)

Key: BMI, body mass index; CVD, cardiovascular disease; HbA1c, haemoglobin A1C; NICE, National Institute for Health and Care Excellence; SD, standard deviation.
Notes: *, indicates variables considered potential effect modifiers for adjustment 1 and the remaining variables were considered in addition to the adjustment 1 variables for adjustment 2.
Source: Novo Nordisk (ITC report), 2021.[97]

B.2.9.1 Methods

Full details of the statistical methods used in the ITCs are provided in the ITC report.[97] The ITCs were conducted using linear regression analyses for the continuous outcomes of change from baseline (listed above).[97] A logistic regression analysis was performed for the binary endpoint of reaching normo-glycemic status.[97] Methods were conducted in accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[98]

B.2.9.1.1 Potential effect modifiers

For both semaglutide 2.4 mg and liraglutide 3.0 mg, exposure is inversely dependent on body weight.[97] In published pharmacokinetic analyses of semaglutide 2.4 mg and liraglutide 3.0 mg, gender was found to have an impact on exposure to liraglutide 3.0 mg, whereas the effect of gender on exposure to semaglutide 2.4 mg was minor. In addition, published evidence indicates that the treatment effect of liraglutide depends on baseline HbA1c in diabetic populations. Race, ethnicity and age were not found to have a clinically relevant effect on exposure for either semaglutide 2.4 mg or liraglutide 3.0 mg. Note that the factors affecting exposure to semaglutide 2.4 mg and liraglutide 3.0 mg were independent of the patient populations (i.e. obese versus diabetic).[97]

Age, dyslipidemia, hypertension and cardiovascular disease (CVD) were also included in the ITC as potential effect modifiers.[97] While these additional included effect modifiers were not thought to be effect modifiers for treatment with GLP-1 receptor agonists, they represent key comorbidity measures where a population adjustment can provide reassurance.[97]

B.2.9.1.2 Analyses conducted

Several analyses were conducted during the ITC. The unadjusted analysis was chosen as the base case because the results of the population adjustment had no impact on the outcomes of the ITC. A series of additional analyses were conducted to explore the impact of adjustments for potential effect modifiers (population adjustment 1 & 2 – see below), time-points, estimands (treatment policy versus trial product) and population (patients with a BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high CV risk versus patients with non-diabetic

hyperglycaemia).[97] The following analyses were conducted for the primary time point of interest (Week 52 for STEP 1 and Week 56 for SCALE 1839):[97]

- Unadjusted analysis – performed on the sub-population of patients with a BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high CV risk, and for the broader subpopulation of patients with non-diabetic hyperglycaemia
- Population adjustment 1 (results adjusted to SCALE 1839 population) – for all endpoints, gender and body weight were included as potential effect modifiers. For HbA1c and glycaemic status endpoints, baseline HbA1c was also included as a potential effect modifier
- Population adjustment 2 (results adjusted to SCALE 1839 population) – in addition to the potential effect modifiers in population adjustment 1, the following potential effect modifiers were also included:
  - Age (in years)
  - Dyslipidaemia (yes/no)
  - Hypertension (yes/no)
  - Cardiovascular disease (CVD) (yes/no)
- Analysis of patients with non-diabetic hyperglycaemia

Additional analyses were conducted at various time-points.[97] It was assumed that if no differences between the results of the unadjusted and adjusted analyses were observed at the primary time point of interest, then adjustment would also have no impact on the results of the analyses at different time points. As this was the case in all analyses (except for the analysis of normo-glycaemic status), only unadjusted analyses were conducted for ITCs considering the following alternative timepoints:[97]

- Week 56 in STEP 1 and Week 56 in SCALE 1839
- Week 68 in STEP 1 and Week 56 in SCALE 1839
- Week 28 in STEP 1 and Week 28 in SCALE 1839

Further scenarios considered the impact of estimands on the ITC and analyses were conducted to explore the impact of using a trial product estimand for all unadjusted analyses conducted (at the primary time point of interest and two alternative time points considered):[97]

- Week 52 in STEP 1 and Week 56 in SCALE 1839 - primary time point considering the trial product estimand
- Week 68 in STEP 1 and Week 56 in SCALE 1839 considering trial product estimand
- Week 28 in STEP 1 and Week 28 in SCALE 1839 considering the trial product estimand

B.2.9.1.3 Outcomes investigated during the indirect comparisons

As a base case, outcomes in STEP 1 at week 52 were compared with outcomes in SCALE 1839 at week 56, corresponding to approximately 1 year after randomisation in each trial.[97] This comparison was considered to be conservative as week 52 in STEP 1 corresponded to 36 weeks of treatment with the maintenance dose of semaglutide 2.4 mg, whereas week 56 in SCALE 1839 corresponded to 52 weeks on the target dose of liraglutide 3.0 mg.[97] The endpoints compared in the ITCs of semaglutide 2.4 mg and liraglutide 3.0 mg included change from baseline to Week 52 (STEP 1) or Week 56 (SCALE 1839) in:[97]

- Body weight (%)
- SBP (mmHg)
- HDL cholesterol (mg/dl)
- Total cholesterol (mg/dl)
- HbA1c (%)
- Waist circumference (cm)

Glycaemic status at the end of treatment was also compared:[97]

- T2D (Yes/No)
- Normo-glycaemic (FPG < 5.5 mmol/L and HbA1c < 6.0%; Yes/No)

Note that lipid data were not collected at week 52 or 56 in STEP 1.[97] Therefore, the lipid values corresponding to week 56 in STEP 1 were obtained using linear interpolation of the values collected at week 20 and week 68.[97]

B.2.9.2 Results

The results of the unadjusted population analysis (base case) at the primary time point of interest (Week 52 for STEP 1 and Week 56 for SCALE 1839) using the treatment policy estimand are presented in Table 12. The results of the unadjusted population analysis at the primary time point of interest using the trial product estimand, and the results of the scenario analyses (population adjustment 1, population adjustment 2, and unadjusted non-diabetic hyperglycaemia population), are provided in Appendix D4.

The results of the ITC suggest that semaglutide 2.4 mg was associated with a statistically significant reduction in change from baseline in body weight, HbA1c and waist circumference compared with liraglutide 3.0 mg.[97] In addition, Semaglutide 2.4 mg was also associated with a numerically greater reduction in SBP compared with liraglutide 3.0 mg, although the results did not reach statistical significance. Furthermore, the results of the ITC suggested that across both trials, treatment with semaglutide 2.4 mg and liraglutide 3.0 mg resulted in similar changes from baseline in HDL and total cholesterol. For the binary endpoint of reversion of T2D status to normo-glycaemic status, semaglutide 2.4 mg was associated with significantly higher odds of achieving normo-glycaemic status compared with liraglutide 3.0 mg. For all but one endpoint, the results were consistent across all analyses conducted. The only exception was the normo-glycaemia analysis, which was no longer statistically significant after adjusting for differences in trial populations.[97] This was driven by a slightly lower baseline HbA1c in SCALE 1839 (5.8%) versus STEP 1 (5.9%); the closer a population is to being normo-glycaemic (i.e. HbA1c < 5.7%), the lower the incremental glycaemic effect of adding a more potent GLP-1 receptor agonist.

Table 12: Base-case results of the indirect comparisons of semaglutide 2.4 mg (STEP 1) versus liraglutide 3.0 mg (SCALE 1839)

Outcome	Estimate of relative treatment effect (semaglutide 2.4 mg vs liraglutide 3.0 mg)
Change from baseline, mean difference (95% CI), p-value	
Weight, %	-5.81 (-7.62, -3.99), p < 0.0001
SBP, mm Hg	-1.64 (-4.60, 1.32), p = 0.2783
HbA1c, %	-0.13 (-0.20, -0.06), p = 0.0002
Waist circumference, cm	-3.59 (-5.56, -1.61), p = 0.0004

Ratio to baseline (95% CI), p-value	
HDL	1.01 (0.98, 1.04), p = 0.5705
Total cholesterol	0.97 (0.94, 1.00), p = 0.0961
OR (95% CI), p-value	
Normo-glycaemic status	1.79 (1.01, 3.16), p = 0.0455
Key: CI, confidence interval; HbA1c; haemoglobin A1c; HDL, high density lipoprotein; OR, odds ratio; SBP systolic blood pressure. **Source**: Novo Nordisk (ITC report), 2021.[97]	

B.2.9.3 Uncertainties from the indirect comparisons

A general uncertainty in anchored indirect treatment comparisons is the potential for bias due to effect modifiers that are in imbalance between trial populations. Since STEP 1 and 1839 were conducted in very similar populations, the potential for imbalance of effect modifiers was low, and unadjusted comparisons were considered as the primary indirect treatment comparisons. However, these were supplemented with population-adjusted analyses, with effect modifiers elicited based on published evidence. As a sensitivity analysis, the population-adjusted analyses were repeated to include further adjustment variables into the model to verify that population-adjusted results were robust to the choice of putative effect modifiers.

Another general uncertainty is related to the handling of intercurrent events of treatment discontinuation and the use of rescue medication in the statistical analysis. To compensate for this, a trial product estimand strategy was applied as an alternative strategy to the primary treatment policy estimand strategy, the results of which were broadly consistent with the base case.

A specific uncertainty in the indirect treatment comparison of STEP 1 and 1839 is the different study duration. This was assessed by means of sensitivity analyses in regard to evaluation time points for the endpoints studied, which again were broadly consistent with the base case.

B.2.9.4 Conclusions from the indirect comparisons

In a population of patients with BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high CV risk, when considering the effect of approximately one year of treatment based on the treatment policy estimand, the results of the ITC suggested that semaglutide 2.4 mg was associated with a statistically significant reduction in body

weight, HbA1c and waist circumference compared with liraglutide 3.0 mg.[97] For the binary endpoint of reversion of T2D status to normo-glycaemic status, semaglutide 2.4 mg was associated with higher odds of achieving normo-glycaemic status compared with liraglutide 3.0 mg. However, the results of the normo-glycaemia analysis were no longer statistically significant after adjusting for differences in trial populations (see Appendix D4). This was driven by the minor population difference in HbA1c of 0.1%-points, because the glycaemic effect of adding a more potent GLP-1 receptor agonists diminishes in a population that is predominantly normo-glycemic.[97]

Across all continuous outcomes, the results of the ITCs which adjusted for potential treatment effect modifiers (population adjustment 1 & 2, Appendix D4) were consistent with the unadjusted analyses.[97] Similarly, the results of the analyses conducted in the pre-diabetic population, using alternative time points, and considering the trial product estimands were consistent with the unadjusted base-case analysis across all outcomes (Appendix D4).[97]

B.2.10. Adverse reactions

This section presents the results of the STEP 1 safety evaluation, which was based on the safety analysis set (see Section B.2.4.1 for a definition). The on-treatment period is used for most evaluations as it represents the period when patients were considered exposed to treatment. AEs with onset during the on-treatment period correspond to treatment-emergent AEs (TEAEs). For deaths and event types with potential long latency to diagnosis, the in-trial period is used (see Section B.2.4.3 for observation period definitions).

Given the 2:1 randomisation for semaglutide 2.4 mg versus placebo, the primary focus of the safety evaluation of AEs and adjudicated events is the proportion of patients with events and event rates to ensure a valid treatment comparison. Whenever the number of patients with events or number of events are looked at, and when evaluating treatment differences for infrequent/rare events, the 2:1 randomisation must be kept in mind.

B.2.10.1 Summary of adverse events

A summary of adverse events that occurred during STEP 1 is provided in Appendix F1. Overall, a similar proportion of patients in the semaglutide 2.4 mg and placebo treatment arms reported AEs (89.7% and 86.4%, respectively).[83]

B.2.10.1.1 Most common adverse events

Table 13 presents the most common AEs reported in ≥ 10% of patients. In the semaglutide 2.4 mg treatment arm, the most common AEs were gastrointestinal disorders, particularly nausea (44.2% of patients), diarrhoea (31.5% of patients), vomiting (24.8% of patients), and constipation (23.4% of patients).[83] In the placebo treatment arm, the most common AEs were nasopharyngitis (20.3% of patients), nausea (17.4% of patients), diarrhoea (15.9% of patients), headache and upper respiratory tract infection (both experienced by 12.2% of patients).[83]

Table 13: Most common adverse events reported in ≥ 10% of patients

	Semaglutide 2.4 mg (n = 1,306)			**Placebo (n = 655)**		
	Patients, n (%)	**Events, n (%)**	**Events/100 person-years**	**Patients, n (%)**	**Events, n (%)**	**Events/100 person-years**
Any AE*	1,171 (89.7)	9,658	566.1	566 (86.4)	3,302	398.0
Nausea	577 (44.2)	1,068 (11.1)	62.6	114 (17.4)	146 (4.4)	17.6
Diarrhoea	412 (31.5)	766 (7.9)	44.9	104 (15.9)	138 (4.2)	16.6
Vomiting	324 (24.8)	636 (6.6)	37.3	43 (6.6)	52 (1.6)	6.3
Constipation	306 (23.4)	390 (4.0)	22.9	62 (9.5)	73 (2.2)	8.8
Nasopharyngitis	281 (21.5)	480 (5.0)	28.1	133 (20.3)	216 (6.5)	26.0
Headache	198 (15.2)	387 (4.0)	22.7	80 (12.2)	104 (3.1)	12.5
Dyspepsia	135 (10.3)	179 (1.9)	10.5	23 (3.5)	30 (0.9)	3.6
Abdominal pain	130 (10.0)	175 (1.8)	10.3	36 (5.5)	41 (1.2)	4.9
URTI	114 (8.7)	158 (1.6)	9.3	80 (12.2)	116 (3.5)	14.0

Key: AE, adverse event; URTI, upper respiratory tract infection.
Notes: *, on-treatment period.
Source: Novo Nordisk (STEP 1 clinical study report), 2020[85]; Wilding et al. 2021.[83]

B.2.10.2 Adverse events of particular interest

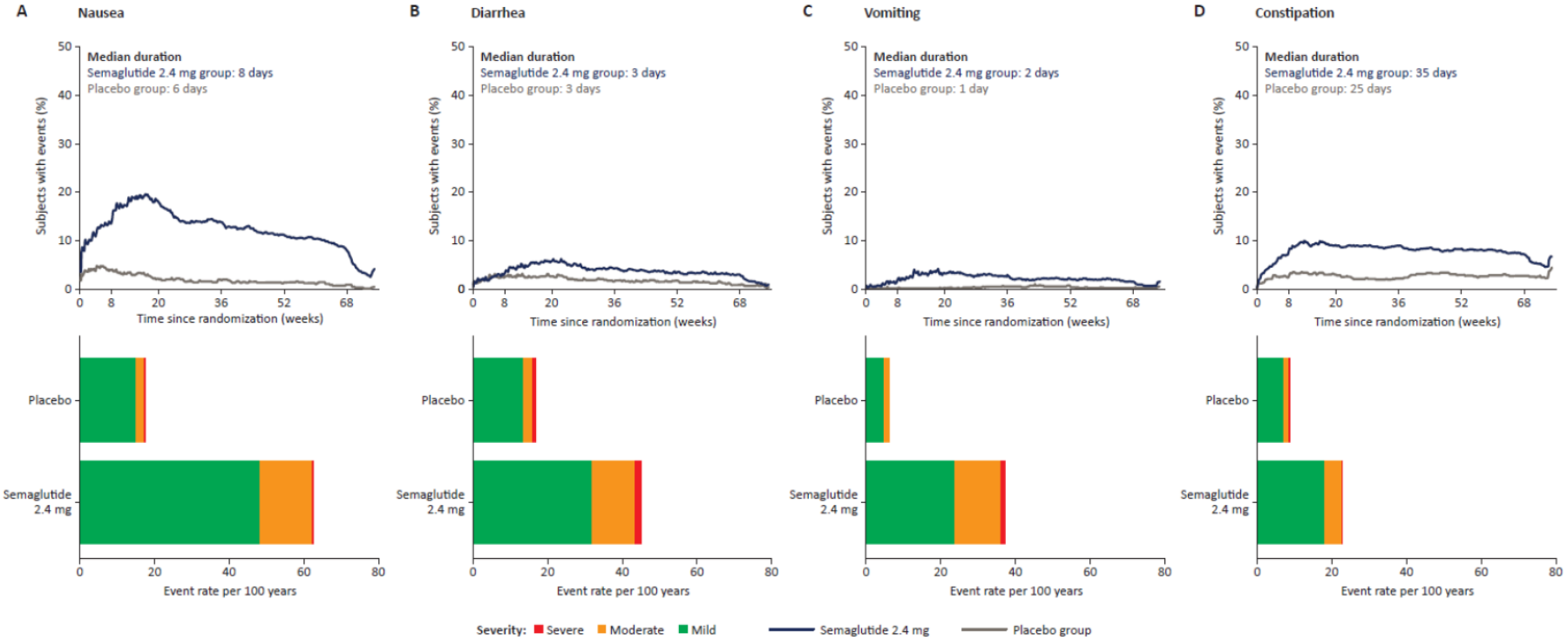
Based on therapeutic experience with GLP-1 receptor agonists and in line with regulatory feedback and requirements, a number of safety focus areas were of special interest in the safety evaluation, as presented in Appendix F2.[83]

B.2.10.2.1 Gastrointestinal disorders

Gastrointestinal disorders (typically nausea, diarrhoea, vomiting, and constipation; Table 13) were the most frequently reported AEs and occurred in more patients receiving semaglutide 2.4 mg than those receiving placebo (74.2% versus. 47.9%; Table 13).

Figure 10 depicts the prevalence and duration of gastrointestinal events by severity. Overall, most gastrointestinal AEs were mild or moderate in severity, were transient, and resolved without permanent discontinuation of the regimen.[83]

Figure 10: Prevalence and duration of gastrointestinal events



Notes: Figure presents the proportion of patients reporting nausea (A), diarrhoea (B), vomiting (C), or constipation (D). Events classed as mild, moderate, or severe, over the course of the treatment period and the median duration of the event. Data are on treatment observation period data (during treatment with trial product [any dose of trial medication administered within the previous 49 days, i.e. any period of temporary treatment interruption with trial product was excluded]). Adverse events were classified by severity as mild (green), moderate (orange) or severe (red).
Source: Wilding et al. 2021.[83]

B.2.10.3 Study withdrawal

Refer to Appendix F3 for a summary of study withdrawals that occurred during STEP 1.

B.2.10.4 Adverse events leading to discontinuation of study treatment, dose interruptions or dose adjustments

Refer to Appendix F4 for a summary of AEs leading to discontinuation of study treatment, dose interruptions or dose adjustments during STEP 1.

B.2.10.5 Use of rescue therapy

Refer to Appendix F5 for a summary of rescue therapy used during STEP 1.

B.2.10.6 Safety summary

Overall, semaglutide 2.4 mg administered once weekly as an adjunct to a reduced-calorie diet and increased physical activity was well tolerated in patients who are overweight or obese, and the majority of reported AEs were mild or moderate in severity. Furthermore, the safety and tolerability profile of semaglutide 2.4 mg was consistent with previous studies of semaglutide as well as with that reported for the GLP-1 receptor agonist class in general; no new safety concerns were identified (further discussed in Section B.2.13).[83, 99, 100]

As is typical of the GLP-1 receptor agonist drug class[99], transient, mild or moderate gastrointestinal disorders were the most frequently reported AEs with semaglutide 2.4 mg.[83] Nausea was the most common gastrointestinal event, occurring primarily during the dose-escalation period, a finding similar to that reported with liraglutide at a dose of 3.0 mg.[101] Gallbladder-related disorders, principally cholelithiasis, were also more common with semaglutide 2.4 than with placebo. Gallbladder-related disorders have been previously reported with GLP-1 receptor agonists and are consistent with the known effects of rapid weight loss.[83]

B.2.11. Ongoing studies

B.2.11.1 STEP programme

Table 14 presents an overview of the STEP clinical trial programme.

Table 14: Summary of STEP trials and rationale for their inclusion in the submission

Study	Study design and status (ongoing/complete)	Included in submission (Yes/No)	Rationale for inclusion/exclusion from the submission
Global Phase IIIa trials			
STEP 1 (weight management)	Phase IIIa, randomised, double-blind, multicentre, placebo-controlled trial in 1,961 adults who were obese (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least one weight-related comorbidity, and without diabetes or HbA1c ≥ 6.5%. **Status**: Complete	Yes	STEP 1 was considered the most appropriate primary evidence source for the target population in this submission, a view shared by clinicians.[23] The patient population was considered highly representative of those patients managed in SWMS in UK clinical practice.[23]
STEP 2 (weight management in T2D)	Phase IIIa, randomised, double-blind, double-dummy, multicentre, placebo- and active-controlled trial in 1,210 adults with T2D, HbA1c 7–10% and who were either overweight or obese (BMI ≥ 27 kg/m^2), who were managed with diet and exercise alone or treated with up to three OADs. **Status**: Complete	No	Trial enrolled patients with T2D and therefore the trial population is not relevant to the submission.
STEP 3 (weight management with IBT)	Phase IIIa, randomised, double-blind, multicentre, placebo-controlled trial of 611 adults who were obese (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least one weight-related comorbidity and without diabetes or HbA1c ≥ 6.5%. **Status**: Complete	No	Semaglutide 2.4 mg was administered in conjunction with IBT. IBT is not considered standard practice in the UK.
STEP 4 (sustained weight management)	Phase IIIa, randomised, double-blind, multicentre, placebo-controlled trial in 902 adults who were obese (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least one	No	NICE scientific advice meeting advised that STEP 4 is not reflective of clinical practice in the UK.

Study	Study design and status (ongoing/complete)	Included in submission (Yes/No)	Rationale for inclusion/exclusion from the submission
	weight-related comorbidity, and without diabetes or HbA1c ≥ 6.5%. **Status**: Complete		
STEP TEENS	Phase IIIa, 68-week double-blind, randomised, parallel group, placebo-controlled, multinational clinical trial comparing semaglutide 2.4 mg once-weekly with placebo in pubertal adolescents, aged 12 to < 18 years, with obesity or overweight with at least one weight-related comorbidity. **Status**: Ongoing	No	Patient population is not relevant to this appraisal.
STEP KIDS	Phase IIIa trial under development (further details not available at this time). **Status**: Ongoing	No	Patient population is not relevant to this appraisal.
STEP HFpEF (obesity)	Phase IIIa trial under development. Primary objective will be to investigate the effects of semaglutide 2.4 mg once-weekly on physical function, disease-specific symptoms, weight-loss, and health related quality of life compared with placebo, both added to standard of care, in patients with obesity and HFpEF (further details not available at this time). **Status**: Ongoing	No	Patient population is not relevant to this appraisal.
STEP HFpEF (T2D)	Phase IIIa trial under development. Primary objective will be to investigate the effects of semaglutide 2.4 mg once-weekly on physical function, disease-specific symptoms, weight-loss, and health related quality of life compared with placebo, both added to standard of care, in patients with	No	Patient population is not relevant to this appraisal.

Study	Study design and status (ongoing/complete)	Included in submission (Yes/No)	Rationale for inclusion/exclusion from the submission
	obesity and T2D and HFpEF (further details not available at this time). **Status**: Ongoing		
Regional Phase IIIa trials			
STEP 6 (East Asian trial)	Regional Phase IIIa, 68-week, randomised, double-blind, placebo-controlled, four-armed, parallel group, multicentre, multinational clinical trial comparing semaglutide 2.4 mg once-weekly with placebo once weekly and semaglutide 1.7 mg once-weekly with placebo once weekly in patients with overweight or obesity. **Status**: Ongoing	No	Patient population and region is not relevant to this appraisal.
STEP 7 (China MRCT)	Regional Phase IIIa, 68-week, randomised, double-blind, placebo-controlled, two-armed, parallel group, multicentre, MCRT comparing semaglutide 2.4 mg once-weekly with placebo in patients with obesity or with overweight and at least one weight-related comorbidity. **Status**: Ongoing	No	Patient population and region is not relevant to this appraisal.
Phase IIIb trials			
STEP 5 (long-term weight management)	Phase IIIa, randomised, double-blind, multicentre, placebo-controlled trial in 304 adults who were obese (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least one weight-related comorbidity, and without diabetes or HbA1c ≥ 6.5%. **Status**: Completed, CTR expected in Q3 2021	No	Data will not be available in time for the submission.

Study	Study design and status (ongoing/complete)	Included in submission (Yes/No)	Rationale for inclusion/exclusion from the submission
STEP 8 (Head-to-head versus liraglutide 3.0 mg)	Phase IIIb, 68-week, randomised, open label, pairwise placebo-controlled, multicentre, US-only clinical trial comparing semaglutide 2.4 mg once weekly with liraglutide 3.0 mg once daily in patinets with obesity or overweight and at least one weight-related comorbidity. Semaglutide once-weekly versus liraglutide once-daily treatment will be open-label, but each of the two active treatment arms will be double blinded against placebo administered at the same dosing frequency. **Status**: Completed, CTR expected Q4 2021	No	Data will not be available in time for the submission.
STEP 9 (Semaglutide in knee osteoarthritis)	Phase IIIb trial under development. Primary objective will be to confirm superiority of semaglutide 2.4 mg once-weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity on body weight and/or knee osteoarthritis-related pain in patients with knee osteoarthritis and obesity (further details not available at this time). **Status**: Ongoing	No	Data will not be available in time for the submission.
STEP 10 (Prediabetes)	Phase IIIb trial under development (further details not available at this time). **Status**: Trial start planned for Q4 2021	No	Data will not be available in time for the submission.
SELECT	Phase IIIb, randomised, double-blind, parallel group, placebo-controlled trial investigating semaglutide 2.4 mg in patients with obesity or overweight and prior cardiovascular disease. The trial population will consist of approximately 17,500 randomised patients, aged ≥ 45 years old with	No	Data will not be available in time for the submission.

Study	Study design and status (ongoing/complete)	Included in submission (Yes/No)	Rationale for inclusion/exclusion from the submission
	established cardiovascular disease and overweight or obesity. **Status**: Ongoing		
Low BMI (Korea/Thailand)	Phase IIIb trial under development (further details not available at this time). **Status**: Ongoing	No	Patient population and region is not relevant to this appraisal.
Phase IV trials			
US employer	Phase IV trial under development (further details not available at this time). **Status**: Ongoing	No	Data will not be available in time for the submission.
Key: HFpEF, heart failure with preserved ejection fraction; IBT, intensive behavioural therapy; MRCT, multiregional clinical trial; OADs, oral anti-diabetic drugs; SWMS, specialist weight management services; T2D, type 2 diabetes.			

B.2.12. Innovation

Over recent years, despite pharmacological advancements for managing patients with obesity, the clinical unmet need in a broad population remains.[23] Previously, patients with obesity who have comorbidities have been unable to receive effective pharmacological intervention within SWMS. Liraglutide 3.0 mg, recently approved by NICE, is restricted for use in a narrow subset of patients with obesity (patients with a BMI ≥ 35 kg/m^2 plus non-diabetic hyperglycaemia plus high CV-risk). However, semaglutide 2.4 mg provides a pharmacological treatment option within SWMS for a broader group of patients with obesity, that could benefit from significantly greater weight loss than previously achieved with other pharmacological interventions.

The weight loss observed with semaglutide 2.4 mg as part of the STEP 1 study (a mean of 15% over 68 weeks) is a significant advancement of more than double the weight loss reported with existing pharmacotherapy options for obesity, which typically provide weight loss of between 5–7%.[23] Furthermore, clinicians have highlighted that there are various weight-related comorbidities impacting patients with obesity that are best placed to benefit from weight loss of 10–15%.[23] As discussed in Section B.1.3.3.1, the benefits of 10–15% weight loss have been demonstrated across a range of weight-related comorbidities, including but not limited to T2D, cardiovascular disease, osteoarthritis, gastroesophageal reflux disease, obstructive sleep apnoea, NASH, hypertension, dyslipidaemia and hyperglycaemia.[17-21, 54] As such, semaglutide 2.4 mg provides a step change in treatment for obesity.

In addition to the direct impact semaglutide 2.4 mg can have in alleviating the current burden of comorbidities in patients with obesity, it can also have additional downstream benefits to patients and wider society by reducing the risk of patients developing future weight-related comorbidities.[22] Weight loss with semaglutide 2.4 mg may also give patients their independence back by allowing them to participate in daily activities, sports and hobbies, or by returning to work.[102] Use of this treatment may also reduce the burden of obesity on the healthcare system through alleviation and prevention of weight-related comorbidities, reducing weight-related hospitalisations and mortality.

B.2.13. Interpretation of clinical effectiveness and safety evidence

In the pivotal STEP 1 study, semaglutide 2.4 mg as an adjunct to lifestyle intervention (diet and exercise) demonstrated considerable benefit over lifestyle intervention alone (placebo arm). On average, patients in the FAS receiving semaglutide 2.4 mg experienced six-times more weight loss compared with patients receiving placebo (−14.9% versus −2.4%, respectively). Moreover, a significantly greater proportion of patients treated with semaglutide 2.4 mg experienced clinically meaningful weight loss of ≥ 5% (86.4% versus 31.5%; $p < 0.001$), ≥ 10% (69.1% versus 12.0%; $p < 0.001$) and ≥ 15% (50.5% versus 4.9%; $p < 0.001$) than with placebo.[83] Greater reductions in waist circumference, systolic blood pressure and HbA1C were also observed with semaglutide 2.4 mg than with placebo.[83] Furthermore, of the patients with non-diabetic hyperglycaemia (i.e. pre-diabetes) at baseline, more than double the proportion of those treated with semaglutide 2.4 mg became normo-glycaemic at 68 weeks compared with those treated with placebo.[95]

The results of the efficacy analyses in the target population (patients with a BMI ≥ 30 mg/kg^2 with at least one weight-related comorbidity) were consistent with those of the FAS, which is unsurprising given the similarities between the two patient populations. In addition, semaglutide 2.4 mg also demonstrated effectiveness in a more severe population of patients with obesity with a BMI ≥ 35 mg/kg^2 with non-diabetic hyperglycaemia and high CV risk (i.e. the liraglutide 3.0 mg eligible population).

Importantly, the clinical benefit obtained with semaglutide 2.4 mg was not achieved at the risk of patient wellbeing. Treatment with semaglutide 2.4 mg resulted in significant and clinically meaningful improvements in HRQoL in patients with obesity. After 68 weeks, semaglutide 2.4 mg was associated with significant improvements in patients' physical functioning, as measured using IWQOL-Lite-CT and SF-36.[83] Regarding safety, semaglutide 2.4 mg was well tolerated and demonstrated a safety profile consistent with that previously reported for semaglutide, and with the GLP-1 receptor agonist class in general, and no new safety concerns were identified.[83, 99, 100] This finding mirrors that of the SUSTAIN 6 trial, a large Phase IIIa pre-approval Cardiovascular Outcomes Trial.[103] SUSTAIN 6 investigated the effects of subcutaneous semaglutide (0.5 mg and 1.0 mg) versus placebo on Major Adverse

Cardiovascular Events (MACE) in patients with T2D and high CV-risk. The trial was designed and conducted in accordance with the US 2008 FDA guidance for evaluating cardiovascular safety in new glucose-lowering therapies. Overall, there was a 26% reduction in the risk of MACE with semaglutide 0.5 mg and semaglutide 1.0 mg relative to placebo (note: these doses are different to that used in obesity [2.4 mg]). In line with STEP 1, the safety profile of semaglutide was overall consistent with that of the GLP-1 RA class, with gastrointestinal adverse events being the most frequently reported adverse drug reactions with semaglutide.[103] It should also be noted that during STEP 1, more patients discontinued treatment due to a lack of efficacy in the placebo arm than in the semaglutide 2.4 mg arm[85], highlighting a desire from patients to be treated with pharmacological intervention.

The results of the indirect treatment comparisons show that in patients with a BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high CV risk, semaglutide 2.4 mg was significantly more effective in reducing body weight, HbA1c and waist circumference compared with liraglutide 3.0 mg.[97] The results also show that patients with non-diabetic hyperglycaemia would benefit greatly from the introduction of semaglutide 2.4 mg.[97] This sentiment is reflected by clinicians who, if approved, would prioritise treatment with semaglutide 2.4 mg ahead of treatment with liraglutide 3.0 mg.[23]

Overall, semaglutide 2.4 mg offers a safe and effective treatment option for patients with a BMI ≥ 30 mg/kg^2 with at least one weight-related comorbidity, offering the potential for weight loss previously unobtainable in SWMS with current pharmacotherapy treatment options.

B.2.13.1 Strengths and limitations of the evidence base

The STEP 1 study was a high-quality trial that enrolled a large and broad population of patients with obesity. STEP 1 included nine clinical trial sites in England and clinicians also considered the patient demographics, disease characteristics and comorbidities to be highly reflective of those patients managed in SWMS in UK clinical practice.[23] Of all the STEP trials, the patient population of STEP 1 was the most reflective of the target population, and therefore STEP 1 was considered the most appropriate primary evidence source for this submission, a view shared by clinicians.[23]

The target population for this submission (patients with a BMI ≥ 30 mg/kg^2 with at least one weight-related comorbidity) was analysed post-hoc and was narrower than the FAS population of the STEP 1 trial. However, the target population represented 75.0% of the FAS and the effiacy results were consistent between the two patient populations. Similarly, although a post-hoc subgroup from STEP 1 was used for the ITC analysis (patients with a BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high CV risk), this population was reflective of the liraglutide 3.0 mg-eligible population and was required for a comparison between semaglutide 2.4 mg and liraglutide 3.0 mg to be made.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

An SLR of cost-effectiveness studies in obesity was conducted in October 2018 with a further update conducted in April 2021. Systematic searches for cost-effectiveness/cost-utility, costs and healthcare resource studies were carried out simultaneously as one combined search to identify all relevant studies on adult patients with obesity. Appendix G provides details of the SLR. In summary, a total of seven published cost-effectiveness analyses which reported results from the UK NHS perspective were identified and reviewed (Table 15). None of the studies identified in the review precisely met the definition of the target population for the present submission, being patients with obesity with a BMI of ≥ 30 mg/kg2 in the presence of at least one weight-related comorbidity (see Section B.1.1 for the full decision problem), nor were any subgroup analyses in this population published. Further, orlistat and bariatric surgery, which were identified as treatments in a number of these studies, were not included as the comparators in this submission.

Of the reviewed studies, one was a piggy-back cost-effectiveness analysis conducted alongside a clinical trial[104]; all other published cost-effectiveness analyses involved some degree of modelling to estimate treatment effect on costs and health outcomes. Cohort, state-transition modelling was used in three of the published cost-effectiveness studies[105-107], two studies used simple decision analyses based on a 1-year and 5-year time horizon,[108, 109] and the final study used a microsimulation state transition model (Monte Carlo simulation) with a 30-year time horizon with computer generated individuals.[110] With the exception of one study published in 2005,[109] and the piggy-back trial analysis[104] – both conducted on a 1-year time-frame analysis – all of the reviewed cost-effectiveness analyses modelled long-term consequences of T2D and CVD in patients with obesity. The association between obesity, onset of T2D and CV disease risk are thus well established in the health-economic literature herein reviewed.[111] One study modelled the association of BMI with colon cancer.[107] The methods used to extrapolate short term changes in BMI to onset of complications differed across studies. For example, Ara et al. 2007[108, 112] used the Framingham risk model to calculate incidence of CVD as a function of BMI. Later, the same authors published a de novo analysis informed by a set of newly

developed risk models;[106] the models were developed on a random sample of adults with data from the General Practice Research Datalink (GPRD) (n = 100,000). Risk models were developed for: onset of type 2 diabetes, incidence of acute myocardial infarction (AMI), stroke and death from any cause as function of BMI, age, gender, smoking status, aspirin, insulin, statin and blood pressure treatment, for T2D and non-T2D cohorts. A natural disease progression model of the BMI trajectory was also estimated by the authors[106] based on the GPRD data.

Table 15: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Foxcroft *et al.* [109]	2005	Decision tree with costs and QALYs assigned to orlistat and placebo responders (assumed zero costs and QALYs in non-responders); time horizon of 1 year; no extrapolation of clinical benefits; assumed a utility gain of 0.017 per unit decrease in BMI;[113] considered costs of obesity pharmacotherapy and GP visits from published NHS tariffs.	Orlistat and placebo responders defined according to NICE or EMA criteria for treatment response	orlistat: 1.498; placebo: 0.567	Incremental: £22,744	£24,431 (SA: £10,856 - £77,197)
Ara *et al.* [108]*	2007	Decision tree analysis on treatment response pathway over 12 months with sibutramine or placebo, followed by a period of up to 5 years natural history weight regain of 1 kg/year; incidence of CHD calculated on trial, patient-level data with Framingham risk model[114] and type 2 diabetes onset using estimates of Colditz et al.[115] and Sjostrom et al.[116]; utility multiplier for CHD of 0.85; assuming diabetes increases mortality by RR 1.33[117] and decreases utility by 0.95; applies a utility gain of 0.00297 per kg lost with sibutramine and 0.00472 gain per kg lost with placebo (unpublished data from SAT trial); assumes 1 GP visit in patients with adverse events; CHD and T2D costs sourced from literature.	Obese individuals free of complications at baseline, mean age 42 years, mean BMI 32.7 kg/m^2, 80% females	Totals not reported; incremental per 1,000 patients 48.5	Totals not reported; incremental per 1,000 patients €572,449	€11,811 (SA: €7,637- €22,701)
Ara *et al.*[105] +	2011	Markov, cohort model comparing orlistat with SoC; obesity complications modelled: first/ recurrent AMI and stroke, T2D; a natural history BMI model was developed on patient-level data (n=100,000) from the GPRD. BMI was linked to onset of cardiovascular disease, T2D and all-cause mortality via risk regression models developed in the same GPRD data; incidence of subsequent cardiovascular events estimated based on the Nottingham Heart Attack register and the South London Stroke register. The authors developed a	Overweight and patients with obesity treated in primary care	not available from the abstract	not available from the abstract	£1,665

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		model for BMI and HRQoL using EQ-5D data controlling for age and comorbidities.				
Ara *et al.* [106]	2012	State-transition Markov model comparing diet and exercise plus one of the following: no active treatment (placebo), orlistat 120mg X3/day, sibutramine 15mg/day, rimonabant 20mg/day. Obesity complications considered: first/ recurrent AMI and stroke, type 2 diabetes; analyses were conducted on a lifetime horizon; BMI effectiveness data from a mixed treatment comparison applied at 3, 6 and 12 months for 1 year; post-active treatment BMI, assumed to return to baseline values linearly over 3 years; post-treatment and weight regain period, a natural disease model was developed with data from the GPRD; transition probabilities to obesity complications (first AMI, and stroke, T2D and all-cause mortality) were estimated based on time-to-event models developed on the GPRD dataset, for type 2 diabetes and non-T2D; BMI, age, gender, use of aspirin, statins and BP treatment were the predictive variables; recurrent CV risk was derived on the Nottingham Heart Attack Register and the South London Stroke Register.	Obese individuals with mean BMI 34.92 kg/m^2, average age 45.5 years, 33.2% having T2D at baseline	• placebo: 5.128 • orlistat: 15.303 • rimonabant: 15.317 • sibutramine 10 mg: 15.376 • sibutramine 15 mg: 15.418	• placebo: £2,806 • orlistat: £3,097 • rimonabant: £3,478 • sibutramine 10 mg: £3,011 • sibutramine 15 mg: £2,967	Results vs placebo: • orlistat £1,665; • rimonabant £3,553; • sibutramine 10mg: £827; • sibutramine 15mg: £557
Lewis *et al.*[107]	2014	Cohort model comparing LighterLife Total, a very low-calorie diet, with: no treatment and other weight management interventions in BMI ≥30 kg/m^2 or with no treatment, gastric banding or gastric bypass in BMI ≥40 kg/m^2; obesity complications modelled: T2D, CHD and colon cancer. Transition probabilities estimated using continuous BMI-dependent trend lines fitted on incidence data from the literature: T2D onset[118], CHD[118], colon cancer[119, 120]. Weight reductions were applied at 12 months; post 12 months, treatment-specific BMI increase was assumed per year until BMI	Separate analyses were conducted for: obese (BMI ≥30 kg/m^2) and morbidly obese (BMI ≥40 kg/m^2)	BMI ≥30 kg/m^2: • No treatment: 6.552 • Slimming World: 6.559 • Counterweight: 6.562 • Weight Watchers: 6.563	Not provided	ICERs vs no treatment: BMI ≥30 kg/m^2: • Slimming World £5,613 • Counterweight £2,618 • Weight Watchers: dominant

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		reached the natural history disease model of no treatment whereby weight increased at a rate of 0.16 kg/m^2 per year.[106] HRQoL was modelled as function of BMI.[121]		• LighterLife Total: 6.691 BMI ≥40 kg/m^2: • No treatment 5.779 • LighterLife Total 6.092 • Gastric banding 6.514 • Gastric bypass 6.824		• LighterLife Total £12,585 BMI ≥40 kg/m^2: • LighterLife Total: £4,356 • Gastric banding: £20,505 • Gastric bypass: £10,627
McRobbie *et al.*[104]	2016	Cost-effectiveness analysis conducted alongside a 1-year clinical trial comparing WAP (n=116) with nurse-led weight management (standard care, n=63). No modelling was conducted.	WAP arm (n=221): 35 kg/m^2, 10% heart disease, 10% T2D; nurse-management (n=109): 35.7 kg/m^2, 6% heart; 8% T2D	Incremental QALYs: 0.0104	Incremental costs: £80	£7,742
Avenell *et al.*[110]	2018	Markov microsimulation model written in the C++ programming language comparing baseline, Look AHEAD intervention, WMP (WMP 1 - less intensive; WMP 2 - more intensive), with or without VLCD and RYGB. Virtual individuals were aged 1 year at a time and progressed through the model over a 30-year time horizon: 2016 until 2046. The model used the future projections of BMI to predict the burden of diseases into the future. Disease events competed to occur in each simulated life. Health states included: healthy, CHD, stroke, hypertension, T2D, knee osteoarthritis and BMI-related	Adult population with a BMI of ≥ 35 kg/m^2 in 2016. Non-surgical comparisons used a sample of 50 million individuals (5.8 million individuals with a BMI of ≥ 35 kg/m^2) Surgery comparison sampled 100 million individuals (11.6 million individuals	• Baseline: 11.36 • WMP1: 11.55 • VLCD added to WMP1: 11.56 • WMP2: 11.58 • Look AHEAD: 11.67 • Bariatric surgery: 12.76	• Baseline: £28,980 • WMP1: £29,090 • VLCD added to WMP1: £30,320 • WMP2: £29,330 • Look AHEAD: £36,430	vs baseline: • WMP1: £557 • VLCD added to WMP1: £6628 • WMP2: £1540 • Look AHEAD: £23,725 • Bariatric surgery: £10,126 vs next best alternative:

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		cancers, including breast, colorectal, endometrial, oesophageal, pancreatic and renal.	with a BMI of ≥ 35 kg/m^2)		• Bariatric surgery: £43,190	• WMP1: £557 • VLCD added to WMP1: Dominated • WMP2: Extendedly dominated • Look AHEAD: Extendedly dominated • Bariatric surgery: £11,648

Key: AMI, acute myocardial infarction; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CV, cardiovascular; GP, general practitioner; GPRD, General Practice Research Datalink; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NHS, National Health Services; QALYs, quality-adjusted life years; RYGB; Roux-en-Y gastric bypass; SoC, standard of care; T2D, type 2 diabetes; VLCD; very low-calorie diets; WAP, Weight Action Programme; WMP; Weight Management Programme.
Notes: *Supplemented with data from Warren et al. 2004[112]; ⁺poster only available.

B.3.2. Economic analysis

The cost-effectiveness model used for this submission was designed to evaluate the treatment of obesity and to reflect the disease's natural history, expected prognostic pathways in the absence of intervention, and treatment effects, is adapted from the model used for the previous NICE appraisal for liraglutide 3.0 mg for managing overweight and obesity (TA664), and uses committee preferred assumptions from that appraisal.[27] The model has undergone numerous improvements and additions during which it was validated against real world data (Section B.3.10). It is a state-transition cohort model that uses risk equations for extrapolation and captures the benefit of weight loss on the key weight-related comorbidities. It is consistent with other models that have been used for obesity and diabetes modelling.[106, 107, 122]

Key results of the economic analysis

ICERs with and without PAS are presented. Where PAS ICERs are presented, these are based on the proposed PAS price.

Semaglutide 2.4mg vs. diet and exercise:

- Patient population: BMI ≥ 30 kg/m^2 patients with one or more obesity related comorbidities
    - Deterministic ICER: [redacted] per QALY (without PAS)
    - Probabilistic ICER[redacted] per QALY (without PAS)
    - Deterministic ICER: £14,827 per QALY (with PAS)
    - Probabilistic ICER: £14,733 per QALY (with PAS)

Semaglutide 2.4mg vs. liraglutide 3.0mg

- Patient population: BMI ≥ 35 kg/m^2, prediabetes and high risk for CVD
    - Deterministic ICER: [redacted](without PAS)
    - Probabilistic ICER: [redacted] (without PAS)
    - Deterministic ICER: Dominant (with PAS)
    - Probabilistic ICER: Dominant (with PAS)

Key: BMI, Body mass index; CVD, Cardiovascular disease; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year.

B.3.2.1 Patient population

Two populations are considered, as discussed in more detail in Sections B.1.1 and B.2.7:

1. BMI ≥ 30 kg/m^2 patients with one or more obesity related comorbidities (base case)
- BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD (subpopulation)

The subpopulation with BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD is considered in order to align with the recommended target population for the pharmacotherapy, liraglutide 3.0 mg which was recommended by NICE in TA664.[27]

The characteristics of the starting cohort in terms of baseline demographic parameters are defined at model entry. The model structure described in detail in Section B.3.2.2, is a cohort model and so average patient characteristics are used as model inputs. These were sourced from a post-hoc analysis of the corresponding subset population in the STEP 1 clinical trial. The baseline characteristics for both populations of interest are shown in Table 16.

Table 16: Baseline characteristics for populations of interest

	Mean	
Patient characteristics	**BMI ≥ 30 kg/m^2 with one or more obesity related comorbidities**	**BMI ≥ 35 kg/m^2, with non-diabetic hyperglycaemia and high risk for CVD**
Used in comparison vs	Diet and exercise	Liraglutide 3.0 mg
Age (years)	[redacted]	[redacted]
BMI (kg/m^2)	[redacted]	[redacted]
Height (m)	[redacted]	[redacted]
SBP (mmHg)	[redacted]	[redacted]
Total cholesterol (mg/dl)	[redacted]	[redacted]
HDL cholesterol (mg/dl)	[redacted]	[redacted]
HbA1c after T2D development (%)*	7.5	7.5
T2D duration (years)*	3.0	3.0
Triglycerides (mg/dl)	146.2	165.9

Proportion Triglyceride level >150 mg/dl (%)	[redacted]	[redacted]
Proportion current smokers (%)	[redacted]	[redacted]
Proportion females (%)	[redacted]	[redacted]
Proportion on lipid-lowering drug (%)	[redacted]	[redacted]
Proportion on antihypertensive medication (%)	[redacted]	[redacted]
Key: BMI, body mass index; HDL, high-density lipoproteins; KOL, key opinion leader; SBP, systolic blood pressure; T2D, type 2 diabetes. **Notes:** *Based on KOL opinion, applied after onset of diabetes. **Source:** STEP 1 trial [90]		

B.3.2.2 Model structure

A Markov cohort model was developed in Microsoft Excel®, based on the model previously used in TA664 for liraglutide 3.0 mg in obesity.[27] The model is a state-transition cohort model that uses risk equations for extrapolation.

B.3.2.2.1 Model heath states

The model includes 11 health states, shown below in Figure 11, and is an updated and simplified version of the model used for TA664.[27] Obesity is associated with numerous possible comorbidities as evidenced by the WHO consultation on obesity, which noted the complications that respond to weight loss and have substantial consequences on healthcare resources and costs, patients' quality of life, and/or life expectancy.[111]

Comorbidities included in the model were those with strong evidence of association with obesity (non-diabetic hyperglycaemia, T2D, OSA, acute coronary syndrome [ACS] and stroke), and osteoarthritis. Cancer health states had limited impact on the cost-effectiveness model used in TA664 for liraglutide 3.0 mg and so were not included.

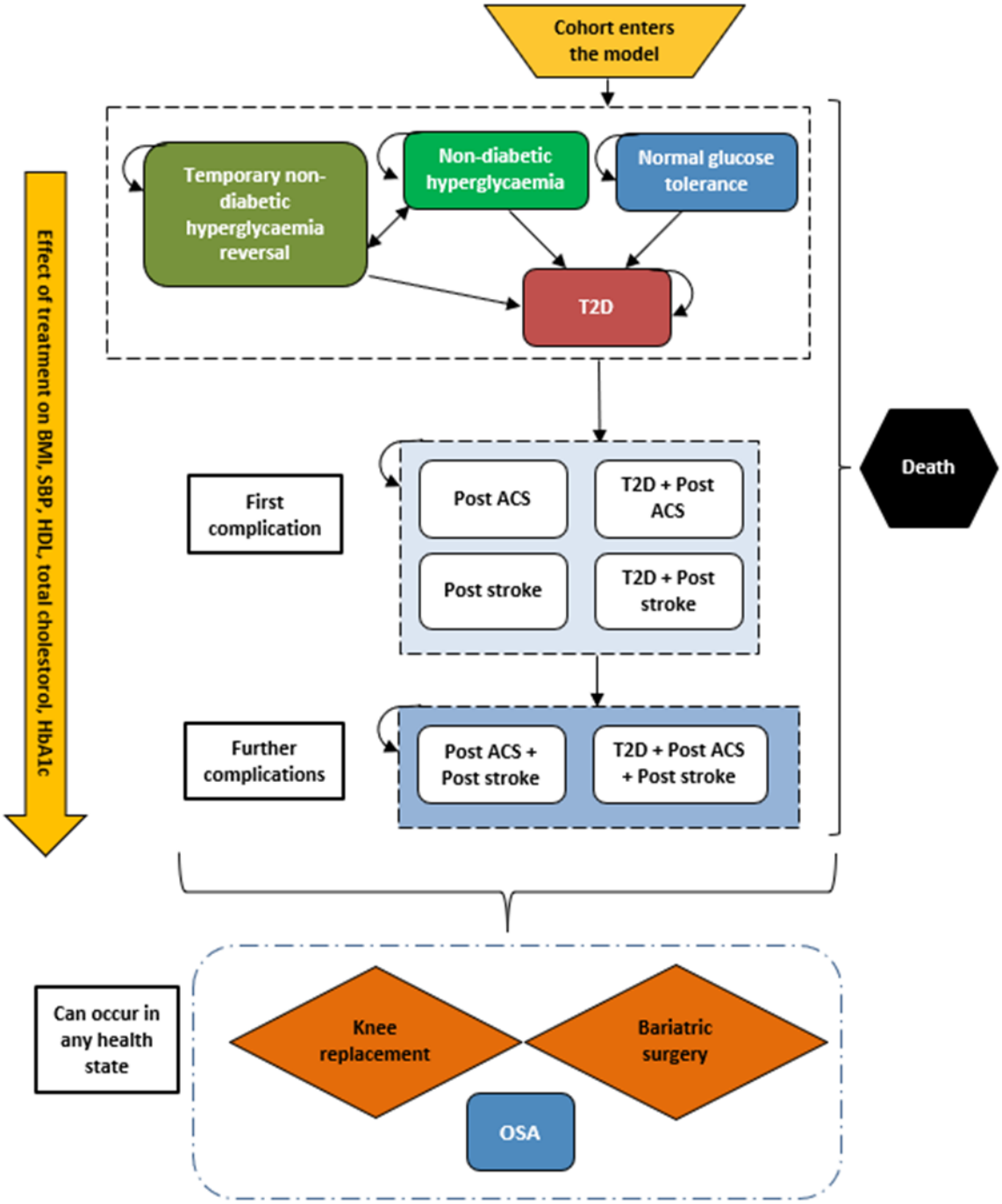
Given that neither all weight related comorbidities from STEP 1 nor all weight-related comorbidities observed in real life are included, the model is expected to be conservative and therefore underestimating the benefit of treatment with semaglutide 2.4 mg.

The majority of the cohort enters the model in the normal glucose tolerance (NGT) or non-diabetic hyperglycaemia health states. In addition, patients in an arm with pharmacotherapy may be ‘on’ or ‘off’ pharmacotherapy. Patients who have discontinued pharmacotherapy treatment still receive diet and exercise. This is tracked by tunnel states that capture time since pharmacotherapy was stopped (to model catch up of surrogate outcomes with control values). Patients in the CV event states are also divided between those with and without diabetes.

The analysed cohort is distributed across the starting health states based on the proportion with non-diabetic hyperglycaemia and proportion with NGT. For each patient population this is based on the observed prevalence in the STEP 1 clinical study.[90] The percentage of patients with history of CVD was [redacted] and was used to inform the number of patients entering the model in a post-CVD health state. [redacted].

The prevalence for obesity-related comorbidities for both populations of interest are shown in Table 17.

Figure 11: Obesity model structure



Key: ACS, Acute coronary syndrome; BMI, body mass index; HDL, high density lipoprotein; OSA, obstructive sleep apnoea; SBP, systolic blood pressure; T2D, type 2 diabetes.

Table 17: Starting non-diabetic hyperglycaemia distribution for both populations of interest

	Mean	
Patient characteristic	**BMI ≥ 30 kg/m^2 with one or more obesity related comorbidities**	**BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD**
Proportion with NGT (%)	[redacted]*	[redacted]
Proportion with non-diabetic hyperglycaemia (%)	[redacted]*	[redacted]
Key: BMI, body mass index; CVD, cardiovascular disease; NGT, normal glucose tolerance. **Notes:** *[redacted] of patients had type 2 diabetes at baseline. These were redistributed into NGT and prediabetes state by scaling up the NGT and the prediabetes health states to 100%		

To limit the number of health states in the model, the following assumptions, which still allow the main costs and benefits of treatment to be captured, were made:

- Non-diabetic hyperglycaemia patients move to T2D + post-ACS or T2D + post-stroke states following an ACS or stroke event respectively. This assumption has previously been used in TA664 where clinical experts explained that people are more likely to be diagnosed with T2D after a cardiovascular event.[27] This assumption is tested in a scenario analysis
- T2D micro-vascular complications are not included as distinct health states. Rather, for a proportion of patients residing in the T2D health state, higher costs apply, reflective of possible micro-vascular complications. This is a conservative assumption as the reduction in micro-vascular complications within T2D is not captured directly from treatment
- Osteoarthritis is not accounted for as a separate health state as this would have tripled the number of health states considered. It is considered in the model in the form of knee replacement event rather than a separate health state. Nonetheless, it is expected that the underestimation from a cost perspective would be low, given that managing osteoarthritis does not involve high medical expenditure (e.g. management with analgesics)
- OSA is not accounted for as a separate health state as this would also have substantially increased the number of health states considered. The costs and quality of life decrements are accounted for by estimated prevalence of OSA each cycle from using a risk equation

- Once individuals develop a condition which bears substantial higher costs, quality of life and/or survival implications, the less 'serious' condition is superseded by the more 'serious' one. For example, if 50% of the cohort are in the temporary non-diabetic hyperglycaemia reversal health state and then experiences non-fatal myocardial infarction (MI) at a rate of 0.3% per year, in the first year, 0.15% of the cohort will then move into the post-ACS state and leave the temporary non-diabetic hyperglycaemia health state

- A small proportion of patients (1.8%) have T2D at baseline. This is due to some of the patients developing T2D between screening and Week 0. As these patients are not in the target population for the submission, they are accounted for in the model scaling up the NGT and prediabetes health states to 100%.

B.3.2.2.2 Transitions and transition probabilities

During every model cycle, the cohort moves between health states or may remain in the same health state. The likelihood of a transition occurring is given by a transition probability. Transition probabilities are derived based on the risk of developing each of the comorbidities associated with obesity included in the analysis (e.g. T2D) or the likelihood of an event occurring (e.g. non-fatal MI is followed by transition of the cohort to post-ACS health states).

In this model, the transition to T2D, ACS, stroke, OSA, osteoarthritis (knee replacement) or death are predicted based on short-term effects of interventions on surrogate outcomes – BMI, SBP, total cholesterol, HDL cholesterol and HbA1c which are typical endpoints in obesity clinical trials and extrapolated over a given time horizon. Effects on surrogate outcomes are translated into lifetime risks of obesity complications through risk-prediction equations or lookup risk tables obtained from published studies.

Demographic and cardio-metabolic risk factor parameters are defined as either static i.e. do not change over time (e.g. sex, height, smoking status, use of lipid-lowering medication) or as dynamic i.e. change over the time horizon of the model. For simplification, some variables which can be dynamic in real-life have been assumed static in this model (e.g. smoking status). Such variables are not believed to be

affected by the interventions considered, and therefore, this simplifying assumption is not expected to affect the outcomes of the cost-effectiveness analyses conducted.

Dynamic variables can change in the model because of

- Time and/or natural progression of the disease (e.g. age);
- Weight reduction interventions (e.g. SBP, cholesterol levels); or
- Both of the above (e.g. BMI, HbA1c in T2D)

Table 18 exhibits the model parameters characterising the starting cohort, and their assumed nature (static or dynamic). A brief description of their behaviour throughout the time horizon of the model is also provided.

Table 18: Definition of baseline cohort characteristics

Parameter	Unit of measure	Parameter nature	Description
Age	Years	Dynamic	Defined at baseline and increasing by 1 unit each year spent alive in the cohort
BMI	kg/m²	Dynamic	Defined at baseline, changes as a result of treatment; when treatment is stopped, weight is regained after a defined period to a value on the natural progression of the disease as if patients had only received diet and exercise. Afterwards BMI has a natural progression (increase) until 68 years old
Height	m	Static	Defined at baseline, does not change
SBP	mmHg	Dynamic	Defined at baseline, changes as a result of treatment. When treatment is stopped, SBP returns to a value on the natural progression of the disease, as if patients had only received diet and exercise after a defined period (catch-up period).
Total cholesterol	mg/dL	Dynamic	Defined at baseline, changes as a result of treatment. When treatment is stopped, total cholesterol returns to a value on the natural progression of the disease, as if patients had only received diet and exercise after a defined period (catch-up period)
HDL-cholesterol	mg/dL	Dynamic	Defined at baseline, changes as a result of treatment. When treatment is stopped, HDL-cholesterol returns to a value on the natural progression of the disease, as if patients had only received diet and exercise after a defined period (catch-up period)

Parameter	Unit of measure	Parameter nature	Description
HbA1c (in cohort with T2D)	%	Dynamic	Defined at baseline, an average HbA1c is applied to proportion of the cohort with baseline T2D or to those developing T2D over time
Triglyceride level	mg/dl	Static	Defined at baseline, does not change
Proportion with triglyceride level ≥150 mg/dL	%	Static	Defined at baseline, does not change
Proportion smokers	%	Static	Defined at baseline, does not change
Proportion females	%	Static	Defined at baseline, changes with mortality
Proportion on lipid-lowering drugs	%	Static	Defined at baseline, does not change
Proportion on antihypertensive medication	%	Dynamic	Defined at baseline, changes as a result of treatment (if decreased due to treatment, catch up after treatment stop is assumed)
Key: BMI, body mass index; HDL, high-density lipoproteins; KOL, key opinion leader; SBP, Systolic blood pressure; T2D, type 2 diabetes.			

In the model, the characteristics of the cohort differ between states. For example, if a therapy impacts BMI, patients in a treated health state will have a different BMI from untreated patients. Transitions depend on cohort characteristics such that if a therapy modifies cardiovascular risk factors, then the transition to a post-CVD event health state is affected by the change in risk of serious cardiovascular disease. State payoffs may also depend on events which do not influence the likelihood of transitioning to a different health state and are included as one-off costs and decrements in the estimated total quality of life.

To reflect the higher likelihood of some obesity co-morbidities occurring simultaneously and to consider the possible lifelong implications of such conditions despite the memory-less feature of Markov cohort models, combinations of co-morbidities have been defined as separate health states. More specifically, if for example, a proportion of the cohort has T2D and goes on to experience an MI event, the respective cohort moves into a health state post-ACS + T2D in the next cycle. If a proportion of this cohort goes on to experience a stroke, this proportion will move

into a post-ACS + post-stroke + T2D health state. This approach allows the model to reflect the chronic nature of most obesity-related conditions.

A limitation of this model is that non-diabetic hyperglycaemia can only be included as a comorbidity at baseline and the cohort with NGT cannot develop non-diabetic hyperglycaemia over the time horizon of the analysis. An SLR was conducted to obtain risk equations for obesity related comorbidities.[123] There are risk equations on development of T2D from any non-diabetic health state, but not for development of non-diabetic hyperglycaemia from NGT. To overcome this limitation, the model allows the user to assign a higher risk of developing T2D to the proportion of the cohort that had non-diabetic hyperglycaemia at baseline and who reverted to NGT during treatment than for those with NGT at baseline. As such, the model includes a temporary non-diabetic hyperglycaemia reversal health state. This adjusts for the fact that reversal of non-diabetic hyperglycaemia to NGT is a temporary situation and after treatment, the cohort would return to have the same risk of T2D as observed in non-diabetic hyperglycaemia, which is higher compared to NGT patients. Therefore, transitions to the temporary non-diabetic hyperglycaemia reversal health state may occur only from non-diabetic hyperglycaemia. This transition is based on the percentage reduction in prevalence observed in STEP 1, applied at the end of the first cycle in the model (3 months from the beginning of the model).

Transition to a post-ACS state occurs following a non-fatal MI or non-fatal unstable angina. Transition to post-stroke occurs following a non-fatal stroke or transient ischemic attack (TIA). The cohort residing in post-ACS can experience further MI or unstable angina events in the next cycles but remains in the same post-ACS state or experiences a cerebrovascular event and transitions to a post-ACS + post-stroke health state. Similarly, the cohort residing in post-stroke can experience a further stroke or TIA event in the next cycles but remains in the same post-stroke state or experiences a cardiovascular event and transitions to a post-ACS + post-stroke health state. Transition to death can occur from any of the model health states either as a fatal event occurs or based on disease specific and general population mortality.

As a general rule, the transitions allowed, and the respective transition probabilities, depend on the health state in which the cohort resides at the end of the previous cycle. That is:

- Higher probability of developing T2D applies to patients residing in a non-diabetic hyperglycaemia health state than for patients with NGT
- Higher rates of MI, unstable angina, stroke or TIA apply to patients residing in the T2D state than patients without T2D
- Higher rates of MI, unstable angina, stroke or TIA apply to patients residing in post-ACS or post-MI health states than patients who did not have a previous CV event
- Higher rates of MI, unstable angina, stroke or TIA apply to patients residing in post-ACS+T2D or post-MI+T2D health states, than for patients in post-ACS or post-MI health states with NGT or in the T2D health state without previous CV event
- Higher rates of mortality apply to T2D, post-ACS, post-stroke health states compared with health states with NGT or no complications

B.3.2.2.3 Time horizon

The base case uses a time horizon of 40 years to capture all costs and consequences of semaglutide 2.4 mg and the comparator. At the end of the model time horizon, a majority of patients are deceased with a difference of less than 0.1% of patients alive between treatment arms. Therefore, any subsequent differences beyond the modelled time horizon are expected to be minimal and discounted such that the model approximates lifetime costs and benefits of the intervention in obesity.

B.3.2.2.4 Cycle length

The cycle length of the model is the time interval elapsing from one transition to another. The cycle length was defined considering the condition analysed and the likely frequency of changes in patients' health status.

For the current decision problem, a cycle length of 3 months was defined for the first year with annual cycles thereafter. Shorter cycles at the start of the model allow a more accurate representation of the treatment effects, dosing schedule, incorporation of treatment stopping rules and changes in disease status after therapy

initiation. Although shorter cycles will always yield more precise estimates, the error becomes very small when the number of cycles increases with increasing time horizon. Thus, for computational efficiency, annual cycles were defined after the first year. Half-cycle correction is applied.

Key features of the economic analysis along with a comparison of the approach to TA664, are summarised in Table 19.

Table 19: Features of the economic analysis

	Previous appraisals	Current appraisal - TA [ID3850] (Semaglutide 2.4 mg)	
Factor	**TA664 (Liraglutide 3.0 mg)**	**Chosen values**	**Justification**
Time horizon	Lifetime (40 years)	Lifetime (40 years)	As per the NICE reference case for modelling chronic conditions such as obesity and TA664 to capture all relevant costs and complications
Extrapolation of treatment effect	Treatment effect is assumed to wane in a linear fashion within three years following treatment discontinuation at a rate of 33%, 67% and 100% applied in Years 1, 2 and 3 following discontinuation	Treatment effect is assumed to wane in a linear fashion within three years following treatment discontinuation at a rate of 33%, 67% and 100% applied in Years 1, 2 and 3 following discontinuation	This assumption is in line with TA664. It follows Ara et al. 2012 [106] and was the preferred assumption by the ERG in TA494
Surrogate outcomes	Risk equations are used to link short term surrogate outcomes to long term clinical outcomes.[124-129]	Risk equations are used to link short term surrogate outcomes to long term clinical outcomes.[124-129]	Long-term clinical outcomes are required for the model but are not available from the clinical trials due to the short duration of the study. This approach was also used for TA664.
Mortality	General population mortality, adjusted for with/without T2D. RRs applies for post-ACS and post-stroke[130, 131] Acute death probabilities for	General population mortality adjusted by excluding mortality of obesity related comorbidities,[135, 136] with HR applied for BMI.[50]	Best available approach to model all potential difference in mortality, both associated change in BMI and with complications.

	Previous appraisals	Current appraisal - TA [ID3850] (Semaglutide 2.4 mg)	
	bariatric surgery, MI, angina, stroke and knee replacement[132-134]	RRs applies for post-ACS and post-stroke[130, 131] Acute death probabilities for bariatric surgery, MI, angina, stroke and knee replacement[132-134]	
Source of HRQoL data	Baseline utility was derived from Søltoft et al. 2009.[137] Health state disutilities were sourced from Søltoft et al. 2009 and Sullivan et al. 2011.[137, 138] Event disutilities were sourced from Campbell et al. 2010, Søltoft et al. 2009 and Sullivan et al. 2011.[137-139]	Baseline utility was derived from Søltoft et al. 2009.[137] Health state disutilities were sourced from Søltoft et al. 2009 and Sullivan et al. 2011.[137, 138] Event disutilities were sourced from Campbell et al. 2010, Søltoft et al. 2009, Sullivan et al. 2011, V Foos, 2018 and NICE TA494, 2017.[137-142]	Søltoft et al. uses data from the Health Survey for England with a sample size over 14,000 people and good representation of the English adult population. Utility was assessed using EQ-5D and adjusted for confounding factors including five obesity-related morbidities thus, utilities applied at baseline are free of any additional effects of obesity-related comorbidities allowing the separation of the effects of comorbidities from a pure effect related to increased weight.
Measure of health effects	QALYs	QALYs	NA
Source of drug acquisition costs	Novo Nordisk	Novo Nordisk	NA
Perspective	NHS/PSS	NHS/PSS	NA
Discounting	3.5% for costs and benefits	3.5% for costs and benefits	NA

Key: HRQoL, Health related quality of life; NHS, National Health Service; PSS, Personal social service; QALY, Quality-adjusted life year.

B.3.2.3 Intervention technology and comparators

The model was developed to allow the comparison of the intervention, semaglutide 2.4 mg in combination with diet and exercise hereby referred to as 'semaglutide 2.4 mg', versus relevant comparators in each population of interest.

B.3.2.3.1 Semaglutide 2.4 mg (Intervention)

Semaglutide 2.4 mg is a once weekly pharmacotherapy which involves a titration phase and a maintenance phase. The titration phase starts at treatment initiation and lasts for 16 weeks during which time the dose is increased every 4 weeks. The applied dosage regime is:

- Week 1–4: 0.25 mg/week
- Week 5–8: 0.5 mg/week
- Week 9–12: 1.0 mg/week
- Week 13–16: 1.7 mg/week
- Week 17 onwards: 2.4 mg/week

Semaglutide 2.4 mg maintenance dose is 2.4 mg subcutaneous (s.c.) injection per week. At the time of writing, it is unclear whether the marketing authorisation for semaglutide 2.4 mg will include a stopping rule where patients not achieving a defined weight loss discontinue treatment. In the model it is assumed that that treatment should be discontinued after 28 weeks if patients have not lost < 5% of their initial body weight, in anticipation of this expected stopping rule in the marketing authorisation (see Section B.1.1).

B.3.2.3.2 Comparators

Diet and exercise

For the population with BMI ≥ 30 kg/m^2 with one or more obesity related comorbidities, no pharmacotherapy is provided in SWMS and thus the relevant comparator to semaglutide 2.4 mg in combination with diet and exercise, is diet and exercise alone.

Diet and exercise refers to the standard management in obesity which includes a reduced calorie diet and increased physical activity.

Liraglutide 3.0 mg

For the population with BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD, liraglutide 3.0 mg in combination with diet and exercise, hereby referred to as 'liraglutide 3.0 mg' is recommended by NICE in TA664. Therefore, this treatment is a relevant comparator to semaglutide 2.4 mg in combination with diet and exercise only in this specific subpopulation.

Liraglutide 3.0 mg (Saxenda, manufactured by Novo Nordisk) is a GLP-1 receptor agonist similar to semaglutide 2.4 mg. Liraglutide 3.0 mg is approved as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients (≥ 18 years) with an initial BMI of:

- ≥ 30 kg/m² (obese), or
- ≥27 kg/m² to <30 kg/m² in the presence of at least one weight-related comorbidity such as dysglycaemia, hypertension, dyslipidaemia, or OSA

Liraglutide 3.0 mg treatment involves a titration phase and a maintenance phase. The titration phase starts at treatment initiation and lasts for 4 weeks during which time the dose is increased each week. The applied dosage regime is:

- Week 1: 0.6mg/day
- Week 2: 1.2mg/day
- Week 3: 1.8mg/day
- Week 4: 2.4 mg/day
- Week 5 onwards: 3.0 mg/day

Liraglutide 3.0 mg maintenance dose is 3 mg s.c. injection per day. In line with the marketing authorisation treatment should be discontinued after 12 weeks on the 3.0 mg daily maintenance dose if patients have not lost at least 5% of their initial body weight (referred to as a stopping rule).[143]

B.3.3. Clinical parameters and variables

B.3.3.1 Treatment effects

The clinical effectiveness of the interventions considered is introduced in the model through changes in BMI and cardio-metabolic risk factors, namely SBP, HDL cholesterol, total cholesterol and HbA1c (in diabetes). These intermediate endpoints are used in risk equations/risk tables to calculate transition probabilities in the model, guiding the progression of the cohort throughout the time horizon of the analysis.

In addition, a temporary reversal of non-diabetic hyperglycaemia in the model is allowed by treatment arm. Finally, adverse events for each treatment are also incorporated.

B.3.3.1.1 Effect on surrogate outcomes

The relative reduction in BMI is the main driver of clinical effectiveness. Changes in BMI influence the risk of all obesity complications in the model (except the incidence of secondary cardiovascular events). Changes in SBP, HDL cholesterol and total cholesterol influence the risk of T2D, CVD in primary prevention and the risk of CVD in secondary prevention. Changes in HbA1c influence the risk of CVD in primary prevention in the cohort with T2D, however, average HbA1c is assumed to not increase over time. Table 20 describes how the effect on surrogate outcomes, measured through changes in physiological parameters, is quantified in the model.

Table 20: Definition of treatment effects on physiological parameters included in the model

Physiological parameters	Treatment effect included in the model
BMI kg/m^2	BMI percentage change from baseline
SBP (mmHg)	SBP absolute change from baseline
HDL cholesterol (mg/dL)	HDL cholesterol absolute change from baseline
Total cholesterol (mg/dL)	Total cholesterol absolute change from baseline
Key: BMI, body mass index; HDL, high density lipoprotein; SBP, systolic blood pressure.	

The initial effect of treatment on the physiological parameters is applied at model start and relative to the baseline values. It should be noted however that the incidence of complications takes over only from Cycle 2 of the model and as such,

the initial weight reduction will start influencing the incidence of complications at the beginning of Cycle 2 of the model (starting from Month 4).

Treatment effects for semaglutide 2.4 mg and diet and exercise for both subgroups were sourced from the population containing all patients of the STEP 1 clinical trial. This population efficacy was assumed to be representative of the subgroups of interest and since this population was defined a priori in the STEP 1 trial, it provided a statistically robust measure of the treatment effect. This assumption was validated in an advisory board with key opinion leaders (KOLs)[23] and the post hoc analysis is explored in a scenario analysis for validation.

The trial product estimand from STEP 1 was used to reflect the efficacy of patients who stay on treatment. This estimand, which estimated the treatment effect of semaglutide 2.4 mg relative to placebo for all randomised patients, assuming they remained on their randomised treatment for the entire planned duration of the trial and had not initiated other anti-obesity therapies, as discussed in more detail in Section B.2.4.4, was considered most appropriate for the modelling of efficacy in the economic model. This estimand in combination with the stopping rule for non-responders provides a clear representation of patients who would receive treatment in a SWMS setting. As described in Section B.3.2.3.1 the stopping rule for semaglutide 2.4 mg is 28 weeks so the full analysis set efficacy is used for Week 20 and Week 28 STEP 1 data. After Cycle 2, early responder efficacy for STEP 1 Week 68 data is used for patients continuing treatment with semaglutide 2.4 mg. The efficacy inputs from the population containing all patients in STEP 1 for semaglutide 2.4 mg and diet and exercise, as used in the base case, are shown in Table 21. Week 28 data for weight change and SBP change and Week 20 data for total cholesterol and HDL cholesterol were used to inform model cycles up to 9 months. Week 68 data informed on treatment model cycles after 9 months.

Table 21: Change in physiological parameter values – STEP 1 – all patients

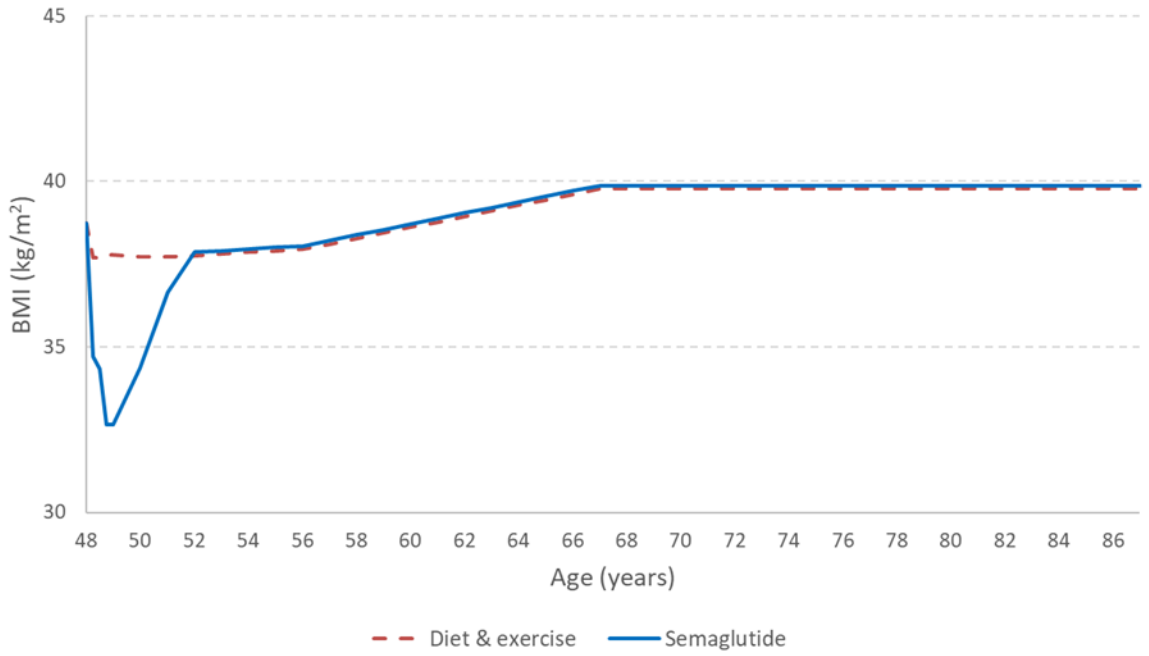
Parameter and timepoint in model	Semaglutide 2.4 mg: full analysis set N = 1306 Early responders N = [redacted]		Diet & exercise: full analysis set N = 655	
	Mean change from baseline	Calculated SE	Mean change from baseline	Calculated SE
Weight change (% change)				
Month 4	-12.04%	0.16%	-2.69%	0.22%
Month 7	-12.04%	0.16%	-2.69%	0.22%
Month 10	-13.22%	0.15%	-2.44%	0.36%
Year 1	-18.47%	0.27%	-2.44%	0.36%
Year 2	-18.47%	0.27%	-2.44%	0.36%
SBP change (mmHg)				
Month 4	-5.93	0.34	-0.56	0.48
Month 7	-5.93	0.34	-0.56	0.48
Month 10	-6.48	0.36	-1.14	0.53
Year 1	-7.63	0.39	-1.14	0.53
Year 2	-7.63	0.39	-1.14	0.53
Total cholesterol change (mg/dl)				
Month 4	-15.27	0.11	1.39	0.01
Month 7	-15.27	0.11	1.39	0.01
Month 10	-15.92	0.12	0.18	0.00
Year 1	-9.20	0.07	0.18	0.00
Year 2	-9.20	0.07	0.18	0.00
HDL cholesterol change (mg/dl)				
Month 4	-4.63	0.03	-0.96	0.01
Month 7	-4.63	0.03	-0.96	0.01
Month 10	-4.76	0.04	1.07	0.01
Year 1	2.97	0.02	1.07	0.01
Year 2	2.97	0.02	1.07	0.01

Key: HDL, high density lipoprotein; SBP, systolic blood pressure.
Note: Early responders are defined as patients that achieve more than 5% weight loss at 28 weeks

Figure 12 illustrates the progression of BMI over time for semaglutide 2.4 mg and diet and exercise, including the additional effect of bariatric surgery, for patients with BMI ≥ 30 kg/m^2 with one or more obesity related comorbidities. Semaglutide 2.4 mg shows a greater reduction in BMI compared to diet and exercise. After age 57 the cohort no longer receives bariatric surgery and the BMI of the cohort increases at a greater rate compared to after the catch up period until age 68 where the cohort no

longer gains a natural increase in BMI (assumptions discussed in more detail in Sections B.3.3.2 and B.3.3.3 respectively).

Figure 12: Projected BMI change for semaglutide 2.4 mg and diet and exercise over time for patients with BMI ≥ 30 kg/m^2 with one or more obesity related comorbidities



Key: BMI, body mass index.

B.3.3.1.2 Reversal of non-diabetic hyperglycaemia to normal glucose tolerance

An immediate effect of interventions in terms of temporary reduction in non-diabetic hyperglycaemia prevalence is applied in the model such that patients temporarily have normal glucose levels.

Non-diabetic hyperglycaemia reversal is applied in the model through a proportion of the cohort with non-diabetic hyperglycaemia transitioning from the non-diabetic hyperglycaemia health state to the temporary non-diabetic hyperglycaemia reversal health state. Patients in the temporary non-diabetic hyperglycaemia reversal health state have normal glucose levels. Following obesity treatment discontinuation, patients return to their pre-treatment glycaemic status as defined in Section B.3.2.1 and therefore transition back to the non-diabetic hyperglycaemia health state.

As in the model used for TA664, non-diabetic hyperglycaemia reversal is applied at Month 3 of the analysis, since it is expected to occur immediately after treatment start, even though observation on glycaemic status from a given trial is available only at 1 year. The parameter is sourced from Week 52 glycaemic status results for the population containing all patients in STEP1 for semaglutide 2.4 mg and diet and exercise. Section B.3.3.1.3 provides detail for the liraglutide 3.0 mg estimate in the BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD population from SCALE 1839. Table 22 shows the percentage of non-diabetic hyperglycaemia patients with glycaemic status reversal for semaglutide 2.4 mg and diet and exercise.

Table 22: Percentage of non-diabetic hyperglycaemia patients with glycaemic status reversal – STEP 1 – all patients

Parameter	Semaglutide 2.4 mg N =1306		Diet & exercise: full analysis set N =655	
	%, reversal	Calculated SE	%, reversal	Calculated SE
Glycaemic status change	90.4%	1.3%	45.8%	3.0%
Key: SE, Standard error. **Source:** Novo Nordisk, STEP 1, data on file[95]				

B.3.3.1.3 Indirect treatment comparison

In the absence of a completed head-to-head trial, an indirect treatment comparison of semaglutide 2.4 mg versus liraglutide 3.0 mg was conducted. A patient-level regression was undertaken including STEP 1 and SCALE 1839 trial data, as discussed in Section B.2.9.

The ITC was not able to produce adjusted estimates for efficacy in responders (further details are contained within Appendix D). The placebo arms of the two trials were very similar in terms of baseline characteristics but did produce slightly different results for change from baseline in BMI and other risk factors. The efficacy of liraglutide 3.0 mg was adjusted in the model to reflect this difference. Observed efficacy in SCALE 1839 for all patients was used for this adjustment.[144]

The adjustment made was to increase the estimated efficacy of liraglutide 3.0 mg on BMI, SBP, HDL and total cholesterol efficacy estimates by the size of difference

between the efficacy estimates in the placebo arms of STEP1 (all patients) and SCALE 1839 (all patients). The percentage of non-diabetic hyperglycaemia patients with glycaemic status reversal was estimated using the odds ratio between liraglutide 3.0 mg (all patients) and placebo (all patients) in SCALE 1839, applied to STEP1 odds for placebo (all patients). Resulting efficacy parameters applied for liraglutide 3.0 mg are presented in Table 23.

Figure 13 illustrates the progression of BMI over time for semaglutide 2.4 mg and liraglutide 3.0 mg, including the additional effect of bariatric surgery, for patients with BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD. Semaglutide 2.4 mg shows a greater reduction in BMI compared to liraglutide 3.0 mg.

Table 23: Change in physiological parameter values – Liraglutide 3.0 mg – all patients

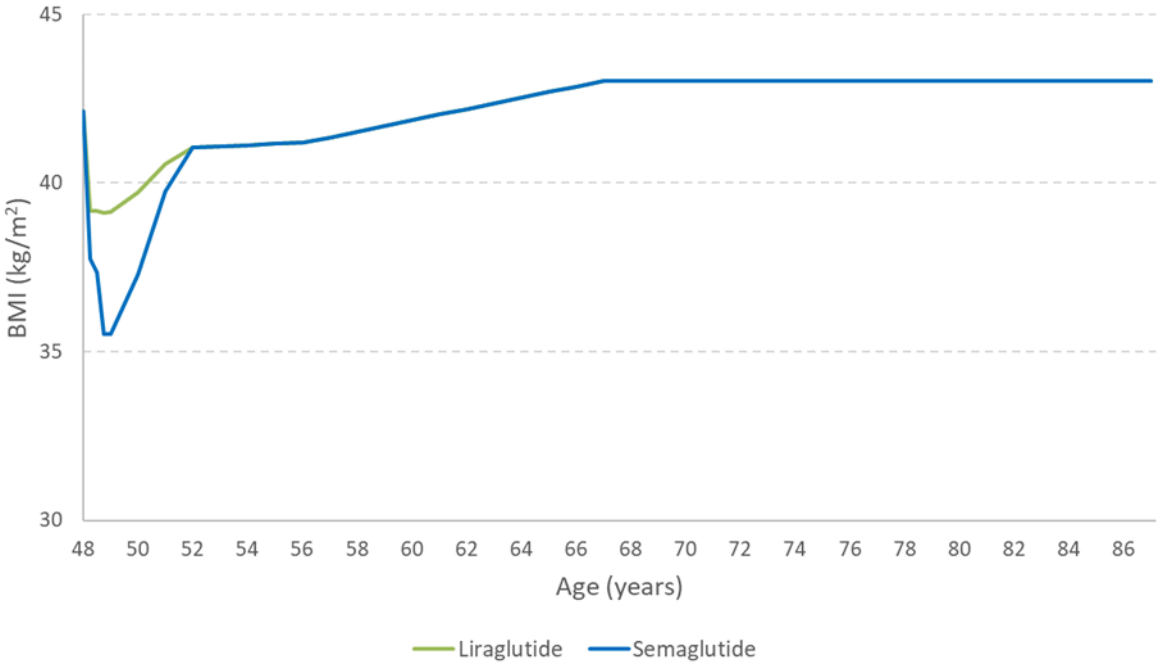
Parameter and time point in model	Liraglutide 3.0 mg: early responders N = 1456 (Week 28) N = [redacted] (Week 56)	
	Mean change from baseline	**Calculated SE**
Weight change (% change)		
Month 4	-10.00%	0.20%
Month 7	-10.00%	0.20%
Month 10	-10.00%	0.20%
Year 1	-10.42%	0.32%
Year 2	-10.24%	0.43%
SBP change (mmHg)		
Month 4	-4.46	0.57
Month 7	-4.46	0.57
Month 10	-4.46	0.57
Year 1	-5.19	0.56
Year 2	-5.96	0.78
Total cholesterol change (mg/dl)		
Month 4	-5.58	1.00
Month 7	-5.58	1.00
Month 10	-5.58	1.00
Year 1	-2.25	1.13
Year 2	-1.11	1.53
HDL cholesterol change (mg/dl)		
Month 4	-3.34	0.28
Month 7	-3.34	0.28

Parameter and time point in model	Liraglutide 3.0 mg: early responders N = 1456 (Week 28) N = [redacted] (Week 56)	
	Mean change from baseline	**Calculated SE**
Month 10	-3.34	0.28
Year 1	2.07	0.32
Year 2	2.17	0.42
	%, reversal	**Calculated SE**
Glycaemic status change	83.6%	1.3%

Key: BMI, body mass index; CVD, cardiovascular disease; HDL, high density lipoprotein; SBP, systolic blood pressure; SE, standard error.

Note: Early responders are defined as patients that achieve more than 5% weight loss at 28 weeks

Figure 13: Projected BMI change for semaglutide 2.4 mg and liraglutide 3.0 mg over time for patients with BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD



Key: BMI, body mass index; CVD, cardiovascular disease.

B.3.3.1.4 Adverse events associated with treatment

Treatment-related AEs are included in the model through a per cycle probability of occurrence in a treatment arm. Adverse events have a disutility and cost that is applied in the cycle that it occurs.

For the semaglutide 2.4 mg and diet and exercise arms, AE rates were sourced from the population containing all patients of the STEP1 trial.[85] The liraglutide 3.0 mg arm AE rates were sourced from the population containing all patients of the SCALE 1839 trial.[145] The AEs included in the model were non-severe hypoglycaemic events as these are most relevant for clinical practice (no severe hypoglycaemic events were observed), and severe gastrointestinal AEs as these were most common. The rate of AEs for each treatment included in the model is shown in Table 24, the resulting incremental probabilities are presented in Table 25. The utilities and costs applied for severe and non-severe hypoglycaemic events and severe gastrointestinal events are described in Section B.3.4.4 and Section B.3.5.3 respectively.

Table 24: Adverse event rates

	Semaglutide 2.4 mg	**Diet & exercise**	**Liraglutide 3.0 mg**
Patient years observed	1856.4	918.5	3218.9
Non-severe hypoglycaemia			
Events	15	7	60
Rate/100 patient years	0.8	0.8	1.9
Severe gastrointestinal events			
Events	91	8	227
Rate/100 patient years	4.9	0.9	7.1

Table 25: Incremental probability of adverse events per cycle for Semaglutide 2.4 mg versus diet and exercise

Adverse event (cycle)	Incremental probability
Non-severe hypoglycaemia	
Cycle 1 (%)	0.008
Cycle 2 (%)	0.024
Cycle 3 (%)	0.024
Cycle 4 (%)	0.024
Cycle 5 (%)	0.035
Cycle 6 (%)	0.035
Severe gastrointestinal events	
Cycle 1 (%)	0.708
Cycle 2 (%)	0.708
Cycle 3 (%)	0.708
Cycle 4 (%)	0.708
Cycle 5 (%)	3.015
Cycle 6 (%)	3.015

B.3.3.2 Bariatric surgery following non-surgical weight management intervention

Bariatric surgery refers to the use of surgical procedures for body weight management. To date, there are three main types of bariatric surgery: gastric banding, gastric bypass and sleeve gastrectomy.[146] Details of how bariatric surgery is included in the model are provided in Appendix L1.

The base case inputs for bariatric surgery eligibility reflect UK data and are shown in Table 26. It should be noted that the minimum BMI level is just to define whether patients are eligible or not. The actual BMI at the time of surgery is higher in clinical practice. The impact of using a higher BMI level for eligibility for bariatric surgery is explored in a scenario analysis. The default model efficacy by type of bariatric surgery on BMI, SBP, total cholesterol, HDL cholesterol and HbA1c, and case fatality are shown in Table 27.

Table 26: Bariatric surgery criteria

Criteria	Model inputs	Comment	Reference
Minimum BMI level	35	The minimum BMI level at which the cohort may be eligible to receive bariatric surgery*	NICE CG189, 2014[77]
Incidence of bariatric surgery per year	1.15%	Proportion of the eligible cohort undergoing bariatric surgery	NICE CG189, 2014 Costing report Section 3.1.11[77]
Maximum age	57	Age limit to undergo bariatric surgery	Gulliford et al. 2017[146]
Incidence of adverse events following surgery	5.95%	Used to weight the costs of adverse events	Borisenko et al. 2018[147]

Key: BMI, body mass index.
Notes: *In the model defaults, the minimum BMI level is set at 35, as 100% of the default population has at least one comorbidity.

Table 27: Bariatric surgery efficacy and case fatality

Parameter	BMI ≥ 30 kg/m^2 patients with one or more obesity related comorbidities	BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD	Source
Proportion by type of surgery			
Gastric bypass	51%		National schedule of NHS reference costs[44]
Laparoscopic banding	18%		
Sleeve gastrectomy	31%		
Percent (%) weight change at 1 year (negative = decrease)	-27.66%		Weighted average
Gastric bypass	-32%		Sjöström 2004[148]
Laparoscopic banding	-20%		Sjöström 2004[148]
Sleeve gastrectomy	-25%		Sjöström 2004[148]
Change in SBP mmHg (positive = increase) at 1 year	-9.10*	-9.32*	Recomputed based on Demssie 2012[149]
Change in total cholesterol mg/dl	-29.69*	-30.87*	Recomputed based on Demssie 2012[149]

Parameter	BMI ≥ 30 kg/m^2 patients with one or more obesity related comorbidities	BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD	Source
(positive = increase) at 1 year			
Change in HDL cholesterol mg/dl (positive = increase) at 1 year	6.34*	5.87*	Recomputed based on Demssie 2012[149]
Change in HbA1c %* (positive = increase) at 1 year (in T2D)	-2.15%*	-2.15%*	Recomputed based on Demssie 2012[149]
Notes: *Recomputed as relative to model baselines based on mean change from baseline reported by Demssie 2012 - values will update depending on the selected baseline parameters corresponding to the studied cohort.			

B.3.3.3 Natural increase in BMI

The STEP 1 trial provided data for the BMI trajectory while on treatment for 68 weeks and an assumption that patients maintain treatment benefit is made for an additional year based on the efficacy plateau seen in the BMI data (Figure 12 and Figure 13).

After the treatment period the path taken for BMI in the arm receiving diet and exercise alone follows natural history of progression, a 0.1447 kg/m^2 (males) and 0.1747 kg/m^2 (females) annual increase in BMI as estimated by Ara et al. from a 100,000 UK Clinical Practice Research Datalink (CPRD) sample of individuals with obesity.[106]

This natural weight increase is a common assumption in obesity models and is supported by a model developed by NICE[150] Support is also found in Heitmann and Garby[151] and the analysis on the UK Clinical Practice Research Datalink.[106] Weight gain reaches a plateau at the ages of 65-70 years on average.[150] As a base case input in the model, weight can increase up to an average of 68 years based on KOL opinion.

B.3.3.4 Treatment discontinuation

Discontinuation is applied in the model in three different ways:

- Non-responder early discontinuation or stopping rule: Close to treatment initiation, i.e. after the first 3-months cycle in the model
- Maximum treatment duration: After a determined duration of treatment (2 years)
- Per cycle discontinuation: During treatment period, patients can discontinue due to any reason such as adverse events

Discontinuation is applied in the semaglutide 2.4 mg and liraglutide 3.0 mg arms of the model only.

B.3.3.4.1 Non-responder discontinuation / Stopping rule

Obesity interventions usually have a regulatory-imposed rule in their label to be stopped early-on in case of lack of response typically defined as <5% weight loss from baseline. In the case of liraglutide 3.0 mg, the regulatory approval by the European Medicines Agency determined that treatment with liraglutide 3.0 mg should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight. This was applied as such in the model.

In the base case analysis, a stopping rule was also used for semaglutide 2.4 mg (in the assumption that semaglutide 2.4 mg marketing authorisation will include such a rule), whereby treatment should be discontinued after 12 weeks on the maintenance dose, i.e. after 28 weeks (16 weeks to reach maintenance dose, 12 weeks on maintenance dose) if patients have not lost <5% of their initial body weight.

A scenario explored no stopping rule for semaglutide 2.4 mg, however as it is a regulatory requirement for liraglutide 3.0 mg, a stopping rule was always enabled for liraglutide 3.0 mg. When enabled, the following will be applicable to the proportion of non-responders in the cohort:

- Liraglutide 3.0 mg has a 4-week titration period before starting the maintenance dose at 3.0 mg/day. Hence, data on the percentage of non-responders from any of the trials of liraglutide 3.0 mg were based on responder-status assessment at 16 weeks after treatment initiation (4-week titration period + 12-week maintenance dose)
- Semaglutide 2.4 mg responder status in STEP 1 was evaluated after 28 weeks (16-week titration period + 12 weeks of maintenance dose)

- Non-responders will discontinue liraglutide 3.0 mg and semaglutide 2.4 mg immediately (i.e. they do not get liraglutide 3.0 mg/semaglutide 2.4 mg efficacy) but the model will account for the initial time on treatment pharmacy costs. Early discontinuation assumes that the non-responder part of the cohort goes on to receive diet and exercise and achieve diet and exercise efficacy

For clarity, Table 28 describes how efficacy parameters are applied to each treatment and proportion of the cohort, responder/non-responder in case of early treatment discontinuation or no early discontinuation. For semaglutide 2.4 mg the stopping rule is assumed to be applied at 28 weeks, so the STEP 1 full analysis set efficacy (responders and non-responders) is used up to and including Cycle 2. After Cycle 2, early responder efficacy is used for patients continuing semaglutide 2.4 mg. The population containing all early responder patients of STEP 1 was assumed to be representative in terms of semaglutide 2.4 mg treatment efficacy for both subgroups. A scenario analysis explores a post hoc analysis of STEP 1 using subgroup data. The proportion of non-responders for liraglutide 3.0 mg is based on the SCALE 1839 trial and is not matched to STEP 1 patient characteristics. Matching was not possible because of the difference in definition of response between the two trials.

Table 28: Efficacy data sources in relation to stopping rules and proportion of responders

Setting	Semaglutide 2.4 mg efficacy source	Liraglutide 3.0 mg efficacy source
Stopping rules apply Discontinuation to diet and exercise	Up to Cycle 2: All patients: full analysis set efficacy Cycle 3 onwards: [redacted]R: early responder efficacy [redacted]NR: full analysis set efficacy with diet and exercise*	All cycles: [redacted]R: early responder efficacy [redacted]NR: full analysis set efficacy with diet and exercise*
Stopping rules do not apply i.e. no early discontinuation	All patients: full analysis set efficacy	Not applicable as stopping rule mandatory
Key: R, responder; NR, non-responder. **Notes:** *diet and exercise using data from STEP1. **Source:** [144, 152]		

B.3.3.4.2 Maximum treatment duration

The base case analysis assumes a maximum treatment duration of 2 years as in SWMS, treatment is typically provided for a maximum of two years.[27] This is also in line with TA664.

B.3.3.4.3 Per cycle discontinuation

In the base case analysis, the probability of discontinuation per cycle was sourced from the Kaplan–Meier curve of time to discontinuation for early 5% responders in the population containing all patients of STEP 1 for semaglutide 2.4 mg and diet and exercise, and this population's discontinuation was assumed to be representative across both subgroups. For liraglutide 3.0 mg, this was sourced from the SCALE 1839 trial, safety analysis set for patients with BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk of CVD in line with TA664.[27] The assumptions around responder discontinuation during treatment are as follows:

- The proportion of the cohort that discontinues before the maximum treatment duration, catches-up to the weight, SBP, total cholesterol and HDL cholesterol level as if patients stayed with diet and exercise according to the catch-up rate. The glycaemic status in patients in the temporary non-diabetic hyperglycaemia reversal health state that discontinue, revert back to the non-diabetic hyperglycaemia health state as defined by the catch-up rate

- After catch-up, physiological parameters will be equal to that in the diet and exercise arm and from there on follow the same path, i.e. both arms have weight going up following natural weight increase.

The catch-up period thus starts sooner for the proportion of the cohort discontinuing before the end of the 2-year treatment duration and defines the rate with which the respective proportion of the cohort will reach the same levels as the diet and exercise arm.

Note that for the proportion of the cohort discontinuing after 6 months, the catch-up duration will be slightly longer than defined by users (e.g. if catch-up period is defined to run over 3 years, the catch-up period for this cohort will be 3.5 years). Similarly, for the cohort discontinuing after 9 months of treatment, catch-up duration

will also be slightly longer than defined by users (e.g. if catch-up period is defined to run over 3 years, the catch-up duration for this cohort will be 3 years and 3 months). The proportion of responders discontinuing after 3 months of treatment for any reason (i.e. at start of Cycle 2) will behave as non-responders (non-responder discontinuation is described in above).

B.3.3.5 Catch-up period after treatment for BMI and glycaemic status

The effect of treatment on BMI, surrogate outcomes (SBP, HDL and total cholesterol) and glycaemic status is not lost immediately after treatment is stopped, but it is initially retained and wanes off over time.

The catch up is implemented so that at the end of the catch-up period BMI and surrogate markers for patients who had received active therapy have returned to the same levels as patients who received diet and exercise alone. The glycaemic status in patients in the temporary non-diabetic hyperglycaemia reversal health state reverts back to the non-diabetic hyperglycaemia health state for all treatments in the model after the catch-up period.

The definition of catch-up rate is provided in Table 29. By default, the catch-up rate for both surrogate outcomes and glycaemic status is assumed to be a cumulative 33% each year until the treatment effect is lost by Year 3 following treatment stop. Treatment effect waning rates are in line with assumptions used in TA664[27], and in line with previously published evidence.[106]

Table 29: Definition of catch-up rate

Definition	Catch-up rate (surrogate outcomes and glycaemic status)
Key assumption	Effect of treatment is gradually lost over a predefined period after treatment stop
Default time to catch-up	3 years
Treatment effect waning % over time (cumulative)	Year 1: 33% Year 2: 67% Year 3 onwards: 100%

B.3.3.6 Post-treatment level of SBP, cholesterol and HbA1c

In the base case analyses, although SBP and cholesterol may also be associated with a natural progression, for reasons of simplicity – as indeed patients may receive

blood pressure and cholesterol lowering drugs – the model only accounts for their evolution related to treatment effects, and there is no natural increase over time. When treatment is discontinued, the cohort returns to the value at baseline which is then maintained over the entire time horizon of the model.

HbA1c in diabetic patients is observed to increase with diabetes duration. The modelled cohort of interest enter the model without T2D but may develop T2D over time. It becomes difficult to represent HbA1c progression because diabetes duration will be different for all those who develop diabetes over the years, and they will all be at a different HbA1c level. This is because diabetes duration will be different for all those who develop diabetes over the years, and they will all be at a different HbA1c level.

Thus, to simplify, when conducting analyses and the cohort do not all have T2D, an average HbA1c of 7.5% is applied to the entire proportion of the cohort with T2D (either since baseline, or developed over time), and this does not increase further with time.

B.3.3.7 Obesity related complications

The model was adapted from the model submitted to NICE as part of TA664 for liraglutide 3.0 mg. This model was constructed from an SLR conducted in 2017 on the links between obesity and complications. This SLR was further updated to validate and identify sources to inform transition probabilities.[123] As described in Section B.3.2.2, not all the benefits of treatment are captured in the model as not all the comorbidities defined in that section could be modelled. Therefore, the risk equations used to extrapolate clinical efficacy parameters in disease outcomes for which data exist are included in Table 30, which presents which risk equation is used for each complication. More details on the risk equations for onset of T2D and CV events are provided in Appendix L.

Table 30: Risk equations used for obesity-related complications

Complication	Risk equation(s) available in model	Justification for base case selection
Onset of T2D	QDiabetes-2018 Model C[124]	QDiabetes allows prediction of 10-year risk and includes BMI and HbA1c as predictive variables. This is in line with assumptions from TA664.
	Framingham Offspring[153]	
First CV event	Qrisk3[125]	The QRisk3 contains a UK cohort and as such is being used in UK. This is in line with assumptions from TA664.
	Framingham Heart Study[154]	
Recurrent CV event	Framingham Recurring Coronary Heart Disease[126]	The only risk equation identified for recurrent CV events in non-diabetic patients. This is in line with assumptions from TA664.
First CV event in T2D	UKPDS82[127]	The UKPDS 82 risk model (outcome model 2) is a large UK study and able to predict both first and recurrent CV events after the onset of T2D. This is in line with assumptions from TA664
	Qrisk3[125]	
Incidence of recurrent CV event in T2D	UKPDS82[127]	
	Framingham Recurring Coronary Heart Disease[126]	
Onset of OSA	Sleep Heart Study[128]	This study preferred to other available studies because it was the largest in sample size (n=5,615), it provided sufficient data to calculate a prevalence rate per unit BMI, and it investigated the prevalence of moderate-to-severe OSA (AHI ≥15), given that in the present health-economic analysis, OSA was assigned a hospital cost for continuous positive airway pressure treatment.
Knee replacement	Wendelboe et al. 2003[129]	The study provided granular data on the association between BMI and incidence of knee surgeries by 2.5 BMI-unit steps for observed BMI levels between 17.50 and 42.49 kg/m^2.

B.3.3.7.1 Cardiovascular events – individual risks

Individual risk models were available for the following outcomes: first ischaemic heart disease (IHD) considered angina herein, first MI and first stroke, recurrent MI and recurrent stroke. There was no model to predict recurrent angina, hence, the estimated risk for recurrent events (MI and stroke) was adjusted based on the proportions of MI and stroke of total CVD exhibited in Table 31.

Table 31: Clinical inputs for calibration of composite cardiovascular endpoints

Model parameter	Value applied in model (mean)
Proportion of MI in all CVD events	33.12% (1)
Proportion of angina in all CVD events	40.22% (2)
Proportion of strokes in all CVD events	26.66% (3)
Proportion of TIA events of total strokes	21.85% (4)

Key: BMI, body mass index; HDL, high density lipoprotein; SBP, systolic blood pressure
Notes: (1): calculated as proportion of initial: MI, sudden and non-sudden CHD of total CHD (excl. coronary insufficiency) in D'Agostino 2000[126] for males and females then multiplied with the proportion of CHD (excl. coronary insufficiency) of total CHD plus stroke from D'Agostino 2008[154]; (2): calculated as proportion of initial angina of total CHD (excl. coronary insufficiency) in D'Agostino 2000[126] for males and females then multiplied with the proportion of CHD (excl. coronary insufficiency) of total CHD plus stroke from D'Agostino 2008[154]; (3): calculated as the proportion of strokes out of total CHD and strokes in D'Agostino 2008[154]; (4): calculated as proportion of TIA in total strokes from Wolf et al. 1991[155] in males and females.

B.3.3.7.2 Obstructive sleep apnoea

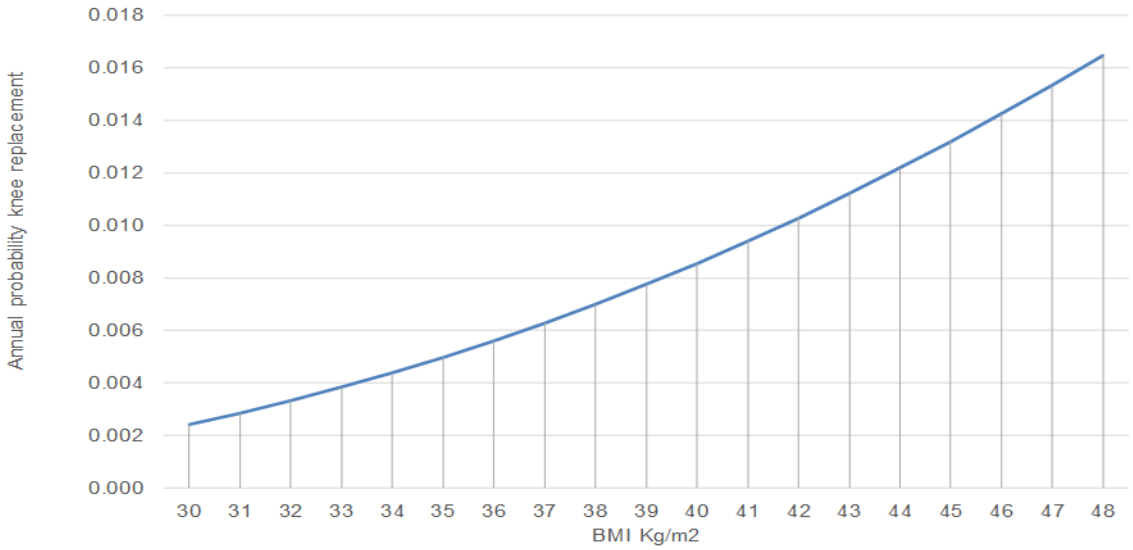
The proportion of the cohort having OSA depends on the BMI level in the cycle. The prevalence of OSA by BMI level was sourced from the Sleep Heart Study.[128] This study found that the prevalence of OSA as defined according to Apnoea-Hypopnea Index (AHI) ≥15 is 13% at BMI levels between 24.4–28.0 kg/m^2 (irrespective of gender). The reported odds ratio corresponding to one standard deviation (SD) increment in BMI was 1.6 (1.45, 1.76). This study was preferred to other available studies because it was the largest in sample size (n=5,615) and it provided sufficient data to calculate a prevalence rate per unit BMI. It was also preferred to other studies as it investigated the prevalence of moderate-to-severe OSA (AHI ≥15), given that in the present health-economic analysis, OSA was assigned a hospital cost for continuous positive airway pressure treatment. The BMI-prevalence table used in the model is illustrated in Appendix L.

Throughout the time horizon, the proportion of the cohort having sleep apnoea may reside in any non-dead health state (i.e. OSA co-occurs with any obesity complication including non-diabetic hyperglycaemia at baseline). This was possible as OSA was assumed not to influence the progression to and from other health states or events.

B.3.3.7.3 Knee replacement

The annual incidence of knee replacement surgeries in the reference BMI group (20-22.5 kg/m^2) for ages <65 years and ≥65 years was sourced from the study of Wendelboe et al. 2003, reporting figures of 0.053% and 0.12%, respectively.[129] The study provided granular data on the association between BMI and incidence of knee surgeries by 2.5 BMI-unit steps for observed BMI levels between 17.50 and 42.49 kg/m^2 and was hence preferred to other studies available in the literature. To derive a continuous function of the BMI-risk of knee replacement, and to extrapolate the association beyond the observed 42.49 kg/m^2 BMI in the study, a second-order polynomial trend was fitted to the calculated probabilities. Separate trend lines were fitted for males and females, and for patients aged 64 years or lower, and above 65 years. Figure 14 illustrates the incidence rate applied corresponding to an average age of the cohort of 48 years. The fitted polynomial trend functions are illustrated in Table 32.

Figure 14: Annual probability of knee replacement surgery by level of BMI



Key: BMI, body mass index.
Source: Wendelboe.[129]

Table 32: BMI-dependent risk functions for knee osteoarthritis

Model parameter	Value applied in model (mean)
Males aged <65 years	0.00002 * $(BMI)^2$ - 0.00095 * BMI + 0.01149
Males aged ≥65 years	0.00005 * $(BMI)^2$ - 0.00213 * BMI + 0.02582
Females aged <65 years	0.00002 * $(BMI)^2$ - 0.00082 * BMI + 0.00847
Females aged ≥65 years	0.00005 * $(BMI)^2$ - 0.00185 * BMI + 0.01902
Key: BMI, body mass index.	

B.3.3.8 Mortality

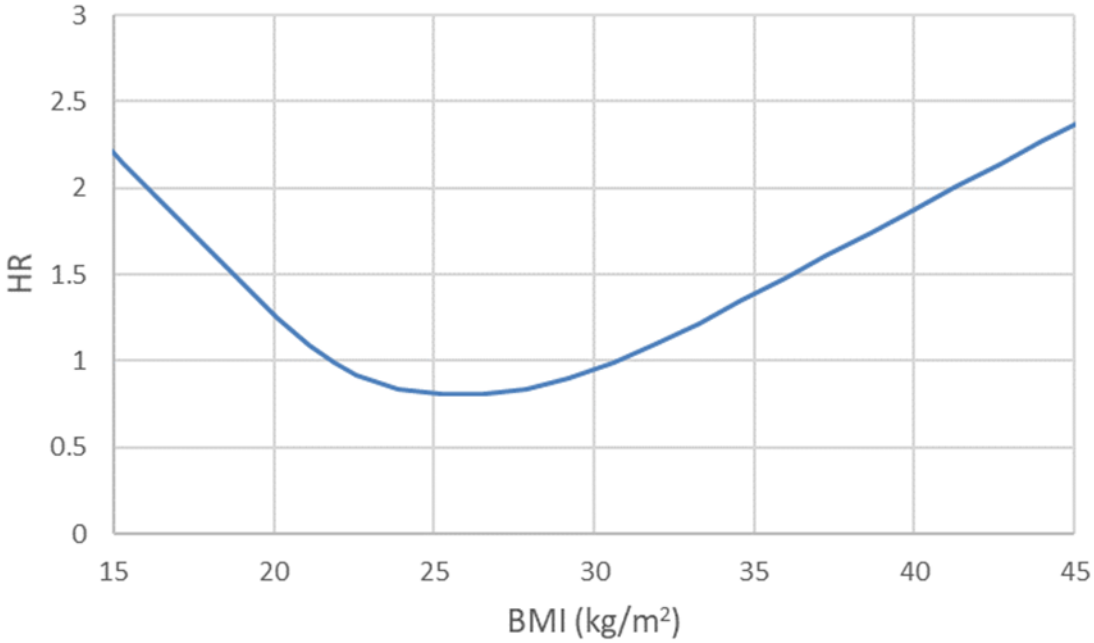
Survival of the model cohort is estimated using a combination of disease specific and BMI adjusted mortality. Disease specific mortality is split into long term mortality, associated with the different comorbidity health states adjusted by BMI and, short-term fatality associated with CVD events and knee replacement.

B.3.3.8.1 Long term mortality

General population mortality, defined as age and gender-specific all-cause mortality, was included in the model based on UK lifetables.[136] The general population mortality was adjusted by excluding the mortality of obesity related comorbidities accounted for elsewhere in the model such as diabetes, IHD, cerebrovascular diseases and arthrosis. The long-term mortality rate associated with obesity complications were obtained from mortality statistics by age, sex and underlying cause of death using ICD10 codes.[135]

The long-term mortality rate for each health state in the model was adjusted by the hazard ratio for BMI. This obtained the long-term disease specific mortality rate specific to the BMI. The association between all-cause mortality and BMI was obtained from Bhaskaran et al. 2018.[50] The digitised curve, used as a model input, is shown in Figure 15.

Figure 15: BMI related HRs from Bhaskaran et al. 2018



Key: BMI, body mass index; HR, hazard ratio.
Source: Bhaskaran. [50]

In addition to all-cause mortality, the model includes a higher risk of mortality associated with obesity complications which is applied to the cohort in each respective health state. The higher long-term mortality risk associated with diabetes and CVD was used to adjust general population mortality for the cohort in health states reflecting such complications.

General population mortality for the cohort who developed CVD was up-adjusted by a factor representing the long-term higher risk of death from having had an ACS or an MI (Table 33).

Table 33: Relative risks used to adjust general population mortality

Obesity complication	RR	Source
Post-ACS	1.3	Johansson et al. 2017 [130]
Post-stroke	2.0	Brammås et al. 2013 [131]
Key: ACS, acute coronary syndrome i.e. angina and MI.		

B.3.3.8.2 Obesity complications short-term mortality

Short-term fatality from CVD events and knee replacement and bariatric surgery is considered in the model at the event occurrence (Table 34).

Case-fatality associated with angina, MI and stroke are considered in the model and used to account for a higher risk of death in the year when the event occurs. Case-fatality associated with angina and MI was weighted and applied to the cohort developing ACS, and stroke related mortality was applied to the cohort developing a stroke event. Case-fatality was defined as death that occurs within 1 month of the event.

Table 34: Short-term mortality from complications

CVD event	Death probability females	Death probability males	Source
Case fatality MI	0.30	0.32	British Heart Foundation. Coronary heart disease statistics 2012. Table 2.12, All ages[133]
Case fatality angina	0.30	0.32	Assumed equal to MI fatality
Case fatality stroke	0.247	0.171	British Heart Foundation. Coronary heart disease statistics 2012. Table 2.12, All ages[133]
Knee replacement	0.003		Sing et al, 2011[134]
Bariatric surgery	0.0007		Alam et al. 2017[132]

B.3.4. Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

The SF-36 and IWQOL-Lite-CT HRQoL measures were administered to patients in the STEP 1 trial at baseline, Week 8, Week 16, Week 20, Week 36, Week 52 and Week 68. For both SF-36 and IWQOL-Lite-CT mean scores (all domains) at baseline were similar between the semaglutide 2.4 mg and placebo treatment arms.

The mean change in SF-36 physical functioning score from baseline to 68 weeks was significantly greater ($p < 0.001$) for semaglutide 2.4 mg compared with placebo (2.21 versus 0.41, respectively; ETD: 1.8; 95% CI: 1.2, 2.4).[83] Figure 8 in Section B.2.6.9.1 shows that the ETDs in change from baseline to Week 68 for all individual

health domain scores and for the physical component summary (PCS) and mental component summary (MCS), scores of SF-36 were all in favour of semaglutide 2.4 mg.

The estimated mean change in IWQOL-Lite-CT physical function score was significantly greater ($p < 0.001$) for semaglutide 2.4 mg compared with placebo (14.67 versus 5.25, respectively; ETD: 9.43; 95% CI: 7.5, 11.35).[83] Figure 9in Section B.2.6.9.2 shows that the ETDs in change from baseline to Week 68 for the physical function, physical, psychological and total scores of the IWQOL-Lite-CT were all in favour of semaglutide 2.4 mg.

Neither SF-36 or IWQOL-Lite-CT HRQoL are representative of the NICE reference case, nor do they yield utilities that can be applied to an economic model. They were therefore not used for the present economic analysis.

B.3.4.2 Mapping

No mapping was performed for this cost-effectiveness model as the model uses published utility values throughout the whole lifetime of the analysis.

B.3.4.3 Health-related quality-of-life studies

Systematic searches for HRQoL studies were carried out to identify all relevant studies on adult patients with obesity. The SLR conducted for semaglutide in April 2021 is an update to the previous SLR that was conducted for the liraglutide NICE TA664 in October 2018. For the original SLR and SLR update combined, a total of 45 records were included for data extraction, corresponding to 26 unique HRQoL studies.

Findings from the SLR demonstrated the lack of comprehensive published utility data, and studies identified in the SLR were therefore not used in the base case analysis. HRQoL inputs used in the base case were instead based on a large UK population-based study that has demonstrated a robust association between BMI and utility (see Section B.3.4.5).[137] Detailed information on the HRQoL literature review and included studies is provided in Appendix H.

B.3.4.4 Adverse reactions

As discussed in Section B.3.3.1.4, the adverse events included in the model are non-severe hypoglycaemia and severe gastrointestinal AEs. Their impact on the cohort of patients is included through disutilities that are applied in the cycle that the event occurs.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

In the model HRQoL is varied by age and BMI level, defined as baseline utility values without obesity complications. Baseline utility values are then adjusted for HRQoL decrements associated with obesity related complications. HRQoL decrements may be associated with the disease, e.g. diabetes or CVD, and therefore applied to baseline utility values to derive health state utilities at each cycle; or may be associated with an event, e.g. MI, and therefore applied in the model as one-off disutilities.

B.3.4.5.1 Baseline utility – per BMI level and age

The model allows the derivation of baseline utility as a function of BMI of the cohort with obesity and no comorbidities based on a polynomial model. The polynomial model reflects clinical opinion that the marginal rate of utility is most likely different from changing BMI from 26 to 25 compared with from 46 to 45. Furthermore, a polynomial model more accurately reflects that HRQoL may increase up to a BMI of around 25kg/m^2.

The source used for deriving such a model is Søltoft et al.[137]. Appendix N describes why this was selected as the most appropriate source. The utility curves were re-estimated using a polynomial of third degree for BMI ranges 15–35 kg/m², as in Søltoft et al.[137] Then, a logarithmic function was fitted to utilities in the BMI range 27–35 kg/m² and extrapolated up to a BMI of 60. The coefficients of the two functions (polynomial and log) for men and women are exhibited in Table 35. The coefficients for the age-adjustment (two scenarios) are reported in Table 36. Details of the two studies are presented in Appendix N.

Table 35: Re-estimate association between BMI and utility

Parameter	(BMI 15-35 kg/m^2)		(BMI 36 kg/m^2 and beyond)	
	Males	Females	Males	Females
BMI3	0.000033	0.000017	.	.
BMI2	-0.003200	-0.001800	.	.
BMI	0.099000	0.057200	-0.105431	-0.147297
Constant	-0.020554	0.401769	1.323834	1.462846
Key: BMI, body mass index.				

Table 36: Coefficients to adjust BMI dependent baseline utility as a function of age from Søltoft et al. 2009 and Burström et al. 2001 studies

Age	Derived coefficient by age			
	Men (Søltoft)	Men (Burström)	Women (Søltoft)	Women (Burström)
16–19	0.0287	-0.06	0.0055	-0.10
20–29	0	-0.062	0	-0.095
30–39	-0.0028	-0.072	-0.0213	-0.115
40–49	-0.0081	-0.112	-0.0336	-0.125
50–59	-0.043	-0.132	-0.0425	-0.155
60–69	-0.0223	-0.142	-0.0619	-0.195
70–79	-0.0565	-0.162	-0.0754	-0.195
80–88	-0.0565	-0.232	-0.0754	-0.235
Source: Søltoft, [137] Burström.[156]				

B.3.4.5.2 Acute decrements in utility

Non-fatal acute events considered in the model include ACS, osteoarthritis, stroke and TIA. Upon the occurrence of one of these events, a one-off disutility is applied in the cycle in which the event occurs. To account for HRQoL impact associated with severe musculoskeletal disorders, the model includes a disutility applied in the year a knee replacement surgery occurs. The disutility is applied once, to the event, and is multiplied with a factor of three to account for three years of living with a chronic, debilitating condition prior to surgery. This assumption was in line with modelling knee replacement in TA664.[27]

A summary of all events for which an acute disutility is included in the model is shown in Table 37. No disutility associated with treatments was included in the model.

Table 37: Disutility values associated with acute events

Parameter	Value	Source
ACS*#	-0.063	Sullivan et al. 2011[138]
Stroke*#	-0.117	Sullivan et al. 2011[138]
TIA*	-0.033	Sullivan et al. 2011[138]
Knee replacement#	-0.194	Søltoft et al.[137]
Key: ACS, acute coronary syndrome; TIA, transient ischemic attack. **Notes:** *HRQoL decrement observed within 30 days of event. #HRQoL decrement for fatal and non-fatal event is considered in the model.		

For fatal events, it is assumed that death occurs in the middle of a cycle. Thus, the total disutility for stroke, for example, for the proportion of the cohort experiencing death from the event, was calculated by multiplying the proportion of the cohort dying within 30 days from the event by half the negative total utility value of the cycle in which the proportion of the cohort died.

The total disutility at each cycle is calculated by taking the sum of non-fatal acute events and fatal acute events.

B.3.4.5.3 Health state utility values

In addition to acute decrements from baseline utility, long-term absolute HRQoL decrements associated with each obesity related complication are considered in the model (Table 38). Such HRQoL 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. By doing so, health state utility values continue to be adjusted for age, gender and BMI level, in addition to HRQoL decrements associated with a given disease.

No HRQoL decrement is assigned for non-diabetic hyperglycaemia.

Table 38: HRQoL decrements of acute events

Health-state*	Value	Source
T2D	-0.037	Søltoft et al.[137]
OSA	-0.038	Søltoft et al.[137]
Post-ACS	-0.037	Sullivan et al. 2011[138]
Post-stroke	-0.035	Sullivan et al. 2011[138]
Key: ACS, acute coronary syndrome; HRQoL, health-related quality of life; OSA, obstructive sleep apnoea; T2D, type 2 diabetes. **Notes:** *excluding acute disutility.		

When health states combine two or more obesity complications, the HRQoL decrement associated with each single complication is summed together and the total is then subtracted from the baseline utility. For example, in the health state 'T2D + Post ASC' the total HRQoL decrement subtracted from the baseline utility is equal to the sum of the HRQoL decrement for T2D and the HRQoL decrement for post ASC. Gough et al. 2009 concluded that the HRQoL decrements associated with T2D and obesity showed no significant interaction and thus could be assumed to be additive.[157] HRQoL decrements associated with each potential combination of obesity complications included in the model are not reported in the literature and so the current approach was therefore seen as the most appropriate solution to account for the HRQoL impact of obesity complications in a transparent way without underestimating the associated severe humanistic burden.

B.3.4.5.4 Disutilities related to bariatric surgery

A one-off disutility is applied to the proportion of the cohort receiving bariatric surgery at each cycle (Table 39). The disutility represents the decrement in quality of life associated with the surgical procedure and related complications.

Table 39: HRQoL decrements for bariatric surgery

Disutility	Model input	Source
Disutility of bariatric surgery	-0.184	Campbell et al. 2010[139]

B.3.4.5.5 Disutilities related to AEs

Table 40 illustrates modelled disutilities per type of treatment-related adverse event in the model.

Table 40: Treatment-related adverse event disutilities

Adverse Event	Model input	Comment/reference
Non-severe hypoglycaemia	-0.0062	V Foos, 2018[141]
Severe gastrointestinal event	-0.0010	-0.05 decrement applied for one week (NICE TA494, 2017) [142]
Key: AE, adverse event.		

B.3.4.5.6 Summary of utility values used in the model

Table 41 provides a summary of utility values used in the model as well as a comparison to values used in TA664.[27] Where values are dependent on BMI and age, the value for the mean of the baseline population is presented.

Table 41: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Utility value in TA664	Justification
Baseline utility	0.901*	*	Section B.3.4.5.1, page 124 to 125	Polynomial model by Søltoft et al.[137]	Allows for HRQoL dependent on BMI, while removing effect of comorbidities. Same as TA664
ACS	-0.063 (0.046)[138]	-0.049, -0.076	Section B.3.4.5.2, page 125	-0.063[138]	Literature value. Same as TA664
Stroke	-0.117 (0.012)[138]	-0.105, -0.129		-0.117[138]	
TIA	-0.033 (0.022)[138]	-0.011, -0.055		-0.033[138]	
Knee replacement	-0.194 (0.048)**[137]	-0.438, -0.243		-0.194**[137]	
T2D	-0.037 (0.009)[137]	-0.028, -0.047	Section B.3.4.5.3, page 126	-0.037[137]	
OSA	-0.038 (0.010)[137]	-0.029, -0.048		-0.038[137]	
Post-ACS	-0.037 (0.026)[138]	-0.011, -0.063		-0.037[138]	
Post-stroke	-0.035 (0.021)[138]	-0.014, -0.056		-0.035[138]	
Bariatric surgery	-0.184 (0.046)[139]	-0.138, -0.230	Section B.3.4.5.4, page 127	-0.184[139]	
Non-severe hypoglycaemia	-0.0062 (0.002)[141]	-0.005, -0.008	Section B.3.4.5.5, page 128	-0.014[158]	Literature value, updated since TA664 to a more recent, better applicable reference
Severe gastrointestinal	-0.050 (0.0002)[142]	-0012, -0.0007		-0.0010 [142]	Annual disutility of -0.0010, decrement of -0.05 applied for one week. Same as TA664

Key: ACS, acute coronary syndrome; OSA, obstructive sleep apnoea; T2D, type 2 diabetes; TIA, transient ischemic attack.
Note: *Baseline for BMI >30 + 1 or more comorbidities is 0.901; Baseline for BMI >35 + prediabetes and high CVD risk is 0.889; Coefficients were not varied; ** Literature value multiplied by three to account for three years of living with osteoarthritis

B.3.5. Cost and healthcare resource use identification, measurement and valuation

Appendix I outlines the SLR to search for studies reporting cost and healthcare resource data for the treatment of patients with obesity in the UK. The SLR conducted for semaglutide in April 2021 is an update to the previous SLR that was conducted for the liraglutide NICE TA664 in October 2018.

Three studies identified in the combined searches were from the UK perspective.[159-161] Information extracted was not found to be relevant for the current economic analysis as studies did not focus on the patient population or treatments identified as relevant to the decision problem, and thus was not utilised (see Appendix G and I).

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Treatment costs

Treatment costs include the acquisition cost of pharmacological treatment and the cost of diet and exercise.

The cost of pharmacological treatment is included in the model based on the dose as per the list price and the proposed confidential discount price (PAS price). Costs for both the titration and maintenance doses are included. The total treatment cost per cycle is calculated by multiplying the cost per mg by the dose in mg required in a given cycle. The cost of needles is provided by Novo Nordisk. To account for the stopping rules used within the 3-month cycle length during the first year of the model, an adjustment is made to the pharmacy cost. For semaglutide 2.4 mg, the adjustment removes 2 weeks of treatment acquisition costs after Cycle 2 (6 months). For liraglutide 3.0 mg, the adjustment adds 1 month of treatment acquisition costs to Cycle 1 (3 months) which is removed in Cycle 2.

The cost of the diet and exercise intervention is included in the obesity monitoring cost. Table 42 reports the annual cost of treatment and monitoring using list prices for semaglutide and liraglutide.

B.3.5.1.2 Obesity monitoring

The cost of obesity monitoring is defined as the average cost of all routine visits, examinations, diet and exercise required for the management of an adult patient with obesity. The routine obesity monitoring cost is included per year; however, it is readjusted automatically to fit the 3-month cycles in the first year of the simulation.

The cost of obesity monitoring is applied to each comparator in the model since all pharmacological treatments are assumed to be administered in conjunction with diet and exercise and to require visits/examination follow-up. Table 42 reports the costs of obesity monitoring, diet and exercise.

Table 42: Annual treatment costs (list price)

Treatment costs	Cost (£)	Description and references
Semaglutide (2.4 mg/ week) – year 1 Titration phase: (week 1-week 16) Maintenance phase: (week 17-52)	[redacted]	Week 1–4 titration period dose: 0.25 mg and £18.31 per week; total: £73.25 Week 5–8 titration period dose: 0.5 mg and £18.31 per week; total: £73.25 Week 9–12 titration period dose: 1.0 mg and £18.31 per week; total: £73.25 Week 13–16 titration period dose: 1.7 mg and £[redacted] per week; total: £[redacted] Week 17-52 maintenance period dose: 2.4mg and £[redacted] per week; total: £[redacted]
Semaglutide (2.4 mg/ week – year 2	[redacted]	Week 1- 52: maintenance period dose: 2.4mg and £[redacted] per week
Liraglutide (3.0 mg/ day) – year 1	2,289.00	Week 1 titration period dose: 0.6 mg per day: total week 1: £ 9.16 Week 2 titration period dose: 1.2 mg per day: total week 2: £18.31 Week 3 titration period dose 1.8 mg per day: total week 3: £27.47 Week 4 titration period dose: 2.4 mg per day: total week4: £36.62 Total Week 1-4: £91.56 Week 5-52: Maintenance period dose: 3.0mg per day: and £45.78 per week, total: £2,197.44
Liraglutide (3.0 mg/ day) – year 2	2,387.10	Week 1-52: Maintenance period dose: 3.0mg per day: and £45.78 per week
Diet & exercise		Included under monitoring costs
Monitoring costs for obesity, annual	248.90	Annual frequency (assumed equal to orlistat and rimonabant) * cost for 3 types of visits:

Treatment costs	Cost (£)	Description and references
		GP visit: GP cost per surgery consultation lasting 9.22 minutes: £39, PSSRU p126.162 Frequency: 4x10 mins106 Nurse visit: Nurse cost / hour: £38, PSSRU p124.162 Frequency: 8x15 mins106 Blood test (1 test): Unit cost: £3.7, Phlebotomy (code DAPS08).44 Frequency: 1x 106
Blood pressure treatment	17.66	Average annual cost of ACE inhibitor treatment: • Enalapril maleate (20mg; 28 tablets; NHS indicative price: £3)= (£3/28)*365.25 = £ 39.13[163] • Lisinopril (20mg; 28 tablets; NHS indicative price: £0.71)= (£0.71/28)*365.25 = £ 9.26[164] • Perindopril Erbumine (4mg; 30 tablets; NHS indicative price: £0.96)= (£0.96/30)*365.25 = £11.69[165] • Ramipril (5mg; 28 tablets; 2.5 mg; NHS indicative price: £0.81)= (£0.81/28)*365.25 = £10.57[166]
List prices used: 0.25mg semaglutide (£73.25 per 4 pen pack) 0.5mg semaglutide (£73.25 per 4 pen pack) 1.0 mg semaglutide (£73.25 per 4 pen pack) 1.7 mg semaglutide (£[redacted] per 4 pen pack) 2.4 mg semaglutide (£[redacted] per 4 pen pack)		

B.3.5.2 Health-state unit costs and resource use

Annual cost of obesity related complications includes costs associated with monitoring and treating a given disease and is used in the model to define health state costs. For T2D, the cost of insulin treatment is considered separately and is based on the dose and type of insulin treatment available in UK practice. The costs of health states including multiple obesity complications are calculated by summing the costs associated with each condition. Obesity related complication costs are derived from UK published studies or real-world data. Table 43 displays annual costs for each health state in the model and the pharmacy costs related to T2D.

Table 43: Annual obesity related complication costs applied to health states in the model

State costs	Cost (£)	Description and references
T2D microvascular	940.86	Annual cost = (a+b+c)/d

State costs	Cost (£)	Description and references
complications costs*		a) Lifetime ophthalmic complications: £6,460[167] b) Lifetime ulcer, amputation, and neuropathy complications: £7,396[167] c) Lifetime renal complications: £5415[167] d) Undiscounted life expectancy (years): 20.935
T2D treatment – average of insulin and oral treatments*	551.89	• Total lifetime per patient, undiscounted T2D pharmacy treatment cost (empagliflozin arm): £11,304[167] • Undiscounted life expectancy (years): 20.935[167] • Annual treatment cost= £11,304/20.935= £539.96
Non-diabetic hyperglycaemia	54.00	Cost of monitoring and educating high risk patients: £270/5 years= £54[168]
MI 1st year, excl. acute event cost	1,174.12	Average costs of: • Non-inpatient cost, Male aged 60 years: £963 (short-term)[169] • Non-inpatient cost, Female aged 60 years: £1,125 (short-term)[169]
Unstable angina 1st year, excl. acute event cost	1,056.18	Average costs of: • Non-inpatient cost, Male aged 60 years: £864[169] • Non-inpatient cost, Female aged 60 years: £1,014 (calculated the ratio of male and female from short-term MI to get the female costs: 54% *864/46%= £1,014)[169]
Post-acute coronary syndrome	846.29	Average costs of: • Non-inpatient cost, Male aged 60 years: £671 (long-term)[169] • Non-inpatient cost, Female aged 60 years: £834 (long-term)[169]
Stroke 1st year, excl. acute event cost	1,333.67	Average costs of: • Non-inpatient cost, Male aged 60 years: £1,091[169] • Non-inpatient cost, Female aged 60 years: £1,281 (calculated the ratio of male and female from short-term MI to get the female costs: 54% *1,091/46%= £ 1,281)[169]
Transient ischaemic attack, 1st year	1,338.77	TIA - from second year: £ 2,447.92/2= £ 1,223.96[170]
Post-stroke (stroke and TIA, in year following the event)	944.69	Average costs of: • Non-inpatient cost, Male aged 60 years: £756[169] • Non-inpatient cost, Female aged 60 years: £924 (calculated the ratio of male and female from long-term MI to get the female costs: 55% *756/45%= £924)[169]
Sleep apnoea cost	1,018.19	Weighted average cost for number of activity and national average unit costs from Total HRGs tab for sleep disorders codes (NHS direct costs): DZ18D, DZ18E, DZ18F, DZ18G[171]
Key: MI, myocardial infarction; T2D, Type 2 diabetes; TIA, transient ischemic attack. **Note:** *Undiscounted costs and life-years were received following communication with the author		

B.3.5.3 Adverse reaction unit costs and resource use

Table 44 illustrates the costs per type of treatment-related adverse event in the model.

Table 44: Costs of treatment-related adverse events

Adverse Events	Cost (£)	Reference
Non-severe hypoglycaemia	4.09	Non-severe hypoglycaemic event (nocturnal or diurnal), table 2[167]
Severe gastrointestinal event	144.01	Cost of Gastroenterology (Code 301) from Total Outpatient Attendance[171]

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 Bariatric surgery costs

As bariatric surgery is included in the model as a downstream event, it has a corresponding one-off cost. The cost is applied to the proportion of the cohort receiving the surgery at each cycle and includes preoperative management, procedure, postoperative follow-up and surgery related complications.[146]

The average procedure cost is calculated as the weighted average cost of the three types of procedures. The cost of leaks is used as a proxy for bariatric surgery related complications [147] and is included in the model as an average across all patients, i.e. already weighted by the incidence of complications. Table 45 reports bariatric surgery costs.

Table 45: Bariatric surgery costs

Event costs	Cost (£)	Description and references
Bariatric surgery, pre-operative management	149.16	Mean cost of the pre-operative assessment visit[172]
Bariatric surgery procedure cost	5,297.28	Weighted average cost of complex surgery, major surgery, laparoscopic banding, sleeve gastrectomy with weights based on number of activities[171]
Gastric bypass procedure	5,931.53	Weighted average cost for number of activity and national average unit costs from Total HRGs: FF10Z, FF11Z[171]
Laparoscopic banding procedure	3,310.84	Cost of Gastric Band Procedures for Obesity from Total HRGs: Code FF13Z[171]
Sleeve gastrectomy procedure	5,404.93	Cost of Sleeve Gastrectomy for Obesity from Total HRGs: Code FF12Z[171]

Bariatric surgery, post-operative follow-up	632.24	Average cost of: • Roux-en-Y gastric bypass: £615[172] • Sleeve gastrectomy: £750[172] • Adjustable gastric banding: £ 428[172]
Bariatric surgery, complications	4,713.74	Cost of bariatric surgery complications; captured leakage and abscess, year 1[173]
TOTAL bariatric surgery, non-fatal	6,359.14	Calculated: sum of preoperative management, procedure costs, postoperative follow-up and 5.95% occurrence of leakage and abscess[147]
TOTAL bariatric surgery, fatal	5,726.90	Assumed same as bariatric surgery, but excluding follow-up costs

B.3.5.4.2 Acute event cost

The model includes the one-off costs of the obesity related acute events angina, MI, stroke, knee replacement and TIA. The costs of obesity related acute events represent the economic burden associated with managing the patient when the acute event occurs, including hospitalisation costs. In the case of knee replacement, this is also associated with pre-surgery visits/examinations and post-surgery follow-up. The cost of managing osteoarthritis before surgery (e.g. analgesics) was considered negligible and not accounted for in the model.

The costs of obesity related acute events are included in the model as one-off, and separately from health state costs. Table 46 reports acute event costs.

Table 46: Acute event costs

Event costs	Cost (£)	Description and references
MI non-fatal event	2,419.26	Weighted average cost for number of FCE's and national average unit costs from Non-Elective Long Stay for codes: EB10A, EB10B, EB10C, EB10D, EB10E[171]
MI fatal	2,419.26	Assumed same as MI non-fatal event cost
Unstable angina non-fatal event	1,698.35	Weighted average cost for number of FCE's and national average unit costs from Non-Elective Long Stay for codes: EB13A, EB13B, EB13C, EB13D[171]
Unstable angina fatal event	1,698.35	Assumed same as Unstable angina non-fatal event cost
Stroke non-fatal event	4,855.71	Weighted average cost for number of FCE's and national average unit costs from Non-Elective Long Stay for codes: AA35A, AA35B, AA35C, AA35D, AA35E, AA35F[171]
Stroke, fatal	4,855.71	Assumed same as Stroke non-fatal event cost

Event costs	Cost (£)	Description and references
TIA event	2,154.92	Weighted average cost for number of FCE's and national average unit costs from Non-Elective Long Stay for codes: AA29C, AA29D, AA29E, AA29F[171]
Knee replacement, non-fatal	6,492.12	Weighted average cost for number of FCE's and national average unit costs from Elective Inpatient for codes: HN22A, HN22B, HN22C, HN22D, HN22E[171]
Fatal knee replacement	6,492.12	Assumed same as knee replacement non-fatal event cost
Key: FCE, finished consultant episode; MI, myocardial infarction; TIA, transient ischemic attack.		

B.3.5.5 Comparison of costs inputs to TA664 costs inputs

Table 47 presents a comparison if cost inputs between the current submission and TA664. Where there is a difference between the costs, this is either because costs sources have been updated, or more appropriate cost sources were identified in a targeted literature review (TLR).

Table 47: Comparison of cost inputs between current submission and TA664

Input	TA664 (Liraglutide 3.0 mg)	Current appraisal - TA [ID3850] (Semaglutide 2.4 mg)	Justification if different
Monitoring costs for obesity, annual	£130.83[106, 174, 175]	£248.90[44, 106, 162]	Updated cost sources
Needles	£5.94[176]	£0 (provided by Novo Nordisk)	Costs now provided by Novo Nordisk
Blood pressure treatment	£33.72	£17.66[163-166]	Updated cost sources
T2D microvascular complications	£468[177]	£940.86[167]	New data available from recent publication
T2D treatment – average of insulin and oral treatments	£316.76[178]	£551.89[167]	New data available from recent publication
Non-diabetic hyperglycaemia	£55[168]	£54[168]	Inflation
MI 1st year, excl. acute event	£3,523[179]	£1,174.12[169]	Updated following TLR
Unstable angina 1st year, excl. acute event	£573[179]	£1,056.18[169]	
Post-acute coronary syndrome	£223[179]	£846.29[169]	
Stroke 1st year, excl. acute event	£6,120[179]	£1,333.67[169]	

Input	TA664 (Liraglutide 3.0 mg)	Current appraisal - TA [ID3850] (Semaglutide 2.4 mg)	Justification if different
TIA, 1st year	£1,385[179]	£1,338.77[170]	
Post-stroke (stroke and TIA, in year following the event)	£2,815[179]	£944,69[169]	
Sleep apnoea	£869[175]	£1,018.19[171]	Updated cost sources
Non-severe hypoglycaemia	£3.16[180]	£4.09[167]	Updated following TLR
Severe gastrointestinal event	£149[175]	£144.01[171]	Updated cost sources
MI event	£2,265[175]	£2,419[171]	
Unstable angina event	£1,466[175]	£1,698[171]	
Stroke event	£4,351[175]	£4,855.71[171]	
TIA event	£1,945[175]	£2,154.92[171]	
Knee replacement	£6,251[175]	£6,492.12[171]	
Bariatric surgery, pre-operative management	£1,024[146]	149.16[172]	Updated following TLR
Gastric bypass procedure	£5,184[175]	5,931.53[171]	Updated cost sources
Laparoscopic banding procedure	£3,076[175]	3,310.84[171]	
Sleeve gastrectomy procedure	£4,823[175]	5,404.93[171]	
Bariatric surgery, post-operative follow-up	£875[146]	632.24[172]	Updated following TLR
Bariatric surgery, complications	£3,158[147]	4,713.74[173]	

Key: excl, excluding; MI, myocardial infarction; T2D, type 2 diabetes; TA, technology appraisal; TIA, transient ischaemic attack; TLR, targeted literature review.

B.3.6. Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A summary of base case model inputs is provided in Table 48 to Table 50. A default margin of error of 25% around the mean estimate was applied where standard errors of the mean were not available/not reported.

Table 48: Summary of baseline cohort characteristics and AE probabilities in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Age	[redacted]	[redacted]	Section B.3.2.1, Table 16
BMI (kg/m^2)	[redacted]	[redacted]	
Height (m)	[redacted]	[redacted]	
SBP (mmHg)	[redacted]	[redacted]	
Total cholesterol (mg/dL)	[redacted]	[redacted]	
HDL cholesterol (mg/dL)	[redacted]	[redacted]	
Average HbA1c after T2D development (%-points)	7.5	No variation	
T2D duration (years)*	3.0	2.0, 4.0$^+$	
Triglycerides (mg/dl)	[redacted]	[redacted]	
Proportion Triglyceride level >150 mg/dl (%)	[redacted]	[redacted]	
Proportion current smokers (%)	[redacted]	[redacted]	
Proportion females (%)	[redacted]	[redacted]	
Proportion on lipid-lowering drug (%)	[redacted]	[redacted]	
Proportion on antihypertensive medication (%)	[redacted]	[redacted]	
Proportion with non-diabetic hyperglycaemia (%)	[redacted]	[redacted]	Section B.3.2.2.1, Table 17
Non-severe hypoglycaemia (incr prob per cycle 1 - %)	0.008	0.010, 0.006 (Beta)	Section B.3.3.1.4, Table 25
Non-severe hypoglycaemia (incr prob per cycle 2 - %)	0.024	0.030, 0.018 (Beta)	
Non-severe hypoglycaemia (incr prob per cycle 3 - %)	0.024	0.030, 0.018 (Beta)	
Non-severe hypoglycaemia (incr prob per cycle 4 - %)	0.024	0.030, 0.018 (Beta)	
Non-severe hypoglycaemia (incr prob per cycle 5 - %)	0.035	0.044, 0.026 (Beta)	
Non-severe hypoglycaemia (incr prob per cycle 6 - %)	0.035	0.044, 0.026 (Beta)	
Severe GI events (incr prob per cycle 1 - %)	0.708	0.885, 0.531 (Beta)	
Severe GI events (incr prob per cycle 2 - %)	0.708	0.885, 0.531 (Beta)	
Severe GI events (incr prob per cycle 3 - %)	0.708	0.885, 0.531 (Beta)	
Severe GI events (incr prob per cycle 4 - %)	0.708	0.885, 0.531 (Beta)	
Severe GI events (incr prob per cycle 5 - %)	3.015	3.769, 2.262 (Beta)	
Severe GI events (incr prob per cycle 6 - %)	3.015	3.769, 2.262 (Beta)	

Key: AE, adverse event; BMI, body mass index; CI, confidence interval; GI, gastrointestinal; HDL, high-density lipoproteins; incr, incremental; KOL, key opinion leader; prob, probability; SBP, systolic blood pressure; T2D, type 2 diabetes.
Notes: *Based on KOL opinion, applied after onset of diabetes. $^+$Not varied in PSA but tested in DSA

Table 49: Summary of efficacy inputs applied in the economic model

Variable	Value		Measurement of uncertainty and distribution: CI (distribution)		Reference to section in submission
	Semaglutide 2.4 mg	Diet and Exercise	Semaglutide 2.4 mg	Diet and Exercise	
Weight change at Month 4 (%)	-12.04	-2.69	-11.73, -12.34 (Normal)	-2.25, -3.12 (Normal)	Section B.3.3.1.1, Table 21
Weight change at Month 10 (%)	-13.22	-2.44	-12.92, -13.52 (Normal)	Equal to Month 4	
Weight change at Year 1 (%)	-18.47	-2.44	-17.95, -18.99 (Normal)	-1.73, -3.15 (Normal)	
SBP change at Month 4 (mmHg)	-5.93	-0.56	-5.27, -6.60 (Normal)	0.39, -1.50 (Normal)	
SBP change at Month 10 (mmHg)	-6.48	-1.14	-5.77, -7.19 (Normal)	Equal to Month 4	
SBP change at Year 1 (mmHg)	-7.63	-1.14	-8.39, -6.87 (Normal)	-2.18, -0.11 (Normal)	
TC change at Month 4 (mg/dl)	-15.27	1.39	-15.06, -15.48 (Normal)	1.41, 1.36 (Normal)	
TC change at Month 10 (mg/dl)	-15.92	0.18	-15.68, -16.16 (Normal)	Equal to Month 4	
TC change at Year 1 (mg/dl)	-9.20	0.18	-9.06, -9.34 (Normal)	0.18, 0.18 (Normal)	
HDL-C change at Month 4 (mg/dl)	-4.63	-0.96	-4.57, -4.70 (Normal)	-0.94, -0.98 (Normal)	
HDL-C change at Month 10 (mg/dl)	-4.76	1.07	-4.69, -4.83 (Normal)	Equal to Month 4	
HDL-C change at Year 1 (mg/dl)	2.97	1.07	3.01, 2.92 (Normal)	1.09, 1.05 (Normal)	
Glycaemic status change (%)	90.4	45.8	92.83, 87.90 (Normal)	51.69, 39.82 (Normal)	Section B.3.3.1.2, Table 22
Maximum treatment duration (years)	2	2	No variation		Section B.3.3.4.2
Per-cycle discontinuation	STEP 1 KM		No variation		Section B.3.3.4.3
Key: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; KM, Kaplan–Meier; SBP, systolic blood pressure; TC, total cholesterol.					

Table 50: Summary of epidemiological inputs, utilities and costs applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Responders Liraglutide 3.0 mg (at 5%, for stopping rule) (%)	83	80, 85 (Beta)	Section B.3.3.1.3, Table 23
Minimum BMI level for bariatric surgery (kg/m^2)	35	Variability assessed in a scenario analysis	Section B.3.3.2, Table 26
Incidence of bariatric surgery per year (%)	1.15	Variability assessed in a scenario analysis	
Maximum age for bariatric surgery (years)	57	No variation	
Incidence of adverse events following bariatric surgery (%)	5.95	No variation	
Proportion of bariatric surgeries that are gastric bypass (%)	51	SE 0.13 (Dirichlet)	Section B.3.3.2, Table 27
Proportion of bariatric surgeries that are laparoscopic banding (%)	18	SE 0.04 (Dirichlet)	
Proportion of bariatric surgeries that are sleeve gastrectomy (%)	31	SE 0.08 (Dirichlet)	
Percentage weight change at 1 year, following gastric bypass (%)	-32	48.6, 17.5 (Beta)	
Percentage weight change at 1 year, following laparoscopic banding (%)	-20	30.6, 11.2 (Beta)	
Percentage weight change at 1 year, following sleeve gastrectomy (%)	-25	38.2, 13.8 (Beta)	
Change in SBP mmHg at 1 year	-9.10	-6.83, -11.38 (Normal)	
Change in total cholesterol mg/dl at 1 year	-29.69	-22.27, -37.11 (Normal)	
Change in HDL cholesterol mg/dl at 1 year	6.34	7.93, 4.76 (Normal)	
Change in HbA1c % at 1 year (in T2D) (%)	-2.15	3.3, 1.2 (Normal)	
Case fatality bariatric surgery	0.0007	0.0009, 0.0005 (Beta)	
Natural weight increases per year, (kg/m^2)	0.46	0.58, 0.35 (Normal)	Section B.3.3.3
Natural weight increases per year, male (kg/m^2)	0.1447	No variation	
Natural weight increases per year, female (kg/m^2)	0.1747	No variation	
Maximum age until which weight increases (years)	68	70.00, 66.00 (Gamma)	
Proportion of MI in all CVD events (%)	34	SE 0.08 (Dirichlet)	Section B.3.3.7.1, Table 31
Proportion of angina in all CVD events (%)	40	SE 0.10 (Dirichlet)	
Proportion of strokes in all CVD events (%)	26	SE 0.07 (Dirichlet)	
Proportion of TIA events of total strokes (%)	22	SE 0.05 (Dirichlet)	
Prevalence of OSA (BMI 24.4-28.0 kg/m^2) (%)	13	No variation	Section B.3.3.7.2
OR for OSA for +1 SD in BMI	1.6	No variation	
RR for mortality post-ACS	1.3	No variation	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
RR for mortality post-stroke	2.0	No variation	Section B.3.3.8.1, Table 33
Case fatality MI	0.31	0.46, 0.17 (Beta)	Section B.3.3.8.2, Table 34
Case fatality MI, males	0.32	No variation	
Case fatality MI, females	0.30	No variation	
Case fatality angina	0.31	0.46, 0.17 (Beta)	
Case fatality angina, females	0.30	No variation	
Case fatality angina, males	0.32	No variation	
Case fatality stroke	0.23	0.35, 0.13 (Beta)	
Case fatality stroke, females	0.247	No variation	
Case fatality stroke, males	0.171	No variation	
Time with osteoarthritis before knee replacement surgery (years)	3	5, 3 (Gamma)	Section B.3.4.5.2
Case fatality knee replacement	0.3	0.5, 0.2 (Beta)	
ACS disutility	-0.063	-0.049, -0.076 (Gamma)	Section B.3.4.5.2, Table 37
Stroke disutility	-0.117	-0.105, -0.129 (Gamma)	
TIA disutility	-0.033	-0.011, -0.055 (Gamma)	
Knee replacement disutility	-0.064	-0.049, -0.081 (Gamma)	
T2D disutility	-0.037	-0.028, -0.047 (Gamma)	Section B.3.4.5.3, Table 38
OSA disutility	-0.038	-0.029, -0.048 (Gamma)	
Post ACS disutility	-0.037	-0.011, -0.063 (Gamma)	
Post stroke disutility	-0.035	-0.014, -0.056 (Gamma)	
Bariatric surgery disutility	-0.184	-0.138, -0.230 (Gamma)	Section B.3.4.5.4, Table 39
Non-severe hypoglycaemia disutility	-0.0062	-0.005, -0.008 (Gamma)	Section B.3.4.5.5, Table 40
Severe gastrointestinal event disutility	-0.0010	-0.0012, -0.0007 (Gamma)	
Semaglutide 2.4 mg/week, Year 1 (£)	[redacted]	N/A	Section B.3.5.1, Table 42
Semaglutide 2.4 mg/week – Year 2 (£)	[redacted]	N/A	
Monitoring costs for obesity, annual (£)	248.90	311.12, 186.67 (Gamma)	
Blood pressure treatment (£)	17.66	22.08, 13.25 (Gamma)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
T2D microvascular complications costs (£)	940.86	1,176.07, 705.64 (Gamma)	Section B.3.5.2, Table 43
T2D treatment – average of insulin and oral treatments (£)	551.89	689.86, 413.92 (Gamma)	
Non-diabetic hyperglycaemia (£)	54.00	67.50, 40.50 (Gamma)	
MI 1st year, excl. acute event cost (£)	1,174.12	1,467.65, 880.59 (Gamma)	
Unstable angina 1st year, excl. acute event cost (£)	1,056.18	1,320.22, 792.13 (Gamma)	
Post-acute coronary syndrome (£)	846.29	1,057.86, 634.72 (Gamma)	
Stroke 1st year, excl. acute event cost (£)	1,333.67	1,667.09, 1,000.25 (Gamma)	
Transient ischaemic attack, 1st year (£)	1,338.77	1,673.47, 1,004.08 (Gamma)	
Post stroke (stroke and TIA, in year following the event) (£)	944.69	1,180.87, 708.52 (Gamma)	
Sleep apnoea cost (£)	1,018.19	1,272.74, 763.64 (Gamma)	
Non-severe hypoglycaemia (£)	4.09	5.11, 3.07 (Gamma)	Section B.3.5.3, Table 44
Severe gastrointestinal event (£)	144.01	180.01, 108.01 (Gamma)	
Bariatric surgery costs, non-fatal (£)	6,359.14	7,948.92, 4,769.35 (Gamma)	Section B.3.5.4.1, Table 45
Bariatric surgery costs, fatal (£)	5,726.90	7,158.63, 4,295.18 (Gamma)	
MI non-fatal event cost (£)	2,419.26	3,024.07, 1,814.44 (Gamma)	Section B.3.5.4.2, Table 46
MI fatal event cost (£)	2,419.26	3,024.07, 1,814.44 (Gamma)	
Unstable angina non-fatal event cost (£)	1,698.35	2,122.94, 1,273.77 (Gamma)	
Unstable angina fatal event cost (£)	1,698.35	2,122.94, 1,273.77 (Gamma)	
Stroke non-fatal event cost (£)	4,855.71	6,069.64, 3,641.78 (Gamma)	
Stroke fatal event cost (£)	4,855.71	6,069.64, 3,641.78 (Gamma)	
TIA event cost (£)	2,154.92	2,693.65, 1,616.19 (Gamma)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Knee replacement, non-fatal event cost (£)	6,492.12	8,115.15, 4,869.09 (Gamma)	
Fatal knee replacement event cost (£)	6,492.12	8,115.15, 4,869.09 (Gamma)	
Key: ACS, acute coronary syndrome; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HbA1c, haemoglobin A1c; MI, myocardial infarction; N/A, not applicable; OSA, obstructive sleep apnoea; OR, odds ratio; RR, relative risk; T2D, type 2 diabetes; TIA, transient ischemic attack.			

B.3.6.2 Assumptions

A summary of the main model assumptions used in the analysis is presented in Table 51. If not stated otherwise, assumptions are the same as in the base case of TA664.

Table 51: Summary of assumption applied in the economic model

Analysis setting	Assumption/Setting	Justification
Assumptions that differ from TA664		
Comorbidities included	ACS T2D Stroke Sleep Apnoea Osteoarthritis	Conservative assumption of limiting to the most economically significant comorbidities to reduce the number of health states and complexity. TA664 also included cancer health states. These were removed to reduce complexity and incorporate feedback provided by the ERG during TA664
Mortality	Disease specific and BMI adjusted mortality (CPRD study)	Mortality was also adjusted by BMI in order to avoid underestimating the mortality and costs. In TA664 no adjustment for BMI was applied
Application of acute and health state disutilities	Acute event and health state disutilities are assumed to be additive.	Assumption, given existing evidence Gough et al. 2009[157] and TA664[27] Some sources are different vs TA664 due to more appropriate sources identified in the literature searches.
Application of acute and health state costs	Acute event costs and health state costs are assumed to be additive.	In line with Ara et al. 2012[106] and TA664[27]. Updated cost sources as well as a new TLR were used, resulting in different cost inputs compared to TA664.
Assumptions consistent with TA664		
Catch up rate for BMI and	Pharmacotherapy returns to value of natural progression	The application of a constant rate of 33.33% per year following treatment cessation is in line with Ara et al.

Analysis setting	Assumption/Setting	Justification
surrogate outcomes	in diet and exercise at a constant rate of 33% per year	2012[106] and TA664[27] which assumed BMI returned to baseline value at 3 years after treatment cessation in a linear fashion.
Natural weight increase after treatment stop	Weight increase following Ara 2012 CPRD, until cohort reaches 68 years old in all treatment arms [106]	Natural weight increase is a common assumption in obesity models supported by a model developed by NICE[150] Support is also found in Heitmann and Garby, 1999[151] and the analysis on the UK CPRD.[106]
Progression of SBP, total cholesterol and HDL cholesterol post-treatment and post waning of treatment effect periods	Post-treatment and waning of treatment effect, systolic blood pressure, total cholesterol, and HDL cholesterol were assumed constant for the remainder of the time horizon.	For reasons of simplicity, the model only accounted for evolution based on treatment effect. The cohort returns to baseline value, corresponding to the average in the cohort, which is then maintained over the entire time horizon of the model when treatment is discontinued. However, as the cohort is assumed to remain treated with antihypertensive medications, and accrues the cost of this, it is plausible to assume the averages would remain stable.
Temporary reversal of non-diabetic hyperglycaemia to a NGT state, maintenance of the glucose status effect over time and risk of T2D in non-diabetic hyperglycaemia vs NGT	All patients in the non-diabetic hyperglycaemia state were assigned a higher risk of developing T2D (vs NGT patients) by modification of the glycaemic status parameter in the corresponding T2D risk equations. In line with changes in glycaemic status observed in the STEP1 and SCALE 1839 trials, a proportion of patients in semaglutide 2.4 mg, liraglutide 3.0 mg and diet and exercise arms temporarily reverted to a normal glycaemic status whereby a lower risk of T2D was applied. All patients reverting to NGT were assumed to return to a non-diabetic hyperglycaemia status at the end of the treatment effect waning period at a constant rate of 33% per year, assuming	According to published risk equations,[124, 153] patients with non-diabetic hyperglycaemia have a higher risk of developing T2D than those with normal glucose tolerance. Changes in glycaemic status observed in STEP1 and SCALE 1839 were applied in the model starting from Cycle 2.[27] Non-diabetic hyperglycaemia reversal was assumed to be a consequence of the initial weight loss and thus applied in the model to occur on the same time, Consequently, the loss of temporary normo-glycaemia was also assumed to occur at the same time with the complete loss of the initial weight loss benefit.

Analysis setting	Assumption/Setting	Justification
	glycaemic status be correlated with weight loss.	
Stopping rule	Semaglutide 2.4 mg (if >5% weight loss not achieved at 28 weeks) Liraglutide 3.0 mg (if >5% weight loss not achieved at 16 weeks)	In line with anticipated semaglutide 2.4 mg marketing approval. In line with regulatory approval for liraglutide 3.0 mg.
Treatment duration	2 years for semaglutide 2.4mg, liraglutide 3.0mg and diet and exercise	This also clinical practice as weight management in SWMS is provided for two years.[27] It is worth noting that after two years patients in the semaglutide arm and the comparator arm transition to diet and exercise alone because diet and exercise is considered to be an integral part of lifelong weight management.
Incidence of first CV event in NGT and non-diabetic hyperglycaemic patients	QRisk3	The QRisk3 equation was used to predict the risk of first cardiovascular event in non-diabetic hyperglycaemia and NGT states and was chosen because it contains a UK cohort and is used in clinical practice in the UK to assess cardiovascular event risk.[181]
Onset of T2D in NGT patients and non-diabetic hyperglycaemic patients	QDiabetes	The QDiabetes risk model was preferred as being the most validated risk score in a UK population, allowing 10 years prediction of risk including prediction of risk in patients with non-diabetic hyperglycaemia.[124]
Incidence of recurrent CV event in NGT	Framingham Recurrent Coronary Heart Disease	This was the best available source for recurrent CV events in NGT.[126]
Incidence of first CV event in T2D	UKPDS82	The UKPDS 82 risk model (outcome model 2) was used, as it is a UK study and able to predict both first and recurrent CV events after the onset of T2D.[127]
Risk of knee replacement	BMI group and per unit increase calculated from Wendelboe et al. 2003[129]	This was the best available source for knee replacement rates.
Treatment discontinuation / retreatment	Patients who discontinued semaglutide 2.4 mg or liraglutide 3.0 mg treatment were assumed to remain on a diet and exercise program for the rest of the analysis time horizon. It was assumed that there would not be any	Diet and exercise was considered an integral part of the treatment of all individuals with obesity, regardless of any pharmacological or surgical intervention co-administered. No published clinical data was available to provide evidence with regards to a

Analysis setting	Assumption/Setting	Justification
	repeated course of treatment with pharmacotherapy	'stop and re-start' type of weight management.
Bariatric surgery	Bariatric surgery was included in the model as an event occurring in all treatment arms. Bariatric surgery does not occur in the first 2 years of treatment	Bariatric surgery is available in England as part of SWMS. Given the placement of semaglutide 2.4 mg, bariatric surgery was included in the model as a downstream event following treatment of interventions provided in SWMS. Thus, patients in both arms can receive bariatric surgery after 2 years. Its occurrence depends however upon a minimum BMI eligibility criterion (which can be reached sooner in the less effective treatment arm) and a maximum age at which patients would be eligible for surgery (which was applied at the same time to both treatment arms).
BMI and age specific HRQoL coefficients	Søltoft et al. 2009[137]	Søltoft et al. 2009 is the same study used to derive the BMI dependent QoL curve.
Key: ACS, acute coronary syndrome; BMI, body mass index; CSPRD, Clinical Practice Research Datalink; CV, cardiovascular; HDL, high-density lipoprotein; HRQoL, health-related quality of life; NGT, normal glucose tolerance; SBP, systolic blood pressure; T2D, type 2 diabetes; TLR, targeted literature review.		

B.3.7. Base-case results

The base case incremental cost-effectiveness ratio (ICER) for semaglutide 2.4mg vs standard management without semaglutide is £[redacted] with the list price of semaglutide 2.4mg applied. The base case ICER with the proposed PAS price of £[redacted] for semaglutide 2.4mg is £14,827. Full results with PAS prices applied are presented in Appendix P. All cost-effectiveness results presented below and for the rest of the dossier, reflect the results with list price applied for semaglutide 2.4 mg.

A comparison of clinical outcomes from the trial and model, and disaggregated cost and quality-adjusted life years (QALYs) results, are presented in Appendix J.

Table 52 provides base case cost-effectiveness results for the population of patients with BMI ≥ 30 kg/m^2 with one or more obesity related comorbidities. Results for patients with BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD are presented in Section B.3.9

Total costs were higher with semaglutide 2.4 mg compared with diet and exercise, respectively £[redacted] versus £[redacted], resulting in an additional cost of £[redacted] with semaglutide 2.4 mg. Semaglutide 2.4 mg was associated with higher total health benefits of 17.957 LYs and 15.361 QALYs, compared with total 17.924 LYs and 15.269 QALYs for diet and exercise, respectively, or an additional 0.034 LYs and additional 0.092 QALYs for semaglutide 2.4 mg. The incremental results for costs and health effects indicate that treatment with semaglutide 2.4 mg was associated with an ICER of £[redacted] per QALY gained compared with diet and exercise. Results are presented in Table 52.

Table 52: Base-case results for semaglutide 2.4 mg versus diet and exercise

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Diet and exercise	[redacted]	17.924	15.269				
Semaglutide 2.4 mg	[redacted]	17.957	15.361	[redacted]	0.034	0.092	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.							

B.3.8. Sensitivity analysis

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to account for multivariate and stochastic uncertainty in the model. One thousand simulations were run. The results are presented as the probability of being cost-effective at willingness-to-pay (WTP) thresholds of £30,000 per QALY.

PSA was conducted to simultaneously take into account the uncertainty associated with parameter values. The implementation of PSA involved assigning specific parametric distributions and repeatedly sampling mean parameter values. No data on the covariance structure between parameters was available, hence parameter correlation could not be implemented in the PSA. Sampling was based on parameter distribution around the mean estimate at a 95% confidence interval.

The mean probabilistic ICER was £[redacted] per QALY gained (95% CI: £[redacted] £[redacted] per QALY gained, Table 53). The ICER scatter plot (Figure 16) showed some degree of uncertainty with regards to the size of the additional QALY gains with semaglutide 2.4 mg. This was due to the few simulations where QALYs of patients on the diet and exercise arm were increased by a relatively large amount due to bariatric surgery. However, all simulations fell in the North-East quadrant showing little uncertainty with regards to the existence of additional benefits as well as no uncertainty with regards to semaglutide 2.4 mg being more costly than diet and exercise, under the current modelling framework, parameter uncertainty and analysis assumptions.

The cost-effectiveness acceptability curve (CEAC) (Figure 17) shows that semaglutide 2.4mg is likely to be considered cost-effective in [redacted]% of cases under a threshold of £30,000 per QALY.

Table 53: Base-case results (probabilistic) for semaglutide 2.4 mg versus diet and exercise

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Diet and exercise	[redacted]	17.901	15.239				
Semaglutide 2.4 mg	[redacted]	17.932	15.330	[redacted]	0.031	0.091	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Figure 16: Cost-effectiveness plane for semaglutide 2.4 mg versus diet and exercise

Key: Incr, incremental; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 17: Cost effectiveness acceptability curve plane for semaglutide 2.4 mg versus diet and exercise

Key: BMI, body mass index; QALY, quality-adjusted life year; WTP, willingness to pay.

B.3.8.2 Deterministic sensitivity analysis

To assess the uncertainty around the base case estimates, deterministic sensitivity analyses have been performed. Confidence intervals were constructed using reported standard errors of the mean (SEM) where these were available, or by calculating a margin of error of 25% around the mean estimate where standard errors were not available or not reported.

Table 54 illustrates the results of the deterministic sensitivity analyses, with the ten most significant drivers listed in descending order. Figure 18 provides a graphical representation of these results. The top three drivers of results were found to be the starting BMI of the cohort, the outcomes discount rate, and the weight reduction at the start of Year 2 with diet and exercise.

Table 54: Deterministic sensitivity analysis for semaglutide 2.4 mg versus diet and exercise

Parameter	Base	Variation (SE or ±25%)		ICER (£/QALY)	
		High	Low	High	Low
Starting BMI	38.7	48.4	30.0	[redacted]	[redacted]
Outcomes discount rate	3.5%	6.0%	0.0%	[redacted]	[redacted]
2-year D&E Weight reduction	-2.4%	-1.7%	-3.2%	[redacted]	[redacted]
Natural Weight Increase	0.46	0.58	0.35	[redacted]	[redacted]
Cost discount rate	3.5%	6.0%	0.0%	[redacted]	[redacted]
% of non-diabetic hyperglycaemia reversal to NGT for D&E	45.8%	51.7%	39.8%	[redacted]	[redacted]
Age threshold for weight increase	68	70	66	[redacted]	[redacted]
Knee replacement incidence under age	0.05%	0.08%	0.03%	[redacted]	[redacted]
T2D disutility	-0.037	-0.028	-0.047	[redacted]	[redacted]
T2D health state cost	941	1,176	706	[redacted]	[redacted]

Key: BMI, body mass index; D&E, diet and exercise; ICER, incremental cost effectiveness ratio; NGT, normal glucose tolerance; QALY, quality-adjusted life year; SE, standard error; T2D, type 2 diabetes.

Figure 18: Deterministic sensitivity analysis for semaglutide 2.4 mg versus diet and exercise

Key: BMI, body mass index; D&E, diet and exercise; ICER, incremental cost effectiveness ratio; NGT, normal glucose tolerance; QALY, quality adjusted life year; T2DM, type 2 diabetes mellitus

B.3.8.3 Scenario analysis

A list summarising the scenarios explored in the analysis is shown in Table 55. The summary results for all scenario analyses are presented in Table 56. Detailed scenario analysis results are provided in Appendix Q. A summary of the PAS ICERs for scenario analyses can be found in Appendix P 2.3. The majority of the PAS ICERs for scenario analyses are below £20,000/QALY gained.

Table 55: Key scenario analyses

Model setting	Base case	Scenario analysis	Justification
Stopping rule	Stopping rule included for semaglutide 2.4 mg using trial product estimand (anticipated license)	No stopping rule for semaglutide 2.4 mg using treatment policy estimand (Appendix O)	To show the impact of not imposing a stopping rule for semaglutide 2.4 mg. The treatment policy estimand reflects ITT efficacy and thus is appropriate with no stopping rule
Efficacy source	All patients in STEP 1 for semaglutide 2.4mg and diet and exercise	Post hoc analysis for each subgroup (Appendix O)	To test the assumption of the population with all patients in STEP 1 being representative of the subgroups of interest
Catch up rate	3 years with linear rate	Linear rate with 2 years and 1 year	To test uncertainty regarding BMI and glycaemic reversal after treatment discontinuation
Time horizon	40 years	20 and 30 years	Shorter time horizons were modelled to test the impact on costs and outcomes over time
Bariatric surgery	Bariatric surgery is included with 1.15% incidence per year at a minimum BMI threshold of 35 kg/m^2	No bariatric surgery, 0.57% incidence per year and BMI threshold of 47 kg/m^2	To test the impact of excluding bariatric surgery as a rescue therapy on cost-effectiveness results; The NICE costing report on implementing CG189, produced in 2014, states that the current incidence of bariatric surgery in patients with recent onset of type 2 diabetes with a BMI of 35 kg/m^2 and over is 0.57%, with future incidence expected to double to 1.15% in these patients[77]; To test the impact of using the actual average BMI level at which patients receive bariatric surgery in the UK, as the BMI level where bariatric surgery is applied in the model
Risk equations	Incidence of first CV event in normal glucose tolerance: QRisk3 Incidence of T2D: QDiabetes	Incidence of first CV event in normal glucose tolerance: Framingham Heart study Incidence of T2D: Framingham Offspring	To test assumptions regarding choice of risk equation on cost-effectiveness results

Model setting	Base case	Scenario analysis	Justification
	Incidence of first CV event in T2D: UKPDS82 Incidence of recurrent CV event in T2D: UKPDS82	Incidence of first CV event in T2D: QRisk3 Incidence of recurrent CV event in T2D: Framingham Recurring Coronary Heart Disease	
T2D development after CVD	Patients with non-diabetic hyperglycaemia develop T2D within the same cycle after a CVD event	Patients with non-diabetic hyperglycaemia do not develop T2D within a cycle after a CVD event	To test the assumption that there is a high correlation between developing T2D and having CVD
Baseline utility	Polynomial model using Søltoft et al. 2009	Alternative baseline utilities – derived as a function of BMI based on SCALE data. A regression analysis conducted on a mapping of SF-36 to EQ-5D utilities was carried out on SCALE. The methods and full results of this analysis are reported in a stand-alone technical report [182]	To test model used to derive baseline utility on cost-effectiveness results
Key: BMI, body mass index; CV/CVD, cardiovascular /disease; ITT, intention to treat T2D, type 2 diabetes.			

Table 56: Summary scenario results for semaglutide 2.4 mg versus diet and exercise

Scenario	Inc. Costs (£)	Inc. LYG	Inc. QALY	ICER (£/QALY)
Base case	[redacted]	0.034	0.092	[redacted]
No stopping rule (using treatment policy estimand)	[redacted]	0.032	0.084	[redacted]
Post hoc analysis efficacy for subgroup	[redacted]	0.037	0.094	[redacted]
1-year catch up rate	[redacted]	0.029	0.069	[redacted]
2-year catch up rate	[redacted]	0.028	0.075	[redacted]
20-year time horizon	[redacted]	0.026	0.086	[redacted]
30-year time horizon	[redacted]	0.032	0.091	[redacted]
No bariatric surgery	[redacted]	0.045	0.108	[redacted]
Bariatric surgery eligibility threshold at BMI 47 kg/m^2	[redacted]	0.045	0.108	[redacted]
Bariatric surgery incidence at 0.57% per year	[redacted]	0.041	0.102	[redacted]
Framingham Offspring risk equation for incidence of T2D	[redacted]	0.031	0.085	[redacted]
Framingham Heart Study risk equation for incidence of first CVD event in NGT	[redacted]	0.040	0.099	[redacted]
Framingham Recurring Coronary Heart Disease risk equation for incidence of recurrent CVD event in T2D	[redacted]	0.031	0.090	[redacted]
QRisk3 risk equation for incidence of first CVD event in T2D	[redacted]	0.041	0.099	[redacted]
Patients with non-diabetic hyperglycaemia do not develop T2D immediately after a CVD event	[redacted]	0.031	0.090	[redacted]
Alternative baseline utilities, derived as a function of BMI based on SCALE data.	[redacted]	0.034	0.083	[redacted]

Key: BMI, body mass index; CVD, cardiovascular disease; FAS, full analysis set; ICER, incremental cost-effectiveness ratio; LYG, life year gained; NGT, normal glucose tolerance; QALY, quality-adjusted life year; T2D, type 2 diabetes.

B.3.8.4 Summary of sensitivity analyses results

Base case deterministic results suggest that semaglutide 2.4 mg is associated with an ICER of £[redacted] when compared with diet and exercise for the treatment of UK patients with a BMI ≥ 30 kg/m^2 with one or more obesity related comorbidities. The PSA results indicate that semaglutide 2.4 mg is approximately [redacted]% likely to be cost-effective at a WTP threshold of £30,000 per QALY, with a mean ICER of £[redacted].

Deterministic sensitivity analysis results demonstrate that the main drivers of semaglutide 2.4 mg cost-effectiveness versus diet and exercise were BMI and weight-related variables as BMI affects risk of comorbidities, mortality, utility and bariatric surgery options. As patients on semaglutide 2.4 mg discontinue and catch up to the diet and exercise arm BMI, any uncertainty in diet and exercise BMI at the end of treatment can cause more of an effect on model results than the uncertainty from semaglutide 2.4 mg weight reduction efficacy. The benefits of treatment are accrued later in life whilst treatment costs are accrued in the first years hence the discount rates also have a large impact on results. It is further noted that when the starting BMI of the cohort is high; there is greater QALY gain from treatment with semaglutide 2.4 mg, than diet and exercise treatment alone. The extreme values tested for starting BMI in deterministic scenario analyses are considered to be implausible in clinical practice, and therefore mainly included to show sensitivity of the model to this input.

The scenario analyses show that a stopping rule would be beneficial for semaglutide 2.4 mg, as treating patients who do not respond increases costs with little added benefit. A stopping rule is more reflective of clinical practice where patients would discontinue treatment if they display little response. The ‘all patients’ population efficacy was assumed representative of the subgroups of interest. This was tested with a scenario using the subgroup post-hoc analysis which produced similar results to the a priori defined population.

The uncertainty regarding waning of treatment effect was tested through varying the catch-up rate. The model shows that the added benefit of treatment is sensitive to assumptions regarding patient weight regain with rapid increase in BMI producing an ICER of £[redacted] per QALY. However, this is an extreme scenario as patients have to gain over 15% of their total BMI within a year of stopping treatment.[106]

The assumptions regarding bariatric surgery show that the base case is conservative for semaglutide 2.4 mg as bariatric surgery offers greater benefit to patients who have a higher BMI i.e. those in the diet and exercise arm. This benefit to the diet and exercise arm is further shown by the skew bariatric surgery causes to the distribution of ICERs in the PSA. The eligibility threshold used in the base case is a conservative estimate as although patients are eligible for bariatric surgery at a BMI of 35 kg/m^2,

in UK practice the median BMI of patients undergoing bariatric surgery is approximately 46 kg/m^2.[183]

The sensitivity analyses regarding risk equations, show a range of ICERs from £[redacted] where the Framingham Heart Study is used to model risk of the first CVD event in T2D to £[redacted] per QALY where Framingham-Offspring risk equation is used to model incidence of T2D. While QRisk3 and Framingham are valid risk equations, UKPDS82 is most appropriate for modelling first CVD events in T2D population. UKPDS82 risk equations are derived from UK patient-level data in patients newly diagnosed type 2 diabetes mellitus. Whereas the Framingham risk equation uses data from a US population which is not as comparable to the UK population. Although QRisk3 estimates CV risk on a sample of patients followed in general practices in England, most patients did not have type 2 diabetes at baseline (1.5% and 1.2% of males and females had type 2 diabetes) and the risk equation was intended as a cardiovascular risk prediction model in the general population.[125]

Overall, the model was robust to all other parameters varied in one-way sensitivity and scenario analyses, showing little uncertainty with regards to semaglutide 2.4 mg cost-effectiveness versus diet and exercise.

B.3.9. Subgroup analysis – semaglutide 2.4mg vs liraglutide 3.0mg in BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD

This subgroup analysis is included to allow for the comparison of semaglutide 2.4 mg to liraglutide 3.0 mg, which was recommended by NICE in TA664[27], for patients with BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD. This subgroup analysis is based on the list price of semaglutide 2.4 mg of £[redacted] per pack and liraglutide 3.0 mg of £196.20 per pack.

In the base case, semaglutide 2.4 mg [redacted] compared to liraglutide 3.0 mg. Semaglutide 2.4 mg was associated with higher total health benefits of an additional 0.018 LYs and additional 0.043 QALYs compared with liraglutide 3.0 mg. [redacted]

[redacted]. Results are presented in Table 57. Similar results are observed when PAS prices are applied for both treatments (Appendix P).

Table 57: Base case results (deterministic) for semaglutide 2.4 mg versus liraglutide 3.0 mg

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Liraglutide 3.0 mg	[redacted]	17.331	14.401				
Semaglutide 2.4 mg	[redacted]	17.349	14.444	[redacted]	0.018	0.043	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.							

B.3.9.1 Probabilistic sensitivity analysis

The ICER scatter plot (Figure 19) and results table (Table 58) show that semaglutide 2.4 mg [redacted].

Table 58: Base-case results (probabilistic) for semaglutide 2.4 mg versus liraglutide 3.0 mg

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Liraglutide 3.0 mg	[redacted]	17.400	14.453				
Semaglutide 2.4 mg	[redacted]	17.418	14.497	[redacted]	0.019	0.044	[redacted]
Key: ICER, incremental cost-effectiveness ratio; incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years.							

Figure 19: Cost-effectiveness plane for semaglutide 2.4 mg versus liraglutide 3.0 mg

Key: Incr, incremental; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

B.3.9.2 Deterministic sensitivity analysis

Table 59 illustrates the results of the deterministic sensitivity analyses, with the ten most significant drivers listed in descending order.

Figure 20 provides a graphical representation of these results. The top three drivers of results were found to be the starting BMI, the outcomes discount rate and the 2-year weight reduction for liraglutide 3.0 mg.

Table 59: 915 analysis for semaglutide 2.4 mg versus liraglutide 3.0 mg

Parameter	Base	Variation (SE or ±25%)		INMB* (£)	
		High	Low	High	Low
Starting BMI	42.1	52.7	35.0	[redacted]	[redacted]
Outcomes discount rate	3.5%	6.0%	0.0%	[redacted]	[redacted]
2-year liraglutide 3.0 mg Weight reduction	-10.2%	-9.4%	-11.1%	[redacted]	[redacted]
% of non-diabetic hyperglycaemia reversal to NGT for liraglutide 3.0mg	82.5%	85.7%	79.4%	[redacted]	[redacted]
1-year liraglutide 3.0 mg Weight reduction	-10.4%	-9.8%	-11.1%	[redacted]	[redacted]
0-7 month liraglutide 3.0 mg Weight reduction	-10.0%	-9.6%	-10.4%	[redacted]	[redacted]
Cost discount rate	3.5%	6.0%	0.0%	[redacted]	[redacted]
% of non-diabetic hyperglycaemia reversal to NGT for semaglutide 2.4mg	90.4%	92.8%	87.9%	[redacted]	[redacted]
2-year semaglutide 2.4 mg Weight reduction	-18.5%	-17.9%	-19.0%	[redacted]	[redacted]
Knee replacement incidence under age 64	0.05%	0.08%	0.03%	[redacted]	[redacted]

Key: BMI, body mass index; CVD, cardiovascular disease; D&E, diet and exercise; INMB, incremental net monetary benefit; NGT, normal glucose tolerance; SE, standard error; T2D, type 2 diabetes.
Notes: *Willingness to pay is £20,000 per QALY.

Figure 20: Deterministic sensitivity analysis for semaglutide 2.4 mg versus liraglutide 3.0 mg

Key: BMI, body mass index; D&E, diet and exercise; ICER, incremental cost effectiveness ratio; NGT, normal glucose tolerance; QALY, quality-adjusted life year; T2DM, type 2 diabetes mellitus.

B.3.9.3 Scenario analysis

The same set of scenario analyses was explored as for the base case analysis (Table 55). The summary results for all scenario analyses are presented in Table 60. Detailed scenario analysis results are provided in Appendix Q.

Table 60: Summary scenario results for semaglutide 2.4 mg versus liraglutide 3.0 mg

Scenario	Inc. Costs (£)	Inc. LYG	Inc. QALY	ICER (£/QALY)
Base case	[redacted]	0.018	0.043	[redacted]
No stopping rule (using treatment policy estimand)	[redacted]	0.019	0.037	[redacted]
Post hoc analysis efficacy for subgroup	[redacted]	0.015	0.034	[redacted]
1-year catch up rate	[redacted]	0.010	0.025	[redacted]
2-year catch up rate	[redacted]	0.017	0.038	[redacted]
20-year time horizon	[redacted]	0.013	0.039	[redacted]
30-year time horizon	[redacted]	0.017	0.042	[redacted]
No bariatric surgery	[redacted]	0.018	0.043	[redacted]
Bariatric surgery eligibility threshold at BMI 47 kg/m^2	[redacted]	0.018	0.043	[redacted]
Bariatric surgery incidence at 0.57% per year	[redacted]	0.018	0.043	[redacted]
Framingham Offspring risk equation for incidence of T2D	[redacted]	0.018	0.042	[redacted]
Framingham Heart Study risk equation for incidence of first CVD event in NGT	[redacted]	0.019	0.044	[redacted]
Framingham Recurring Coronary Heart Disease risk equation for incidence of recurrent CVD event in T2D	[redacted]	0.017	0.042	[redacted]
QRisk3 risk equation for incidence of first CVD event in T2D	[redacted]	0.021	0.045	[redacted]
Patients with non-diabetic hyperglycaemia do not develop T2D immediately after a CVD event	[redacted]	0.017	0.043	[redacted]
Alternative baseline utilities, derived as a function of BMI based on SCALE data.	[redacted]	0.018	0.039	[redacted]

Key: BMI, body mass index; CVD, cardiovascular disease; FAS, full analysis set ; ICER, incremental cost-effectiveness ratio; LYG, life year gained; NGT, normal glucose tolerance; QALY, quality-adjusted life year; T2D, type 2 diabetes.

B.3.9.4 Summary of sensitivity analyses results

For the comparison versus liraglutide 3.0 mg in BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD, semaglutide 2.4 mg showed [redacted] and increased QALYs. Therefore semaglutide 2.4 mg is a dominant option compared to liraglutide 3.0 mg. Sensitivity analysis showed that 100% of simulations in the PSA were [redacted] for semaglutide 2.4 mg with increased benefits. [redacted]

B.3.10. Validation

The economic model used in this submission was based on from the model submitted to NICE during TA664 for liraglutide 3.0mg.[27] which has been validated against real world data. These validations have shown the model predictions using risk equations have good concordance studies included in the validation.[184] The latest published external validation of the model showed it predicted CVD and T2D with a good degree of accuracy.[185] Further updates to the model underwent a quality control process. This involved checks on the selection and results of different modelling options, calculation spot checks, cross checks against source data and extreme value scenarios to check if the model behaved logically.

The quality check explored the following general aspects of the model:

- Top-down tests. This involved systematic variation of the model input parameters to establish whether changes in inputs, result in predictable changes in the model outputs. These tests were designed to identify failures in model logic or material computation errors
- Model internal functionality (e.g. testing of all key model parameters, extreme value testing). The following aspects of the spreadsheet were identified as key areas for detailed checking: Markov traces; translation of drug prices, complications and resource use into state costs
- Internal consistency. Accuracy of input data. This was checked by comparing the model inputs in Excel against the data sources referenced

B.3.11. Interpretation and conclusions of economic evidence

Obesity is a complex condition which affects an individual's immediate quality of life and increases the risk of certain conditions which themselves impact life expectancy and quality of life. By necessity, the economic model in this submission is a simplification of the impact obesity has on quality-adjusted life year calculations. Moreover, an attempt has been made to quantify the impact of obesity related comorbidities that were the most economically significant to the decision problem. Cefalu et al. 2015 presents evidence from the literature regarding the therapeutic benefit of weight loss for complications of obesity as shown in Table 61.[54] The efficacy of semaglutide 2.4 mg shows up to 15% reduction in weight from baseline in STEP1 demonstrating that it would show therapeutic benefit in the obesity complications mentioned in Cefalu et al. 2015. Patients with NAFLD, stress incontinence, gastroesophageal reflex disease and polycystic ovary syndrome would benefit from treatment, however these were not included in the model. Furthermore, other obesity related complications defined in STEP 1 such as kidney disease, gout and asthma have not been captured by the model. To this end, the model is a conservative estimate to the relevant costs and benefits attributable to weight loss management in terms of its impact on the reversal and/or prevention of obesity-related complications.

Table 61: Summary of evidence regarding therapeutic weight loss for complications of obesity from Cefalu et al. 2015

Obesity complication	Weight loss required for therapeutic benefit (%)	Notes
Diabetes (prevention)	3-10	Maximum benefit at 10%
Hypertension	5 to >15	Blood pressure still decreasing at >15%
Dyslipidaemia	3 to >15	Triglycerides still decreasing at >15%
Hyperglycaemia (elevated A1C)	3 to >15	A1C still decreasing at >15%
NAFLD	10	Improves steatosis, inflammation, and mild fibrosis
Sleep apnoea	10	Little benefit at 5%
Osteoarthritis	5–10	Improves symptoms and joint stress mechanics
Stress incontinence	5–10	
Gastroesophageal reflex disease	5–10 in women; 10 in men	

Polycystic ovary syndrome	5–15 (>10 optimal)	Lowers androgens, improves ovulation, and increases insulin sensitivity
Key: NAFLD, Non-alcoholic fatty liver disease. **Source:** Cefalu 2015[54]		

There are a few limitations to the current modelling approach that should be considered. To keep the model complexity to a minimum, a number of simplifying assumptions have been made. A further limitation is the absence of longer-term data to model what happens when patients stop treatment (i.e. waning of treatment effect). The model was validated as described in Section B.3.10.

There is uncertainty regarding the comparison with liraglutide 3.0 mg as there was no robust way to conduct an ITC that compares outcomes for responders in the semaglutide study with outcomes among differently defined responders in the liraglutide study.

Mortality in the model was adjusted to consider not only the specific diseases and complications but also the BMI of the cohort. The disease specific mortality rates may already factor in some of the increased mortality due to obesity and therefore, mortality in the model may be overestimated.

Notwithstanding the limitations mentioned above, based on the currently available evidence, the results shown here demonstrate that semaglutide 2.4 mg is a clinically and cost-effective alternative to diet and exercise in patients with BMI ≥ 30 kg/m^2 with one or more obesity related comorbidities and to liraglutide 3.0 mg in patients with BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Semaglutide for managing overweight and obesity (ID3850)

Clarification questions

July 2021

File name	Version	Contains confidential information	Date
[ID3850] Semaglutide ERG clarification questions	**V0.1**	**No**	**25.08.21**

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Submission population

A1. Priority question: CS, Section B.2.11.1, Table 14, states that the STEP 2 trial population – people with type 2 diabetes – is not relevant to the submission. Please clarify why this population is not considered relevant.

The focus of this appraisal is the treatment of obesity and the substantial downstream benefits associated with weight loss, and not the active treatment of T2D, for which semaglutide is already available in a different dose. This submission focuses on patients with obesity (body mass index [BMI] of ≥ 30 kg/m^2) who have one or more weight related comorbidities, a broad and diverse patient population with a high level of unmet need. As observed in the pivotal STEP 1 study, semaglutide 2.4 mg will provide this patient group – the vast majority of which would otherwise have no pharmacological intervention available – with the opportunity for significant and clinically meaningful weight loss. The benefits of weight loss in this population include improvements in complications and comorbidities that are associated with obesity, which themselves have substantial consequences on healthcare resources and costs, patients' quality of life, and/or life expectancy.

Thus, this appraisal targets a population where there is significant need, and for which the greatest clinical benefit has been observed for the 2.4 mg formulation of semaglutide. This could potentially include people living with T2D, but also reflects a wealth of other comorbidities such as hip or knee osteoarthritis, liver disease and obstructive sleep apnoea. Whilst we would not expect people with T2D to be excluded from treatment, advice from clinical experts suggested that these patients would typically be treated as a person living with T2D and follow a diabetes treatment pathway where semaglutide is available at a lower dose. This treatment would focus on multiple factors, such as glycaemic control, weight, cardiovascular (CV) risk and hypoglycaemia.

Systematic literature review

A2. No reference citation numbers are given for the excluded references listed in CS, Appendix D, Section D1.2.1, Table 5, and copies of these references have not been provided in the reference pack (for example excluded studies by Astrup et al. are not in the bibliography, nor the reference pack, but are referred to in CS, Appendix H, Section H.7.1). Please provide a bibliography for the excluded references and, if possible, the PDFs.

We provide, as separate documents, the bibliography for all 153 excluded references (see Attachment A: 'Bibliography of the excluded references') with the EndNote™ library (see Attachment B: 'Sema_Excludes') and the PDF versions of the 63 studies the ERG specifically requested at the ERG clarifications call (see Attachment C: 'NICE Excluded studies') . As requested, we also provide an Excel® file with additional details on the reason for excluding 112 of the 153 studies (see Attachment D: 'Excluded Studies'). The other 39 excluded studies did not match the population of this submission mainly on the basis of intervention or population.

A3. CS, Appendix D, Section D.1.2, Table 4, presents the systematic literature review inclusion criteria. It states the primary population of interest to the submission was adults with a BMI ≥ 30 kg/m^2 and one or more comorbidities, as aligned with those in the STEP 1 trial (specifically, dyslipidaemia, hypertension, coronary artery disease, obstructive sleep apnoea, non-diabetic hyperglycaemia, reproductive system, liver disease, kidney disease, osteoarthritis, gout and asthma, cerebrovascular disease). Does this mean that

studies including people with a BMI ≥ 30 kg/m^2 and who did not have one of the co-morbidities listed here were excluded?

Yes, this is correct.

A4. CS, Appendix D, Section D.3, Table 9, provides a quality assessment for the STEP 1 and SCALE trials. A quality assessment judgement for the criterion "Is there any evidence to suggest that the authors measured more outcomes than they reported?" is missing for the STEP 1 study. Please provide the company's judgement.

There is no evidence to suggest that the authors measured more outcomes than they reported for the STEP 1 study. The risk of bias in the study was considered to be low.

STEP 1 trial

A5. Priority question: Please provide the reason(s) for missing data at each time point in each STEP 1 trial arm for each outcome, as this is not clear from the way the data are presented in the CS and Appendices. The number of missing data differs between outcomes and is not explained directly by reference to the participant flow chart in Appendix D2.

Information on reasons for missing data in STEP 1 for each outcome at each landmark visit is presented in Attachment E: 'Exploratory-clarification_questions.doc output number 23'.

A6. Please clarify why the baseline characteristics data for the race and BMI categories above 30 kg/m^2 are missing from CS, Section B.2.3.2, Table 5, for the STEP 1 target population subgroup (BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity)? Please provide these data, if possible, and complete Table 5.

The missing information on number of patients according to race/ethnicity and BMI categories is presented in Attachment E: 'Exploratory-clarification_questions.doc output number 24'.

A7. Please explain what the placebo was (that is, the ingredients used in the placebo injection pen) in the STEP 1 trial, as this cannot be identified in the CS, Appendices, trial publications or clinical study report.

The placebo product contains the same excipients as the semaglutide B solution for injection but with the absence of the active ingredient. The placebo product is a colourless or almost colourless liquid, free from turbidity and essentially free from particulate matter. The solution is isotonic with a pH of 7.4. It consists of the following ingredients:

- Disodium hydrogen phosphate, dihydrate (buffering agent)
- Propylene glycol (isotonic agent)
- Phenol (preservative agent)
- Hydrogen chloride (pH adjustment)
- Sodium hydroxide (pH adjustment)
- Water for injection (solvent)

Indirect treatment comparison

A8. Priority question: Please provide the statistical code and individual patient data used for the indirect treatment comparison (ITC) analyses. The ERG would like to review the code and validate the results.

SAS® statistical code for the ITC analyses together with a description of the dataset are provided in separate files (see Attachment F 'NovoNordisk_Sema_IPD_ITC-documentation-of-data-structure' and Attachments G-L). As discussed with the ERG at the clarifications call, the company cannot provide the individual patient data used for the ITC.

A9. The number of participants included from each trial in the comparison of baseline characteristics of the BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high CV risk sub-populations of the SCALE 1839 and STEP 1 trials in CS, Section B.2.9, Table 11 is unclear. The patient numbers in the table header (SCALE n=3731, STEP 1 n=1961) refer to the full analysis set (FAS) population for STEP 1 and total randomised participants for SCALE. However, rows 5 to 8 refer to 421 patients for STEP 1 and 800 patients for

SCALE. Please clarify the number of participants included in the comparison and correct the numbers in the column headings if they are incorrect.

The ITC results pertain to the TA664 subgroup of patients with BMI ≥ 35 kg/m^2, with non-diabetic hyperglycaemia, and high risk of cardiovascular disease (CVD) at baseline. We acknowledge that CS, Section B.2.9, Table 11 could be clearer. The first line in Table 11 in Section B.2.9 of the CS refers to the size of the FAS in the SCALE 1839 and STEP 1 trials prior to subsetting to the subpopulation of patients with BMI ≥ 35 kg/m^2, with non-diabetic hyperglycaemia and high CV risk. The subsequent rows in the table all pertain to this subgroup (consisting of 800 patients both in the FAS and the subgroup for SCALE 1839; and 421 both in the FAS and the subgroup for STEP 1).

A10. Tables 3 and 4 in the indirect treatment comparison (ITC) report are labelled as 'full analysis set'; please confirm the data refer to the TA664 subgroup.

Yes, we confirm that the ITC pertains to the TA664 subgroup of patients with BMI ≥ 35 kg/m^2, with non-diabetic hyperglycaemia, and high risk of CVD at baseline, as also described in Section 2.2 of the ITC report.

Specifically, table legends in the ITC report generally follow the format *'output description - subgroup - analysis set'*, specifying both the subgroup, but also the analysis set from which the subgroup is elicited.

A11. Please provide baseline characteristic ethnicity and pre-diabetes data for the BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high CV risk subgroups in each of the SCALE 1839 and STEP 1 trials, if available.

The ethnicity baseline characteristics regarding racial attributes is presented in Attachment E: *'*Exploratory-clarification_questions.doc output number 1*'*. Please note that for the analyses presented in this submission, pre-diabetes was defined according to the NICE-preferred definition (as used in TA664) – that is, non-diabetic hyperglycaemia, defined as a glycated haemoglobin (HbA1c) level of 42–47 mmol/mol (6.0–6.4%) or a fasting plasma glucose (FPG) level of 5.5–6.9 mmol/L (see also Section B.3.5.5 of the company evidence submission). Therefore, all patients in the subgroup defined in Question A11 are characterized as pre-diabetic.

A12. As noted above, the ITC report (Section 2.5.2) states the ITC analysis was based on the FAS for each trial. Did the company run a scenario analysis using the TA664 subgroup data? If not, please repeat the analysis using the relevant subgroup data for the unadjusted analysis.

See the response to A10: the base case ITC analysis was based on the TA664 subgroup of patients with BMI ≥ 35 kg/m^2, with non-diabetic hyperglycaemia, and high risk of CVD at baseline.

A13. The ERG has a number of questions related to the handling of missing data for the ITC treatment policy and trial product estimands:

(a) Sections 2.5.3.1 and 2.5.3.2 of the ITC report show differences in the approaches to handling missing data for the STEP 1 and SCALE 1839 trials for both the treatment policy and trial product estimands. Given the company has access to individual patient data (IPD) for both studies, would it have been possible to use identical methods? If it is possible, please conduct these analyses. If it is not possible, please clarify why.

(b) Please summarise the amount of data which was imputed for each arm for both trials.

(c) Please present the baseline characteristics for those subjects with missing data compared to those without.

(d) Please explain why it was not possible to use the McEvoy approach for patients off-treatment at a specific visit in SCALE 1839 (ITC report, Section 2.5.3.1).

a) For the base case ITC based on the treatment policy estimand, the approaches to handling missing data are the same. Specifically, the McEvoy approach was used to impute data for patients missing on-treatment at a given visit (i.e. imputing based on observed data from patients on-treatment at that visit), whereas a linear extrapolation approach was used to impute data for patients missing off-treatment at a given visit.

The hypothetical estimand was included as a scenario analysis in the ITC. Here, the approaches to missing data handling reflect those that were used in the pre-planned

analysis of the hypothetical estimand for STEP 1, and in the pre-planned primary statistical analysis in SCALE 1839 (as also reflected in the European label for liraglutide and in the TA664 CS for liraglutide) since this was considered the more transparent solution. However, it is possible to align this scenario analysis more between the two trials – for example, by imputing missing data from a mixed model for repeated measures, as done for STEP 1. The results are provided in Attachment E: 'Exploratory-clarification_questions.doc output number 2-8' and are consistent with the results provided in the ITC report.

b) The amount of missing data which was imputed for each arm is presented for both estimands in Attachment E: 'Exploratory-clarification_questions.doc output number 9-22'.

c) Baseline characteristics are presented for subjects with missing data compared with those without missing data for both estimands for all endpoints in Attachment E: 'Exploratory-clarification_questions.doc output number 26-53'.

d) In SCALE 1839, patients who discontinued trial product before the landmark visit at 56 weeks were asked to return only at 56 weeks for an assessment of the primary endpoint (body weight). This implies that for those patients, data between discontinuation and Week 56 are missing, and that retrieved dropout data at Week 56 are available for body weight only. Accordingly, a McEvoy approach (imputing missing data for patients off-treatment at each visit based on retrieved dropouts at that visit) is not applicable across the visits and endpoints relevant for the SCALE 1839 ITC.

A14. The ANCOVA used for the ITC relies on several assumptions about the data, namely linearity between covariate and outcome variables across groups, homogeneity of regression slopes, normality of residuals, and that there are no significant outliers. Please provide evidence that these assumptions were met.

We have provided regression diagnostics for the ANCOVA models for the primary analyses (see Attachments M-V: 'ANCOVA_assumption_check.pdf'). The choice of ANCOVA is aligned with the focus on estimating effect sizes as mean differences. In moderately large data sets such as the present ITC data set (N = 800 SCALE 1839;

N = 421 STEP 1), ANCOVA is generally considered a robust way to perform inferences about mean differences.[1]

A15. Please present the coefficients from the ANCOVA and multiple logistic regression analyses for the ITC population adjusted models.

The coefficients from the ANCOVA and multiple logistic regression analyses are presented in Attachment E: *'*Exploratory-clarification_questions.doc output number 54-60' for the ITC population-adjusted models. Analyses were conducted for each of the 500 imputed complete data sets and pooled by Rubin's rule to draw inference on the coefficients.

A16. Priority question: Please provide a plot of participants' use of rescue medications, and discontinuations over time for both STEP 1 and SCALE 1839 (akin to Figure 3 in Aroda et al 2019 [CS Document B, reference 89]). The ERG wishes to understand how incidence of these intercurrent events differed by treatment arm and between trials.

Figure 3 in Aroda et al. (2019) uses a band plot to show frequency and timing of intercurrent events affecting the estimand of interest. For STEP 1, band plots do not provide a complete picture of the frequency and timing of intercurrent events since patients were allowed to temporarily discontinue (and later resume) treatment. We have instead provided plots of time to first treatment discontinuation, permanent treatment discontinuation, and time to trial withdrawal, alongside a listing of patients initiating rescue medication provided in Attachment E: *'*Exploratory-clarification_questions.doc table 25 and CS, STEP 1 CTR, *Section 14.1.10-14.1.12'.*

In SCALE 1839, there was no notion of anti-obesity rescue intervention (i.e., starting weight management drugs or undergoing bariatric surgery), and there was no distinction between discontinuation of treatment and withdrawal from trial. The available information about intercurrent events in this trial can therefore be summarized by a plot of time to discontinuation and is provided in Attachment W: *'CTR_1839-ext01-report-body Section 14.1.7'.*

A17. The scenario analyses results for weight, systolic blood pressure (SBP), high density lipoprotein (HDL), and total cholesterol in CS, Appendix D,

Section D.1.3.5, Table 8, do not agree with the ITC report Tables 5, 6, 7, and 8. Please clarify which values are correct.

The results of the scenario analyses provided in CS, Appendix D Table 8 were provided in error. The results presented in Version 3.0 of the ITC report (see Attachment X: 'DOF_NovoNordisk_Sema_IPD_ITC_report_v3) are correct, and the reference has been provided again for clarity.

A18. The ITC report (Section 2.5.2) states that the analyses used the FAS dataset (section 2.5.2). However, the semaglutide outcome results in Table 5 of the ITC report do not correspond to those of the Wilding 2021 paper (Table 2) for the treatment policy estimand. For example, the difference in body weight % change between semaglutide and placebo from baseline to week 68 is -12.44 in Wilding, contrasted with -11.58 in Table 5 of the ITC report. Similarly, there are also differences between the results reported in Table 5 of the ITC report for the liraglutide versus placebo and the SCALE trial paper (Pi-Sunyer et al., 2015). For example, the difference in body weight % change between liraglutide and placebo from baseline to week 56 is -5.4 in the paper (Table 2), contrasted with -5.07 in Table 5 of the ITC report. Please clarify and explain these differences.

Please see the response to A10: The ITC results pertain to the TA664 subgroup of patients with BMI ≥ 35 kg/m^2, with non-diabetic hyperglycaemia, and high risk of CVD at baseline. This is why the results do not correspond to the results for the full population reported in the primary publications for the STEP 1 and SCALE 1839.

A19. There is an inconsistency between the trial product estimand results used in the economic model (CS, Section B.3.3.1.1, Table 21) and those reported in Wilding et al 2021 (Appendix, Table S2). Specifically, body weight change (% change) from baseline for semaglutide at years 1 and 2 in Table 21 is given as -18.47% whilst it is reported in the paper's Table S2 as -16.86% at week 68. Notably the placebo figures are identical in both tables as -2.44%. Please explain this apparent discrepancy.

The model uses treatment efficacy data from all patients in the trial for the cycles in the model before any treatment-specific stopping rule. These data are located in the "Time dependent" sheet and are relevant for the diet and exercise arm (which has no

stopping rule) and for the Month 4 and 7 cycles in the model for semaglutide 2.4 mg as these occur before the semaglutide 2.4 mg stopping rule. The responder treatment efficacy data are used for the cycles in the model after a treatment-specific stopping rule for those patients that continue treatment. These data are located in the "Early responders" sheet and are relevant for liraglutide 3.0 mg for all treatment cycles and for semaglutide 2.4 mg for the Month 10 cycle onwards.

Table 21 in the CS, Section B.3.3.1.1 reports the treatment efficacy used at each time point. Since the Year 1 and 2 data for semaglutide 2.4 mg use the Week 68 data point for responders, this should be -18.47% as reported. The value reported in the Appendix, Table S2 of Wilding et al. (2021) reports the data for all patients.

A20. The effect estimates for HbA1c, HDL and total cholesterol and waist circumference are discussed in CS, Section B.2.9.2, page 62, but the clinical significance of the findings is not discussed. Please explain what the minimum clinically important difference and minimum clinically important change from baseline would be for these outcomes.

Waist Circumference:

Increasing abdominal adiposity is associated with individual cardiometabolic risk factors and their aggregation in the metabolic syndrome in both men and women. A changing waist circumference affected cardiometabolic risk factors, and this was most clearly seen for the metabolic syndrome, which accumulates the effects of individual abnormalities. After accounting for changes in BMI, reducing waist by 3 cm had a significant beneficial effect on the metabolic syndrome in women, and increasing waist by 7 cm had a detrimental effect in both sexes.[2] Waist reductions of 5–10 cm in Caucasian women, across a range of baseline BMI 25–50 kg/m^2 or waist circumference 72–133 cm, may be used as guideline to encourage overweight women to achieve a realistic target with a high probability of health benefits.[3]

Objectively measured waist circumference gains of greater than 5 cm are associated with subsequent higher total mortality risk and higher CVD mortality risk in men. Interventions focusing on preventing increase in central adiposity rather than lowering weight per se in later life may potentially have greater health benefits.[4]

HbA1c:

A decrease of at least 0.5% (5.5 mmol/mol) or 1.0% (11 mmol/mol) at an HbA1c value of 9.0% (75 mmol/mol) after adjustment of therapy is considered sufficient by all healthcare professionals to allow the conclusion that glucose regulation has improved. In general, guidelines consider a difference of 0.5% (5.5 mmol/mol) to be clinically significant.[5]

Lipids:

Meta-analyses reported by Gould et al. found, for every 1 mmol/L decrease in total cholesterol, there was a 17.5% reduction in relative risk (RR) for all-cause mortality, 24.5% reduction in RR for coronary heart disease (CHD)-related mortality, and 29.5% reduction in RR for any CHD event. Corresponding reductions for every 1 mmol/L decrease in low-density lipoprotein cholesterol (LDL-C) were 15.6%, 28.0% and 26.6%, respectively.[6] Similar relationships were observed in patients without CHD. The primary treatment goal for people with diabetes is LDL-C consistently < 2.0 mmol/L or > 50% reduction from baseline. Alternative targets and goals are non-high-density lipoprotein cholesterol (non-HDL-C) < 2.6 mmol/L or apolipoprotein B < 0.8 g/L.[7] An HDL-C of 1.6 mmol/L or above is considered desirable.

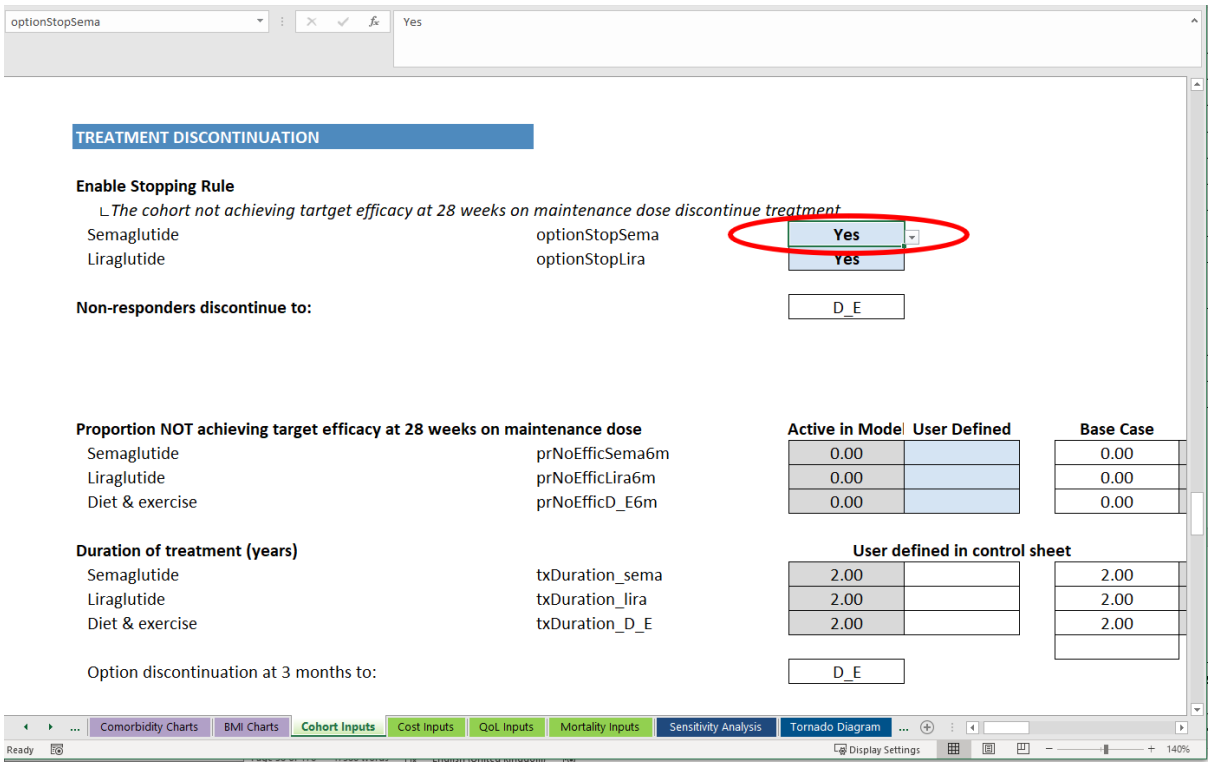
Section B: Clarification on cost-effectiveness data

B1. Priority question: Please provide brief instructions of how to run the following scenarios in the model in order to obtain the results reported in CS, Section B.3.8.3, Table 56: no stopping rule; post hoc efficacy analysis for subgroups; 1 and 2-year catch-up rate; patients with non-diabetic hyperglycaemia do not develop T2D immediately after a CVD event; and alternative baseline utilities derived as a function of BMI based on SCALE data.

Scenario: No stopping rule.

This scenario is conducted by setting “optionStopSema” to “No” in order to disable the stopping rule for semaglutide. This is located on the “Cohort inputs” sheet in cell F244 (Figure 1).

Figure 1: Semaglutide 2.4 mg stopping rule option



The treatment policy estimand efficacy data are located in CS, Appendix O, Table 73 for both semaglutide 2.4 mg and diet and exercise and CS, Appendix O, Table 74 for liraglutide 3.0 mg. Either efficacy data can be entered into the user-defined cells in the “Cohort inputs” sheet, or semaglutide 2.4 mg and diet and exercise data can be entered into the “Time dependent” sheet (Figure 2) and liraglutide 3.0 mg data into the “Early responders” sheet (Figure 3).

Figure 2: Semaglutide 2.4 mg and diet and exercise treatment policy estimand data option

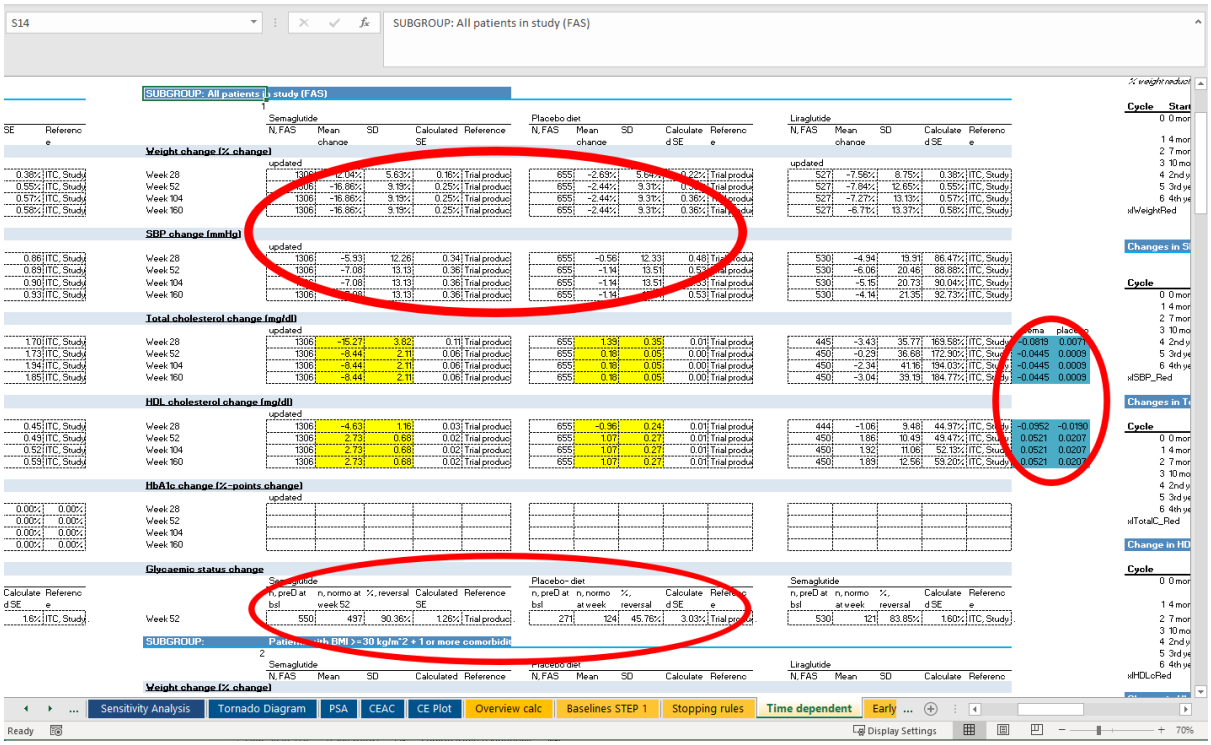
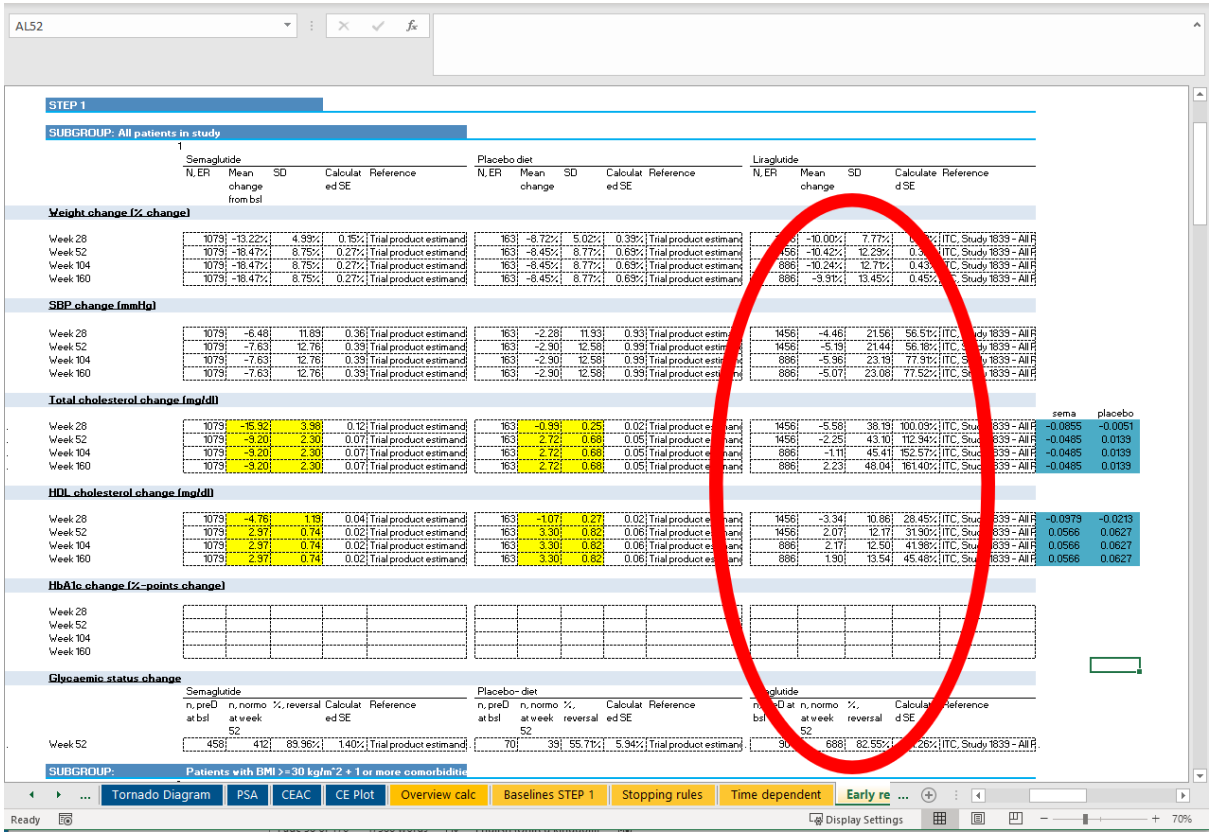


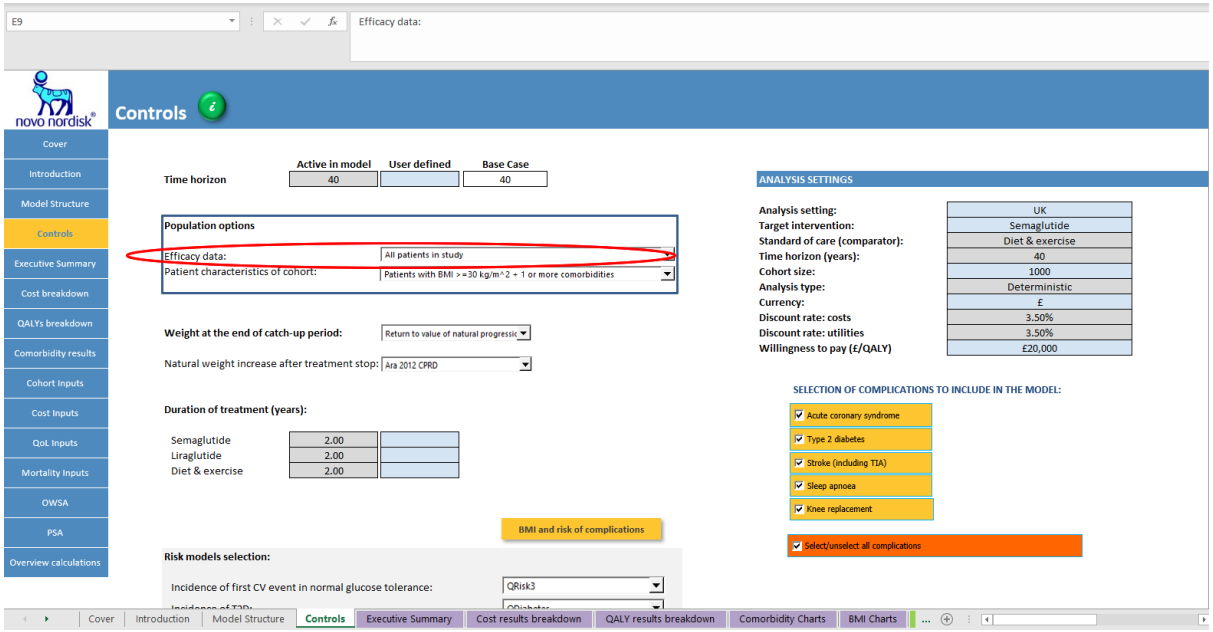
Figure 3: Liraglutide 3.0 mg ITC using treatment policy estimand data option



Scenario: Post-hoc efficacy analysis for subgroups.

This scenario is conducted by selecting the subgroup efficacy data for the subgroup of interest. This can be found in the “Controls” sheet for the dropdown next to “Efficacy data” (Figure 4).

Figure 4: Post-hoc efficacy subgroup dropdown

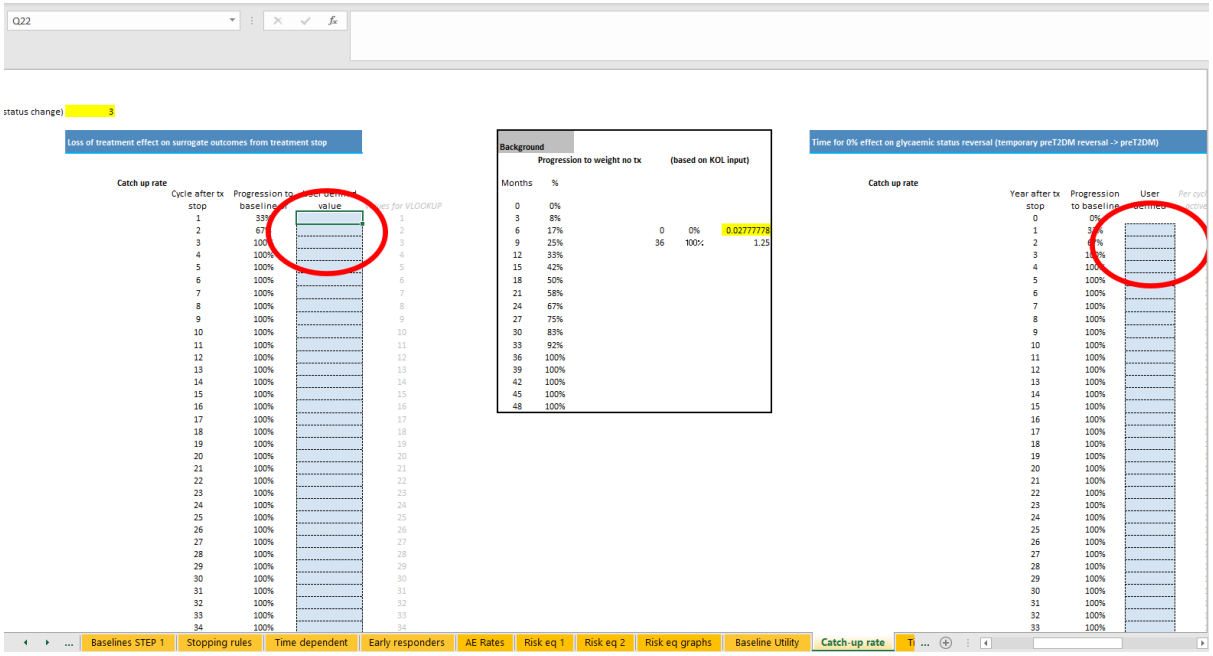


Scenario: 1- and 2-year catch-up rate.

1-year catch-up rate is selected by going to the “Catch up rate” sheet and setting Q22:Q23 to 100%.and AE23:AE24 to 100% (see Figure 5).

2-year catch-up rate is selected by setting Q22 to 50%, Q23 to 100%, AE23 to 50% and AE24 to 100% (Figure 5).

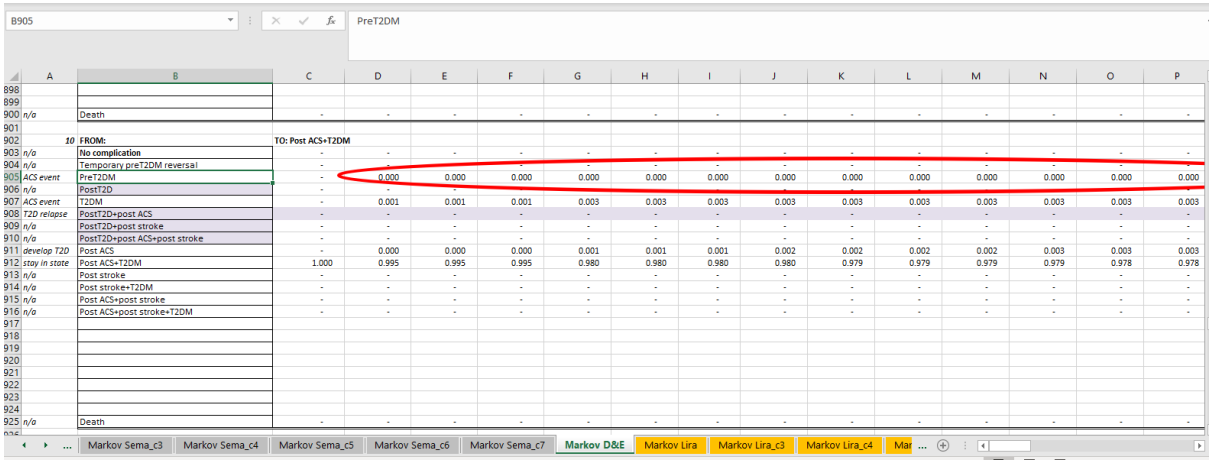
Figure 5: Catch-up rate user inputs



Scenario: Patients with non-diabetic hyperglycaemia do not develop T2D immediately after a CVD event.

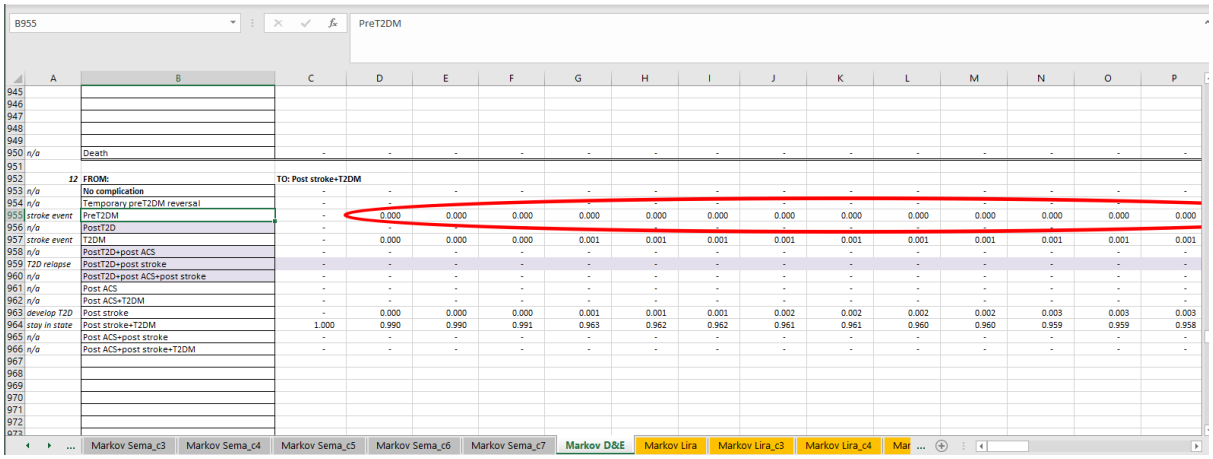
This scenario can be run by editing the transition matrices in Markov sheets (Markov Sema, Markov_Sema_c3:Markov_Sema_c7, Markov_D&E, Markov Lira, Markov_Lira_c3:Markov_Lira_c7). The transitions from non-diabetic hyperglycaemia to Post ACS+T2D (row 905) and Post stroke+T2D (row 955) are set to 0 and the probability is transferred to the Post ACS (row 880) and Post stroke (row 930) transition. The transition matrices in the Markov engine are shown in Figure 6 to Figure 9.

Figure 6: Markov engine transition probabilities (to be set to zero)



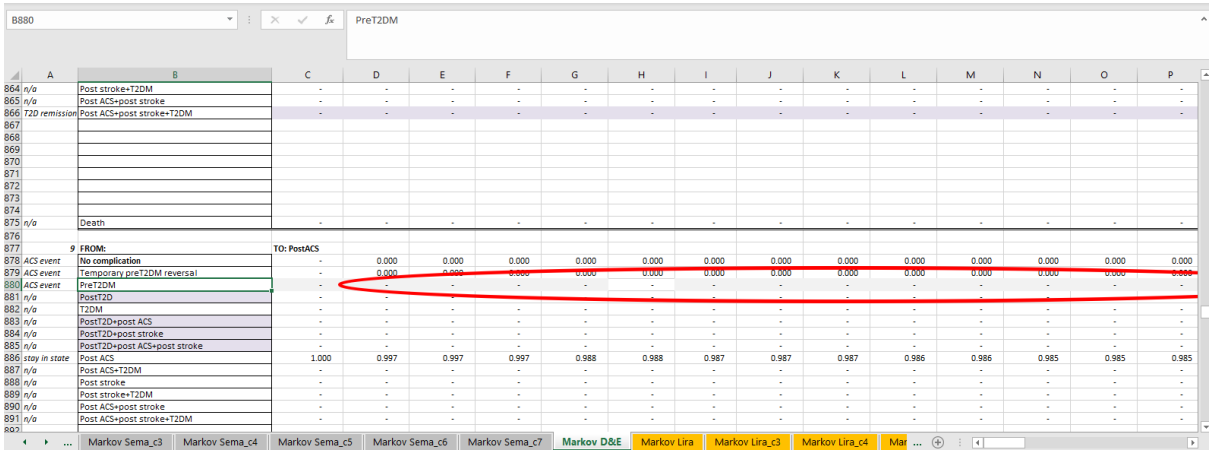
900	n/a	Death	-	-	-	-	-	-	-	-	-	-	-	-	-	-
902	10	FROM:	TO: Post ACS+T2DM													
903	n/a	No complication	-	-	-	-	-	-	-	-	-	-	-	-	-	-
904	n/a	Temporary preT2DM reversal	-	-	-	-	-	-	-	-	-	-	-	-	-	-
905	ACS event	PreT2DM	-	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
906	n/a	PostT2D	-	-	-	-	-	-	-	-	-	-	-	-	-	-
907	ACS event	T2DM	-	0.001	0.001	0.001	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003
908	T2D relapse	PostT2D+post ACS	-	-	-	-	-	-	-	-	-	-	-	-	-	-
909	n/a	PostT2D+post stroke	-	-	-	-	-	-	-	-	-	-	-	-	-	-
910	n/a	PostT2D+post ACS+post stroke	-	-	-	-	-	-	-	-	-	-	-	-	-	-
911	develop T2D	Post ACS	-	0.000	0.000	0.000	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.003	0.003	0.003
912	stay in state	Post ACS+T2DM	1.000	0.995	0.995	0.995	0.980	0.980	0.980	0.980	0.979	0.979	0.979	0.979	0.978	0.978
913	n/a	Post stroke	-	-	-	-	-	-	-	-	-	-	-	-	-	-
914	n/a	Post stroke+T2DM	-	-	-	-	-	-	-	-	-	-	-	-	-	-
915	n/a	Post ACS+post stroke	-	-	-	-	-	-	-	-	-	-	-	-	-	-
916	n/a	Post ACS+post stroke+T2DM	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Figure 7: Markov engine transition probabilities (to be set to zero)



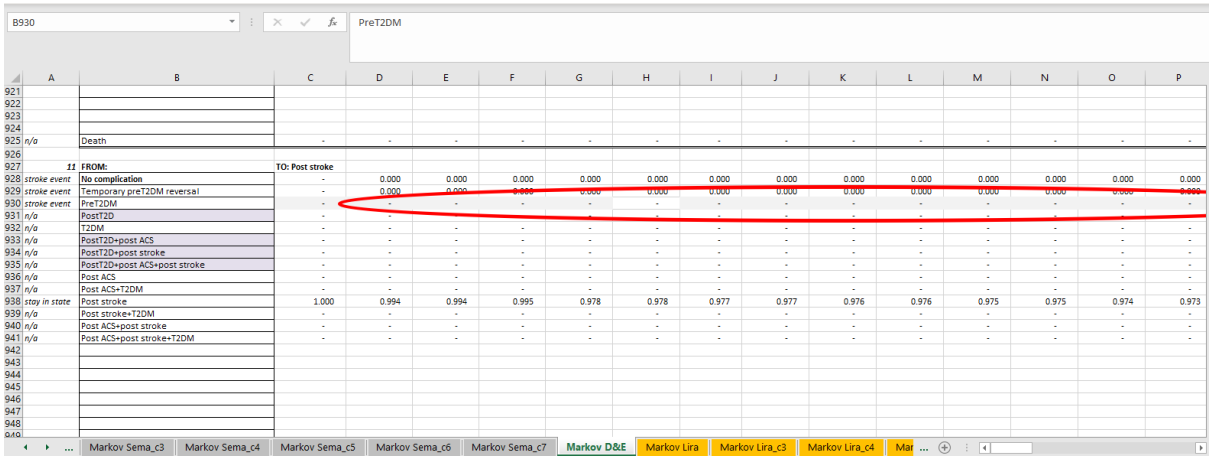
950	n/a	Death	-	-	-	-	-	-	-	-	-	-	-	-	-	-
952	12	FROM:	TO: Post stroke+T2DM													
953	n/a	No complication	-	-	-	-	-	-	-	-	-	-	-	-	-	-
954	n/a	Temporary preT2DM reversal	-	-	-	-	-	-	-	-	-	-	-	-	-	-
955	stroke event	PreT2DM	-	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
956	n/a	PostT2D	-	-	-	-	-	-	-	-	-	-	-	-	-	-
957	stroke event	T2DM	-	0.000	0.000	0.000	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
958	n/a	PostT2D+post ACS	-	-	-	-	-	-	-	-	-	-	-	-	-	-
959	T2D relapse	PostT2D+post stroke	-	-	-	-	-	-	-	-	-	-	-	-	-	-
960	n/a	PostT2D+post ACS+post stroke	-	-	-	-	-	-	-	-	-	-	-	-	-	-
961	n/a	Post ACS	-	-	-	-	-	-	-	-	-	-	-	-	-	-
962	n/a	Post ACS+T2DM	-	-	-	-	-	-	-	-	-	-	-	-	-	-
963	develop T2D	Post stroke	-	0.000	0.000	0.000	0.001	0.001	0.001	0.002	0.002	0.002	0.002	0.003	0.003	0.003
964	stay in state	Post stroke+T2DM	1.000	0.990	0.990	0.991	0.963	0.962	0.962	0.961	0.961	0.960	0.960	0.959	0.959	0.958
965	n/a	Post ACS+post stroke	-	-	-	-	-	-	-	-	-	-	-	-	-	-
966	n/a	Post ACS+post stroke+T2DM	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Figure 8: Markov engine transition probabilities (to be set to row 880)



875	n/a	Death	-	-	-	-	-	-	-	-	-	-	-	-	-	-
877	9	FROM:	TO: PostACS													
878	ACS event	No complication	-	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
879	ACS event	Temporary preT2DM reversal	-	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
880	ACS event	PreT2DM	-	-	-	-	-	-	-	-	-	-	-	-	-	-
881	n/a	PostT2D	-	-	-	-	-	-	-	-	-	-	-	-	-	-
882	n/a	T2DM	-	-	-	-	-	-	-	-	-	-	-	-	-	-
883	n/a	PostT2D+post ACS	-	-	-	-	-	-	-	-	-	-	-	-	-	-
884	n/a	PostT2D+post stroke	-	-	-	-	-	-	-	-	-	-	-	-	-	-
885	n/a	PostT2D+post ACS+post stroke	-	-	-	-	-	-	-	-	-	-	-	-	-	-
886	stay in state	Post ACS	1.000	0.997	0.997	0.997	0.988	0.988	0.987	0.987	0.987	0.986	0.986	0.985	0.985	0.985
887	n/a	Post ACS+T2DM	-	-	-	-	-	-	-	-	-	-	-	-	-	-
888	n/a	Post stroke	-	-	-	-	-	-	-	-	-	-	-	-	-	-
889	n/a	Post stroke+T2DM	-	-	-	-	-	-	-	-	-	-	-	-	-	-
890	n/a	Post ACS+post stroke	-	-	-	-	-	-	-	-	-	-	-	-	-	-
891	n/a	Post ACS+post stroke+T2DM	-	-	-	-	-	-	-	-	-	-	-	-	-	-

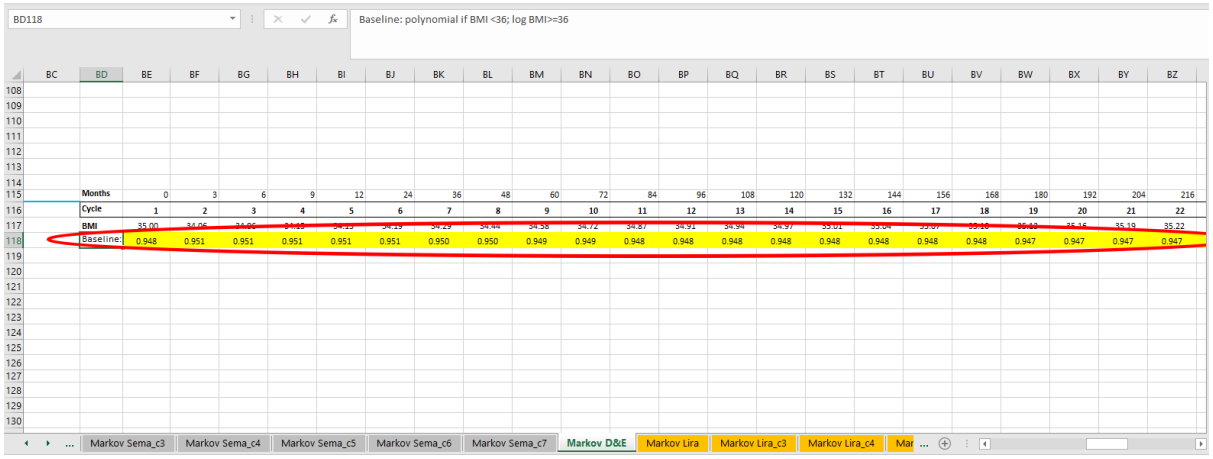
Figure 9: Markov engine transition probabilities (to be set to row 930)



Scenario: Alternative baseline utilities derived as a function of BMI based on SCALE data.

This scenario can be run by editing the utility used in each cycle in the Markov sheets (Markov Sema, Markov_Sema_c3:Markov_Sema_c7, Markov_D&E, Markov Lira, Markov_Lira_c3:Markov_Lira_c7) cells BE118:CU118 (Figure 10).

Figure 10: Markov engine utilities for each cycle



The utilities can be derived by averaging male and female regression models using the proportion female. The proportion female is reported for each population in the "Baseline STEP 1" sheet row 25 (also see CS, Section B.3.2.1, Table 16). The regression coefficients used as per TA664 for male and female patients are reported in Table 1 and Table 2, respectively.

Table 1: Regression model on EQ-5D for males

Parameter	Estimate	SE	95% CI	p-value
Model Intercept	1.1129	0.3279	[0.4682; 1.7575]	0.0008
Age Groups				
Age 18-24 years	0.0038	0.0195	[-0.0345; 0.0422]	0.8446
Age 35-44 years	-0.0012	0.0115	[-0.0238; 0.0213]	0.9140
Age 45-54 years	-0.0213	0.0111	[-0.0431; 0.0006]	0.0567
Age 55-64 years	-0.0192	0.0120	[-0.0429; 0.0045]	0.1113
Age 65-74 years	-0.0279	0.0140	[-0.0555; -0.0003]	**0.0474**
Age 75 years or more	-0.0824	0.0591	[-0.1987; 0.0339]	0.1643
Age 25-34 years	[Reference Category]			
Heart or Circulatory Diseases (excl. Hypertension)	-0.0032	0.0076	[-0.0181; 0.0117]	0.6707
Hypertension	-0.0005	0.0064	[-0.0130; 0.0120]	0.9355
Smoking Status				
Current Smoker	-0.0045	0.0078	[-0.0199; 0.0108]	0.5616
Previous Smoker	-0.0129	0.0067	[-0.0261; 0.0004]	0.0572
Never Smoked	[Reference Category]			
Body Mass Index				
Linear Effect	-0.002780	0.0225	[-0.0470; 0.0415]	0.9017
Quadratic Effect	-0.000080	0.0005	[-0.0011; 0.0009]	0.8709
Cubic Effect	0.0000012	0.0000	[-0.0000; 0.0000]	0.7502

Key: BMI, body mass index; CI, confidence interval; SE, standard error.
Notes: Bold indicates statistically significant result.
Population mean used for non BMI variables if not 0:

- Hypertension: 0.491
- Current smoker: 0.209
- Previous smoker: 0.369

Table 2: Regression model on EQ-5D for females

Parameter	Estimate	SE	95% CI	p-value
Model Intercept	1.1430	0.1600	[0.8291; 1.4569]	<.0001
Age Groups				
Age 18-24 years	0.0013	0.0116	[-0.0214; 0.0241]	0.9078
Age 35-44 years	-0.0033	0.0060	[-0.0151; 0.0086]	0.5893
Age 45-54 years	-0.0125	0.0059	[-0.0242; -0.0009]	**0.0343**
Age 55-64 years	-0.0198	0.0064	[-0.0324; -0.0071]	**0.0022**
Age 65-74 years	-0.0206	0.0090	[-0.0382; -0.0030]	**0.0218**
Age 75 years or more	-0.0449	0.0285	[-0.1008; 0.0109]	0.1147
Age 25-34 years	[Reference Category]			
Heart or Circulatory Diseases (excl. Hypertension)	-0.0047	0.0054	[-0.0154; 0.0059]	0.3824
Hypertension	-0.0115	0.0037	[-0.0188; -0.0042]	**0.0021**
Smoking Status				
Current Smoker	-0.0082	0.0051	[-0.0182; 0.0018]	0.1092
Previous Smoker	-0.0016	0.0040	[-0.0095; 0.0064]	0.6966
Never Smoked	[Reference Category]			
Body Mass Index				
Linear Effect	-0.0086	0.0109	[-0.0299; 0.0127]	0.4284
Quadratic Effect	0.0001	0.0002	[-0.0004; 0.0006]	0.6570
Cubic Effect	-0.0000005	0.0000	[-0.0000; 0.0000]	0.7614

Key: CI, confidence interval; SE, standard error.
Notes: Bold indicates statistically significant result.
Population mean used:

- Hypertension: 0.377
- Current smoker: 0.135
- Previous smoker: 0.247

The resulting utilities for BMI are shown in Table 3.

Table 3: Baseline utilities per BMI for male and female

BMI	Female	Male
27	0.972	0.997
28	0.968	0.992
29	0.965	0.988
30	0.961	0.983
31	0.957	0.979
32	0.954	0.974

BMI	Female	Male
33	0.951	0.970
34	0.947	0.966
35	0.944	0.962
36	0.941	0.958
37	0.938	0.954
38	0.936	0.950
39	0.933	0.946
40	0.930	0.943
41	0.928	0.939
42	0.925	0.936
43	0.923	0.932
44	0.921	0.929
45	0.918	0.926
46	0.916	0.924
47	0.914	0.921
48	0.912	0.918
49	0.910	0.916
50	0.908	0.914
51	0.906	0.912
52	0.905	0.910
53	0.903	0.909
54	0.901	0.908
55	0.900	0.907
56	0.898	0.906
57	0.896	0.905
58	0.895	0.905
59	0.893	0.905
60	0.892	0.905
Key: BMI, body mass index.		

B2. Priority question: Please clarify whether the changes in physiological parameter values for the FAS (CS, Section B.3.3.1.1, CS table 21) have also been used for the subgroup comparison with liraglutide (i.e. patients with BMI ≥35 kg/m^2).

The values reported in CS, Section B.3.3.1.1, Table 21 have also been used for the subgroup comparison with liraglutide 3.0 mg. This is in line with our rationale described in CS, Section B.3.3.1.1:

"Treatment effects for semaglutide 2.4 mg and diet and exercise for both subgroups were sourced from the population containing all patients of the STEP 1 clinical trial. This population efficacy was assumed to be representative of the subgroups of interest and since this population was defined a priori in the STEP 1 trial, it provided a statistically robust measure of the treatment effect. This assumption was validated in an advisory board with key opinion leaders and the post hoc analysis is explored in a scenario analysis for validation."

B3. Please indicate which of the cohort characteristics for the patients with BMI ≥35 kg/m^2 differ from the parameter values shown for the baseline cohort characteristics in CS, Section B.3.6.1, Table 48.

Table 16 in B.3.2.1 of the CS provides the characteristics for both populations alongside each other.

B4. Priority question: The weight change (% change) for semaglutide at 6 months used in the model (-13.22% in sheet cohort inputs!i100) differs from that reported in CS, Section B.3.3.1.1, Table 21 (-12.04%). There are similar differences for SBP change, and Total and HDL cholesterol change. Please clarify whether CS Table 21 or the model is correct.

Please see the company response in clarification A19 as this further explains the use of all patient and responder data in the model. As described in CS, Section B.3.3.1.1, the stopping rule for semaglutide 2.4 mg is at 28 weeks, so the all-patients efficacy is used from Week 20 and Week 28 STEP 1 data for the first 2 cycles. After Cycle 2, early responder efficacy from STEP 1 Week 68 data is used for patients continuing treatment with semaglutide 2.4 mg. This is reflected in the model using the variable "weightReduction_sema6m_fs" (-12.04%, located in the "Cohort inputs" sheet cell F103) for Months 4 and 7 and "weightReduction_sema6m" (-13.22%, located in the "Cohort inputs" sheet cell F100) for Month 10. The same applies to the other listed variables, which are also located in the "Cohort inputs" sheet.

B5. The proportions of patients who receive different types of bariatric surgery differs between CS, Section B.3.3.2, Table 27, and the model (sheet cohort

inputs!49,i50) for laparoscopic banding and sleeve gastrectomy. Please clarify whether CS Table 27 or the model is correct.

The model is correct. Table 27 in the CS should be 18% for sleeve gastrectomy and 31% for laparoscopic banding.

B6. Priority question: Please provide a table of the coefficients used in the model for the QRisk3, QDiabetes and UKPDS82 risk equations.

Full details of the Visual Basic® for Applications (VBA) code for the risk equations are included in CS, Appendix M. The VBA code contains the coefficients used and transformations performed on each variable such as any centring for continuous variables. CS, Appendix L provides a description of the variables used and any abbreviations for the risk equations.

The coefficients for the QRisk3 model are shown in Table 4. Variable definitions are provided in CS, Appendix L.3.1.1 Table 61.

Table 4: QRisk3 coefficients

Variable in VBA	Female coefficient	Male coefficient
ethrisk:		
White / not recorded	0	0
Indian	0.280	0.277
Pakistani	0.563	0.474
Bangladeshi	0.296	0.530
Other Asian	7.28E-02	0.035
Black Caribbean	-0.171	-0.358
Black African	0.394	-0.401
Chinese	0.326	-0.415
Other	0.171	-0.263
smoke_cat:		
Non smoker	0	0
Ex smoker	0.134	0.191
Light smoker	0.562	0.552
Moderate smoker	0.667	0.638
Heavy smoker	0.849	0.790
age_1	-8.14	-17.840
age_2	0.797	0.002
bmi_1	0.292	2.456
bmi_2	-4.15	-8.301
rati	0.153	0.173

Variable in VBA	Female coefficient	Male coefficient
sbp	1.31E-02	0.013
sbps5	7.89E-03	0.010
town	7.72E-02	0.033
b_af	1.592	0.882
b_typicalantipsy	0.252	0.130
b_corticosteroids	0.595	0.455
b_migraine	0.301	0.223
b_ra	0.214	0.256
b_renal	0.652	0.210
b_semi	0.126	0.719
b_sle	0.759	0.121
b_treatedhyp	0.509	0.440
b_type1	1.73	0.517
b_type2	1.07	1.234
b_fh_cvd	0.454	0.859
age_1 * (smoke_cat = Ex smoker)	-4.71	-0.210
age_1 * (smoke_cat = Light smoker)	-2.74	0.753
age_1 * (smoke_cat = Moderate smoker)	-0.866	0.993
age_1 * (smoke_cat = Heavy smoker)	0.902	2.133
age_1 * b_af	19.9	3.490
age_1 * b_corticosteroids	-0.984	1.171
age_1 * b_migraine	1.763	-1.506
age_1 * b_renal	-3.59	2.349
age_1 * b_sle	19.7	-0.507
age_1 * b_treatedhyp	11.9	6.511
age_1 * b_type1	-1.24	5.338
age_1 * b_type2	6.87	3.646
age_1 * bmi_1	23.8	31.005
age_1 * bmi_2	-71.2	-111.292
age_1 * fh_cvd	0.995	2.781
age_1 * sbp	0.034	0.019
age_1 * town	-1.03	-0.101
age_2 * (smoke_cat = Ex smoker)	-0.076	-4.99E-04
age_2 * (smoke_cat = Light smoker)	-0.120	-7.99E-04
age_2 * (smoke_cat = Moderate smoker)	-0.104	-8.37E-04
age_2 * (smoke_cat = Heavy smoker)	-0.140	-7.84E-04
age_2 * b_af	-0.076	-3.50E-04
age_2 * b_corticosteroids	-0.120	-2.50E-04
age_2 * b_migraine	-0.066	-1.11E-03
age_2 * b_renal	-0.227	1.99E-04
age_2 * b_sle	0.077	-1.83E-03
age_2 * b_treatedhyp	0.001	6.38E-04

Variable in VBA	Female coefficient	Male coefficient
age_2 * b_type1	-1.24	6.41E-04
age_2 * b_type2	6.87	-2.47E-04
age_2 * bmi_1	23.8	5.04E-03
age_2 * bmi_2	-71.2	-1.31E-02
age_2 * fh_cvd	0.995	-2.48E-04
age_2 * sbp	0.034	-1.27E-05
age_2 * town	-1.03	-9.33E-05
Key: VBA, Visual Basic for Applications. Note, for female: age_1 = (Age/10)^-2 age_2 = Age/10 bmi_1 = (BMI/10)^-2 bmi_2 = (BMI/10)^-2 * ln(BMI/10)) for male: age_1 = (Age/10)^-1 age_2 = (Age/10)^3 bmi_1 = (BMI/10)^-2 bmi_2 = (BMI/10)^-2 * ln(BMI/10))		

The coefficients for the QDiabetes model are shown in Table 5. Variables definitions are provided in CS, Appendix L.2.1 Table 58.

Table 5: QDiabetes model coefficients

Variable in VBA	Female coefficient	Male coefficient
ethrisk:		
White / not recorded	0	0
Indian	0.599	0.676
Pakistani	0.783	0.831
Bangladeshi	1.195	1.097
Other Asian	0.714	0.768
Black Caribbean	0.120	0.209
Black African	0.014	0.381
Chinese	0.571	0.342
Other	0.171	0.220
smoke_cat:		
Non smoker		
Ex smoker	0.066	0.116
Light smoker	0.146	0.146
Moderate smoker	0.153	0.108
Heavy smoker	0.308	0.198
age_1	3.566	4.019
age_2	-5.62E-03	-4.84E-03
bmi_1	2.504	0.818
bmi_2	-0.043	-0.126

Variable in VBA	Female coefficient	Male coefficient
hba1c_1	8.737	8.051
hba1c_2	-0.078	-0.147
town	0.036	0.025
b_typicalantipsy	0.550	0.455
b_corticosteroids	0.169	0.138
b_cvd	0.164	0.145
b_gestdiab	1.125	0
b_learning	0.289	0.260
b_manicschiz	0.318	0.285
b_pos	0.338	0
b_statin	0.456	0.426
b_treatedhyp	0.404	0.332
fh_Diab	0.443	0.566
age_1 * b_atypicalantipsy	-0.813	-1.00
age_1 * b_learning	-0.908	-0.892
age_1 * b_statin	-1.856	-1.707
age_1 * bmi_1	0.602	0.451
age_1 * bmi_2	-3.45E-02	-0.109
age_1 * fh_Diab	-0.273	-0.678
age_1 * hba1c_1	25.4	27.7
age_1 * hba1c_2	-6.808	-7.401
age_2 * b_atypicalantipsy	4.67E-04	2.25E-04
age_2 * b_learning	8.52E-04	6.60E-04
age_2 * b_statin	2.26E-03	1.39E-03
age_2 * bmi_1	-4.34E-03	-1.22E-03
age_2 * bmi_2	1.16E-04	2.27E-04
age_2 * fh_Diab	4.35E-04	5.06E-04
age_2 * hba1c_1	-5.23E-02	-5.92E-02
age_2 * hba1c_2	1.41E-02	1.56E-02

Key: VBA, Visual Basic for Applications.
Note, for female: age_1 = (Age/10)^0.5
age_2 = (Age/10)^3
bmi_1 = BMI/10
bmi_2 = (BMI/10)^3
hba1c_1 = (HbA1c/10)^0.5
hba1c_2 = HbA1c/10
for male: age_1 = ln(Age/10)
age_2 = (Age/10)^3
bmi_1 = (BMI/10)^2
bmi_2 = (BMI/10)^3
hba1c_1 = (HbA1c/10)^0.5
hba1c_2 = HbA1c/10

The coefficients for the UKPDS82 model are shown in CS Appendix L.3, Table 64 and Table 67.

B7. Please confirm that all the costs reported in CS, Section B.3.6.1, Table 48, have been inflated to 2020/21 prices.

There are no costs reported in CS, Table 48. However, all costs have been inflated to 2020/21 prices and are reported in CS, Table 50. The cost year of the data and uninflated vales are reported in the "Cost Calculations" sheet in the model.

B8. Please confirm that the adverse event rates in CS, Section B.3.3.1.4, Table 24, are grade 3-4 adverse events. Also please explain what events are classified as non-severe hypoglycaemia and severe gastrointestinal events in CS Table 24 and provide a reference to the source of these data.

Severity classification in STEP 1 was an assessment performed by the investigator based on the protocol-defined criteria[8] and not utilizing the Common Terminology Criteria for Adverse Events (CTCAE) grading. We cannot confirm that these events correspond exactly to the specific gradings in other classification systems.

The gastrointestinal events were classified as severe. The hypoglycaemia events were classified as mild and moderate; there were no severe hypoglycaemia events. The STEP 1 CSR reports these data in Table 14.3.1.25 and Table 14.3.1.58. The AE event rates for liraglutide 3.0mg were calculated using the data reported in the study by le Roux et al. (2017)[9]. The publication reports 7% of gastrointestinal events were identified as severe. In the publication, the number of gastrointestinal events is reported in Table 3 and the number of hypoglycaemia events are reported in the appendix table S17. Only spontaneously reported hypoglycaemia events were used as the majority of hypoglycaemic events were recorded as hypoglycaemia per protocol. The total years of observation was calculated using the total number of adverse events and event rate per 100 years of observation in Table 3 of the publication.

The AEs were defined using the Medical Dictionary for Regulatory Activities version 22.1. The seriousness, severity, causality and final outcome of AEs followed definitions in the trial protocol.

B9. Priority question: Please summarise the main differences between the current model and the model used in the validation paper by Lopes et al (Lopes S, Meincke HH, Lamotte M, et al. A novel decision model to predict the impact of weight management interventions: The Core Obesity Model. Obesity Science & Practice. 2021; 7(3):269-80.) Please comment on whether these differences would affect the relevance of the Lopes et al model validations for the current appraisal.

The current model shares with the validation model, the implementation of the risk equations, health states (excluding cancer health states) and the cost, utility and treatment efficacy structural calculations. Therefore, the validation conclusions regarding the obesity related comorbidities are transferable to the current appraisal.

The mortality in the model used in Lopes et al was low compared to the validation data. Therefore, the current model was updated to include BMI adjusted mortality. The current model also includes an update to incorporate treatment discontinuation as well as uses updated inputs. As described in CS, Section B.3.2.2.1 the current model does not include the cancer health states that were in the previous Lopes et al model.

The main drivers identified in the current appraisal through sensitivity analysis, namely the starting BMI, discount rates and weight reduction from treatment, are all variables that interact structurally with the risk equations in the same way between the validation model and current appraisal model.

B10. Priority question: Please verify that the trial product estimands produce the correct treatment outcomes in the model by comparing the mean BMI, SBP and total cholesterol for the first two years in the model against the trial outcomes reported in CS Section 2.6.

The data from the CSR for the treatment policy estimand is reported in CS Section 2.6, whereas the trial product estimand is reported in CS, Appendix E.2. The model uses the trial product estimand, and therefore the model output is compared with the trial product estimand data from the CSR. The validation for each treatment arm was conducted separately by setting the patient characteristics in the model to the patient characteristics of the treatment arm being validated (CS Section B2.3.2 Table 5). Furthermore, only the cohort of patients on treatment in the model were analysed to

provide similarity to the descriptive statistics reported in the CSR. Table 6 and Table 7 (below) show the modelled outcomes versus the trial outcomes for the FAS population using the trial product estimand for semaglutide 2.4 mg and for diet and exercise, respectively. The difference in results is small, which can be attributed to the CSR reporting descriptive statistics, whereas the model input uses statistical modelling guided by the estimand and considers data selection and imputation of missing data.

Table 6: Semaglutide 2.4 mg modelled outcomes versus STEP 1 trial reported outcomes

Parameter	Modelled outcome change at 2 years from baseline	Trial outcome change at 68 weeks from baseline
	Semaglutide 2.4 mg	Semaglutide 2.4 mg
BMI (kg/m^2)	-6.37	-6.27
SBP (mmHg)	-7.08	-7.08
Total cholesterol (mg/dL)	-8.44	-7.45
Key: BMI, body mass index; SBP, systolic blood pressure.		

Table 7: Diet and exercise modelled outcomes versus STEP 1 trial reported outcomes

Parameter	Modelled outcome change at 2 years from baseline	Trial outcome change at 68 weeks from baseline
	Diet and exercise	Diet and exercise
BMI (kg/m^2)	-0.92	-0.95
SBP (mmHg)	-1.14	-1.14
Total cholesterol (mg/dL)	0.18	-1.49
Key: BMI, body mass index; SBP, systolic blood pressure.		

B11. Priority question: Please compare the results of the economic analysis for the comparator arm, i.e. the total costs and the total QALYs for diet and exercise, between the current semaglutide appraisal and TA664 for liraglutide. Please comment on the reasons for any differences between the results.

Table 8 (below) shows the results for the BMI ≥ 35kg/m^2 + non-diabetic hyperglycaemia + high risk of CVD scenario using the diet and exercise comparator from the current appraisal and from TA664.

Table 8: Diet & exercise results from current appraisal and TA664

Technologies	Costs (£)	QALYs
Diet & exercise (SCALE-TA664)	£19,992	15.18
Diet & exercise (STEP 1)	£28,371	14.31
Key: QALY, quality-adjusted life year.		

The current model shares many similarities with the model used in TA664. The most notable differences are inclusion of mortality adjusted for BMI, update of the costs, and inclusion of the option for the weight to return to the value of natural progression at the end of the catch-up period. Therefore, to make a fair comparison of the diet and exercise data, the SCALE diet and exercise efficacy data and patient characteristics were implemented into the semaglutide 2.4 mg appraisal model. The results provided in Table 9 (below) show similar cost and QALYs. This is as expected given the similarities of the patient populations between STEP1 and SCALE, and the results of the ITC in CS, Section B.2.9. The ITC showed that population adjustment had no impact on the outcomes of the ITC. The SCALE diet and exercise arm has similar but improved efficacy for SBP and HDL and total cholesterol. This explains the small difference in results as the SCALE diet and exercise arm has a reduced number of CV events compared to STEP1.

Table 9: Diet & exercise results using current appraisal model

Technologies	Costs (£)	QALYs
Diet & exercise (SCALE-TA664)	£27,597	14.60
Diet & exercise (STEP 1)	£28,371	14.31
Key: QALY, quality-adjusted life year.		

B12. Please explain the data sources for CS, Section B.3.3.1.1, Table 21, as these are not obvious from the submission. For instance, the pattern of change in HDL and total cholesterol indicated in CS Table 21 does not appear to agree with the data presented in clinical study report Table 11-4 or in clinical study report sections 14.2.9.6 and 14.2.151.

Please see the company response in clarification A19 as this further explains the use of all patient and responder data in the model. The CSR sections and tables

mentioned in the clarification detail the efficacy for all patients. CS, Section B.3.3.1.1 Table 21 reports the treatment efficacy data used in the model, which includes a combination of treatment efficacy data derived from both all patients and early responders.

B13. Please explain why knee replacement is included in the model but hip replacement is not included.

As noted in CS, Section B.3.2.2, obesity is associated with numerous possible comorbidities, and the model will inevitably be a simplification of reality. The model encompasses the key comorbidities and complications that are associated with obesity, noted to respond to weight loss and having substantial consequences on healthcare resource use and costs, patients' quality of life, and/or life expectancy. Reviews of the literature were conducted in 2014 and 2017 to identify such conditions and also to inform transition probabilities in the model. The reviews identified a report by the World Health Organization[10] that classified the relative risk of health problems associated with obesity into three categories: greatly, moderately, and slightly increased risk. This was used to help inform which complications and comorbidities were incorporated into the model, focusing on those associated with a greatly or moderately increased risk. Osteoarthritis (knees) is identified in the report as having a moderately increased risk of health problems associated with obesity (relative risk 2–3 times greater) and was therefore included in the model. However, as explained in CS, Section B.3.2.2.1, it was not accounted for separately but rather was included in the form of a 'knee replacement' event. Since hip replacement was not described in the aforementioned WHO report as being associated with greatly or moderately increased risk, it was not included in the model.

Of note, the data used to model knee replacement were based on a study by Wendelboe et al. 2003[11], which provides data on the association between BMI and the incidence of knee surgeries (see CS, Section B.3.3.7.3). Whilst this paper does also demonstrate an association between BMI and hip replacement, it is less marked than the association between BMI and knee replacement. As the model does not account for all weight-related comorbidities, it is expected to be conservative in estimating the benefits of treatment.

Section C: Textual clarification and additional points

C1. The superscript footnote letters in CS, Section B.1.1, Table 1, do not appear within the text of the table. Please clarify to which text the footnotes relate.

The footnotes in Document B, Table 1 of the CS were added in error, please ignore these footnotes.

C2. Please provide Supplement 1 to the STEP 3 trial paper (Wadden et al, 2021. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. JAMA 325(14):1403-1413).

We have attached supplement 1 to the STEP 3 trial paper to this response (see Attachment Y: Wadden_JAMA_2021_Suppl1).

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Semaglutide for managing overweight and obesity [ID3850]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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About you	
1.Your name	[redacted]
2. Name of organisation	Obesity UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The organisation delivers support via a combination of online and face to face support groups. Funding has been obtained over the years from a combination of project grants from Public Health England, Pharmaceutical Companies, Medical Device Companies and sone personal donations. At the time of the merger of WLSinfo and HOOP in April 2019 there was a total of 40,000 notional members. Although there is a no formal membership system and by its the nature online support group actual membership is difficult to quantify.

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	In July 2021 Obesity UK received 6500 pounds from Novo Nordisk. This was for the creation and storage of training videos and materials for volunteers
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Through our online support groups and through our closed facebook community groups.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Obesity can also diminish a person's overall quality of life as they may avoid public places and, in some cases, encounter discrimination. People living with Obesity may experience depression, difficulty in hygiene practices, disability, sexual problems, shame and guilt, social isolation and due to this, lower work achievements. In some cases, Obesity is physically debilitating. They may experience joint pain and require mobility access assistance e.g. wheelchair usage and modified bathroom facilities in their home. They can have

	skin issues with infection and odour, with basic tasks like showering and bathing becoming impossible without assistance. Obesity may affect fertility with the ability to have biological children greatly reduced. This may also be compounded by treatments for infertility being withdrawn for patients over a specific BMI. People living with Obesity can often been seen as lazy, unmotivated and having a lower IQ, this increased social stigma may affect career prospects, meaning

	that confidence lowered, and financial detriment is vastly increased. Obesity can affect people of any ethnic group or sex, it is also seen in both adults and children. These are some examples of what are members told us. “I hate not being able to shop in ordinary stores, the normal shops don't cater for me, I have to buy online." "When I go out with the kids I worry if the seating will be able to take my weight, will I be able to fit in a booth? Will everyone be looking at me?"

	"Living with obesity is a life of exhaustion, worry and shame. Exhaustion from trying to lose the weight and the shame; worry in case you won't fit somewhere like a plane seat or pub seat or that people will mock you for your size; shame because you feel you're not 'normal' and somehow you're less worthy of love and respect." "Obesity is a significant contributor to my depression and anxiety. It makes me want to stay indoors and hide away because people presume we are obese due to continual bingeing and eating the 'wrong' foods." “Horrible, uncomfortable, constantly being

	called names like fat, lazy, ugly greedy to name a few." "Life is an emotional rollercoaster at times. Lack of support and negativity from others can undo any good progress made." "Living with obesity is soul-destroying, painful, difficult, embarrassing, stressful and thoroughly depressing. People who have not lived with obesity do not understand how desperate for help we feel." "There is not any element of my life that is not affected by my obesity. Physical and mental. My education, my work and my relationships."

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Sometimes some drugs are only available from specialist weight management services – we don't have one nearby. Not good at all, too many General Practitioners have no clue or understanding the how or why saying eat less and move more doesn't work for everyone. Some hospital specialists like orthopaedic doctors dont offer solutions to my joint problems and just say lose weight. There is a lack of understanding and support early on for treatments or support for those increasing in weight until you become extremely obese and possibly require surgical intervention which you only qualify for if you obese enough. Many people expressed their concern at the lack of access to liraglutide. This seems to only be available in specialist weight management centres and there are areas that are not covered by these clinics. Many people told us they had used orlistat with little effect and poor outcomes. Bariatric surgery is available but not everyone wants to go down that road, and even if they do its often difficult to access and hard to get. Many members expressed the desire for more psychological support and for longer term care.

8. Is there an unmet need for patients with this condition?	Universally our members agreed that there is a need for better access to and more treatments available. There are disparities around the country. These are some of the things our members said "Is there an unmet need Yes, hell yes" "There is a need for early diagnosis (instead of going undiagnosed for years) and support of medical conditions which contribute to weight gain, to address all issues and not just weight loss (by diet and exercise)." "Weight loss support required early on, and not when some becomes a certain weight where they meet criteria for weight loss surgery. People need treatment when they are younger." "There is a need for non-judgemental emotional support and for somebody to come alongside them. There is also an unmet physical need and probably the two needs are linked." "We need good quality services with a range of tools at there disposal. Everyone should have full access to all the treatments for as long as they are needed."

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	In assisting the patient to lose weight, it may increase the overall physical health of the patient e.g. lowering elevated blood pressure, blood sugar and cholesterol. It may also help by giving the patient more energy in their daily lives with the goal of a more stable and manageable home life for not only the patient, but their family also. Benefits include offering patients choice in their treatment of Obesity. A "one size fits all" approach to medicines is not best practice. The treatment for Obesity must be suited to the patient, their lifestyle dietary requirements and overall health. Patients living with more severe Obesity may require less assistance in their day to day lives with personal hygiene and other daily tasks. This would give the patient more independence in their own home. They may feel more secure about socialising and interacting with other people. By using this medicine people would hope to lose weight and increase their quality of life. This can improve confidence and improve life chances in employment and education. Living with Obesity impacts on relationships, education, economic chances and employment. If the burden of obesity can be lifted huge changes can be made. As a person living with obesity loses weight, the psychological burden on the whole family decreases. Life gets easier for all family members. The person living with obesity can take a more active part in family life. Our members said “It would help me to control blood sugars and lose weight.” “I need more information about this drug before I decide” “Even though there may be side effects this might give me the kick start I need” “This could reduce my appetite” “Maybe I wont need bariatric surgery if I have this”

	"It's only a once weekly jab with a tiny needle" "By helping people to lose weight it could make them more independent"

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	This medicine would be best started as part of a package of ongoing support from a multidisciplinary team. Patients may need guidance on how to administer the medication. We asked our members. "I am worried about some of the serious side effects I have seen listed in the internet about this drug." "I have read about side effects like feeling sick – but I would tolerate a high level of discomfort if it helped me lose weight."
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We had a lengthy online discussion about who this could help. Groups that came up included young people. People living with mental health problems. People who are house bound. People awaiting bariatric and other types of surgery. People with joint problems awaiting joint replacement surgery.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Obesity UK feel it should be ensured that equality of access to this treatment for members of the BAME community is essential.
Other issues	
13. Are there any other issues that you would like the committee to consider?	We would like the committee to consider the use of this treatment for people who have weight regain after bariatric surgery,

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • Overall approval for the introduction of a better drug treatment for people living with obesity • Ensuring access to treatment is equitable across the country • Drug treatments work best as part of a full multi-disciplinary care team package • Care packages including this treatment should last long enough for people to get the most from treatment. •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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Evidence Review Group Report commissioned by the NIHR Systematic Reviews Programme on behalf of NICE

Semaglutide for managing overweight and obesity

ERRATUM

Post factual accuracy check version with corrections and updated confidentiality marking

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Declared competing interests of the authors and advisors

The authors and their advisors report none.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Karen Pickett critically appraised the clinical effectiveness systematic review, drafted the report, project managed the review and is the project guarantor; Geoff Frampton critically appraised the clinical effectiveness systematic review, critically appraised the indirect treatment comparison, and drafted the report; Neelam

Kalita critically appraised the economic evaluation, and drafted the report; David Alexander Scott critically appraised the indirect treatment comparison, and drafted the report; Emma Maund critically appraised the clinical effectiveness systematic review, and drafted the report; Jo Lord critically appraised the economic evaluation, and drafted the report.

[redacted]

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LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AE	Adverse event
AIC	Academic in confidence
BMI	Body mass index
BNF	British National Formulary
CI	Confidence interval
CIC	Commercial in confidence
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CVD	Cardiovascular disease
DSU	Decision Support Unit
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
ERG	Evidence Review Group
FAS	Full analysis set
FPG	fasting plasma glucose
GI	Gastrointestinal
HbA1c	Haemoglobin A1c
HDL	High density lipoprotein
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IBT	Intensive behavioural therapy
IPD	Individual patient level data

ITC	Indirect treatment comparison
ITT	Intent to treat
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trials Version
KOL	Key opinion leader
MI	Myocardial infarction
mITT	Modified intent to treat
NGT	Normal glucose tolerance
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
OSA	Obstructive sleep apnoea
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
QS	Quality standard
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SF-36	Short Form-36
SLR	Systematic literature review
SmPC	Summary of product characteristics
SWMS	Specialist weight management services
T2D	Type 2 diabetes
TA	Technology appraisal
TLR	Targeted literature review
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

Here, and throughout our report, we refer to semaglutide 2.4 mg/week in combination with a lifestyle intervention (including increased physical activity and a reduced-calorie diet) as 'semaglutide 2.4 mg' and placebo in combination with a lifestyle intervention (including increased physical activity and a reduced-calorie diet) as 'diet and physical activity'. We refer to liraglutide 3.0 mg in combination with a reduced-calorie diet and increased physical activity as 'liraglutide 3.0 mg'.

1.1 Overview of the ERG's key issues

Table 1 Summary of key issues

Issue number	Summary of issue	Report sections
1	Decision problem target population	2.2.3 and 2.3
2	Exclusion of orlistat as a comparator	2.2.1 and 2.3
3	Exclusion of the STEP 2 trial from the CS	3.2.1
4	Exclusion of the STEP 3 trial from the CS	3.2.1
5	The ITC results are not used in the economic model	3.4.3
6	Treatment stopping rule	4.2.6
7	Assumption that all patients with non-diabetic hyperglycaemia develop type 2 diabetes after an initial cardiovascular (CVD) event	4.2.2
8	Differences in how intercurrent events are recorded across trials may impact imputation	3.4.1
9	Results from the completed STEP 5 and STEP 8 trials are expected this year	3.2.1 and 3.2.1.3

10	Treatment duration and retreatment	2.2.2 and 4.2.2.1

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are:

- The company assumes that all patients develop type 2 diabetes after an initial CVD event, whereas the ERG does not agree with this assumption.
- The ERG assumes a different natural weight increase for the population.
- The ERG prefers to include the STEP 3 trial, which the company excluded.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Table 2 reports the base case results for semaglutide 2.4 mg versus diet and physical activity in the population with a BMI ≥ 30 and at least one co-morbidity. The incremental cost effectiveness ratio (ICER) for semaglutide vs diet and physical activity is [redacted] per QALY. Table 3 reports the base case results for semaglutide 2.4 mg versus diet and physical activity and liraglutide 3.0 mg. Semaglutide 2.4 mg is [redacted] compared to liraglutide 3.0 mg [redacted]

Table 2 Company base-case results for semaglutide 2.4 mg versus diet and physical activity (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Diet and physical activity	[redacted]	17.924	15.269				
Semaglutide 2.4 mg	[redacted]	17.957	15.361	[redacted]	0.034	0.092	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.							

Source: Reproduced from CS Table 52

Table 3 Subgroup results for semaglutide 2.4 mg versus liraglutide 3.0mg (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Diet and physical activity	[redacted]	17.288	14.311				
Liraglutide 3.0 mg	[redacted]	17.331	14.401	[redacted]	0.043	0.090	[redacted]
Semaglutide 2.4 mg	[redacted]	17.349	14.444	[redacted]	0.018	0.043	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

Source: Reproduced from CS Table 57

The model results were most sensitive to the starting BMI.

1.3 The decision problem: summary of the ERG's key issues

Issue 1 Decision problem target population

Report section	2.2.3 and 2.3
Description of issue and why the ERG has identified it as important	The company has partly focused in their decision problem on a sub-population of the population specified in the NICE scope and draft marketing authorisation: people with a BMI ≥ 30 with at least one comorbidity (the 'target subgroup'). While we consider the focus on this subgroup is acceptable, we understand that semaglutide 2.4 mg will likely be used primarily within tier 3 services. If it is most likely to be used in this context, the NICE criteria for eligibility for bariatric surgery may more suitably define the target population (BMI ≥ 35 with at least one co-morbidity or ≥ 40 with or without comorbidities, unless new onset diabetes, in which case BMI ≥ 30, or lower for people of Asian family origin).[1] We acknowledge that NICE quality standard (QS) 127 states that adults with a BMI of ≥ 30 mg/kg^2 who have not had successful outcomes in tier 2 may be referred to tier 3, but we understand that few people with a BMI of 30 to 35 are currently treated in tier 3. An analysis of the cost-effectiveness for the bariatric surgery-eligible subgroup may be appropriate and informative.
What alternative approach has the ERG suggested?	To include a scenario analysis for this subgroup to illustrate cost-effectiveness in this population.
What is the expected effect on the cost-effectiveness estimates?	We have not been able to run a scenario analysis for this proposed subgroup, as to do this we would need to know the mean starting BMI for the starting cohort for the group from the STEP 1 trial. We have run a scenario analysis for a mean starting BMI of 42.5 (which models the cost-effectiveness for people with a BMI between 40 to 45). This resulted in more favourable ICERs for semaglutide 2.4 mg in comparison to

	physical activity and diet than when lower mean starting BMI values were used. A mean starting BMI of 42.5 may approximate that likely to be seen in our suggested subgroup. If that is the case, we expect that focusing on the subgroup is likely to result in lower ICERs for semaglutide 2.4 mg.
What additional evidence or analyses might help to resolve this key issue?	Provision of an illustrative cost-effectiveness scenario analysis for the bariatric surgery-eligible subgroup. Discussion with clinical experts about the company's positioning of semaglutide 2.4 mg in the care pathway and the clinical relevance of the company's target population, the bariatric surgery-eligible subgroup and the STEP 1 trial full analysis set population, will help resolve uncertainties about the positioning of semaglutide 2.4 mg in the care pathway and which population is most suitable for decision making.

Issue 2 Exclusion of orlistat as a comparator

Report section	2.2.1 and 2.3
Description of issue and why the ERG has identified it as important	The company have excluded orlistat as a comparator from their decision problem, as it is not widely used. We agree with the company's decision. However, as orlistat is included in the NICE scope as a comparator, this may require further consideration.
What alternative approach has the ERG suggested?	We have not suggested an alternative approach, as we agree with the company's exclusion of orlistat.
What is the expected effect on the cost-effectiveness estimates?	It is unknown what effect this might have on the cost-effectiveness estimates, as this comparator has not been included in the CS.
What additional evidence or analyses might help to resolve this key issue?	Through discussion with clinical experts about the relevance of this comparator and whether or not experts consider the company's exclusion of it from the decision problem is reasonable.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 3 Exclusion of the STEP 2 trial from the CS

Report section	3.2.1
Description of issue and why the ERG has identified it as important	The STEP 2[2] trial meets the NICE scope, but the company has not included data from it in their submission. The trial compared the efficacy of semaglutide 2.4mg to placebo, both as adjuncts to a lifestyle intervention that included a reduced-calorie diet and increased physical activity, in people with a BMI ≥ 27 kg/m^2 (overweight) or BMI ≥ 30 kg/m^2 (obese) with at least one weight-related co-morbidity who had glycated haemoglobin 7-10% (53-

	86 mmol/mol) and who had been diagnosed with type 2 diabetes. We are unclear, having only spoken to one clinical expert, whether people with type 2 diabetes might be treated with the 2.4 mg dose in practice for the purposes of weight loss and maintenance. Without inclusion of this trial, there is no data in the submission on the clinical and cost-effectiveness of semaglutide 2.4 mg for people with type 2 diabetes.
What alternative approach has the ERG suggested?	We have not suggested an alternative approach, but we believe further discussion about whether or not people with type 2 diabetes will be treated with the 2.4 mg dose of semaglutide 2.4 mg is warranted.
What is the expected effect on the cost-effectiveness estimates?	We note that the difference in percentage weight change between semaglutide 2.4 mg and placebo (diet and physical activity) was qualitatively smaller in the STEP 2 trial than the STEP 1 trial. This might indicate that ICER estimates for people who have type 2 diabetes may be higher than for those with other comorbidities.
What additional evidence or analyses might help to resolve this key issue?	Through discussion with clinical experts about whether or not the semaglutide 2.4 mg dose may be used in clinical practice for the purposes of weight loss and maintenance in people with type 2 diabetes. This will resolve whether or not the STEP 2 trial should have been included in the submission.

Issue 4 Exclusion of the STEP 3 trial from the CS

Report section	3.2.1
Description of issue and why the ERG has identified it as important	The STEP 3[3] trial meets the NICE scope and we believe data from it should have been included in the submission. The trial compared the efficacy of semaglutide 2.4mg to placebo, with both interventions administered as an adjunct to intensive behavioural therapy as part of a lifestyle intervention which included a reduced-calorie diet and increased physical activity. The trial included people with a BMI of ≥ 27 kg/m^2 (overweight) or BMI of ≥ 30 kg/m^2 (obese) with at least one weight-related co-morbidity. The company argue that IBT is not standard clinical practice in the UK. We suggest that in clinical practice, standard management is variable and so it is unlikely that a trial intervention will fully reflect clinical practice. Exclusion of this trial means that not all relevant data on the clinical effectiveness of semaglutide 2.4 mg has been included in the submission.
What alternative approach has the ERG suggested?	We suggest that the STEP 3 trial should have been included in the company's systematic literature review.
What is the expected effect on the cost-effectiveness estimates?	In the STEP 3 trial, the difference in percentage change in weight from baseline between semaglutide 2.4 mg and placebo (diet and physical activity) was qualitatively smaller than in the STEP 1 trial. As such, the trial may provide a more conservative estimate of the effectiveness of semaglutide 2.4 mg, which could potentially increase the ICERs.
What additional evidence or	Provision of scenario analyses that use both the STEP 1 trial and STEP 3 trial data to compare the cost-effectiveness of

analyses might help to resolve this key issue?	semaglutide 2.4 mg with diet and physical activity, and to compare the cost-effectiveness of semaglutide 2.4 mg with liraglutide 3.0 mg.

Issue 5 The ITC results are not used in the economic model

Report section	3.4.3
Description of issue and why the ERG has identified it as important	The unadjusted or adjusted ITC results are not used to inform the economic model. Instead, a separate calculation was performed. The mean changes from baseline from the STEP 1 trial product estimand are used directly in the economic model (CS Table 21), whilst for liraglutide 3.0 mg an odds ratio from SCALE 1839 was applied to the placebo and diet and physical activity arm from STEP 1 to give the adjusted estimates for liraglutide 3.0 mg (CS Table 23). This calculation is unclear to the ERG. It is also unclear why the unadjusted ITC could not have been used in the economic model, negating the need for this ad hoc calculation. The Company note that the ITC was "not able to produce adjusted estimates for efficacy in responders (further details are provided in Appendix D)" (CS section B.3.3.1.3). However, the ERG was unable to find any reference to this in Appendix D.
What alternative approach has the ERG suggested?	We suggest including the ITC results in the economic model.
What is the expected effect on the cost-effectiveness estimates?	The relative treatment effect values currently used in the economic model are more favourable for semaglutide 2.4 mg compared to placebo (diet and physical activity) or liraglutide 3.0 mg than the values from the ITC would be. For example, the mean weight change from baseline at 1 year used in the model is -18.47% for semaglutide 2.4 mg, -2.44% for placebo plus diet and physical activity (CS Table 21) and -10.42% for liraglutide 3.0 mg (CS Table 23). This gives higher differences in favour of semaglutide 2.4 mg (-16% vs placebo plus diet and physical activity, -8% vs liraglutide 3.0 mg) than the ITC (-12% vs placebo plus diet and physical activity, -6% vs liraglutide 3.0 mg) (ITC report Table 5). Utilising the ITC results in the economic model may therefore increase the ICERs.
What additional evidence or analyses might help to resolve this key issue?	We suggest the company should include the ITC results in the economic model. If this is not possible, they should provide a clear rationale as to why. The calculation currently used to generate the liraglutide 3.0 mg estimates used in the model should also be explained.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 6 Treatment stopping rule

Report section	4.2.6
Description of issue and why the ERG has identified it as important	The company has included a stopping rule for semaglutide 2.4 mg, whereby non-responders, i.e. people who have not lost at least 5% of their initial body weight after six months of taking the maintenance dose, would discontinue treatment. The ERG notes that a stopping rule was not included within the STEP 1 clinical trial. The CS states that it is unclear whether the marketing authorisation will include a stopping rule for semaglutide 2.4 mg (CS B3.2.3.1).
What alternative approach has the ERG suggested?	The ERG has not suggested an alternative approach; however, we feel that due to the relatively large impact of this issue on model results that it warrants further discussion.
What is the expected effect on the cost-effectiveness estimates?	The CS reports an analysis where there is no stopping rule and the treatment policy estimand has been used (CS Table 56). In this scenario, the ICER increases from [redacted] per QALY to [redacted] per QALY for semaglutide 2.4 mg vs diet and physical activity.
What additional evidence or analyses might help to resolve this key issue?	Through discussion with clinical experts and publication of the marketing authorisation for semaglutide 2.4 mg.

Issue 7 Assumption that all patients with non-diabetic hyperglycaemia develop type 2 diabetes after initial CVD event

Report section	4.2.2
Description of issue and why the ERG has identified it as important	Patients with non-diabetic hyperglycaemia are assumed to develop type 2 diabetes (T2D) following an initial CVD event. Clinical advice to the ERG suggests that it is not possible to assume that all patients will develop T2D after a CVD event. Whilst this assumption was previously used in TA664, we note that the NICE committee had reservations about this assumption and there was no good evidence to determine the proportion of people who develop type 2 diabetes after a CVD event.
What alternative approach has the ERG suggested?	The ERG prefers to assume that patients with non-diabetic hyperglycaemia would not develop T2D after an initial CVD event.
What is the expected effect on the cost-effectiveness estimates?	The CS reports an analysis where patients with non-diabetic hyperglycaemia do not develop T2D immediately after a CVD event (CS Table 56). In this scenario, the ICER increases from [redacted] per QALY to [redacted] per QALY for semaglutide 2.4 mg vs diet and physical activity.

What additional evidence or analyses might help to resolve this key issue?	Through discussion with clinical experts on the validity of this assumption

The following issues identified by the ERG in the cost-effectiveness evidence where we disagree with the company (summarised in Table 48). These are not considered key issues as they only have a relatively small impact on the model results:

- Mean increase of weight by 0.106kg/m^2 (0.296 kg) per year
- Maximum age of weight increase, 66 years
- Weight decreases after attaining the maximum age for weight increase
- Cost of microvascular complication £398
- Cost of sleep apnoea £274

1.6 Other key issues: summary of the ERG's view

Issue 8 Differences in how intercurrent events are recorded across trials may impact imputation

Report section	3.4.1
Description of issue and why the ERG has identified it as important	Differences in how or whether intercurrent events are recorded between trials raise questions about how they can be consistently handled in the missing data imputation used to calculate the trial product estimand. In SCALE 1839 the company noted there was "no notion of anti-obesity rescue medication" (clarification response A16) nor any distinction between treatment discontinuation and trial withdrawal. It is unclear to the ERG whether this means rescue medications were not recorded or not permitted.
What alternative approach has the ERG suggested?	The ERG prefer the treatment policy estimate since this uses less imputation but we realise this may not be appropriate for the economic model.
What is the expected effect on the cost-effectiveness estimates?	It is unclear whether this could have impacted the economic model nor any direction of effect.
What additional evidence or analyses might help to resolve this key issue?	It is unclear how this issue could be resolved.

Issue 9 Results from the completed STEP 5 and STEP 8 trials are expected this year

Report section	3.2.1 and 3.2.1.3
Description of issue and why the ERG has identified it as important	The company has not included data from the completed STEP 5 and STEP 8 trials in the CS, as they stated data from the trials were not available in time for this submission. The STEP 8 trial was a head-to-head comparison of semaglutide 2.4 mg with liraglutide 3.0 mg and also with placebo (all as adjuncts to a lifestyle intervention) in people living with obesity (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2) with at least one weight-related comorbidity. Currently, there are no other head-to-head trials available comparing semaglutide 2.4 mg and liraglutide 3.0 mg. In the CS, the company compares the clinical efficacy of the drugs in the liraglutide-eligible subgroup using an indirect treatment comparison. The STEP 5 trial compares semaglutide 2.4 mg against placebo (both as adjuncts to a lifestyle intervention) in people living with obesity (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2) with ≥ 1 weight-related comorbidity. The drugs are administered during a 104-week period. The STEP 1 trial used a 68-week treatment period, so the STEP 5 trial will provide evidence of efficacy when it is used over a longer period. Both trials are relevant to the NICE scope for this appraisal, albeit it is unclear how many people in the STEP 8 trial might be included in a 'liraglutide-eligible' subgroup. Data from these trials could potentially have a bearing on conclusions about the clinical effectiveness and cost-effectiveness of semaglutide 2.4 mg.
What alternative approach has the ERG suggested?	None. The company states the results of these studies are not currently available and the clinical study reports are expected in Q4 (STEP 8) and Q3 (STEP 5) this year.
What is the expected effect on the cost-effectiveness estimates?	The results of these studies are not available, so it is unknown what impact they may have on the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Provision of the results of these trials when they are available.

Issue 10 Treatment duration and retreatment

Report section	2.2.2 and 4.2.2.1
Description of issue and why the	In their economic model, the company has assumed that people are treated with semaglutide 2.4 mg for a maximum of two years and do not receive retreatment with pharmacotherapy. We agree that these assumptions are reasonable. We note,

ERG has identified it as important	however, from a discussion with our clinical expert that there are uncertainties about whether people would receive a single course of treatment and if it could be repeated. We also note that in TA664[4] the committee discussed that limiting treatment to two years was not ideal for a long-term condition such as obesity, although the committee accepted this assumption. Treatment duration and retreatment are therefore areas of uncertainty.
What alternative approach has the ERG suggested?	We have not suggested an alternative approach, but we believe further discussion about length of treatment and whether people might be retreated is warranted.
What is the expected effect on the cost-effectiveness estimates?	The ERG conducted a scenario with the ERG's preferred assumptions using a treatment duration for 3 years. In this scenario the ICER for semaglutide 2.4mg increased from [redacted] per QALY to [redacted] per QALY.
What additional evidence or analyses might help to resolve this key issue?	Through discussion with clinical experts about length of treatment and whether it is possible that some people may be retreated with semaglutide or receive treatment beyond 2 years.

1.7 Summary of ERG's preferred assumptions and resulting ICER

Based on the ERG critique of the company's model (discussed in section 4), we have identified the following aspects of the company base case with which we disagree. Our preferred assumptions are the following:

- **Patients with non-diabetic hyperglycaemia transitioning to T2D after CVD events**: We assume that these patients do not transition to T2D after CVD events.
- **Natural weight increase:** We use a natural weight increase of 0.296 kg per year.
- **Age at weight increase:** We assume weight does not increase after age 66 years.
- **Weight increase after age 66 years:** We assume that individuals lose 0.296 kg per year after age 66 years.
- **Annual cost of microvascular complications:** We use an annual cost of £398.
- **Annual cost of sleep apnoea:** We use an annual cost of £274.

Table 4 reports the ERG preferred base case results for semaglutide 2.4 mg versus diet and physical activity in the population with a BMI ≥ 30 and at least one co-morbidity. The incremental cost-effectiveness ratio (ICER) for semaglutide 2.4mg vs diet and physical activity is [redacted] per QALY. Table 5 reports the results for semaglutide 2.4mg versus diet and physical activity and liraglutide 3.0 mg for the liraglutide-eligible subgroup. Semaglutide 2.4mg is [redacted] compared to liraglutide 3.0mg [redacted]

Table 4 ERG's preferred model assumptions

Assumption	Treatments	Total costs	Total QALYs	ICER (£/QALY)
Company base-case	Diet & physical activity	[redacted]	15.269	
	Semaglutide 2.4mg	[redacted]	15.361	[redacted]
Patients with pre-diabetes do not transition to T2D after CVD events	Diet & physical activity	[redacted]	15.329	
	Semaglutide 2.4mg	[redacted]	15.419	[redacted]
+ Mean increase of weight by 0.296 kg per year	Diet & physical activity	[redacted]	15.484	
	Semaglutide 2.4mg	[redacted]	15.582	[redacted]
+ Mean decrease in weight after age 66 years: 0.296 kg per year	Diet & physical activity	[redacted]	15.540	
	Semaglutide 2.4mg	[redacted]	15.634	[redacted]
+ Age at which weight no longer increases: 66 years	Diet & physical activity	[redacted]	15.562	
	Semaglutide 2.4mg	[redacted]	15.656	[redacted]
+ Annual cost of microvascular complication, £398	Diet & physical activity	[redacted]	15.562	
	Semaglutide 2.4mg	[redacted]	15.656	[redacted]
+ Annual cost of sleep apnoea, £274	Diet & physical activity	[redacted]	15.562	
	Semaglutide 2.4mg	[redacted]	15.656	[redacted]
ERG base case	Diet & physical activity	[redacted]	15.562	
	Semaglutide 2.4mg	[redacted]	15.656	[redacted]

Table 5 ERG's preferred model assumptions- liraglutide eligible subgroup

Assumption	Treatments	Total costs	Total QALYs	Incremental ICER (£/QALY)
Company base-case	Diet & physical activity	[redacted]	14.311	
	Liraglutide 3.0mg	[redacted]	14.401	[redacted]
	Semaglutide 2.4mg	[redacted]	14.444	[redacted]
Patients with pre-diabetes do not transition to T2D after CVD events	Diet & physical activity	[redacted]	14.419	
	Liraglutide 3.0mg	[redacted]	14.505	[redacted]
	Semaglutide 2.4mg	[redacted]	14.548	[redacted]
+ Mean increase of weight by 0.296 kg per year	Diet & physical activity	[redacted]	14.562	
	Liraglutide 3.0mg	[redacted]	14.648	[redacted]
	Semaglutide 2.4mg	[redacted]	14.690	[redacted]
+ Mean decrease in weight after age 66 years: 0.296 kg per year	Diet & physical activity	[redacted]	14.642	
	Liraglutide 3.0mg	[redacted]	14.727	[redacted]
	Semaglutide 2.4mg	[redacted]	14.770	[redacted]
+ Age at which weight no longer increases: 66 years	Diet & physical activity	[redacted]	14.659	
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]
+ Annual cost of microvascular complication, £398	Diet & physical activity	[redacted]	14.659	
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]
+ Annual cost of sleep apnoea, £274	Diet & physical activity	[redacted]	14.659	
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]
ERG base case	Diet & physical activity	[redacted]	14.659	
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Novo Nordisk on the clinical effectiveness and cost-effectiveness of semaglutide 2.4 mg for managing overweight and obesity. It identifies the strengths and weakness of the CS. A clinical expert was consulted to advise the evidence review group (ERG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 5th August 2021. A response from the company via NICE was received by the ERG on 26th August 2021 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on overweight and obesity

The CS (section B.1.3) provides a clear and accurate overview of obesity (BMI ≥ 30 kg/m^2), including its definition, causes, prevalence, effect on health-related quality of life (HRQoL) and the morbidity and mortality associated with it. The CS outlines some of the weight-related co-morbidities people living with obesity may experience, including prediabetes, type 2 diabetes and cardiovascular disease, acknowledging that it is not an exhaustive list due to the range of complications that exist. The company do not mention eating disorders, such as binge eating (which our clinical expert states are common in this population) and the process by which mental health co-morbidities should be addressed. The ERG's clinical expert stated that screening people for mental health issues, such as depression and eating disorders, is central to their work in weight services. They see many people with eating disorders and the majority of people living with obesity who they treat have a history of depression (up to 70%). Our expert stated that whilst there may be regional variation, other services also report a high incidence of depression and anxiety. The PHQ depression screening tool was used in the pivotal semalutide trial[5] and people were only included in the trial if they had a score of < 15 on this (see CS Table 4) (scores of 15 and 20 represent moderately severe and severe depression, respectively[6]). Our expert commented that it is unclear how this should influence clinicians' prescribing in clinical practice when using semaglutide.

The CS provides information about how weight losses of 5%, 5-10% and ≥15% can positively impact co-morbidities. We understand from our clinical expert that many people achieve a weight loss of 5% in one year when under the treatment of weight management

services. For example, one evaluation of a weight management service found that 60.0% of the participants included achieved a 5% or more weight loss at 12 months.[7]

The company's description of the health condition does not include information about overweight. As discussed in section 2.3, the company have focused their decision problem on people with obesity (BMI ≥ 30 kg/m^2) who have at least one co-morbidity and have not included people living with overweight. We consider that this is acceptable (see section 2.2.3 for further discussion about this).

CS section B.1.3.4 provides information on current service provision in the NHS in England for overweight and obesity. As outlined in the CS, care is provided through four weight management tiers (tiers 1 to 4). These are shown in CS Figure 1. The CS states the tiers are a guide only and definitions can vary locally.

The CS accurately indicates that lifestyle intervention to change people's diet and physical activity is a central part of treating obesity. The CS does not provide information about the form this typically takes in practice. We understand from our clinical expert that in tier 2 services are typically managed in primary care, although provision can vary regionally. Tier 2 lifestyle interventions may take the form of, for example, referral to an exercise scheme or commercial weight management programme. People need to have taken part in tier 2 interventions before attending tier 3 services (although tier 2 services are not universally nationally available). Our expert stated that in tier 3 services, run by multidisciplinary teams, standard management of obesity involves a full assessment of an individual's mental health (including eating disorders), co-morbidities and readiness to engage with treatment. Some patients may need mental health services/treatments first as mental health issues can be a barrier to engagement with lifestyle interventions. This is one example of a service and our expert stated that there is some variation in local pathways. After assessments of suitability and readiness of engagement in lifestyle interventions, weight loss interventions are primarily delivered by dietetic services. These usually consist of group sessions with some behavioural intervention (such as motivational interviewing). They address healthy eating, having a balanced diet and eating behaviour. Emotional eating and psychological barriers such as dealing with setbacks are discussed in these sessions, which are supervised by a psychologist. People typically take part in one or two group sessions a month over six months (typically six to nine sessions over this period). Some patients are also referred for physical activity intervention.

CS section 1.3.4.1 suggests the main aim of tier 3 is to achieve clinically meaningful weight loss, and that another part of its aim is to prepare some selected patients for bariatric surgery. Expert advice to the ERG is that a key purpose of tier 3 services is to assess people's readiness for weight loss (bariatric) surgery and to prepare them for this. If people chose to undergo surgery, surgical referral takes place around six months to a year into treatment. Our clinical expert stated that around 25% to 30% of people treated in tier 3 services progress to weight loss surgery. Prior to surgical referral, prebariatric patients may require additional psychological assessment to ensure they have adequate coping mechanisms to undergo the surgical route.

The CS accurately outlines that the only pharmacological treatments currently available for people with obesity are orlistat and liraglutide 3.0 mg. The CS states NICE recommends liraglutide 3.0 mg for people with a BMI of ≥ 35 kg/m^2 who have non-diabetic hyperglycaemia and a high risk of cardiovascular disease.[4] We additionally note that liraglutide 3.0 mg is recommended by NICE for members of some minority ethnic groups at a lower BMI threshold of 32.5 kg/m^2. The recommended population in the NICE guidance is a subpopulation of the people in whom liraglutide 3.0 mg is recommended in its marketing authorisation.[8] It is indicated for people with a BMI of ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) with at least one weight-related comorbidity or people with a BMI ≥ 30 kg/m^2. The company (Novo Nordisk) markets liraglutide 3.0 mg.

The company outline that orlistat is not widely used, and that many people decide not to use it or stop taking it due to undesirable side effects. We understand from our clinical expert that orlistat has undesirable gastrointestinal side effects and that it is not used in specialised services but is still prescribed by some GPs. We also note that clinical experts informed the liraglutide 3.0 mg, TA664 appraisal committee that many people decide not to take orlistat or cease treatment with it due to side effects.[4] In the liraglutide 3.0 mg appraisal, the experts stated that most people who are referred to tier 3 services will have previously been treated with orlistat. The committee concluded that orlistat was not an alternative treatment to liraglutide 3.0 mg.[4]

2.2.2 Background information on semaglutide

The company describe semaglutide in CS section B.1.2. Semaglutide is a GLP-1 analogue that has effects on areas of the brain involved in regulation of food intake. The maintenance dose for treating overweight and obesity is 2.4 mg/week and the company refer to the intervention specifically as 'semaglutide 2.4 mg' throughout the CS (they indicate that they

do this to distinguish it from its diabetes indication). The CS states the semaglutide 2.4 mg marketing authorisation application was submitted to the EMA on 18 December 2020, with the result expected on 22 January 2022 (CS Table 2). The company provided the draft summary of product characteristics (SmPC) with the submission (CS Appendix C).

In line with the draft SmPC, the CS states that semaglutide 2.4 mg is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and maintenance, in adults with a BMI of:

- ≥30 kg/m^2 (obesity), or
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) who have at least one weight-related co-morbidity.

It is self-administered once-weekly by subcutaneous injection. The dose is escalated over a 16-week period to reach a maintenance dose of 2.4 mg once weekly.

The company state in the CS that it is unclear whether the marketing authorisation will include a stopping rule for semaglutide 2.4 mg. As outlined in CS section B.1.1, the draft SmPC states that if people have not lost at least 5% of their initial body weight after six months of taking the maintenance dose, a decision should be made about whether or not to continue treatment, based on the risks and benefits to the individual person. The company applied this stopping rule to semaglutide 2.4 mg treatment in their CS base case economic model, and also conducted a scenario analysis in which no stopping rule was applied (CS section B.3.3.4.1). In both the base case and scenario analysis, the comparator's (liraglutide's) stopping rule was applied. The ERG's clinical expert commented that there is also a question about whether to continue semaglutide 2.4 mg prescriptions for people who do not engage in lifestyle intervention and discontinue their engagement in tier 3 services.

The draft SmPC does not state for how long people should be treated with semaglutide 2.4 mg. In the company's CS economic model base case, they have applied a maximum treatment duration of two years (CS section B.3.3.4). The company state treatment is typically provided in weight management services for two years and that this assumption is in line with the liraglutide, TA664 appraisal.[4] We note that in TA664, the committee discussed that limiting treatment to two years was not ideal for a long-term condition such as obesity. They noted the clinical need to reduce weight and then maintain weight loss. In the end, the committee accepted a treatment duration of two years for a single course of treatment and decided that the assumption was reasonable in the context of tier 3 weight management services.[4] Based on the committee's conclusion in TA664 and advice from our

clinical expert, we consider it is also a reasonable assumption for treatment with semaglutide 2.4 mg. Our clinical expert noted, however, that it is currently unclear what would happen regarding pharmacological treatment with liraglutide 3.0 mg or semaglutide 2.4 mg after two years. For example, it is unclear if people should receive a single course of treatment with semaglutide 2.4 mg or whether, and when, it could be repeated.

2.2.3 The position of semaglutide 2.4 mg in the treatment pathway

The company detail their proposed positioning of semaglutide 2.4 mg in the clinical care pathway in CS section B.1.3.4. The company appear to suggest (we found the text to be unclear) that semaglutide 2.4 mg would be used in tier 3 and 4 multidisciplinary team weight assessment and management clinics, where pharmacotherapy can be provided under the guidance of such a team. The company refer to these settings as specialist weight management services (SWMS). The CS states there is a need for additional pharmacological treatments within SWMS. It states orlistat is rarely used and there is an unmet clinical need for people who would not be eligible for liraglutide 3.0 mg (which is recommended by NICE for people with a BMI ≥ 35 kg/m^2 [or ≥ 32.5 kg/m^2 for members of some minority ethnic groups] who have non-diabetic hyperglycaemia and a high risk of cardiovascular disease). They state semaglutide 2.4 mg should be used as an adjunct to a reduced-calorie diet and increased physical activity in people with a BMI of ≥ 30 mg/kg^2 and at least one weight-related comorbidity. The company suggest this population is anticipated to benefit the most within SWMS from pharmacological treatment.

As noted in section 2.3, the population of people with a BMI of ≥ 30 mg/kg^2 and at least one weight-related comorbidity in whom the company proposes semaglutide 2.4 mg will be used is narrower than the draft marketing authorisation indication and the population defined in the NICE scope. The proposed population also does not fully match the population we understand to be eligible for treatment within SWMS. We note from published reports and our clinical expert that SWMS are usually provided for people with a BMI of ≥ 35 with co-morbidities or of ≥ 40 with or without comorbidities.[9 10] The company mention that NICE quality standard (QS) 127 states that adults with a BMI of ≥ 30 mg/kg^2 who have not had successful outcomes from tier 2 services should be offered a discussion about alternative weight management interventions, including referral to SWMS (i.e. tier 3). We acknowledge that NICE QS 127[11] states this, but we understand from our clinical expert that people with a BMI of 30 to 35 are currently only treated in tier 3 services if they have new onset diabetes and are preparing for weight loss surgery, which is in line with the NICE pathway for referral of people suitable for bariatric surgery into tier 3 and onwards.[1] Our clinical expert stated that

if semaglutide 2.4 mg were to be recommended for people with a BMI of ≥ 30 with other co-morbidities, this would expand the patient population for tier 3 services, which would result in additional costs.

The company have also not explicitly explained why they have not positioned semaglutide 2.4 mg as a tier 2 pharmacological intervention, as well as one that can be used in tiers 3 and 4. Clinical expert advice to the ERG is that lifestyle interventions would need to be deliverable when using semaglutide 2.4 mg and specialist assessments made. Given that the company expect semaglutide 2.4 mg to be used in SWMS, based on clinical expert advice we consider it is reasonable in this context for the company not to have positioned semaglutide 2.4 mg as an intervention for people with a BMI between 27 and 30 who have at least one weight-related co-morbidity (part of the population of interest specified in the NICE scope and draft SmPC), as they are not treated in tier 3 services.

Overall, we suggest that the company's positioning of semaglutide 2.4 mg as a treatment specifically for people with a BMI ≥ 30 who have at last one weight-related comorbidity is acceptable, if it is to be used in the NHS only within SWMS. It should be acknowledged, though, that most people who are seen in these services will have a BMI of ≥ 35 – few people currently treated within these services will have a BMI of 30 to 35.

We note that whilst the company have set out that there is an unmet need for other pharmacological treatment options within SWMS, they have not outlined in the CS how treatment with semaglutide 2.4 mg may potentially fit with weight loss surgery in the clinical pathway. It is unclear from the CS when weight loss surgery would be offered to people taking semaglutide 2.4 mg. Our clinical expert indicated that pharmacological treatment options becoming available may mean that some people may wish to try weight loss drugs before having surgery. This may make it difficult to assess people's readiness for surgery, as it will be less clear how prepared people are to change lifestyle behaviours than when treated by standard management alone. Clinical expert advice to the ERG is that, in their opinion, semaglutide 2.4 mg should be positioned for people who are eligible for but will not consider surgery or who are not fit enough to undergo it, as well as for those with a BMI of 30 to 35 with comorbidities. If people take semaglutide 2.4 mg and then decide they wish to have surgery after all, a reasonable aim could be that their weight remains stable for six months after ceasing the maintenance semaglutide 2.4 mg dose before being referred for surgery. Our expert noted that a time interval between completing pharmacological therapy with a GLP-1 analogue and commencing the surgical pathway would aid pre-bariatric surgery assessment.

ERG conclusion

The company's positioning of semaglutide 2.4 mg as a treatment specifically for people with a BMI ≥ 30 who have at last one weight-related comorbidity is acceptable, if it is intended that semaglutide 2.4 mg will only be provided in the NHS in tier 3 and 4 services (we note it is most likely to be used within tier 3). We note, though, that this would expand the patient population typically treated in tier 3 services to include more people with a BMI of 30 to 35. Currently few people with a BMI in this range are treated within tier 3 services. The company's assumption that maximum treatment duration with semaglutide 2.4 mg would be two years appears reasonable, given the precedence set by the liraglutide appraisal (TA 664),[4] but it is unclear if people would receive a single course of treatment or whether, and when, it could be repeated.

2.3 Critique of the company's definition of the decision problem

Table 6 compares the company's decision problem to the final scope for this appraisal issued by NICE. The ERG consider that the decision problem adheres to the NICE scope with the following exceptions:

- **Population**:
    - The population specified in the NICE scope and the anticipated marketing authorisation (provided by the company in CS Appendix C) is adults who have a BMI of ≥30 kg/m^2 (obese) or a BMI of ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity. The company have focused their submission on a narrower population: namely, adults who have a BMI of ≥30 kg/m^2 and at least one weight-related comorbidity.
    - We believe it is acceptable to focus on this subgroup, as it is still within the draft SmPC indication, the NICE scope and, as we concluded in section 2.2.3, it to some extent reflects the people who are typically treated within SWMS (where the company appears to be positioning semaglutide 2.4 mg in the clinical pathway). We understand, however, that few people with a BMI of 30 to 35 are currently treated in SWMS. Focusing on this subgroup is inclusive of these few, but overall, we consider data on the clinical efficacy of semaglutide 2.4 mg in people who have a BMI of ≥ 35 might be more representative of the clinical effectiveness likely to be achieved in practice. In this regard, the NICE criteria for eligibility for bariatric surgery may more suitably define the target

population (BMI ≥ 35 with at least one co-morbidity or ≥ 40 with or without comorbidities, unless new onset diabetes, in which case BMI ≥ 30, or lower for people of Asian family origin).[1] We understand from our clinical expert that this is the patient group that is typically treated in tier 3. Although, we acknowledge that trial data is only available for people who had co-morbidities.

  - Regarding comorbidities, efficacy evidence for people with diabetes as a comorbidity is not included (we discuss this further in section 3.2.1). Clinical expert advice to the ERG is that they expect semaglutide 2.4 mg to be used to treat overweight and obesity in people who have type 2 diabetes as a comorbidity. The company state in CS Table 14 that this population is not relevant to the submission, but they do not explain why. NICE and the ERG sought clarification from the company about the reason for this. In clarification response A1, the company explained that semaglutide 2.4 mg could potentially be used in people living with type 2 diabetes, but clinical expert advice suggested that treatment for this group would typically follow a diabetes treatment pathway where semaglutide is indicated at a lower dose. We understand from our clinical expert that, in this context, semaglutide would be used without specialist lifestyle interventions as offered in tier 3 services. The expert stated that diabetes specialists would need to refer people to obesity services for lifestyle intervention if semaglutide 2.4 mg were to be used for the management of weight at the highest dose. We suggest that, overall, it is unclear if semaglutide 2.4 mg in combination with lifestyle intervention might be used for weight loss or management in some people with type 2 diabetes. We have only been able to obtain one expert's opinion about this. It is therefore unclear if data relating to this population should have been included in the CS.

- **Comparators.** The company have excluded orlistat as a comparator, as it is not widely used. As we outlined in section 2.2.1, we understand that orlistat is not typically used in tier 3 services. We therefore consider it is reasonable for the company to have excluded it as a comparator, given the company appears to be positioning semaglutide 2.4 mg as a treatment option within SWMS.

Table 6 Summary of the decision problem

Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
Population			
Adults who have a BMI of: • ≥30 kg/m^2 (obese) or • ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity	Adults who have a BMI of ≥ 30 kg/m^2 (obese) in the presence of at least one weight-related comorbidity	The company state that it is anticipated that this subgroup of people will benefit the most from pharmacological treatment within SWMS. They state that there is an unmet clinical need for this patient group, because patients have limited treatment options and many do not meet the criteria for pharmacological treatment with liraglutide 3.0 mg.	The company's focus on this subgroup is acceptable, given the company's positioning of semaglutide 2.4 mg as a treatment option within SWMS – see our discussion about this in this section and section 2.2.3.
Intervention			
Semaglutide	Semaglutide 2.4 mg	The company outline that semaglutide 2.4 mg (used as an adjunct to diet and physical activity) is an approved treatment for adults with type 2 diabetes mellitus, at doses of 0.25 mg, 0.5 mg and 1 mg. Semaglutide 2.4 mg is the specific maintenance dose for treatment of obesity.	The intervention reflects the NICE scope and is appropriate. We note the draft SmPC states that semaglutide 2.4 mg is indicated as an adjunct to a reduced-calorie diet and increased physical activity when used for weight management in people living with overweight in the presence of at least one weight-related comorbidity or living with obesity.

Comparators			
• Standard management without semaglutide (including a reduced calorie diet and increased physical activity) • Liraglutide (for the population for whom liraglutide is recommended in technology appraisal 664: patients with a BMI ≥ 35 mg/kg^2 with non-diabetic hyperglycaemia and high risk of cardiovascular disease) • Orlistat (prescription dose)	• Standard management without semaglutide (including a reduced calorie diet and increased physical activity) • Liraglutide 3.0 mg (for the population for whom liraglutide is recommended in TA664: patients with a BMI ≥ 35 mg/kg^2 with prediabetes and high cardiovascular risk)	The company state orlistat is not a relevant comparator. They suggest it is not widely used and that many people decide not to use it or stop taking it due to undesirable side effects, citing discussions held during the TA494[12] and TA664[4] appraisals and trends in prescription data.	The company's inclusion of standard management and liraglutide 3.0 mg as comparators matches the NICE scope. The company have accurately outlined the population in whom liraglutide 3.0 mg is recommended, but we additionally note that liraglutide is recommended for members of some minority ethnic groups at a lower BMI threshold of 32.5 kg/m^2.[4] We agree that orlistat is not a relevant comparator and therefore the company's exclusion of it from the decision problem is appropriate.
Outcomes			
• BMI • weight loss • waist circumference • incidence of type 2 diabetes • glycaemic status • cardiovascular events • mortality • adverse effects of treatment • health-related quality of life.	As per scope	Not applicable	Decision problem matches the NICE scope.
Economic analysis			
See CS Table 1 – text not replicated here to reduce table size	Same as NICE scope	Not applicable	The CS economic analysis has been conducted in line with the reference case stipulations outlined in the scope. The economic model base case outcomes and costs are estimated over a lifetime horizon of 40 years. Semaglutide 2.4 mg does not currently have an agreed patient access scheme (PAS)

			(discussions are ongoing with NHS England). Liraglutide 3.0 mg has a commercial access agreement and the company have provided the results of cost-effectiveness analyses with this applied.
Subgroups			
None	The submission will also address the subset of patients who are eligible to receive treatment with liraglutide 3.0 mg (patients with a BMI ≥ 35 mg/kg^2 with prediabetes and high CVD risk) following its approval in TA664.	Not applicable (specified in final scope under comparators)	Inclusion of this subgroup is appropriate.
Special considerations including issues related to equity or equality			
None	Company stated 'N/A'. We note that the company outline equality considerations in CS section B.1.4, including BMI threshold variations between different ethnicities related to their risks of developing health conditions and for intervening to prevent type 2 diabetes.	Not applicable	Clinical expert advice to the ERG is that BMI thresholds for intervention should be adjusted to take into account ethnicity, as was done in NICE's liraglutide 3.0 mg guidance.[4] Neither we nor our expert identified any other equity or equality issues.

Source: adapted version of CS Table 1

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company report three systematic literature reviews in the CS:

1. a clinical effectiveness evidence review that identified semaglutide 2.4 mg studies for inclusion in the CS and semaglutide 2.4 mg and/or liraglutide 3.0 mg studies for inclusion in an indirect treatment comparison (ITC) the company included in the CS,
2. a review of cost-effectiveness/cost-utility, costs and healthcare resource studies, and,
3. a review of HRQoL studies. A brief critique of the company's review of clinical effectiveness studies is provided in Table 7 below.

Across these reviews, we identified some concerns about the company's approach to searching for literature, study selection and the processes of data extraction and risk of bias assessment, which we detail below.

3.1.1 Searches

The CS reports three systematic searches:

- Clinical effectiveness studies (CS Appendix D.1)
- Cost-effectiveness studies, costs and resource use (CS Appendices G and I)
- HRQoL studies (CS Appendix H)

Each search had some limitations to the sources searched and search terms used (see Table 7). However, overall, the ERG consider the searches to be broadly fit for purpose, and it is unlikely that key studies have been missed. Clinical experts advising the ERG were not aware of any relevant studies that have not been identified. As the company did not search trial registries, the ERG searched ClinicalTrials.gov and the EU Clinical Trials Register for ongoing or recently completed studies of semaglutide 2.4 mg and/or liraglutide 3.0 mg. The results are discussed in section 3.2.1.3.

3.1.2 Study selection

For the cost-effectiveness and HRQoL reviews, one reviewer conducted study selection for each review, with a second reviewer checking only in cases of uncertainty (CS Appendices D.1.2, G.4 and H.3). Ideally dual reviewer screening would have been preferable to reduce the risk of errors or bias being introduced.

CS Appendix D Table 5 provides a list of studies excluded during full text screening from the clinical effectiveness review. The company did not provide the full reference citations for

these or PDFs of the references. These were requested in clarification question A2. After considering clarification response A2 we believe the reasons for excluding clinical effectiveness studies listed in CS Appendix Table 5 are appropriate.

For the clinical effectiveness review the company excluded a trial of semaglutide 2.4 mg/week which included people with type 2 diabetes who were living with overweight r obesity (STEP 2) because they considered people with type 2 diabetes would not be managed under a weight management pathway. It is unclear whether or not this trial should have been included in the CS (see further discussion in section 2.3 and section 3.2.1). The company identified another trial (STEP 3) as being eligible for inclusion in the review but excluded the trial post hoc, arguing that intensive behavioural therapy (IBT) support for diet and physical activity in the trial was not reflective of NHS practice. As explained in section 3.2.1 below, the ERG disagree with the company and believe the STEP 3 trial should have been included in the review. The ERG have no concerns with study selection in the other reviews.

3.1.3 Data extraction and risk of bias assessment

The company do not report the number of reviewers involved in the data extraction process for the HRQoL and cost-effectiveness reviews; and they do not report the number of reviewers involved in the risk of bias assessments for any of the reviews.

3.1.4 Summary of the ERG's critique

Overall, despite our concerns listed here, the company's evidence reviews are broadly fit for purpose and appear to have identified all relevant studies. However, the ERG disagree with the company's exclusion of the STEP 3 trial.

Table 7 ERG appraisal of systematic review methods

Systematic review components and processes	ERG response	ERG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The PICOS is defined in CS Appendix D.1.2 table 4 for the eligibility criteria.
Were appropriate sources of literature searched?	Yes but sources could have been	The company's searches included Medline, Embase, Cochrane Central

	more comprehensive	Register of Controlled Trials, HTA Database, Database of Abstracts of Reviews of Effectiveness, but not clinical trial registries, websites, or reference lists of relevant papers or systematic reviews.
Was the time period of the searches appropriate?	Yes	Databases were searched from inception, and conferences for the past 3-4 years. Searches were updated 26th April 2021.
Were appropriate search terms used and combined correctly?	Partly	Search strategies in CS Appendix Tables 1 to 3 contain no search terms for the comparator (diet and physical activity). This is likely inconsequential as relevant RCTs would be captured by the drug search terms. However, synonyms for overweight and obesity are inadequate, and some relevant subject headings for population and comparator are missing, meaning that some relevant studies might have been missed.
(1) Were inclusion and exclusion criteria specified? (2) If so, were these criteria appropriate and relevant to the decision problem?	(1) Yes (2) Partly	(1) CS Appendix Table 4 lists the eligibility criteria. (2) BMI and HRQoL are specified outcomes in the decision problem but are not listed in the eligibility criteria. As far as the ERG are aware this did not result in the exclusion of any RCTs that would have otherwise been eligible (relevant RCTs would be captured on other PICO terms).
Were study selection criteria applied by two or more reviewers independently?	Yes	CS Appendix D.1.2 Both title and abstract screening and full text assessment were

		undertaken by two independent reviewers. Disagreements were resolved through discussion, or arbitration with a third independent reviewer when necessary.
Was data extraction performed by two or more reviewers independently?	Yes	CS Appendix D.1.2 Data extraction was performed by a single reviewer and checked by a second reviewer. Discrepancies between the reviewer and the person checking were resolved by a third independent reviewer
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	CS Appendix Table 9 Study quality was assessed using seven criteria. No reference is provided in the CS, but this appears to be the CRD assessment tool.[13]
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Unclear	The CS does not provide details of who performed the risk of bias assessment.
Is sufficient detail on the individual studies presented?	Partly	Yes for the semaglutide 2.4 mg trial (CS section B.2.3) but limited information given for the liraglutide 3.0 mg trial used in the indirect treatment comparison (ITC) (CS Appendix D.1.3.1). Some baseline characteristics were missing for the STEP 1 trial (clarification responses A6 & A11). Only aggregate baseline characteristics (pooled intervention and diet and physical activity arms) reported for liraglutide-eligible population in the ITC analysis (section 3.3.3.1).

If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	An ITC was undertaken, and we consider the methodology followed by the company is appropriate (see section 3.4).

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The company's systematic literature review identified two potentially relevant phase 3 trials evaluating the efficacy of semaglutide 2.4 mg: STEP 1 and STEP 3 (CS section B.2.2). Both trials were conducted as part of the company's STEP clinical trial programme and were used to support the draft marketing authorisation. Both were sponsored by the company (Novo Nordisk). The company additionally provided information about 15 other ongoing or completed studies carried out as part of the STEP programme in CS section B.2.11, including reasons why the studies were excluded from the submission.

STEP 1 was an RCT comparing the efficacy of semaglutide 2.4 mg to placebo, both as adjuncts to a lifestyle intervention, in adults living with obesity (BMI ≥ 30 kg/m^2) or with overweight (BMI ≥ 27 kg/m^2) with at least one weight-related comorbidity. The trial did not include people with diabetes or HbA1c ≥ 6.5%. The company included STEP 1 in the CS review and use data from it in the economic model. The company provided the trial paper[5] and clinical study report[14] with the submission.

Throughout this report, we refer to semaglutide 2.4 mg in combination with the lifestyle intervention as 'semaglutide 2.4 mg' and placebo in combination with the lifestyle intervention as 'diet and physical activity'.

The design of the STEP 3 trial was the same as the STEP 1 trial, except that semaglutide 2.4 mg and placebo were given as adjuncts to intensive behavioural therapy (IBT). The trial was conducted solely in the United States.[3] The company state in CS section B.2.2 that IBT is not standard clinical practice in the UK, and, for this reason, they have excluded it from the CS review.

We have outlined what constituted IBT in the STEP 3 trial in Table 8, which also compares this intervention to standard management in the England and the lifestyle intervention used in the STEP 1 trial. In both the STEP 1 and STEP 3 trials, participants received individual counselling or IBT sessions. The ERG's clinical expert's advice indicates that neither of the interventions used in the STEP 1 and STEP 3 trials fully matches standard management in clinical practice. Clinical expert advice is that one-to-one counselling is not realistic in practice in England and people typically attend dietetics group sessions. We suggest the frequency of sessions offered in the STEP 1 trial more closely aligns to clinical practice in England than that in the STEP 3 trial. Clinical expert advice to the ERG is also that people's diet and activity levels, and therefore adherence, cannot be as closely monitored in practice as they were in the STEP 1 trial (in which participants recorded these daily in a diary or a smartphone application or other tools, which were then reviewed during counselling sessions).

We suggest that overall the standard management used in the STEP 1 trial more closely reflects practice in England than the IBT intervention used in STEP 3. Clinical expert advice to the ERG is that it is unlikely an NHS service could fund and provide the level of intervention delivered in the STEP 3 trial. However, whilst acknowledging this, we do not agree with the company's post-hoc exclusion of the STEP 3 trial from their systematic literature review. We believe the company should have included data from this trial in their submission. The trial met the inclusion criteria for the review and in our opinion, the comparator reflects the comparator specified in the NICE scope, in the sense that it was management of overweight and obesity without semaglutide that included a reduced calorie diet and increased physical activity. We suggest that standard management clinical practice is variable in England and so it is unlikely that an intervention used in a trial will fully reflect clinical practice. We provide selected results from the STEP 3 trial in section 3.6.

Table 8 Description of the standard management approaches used in clinical practice in England, the STEP 1 trial and the STEP 3 trial

Clinical practice [a]	STEP 1 [5]	STEP 3 [3]
People usually take part in one or two dietetics group sessions over 6 months (typically 6 to 9 sessions). They address healthy eating, having a balanced diet and eating behaviour,	Individual counselling sessions every 4 weeks during the 68-week intervention period of trial. The aim of these sessions was to help participants adhere to a reduced calorie	30 individual intensive behavioural therapy sessions with a dietician during the 68-week trial. The dietician gave the participants directions in physical activity, diet and

and include some behavioural intervention (motivational interviewing). One-to-one counselling is not realistic in practice, although some patients may receive one-to-one support for eating disorders. Some patients are also referred for physical activity intervention. Diet and physical activity are not recorded, so it is not possible to know how well people are adhering to this.	diet and increased physical activity. The aim of the diet element was to have a 500-kcal deficit per day compared to energy expenditure at baseline. Participants were encouraged to do 150 minutes of physical activity per week. Physical activity and diet were recorded daily and this record was reviewed during the counselling sessions.	behavioural strategies. Participants also had a hypo-caloric diet (1200-1800 kcal/d, depending on body weight at randomisation, after an initial 8-week low-calorie diet [1000-1200 kcal/d provided as meal replacements]) and were instructed to do 100 minutes of physical activity per week, titrated to 200 min/week during the trial.
[a] Our description of clinical practice here is based on information from our clinical expert about the form this typically takes.		

We have reviewed the other 15 ongoing or completed trials conducted as part of the STEP programme, which were outlined in CS section B.2.11. We agree with the company's exclusion of all them (the majority because they are ongoing or because the company stated data were not available in time for inclusion in the submission) except we are unclear whether or not the STEP 2 trial should have been included – we discuss this further in the next paragraph. As we discuss in section 3.2.1.3, we also note that the completed phase 3 trials STEP 5 and STEP 8 are relevant to the NICE scope and the decision problem, but the company stated data were not yet available for inclusion in the CS. The clinical trial reports for these studies are expected this year. We suggest data from these trials could potentially have a bearing on conclusions about the clinical effectiveness and cost-effectiveness of semaglutide 2.4 mg.

The STEP 2 trial evaluated the efficacy of semaglutide 2.4mg, 1.0 mg or placebo (all delivered alongside a lifestyle intervention, which involved a reduced-calories diet and increased physical activity) for weight management in people who were either overweight or obese (BMI ≥ 27 mg/m^2), had glycated haemoglobin 7-10% (53-86 mmol/mol) and who had been diagnosed with type 2 diabetes.[2] The STEP 2 trial semaglutide 2.4 mg and placebo arms meet the NICE scope and the decision problem. The company, however, state in CS Table 14 that the trial has not been included in the CS as the population – adults with type 2 diabetes – is not relevant to the submission. As outlined in section 2.3, in their clarification

response A1, the company explained that while semaglutide 2.4 mg might be used to treat weight in people with type 2 diabetes, clinical experts consulted by the company suggested that treatment for these patients would typically follow a diabetes treatment pathway where semaglutide would be used at a lower dose. We are unclear, having only spoken to one clinical expert, whether people with type 2 diabetes might be treated with the 2.4 mg dose in practice for the purposes of weight loss and maintenance. The company's clarification response and our clinical expert indicate this is possible. We suggest it is uncertain if the STEP 2 trial should have been included in the review, and further discussion with clinical experts during the appraisal process may help resolve this uncertainty.

We otherwise believe it is likely that all relevant studies of semaglutide 2.4 mg have been included in the CS (see section 3.2.1.3 for details about the ERG's additional searches for studies).

The trials identified for and included in the ITC are detailed in section 3.3.2.1.

3.2.1.1 Study characteristics

The company summarise the characteristics and methodology of the STEP 1 trial in CS section B.2.3.1. We have summarised the key characteristics of the trial in Table 14 and the outcomes assessed in Table 12 (in section 3.2.3 of this report), indicating which outcomes informed the CS economic model. The trial meets the decision problem and systematic literature review inclusion criteria. Semaglutide 2.4 mg was administered in line with the anticipated SmPC.

To be included in the trial, participants had to have one of the following weight-related comorbidities: hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease. Clinical expert advice to the ERG is that these comorbidities are reflective of those seen in patients in practice who are likely to be treated with semaglutide 2.4 mg.

Table 9 STEP 1 trial characteristics

Trial characteristic	Description
Study design	Phase 3 double-bind, placebo-controlled RCT
Number and location of centres	129 sites in 16 countries, including 10 in the UK
Participant numbers	1,961 adults

Study population	Adults with obesity (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least one weight-related comorbidity, and without diabetes or HbA1c ≥ 6.5%
Comorbidities – eligibility criteria	To be included in the trial, participants with overweight had to have at least one of these weight-related co-morbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease
Intervention	Semaglutide 2.4 mg once weekly given as an adjunct to a lifestyle intervention[a]. Dose was titrated from a starting dose of 0.25 mg every four weeks to reach the maintenance dose.
Comparator	Matching placebo given as an adjunct to a lifestyle intervention [a].
Treatment and trial duration	Participants received semaglutide for 68 weeks, including 16 weeks of dose titration to reach the maintenance dose of 2.4 mg and a 52-week period of receiving the maintenance dose. A subset of participants then took part in a 52-week off-treatment extension phase where they did not receive semaglutide 2.4 mg or placebo nor the lifestyle intervention.
Stopping rule	A treatment non-responder stopping rule does not appear to have been used in the STEP 1 trial, but is applied in the CS economic model base case (see section 4.2.2).
Source: CS Table 3, CS Table 4, CS section B.2.3.1, STEP 1 trial paper,[5] CS Figure 3. [a] Details of the lifestyle intervention are given in our Table 8	

The company provide clinical efficacy results from the STEP 1 trial in the CS for the following population and subgroups:

- The whole trial population (full analysis set): people with a BMI ≥ 30 or ≥ 27 who have at least one of comorbidity (hypertension, dyslipidaemia, obstructive sleep apnoea [OSA] or cardiovascular disease [CVD])
- Subgroup: people with a BMI ≥ 30 plus at least one weight-related comorbidity
- Subgroup: people with a BMI ≥ 35 with non-diabetic hyperglycaemia and high CVD risk (this population matches the group of people for whom NICE recommends liraglutide 3.0 mg for the treatment of obesity in TA 664)[4]

3.2.1.2 Patients' baseline characteristics

The company present baseline characteristics for the STEP 1 trial full analysis set and the BMI ≥ 30 kg/m^2 plus ≥ one comorbidity subgroup in CS Table 5 and comment on these in CS

section B.2.3.2. In CS Table 5, race and BMI category characteristics were not reported for the subgroup, while they were provided for the full analysis set. The company provided this information in clarification response A6, attachment E. We have presented selected baseline characteristics in Table 10. Baseline characteristics for the BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high CVD risk subgroup are provided in CS Table 11 and discussed in section 3.3.3.1 of this report.

We agree with the company that baseline characteristics were well balanced between the semaglutide 2.4 mg and diet and physical activity arms of the trial for both the BMI ≥ 30 kg/m^2 plus ≥ one comorbidity subgroup and full analysis set. We also agree with their conclusion that characteristics were similar across the full analysis set and the subgroup, with some expected higher rates of some disease characteristics in the subgroup, given their higher BMI.

The company state that clinicians considered the baseline characteristics of the trial reflected the UK obesity population, including the people who would typically be referred to SWMS. We understand from our clinical expert that in tier 3 services, people with higher BMIs than those in the STEP 1 trial are typically seen in practice and thus people have more comorbidities.

Table 10 Selected baseline characteristics of participants in the STEP 1 trial

	Trial population			
	BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity (n = 1,470)		**Full analysis set (n = 1,961)**	
	Semaglutide 2.4 mg (n = 974)	**Diet and physical activity (n = 496)**	**Semaglutide 2.4 mg (n = 1,306)**	**Diet and physical activity (n = 655)**
Mean age, years (range)	[redacted]	[redacted]	46 (18–86)	47 (18–82)
Female, n (%)	696 (71.5)	375 (75.6)	955 (73.1)	498 (76.0)
Race, n (%)				
White	768 (78.9)	394 (79.4)	973 (74.5)	499 (76.2)
Asian	92 (9.4)	43 (8.7)	181 (13.9)	80 (12.2)
Black or African American	56 (5.7)	31 (6.3)	72 (5.5)	39 (6.0)
Other*	58 (6.0)	28 (5.6)	80 (6.1)	37 (5.6)
Hispanic or Latino ethnic group, n (%)	108 (11.1)	67 (13.5)	150 (11.5)	86 (13.1)
BMI				

	Trial population			
	BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity (n = 1,470)		Full analysis set (n = 1,961)	
	Semaglutide 2.4 mg (n = 974)	Diet and physical activity (n = 496)	Semaglutide 2.4 mg (n = 1,306)	Diet and physical activity (n = 655)
Mean BMI, kg/m^2 (SD)	[redacted]	[redacted]	37.8 (6.7)	38.0 (6.5)
< 30 kg/m^2, n (%)	0	0	81 (6.2)	36 (5.5)
≥ 30 – < 35 kg/m^2, n (%)	319 (32.8)	158 (31.9)	436 (33.4)	207 (31.6)
≥ 35 – < 40 kg/m^2, n (%)	339 (34.8)	168 (33.9)	406 (31.1)	208 (31.8)
≥ 40 kg/m^2, n (%)	316 (32.4)	170 (34.3)	383 (29.3)	204 (31.1)
Patients with at least one comorbidity, n (%)	974 (100)	496 (100)	1048 (80.2)	532 (81.2)
Non-diabetic hyperglycaemia[a]	518 (53.2)	253 (51.0)	550 (42.1)	271 (41.4)

Source: this is a shortened version of CS Table 5, with additional information from the company's clarification response A6, attachment E.
[a] defined as haemoglobin A1c (HbA1c) levels in the range 6.0–6.4%, or fasting plasma glucose (FPG) levels in the range 5.5–6.9 mmol/L.

3.2.1.3 Ongoing studies

As discussed in section 3.2.1, the company provide a list of completed and ongoing studies on semaglutide 2.4 mg that are part of their STEP research programme. Among the studies listed are the completed phase 3 trials STEP 8 and STEP 5 (summarised in Table 11). The STEP 8 trial was a head-to-head comparison of semaglutide 2.4 mg with liraglutide 3.0 mg in people living with obesity or people with overweight who have at least one weight-related comorbidity. The company state that data from these trials were not available in time for this submission. Both the STEP 5 and STEP 8 trials are relevant to the decision problem for this appraisal, albeit it is unclear how many people in the STEP 8 trial might be included in a 'liraglutide-eligible' subgroup as per the NICE scope and decision problem.

Table 11 Details of the completed STEP 8 and STEP 5 trials

Trial (trial identifier), number of participants enrolled [a]	Population	Intervention and comparator(s)	Date clinical trial reports expected [b]
STEP 8 (NCT04074161) N = 338 participants	People living with obesity (BMI ≥ 30 kg/m^2) or people living with overweight (BMI ≥ 27 kg/m^2) with ≥ 1 weight-related comorbidity	• Semaglutide 2.4 mg • Liraglutide 3.0 mg • Placebo All administered during a 68-week treatment period and as an adjunct to a reduced-calorie diet and increased physical activity	Q4 2021
STEP 5 (NCT03693430) N = 304 participants	People living with obesity (BMI ≥ 30 kg/m^2) or people living with overweight (BMI ≥ 27 kg/m^2) with ≥ 1 weight-related comorbidity	• Semaglutide 2.4 mg • Placebo Both administered during a 104-week treatment period and as an adjunct to a reduced-calorie diet and increased physical activity	Q3 2021

Source: Table 14 and ClinicalTrials.gov

[a] The stated number of participants enrolled here is extracted from the number recorded under 'actual enrollment' on the ClinicalTrials.gov trial record.

[b] As stated in CS Table 14.

The company do not appear to have searched for other ongoing studies. For example, they have not searched trial registries. Given this gap in their searches, the ERG searched clinicaltrials.gov and the EU Clinical Trials Register for ongoing or recently completed trials of both semaglutide 2.4 mg and liraglutide 3.0 mg to check if any studies of either drug were missing from the submission and to check if there were any ongoing studies from which results may potentially be available soon. We did not identify any completed semaglutide 2.4 mg trials that had not been mentioned by the company in their submission or any additional

ongoing studies due to complete within the next 12 months. We did not identify any completed trials of liraglutide 3.0 mg or any that are due to complete within the next 12 months that could potentially inform the company's ITC.

ERG conclusion on included studies

The company have included one trial of semaglutide 2.4 mg in their systematic literature review; the STEP 1 trial. Baseline characteristics were well balanced between treatment arms. We understand from our clinical expert that in tier 3 services, people with higher BMIs than those in the STEP 1 trial are typically seen and thus people have more comorbidities. In this sense, we suggest the trial is not fully representative of the people who will likely be treated with semaglutide 2.4 mg in practice. We believe the company's exclusion of the STEP 3 trial was inappropriate and that data from the trial should have been included in the CS. It is uncertain whether or not semaglutide 2.4 mg will be used for weight loss and maintenance in people with type 2 diabetes in practice and therefore whether or not the STEP 2 trial should have been included in the submission. We consider the completed STEP 5 and STEP 8 trials are relevant to the appraisal (albeit it is unclear how many people in the STEP 8 trial might be included in a 'liraglutide-eligible' subgroup) but note that data from the trials are not yet available.

3.2.2 Risk of bias assessment

The company's quality (i.e. risk of bias) assessment for the STEP 1 trial is presented in CS Appendix D.3, based on Centre for Reviews and Dissemination (CRD) criteria.[13] The ERG assessed the STEP 1 trial using the same criteria, and the company's and ERG's judgements are provided in Appendix 1. The company and ERG conclude that STEP 1 was a well-conducted trial of good methodological quality and in general the ERG agree with the company's risk of bias judgements. However, the ERG are unclear about the risk of attrition bias in the company's analysis of STEP 1 (further details are provided in section 3.3.5).

In summary, the STEP 1 trial was generally well-conducted, but the ERG are unclear about the risk of attrition bias which introduces some uncertainty (of unknown magnitude and direction) to the outcome estimates reported in the CS.

3.2.3 Outcomes assessment

The efficacy outcomes assessed in the STEP 1 trial are summarised in CS Tables 3 and 4 and in Table 12 here. The company have included all the outcomes specified in the decision

problem and NICE scope in the CS, except for the incidence of type 2 diabetes (only reported at baseline) and cardiovascular events. Cardiovascular events do not appear to have been measured in the STEP 1 trial. The ITC report (section 3.2) states that there were few cases of type 2 diabetes to conduct statistical analyses.[15] In the economic model, longer-term benefit of weight loss on the incidence of diabetes and cardiovascular events is estimated using risk equations (CS section B.3.3.7). The company present changes in systolic blood pressure and fasting lipid profile from baseline as additional outcomes in the CS. These are not specified in the decision problem or the NICE scope, but are included in the CS as they inform the economic model. Efficacy results are presented as changes from baseline to week 68 (i.e. the end of the maintenance treatment period of the trial) or as status at week 68.

Table 12 Primary and other outcomes assessed in the STEP 1 trial

Outcome type	Outcomes assessed
Primary outcomes	• **Percentage change in body weight** from baseline to 68 weeks (the CS economic model uses the results of this outcome from the trial as efficacy inputs at months 4, 7 and 10, and years 1 and 2 in the economic model) Checking reviewer, please see CS section B.3.3.1.1. • Proportion of participants achieving a baseline body weight loss of ≥ 5% at 68 weeks
Other outcomes	• BMI (specifically, BMI change from baseline) • Weight loss (specifically: change in body weight in kg; and weight change ≥ 10%, ≥ 15% and ≥ 20%) • Incidence of type 2 diabetes (only reported at baseline) • Waist circumference • Glycaemic status (specifically: HbA1c (%) change from baseline; and, **percentage of participants with prediabetes or non-diabetic hyperglycaemia at baseline who achieved normoglycaemia** at 68 weeks) • Mortality • Adverse effects of treatment • Health-related quality of life • **Change in systolic blood pressure from baseline** • **Change in fasting lipid profile from baseline (specifically, HDL and total cholesterol)**
Source: CS Tables 3 and 4 Notes: Bold text shows the outcomes used in the economic model.	

The outcomes measured are appropriate and clinically relevant. Clinical expert advice to the ERG is that the key clinical outcomes for assessing the efficacy of treatment for obesity are weight loss, HbA1c and psychological and physical wellbeing. We suggest the latter would

be captured in the HRQoL outcomes included in the CS. One of the primary outcomes was the proportion of participants who achieved a ≥ 5% weight loss. This outcome is clinically meaningful. As referenced in the CS, a NICE clinical knowledge summary for the management of obesity[16] suggests a clinical aim of an overall reduction of 5-10% in body weight or higher in a person living with obesity. As we note in section 2.2.1, clinical expert advice to the ERG is that people typically achieve a weight loss of 5% in practice with the motivation of weight loss surgery and if they are able to engage with treatment.

The STEP 1 trial used the American Diabetes Association definition of prediabetes.[5] This defines prediabetes as an HbA1c level of 5.7 to 6.4% or FPG ≥ 5.6 mmol/L and ≤ 6.9 mmol/L, or two-hour post challenge (OGTT) FPG ≥ 7.8 mmol/L and ≤ 11.0 mmol/L. As outlined in CS section B.2.4.5, in the submission, the company have defined prediabetes in line with the definition of non-diabetic hyperglycaemia used in the NICE liraglutide appraisal (TA 664),[4] when presenting the achievement of normoglycaemia among participants who had non-diabetic hyperglycaemia at baseline in the STEP 1 trial for the FAS population, the target subgroup and the liraglutide-eligible subgroup. The CS states the TA 664 definition was an HbA1c level of 42 to 47 mmol/mol (6.0 to 6.4%) or a FPG level of 5.5 mmol/L. This is correct, but the upper bound FPG of 6.9 mmol/L[4] was missing from the definition in this section of the CS.

HRQoL was measured in the trial using the 36-Item Short Form Survey (SF-36) and the short form of Impact of Weight on Quality of Life-Lite for Clinical Trials (IWQOL-Lite-CT). The results of these measures were not used in the economic model, so we do not consider how these outcomes were measured further here. The model used published utility values (CS section B.3.4). We consider that the company's approach to estimating utility values is generally reasonable (see section 4.2.7).

ERG conclusion on outcomes assessment

The outcome measures included from the STEP 1 trial in the CS are appropriate and clinically relevant. No data are available from the trial on the longer-term outcomes of diabetes incidence and cardiovascular events. We have no concerns about how the outcomes were defined or measured.

3.2.4 Statistical methods of the included studies

3.2.4.1 Statistical procedures

The statistical procedures used in the STEP 1 trial are described in CS section B.2.4. The ERG have no concerns about the sample size calculation, the statistical approaches used for analysing each outcome or the methods used to impute missing data. The trial appears to be adequately powered.

3.2.4.2 Analysis sets

The company define the full analysis (FAS) and safety analysis sets in CS section B.2.4.1. The STEP 1 efficacy analysis used the FAS, which the company stated included all randomised participants in line with the intention-to-treat principal. The company defines two post-hoc subgroup analyses in section B.2.4.2.

The company provide clinical efficacy results in the submission for three trial populations:

- the whole trial population (FAS) (n = 1,961),
- the two post-hoc subgroups:
    - BMI ≥ 30 plus at least one weight-related comorbidity (n = 1,470), and
    - BMI ≥ 35 with non-diabetic hyperglycaemia and high CVD risk subgroup (n = 421).

The CS economic model base case, however, does not use the BMI ≥ 30 plus at least one weight-related comorbidity subgroup data and uses the FAS results instead for this population. The efficacy results from the subgroup are used in a company scenario analysis (see section 5.2.3).

3.2.4.3 Treatment estimands

Efficacy results are provided in the CS for two treatment estimands, shown in Table 13 and explained in CS section B.2.4.4. The company details what the term 'estimand' means in section B.1.2.4.4. Briefly, they are a way of handling intercurrent events that occur during a trial that might affect how the results are interpreted, such as a participant starting other medications (e.g. a rescue medication, a medication that the protocol prohibits or a subsequent therapy line).[17 18] A treatment policy estimand provides the treatment effect in the target population regardless of participants' discontinuation of the trial drug or use of other medications. The trial product estimand shows the treatment effect in the target population in the hypothetical situation that participants had continued using the trial medication and had not discontinued.[18] Therefore, the treatment policy estimand only

imputes data for participants who withdrew from the trial, while the trial product imputes data for participants using rescue medication, discontinuing the trial product, and withdrawing from the trial.

In the STEP 1 trial, the estimands were used to take into account the intercurrent events of participants starting other anti-obesity therapies (i.e. weight management drugs or weight loss surgery) and premature discontinuation.

Table 13 STEP 1 trial treatment estimands

Estimand (number of FAS participants included)	Definition
Treatment policy estimand (n = 1,961)	Estimated the effect of semaglutide 2.4 mg relative to diet and physical activity for all randomised participants regardless of starting other therapies, treatment adherence or premature discontinuation.
Hypothetical (trial product) estimand (n = 1,961)	Estimated the effect of semaglutide 2.4 mg relative to diet and physical activity for all randomised participants, assuming they remained on treatment and did not start other anti-obesity therapies (i.e. this estimand excludes the effects of other anti-obesity therapies and any effects after treatment discontinuation)
Source: CS section B.2.4.4.	

The treatment policy estimand was used for regulatory approval. We believe, and clinical advice to the ERG suggests, that the treatment policy estimand results are the most relevant to clinical practice. The trial product estimand was used in the economic model alongside a treatment stopping rule. The effects of other anti-obesity therapies are estimated in the model using published literature. The ERG considers the use of the trial product estimand to incorporate the effect of treatment discontinuation to be a reasonable and appropriate approach (section 4.2.6.1). The company have conducted a scenario analysis with no stopping rule applied, which uses the treatment policy estimand (section 5.2.3).

The company do not compare baseline characteristics between the participants included in each of these estimands, so it is not possible to determine how the participants whose data generated the trial product estimands differed from or were similar to participants in the treatment policy estimand.

ERG comment on study statistical methods

We have not identified any issues with the statistical methods of the STEP 1 trial.

3.2.5 Efficacy results of the intervention studies

Here we provide the results of the outcomes from the STEP 1 trial that inform the economic model, namely:

- Percentage change in body weight
- Percentage of participants with prediabetes or non-diabetic hyperglycaemia at baseline who achieved normoglycaemia
- Change in systolic blood pressure
- Change in HDL and total cholesterol

See Appendix 2 of this report for the results of the following other outcomes measured in the STEP 1 trial: other weight loss outcomes, percentage of participants with a specified weight change from baseline, waist circumference change, incidence of type 2 diabetes (only reported at baseline and as a safety outcome), HbA_{1c} (%) change from baseline, and HRQoL.

3.2.5.1 Percentage change in weight from baseline at 68 weeks

Across the three populations and two estimands analysed, the percentage decrease in weight from baseline to 68 weeks ranged from 14.2 to 16.9 percentage points in the semaglutide 2.4 mg arm, and from 2.41 to 2.82 percentage points in the diet and physical activity arm (Table 14). The difference between trial arms was statistically significant for the FAS population (95% CIs exclude zero) but confidence intervals were not reported for the other analysis populations.

Table 14 Percentage change in weight from baseline at 68 weeks

Estimand (Data source)	Semaglutide 2.4 mg		Diet and physical activity		Difference (95% CI)
	Mean (SD[a]) change	N	Mean (SD[a]) change	N	
FAS (BMI≥30 or BMI≥27 plus ≥1 of hypertension, dyslipidaemia, OSA or CVD)					
Treatment policy (CSR 14.2.9)	-14.85 %-points	1306	-2.41 %-points	655	-12.44% (-13.37 to -11.51); p<0.0001

Trial product (CSR 14.2.20)	-16.86 %-points	1306	-2.44 %-points	655	-14.42 (-15.29 to -13.55); p<0.0001
Target subgroup (BMI ≥30 plus ≥1 weight-related comorbidity) (post hoc analysis)					
Treatment policy (CS B.2.7.1)	-14.8 %-points	974	-2.6 %-points	496	-12.2 [b]
Trial product (Appendix E.2)	-16.59 (8.85) %-points	974	-2.56 (8.99) %-points	496	-14.03 [b]
Liraglutide-eligible subgroup (BMI≥35 with non-diabetic hyperglycaemia and CVD risk) (post hoc analysis)					
Treatment policy (CS B.2.7.2)	-14.2 %-points	273	-2.8 %-points	148	-11.4 [b]
Trial product (Appendix E.2)	-15.89 (8.87) %-points	273	-2.82 (9.00) %-points	148	-13.07 [b]
FAS: full analysis set [a] SD reported for some analyses [b] Not reported; raw difference calculated by reviewer					

3.2.6 Glycaemic status

The proportion of patients with prediabetes or non-diabetic hyperglycaemia at baseline who achieved normoglycaemia at week 68 was clearly higher for the semaglutide 2.4 mg arm than the diet and physical activity arm (Table 15). NB this outcome was not reported for the trial product estimand. The proportion who achieved normoglycaemia informs the economic model (CS section B.3.3.1.2) although there is a discrepancy between the data used in the model (CS Table 22) and those reported from the STEP 1 trial.

Table 15 Percentage of participants with prediabetes or non-diabetic hyperglycaemia at baseline who achieved normoglycaemia at 68 weeks (treatment policy estimand)

Baseline population	Semaglutide 2.4 mg		Diet and physical activity		Difference
	%	N [a]	%	N [a]	
FAS (BMI≥30 or BMI≥27 plus ≥1 of hypertension, dyslipidaemia, OSA or CVD)					
Participants shifting from prediabetes to normo-glycaemic (trial publication)	84.1%	593	47.8%	263	36.3 [b]

Participants shifting from non-diabetic hyperglycaemia to normo-glycaemic (CS Table 10)	79.8%	550	39.1%	271	40.7 [b]
Target subgroup (BMI ≥30 plus ≥1 weight-related comorbidity) (post hoc analysis)					
Participants shifting from non-diabetic hyperglycaemia to normo-glycaemic	79.2%	518	20.0%	253	59.2 [b]
Liraglutide-eligible subgroup (BMI≥35 with non-diabetic hyperglycaemia and CVD risk) (post hoc analysis)					
Participants shifting from non-diabetic hyperglycaemia to normo-glycaemic (CS Table 10)	78.4%	273	36.5%	148	41.9 [b]

FAS: full analysis set

[a] The denominator is the number of patients with prediabetes or non-diabetic hyperglycaemia at baseline

[b] Not reported; raw difference calculated by reviewer

3.2.6.1 Systolic blood pressure

Across the analyses conducted, mean systolic blood pressure decreased from baseline to week 68 by 6.2 to 8.6 mmHg in the semaglutide 2.4 mg arm and by 1.0 to 2.2 mmHg in the diet and physical activity arm (Table 16). The difference between trial arms was statistically significant for the FAS population (95% CIs exclude zero) but confidence intervals were not reported for the other analysis populations. The company do not comment on the clinical significance of these changes in systolic blood pressure, which we note are relatively small.

Table 16 Systolic blood pressure change from baseline at 68 weeks

Estimand (Data source)	**Semaglutide 2.4 mg**		**Diet and physical activity**		**Difference (95% CI)**
	Mean (SD[a]) change	**N**	**Mean (SD[a]) change**	**N**	
FAS (BMI≥30 or BMI≥27 plus ≥1 of hypertension, dyslipidaemia, OSA or CVD)					
Treatment policy (CSR 14.2.87)	-6.16 mmHg	1306	-1.06 mmHg	655	-5.10 (-6.34 to -3.87); p<0.0001

Trial product (CSR 14.2.150)	-7.08	1306	-1.14	655	-5.93 (-7.19 to -4.68); p<0.0001
Target subgroup (BMI ≥30 plus ≥1 weight-related comorbidity) (post hoc analysis)					
Treatment policy (CS B.2.7.1)	-6.4 mmHg	974	-1.0 mmHg	496	-5.4 [b]
Trial product (Appendix E.2)	-7.25 (13.08) mmHg	974	-1.39 (13.50) mmHg	496	-5.86 [b]
Liraglutide-eligible subgroup (BMI≥35 with non-diabetic hyperglycaemia and CVD risk) (post hoc analysis)					
Treatment policy (CS B.2.7.2)	-7.7 mmHg	273	-1.6 mmHg	148	-6.1 [b]
Trial product (Appendix E.2)	-8.55 (13.06)	273	-2.23 (13.27)	148	-6.32 [b]
FAS: full analysis set [a] SD reported for some analyses [b] Not reported; raw difference calculated by reviewer					

3.2.6.2 Fasting HDL and total cholesterol

HDL cholesterol

The company do not consistently report the change in fasting HDL cholesterol from baseline to 68 weeks for all the subgroups and estimands analysed. Where reported, the data suggest that in the FAS population HDL cholesterol increased marginally from baseline up to week 68, slightly more so in the semaglutide 2.4 mg arm (Table 17). But the changes appear very small (<0.5 mg/dL, with ratios close to 1.0). The company do not comment on the clinical significance of these changes in HDL cholesterol, although they report that the difference between trial arms is statistically significant.

Table 17 Geometric mean fasting HDL cholesterol (mg/dL) ratio to baseline and mean change at 68 weeks

Estimand (Data source)	**Semaglutide 2.4 mg**		**Diet and physical activity**		**Ratio difference (95% CI)**
	Ratio (mean [SD] change [a])	**N**	**Ratio (mean [SD] change [a])**	**N**	
FAS (BMI≥30 or BMI≥27 plus ≥1 of hypertension, dyslipidaemia, OSA or CVD)					

Treatment policy (CSR 14.2.96) (CS B.2.6.5)	1.05 (0.04 mg/dL [a])	1306	1.01 (0.01 mg/dL [a])	655	1.04 (1.02 to 1.05); p<0.0001
Trial product (CSR 14.2.151; Appendix E.2)	1.05 (0.05 [0.16] mg/dL)	1306	1.02 (0.02 [0.17] mg/dL)	655	1.03 (1.02 to 1.05); p<0.0001
Target subgroup (BMI ≥30 plus ≥1 weight-related comorbidity) (post hoc analysis)					
Treatment policy (CS B.2.7.1)	1.0 [b] (0.0 mg/dL)	974	1.0 [b] (0.00 mg/dL)	496	1.0 [b]
Trial product (Appendix E.2)	NR (0.05 [0.16] mg/dL)	974	NR (0.02 [0.17] mg/dL)	496	NR
Liraglutide-eligible subgroup (BMI≥35 with non-diabetic hyperglycaemia and CVD risk) (post hoc analysis)					
Treatment policy (CS.B.2.7.2)	NR (0.1 mg/dL)	273	NR (0.0 mg/dL)	148	NR
Trial product (Appendix E.2)	NR (0.08 [0.16] mg/dL)	273	NR (0.02 [0.16] mg/dL)	148	NR

FAS: full analysis set; NR: not reported

[a] log scale; SD reported for some analyses

[b] Not reported; calculated by reviewer

Total cholesterol

The company do not consistently report the change in fasting total cholesterol from baseline to 68 weeks for all the subgroups and estimands analysed. Where reported, the data across the analyses conducted suggest that in the FAS population total cholesterol decreased marginally or remained stable from baseline up to week 68, changing by 0 to -0.04 mg/dL in the semaglutide 2.4 mg arm and with no change in the diet and physical activity arm (Table 58). The company do not comment on the clinical significance of these changes in HDL

cholesterol, although they report that the difference between trial arms is statistically significant.

Table 18 Geometric mean fasting total cholesterol (mg/dL) ratio to baseline and mean change at 68 weeks

Estimand (Data source)	Semaglutide 2.4 mg		Diet and physical activity		Ratio difference (95% CI)
	Ratio (mean [SD] change [a])	N	Ratio (mean [SD] change [a])	N	
FAS (BMI≥30 or BMI≥27 plus ≥1 of hypertension, dyslipidaemia, OSA or CVD)					
Treatment policy (CSR 14.2.96) (CS B.2.6.5)	0.97 (-0.04 mg/dL)	1306	1.00 (0.00 mg/dL)	655	0.97 (0.95 to 0.98); p<0.0001
Trial product (CSR 14.2.151; Appendix E.2)	0.96 (-0.04 [0.16] mg/dL)	1306	1.00 (0.00 [0.16] mg/dL)	655	0.96 (0.94 to 0.97)
Target subgroup (BMI ≥30 plus ≥1 weight-related comorbidity) (post hoc analysis)					
Treatment policy (CS B.2.7.1)	1.0 [c] (-0.0 mg/dL)	974	1.0 [c] (0.0 mg/dL)	496	1.0 [b]
Trial product (Appendix E.2)	NR (-0.04 [0.16] mg/dL)	974	NR (0.00 [0.16] mg/dL)	496	NR
Liraglutide-eligible subgroup (BMI≥35 with non-diabetic hyperglycaemia and CVD risk) (post hoc analysis)					
Treatment policy (CS.B.2.7.2)	1.0 [c] (0.0 mg/dL)	273	1.0 [c] (0.0 mg/dL)	148	1.0 [b]
Trial product (Appendix E.2)	NR (-0.04 [0.17] mg/dL)	273	NR (-0.02 [0.17] mg/dL)	148	NR

FAS: full analysis set; NR: not reported

[a] log scale; SD reported for some analyses

[b] Not reported; calculated by reviewer

3.2.6.3 Subgroup analyses

The STEP 1 trial results for the target and liraglutide-eligible subgroups have been reported alongside those for the full analysis set population above, to make it easier for the reader to make comparisons between the groups.

3.2.7 Safety outcomes

The majority of participants (>85%) in both the semaglutide 2.4 mg arm and the diet and physical activity (plus placebo) arm of the STEP 1 trial experienced adverse events. The rate of any adverse events was marginally more frequent in the semaglutide 2.4 mg arm than the diet and physical activity arm (89.7% versus 86.4%), as was the rate of serious adverse events (9.8% versus 6.4%). Overall, the rate of adverse events per 100 person-years was higher in the semaglutide 2.4 mg arm (566.1) than the diet and physical activity arm (398.0) (Table 19).

Adverse events led to discontinuations in 7.0% of those receiving semaglutide 2.4 mg and 3.1% of those receiving diet and physical activity, with discontinuations due to gastrointestinal disorders being the main adverse event leading to discontinuation.

One death was reported in each trial arm, neither of which was considered by the independent external event adjudication committee to be related to semaglutide 2.4 mg or diet and physical activity (CS Appendix F.1).

The rate of adverse events considered probably related to treatment was relatively high for the diet and physical activity arm, i.e. for participants receiving placebo and the lifestyle intervention (22.4%).

The CS reports the most frequent adverse events, i.e. those which affected ≥10% of participants in either trial arm (Table 19) but does not specify the rates of grade 3 or grade 4 events. Rates of nasopharyngitis and upper respiratory tract infection did not differ between the trial arms whereas the other common adverse events, which were mostly gastrointestinal disorders, were more frequent in the semaglutide 2.4 mg arm.

Table 19 Summary of adverse events

Adverse event (AE)	Semaglutide 2.4 mg		Diet and physical activity	
	Participants N (%)	Events per 100 person-years	Participants N (%)	Events per 100 person-years
Any AE	1171 (89.7)	566.1	566 (86.4)	398.0
Serious AE	128 (9.8)	9.6	42 (6.4)	6.4
AE leading to discontinuation	92 (7.0)	7.2	20 (3.1)	2.8
GI disorders leading to discontinuation	59 (4.5)	4.6	5 (0.8)	0.6
Mortality	1 (0.1)	0.1	1 (0.2)	0.3
Treatment-related AE				
Probably related	571 (43.7)	125.9	147 (22.4)	39.8
Possibly related	726 (55.6)	158.3	223 (34.0)	66.9
AE reported in ≥10% of participants in either trial arm				
Nausea	577 (44.2)	62.6	114 (17.4)	17.6
Diarrhoea	412 (31.5)	44.9	104 (15.9)	16.6
Vomiting	324 (24.8)	37.3	43 (6.6)	6.3
Constipation	306 (23.4)	22.9	62 (9.5)	8.8
Nasopharyngitis	281 (21.5)	28.1	133 (20.3)	26.0
Headache	198 (15.2)	22.7	80 (12.2)	12.5
Dyspepsia	135 (10.3)	10.5	23 (3.5)	3.6
Abdominal pain	130 (10.0)	10.3	36 (5.5)	4.9
Upper RT infection	114 (8.7)	9.3	80 (12.2)	14.0

GI: gastrointestinal; RT: respiratory tract Source: CS Table 13 and CS Appendix F.2

The company report a set of adverse events which they refer to as being of "particular interest" (CS Appendix F.2) or "safety focus areas" (trial publication), which were selected "based on therapeutic experience with glucagon-like peptide-1 receptor agonists and in line with regulatory feedback and requirements" (CS section B.2.10.2). The most frequent events of particular interest were gastrointestinal disorders, which occurred in 74.2% of participants in the semaglutide 2.4 mg arm and 47.9% of participants in the diet and physical activity arm (Table 20). Cardiovascular events, which are specified as an outcome in the Decision Problem (CS section B.1.1) and inform the economic analysis (section B.3.3.71), are

included among the events of particular interest. However, cardiovascular events are only presented at an aggregate level for each arm of the STEP 1 trial and are not defined explicitly.

Table 20 Safety focus areas

Adverse event	Semaglutide 2.4 mg		Diet and physical activity	
	Participants N (%)	Events per 100 person-years	Participants N (%)	Events per 100 person-years
GI disorders	969 (74.2)	252.6	314 (47.9)	89.1
Gallbladder-related	34 (2.6)	2.5	8 (1.2)	1.0
> Hepatobiliary	33 (2.5)	2.3	5 (0.8)	0.6
>> Cholelithiasis	23 (1.8)	1.4	4 (0.6)	0.5
Hepatic disorders	31 (2.4)	2.2	20 (3.1)	2.9
Acute pancreatitis	3 (0.2)	0.2	0	0
Cardiovascular disorders	107 (8.2)	7.2	75 (11.5)	10.5
Allergic reactions	96 (7.4)	6.3	54 (8.2)	7.6
Injection site reactions	65 (5.0)	5.8	44 (6.7)	9.9
Malignant neoplasms	14 (1.1)	0.8	7 (1.1)	0.8
Psychiatric disorders	124 (9.5)	9.4	83 (12.7)	13.6
Acute renal failure	3 (0.2)	0.2	2 (0.3)	0.2
Hypoglycaemia	8 (0.6)	0.9	5 (0.8)	0.8

GI: gastrointestinal Source: CS Appendix F.2 and trial publication

3.2.8 Pairwise meta-analysis of intervention studies

As the company only included one trial (STEP 1) comparing semaglutide 2.4 mg to diet and physical activity, the company did not undertake a meta-analysis.

3.3 Critique of studies included in the indirect comparison and/or multiple treatment comparison

The company conducted an indirect treatment comparison (ITC) to compare semaglutide 2.4 mg/week against liraglutide 3.0 mg/day using the placebo plus diet and physical activity arms of the STEP 1 and SCALE 1839 trials as the common comparator. The ITC utilised

data from the liraglutide-eligible subgroup of patients, i.e. those with BMI≥35 kg/m^2 with non-diabetic hyperglycaemia and high CVD risk (clarification response A12).

3.3.1 Rationale for the ITC

A direct comparison of semaglutide 2.4mg vs liraglutide 3.0mg is being conducted in the recently completed STEP 8 trial; however, STEP 8 results will not be available until Q4 2021. In the absence of any direct comparisons, an indirect comparison was deemed appropriate by both the company (CS section B.2.9) and the ERG. We assume that when results of the STEP 8 trial become available they would supersede the results of the ITC, i.e. the role of the ITC is for interim decision making.

3.3.2 Identification, selection and feasibility assessment of studies for the ITC

3.3.2.1 Identification of studies

A SLR was conducted to identify relevant studies for inclusion in the indirect comparisons of semaglutide 2.4 mg versus liraglutide 3.0 mg (CS section B.2.9). Details of the SLR and a summary of the included studies are provided in CS Appendix D.1.2, CS Appendix D.1.3 and an ITC Report.[15] The search was conducted in September 2020 and updated in April 2021 and was considered by the ERG to be broadly up to date and fit for purpose. We consider it is unlikely that key studies have been missed.

3.3.2.2 Selection of studies

Study selection is reported in CS Appendix D.1.2. The company's eligibility criteria (summarised in Table 21) are generally broader than the decision problem. Apart from HRQoL, all outcomes specified in the decision problem are captured in the eligibility criteria. Broad reasons for excluding studies at full text screening are provided in CS Appendix Table 5. The ERG requested further details of the excluded studies in order to check whether the company's exclusions were appropriate (clarification response A2).

Table 21 Eligibility criteria for the indirect treatment comparison

PICOD criterion	Inclusion criteria
Population	Adults with: • BMI ≥ 27 kg/m^2 and one weight-related co-morbidity • BMI ≥ 30 kg/m^2 (with weight-related co-morbidities) NB CS Appendix Table 4 states people with "BMI ≥ 30 kg/m^2 (without weight-related co-morbidities)" were included; however according to

	clarification response A3 people without weight-related comorbidities were excluded.
Intervention	Semaglutide 2.4 mg
Comparators	**As per the decision problem:** • Standard management without semaglutide (including a reduced calorie diet and increased physical activity) • Liraglutide, 3.0 mg (Saxenda)
Outcomes	**Outcomes consistent with the decision problem:** • Proportion of subjects losing at least 5%, 10%, and 15% of baseline fasting body weight • Weight loss in kg • Mean % change in weight • HbA1c - Mean % change in HbA1c versus baseline HbA1c • % reversing from prediabetes to normal glucose tolerance • Waist circumference • Safety outcomes (incidence of hypoglycaemia, incidence of SAEs and discontinuations due to AEs) **Outcomes additional to the decision problem:** • Systolic blood pressure (SBP) - Absolute change in mm Hg vs baseline • HDL – Absolute change in mg/dl versus baseline • Total cholesterol - Absolute change in mg/dl versus baseline • % reduction in antihypertensive treatment • % change in glucose lowering drugs **Outcomes stated in the decision problem but not included:** • HRQoL
Design	RCTs with data following >9 months of treatment duration
Source: summary of CS Appendix Table 4. This table gives a shortened overview of the key criteria and is not exhaustive (i.e. the language criteria are not included here).	

The company's process for eligibility screening followed good practice, with titles, abstracts and full-text articles assessed by two reviewers independently.

3.3.2.3 Studies eligible for inclusion in the ITC

Following the study selection process, the company identified 3 relevant RCTs (reported in 7 references):

- STEP 1 and STEP 3 trials of semaglutide 2.4 mg versus placebo, both used as adjuncts to diet and physical activity in overweight or obese patients;
- The SCALE 1839 Obesity and Prediabetes study of liraglutide 3.0 mg/day versus placebo, both used as adjuncts to diet and physical activity in overweight or obese patients. For simplicity, we refer to liraglutide 3.0 mg/day in combination with diet and physical activity as 'liraglutide 3.0 mg' throughout this report.

The company excluded the STEP 3 trial post-hoc because all enrolled patients received IBT in addition to their randomised treatment (i.e. placebo or semaglutide 2.4 mg), which the company argue is not considered standard practice in the UK (CS Appendix section D.1.3). As explained in section 3.2.1 above the ERG disagree with the company and believe the STEP 3 trial meets the NICE scope and decision problem and should have been included in the company's analyses.

3.3.2.4 Included studies and populations

Following the selection process outlined above the ITCs included data from two trials: STEP 1, providing patient data for semaglutide 2.4 mg; and SCALE 1839 obesity and pre-diabetes, providing patient data for liraglutide 3.0 mg. Both trials were conducted by the company, and the company used individual participant data (IPD) for the ITC analyses.

Dose escalation and study duration for patients with prediabetes

In STEP 1 the target dose (2.4mg semaglutide) was achieved after 16 weeks and end of treatment was at 68 weeks, i.e. after 52 weeks on the target dose. In SCALE 1839 the target dose (3.0mg liraglutide) was achieved after 4 weeks and end of treatment was at 56 weeks, i.e. after 52 weeks on the target dose (CS Appendix D.1.3.1). The company conducted a base case comparison based on time after randomization (approximately 1 year) rather than weeks on the target dose of treatment: the analysis was conducted for 52 weeks after randomization in STEP 1 and 56 weeks after randomization in SCALE 1839 (ITC Report), with scenario analyses at other time points. The company do not provide a rationale for this approach, which does not reflect the full treatment duration in STEP 1 (36 weeks of the target dose rather than 52 weeks, and hence the company regard this as a conservative comparison; ITC Report). The ERG note that the benefit of semaglutide 2.4 mg appears to be established before the full 68-week trial duration and therefore the company's analysis approach appears reasonable and conservative.

Subgroups analysed

The company's main population of interest, referred to as the ITC base case, was the sub-population of participants in each trial who had BMI≥35 kg/m^2, non-diabetic hyperglycaemia (high risk of` diabetes – NICE definition), and high risk of cardiovascular disease (CVD). The ITC report states that in addition to the base case, (unadjusted) analyses were also conducted for the "broader subpopulation of patients with pre-diabetes" (specific BMI range not stated) (these analyses are not relevant to this appraisal).

Definitions

In both trials **prediabetes** was defined according to American Diabetes Association criteria: HbA1c 5.7−6.4% both inclusive or 5.5 mmol/L ≤FPG ≤6.9 mmol/L or 2-hour post-challenge (oral glucose tolerance test [OGTT]) plasma glucose ≥7.8 mmol/L and ≤11.0 mmol/L. **Normoglycaemia** is not explicitly defined in the ITC Report,[15] but the ITC report states **high risk of diabetes** is defined by NICE as having 5.5 mmol/L ≤FPG ≤6.9 mmol/L or 6.0% ≤HbA1c ≤6.4% (this definition was used in the liraglutide appraisal [TA664]). The ITC report states the definition of **high risk of CVD** in the liraglutide appraisal was total cholesterol >5 mmol/L or systolic blood pressure >140 mmHg or HDL <1.0 mmol/L for men and <1.3 mmol/L for women, and this is correct.

3.3.3 Clinical heterogeneity assessment

3.3.3.1 Trial baseline characteristics

The CS presents baseline characteristics for STEP 1 (CS Tables 5 and 6; CS Appendix Table 10) and SCALE 1839 (CS Table 11). However, comparisons of baseline characteristics across both arms in both trials is only possible for the FAS population (Table 22). An aggregate comparison (intervention and placebo arms pooled) between STEP 1 and SCALE 1839 for the liraglutide-eligible subgroup is provided in CS Table 11, reproduced in Table 23 below.

Overall, the STEP 1 and SCALE 1839 trial populations were similar, although STEP 1 had a slightly higher proportion of Asian participants and lower proportion of people with prediabetes (Table 22). Fewer baseline characteristics are reported for the liraglutide-eligible subgroup, which is the primary population of interest for the ITC (Table 23), as the company have only presented variables which they believe are potential effect modifiers. Where reported, the baseline characteristics of the liraglutide-eligible subgroup of participants were also generally similar between STEP 1 and SCALE 1839; the largest differences were in

white ethnicity (6.2%-points higher in SCALE 1839), dyslipidaemia (5%-points higher in STEP 1), Asian ethnicity (4.5%-points higher in STEP 1) and mean weight (1.3 kg higher in STEP 1).

Table 22 Baseline characteristics of STEP 1 and SCALE 1839 trials: FAS populations

Variable **Mean (SD) unless stated otherwise**		**STEP 1**		**SCALE 1839**	
		Semaglutide 2.4 mg N=1306	**Diet and physical activity N=655**	**Liraglutide 3.0 mg N=2487**	**Diet and physical activity N=1244**
Age, years		46 (13)	47 (12)	45.2 (12.1)	45.0 (12.0)
Female sex, %		73.1	76.0	78.7	78.1
Self-reported race or ethnic group, %	White	74.5	76.2	84.7	85.3
	Black [a]	5.5	6.0	9.7	9.2
	Asian	13.9	12.2	3.6	3.7
	Other	6.1	5.6	1.9	1.8
Body weight, kg		105.4 (22.1)	105.2 (21.5)	106.2 (21.2)	106.2 (21.7)
BMI, kg/m^2		37.8 (6.7)	38.0 (6.5)	38.3 (6.4)	38.3 (6.3)
Waist circumference, cm		114.6 (14.8)	114.8 (14.4)	115.0 (14.4)	114.5 (14.3)
HbA1c %		5.7 (0.3)	5.7 (0.3)	5.6 (0.4)	5.6 (0.4)
Prediabetes, %		45.4	40.2	61.4	60.9
Systolic BP, mmHg		126 (14)	127 (14)	123.0 (12.9)	123.2 (12.8)
Total cholesterol, mg/dL (% CV [b])		189.6 (20.5) [b]	192.1 (19.4) [b]	193.7 (19.1) [b]	194.3 (18.8) [b]
HDL cholesterol, mg/dL (% CV [b])		49.4 (25.6) [b]	49.5 (25.0) [b]	51.4 (26.2) [b]	51.0 (26.4) [b]
Dyslipidaemia, %		38.2	34.5	29.6	28.9
Hypertension, %		36.1	35.7	34.2	35.9
On anti-hypertensive drug, %		23.8	23.2	NR [c]	NR [c]
On lipid-lowering drug, %		19.1	17.4	NR [c]	NR [c]

Sources: STEP 1: trial publication[5] and CS Table 5; SCALE 1839: trial publication[19]
BP: blood pressure; CV: coefficient of variation; NR: not reported
[a] reported as Black or African American in the STEP 1 trial
[b] geometric mean and % coefficient of variation
[c] reported for prediabetic and normoglycaemia groups but not FAS population

Table 23 Baseline characteristics of STEP 1 and SCALE 1839 trials: liraglutide-eligible populations (BMI≥35, non-diabetic hyperglycaemia and high cardiovascular risk)

Variable		STEP 1 N=421 [a]	SCALE 1839 N=800 [a]
Age, years, mean (SD)		48.1 (12.06)	48.2 (11.24)
Female, n/N (%) [b]		314/421 (74.6)	606/800 (75.8)
Race / ethnicity, n/N (%) [c]	White	334/421 (79.3)	684/800 (85.5)
	Black or African American	23/421 (5.5)	74/800 (9.3)
	Asian	34/421 (8.1)	29/800 (3.6)
	Other	18/421 (4.3)	13/800 (1.6)
	Not reported	12/421 (2.9)	0/800 (0)
Weight, kg, mean (SD) [b]		117.2 (21.91)	115.9 (19.76)
BMI, kg/m^2, mean (SD)		42.1 (6.28)	41.7 (5.35)
Waist circumference		Not reported	Not reported
HbA_{1c}, %, mean (SD) [b]		5.9 (0.28)	5.8 (0.34)
Systolic BP		Not reported	Not reported
Total cholesterol		Not reported	Not reported
HDL cholesterol		Not reported	Not reported
CVD, n/N (%)		36/421 (8.6)	88/800 (11.0)
Dyslipidaemia, n/N (%)		164/421 (39.0)	272/800 (34.0)
Hypertension, n/N (%)		190/421 (45.1)	389/800 (48.6)

Source: reproduction of CS Table 11 with minor modification
[a] The sample sizes given in CS Table 11 are for the FAS populations. The correct subgroup sample sizes were confirmed by the company in clarification response A9
[b] The CS states that these variables were considered potential effect modifiers and included in adjustment 1; age, dyslipidaemia, hypertension and cardiovascular disease were additionally included in adjustment 2.
[c] From clarification response A11 (not reported in the CS)

Overall the trials appear generally well-balanced in terms of the key prognostic variables that are relevant in obesity management.

3.3.3.2 Effect modifiers

3.3.3.2.1 Potential effect modifiers of drug exposure

The company explored the factors which affect exposure to semaglutide and liraglutide (ITC Report section 2.4.1). They considered exposure to semaglutide up to 1.0 mg/week in a diabetic population in a study by Carlsson Petri et al.[20] (ITC Report Figure 4) and exposure to liraglutide up to 3.0 mg/day in a population with obesity, in a study by Overgaard et al.[21] (ITC Report Figure 3). The company do not comment on whether other data sources were available or whether the factors affecting semaglutide exposure to a maximum of 1.0

mg/week would also apply to the intended 2.4 mg/week dose. As reported in the literature,[20] [21] the company conclude that baseline body weight (inversely related to exposure) and, for liraglutide only, sex (lower exposure in men) were the only effect modifiers for drug exposure (the reason why sex should be an effect modifier for liraglutide but not semaglutide is not discussed). For both drugs there were statistically significant effects on exposure of age, race, ethnicity, baseline glycaemic status, injection site and renal function (ITC Report Figures 3 and 4), but the company state race, ethnicity and age were not found to have a clinically relevant effect on exposure, which is consistent with the conclusions of the cited studies[20] [21] (the studies also reported no clinically relevant effects of sex, age, race, ethnicity, renal function, or injection site on exposure to semaglutide 1.0 mg;[20] and no clinically relevant effects of age ≥70 years, race, ethnicity and glycaemic status on exposure to liraglutide 3.0 mg[21]). As noted above, we believe there is some uncertainty in how generalisable these findings are beyond the specific populations and drug dosing in these studies.

3.3.3.2.2 Potential effect modifiers of relative weight change

The company identified baseline body weight/BMI and gender as potential effect modifiers of relative change in body weight based on subgroup analyses for semaglutide and liraglutide respectively versus placebo (ITC Report section 2.4.2.2). However, these subgroup analyses are not presented.

3.3.3.2.3 Potential effect modifiers of waist circumference, systolic blood pressure and lipids

The company argue that the treatment effect of liraglutide versus placebo on waist circumference, systolic blood pressure and lipids was predominantly impacted by the treatment effect on relative weight loss (ITC Report section 2.4.2.3). Accordingly, the effect modifiers for waist circumference, systolic blood pressure and lipids would be the same as those for weight loss. This observation is based on analysis of data from a series of SCALE trials by Bays et al.[22] (ITC Report Figure 5).

3.3.3.2.4 Potential effect modifiers of HbA1c and glycaemic status

The company cite evidence that the treatment effect of liraglutide versus placebo depends on baseline HbA_{1c} in diabetic populations[23] and they argue that the exposure of GLP-1 RAs is not expected to differ between diabetic and non-diabetic populations. The company's conclusion is that, in addition to gender and weight, baseline HbA_{1c} is a relevant effect modifier to consider in the ITC (ITC Report section 2.4.2.4).

As shown in Table 23 above, the effect modifiers weight, sex and HbA_{1c} were similar for the liraglutide-eligible subgroup in the STEP 1 and SCALE 1839 trials, apart from a slight difference in mean weight (1.3 kg higher in STEP 1).

3.3.4 Similarity of treatment effects

The ITC uses the placebo plus diet and physical activity arm of each trial as the common comparator. The CS and ITC report do not comment on the similarity of diet and physical activity prescriptions.

In both trials patients were advised to increase their physical activity to at least 150 minutes per week and adhere to a 500kcal deficit diet relative to their estimated individualised energy requirements. However, there were some differences between the trials, e.g. in the frequency and nature of the counselling sessions (individual sessions in STEP 1 every 4 weeks; individual or group sessions in SCALE 1839, frequency not reported).

Although the trials had different durations, as discussed above the company base their ITC analysis on outcomes measured approximately 1 year following randomisation. This was 52 weeks after randomisation for the STEP 1 trial (of which 36 weeks were on the full 2.4mg dose in the semaglutide 2.4 mg arm) and 56 weeks after randomisation for the SCALE 1839 trial (of which 52 weeks were on the full 3.0 mg dose in the liraglutide arm). However, the CS does not report outcomes for STEP 1 at 52 weeks after randomisation but instead reports them at 68 weeks after randomisation (the end of treatment). It is therefore not possible for the ERG to compare the outcomes in the placebo plus diet and physical activity arms of the trials at the same timepoints as used in the ITC.

The only comparison of the placebo plus diet and physical activity arms that the ERG can make based on the data provided by the company is for the FAS populations and the change from baseline to end of treatment, i.e. 68 weeks after randomisation in STEP 1 and 56 weeks after randomisation in SCALE 1839 (Table 24). NB the data reported in Table 24 are for the treatment policy estimand.

Table 24 Changes from baseline for outcomes at end of treatment in the placebo plus diet and physical activity arms of STEP 1 and SCALE 1839: FAS populations

Outcome, mean change from baseline	STEP 1 (68 weeks) placebo + DPA arm [a]	SCALE 1839 (56 weeks) Placebo + DPA arm [b]
Weight change	-2.61 kg	-2.8 kg

Proportional weight change		-2.41 %-points	-2.6 %-points
BMI change		-0.92 kg/m^2	-1.0 kg/m^2
Waist circumference change		-4.13 cm	-3.9 cm
HbA_{1c} change		-0.15 %-points	-0.06 %-points
Systolic blood pressure change		-1.06 mmHg	-1.50 mmHg
Ratio to baseline [c]	HDL cholesterol	1.01	0.7
	Total cholesterol	1.00	1.0

DPA: diet and physical activity
[a] Source: data as reported in section 3.2.5. above, using the treatment policy estimand
[b] Source: trial publication[19]
[c] analysis based on log scale and geometric means

CS section B.3.3.1.3 states that the placebo arms of the two trials were very similar in terms of baseline characteristics but did produce slightly different results for change from baseline in BMI and other risk factors. The effects of placebo plus diet and physical activity do appear broadly similar for both trials, with the changes in outcomes from baseline being generally consistent across the trials in their direction and magnitude (Table 24). The decrease in weight and BMI was marginally smaller in the STEP 1 placebo plus diet and physical activity arm; however, there is uncertainty in how applicable these FAS results are to the population subgroup and timepoints analysed in the ITC.

3.3.5 Risk of bias assessment for studies included in the ITC

The company used seven criteria to assess the risk of bias for the two studies, SCALE 1839 and STEP 1, included in the ITC (CS Appendix Table 9). The ERG independently assessed the studies using the same criteria as the company and our judgements are reported in Appendix 1. Overall, the ERG consider both trials to be of good methodological quality but the risk of attrition bias is unclear in both trials. The reasons for the risk of attrition bias being unclear to the ERG in the STEP 1 and SCALE 1839 trials are:

- The company provide data which show some systematic differences in baseline characteristics between patients with observations and those with missing data (clarification response A13, attachment E, Tables 26 to 53) for the liraglutide-eligible subgroup. Patients with missing data had a mean age that was 2.5 to 4.8 years lower (treatment policy estimand) or 3.3 to 4.0 years lower (trial product estimand) than those who provided observations for analysis. Also, a lower proportion of the patients with missing data had dyslipidaemia and hypertension than those who provided data for analysis. It is unclear whether these differences would be clinically important and whether, after imputation, they would favour one trial over the other.

- The company did not provide a similar comparison of baseline characteristics for patients with missing/non-missing data for the FAS population.

ERG conclusion: The company's inclusion of the STEP 1 and SCALE 1839 trials in the ITC is appropriate, although the ERG believe the STEP 3 trial should also have been included. The baseline characteristics of the STEP 1 and SCALE 1839 trials are broadly homogeneous, supporting the combining of these trials in an ITC. The risk of attrition bias is unclear in both trials, introducing uncertainty (of unknown magnitude and direction) around the efficacy outcome estimates from the ITC.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Overview of the ITC

Two relevant comparators were defined by the decision problem: standard management with diet and physical activity; and liraglutide. Whilst diet and physical activity formed the comparator arm of STEP 1 (along with placebo), an indirect treatment comparison (ITC) was required to compare semaglutide 2.4 mg to liraglutide 3.0 mg.

The population for the liraglutide ITC (BMI≥35, non-diabetic hyperglycaemia, and high risk of CVD) was aligned with TA664[4] (clarification responses A9-A12 and A18). As the company own both semaglutide 2.4 mg and liraglutide 3.0 mg, the analysis methodology was informed by the company's access to individual patient data (IPD) for both the STEP 1 and SCALE 1839 trials.

A series of unadjusted and adjusted analyses were conducted for the ITC, as explained in section 3.4 below). The following outcomes were included:

- Change from baseline – continuous outcomes:
    - Body weight (%)
    - Waist circumference
    - HbA1c
    - Systolic blood pressure
    - Fasting HDL cholesterol
    - Fasting total cholesterol
- Dichotomous outcomes:
    - Type 2 diabetes incidence
    - Proportion achieving normoglycaemic status

The type 2 diabetes incidence endpoint was not reported due to too few events (ITC report, section 3.2). BMI was not included; no explanation is provided in the CS. The economic model, however, does not use this outcome. The model uses % change in body weight, which is synonymous to % change in BMI.

As noted in section 3.2.4.3, two estimands were employed, which differ in how they address intercurrent events (rescue medication use and treatment discontinuation). The base case in the ITC uses the treatment policy estimand, that is, participants were included irrespective of whether they used rescue medications or discontinued treatment. This may be viewed as the more conservative approach as it would not adjust for a higher use of rescue medications in the comparator arm and discontinuations in the treatment arm, both of which might be expected to favour the comparator arm.

The trial product estimand was used as a scenario analysis in the ITC. The aim of this analysis is to reduce bias arising from differences in treatments and dropouts between trial arms by adjusting, through imputation methods, for use of rescue medications, treatment switching, or treatment discontinuation. The trial product estimand analysis produced similar outcomes to the treatment policy estimand, and where there were differences generally the treatment policy results are the more conservative (section 3.5).

The ERG requested band plots of the use of rescue medications, and discontinuations over time for both STEP 1 and SCALE 1839 (akin to Figure 3 in Aroda et al 2019[18]) to try to understand how the incidence of these intercurrent events differed by treatment arm and between trials and thus impacted the estimands (clarification question A16). The company did not provide these, arguing that they would not provide a complete picture of STEP 1 due to subjects being able to discontinue then resume treatment. It is unclear to the ERG how this could not be presented as a band plot. Nevertheless, the STEP 1 data provided by the company show a higher use of rescue medications in the diet & physical activity arm (N=13 [1%] vs 7 [1%], clarification response document E, Table 25) and a higher rate of treatment discontinuation in the placebo (diet and physical activity) arm (~18% vs 12% at week 52, CSR Figure 14.1.11). It is unlikely the higher rate of placebo discontinuations would impact the results (reasons for discontinuations appeared broadly similar for both trials – see flow charts in CS Appendix and SCALE 1839 trial paper[19]).

For the SCALE 1839 trial, the company noted there was “no notion of anti-obesity rescue medication” nor any distinction between treatment discontinuation and trial withdrawal (clarification response A16). It is unclear to the ERG whether this means rescue

medications were not recorded or not permitted. The data provided (clarification responses, attachment W, Figure 14.1.7) show a higher rate of (any-cause) discontinuation in the liraglutide 3.0 mg arm compared to placebo (approximately 10% vs 3%).

The ERG were concerned that the approaches to handling missing data differed between trials (clarification question A13). The company clarified that the missing data approaches were equivalent for the treatment policy estimand across both trials but differed due to using pre-planned analyses for each of STEP 1 and SCALE 1839 for the trial product estimand. In response to the ERG question, the company aligned the approach to the trial product estimand by applying the same mixed model for repeated measures as used for STEP 1 to SCALE 1839. This resulted in similar though slightly less favourable estimates in favour of semaglutide 2.4 mg for body weight (%), waist circumference, and glycaemic status (clarification responses document E, Tables 2-9).

Less imputation was required for STEP 1 using the treatment policy estimand (~10% semaglutide 2.4 mg, 16% diet and physical activity) compared to SCALE 1839 (~23% liraglutide 3.0 mg, ~31% diet and physical activity). By definition, the trial product estimand requires more imputation, but again this was less in STEP 1 (~22% semaglutide 2.4 mg, ~26% diet and physical activity) compared to SCALE 1839 (~32% liraglutide 3.0 mg, 33% diet and physical activity).

The differences in how or whether intercurrent events are recorded in the two trials raise questions about how they can be consistently handled in the missing data imputation used to calculate the estimands. The trial product approach

- requires more imputation, and therefore introduces more uncertainty than the treatment policy estimand
- relies on poorer recording of intercurrent events in SCALE 1839
    - There is no distinction between treatment discontinuations and other trial withdrawals (patients are therefore grouped together)
    - Use of rescue medications was not permitted or not recorded
- requires more imputation in SCALE 1839 than STEP 1

We conclude that the treatment policy estimand is likely to be a more conservative scenario for the efficacy of semaglutide 2.4 mg and is also less uncertain as less imputation is required. (As discussed in section 4.2.6.1, the economic model uses the trial product estimand from the STEP 1 trial and we believe this is appropriate for the purposes of the

economic model; note, however, that neither the treatment policy not trial product estimand results from the ITC have been used in the model.)

Whilst the Company's ITC base case compared outcomes at week 52 for STEP 1 versus week 56 for SCALE 1839, scenarios considered week 56 for both trials, and week 68 for STEP 1 versus week 56 for SCALE 1839. Results for these scenarios are relatively consistent across outcomes (section 3.3.3.2).

3.4.2 Data inputs for the ITC

The ERG agree that the patients' characteristics are relatively homogeneous between the semaglutide 2.4 mg and liraglutide populations (section 3.3.3.1 above). This applies both the FAS (STEP 1[5] and SCALE 1839[19] trial publications) and the liraglutide-eligible subgroup (CS Table 11). There were some minor differences in Asian and black/African American ethnicity (clarification response A11, attachment E, Table 1) but this was not identified as an effect modifier by the company and therefore not included in the adjusted analysis.

The company identified body weight, gender, baseline hbA_{1c}, and age as effect modifiers, and dyslipidaemia, hypertension, and CVD as potential effect modifiers (CS, section B.2.9.1.1). They note that neither race nor ethnicity were found to be effect modifiers for semaglutide or liraglutide (see section 3.3.3.2 above). The ERG's expert did not identify any missing effect modifiers.

3.4.3 Statistical methods for the ITC

The company conducted a series of adjusted and unadjusted analyses for the ITC. The adjusted analyses used established methods, linear regression (for continuous outcomes) and logistic regression (for dichotomous outcomes) to control for effect modifiers (body weight, gender and baseline hbA_{1c}) and potential effect modifiers (dyslipidaemia, hypertension, and CVD). Given the similarity in results and the similarity between the semaglutide 2.4 mg and liraglutide populations, the company preferred the unadjusted analysis as their base case (CS section B.2.9.1.2).

The ERG agree the unadjusted ITC is adequate to compare semaglutide 2.4 mg and liraglutide 3.0 mg. The semaglutide 2.4 mg and liraglutide 3.0 mg populations are homogeneous in terms of baseline characteristics and effect modifiers (CS Table 11) hence any adjusted ITC would not be expected to have a material impact on relative treatment effects.

The company provided the SAS code used for the ITC in clarification response A8. They declined to provide the IPD, and hence the ERG were unable to validate the adjusted ITC results. However, we were able to confirm the unadjusted ITC results using the Bucher method using the data reported in the ITC report, for all outcomes and both estimands.

Finally, neither the adjusted nor unadjusted ITC results inform the economic model. Instead, a separate ad hoc calculation was performed by the company to adjust for "slightly different results for change from baseline in BMI and other risk factors" (which were not specified) (CS section B.3.3.1.3). The company's calculation adjusts the efficacy of liraglutide 3.0 mg in the economic model to reflect this difference using observed efficacy in SCALE 1839. The mean changes from baseline in STEP 1 (trial product estimand) are used directly in the economic model (CS Table 21), whilst for liraglutide an odds ratio from SCALE 1839 was applied to the diet and physical activity arm of STEP 1 to give the adjusted estimates for liraglutide (CS Table 23). However, the details of this calculation are unclear to the ERG. As we note above, the differences in the changes from baseline for BMI and other outcomes between the diet and physical activity arms are relatively small (section 3.3.4), but the company do not provide a rationale for why the unadjusted ITC could not have been used in the economic model (i.e. avoiding the need for this ad hoc calculation). The company state in CS section 3.3.1.3 that the ITC was "not able to produce adjusted estimates for efficacy in responders (further details are provided in Appendix D)". However, there is no reference to this in CS Appendix D.

3.4.4 Summary of the ERG's critique of the ITC

- The ITC methodology followed by the company is appropriate given the available data.
- The methodology has been described and applied correctly.
- All effect modifiers have been included in the analysis.
- The adjusted ITC could not be validated as IPD were not provided.
- The unadjusted ITC results are preferred for the ITC since the STEP 1 and SCALE 1839 trial populations are homogeneous.
- A comprehensive range of scenario analyses were conducted by the company.
- The treatment policy estimand (company ITC base case) is likely to be the most conservative; the trial product estimand makes more use of data imputation which may introduce bias (or at least uncertainty) since missing data are inconsistently reported between trials. Use of the trial product estimand in the economic model is

appropriate, as it takes into account treatment stopping, which the treatment policy estimand does not (see section 4.2.6.1).

- It is unclear why the ITC results were not implemented in the economic model.
- The company's adjustment calculation in the economic model, used in lieu of relative effectiveness data from the ITC, is unclear to the ERG.

3.5 Results from the indirect comparison

The CS states (section B.2.9.2) that results of the unadjusted population analysis at the primary time point of interest using the trial product estimand, and the results of the scenario analyses (population adjustment 1, population adjustment 2, and unadjusted non-diabetic hyperglycaemia population), are provided in Appendix D4. However, Appendix D4 was not provided with the submission. The available ITC results presented below are from the ITC Report and CS Table 12. We report results below for the outcomes that inform the economic model (although, note, none of the ITC results were used in the model). We report the ITC results for other outcomes in Appendix 3.

3.5.1 Body weight

The unadjusted analyses for both the treatment policy estimand and trial product estimand indicate a statistically greater weight reduction with semaglutide 2.4 mg than with liraglutide 3.0 mg (Table 25). Adjusted analyses are only reported for the treatment policy estimand and these were also significantly in favour of semaglutide 2.4 mg. The treatment effect in unadjusted analyses was consistently larger for the trial product estimand than for the treatment policy estimand.

Table 25 ITC results: effect on % weight change from baseline

Analysis (STEP 1/SCALE 1839: week 52/56 unless stated)	**Relative treatment effect (95% CI), %-points semaglutide 2.4 mg vs liraglutide 3.0 mg**	
	Treatment policy estimand	**Trial product estimand**
Unadjusted [a]	-5.81 (-7.62 to -3.99), p < 0.0001 [a,b]	-6.62 (-8.28, -4.96), p<0.0001 [b]
Population adjustment 1	-5.87 (-7.69, -4.06), p<0.0001 [b]	Not reported
Population adjustment 2	-5.72 (-7.56, -3.89), p<0.0001 [b]	Not reported
Unadjusted, pre-diabetes	-5.78 (-7.06, -4.49), p<0.0001 [b]	Not reported
Week 56/56, unadjusted	-5.98 (-7.83, -4.14), p<0.0001 [b]	Not reported
Week 68/56, unadjusted	-6.51 (-8.51, -4.51), p<0.0001 [b]	-7.59 (-9.40, -5.79) [b]
Week 28/28, unadjusted	-2.92 (-4.22, -1.61), p<0.0001 [b]	-3.35 (-4.57, -2.13), p<0.0001 [b]

[a] From CS Table 12

[b] From ITC Report Table 5

3.5.2 Glycaemic status

The CS states that semaglutide 2.4 mg was associated with a statistically significantly higher odds of achieving normo-glycaemic status compared to liraglutide 3.0 mg (CS section B.2.9.2). However, the odds ratio was not statistically significant for all the analyses conducted (Table 26). Notably, the primary unadjusted analysis (week 52 in STEP 1 compared against week 56 in SCALE 1839) was only marginally significant for the treatment policy estimand analysis, with the lower limit of the 95% confidence interval of the odds ratio being fractionally above 1.0). The odds ratio for the trial product estimand analysis was higher and statistically significant, but with a relatively wide 95% confidence interval. Odds ratios for the adjusted analyses were reported only for the treatment policy estimand analysis and were not statistically significant.

The CS states that the lack of a difference after adjusting for trial populations "was driven by a slightly lower baseline HbA1c in SCALE 1839 (5.8%) versus STEP 1 (5.9%); the closer a population is to being normo-glycaemic (i.e. HbA_{1c} < 5.7%), the lower the incremental glycaemic effect of adding a more potent GLP-1 receptor agonist" (CS section B.2.9.2).

Table 26 ITC results: effect on normoglycaemic status change from baseline

Analysis (STEP 1/SCALE 1839: week 52/56 unless stated)	**Odds ratio (95% CI), semaglutide 2.4 mg vs liraglutide 3.0 mg**	
	Treatment policy estimand	**Trial product estimand**
Unadjusted	1.79 (1.01, 3.16), p=0.0455 [a,b]	2.36 (1.26, 4.43), p=0.0073 [b]
Population adjustment 1	1.52 (0.82, 2.79), p=0.1804 [b]	Not reported
Population adjustment 2	1.56 (0.84, 2.92), p=0.1618 [b]	Not reported
Unadjusted, pre-diabetes	1.61 (1.07, 2.41), 0.0220 [b]	Not reported
Week 56/56, unadjusted	1.86 (1.05, 3.29), p=0.0327 [b]	Not reported
Week 68/56, unadjusted	1.32 (0.76, 2.30), p=0.3263 [b]	2.44 (1.30, 4.60), p=0.0055 [b]
Week 28/28, unadjusted	2.03 (1.13, 3.65), p=0.0178 [b]	1.86 (1.03, 3.38), p=0.0405 [b]

[a] From CS Table 12
[b] From ITC Report Table 11

3.5.3 Systolic blood pressure

There was no statistically significant effect of semaglutide 2.4 mg compared to liraglutide 3.0 mg on systolic blood pressure, apart from in an unadjusted analysis for the treatment policy estimand in a prediabetes subgroup (Table 27). The CS comments that although differences were not significant, the reduction in SBP was numerically greater with semaglutide 2.4 mg than with liraglutide 3.0 mg (CS section B.2.9.2). We note that the difference in all analyses was very small, in all cases less than 3.0 mmHg.

Table 27 ITC results: effect on systolic blood pressure change from baseline

Analysis (STEP 1/SCALE 1839: week 52/56 unless stated)	**Relative treatment effect (95% CI), mmHg, semaglutide 2.4 mg vs liraglutide 3.0 mg**	
	Treatment policy estimand	**Trial product estimand**
Unadjusted	-1.64 (-4.60, 1.32), p=0.2783 [a,b]	-1.36 (-4.04, 1.32), p=0.3197 [b]
Population adjustment 1	-1.92 (-4.87, 1.04), p=0.2032 [b]	Not reported
Population adjustment 2	-1.59 (-4.53, 1.34), p=0.2874 [b]	Not reported
Unadjusted, pre-diabetes	-2.82 (-4.89, -0.74), p=0.0078 [b]	Not reported
Week 56/56, unadjusted	-1.56 (-4.32, 1.20), p=0.2672 [b]	Not reported
Week 68/56, unadjusted	-1.32 (-4.25, 1.60), p=0.3751 [b]	-1.26 (-3.88, 1.37), p=0.3477 [b]
Week 28/28, unadjusted	-1.36 (-4.25, 1.54), p=0.3582 [b]	-1.55 (-4.33, 1.22), p=0.2730 [b]

[a] From CS Table 12
[b] From ITC Report Table 6

3.5.4 Fasting HDL and total cholesterol

The CS concludes that semaglutide 2.4 mg and liraglutide 3.0 mg resulted in similar changes from baseline in HDL and total cholesterol (CS section B.2.9.2). This is corroborated by results reported in the CS and ITC Report for HDL cholesterol (Table 28) and for total cholesterol (Table 29). We note that the change from baseline in HDL and total cholesterol was very small, with ratios to baseline being very close to 1.0 for semaglutide 2.4 mg[5] and change from baseline being ≤3.1 %-points for liraglutide 3.0 mg.[19]

Table 28 ITC results: effect on fasting HDL cholesterol change from baseline

Analysis (STEP 1/SCALE 1839: week 52/56 unless stated)	**Ratio to baseline (95% CI), semaglutide 2.4 mg vs liraglutide 3.0 mg**	
	Treatment policy estimand	**Trial product estimand**
Unadjusted	1.01 (0.98, 1.04), p=0.5696 [b]	1.01 (0.98, 1.04), p=0.5843 [b]

Population adjustment 1	1.01 (0.98, 1.04), p=0.4430 [b]	Not reported
Population adjustment 2	1.01 (0.98, 1.04), p=0.5028 [b]	Not reported
Unadjusted, pre-diabetes	1.00 (0.98, 1.02), p=0.9010 [b]	Not reported
Week 56/56, unadjusted	Not reported	Not reported
Week 68/56, unadjusted	1.03 (1.00, 1.07), p=0.0523 [b]	1.04 (1.00, 1.07), p=0.0437 [b]
Week 28/28, unadjusted	0.97 (0.94, 1.00), p=0.0261 [b]	0.96 (0.94, 0.99), p=0.0146 [b]
[a] p-value is from an updated version of the ITC Report and differs from that reported in CS Table 12 and the original version of the ITC Report (clarification response A17) [b] From ITC Report Table 7		

Table 29 ITC results: effect on fasting total cholesterol change from baseline

Analysis (STEP 1/SCALE 1839: week 52/56 unless stated)	**Ratio to baseline (95% CI), semaglutide 2.4 mg vs liraglutide 3.0 mg**	
	Treatment policy estimand	**Trial product estimand**
Unadjusted	0.97 (0.94, 1.00), p=0.0961 [a,b]	0.96 (0.93, 1.00), p=0.0278 [b]
Population adjustment 1	0.97 (0.94, 1.00), p=0.0955 [b]	Not reported
Population adjustment 2	0.97 (0.94, 1.00), p=0.0857 [b]	Not reported
Unadjusted, pre-diabetes	0.96 (0.94, 0.98), p=0.0004 [b]	Not reported
Week 56/56, unadjusted	Not reported	Not reported
Week 68/56, unadjusted	0.99 (0.95, 1.02), p=0.4096 [b]	0.98 (0.94, 1.01), p=0.1584 [b]
Week 28/28, unadjusted	0.97 (0.94, 1.00), p=0.0741 [b]	0.96 (0.93, 1.00), p=0.0261 [b]
[a] From CS Table 12 [b] From ITC Report Table 8		

3.6 Additional work on clinical effectiveness undertaken by the ERG

As we suggest the STEP 3 trial should have been included in the CS (see discussion in section 3.2.1), we have summarised results from the STEP 3 trial in Table 34 for outcomes that are used in the economic model.

Table 30 Summary of selected STEP 3 trial results

Estimand	Semaglutide 2.4 mg + IBT		Placebo + IBT		Difference (95% CI)
	Mean change	N	Mean change	N	
% body weight reduction					
Treatment policy	-16.0	407	-5.7	204	-10.3 (-12.0 to -8.6); p<0.001
Trial product	-17.6	407	-5.0	204	-12.7 (-14.3 to -11.0), p <0.001
Systolic blood pressure, mm Hg					
Treatment policy	-5.6	407	-1.6	204	-3.9 (-6.4 to -1.5); p = 0.001
Trial product	-6.21	407	-3.47	204	-2.74 (-5.12 to -0.36), p = 0.02
Total cholesterol					
Treatment policy	-3.8	407	2.1	204	-5.8 (-8.4 to -3.2); p < 0.001
Trial product	-4.5	407	2.1	204	-6.4 (-8.8 to -4.0), p < 0.001
HDL cholesterol					
Treatment policy	6.5	407	5.0	204	1.5 (-1.8 to 4.9), p = 0.39
Trial product	6.2	407	6.5	204	0.2 (-2.5 to 3.0), p = 0.860
Percentage of participants with prediabetes or non-diabetic hyperglycaemia at baseline who achieved normoglycaemia					
Treatment policy	NR	NR	NR	NR	NR
Trial product	NR	NR	NR	NR	NR

Source: Wadden et al. (2021)[3]

IBT: intensive behavioural therapy

3.7 Conclusions on the clinical effectiveness evidence

The company provided evidence in the CS that compares the clinical efficacy of semaglutide 2.4 mg in addition to standard weight management against two of the three comparators specified in the NICE scope:

- Standard management without semaglutide – referred to as 'diet and physical activity' in this report.
- Liraglutide (for the population for whom liraglutide is recommended in technology appraisal 664[4]), i.e. people with a BMI of ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and a high risk of cardiovascular disease. In the included liraglutide trial (SCALE 1839) liraglutide was administered as an adjunct to standard management.

The company did not include the NICE scope specified comparator orlistat, and we believe that this is reasonable (see section 2.3).

The population specified in the NICE scope was adults living with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) who had at least one comorbidity or living with obesity (BMI ≥ 30 kg/m^2). In their decision problem, the company have focused on a sub-population of the scope-specified population (see section 2.3). The company focus on people with a BMI of ≥ 30 kg/m^2 with at least one weight-related co-morbidity. However, the CS provides trial results for both this subgroup and the scope-specified population.

The company included one trial in their review, STEP 1, that directly compared semaglutide 2.4 mg plus standard management against a placebo arm that included standard management without semaglutide 2.4 mg. The STEP 1 trial participants were those living with overweight (BMI ≥ 27 kg/m^2) or obesity (BMI ≥ 30 kg/m^2) who had at least one weight-related co-morbidity. People with type 2 diabetes were not included in the trial. The company provided trial results for the full analysis set (n = 1,961) and two post-hoc subgroups: people with a BMI ≥ 30 plus at least one weight-related comorbidity (n = 1,470) (the 'target subgroup') and people with a BMI ≥ 35 with non-diabetic hyperglycaemia and high CVD risk (n = 421) (the liraglutide-eligible subgroup).

Regarding the representativeness of the STEP 1 trial participants' baseline characteristics, expert advice to the ERG was that in clinical practice, people with a higher BMI than those included in the trial are typically seen in tier 3 weight management services and thus people have more comorbidities. The trial may therefore not be fully representative of the people treated in practice in these respects. We considered the trial to have been generally well-

conducted, but the ERG are unclear about the risk of attrition bias which introduces some uncertainty (of unknown magnitude and direction) to the outcome estimates reported in the CS.

The trial found participants treated with semaglutide 2.4 mg showed a consistently higher percentage decrease in weight from baseline at 68 weeks than those treated with standard management in the FAS population and both subgroups. The proportion of patients with prediabetes or non-diabetic hyperglycaemia at baseline who achieved normoglycaemia at week 68 was higher for the semaglutide 2.4 mg arm than with standard management for the FAS and liraglutide-eligible groups. This outcome was not reported for the target subgroup. There were greater improvements in systolic blood pressure from baseline up to week 68 semaglutide 2.4 mg than with standard management in the FAS population and both subgroups. In the FAS population, changes in HDL and total cholesterol from baseline to week 68 favoured semaglutide 2.4mg. HDL and total cholesterol results were not reported for the target and liraglutide-eligible subgroups.

In terms of adverse events, gastrointestinal disorders were more common in the semaglutide 2.4 mg plus standard management arm than with standard management (74.2% versus 47.9%). There were three cases of acute pancreatitis in the semaglutide 2.4 mg plus standard management arm (0.2%), versus none with standard management alone.

The ERG have identified the following concerns and uncertainties about the decision problem and clinical effectiveness evidence included in the CS for the comparison of semaglutide 2.4 mg against diet and physical activity:

- We consider that the company's focus on the BMI ≥ 30 plus at least one weight-related comorbidity target subgroup in their decision problem is acceptable (see section 2.3 for a discussion about this). We suggest, however, that the NICE criteria for eligibility for bariatric surgery may more suitably define the target population (BMI ≥ 35 with at least one co-morbidity or ≥ 40 with or without comorbidities, unless new onset diabetes, in which case BMI ≥ 30, or lower for people of Asian family origin).[1] These criteria reflect the patient group that is typically treated within tier 3 services where we understand semaglutide 2.4 mg is most likely to be used.
- It is uncertain if the STEP 2 trial of semaglutide 2.4 mg in people with type 2 diabetes should have been included in the CS. If it is expected that the 2.4 mg dose might be used in practice in people with type 2 diabetes for weight loss and maintenance, then

data from STEP 2 trial will be relevant. There are currently no efficacy data for this population in the submission.

- The company post-hoc excluded the STEP 3 trial from their review, as it used IBT as part of the standard care arm (i.e. alongside a reduced calorie diet and increased physical activity). We believe the trial meets the NICE scope and it would have been appropriate to include it in the review. Omission of it means it is uncertain how effective semaglutide 2.4 mg would be when all relevant evidence has been considered.
- Two completed semaglutide 2.4 mg trials (STEP 5 and STEP 8) are relevant to the NICE scope and the company states clinical study reports for these trials are expected in Q3 and Q4 of this year. These studies' data could potentially have a bearing on conclusions about the clinical effectiveness and cost-effectiveness of semaglutide 2.4 mg.

A further issue we note is that there are uncertainties around how long people should be treated with semaglutide 2.4 mg, given that obesity is a long-term condition, and whether treatment could be repeated.

The company conducted an ITC, using individual patient data, to compare semaglutide 2.4 mg to liraglutide 3.0 mg. The company included the STEP 1 and SCALE 1839 trials. The ITC utilised data from the liraglutide-eligible subgroup of patients, i.e. those with BMI≥35 kg/m^2 with non-diabetic hyperglycaemia and high CVD risk. Like the STEP 1 trial, we considered the SCALE 1839 trial to have been well-conducted but at risk of attrition bias.

The results indicated statistically significant greater weight reduction with semaglutide 2.4 mg than with liraglutide 3.0 mg. The CS states that semaglutide 2.4 mg was associated with a statistically significantly higher odds of achieving normo-glycaemic status compared to liraglutide 3.0 mg. However, the odds ratio was not statistically significant for all the analyses conducted. There was no statistically significant effect of semaglutide 2.4 mg compared to liraglutide 3.0 mg on systolic blood pressure, apart from in an unadjusted analysis for the treatment policy estimand in a prediabetes subgroup. Semaglutide 2.4 mg and liraglutide 3.0 mg resulted in similar changes from baseline in HDL and total cholesterol.

The ITC methodology followed by the company is appropriate, but we have identified the following concerns and uncertainties:

- It is unclear why the ITC results were not implemented in the economic model.

- The company's adjustment calculation in the economic model, used in lieu of relative effectiveness data from the ITC, is unclear to the ERG.

4 COST EFFECTIVENESS

4.1 ERG critique on the company's review of cost-effectiveness evidence

The company conducted a systematic literature review (SLR) to identify all relevant economic evaluation studies, and resource use and cost studies for adults with obesity (CS section B.3.1 and CS Appendix G). The company updated searches that had previously been conducted for liraglutide for NICE technical appraisal (TA664)[4] and conducted new searches related to semaglutide.

The company performed their searches in relevant electronic databases and conferences (CS Appendix G Table 16 and section G.2.) The searches were conducted in April 2021. The ERG note that Health Technology Assessment (HTA) databases were not searched. The inclusion and exclusion criteria are presented in CS Appendix G Table 27. The original inclusion criteria for TA664[4] were for patients treated with liraglutide, orlistat or usual care (diet and physical activity) and the new searches for this appraisal included patients treated with semaglutide. Studies were only included if they were conducted in the UK.

From the 58 publications that met the inclusion criteria, seven were included in the company's review of cost-effectiveness / cost utility studies. None of the studies were for treatment with liraglutide or semaglutide. More details of the studies are reported in CS section 3.1 and CS Appendix G.7.

ERG conclusion

The ERG considers the company's review may have missed some potentially useful studies because they have not included studies outside the UK and they do not appear to have searched the grey literature, e.g. HTA reports. Studies conducted outside the UK may have been useful if they had reported the cost-effectiveness for semaglutide or liraglutide. Nevertheless, the ERG considers the most relevant published publication to be the NICE appraisal for liraglutide (TA664)[4] and the company based their cost-effectiveness model on the one developed for TA664.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

The NICE reference case checklist for the company's model is shown in Table 31. The ERG considers that the company model meets all the criteria of the NICE reference case.

Table 31 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, although would be better as 50 year time horizon.
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of	Yes

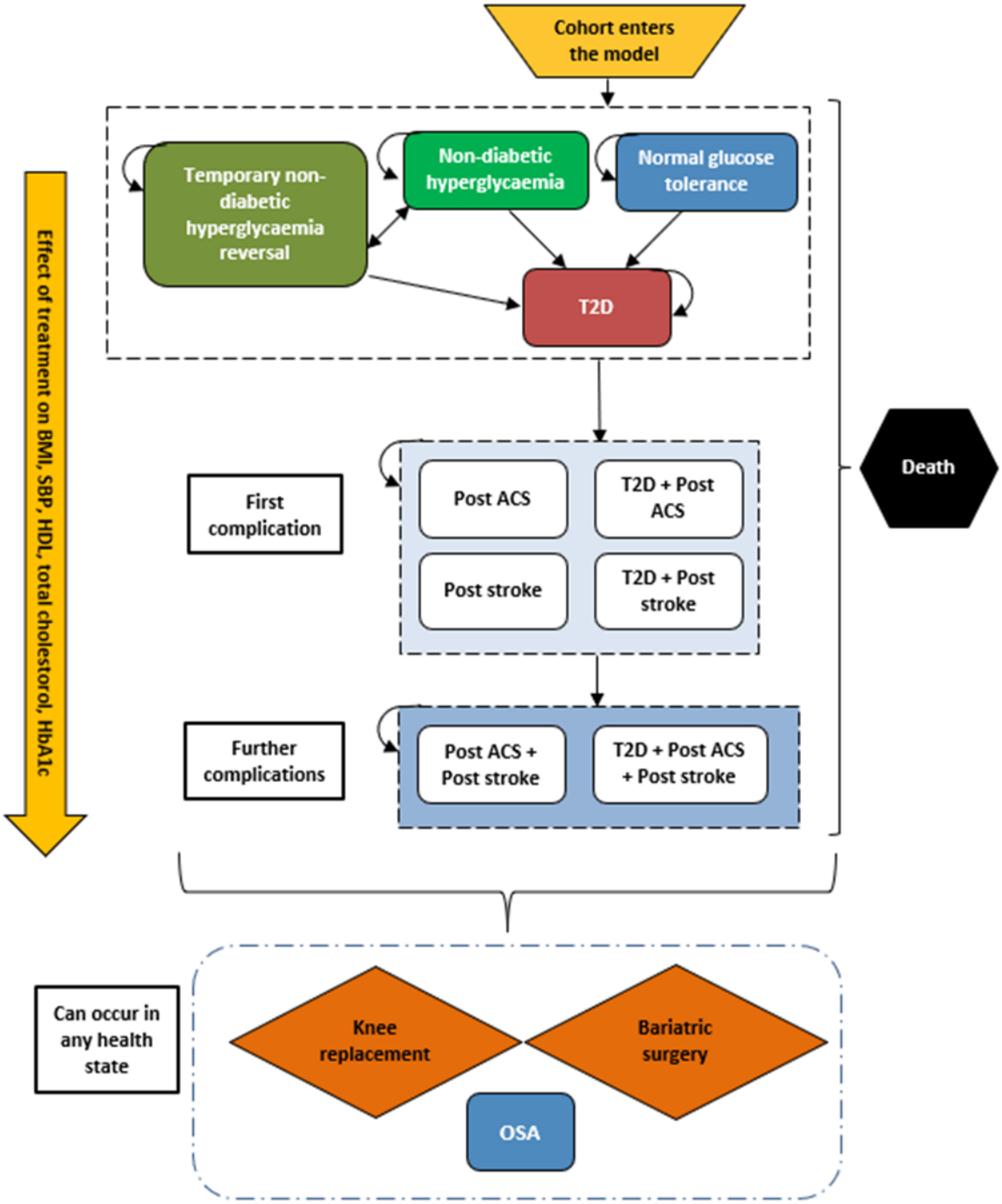
	the other characteristics of the individuals receiving the health benefit	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company developed a cohort state transition model using Microsoft Excel. The model structure is shown in Figure 1 (CS figure 11). The model was adapted from the model submitted to NICE as part of TA664 for liraglutide.[4] The model has a cycle length of three months for the first year, to allow for the incorporation of treatment discontinuation and then annual cycles thereafter. The model consists of 11 health states: Temporary non-diabetic hyperglycaemia reversal, Non-diabetic hyperglycaemia, Normal glucose tolerance (NGT), type 2 diabetes (T2D), Post acute coronary syndrome (ACS), Post stroke, T2D + post ACS, T2D + Post stroke, Post ACS + Post stroke, T2D + post ACS + post stroke. In addition to the health states, there are acute events that may occur from any health states for knee replacement, bariatric surgery and obstructive sleep apnoea (OSA).

Figure 1 Obesity model structure



Key: ACS, Acute coronary syndrome; BMI, body mass index; HDL, high density lipoprotein; OSA, obstructive sleep apnoea; SBP, systolic blood pressure; T2D, type 2 diabetes.
Source: reproduction of CS Figure 11.

Individuals enter the model in the NGT or non-diabetic hyperglycaemia health states, according to the observed prevalence in the STEP 1 clinical trial. In the base case analysis (BMI ≥ 30 kg/m^2 with one or more obesity related comorbidities) 46.6% of patients have NGT and 53.4% have non-diabetic hyperglycaemia. For the subgroup analysis all patients have non-diabetic hyperglycaemia.

During each model cycle, the cohort moves between health states or may remain in the same health state. The likelihood of transition between health states is given by the transition probabilities and these are calculated from risk functions using surrogate outcomes (BMI, SBP, total cholesterol, HDL cholesterol and HbA1c). The risk functions are described in more detail in section 4.2.6. Individuals in the non-diabetic hyperglycaemia health state may have a temporary reversal of their hyperglycaemia (in month 3) and move to the temporary reversal of non-diabetic hyperglycaemia health state. After cessation of treatment, individuals who remain in this state return to the non-diabetic hyperglycaemia health state.

Following an ACS event (non-fatal MI or non-fatal unstable angina event), individuals transition to a post ACS state. They transition to a post-stroke health state following a cerebrovascular event (non-fatal stroke or transient ischemia attack (TIA)). Those individuals in the post ACS health state remain in the same state if they experience further MI or unstable angina events in the next cycles. If they experience a cerebrovascular event they transition to the post ACS + post-stroke health state. Similarly, individuals residing in the post-stroke health state can experience a further stroke or TIA event in the next cycles but remain in the same post-stroke state or experience a cardiovascular event and transition to a post ACS + post-stroke health state. Patients in the cardiovascular health states described above are divided between those with and without diabetes. Transition to death can occur from any of the model health states either as a fatal event occurs or based on disease specific and general population mortality.

Patients with non-diabetic hyperglycaemia move to T2D + post-ACS or T2D + post stroke states following an ACS or stroke event respectively. The CS states that this assumption was previously used in TA664. The ERG notes that the NICE committee had reservations about this assumption and there was no good evidence to determine the proportion of people who develop type 2 diabetes after a cardiovascular event. The company includes a scenario analysis (CS Table 56) where patients do not develop T2D after a CVD event. Clinical advice to the ERG suggests that it is not possible to assume that patients will develop T2D after a CVD event. Therefore, in the ERG base case in section 6, we assume that patients do not develop T2D after a CVD event.

The benefits of treatment are introduced into the model through changes in the intermediate clinical outcomes (BMI, SBP, total cholesterol, HDL cholesterol) from the STEP 1 trial (described in more detail in section 4.2.6). Patients discontinue treatment after three months on the maintenance dose if they are a non-responder (defined as less than 5% weight loss

from baseline) or for other reasons such as adverse events. There is a maximum treatment duration of two years. Patients who discontinue treatment assume the same treatment efficacy as the diet and physical activity arm. Treatment effect is assumed to wane in a linear fashion over three years after discontinuation of treatment. Patients' clinical outcomes (BMI, SBP, total cholesterol and HDL cholesterol) gradually revert to be equal to those in the diet and physical activity arm and from there follow on the same path (CS Figure 12 and 13).

The model assumes a natural BMI increase after the treatment period of 0.1447 kg/m^2 for males and 0.1747 kg/m^2 for females per year for the diet and physical activity arm, as estimated by Ara et al.[24] After individuals reach 68 years, no further weight increase is assumed. Projected BMI change for semaglutide 2.4 mg and diet and physical activity over time is shown in CS Figure 12.

There are more recent studies estimating natural weight gain, such as Iyen et al. [25]. Iyen et al estimated BMI trajectories for a cohort of 264,230 individuals in the UK followed for 10 years. There was a mean increase of 1.06 kg/m^2 over 10 years. Zaninotto et al[26] explored BMI trajectories in the English Longitudinal Study of Ageing. They reported that after age 66 years, there was a steep decrease in individual's BMI, in contrast to the company's assumption of no change in weight after age 68 years. We conduct scenario analyses using these sources (section 6).

OSA is accounted for by calculating costs and quality of life decrements for the estimated prevalence of OSA each cycle. Osteoarthritis is not included in the model except for related to knee replacement. T2D microvascular complications are not included as distinct health states. For a proportion of patients with T2D, higher costs apply reflective of microvascular conditions.

Assumptions

An abridged summary of the main model assumptions is presented in Table 32.
Assumptions related to risk functions are discussed in section 4.2.6.

Table 32 Summary of assumptions applied in the economic model

Analysis setting	Assumption / Setting	Company justification	ERG comments
Assumptions that differ from TA664[4]			
Comorbidities included	ACS T2D Stroke Sleep apnoea Osteoarthritis	Conservative assumption of limiting to the most economically significant comorbidities to reduce the number of health states and complexity. TA664 also included cancer health states. These were removed to reduce complexity and incorporate feedback provided by the ERG during TA664.	We agree it is reasonable to focus on those health states that are mostly impacted by reducing obesity and thus have the most impact on model results.
Mortality	Disease specific and BMI adjusted mortality (CPRD study)	Mortality was also adjusted by BMI in order to avoid underestimating the mortality and costs. In TA664 no adjustment for BMI was applied	We agree
Application of acute and health state disutilities	Acute event and health state disutilities are assumed to be additive.	Assumption, given existing evidence Gough et al. 2009 and TA664. Some disutilities have been updated since TA664 due to more appropriate sources identified in the literature searches.	Although TSD 12 recommends that disutilities should be multiplicative, we consider there is evidence that using additive disutilities are appropriate, see section 4.2.7.3.
Application of acute and health state costs	Acute event costs and health state costs are assumed to be additive.	Additive health state costs is in line with Ara et al. 2012[24] and TA664.[4] Cost sources were updated as a new targeted literature review were used, resulting in different cost inputs compared to TA664.	We agree.
Assumptions consistent with TA664			
Catch up rate for BMI and surrogate outcomes	Pharmacotherapy returns to value of natural progression in diet and physical activity at a constant rate of 33% per year	The application of a constant rate of 33% per year following treatment cessation is in line with Ara et al. 2012 and TA664 which assumed BMI	We consider the rate of weight gain after treatment cessation is uncertain as

Analysis setting	Assumption / Setting	Company justification	ERG comments
		returned to baseline value at 3 years after treatment cessation in a linear fashion.	there are no available follow-up in the STEP 1 or pharmacological weight loss clinical trials.
Natural weight increase after treatment discontinuation	Weight increase following Ara 2012 in the CPRD dataset, until the cohort reaches 68 years old in all treatment arms	Natural weight increase is a common assumption in obesity models supported by a model developed by NICE. Support is also found in the study by Heitmann and Garby, 1999 and the analysis on the UK CPRD.	There are more recent studies estimating natural weight gain, such as Iyen et al.[25] and Zaninotto.[26] We conduct scenario analyses using these sources (section 6).
Progression of SBP, total cholesterol and HDL cholesterol post-treatment and post waning of treatment effect periods	Post-treatment and waning of treatment effect, SBP, total cholesterol, and HDL cholesterol were assumed constant for the remainder of the time horizon.	For reasons of simplicity, the model only accounted for evolution based on the treatment effect. The cohort returns to baseline value, corresponding to the average in the cohort, which is then maintained over the entire time horizon of the model when treatment is discontinued. However, as the cohort is assumed to remain treated with antihypertensive medications, and accrues the cost of this, it is plausible to assume the averages would remain stable.	We agree.
Temporary reversal of non-diabetic hyperglycaemia to a NGT state, maintenance of the glucose status effect over time and risk of T2D in non-diabetic	All patients in the non-diabetic hyperglycaemia state were assigned a higher risk of developing T2D (vs NGT patients) by modification of the glycaemic status parameter in the corresponding T2D risk equations. In line with changes in glycaemic status	According to published risk equations, patients with non-diabetic hyperglycaemia have a higher risk of developing T2D than those with normal glucose tolerance. Changes in glycaemic status observed in STEP 1 and SCALE 1839 were applied in the model starting from Cycle 2.	We agree.

Analysis setting	Assumption / Setting	Company justification	ERG comments
hyperglycaemia vs NGT	observed in the STEP 1 and SCALE 1839 trials, a proportion of patients in semaglutide 2.4 mg, liraglutide 3.0 mg and diet and physical activity arms temporarily reverted to a normal glycaemic status whereby a lower risk of T2D was applied. All patients reverting to NGT were assumed to return to a non-diabetic hyperglycaemia status at the end of the treatment effect waning period at a constant rate of 33% per year, assuming glycaemic status be correlated with weight loss.	Non-diabetic hyperglycaemia reversal was assumed to be a consequence of the initial weight loss and thus applied in the model to occur at the same time. Consequently, the loss of temporary normo-glycaemia was also assumed to occur at the same time with the complete loss of the initial weight loss benefit.	
Stopping rule	Semaglutide 2.4 mg (if >5% weight loss not achieved at 28 weeks) Liraglutide 3.0 mg (if >5% weight loss not achieved at 16 weeks)	In line with anticipated semaglutide 2.4 mg marketing approval. In line with regulatory approval for liraglutide 3.0 mg.	We agree. We note that a stopping rule was not included in the STEP 1 clinical trial.
Treatment duration	2 years for semaglutide 2.4mg, liraglutide 3.0mg and diet and physical activity	This reflects clinical practice as weight management in SWMS is provided for two years. It is worth noting that after two years patients in the semaglutide 2.4 mg arm and the comparator arm transition to diet and physical activity alone because diet and physical activity is considered to be an integral part of lifelong weight management.	We agree.
Treatment discontinuation / retreatment	Patients who discontinued semaglutide 2.4 mg or liraglutide 3.0 mg treatment were assumed to remain on a diet and physical activity	Diet and physical activity was considered an integral part of the treatment of all individuals with obesity, regardless of any pharmacological or surgical intervention co-	We agree.

Analysis setting	Assumption / Setting	Company justification	ERG comments
	program for the rest of the analysis time horizon. It was assumed that there would not be any repeated course of treatment with pharmacotherapy	administered. No published clinical data was available to provide evidence with regards to a 'stop and re-start' type of weight management.	
Key: ACS, acute coronary syndrome; BMI, body mass index; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; HDL, high-density lipoprotein; HRQoL, health-related quality of life; NGT, normal glucose tolerance; SBP, systolic blood pressure; T2D, type 2 diabetes; TLR, targeted literature review.			

Source: CS Table 51

ERG conclusion

The ERG considers that the model structure is appropriate and reasonable. It is based on the model submitted to NICE for the appraisal of liraglutide 3.0 mg for managing overweight and obesity (TA664) which was considered by the NICE committee to be suitable for decision making. The previous model also included cancer health states. The CS comments that this state was removed to reduce complexity and following comments of the ERG during TA664. There remains uncertainty around the rate of weight gain following treatment cessation and the assumption that patients with non-diabetic hyperglycaemia would develop type 2 diabetes after a cardiovascular event.

4.2.3 Population

The target population for the economic evaluation comprised of adult patients with a BMI of ≥ 30 kg/m^2 with at least one weight-related comorbidity (base case) and ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and high risk for CVD. We refer to this subgroup in this report as the liraglutide-eligible subgroup.

The subgroup population is so defined in order to align with the recommended target population for liraglutide 3.0 mg (TA664).[4] The characteristics of the starting cohort for both populations are shown in Table 33 (CS Table 16) and were sourced from a post-hoc analysis of these subgroups in the STEP 1 clinical trial.

Table 33 Baseline characteristics for populations of interest

	Mean	
Patient characteristics	**BMI ≥ 30 kg/m^2 with one or more obesity related comorbidities**	**BMI ≥ 35 kg/m^2, with non-diabetic hyperglycaemia and high risk for CVD**
Used in comparison vs	Diet and physical activity	Liraglutide 3.0 mg
Age (years)	[redacted]	[redacted]
BMI (kg/m^2)	[redacted]	[redacted]
Height (m)	[redacted]	[redacted]
SBP (mmHg)	[redacted]	[redacted]
Total cholesterol (mg/dl)	[redacted]	[redacted]
HDL cholesterol (mg/dl)	[redacted]	[redacted]
HbA1c after T2D development (%)*	7.5	7.5
T2D duration (years)*	3.0	3.0
Triglycerides (mg/dl)	[redacted]	[redacted]
Proportion Triglyceride level >150 mg/dl (%)	[redacted]	[redacted]
Proportion current smokers (%)	[redacted]	[redacted]
Proportion females (%)	[redacted]	[redacted]
Proportion on lipid-lowering drug (%)	[redacted]	[redacted]
Proportion on antihypertensive medication (%)	[redacted]	[redacted]

Key: BMI, body mass index; HDL, high-density lipoproteins; KOL, key opinion leader; SBP, systolic blood pressure; T2D, type 2 diabetes.
Notes: *Based on KOL opinion, applied after onset of diabetes.
Source: STEP 1 trial [27]

Source: Reproduction of CS Table 16

ERG conclusion

The population chosen by the company differs from that in the final scope issued by NICE, which is adults who have a BMI of ≥30 kg/m^2 (obese) or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity. The CS states that a different population has been chosen as adult patients with a BMI of ≥ 30 kg/m^2 with at least one weight-related comorbidity are likely to benefit most from pharmacological treatment with SWMS in NHS clinical practice.

The ERG notes that tier 3 SWMS currently only see people with a BMI ≥35 kg/m^2 (obese); few people with a BMI of 30 to 35 kg/m^2 are treated within these services (see discussion in section 2.2.3). The ERG's clinical expert commented that that

people with higher BMIs than those included in the STEP 1 trial are typically seen in practice and thus people have more comorbidities (see section 3.2.1.2).

We also note the cost-effectiveness of semaglutide 2.4 mg is sensitive to the starting BMI of individuals (CS Figure 20). We have therefore presented results for different starting BMI cohorts in section 6**Error! Reference source not found.**.

4.2.4 Interventions and comparators

Semaglutide 2.4 mg is compared to diet and physical activity (for the population with BMI ≥ 30 kg/m^2 with at least one weight-related comorbidity) and liraglutide 3.0 mg (for the subgroup population with BMI ≥ 35 kg/m^2 non-diabetic hyperglycaemia and high risk for CVD).

The NICE scope also includes orlistat as a comparator which was not been included in the CS. The CS states that orlistat is not a relevant comparator for semaglutide 2.4 mg as it is no longer widely used in clinical practice. Further, in the NICE appraisal TA664,[4] orlistat was not considered as an alternative to liraglutide 3.0 mg by the NICE committee and was therefore not included as a comparator. As discussed in section 2.3, we agree it is reasonable to exclude orlistat as a comparator.

4.2.5 Perspective, time horizon and discounting

Costs are estimated from the NHS and Personal Social Services (PSS) perspective. Costs and QALYs are discounted at 3.5% in the base case (CS Tables 19). The model outcomes and costs are estimated over a lifetime horizon (40 years). Alternative time horizons of 20, and 30 years are considered in scenario analyses, but this assumption does not have a significant impact on the model results (CS Tables 56). We note that the most recent NICE appraisal for liraglutide 3.0 mg (TA664)[4] also applied a 40-year time horizon. The CS comments that there is a difference of less than 0.1% of patients alive between treatment arms after 40 years and therefore any subsequent differences beyond the modelled time horizon are expected to be minimal. The ERG considers that the lifetime horizon would be better for 50 years (until mean age of patients is 99 years), however we do not expect the results to change significantly with a longer time horizon.

ERG conclusion on perspective, time horizon and discounting

The company adopted the recommended perspective and discounting rates and an appropriate time horizon, which are all in line with NICE guidelines and previous NICE appraisals.

4.2.6 Treatment effectiveness and extrapolation

Transition probabilities between health states used in the model for T2D and cardiovascular events are based upon risk functions. The risk functions use intermediate endpoints, i.e. BMI, SBP, HDL and total cholesterol and HB1A1c to calculate transition probabilities. The treatment effect of the intervention is incorporated through a reduction in these intermediate clinical outcomes in the STEP 1 trial.

4.2.6.1 Treatment effect

The treatment effect is applied by a reduction in the clinical outcomes to the mean baseline values in each treatment arm. The outcomes used in the model are BMI, SBP, total cholesterol and HDL cholesterol and change in glycaemic status. The treatment effects for semaglutide 2.4mg and diet and physical activity for both subgroups were sourced from the FAS population of the STEP 1 clinical trial. The company state that this is reasonable as the population was defined a priori in the STEP 1 trial and therefore is a statistically robust measure of the treatment effect. The company conducted scenarios using the treatment effect specific to each of the subgroups, rather than using the FAS treatment effect (CS Table 56 and CS Table 60) and the results were similar to using the FAS treatment effect.

The trial product estimand is used in the model to reflect the treatment effect of those patient who remain on treatment. Note this differs from the treatment effect seen in the trial, reported in CS section 2.6. The model uses a stopping rule for non-responders which was not included in the STEP 1 trial. The trial product estimand used in the model is an adjusted treatment effect to incorporate this stopping rule. The trial product estimands for BMI (% weight change), SBP, total cholesterol and HDL cholesterol are shown in Table 34 (CS Table 21) for semaglutide 2.4 mg, diet and physical activity and liraglutide 3.0 mg (CS Table 23). The ERG considers the use of the trial product estimand to incorporate the effect of treatment discontinuation to be a reasonable and appropriate approach. The trial product estimand appears to be consistent with the treatment effect reported in the trial (see section 5.3). We note that the company STEP 1 trial did not include a stopping rule and there is some uncertainty about whether this will be included in the marketing authorisation for semaglutide 2.4mg (CS B3.2.3.1).

The treatment effect for liraglutide 3.0 mg was taken from the SCALE 1839 trial. In the absence of head-to-head data, the efficacy of liraglutide was adjusted based on the results of an indirect treatment comparison (discussed in section 3.4). The CS states that the adjustment was made to increase the estimated efficacy estimates of liraglutide by size of the difference between the efficacy estimates in the placebo arms (all patients) of STEP 1 and SCALE 1839.

Table 34 Change in physiological parameter values – STEP 1 and SCALE 1839 early responders

Parameter and timepoint in model	Semaglutide 2.4 mg: full analysis set N = 1306 Early responders n = [redacted]	Diet & physical activity: full analysis set N = 655	Liraglutide 3.0 mg: early responders N = 1456 (Week 28) Early responders n = [redacted] (Week 56)
	Mean change from baseline	Mean change from baseline	Mean change from baseline
Weight change (% change)			
Month 4	-12.04%	-2.69%	-10.00%
Month 7	-12.04%	-2.69%	-10.00%
Month 10	-13.22%	-2.44%	-10.00%
Year 1	-18.47%	-2.44%	-10.42%
Year 2	-18.47%	-2.44%	-10.24%
SBP change (mmHg)			
Month 4	-5.93	-0.56	-4.46
Month 7	-5.93	-0.56	-4.46
Month 10	-6.48	-1.14	-4.46
Year 1	-7.63	-1.14	-5.19
Year 2	-7.63	-1.14	-5.96
Total cholesterol change (mg/dl)			
Month 4	-15.27	1.39	-5.58
Month 7	-15.27	1.39	-5.58
Month 10	-15.92	0.18	-5.58
Year 1	-9.20	0.18	-2.25
Year 2	-9.20	0.18	-1.11
HDL cholesterol change (mg/dl)			
Month 4	-4.63	-0.96	-3.34
Month 7	-4.63	-0.96	-3.34
Month 10	-4.76	1.07	-3.34
Year 1	2.97	1.07	2.07
Year 2	2.97	1.07	2.17

Key: HDL, high density lipoprotein; SBP, systolic blood pressure.
Note: Early responders are defined as patients that achieve more than 5% weight loss at 28 weeks

Source: CS Table 21 and Table 23

The company assumes that the effect of treatment on BMI, surrogate outcomes (SBP, HDL and total cholesterol) and glycaemic status reduces linearly over three years after treatment cessation. At the end of three years, clinical parameters have returned to the same level as patients who received diet and physical activity alone. After the first model cycle (3 months), a proportion of patients with non-diabetic hyperglycaemia have glycaemic status reversal (90.4% for those treated with semaglutide 2.4 mg, 45.8% for diet and physical activity and 83.6% for liraglutide 3.0 mg). These patients will revert back to a non-diabetic hyperglycaemic status at the end of the treatment effect waning period at a constant rate of 33% per year. The proportions with glycaemic reversal for semaglutide 2.4 mg and diet and physical activity has been adjusted with an odds ratio between liraglutide and placebo (all patients) in the SCALE 1839.

4.2.6.2 Estimation of transition probabilities (risk equations)

The risk equations used to estimate transition probabilities between health states and for acute events are shown in Table 35 (CS Table 30). The risk equations use the cohort's mean clinical parameters combined with coefficients to estimate the risk of T2D and cardiovascular events. Where variables in the risk equations are not included as cohort characteristics or surrogate outcomes in the model, the average values of the derivation cohort of the risk equations were used and maintained constant over the time horizon of the analysis. The QRisk3,[28] QDiabetes[29] and UKPDS82[30] were large UK-based studies. The risk equations are described in more details in CS Appendix L.

Table 35 Risk equations used for obesity-related complications

Complication	Risk equation(s) available in model	Company justification for base case selection
Onset of T2D	QDiabetes-2018 Model C [29]	QDiabetes allows prediction of 10-year risk and includes BMI and HbA1c as predictive variables. This is in line with assumptions from TA664. [4]
	Framingham Offspring (scenario) [31]	
First CVD event	Qrisk3[28]	QRisk3 was estimated from a UK cohort and as such is being used in UK. This is in line with assumptions from TA664.[4]
	Framingham Heart Study (scenario) [32]	
Recurrent event	Framingham Recurring Coronary Heart Disease[32]	The only risk equation identified for recurrent CVD events in non-diabetic

		patients. This is in line with assumptions from TA664.[4]
First CVD event in T2D	UKPDS82[30]	The UKPDS 82 risk model (outcome model 2) is a large UK study and able to predict both first and recurrent CVD events after the onset of T2D. This is in line with assumptions from TA664[4]
	QRisk3[28]	
Incidence of recurrent CVD event in T2D	UKPDS82[30]	
	Framingham Recurring Coronary Heart Disease (scenario) [32]	
Onset of OSA	Sleep Heart Study[33]	This study was preferred to other available studies because it was the largest in sample size (n=5,615), it provided sufficient data to calculate a prevalence rate per unit BMI, and it investigated the prevalence of moderate-to-severe OSA (AHI ≥15), given that in the present health-economic analysis, OSA was assigned a hospital cost for continuous positive airway pressure treatment.
Knee replacement	Wendelboe et al. 2003[34]	The study provided granular data on the association between BMI and incidence of knee surgeries by 2.5 BMI-unit steps for observed BMI levels between 17.50 and 42.49 kg/m^2.

Source: reproduction of CS Table 30

Based on the QDiabetes equation the risk of developing T2D is higher in the cohort with non-diabetic hyperglycaemia than the NGT cohort. The risk factors for T2D included in the QDiabetes algorithm are shown in CS Appendix Table 58. HBA1c levels (blood sugar levels) were set constant in the model at 37 mmol/mol in NGT and 47 mmol/mol in non-diabetic hyperglycaemia. The ERG notes that HBA1c levels were recorded in the STEP 1 study (CS section 2.6.6).

The QRisk3 equation is used to derive the absolute risk of CVD in primary prevention in the base case. The risk factors for CVD in primary prevention used in the QRisk3 prediction model are shown in CS Appendix Table 61. The model stratifies the risk of CVD into the risk of angina, MI, stroke and TIA according to the proportions shown in CS Table 31.

The UKPDS 82 risk model is used to predict both first and recurrent CVD events after the onset of T2D. The risk factors and coefficients from UKPDS82 for CVD in primary prevention in the T2D cohort are shown in CS Appendix 64 and for 2nd MI and 2nd stroke are shown in CS Appendix Table 67. Generally, the ERG prefers the QRisk3 risk model to UKPDS 82 as this study is more recent so it is our view that the QRisk3 risk model should be used for the

prediction of CVD in individuals with T2D. This is also consistent with the risk model used for 1st CVD events for individuals without T2D.

Sleep apnoea is included as a comorbidity in the model with the prevalence of OSA dependent on BMI according to the Sleep Heart Health Study. Sleep apnoea prevalence by BMI level is shown in CS Appendix Table 48.

The risk of knee replacement is stratified by BMI, gender and age (<65; >65 years). The annual incidence was sourced from the study of Wendelboe et al.[34]. The risk functions for knee osteoarthritis are shown in CS Table 32.

Bariatric surgery is an option for people with severe obesity in whom non-surgical interventions have been tried but the individuals did not achieve the required weight loss. The criteria for bariatric surgery in the England is BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with at least one comorbidity such as T2D or CVD. The company assumes the proportion of eligible patients undergoing bariatric surgery is 1.15% per year.[1] The model treats bariatric surgery as an annual event for patients who fulfil the above criteria. There are three types of bariatric surgery currently used available: gastric bypass, laparoscopic banding and sleeve gastrectomy. The prevalence of the types of bariatric surgery and their efficacy are shown in CS Table 27.

4.2.6.3 Mortality

Patients may die from any health state and mortality is split into short (associated with acute events) and long-term mortality. Mortality from CVD events, knee replacement and bariatric surgery are shown in CS Table 34. General population mortality from UK lifetables[35] was adjusted by excluding mortality of obesity related complications. Mortality was adjusted by a hazard ratio for BMI, based on Bhaskaran et al.[36] For patients in the Post ACS and Post stroke health states, a relative risk was applied to the mortality rate (CS Table 33).

The model does not include a hazard ratio for Type 2 diabetes mortality. A study by Mulnier et al[37] followed a cohort of patients with and without diabetes from the General Practice Research Database. They found higher mortality in individuals with diabetes than without. The HR for all-cause mortality in Type 2 diabetes compared with no diabetes was 1.93. However, we consider this HR for all-cause mortality may already be included within the hazard ratio for BMI and post-MI and post stroke and so we consider it is appropriate not to include a separate HR for Type 2 diabetes.

4.2.6.4 Treatment discontinuation

Treatment discontinuation occurs in the model due to:

i) Per cycle discontinuation due to any reason, such as adverse events,

ii) Non-responder early discontinuation or stopping rule,

iii) Maximum treatment duration of two years.

The probability of discontinuation per cycle was taken from the Kaplan-Meier curve of time to discontinuation.

The non-responder discontinuation / stopping rule applies to individuals who do not lose 5% of their initial body weight after 12 weeks of the maintenance dose. Thus, the stopping rule occurs after 28 weeks for semaglutide (16 weeks titration period, 12 weeks maintenance dose) and 16 weeks for liraglutide (4 weeks titration period, 12 weeks maintenance dose). The CS states that the company is expecting the marketing authorisation for semaglutide 2.4 mg to include a stopping rule that treatment would be discontinued for non-responders after 12 weeks on the maintenance dose, as is the case for liraglutide 3.0 mg.

4.2.6.5 Adverse events

Treatment related adverse events are included in the model for non-severe hypoglycaemia and severe gastrointestinal events. The incidence of the adverse events during the treatment period are shown in CS Table 25. AE rates were sourced from the STEP 1 trial for semaglutide 2.4 mg and the SCALE 1839 trial for liraglutide 3.0 mg.

ERG conclusion on treatment effectiveness and extrapolation

The company uses a trial product estimand for those patients who remain on treatment. The ERG considers the use of the trial product estimand to incorporate the effect of treatment discontinuation to be reasonable and appropriate. The company has provided validation to show that the trial product estimand appears to be consistent with the treatment effect reported in the trial (see section 5.3). We note that the company STEP 1 trial did not include a stopping rule and there is some uncertainty about whether this will be included in the marketing authorisation for semaglutide 2.4mg (CS B3.2.3.1).

The company used risk equations to estimate the long-term risk of morbidity. We consider that the use of these risk equations is appropriate to model diabetes and

cardiovascular outcomes based on surrogate outcomes. The same risk equations were used as in TA664. For that appraisal, the NICE committee accepted that the risk equations selected in the company's and ERG's base case were both suitable for decision making.

4.2.7 Health-related quality of life

4.2.7.1 Systematic literature review for utilities

The company conducted a systematic literature search to identify HRQoL studies for adults with obesity by updating searches that had previously been conducted for liraglutide for NICE technical appraisal (TA664)[4] and conducting new searches related to semaglutide. The search strategy is described in CS Appendix H. The searches were conducted on 14 April 2021. The company searched relevant database (see CS Appendix Table 32 and 33).

The eligibility criteria for the HRQoL studies included adults with BMI ≥35 kg/m^2 with treatment with liraglutide, orlistat, usual care (diet and physical activity) in the original review for TA664 and semaglutide for the current appraisal. (CS Appendix Table 44 and 45). The searches identified 26 unique HRQoL studies after abstract and full-text screening. The company comments that the studies identified were not relevant for the current economic analysis and were therefore not used.

4.2.7.2 Study-based health-related quality of life

The SF-36 and IWQOL-lite-CT HRQoL measures were collected from patients in the STEP 1 trial. These are reported in more detail in CS section B 2.6.9. The company comments that these measures are not consistent with the NICE reference case and do not yield utilities that could be used in the economic model.

4.2.7.3 Health-related quality of life data used in the company's cost-effectiveness analysis

The approach the company used for health-related quality of life was to use a baseline utility for individuals with no complications (in the normal glucose tolerance, non-diabetic hyperglycaemia and temporary non-diabetic hyperglycaemic reversal health states), based on age and BMI. Individuals in other health states or who suffer an acute event (such as stroke, TIA or knee replacement) are assigned a utility decrement associated with that health state or event.

4.2.7.3.1 Baseline utility

The company uses the study by Søltoft et al[38] for the baseline utility values. This study analysed the EQ-5D responses of 14,416 adults in the 2003 Health Survey for England. The company chose this study because it adjusted the utilities so that they are free of any additional obesity related comorbidities and the utility values are reported with coefficients for age and BMI. The ERG consider this to be an appropriate approach.

The utility curves related to BMI from Søltoft et al[38] are shown in CS Appendix Figure 15. The company notes that utility values appear to decline linearly after a BMI level of 25 kg/m^2. They therefore fit a linear function to the curve after this point. The coefficients used for utility based on BMI are shown in Table 36 (CS Table 35).

Table 36 Coefficient used to estimate baseline utility values based upon BMI

Parameter	(BMI 15-35 kg/m^2)		(BMI 36 kg/m^2 and beyond)	
	Males	**Females**	**Males**	**Females**
BMI3	0.000033	0.000017	.	.
BMI2	-0.003200	-0.001800	.	.
BMI	0.099000	0.057200	-0.105431	-0.147297
Constant	-0.020554	0.401769	1.323834	1.462846
Key: BMI, body mass index.				

Source: reproduction of CS Table 35

In a similar way utility values were adjusted for age based on the coefficients reported in Søltoft et al[38]. The coefficients from the Søltoft et al study are shown in CS Table 36.

4.2.7.3.2 Decrements in utility associated with acute events

Non-fatal acute events considered in the model include ACS, knee replacement, stroke and TIA. A one-off disutility is applied for these events in the first cycle in which the event occurs. To account for the impact of living with musculoskeletal disorder, patients receiving knee replacement are assumed to have the disutility applied for three years. Disutility values are taken from Søltoft et al[38] and Sullivan et al.[39]

Sullivan et al compiled a UK-based catalogue of EQ-5D index scores based on 79,522 individuals with completed EQ-5D scores. Utilities from the Søltoft et al. and Sullivan et al. sources are consistent with the NICE reference case. If a fatal event occurs in the acute event state then the fatal event is assumed to occur at the mid-point of the cycle so only half

the acute event disutility is applied and the patient moves to the dead health state. The disutility values associated with acute events are shown in Table 37(CS Table 37).

Disutilities related to bariatric surgery are treated in the model as one-off disutilities applied to the proportion of patients receiving bariatric surgery in each cycle. The disutility represents the decrement in quality of life associated with the surgical procedure and the related complications, based upon Campbell et al[40] and was estimated to be -0.184.

Two adverse events were included in the model for non-severe hypoglycaemia and severe gastrointestinal event. The disutilities for these two adverse events are shown in Table 37(CS Table 40).

4.2.7.3.3 Health state utility values

Health state values for T2D, OSA, Post ACS and Post-stroke are shown in Table 37 (CS Table 38) and use the same sources as the acute events.[38 39] When health states combine two or more obesity complications (e.g. T2D + Post ACS), the utility decrement for this health state is calculated by adding the utility decrements for each of the individual complications. The CS states that Gough et al.[41] concluded that HRQoL decrements associated with T2D and obesity showed no significant interaction and thus could be assumed to be additive. We note that the NICE technical support document 12[42] recommends multiplicative decrements. However, from studies that have reported multiple co-morbidities for diabetes,[39 43] we agree with the company and consider it is reasonable to treat co-morbidities as independent and add utility decrements. In addition, we note that this approach was also taken in TA664.[4]

We note that the decrement for type 2 diabetes is lower than reported in other studies such as Sullivan et al and Ara et al.[44] We use the utility decrement from Sullivan et al[39] (-0.0714) in a scenario in section 6. The decrement for knee replacement is lower in other sources, such as Sullivan et al.[39] (decrement -0.099). We conduct a scenario analysis using the value from Sullivan et al in section 6.

Table 37 Summary of utility values for cost-effectiveness analysis in the company's economic model

State	Utility value: mean (standard error)	Source
Baseline utility	0.901*	Søltoft et al. [38]
ACS	-0.063 (0.046)	Sullivan et al. [39]

Stroke	-0.117 (0.012)	Sullivan et al. [39]
TIA	-0.033 (0.022)	Sullivan et al. [39]
Knee replacement	-0.194 (0.048)**	Søltoft et al. [38]
T2D	-0.037 (0.009)	Søltoft et al. [38]
OSA	-0.038 (0.010)	Søltoft et al. [38]
Post ACS	-0.037 (0.026)	Sullivan et al. [39]
Post-stroke	-0.035 (0.021)	Sullivan et al. [39]
Bariatric surgery	-0.184 (0.046)	Campbell et al[40]
Non-severe hypoglycaemia	-0.0062 (0.002)	Foos et al[45]
Severe gastrointestinal	-0.050 (0.0002)	TA494[12]
Key: ACS, acute coronary syndrome; OSA, obstructive sleep apnoea; T2D, type 2 diabetes; TIA, transient ischemic attack. **Note:** *Baseline for BMI >30 + 1 or more comorbidities is 0.901; Baseline for BMI >35 + non-diabetic hyperglycaemia and high CVD risk is 0.889; Coefficients were not varied; ** Literature value multiplied by three to account for three years of living with osteoarthritis		

Source: CS Table 41

ERG conclusion on HRQoL

The company's approach to estimating utility values is generally reasonable and consistent with the NICE reference case. The ERG notes that the utilities used in this appraisal are largely the same as those used in TA664[4], with the exception of the utility values used for non-severe hypoglycaemia adverse event.

4.2.8 Resources and costs

The costs included in the economic model consist of drug acquisition costs for weight loss treatments, costs for obesity monitoring, health state management costs, acute event costs (including knee replacement and bariatric surgery) and costs for managing AEs.

The company conducted a SLR to identify studies reporting cost and health care resource use data for the treatment of patients with obesity. More details on the review are discussed briefly in this report in section 4.1 and CS Appendix G and I. Three studies were identified but the company reports that the studies did not focus on the patient population or treatments identified as relevant to the decision problem and were therefore not used in the model. The ERG considers that the company's literature review is likely to reflect the available evidence and agrees that the identified studies are not relevant for this appraisal.

The company has conducted a targeted literature review for the costs used in the model. CS Table 47 shows a comparison between the costs used in the current appraisal with those used TA664[4] for liraglutide 3.0 mg.

4.2.8.1 Drug acquisition and monitoring costs

As detailed in section 2.2.2, semaglutide is self-administered once weekly as a subcutaneous injection. The maintenance dose of semaglutide is 2.4 mg (Table 38). The dose is gradually increased over 16 weeks. The titration dose of each of the 16 weeks is shown in CS Table 42. Semaglutide has a list price of [redacted] per pack and each pack contains four pre-filled pens containing a 2.4mg dose.

Liraglutide is administered daily in a similar manner to semaglutide 2.4 mg. The maintenance dose of liraglutide is 3.0 mg and the dose is increased over the first four weeks of treatment. The titration dose of each of the four weeks is shown in CS Table 42. The list price for liraglutide 3.0mg is £196.20 per pack and each pack contains five pre-filled pens containing 18mg of liraglutide (Table 38).

Liraglutide 3.0 mg is available with a confidential price discount (PAS price). Semaglutide 2.4 mg does not currently have an agreed PAS (discussions are ongoing with NHS England). All analyses in this report are for the list price with additional analyses with the PAS prices reported by the ERG in a confidential appendix.

The cost of obesity monitoring includes cost for routine visits, examinations (GP visits and nurse visits and blood tests, see Table 38). The annual monitoring costs is £248.90. The breakdown of the monitoring costs is shown in CS Table 42. There is also an annual cost for blood pressure treatment of £17.66. The ERG considers that monitoring costs have been underestimated as they do not include the costs for dietitian and specialist consultations. In response to the ERG's question B20 in the appraisal for liraglutide 3.0 mg (TA664), the company estimated an annual cost of £353.60. However, we note that as monitoring costs are applied equally across arms, changes to the monitoring costs will have no effect on the ICERs.

Table 38 Treatment and monitoring costs (list price)

Treatment costs	Cost (£)	Description and references
Semaglutide (2.4 mg/ week)	[redacted]	4 pens, 2.4mg per pen Maintenance dose 2.4mg / week
Liraglutide (3.0 mg/ day)	£196.20 per pack	Maintenance period dose: 3.0mg per day:
Monitoring costs for obesity, annual	£248.90	Annual frequency (assumed equal to orlistat and rimonabant) * cost for 3 types of visits:

Treatment costs	Cost (£)	Description and references
		• GP visit: Frequency: 4x10 mins • Nurse visit: Frequency: 8x15 mins • Blood test (1 test)
Blood pressure treatment	17.66	Average annual cost of ACE inhibitor treatment.

Source: CS Table 42

4.2.8.2 Health state costs

The annual health state costs for obesity related complications include the costs for monitoring and treating a given disease and are shown in Table 39 (CS Table 43). In addition to the diabetes health state costs, there is a cost for insulin treatment and oral drugs for diabetes. The costs of health states including multiple obesity complications are calculated by summing the costs associated with each condition. The costs are derived from UK published studies. Costs are updated to 2020 costs using PSSRU[46] inflation indices. The costs of T2D microvascular complications are estimated by summing the costs associated with each condition from the study by Capehorn et al.[47] The ERG notes that costs of T2D microvascular complications are applied from onset of T2D. However, the ERG consider this unlikely as the risk of complications increase with the time since diagnosis.[48] The ERG has estimated the costs reported in Capehorn et al to be lower than used by the company of £507 per year and use these costs in the ERG base case in section 6.

Table 39 Annual obesity related complication costs applied to health states in the model

State costs	Cost (£)	Source
T2D microvascular complications costs	940.86	Capehorn et al[47]
T2D treatment – average of insulin and oral treatments	551.89	Capehorn et al[47]
Non-diabetic hyperglycaemia	54.00	NHS diabetes prevention programme
MI 1st year, excl. acute event cost	1,174.12	Alva et al[49]
Unstable angina 1st year, excl. acute event cost	1,056.18	Alva et al[49]
Post-acute coronary syndrome	846.29	Alva et al [49]
Stroke 1st year, excl. acute event cost	1,333.67	Alva et al[49]
Transient ischaemic attack, 1st year	1,338.77	Danese et al [50]
Post-stroke (stroke and TIA, in year following the event)	944.69	Alva et al[49]
Sleep apnoea cost	1,018.19	NHS reference costs 2018/19 [51]

State costs	Cost (£)	Source
Key: MI, myocardial infarction; T2D, Type 2 diabetes; TIA, transient ischemic attack.		

The sleep apnoea cost is applied to the proportion of patients with sleep apnoea. The cost is taken from NHS reference costs [51]. However, we consider the costs may be overestimated. The long-term annual costs for continuous positive airway pressure machines for sleep apnoea were estimated in Sharples et al[52] as £251.99 per year. We use this cost (inflated to 2020 prices) in the ERG base case in section 6.3.

4.2.8.3 Acute event costs, bariatric surgery and adverse event costs

The model includes one-off costs for the obesity related acute events unstable angina, MI stroke, TIA and knee replacement. These costs include the cost of management, including hospitalisation for the acute event. The cost of knee replacement also includes the cost of pre-surgery visits and examinations and post-surgery follow-up. Costs are taken from NHS reference costs 2018/19 and inflated to 2020 prices. The acute event costs are shown in CS Table 46.

Bariatric surgery is applied as a one-off cost and includes preoperative management, post-operative follow-up and surgery related complications. The average -procedure cost is calculated as the weighted average of the three types of procedure. Bariatric surgery costs are shown in CS Table 45.

The one-off costs for adverse events for non-severe hypoglycaemia and severe gastrointestinal events are £4.09 and £144.01 respectively.

ERG conclusion on resources and costs

The company's approach to resources and costs in the economic model are consistent with the NICE reference case and the previous technology appraisal for liraglutide 3.0 mg (TA664). Some of the cost estimates in TA664 have been updated based on a targeted literature search (CS Table 47). The approach is largely reasonable, with the exception of i) the costs for sleep apnoea and ii) applying the microvascular complication costs from onset of T2D.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company reported their base case results in CS Table 52, reproduced below in Table 40**Error! Reference source not found.** for the population of people with BMI ≥ 30 kg/m^2 with one or more obesity related co-morbidities. They also conducted a subgroup analysis for the population of people with BMI ≥ 35 kg/m^2, non-diabetic hyperglycaemia and high risk for CVD, comparing the cost-effectiveness of semaglutide 2.4mg versus liraglutide 3.0mg (CS Table 53). The company did not include diet and physical activity as a comparator for this analysis. We present the incremental results for all the comparators below.

The cost-effectiveness results, reproduced below in Table 40 and Table 41, are presented with list prices for all the treatment arms. The results with the PAS price discount for liraglutide 3.0mg is presented in a confidential addendum to this report.

Table 40 Company base case results for semaglutide 2.4 mg versus diet and physical activity (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Diet and physical activity	[redacted]	17.924	15.269				
Semaglutide 2.4 mg	[redacted]	17.957	15.361	[redacted]	0.034	0.092	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.							

Source: Reproduced from CS Table 52

Table 41 Subgroup results for semaglutide 2.4 mg versus liraglutide 3.0mg (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Diet and physical activity	[redacted]	17.288	14.311				
Liraglutide 3.0 mg	[redacted]	17.331	14.401	[redacted]	0.043	0.090	[redacted]
Semaglutide 2.4 mg	[redacted]	17.349	14.444	[redacted]	0.018	0.043	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.							

Source: Reproduced from CS Table 57

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The CS reports results for the one-way, deterministic sensitivity analysis in the tornado plots for: the base case in CS Figure 18 and the liraglutide-eligible subgroup in CS Figure 20 respectively. The ranges of variation for input parameters were based on confidence intervals obtained from standard errors of the mean (where available), or simple assumed percentages where empirical evidence was unavailable. The results indicated that the starting BMI of the cohort, the discount rate for QALYs, and the weight reduction at the start of Year 2 with diet and physical activity have the largest impact on the cost-effectiveness results.

5.2.2 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA), with input parameter distributions as reported in CS Tables 48-50. The company's probabilistic results are reported in CS Table 53 (base case) and Table 58 (liraglutide-eligible subgroup analysis). The cost-effectiveness scatter plot and acceptability curve for the base case are shown in CS Figures 16 and 17 respectively. For the liraglutide-eligible subgroup analysis, they presented the scatter plot in CS Figure 19. The ERG confirms that the probabilistic results for the base case are similar to the deterministic results. The probabilistic ICER for semaglutide 2.4mg compared with diet and physical activity is [redacted] per QALY gained compared with [redacted] per QALY for the deterministic ICER.

5.2.3 Scenario analysis

The company presented fifteen scenario analyses (CS Table 56 for the base case and Table 60 for the liraglutide-eligible subgroup analyses). We reproduce the results of the scenario analyses for the base case and the scenario analyses in Table 42 below.

Table 42: Scenario analyses explored in the economic model (list price)

Scenario	Base case (semaglutide 2.4 mg vs diet and physical activity)	Liraglutide-eligible subgroup (semaglutide 2.4 mg vs liraglutide 3.0mg)
	ICER (£/QALY)	ICER (£/QALY)
Base case	[redacted]	[redacted]
No stopping rule (using treatment policy estimand)	[redacted]	[redacted]
Post hoc analysis efficacy for subgroup (using efficacy data from patients with BMI ≥30 and one or more comorbidities.)	[redacted]	[redacted]
1-year catch up rate	[redacted]	[redacted]
2-year catch up rate	[redacted]	[redacted]
20-year time horizon	[redacted]	[redacted]
30-year time horizon	[redacted]	[redacted]
No bariatric surgery	[redacted]	[redacted]
Bariatric surgery eligibility threshold at BMI 47 kg/m^2	[redacted]	[redacted]
Bariatric surgery incidence at 0.57% per year	[redacted]	[redacted]
Framingham Offspring risk equation for incidence of T2D	[redacted]	[redacted]
Framingham Heart Study risk equation for incidence of first CVD event in NGT	[redacted]	[redacted]
Framingham Recurring Coronary Heart Disease risk equation for incidence of recurrent CVD event in T2D	[redacted]	[redacted]
QRisk3 risk equation for incidence of first CVD event in T2D	[redacted]	[redacted]
Patients with non-diabetic hyperglycaemia do not develop T2D immediately after a CVD event	[redacted]	[redacted]
Alternative baseline utilities, derived as a function of BMI based on SCALE data.	[redacted]	[redacted]

Source: reproduction of CS Table 56

For the base case, the model results are most sensitive to using a one year catch-up rate related to BMI and glycaemic reversal after treatment discontinuation, followed by the scenario with no stopping rule, the two year-catch up rate and using the risk equation using Framingham Offspring risk equation for the incidence of T2D. For these scenarios, the base case ICER [redacted]. Using a bariatric surgery eligibility threshold of BMI 47kg/m^2 as well the scenario with no bariatric surgery [redacted].

For the liraglutide-eligible subgroup analyses, semaglutide 2.4 mg remained [redacted].

5.3 Model validation and face validity check

The company approach to validation is described in CS section B.3.10. For quality control, the model checks included conducting top-down tests (i.e. changing input parameters), model functionality (i.e. testing all key parameters, extreme value tests), and internal consistency (i.e. accuracy of input data against source data). For external validation, the company cited the publication by Lopes et al [53] that reported that the model predicted CVD and T2D with a good degree of accuracy. They did not provide any information on internal validity, i.e. comparing the model results with outputs from the phase 3 STEP 1 trial or the SCALE 1839 trial.

The ERG conducted a series of quality checks of the company model. These included: checking that the input parameters in the model matched the values in the CS and in the original sources; and validating the results of the scenario and sensitivity analyses as reported by the company. We also conducted a series of 'white box' and 'black box' checks to validate the model. We did not identify any errors in the model. However, the ERG were unable to replicate the scenario using alternative baseline utilities, derived as a function of BMI based on SCALE data.

5.3.1 Internal validation

For internal validation, the company provided a comparison of the modelled estimated clinical events (mean BMI, SBP and total cholesterol) for the first two years with the trial product estimand data, as response to clarification question B10. We note that the change in the clinical outcomes for semaglutide 2.4mg at 2 years from baseline are slightly higher compared to that of the change in the trial outcomes at 68 weeks from baseline. However, we do not anticipate these differences to impact the overall cost-effectiveness results.

Table 43: Comparison of modelled outcomes versus STEP 1 trial reported outcomes

Parameter	Modelled outcome change at 2 years from baseline	Trial outcome change at 68 weeks from baseline	Modelled outcome change at 2 years from baseline	Trial outcome change at 68 weeks from baseline
	Semaglutide 2.4 mg		Diet and physical activity	
BMI (kg/m^2)	-6.37	-6.27	-0.92	-0.95

Parameter	Modelled outcome change at 2 years from baseline	Trial outcome change at 68 weeks from baseline	Modelled outcome change at 2 years from baseline	Trial outcome change at 68 weeks from baseline
SBP (mmHg)	-7.08	-7.08	-1.14	-1.14
Total cholesterol (mg/dL)	-8.44	-7.45	0.18	-1.49
Key: BMI, body mass index; SBP, systolic blood pressure.				

Source: Reproduced from Tables 6 and 7 from the company's response to ERG clarification B10.

5.3.2 External validation

In their response to clarification question B11, the company compared the costs and QALYs associated with the comparator arm – diet and physical activity – of the current appraisal with previous TA664 for the subgroup with BMI ≥ 35kg/m^2 and non-diabetic hyperglycaemia and high risk of CVD, reproduced below in Table 44. They argued the difference in results were attributed to the inclusion of mortality adjusted for BMI, updated costs and the inclusion of the provision for weight to return to the value of natural progression at the end of the catch-up period.

Table 44 Comparison of results from current appraisal and TA664

Technologies	Costs (£)	QALYs
Diet & physical activity (SCALE-TA664)	£19,992	15.18
Diet & physical activity (STEP 1)	£28,371	14.31
Key: QALY, quality-adjusted life year.		

Source: Reproduced from Table 8 from company's response to clarification question B11

The company used the patient characteristics and efficacy data for diet and physical activity from the SCALE 1839 trial in the current appraisal, results are reproduced in Table 45 below. We agree with the company's conclusion that the results between the two appraisals are similar when adjusted for patient characteristics and efficacy data.

Table 45 Comparison of results from current appraisal and TA664 (adjusted for patient characteristics and efficacy data)

Technologies	Costs (£)	QALYs
Diet & physical activity (SCALE-TA664)	£27,597	14.60
Diet & physical activity (STEP 1)	£28,371	14.31
Key: QALY, quality-adjusted life year.		

Source: Reproduced from Table 9 from company's response to clarification question B11

6 ERG'S ADDITIONAL ANALYSES

6.1 Corrections to the company's base case

The ERG did not identify any errors that affected the company's base case analysis. However, we conducted further scenarios for those aspects where we considered uncertainties remained. These are discussed in section 6.2.

6.2 Impact on the ICER of additional analyses undertaken by the ERG

The ERG conducted a series of scenarios on the company's base case and liraglutide-eligible subgroup analyses. These are listed in Table 46 and Table 49 below respectively. We note that change in mean starting BMI has the most significant impact on the cost-effectiveness results. Across the scenarios conducted for the company's base case, the ICERs for semaglutide 2.4mg vs diet and physical activity vary between [redacted] (Scenario: Mean BMI of 42.5kg/m^2) and [redacted] (Scenario: Mean BMI of 32.5 kg/m^2).

Table 46 Scenarios conducted by the ERG on the company's base case

Assumption	Treatments	Total costs	Total QALYs	ICER (£/QALY)
Company base-case	Diet & physical activity	[redacted]	15.269	[redacted]
	Semaglutide 2.4mg		15.361	
Using the patient characteristics for all patients in STEP 1	Diet & physical activity	[redacted]	15.943	[redacted]
	Semaglutide 2.4mg		16.041	
Using the subgroup efficacy for those with BMI >=30 and one or more comorbidities.	Diet & physical activity	[redacted]	15.273	[redacted]
	Semaglutide 2.4mg		15.367	
Yearly increase in weight of 0.296kg (Iyen et al.)	Diet & physical activity	[redacted]	15.422	[redacted]
	Semaglutide 2.4mg		15.521	
Age at which weight no longer increases: 66 years	Diet & physical activity	[redacted]	15.276	[redacted]
	Semaglutide 2.4mg		15.369	
Using QRISK3 for incidence of first CVD event in T2D	Diet & physical activity	[redacted]	15.136	[redacted]
	Semaglutide 2.4mg		15.235	
Disutility for T2D: -0.0714 (Sullivan et al.)	Diet & physical activity	[redacted]	15.138	[redacted]
	Semaglutide 2.4mg		15.240	
Disutility for knee replacement: -0.099 (Sullivan et al.)	Diet & physical activity	[redacted]	15.323	[redacted]
	Semaglutide 2.4mg		15.414	
Mean starting BMI of 32.5 kg/m^2	Diet & physical activity	[redacted]	16.453	[redacted]
	Semaglutide 2.4mg		16.533	
Mean starting BMI of 37.5 kg/m^2	Diet & physical activity	[redacted]	15.510	[redacted]
	Semaglutide 2.4mg		15.615	
Mean starting BMI of 42.5 kg/m^2	Diet & physical activity	[redacted]	14.495	[redacted]
	Semaglutide 2.4mg		14.617	

For the liraglutide-eligible subgroup, the scenario with Mean starting BMI of 37.5 kg/m^2 has the most significant impact on the model results with the ICER for liraglutide 3.0mg vs diet and physical activity increasing from £[redacted] to £[redacted].

Table 47 Scenarios conducted by the ERG on the company's liraglutide-eligible subgroup

Assumption	Treatments	Total costs	Total QALYs	ICER (£/QALY)
Company base-case	Diet & physical activity	[redacted]	14.311	
	Liraglutide 3.0mg	[redacted]	14.401	[redacted]
	Semaglutide 2.4mg	[redacted]	14.444	[redacted]
Using efficacy data for those with BMI >=35 and one or more comorbidities.	Diet & physical activity	[redacted]	14.420	
	Liraglutide 3.0mg	[redacted]	14.509	[redacted]
	Semaglutide 2.4mg	[redacted]	14.543	[redacted]
Yearly increase in weight of 0.296kg (Iyen et al.)	Diet & physical activity	[redacted]	14.450	
	Liraglutide 3.0mg	[redacted]	14.540	[redacted]
	Semaglutide 2.4mg	[redacted]	14.583	[redacted]
Age at which weight no longer increases: 66 years	Diet & physical activity	[redacted]	14.380	
	Liraglutide 3.0mg	[redacted]	14.470	[redacted]
	Semaglutide 2.4mg	[redacted]	14.513	[redacted]
Using QRISK3 for incidence of first CVD event in T2D	Diet & physical activity	[redacted]	14.106	
	Liraglutide 3.0mg	[redacted]	14.206	[redacted]
	Semaglutide 2.4mg	[redacted]	14.251	[redacted]
Disutility for T2D: -0.0714 (Sullivan et al.)	Diet & physical activity	[redacted]	14.114	
	Liraglutide 3.0mg	[redacted]	14.216	[redacted]
	Semaglutide 2.4mg	[redacted]	14.261	[redacted]
Disutility for knee replacement: -0.099 (Sullivan et al.)	Diet & physical activity	[redacted]	14.380	
	Liraglutide 3.0mg	[redacted]	14.469	[redacted]
	Semaglutide 2.4mg	[redacted]	14.511	[redacted]
Mean starting BMI of 37.5 kg/m^2	Diet & physical activity	[redacted]	15.260	
	Liraglutide 3.0mg	[redacted]	15.334	[redacted]
	Semaglutide 2.4mg	[redacted]	15.377	[redacted]

6.3 ERG's preferred assumptions

The ERG's preferred assumptions are listed in the Table 48.

Table 48 ERG preferred assumptions

Model aspect	Company's assumption	ERG preferred assumption
Transition of patients with non-hyperglycaemia	Patients develop T2D immediately after a CVD event.	The NCE committee from TA664 concluded that there was no good evidence to determine the proportion of people who develop type 2 diabetes after a cardiovascular event. Furthermore, clinical advice to the ERG suggest that it is not possible to assume that patients will develop T2D

		after a CVD event. Further details in section 4.2.2.
Body weight	Patients undergo a natural increase of weight per year of 0.463kg. This is based on an increase in BMI of 0.1447 kg/m^2 for males and 0.1747 kg/m^2 for females per year for the diet and physical activity arm from the study by Ara et al.[24]	Patients undergo a natural increase of weight per year of 0.296 kg. This is based on a more recent study by Iyen et al.[25] that included a cohort of 264,230 individuals in the UK. The study estimated a mean increase in BMI of 1.06 kg/m^2 per 10 years. Further details in section 4.2.2**Error! Reference source not found.**.
Maximum age of weight increase	68 years	66 years.
Direction of weight change at maximum age	Weight remains constant after the maximum age of 68 years.	There is a steep decrease in individuals' BMI based on the study by Zaninotto et al[26] that explored BMI trajectories in the English Longitudinal Study of Ageing. We assume that the weight decrease post maximum age is similar to that of weight increase before reaching maximum age of weight gain. Further details in section 4.2.2.**Error! Reference source not found.**
Costs of microvascular complication and sleep apnoea	Microvascular complication: £941 Sleep apnoea: £1018	Microvascular complication: £398[47] Sleep apnoea: £274[52]

The cumulative effect of the ERG's preferred assumptions to the company's analyses are shown in Table 49 and Table 50. Applying the ERG preferred assumptions increases the company's base case ICER for semaglutide 2.4mg versus diet and physical activity from [redacted] to [redacted] per QALY. For the liraglutide-eligible subgroup, while the ICER for liraglutide 3.0mg versus diet and physical activity increases from [redacted] to [redacted] semaglutide 2.4mg [redacted] compared to liraglutide 3.0mg.

Table 49 Cumulative change from the company base case to ERG base case with ERG's preferred assumptions

Assumption	Treatments	Total costs	Total QALYs	ICER (£/QALY)
Company base-case	Diet & physical activity	[redacted]	15.269	[redacted]
	Semaglutide 2.4mg	[redacted]	15.361	
Patients with pre-diabetes do not transition to T2D after CVD events	Diet & physical activity	[redacted]	15.329	[redacted]
	Semaglutide 2.4mg	[redacted]	15.419	
	Diet & physical activity	[redacted]	15.484	[redacted]

+ Mean increase of weight by 0.296 kg per year	Semaglutide 2.4mg	[redacted]	15.582	
+ Mean decrease in weight after age 66 years: 0.296 kg per year	Diet & physical activity	[redacted]	15.540	[redacted]
	Semaglutide 2.4mg	[redacted]	15.634	
+ Age at which weight no longer increases: 66 years	Diet & physical activity	[redacted]	15.562	[redacted]
	Semaglutide 2.4mg	[redacted]	15.656	
+ Annual cost of microvascular complication, £398	Diet & physical activity	[redacted]	15.562	[redacted]
	Semaglutide 2.4mg	[redacted]	15.656	
+ Annual cost of sleep apnoea, £274	Diet & physical activity	[redacted]	15.562	[redacted]
	Semaglutide 2.4mg	[redacted]	15.656	
ERG base case	Diet & physical activity	[redacted]	15.562	[redacted]
	Semaglutide 2.4mg	[redacted]	15.656	

Table 50 Cumulative change from company liraglutide-eligible subgroup results to the ERG liraglutide-eligible subgroup results with the ERG's preferred assumptions

Assumption	Treatments	Total costs	Total QALYs	Incremental ICER (£/QALY)
Company base-case	Diet & physical activity	[redacted]	14.311	
	Liraglutide 3.0mg	[redacted]	14.401	[redacted]
	Semaglutide 2.4mg	[redacted]	14.444	[redacted]
Patients with pre-diabetes do not transition to T2D after CVD events	Diet & physical activity	[redacted]	14.419	
	Liraglutide 3.0mg	[redacted]	14.505	[redacted]
	Semaglutide 2.4mg	[redacted]	14.548	[redacted]
+ Mean increase of weight by 0.296 kg per year	Diet & physical activity	[redacted]	14.562	
	Liraglutide 3.0mg	[redacted]	14.648	[redacted]
	Semaglutide 2.4mg	[redacted]	14.690	[redacted]
+ Mean decrease in weight after age 66 years: 0.296 kg per year	Diet & physical activity	[redacted]	14.642	
	Liraglutide 3.0mg	[redacted]	14.727	[redacted]
	Semaglutide 2.4mg	[redacted]	14.770	[redacted]
+ Age at which weight no longer increases: 66 years	Diet & physical activity	[redacted]	14.659	
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]
+ Annual cost of microvascular complication, £398	Diet & physical activity	[redacted]	14.659	
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]
+ Annual cost of sleep apnoea, £274	Diet & physical activity	[redacted]	14.659	
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]
ERG base case	Diet & physical activity	[redacted]	14.659	
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]

The ERG conducted a series of scenario analyses on the base case and the liraglutide-eligible subgroup, shown below in Table 51 and Table 52. For the base case, the ICER for semaglutide 2.4mg versus diet and physical activity varied between [redacted] (Scenario: Mean starting BMI of 42.5 kg/m^2) and [redacted] (Scenario: catch up rate of 1 year). For the liraglutide-eligible subgroup, semaglutide 2.4mg was [redacted] compared to liraglutide 3.0mg for all scenarios.

Table 51 Scenarios conducted on the ERG base case

Assumption	Treatments	Total costs	Total QALYs	ICER (£/QALY)
ERG base-case	Diet & physical activity	[redacted]	15.562	[redacted]
	Semaglutide 2.4mg	[redacted]	15.656	
Mean starting BMI of 32.5 kg/m^2	Diet & physical activity	[redacted]	16.762	[redacted]
	Semaglutide 2.4mg	[redacted]	16.839	
Mean starting BMI of 37.5 kg/m^2	Diet & physical activity	[redacted]	15.766	[redacted]
	Semaglutide 2.4mg	[redacted]	15.870	
Mean starting BMI of 42.5 kg/m^2	Diet & physical activity	[redacted]	14.775	[redacted]
	Semaglutide 2.4mg	[redacted]	14.895	
No stopping rule	Diet & physical activity	[redacted]	15.569	[redacted]
	Semaglutide 2.4mg	[redacted]	15.651	
Catch-up rate: 1 year	Diet & physical activity	[redacted]	15.541	[redacted]
	Semaglutide 2.4mg	[redacted]	15.609	
Catch-up: 2 years	Diet & physical activity	[redacted]	15.557	[redacted]
	Semaglutide 2.4mg	[redacted]	15.634	
Catch-up: 4 years	Diet & physical activity	[redacted]	15.578	[redacted]
	Semaglutide 2.4mg	[redacted]	15.685	
Treatment duration: 3 years	Diet & physical activity	[redacted]	15.563	[redacted]
	Semaglutide 2.4mg	[redacted]	15.693	
Using QRISK3 for incidence of first CVD event in T2D	Diet & physical activity	[redacted]	15.423	[redacted]
	Semaglutide 2.4mg	[redacted]	15.524	

Table 52 Scenarios conducted on the ERG liraglutide-eligible subgroup

Assumption	Treatments	Total costs	Total QALYs	Incremental ICER (£/QALY)
ERG base-case	Diet & physical activity	[redacted]	14.659	
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]
Mean starting BMI of 37.5 kg/m^2	Diet & physical activity	[redacted]	15.580	
	Liraglutide 3.0mg	[redacted]	15.651	[redacted]
	Semaglutide 2.4mg	[redacted]	15.694	[redacted]
Mean starting BMI of 42.5 kg/m^2	Diet & physical activity	[redacted]	14.596	
	Liraglutide 3.0mg	[redacted]	14.672	[redacted]
	Semaglutide 2.4mg	[redacted]	14.726	[redacted]
No stopping rule	Diet & physical activity	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	14.743	[redacted]
	Semaglutide 2.4mg	[redacted]	14.802	[redacted]
Catch-up rate: 1 year	Diet & physical activity	[redacted]	14.638	
	Liraglutide 3.0mg	[redacted]	14.694	[redacted]
	Semaglutide 2.4mg	[redacted]	14.718	[redacted]
Catch-up rate: 2 years	Diet & physical activity	[redacted]	14.649	
	Liraglutide 3.0mg	[redacted]	14.722	[redacted]
	Semaglutide 2.4mg	[redacted]	14.760	[redacted]
Catch-up rate: 4 years	Diet & physical activity	[redacted]	14.667	
	Liraglutide 3.0mg	[redacted]	14.765	[redacted]
	Semaglutide 2.4mg	[redacted]	14.814	[redacted]
Treatment duration: 3 years	Diet & physical activity	[redacted]	14.659	
	Liraglutide 3.0mg	[redacted]	14.768	[redacted]
	Semaglutide 2.4mg	[redacted]	14.830	[redacted]
	Diet & physical activity	[redacted]	14.439	

Using QRISK3 for incidence of first CVD event in T2D	Liraglutide 3.0mg	[redacted]	14.535	[redacted]
	Semaglutide 2.4mg	[redacted]	14.580	[redacted]

6.4 Conclusions on the cost effectiveness evidence

The company developed a de novo model, based on the model developed for the NICE technology appraisal TA664 for liraglutide 3.0 mg for managing overweight and obesity.[4] The ERG considers the model structure is appropriate to reflect this condition and the treatment pathway and is consistent with the NICE reference case.

The model uses intermediate clinical outcomes to extrapolate to morbidity events and mortality beyond the trial period. As such, there is inherent uncertainty in the cost-effectiveness results from the modelling. However, it is reassuring that the company has provided validation of the extrapolation of clinical outcomes.

The company base case ICER for semaglutide 2.4mg vs diet and physical activity is [redacted] per QALY. The results are most sensitive to changes to the starting BMI of the cohort, the catch-up rate (time for patients to regain weight) and the incorporation of the stopping rule for non-responders. Semaglutide 2.4mg is more cost-effective for those with higher BMI, therefore in the base case cost-effectiveness estimate, those with higher BMI are compensating for those with lower BMI. For this reason, the ERG presents the results for different BMI ranges. The catch-up rate is uncertain as no follow-up data were available for weight gain in the three years after stopping treatment. However, this duration of catch-up has previously been accepted by the NICE committee in TA664. There is some uncertainty around the inclusion or the stopping rule for non-responders as it was not included in the company's clinical trial and it is still unclear whether the marketing authorisation for semaglutide 2.4mg will include it.

The ERG suggests the following changes to the parameters and assumptions used in the company model:

i) Patients with pre-diabetes do not transition to T2D after CVD events,
ii) Alternative natural history increase in population's weight over time,
iii) Reduced annual cost of microvascular complications for T2D and sleep apnoea.

The ERG base case including these changes is [redacted] per QALY for semaglutide 2.4mg versus diet and physical activity.

7 END OF LIFE

Semaglutide 2.4mg is not suitable to be considered as an end-of-life treatment as the population to be treated with it does not fulfil the criteria to have an expected life expectancy of less than 24 months.

8 References

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9 Appendices

9.1 Company and ERG risk of bias assessments for the STEP 1 and SCALE 1839 trials

Appendix 9.1 Table 1A Company and ERG risk of bias assessments for the STEP 1 trial

Criterion	Company judgement	ERG judgement
Was randomisation carried out appropriately?	**Yes** Performed using an interactive web-based response system	**Yes (=low risk of selection bias)** Centrally randomised…. using an IWRS [interactive web-based response system] (CSR section 9.4.2.1)
Was the concealment of treatment allocation adequate?	**Yes** No rationale reported	**Yes (=low risk of selection bias)** Interactive voice or interactive web-based response system would have concealed allocation
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes** There were no noteworthy differences in baseline characteristics or medical history	**Yes (=low risk of selection bias)** Baseline characteristics were similar in the two treatment groups (CSR Tables 10-2 and 10-3)
Were the care providers, participants, and outcome assessors blind to treatment allocation?	The company did not report an assessment – **assumed "yes"** by ERG Participants & investigators were masked to treatment allocation during the entire trial	**Yes (=low risk of performance and detection biases)** Treatment allocation remained blinded to the subjects, the investigators and to Novo Nordisk during the entire treatment and follow-up period in the main phase of the trial and until after DBL for the main phase of the trial. Semaglutide and diet and physical activity were identical in appearance and were packed and labelled to fulfil the requirements for double-blind procedures (CSR section 9.4.2.2)
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The company did not report an assessment – **assumed "yes" by ERG**	**Yes (=unclear risk of attrition bias in relation to this aspect of imbalances in missing data)**

	A greater proportion of participants in the semaglutide 2.4 mg group withdrew due to AEs (92 [7%] of 1306 participants) than did in the diet and physical activity group (21 [3.2%] of 655 participants).	A total of 66 patients (5.1%) in the semaglutide 2.4 mg arm and 46 patients (7.0%) in the diet and physical activity arm were withdrawn or withdrew from the STEP 1 study. Differences in the proportion of missing data between trial arms were small and reasons for data missing similar for the two arms (CS Appendix Figure 3) However, in the liraglutide eligible subgroup, participants with missing data had a lower age, and rates of cardiovascular disease, dyslipidaemia, and hypertension than those without missing data (clarification response attachment E). The ERG are unclear whether this would be a source of attrition bias (see section 3.3.5).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No**[a] There is no evidence to suggest that the authors measured more outcomes than they reported for the STEP 1 study (clarification response A4)	**No (=low risk of reporting bias)** Protocol specified outcomes were checked by the ERG against the CSR and trial publication. All primary and secondary outcomes were reported
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes** Details of the imputation methods for missing data are given in CS Appendix Table 9.[b]	**Yes (=low risk of attrition bias in relation to this aspect of imbalances in missing data)** The ITT principle was followed in the trial (CSR, section 9.7.1.1), and the imputation methods appear generally appropriate.
[a] Reported in clarification response A4. [b] The methods used to account for missing data in the ITC have been transposed for the SCALE 1839 trial and STEP 1 trial in Appendix Table 9 compared to the descriptions in the ITC report. Source: partly reproduced from CS Appendix Table 9.		

Appendix 9.1 Table 1B Company and ERG risk of bias assessments for the SCALE 1839 trial

Criterion	Company judgement	ERG judgement
Was randomisation carried out appropriately?	**Yes** Performed using a funder-provided telephone or web-based system	**Yes (=low risk of selection bias)** Randomization was performed with the use of a telephone or Web-based system provided (trial publication)
Was the concealment of treatment allocation adequate?	**Yes** No rationale reported	**Yes (=low risk of selection bias)** Interactive voice or interactive web-based response system would have concealed allocation
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes** There were no noteworthy differences in baseline characteristics or medical history.	**Yes (=low risk of selection bias)** Baseline characteristics were similar in the two groups (trial publication)
Were the care providers, participants, and outcome assessors blind to treatment allocation?	**Yes** Participants & investigators were masked to treatment allocation during the entire trial	**Yes (=low risk of performance and detection biases)** Participants and investigators were masked to treatment allocation during the entire trial…. and visually identical devices were used for subcutaneous injection (Le Roux et al., 2017, page 2)
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	**Yes** A greater proportion of participants in the liraglutide group withdrew due to AEs (199 [13%] of 1501 participants) than did in the diet and physical activity group (46 [6%] of 747)	**Yes (=unclear risk of attrition bias in relation to this aspect of imbalances in missing data)** A total of 1789 patients (71.9%) in the liraglutide group, as compared with 801 patients (64.4%) in the diet and physical activity group, completed 56 weeks of treatment. Differences in the proportion of missing data between trial arms were small and reasons for data missing similar for the two arms (trial publication). However, in the liraglutide eligible subgroup, participants with missing data had a lower

		age, weight and rates of dyslipidaemia, and hypertension than those without missing data (Clarification response attachment E). The ERG are unclear whether this would be a source of attrition bias (see section 3.3.5).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No** No rationale reported	**No (=low risk of reporting bias)** Protocol specified outcomes were checked by the ERG against the trial publications (Pi-Sunyer et al., 2015 and Le Roux et al., 2017). All primary and secondary outcomes were reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**No** The pre-specified efficacy analyses used data from the full analysis set of all randomised individuals who received at least one treatment dose and had at least one post-baseline assessment. Details of the imputation methods for missing data are given in CS Appendix Table 9.[a]	**No (but ERG conclude low risk of attrition bias in relation to this aspect of imbalances in missing data)** The FAS in this trial included all patients who underwent randomisation and received at least one dose of a study drug and had at least one assessment after baseline ("modified ITT" population). However, >97% of patients in the randomised population were included in the modified ITT population, suggesting risk of attrition bias would be low. The methods used to impute missing data appear appropriate.
[a] The methods used to account for missing data in the ITC have been transposed for the SCALE 1839 trial and STEP 1 trial in Appendix Table 9 compared to the descriptions in the ITC report. Source: partly reproduced from CS Appendix Table 9		

9.2 Results of other outcomes reported in the STEP 1 trial

This appendix reports the results of the following other outcomes measured in the STEP 1 trial: other weight loss outcomes, percentage of participants with a specified weight change from baseline, waist circumference change, incidence of type 2 diabetes (only reported at baseline and as a safety outcome), HbA_{1c} (%) change from baseline, and HRQoL

9.2.1 Weight loss

Body weight at baseline in kg was reported only for the FAS population. The mean (SD) baseline weight of participants was 104.5 (22.1) kg in the semaglutide 2.4 mg arm and 105.2 (21.5) kg in the diet and physical activity arm.

The change in body weight in kg from baseline to 68 weeks was only reported for the FAS population. The semaglutide 2.4 mg arm experienced a mean decrease of more than 15kg whilst the diet and physical activity arm experienced a mean decrease of less than 3 kg (Table 53). The difference between arms was statistically significant (95% CIs exclude zero).

Table 53 Weight change from baseline at 68 weeks

Estimand (Data source)	Semaglutide 2.4 mg		Diet and physical activity		Difference (95% CI)
	Mean change	N	Mean change	N	
FAS (BMI≥30 or BMI≥27 plus ≥1 of hypertension, dyslipidaemia, OSA or CVD)					
Treatment policy (CSR 14.2.14)	-15.33 kg	1306	-2.61 kg	655	-12.71 kg (-13.68 to -11.74);p<0.0001
Trial product (CSR 14.2.22)	-17.36 kg	950	-2.70 kg	443	-14.66 (-15.58 to -13.74); p<0.0001
FAS: full analysis set					

The percentage of participants who achieved a weight decrease of ≥5%, ≥10%, ≥15% or ≥20% at 68 weeks relative to baseline was consistently higher in the semaglutide 2.4 mg arm than the diet and physical activity arm (Table 54). Odds ratios were statistically significant (95% CIs exclude 1.0) and were higher for the trial product estimand than for the treatment policy estimand (NB the trial policy estimand, which includes discontinuations and use of rescue medication, is likely to be more reflective of weight loss in clinical practice).

Table 54 Percentage of participants with specified weight change from baseline at 68 weeks (FAS population)

Estimand	Semaglutide 2.4 mg		Diet and physical activity		Odds ratio (95% CI)
	%	N	%	N	
Weight change ≥5%					
Treatment policy	86.4%	1212	31.5%	577	11.2 (8.9 to 14.2); p<0.001

Trial product	92.4%	1059	33.1%	499	37.0 (28.0 to 49.0)
Weight change ≥10%					
Treatment policy	69.1%	1212	12.0%	577	14.7 (11.1 to 19.4); p<0.001
Trial product	74.8%	1059	11.8%	499	30.0 (22.5 to 40.0)
Weight change ≥15%					
Treatment policy	50.5%	1212	4.9%	577	19.3 (12.9 to 28.8); p<0.001
Trial product	54.8%	1059	5.0%	499	31.8 (21.0 to 48.3)
Weight change ≥20%					
Treatment policy	32.0%	1212	1.7%	577	26.9 (14.2 to 51.0)
Trial product	34.8%	1059	2.0%	499	42.2 (20.8 to 85.6)
FAS: full analysis set Source: CS Figure 5 and trial publication					

9.2.2 BMI loss

The change in BMI from baseline to 68 weeks was reported only for the FAS population. The change was larger for the semaglutide 2.4 mg arm (a decrease of more than 5 kg/m^2) than for the diet and physical activity arm (a decrease of less than 1 kg/m^2), with the difference between arms statistically significant (95% CIs exclude zero) (Table 55).

Table 55 BMI change from baseline at 68 weeks

Estimand (Data source)	Semaglutide 2.4 mg		Diet and physical activity		Difference (95% CI)
	Mean change	N	Mean change	N	
FAS (BMI≥30 or BMI≥27 plus ≥1 of hypertension, dyslipidaemia, OSA or CVD)					
Treatment policy (CSR 11.3.4.3)	-5.54 kg/m^2	1306	-0.92 kg/m^2	655	-4.61 (-4.96 to -4.27) (p NR)
Trial product (CSR 14.2.48)	-6.27 kg/m^2	1306	-0.95 kg/m^2	655	-5.33 (-5.65 to -5.00); p<0.0001
FAS: full analysis set; NR: not reported					

9.2.3 Waist circumference

Across the analyses conducted, mean waist circumference decreased from baseline to 68 weeks by 13.1 to 15.2 cm in the semaglutide 2.4 mg arm and by 4.1 cm to 6.1 cm in the diet and physical activity arm (Table 56). The difference between trial arms was statistically

significant for the FAS population (95% CIs exclude zero) but confidence intervals were not reported for the other analysis populations. The CS does not comment on the clinical significance of these changes in waist circumference, but the company explained in clarification response A20 that they are likely to be clinically meaningful. However, the ERG's clinical expert suggested that waist circumference is difficult to reliably measure in practice due to variations in waist shape and measurement errors, especially at higher BMIs. Waist circumference is not used in the company's economic analysis.

Table 56 Waist circumference change from baseline at 68 weeks

Estimand (Data source)	Semaglutide 2.4 mg		Diet and physical activity		Difference (95% CI)
	Mean (SD[a]) change	N	Mean (SD[a]) change	N	
FAS (BMI≥30 or BMI≥27 plus ≥1 of hypertension, dyslipidaemia, OSA or CVD)					
Treatment policy (Appendix R.3)	-13.54 cm	1306	-4.13 cm	655	-9.42 (-10.30 to -8.53) (p NR)
Trial product (CSR 14.2.60)	-15.22 cm	1306	-4.48 cm	655	-10.75 (-11.6 to -9.88); p<0.0001
Target subgroup (BMI ≥30 plus ≥1 weight-related comorbidity) (post hoc analysis)					
Treatment policy (CS B.2.7.1)	-13.6 cm	974	-4.3 cm	496	-9.3 [b]
Trial product (Appendix E.2)	-15.22 (9.11) cm	974	-4.66 (9.28) cm	946	10.56 [b]
Liraglutide-eligible subgroup (BMI≥35 with non-diabetic hyperglycaemia and CVD risk) (post hoc analysis)					
Treatment policy (CS B.2.7.2)	-13.1 cm	273	-5.4 cm	148	-7.7 [b]
Trial product (Appendix E.2)	-14.69 (9.39) cm	273	-6.08 (9.52) cm	148	-8.61 [b]

FAS: full analysis set; NR: not reported
[a] SD reported for some analyses
[b] Not reported; raw difference calculated by reviewer

9.2.4 Incidence of type 2 diabetes

The incidence of type 2 diabetes is specified as an outcome in the NICE scope and decision problem but was reported only at baseline in the CS due to too few cases (ITC Report section 3.2). Although type 2 diabetes was an exclusion criterion in the STEP 1 trial, 18

patients in the semaglutide 2.4 mg arm (1.4%) and 17 in the diet and physical activity arm (2.6%) had type 2 diabetes at baseline (CS Table 8). According to the CSR, the incidence of diabetes in the STEP 1 trial safety analysis set was <0.1% (n=1 patient) in the semaglutide 2.4 mg arm and 0.9% (n=6 patients) in the diet and physical activity arm (CSR section 14.3.1.5).

9.2.5 Glycaemic status

Across the analyses conducted, mean % HbA_{1c} decreased from baseline to week 68 by 0.45 to 0.60 percentage points in the semaglutide 2.4 mg arm and by 0.1 to 0.2 percentage points in the diet and physical activity arm (Table 57). The difference between trial arms was statistically significant for the FAS population (95% CIs exclude zero) but confidence intervals were not reported for the other analysis populations.

The reductions in HbA1c in the semaglutide 2.4 mg arm were close to 0.50 %-points. The company's clarification response A20 states that according to clinical guidelines, a reduction of 0.5% (5.5 mmol/mol) is considered to be clinically significant (reference cited).

Table 57 HbA_{1c} (%) change from baseline at 68 weeks

Estimand (Data source)	Semaglutide 2.4 mg		Diet and physical activity		Difference (95% CI)
	Mean (SD[a]) change	N	Mean (SD[a]) change	N	
FAS (BMI≥30 or BMI≥27 plus ≥1 of hypertension, dyslipidaemia, OSA or CVD)					
Treatment policy (CSR 11.6.1)	-0.45 %-points	1306	-0.15 %-points	655	-0.29 (-0.32 to -0.26) (p NR)
Trial product (CSR 14.2.150)	-0.50 %-points	1306	-0.16 %-points	655	-0.34 (-0.37 to -0.31); p<0.0001
Target subgroup (BMI ≥30 plus ≥1 weight-related comorbidity) (post hoc analysis)					
Treatment policy (CS B.2.7.1)	-0.5 %-points	974	-0.1 %-points	496	-0.4 [b]
Trial product (Appendix E.2)	-0.52 (0.28) %-points	974	-0.17 (0.29) %-points	496	-0.35 [b]
Liraglutide-eligible subgroup (BMI≥35 with non-diabetic hyperglycaemia and CVD risk) (post hoc analysis)					
Treatment policy (CS B.2.7.2)	-0.5 %-points	273	-0.2 %-points	148	-0.3 [b]

Trial product (Appendix E.2)	-0.60 (0.28)	273	-0.16 (0.29)	148	-0.44 [b]
FAS: full analysis set; NR: not reported [a] SD reported for some analyses [b] Not reported; raw difference calculated by reviewer					

9.2.6 HRQoL outcomes

The HRQoL outcomes reported in STEP 1 are not used in the company's economic evaluation which instead draws upon HRQoL data from alternative sources considered more relevant to the longer time horizon of the economic model (see section 4.2.7). Only a brief summary of the STEP 1 HRQoL outcomes is therefore provided here.

Baseline HRQoL scores were comparable between the semaglutide 2.4 mg and diet and physical activity arms for each of the HRQoL scales assessed (trial publication).

In the FAS population the proportion of patients who achieved a clinically meaningful within-person improvement in HRQoL from baseline to week 68 was higher for the semaglutide 2.4 mg arm than the diet and physical activity arm when assessed using both the SF-36 physical functioning scale and the IWQOL-Lite-CT physical function scale (CS sections B.2.6.9.1 and B.2.6.9.2):

- SF-36 physical functioning (≥3.7 points): semaglutide 2.4 mg 40.0%, diet and physical activity 27.0%; OR=2.08 (95% CI 1.60 to 2.70)
- IWQOL-Lite-CT physical function (≥14.6 points: semaglutide 2.4 mg 51.2%, diet and physical activity 32.9%; OR=2.72 (95% CI 2.14 to 3.47)

However, the difference between semaglutide 2.4 mg and diet and physical activity was smaller for the improvement in the SF-36 Mental Component Summary (the company do not discuss the clinical significance of this) (trial publication).

9.3 Other ITC results

This appendix reports the results of outcomes from the ITC for the outcomes that are not used in the economic model. Note: none of the ITC results were used directly in the model.

9.3.1 BMI

BMI change was reported for STEP 1[5] and SCALE 1839,[19] but not included in the ITC analysis. We note, though, that percentage weight change and percentage BMI change are synonymous outcomes.

9.3.2 Waist circumference

The unadjusted analyses for both the treatment policy estimand and trial policy estimand indicate a statistically greater reduction waist circumference with semaglutide 2.4 mg than with liraglutide 3.0 mg except when the comparison was made at half a year (28 weeks in each trial) (Table 58). Adjusted analyses are only reported for the treatment policy estimand and these were also significantly in favour of semaglutide 2.4 mg except at the 28 weeks analysis. The treatment effect in unadjusted analyses was consistently larger for the trial product estimand than for the treatment policy estimand.

The CS does not discuss the clinical significance of the changes in waist circumference. Clarification response A20 states that after accounting for changes in BMI, reducing waist by 3 cm had a significant beneficial effect on the metabolic syndrome in women, and waist reductions of 5–10 cm in Caucasian women, across a range of baseline BMI 25–50 kg/m^2 or waist circumference 72–133 cm, may be used as guideline to encourage overweight women to achieve a realistic target with a high probability of health benefits (references cited). However, the company do not explicitly define a minimal clinically important change in waist circumference.

Table 58 ITC results: effect on waist circumference change from baseline

Analysis (STEP 1/SCALE 1839: week 52/56 unless stated)	**Relative treatment effect (95% CI), cm, semaglutide 2.4 mg vs liraglutide 3.0 mg**	
	Treatment policy estimand	**Trial product estimand**
Unadjusted	-3.59 (-5.56, -1.61), p=0.0004 [a,b]	-4.27 (-6.08, -2.45), p<0.0001 [b]
Population adjustment 1	-3.83 (-5.77, -1.88), p=0.0001 [b]	Not reported
Population adjustment 2	-3.75 (-5.72, -1.78), p=0.0002 [b]	Not reported
Unadjusted, pre-diabetes	-4.12 (-5.48, -2.76), p<0.0001 [b]	Not reported
Week 56/56, unadjusted	-3.57 (-5.54, -1.59), p=0.0004 [b]	Not reported
Week 68/56, unadjusted	-3.50 (-5.60, -1.40), p=0.0011 [b]	-4.47 (-6.39, -2.55), p<0.0001 [b]
Week 28/28, unadjusted	-0.59 (-2.15, 0.97), p=0.4586 [b]	-1.00 (-2.48, 0.48), p=0.1840 [b]

[a] From CS Table 12
[b] From ITC Report Table 10

9.3.3 HbA_{1c}

The unadjusted analyses for both the treatment policy estimand and trial product estimand indicate a statistically greater reduction in HbA_{1c} with semaglutide 2.4 mg than with liraglutide 3.0 mg (Table 59). Adjusted analyses are only reported for the treatment policy estimand and these were also significantly in favour of semaglutide 2.4 mg. The treatment effect in unadjusted analyses was similar for the trial product estimand than for the treatment policy estimand.

The reductions in HbA1c were relatively small (≤0.14 percentage point) but the CS does not discuss the clinical significance of these changes. In clarification response A20 the company state that in general, guidelines consider a difference of 0.5% (5.5 mmol/mol) to be clinically significant (reference cited).

Table 59 ITC results: effect on HbA_{1c} change from baseline

Analysis (STEP 1/SCALE 1839: week 52/56 unless stated)	**Relative treatment effect (95% CI), %-points, vs liraglutide**	
	Treatment policy estimand	**Trial product estimand**
Unadjusted	-0.13 (-0.20, -0.06), p=0.0002 [a,b]	-0.12 (-0.18, -0.06), p<0.0001 [b]
Population adjustment 1	-0.08 (-0.15, -0.01), p=0.0207 [b]	Not reported
Population adjustment 2	-0.08 (-0.15, -0.01), p=0.0324 [b]	Not reported
Unadjusted, pre-diabetes	-0.14 (-0.19, -0.09), p<0.0001 [b]	Not reported
Week 56/56, unadjusted	-0.13 (-0.19, -0.06), p=0.0002 [b]	Not reported
Week 68/56, unadjusted	-0.12 (-0.19, -0.05), p=0.0008 [b]	-0.13 (-0.18, -0.07), p<0.0001 [b]
Week 28/28, unadjusted	-0.06 (-0.12, -0.01), p=0.0293 [b]	-0.05 (-0.10, -0.00), p=0.0366 [b]

[a] From CS Table 12
[b] From ITC Report Table 9

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

ERG RESPONSE TO THE FACTUAL ACCURACY CHECK

Semaglutide for managing overweight and obesity [ID3850]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 5 October 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Use of ITC in model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report page 16 – The ERG state in regard to the ITC – 'This calculation is unclear to the ERG. It is also unclear why the unadjusted ITC could not have been used in the economic model, negating the need for this ad hoc calculation. The Company note that the ITC was "not able to produce adjusted estimates for efficacy in responders (further details are provided in Appendix D)" (CS section B.3.3.1.3). However, the ERG was unable to find any reference to this in Appendix D'	Novo Nordisk recommend removal of the term 'ad hoc' from the ERG report as this misrepresents the analyses performed by Novo Nordisk and the rationale for those analyses. A further explanation is provided below. An estimate for liraglutide 3.0mg responder efficacy which was both compatible with the model and appropriate, was generated as described in CS Section B.3.3.1.3. page 104. This calculation for weight change, SBP change, total cholesterol and	Firstly, we would like to apologise for the lack of further details on this issue in Appendix D. However, Novo Nordisk feel that the ERG have not acknowledged the explanations provided for why incorporation of the ITC into the model is not appropriate. The economic model includes efficacy estimates for responders. Semaglutide 2.4mg responders are defined as patients who have lost at least 5% of their initial body weight at week 28 of treatment and liraglutide 3mg responders are defined as patients who have lost at least 5% of their initial body weight at week 16 of treatment. The study designs of the two trials on which the ITC was based (STEP1 and SCALE 1839) preclude meaningful estimation of treatment effect in responders. Responders can be identified in the active treatment arms in both trials but not in the placebo arms. In a placebo arm, the apparent responders are those that do well on placebo alone. This population of patients that spontaneously improve is a highly selected population, and a comparison between active treatment responders and placebo responders would not have	We have removed the term "ad hoc" on page 16 in response to the formulae provided. However, we remain unable to reconcile the calculations based on these formulae with the data provided in the CS.

	HDL cholesterol change is as follows: Parameter value for Liraglutide 3.0mg in ITC = Parameter value for Liraglutide 3.0mg in SCALE 1839 + [Parameter value for Diet & exercise in STEP1 – Parameter value for Diet & exercise in SCALE 1839] The rationale for this adjustment is to transfer the incremental benefit of liraglutide over diet and exercise. This is achieved through the adjustment for differences between the trials diet and exercise arms, and was felt more appropriate than by a naïve comparison. The differences between BMI outcomes in the diet and exercise groups in STEP 1 and SCALE 1839 were small when compared with the treatment effects. Therefore, this adjustment has limited effect and modelling results using the naïve comparison are similar. The calculation for the percentage with glycaemic status change is as follows:	the benefit of randomisation. Instead, it would represent a biased post-randomization comparison. Analogously, an indirect comparison between semaglutide and liraglutide responders via placebo responders in the two trials would be a biased comparison. Specifically, it would not estimate the effect that could be expected in a randomized head-to-head trial comparing semaglutide and liraglutide under a given stopping rule. In issue 5 it was suggested to include the ITC results in the economic model. The economic model accounts for stopping rules by explicitly modelling the behaviour of patients upon discontinuation of semaglutide and liraglutide in case of non-response. Due to the issues described above it is not appropriate to use the ITC results in the economic model.	

	Parameter value for Liraglutide 3.0mg in ITC= Parameter value for Liraglutide 3.0mg in SCALE 1839 * Parameter value for Diet & exercise in STEP 1 / Parameter value for Diet & exercise in SCALE 1839 The rationale here is similar, that the effect of liraglutide is better represented by transferring the benefit over diet and exercise rather than by a naïve comparison.		

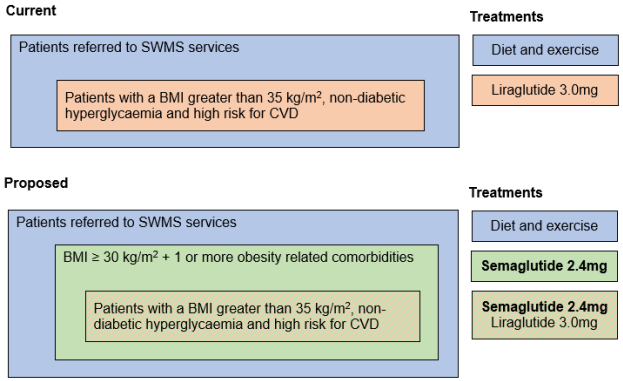
Issue 2 Cost of sleep apnoea

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report page 18 - The ERG have lowered the cost for managing obstructive sleep apnoea without justification or acknowledgement of why their preferred source was used over the company estimate. The use of the ERG preferred source is a factually inaccurate representation of the cost of	We ask that the ERG describe and justify how the cost estimate of £274, derived from Sharples et al as the annual cost for continuous positive airway pressure machine is more reflective of the overall cost of obstructive sleep apnoea than the NHS reference cost used by the company.	The company estimate of the cost of sleep apnoea has been derived from NHS reference cost as per standard NICE guidance. This estimates the total cost to the NHS of managing this condition and is the appropriate source to use. The cost used by the ERG is simply a cost for use of the positive airway pressure machine and does not capture the wider NHS cost associated with obstructive sleep apnoea, vastly	Not a factual inaccuracy. We justify our estimate below. In the ERG analyses, we use the ongoing annual costs of Continuous Positive Airway Pressure (CPAC) which includes annual equivalent cost of CPAC machine, annual equivalent cost of CPAC mask, annual sundries, and cost of follow-up outpatient visit. The estimate of £251.99 was based on 2011/12 prices and obtained from Table 47 of the study

managing obstructive sleep apnoea.		underestimating the cost of this condition. Given the impact on model results it is appropriate for the ERG to sufficiently justify why their preferred source is more appropriate than the standard source used by the company.	by Sharples et al (reference 52 in the ERG report). This estimate was inflated to 2020/21 prices that gave the value of £274. We believe it is appropriate to use the annual costs of CPAC alone for managing sleep apnoea to avoid double-counting. This is because the costs associated with other direct impacts of the condition, i.e., strokes and CVDs, are included in the analyses.

Issue 3 Positioning of semaglutide 2.4mg

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report page 27 – Mischaracterisation of the positioning of semaglutide 2.4mg in relation to liraglutide 3.0mg	ERG report page 27 states 'We note that whilst the company have set out that there is an unmet need for other pharmacological treatment options within SWMS, they have not outlined in the CS how treatment with semaglutide 2.4 mg may potentially fit with liraglutide 3.0 mg and weight loss surgery in the clinical pathway'. We	Liraglutide 3.0mg has been approved by NICE for treatment in a patient population who are BMI ≥35 with high CV risk and pre-diabetes. This population is a subset of the semaglutide 2.4mg population as described in CS Table 1 page 15. As discussed throughout the company submission, and through the company Budget Impact Template, the use of semaglutide 2.4 is expected to displace the use of liraglutide 3.0mg in the liraglutide approved subpopulation. We therefore believe this statement is inaccurate and should be removed, as Novo Nordisk have made it clear that the intention would be for liraglutide 3.0mg use to be displaced by the introduction of semaglutide 2.4mg. The positioning of semaglutide 2.4mg in relation to liraglutide 3.0mg	Thank you for outlining here that the intention is for liraglutide 3.0 mg to be displaced by the introduction of semaglutide 2.4 mg. The ERG did not receive a copy of the Budget Impact Template/Submission with the CS. We have reviewed the CS again and we do not believe it was clearly stated that it is expected that semaglutide 2.4 mg will displace liraglutide 3.0 mg. For example, CS section B.1.3 outlines that there is an unmet clinical need for pharmacological treatments for people with obesity and comorbidities who do not meet the criteria for liraglutide 3.0

	propose that this statement is removed.	was also outlined clearly in Figure 2 of the company Budget Impact Submission and is reproduced here for clarity, and Table 15 in the company Budget Impact Submission which shows declining use of liraglutide 3.0mg over the first 5-years following the introduction of semaglutide 2.4mg.  	mg treatment, but we do not believe it discusses whether semaglutide would replace liraglutide 3.0 or whether it would be another pharmacological treatment option for the liraglutide approved subpopulation. We acknowledge, though, that CS section B.2.13 states clinicians would prioritise treatment with semaglutide 2.4 mg over liraglutide 3.0 mg, if semaglutide 2.4 mg is approved. Given this, and your clear statement here that semaglutide 2.4 mg is expected to displace treatment with liraglutide 3.0 mg, we agree to remove the statement on page 27 that the company has not outlined in the CS how treatment with semaglutide 2.4 mg may potentially fit with liraglutide 3.0 mg. We have altered the text as follows: “We note that whilst the company have set out that there is an unmet need for other pharmacological treatment options within SWMS, they have not outlined in the CS how treatment with semaglutide 2.4 mg may potentially fit with ~~liraglutide 3.0 mg and~~ weight loss surgery in the clinical pathway. It is unclear from the CS ~~if it is intended that semaglutide 2.4 mg would replace liraglutide 3.0 mg or be another pharmacological treatment option for people with a BMI of ≥ 35 mg/kg² who have non-diabetic hyperglycaemia and a high risk of cardiovascular disease. It is also unclear~~ when weight loss

			surgery would be offered to people taking semaglutide 2.4 mg." We have kept our reference to and discussion of weight loss surgery, as the company's justification for amending this text relates to the positioning of semaglutide 2.4 mg in relation to liraglutide 3.0 mg, rather than weight loss surgery.

Issue 4 STEP trial population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report page 42 – Incorrect description of evidence included within company submission.	ERG page 42 states that 'the trial inclusion criteria specified participants needed to have at least one weight-related comorbidity to be included in the trial, only 80.2% to 81.2% of the full analysis set did so. It is unclear why this is the case'. The pivotal Ph-III RCT STEP-1 included patients with a BMI>=30 (this can be with or without comorbidities) or BMI>= 27 with one of the following comorbidities: hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease. In	To avoid a misrepresentation of the evidence provided by the company we ask the ERG to amend the statement to make it clear that the difference between full analysis set and BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity subgroup is clear and stems from patients with a BMI ≥27 to 30 with comorbidities or patients with a BMI ≥30 without comorbidities.	Thank you for clarifying this. We believe the STEP 1 trial inclusion criteria wording in both the CS and trial paper are ambiguous regarding whether or not people with a BMI of ≥ 30 needed to have at least one weight-related comorbidity to be included in the trial. Your proposed amendment here has clarified to us that people were included if they had a BMI of ≥ 27 with one of the specified comorbidities or a BMI of ≥ 30 with or without comorbidities. To address this, we have now entirely removed the following sentences on page 42 of the ERG report: "We note that although the trial inclusion criteria specified participants needed to have at least one weight-related comorbidity to be included

	addition, a total of 12 comorbidities were measured at baseline (see Issue 6). The difference between full analysis set and the BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity subgroup which was observed by the ERG stems from the following subgroups • Patients with a BMI ≥27 to 30 with comorbidities • Patients with a BMI ≥30 without comorbidities		in the trial, only 80.2% to 81.2% of the full analysis set did so. It is unclear why this is the case. All participants in the company's target subgroup of BMI ≥ 30 kg/m2 plus ≥ one comorbidity, where the company are positioning treatment with semaglutide 2.4 mg, did, however, have at least one comorbidity."

Issue 5 Evidence included within the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report page 43 – Incorrect description of evidence included within company submission.	ERG page 43 states that 'The STEP 8 trial was a head-to-head comparison of semaglutide 2.4 mg with liraglutide 3.0 mg in people living with overweight or obesity who have at least one weight-related comorbidity' The company proposes to amend to 'The STEP 8 trial was a head-	To avoid a misrepresentation of the evidence provided by the company we ask the ERG to amend the statement to make it clear that STEP-5 and STEP 8 include people with overweight who have at least one weight related comorbidity or people living with obesity (who may or may not have a comorbidity).	Thank you for bringing this to our attention. We have now amended the text on ERG report page 43 and page 44 (Table 11) exactly as the company has suggested. We have also corrected similar text describing the STEP 5 and 8 trials in the Issue 9 table in the Executive Summary of the report.

	to-head comparison of semaglutide 2.4 mg versus liraglutide 3.0 mg in people living with obesity or people with overweight who have at least one weight-related comorbidity.' ERG page 44 table 11 states that STEP 8 includes 'People living with overweight (BMI ≥ 27 kg/m^2) or obesity (BMI ≥ 30 kg/m^2) with ≥ 1 weight-related comorbidity' The company proposes to amend to 'STEP 8 includes 'People living with obesity (BMI ≥ 30 kg/m^2) or people living with overweight (BMI ≥ 27 kg/m^2) with ≥ 1 weight-related comorbidity'.' ERG page 44 table 11 states that STEP-5 includes 'People living with overweight (BMI ≥ 27 kg/m^2) or obese (BMI ≥ 30 kg/m^2) with ≥ 1 weight-related comorbidity' The company proposes to amend to 'STEP 5 includes 'People living with obesity (BMI ≥ 30 kg/m^2) or people living with overweight (BMI ≥ 27 kg/m^2) with ≥ 1 weight-related comorbidity'.'		

Issue 6 Evidence included within the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report page 29 – Incorrect description of evidence included within company submission.	ERG page 29 states that 'the company's submission in practice only includes evidence for people with hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease'. This statement is inaccurate. This submission and associated economic analyses utilised data from the pivotal Ph-III RCT STEP-1. Patients in STEP-1 had various comorbidities including: • Pre-diabetes • Dyslipidaemia • Hypertension • Coronary artery disease • Cerebrovascular disease • Obstructive sleep apnoea • Disorder of reproductive system (polycystic ovary syndrome, irregular intermenstrual bleeding, infertility), • Liver disease (non-alcoholic steatohepatitis [NASH] or non-	To avoid a misrepresentation of the evidence provided by the company we ask the ERG to amend the statement to make it clear that the clinical evidence used in the submission does include patients with a range of comorbidities relevant to clinical practice.	We agree with the company that our original text on page 29 provides an incorrect description of the evidence. To address this, we have now deleted the following text, "the company's submission in practice only includes evidence for people with hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease", rather than using the wording change suggested by the company here. We have additionally clarified in ERG report Table 9 ('STEP 1 trial characteristics') in section 3.2.1.1 that the comorbidities eligibility criteria only applied to participants with overweight.

	alcoholic fatty liver disease [NAFLD]) • Kidney disease • Hip or knee osteoarthritis • Gout (including hyperuricaemia) • Asthma Novo Nordisk propose the following wording change: 'the company's submission includes evidence from the STEP-1 trial which enrolled patients with a wide variety of clinically relevant comorbidities, although the impact of treatment on all of these comorbidities could not be explicitly modelled'		

Issue 7 Outcome assessments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 47 of the report, the ERG state "The STEP 1 trial used the American Diabetes Association (ADA) definition of prediabetes. This defines prediabetes as an HbA1c level of 5.7 to 6.4% or FPG ≥ 5.6	The CS does not present the proportion of participants who had prediabetes at baseline according to the ADA definition who achieved normoglycaemia for the FAS population. In Section B.2.6.8 of the CS, the company	To correct a misreporting of the data included in the company submission	We agree with the company that the CS does not present the proportion of participants who had prediabetes at baseline according to the ADA definition who achieved normoglycaemia for the FAS population. We have now corrected the text on page 47 of the ERG report by

mmol/L and ≤ 6.9 mmol/L, or two-hour post challenge (OGTT) FPG ≥ 7.8 mmol/L and ≤ 11.0 mmol/L. In the submission, the company presents the proportion of participants who had prediabetes at baseline according to this definition who achieved normoglycaemia for the FAS population. Additionally, as outlined in CS section B.2.4.5, in the submission, the company have defined prediabetes in line with the definition of non-diabetic hyperglycaemia used in the NICE liraglutide appraisal (TA 664), when presenting the achievement of normoglycaemia among participants who had non-diabetic hyperglycaemia at baseline in the STEP 1 trial for the FAS population and the liraglutide-eligible subgroup (this outcome is not reported for the target subgroup).” The description of the presented results is incorrect.	presents the proportion of participants who had non-diabetic hyperglycaemia at baseline (per the TA664 definition) who achieved normoglycaemia for the FAS population. The text should be updated to reflect this The claim that the CS does not report the achievement of normoglycaemia among participants who had non-diabetic hyperglycaemia (per the TA664 definition) at baseline in the STEP 1 trial for target subgroup, is incorrect. In Section B.2.7.1 of the CS, the company presents the proportion of participants in the target subgroup who had prediabetes at baseline according to the NICE preferred definition who achieved normoglycaemia. The text should be updated to reflect this		deleting the following text: “In the submission, the company presents the proportion of participants who had prediabetes at baseline according to this definition who achieved normoglycaemia for the FAS population.” We also agree with the company that the achievement of normoglycaemia among participants who had non-diabetic hyperglycaemia at baseline outcome is reported for the target subgroup in the CS. We have now corrected the text on page 47 of the ERG report to read that this outcome is reported “for the FAS population, the target subgroup and the liraglutide-eligible subgroup. We have deleted the text stating “this outcome is not reported for the target subgroup”.
The reporting of Glycaemic status (Section 3.2.6 of the ERG report) is incorrect.	In the first column of table 15, Novo Nordisk proposes that the text should be amended to “Proportion of patients shifting	The text should be updated because the percentages reported in the row are the proportions of patients shifting from non-diabetic hyperglycaemia to normo-	The ERG’s intention was that the interpretation of Table 15 would make sense according to the table caption. However, in hindsight we appreciate that

	from non-diabetic hyperglycaemia to normo-glycaemic" instead of "Non-diabetic hyperglycaemia at baseline". The table heading and reported data should be checked to ensure they are aligned and accurate. Table 15 also states that the results are not reported for the target subgroup (BMI ≥30 plus ≥1 weight-related comorbidity), which is incorrect. These data are reported in Section B.2.7.1 and therefore the text should be updated to reflect this.	glycaemic, and not the proportion of patients with non-diabetic hyperglycaemia at baseline. In Section B.2.7.1 of the CS, the company presents the proportion of participants in the target subgroup who had prediabetes at baseline according to the NICE preferred definition who achieved normoglycaemia.	readers may interpret the row labels independently of the caption. We thank the company for pointing this out and have amended the row labels in ERG Report Table 15 as suggested, except that we have used the word 'participants' instead of 'patients'. Thank you for highlighting that data for the target subgroup are missing from ERG Table 15. We have updated the table and accompanying text to correct this.

Issue 8 HbA1C variable in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96 of the ERG report says 'We note that previous versions of the model have included HBA1c as a dynamic variable and we are unclear why HBA1c has not been included as a dynamic variable in this version of the model.	Both the structure and inputs for the HbA1c variable remain unchanged from the version of the model used in TA664. The variable can change over time in the CS model. However, a simplification was applied in both TA664 and the CS model for cohorts that do not have 100% of patients with T2D at baseline, to	Novo Nordisk wish to clarify the functionality and application of the HbA1c variable in the CS model.	Thank you for the clarification. We have noted this and revised the text accordingly on page 96 of the ERG report (by deleting the sentence highlighted by the company).

	not change the average HbA1c over time. The patients that undergo bariatric surgery receive a reduction in HbA1c as described in CS Section B3.3.2 Table 27 page 109. The CS describes the HBA1c variable as dynamic in CS Section B.3.2.2 Table 18 page 93. The CS Section B.3.3.6 page 115 describe the following: "HbA1c in diabetic patients is observed to increase with diabetes duration. The modelled cohort of interest enter the model without T2D but may develop T2D over time.		

Issue 9 Costs of microvascular complications

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 104 of the ERG report it is stated that the ERG has estimated the annual costs of microvascular complications to be £507, based on Capehorn et al, however, they do not state how these costs were calculated. Without further detail or justification the ERG	Describe how the cost estimate of £507 per year was derived and provide justification for why the use of this cost is more appropriate.	The ERG noted that the issue with microvascular complications costs in the company model is that it was applied from the onset of T2D. The ERG has 'addressed' the issue by lowering the annual costs, but still apply this cost from the onset of T2D. It is unclear how this adjustment was derived and how it addresses the issue noted by the ERG.	Not a factual inaccuracy. The ERG estimated the cost of microvascular complications by averaging the costs of ophthalmic complications, ulcer, amputation and neuropathy complications and renal complications over patients' lifetime for semaglutide and empaglifloxin arms in the study by Capehorn et al. (obtained from Figure1) (reference 47 in the ERG report). The lifetime estimate was

cost risks presenting a factually inaccurate representation of the cost of managing microvascular complications			converted to cost per year and inflated to 2020/21 prices.

Issue 10 Reporting of diet and physical activity results for the subgroup analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Tables 41 (page 106), 47 (page 112), 50 (page 114) and 52 9Page 115) - The results of diet and physical activity as well as the incremental results of liraglutide 3.0mg versus diet and physical activity are reported. The reporting of these results is not appropriate.	Novo Nordisk proposes that the Diet and physical activity results should be removed as well as the incremental results for liraglutide 3.0mg versus diet and physical activity from Tables 41, 47, 50 and 52.	The subgroup was explicitly included to allow for the comparison of semaglutide 2.4mg versus liraglutide 3.0, and the comparison of semaglutide versus diet and physical activity for the subgroup is already included in the base case analysis.	Not a factual inaccuracy. We disagree with the company's justification for their proposed amendment. Therefore, we have not made any change to text.

Issue 11 Minor text/marking clarifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report Page 71 – Error in reporting of outcomes for linear and logistic regression	On page 71 of the ERG report the text reads: 'The company conducted a series of adjusted	Minor wording alteration to correctly describe the outcomes included in the linear and logistic regressions.	Thank you for highlighting this typographic error. We have corrected this in the first paragraph of section 3.4.3 on page 71.

	and unadjusted analyses for the ITC. The adjusted analyses used established methods, linear regression (for dichotomous outcomes) and logistic regression (for continuous outcomes) methods to control for effect modifiers (body weight, gender and baseline hbA1c)' The use of dichotomous and continuous are used incorrectly (the wrong way around). Novo Nordisk propose the following amendment to the wording: 'The company conducted a series of adjusted and unadjusted analyses for the ITC. The adjusted analyses used established methods, linear regression (for **continuous** outcomes) and logistic regression (for **dichotomous** outcomes) methods to control for effect modifiers (body weight, gender and baseline hbA1c)'		
ERG report Page 72-73 – Error in reporting of estimands	In the 7th bullet of section 3.4.4 we believe that the reporting of the estimands by the ERG is incorrect. The text reads 'Use of the **treatment policy** estimand in	Minor wording alteration to correctly describe the estimands and the ERGs preferred approach. The company would be happy to answer any questions or clarify anything further to	Thank you for highlighting this typographic error. We have corrected this in the bullets listed under section 3.4.4 on page 72/73.

	the economic model is appropriate, as it takes into account treatment stopping, which the **treatment policy** estimand does not (see section 4.2.6.1)' The company model base case uses the trial product estimand which incorporates the stopping rule. The treatment policy estimand (no stopping rule) is explored in scenario analyses. The above text refers to the treatment policy estimand twice, so we assume one of these is an error/typo. We propose that the ERG review and update the wording accordingly to reflect their preferred view.	help the ERGs interpretation of the estimands as we appreciate this is not straightforward.	
ERG report page 13 and 14 – Incorrect marking	On page 13 and 14 of the ERG report the direction of the ICER change associated with a change suggested by the ERG is marked as CiC. This CiC marking is not needed and should be removed.	This resulted in more favorable ICERs for semaglutide 2.4 mg in comparison to physical activity and diet than when lower mean starting BMI values were used. A mean starting BMI of 42.5 may approximate that likely to be seen in our suggested subgroup. If that is the case, we expect that focusing on the subgroup is likely to result in lower ICERs for semaglutide 2.4 mg.	Thank you for noting this. We have now removed the CiC marking.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Semaglutide for managing overweight and obesity [ID3850]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **15 November 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the issues below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

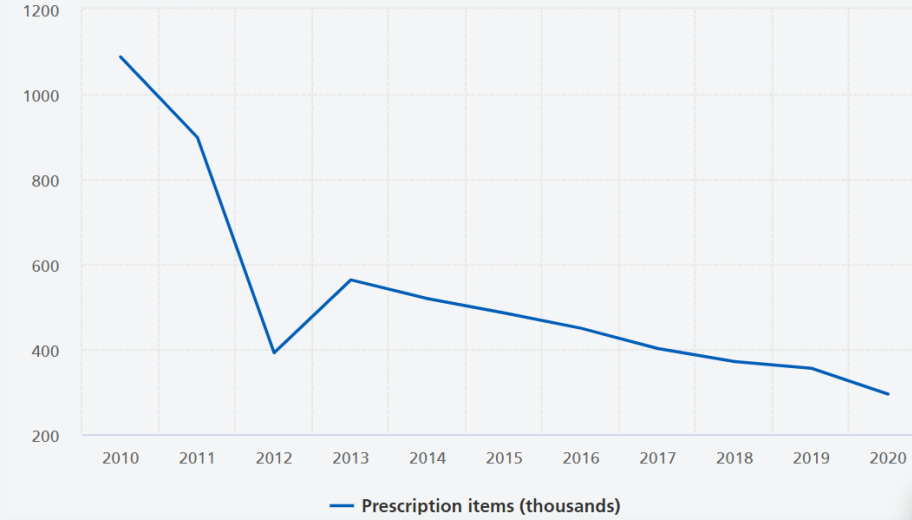
Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novo Nordisk**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

Please use the table below to respond to the issues raised in the ERG report.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Decision problem target population	**NO**	The ERG highlight that the Company Submission (CS) has focused on a sub-population of the population specified in the NICE scope and marketing authorisation: people with a BMI ≥ 30 with at least one weight related comorbidity (the 'target population'). This is a population with a high unmet need where the vast majority of patients are not currently able to access efficacious pharmacotherapy. Furthermore, it aligns with current service provisions for weight management and has enabled Novo Nordisk to propose a confidential commercial arrangement with NHS England. Because Novo Nordisk has demonstrated clinical and cost-effectiveness in the target population and the pivotal STEP 1 trial population is considered reflective of clinical practice, we do not feel that further, more granular subgroup analyses would add value to the Committee. With the proposed confidential commercial arrangement, the Company base case ICER is £14,827. It is not clear why the ERG would on the one hand agree with the focus on the target population, whilst also requesting that additional analyses be performed on a narrower subset of 'bariatric surgery eligible' patients. Adopting a further subgroup analysis with the goal of potentially narrowing the eligible population further, as requested by the ERG, suggests unnecessarily excluding patients with a clear clinical need and for whom semaglutide 2.4mg could provide substantial clinical benefits and for whom treatment would normally be considered cost effective. The current service provision within SWMS is considered suboptimal when compared with the growing needs of the UK patient population. Considering the NHS priority for the expansion of obesity management services (Department of Health and Social Care, 2021) and the future availability of treatments such as semaglutide 2.4mg it is our expectation that the use of SWMS are likely to expand further. Novo Nordisk have heard from NHS England and the clinical community that treatment in a broader population is desired (Br J Diabetes, 2021), which is in alignment with the government's obesity strategy and the NHS Long Term Plan (NHS Long Term Plan, Section 2.14, 2019). Just recently, the government has announced significant investments to

		advance obesity care, most notably £20 million for innovations in obesity (Government Spending Review, 2021) and £12 million for the evolution of weight management services (Press Release, Department of Health and Social Care, 2021). Novo Nordisk are currently trying to find a solution to negate the need for a confidential commercial arrangement. Given this and the expectation that obesity services are likely to expand in the future, the ICER using the FAS from STEP 1 (£15,111) may become more relevant for the committee deliberations, reflecting the full license population. This ICER can be produced by switching the patient characteristics to "All patients in study" (Cell E10) which can be found in the "Controls" sheet of the model. In conclusion, Novo Nordisk do not understand why the ERG have suggested an analysis based on a narrower population than the target population given the data on clinical and cost effectiveness presented within the CS. Furthermore, whilst the target population is reflective of current service provisions for weight management and has enabled confidential commercial arrangement discussions with NHS England, the likely expansion of weight management services in the future could permit access for a broad population covered by the license.
Key issue 2: Exclusion of orlistat as a comparator	**NO**	Orlistat use today is very limited. Orlistat is associated with low success rates, undesirable side effects and poor adherence which means that its use has been declining for many years. During response to the NICE draft scope, Decision Problem and in CS sections B.1.1 and B.1.3.4 Novo Nordisk have explained using both empirical data on the decline in orlistat use, and qualitative insight received via engagement with clinicians' that orlistat is not an appropriate comparator. These sentiments have been echoed in the two most recent appraisals of treatments for obesity, TA494 (Naltrexone–bupropion for managing overweight and obesity) and TA664 (Liraglutide for managing overweight and obesity). Novo Nordisk appreciate that the ERG has acknowledged this information in their report and agree with the company's decision. Novo Nordisk also note that as part of the consultation on this appraisal, Obesity UK provided some feedback on the use of both orlistat and bariatric surgery, which in both cases suggests they are not widely used and unlikely to be considered relevant comparators as per the clinical feedback already provided: *'Many people told us they had used orlistat with little effect and poor outcomes. Bariatric surgery is available but not everyone wants to go down that road, and even if they do its often difficult to access and hard to get'.* Further, semaglutide 2.4mg is intended for use in patients who have been referred to SWMS where conventional interventions (such as orlistat) have been unsuccessful or not considered appropriate. We also refer to Figure 1 (below and referenced as Figure 2 in the CS), which demonstrates declining use of orlistat over time. Given orlistat was not deemed an appropriate comparator in prior HTA decision making and given the use of orlistat is likely to

		have declined further since those appraisals, we believe the Committee have been provided with enough information to consider this issue resolved. **Figure 1: Number of NHS prescriptions of orlistat in England** 
Key issue 3: Exclusion of the STEP 2 trial from the CS	**YES**	In response to this issue Novo Nordisk have shared the publication and Clinical Trial Report Synopsis of STEP 2 to help inform the Committee discussion around treatment in people with obesity and T2D. This submission focuses on people with obesity (body mass index [BMI] of ≥ 30 kg/m2) who have one or more weight related comorbidities, a broad and diverse patient population with a high level of unmet need. Semaglutide 2.4mg will provide this patient group with the opportunity for significant and clinically meaningful weight loss. The STEP 1 trial was included within the CS as the primary evidence source to address this decision problem given the large degree with which the patients enrolled, and outcomes observed represents the target population to be treated in NHS clinical practice (people with BMI ≥30 with one or more weight related comorbidity). The relevance and representativeness of this trial has been discussed with numerous clinical experts, as noted in the CS. Novo Nordisk have, however, acknowledged the importance of T2D as a comorbidity, and note that approximately one third of patients currently receiving SWMS have T2D. Novo Nordisk does not seek to exclude patients

		with obesity and T2D from the target population, a group for which semaglutide 2.4mg could be considered a relevant and important treatment option. Semaglutide 2.4mg has been investigated as a treatment for obese patients with T2D as part of the STEP 2 trial. These data show the continued superiority of semaglutide 2.4mg compared with placebo: • Estimated change in mean bodyweight from baseline to week 68 was –9·6% (SE 0·4) with semaglutide 2.4mg vs –3.4% (0.4) with placebo. Estimated treatment difference for semaglutide 2·4mg versus placebo was −6.2 percentage points (95% CI −7.3 to −5.2; p<0·0001). • At week 68, more patients on semaglutide 2·4mg than on placebo achieved weight reductions of at least 5% (267 [68.8%] of 388 vs 107 [28.5%] of 376; odds ratio 4.88, 95% CI 3·58 to 6·64; p<0·0001) Novo Nordisk acknowledge that the weight loss observed within STEP 2 is less than that in STEP 1, but this is accompanied with other benefits such as a reduction in glucose lowering medication and improved glycaemic control. We have heard from clinical experts that weight loss in a T2D population may be expected to be lower than in a non-T2D population. This has also been demonstrated in other pharmacological intervention trials such as liraglutide 3.0mg in SCALE Diabetes (Clinical Trials, 2013). Despite this, it is clear that substantial clinical benefits can be achieved for patients who are both obese and have T2D and this population should not be excluded by the ERG from the company target population. We acknowledge the ERG view that the STEP-2 data are informative, given the potential use of semaglutide 2.4mg in an obese population with T2D. However, explicitly modelling the cost-effectiveness of semaglutide 2.4mg in an obeseT2D population in the company obesity model comes with inherent limitations and challenges which are likely to underestimate the real value of semaglutide 2.4mg in people with obesity and T2D. The management of people with diabetes is important, i.e., the primary aim of diabetes treatment is glycaemic control without increasing weight or risk of hypoglycaemia. The company model focuses on the value of weight loss and does not focus on glycemia, as such there are a number of limitations which should be taken into consideration resulting in an underestimation of the cost-effectiveness in the T2D population, such as: • T2D is a progressive disease and typically modelled via a number of different health states associated with different treatments, glycaemic status, increasing duration of T2D, risks and costs. In the company model T2D patients enter the model with the same baseline characteristics therefore vastly simplifying the progressive nature of disease and underestimating the benefit of slowing T2D progression. However, STEP 2 contained a mixture of patients at baseline whose T2D was managed with diet and exercise, or with a stable dose of up to three oral glucose lowering agents. Therefore, the heterogeneity of patients within STEP 2 data cannot be reflected adequately within the company model.

- In STEP 2 glucose lowering medication was adjusted to control the patient's HbA1c in both arms. Patients in the placebo arm had much greater adjustment of their medication than patients receiving semaglutide 2.4mg, which is not adequately reflected in the company model. However, despite this, HbA1c was much better controlled in patients receiving semaglutide 2.4mg. The differences in costs for glucose lowering medication between placebo and the semaglutide 2.4mg arm are not incorporated with sufficient granularity in the company model
- In addition, the company model does not model individual health states for microvascular complications associated with T2D such as retinopathy, nephropathy and neuropathy all of which are relevant long-term complications of diabetes used in established diabetes models to reflect the complex nature of the disease.

Despite these limitations, as agreed during the Technical Engagement call Novo Nordisk have provided ICER estimates for semaglutide 2.4mg using data from STEP 2 in the company model. Given the limitations of the company model in capturing benefits in a T2D population, we also provide, for illustrative purposes, the ICER for semaglutide 2.4mg plus diet and exercise vs diet and exercise alone, using an established, well-validated diabetes model (Phil McEwan, 2014; IQVIA, 2021) which is able to more comprehensively capture the impact of treatment on weight loss, glycaemic control and other glucose lowering medications. The CORE diabetes model has been part of a number of technology appraisals in diabetes to NICE (TA203; TA622) and SMC (748/11; 785/12; 1044/15; 1088/15; SMC2287; SMC2235).

For patients with a BMI ≥ 30 and T2D (using data from STEP 2) the ICER is £21,277/QALY in the base case (Table 1).

Table 1: ICERs for BMI ≥ 30 plus comorbidity using data from STEP 2, Company Model (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Diet and exercise	[redacted]	15.468	[redacted]				
Semaglutide 2.4mg	[redacted]	15.536	[redacted]	[redacted]	0.068	[redacted]	21,277
Key: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.							

The analysis in the Diabetes Model provides an ICER of £16,613/QALY (Table 3). The Diabetes Model has been built explicitly to model the clinical pathway of T2D patients but is not targeted to therapies with weight loss as the key outcome of interest. It is important to note that neither estimate takes into account the changes in T2D medication costs. Table 2 below details the differences between the company obesity model and the diabetes model ('herein referenced as the 'Core Diabetes Model'[CDM]).

Table 2 Comparison of company obesity model and the CDM

Model components	Company obesity model	Core Diabetes Model
Model purpose	The company obesity model (COM) has been designed with the purpose to evaluate the cost-effectiveness of obesity interventions aimed to prevent and delay the occurrence of obesity complications. Thus, treatment benefits are best captured before the onset of such complications. When designing the model, the focus has been to capture a broad spectrum of complications, seen to be associated with obesity, and respond to weight loss, rather modelling further complexities associated with each. This is the case for type 2 diabetes (T2D), but also for sleep apnoea.	The Core Diabetes model (CDM) has been designed to evaluate the cost effectiveness of diabetes interventions that manage type 2 diabetes (T2D) and prevent and delay the occurrence of diabetes related complications.
Impact of glycaemic effect	The benefits of blood glucose control beyond the onset of T2D are likely underestimated with the COM. This is because the glycaemic effect (when analysing a single T2D cohort in the COM) have an impact only: • on the modelled cardiovascular events i.e., myocardial infarction, unstable angina, stroke and transient ischaemic attacks	The CDM captures the impact of the glycaemic effect: • on the modelled cardiovascular events i.e., myocardial infarction, unstable angina, stroke and transient ischaemic attacks It additionally captures the impact of the glycaemic effect in delaying the incidence of: • end-stage renal disease • heart failure • peripheral vascular disease • diabetic eye disease • foot ulcers or amputations

				• diabetic neuropathy and their associated mortality.
		Treatment discontinuation due to a stopping rule	The COM can implement a stopping rule by applying responder efficacy to the proportion of the cohort achieving response	The CDM does not have the ability to implement an early responder stopping rule
		Modelling of next line therapies	It is not possible in the COM	The CDM uses treatment intensification to basal insulin for patients that discontinue treatment with semaglutide 2.4mg
		Modelling of treatment effects	The COM models treatment effects via changes in: • Weight loss • Systolic blood pressure (SBP) • total cholesterol • HDL cholesterol • HbA1c	The COM models treatment effects via changes in: • Systolic blood pressure (SBP) • total cholesterol • HDL cholesterol • HbA1c • Diastolic blood pressure (DBP) • LDL cholesterol • triglycerides • BMI • estimated glomerular filtration rate
		Implementation of disutility related to BMI	The COM applies BMI-related disutilities based on the paper of Soltoft et al (2009) which relates change in utility based on the starting BMI. Disutiluty per BMI point is approximately 0.003. the COM yields more conservative cost-effectiveness estimates compared to CDM	The CDM uses a fixed disutility of 0.0061 per unit BMI from Bagust and Beale (2006).
		Mortality	The COM includes BMI adjusted mortality and obesity complication mortality	The CDM includes mortality related to complications, adjusted for patient characteristics, time since the event

		occurred and use of medication (e.g. ACE inhibitors, aspirin, statins).

Table 3: Illustrative ICERs for BMI ≥ 30 using data from STEP 2, Diabetes Model (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Diet and exercise	[redacted]	14.87	[redacted]				
Semaglutide 2.4mg	[redacted]	14.98	[redacted]	[redacted]	0.11	[redacted]	16,613
Key: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.							

The T2D population represents up to a third of the obese patient population referred to SWMS, a population in which STEP-2 has demonstrated a clinical benefit of treatment with semaglutide 2.4mg, and despite some limitations in modelling this population, data suggests that the treatment of these patients is likely to be cost-effective.

Key issue 4: Exclusion of the STEP 3 trial from the company submission	**YES**	STEP 3 was a Phase IIIa randomised, double-blind, multicentre, placebo-controlled trial of 611 adults who were obese (BMI ≥ 30 kg/m2), or, alternatively are overweight (BMI ≥ 27 kg/m2) with at least one weight-related comorbidity and without diabetes or HbA1c ≥ 6.5%. During the study, semaglutide 2.4mg was administered in conjunction with intensive behavioural therapy (IBT), which consisted of combined behavioural counselling, reduced-calorie diet, and increased physical activity. This trial was conducted with enrolment sites exclusively in the United States. As described in the company submission (and as was determined as part of TA664 where the SCALE IBT, similar in design to STEP-3, was not considered relevant to the Decision Problem) this kind of extended and intensive management is not reflective of how patients are treated in the United Kingdom and therefore the results are not generalisable to the Decision Problem being evaluated. Below includes a description of the IBT administered as part of the trial: *'Each IBT counselling session covered a specific topic, for example, advice on modifying diet or physical activity as well as behavioural strategies to facilitate these changes (e.g., monitoring food intake, challenging negative thoughts, obtaining social support)* (Journal of American Medical Association, 2021). *From the randomization visit through week 12, participants received weekly IBT counselling from a dietitian (or a similarly qualified healthcare professional) who discussed participants' progress, reviewed food and activity diaries, addressed any adherence problems, and prepared for transition to the next phase of the diet. Most of the topics were accompanied by a homework assignment, found in the participant hand-outs to be completed before*

		the next visit according to the visit schedule. From weeks 12 to 24, IBT counselling visits decreased to every other-week, and from weeks 24 to 68 were every 4 weeks (for a total of 30 IBT visits over the 68 weeks. Data from the activity tracker collected in this trial were used for exploratory purposes. Participants were allowed to keep the activity tracker after approval by the independent ethics committee/institutional review board. Participants could use a food diary of their choice (eg, paper/app/other tool) for dietary recording, provided it could be reviewed during the counselling sessions. All participants were instructed on how to capture food intake and were encouraged to keep the diary on a daily basis.' The ERG themselves describe the intensity of standard management approaches in clinical practice in Table 8 of the ERG report. In doing so they highlight that over a 6-month period, 6-9 sessions with a dietician are to be expected. In STEP-1 counselling sessions are conducted every 4 weeks, which is aligned to the amount of contact time expected in clinical practice over the same period. In STEP-3 weekly sessions are conducted for the first 12 weeks, and every other week for the following 12 weeks, vastly exceeding the contact time expected in clinical practice. As such, the data provided from STEP-1 represents the most generalisable significant and informative data source for standard management in England and the primary data source for which the Committee should base its recommendation. In response to this Issue Novo Nordisk have shared the top-level results from the STEP 3 trial (Wadden et al, 2021). Data show the continued superiority of semaglutide 2.4mg in comparison with placebo: • At week 68, the estimated mean body weight change from baseline was –16.0% for semaglutide 2.4mg vs –5.7% for placebo (difference, −10.3 percentage points [95% CI, −12.0 to −8.6]; P < .001). • More participants treated with semaglutide 2.4mg vs placebo lost at least 5% of baseline body weight (86.6% vs 47.6%, respectively; P < .001). The ERG point out that the difference in percentage change in weight from baseline between semaglutide 2.4mg and placebo (IBT) was qualitatively smaller than between semaglutide 2.4mg and placebo (standard diet and exercise) as observed in the STEP 1 trial. However, this difference is marginal with overlapping confidence intervals (note from page 47 of CS '*The estimated mean weight change at 68 weeks (based on observed data) was −14.9% with semaglutide 2.4 mg, compared to −2.4% with placebo (estimated treatment difference [ETD]: −12%; 95% CI: −13.4, −11.5; p < 0.001)'.* Given both the ERG and company highlight that IBT is not reflective of UK clinical practice, and the broad consistency of results between STEP-1 and STEP-3 Novo Nordisk maintain the view that STEP-1 is the primary data source upon which the Committee should base their decision making, and that no further consideration of data from STEP-3 is required.

Key issue 5: The ITC results are not used in the economic model

NO

The ITC calculation for weight change, SBP change, total cholesterol and HDL cholesterol change is as follows:

- *Parameter value for liraglutide 3.0mg in ITC = Parameter value for liraglutide 3.0mg in SCALE 1839 + [Parameter value for Diet & exercise in STEP1 – Parameter value for Diet & exercise in SCALE 1839]*

The ITC calculation for the percentage with glycaemic status change is as follows:

- *Parameter value for liraglutide 3.0mg in ITC= Parameter value for liraglutide 3.0mg in SCALE 1839 *Parameter value for Diet & exercise in STEP 1 /Parameter value for Diet & exercise in SCALE 1839*

Table 4 below show the adjusted liraglutide 3.0mg efficacy for the base case. The tables on no stopping rule scenario (Table 7) and post hoc subgroup efficacy scenario (Table 8) can be found in Appendix 2. The values for the adjusted liraglutide 3.0mg efficacy use non rounded inputs in the calculation and therefore the values calculated using the reported table values may be slightly different.

Table 4 Base case ITC values

	Liraglutide 3.0mg (SCALE 1839) all patients, early responders	**D&E (SCALE 1839) – all patients, early responders**	**D&E (STEP1) – all patients, early responders, trial product estimand**	**ITC Adjusted liraglutide 3.0mg**
Body weight (%) - relative change from baseline				
Change at 4, 7, 10 months	-10.32%	-9.04%	-8.72%	-10.00%
Change at year 1	-11.14%	-9.17%	-8.45%	-10.42%
Change at year 2	-9.76%	-7.97%	-8.45%	-10.24%
Change in SBP				
Change at 4, 7, 10 months	-5.57	-3.39	-2.28	-4.46
Change at year 1	-5.26	-2.97	-2.90	-5.19
Change at year 2	-4.98	-1.92	-2.90	-5.96
Change in total cholesterol				
Change at 4, 7, 10 months	-9.6	-5.06	-1.04	-5.58
Change at year 1	-6.3	-1.19	2.86	-2.25

		<table><tr><td>Change at year 2</td><td>-5.43</td><td>-1.46</td><td>2.86</td><td>-1.11</td></tr><tr><td></td><td></td><td></td><td></td><td></td></tr><tr><td colspan="5">Change in HDL cholesterol</td></tr><tr><td>Change at 4, 7, 10 months</td><td>-0.82</td><td>1.53</td><td>-0.99</td><td>-3.34</td></tr><tr><td>Change at year 1</td><td>1.96</td><td>2.93</td><td>3.04</td><td>2.07</td></tr><tr><td>Change at year 2</td><td>3.01</td><td>3.88</td><td>3.04</td><td>2.17</td></tr><tr><td></td><td></td><td></td><td></td><td></td></tr><tr><td colspan="5">Glycaemic status change</td></tr><tr><td>Odds (>1 is improvement)</td><td>4.8</td><td>1.2</td><td>1.3</td><td>5.5</td></tr><tr><td>% reversing</td><td></td><td></td><td></td><td>83.6%</td></tr></table> Novo Nordisk have provided the Clinical Trial Report Synopsys for the STEP-8 study and top-level results in response to this issue and Key Issue 9. The results show a substantial improvement in weight loss for those treated with semaglutide 2.4mg when compared with liraglutide 3.0mg, the magnitude of which is similar to the difference as calculated in the ITC. At time of submission, STEP 8 data was not available but now validates the results of the ITC and reduces the uncertainty associated with the analysis. As such it would be reasonable to assume that the conclusion that semaglutide 2.4mg is dominant over liraglutide 3.0mg would be unlikely to change.
Key issue 6: Treatment stopping rule	**YES**	The MHRA marketing authorisation is now available for semaglutide 2.4mg (Wegovy®) and reads as follows: ‘Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance in adults with an initial Body Mass Index (BMI) of ≥30kg/m^2 (obesity), or ≥27kg/m^2 to <30kg/m^2 (overweight) in the presence of at least one weight-related comorbidity.’ In addition, it includes the following wording on treatment stopping rule: ‘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, taking into account the benefit/risk profile in the individual patient'. (MHRA: Semaglutide 2.4mg SPC, 2021) The wording of the marketing authorisation is aligned with how Novo Nordisk have modelled treatment with semaglutide 2.4mg, and how we expect semaglutide 2.4mg to be used in clinical practice. At the request of the ERG Novo Nordisk have again consulted with clinical experts on this topic and received additional confirmation that the application of non-responder stopping rules is common clinical practice for every approved anti-obesity medication and is aligned with various other appraisals in this area, in particular GLP-1 agonist, liraglutide 3.0mg, evaluated as part of TA664. Further, clinician feedback suggests that in the vast majority of cases patients who do not achieve the 5% weight loss threshold within 6-months would voluntarily seek to discontinue treatment. As such it is appropriate to include such a stopping rule in the economic analyses to reflect how semaglutide 2.4mg will be used in practice.
Key issue 7: Assumption that all patients with non-diabetic hyperglycaemia develop type 2 diabetes after initial CVD event	**NO**	We rely on risk equations for the modelling, and there isn't one to predict cardiovascular risk for a population with non-diabetic hyperglycaemia. In the absence of such, an assumption on whether patients develop T2D after a CV event is necessary. As such, in the CS base case, patients with non-diabetic hyperglycaemia are assigned to a history of ACS/stroke and assumed to have T2D after the first CV event occurs. Patients treated for the management of obesity are likely to have risk factors for long term complications like diabetes. It is likely that while some patients will not develop type 2 diabetes after a CV event, some patients may go on to develop this. On balance, clinical experts have told the company that the truth probably lies somewhere on this continuum, leaning more towards the company's assumption. With that said, the impact of removing this assumption on the base case ICER is minimal (about [redacted]). The inclusion of this assumption is in line with the approach used in TA664 which was considered acceptable for decision making. In addition, it has been demonstrated in Lopes et al 2020 that the model does not overestimate the incidence of T2D which ultimately indicates that the model, to a large extent reflects reality, and there is no reason for the Committee to conclude an alternative approach, as suggested by the ERG more appropriately reflects clinical reality.
Key issue 8: Differences in how intercurrent events are	**NO**	The ERG notes differences in how or whether intercurrent events are recorded across trials (STEP 1 and SCALE 1839). SCALE 1839 was conducted more than 5 years ago (2015) and at the time of study completion, the use of different methodologies for the imputation of intercurrent events was preferred. This is an inherent limitation associated with synthesising evidence from multiple clinical trials conducted at different points in time. We appreciate the ERG view that it is unclear how this issue could be resolved but expect that the risk of bias is low. Further, as data are available from STEP 8 (provided as part of

recorded across trials may impact imputation		our Technical Engagement responses), which provides a randomised comparison between semaglutide 2.4mg and liraglutide 3.0mg, Novo Nordisk feel as though the Committee are likely to have sufficient evidence to draw conclusions around the benefit semaglutide 2.4mg provides over liraglutide 3.0mg without further consideration of this issue.
Key issue 9: Results from the completed STEP 5 and STEP 8 trials are expected this year	**YES**	STEP 5 is a completed Phase IIIa, 104-week, randomised, double-blind, multicentre, placebo-controlled trial in 304 adults who were obese (BMI ≥ 30 kg/m2), or overweight (BMI ≥ 27 kg/m2) with at least one weight-related comorbidity, and without diabetes or HbA1c ≥ 6.5%. Novo Nordisk have shared the Clinical Trial Report Synopsis with the ERG as part of our Technical Engagement responses. These data support the superiority of semaglutide 2.4mg vs placebo over the 104-week treatment duration. The data show: • Body weight change (%) from baseline to week 104: −15.18% vs −2.62%; ETD: −12.55% [−15.33; −9.77]$_{95\%CI}$ • Proportion of subjects achieving the pre-defined categorical weight reductions of ≥10%: 61.6% vs 13.3%; odds ratio: 7.23 [3.95;13.23]$_{95\%\ CI}$ STEP 8 is a completed Phase IIIb, 68-week, randomised, open label, US-based, pairwise placebo-controlled, multicentre, clinical trial of 338 patients, comparing semaglutide 2.4mg once weekly with liraglutide 3.0 mg once daily in patients with obesity or overweight and at least one weight-related comorbidity. Novo Nordisk have shared the Clinical Trial Report Synopsis with the ERG as part of our Technical Engagement responses. These data support the superiority of semaglutide 2.4mg vs liraglutide 3.0 mg. The data show: • Body weight change (%) from baseline to week 68: −15.78% with semaglutide 2.4mg and −6.4% with liraglutide 3.0 mg and the estimated treatment difference (ETD) was −9.38% [−11.97; −6.80]$_{95\%CI}$. • The proportion of subjects achieving the pre-defined categorical weight reductions of ≥10%: 70.9% vs 25.6%; odds ratio: 6.28 [3.53; 11.18]$_{95\%CI}$ The data provided continue to support the use of semaglutide 2.4mg as a highly efficacious and tolerable treatment option for patients with obesity.

Key issue 10: Treatment duration and retreatment	**NO**	The base case analysis assumes a maximum treatment duration of 2 years as in SWMS, treatment is provided for a maximum of two years, and this is not expected to change following the introduction of semaglutide 2.4mg. In TA664, the committee accepted a treatment duration of two years for a single course of treatment with GLP-1 agonist and decided that the assumption was reasonable and appropriate in the context of weight management services. The ERG have confirmed in their report (page 19) that this assumption is also considered reasonable for this appraisal of semaglutide 2.4mg. As such we believe there is no reason for the Committee to conclude an alternative approach is more appropriate.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Annual cost of microvascular complications	Section 4.2.8 Resources and costs	YES	As discussed during the Technical Engagement call, the ERG have used the discounted costs of microvascular complications at £507, and further lowered to £398 which is significantly lower than the company's undiscounted estimate (£940.86). It is important to use the undiscounted cost estimate, as otherwise the cost estimate will be double discounted when applied alongside standard discounting within the company model. To avoid double discounting, Novo Nordisk has approached the authors of the Capehorn et al (2021) paper to retrieve the (unpublished) undiscounted estimates which the company is open to share with the ERG and NICE for clarification. This information is enclosed and shows that the use of undiscounted costs for a) ophthalmic b) ulcer, amputation and neuropathy and c) renal complications which are annualised over the undiscounted life expectancy add to annual microvascular complication costs of £940.86. Thus, we believe that the company estimate of microvascular complication costs are more appropriate.

Additional issue 2: Annual costs of sleep apnoea	Section 4.2.8 Resources and costs	NO	It remains unclear why the use of alternative cost data from the Sharples et al (2014) publication is preferred over the use of established NHS reference cost data from a more recent reference time point. The methodology used in the CS for calculating sleep apnoea costs is in line with existing NICE guidance on cost estimates and has been used and accepted in TA664 (guidance issued recently, in December 2020). Additionally, as discussed during the Technical Engagement call, Novo Nordisk would like to clarify that no stroke or CVD related costs have been included in the company's calculation of sleep apnoea costs. The costs used to derive the annual costs of sleep apnoea are directly sourced from the National schedules of NHS costs and show the national average unit cost for sleep apnoea, based on the four sleep disorder codes available in NHS costs (DZ18D, DZ18E, DZ18F, DZ18G). Clinical experts consulted by the company have stated that the annual costs of treating sleep apnoea are likely to be much closer to the company estimate of £1,018.19 than the ERG proposed £274. The company's approach is in line with NICE methodology and preferred over the use of alternative cost data from literature (NICE Methods Guide, 2013), which is why we believe that the use of the company estimate is more appropriate than the ERG proposed cost estimates.

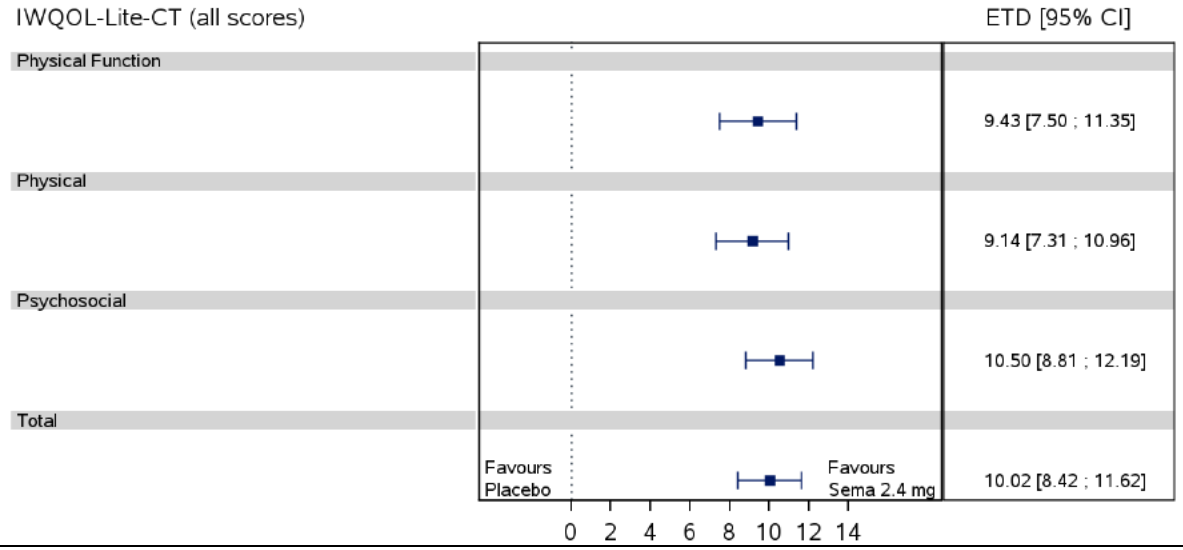
Additional issue 3: Presence of eating disorders and mental health issues	Section 2.2.1 Background information on overweight and obesity	NO	Section 2.2.1 of the ERG report states 'The company do not mention eating disorders, such as binge eating (which our clinical expert states are common in this population) and the process by which mental health co-morbidities should be addressed'. Although the direct impact of treatment with semaglutide 2.4mg on these factors is not explicitly discussed in the CS, Novo Nordisk would like to point out that key HRQL endpoints collected within STEP-1 show improvement in overall scores for which data on mental health are collected. As detailed in Appendix R of the CS additional results from the STEP 1 clinical trial are presented, including the Impact of weight on Quality of life (IWQoL) questionnaire and SF-36v2. The IWQoL tool includes domains linked to self-esteem, sexual life, public distress and binge eating, and the SF-36v2 includes questions relating to emotional, and mental health in addition to physical functioning and general health. **Figure 2: IWQOL-Lite-CT change from baseline to 68 weeks** 

			Figure 27 in Appendix R (and above) presents the change from baseline to Week 68 for semaglutide 2.4mg and placebo for the physical function, physical, psychological and total scores of the IWQOL-Lite-CT; all were in favour of semaglutide 2.4mg.

Additional issue 4: CIC marking		NO	The following parts of the ERG report should be marked as CIC:
			• Table 2, Total costs (£) of Diet and physical activity
			• Table 3, Total costs (£) of Diet and physical activity and Total costs, Incr. costs and ICER of liraglutide 3.0 mg
			• Table 4, Total costs (£) of Diet and physical activity for all scenarios
			• Table 5, Total costs (£) of Diet and physical activity and Total costs, Incr. costs and ICER of liraglutide 3.0 mg for all scenarios
			• Table 10, the values for the below parameters for BMI ≥ 30 mg/kg^2 plus ≥ 1 comorbidity:
			  ○ Age (years)
			  ○ Mean BMI (kg/m^2)
			• Table 33, the values for the below parameters for both populations:
			  ○ Age (years)
			  ○ BMI (kg/m2)
			  ○ Height (m)
			  ○ SBP (mmHg)
			  ○ Total cholesterol (mg/dl)
			  ○ HDL cholesterol (mg/dl)
			  ○ Triglycerides (mg/dl)
			  ○ Proportion Triglyceride level >150 mg/dl (%)
			  ○ Proportion current smokers (%)
			  ○ Proportion females (%)
			  ○ Proportion on lipid-lowering drug (%)
			  ○ Proportion on antihypertensive medication (%)
			• Table 34, number of early responders for semaglutide 2.4mg and liraglutide 3.0mg
			• Table 40, Total costs (£) of Diet and physical activity
			• Table 41, Total costs (£) of Diet and physical activity and Total costs, Incr. costs and ICER of liraglutide 3.0 mg
			• Table 46, Total costs (£) of Diet and physical activity for all scenarios
			• Table 47, Total costs (£) of Diet and physical activity and Total costs, Incr. costs and ICER of liraglutide 3.0 mg for all scenarios
			• Table 49, Total costs (£) of Diet and physical activity for all scenarios

			• Table 50, Total costs (£) of Diet and physical activity and Total costs, Incr. costs and ICER of liraglutide 3.0 mg for all scenarios • Table 51, Total costs (£) of Diet and physical activity for all scenarios • Table 52, Total costs (£) of Diet and physical activity and Total costs, Incr. costs and ICER of liraglutide 3.0 mg for all scenarios

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Novo Nordisk have not made any changes to the proposed base case

Appendix 1 - List price ICERs

Table 5: ICERs using data from STEP 2, Company Model (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Diet and exercise	[redacted]	15.468	12.729				
Semaglutide 2.4mg	[redacted]	15.536	12.816	[redacted]	0.068	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.							

Table 6: Illustrative ICERs using data from STEP 2, Diabetes Model (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Diet and exercise	[redacted]	14.87	7.31				
Semaglutide 2.4mg	[redacted]	14.98	7.41	[redacted]	0.11	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.							

Appendix 2 - Tables showing the adjusted liraglutide 3.0mg efficacy for the no stopping rule scenario and post hoc subgroup efficacy scenario

Table 7: No stopping rule with treatment policy estimand ITC values

	Liraglutide 3.0mg (SCALE 1839) – all patients, early responders	D&E (SCALE 1839) – all patients, early responders	D&E (STEP1) – all patients, early responders, treatment policy estimand	ITC Adjusted liraglutide 3.0mg
Body weight (%) - relative change from baseline				
Change at 4, 7, 10 months	-10.32%	-9.04%	-8.78%	-10.06%
Change at year 1	-11.14%	-9.17%	-8.27%	-10.24%
Change at year 2	-9.76%	-7.97%	-8.27%	-10.06%
Change in SBP				
Change at 4, 7, 10 months	-5.57	-3.39	-2.03	-4.21

	Liraglutide 3.0mg (SCALE 1839) – all patients, early responders	D&E (SCALE 1839) – all patients, early responders	D&E (STEP1) – all patients, early responders, treatment policy estimand	ITC Adjusted liraglutide 3.0mg
Change at year 1	-5.26	-2.97	-2.48	-4.77
Change at year 2	-4.98	-1.92	-2.48	-5.54
Change in total cholesterol				
Change at 4, 7, 10 months	-9.6	-5.06	-1.23	-5.77
Change at year 1	-6.3	-1.19	4.45	-0.66
Change at year 2	-5.43	-1.46	4.45	0.48
Change in HDL cholesterol				
Change at 4, 7, 10 months	-0.82	1.53	-1.01	-3.36
Change at year 1	1.96	2.93	3.38	2.41
Change at year 2	3.01	3.88	3.38	2.51
Glycaemic status change				
Odds (>1 is improvement)	3.2	0.8	1.1	4.0
% reversing				79.2%

Table 8: Post hoc efficacy analysis for subgroups ITC values

	Liraglutide 3.0mg (SCALE 1839) – BMI ≥ 35 kg/m^2, prediabetes and high risk for CVD, early responders	D&E (SCALE 1839) – BMI ≥ 35 kg/m^2, prediabetes and high risk for CVD, early responders	D&E (STEP1) – BMI ≥ 35 kg/m^2, prediabetes and high risk for CVD, early responders, treatment policy estimand	ITC Adjusted liraglutide 3.0mg
Body weight (%) - relative change from baseline				
Change at 4, 7, 10 months	-9.96%	-9.15%	-9.08%	-9.89%

	Liraglutide 3.0mg (SCALE 1839) – BMI ≥ 35 kg/m^2, prediabetes and high risk for CVD, early responders	D&E (SCALE 1839) – BMI ≥ 35 kg/m^2, prediabetes and high risk for CVD, early responders	D&E (STEP1) – BMI ≥ 35 kg/m^2, prediabetes and high risk for CVD, early responders, treatment policy estimand	ITC Adjusted liraglutide 3.0mg
Change at year 1	-10.91%	-8.82%	-9.36%	-11.45%
Change at year 2	-9.46%	-8.07%	-9.36%	-10.75%
Change in SBP				
Change at 4, 7, 10 months	-6.22	-3.59	-3.14	-5.77
Change at year 1	-7.58	-3.53	-3.88	-7.93
Change at year 2	-6.21	-3.89	-3.88	-6.20
Change in total cholesterol				
Change at 4, 7, 10 months	-6.8	-0.72	-7.32	-13.40
Change at year 1	-3.84	-5.43	-2.37	-0.78
Change at year 2	-6.41	-2.54	-2.37	-6.24
Change in HDL cholesterol				
Change at 4, 7, 10 months	0.88	1.44	-1.46	-2.38
Change at year 1	2.8	1.85	3.44	4.39
Change at year 2	3.53	3.75	3.44	3.22
Glycaemic status change				
Odds (>1 is improvement)	4.8	1.2	1.1	4.5
% reversing				81.7%

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Semaglutide for managing overweight and obesity [ID3850]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **15 November 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with overweight or obesity and current treatment options	
About you	
1.Your name	**Beverley Burbridge**
2. Are you (please tick all that apply):	☒ a patient with overweight or obesity? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with overweight or obesity? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Obesity UK
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with overweight or obesity? If you are a carer (for someone with overweight or obesity) please share your experience of caring for them.	I have lived with the experience of obesity every day of my life. The earliest memory of obesity was in infant school, on school sports day trying to squeeze through a sports bench. Even now, 50 years later, my heart begins to race when I see them. The psychological scars are still there as fresh as the day they happened and it still continues. They might dim but never go away. The victim of bullying, being ostracized by society all for being fat. Feeling worthless, an outsider, people treating you as thick and lazy. The look of disgust in people's faces. These are the "nice" names. It doesn't matter how thick skinned you are, they are like a knife in the back every time. I've never been attacked for being fat but I know people who have been. I was offered through work to go to Israel but I wasn't allowed to go because "you are not what our company is about". Being passed over for promotion at work, it happens quite often. Not attending social functions because you've literally got nothing to wear, and what clothes you have got, they are men's clothes as they are only the ones that would fit. When I was a teenager, it was the days before internet, I only had Evans and the Littlewoods catalogue, I wanted to dress my age, I didn't want to dress as a 50-year-old but I had no choice. It's a case of you wear what fits

	you. You can't go anywhere as you don't know if you will fit through the gates/turnstiles and the utter embarrassment of being turned away "as you're too fat". Will I fit in the chairs or will they hold my weight or will they break? I can't go to that restaurant as I don't fit in the chairs or booths. So, you stay at home. You don't socialise. Boyfriends, never! If someone does take an interest in you, you take it even though you know it's the wrong choice, they're abusive, controlling, but you put up with it because you are lonely. No confidence, low self-esteem. You don't take on things to do because of the fear of failure down to the fact, I'm fat and I won't be able to do it as I can't bend down, I didn't do a First aid course as I knew that whoever drew the short straw to work with me would have to put me in the recovery position and there wouldn't be a long enough bandage to go round my arm. The pain in my knee matches the pain in my hip, due to being super morbidly obese for not just a couple of years but for the best part of my adult life, that will never be repaired. Living with Obesity is not a happy existence. You live half a life, you live with stress, anxiety, anger, suicidal thoughts, every emotion going every day of your obese life. Not only does it affect you, it affects your family and friends, how you react with them, how you take your anger and sadness out on them. My BMI was 55, no co-morbidities just super morbidly obese. Knees and hips painful, potentially wheelchair bound in the next 10 years due to weight. But I could drop down dead from a massive heart attack. If I'm lucky I will die from it, unlucky and I need assistance and help for the rest of my life.

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for overweight and obesity on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	In the first place you have to access primary care for any treatment, this in itself is extremely difficult and then you need a sympathetic practitioner to help you. You have to have the knowledge to be able to ask for the appropriate treatment. In some cases, this is not forthcoming. Being told that sinusitus is due to the fact that you are overweight, is not helpful and is demeaning to the patient when they have sought the courage to come to ask for help. Being told to do a food diary, join a slimming club, do more exercise, eat less and do more. Do you not think, that in most cases people have been doing this for years if not decades? That they are at the end of their tether, desolate, depressed, despondent, possibly suicidal. Access to drugs as well as psychological help is needed, a 2 way approach is vital. In some cases, dependant on your location, access to these treatments is readily available, in others it's never an option. Consistency is needed throughout the NHS. Community or surgery treatments need to be flexible and not restricted to a Monday to Friday 9am to 1.00pm time frame. These are my experiences as well as of others in a similar situation.
8. If there are disadvantages for patients of **current NHS treatments** for overweight and obesity (for example how treatments given or taken, side effects of treatment etc) please describe these.	Drugs need to be taken by the patient themselves and not to rely on a GP surgery-based treatment. You need to have the confidence in the drug that you are going to take that it works. The mind is a great deceiver, in some patients if you think you might have side effects there is a great possibility you will have. You need to have hope and a conviction that it will work.
Advantages of this treatment	
9a. If there are advantages of semaglutide over current treatments on the NHS please describe these. For example, the impact on your quality of life, your	If I had the option to take an injection was a week or a daily tablet I would opt for the injection. For me it would be quick, easy and I would remember to take it with a reminder on my phone. Especially now, a lot more people work either irregular shift patterns, split shifts, 2 or 3 jobs, current lifestyles don't allow the continuity to enable people to get into a routine. If obese people are taking a lot more medicines

ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does semaglutide help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	to combat high blood pressure, arthritis, diabetes this would be another one to the list. It would be a small price to pay for living your whole life instead of half a life. If you told me I would have to inject myself with a drug, once a day, once a week, whatever time frame, but I might, maybe, possibly short term, for an hour out of a day feel a bit nauseous, then I would say I will take that and I will work with it.
Disadvantages of this treatment	
10. If there are disadvantages of semaglutide over current treatments on the NHS please describe these? For example, are there any risks with semaglutide? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	Depending on how badly the side affects were for me, as an individual and probably for a lot of people living with obesity I would put up with the side affects as the advantages would far outweigh the disadvantages.

Patient population	
11. Are there any groups of patients who might benefit more from semaglutide or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments.	All patients will benefit from Semaglutide and you certainly can't discriminate. I could say that I need it more as I am able bodied and it would be more beneficial to me. Be proactive instead of reactive. Better financially in the long term. A long-term investment. If people have disabilities, then a carer might have to administer the injection. If someone is visually impaired or not very dextrous then training or an aid to be made available. Drugs to should be available in different formats so as not to eliminate people from treatment.
Equality	
12. Are there any potential equality issues that should be taken into account when considering overweight and obesity and semaglutide? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race,	

religion or belief, sex, and sexual orientation or people with any other shared characteristics. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Is semaglutide a suitable treatment option for the population suggested by the company (people with a BMI of 30 or more with at least one comorbidity)? Are there other groups of people with overweight or obesity who would benefit from semaglutide?	I think that anybody who suffers with obesity should be allowed to take it as a maintenance programme to keep within a healthy BMI. Perhaps the dosage or the frequency could be different for those people looking at maintain rather than loosing. Or administered on a “as and when” requirement.
Is orlistat a potential alternative treatment for the management of overweight and obesity? If not, please explain why.	In the first instance, as a form of treatment it is an option. But from personal experience the side effects are unpleasant and are continuous throughout the day. It is not just for 30 minutes in the morning and it passes so it’s very difficult to use and has a detrimental effect not only physical but mental health as well.
Do you think it would usually be appropriate to stop treatment with semaglutide after 6 months with less than 5% weight loss?	I don’t think it would be appropriate to stop after 6 months, 6 months in the grand scheme of things is nothing. When you are a slave to the scales you are putting more and more stress and unnecessary pressure on the patient. The question would have to be asked why it’s not working BUT not to take the patient off the treatment. Not to threaten the patient with removing treatment. This is cruel and actually has the opposite effect to what you and the patient want to achieve. No-one wants to be obese.

How long would it be appropriate to take semaglutide for?	Rest of your life. Quite simple really. Obesity is a disease. There is no quick fix, no short-term fix. Over the years I have lost weight, gained, lost and gained more than I've lost most of my adult life, it's a vicious circle and it doesn't stop. You always think that "this is the last time, gone forever" but it hasn't.
Do you think it would be appropriate to have multiple courses of semaglutide?	I think different strengths would be ideal. A dosage for the initial weight loss and then reduce the strength as a maintenance dose.
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- You need hope for the future.
- You want to know that there is some help for you, both for physical and mental well-being.
- You want to know that you are not alone, that there is someone looking out for you.
- That you are being taken seriously and not being put at the bottom of the pile.
- You want to know there is a "cure" for obesity or at least an aid.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Semaglutide for managing overweight and obesity [ID3850]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Kenneth Clare**

2. Name of organisation	Obesity UK
3. Job title or position	Director of Bariatric and Metabolic Surgery Support
4a. Brief description of the organisation (including who funds it). How many members does it have?	Obesity UK is a registered charity which operates as a membership organisation to represent the voice of people with obesity. Obesity UK members form a mutual support group and provide a valuable link between those who struggle on a daily basis and the healthcare organisations that provide evidence-based weight management services. At the time of the launch there was an estimated >30,000 membership. Funding is almost exclusively from partnerships with commercial organisations.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Yes. Novo Nordisk pledged funds for a project compiling training videos for volunteers. The total is £6500 the company will be invoiced for this amount on completion of the project – forecast at the end of December.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Via our closed facebook groups, by email submission and in virtual support group discussion groups.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Obesity is a complex disease which if left untreated, can lead to other conditions including (but not limited to), diabetes, hypertension, high cholesterol, stroke, heart disease, certain types of cancer, and arthritis.

	Obesity can also diminish a person's overall quality of life as they may avoid public places and, in some cases, encounter discrimination. People living with Obesity may experience depression, difficulty in hygiene practices, disability, sexual problems, shame and guilt, social isolation. In some cases, Obesity is physically debilitating. They may experience joint pain and require mobility access assistance e.g. wheelchair usage and modified bathroom facilities in their home. They can have skin issues with infection and odour, with basic tasks like showering and bathing becoming impossible without assistance. Obesity may affect fertility with the ability to have children greatly reduced. This may also be compounded by treatments for infertility being withdrawn for patients over a specific BMI. People living with Obesity can often been seen as lazy, unmotivated and having a lower IQ, this increased social stigma may affect career prospects, meaning that confidence lowered, and financial burden is greatly increased. It can affect peoples opportunities in every aspect of life, social, educational and employment. Obesity can affect people of any ethnic group or sex, it is also seen in both adults and children. Caring for a person living with obesity can have a draining effect on the carer. Reduced quality of life and a reduced social life can affect the physical and mental health of a carer too.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The are two non-surgical/drug treatments currently offered by prescription on the NHS. These are Orlistat and Liraglutide Orlistat decreases the amount dietary fat absorbed in the body; this helps by breaking it down to smaller components in turn leading to weight loss. It is "usually" prescribed for 3 months, then, if the patient is seen to be losing weight, a further 12-month usage is recommended PROS - Tablet form, taken along with meals. Easy to take. Weight loss (though small %age) CONS - Reduced effectiveness of the contraceptive pill, faecal incontinence/urgent bowel movements, abdominal pain, and flatulence. These side effects can exacerbate an already socially anxious persons increased feelings of shame, guilt, and hopelessness in the treatment of their Obesity. Patients are counselled that these effects are brought on and worsened by ingestion of fat. But still the drug does not have a great reputation in the patient community. Liraglutide works by increasing feelings of being full and decreasing hunger in the brain this can lead to eating fewer calories. PROS – Liraglutide seems to have good results in some people who can get access to the drug. CONS NHS access is limited under current guidelines to people with an BMI in a certain range, with certain blood test results, type 2 diabetes or other high risk factors and they must attending a Tier 3 weight management clinic. These clinics are limited access depending on where you live.

	Many patients experience nausea initially but this often subsides. Some patients don't like injecting themselves daily. Some patients have resorted to buying their own medication, either from a pharmacy or an online source, as it is not available on the NHS. Bariatric surgery is currently the method of treatment favoured by the majority of people who wish to lose a significant amount of weight (and have a sustained weight loss). PROS – It is increasingly well known and its benefits are discussed in the media and in general conversations. There is a favourable degree of weight loss and weight maintenance. CONS – Access via the NHS is limited around the country. There can be a long process via Tier 3 weight management clinics, which are not available everywhere. People perceive this as a process with significant risks. There are potential risks. There are also measures which require life long changes in behaviour for example taking vitamin and mineral supplements.
8. Is there an unmet need for patients with this condition?	There is a large unmet need for people who are living with obesity. As stated above, for many Orlistat is not desirable option. Liraglutide is not available and Bariatric surgery may be unavailable or a person may not think the risks outweigh the benefits. There are also people who doctors consider unfit for bariatric surgery who need another treatment option.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients are anticipating a new medication being available. They hope that there will be easier access than current injectable medication. Many people think the once weekly dose is a lot better than the daily dose of other injectable medicines. People are aware that this drug may offer better weight loss than other medicines.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Some people are concerned about vomiting and nausea. There are a very small number of patients who say they would not take an injection due to needle phobia or other anxieties.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People who are not suitable for bariatric surgery. People with regain following bariatric surgery. People who live with severe and enduring mental health problems whose medication can contribute to weight gain. People living with learning difficulties.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Steps should be taken to ensure that people from BAME communities get equitable to this medication if it is made available.
Other issues	
13. Are there any other issues that you would like the committee to consider?	To restate - the low compliance with orlistat, and the difficulty in access to liraglutide, and bariatric surgery.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • More treatments for people living with obesity • Improved access to treatments for people living with obesity • The currently available treatments are considered either, high risk, unpleasant side effects or inaccessible by many people living with obesity.	

- Offering improved results from a new treatment with less frequent injections.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Your privacy

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Semaglutide for managing overweight and obesity [ID3850]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **15 November 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with overweight or obesity and current treatment options	
About you	
1. Your name	**Carel le Roux**
2. Name of organisation	**Ulster University**
3. Job title or position	**Professor of Metabolic Medicine**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with overweight and obesity? ☐ a specialist in the clinical evidence base for overweight and obesity or the technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for overweight and obesity	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent the complications of obesity
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	>15% weight loss

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Tier 3 and Tier 4 services providing nutritional therapies, pharmacotherapies and surgical therapies.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Currently the best guidelines are those of the Obesity Canada
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined but the provision is suboptimal.
• What impact would the technology have on the current pathway of care?	The medication would facilitate the pathway and deliver significant improvement in quality of life while at the same time reducing the complications of obesity.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes it would be a substantial improvement on the current best pharmacotherapy (liraglutide)
• How does healthcare resource use differ between the technology and current care?	Similar
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tier 3 and 4 services initially but the largest impact will be once it can be used by primary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes it is twice as good as the current best treatment.
• Do you expect the technology to increase	Yes

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or	No

ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I suggest that the same stopping rules are used as are currently in place, ie if patients don't lose 5% of their weight after 16-20 weeks on treatment then the drug should be stopped. This will stop the use of the medication in patients who do not respond.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I think people with diabetes and obesity treated with this drug will achieve glycaemic levels that will be below the threshold of diagnosing diabetes – thus effectively their diabetes will be in remission. The health economic models struggle to calculate the utility gain of such a benefit.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Most people will achieve double digit weight loss which appears to be required to reverse many of the complications of obesity.

• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes, patients at high risk of the complications of obesity are not provided treatments which can reverse the existing complications.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are similar to the existing treatments thus no change in management required.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes,	Yes, weight loss and prevention of type 2 diabetes.

and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate measures were used for cardiovascular event prevention. These are the standard measures used.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA664?	Not specifically for obesity.

23. How do data on real-world experience compare with the trial data?	Real world data is very similar to trial data
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	The majority of the trial population were female, but the ethnic mix was similar to the UK. If the medication is not available in the NHS then it will increase inequality.
24b. Consider whether these issues are different from issues with current care and why.	Similar to current care.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. Please also refer to the key issues summary in ERG report for further detail on each issue. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Decision problem target population Is semaglutide appropriate for the 'target population' suggested by the company (people with a BMI ≥ 30 with at least one comorbidity)? In which clinical setting is semaglutide likely to be used and does this impact the population who would be able to receive semaglutide in practice?	Yes, a BMI>30 reflects the population treated in Tier 3 services and are the population which would benefit most if a wide range of comorbidities, which does include type 2 diabetes can be prevented. There are no difference in clinical response between patients with a BMI>30 or <30 kg/m^2.

Exclusion of orlistat as a comparator Is orlistat a relevant comparator for semaglutide in this condition?	Orlistat already has NICE approval and should be used first line in primary care or obesity services. If patients have not responded to orlistat or are not able to tolerate orlistat then semaglutide should be considered. Thus semaglutide should be the second line medication used and for this reason a comparison with orlistat is not relevant. In addition, tolerability and efficacy issues have led to a significant decline of orlistat use.
Exclusion of the STEP 2 trial from the company submission STEP 2 compares semaglutide 2.4mg to placebo, both in conjunction with a lifestyle intervention, in people with overweight or obesity who had been diagnosed with type 2 diabetes. Is it appropriate to include data from this trial in the appraisal of semaglutide in this population (people with a BMI ≥ 30 with at least one comorbidity)? Would semaglutide 2.4mg be used in clinical practice for the purposes of weight loss and	Semaglutide 1mg is already NICE approved and available in the NHS for the treatment of people with diabetes. There was no different in glycaemic benefit between semaglutide 1mg and 2.4mg. Semaglutide 1mg also has cardiovascular outcome data showing a mortality benefit. The weight loss difference was clinical and statistically significant between 1mg and 2.4mg. In clinical practice, semaglutide 1mg would thus be offered to people with obesity and T2D whose primary focus is on glycaemic control. In other people with obesity and T2D, whose primary goal is to lose weight, a treatment with semaglutide 2.4mg could provide a good alternative.

maintenance in people with type 2 diabetes?	
Exclusion of the STEP 3 trial from the company submission STEP 3 compares semaglutide 2.4mg to placebo, both in conjunction with intensive behavioural therapy as part of a lifestyle intervention, in people with overweight or obesity. Given the inclusion of intensive behavioural therapy in both arms of the STEP 3 trial, is it appropriate to include data from this trial in the appraisal?	STEP 1 reflected the lifestyle changes and behaviour therapy approaches used in Tier 3 NHS services. STEP 3 used lifestyle changes and behaviour therapy which is only available in research settings in the UK and can thus not be implemented in the NHS because of the extra-ordinary cost of these interventions. The weight loss achieved in STEP 1 and STEP 3 were also not statistically different.
Treatment stopping rule The summary of product characteristics includes a stopping rule that specifies that a decision is required at 6 months on whether to continue treatment based on the benefit/risk profile of the individual, if 5% of initial body	I think all patients should be encouraged to stop the medication if they haven't lost >5% weight at 6 months. I don't think this will be a challenge because patients are unlikely going to continue injecting themselves every week if they do not experience any benefit. In fact I think the "stay time" of patients losing <10% weight with semaglutide 2.4 will be poor because I don't think patients would like to continue the injections unless they achieve >10% weight loss. This will further improve the health economic benefit of semaglutide.

weight has not been lost. Based on this, what proportion of individuals who have not lost 5% of their initial body weight after 6 months treatment would you expect to discontinue semaglutide at this point?	
Assumption that all patients with non-diabetic hyperglycaemia develop type 2 diabetes after initial CVD event How common is it that people with overweight or obesity and non-diabetic hyperglycaemia develop type 2 diabetes immediately or shortly after a CVD event?	Approximately 29% of patients at time of myocardial infarction are newly diagnosed with Type 2 diabetes. Almost all of these patients had prediabetes prior to myocardial infarction. Up to 69% of patients are diagnosed with prediabetes at the time of myocardial infarction, but it is unclear how many of them had prediabetes prior to myocardial infarction https://pubmed.ncbi.nlm.nih.gov/25670820/ I think it is an overestimate to say that everyone of prediabetes will develop type 2 diabetes after a myocardial infarction but the physiological stress of the infarction would tip many if not most over to type 2 diabetes.
Treatment duration and retreatment Will semaglutide be given as a single course of treatment, or will retreatment be offered? How long will a course of semaglutide be in clinical	Single course of treatment while in Tier 3 obesity services. Patients are only allowed to remain in Tier 3 services for 2 years thus the treatment course of the medication is thus likely also to be only 2 years.

practice (will this be restricted to 2 years)?	
Are there any important issues that have been missed in the ERG report?	No
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement: • Obesity as a disease can be effectively treated with semaglutide 2.4mg • The variety of complications of obesity which does include type 2 diabetes can be prevented by semaglutide 2.4mg • Weight related comorbidities and quality of life will significantly improve in patients with >15% weight loss • Tier 3 services are currently equipped and in a position to provide this treatment safely and effectively • Semaglutide can change complications of obesity in a similar way that statins changed the complications of dyslipidaemia	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Semaglutide for managing overweight and obesity [ID3850]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **15 November 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with overweight or obesity and current treatment options	
About you	
1. Your name	**Professor John Wilding**
2. Name of organisation	**University of Liverpool**
3. Job title or position	**Professor of Medicine**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? x a specialist in the treatment of people with overweight and obesity? **x** a specialist in the clinical evidence base for overweight and obesity or the technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x** other (they didn't submit one, I don't know if they submitted one etc.) I withdrew from RCP and ABCD processes as I was already providing input as a clinical expert on behalf of the company and did not want to be conflicted.

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for overweight and obesity	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aims of treatment for obesity are to improve / reduce the complications of obesity such as development of type 2 diabetes and its complications, cardiovascular disease, sleep apnoea. It is also hoped that weight loss will improve quality of life in relation to both physical and mental function, which is partly, but not completely dependent on the improvement of complications.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	In general a weight loss of 5% or more will produce clinically relevant improvements in some conditions (for example it is associated with at least a 50% reduction in progression to diabetes in people with impaired glucose regulation), and improvements in cardiovascular risk factors. At the same time greater weight losses of 10%, 15% or more may be needed to improve other complications (such as remission of diabetes, or improvements in sleep apnoea), as well as result in a greater improvement in risk factors. Observational data and data from studies of people who have lost weight from bariatric surgery show that weight loss of 15-20% or more is associated with reduced cardiovascular events, reduced cancer risk, and lower mortality as well as substantial improvements in quality of life.

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – very much so - the only treatments we have other than lifestyle (which produces less than 3% weight loss on average, with only about a third of people achieving clinically relevant weight loss of 5% or more) is orlistat, and for a limited number of people liraglutide 3mg. Bariatric surgery is highly effective but only about 6000 operations per year for over a million eligible. This is particularly the case for people with severe and complex obesity attending tier 3 services.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	People with obesity are supported in
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines are the most widely used.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are well defined pathways for tier 3 (specialist weight management) and tier 4 (bariatric services), but availability is somewhat variable across the UK. There are a mixture of providers - mostly secondary care, but some provided by secondary care and delivered in community, and some private providers. Most people (but not everyone) has access to a tier 3 service. NHS England and GIRFT have recently surveyed this comprehensively but this information is not yet publicly available.
• What impact would the technology have on the current pathway of care?	

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not currently available. I would see it as being used as an adjunct to lifestyle intervention in people with severe obesity accessing tier 3 services. This is similar to the current TA for liraglutide but as semaglutide is at least twice as effective it is hoped more people (with broader inclusion criteria – ie not just those with impaired glucose regulation at high CV risk).
• How does healthcare resource use differ between the technology and current care?	The additional cost of the medication (and a small cost for education about injections and its use) would be the major additional resource. This may be offset by lower resource use in other areas as complications of obesity would be reduced / ameliorated.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	I would envision it being mainly used in specialist (tier 3 services) for people with severe and complex obesity. Most of these people will have a BMI > 35 kg/m^2, with some lower if significant complications / co-morbidity and with appropriate adjustment for ethnicity.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Minimal training as most clinicians are already familiar with this drug and others in the class as used for treatment of type 2 diabetes (albeit at a lower dose), and there is also growing experience with the use of liraglutide as per relevant NICE guidance.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes very much so as evidenced by clinical trials, especially STEP 1 trial (Wilding et al *N Engl J Med* 2021;384:989-1002.DOI: 10.1056/NEJMoa2032183), which shows effects on weight, CV risk factors and quality of life, that are much greater than are seen with lifestyle alone.
• Do you expect the technology to increase	We do not have data on life expectancy. There may be some data in the future from the ongoing SELECT CVOT in people with obesity without diabetes with established cardiovascular disease (17500 people randomised)

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – see published papers (eg STEP 1) for this. Improvements were seen in all domains of SF36 and IWQOL for clinical trials measures.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The STEP 2 trial suggest semaglutide 2.4mg is less effective for people with T2DM. Less weight loss is seen in most trials of weight loss medication in this population. Semaglutide 1mg already available for diabetes and gives about 70% of the effect. 2mg dose may also soon be available for T2DM plus other technologies (tirzepatide) with greater weight loss so this may not be the right population for this medication.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or	Should be straightforward and as much of the medical support for tier 3 care is given by specialists in diabetes and endocrinology who are already very familiar with this drug and the class in general.

ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Weight loss of 5% or more at 16 weeks might be expected for continuation. In trials more than 80% met this milestone.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes – see comments above
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, this is substantially more effective than anything that has been available up to this time. There is a huge unmet need for treatments for obesity.

• Is the technology a 'step-change' in the management of the condition?	Yes – see above
• Does the use of the technology address any particular unmet need of the patient population?	Yes - Need for a non-surgical treatment that delivers substantial weight loss benefit
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Most yes, although STEP 3 included a very intensive behavioural intervention that would not normally be used in the UK.. It is relevant that although this produced slightly faster initial weight loss, the net results at 68 weeks were very similar to STEP 1 that used a much more light touch lifestyle intervention that is closer to current UK practice.
• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes,	Weight loss, improvement in CV risk factors and measures of glycaemia / metabolic risk in the non-diabetic population and improvements in quality of life as measured in clinical trials.

and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	It is likely that they do and there is evidence from trials in people with T2DM that the CV benefits from this class may actually be greater than expected from improvements in surrogate markers such as lipids, BP, and glucose.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA664?	No

23. How do data on real-world experience compare with the trial data?	Too early to tell as semaglutide only just licensed (and not yet marketed) in UK and has only been available in USA for a few months.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Need to ensure ethnicity specific BMI criteria are used when deciding on eligibility.
24b. Consider whether these issues are different from issues with current care and why.	Similar to current care

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. Please also refer to the key issues summary in ERG report for further detail on each issue. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Decision problem target population Is semaglutide appropriate for the 'target population' suggested by the company (people with a BMI ≥ 30 with at least one comorbidity)? In which clinical setting is semaglutide likely to be used and does this impact the population who would be able to receive semaglutide in practice?	It is appropriate for the target population, but I think it will be most effectively used in people accessing 'tier 3' services for severe and complex obesity. In general these will have a BMI > 35, with co-morbidity or > 40 without. Absence of co-morbidity is uncommon in BMI > 40. These people have the greatest need and can be cared for by teams with appropriate knowledge about treatment of obesity in tier 3 services. It should be noted that such specialist care can and is delivered in a variety of settings that includes hospitals but also community and primary care settings (this has been a problem for implementation of TA 664 as liraglutide can only be used in hospital settings- this creates inequality of access depending on how local services are configured).

Exclusion of orlistat as a comparator Is orlistat a relevant comparator for semaglutide in this condition?	Not really as rarely used now and is available OTC.
Exclusion of the STEP 2 trial from the company submission STEP 2 compares semaglutide 2.4mg to placebo, both in conjunction with a lifestyle intervention, in people with overweight or obesity who had been diagnosed with type 2 diabetes. Is it appropriate to include data from this trial in the appraisal of semaglutide in this population (people with a BMI ≥ 30 with at least one comorbidity)? Would semaglutide 2.4mg be used in clinical practice for the purposes of weight loss and	The STEP 2 trial suggest semaglutide 2.4mg is less effective for people with T2DM. Less weight loss is seen in most trials of weight loss medication in this population. Semaglutide 1mg already available for diabetes and gives about 70% of the effect. 2mg dose amy also soon be available for T2DM plus other technologies (tirzepatide) with greater weight loss so this may not be the right population for this medication. I think that in practice the 2.4 mg dose would rarely be offered for people with T2DM as the additional benefit is relatively small (+ also should be noted that at present the 1mg dose shows CV risk reduction for the highest risk patients and this has not yet been shown for the 2.4mg dose).

maintenance in people with type 2 diabetes?	
Exclusion of the STEP 3 trial from the company submission STEP 3 compares semaglutide 2.4mg to placebo, both in conjunction with intensive behavioural therapy as part of a lifestyle intervention, in people with overweight or obesity. Given the inclusion of intensive behavioural therapy in both arms of the STEP 3 trial, is it appropriate to include data from this trial in the appraisal?	The STEP 3 trial included a highly intensive behavioural intervention. This is not available or used in the NHS or even in the private sector in the UK. Although it resulted in slightly greater weight loss initially in those treated with semaglutide, the end result was very similar to that seen with a less intensive intervention in STEP 1. Although the placebo weight loss was greater in STEP 3, this type of intervention and the outcomes are not typical of what is seen in UK practice in tier 3 services, so in my view this is not a relevant comparator.
Treatment stopping rule The summary of product characteristics includes a stopping rule that specifies that a decision is required at 6 months on whether to continue treatment based on the benefit/risk profile of the individual, if 5% of initial body	Seems reasonable. From the clinical trial data I would expect less than 15% of people to discontinue at 6 months.

weight has not been lost. Based on this, what proportion of individuals who have not lost 5% of their initial body weight after 6 months treatment would you expect to discontinue semaglutide at this point?	
Assumption that all patients with non-diabetic hyperglycaemia develop type 2 diabetes after initial CVD event How common is it that people with overweight or obesity and non-diabetic hyperglycaemia develop type 2 diabetes immediately or shortly after a CVD event?	I don't have specific information on this point and am not sure if that information is available. I would expect that it would be high – probably more than 50% but less than 100% as the stress of an acute event is very likely to result in a rise in glucose that would mean that many people would cross the threshold and now be classed as having diabetes. We do see very high rates of new diabetes in people presenting with an acute cardiac event (around 12-15% in literature) and those with IGR are most at risk.
Treatment duration and retreatment Will semaglutide be given as a single course of treatment, or will retreatment be offered? How long will a course of semaglutide be in clinical	At present obesity is treated differently to other chronic diseases, in that it is expected that it will resolve after a 'course' of treatment. This represents a fundamental misunderstanding of biology. The physiology of weight regulation, and multiple studies, have shown that similar to blood glucose in diabetes, blood pressure in hypertension and lipid levels in dyslipidaemia, weight will slowly regain once treatment has stopped. Some people will be able to maintain weight loss for longer than others and a few (perhaps 10-15%) can maintain it long-term. We now have data (from STEP 5) that shows that semaglutide can maintain weight loss for up to 2 years. I would therefore advise (at present) 2 years treatment, and consideration of a further course of treatment if significant (say more than half the weight lost) is regained. This is a pragmatic suggestion in relation to a difficult question. If we have data in the future (eg from the

practice (will this be restricted to 2 years)?	ongoing SELECT trial) that shows longer term efficacy, perhaps together with CV benefit, then a longer course of treatment may be justified.
Are there any important issues that have been missed in the ERG report?	No

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Semaglutide 2.4 mg represent a real step change in the pharmacological treatment of people with obesity
- Clinical benefits are likely to be greatest in those with higher weight and more complications.
- Benefits include improvement in a range of complications and quality of life
- Treatment would best be offered in specialist care, but across a range on settings
- This has the potential to improve the lives of many people living with obesity

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NHSE COMMENTARY

SEMAGLUTIDE FOR MANAGING OVERWEIGHT OR OBESITY

1. Obesity (defined as a BMI>30Kg/M^2) is a complex chronic condition of multifactorial origin that increases risk for Type 2 diabetes mellitus, cardiovascular disease, other co-morbid conditions (eg OSA, NAFLD), and lowers life expectancy.

2. In England, 64% of adults are overweight or obese. The proportion of adults who are obese is 28% (26% male and 29% female) with approximately 36% of adults in NHSE in the BMI overweight category. In the obese population, approximately 19% are categorised as Obesity 1 (BMI- 30-34.9); 6% are categorised as Obesity 2 (BMI- 35-39.9) and 3% are categorised as Obesity 3 (BMI > 40Kg/ M^2).

3. NHSE note the MA for Semaglutide is "as an adjunct to a reduced calorie diet and increased physical activity for weight management, including weight loss and weight maintenance in adults with an initial BMI >30Kg/ M^2 (obesity) or >27to 29.9 Kg/ M^2 (overweight) in the presence of 1 or more comorbidities".

4. In line with NICE guidance CG189, NHSE supports use of Semaglutide only when used as part of multicomponent interventions that includes appropriate dietary (reduced calorie, healthy diet) and physical activity interventions. NHSE note improving fitness and physical activity can reduce the development of Type 2 diabetes mellitus and favourably influence a range of cardiovascular risk factors , independently of weight loss. NHSE would appreciate comment from clinical experts if it would be appropriate to prescribe Semaglutide for people who are overweight or obese and who do not engage with the appropriate weight management programme. The NHSE view is that this situation would be outside the MA for Semaglutide.

5. In the NHS high risk people with a BMI>35Kg/ M^2 and 1 comorbidity and those with a BMI>40Kg/ M^2 (with appropriate adjustment for members of minority ethnic groups) are seen within a TIER 3 weight management service. Under some, albeit rare circumstances, people with a BMI-30-35Kg/ M^2 can be transferred from a TIER 2 weight management service (a time-limited diet/physical activity programme) to a TIER 3 service.

6. The main clinical evidence considered for this appraisal was from the STEP1 trial. Participants who were obese (BMI>30) and overweight patients (BMI >27) with at least 1 weight related comorbidity were randomly allocated to either Semaglutide 2.4mg once weekly or placebo for 68 weeks. Diet and exercise counselling occurred every 4 weeks and participants kept a food and activity dairy (target diet - minus 500 calorie/day plus 150 minutes/week physical activity). The co-primary end points were percentage change body weight and weight reduction of at least 5%; both assessed from baseline to week 68. At the end of study body weight change (- 14.9% Vs – 2.4%) and proportion achieving >5% weight loss (86.4% Vs 31.5%) favoured Semaglutide Vs placebo. Secondary end points, not controlled for multiple comparisons, also favoured the Semaglutide group.

7. NHSE note the following:

    1. The proportion of people within each BMI weight category in the STEP 1 trial was overweight 6% (BMI-27-29.9); Obesity 1 33% (BMI 30-34.9); Obesity 2 31% (BMI 35-39.9) and Obesity 3 29% (BMI >40). The mean BMI was 38Kg/M^2 and

44% of the population were defined as having prediabetes . NHSE considers the majority of trial participants represent a very severely obese population and note the distribution by BMI weight category to be very different from the distribution by BMI category in the NHS; with 60% of the trial population in obese categories 2 and 3 compared with approximately 9% in the NHS. As BMI increases the greater the risk for obesity related comorbid conditions and NHSE note the economic analysis was sensitive to the starting BMI.

2. Participants in the trial were volunteers who were highly motivated (approximately 90% complete follow up) with a mean age of 46 and 73% female and 74% white Caucasian. The male: female distribution in NHSE is much closer to 1:1. The trial population does not fully represent those with highest needs were increased support may be required to ensure underserved populations get into services to fully benefit from weight management interventions.

8. NHSE note the company propose a stopping rule at 28 weeks (ie a 16week titration and 12 week maintenance phase) for people who have not achieved at least 5% weight loss from baseline. NHSE note 5% weight loss is generally accepted as being clinically meaningful but note some regulatory bodies ,in guidance for medications for the management of obesity, indicate medicines should produce an average weight loss of at least 5% more than placebo.

9. NHSE accepts that improvement in glycaemic control measures and triglycerides are seen with small amounts of weight loss (3%-5%) and there can be further improvement with greater amounts of weight loss. Beyond weight loss of 10kg, there appears to be little additional benefit in terms of preventing progression of impaired glucose tolerance to Type 2 diabetes. In general, 5-10% weight loss is associated with improvement in systolic blood pressure and HDL-C but for some comorbid conditions(eg OSA, NAFLD) a greater degree of weight loss (10-15%) may be required to translate into a clinically meaningful benefit.

10. NHSE note the company support a stopping rule for responders to Semaglutide at 2 years. NHSE note a 2 year stopping rule was accepted by NICE in the appraisal of Liraglutide (TA 664) presumably on advice from clinical experts that patients would be discharged from a TIER 3 weight management service at this time. NHSE note the committee did not feel this to be an ideal situation for management of a chronic condition. NHSE note the target population for treatment in the TA664 appraisal included trial participants with a BMI>35Kg/$M^2$with prediabetes and a further cardiovascular risk factor whereas the target population proposed by the company for consideration in this appraisal is broader and includes participants with a BMI 30-34.9 with 1 obesity related comorbidity. The latter subpopulation would typically be managed in a TIER 2 weight management service.

11. NHSE is aware of preliminary results from the STEP5 and STEP 8 clinical trials:

    1. In STEP 5 , combined with dietary and physical advice, weekly injection of 2.4mg Semaglutide led to

        : 15.2% weight loss compared with 2.6% weight loss with placebo at 2 years

        :77% Vs 34% losing at least 5% body weight at 2 years

2. In STEP 8, mean body weight at 68 weeks was 15.8% lower with 2.4mg/weekly SC Semaglutide plus lifestyle changes Vs 6.4% lower with 3.0mg/day SC Liraglutide plus lifestyle changes.

12. NHSE note that the preliminary evidence indicates weight loss is maintained over a 2 year period for people who continue on 2.4mg of Semglutide and more than 3 in 4 people will have a clinically meaningful decrease in body weight of 5%. NHSE note that clinical expert advice and patient testimony in the appraisal of Liraglutide and clinical expert advice to the ERG suggests that patients responding to, and tolerating Semaglutide, may be unwilling to stop the drug at 2 years. Further, NHSE expect a proportion of patients who agree to stop Semaglutide at 2 years, and who subsequently regain weight after discontinuation, would wish to be retreated with the drug.

13. In relation to the imposition an arbitrary 2 year stopping rule NHSE note the following:

In the STEP 4 study, overweight or obese adults who had reached a target dose of 2.4mg of Semaglutide after a 20 week run-in period were randomised to continued treatment or switched to placebo for a further 48 weeks. NHSE note the percentage change in body weight on active treatment was -10.6% at week 20 compared with baseline values. The percentage change in body weight was mean -5% for participants who switched from active treatment to placebo at week 20 after a further 48 weeks follow up compared with baseline values, with no indication of a slowing in weight regain. NHSE notes a 5% reduction in body weight compared with baseline is the minimum accepted for a clinically meaningful benefit and, if not achieved, is the threshold proposed for not continuing Semaglutide following the dose titration and maintenance schedule at week 28 following treatment initiation. The results suggest that within a year of discontinuing Semaglutide weight loss is verging on no longer being clinically meaningful, and with weight regain, the corresponding benefit on surrogate end-points were also largely lost compared with baseline measures.

NHSE note that a 2 year stopping rule was not part of the protocol in any of the STEP trials. In the ongoing Semaglutide cardiovascular outcome trial in people with established cardiovascular disease (prior MI, Stroke or symptomatic intermittent claudication) participants are expected to remain on Semaglutide for 31 to 50 months.

NHSE note regulators accept LDL-C and blood pressure as valid surrogates for future cardiovascular events. NHSE note weight loss associated with the use of Semaglutide has a minimal effect on LDL-C and know of no trials , prior to the introduction of statins, that produced much larger benefits in terms of LDL-C reduction, had no benefit in terms of reducing hard cardiovascular outcomes. Further, medicines associated with a 100% or more increase in HDL-C failed to show a benefit in reducing cardiovascular events (CTEP inhibitors). Finally, medicines employed to reduce blood pressure in patients with hypertension and LDL-C in patients with hypercholesterolemia are not discontinued if effective and tolerated for these chronic conditions. Similarly, GLP-1 inhibitors are not discontinued if effective and tolerated in patients with Type 2 diabetes.

14. NHSE note and accept the company comment (page 21 company submission) relating to real world evidence from the UK CPRD GOLD database relating to the benefit of intentional weight loss (median reduction in body weight of 13% versus people who maintained a stable baseline weight) on reducing the risk for obesity related outcomes of Type 2 , hypertension and dyslipidaemia. Importantly, NHSE would wish to emphasise that after a median follow-up of more than 6 years in people with sustained and intentional weight loss the benefits on risk factors were NOT accompanied by reduction in hard cardiovascular outcomes (heart failure, atrial fibrillation, unstable angina or Myocardial infarction).

15. NHSE recognise obesity as a chronic condition for which long-term therapy and management is required. NHSE note the MA for Semaglutide includes an indication for both weight loss and weight maintenance. While the results of the short-term STEP trials are encouraging, the longer term benefits of Semaglutide on hard clinical outcomes are unknown. Given the considerations outlined above, NHSE views the introduction of an arbitrary 2 year stopping rule, with an inevitable return of weight and obesity related comorbidities, adds to the uncertainty relating to any potential benefit for long term clinical outcomes. Further, with a broader population with lesser degrees of obesity proposed for treatment access for this appraisal compared with that proposed inTA664, NHSE would comment that as the eligible population numbers increase and the likely benefits of treatment decrease outcome uncertainties become more important considerations.

16. NHSE note the recommendation for Liraglutide (TA664) for treatment of overweight and obesity was an optimised recommendation that focussed on a subgroup with a BMI>35Kg/M2 , with prediabetes and the presence of a further cardiovascular risk factor. NHSE note for this population the drug would be prescribed in secondary care via a multidisciplinary Tier 3 weight management service. NHSE do not fully understand the rationale for a prerequisite to meet the definition of prediabetes to enable access to Liraglutide given access to a TIER 3 weight management service is open to people with a BMI 35-39.9Kg/ M^2 with any additional obesity related comorbidity. In the TA664 appraisal, the company proposed this subgroup for consideration " as these people are at high risk of experiencing the adverse consequences of obesity and likely to gain the most from Liraglutide". NHSE agree but note that the population eligible for a TIER 3 weight management service in the highest BMI categories represent a very high risk population would also be expected to gain most from use of Semaglutide, without necessarily requiring a prerequisite for meeting the definition for prediabetes which could potentially limit access to the drug.

Professor Gary McVeigh
Clinical advisor NHSE

NICE National Institute for Health and Care Excellence

Professional organisation submission

Obesity, overweight - semaglutide [ID3850]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	ASSOCIATION FOR THE STUDY OF OBESITY
3. Job title or position	Senior Clinical Lecturer and Consultant in Endocrinology

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? **x** other (please specify):representative of ASO representing clinicians and non-clinicians with expertise in Obesity.
5a. Brief description of the organisation (including who funds it).	The ASO is the UK's foremost charitable organisation dedicated to the understanding, prevention and treatment of obesity.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	The organisation has received funding from Novo Nordisk to find the administrative costs of the provision of online educational webinars and sponsorship of the online Annual Congress. Annual Congress sponsorship £10k The total sums to be paid by December 2021 in relation to online Webinars £70,827 (plus VAT in the sum of £8585).

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent the complications of obesity
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	>10% weight loss

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The need is urgent and major
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Treated through the tiered system, with lifestyle modification, limited pharmacotherapy and bariatric surgery
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The pathway is well defined but the provision is suboptimal and variable.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	The medication would facilitate the pathway and deliver significant improvement in quality of life while at the same time reducing the complications of obesity.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes it would be a substantial improvement on the current best pharmacotherapy (liraglutide)
• How does healthcare resource use differ between the technology and current care?	similar
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The implementation of the NICE guidance on Saxenda has unfortunately been problematic and we highlight the reasons so that they are avoided with Semaglutide. Saxenda can only be prescribed by a hospital Tier 3 service and for a duration of 2 years. This has disadvantaged patients who are being looked after in a *community* tier 3 service, whom the medication should also be available to. The committee should also consider other health economic models for Semaglutide that may make it more cost-effective. This includes its use in the primary care setting (Tier 2) and led by General practitioners, instead of purely in specialist weight management service (Tier 3). A similar successful model has been applied to the care of people with diabetes who are now predominantly looked after in the community, but have access to a Community Consultant Diabetologist when necessary.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	none
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, it is the most effective medication for obesity
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or	No

less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The stopping rules are currently in place, ie if patients don't lose 5% of their weight after 16-20 weeks on treatment then the drug should be stopped. This will stop the use of the medication in patients who do not respond. The implementation of the NICE guidance on Saxenda has unfortunately been problematic and we highlight the reasons so that they are avoided with Semaglutide. Saxenda can only be prescribed by a hospital Tier 3 service and for a duration of 2 years. Whilst we appreciate the health economic analyses, it is uncommon to treat a chronic disease like Obesity for 2 years and then stop. Discontinuation of the medication almost inevitably leads to disease relapse. We therefore recommend that if Semaglutide is effective, it should be continued long term. No additional testing needed.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	Some people with diabetes and obesity treated with Semaglutide will achieve diabetes remission. The health economic models are not always able to capture this benefit.

quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Most people will achieve >10% weight loss which appears to be required to reverse many of the complications of obesity.
• Is the technology a 'step-change' in the management of the condition?	Semaglutide at 2.4mg weekly is by far the most effective treatment for Obesity at the current moment, causing approximately double the weight loss observed by Saxenda. It is therefore a step-change in the management of the condition as this weight loss is expected to improve quality of life, ameliorate obesity-related complications and avoid the need for bariatric surgery for some patients. It is also likely to facilitate other treatments these patients need for obesity-related complications e.g. in vitro fertilisation, joint replacement surgery.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, patients at high risk of the complications of obesity are not provided treatments which can reverse the existing complications.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are similar to the existing treatments thus no change in management required.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes, weight loss and prevention of type 2 diabetes.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate measures were used for cardiovascular event prevention. These are the standard measures used.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	Not specifically for obesity.
21. How do data on real-world experience compare with the trial data?	Real world data are very similar to trial data
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The implementation of the NICE guidance on Saxenda has unfortunately been problematic and we highlight the reasons so that they are avoided with Semaglutide. Saxenda can only be prescribed by a hospital Tier 3 service and for a duration of 2 years. This has disadvantaged patients who are being looked after in a *community* tier 3 service, whom the medication should also be available to.
22b. Consider whether these issues are different from issues with current care and why.	Similar to current care.
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to	

be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Obesity as a disease can be effectively treated with semaglutide 2.4mg
- The variety of complications of obesity which does include type 2 diabetes can be prevented by semaglutide 2.4mg
- Weight related comorbidities and quality of life will significantly improve in patients with >10% weight loss
- Tier 3 services are currently equipped and in a position to provide this treatment safely and effectively

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Semaglutide for managing overweight and obesity [ID3850]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **15 November 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the issues below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Obesity Group of the British Dietetic Association**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to the issues raised in the ERG report.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Decision problem target population	No	Could example be given of obesity-related co-morbidities to allow referrer to see what this means please? It is currently very broad. Could People first language be used please? (e.g. “people living with obesity” not “obese”).
Key issue 2: Exclusion of orlistat as a comparator	No	We agree with this exclusion.
Key issue 3: Exclusion of the STEP 2 trial from the company submission	No	We agree with this exclusion since the purpose of this submission is related to the management of obesity and not the direct treatment of type 2 diabetes.
Key issue 4: Exclusion of the STEP 3 trial from the company submission	No.	We agree with this exclusion.
Key issue 5: The ITC results are not used in the economic model	No	We are unable to comment on this issue.
Key issue 6: Treatment stopping rule	No	We are unable to comment on this issue.
Key issue 7: Assumption that all patients with non-diabetic hyperglycaemia develop type 2 diabetes after initial CVD event	No.	We are unable to comment on this issue.

Key issue 8: Differences in how intercurrent events are recorded across trials may impact imputation	No.	We are unable to comment on this issue.
Key issue 9: Results from the completed STEP 5 and STEP 8 trials are expected this year	No.	We are unable to comment on this issue.
Key issue 10: Treatment duration and retreatment	No.	At the present time there is a suggested maximum 2 years for treatment. As within any weight loss treatment once it is removed there is a compensatory biological response to drive weight regain, as a result there is a strong likelihood that patient would regain the weight they lost. It would therefore be suggested that if this occurred that retreatment is considered. In addition, there should be consideration, if safe, for longer term use of the medication past 2 years to ensure that the weight loss in maintained in the long-term. We also note that behavioural changes are important throughout and after treatment.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

NICE National Institute for Health and Care Excellence

Professional organisation submission

Semaglutide for managing overweight and obesity [ID3850]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Obesity and Metabolic Surgery Society**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	yes an employee or representative of a healthcare professional organisation that represents clinicians? yes a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	BOMSS is the UK internationally recognised society representing multidisciplinary specialists(surgeons, dieticians, nurses and psychologists) with a special interest in the surgical and medical management of severe obesity and its complications. (https://bomss.org/about/) BOMSS receives financial support through membership subscriptions and from a wide range of industry partners including 4 major corporate sponsors who in 2021 each contributed £50K. Novo Nordisk were one of these major sponsors in 2021.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	Yes see 5a above

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of interventions for people living with obesity or severe and complex obesity is to help them to lose weight and improve quality of life. Obesity has a complex multifactorial aetiology, and can adversely affect all organ systems. Improvement in quality of life is generally achieved if people lose weight as this reduces burden of obesity related disease such as type 2 diabetes, sleep apnoea, mobility issues and psychological well-being. Until recently the only effective intervention has been bariatric surgery. Semaglutide and other GLP-1 agonists such as liraglutide 3mg are currently the only effective drugs for promoting weight loss. The likely outcome of treatment with Semaglutide will be dependent on the precise clinical scenario at presentation.

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinically meaningful and measurable improvement in quality of life for those living with severe and complex obesity can be achieved with 10% total body weight loss
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes There are over 2 million people in the UK who suffer with severe and complex obesity. Whilst surgery can be an effective treatment for these people, the NHS performs approximately 6,000 procedures per annum in the UK. The vast majority of people with this condition do not currently undergo effective treatment for this condition. There are significant barriers to effective treatment for many people for reasons which are complex and interlinked including: Lack of knowledge amongst the general population Lack of knowledge amongst clinicians in both primary and secondary care Stigma against those with Obesity, and widespread belief that this is a self-inflicted condition
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Obesity and severe and complex obesity is treated in primary care, secondary care and also in specialist weight management services including tier 3 and tier 4 services.

	Tier 4 services provide bariatric surgery to some patients who have already been managed in a tier 3 service Medical treatment of obesity with Liraglutide was supported by NICE in Technology appraisal guidance [TA664] published in December 2020
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Obesity: identification, assessment and management. CG 189 Nov 2014 Guidance for treatment of obesity is currently in the process of being updated (GID-NG10182) and is expected to be published in 2023
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care for management of obesity has been defined by NICE for adults and was last updated in August 2021: http://pathways.nice.org.uk/pathways/obesity Use of Liraglutide is defined within this pathway Whilst pathways of care well defined there is a marked post-code lottery in terms of implementation due to lack of commissioning of services.
• What impact would the technology have on the current pathway of care?	The technology would fill the current treatment gap that exists between lifestyle interventions and bariatric surgery. This would provide ≥10% weight loss to patients with obesity leading to improve health. More patients may be referred into tier 3 services
10. Will the technology be used (or is it already used) in	The technology will be used in the same way as Liraglutide albeit with wider indications for use than Liraglutide 3mg

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The technology will be used by current weight management services. The only two drugs that are approved by NICE are orlistat and liraglutide 3mg (for people with pre-diabetes, a BMI ≥35 or more plus a CV risk factor). The new technology in light of its markedly greater weight loss will be available to greater proportion of people living with obesity. Introduction of the technology will require increased financial and human resource in the short term. This may well be offset and exceeded by reduced NHS costs in the future as well as increased levels of economic activity amongst those having this treatment
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist weight management services Semaglutide 2.4 mg once weekly should be used within the context of a multi-disciplinary specialist weight management team with access to a physician/surgeon with expertise in obesity management, psychology and specialist dietitians. It is important that people with obesity are triaged appropriately to the appropriate treatment.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Increased commissioning and provision of tier 3 services. Training of GPs and other healthcare professionals so that they refer patients who fulfil the eligibility criteria
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes This is the most effective medication for obesity to date leading to on average 14.9% weight loss in people with overweight/obesity without type 2 diabetes compared to current treatment which leads to at best 6% weight loss.

• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More appropriate for: People with a BMI of ≥35 or more and people with a BMI of 30-34.9 with obesity related complication. People who need to reduce their weight in order to have another procedure e.g., knee replacement Less appropriate for: People with sarcopenia
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	The technology will be more difficult to use than currently available non-surgical therapies. Patients will need to be trained to inject and also supported to deal with the side effects during the dose escalation

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	phase. Patients with gallstones will require more monitoring due to increased risk of cholecystitis. Patients with pre-existing gastro-intestinal symptoms will need increased monitoring.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The SmPc states that people who do not achieve ≥5% weight loss or more at 6 months should stop the treatment, This will be based upon weighing.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	This technology is likely to mean that people will be able to return to work and have fewer sick days, and this may only show up indirectly in QALY calculations

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Most people will achieve >10% weight loss which appears to be required to reverse many of the complications of obesity.
• Is the technology a 'step-change' in the management of the condition?	Semaglutide 2.4mg once weekly represents a step-change in the management of people living with obesity due to its efficacy.
• Does the use of the technology address any particular unmet need of the patient population?	At the moment there are no obesity medications to fill the gap between lifestyle interventions and bariatric surgery.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Gastrointestinal side effects are common during the first 16 weeks and patients will need telephone support to deal with these. These are usually minor and settle with support and time

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	% weight loss, improvement in cardiometabolic risk factors and improved quality of life.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance ?	No
21. How do data on real-world experience compare with the trial data?	Real world data are very similar to trial data
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The provision of specialist weight management services and referral of people with obesity is patchy. This needs improving.

22b. Consider whether these issues are different from issues with current care and why.	Similar

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Obesity is associated with multiple co-morbidities that reduce health, quality of life and lead to marked healthcare and social care costs. These can be reduced by weight loss but for the majority of conditions at least 10% weight loss is needed.
- Currently, available obesity medications do not lead to 10% weight loss
- Semaglutide 2.4 mg is based on a naturally occurring hormone, GLP-1 and leads to > 10% weight loss in people without type 2 diabetes.
- Semaglutide 2.4 mg is a game changer for people with obesity
- Additional resources and training will be required to ensure equitable access

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Semaglutide for managing overweight and obesity [ID3850]

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Deadline for comments by **5pm** on **15 November 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

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- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
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- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Royal College of Physicians (RCP)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to the issues raised in the ERG report.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Decision problem target population	Yes	Our experts agree that a cost-effectiveness analysis of people who are eligible to attend Tier 3 may provide useful information. However, this will result in a postcode lottery in terms of access as many areas of England do not have access to a Tier 3 weight management service. We already have this issue with NICE liraglutide 3mg which is limited to hospital-based Tier 3 services Our experts recommend that any Tier 3 service with access to a physician/GP with a special interest in weight management and appropriate multi-disciplinary support should be able to offer semaglutide 2.4 mg to the appropriate patients. NICE guidelines are unclear regarding which ethnic groups should have their BMI threshold lowered, this would need to be clarified. Another group that should be considered here includes people who need to lose weight in order to have another surgery.
Key issue 2: Exclusion of orlistat as a comparator	No	Our experts agree with the exclusion of orlistat as a comparator

Key issue 3: Exclusion of the STEP 2 trial from the company submission	Yes	The weight loss in the STEP 2 trial (people with type 2 diabetes) was significantly lower that STEP1, 3 and 4 and lower that the published tirzepatide data. If these data are not included then patients with T2D will need to be excluded People with T2D and obesity are more likely to be treated with the diabetes dose of semaglutide or tirzepatide when licensed. Our experts recommend a separate analysis looking only at people with T2D and obesity and to look at those with a BMI <35 and ≥35 kg/m^2.
Key issue 4: Exclusion of the STEP 3 trial from the company submission	N0	The IBT programme is not standard practice in England and current Tier 3 service staffing would not be able to delivery this. The addition of IBT to semaglutide 2.4 mg did not improve overall % weight loss despite the increased costs so we agree with STEP 3 being excluded.
Key issue 5: The ITC results are not used in the economic model	Yes	Our experts agree with the ERG and that the ITC results should be used.
Key issue 6: Treatment stopping rule	No	The marketing authorisation includes a stopping rule at 6 months is a person has not lost 5% of their total body weight.
Key issue 7: Assumption that all patients with non-diabetic hyperglycaemia develop type 2 diabetes after initial CVD event	Yes	Our experts agree with the ERG.
Key issue 8: Differences in how intercurrent events are recorded across trials may impact imputation	No	Our experts are unsure how to resolve this
Key issue 9: Results from the completed STEP 5 and STEP 8 trials are expected this year	YES	The results from STEP 5 and STEP 8 were reported at obesity week so are available and should be included.

Key issue 10: Treatment duration and retreatment		Obesity is a chronic progressive medical treatment that requires life-long management similar to other chronic disease such as T2D and hypertension. Termination of treatment will lead to weight regain in the majority of people and strategies will need to be put in place (either behavioural support or reintroduction of semaglutide 2.4mg) to prevent this from happening as this would adversely impact on physical and mental health.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

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Technical engagement response form

Semaglutide for managing overweight and obesity [ID3850]

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**The UK Obesity Organisation**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to the issues raised in the ERG report.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Decision problem target population	No	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 2: Exclusion of orlistat as a comparator	**N**o	Agree fully that orlistat should not be used as a comparator.
Key issue 3: Exclusion of the STEP 2 trial from the company submission	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 4: Exclusion of the STEP 3 trial from the company submission	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 5: The ITC results are not used in the economic model	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 6: Treatment stopping rule	**N**o	Agree that if little or no weight loss is seen within the 6 months then a stopping rule should be applied.
Key issue 7: Assumption that all patients with non-diabetic hyperglycaemia develop type 2 diabetes after initial CVD event	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

Key issue 8: Differences in how intercurrent events are recorded across trials may impact imputation	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 9: Results from the completed STEP 5 and STEP 8 trials are expected this year	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 10: Treatment duration and retreatment	**N**o	Agree with the ERG's comments around 'should a chronic condition have a treatment duration cut off'. However, the data shows us that within 2 years patients may have had a weight loss of equal to or greater than 10%, so it could be appropriate to stop treatment once they reach a healthier weight, that may allow them to re-engage or adopt exercise or other management tools to help maintain the weight loss.

Additional issues

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..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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Evidence Review Group Report commissioned by the NIHR Systematic Reviews Programme on behalf of NICE

Semaglutide for managing overweight and obesity (ID3850)

Evidence Review Group's summary and critique of the company's response to technical engagement

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Keith Cooper, Senior Research Fellow, Health Economics Karen Pickett, Research Fellow, Evidence Synthesis Geoff Frampton, Senior Research Fellow, Evidence Synthesis Neelam Kalita, Senior Research Fellow, Health Economics David Alexander Scott, Principal Research Fellow, Statistics
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Date completed	03/12/2021

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[redacted]

LIST OF ABBREVIATIONS

BMI	Body mass index
CPAP	Continuous positive airway pressure
CS	Company submission
CVD	Cardiovascular disease
ERG	Evidence Review Group
FAS	Full analysis set
HRQoL	Health-related quality of life
IBT	Intensive behavioural therapy
ICER	Incremental cost-effectiveness ratio
IWQoL	Impact of Weight on Quality of Life
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAS	Patient access scheme
SWMS	Specialist weight management services
TA	Technology appraisal
TE	Technical engagement
T2D	Type 2 diabetes

1. Introduction

This document is the Evidence Review Group (ERG)'s summary and critique of the response by the company, Novo Nordisk, to the key issues for technical engagement (TE) proposed in the ERG report for this appraisal (submitted to NICE on 23rd September 2021). The ERG received the company's response on 17th November 2021.

The company's TE response form contains the following information:

- A written response to each of the 10 key issues, four of which include new evidence, data and/or analyses (see Table 1).
- Written responses to four additional issues raised by the company, one of which contains new evidence (see Table 1).
- Selected cost-effectiveness results in response to key Issue 3. NB the company have not made any changes to their preferred base case analysis.

In this report we present the following:

- Our critique of the company's response to each of the 10 issues for technical engagement (section 2).
- A critique of or response to each of the company's responses to each of the four additional issues they raised (section 2).
- An update of the ERG's base case analyses (section 3.1) and scenario analyses (section 3.4). NB these analyses are provided using the list prices for semaglutide and liraglutide in section 3 and are repeated using the proposed patient access scheme (PAS) price for semaglutide and list price for liraglutide in Appendix 4.1.

Table 1 Summary of key issues for technical engagement

Issue number	Summary of issue	Does this response contain new evidence, data or analyses?
1	Decision problem target population	No
2	Exclusion of orlistat as a comparator	No
3	Exclusion of the STEP 2 trial from the CS	Yes, new data and analyses
4	Exclusion of the STEP 3 trial from the CS	Yes, new data
5	The ITC results are not used in the economic model	No
6	Treatment stopping rule	Yes, new evidence [a]
7	Assumption that all patients with non-diabetic hyperglycaemia develop type 2 diabetes after an initial cardiovascular (CVD) event	No
8	Differences in how intercurrent events are recorded across trials may impact imputation	No
9	Results from the completed STEP 5 and STEP 8 trials are expected this year	Yes, new evidence
10	Treatment duration and retreatment	No
Additional issue 1	Annual cost of microvascular complications	Yes, new evidence
Additional issue 2	Annual costs of sleep apnoea	No
Additional issue 3	Presence of eating disorders and mental health issues	No
Additional issue 4	CIC marking	No

[a] The company provided the final version of the marketing authorisation

2. Critique of the company's response to key issues for technical engagement

2.1 Issue 1 – Decision problem target population

2.1.1 Summary of the issue

The ERG proposed a scenario analysis to more closely reflect the population that is currently treated in tier 3 services (based on our expert's opinion and published reports[1 2]). We suggested that the NICE criteria for eligibility for bariatric surgery may more suitably define the target population (BMI ≥ 35 kg/m^2 with at least one co-morbidity or ≥ 40 kg/m^2 with or without comorbidities, unless new onset diabetes, in which case BMI ≥ 30 kg/m^2, or lower for people of Asian family origin).[3] Our clinical expert noted that if semaglutide were to be approved for the company's target population, this would potentially expand the patient population who can be referred to tier 3 weight management services. Currently, few people with a BMI 30-35 kg/m^2 are treated in tier 3 (people with a BMI in this range are generally only referred if they have new onset diabetes, in line with the NICE pathway for referral of people suitable for bariatric surgery into tier 3 and onwards[3]).

In the ERG report we provided scenarios using different starting BMI values which give an indication of the cost effectiveness for the group with BMI ≥ 35 kg/m^2 (see ERG report section 6). However, these scenarios were defined only by the BMI value, as we are unclear which other population characteristics we would need to change in the economic model. Our suggested scenario analysis for the bariatric surgery eligible group aimed to provide a more accurate characterisation of this population.

2.1.2 Critique of the company's response

In their response to technical engagement (TE) the company have not provided the illustrative scenario analysis suggested by the ERG for the bariatric surgery eligible subgroup. The company have presented several arguments for not providing this analysis. However, these arguments primarily justify why the company's target population analysis is relevant to clinical decision making (which, as stated in Issue 1 in the ERG report we do not disagree with).

Our scenario analyses (ERG report section 6) showed that the ICER would be [redacted] for groups with higher BMI. We accept that the proposed scenario on the bariatric surgery eligible subgroup may not be informative unless NICE would prefer to see a more accurate estimate of the ICER in this group.

2.2 Issue 2 – Exclusion of orlistat as a comparator

2.2.1 Summary of the issue

Orlistat is specified as a comparator in the NICE scope but the company excluded orlistat from their CS decision problem as it is not widely used in clinical practice. In our ERG report we agreed with excluding orlistat due to its limited use. However, as we received advice from a single clinical expert we included this issue to enable NICE to consider additional clinical opinion on the extent to which orlistat is used in practice.

2.2.2 Critique of the company's response

The company note that the limited use of orlistat is reflected in two recent technology appraisals (TAs) of drug interventions for managing overweight and obesity (Naltrexone–bupropion for managing overweight and obesity [TA494],[4] and liraglutide for managing overweight and obesity [TA664][5]). The company also cite feedback provided by Obesity UK during the consultation for the appraisal: 'Many people told us they had used orlistat with little effect and poor outcomes'. The company state that, as orlistat is intended for use within specialist weigh management services (SWMS), orlistat will have been among the conventional interventions already tried by patients.

The company's response has not changed the ERG's position: We agree that orlistat is not a relevant comparator, if it is intended that semaglutide 2.4 mg will be used in SWMS.

2.3 Issue 3 – Exclusion of the STEP 2 trial from the CS

2.3.1 Summary of the issue

In our ERG report, we noted that the STEP 2 trial[6] met the NICE scope and the company's decision problem, but that the company did not include results from the trial in their evidence synthesis in the CS. The trial compared the efficacy of semaglutide 2.4mg to placebo, both as adjuncts to a lifestyle intervention that included a reduced-calorie diet and increased physical activity, in people with a BMI ≥ 27 kg/m^2 (overweight) or BMI ≥ 30 kg/m^2 (obese) with at least one weight-related co-morbidity and who had been diagnosed with type 2 diabetes (T2D). The company stated in their CS that the STEP 2 trial[6] population was not relevant to the submission. In their clarification response, the company explained that it is possible that semaglutide 2.4 mg may be used to treat weight in people with T2D but use of semaglutide would typically follow a diabetes treatment pathway where semaglutide would be used at a lower dose. Our clinical expert indicated it was possible that the 2.4 mg dose

might be used in this population for the purposes of weight loss and maintenance. However, as we had only spoken to one clinical expert there was some uncertainty about whether semaglutide would be used for this purpose. We suggested that further discussion with clinical experts about whether or not semaglutide 2.4 mg would be used for this purpose would help resolve this uncertainty and, therefore, clarify whether or not the STEP 2 trial[6] should have been included in the company's submission.

2.3.2 Critique of the company's response

The company have provided additional information that around one third of the people treated in SWMS have T2D and they state that semaglutide 2.4 mg is a potential treatment option for this patient group. This clarifies that people living with obesity who have T2D as a co-morbidity would be a part of the target population and hence the STEP 2 trial[6] results are relevant to the appraisal.

Critique of the clinical evidence

The company provided a paper[6] and a Clinical Trial Report Synopsis[7] reporting the results of the STEP 2 trial. The company note that the weight loss observed in the STEP 2 trial[6] was less than in the STEP 1 trial,[8] but that weight loss in people with T2D is accompanied by other benefits and that clinical experts have indicated that lower weight loss in people with T2D compared to those without is to be expected. The ERG agree with this interpretation.

STEP 2 was a blinded trial and the ERG judged the trial to have an overall low risk of bias. The key difference between the STEP 2 trial and STEP 1 trial is that STEP 2 included participants with T2D (and hence also diabetes medication in addition to semaglutide) whereas STEP 1 did not. The mean duration of diabetes was 8.2 years. Mean age of participants at baseline in STEP 2 was slightly higher (55 years)[6] compared to the STEP 1 trial (46 to 47 years) (ERG report Table 10) whilst mean baseline BMI in STEP 2 (35.9 kgm^{-2})[6] was slightly lower than in STEP 1 (38 kgm^{-2}). The diet and physical activity component of STEP 2 was similar to that of STEP 1, i.e. consisting of individual counselling at 4-weekly intervals (as summarised in ERG report Table 8). We noted in ERG report section 3.2.1 that the STEP 1 trial would probably not fully match NHS clinical practice since individual counselling sessions are impractical in the NHS, and the same consideration applies to STEP 2.

Critique of the company's economic analyses

During TE the company had noted several obstacles to modelling weight loss in a diabetic population, due to differences in the general approaches that are used for modelling weight

loss and for modelling T2D. The company agreed to provide an illustrative analysis using the CORE Diabetes model which is an established and validated diabetes model that has been used in previous technology appraisals in diabetes such as TA203 and TA622.

In their response to TE the company conducted two analyses for the comparison of semaglutide 2.4mg against placebo for patients with a BMI ≥ 30 kg/m^2 and T2D:

1. Using data from the STEP 2 trial in the current company model.
2. An illustrative analysis using the CORE Diabetes model.

Results of these analyses are shown in Table 2 below.

Table 2 Results from the company's additional analyses for patients with BMI ≥ 30 kg/m^2 and T2D (PAS price)

Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
1. Company model results using STEP2 data					
Diet and physical activity	[redacted]	[redacted]			
Semaglutide 2.4mg	[redacted]	[redacted]	[redacted]	[redacted]	21,277
2. Illustrative scenario using the CORE Diabetes model					
Diet and physical activity	[redacted]	[redacted]	[redacted]	[redacted]	
Semaglutide 2.4mg	[redacted]	[redacted]	[redacted]	[redacted]	16,613
Source: Tables 1 & 3 of the company's response to TE					

The ERG checked the company's revised analyses. In summary:

- We replicated the company's cost effectiveness results for people with BMI ≥ 30 kg/m^2 plus comorbidity using data from STEP 2 and the semaglutide PAS price as reported in Table 1 of their response to TE. However, we have not validated the data from the STEP 2 trial used in this analysis.
- We note that the company model uses the following information from STEP 2: the STEP 2 cohort characteristics; discontinuation rates in STEP 2 (Sheet!Time-to-discontinuation cell$D$7:$D$24) and the relative treatment effect for the change in weight in STEP 2.
- The company compare the features of their obesity economic model against those of the CORE Diabetes model in Table 2 of their response to TE. However, the company have not provided an economic model for their illustrative scenario that uses the CORE Diabetes model. Therefore, the ERG could not verify the company's reported

cost effectiveness results for this scenario (reported in Table 3 in the company's response to TE) and we are unable to comment on the validity of this scenario.

2.4 Issue 4 – Exclusion of the STEP 3 trial from the CS

2.4.1 Summary of the issue

In the CS, the company identified that the STEP 3 trial[9] met their systematic literature review inclusion criteria, but excluded it post-hoc from the review. The company excluded the trial because they considered that the intensive behavioural therapy (IBT) employed for diet and physical activity is not standard clinical practice in the UK. We noted in our ERG report that the trial meets the NICE scope and we believed data from it should have been included in the CS. We acknowledged that the standard management used in the STEP 1 trial[8] included in the CS more closely reflects practice in England than the IBT intervention used in the STEP 3 trial.[9] We suggested, however, that standard clinical management is variable in practice, so it was unlikely that an intervention used in a trial would fully reflect clinical practice.

2.4.2 Critique of the company's response

The company have highlighted that the IBT approach employed in STEP 3 was considerably more intensive than the counselling approach for diet and physical activity that would likely be achievable in NHS clinical practice. On re-checking details of the IBT approach employed in STEP 3 (eAppendix 4 in the trial publication[9]) we agree with the company that the IBT approach employed in STEP 3 is unlikely to be generalisable to NHS practice.

The company argued that the difference in percentage change in weight from baseline between semaglutide 2.4mg and placebo in each trial is marginal with overlapping confidence intervals. We agree that the STEP 3 and STEP 1 trials show broadly similar efficacy of semaglutide 2.4mg versus placebo.

In summary, following reconsideration of the information presented in the STEP 3 trial publication.[9] and its supplementary Appendix, we agree with the company that it is appropriate to exclude the STEP 3 trial from the analysis because: (i) STEP 3 is unlikely to be generalisable to NHS clinical practice; and (ii) the inclusion/exclusion of STEP 3 would have minimal impact on clinical efficacy outcomes compared to the data already available from STEP 1.

2.5 Issue 5 – The ITC results are not used in the economic model

2.5.1 Summary of the issue

The ERG were unclear about the calculations used for the ITC of semaglutide versus liraglutide used in the economic model.

2.5.2 Critique of the company's response

The formulae provided by the company are appropriate, but we cannot validate the numbers provided in the first three columns of Table 4 in the company's response to TE Issue 5 against those provided in the CS or publications.

The STEP 8 trial now provides a head-to-head comparison of semaglutide versus liraglutide (see Issue 9 below), so we believe that the ITC is outdated. We recommend that the results from STEP 8 for those participants eligible for liraglutide in the NHS (BMI ≥ 35 kg/m^2 with non-diabetic hyperglycaemia and CVD risk) should be used directly in the economic model to replace the ITC. However, the STEP 8 trial included people with BMI ≥ 30.0 kg/m^2 or ≥ 27.0 kg/m^2 with the presence of at least one weight-related comorbidity, i.e. a wider population than those eligible for liraglutide in the NHS. The company have not provided results from STEP 8 for the NHS relevant liraglutide-eligible subgroup and it is unclear how many of the participants in STEP 8 were in this subgroup.

The company report change in body weight at 68 weeks in the STEP 8 trial as -9.38% (95% CI -11.97, -6.80) which is comparable to the result from the ITC, but it is unclear if these results from STEP 8 apply to the early responders. Also, as noted above, the STEP 8 results apply to the full analysis population rather than the liraglutide-eligible subgroup.

2.6 Issue 6 – Treatment stopping rule

2.6.1 Summary of the issue

The company's economic analysis assumed that patients who did not respond to treatment would discontinue treatment (stopping rule). At the time that the ERG report was written, the marketing authorisation for semaglutide had not been published. There remained uncertainty whether the marketing authorisation would include a stopping rule for semaglutide 2.4 (CS section B3.2.3.1). In addition, the ERG noted that a stopping rule was not included within the STEP 1 clinical trial.

2.6.2 Critique of the company's response

The company in their response to technical engagement state that the MHRA marketing authorisation for semaglutide 2.4 mg has now been published and includes a stopping rule described as follows:

- '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, taking into account the benefit/risk profile in the individual patient'.

The company state that the wording of the marketing authorisation is aligned with how treatment has been modelled.

The ERG welcome the publication of the marketing authorisation and we note that clinical experts consulted as part of this technology appraisal have confirmed that the application of the non-responder stopping rules would be appropriate in this population. However, we note that there remains uncertainty in the model results for which the company trial did not include a stopping rule.

2.7 Issue 7 – Assumption that all patients with non-diabetic hyperglycaemia develop type 2 diabetes after an initial cardiovascular (CVD) event

2.7.1 Summary of the issue

The company model included the assumption that patients with non-diabetic hyperglycaemia are assumed to develop T2D following an initial CVD event. Based on our clinical advice, the ERG considered that this assumption was not representative of clinical practice and a better assumption would be to assume that these patients do not develop T2D following an initial CVD event.

2.7.2 Critique of the company's response

The company state that while it is likely that some patients with non-diabetic glycaemia will not develop T2D after a CV event some patients may go on to develop this. Further the impact of removing this assumption on the base case is small, this assumption was included in TA664 and the validation paper Lopes et al 2020[10] did not indicate an overestimation of the incidence of T2D.

The ERG agree that the impact of this assumption is small (increase in ICER of ~£[redacted]), however we believe this assumption is unrealistic and overestimates the incidence of T2D.

2.8 Issue 8 – Differences in how intercurrent events are recorded across trials may impact imputation

2.8.1 Summary of the issue

We raised the question of differences between the SCALE 1839 and STEP 1 trials in how the intercurrent events were recorded and whether this may have impacted the missing data imputation used in the trial product estimand.

2.8.2 Critique of the company's response

The company state that they expect the risk of bias arising from these differences to be low but they have not provided a justification for their assertion.

This issue would be superseded by using the STEP 8 trial results to directly inform the economic model, instead of using the ITC results, subject to data for the NHS-relevant liraglutide-eligible subgroup in STEP 8 being available (see Issue 5 above).

2.9 Issue 9 – Results from the completed STEP 5 and STEP 8 trials are expected this year

2.9.1 Summary of the issue

The company included details about two completed trials on semaglutide 2.4 mg (STEP 5 and STEP 8) in their CS, but noted that results were not available in time to be included in the submission:

- The STEP 8 trial: a head-to-head comparison of semaglutide 2.4 mg with liraglutide 3.0 mg and also with placebo (all as adjuncts to a lifestyle intervention) in people living with obesity (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2) with ≥ 1 weight-related comorbidity.
- The STEP 5 trial: a comparison of semaglutide 2.4 mg against placebo (both as adjuncts to a lifestyle intervention) in people living with obesity (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2) with ≥ 1 weight-related comorbidity. The drugs were administered during a 104-week period.

We noted in our ERG report that both trials were relevant to the NICE scope, albeit it was unclear how many people in the STEP 8 trial might be included in a 'liraglutide-eligible' subgroup. We suggested that results of the trials could potentially have a bearing on conclusions about the clinical and cost-effectiveness of semaglutide 2.4 mg, and suggested that the company provide the results when they were available.

2.9.2 Critique of the company's response

The company shared the Clinical Study Report Synopses for both the STEP 5[11] and STEP 8[12] trials with their TE response and summarised the weight change results (% weight change from baseline to week 104 (STEP 5) or to week 68 (STEP 8), and the % of participants achieving a weight reduction of at least 10%) from the trials in their response. The company state that the results support superiority of semaglutide 2.4 mg over the comparators in these trials in terms of these outcomes. We agree this is the case. The % weight change in the STEP 5 trial at 104 weeks is consistent with that in the STEP 1 trial at 68 weeks. This result supports the efficacy of semaglutide 2.4 mg when it is used over a longer period than in the STEP 1 trial. We reviewed the results provided in the STEP 5 and STEP 8 trial synopses for other outcomes that inform the economic model, where these were available, and noted results were generally in favour of semaglutide 2.4 mg (but not always statistically significantly so). As noted above under Issue 5, the results available in the STEP 8 trial Synopsis were for the whole trial population (BMI ≥ 30.0 kg/m^2 or ≥ 27.0 kg/m^2 with the presence of ≥ 1 weight-related comorbidity) and not the liraglutide-eligible subgroup specified to be of interest in the NICE scope.

2.10 Issue 10 – Treatment duration and retreatment

2.10.1 Summary of the issue

We noted that the company's assumptions in the economic model that people would receive treatment with semaglutide 2.4 mg for a maximum of two years and they would not receive retreatment with pharmacotherapy were reasonable. We also noted, however, that potential length of treatment and the possibility of retreatment with semaglutide were areas where there was some clinical uncertainty. We suggested that this could be resolved through further discussion with clinical experts about these factors.

2.10.2 Critique of the company's response

The company state in their TE response that treatment in SWMS is provided for a maximum of two years and that introduction of semaglutide 2.4 mg into the treatment pathway is not expected to change this.

We maintain our position that the assumptions used in the model are reasonable.

2.11 Additional issue 1 – Annual cost of microvascular complications

The ERG used a lower cost for microvascular complications (£398) than the company's estimate (£940.86), based on the cost estimates reported in Capehorn et al.[13] The company in their response to technical engagement note that the cost estimates in the study by Capehorn et al were discounted estimates. When these costs are used in the company model they will be double discounted and therefore undiscounted cost estimates should be used. The company have retrieved the unpublished undiscounted estimates from the study authors.

We agree that the cost estimates used by the ERG are erroneous because they are discounted estimates and the estimates from the company are more appropriate.

2.12 Additional issue 2 – Annual cost of sleep apnoea

2.12.1 Summary of the issue

The ERG suggested a lower cost for treating patients with sleep apnoea of £274, compared to the company estimate of £1,019. In the company response, they defend the use of their cost estimate by stating that it is based upon NHS reference cost data which they contend is more appropriate than the source used by the ERG.

We disagree with the company's use of NHS reference costs for the cost of sleep apnoea. The NHS reference costs relate to secondary care costs such as hospitalisation costs. The cost of CPAP reported in Sharples et al[14] is more representative of the cost of sleep apnoea. Further we note that the NHS reference costs only relate to 6,041 patients compared to the estimated 667,000 people with moderate or severe sleep apnoea,[15] i.e. those reported in the NHS Reference costs represent the cost of acute sleeping disorder episodes, rather than average cost of sleep apnoea.

2.13 Additional issue 3 – Presence of eating disorders and mental health issues

2.13.1 Summary of the issue

This is an additional issue raised in the company's technical engagement response that does not relate to a key issue raised in the ERG report. In this additional issue, the company highlight the following comment in section 2.2.1 of the ERG report: 'The company do not mention eating disorders, such as binge eating (which our clinical expert states are common

in this population) and the process by which mental health co-morbidities should be addressed'. The company note that the potential effects of semaglutide 2.4 mg on mental health were captured in the health-related quality of life (HRQoL) results presented in the CS. They also note that the Impact of Weight on Quality of Life (IWQoL) tool domains capture binge eating and other aspects of psychosocial well-being. The company reiterate results originally presented in the CS that show results were in favour of semaglutide across the HRQoL domains assessed.

2.13.2 Critique of the company's response

The ERG statement highlighted by the company is in the background section of our ERG report. Our statement reflects an observation that while the company provided information in the background section of their CS about physical health weight-related co-morbidities, they did not include information about mental health co-morbidities. We noted in section 3.2.3 of the ERG report that clinical advice to the ERG was that psychological and physical well-being outcomes were among those considered most important in assessing the efficacy of treatments for people living with obesity. We suggested these outcomes would be captured by the HRQoL outcomes included in the CS. Therefore, we have already acknowledged that the CS contained information on psychological well-being outcomes.

2.14 Additional issue 4 – CIC marking

2.13.1 Summary of the issue

This is an additional issue, the company provided updated confidentiality marking for the ERG report.

2.13.2 Critique of the company's response

We have updated the confidentiality marking in our ERG report in line with instructions in the company's technical engagement response. We have submitted the updated report to NICE, along with this critique of the company's TE response.

3. Updated cost-effectiveness results - ERG summary and critique

3.1 Company's revised base case cost-effectiveness results

The company have not made any changes to their proposed base case in response to TE.

3.2 ERG's revised preferred assumptions

We have updated our preferred base case, keeping all preferred assumptions, as outlined in the ERG report, except for the cost of microvascular complications, where we used the company cost (£908.46), as discussed in Additional issue 1 (section 2.11). Results are shown here using the list prices for semaglutide 2.4mg and liraglutide 3.0mg. Results are shown in Appendix 4 using the proposed PAS price for semaglutide 2.4mg.

3.3 Cost-effectiveness results based on ERG preferred model assumptions

The cumulative effect of the ERG's preferred assumptions on the company's analyses are shown in Table 3 and Table 4. Applying the ERG updated preferred assumptions increases the company's base case ICER for semaglutide 2.4mg versus placebo (i.e. diet and physical activity) from [redacted] to [redacted] per QALY. For the liraglutide-eligible subgroup, while the ICER for liraglutide 3.0mg versus placebo increases from £[redacted] to £[redacted], semaglutide 2.4mg [redacted] compared to liraglutide 3.0mg.

Table 3 Cumulative change from the company base case to ERG base case with ERG's preferred assumptions (with list price for semaglutide 2.4mg)

Assumption	Treatments	Total costs	Total QALYs	ICER (£/QALY)
Company base-case	Placebo	[redacted]	15.269	[redacted]
	Semaglutide 2.4mg	[redacted]	15.361	
Patients with pre-diabetes do not transition to T2D after CVD events	Placebo	[redacted]	15.329	[redacted]
	Semaglutide 2.4mg	[redacted]	15.419	
+ Mean increase of weight by 0.296 kg per year	Placebo	[redacted]	15.484	[redacted]
	Semaglutide 2.4mg	[redacted]	15.582	
+ Mean decrease in weight after age 66 years: 0.296 kg per year	Placebo	[redacted]	15.540	[redacted]
	Semaglutide 2.4mg	[redacted]	15.634	
+ Age at which weight no longer increases: 66 years	Placebo	[redacted]	15.562	[redacted]
	Semaglutide 2.4mg	[redacted]	15.656	
+ Annual cost of sleep apnoea, £274	Placebo	[redacted]	15.562	[redacted]
	Semaglutide 2.4mg	[redacted]	15.656	
ERG base case	Placebo	[redacted]	15.562	[redacted]
	Semaglutide 2.4mg	[redacted]	15.656	

Table 4 Cumulative change from company liraglutide-eligible subgroup results to the ERG liraglutide-eligible subgroup results with the ERG's preferred assumptions (with list price for semaglutide 2.4mg)

Assumption	Treatments	Total costs	Total QALYs	Incremental ICER (£/QALY)
Company base-case	Placebo	[redacted]	14.311	

	Liraglutide 3.0mg	[redacted]	14.401	[redacted]
	Semaglutide 2.4mg	[redacted]	14.444	[redacted]
Patients with pre-diabetes do not transition to T2D after CVD events	Placebo	[redacted]	14.419	[redacted]
	Liraglutide 3.0mg	[redacted]	14.505	[redacted]
	Semaglutide 2.4mg	[redacted]	14.548	[redacted]
+ Mean increase of weight by 0.296 kg per year	Placebo	[redacted]	14.562	[redacted]
	Liraglutide 3.0mg	[redacted]	14.648	[redacted]
	Semaglutide 2.4mg	[redacted]	14.690	[redacted]
+ Mean decrease in weight after age 66 years: 0.296 kg per year	Placebo	[redacted]	14.642	[redacted]
	Liraglutide 3.0mg	[redacted]	14.727	[redacted]
	Semaglutide 2.4mg	[redacted]	14.770	[redacted]
+ Age at which weight no longer increases: 66 years	Placebo	[redacted]	14.659	[redacted]
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]
+ Annual cost of sleep apnoea, £274	Placebo	[redacted]	14.659	[redacted]
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]
ERG base case	Placebo	[redacted]	14.659	[redacted]
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]

3.4 Scenario analyses conducted on the ERG's revised preferred assumptions

The ERG updated the scenario analyses on the base case and the liraglutide-eligible subgroup, shown below in Table 5 and Table 6. For the base case, the ICER for semaglutide 2.4mg versus placebo (i.e. diet and physical activity) varied between [redacted] (Scenario: Mean starting BMI of 42.5 kg/m^2) and [redacted] (Scenario: catch up rate of 1 year). For the liraglutide-eligible subgroup, semaglutide 2.4mg was [redacted] compared to liraglutide 3.0mg for all scenarios.

Table 5 Scenarios conducted on the ERG base case (with list price for semaglutide 2.4mg)

Assumption	Treatments	Total costs	Total QALYs	ICER (£/QALY)
ERG base-case	Placebo	[redacted]	15.562	[redacted]
	Semaglutide 2.4mg	[redacted]	15.656	
Mean starting BMI of 32.5 kg/m^2	Placebo	[redacted]	16.762	[redacted]
	Semaglutide 2.4mg	[redacted]	16.839	
Mean starting BMI of 37.5 kg/m^2	Placebo	[redacted]	15.766	[redacted]
	Semaglutide 2.4mg	[redacted]	15.870	
Mean starting BMI of 42.5 kg/m^2	Placebo	[redacted]	14.775	[redacted]
	Semaglutide 2.4mg	[redacted]	14.895	
Catch-up rate: 1 year	Placebo	[redacted]	15.541	[redacted]
	Semaglutide 2.4mg	[redacted]	15.609	

Catch-up: 2 years	Placebo	[redacted]	15.557	[redacted]
	Semaglutide 2.4mg	[redacted]	15.634	
Catch-up: 4 years	Placebo	[redacted]	15.578	[redacted]
	Semaglutide 2.4mg	[redacted]	15.685	
Treatment duration: 3 years	Placebo	[redacted]	15.563	[redacted]
	Semaglutide 2.4mg	[redacted]	15.693	
Using QRISK3 for incidence of first CVD event in T2D	Placebo	[redacted]	15.423	[redacted]
	Semaglutide 2.4mg	[redacted]	15.524	

Table 6 Scenarios conducted on the ERG liraglutide-eligible subgroup (with list price for semaglutide 2.4mg)

Assumption	Treatments	Total costs	Total QALYs	Incremental ICER (£/QALY)
ERG base-case	Placebo	[redacted]	14.659	
	Liraglutide 3.0mg	[redacted]	14.745	[redacted]
	Semaglutide 2.4mg	[redacted]	14.788	[redacted]
Mean starting BMI of 37.5 kg/m^2	Placebo	[redacted]	15.580	[redacted]
	Liraglutide 3.0mg	[redacted]	15.651	[redacted]
	Semaglutide 2.4mg	[redacted]	15.694	[redacted]
Mean starting BMI of 42.5 kg/m^2	Placebo	[redacted]	14.596	[redacted]
	Liraglutide 3.0mg	[redacted]	14.672	[redacted]
	Semaglutide 2.4mg	[redacted]	14.726	[redacted]
Catch-up rate: 1 year	Placebo	[redacted]	14.638	[redacted]
	Liraglutide 3.0mg	[redacted]	14.694	[redacted]
	Semaglutide 2.4mg	[redacted]	14.718	[redacted]
Catch-up rate: 2 years	Placebo	[redacted]	14.649	[redacted]
	Liraglutide 3.0mg	[redacted]	14.722	[redacted]
	Semaglutide 2.4mg	[redacted]	14.760	[redacted]
Catch-up rate: 4 years	Placebo	[redacted]	14.667	[redacted]
	Liraglutide 3.0mg	[redacted]	14.765	[redacted]
	Semaglutide 2.4mg	[redacted]	14.814	[redacted]
Treatment duration: 3 years	Placebo	[redacted]	14.659	[redacted]
	Liraglutide 3.0mg	[redacted]	14.768	[redacted]
	Semaglutide 2.4mg	[redacted]	14.830	[redacted]
Using QRISK3 for incidence of first CVD event in T2D	Placebo	[redacted]	14.439	[redacted]
	Liraglutide 3.0mg	[redacted]	14.535	[redacted]
	Semaglutide 2.4mg	[redacted]	14.580	[redacted]

4. Appendices

Appendix 4.1 ERG results using proposed PAS price for semaglutide 2.4mg

We have updated our preferred base case, keeping all preferred assumptions except for the cost of microvascular complications, where we used the company's cost (£908.46), as explained in section 2.11 above. Results are shown here with the proposed PAS price for semaglutide 2.4mg and list price for liraglutide 3.0mg.

The cumulative effect of the ERG's preferred assumptions in the company's analyses are shown in Table 7 and Table 8. Applying the ERG updated preferred assumptions increases the company's base case ICER for semaglutide 2.4mg versus placebo (i.e. diet and physical activity) from £14,627 to £16,337 per QALY. For the liraglutide-eligible subgroup, while the ICER for liraglutide 3.0mg versus placebo increases from £32,439 to £38,969, semaglutide 2.4mg [redacted] compared to liraglutide 3.0mg.

Table 7 Cumulative change from the company base case to ERG base case with ERG's preferred assumptions (proposed PAS price for semaglutide 2.4mg)

Assumption	Treatments	Total costs	Total QALYs	ICER (£/QALY)
Company base-case	Placebo	[redacted]	[redacted]	£14,827
	Semaglutide 2.4mg	[redacted]	[redacted]	
Patients with pre-diabetes do not transition to T2D after CVD events	Placebo	[redacted]	[redacted]	£15,336
	Semaglutide 2.4mg	[redacted]	[redacted]	
+ Mean increase of weight by 0.296 kg per year	Placebo	[redacted]	[redacted]	£13,925
	Semaglutide 2.4mg	[redacted]	[redacted]	
+ Mean decrease in weight after age 66 years: 0.296 kg per year	Placebo	[redacted]	[redacted]	£14,393
	Semaglutide 2.4mg	[redacted]	[redacted]	
+ Age at which weight no longer increases: 66 years	Placebo	[redacted]	[redacted]	£14,414
	Semaglutide 2.4mg	[redacted]	[redacted]	
+ Annual cost of sleep apnoea, £274	Placebo	[redacted]	[redacted]	£16,337
	Semaglutide 2.4mg	[redacted]	[redacted]	
ERG base case	Placebo	[redacted]	[redacted]	£16,337
	Semaglutide 2.4mg	[redacted]	[redacted]	

Table 8 Cumulative change from company liraglutide-eligible subgroup results to the ERG liraglutide-eligible subgroup results with the ERG's preferred assumptions (proposed PAS price for semaglutide 2.4mg)

Assumption	Treatments	Total costs	Total QALYs	Incremental ICER (£/QALY)
Company base-case	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£32,439
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant

Patients with pre-diabetes do not transition to T2D after CVD events	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£34,287
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant
+ Mean increase of weight by 0.296 kg per year	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£34,891
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant
+ Mean decrease in weight after age 66 years: 0.296 kg per year	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£34,763
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant
+ Age at which weight no longer increases: 66 years	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£34,656
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant
+ Annual cost of sleep apnoea, £274	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£37,412
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant
ERG base case	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£37,412
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant

The ERG updated the scenario analyses on the base case and the liraglutide-eligible subgroup, shown below in Table 9 and Table 10. For the base case, the ICER for semaglutide 2.4mg versus placebo (i.e. diet and physical activity) varied between £12,867 (Scenario: Mean starting BMI of 42.5 kg/m^2) and £25,746 (Scenario: catch up rate of 1 year). For the liraglutide-eligible subgroup, semaglutide 2.4mg was dominant (i.e. cheaper and more effective) compared to liraglutide 3.0mg for all scenarios.

Table 9 Scenario analyses conducted on the ERG base case (proposed PAS price for semaglutide 2.4mg)

Assumption	Treatments	Total costs	Total QALYs	ICER (£/QALY)
ERG base-case	Placebo	[redacted]	[redacted]	£16,337
	Semaglutide 2.4mg	[redacted]	[redacted]	
Mean starting BMI of 32.5 kg/m^2	Placebo	[redacted]	[redacted]	£22,192
	Semaglutide 2.4mg	[redacted]	[redacted]	
Mean starting BMI of 37.5 kg/m^2	Placebo	[redacted]	[redacted]	£14,980
	Semaglutide 2.4mg	[redacted]	[redacted]	
Mean starting BMI of 42.5 kg/m^2	Placebo	[redacted]	[redacted]	£12,867
	Semaglutide 2.4mg	[redacted]	[redacted]	
Catch-up rate: 1 year	Placebo	[redacted]	[redacted]	£25,746
	Semaglutide 2.4mg	[redacted]	[redacted]	
Catch-up: 2 years	Placebo	[redacted]	[redacted]	£21,060
	Semaglutide 2.4mg	[redacted]	[redacted]	
Catch-up: 4 years	Placebo	[redacted]	[redacted]	£13,501
	Semaglutide 2.4mg	[redacted]	[redacted]	
Treatment duration: 3 years	Placebo	[redacted]	[redacted]	£17,747

	Semaglutide 2.4mg	[redacted]	[redacted]	
Using QRISK3 for incidence of first CVD event in T2D	Placebo	[redacted]	[redacted]	£15,157
	Semaglutide 2.4mg	[redacted]	[redacted]	

Table 10 Scenario analyses conducted on the ERG liraglutide-eligible subgroup (proposed PAS price for semaglutide 2.4mg)

Assumption	Treatments	Total costs	Total QALYs	Incremental ICER (£/QALY)
ERG base-case	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£37,412
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant
Mean starting BMI of 37.5 kg/m^2	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£45,336
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant
Mean starting BMI of 42.5 kg/m^2	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£42,443
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant
Catch-up rate: 1 year	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£61,395
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant
Catch-up rate: 2 years	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£45,736
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant
Catch-up rate: 4 years	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£31,833
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant
Treatment duration: 3 years	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£42,626
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant
Using QRISK3 for incidence of first CVD event in T2D	Placebo	[redacted]	[redacted]	
	Liraglutide 3.0mg	[redacted]	[redacted]	£33,646
	Semaglutide 2.4mg	[redacted]	[redacted]	Dominant

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