NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Semaglutide for reducing the risk of major adverse cardiovascular events in people with cardiovascular disease and overweight or obesity [ID6441]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Semaglutide for reducing the risk of major adverse cardiovascular events in people with cardiovascular disease and overweight or obesity [ID6441]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Novo Nordisk Ltd:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. HEART UK – The Cholesterol Charity
   b. Kidney Care UK
   c. Kidney Research UK
   d. Pumping Marvellous Foundation
   e. British & Irish Association of Stroke Physicians
   f. British Obesity and Metabolic Specialist Society
   g. Royal College of General Practitioners
   h. NHS England

4. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group (LRIG)

5. **External Assessment Group response to factual accuracy check of EAR**
   a. First factual accuracy check response
   b. Second factual accuracy check response

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

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and living with overweight or obesity [ID6441]

Company evidence submission

12th August 2025

File name	Version	Contains confidential information	Date
ID6441 semaglutide_CV prevention_obesity_consolidated doc_[REDACTED].docx	v1.0	No (redacted)	12th August 2025

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Abbreviations

ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AE	adverse event
AFT	accelerated failure time
AJ	Aalen-Johansen
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
BNF	British National Formulary
CAA	Commercial Access Agreement
CCS	chronic coronary syndrome
CEAC	cost-effectiveness acceptability curve
CEAF	cost-effectiveness acceptability frontier
CEP	cost-effectiveness plane
CHD	coronary heart disease
CI	confidence interval
CIF	cumulative incidence function
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
CPRD	Clinical Practice Research Datalink
CR	coronary revascularisation
CTR	clinical trial report
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcome trial
DALY	disability-adjusted life year
DBP	diastolic blood pressure
DSA	deterministic sensitivity analysis
EAC	event adjudication committee
eCRF	electronic case report form
eCVD	established cardiovascular disease
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
ESRD	end-stage renal disease

ETD	estimated treatment difference
ETR	estimated treatment ratio
FAS	full analysis set
FDA	US Food and Drug Administration
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HbA1c	glycated haemoglobin
HDL	high-density lipoprotein
HF	heart failure
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with Reduced ejection fraction
HHF	hospitalisation for heart failure
HR	hazard ratio
HRQoL	health-related quality of life
hsCRP	high-sensitivity C-reactive protein
HSUV	health state utility value
HTA	health technology assessment
HUA	hospitalisation for unstable angina
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
KCCQ CSS	Kansas City Cardiomyopathy Questionnaire clinical summary score
KDIGO	Kidney Disease: Improving Global Outcomes
LDL	low-density lipoprotein
LTFU	lost to follow-up
LV	left ventricular
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular event
MI	myocardial infarction
NHB	net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NSTEMI	non-ST segment elevation myocardial infarction
NYHA	New York Heart Association

OWSA	one-way sensitivity analysis
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PH	proportional hazards
PPPY	per patient per year
PRO	patient-reported outcomes
PSA	probabilistic sensitivity analysis
PTSD	post-traumatic stress disorder
PY	person year
QALY	quality-adjusted life year
RA	receptor agonist
RCT	randomised controlled trial
SAE	serious adverse event
SBP	systolic blood pressure
s.c.	subcutaneous(ly)
SLR	systematic literature review
SMI	severe mental illness
SmPC	summary of product characteristics
SoC	standard of care
SOC	system organ class
STEMI	ST segment elevation myocardial infarction
T2D	type 2 diabetes
TA	technology appraisal
TIA	transient ischaemic attack
UACR	urinary albumin-to-creatinine ratio
UK	United Kingdom
US	United States
VAS	visual analogue scale
VBA	Visual Basic for Application
WHO	World Health Organization
WRSSM	weight-related signs and symptoms measure
WTP	willingness to pay
YLL	years of life lost

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

Cardiovascular disease (CVD) is a leading cause of mortality and disability

- CVD describes a group of serious, chronic conditions affecting the heart and blood vessels, including coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease (PAD) (1)
- CVD can result in severe acute events such as myocardial infarction (MI) and strokes; CHD may also result in chronic conditions such as heart failure (HF) (2). PAD not only increases the risk of MI, stroke, vascular dementia, and renovascular disease, but is also associated with intermittent claudication and chronic limb-threatening ischaemia, leading to significant morbidity (3-5)
- Atherosclerosis is the common denominator in the pathophysiology of CHD, cerebrovascular disease and PAD (6). Modifiable risk factors for the development of atherosclerosis include diabetes, hypertension, hypercholesterolaemia, tobacco use and living with overweight and obesity (2). A raised body mass index (BMI), independent to other cardiovascular (CV) risk factors, increases the risk of developing CVD and the risk of death from CVD (7, 8)
- Atherosclerotic CVD is often mediated by systemic inflammation; there is a high prevalence of residual inflammatory risk, despite conventional pharmacological standard of care (SoC), among people with established CVD (eCVD) (9)
- Survivors of MI and stroke often have to live with long-term sequelae or disability, have an increased risk of subsequent, including more severe, CV events and face increased mortality after the first event (2, 6, 10-13).

CVD poses a heavy clinical, humanistic and economic burden

- CVD is the second most common cause of mortality in the United Kingdom (UK), with over 174,000 deaths a year (14), and the biggest cause of premature mortality (15). CVD is also the leading cause of death and disability in people living with overweight or obesity (16)
- In the United Kingdom (UK), around 1.4 million people (2.2% of the population) have survived an MI, just under 1.2 million (1.9%) have had a stroke or transient ischaemic attack (TIA), and just over 350,000 (0.6%) have PAD (2, 17)
- CV events lead to significant chronic impairments in health-related quality of life (HRQoL), caused by long-lasting functional impairments and psychosocial limitations (18). The quality of life burden on people with residual CV risk is particularly marked, as experiencing multiple CV events will lead to further deterioration in HRQoL (19)

- The total annual healthcare cost of CVD is estimated at £12 billion, and the total cost to the UK economy (including premature death, disability and informal costs) is estimated to be £28 billion each year (2)
- The NHS England 10-year Health Plan (2025) lists CVD as one of its early clinical priorities, and aims to reduce premature CVD mortality (20).

Despite treatment with contemporary therapies and risk factor management, people with eCVD are at high risk of additional CV events (21).

- People with eCVD are at high risk of subsequent events, with the highest risk in the 12 months following the first event, decreasing thereafter (22-24). People with eCVD are recognised as being at "highest" risk in the European Society of Cardiology (ESC) 2021 guidelines (25)
- Current guidelines recommend interventions that have been shown to reduce recurrent CV events by modifying lipids, blood pressure, diet and physical exercise, and controlling chronic kidney disease (CKD) and glycaemia in relevant populations. In spite of substantial reductions in CV mortality over decades, residual risk remains high (2, 9, 26); additionally, rates of premature mortality due to CVD have started to rise again since 2022, with more people under the age of 75 dying from CVD than at any time in the last 14 years (14, 27)

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist (RA) already used extensively in clinical practice for type 2 diabetes (T2D) and weight management, and is known to be generally well-tolerated.

- Semaglutide has been granted a UK marketing authorisation for the risk reduction of major adverse cardiovascular events (MACE; cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with eCVD and either obesity or overweight (BMI ≥27 kg/m^2) based on data from the SELECT trial (28)
- Semaglutide is also the only GLP-1 RA to be recommended by the ESC for the reduction of CV mortality, MI, or stroke in people with chronic coronary syndrome (CCS) and BMI >27 kg/m^2 (29)
- In addition to improving glycaemic control in T2D and contributing to weight reduction, semaglutide has been shown to exert beneficial effects on the CV system by decreasing blood pressure, reducing levels of blood lipids, attenuating the development of atherosclerotic plaques and reducing systemic inflammation (30-32).

1.1 Decision problem

The submission covers the technology's full marketing authorisation for cardiovascular risk reduction in adults with established cardiovascular disease (eCVD) and body mass index (BMI) ≥27 kg/m^2. The decision problem addressed in this submission is provided in Table 1, which outlines any differences from the National Institute for Health and Care Excellence (NICE) final scope (33).

Table 1: The decision problem

	Final scope issued by NICE /reference case (33)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with established cardiovascular disease (previous myocardial infarction, stroke or symptomatic peripheral arterial disease) and a BMI of at least 27 kg/m^2	As per scope	–
Intervention	Semaglutide (Wegovy)	As per scope	
Comparator(s)	Established clinical management for the prevention of CV events without semaglutide	As per scope	
Outcomes	The outcome measures to be considered include: • Heart function • Non-fatal stroke • Non-fatal myocardial infarction • Symptoms of heart failure • Hospitalisation for heart failure • All-cause hospitalisation • Mortality • Cardiovascular mortality • Kidney function • Development of diabetes	As per scope, except for “heart function”	The clinical studies identified did not include formal measures of heart function (such as ejection fraction) as outcomes

	Final scope issued by NICE /reference case (33)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Treatment discontinuation • Health-related quality of life • Adverse effects of treatment		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • People with BMI > 35 • People with previous myocardial infarction • People with previous stroke • People with symptomatic peripheral arterial disease • People with heart failure • People with chronic kidney disease • Subgroups according to calculated baseline risk of cardiovascular events	Cost-effectiveness in the following subgroups is reported: • People with BMI ≥35 • People with previous myocardial infarction • People with previous stroke • People with symptomatic peripheral arterial disease • People with heart failure • People with chronic kidney disease. Cost-effectiveness in subgroups according to calculated baseline risk of cardiovascular events is addressed through scenario analyses in the economic model.	Baseline risk of cardiovascular events was not calculated for individuals in SELECT and the study did not report findings stratified by risk. Other subgroups in the scope are identifiable from the SELECT data.
Special considerations including issues related to equity or equality	None	There is a known and acknowledged elevated cardiovascular risk in people of South Asian or sub-Saharan African ethnic origin (34, 35).	The overall population under consideration, namely people living with established cardiovascular disease and BMI ≥27 kg/m^2, represent a high-risk group where CVD and

	Final scope issued by NICE /reference case (33)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		Socioeconomic status and deprivation has an influence on the incidence and impact of obesity, compounded by the understanding that people living in England's most deprived areas are almost four times more likely to die prematurely from cardiovascular disease than those in the least deprived (36-38). Compared with the general population, people with severe mental illness are more likely to develop and die from preventable conditions such as cardiovascular disease (36).	BMI are both markers and drivers of inequality, relative to the UK population. In England, CVD is more prevalent in lower income households: 23% of adults aged 35 and over in the lowest income quintile reported any CVD, vs 16% in the 1st (highest income) quintile (39) Within this overall population there are further populations including but not limited to people of South Asian and sub-Saharan ethnicities, people who have a high deprivation index and those with co-existent severe mental illness who have elevated CV risk associated with poor health (34-38).

Abbreviations: BMI, body mass index; CV(D), cardiovascular (disease); MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; UK, United Kingdom.

1.2 Description of the technology being evaluated

The current assessment focuses on the use of semaglutide (Wegovy®) within its licensed indication for cardiovascular risk reduction in adults with established cardiovascular disease and BMI ≥27 kg/m^2, as reported in Table 2.

Semaglutide is administered subcutaneously (s.c.), starting with 0.25 mg and escalating to a target maintenance dose of 2.4 mg once weekly. Details of other indications associated with semaglutide can be found outlined in the summary of product characteristics (SmPC) documents, provided in the reference pack (28).

Table 2: Technology being evaluated

UK approved name and brand name	**Semaglutide 2.4 mg (Wegovy®)**
Mechanism of action	Semaglutide is a GLP-1 analogue that acts as a GLP-1 RA and selectively binds to and activates the GLP-1 receptor, the target for native GLP-1 (40). GLP-1 is a hormone that has multiple actions, which include maintaining glucose homeostasis, and regulating cardiovascular function, gastric motility and food intake (41). GLP-1 receptors are expressed in the pancreas, the central nervous system, the cardiovascular system, the kidneys, the gastrointestinal tract and the lungs (30). Semaglutide has been shown to exert beneficial effects on the CV system by decreasing blood pressure, reducing levels of blood lipids, attenuating the development of atherosclerotic plaques and reducing systemic inflammation, independently of body weight changes (30-32).
Marketing authorisation/CE mark status	Wegovy® has a UK marketing authorisation from the MHRA (granted in July 2024) (28).
Indications and any restriction(s) as described in the summary of product characteristics†	**Cardiovascular Risk Reduction** Wegovy® is indicated as an adjunct to a reduced-calorie diet and increased physical activity to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight (BMI ≥27 kg/m^2). Wegovy® is also indicated for weight management in adults and adolescents (28). Details of other indications associated with Wegovy® can be found in the SmPC, provided in the reference pack (See Appendix A).

<table>
<tr><td>Method of administration and dosage</td><td>
Method of administration
Wegovy® is administered once weekly at any time of the day, with or without meals.
It is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed. It should not be administered intravenously or intramuscularly.
The day of weekly administration can be changed if necessary, as long as the time between two doses is at least 3 days (>72 hours). After selecting a new dosing day, once-weekly dosing should be continued.

Posology
The maintenance dose of semaglutide 2.4 mg once-weekly is reached by starting with a dose of 0.25 mg. To reduce the likelihood of gastrointestinal symptoms, the dose should be escalated over a 16-week period to a maintenance dose of 2.4 mg once weekly (see Table 3). In case of significant gastrointestinal symptoms, consider delaying dose escalation or lowering to the previous dose until symptoms have improved. Weekly doses higher than 2.4 mg are not recommended.
Table 3: Dose escalation schedule
<table>
<tr><th>Dose escalation</th><th>Weekly dose</th></tr>
<tr><td>Week 1–4</td><td>0.25 mg</td></tr>
<tr><td>Week 5–8</td><td>0.5 mg</td></tr>
<tr><td>Week 9–12</td><td>1 mg</td></tr>
<tr><td>Week 13–16</td><td>1.7 mg</td></tr>
<tr><td>Maintenance dose</td><td>2.4 mg</td></tr>
</table>
</td></tr>
<tr><td>Additional tests or investigations</td><td>Not applicable</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>
Maintenance (28, 42)
2.4 mg presentation: £175.80 per pack. Each pack contains 1 pre-filled pen of 4 x 0.75 ml doses. Each dose contains 2.4 mg of semaglutide.

Titration (42)
1.7 mg presentation: £124.53 per pack (1 pre-filled pen)
1.0 mg presentation: £73.25 per pack (1 pre-filled pen)
0.5 mg presentation: £73.25 per pack (1 pre-filled pen)
0.25 mg presentation: £73.25 per pack (1 pre-filled pen)
Annual cost of treatment is as follows:‡
• Price list:
Year 1: £1,926
Year 2 onwards: £ 2,285
• CAA price:
</td></tr>
</table>

	Year 1: £[redacted] Year 2 onwards: £[redacted] Treatment with semaglutide is chronic.
Patient access scheme (if applicable)	There is no PAS in place for semaglutide (Wegovy®). Instead, a confidential CAA between Novo Nordisk and NHS England exists for semaglutide (Wegovy®), allowing the NHS to procure semaglutide [redacted]. The 1.7 mg and 2.4 mg presentations of semaglutide (Wegovy®) are provided to the NHS at a [redacted] of £[redacted] and £[redacted], respectively, and this price has been included in the economic analysis of this submission.

†Please that note that for type 2 diabetes semaglutide is branded as Ozempic® and has a different dose escalation schedule and maintenance dose; ‡Cost of treatment assuming maintenance dose of 2.4 mg. Please note that in practice the cost is likely to be lower, as not all people would be titrated to the highest dose.
Abbreviations: BMI, body mass index; CAA, commercial access agreement; CE, conformité Européenne; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; PAS, Patient Access Scheme; UK, United Kingdom.

1.2.1 Current submission and TA875

This current submission is distinct from TA875, with the key differences as follows:

- The population of interest, people living with eCVD and with BMI ≥27 kg/m^2, is different from the population covered by TA875 (people accessing weight management services)
- The indication in this submission is the prevention of secondary major adverse cardiovascular events (MACE), such as MI and stroke, which has already been recognised by the Medicines and Healthcare products Regulatory Agency (MHRA) as a separate indication from weight management (28). The eCVD population, as per the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial (Section 2.3.5), is expected to predominantly have a BMI <35 kg/m^2, and many of these people would therefore not be eligible for semaglutide treatment via current pathways for managing overweight/obesity, which have strict BMI eligibility criteria. Notably, analyses of SELECT have suggested that semaglutide may exert its beneficial effects on the CV system through mechanisms other than weight loss alone (Section 2.6.1.6)

- The care pathway for weight management is clearly different from that for CV risk reduction; the two indications have vastly different settings of care, adjuncts to care, prescribers, standard of care (SoC) and therapeutic aims. Notably, weight management pathways include specific and intensive diet and exercise-related interventions, whereas CV risk reduction SoC includes lifestyle advice and guidance alongside other therapeutic interventions.

Based on the above key differences, and considering there are distinctly different pathways for CV and weight management, it is expected that risk reduction of CV events in people with eCVD and a BMI ≥27 kg/m^2 should follow distinct, specific, mature CV care pathways.

1.3 Health condition and position of the technology being evaluated

1.3.1 Disease overview

Cardiovascular disease (CVD) is a general term used to describe a group of serious, chronic conditions affecting the heart and blood vessels, including coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease (PAD) (1). CHD can result in myocardial infarction (MI) and/or heart failure (HF), and increases the risk of having a stroke (2). Cerebrovascular disease can result in stroke, transient ischaemic attack (TIA), cognitive impairment and vascular dementia (2, 43). PAD not only increases the risk of MI, stroke, vascular dementia, and renovascular disease, but is also associated with intermittent claudication and chronic limb-threatening ischaemia, leading to significant morbidity (3-5). In the Phase 3 cardiovascular outcomes trial (CVOT) SELECT, which provides the main evidence base for this submission, the inclusion criteria required evidence of eCVD defined as at least one of the following: prior MI, prior stroke or symptomatic PAD (44). While this definition of eCVD was specific to the trial, the participants in SELECT constitute an easily identifiable, distinct population which aligns with the population covered by existing guidance for the secondary prevention of CV events (Section 1.3.4), such as the European Society of Cardiology (ESC) guidelines, which classify people with established atherosclerotic cardiovascular disease (ASCVD) as being in the “very-high-risk” group, the highest risk category in their classification (25).

Both MIs and strokes are medical emergencies, requiring immediate medical treatment (11, 45). An MI occurs when there is a decreased or complete cessation of the blood supply to a portion of the myocardium (heart muscle), resulting in myocardial injury (11). MIs can present as ST segment elevation MIs (STEMIs), where there is total occlusion of the coronary artery, or non-ST segment elevation MI (NSTEMI), where the obstruction may be partial (46). People experiencing an MI commonly present with chest pain or tightness which may radiate to the shoulder, jaw or arm which can be associated with nausea, sweating and shortness of breath (47). The overall prognosis depends on the extent of heart muscle damage, which can be measured by ejection fraction, i.e. the percentage of blood pumped out with each heartbeat (11, 48). People with preserved left ventricular (LV) function tend to have better outcomes, whereas people with reduced LV function, and therefore reduced ejection fraction, tend to have a worse prognosis (11). Nowadays, most people will survive an MI, but they are at high risk of experiencing a subsequent MI or other CV event (10), and/or develop HF due to myocardial damage impairing the heart's ability to pump: MI remains the most common cause of HF, which is diagnosed in approximately 13% of people at 30 days and 20–30% at 1 year after an MI (49). Survivors of MI may go on to experience complications, further described in Section 1.3.3.1.

HF is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise (50). Overall, HF can be divided into three distinct phenotypes, mostly based on the measurement of left ventricular ejection fraction (LVEF):

- HF with reduced ejection fraction (HFrEF): LVEF ≤40%
- HF with mildly reduced ejection fraction (HFmrEF): LVEF 41–49%
- HF with preserved ejection fraction (HFpEF): LVEF ≥50%

Severity of HF is usually graded using the New York Heart Association (NYHA) functional classification, where people in the least symptomatic group (Class I) have no limitation of physical activity, whereas people in the most symptomatic group (Class IV) are unable to carry any physical activity without discomfort (50).

A stroke, or cerebrovascular accident, is the result of ischaemia in an area of the brain, which results in cerebral infarction (45). People experiencing a stroke may present with dysarthria (slurred speech), facial and/or arm paralysis, and ataxia, depending on the area of the brain that is affected. Complications after a stroke are common and are further described in Section 1.3.3.1. Nowadays, the majority of people survive strokes, but their recovery is prolonged and most will remain disabled or experience neurological deficits (45).

PAD is a term used to describe a narrowing or occlusion of the peripheral arteries affecting the blood supply to the lower limbs (51). Intermittent claudication is the most common symptom of PAD: diminished circulation leads to pain in the lower limb on walking or exercise, which is relieved by rest (51, 52). Limb ischaemia can be either acute, when symptoms develop over less than two weeks, or chronic; in some cases, gangrene can develop in the toes or entire forefoot. The most severe cases can lead to limb-threatening ischaemia, necessitating emergency surgery, including amputation (2, 52). Even with treatment, the prognosis of PAD is generally guarded. If modifiable risk factors are left untreated, the disease is progressive. In addition, most people with PAD also have co-existence of cerebrovascular disease or CHD, which also increases the mortality rate, due to a higher risk of MI and stroke (3, 4, 52).

Although CVD may arise from different aetiologies, atherosclerosis is the common denominator in the pathophysiology of MI, strokes and PAD (6). Modifiable risk factors for atherosclerosis include diabetes, hypertension, hypercholesterolaemia, tobacco use, diet, lack of exercise and living with overweight and obesity; non-modifiable risk factors include age, sex and genetics (2). A raised BMI, independent of other CV risk factors, increases the risk of developing CVD and the risk of death from CVD (7, 8, 16). Multiple direct and indirect pathophysiological mechanisms link increased adiposity (body fat), particularly visceral/abdominal fat, to inflammation, CV risk and CVD (16).

Inflammation is a key driver of the steps involved in the formation of atherosclerotic plaque and the triggering of plaque rupture events (9). Furthermore, there is evidence that inflammation plays a significant role in accelerating atherosclerotic plaque growth in the immediate period after an MI. Despite conventional

pharmacological SoC, there is a high prevalence of residual inflammatory risk among people with eCVD, who have an increased risk of subsequent, more severe, CV events following the first event (6, 9).

1.3.2 Epidemiology

In the United Kingdom (UK), around 1.4 million people (2.2% of the population) have survived an MI, just under 1.2 million (1.9%) have had a stroke or TIA, and just over 350,000 (0.6%) have PAD (2, 17). Between 2003 and 2017, the prevalence (prevalence of ever having had a condition, in people aged 16 and over) of MIs in England (from 2.8% in 2003 to 2.5% in 2017) and strokes (2.3% in 2003 to 2.4% in 2017) has overall remained constant (14, 39). In 2017, the prevalence of MIs in England was almost 3 times higher in men than in women (3.8% vs 1.3%) but the difference was less pronounced for strokes (men: 2.7%, women: 2.0%). The incidence of MI and stroke was highest in people aged ≥75 (8.5% and 8.8%, respectively), followed by those aged 65–74 (7.4% and 5.1%, respectively) (39).

In 2023/2024, there were 81,814 confirmed MIs in England, Wales and Northern Ireland, of which 29,282 were higher-risk STEMIS and 52,632 were lower-risk NSTEMIs (53). There are around 100,000 strokes each year in the UK, accounting for 150,000 hospital admissions, of which 126,000 are in England and 8,000 in Wales (2, 54). Additionally, in England there are over 100,000 hospital admissions a year due to HF (55).

The mortality rates for CHD and cerebrovascular disease have decreased by around 60% in the past 20 years, and this has been a significant contributor to increased life expectancy for men and women in the UK (2, 26). In 2001, there were 251 deaths and 141 deaths per 100,000 from CHD and strokes, respectively; this fell to 102 deaths and 51 deaths per 100,000, respectively, in 2022 (14). This decrease is partly due to increased use of interventional procedures in the acute setting, i.e. thrombolysis in stroke care and percutaneous coronary intervention (PCI) in MI, to limit or prevent infarction (56, 57). However, demographic shifts mean that CVD-related mortality is increasing (26). Improvements in rates of premature mortality due to CVD have slowed down since 2010 and, alarmingly, have started to rise again since 2022 (27). More people under the age of 75 are dying from CVD

than at any time in the last 14 years, with the number of deaths in 2010 (46,672 deaths) steadily decreasing until 2017 (43,486), then increasing up to 2022 (48,637) (14).

More people surviving MIs and strokes (despite increases in CVD-related early mortality) means there is a growing population of people living with eCVD but, while 70% of people survive an MI (2), recurrent CV events are common for these people: recurrence rates for any CVD event or for subsequent revascularisation in the year after an MI are close to 50%, and up to 75% of people have a recurrent event within three years (10). In people surviving a first stroke, the risk of experiencing a recurrent stoke increases from 11.1% at 1 year to 39.2% at 10 years following that initial stroke (58). Overall, the highest risk of experiencing a subsequent CV event is in the 12 months following the first event, decreasing thereafter (22-24, 59). A Finnish retrospective study looking at outcomes post MI, unstable angina and stroke found that after the first CV event, there were rapid increases both in recurrent CV events and deaths during the next six months: after 180 days, 14.0% of people had suffered a recurrent CV event or had died (any cause). After the initial surge, the occurrence of both CV event recurrence and deaths stabilised to a relatively constant rate; at 5 years after the first CV event, 41.5% of people had suffered a recurrent CV event or died. Of those, 31.1% had died (26.8% without CV event recurrence and 4.2% post recurrence) and 10.4% had suffered a non-fatal recurrent event and were still alive (59). As described earlier, around 1.4 million people in the UK have had an MI, and almost 1.2 million people are on the stroke register, meaning there is a large population at high risk of experiencing a subsequent CV event (2, 10).

People living with a raised BMI are over-represented in these populations as overweight and obesity are independent risk factors for the development and progression of CVD, putting adults at increased risk of cardiovascular events (7, 8). Approximately 64% of people in the UK are considered to be overweight (BMI of ≥25–<30 kg/m^2) or obese (BMI ≥30 kg/m^2) (60-63). It is estimated that over 80% of people with CHD are overweight or obese (64). Similarly, people with diabetes are also over-represented in the eCVD population as diabetes increases the relative risk for CVD morbidity and mortality from up to 3-fold in men and up to 5-fold in women

compared with people without diabetes (65). In the UK, 4.4 million people are living with diabetes, and it is estimated that an additional 1.2 million could be living with undiagnosed type two diabetes (T2D) (66). Globally, CVD affects approximately 32% of all people with T2D (67).

1.3.2.1 CPRD analysis

To support this appraisal, data from a Clinical Practice Research Datalink (CPRD) analysis were used to explore the current epidemiology of eCVD in the UK (68). The CPRD collects data from a network of GP practices and links it to other health-related data to create a representative dataset of the UK population. A cohort of people with eCVD were identified and information extracted on their demographic characteristics and risk of CV events. The analysis found that:

- People with eCVD could be readily identified from routinely collected GP data: it is estimated that in 2017, [redacted]% of adults in the UK were living with eCVD and with overweight or obesity. By applying exclusion criteria from SELECT (Section 2.3.2), a SELECT-like population was identified, which accounted for around [redacted]% of the overall adult population
- In the SELECT-like population:
    - The mean age at index event (first CV event) was around [redacted] years for MI and [redacted] years for stroke
    - For all non-fatal CV events considered, event rates were highest in the first year post index event.

The CPRD data, including baseline characteristics, are explored further in Sections 2.3.5, 2.13 and in the economic analysis (Sections 3.3, 3.9.2, 3.11.3.1 and 3.14).

1.3.3 Disease burden

1.3.3.1 Clinical burden

CVD is the leading cause of death globally (1) and the second most common in the UK, with over 174,000 deaths a year (14). Furthermore, CVD is the biggest cause of premature mortality in the UK and, as described in Section 1.3.2, rates of mortality in people under the age of 75 have risen in the past few years (14, 27); it is estimated that one in four premature deaths in the UK are attributable to CVD (69). The NHS

England 10-year Health Plan (2025) lists CVD as one of its early clinical priorities, and states that one of its Plan for Change ambitions is to reduce premature CVD mortality (20). The overall number of deaths from CVD is slightly higher in men than in women (92,713 male deaths vs 82,114 female deaths), but the difference is much greater when it comes to premature mortality: twice as many men (33,031) than women (15,606) under the age of 75 died of CVD in 2022 (14). A study looking at years of life lost (YLL) due to premature mortality in the UK found that CHD was the leading cause of YLL for both men (1,637 YLL per 100,000 people) and women (610 YLL per 100,000 people); cerebrovascular disease accounted for 511 YLL and 401 YLL per 100,000 people in men and women, respectively (70). CVD is also the leading cause of death and disability in people living with overweight or obesity (16); in England (2019 data), mortality rates from CVD in people living with obesity were 4.4 deaths per 1,000 person years (PY) for men (30.1% of all-cause deaths) and 3.0 deaths per 1,000 PYs for women (31.9% of all-cause deaths) (71).

The clinical burden associated with eCVD is significant: the all-cause mortality rate in a cohort of UK patients who had experienced a single CV event was found to be 28.5 per 100 PYs in the 6 months following the first CV event, rising to 36.5 per 100 PYs following a second event (13). Mortality rates for people with HF are also high: despite optimal medical therapy including cardiac re-synchronisation therapy, only 65% of people in NYHA class IV HF are alive at a mean follow-up of 17 months (72). Mortality rates for HF overall are approximately 50% within five years of diagnosis (73).

Major cardiovascular events associated with eCVD, such as MI or stroke, have a high rate of morbidity. Survivors of MI may go on to experience complications of the original infarction (11, 74, 75), such as:

- Ischaemic complications: angina, re-infarction and/or infarct extension
- Mechanical complications: LV dysfunction and HF, cardiogenic shock, LV aneurysm, cardiac rupture, ischaemic ventricular septal defect and/or acute mitral regurgitation
- Thromboembolic complications: LV thrombus and/or in-stent thrombosis (following stent placement in PCI)

- Pericardial complications: early infarct-associated pericarditis, late pericarditis or post-cardiac injury syndrome, and/or pericardial effusion
- Arrythmias (irregular heartbeat): tachyarrhythmias, bradyarrhythmias, atrioventricular blocks, and/or ventricular arrhythmias.

Complications after a stroke are common. Complications in the early period following a stroke include (76):

- Haemorrhagic transformation of ischaemic stroke: one of the complications most likely to result in death in people with acute ischaemic stroke (77)
- Cerebral oedema
- Delirium
- Seizures
- Venous thromboembolism – pulmonary embolism has been associated with 13–25% of deaths in the early period following stroke
- Cardiac complications such as myocardial ischemia, congestive heart failure, atrial fibrillation, and arrhythmias
- Infection – people with stroke are at increased risk of infection including aspiration pneumonia, urinary tract infection, and cellulitis from infected pressure sores.

Long-term complications include (76):

- Mobility problems: hemiparesis or hemiplegia (80% of people with stroke; 40% have persistent altered arm function), ataxia (lack of coordination; 3% of people with ischaemic stroke), falls (73% of people), and/or spasticity and contractures (60% of people with stroke and hemiparesis)
- Sensory problems: up to 80% of people have some loss or alteration in sensations such as touch, temperature, and pain
- Problems with swallowing, hydration, and nutrition: dysphagia (difficulty in swallowing foods, fluids, and saliva) occurs in 40–78% of people with stroke

and is associated with aspiration pneumonia, disability, and death. Dehydration and malnutrition can also occur due to swallowing problems

- Fatigue (up to 53% of people)
- Pain: neuropathic pain or central post-stroke pain (5–20% of people), and/or musculoskeletal pain (shoulder pain affects 17–25% of people at 6 months following stroke)
- Other long-term complications include aphasia (impairment of language function), dysarthria, cognitive impairment, continence problems (urinary and faecal), anxiety and depression, sexual dysfunction and visual problems.

In the UK, strokes are the single biggest cause of severe disability (2). It is important to note that recurrent strokes are often more severe and disabling than the first event, and recurrent strokes continue to account for 25–30% of all strokes (12).

1.3.3.2 Quality of life burden

CV events can lead to significant chronic impairments in health-related quality of life (HRQoL), caused by long-lasting functional impairments and psychosocial limitations (18). The quality of life burden on people with residual CV risk is particularly high, as experiencing multiple CV events leads to further deterioration in HRQoL (19). Clinical expert feedback (received as part of individual interviews conducted by Novo Nordisk in 2025) has confirmed that following each CV event, the risk of another event increases alongside progression to frailty, and that more events result in a faster progression along the frailty continuum (78).

The sudden onset of an acute CV event, the actual risk of dying, and the perceived loss of control and helplessness during the event combine to represent a potentially traumatic situation, which can lead to the development of post-traumatic stress disorder (79). Even if they do not go on to develop PTSD, people who have experienced a CV event are still likely to develop anxiety and live in fear of a recurrent event, and have to cope with a change in their social status due to the reduction, suspension or removal of certain physical activities (18). According to the latest Health Survey for England, which used the EQ-5D questionnaire, 31% of adults aged 35 and over with CHD or stroke reported at least one severe health

problem, compared with 14% of those who reported diagnosed diabetes or hypertension (but no CHD or stroke) and 8% of those with none of these conditions (39).

People who have experienced an MI will often develop illness-related symptoms and post-MI fatigue in the recovery period (18). As previously described (Section 1.3.1), MI remains the most common cause of HF (49), and symptoms of HF such as shortness of breath, fatigue, and ankle swelling can significantly impact an individual's HRQoL (80). Additionally, depression affects 20% of people with HF and is severe in half of them; cachexia, a generalised wasting process characterised by loss of muscle with or without loss of fat mass, may be present in up to 15% of people with HF (50). A study looking at perceived HRQoL in MI survivors in England found that over two-thirds reported one or more problems affecting their HRQoL at baseline, and 30 days after MI. Moderate or severe problems were frequently reported for usual activities, pain, anxiety and mobility, both at baseline and at 12 months of follow-up. It was found that HRQoL more frequently declined in women, the elderly and people with comorbidities (81). In another study looking at HRQoL in survivors of MI, people with a recent MI were administered the EQ-5D questionnaire at 6-months intervals during their 2-year follow-up. The study found that people who suffered a non-fatal CV event during that period experienced a significant deterioration in their HRQoL (82). The study provided a consistent set of estimates of disutility observed after MI, stroke and HF, and therefore, the reported disutilities associated with CV events were selected for the economic model (Section 3.4.4).

As described in Section 1.3.2, improvements in the acute care setting means that a greater proportion of people are now surviving an acute stroke episode (56, 57). For many survivors and their families, this results in living a life affected by the long-term consequences of stroke, such as physical disability, cognitive impairment, fatigue and psychological problems such as depression and anxiety (57). A study looking at long-term data from the South London stroke register found that one in five people lived at least 15 years after a stroke and that poor functional, cognitive and psychological outcomes affected a substantial proportion of these long-term survivors. Fewer than one in five survivors were active in their daily lives at both 10 and 15 years, and psychological impairments were identified in approximately one-

third of survivors: at 15 years, 39.1% (95% confidence interval [CI]: 30.9%, 47.9%) screened positively for depression, 34.9% (95% CI: 27.0%, 43.8%) screened positively for anxiety, and 30.0% (95% CI: 19.5%, 43.1%) screened positively for cognitive impairment (57).

Similarly, CVD is a leading cause of disability in people living with obesity, and people living with both conditions often have concurrent chronic physical conditions, such as obstructive sleep apnoea and joint stress or damage, and/or psychological disorders, such as depression, other mood disturbances and eating disorders (16). A prospective study looking at HRQoL, as measured by the EQ-5D-5L and visual analogue scale (VAS) surveys, in people with established CHD found that increased BMI was strongly associated with poor QoL (BMI 29.6 ± 5.9 for poor QoL vs 28.8 ± 4.8 for good QoL, p<0.001) (83). Additionally, poor HRQoL has been reported to increase the risk of hospitalisations and subsequent CV events in survivors of MI, and people with obesity reported significantly lower EQ-5D index scores than those with a lower BMI (BMI <30: mean index score 0.86, standard deviation [SD]: 0.19 vs BMI ≥30: mean index score 0.75, SD: 0.25; p<0.001) (84).

1.3.3.3 Economic burden

In the UK, CVD poses a significant economic burden, with the total annual healthcare cost of CVD estimated at £12 billion, and the total cost to the UK economy (including premature death, disability and informal costs) estimated to be £28 billion each year (2). In England, there were about 1 million hospital admissions for CVD in 2023/24 (5.7% of all admissions), leading to almost 6 million bed days (12.3% of total bed days) (55). In the UK, costs associated with CV events are high and increase with subsequent events: in the 2006–2012 period, incremental CV event costs in the acute period (6 months post-event) were £3,504 after a first event and £3,968 after the second event. In the subsequent 30 months, incremental costs per year increased from £361 after a first event to £1,018 after a second event (13). Hospitalisation accounted for 95% of acute and 61% of long-term incremental costs. Notably, those data relate to people receiving lipid-modifying therapy prior to their first CV event, demonstrating that despite treatment, those people still carry a high risk of experiencing a CV event. Clinical expert opinion has confirmed that following

each CV event, the risk of another event impacts length of hospital stay and cost (78).

As described in Section 1.3.3.1, strokes are the single biggest cause of severe disability in the UK and are associated with long-term costs. In the UK, the mean cost of a new-onset stroke has been estimated at £45,409 (95% CI: 42,054–48,763) in the first year after stroke and £24,778 (95% CI: 20,234–29,322) in subsequent years. The aggregate societal cost of stroke is estimated to be £26 billion per year, including £8.6 billion for NHS and social care. The largest component of total cost is unpaid care (61%) and, given the high survival rates, £20.6 billion is related to ongoing care (85).

1.3.4 Clinical pathway of care

NICE has issued several guidelines for the risk assessment and reduction, including secondary prevention, of CV events. No NICE guidelines have been identified for the management of CV risk after a stroke, but in the UK, there are guidelines available from the Stroke Association and in Europe, from the ESC. However, there is not one standardised pathway for the secondary prevention of CV events, and guidelines vary depending on the type of CV event and where care is accessed (primary and/or secondary care). There are, however, similarities between all guidelines, notably in that they all recommend lipid-modifying therapy (statins) and lifestyle changes (including advice on diet and physical exercise) for risk reduction (Table 4). Notably, it is common for CV medication to be indicated as an adjunct to diet modification, when response to initial dietary and other non-pharmacological approaches (exercise, weight reduction) has been inadequate (86).

Table 4: Guidelines for the secondary prevention of CV events

Guideline	Condition	Setting	Population for secondary prevention	Drug therapy for secondary prevention	Non-pharmacological secondary prevention	Comment
NICE NG185 (87)	ACS	Primary and secondary care	People who have had an MI	• ACE inhibitors • ***Anti-platelet therapy*** • Beta blockers • ***Statins*** • Aldosterone antagonists (if HF and reduced LVEF) • DOAC	• Cardiac rehabilitation • ***Lifestyle changes***	NG185 covers both acute and long-term management of ACS. Most of the recommendations for secondary prevention of further events fall under long-term management. Not all people with ACS have had an MI, some have experienced an episode of unstable angina only

NICE NG238 (88)	CVD	Primary care	People who have CVD	• ***Lipid-lowering therapy:***
				  ○ ***Statins***
				  ○ PCSK9 inhibitors (alirocumab or evolocumab), ezetimibe and inclisiran¶
				• ***Anti-platelet therapy***
					• ***Lifestyle changes***	Although the guideline states that it "covers identifying and assessing risk of adults without eCVD", it also "covers…primary and secondary prevention of CVD"

NICE CG147 (89)	PAD	Primary and secondary care	People with PAD	• ***Statins*** • ***Anti-platelet therapy***	• ***Lifestyle changes***	

Guideline	Condition	Setting	Population for secondary prevention	Drug therapy for secondary prevention	Non-pharmacological secondary prevention	Comment
National Clinical Guideline for Stroke (90)	Stroke and TIA	Primary and secondary care	People who have had a stroke or TIA	• Blood pressure-lowering therapy (including, but not limited to ACE inhibitors) • ***Anti-platelet therapy*** • ***Statins***	• ***Lifestyle changes***	

2021 ESC Guidelines on CVD prevention in clinical practice (25)†	CVD prevention	Primary and secondary care	People who are at risk of CVD or who have CVD	• ***Lipid-lowering therapy:***
				  ○ ***Statins***
				  ○ Additional PCSK9 inhibitors and/or ezetimibe¶
				• ***Anti-platelet therapy***
				• Anti-coagulant therapy
				• Blood pressure-lowering therapy
				• Beta blockers (if LV dysfunction or systolic HF)
				• In patients with T2D and:
				  • ASCVD: GLP-1 RA or SGLT2 inhibitor
				  • CKD or HFrEF: SGLT2 inhibitor
					• ***Lifestyle changes***	

Guideline	Condition	Setting	Population for secondary prevention	Drug therapy for secondary prevention	Non-pharmacological secondary prevention	Comment
2024 ESC Guidelines for the management of CCS (29)†	CCS	Primary and secondary care	People who have had an MI	• ***Anti-platelet therapy*** • Anti-coagulant therapy • ***Lipid-lowering therapy:*** ○ ***Statins*** ○ PCSK9 inhibitors and/or ezetimibe¶ ○ Bempedoic acid§ • Blood pressure-lowering therapy • In patients with T2D: GLP-1 RA or SGLT2 inhibitor	• ***Lifestyle changes***	• There is a type IIa recommendation (defined as based on "weight of evidence/ opinion is in favour of usefulness/efficacy") that states "The GLP-1 RA semaglutide should be considered in CCS patients without diabetes, but with overweight or obesity (BMI >27 kg/m^2), to reduce CV mortality, MI, or stroke". In the CCS guidelines, GLP-1 RAs are recommended for management of T2D and obesity, but semaglutide is the only named GLP-1 RA for CV risk reduction • CCS refers to a range of conditions associated with myocardial ischaemia, but not all people with CCS have had an MI: some are

Guideline	Condition	Setting	Population for secondary prevention	Drug therapy for secondary prevention	Non-pharmacological secondary prevention	Comment
						asymptomatic, others have angina and others have LVD or HF of ischaemic origin
2024 ESC guidelines for the management of peripheral arterial and aortic diseases (91)	PAD	Primary and secondary care	People with PAD	• ***Anti-platelet therapy*** • Blood pressure-lowering therapy • ***Lipid-lowering therapy:*** ○ ***Statins*** ○ PCSK9 inhibitors and/or ezetimibe¶ ○ Bempedoic acid +/– PCSK9 inhibitor§ • In patients with T2D: GLP-1 RA or SGLT2 inhibitor	• ***Lifestyle changes***	
2023 ESC Guidelines for the management of ACS (92)	ACS	Primary and secondary care	People who have had an MI	• ***Anti-platelet therapy*** • Anti-coagulant therapy • ***Lipid-lowering therapy:*** ○ ***Statins*** ○ PCSK9 inhibitors and/or ezetimibe¶ • Beta blockers (if LVEF ≤40% regardless of HF symptoms)	• Cardiac rehabilitation • ***Lifestyle changes***	The guidelines cover both acute and long-term management of ACS. Most of the recommendations for secondary prevention of further events fall under long-term management. Not all people with ACS have had an MI, some have experienced an

Guideline	Condition	Setting	Population for secondary prevention	Drug therapy for secondary prevention	Non-pharmacological secondary prevention	Comment
				• ACE inhibitors • Aldosterone antagonists (if LVEF ≤40% and HF or diabetes) • Influenza vaccination		episode of unstable angina only

Interventions in bold italics are those common to all guidelines.
Lifestyle changes include changes to diet, physical exercise, alcohol consumption and smoking cessation.
†Class I recommendations only (except where otherwise stated): there is evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. (intervention is "recommended" or is "indicated"); ‡Specialist weight management services are usually tier 3 services, which are traditionally offered in secondary care but there are equivalent services with similar multidisciplinary team support in community settings in some places; ¶If lipid target not met with, or intolerance/contraindication to, statins; §If lipid target not met with ezetimibe, and intolerance to statins.
Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; CCB, calcium channel blocker; CCS, chronic coronary syndrome, CV, cardiovascular; CKD, chronic kidney disease; CVD, cardiovascular disease; DOAC, direct oral anti-coagulant; ESC, European Society of Cardiology; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes; TIA, transient ischaemic attack.

The NICE clinical guideline 185 provide recommendations for secondary prevention of acute coronary syndromes (ACS) for people who have had an MI (87). This includes treatment with angiotensin-converting enzyme (ACE) inhibitors, dual anti-platelet therapy (aspirin plus a second anti-platelet) unless they have a separate indication for anti-coagulation, beta-blockers, and statins. All patients should be given advice about and offered a cardiac rehabilitation program with an exercise component, including health education and stress management components, psychological and social support, and advice on sexual activity. A changed diet should be advised as part of lifestyle changes after an MI (specifically a Mediterranean-style diet), and advice should be given on alcohol consumption, regular physical activity, smoking cessation, and weight management in line with CG43 (now updated as CG189) (93).

The NICE clinical guideline 238 makes recommendations for the risk assessment and reduction of CV events including lipid modification to manage dyslipidaemia for people at risk of CVD and those who have CVD. Recommendations associated with secondary prevention focus on lifestyle changes, including behaviour change, cardioprotective diet, physical activity, weight management, alcohol consumption, smoking cessation, and avoidance of plant stanols/sterols. Lipid-lowering therapy is recommended for the secondary prevention of CVD, aiming for a low-density lipoprotein (LDL) cholesterol target of 2.0 mmol/l or less, or non-high-density lipoprotein (non-HDL) levels of 2.6 mmol/l or less. Initial treatment is recommended as atorvastatin, escalated to additional lipid-lowering treatments (such as alirocumab, evolocumab, ezetimibe and inclisiran) if targets are not met (88).

The National Clinical Guideline for Stroke states that people with a stroke should receive a comprehensive and personalised strategy for vascular prevention including medication and lifestyle factors, which should be implemented as soon as possible after the event and should continue long-term (90).

The NICE clinical guideline 147 states that people with PAD should be given information, advice, support and treatment regarding the secondary prevention of CVD, including smoking cessation, diet and exercise, lipid-lowering and anti-platelet therapies, and the prevention, diagnosis and management of diabetes and hypertension (89).

The 2021 ESC guidelines on CVD prevention, which concern people at risk of CVD and those who have CVD, state that anti-obesity medications with protective CVD effects may be considered for risk reduction (25). For people who have had an MI, the ESC recommends that secondary prevention should start as early as possible after the first event, and should aim to support healthy lifestyle choices, continue optimal pharmacological and cardio-protective treatment, and reach and sustain risk factor treatment targets (92). Finally, the 2024 ESC guidelines for the management of chronic coronary syndromes (CCS) state that semaglutide is the only GLP-1 RA that should be considered to reduce CV mortality, MI, or stroke in people with CCS and without diabetes, but with overweight or obesity (BMI >27 kg/m^2) (29). Additional ESC guidelines include management of ACS (92) peripheral and aortic arterial disease (91).

There are tools/risk calculators available for the assessment of risk on people with eCVD, such as the SMART-REACH model (94). The SMART-REACH model estimates life expectancy for individual people with eCVD, based on their clinical characteristics. To enable use of the SMART-REACH model in daily clinical practice, a calculator that allows estimation of life expectancy without recurrent CV events as well as 10-year CV risk has been developed, which can be also used to estimate potential gain in life expectancy by initiating additional therapy or increasing statin dose (the calculator is available at: https://uprevent.com/calculators/smartReach). Although not explicitly recommended for use, the SMART-REACH model is mentioned in the 2021 ESC guidelines for CVD prevention (Table 4 Patient categories and associated cardiovascular disease risk (25)). The SMART-REACH model is used to calculate lifetime risk in the economic model, in some of the scenario analyses (see Section 3.11.3).

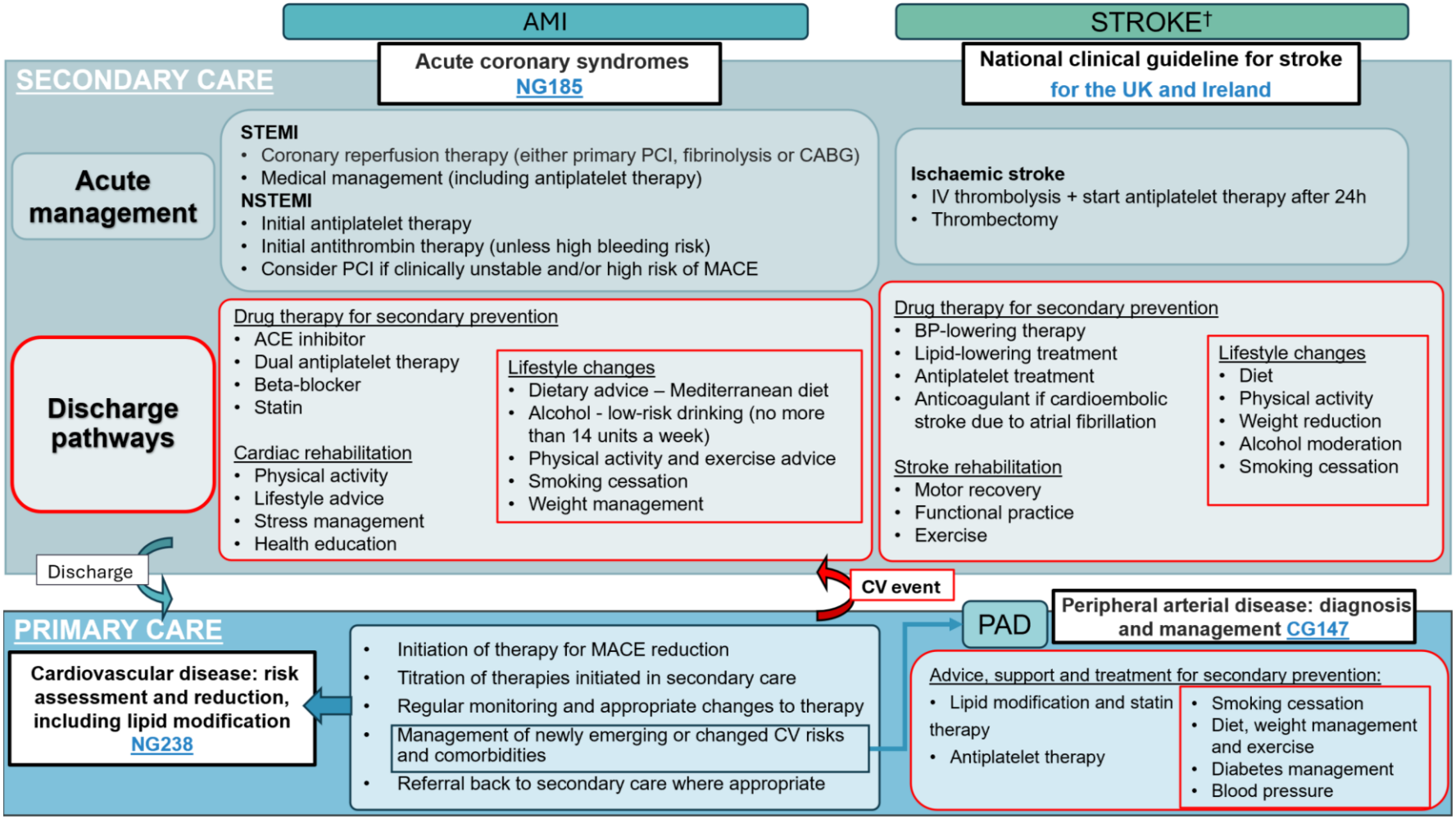
1.3.4.1 Current treatment pathway

Mortality rates from CVD fell substantially and consistently between the 1980s and around 2018 (2, 14). These improvements were associated with population level interventions for screening, risk assessment, and treatment. Therapies that have been shown to reduce CV event rates include drugs to modify lipids and blood pressure, lifestyle factors such as smoking and disease specific factors such as kidney function and glycaemia in relevant populations. The services available for

secondary prevention are therefore well established and people with eCVD and with BMI ≥27 kg/m^2 would already be eligible for these existing standard clinical care pathways. The pathways include (but are not necessarily limited to) cardiology clinics, primary care, cardiac rehabilitation, lipid-lowering services, cardiometabolic clinics and hypertension services, and are focused on long-term management of risk factors, including diet and physical exercise advice, with the intent of reducing future CV events and improving patient function.

The current treatment pathway for CV risk reduction in people with eCVD is depicted in Figure 1.

Figure 1: Current treatment pathway for CV risk reduction in eCVD, excluding semaglutide



†Acute management of TIA and subarachnoid haemorrhage not described in this diagram but available for National clinical guideline for stroke. For haemorrhagic strokes (ICH), acute management includes reversal of anticoagulant therapy if indicated, and BP lowering therapy if spontaneous ICH and SBP 150–200 mmHg.
Abbreviations: ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CV, cardiovascular; ICH, intracerebral haemorrhage; IV, intravenous; MACE, major adverse cardiovascular event; (N)STEMI, (non-)ST elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; (S)BP, (systolic) blood pressure; TIA, transient ischaemic attack; UK, United Kingdom.

1.3.5 Unmet need

Despite treatment with evidence-based pharmacotherapy, people with eCVD have residual CV risk, which is associated with more severe, recurrent CV events and the risk of morbidity and mortality they carry (21, 59). The risk of recurrent CV events is highest in the 12 months following the first event, therefore, there is an unmet need for prompt treatment to reduce morbidity associated with subsequent CV events and mortality (22-24, 59); the need to start treatment early after the first CV event was highlighted by clinical experts consulted at an advisory board conducted by Novo Nordisk in March 2024 (95). People with HF, which is diagnosed in up to 30% of people in the year following MI (49), still experience high morbidity and mortality: they are 2 to 3 times more likely to experience a stroke than people without HF (2), and only 50% are alive 5 years after diagnosis (73). Additionally, the symptoms associated with HF pose a heavy burden that significantly affects their HRQoL (80).

As described in Section 1.3.1, residual inflammation persists even with CV therapies such as statins and people with a raised BMI are at an even greater risk of subsequent CV events, as they have elevated levels of pro-inflammatory cytokines and high-sensitivity C-reactive protein (hsCRP), both of which are associated with an increased CV risk (7, 8, 96, 97). For people with eCVD who are living with overweight or obesity, the increased risk associated with obesity is an important therapeutic target for this high-risk population. However, most CVOTs in obesity have been inconclusive, with several trials being terminated prematurely (due to safety concerns, futility or where the study integrity had been compromised) and others failing to show superiority or efficacy of the trial drug (98-103). Therefore, there are no presently available treatments, other than semaglutide, with both evidence and licence supporting benefit in reducing MACE in people with eCVD and living with overweight and obesity.

1.3.6 Proposed positioning of semaglutide

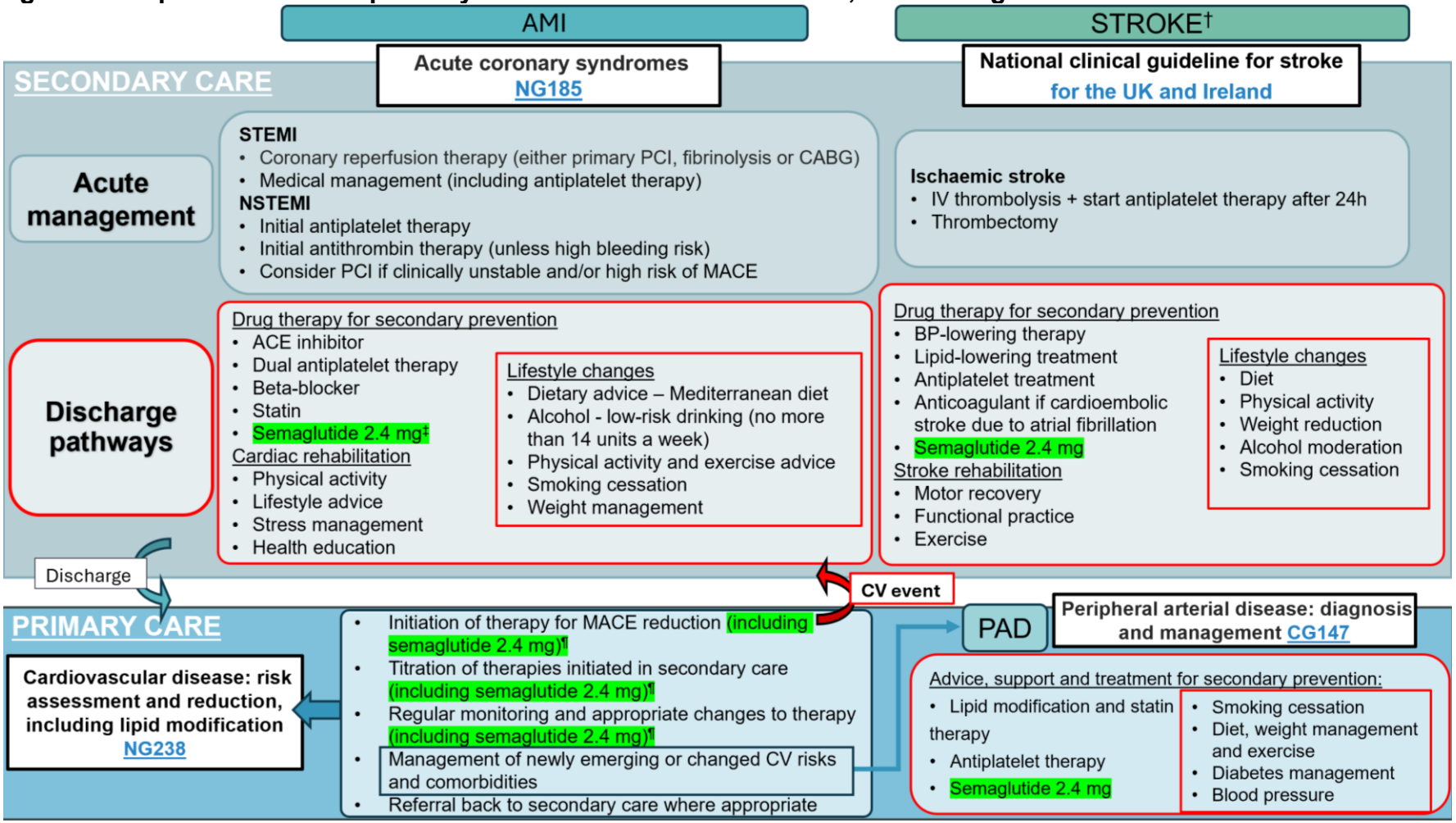
Management of eCVD aims to reduce mortality, morbidity and improve QoL by reducing the overall relative risk of secondary events and associated comorbidities. As people with eCVD are managed in both secondary and primary care, semaglutide could be prescribed in the following settings:

- Given the time-sensitive aspect of CV event management, as people are at highest risk of a recurrent event in the 12 months following the index event (22-24, 59), semaglutide would be well placed to be available as a treatment option in the post-event secondary care pathways
- Increasingly, CV risk reduction is undertaken in primary care as part of broader prevention strategies and management of high-risk populations. Therefore, semaglutide may also be initiated in this setting.

Semaglutide would not displace any of the current treatments for secondary prevention of CV events, and as semaglutide is expected to be added to the existing pathway of care, no additional services would have to be created.

The proposed positioning of semaglutide for risk reduction of MACE (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with eCVD and either obesity or overweight (BMI ≥27 kg/m^2) is presented in Figure 2.

Figure 2: Proposed treatment pathway for CV risk reduction in eCVD, with semaglutide



†Acute management of TIA and subarachnoid haemorrhage not described in this diagram but available for National clinical guideline for stroke. For haemorrhagic strokes (ICH), acute management includes reversal of anticoagulant therapy if indicated, and BP lowering therapy if spontaneous ICH and SBP 150–200 mmHg; ‡As per the 2024 European Society of Cardiology Chronic Coronary Syndrome Guidelines; ¶For CV indication only in people with BMI ≥27 kg/m^2.
Abbreviations: ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; CV, cardiovascular; ICH, intracerebral haemorrhage; IV, intravenous; MACE, major adverse cardiovascular event; (N)STEMI, (non-)ST elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; (S)BP, (systolic) blood pressure; TIA, transient ischaemic attack; UK, United Kingdom.

1.4 Equality considerations

CVD disproportionately affects already disadvantaged populations, widening existing health inequalities (7). In England, CVD is more prevalent in lower income households: 23% of adults aged 35 and over in the lowest income (5th) quintile reported any CVD, vs 16% in the 1st (highest income), 2nd and 3rd quintile each, and 18% in the 4th quintile (39). People living in England's most deprived areas are almost four times more likely to die prematurely from CVD than those in the least deprived (36, 37). If introduced into usual practice in the NHS, the health benefits of semaglutide would most likely benefit people in England's more deprived areas and of low socio-economic status.

There is a known and acknowledged elevated cardiovascular risk in people of South Asian or sub-Saharan African ethnic origin (34, 35). People of South Asian ethnicities have an increased risk of ischaemic heart disease, HF and hypertension, compared with people of White European origin (35). In England, data from the King's Fund have shown that the Black population has a higher prevalence of CVD and obesity (104); this is corroborated by findings from an American study which has found that age-adjusted obesity-related CVD mortality is greater in Black individuals than any other racial group (105). Additionally, people from Black, Asian and minority ethnic family backgrounds face an increased risk of chronic health conditions (including CVD) at a lower BMI (below BMI 25 kg/m^2) than people from a White family background, and NICE has issued targeted advice for these populations to increase awareness (93).

Additionally, there are gender inequalities with regards to CVD prevalence, outcomes and specific disease characteristics. Men are almost twice as likely to develop CHD than women, but women have higher mortality rates and worse prognosis after CV events (39, 106); women are often underdiagnosed for MIs, with the result that they do not always get the same timely interventions as men (27). In PAD, the outcomes in women tend to be worse than in men, chiefly because of the smaller diameter of the arteries, and women are more likely to develop complications and embolic events than men (52).

Finally, people with severe mental illness (SMI) are more likely to develop and die from preventable conditions such as cardiovascular disease compared with the general population (36). People with SMI have a 53% higher risk of developing CVD and a 85% higher risk of dying from CVD than the general population (69).

2 Clinical effectiveness

SELECT is the first Phase 3 study demonstrating that semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist (RA), improved cardiovascular (CV) outcomes in a non-diabetic population with established cardiovascular disease (eCVD) and body mass index (BMI) ≥27 kg/m^2, independent of weight loss (44)

- SELECT assessed CV outcomes with semaglutide added to standard of care (SoC) vs placebo + SoC
- In SELECT, semaglutide once weekly showed a statistically significant and clinically relevant benefit in reduction of major adverse cardiovascular events (MACE; hazard ratio [HR]: 0.80; 95% confidence interval [CI]: 0.72, 0.90; p<0.0001) vs placebo
- The beneficial effect of semaglutide was consistent across other endpoints including components of expanded MACE, with similar HRs for non-fatal myocardial infarction (MI; HR: 0.72; 95% CI: 0.61, 0.85), non-fatal stroke (HR: 0.93; 95% CI: 0.74, 1.15), a composite heart failure (HF) endpoint (HR: 0.82; 95% CI: 0.71, 0.96) and all-cause mortality (HR: 0.81; 95% CI: 0.77, 0.93)
- Semaglutide offered improvements in cardiometabolic risk factors, including glucose metabolism, blood pressure, lipid profile, and high-sensitivity C-reactive protein (hsCRP) vs placebo.

In SELECT, semaglutide was well tolerated, with a safety profile consistent with what has been observed in clinical practice, where it is used extensively

- Overall, the adverse events (AEs) reported in the trial were as expected for the enrolled trial population and the trial product
- The proportion of participants with serious adverse events (SAEs) was significantly lower with semaglutide than with placebo (33.4% vs 36.4% of participants, p<0.001). Most SAEs had resolved by the end of the trial.

Additional analyses of SELECT data and results from other trials of semaglutide in people with eCVD provide supportive evidence for the CV benefits of semaglutide

- The CV benefits shown in SELECT are supported by data from smaller trials of semaglutide showing consistent improvements in CV risk factors and improved quality of life in people with heart failure with preserved ejection fraction (HFpEF) (107, 108), and a trial of lower dose semaglutide showing CV benefits in people with diabetes (109)
- The CV benefits of semaglutide were applied to a population at high risk of recurrent CV events, on top of existing SoC; those benefits were consistent across endpoints and across pre-specified subgroups

- Pre-specified analyses using data from SELECT suggest that the magnitude of treatment effect with semaglutide on CV outcomes was independent of body weight at baseline and the extent of weight loss (<5% vs ≥5% at week 20), and that the CV benefits of semaglutide were first observed early in the trial (110, 111).

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify efficacy, safety, and health-related quality of life (HRQoL) data from clinical trials investigating semaglutide for the treatment of adults (≥18 years) with eCVD and overweight or obesity (BMI ≥27 kg/m^2). The SLR consisted of a de novo SLR conducted in September 2024 and an SLR update performed in May 2025. See Appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

In the de novo SLR, 1,804 publications were identified through the electronic database searches. After the removal of 500 duplicates, 1,304 publications were reviewed based on their titles and abstracts. A total of 1,090 publications were excluded at the title/abstract review stage, leaving 214 potentially relevant publications that were procured for full-text review. By reviewing the full-text publications, a further 185 publications were excluded. Hand-searching yielded 1 additional relevant publication, resulting in a total of 30 publications.

The 30 publications included in the de novo SLR reported on three unique trials. Thirteen publications reported on the SELECT trial, seven on the STEP-HFpEF trial, and one on the STEP-HFpEF DM trial. There were an additional nine publications reporting on pooled analyses, eight of which reported on STEP-HFpEF and STEP-HFpEF DM and the remaining publication reported on SELECT, STEP-HFpEF, STEP-HFpEF DM, and FLOW. Data from the FLOW trial (NCT03819153), which studied the effects of semaglutide on CKD in people with T2D, were not relevant to the SLR due to the use of a lower semaglutide dose (1.0 mg rather than 2.4 mg). The SLR update identified an additional 10 publications, eight of which reported on SELECT and two on STEP-HFpEF DM. Therefore, only the efficacy data for SELECT, STEP-HFpEF, and STEP-HFpEF DM are considered relevant to this appraisal. A summary of identified studies and primary publications is provided in Table 5; secondary publications for the identified studies are listed in Appendix B.

Table 5: Identified clinical effectiveness evidence

Study name, trial number, phase	Intervention	Comparator	Primary publication – Author, year/source†
SELECT (NCT03574597) Phase 3 RCT	Semaglutide 2.4 mg	Placebo	Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. New England Journal of Medicine. 2023;389(24):2221-32 (44)
STEP-HFpEF (NCT04788511) Phase 3 RCT			Kosiborod MN, Abildstrom SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. New England Journal of Medicine. 2023;389(12):1069-84 (107)
STEP-HFpEF DM (NCT04916470) Phase 3 RCT			Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, Hovingh GK, et al. Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. New England Journal of Medicine. 2024;390(15):1394-407 (108)

†All other publications are reported in Appendix B.
Abbreviations: RCT, randomised controlled trial.

There are a number of trials of semaglutide, some reporting CV-related outcomes, which are not considered relevant to the submission since the indications, populations studied, semaglutide doses and/or primary outcomes differ from those in the decision problem, and were therefore excluded from the SLR. An overview of other trials of semaglutide with CV-related outcomes is presented in Section 2.6.3 and Appendix J.

2.2 List of relevant clinical effectiveness evidence

As described in Section 2.1, the following three randomised controlled trials (RCTs) evaluating semaglutide were identified by the clinical SLR: SELECT, STEP-HFpEF and STEP-HFpEF DM.

Data from the Phase 3 trial SELECT form the main evidence base for this submission (Table 6). SELECT was prioritised as it aligns with the population of

interest in this submission; SELECT was also used to inform clinical parameters in the cost-effectiveness model.

Data from the Phase 3 trials STEP-HFpEF and STEP-HFpEF DM are presented as supportive evidence for the clinical CV benefit of semaglutide in people with HFpEF and BMI ≥30 kg/m^2, without and with T2D, respectively (Section 2.6.2).

Table 6: Clinical effectiveness evidence

Study	**SELECT (NCT03574597)**
Study design	Phase 3, randomised, double-blind, placebo-controlled, global, multicentre trial
Population	Adults with eCVD† and overweight or obesity (BMI ≥27 kg/m^2)
Intervention(s)	Semaglutide s.c., once weekly + SoC‡
Comparator(s)	Placebo s.c., once weekly + SoC‡
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem (in bold if used in model)	*Primary endpoint* • Time from randomisation to first occurrence of a composite endpoint consisting of CV death, non-fatal MI, or non-fatal stroke *Confirmatory secondary endpoints* • **Time from randomisation to CV death** • Time from randomisation to first occurrence of a composite HF endpoint consisting of: HF hospitalisation, urgent HF visit or CV death • **Time from randomisation to all-cause death** *Supportive secondary endpoints* • Time from randomisation to first occurrence of: o An expanded composite CV endpoint consisting of: CV death, non-fatal MI, non-fatal stroke, coronary revascularisation or unstable angina requiring hospitalisation o A composite endpoint consisting of all-cause death, non-fatal MI, or non-fatal stroke o **Non-fatal MI** o **Non-fatal stroke**

	○ **HF requiring hospitalisation or urgent HF visit** • Time from randomisation to first occurrence of: ○ A 5-component composite nephropathy endpoint[¶] consisting of: onset of persistent macroalbuminuria (UACR >300 mg/g), persistent 50% reduction in eGFR compared with baseline, onset of persistent eGFR <15 ml/min/1.73 m^2, initiation of chronic renal replacement therapy (dialysis or transplantation) or renal death ○ **HbA1c ≥48 mmol/mol (6.5%)** • For participants with a screening HbA1c <39 mmol/mol (5.7%): ○ Time from randomisation to HbA1c ≥39 mmol/mol (5.7%) • For participants with a screening HbA1c ≥39 mmol/mol (5.7%): ○ Proportion of participants with HbA1c <39 mmol/mol (5.7%) at each visit where HbA1c is assessed • Change from randomisation to Week 117 in glycaemic status (normoglycaemia, prediabetes or T2D) • Change from randomisation to Year 2/Week 104 (visit 14) in: ○ SBP (mmHg) ○ DBP (mmHg) ○ Heart rate (bpm) ○ hsCRP (mg/l) ○ **Body weight (%)** ○ Waist circumference (cm) ○ HbA1c (%, mmol/mol) change from screening (visit 1) to Year 2/Week 104 (visit 14) ○ Lipids (mg/dl): Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides • Patient reported outcome: Change from randomisation to Year 2/Week 104 (visit 14) in: ○ EQ-5D-5L questionnaire (EQ-5D index score (range 0 to 1) and EQ-5D-VAS (range 0 to 100) ○ Total score WRSSM • **Adverse effects of treatment**
All other reported outcomes	• Time from randomisation to first occurrence of: ○ **Coronary revascularisation** ○ **Unstable angina requiring hospitalisation** • Being current smoker at Year 2/Week 104 (visit 14) (yes/no) • Total number of hospitalised days from randomisation to end of trial

	• Total number of hospitalisations from randomisation to end of trial

†eCVD was defined as having one of the following: prior MI, prior stroke (ischaemic or haemorrhagic) or symptomatic PAD; ‡SoC covers the management of CV risk factors including medical treatment and healthy lifestyle counselling (including a reduced-calorie diet and physical activity). The comparator in the economic model is referred to as "established clinical management"; ¶The economic model uses a different nephropathy outcome and instead tracks chronic kidney disease stage (1–5).
Abbreviations: CV, cardiovascular; DBP, diastolic blood pressure; eCVD, established cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; HF, heart failure; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral arterial disease; SBP, systolic blood pressure; s.c., subcutaneously; SoC, standard of care; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio; VAS, visual analogue scale; WRSSM, weight-related sign and symptom measure.

2.2.1 Data presented in the submission

The primary evidence considered in this submission is based on the primary analysis of SELECT. Non-interventional follow-up of some of the SELECT participants is ongoing to confirm the long-term benefit of semaglutide (SELECT-LIFE, described in Sections 2.12, 2.13 and Appendix J). The SELECT data presented are from the publication by Lincoff et al, 2023 (44) and from the SELECT final clinical trial report (CTR) (112), and were used to support the application to the MHRA for marketing authorisation (28).

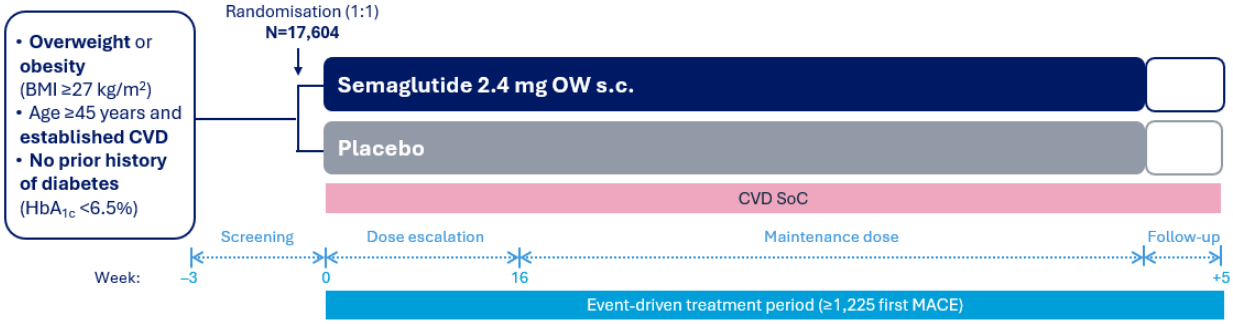
2.3 Summary of methodology of the relevant clinical effectiveness evidence – SELECT

2.3.1 Study design

SELECT was a Phase 3, multinational, multicentre, randomised, double-blind, placebo-controlled study comparing semaglutide with placebo both administered s.c. in 17,604 adults aged ≥45 years with eCVD (defined as having one of the following: prior MI, prior stroke or symptomatic PAD) and BMI ≥27 kg/m^2, without diabetes (44). The exclusion from SELECT of people with diabetes is discussed in Section 2.13; it is important to note that the licence for semaglutide covers people with eCVD and BMI ≥27 kg/m^2, with and without diabetes, as evidence for the CV benefits of semaglutide in people with T2D is available from the SUSTAIN-6 trial (NCT01720446), as described in Section 2.6.3. The primary objective of SELECT was to demonstrate that semaglutide s.c. once weekly lowers the incidence of MACE vs placebo, when added to SoC, in people with eCVD and BMI ≥27 kg/m^2. The details of SoC are described in Sections 2.3.3 and 2.3.4.

The SELECT participants represented a clinically relevant population as they were at an increased risk of a future CV event, due to having eCVD and BMI ≥27 kg/m^2 (as described in Section 1.3.5). The study was conducted across 804 sites in 41 countries, including 42 sites in the UK (of which 37 were in England and 1 in Wales) where a total of 933 participants were included in the full analysis set (FAS) (112). Figure 3 presents a study design schematic for SELECT.

Figure 3: SELECT study design



Source: Novo Nordisk data on file (113).
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; MACE, major adverse cardiovascular event; OW, once-weekly; s.c., subcutaneous; SoC, standard of care.

The trial included a 16-week dose escalation period, a maintenance period of 218 weeks, and a 5-week follow-up period. The trial was event driven, with trial closure occurring when the targeted number (≥1,225) of primary endpoint events was reached. A summary of the methodology for SELECT is presented in Table 7.

Table 7: SELECT study design and methodology

Primary objective	To demonstrate that semaglutide once weekly lowers the incidence of MACEs vs placebo both added to SoC in people with eCVD and overweight or obesity
Location	804 sites in 41 countries (Algeria, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Colombia, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Latvia, Malaysia, Mexico, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, UK, US)
Design	Randomised, double-blind, placebo-controlled trial
Randomisation	1:1
Population	People with BMI ≥27 kg/m^2 aged ≥45 years with eCVD (≥1 prior MI, prior stroke [ischaemic or haemorrhagic] or symptomatic PAD)
Intervention	Semaglutide (planned N of 8,750) Placebo (planned N of 8,750)
Study duration	Event-driven

Primary endpoint	Time from randomisation to first occurrence of MACE (composite endpoint consisting of CV death, non-fatal MI, or non-fatal stroke)
Confirmatory secondary endpoints of primary endpoint	Time from randomisation to: • CV death • First occurrence of a composite HF endpoint consisting of: HF hospitalisation, urgent HF visit, or CV death • All-cause death
Supportive secondary endpoints of primary endpoint	Time from randomisation to first occurrence of: • An expanded composite CV endpoint consisting of: CV death, non-fatal MI, non-fatal stroke, coronary revascularisation or unstable angina requiring hospitalisation • A composite endpoint consisting of: all-cause death, non-fatal MI, or non-fatal stroke • Non-fatal MI • Non-fatal stroke • Coronary revascularisation • Unstable angina requiring hospitalisation • HF requiring hospitalisation or urgent HF visit
Estimands	**Primary estimand** The primary estimand for all objectives is the intention-to-treat estimand, evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment and changes to background medication. **Secondary estimand** The secondary estimand (for primary and confirmatory secondary endpoints, as well as body weight) evaluates the effect of the randomised treatment intervention in all randomised participants had they remained on their randomised treatment for the entire trial. The estimand is addressed using the FAS and the first on-treatment observation period.

Source: SELECT final CTR (112).
Abbreviations: BMI, body mass index; CTR, clinical trial report; CV, cardiovascular; eCVD, established cardiovascular disease; FAS, full analysis set; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; PAD, peripheral arterial disease; SoC, standard of care; UK, United Kingdom; US, United States.

2.3.2 Eligibility criteria

A summary of the key eligibility criteria for SELECT is provided in Table 8.

Table 8: SELECT eligibility criteria

Key inclusion criteria	• Adults aged ≥45 years at the time of signing informed consent
	• BMI ≥27 kg/m^2
	• Established CVD as evidenced by at least one of the following:
	  ○ Prior MI
	  ○ Prior stroke (ischaemic or haemorrhagic)
	  ○ Symptomatic PAD, as evidenced by intermittent claudication with ABI <0.85 (at rest), or peripheral arterial revascularisation procedure, or amputation due to atherosclerotic disease

Key exclusion criteria	• MI, stroke, or hospitalisation for unstable angina or TIA within past 60 days prior to the day of screening • Presently classified as class IV HF (NYHA) • HbA1c ≥48 mmol/mol (6.5%) as measured by the central laboratory at screening • History of T1D or T2D (history of gestational diabetes was allowed) • Treatment with glucose-lowering agent(s) or GLP-1 RA within 90 days before screening
Randomisation criteria	People who fulfilled all inclusion criteria and who did not meet any exclusion criteria were eligible to be randomised in the trial provided that no MI, stroke, hospitalisation for unstable angina or TIA had occurred and no revascularisation had been planned between screening and randomisation

Source: Lincoff 2023 (44), SELECT final CTR (112).
Abbreviations: ABI, ankle-brachial index; BMI, body mass index; CTR, clinical trial report; CV(D), cardiovascular (disease); HbA1c, glycated haemoglobin; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral arterial disease; SoC, standard of care; TIA, transient ischaemic attack; T1D, type 1 diabetes; T2D, type 2 diabetes; UK, United Kingdom; US, United States.

2.3.3 Treatments administered

Participants followed a fixed dose escalation scheme, which aimed at participants reaching the maintenance dose of 2.4 mg after 16 doses (16 weeks). Dosing was once weekly with dose escalation every 4th week until the maintenance dose was reached. The dose escalations were: 0.24 mg, 0.5 mg, 1.0 mg, 1.7 mg, and 2.4 mg. If a participant did not tolerate the recommended target dose of 2.4 mg once-weekly, the participant could stay at a lower dose level, preferably 1.7 mg once-weekly. Extension of dose escalation intervals and treatment pauses could be considered if treatment with the trial product was associated with unacceptable adverse events (AE) or due to other circumstances.

Participants were instructed to inject semaglutide or placebo once weekly at the same day of the week (to the extent possible) throughout the trial (44). Semaglutide

or placebo were administered on top of SoC (referred to as “established clinical management” in the economic model, Section 3) which covers the management of CV risk factors including medical treatment and healthy lifestyle counselling (including a reduced-calorie diet and physical exercise).

2.3.4 Prior and concomitant therapies

Concomitant therapy (112): as described above, the trial evaluated semaglutide relative to placebo when added to current SoC. Investigators were encouraged to optimise treatment with medications affecting CV risk in accordance with treatment guidelines or local clinical practice. At randomisation, approximately [redacted]% of participants in each treatment group were receiving CV medication, primarily beta blockers, ACE inhibitors or angiotensin receptor blockers, and around 90% were receiving lipid-lowering drugs, as expected for a population with eCVD (Table 9). Additionally, leaflets providing healthy lifestyle advice were offered to participants, consistent with existing local SoC (related to diet, physical exercise, smoking and alcohol consumption) for adults with eCVD and BMI ≥27 kg/m^2 (114).

Table 9: Concomitant cardiovascular related medication ongoing at randomisation – FAS

	Semaglutide (N=8,803) n (%)	Placebo (N=8,801) n (%)
Cardiovascular medications	[redacted]	[redacted]
Beta blockers	6,182 (70.2)	6,175 (70.2)
ACE inhibitors	3,963 (45.0)	3,966 (45.1)
Angiotensin receptor blockers	2,618 (29.7)	2,569 (29.2)
Calcium channel blockers	2,407 (27.3)	2,331 (26.5)
ARNI	[redacted]	[redacted]
Lipid-lowering drugs	**7,928 (90.1)**	**7,929 (90.1)**
Statins	7,716 (87.7)	7,709 (87.6)
Bile acid sequestrants	[redacted]	[redacted]
Fibrates	213 (2.4)	266 (3.0)
Ezetimibe	1,188 (13.5)	1,144 (13.0)
PCSK9 inhibitors	177 (2.0)	162 (1.8)
Eicosapentaenoic acid ethyl ester	[redacted]	[redacted]
Bempedoic acid	[redacted]	[redacted]
Omega-3-acid ethyl ester	[redacted]	[redacted]
Other omega 3-triglycerides	[redacted]	[redacted]
Diuretics	[redacted]	[redacted]

	Semaglutide (N=8,803) n (%)	Placebo (N=8,801) n (%)
Thiazides	[redacted]	[redacted]
Loop diuretics	[redacted]	[redacted]
Aldosterone antagonists	[redacted]	[redacted]
Other potassium-sparing diuretics	[redacted]	[redacted]
Thiazide-like diuretics	[redacted]	[redacted]
Platelet aggregation inhibitors	**7,612 (86.5)**	**7,569 (86.0)**
Acetylsalicylic acid	6,909 (78.5)	6,860 (77.9)
$P2Y_{12}$ inhibitors	2,925 (33.2)	2,998 (34.1)
Other	77 (0.9)	104 (1.2)
Anti-thrombotic medications	**1,086 (12.3)**	**1,150 (13.1)**
Vitamin K antagonists	336 (3.8)	340 (3.9)
DOAC	738 (8.4)	784 (8.9)
Heparin	[redacted]	[redacted]
Anti-arrhythmic agents	[redacted]	[redacted]
Anti-angina agents	[redacted]	[redacted]

Source: Lincoff 2023 appendix (44), SELECT final CTR (112).
Abbreviations: ACE, angiotensin-converting enzyme; ARNI, angiotensin receptor-neprilysin inhibitor; CTR, clinical trial report; DOAC, direct oral anti-coagulant; FAS, full analysis set; PCSK9, proprotein convertase subtilisin/kexin type 9.

Only medication, other than trial product, that the participant was receiving at the time of screening or received during the trial for the following reasons was to be recorded in the electronic case report form (eCRF):

- To treat or prevent CV diseases (for example anti-hypertensives, lipid-lowering agents, anticoagulants, aspirin and other antiplatelet agents)
- To treat overweight or obesity (centrally acting anti-obesity drugs, peripherally-acting anti-obesity drugs, and herbal anti-obesity preparations were allowed; initiation of another GLP-1 RA was not allowed)
- To treat diabetes and diabetes complications (for participants who developed diabetes during the trial)
- To treat a SAE or medication which may provide further information on the SAE i.e. alternative aetiology
- In relation to a clinical trial for coronavirus disease 2019 (COVID-19) prevention or treatment

- In relation to an approved COVID-19 vaccine.

Prior therapies: the following prior therapies or planned procedures were not allowed (112):

- Treatment with glucose-lowering agent(s) within 90 days before screening
- Treatment with any GLP-1 RA within 90 days before screening
- Receipt of any investigational medicinal products within 30 days before screening
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.

2.3.5 Baseline characteristics

In SELECT, the baseline characteristics and demographics were overall well balanced across the treatment groups, with no obvious outliers (Table 10). Many of the baseline characteristics considered relevant to CV risk factors such as blood pressure, lipid levels and HbA1c were similar between the two groups.

Clinical experts at the advisory board considered that the SELECT population was broadly representative of people in the UK (95). Additional clinical expert opinion has confirmed that overall, there was no significant difference in the baseline characteristics of the SELECT population and those of a UK population with eCVD. They did note that there were some differences in ethnicity, reflecting North American trial inclusion, and that in the UK, there is a greater South-East Asian population, and a smaller Black American population than in North America. However, they thought the cohorts were very similar and therefore applicable to the UK as representative data (78).

The SELECT-like population identified from the CPRD analysis (Section 1.3.2.1) was similar to that of SELECT in terms of mean BMI (CPRD: [redacted]; SELECT: 33.3), percentage of those with multiple types of eCVD ([redacted]%; 8%) and percentage with chronic HF (CHF; [redacted]%; 24%). Differences between the two populations were seen in:

- Mean age: participants in SELECT were younger than the CPRD population (SELECT: 61.6 years; CPRD: [redacted] years). This could be partly because participants enrolled in clinical trials tend to be younger, but also because the CPRD dataset included those with long-term stable eCVD, as noted by a clinical expert (115); people in the CPRD cohort had experienced their first CV event between [redacted] years prior to inclusion in the database and therefore had had eCVD for longer than participants enrolled in SELECT (median time from qualifying CV event to randomisation: [redacted] years) (116)
- Types of eCVD: more participants had a previous MI in SELECT than in the CPRD cohort (SELECT: 67.7%; CPRD: [redacted]%), and fewer participants had a previous stroke (17.9% vs [redacted]%) or PAD (4.3% vs [redacted]%) in SELECT than in the CPRD cohort.

Despite those differences, the SELECT population represents the best available evidence and clinical feedback has confirmed it is broadly representative of what they see in practice (78, 95, 115).

Table 10: Baseline demographic and clinical characteristics – FAS

	Semaglutide (N=8,803)	Placebo (N=8,801)
Age, years, mean (SD)	61.6 (8.9)	61.6 (8.8)
Age group, years, n (%)		
<55	2,057 (23.4)	2,094 (23.8)
55 to <65	3,387 (38.5)	3,338 (37.9)
65 to <75	2,656 (30.2)	2,706 (30.7)
≥75	703 (8.0)	663 (7.5)
Sex, n (%)		
Female	2,448 (27.8)	2,424 (27.5)
Male	6,355 (72.2)	6,377 (72.5)
Region, n (%)		
Asia	1,100 (12.5)	1,101 (12.5)
Europe	3,326 (37.8)	3,366 (38.2)
North America	2,200 (25.0)	2,201 (25.0)
Other	2,177 (24.7)	2,133 (24.2)
Race or ethnicity, n (%)		
White	7,387 (83.9)	7,404 (84.1)
Asian	720 (8.2)	727 (8.3)
Black or African American	348 (4.0)	323 (3.7)

	Semaglutide (N=8,803)	Placebo (N=8,801)
Other	227 (2.9)	247 (3.1)
Hispanic or Latino	914 (10.4)	908 (10.3)
Not reported	95 (1.1)	76 (0.9)
Body weight, kg, mean (SD)	96.5 (17.5)	96.8 (17.8)
BMI, kg/m^2, mean (SD)	33.3 (5.0)	33.4 (5.0)
BMI, kg/m^2, n (%)		
27 to <30	2,555 (29.0)	2,469 (28.1)
30 to <35	3,693 (42.0)	3,781 (43.0)
35 to <40	1,687 (19.2)	1,659 (18.9)
40 to <45	579 (6.6)	595 (6.8)
≥45	289 (3.3)	297 (3.4)
Waist circumference, cm, mean (SD)	111.3 (13.1)	111.4 (13.1)
HbA1c, %, mean (SD)	5.78 (0.34)	5.78 (0.33)
<5.7%	2,925 (33.2)	2,980 (33.9)
≥5.7%	5,877 (66.8)	5,879 (66.1)
NR	1 (<0.1)	2 (<0.1)
Median high-sensitivity CRP level (IQR) – mg/l	1.87 (0.89–4.18)	1.80 (0.86–4.06)
CV inclusion criteria		
Only MI	5,962 (67.7)	5,944 (67.5)
Only stroke	1,578 (17.9)	1,556 (17.7)
Only PAD	376 (4.3)	401 (4.6)
Two or more inclusion criteria	718 (8.2)	719 (8.2)
Other[†]	181 (2.1)	193 (2.2)
Chronic heart failure, n (%)		
Yes	2,155 (24.5)	2,131 (24.2)
No	[redacted]	[redacted]
NR	[redacted]	[redacted]
Subclass		
HFpEF	[redacted]	[redacted]
HFrEF	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
NR	[redacted]	[redacted]
eGFR, ml/min/1.73 m^2, mean (SD)	82.4 (17.5)	82.5 (17.3)
Median lipid level (IQR) – mg/dl		
Total cholesterol	153 (131–182)	153 (131–183)
HDL cholesterol	44 (37–52)	44 (37–52)
LDL cholesterol	78 (61–102)	78 (61–102)
Triglycerides	134 (99–188)	135 (100–190)

	Semaglutide (N=8,803)	Placebo (N=8,801)
Mean systolic blood pressure (SD) – mmHg	131.0 (15.6)	130.9 (15.3)
Mean diastolic blood pressure (SD) – mmHg	79.4 (10.0)	79.2 (9.9)
Pulse – beats/min	68.9 (10.6)	68.6 (10.7)

Source: Lincoff 2023 including appendix (44), SELECT final CTR (112).
†This category included participants where it is unknown if they fulfilled only one or several criteria and participants who were randomised in error and did not fulfil any criteria.
Abbreviations: CRP, C-reactive protein; CTR, clinical trial report; CV, cardiovascular; FAS, full analysis set; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; NR, not reported; PAD, peripheral arterial disease; SD, standard deviation.

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

2.4.1 Analysis population and participant flow

All analyses (including safety) were based on the FAS, which comprised 17,604 participants (8,803 participants in the semaglutide group and 8,801 participants in the placebo group). Five randomised participant IDs were not included in the FAS because the participants had been randomised more than once. The FAS included 28 randomised participants (9 randomised to semaglutide and 19 to placebo) who were not exposed to the trial product. No participants in the FAS were excluded from the analyses.

Appendix B contains the participant flow for SELECT.

2.4.2 Observation periods

Participants were expected to visit the trial centre for assessment every 4 weeks during the first 26 weeks of treatment, then every 13 weeks until end of treatment. End of treatment and end of trial follow-up visits were scheduled according to trial completion. A trial completer was defined as a participant who either attended the end-of-trial follow-up visit or who died while active in the trial. A participant was considered lost to follow-up (LTFU) if the participant did not complete the trial and did not withdraw consent. The date of last contact with participant and status for LTFU were determined by investigator at trial completion.

The **in-trial observation period** was defined as the period from date of randomisation to one of the following dates, whichever came first:

- Date of follow-up visit
- Date when participant withdrew consent
- Date of last contact with participant for LFTU participants
- Date of death.

The in-trial observation period covered the time from randomisation to the last day of the trial, regardless of treatment adherence.

The **on-treatment period** was defined as the sum of all time points in the in-trial period where a participant had taken trial product within the previous 5 weeks. The on-treatment observation period for a participant could therefore consist of several time intervals with gaps between, if treatment had been paused for >35 consecutive days.

The **first on-treatment observation period** was defined as the on-treatment observation period until first time being off treatment for >35 days.

The end of trial occurred when the follow-up visit of the last participant, which took place 7 weeks after end of treatment, was completed.

2.4.3 Summary of statistical analyses

A summary of the statistical analyses undertaken in SELECT is provided in Table 11.

Table 11: Summary of statistical analyses

Hypothesis objective	The following superiority hypothesis was tested: H0: HR ≥1.0 against Ha: HR <1.0 in which HR is the hazard ratio for the comparison of semaglutide vs placebo. Superiority of semaglutide vs placebo was considered confirmed if the associated H0 is rejected based on nominal significance level derived from the pre-specified alpha spending based on the actual observed number of events available for the analysis. Final inference on termination was adjusted for the group sequential design using the likelihood ratio ordering for the p-value, 95% CI, and HR.
Statistical analysis	**Primary outcome** Analysis of the primary endpoint (time from randomisation to first occurrence of the composite MACE endpoint) was based on the FAS using the in-trial observation period. The HR comparing semaglutide vs placebo was estimated from a Cox proportional hazards model with treatment group as a fixed factor. Participants without a primary endpoint event prior to the in-trial end date were censored. **Secondary outcomes** Secondary endpoints were categorised as being confirmatory when they were analysed under multiplicity control, and as supportive if the endpoints were analysed without multiplicity control. • **Confirmatory secondary endpoints** The superiority hypothesis previously described was tested for all confirmatory endpoints under multiplicity control via a hierarchical testing scheme. The confirmatory endpoints were prioritised according to the below ordering and the testing procedure was stopped the first time an analysis failed to confirm superiority of the endpoint in question. The statistical significance levels of the confirmatory secondary endpoint analyses were pre-specified (see statistical analysis plan). The confirmatory secondary endpoints were defined as time from randomisation to: o CV death o HF composite o All-cause death. The confirmatory secondary endpoints were analysed using the same proportional hazards regression model described for the primary endpoint.

	• **Supportive secondary endpoints** Each supportive secondary time to event endpoint was analysed with the same Cox proportional hazards model as the primary endpoint. The estimated HR for the effect of semaglutide vs placebo was presented. Continuous supportive secondary endpoints (change from baseline to Year 2 [Week 104]) were analysed using multiple imputation. Missing values were defined as data that were planned to be observed but were not present in the database. The imputation model included baseline value as a covariate and was fitted to participants that were off treatment for the first time but had an observed data point at the specific visit. The fitted model was used to impute values for all participants that did not have an observed data point at the specific visit. Each of the completed data sets was analysed separately for Year 1 and Year 2 assessments by an analysis of covariance (ANCOVA) adjusted for treatment group as fixed factor and baseline value as covariate. Rubin's rule was used to combine the results to draw inference. Analysis of lipids and hsCRP were on logarithmic scale. The ETD (ETR for lipid and hsCRP endpoints) for the effect of semaglutide vs placebo was presented. The following endpoint was defined only for participants with a screening HbA1c ≥39 mmol/mol (5.7%): o HbA1c <39 mmol/mol (5.7%) at each visit where HbA1c was assessed The endpoint was analysed separately at Year 1 and Year 2 using a logistic regression model with treatment group as fixed factor and baseline HbA1c as covariate. The ratio (semaglutide vs placebo) between the estimated odds was presented together with 95% CIs. The following endpoint was defined only for participants with a screening HbA1c <39 mmol/mol (5.7%): o Time from randomisation to HbA1c ≥39 mmol/mol (5.7%) The endpoint was analysed using a Cox proportional hazards model with treatment group as fixed factor. The ratio (semaglutide vs placebo) between the estimated hazards was presented together with 95% CIs. • **Exploratory endpoints** The exploratory smoking endpoint was analysed separately at Year 1 and Year 2 using a binomial regression model with treatment group and baseline smoking status as fixed factors. The ratio (semaglutide vs placebo) between the estimated odds were presented alongside 95% CIs. Deterioration from baseline to Week 117 in glycaemic category (yes/no, where "yes" was determined by a change from normoglycaemia at baseline to prediabetes/diabetes at Year 2 or from prediabetes at baseline to diabetes at Year 2) was analysed using binomial regression model with treatment group as fixed factor and baseline HbA1c as covariate. The ratio (semaglutide vs placebo) between the estimated odds was presented with 95% CIs.

Sample size, power calculation	SELECT was designed to have 90% power to confirm superiority of semaglutide vs placebo for the primary endpoint. An assumed true HR for MACE was 0.83, which was based on a conservative assessment of the observed point estimate for the HR in the CVOT for semaglutide 1.0 mg in T2D (SUSTAIN-6), which was 0.74 (95% CI: 0.58, 0.95) for a similar definition of MACE. The number of events needed to be accrued was determined based on the log-rank test and the group sequential design allowing for interim testing. The Lans-DeMets alpha spending function, approximating O'Brien Fleming's stopping boundaries, was used with a study-wise (cumulative) one-sided type I error rate of 2.5%. In total, it was calculated that 1,225 first MACE would provide 90% power to confirm superiority. The annualised event rate for first MACE was based on the event rates observed in SUSTAIN-6 and LEADER, compared with event rates in other non-T2D trials (FOURIER, SCOUT, and IRIS) and adjusted to the inclusion and exclusion criteria of SELECT. In the SCOUT trial, which was conducted in people with overweight or obesity, the subgroup that only had eCVD had ~30% fewer MACE compared with the subgroup that had eCVD and T2D. Based on this literature, an event rate around half of that seen in LEADER and SUSTAIN-6 is assumed when including people with prior MI, prior stroke or symptomatic PAD but without T2D. Accordingly, the overall annualised event rate across the two treatment arms was assumed to be 2.0% (1.8% in the semaglutide arm and 2.2% in the placebo arm). Therefore, with a sample size of 17,500 participants randomised to either semaglutide or placebo, the 1,225 events were expected to be accrued at Month 59 (approximately 5 years).
Data management	Novo Nordisk was responsible for the data management of this trial including quality checking of the data. All participants' data relating to the trial were recorded on eCRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator was responsible for verifying that data entries were accurate and correct by signing the eCRF.

Source: Lincoff 2023 (44), SELECT final CTR (112).
Abbreviations: CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; eCRF, electronic case report form; eCVD, established cardiovascular disease; ETD, estimated treatment difference; ETR, estimated treatment ratio; FAS, full analysis set; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular event; MI, myocardial infarction; PAD, peripheral arterial disease; T2D, type 2 diabetes.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of SELECT, STEP-HFpEF and STEP-HFpEF DM was conducted using the NICE 7-item checklist for RCTs (117), the full details of which are provided in Appendix B. All three trials were clearly reported, with a low risk of bias. The trial with the lowest risk of bias was SELECT, which had no limitations when quality assessed using the NICE 7-item checklist. The only limitations of STEP-HFpEF and STEP-HFpEF DM were some limited differences in baseline characteristics between treatment arms, described in Appendix B.

The strengths and limitations of the clinical effectiveness evidence are discussed in Section 2.13.

2.6 Clinical effectiveness results

2.6.1 SELECT

This section presents the data for the analyses performed on the FAS, as described in Section 2.4.1. Primary endpoint data for both primary estimand (intention-to-treat estimand) and secondary estimands are presented here; secondary estimand data for all other endpoints are presented in Appendix K.

Primary estimand data from analyses performed on the FAS are the focus of this submission and are used in the economic model to demonstrate the effectiveness of semaglutide vs SoC.

2.6.1.1 Treatment dosing and discontinuation

As described in Section 2.3.3, participants followed a fixed-dose escalation scheme, which aimed at participants reaching the maintenance dose of 2.4 mg after 16 doses. After the initial 16 weeks of dose escalation, approximately [redacted]% of participants who were on-treatment at that time in the semaglutide group were receiving the planned 2.4 mg dose (112); this rose to approximately 77% after 104 weeks (44).

The median time from treatment initiation to discontinuation, i.e. the on-treatment observation period until first time being off treatment for over 35 days (Section 2.4.2), was [redacted]. In terms of permanent discontinuation of treatment, overall

discontinuation rates were marginally higher in the semaglutide group than in the placebo group (30.6% vs 27.0%). The most common reason for discontinuing treatment in both groups was AEs (semaglutide: 16.6%, placebo: 8.2%).

2.6.1.2 Primary endpoint: Time from randomisation to first occurrence of MACE

SELECT met its primary endpoint, showing a statistically significant reduction in the incidence of MACE with semaglutide vs placebo.

Primary estimand: during the in-trial observation period (median follow-up of [redacted]), there were 1,270 occurrences of first event adjudication committee (EAC)-confirmed MACE (semaglutide: 569 [6.5% of participants with ≥1 event]; placebo: 701 [8.0% of participants with ≥1 event] – Table 12). The estimated risk of experiencing a first MACE within any certain time from randomisation was lower for semaglutide compared with placebo, as supported by the separation of the curves shortly after trial initiation, and sustained throughout the trial (Figure 4). Primary analysis confirmed the superiority of semaglutide for time from randomisation to first MACE, with a 20% relative reduction in risk compared with placebo (hazard ratio [HR]: 0.80, 95% CI: 0.72, 0.90; p<0.0001).

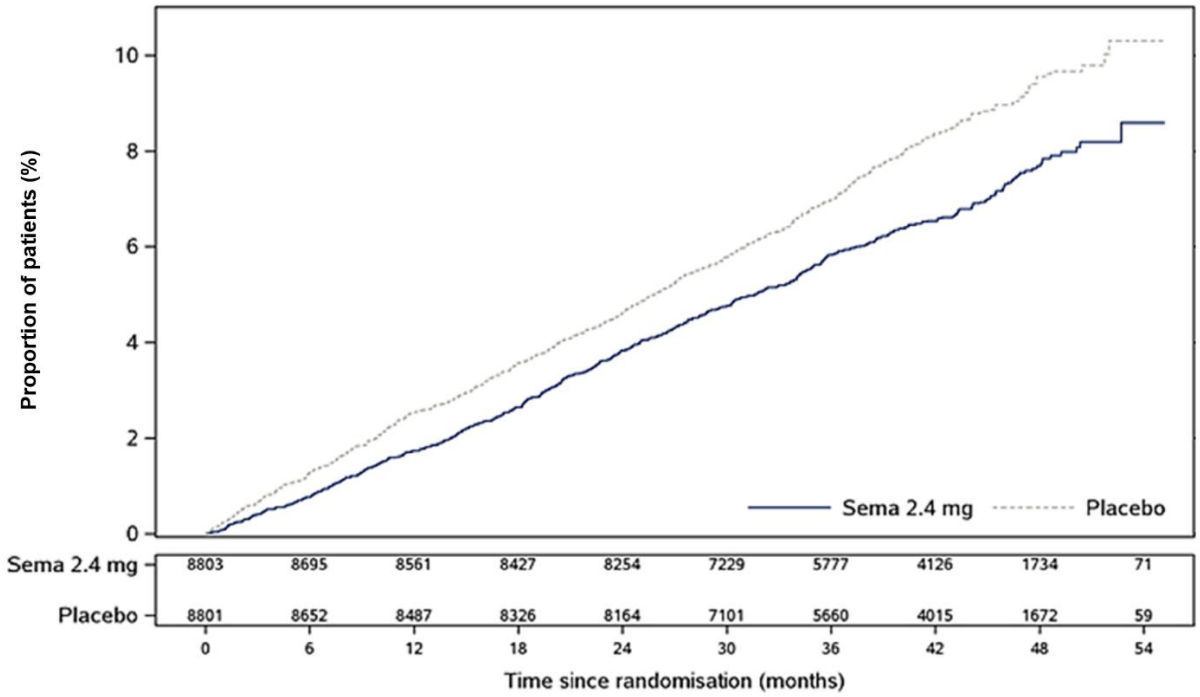
All three components of the primary endpoint contributed to the superior MACE reduction demonstrated by semaglutide vs placebo (Table 12).

Table 12: First EAC-confirmed MACE – distribution of events – primary estimand (FAS – in-trial)

	Semaglutide N=8,803	Placebo N=8,801	Hazard ratio (95% CI)	p-value
First EAC-confirmed MACE – n (%)†	569 (6.5)	701 (8.0)	0.80 (0.72, 0.90)	<0.0001
CV death	[redacted]	[redacted]	–	–
Non-fatal MI	[redacted]	[redacted]	–	–
Non-fatal stroke	[redacted]	[redacted]	–	–

Source: Lincoff 2023 (44), SELECT final CTR (112).
†The primary efficacy end point was a composite of death from cardiovascular causes, non-fatal MI, or non-fatal stroke. The hazard ratio, 95% CI, and p-value were adjusted for the group sequential design with the use of likelihood-ratio ordering, and the nominal two-sided significance level was 0.046
Abbreviations: CI, confidence interval; CTR, clinical trial report; CV, cardiovascular; EAC, event adjudication committee; FAS, full analysis set; MACE, major adverse cardiovascular event; MI, myocardial infarction.

Figure 4: Time from randomisation to first occurrence of EAC-confirmed MACE – cumulative incidence plot – primary estimand (FAS – in-trial)



Source: SELECT final CTR (112).
Abbreviations: CTR, clinical trial report; EAC, event adjudication committee; FAS, full analysis set; MACE, major adverse cardiovascular event; sema, semaglutide.

Secondary estimand: results of the supplementary analysis of data from the first on-treatment period were consistent with the primary estimand (Table 13 and Figure 5). During the first on-treatment observation period (median follow-up of [redacted]), there were [redacted] occurrences of first EAC-confirmed MACE (semaglutide: [redacted] [redacted]% of participants with ≥1 event]; placebo: [redacted] [redacted]% of participants with ≥1 event]); corresponding to a [redacted]% relative reduction in risk compared with placebo (HR: [redacted], 95% CI: [redacted]; p[redacted]). The distribution of the composite outcome events is shown in Table 13.

Table 13: First EAC-confirmed MACE – distribution of events – secondary estimand (FAS – first on-treatment period)

	Semaglutide N=8,794	Placebo N=8,782	Hazard ratio (95% CI)	p-value
First EAC-confirmed MACE – n (%)	[redacted]	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	–	–
Non-fatal MI	[redacted]	[redacted]	–	–

	Semaglutide N=8,794	Placebo N=8,782	Hazard ratio (95% CI)	p-value
Non-fatal stroke	[redacted]	[redacted]	–	–

Source: SELECT final CTR (112).
Abbreviations: CI, confidence interval; CTR, clinical trial report; CV, cardiovascular; EAC, event adjudication committee; FAS, full analysis set; MACE, major adverse cardiovascular event; MI, myocardial infarction.

Figure 5: Time from randomisation to first occurrence of EAC-confirmed MACE – cumulative incidence plot – secondary estimand (FAS – first on-treatment period)

Source: SELECT final CTR (112).
Abbreviations: CTR, clinical trial report; EAC, event adjudication committee; FAS, full analysis set; MACE, major adverse cardiovascular event; sema, semaglutide.

2.6.1.2.1. Supportive secondary endpoint of primary objective: First occurrence of EAC-confirmed events

The supportive secondary endpoint of the primary objective showed that semaglutide was more strongly associated with a reduced risk of EAC-confirmed events (upper bounds of 95% CI of HR were below 1) for Expanded MACE (CV death, non-fatal MI, non-fatal stroke, coronary revascularisation (CR), or unstable angina requiring hospitalisation), as well as the composite endpoint of All-cause death, non-fatal MI, or non-fatal stroke, and the individual, separate categories of Non-fatal MI and CR (from randomisation to the first occurrence of each event) (Table 14).

Table 14: First occurrence of EAC-confirmed events (FAS – in trial)

	Semaglutide (N=8,803) n (%)	Placebo (N=8,801) n (%)	Hazard ratio (95% CI)	p-value†
Expanded MACE‡	873 (9.9)	1,074 (12.2)	0.80 (0.73, 0.87)	[redacted]
All-cause death, non-fatal MI, or non-fatal stroke	710 (8.1)	877 (10.0)	0.80 (0.72, 0.88)	[redacted]
Non-fatal MI	234 (2.7)	322 (3.7)	0.72 (0.61, 0.85)	[redacted]
Non-fatal stroke	154 (1.7)	165 (1.9)	0.93 (0.74, 1.15)	[redacted]
CR	473 (5.4)	608 (6.9)	0.77 (0.68, 0.87)	[redacted]
Hospitalisation for unstable angina	109 (1.2)	124 (1.4)	0.87 (0.67, 1.13)	[redacted]
HF hospitalisation or urgent HF visit	97 (1.1)	122 (1.4)	0.79 (0.60, 1.03)	[redacted]

Source: Lincoff 2023 (44), SELECT final CTR (112).
†Two-sided p-value for test of no difference; ‡The Expanded MACE outcome included CV death, non-fatal MI, non-fatal stroke, CR, or unstable angina requiring hospitalisation.
Abbreviations: CI, confidence interval; CR, coronary revascularisation; CTR, clinical trial report; CV, cardiovascular; EAC, event adjudication committee; FAS, full analysis set; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction.

2.6.1.3 Confirmatory secondary endpoints

The confirmatory endpoints of time to CV death, time to first occurrence of HF composite endpoint and time to all-cause death all showed a consistent and beneficial effect of semaglutide vs placebo.

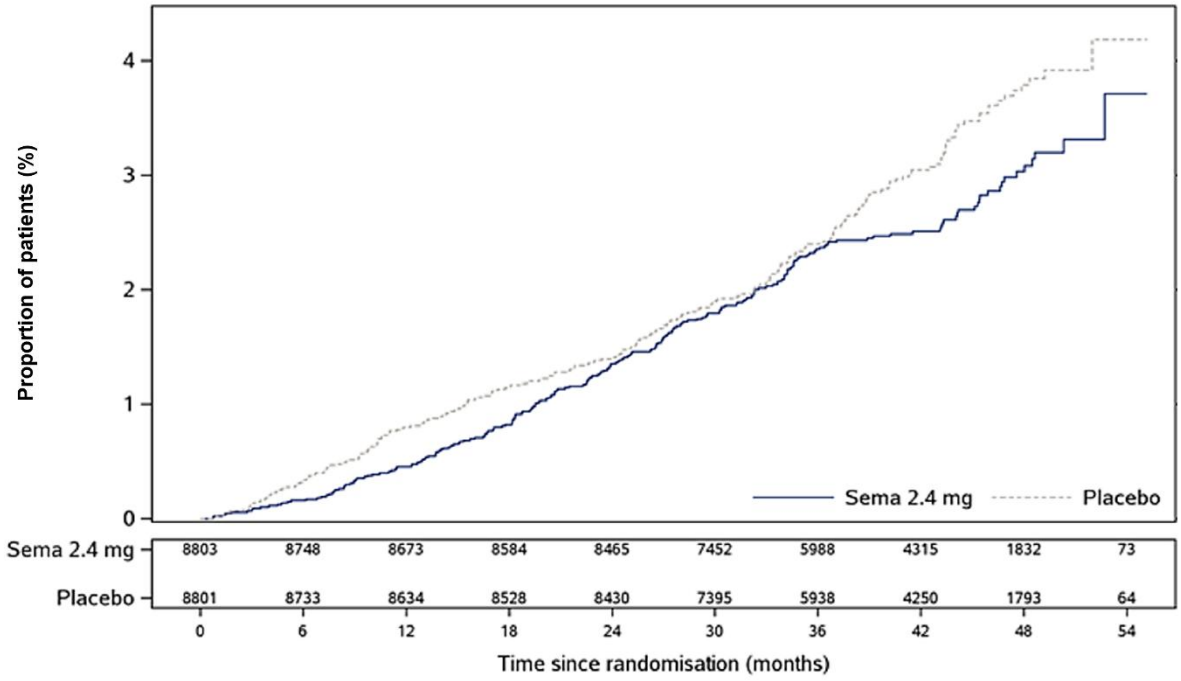
2.6.1.3.1. Time from randomisation to CV death

EAC-confirmed CV deaths occurred from time of randomisation and throughout the entire in-trial observation period (Figure 6); the potential impact of the COVID-19 pandemic on CV deaths is discussed in Section 2.6.1.7. There were fewer occurrences of EAC-confirmed CV death (including undetermined cause of death[a] (118)) among people receiving semaglutide (223 events [2.5% of participants with ≥1 event]) vs those receiving placebo (262 events [3.0% of participants with ≥1 event]). The estimated risk of CV death within any certain time was lower with semaglutide than with placebo as reflected in the separation of the curves from shortly after trial

[a] In SELECT, deaths of undetermined cause (i.e. deaths for which the EAC could not determine the cause) were presumed to be CV deaths in the statistical analyses of CV outcomes in accordance with Clinical Data Interchange Standards Consortium 2014 guidelines

initiation, and through the majority of the trial. Statistical analysis of time from randomisation to EAC-confirmed CV death resulted in an estimated HR of 0.85 (95% CI: 0.71, 1.01) for semaglutide relative to placebo. However, superiority of semaglutide over placebo was not confirmed (one-sided p[redacted]; nominal significance level [derived from the relevant alpha spending function]: 0.01148). The EAC-confirmed CV deaths during the in-trial period are summarised in Table 15.

Figure 6: Time from randomisation to EAC-confirmed CV death – cumulative incidence plot – primary estimand (FAS – in trial)



Source: SELECT final CTR (112).
Abbreviations: CTR, clinical trial report; CV, cardiovascular; EAC, event adjudication committee; FAS, full analysis set; sema, semaglutide.

Table 15: EAC-confirmed CV death (including undetermined cause of death) – primary estimand (FAS – in trial)

	Semaglutide N=8,803	Placebo N=8,801	Hazard ratio (95% CI)	p-value†
EAC-confirmed CV death – n (%)	223 (2.5)	262 (3.0)	0.85 (0.71, 1.01)	[redacted]
CV death	[redacted]	[redacted]	–	–
Sudden cardiac death	[redacted]	[redacted]	–	–
Stroke	[redacted]	[redacted]	–	–
HF	[redacted]	[redacted]	–	–
MI	[redacted]	[redacted]	–	–
CV procedure	[redacted]	[redacted]	–	–

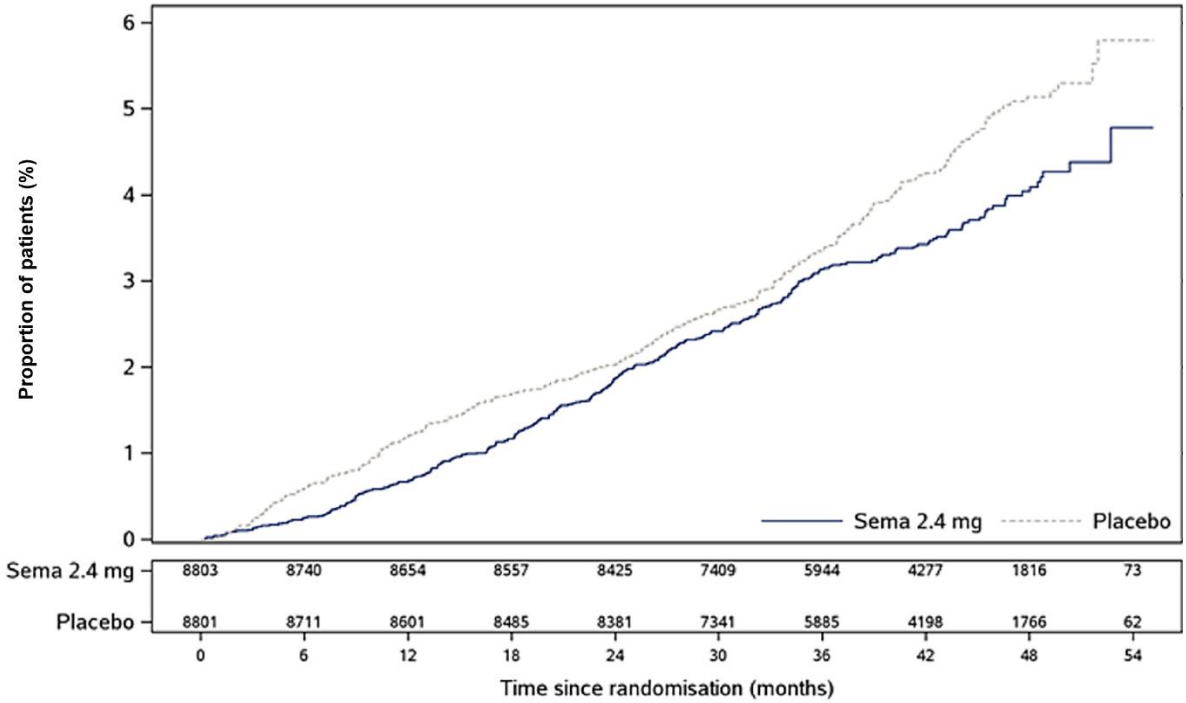
	Semaglutide N=8,803	Placebo N=8,801	Hazard ratio (95% CI)	p-value†
CV haemorrhage	[redacted]	[redacted]	–	–
Other	[redacted]	[redacted]	–	–
Undetermined cause of death	[redacted]	[redacted]	–	–

Source: Lincoff 2023 (44), SELECT final CTR (112).
†One-sided p-value. The nominal significance level was updated to 0.01148 using the alpha spending function described in the supplementary appendix of Lincoff 2023.
Abbreviations: CI, confidence interval; CV, cardiovascular; EAC, event adjudication committee; FAS, full analysis set; HF, heart failure; MI, myocardial infarction.

2.6.1.3.2. First occurrence of a composite HF endpoint

Throughout the trial, the estimated risk of experiencing a first composite HF event (defined as HF hospitalisation, urgent HF visit, or CV death) was lower for semaglutide than for placebo (Figure 7). First occurrence of a composite HF endpoint was reported in 3.4% (300 events) of participants in the semaglutide group and 4.1% (361 events) of participants in the placebo group (both proportions were among participants with ≥1 event) (Table 16). Semaglutide was associated with a 18% lower relative risk of composite HF outcome events compared with placebo – estimated HR of 0.82, 95% CI: 0.71, 0.96 (superiority of semaglutide vs placebo for time from randomisation to first composite HF outcome was not tested as per the pre-specified hierarchical testing scheme – described in Table 11).

Figure 7: Time from randomisation to first EAC-confirmed composite heart failure outcome – cumulative incidence plot – primary estimand (FAS – in trial)



Source: SELECT final CTR (112).
Abbreviations: CTR, clinical trial report; CV, cardiovascular; EAC, event adjudication committee; FAS, full analysis set; sema, semaglutide.

Table 16: First EAC-confirmed composite HF outcome – primary estimand (FAS – in trial)

	Semaglutide N=8,803	Placebo N=8,801	Hazard ratio (95% CI)	p-value
First EAC-confirmed composite HF event – n (%)	300 (3.4)	361 (4.1)	0.82 (0.71, 0.96)	Not tested
CV death	[redacted]	[redacted]	–	–
HF	[redacted]	[redacted]	–	–
HF requiring hospitalisation	[redacted]	[redacted]	–	–
Urgent HF visit	[redacted]	[redacted]	–	–

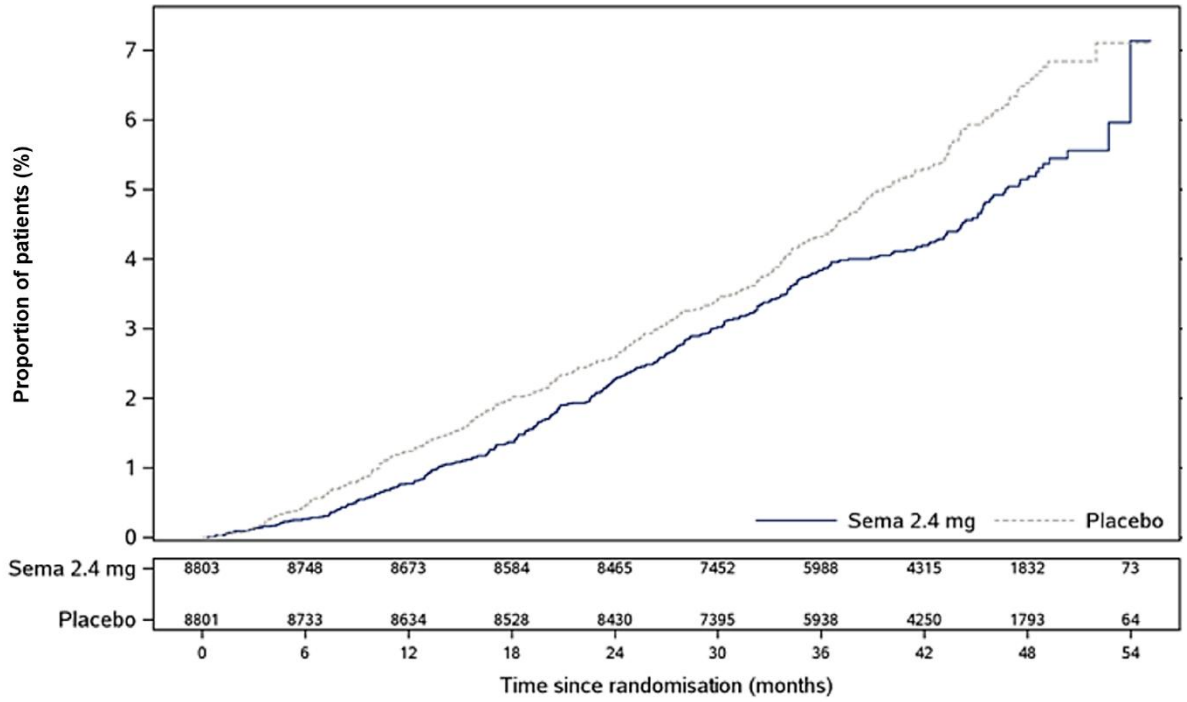
Source: Lincoff 2023 (44), SELECT final CTR (112).
Abbreviations: CI, confidence interval; CTR, clinical trial report; CV, cardiovascular; EAC, event adjudication committee; FAS, full analysis set; HF, heart failure.

Further evidence of the clinical benefits of semaglutide on HF outcomes is presented in Section 2.6.2.

2.6.1.3.3. Time from randomisation to all-cause death

As confirmed by the EAC, 833 participants in total died during the in-trial observation period. In comparison with placebo, the estimated risk of all-cause death was lower for semaglutide, as illustrated in the separation of the curves from shortly after trial initiation, and throughout the trial (Figure 8). All-cause deaths observed were lower with semaglutide (375 [4.3%] participants) compared with placebo (458 [5.2%] participants). Statistical analysis resulted in an estimated HR of 0.81, 95% CI: 0.71, 0.93 for semaglutide relative to placebo, corresponding to a 19% lower relative risk of all-cause death with semaglutide (the superiority of semaglutide vs placebo for time from randomisation to all-cause death was not tested, as per the pre-specified hierarchical testing scheme described in Table 11). The distribution of events for EAC-confirmed all-cause death can be found in Table 17.

Figure 8: Time from randomisation to EAC-confirmed all-cause death – cumulative incidence plot – primary estimand (FAS – in trial)



Source: SELECT final CTR (112).
Abbreviations: CTR, clinical trial report; EAC, event adjudication committee; FAS, full analysis set; sema, semaglutide.

Table 17: EAC-confirmed all-cause death – primary estimand (FAS – in trial)

	Semaglutide N=8,803 n (%)	Placebo N=8,801 n (%)	Hazard ratio (95% CI)	p-value
All-cause death	375 (4.3)	458 (5.2)	0.81 (0.71, 0.93)	Not tested
CV death	[redacted]	[redacted]	–	–
Undetermined cause of death	[redacted]	[redacted]	–	–
Non-CV death	[redacted]	[redacted]	–	–
Infection	[redacted]	[redacted]	–	–
Malignancy	[redacted]	[redacted]	–	–
Trauma	[redacted]	[redacted]	–	–
Pulmonary causes	[redacted]	[redacted]	–	–
Suicide	[redacted]	[redacted]	–	–
Neurological causes	[redacted]	[redacted]	–	–
GI causes	[redacted]	[redacted]	–	–
Haemorrhage	[redacted]	[redacted]	–	–
Hepatobiliary causes	[redacted]	[redacted]	–	–

	Semaglutide N=8,803 n (%)	Placebo N=8,801 n (%)	Hazard ratio (95% CI)	p-value
Non-CV procedure or surgery	[redacted]	[redacted]	–	–
Prescription drug reaction or overdose	[redacted]	[redacted]	–	–
Renal	[redacted]	[redacted]	–	–
Other	[redacted]	[redacted]	–	–

Source: Lincoff 2023 (44), SELECT final CTR (112).
Abbreviations: CI, confidence interval; CTR, clinical trial report; CV, cardiovascular; EAC, event adjudication committee; FAS, full analysis set; GI, gastrointestinal.

2.6.1.4 Supportive secondary endpoints of secondary objective

Supportive secondary endpoints of the secondary objective measured the effect of semaglutide relative to placebo in terms of kidney function, glucose metabolism, CVD risk-related factors, body weight and patient-reported outcomes (PRO). Treatment with semaglutide showed beneficial effects on:

- Kidney function, as demonstrated by a lower risk of kidney function deterioration vs placebo
- Glucose metabolism, as demonstrated by a reduction in HbA1c from baseline and by fewer participants developing prediabetes and T2D vs placebo
- CVD-risk related factors, with greater decreases in systolic blood pressure (SBP), diastolic blood pressure (DBP) and hsCRP vs placebo
- Body weight changes, with significantly greater decreases in body weight (%) and waist circumference (cm) vs placebo
- HRQoL, as demonstrated by greater improvements in EQ-5D-5L, EQ-5D-VAS and weight-related signs and symptoms measure (WRSSM) scores vs placebo.

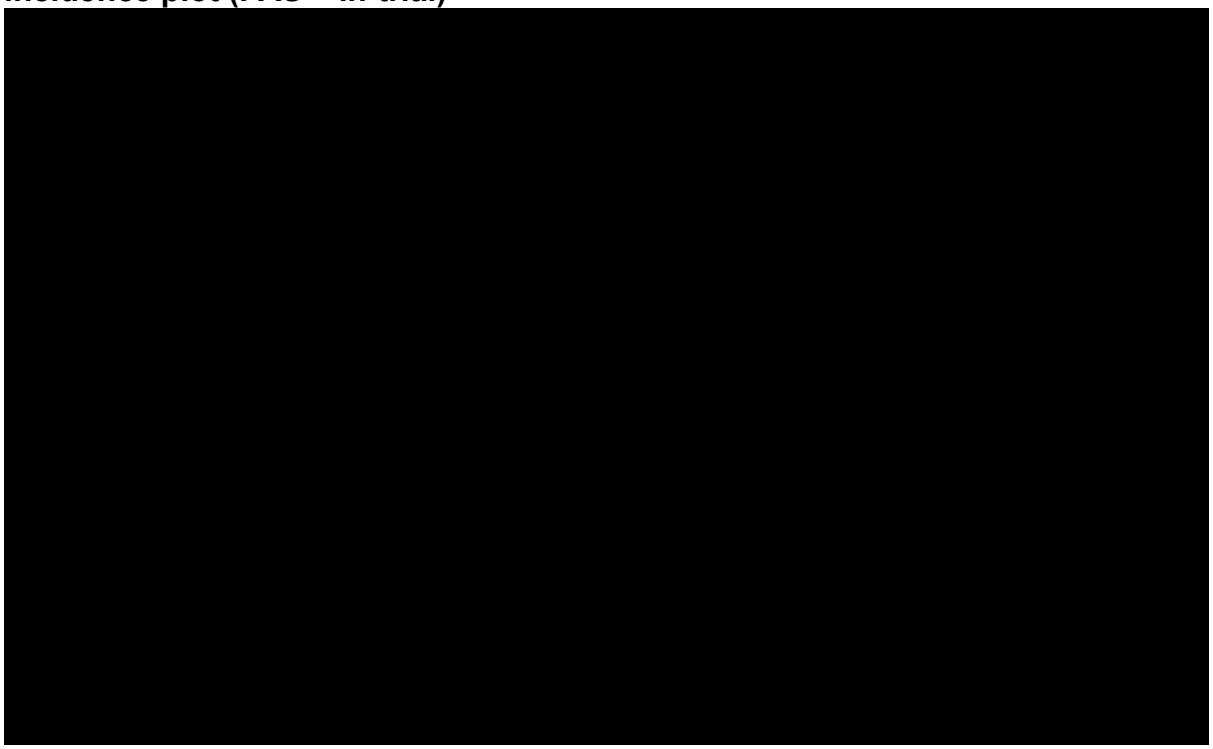
2.6.1.4.1. Kidney function

The semaglutide effects on kidney function were assessed by the time from randomisation to first occurrence of a 5-component composite nephropathy endpoint. The composite nephropathy endpoint consisted of the first occurrence of: onset of persistent macroalbuminuria (urinary albumin-to-creatinine ratio [UACR] >300 mg/g), persistent 50% reduction in estimated glomerular filtration rate (eGFR)

compared with baseline, onset of persistent eGFR <15 ml/min/1.73 m^2, initiation of chronic renal replacement therapy (dialysis or transplantation), or renal death.

Composite nephropathy events occurred throughout the entire observation period, with clustering of events at times of scheduled albumin and eGFR assessments (collected at Week 0, 20, 52 and hereafter every 52 weeks). Composite nephropathy events occurred in a lower proportion of semaglutide-treated participants (155 [1.8% of participants with ≥1 event]) compared with those receiving placebo (198 [2.2% of participants with ≥1 event]), as reflected in the separation of the curves (Figure 9). The analysis of time to first composite nephropathy events resulted in an estimated HR of 0.78, 95% CI: 0.63, 0.96; p[redacted] for semaglutide relative to placebo hence, the risk of kidney function deterioration was significantly lower with semaglutide. The reduction in risk was mainly driven by the component persistent macroalbuminuria (Table 18).

Figure 9: Time from randomisation to first nephropathy outcome – cumulative incidence plot (FAS – in-trial)



Source: SELECT final CTR (112).
Abbreviations: CTR, clinical trial report; FAS, full analysis set; sema, semaglutide.

Table 18: First composite nephropathy events (FAS – in trial)

	Semaglutide N=8,803 n (%)	Placebo N=8,801 n (%)	Hazard ratio (95% CI)	p-value
Composite nephropathy events	155 (1.8)	198 (2.2)	0.78 (0.63, 0.96)	[redacted]
Persistent macroalbuminuria	[redacted]	[redacted]	–	–
Persistent reduction in eGFR	[redacted]	[redacted]	–	–
Onset of persistent eGFR <15 ml/min/1.73 m^2	[redacted]	[redacted]	–	–
Initiation of chronic RRT	[redacted]	[redacted]	–	–
Dialysis	[redacted]	[redacted]	–	–
Renal death	[redacted]	[redacted]	–	–

Source: SELECT final CTR (112).
Abbreviations: CI, confidence interval; CTR, clinical trial report; eGFR, estimated glomerular filtration rate; FAS, full analysis set; RRT, renal replacement therapy.

2.6.1.4.2. Glucose metabolism

In SELECT, development of prediabetes was defined as blood levels of HbA1c of 5.7–6.4% (39–47 mmol/mol) and T2D was defined as levels ≥6.5% (≥48 mmol/mol) (44). Please note that in the UK, prediabetes is defined as blood levels of HbA1c of 6.0–6.4% (42–47 mmol/mol) (119); however, the definition of T2D is the same, which means the difference in definition of prediabetes has no impact on the economic model (Section 3.2). In SELECT, changes in HbA1c were investigated as follows:

- **Change in HbA1c (%, mmol/mol) at Year 2 (Week 104):** Baseline HbA1c was similar between the two treatment groups, with a mean value of 5.8% (39.7 mmol/mol) (120). Only the semaglutide treatment arm saw a reduction in mean HbA1c. At Week 104, the estimated mean change in HbA1c from baseline was −0.31% ([redacted] mmol/mol) for semaglutide and 0.01% [redacted] mmol/mol) for placebo (Table 19). The estimated treatment difference (ETD; semaglutide vs placebo) was −0.32 %-points (95% CI: −0.33, −0.31) ([redacted] mmol/mol; 95% CI: [redacted]) in favour of semaglutide.

Table 19: HbA1c (%) change from baseline at Year 2 (Week 104) (FAS – in trial)

HbA1c (%)	FAS	N	Estimate	95% CI	p-value†
Change from baseline (%) at Year 2 (Week 104)					
Semaglutide	8,803	[redacted]	−0.31		
Placebo	8,801	[redacted]	0.01		
Treatment difference at Week 104 (%-points)					
Semaglutide vs placebo			−0.32	−0.33, −0.31	[redacted]
HbA1c (mmol/mol)	**FAS**	**N**	**Estimate**	**95% CI**	**p-value†**
Change from baseline at Year 2 (Week 104)					
Semaglutide	8,803	[redacted]	[redacted]		
Placebo	8,801	[redacted]	[redacted]		
Treatment difference at Week 104					
Semaglutide vs placebo			[redacted]	[redacted]	[redacted]

Source: Lincoff 2023 (44), SELECT final CTR (112).
Notes: the baseline measurement for HbA1c is made at the screening visit.
Abbreviations: CI, confidence interval; CTR, clinical trial report; FAS, full analysis set; HbA1c, glycated haemoglobin.

- **Time from randomisation to first occurrence of HbA1c ≥6.5%:** Since HbA1c was mostly measured at pre-specified visits, analysis of time from randomisation to first occurrence of HbA1c level ≥6.5% (48 mmol/mol) showed that both curves in the cumulative incidence plot had clear steps at time of visits (Figure 10). There was a clear separation between the two treatment groups, with fewer events among participants receiving semaglutide (306 [3.5% of participants with ≥1 event]) vs placebo (1,059 [12.0% of participants with ≥1 event]). In comparison with placebo, the HR for semaglutide was 0.27 (95% CI: 0.24, 0.31) demonstrating that the risk of having an HbA1c ≥6.5% (indicating T2D development) was lower for the semaglutide group.

Figure 10: Time from randomisation to first occurrence of HbA1c ≥6.5% (48 mmol/mol) – cumulative incidence plot (FAS – in trial)

Source: SELECT final CTR (112).
Abbreviations: CTR, clinical trial report; FAS, full analysis set; HbA1c, glycated haemoglobin; sema, semaglutide.

- **For participants with a screening HbA1c <5.7%: Time from randomisation to first occurrence of HbA1c ≥5.7%.** Time from randomisation to first occurrence of HbA1c level ≥5.7% (39 mmol/mol) was analysed among the subpopulation of participants with screening HbA1c <5.7%. The cumulative incidence plot in Figure 11 shows a clear separation between the two treatment groups in favour of semaglutide, with fewer events among participants in the active treatment group (623 [21.3% of participants with ≥1 event among those in the FAS with screening HbA1c <5.7%]) compared with placebo (1,501 [50.4% of participants with ≥1 event among those in the FAS with screening HbA1c <5.7%]). Based on analysis of in-trial data, the HR for semaglutide relative to placebo was 0.33 (95% CI: 0.30, 0.36) showing that the risk of having an HbA1c ≥5.7% (indicating prediabetes development) was significantly lower for the semaglutide group than for the placebo group.

Figure 11: Time from randomisation to first occurrence of HbA1c ≥5.7% (39 mmol/mol)† – cumulative incidence plot (FAS – in trial)

Source: SELECT final CTR (112).
†For participants with a screening HbA1c <5.7% (39 mmol/mol).
Abbreviations: CTR, clinical trial report; FAS, full analysis set; HbA1c, glycated haemoglobin; sema, semaglutide.

- **For participants with a screening HbA1c ≥5.7%: Reduction in HbA1c to <5.7% at Year 2 (Week 104).** At the time of screening, 66.8% of participants in the semaglutide group and 66.1% of participants in the placebo group had a screening HbA1c ≥5.7% (39 mmol/mol), indicative of prediabetes. A greater proportion of participants achieved HbA1c <5.7% (39 mmol/mol) at Week 104 with semaglutide (% of participants who met the criterion among those in the FAS with prediabetes at screening) compared with placebo (% of participants who met the criterion among those in the FAS with prediabetes at screening). The odds of achieving an HbA1c <5.7% at Week 104 were higher for the semaglutide group than the placebo group (odds ratio [OR]: 8.74; 95% CI: 7.91, 9.65), indicating that significantly more individuals in the semaglutide group returned to normoglycaemia during the trial (Table 20).

Table 20: Odds of HbA1c <5.7% (39 mmol/mol)† at Year 2 (Week 104) (FAS – in trial)

HbA1c <5.7% (39 mmol/mol)	FAS	N	Estimate	95% CI	p-value‡
Odds at Week 104					
Semaglutide	[redacted]	[redacted]	[redacted]		
Placebo	[redacted]	[redacted]	[redacted]		
Odds ratio at Week 104					
Semaglutide vs placebo			8.74	7.91, 9.65	[redacted]

Source: Lincoff 2023 (44), SELECT final CTR (112).
†For participants with a screening HbA1c ≥5.7% (39 mmol/mol); ‡Two-sided p-value for test of no difference.
Abbreviations: CI, confidence interval; CTR, clinical trial report; FAS, full analysis set; HbA1c, glycated haemoglobin.

2.6.1.4.3. CVD risk-related outcomes

At baseline, mean observed SBP was similar across the two treatment groups (semaglutide: 131.0 mmHg, placebo: 130.9 mmHg). However, at Week 104, a greater reduction in mean SBP was observed in the semaglutide group (−3.82 mmHg) vs the placebo group (−0.51 mmHg). The estimated treatment difference ETD (semaglutide vs placebo) was −3.31 mmHg (95% CI: −3.75, −3.88) in favour of semaglutide.

Mean observed DBP at baseline was similar across the two treatment groups (semaglutide: 79.4 mmHg, placebo: 79.2 mmHg). At Week 104, average DBP decreased in both the semaglutide and placebo groups; however, the estimated change in DBP was greater with semaglutide (−1.02 mmHg) than with placebo (−0.47 mmHg). The ETD (semaglutide vs placebo) was −0.55 mmHg (95% CI: −0.83, −0.27) in favour of semaglutide.

Heart rate increase is a well-known side effect associated with GLP-1 RA treatment. In the semaglutide group, mean observed pulse at baseline was 68.9 bpm and in the placebo group, 68.6 bpm. The estimated change from baseline at Week 104 was greater with semaglutide (3.79 bpm) than with placebo (0.69 bpm), corresponding to an ETD of 3.10 bpm (95% CI: 2.80, 3.39).

At baseline, geometric mean hsCRP was 1.96 mg/l for the semaglutide group and 1.91 mg/l for the placebo group. In the semaglutide group, the mean hsCRP [redacted]

[redacted].

The estimated hsCRP ratio to baseline at Week 104 for the two treatment groups (semaglutide: [redacted] vs placebo: [redacted]) as well as the estimated treatment ratio (ETR) show that the result was in favour of semaglutide (ETR: 0.62, 95% CI: 0.60, 0.64) (44, 112).

Changes at Year 2 (Week 104) in SBP, DBP, pulse and hsCRP from baseline are shown in Table 21.

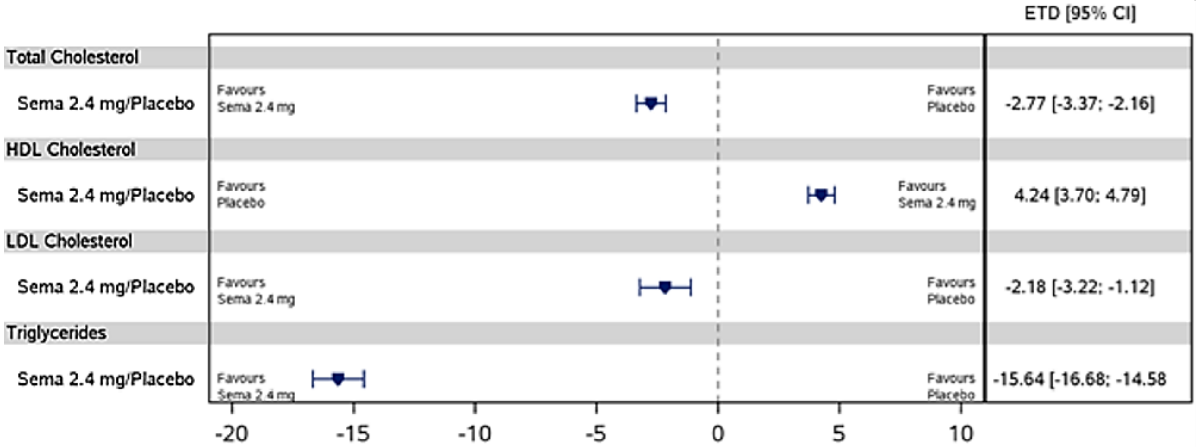
Table 21: SBP, DBP, pulse and hsCRP change from baseline at Year 2 (Week 104) (FAS – in trial)

	FAS	N	Estimate	95% CI	p-value†
SBP (mmHg)					
Change from baseline at Year 2 (Week 104)					
Semaglutide	8,803	[redacted]	−3.82		
Placebo	8,801	[redacted]	−0.51		
Treatment difference at Week 104					
Semaglutide vs placebo			−3.31	−3.75, −2.88	[redacted]
DBP (mmHg)					
Change from baseline at Year 2 (Week 104)					
Semaglutide	8,803	[redacted]	−1.02		
Placebo	8,801	[redacted]	−0.47		
Treatment difference at Week 104					
Semaglutide vs placebo			−0.55	−0.83, −0.27	[redacted]
Pulse (bpm)					
Change from baseline at Year 2 (Week 104)					
Semaglutide	8,803	[redacted]	3.79		
Placebo	8,801	[redacted]	0.69		
Treatment difference at Week 104					
Semaglutide vs placebo			3.10	2.80, 3.39	[redacted]
hsCRP (mg/l)					
Ratio to baseline at Year 2 (Week 104)					
Semaglutide	[redacted]	[redacted]	[redacted]		
Placebo	[redacted]	[redacted]	[redacted]		
Treatment ratio at Week 104					
Semaglutide vs placebo			0.62	0.60, 0.64	[redacted]

Source: Lincoff 2023 (44), SELECT final CTR (112).
†Two-sided p-value for test of no difference.
Abbreviations: CI, confidence interval; CTR, clinical trial report; DBP, diastolic blood pressure; FAS, full analysis set; hsCRP, high sensitivity C-reactive protein; SBP, systolic blood pressure.

Treatment with semaglutide resulted in greater decreases in total cholesterol, LDL cholesterol and triglycerides, and a greater increase in HDL cholesterol (also known as “good” cholesterol) than placebo. Change in lipids at Year 2 (Week 104) from baseline are shown in Figure 12. At baseline, geometric mean lipid levels (mmol/l, mg/dl) were overall within normal range and similar across the two treatment groups. The ETDs (semaglutide/placebo) were consistently in favour of semaglutide for all lipids.

Figure 12: Lipids (%) change from baseline at Year 2 (Week 104) (FAS – in trial)



Source: Figure from SELECT final CTR (112), data available from Lincoff 2023 (44).
Abbreviations: CI, confidence interval; CTR, clinical trial report; ETD, estimated treatment difference; FAS, full analysis set; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sema, semaglutide.

2.6.1.4.4. Body weight changes

At baseline, the mean body weight was 96.5 kg in the semaglutide group and 96.8 kg in the placebo group. At Week 104, a reduction in mean body weight was observed in both groups, although greater weight reduction was seen with semaglutide than with placebo. The estimated mean change in body weight (%) from baseline (randomisation) to Year 2 (Week 104) was −9.39% in the semaglutide group vs −0.88% in the placebo group. The ETD was −8.51 %-points (95% CI: −8.75, −8.27) for semaglutide vs placebo, in favour of semaglutide (Table 22).

The mean waist circumference at baseline was 111.3 cm for the semaglutide group and 111.4 cm for the placebo group. A reduction in mean waist circumference was observed in both groups; however, a greater reduction in mean waist circumference was observed with semaglutide than with placebo. The estimated mean change in waist circumference from baseline to Year 2 was −7.56 cm in the semaglutide group

compared with −1.03 cm in the placebo group. The ETD (semaglutide/placebo) was −6.53 cm (95% CI: −6.79, −6.27) in favour of semaglutide (Table 22).

Table 22: Change in body weight (%) and waist circumference (cm) at Year 2 (Week 104) (FAS – in trial)

	FAS	N	Estimate	95% CI	p-value†
Body weight					
Change from baseline (%) at Year 2 (Week 104)					
Semaglutide	8,803	[redacted]	−9.39		
Placebo	8,801	[redacted]	−0.88		
Treatment difference at Week 104 (%–points)					
Semaglutide vs placebo			−8.51	−8.75, −8.27	[redacted]
Waist circumference					
Change from baseline (cm) at Year 2 (Week 104)					
Semaglutide	8,803	[redacted]	−7.56		
Placebo	8,801	[redacted]	−1.03		
Treatment difference at Week 104 (cm)					
Semaglutide vs placebo			−6.53	−6.79, −6.27	[redacted]

Source: Lincoff 2023 (44), SELECT final CTR (112).
†Two-sided p-value for test of no difference.
Abbreviations: CI, confidence interval; CTR, clinical trial report; FAS, full analysis set.

2.6.1.4.5. Patient-reported outcomes

The EQ-5D-5L questionnaire is used to estimate the impact on patients' HRQoL and provides a description of patients' problems by dimensions (descriptive system), a score for overall self-rated health (VAS, range: 0–100) as well as an index score (EQ-5D-5L index, range: 0–1). A higher score indicates better self-reported health status. The WRSSM is a PRO questionnaire designed to assess symptoms commonly associated with overweight and obesity. The WRSSM total scores range from 0 to 4, with higher scores reflecting worse symptomatology. Questionnaires were collected and scored at baseline (visit 2), Week 20 (visit 7), Week 52 (visit 10) and thereafter every 52 weeks, until the end of trial.

Change in EQ-5D-5L index score at Year 2 (Week 104)

At baseline, mean EQ-5D-5L index score was identical for the semaglutide and placebo treatment groups (0.88). The result from the analysis of change in mean EQ-5D-5L index score from baseline at Week 104 was in favour of semaglutide, with

a statistically significant ETD (semaglutide/placebo) of 0.01; 95% CI: 0.01, 0.02; p[redacted] (Table 23).

Change in EQ-5D-VAS score at Year 2 (Week 104)

At baseline, mean score on the VAS was 77.15 in both the semaglutide and placebo groups. Although there was an increase from baseline with both treatments, the increase in mean EQ-5D-VAS score was higher in the semaglutide group (2.52) compared with placebo (0.920), resulting in a statistically significant ETD (semaglutide/placebo) of 1.60; 95% CI: 1.16, 2.04; p[redacted] (Table 23).

Table 23: EQ-5D-5L index and VAS score change from baseline at Year 2 (Week 104) (FAS – in trial)

	FAS	N	Estimate	95% CI	p-value†
EQ-5D-5L index score					
Change from baseline at Year 2 (Week 104)					
Semaglutide	8,803	[redacted]	0.01		
Placebo	8,801	[redacted]	−0.01		
Treatment difference at Week 104					
Semaglutide vs placebo			0.01	0.01, 0.02	[redacted]
EQ-5D-5L VAS score					
Change from baseline at Year 2 (Week 104)					
Semaglutide	8,803	[redacted]	2.52		
Placebo	8,801	[redacted]	0.92		
Treatment difference at Week 104					
Semaglutide vs placebo			1.60	1.16, 2.04	[redacted]

Source: Lincoff 2023 (44), SELECT final CTR (112).
†Two-sided p-value for test of no difference.
Note: Score ranges from 0 to 1 and a higher score indicates better self-reported health status.
Abbreviations: CI, confidence interval; CTR, clinical trial report; FAS, full analysis set; VAS, visual analogue score.

Exploratory endpoint: Change in WRSSM score at Year 2 (Week 104)

At baseline, mean WRSSM total score was [redacted] and [redacted] for the semaglutide group and the placebo group, respectively. The WRSSM total score decreased in both groups, although a [redacted] was observed in the semaglutide group vs placebo (mean change from baseline to Week 104: [redacted] vs [redacted]) (112).

2.6.1.5 Exploratory endpoints

2.6.1.5.1. Exploratory endpoints of secondary objective

Change in glycaemic status at Week 117

Deterioration in glycaemic status from baseline at Week 117 was determined by a change from normoglycaemia to prediabetes/diabetes or from prediabetes to diabetes. The risk of deterioration in glycaemic status was [redacted] for the semaglutide group compared with the placebo group (OR: [redacted]; 95% CI: [redacted]) (112).

2.6.1.5.2. Other exploratory endpoints

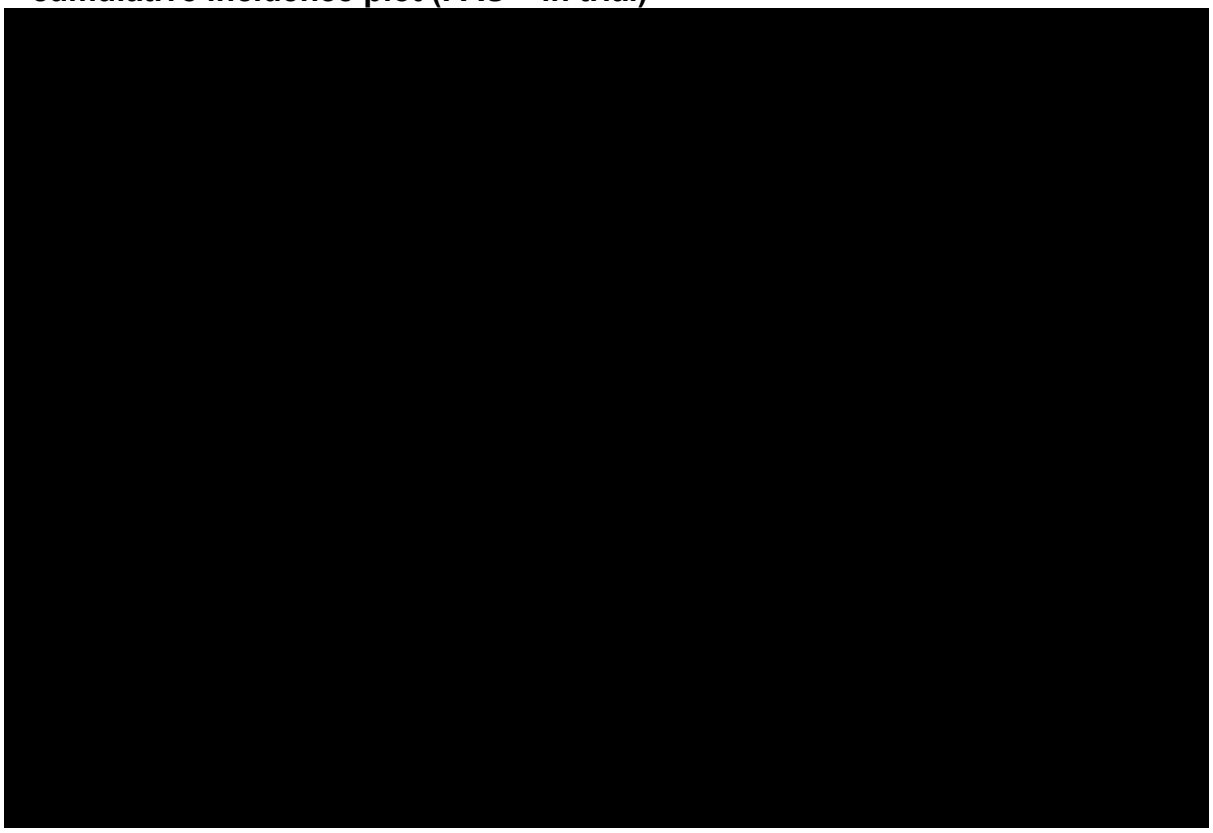
Smoking status at Year 2 (Week 104)

The risk of being a current smoker at Week 104 was [redacted] (OR: [redacted], 95% CI: [redacted]; p[redacted]).

Number of hospitalisations from randomisation to end of trial

There were [redacted] hospitalisations among individuals treated with semaglutide ([redacted]) compared with those receiving placebo ([redacted]), corresponding to a mean ratio (semaglutide/placebo) of [redacted], 95% CI: [redacted]; p[redacted] (Figure 13).

Figure 13: Mean number of hospitalisations from randomisation to end of trial – cumulative incidence plot (FAS – in trial)



Source: SELECT final CTR (112).
Abbreviations: CTR, clinical trial report; FAS, full analysis set; sema, semaglutide.

Number of hospitalised days from randomisation to end of trial

The mean time spent in hospital (weeks) from randomisation to the end of in-trial period is shown in Figure 14. For both treatment groups, the number of hospitalisation days per participant was estimated based on data observed for Weeks 52, 104, 156, and 208. All estimated ratios were [redacted]. At Week 104, the estimated mean ratio was [redacted], 95% CI: [redacted]; p[redacted].

Figure 14: Mean time spent in hospital (weeks) from randomisation to end of trial – cumulative incidence plot (FAS – in trial)

Source: SELECT final CTR (112).
Abbreviations: CTR, clinical trial report; FAS, full analysis set; sema, semaglutide.

2.6.1.6 Pre-specified analyses

A number of pre-specified analyses were conducted on SELECT data to investigate the relationship between baseline characteristics, weight changes and CV outcomes, and time to onset of treatment effect.

The focus of the Deanfield et al, 2024 analysis (110) was to evaluate the possible relationship between baseline weight, early weight loss (from baseline to Week 20) and time to first MACE. Using a Cox model, the analyses assessed how many MACE occurred in relation to subgroups of early weight loss (<5% vs ≥5%) for each treatment arm during trial follow-up. Only MACE occurring after Week 20 were included in the analyses to ensure evaluation of the effect of early weight loss on future MACE. The rationale for choosing Week 20 as a cut-off timepoint was to allow sufficient MACE events to occur in the follow-up period after early weight loss, such that the event numbers would yield reliable analyses. Had a later timepoint been chosen, e.g. Week 104, MACE that occurred *before* this timepoint would need to be disregarded, resulting in most of the observed events being excluded from the analyses. Similarly, measuring MACE from the beginning of the trial and evaluating

weight loss at Week 104, would have prohibited demonstrating the relationship between weight loss and MACE. This would also have added survival bias to the analyses as only participants who were alive at Week 104 would be included. Additionally, participants were on dose titration for the first 16 weeks of treatment, which means that the earliest they could reach the target dose of 2.4 mg was Week 17; it is reasonable to expect it would take a few weeks to see the benefit achieved with the full dose of semaglutide.

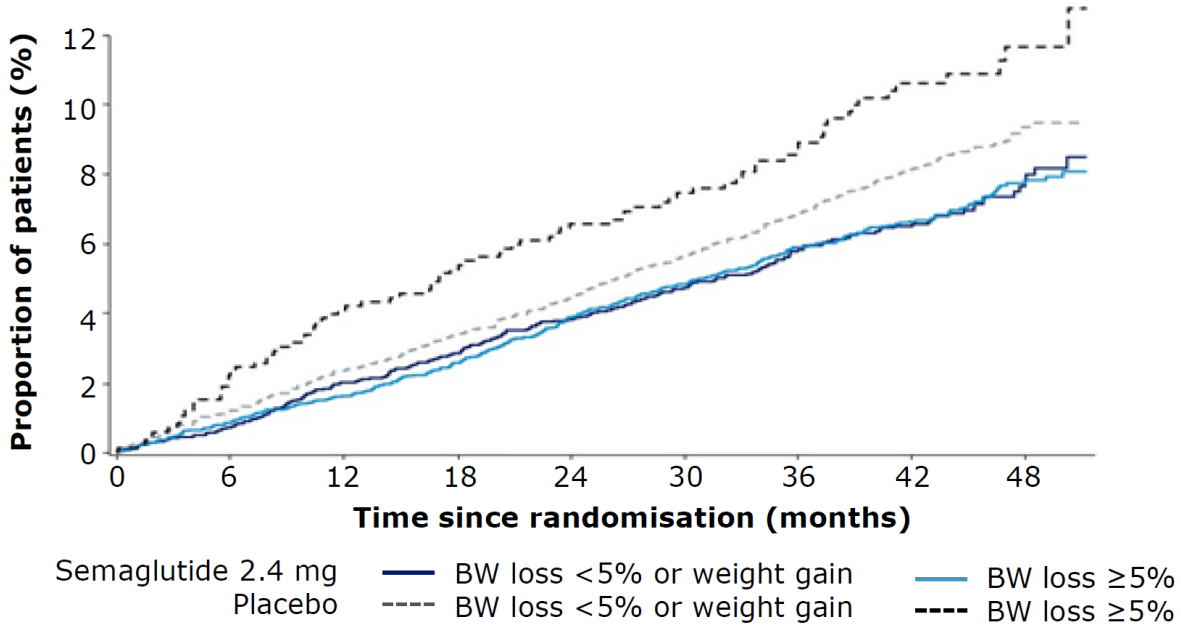
A weight loss cut-off of 5% was chosen as it is a threshold widely used to indicate a clinically meaningful response to therapy and is recommended by clinical treatment guidelines (121). By Week 20, 62% of semaglutide and 10% of placebo participants had lost ≥5% of their body weight. The reduction in the MACE rates by semaglutide vs placebo was similar in participants who lost ≥5% and those who lost <5% or gained weight (HR: 0.67; 95% CI: 0.52, 0.87 and HR: 0.85, 95% CI: 0.72, 1.00, respectively; interaction p-value >0.10 between weight loss subgroups). MACE rates among participants on semaglutide were identical in the two weight loss categories (5.9% in both groups), and for participants on placebo who lost ≥5% weight had higher MACE rates than those who lost <5% or gained weight (8.5% vs 7.0%, respectively; Table 24 and Figure 15). Additionally, the consistent reduction in MACE with semaglutide vs placebo was achieved regardless of the level of baseline adiposity, as measured across all subgroup categories of baseline weight (BMI, body weight) and anthropometric (waist circumference, waist:height ratio) (p-values >0.1) (110).

Table 24: MACE after Week 20 by % change in body weight (Baseline to Week 20; FAS, in-trial)

	Semaglutide N=8,803 n (%)	Placebo N=8,801 n (%)	Hazard ratio (95% CI)	Interaction p-value
Body weight loss <5% or weight gain	199 (5.9)	551 (7.0)	0.85 (0.72, 1.00)	0.1334
Body weight loss ≥5%	318 (5.9)	72 (8.5)	0.67 (0.52, 0.87)	

Source: Deanfield 2024 (110).
Abbreviations: CI, confidence interval; FAS, full analysis set; MACE, major adverse cardiovascular event.

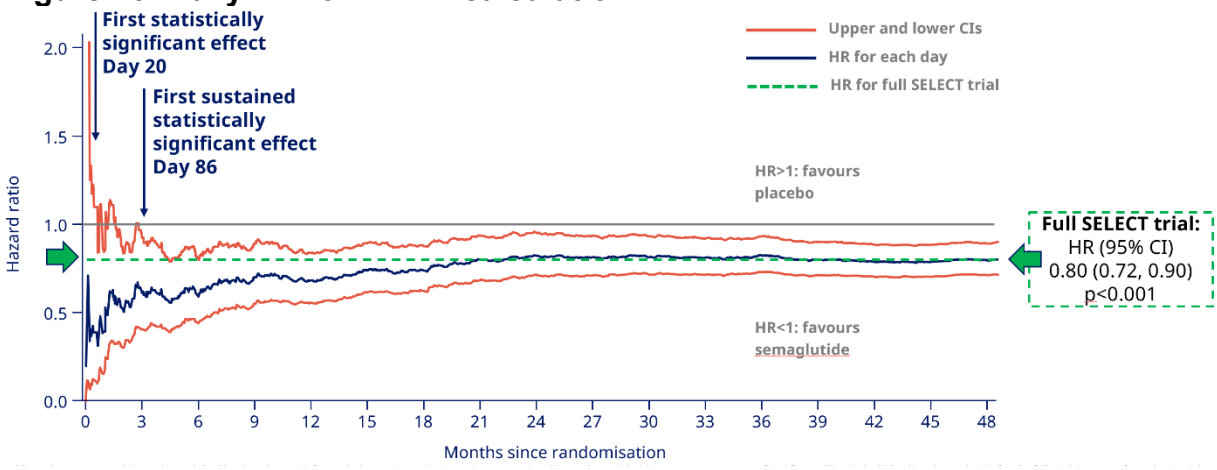
Figure 15: Time to first MACE by % change in body weight (baseline to Week 20)



Source: Deanfield 2024 (110).
Abbreviations: BW, body weight; MACE, major adverse cardiovascular event.

Another pre-specified analysis by Plutzky et al, 2025, investigated the time to onset of benefit of semaglutide on MACE (111). The analysis estimated an updated HR for MACE each day (using cumulative number of events) with corresponding 95% CIs, and found that treatment with semaglutide reduced the risk of MACE soon after randomisation, and that the first sustained, statistically significant effect (HR and upper CI below 1) was observed within 3 months of randomisation (Figure 16), with an overall HR of 0.62 (95% CI: 0.41, 0.93) for those first 3 months.

Figure 16: Daily HR for MACE calculation



Source: Plutzky 2025 (111).
Red lines show upper and lower CIs and the blue line shows HR for each day, estimated using a Cox

proportional hazards model with treatment group as a fixed factor. The dashed blue line shows the HR for the full trial. Data are from the in-trial period for the full analysis set. Estimated HRs and 95% CIs are shown from Week 0 to Week 208 post-randomisation. A two-sided significance level of 5% was used. No adjustments for multiplicity were performed. First sustained statistically significant effect defined as the time-point at which the upper limit of the 95% CI is below 1 and subsequently remains below 1.
Abbreviations: CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event.

The results from the two analyses show that the magnitude of the treatment effect with semaglutide on the primary endpoint MACE was independent of the extent of weight loss (<5% and ≥5% at Week 20), as participants in both weight loss groups experienced similar MACE rates (which were significantly lower than with placebo), and that the CV benefits of semaglutide were first observed early in the trial. This suggests that weight reduction may not be driving the improvements in CV outcomes seen with semaglutide, supporting the hypothesis that semaglutide exerts its beneficial effects on the CV system through alternative mechanisms.

2.6.1.7 Potential impact of COVID-19 on CV outcomes

SELECT ran from October 2018 to June 2023 and therefore it is reasonable to expect that the COVID-19 pandemic may have impacted some of the mortality outcomes in the trial. In Section 2.6.1.3.1 Time from randomisation to CV death, the survival curves were seen to converge from 24 months after randomisation to approximately 36 months (Figure 6), which could be due to COVID-19. It is possible that non-CV death may have acted as a competing risk, i.e. an event which occurrence precludes the occurrence of the primary event of interest, for CV death. Participants who reported a COVID-19 infection were more likely to die from non-CV causes, whereas participants without a COVID-19 event died predominantly from CV causes, as expected in this population. The relatively high number of non-CV deaths in participants with COVID-19 combined with fewer non-CV deaths with semaglutide vs placebo meant that more participants in the semaglutide arm than in the placebo arm survived to remain “at risk” for CV death. Therefore, the competing risk of non-CV death (which prevents the occurrence of CV death) combined with the lower rates of non-CV death in the semaglutide arm may have resulted in the unanticipated convergence of survival curves for CV death, which corresponds to the most severe periods of the COVID-19 pandemic (March 2020 – March 2022) (122).

2.6.2 Supportive evidence: STEP-HFpEF and STEP-HFpEF DM

The supportive evidence presented in this section is from the two other studies which were identified by the clinical SLR as relevant to this submission (Section 2.1): STEP-HFpEF and STEP-HFpEF DM. The population of interest in the studies had a specific type of CVD, namely HFpEF, and a BMI ≥30 kg/m^2. As described in Section 1.3.3, symptoms associated with HF pose a heavy burden on patients' HRQoL (80); HFpEF accounts for up to 50% of all people with HF, and is associated with significant morbidity and mortality (123).

The two studies were of similar design, with the main difference being that the participants enrolled in STEP-HFpEF DM had T2D as well as HFpEF and a BMI ≥30 kg/m^2. Both studies were part of the STEP clinical trial programme, which investigated semaglutide 2.4 mg for the management of obesity and overweight (Appendix J). Although results from the STEP trials have shown a consistent picture of improvement in CV risk factors with semaglutide, STEP 1 to STEP 10 are not included in this submission as they did not have a primary CV outcome, and they provided limited direct evidence of the CV benefits of semaglutide in people with eCVD. The main outcomes that are relevant to the decision problem are presented here, namely HRQoL, body weight, CV risk factors and HF events. Additional efficacy data provided in Appendix K, and an overview of the methodology for both trials is presented in Appendix L.

2.6.2.1 Overview of study design and methodology

The Phase 3 trials STEP-HFpEF and STEP-HFpEF DM investigated the effects of semaglutide once weekly on physical function, symptoms, and body weight compared with placebo, both added to SoC, in people with HFpEF and BMI ≥30 kg/m^2, without and with T2D, respectively. STEP-HFpEF enrolled 529 participants who were randomised 1:1 to receive either semaglutide (n=263) or placebo (n=266); STEP-HFpEF DM enrolled 617 participants who were randomised 1:1 to receive either semaglutide (n=310) or placebo (n=307).

Similarly to SELECT, two estimands were pre-specified in both STEP-HFpEF and STEP-HFpEF DM: the primary estimand ("treatment policy" estimand) for all objectives was the intention-to-treat estimand, evaluating the effect of the

randomised treatment intervention irrespective of adherence to treatment and regardless of initiation of other anti-obesity therapies. The secondary estimand ("hypothetical" estimand) assessed treatment effect under the assumption that participants receive their assigned treatment for the duration of the trial, without initiating other anti-obesity therapies. Primary endpoint data for both primary estimand and secondary estimands are presented here; secondary estimand data for other endpoints described in this section are presented in Appendix K.

2.6.2.2 Primary efficacy outcomes

STEP-HFpEF and STEP-HFpEF DM both met their dual primary endpoints, showing a statistically significant reduction in body weight and increase in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ CSS) from baseline (Week 0) to end of treatment (Week 52) (107, 108, 124, 125).

2.6.2.2.1. STEP-HFpEF

2.6.2.2.1.1. Change in body weight

- Primary estimand (treatment policy estimand): At Week 52, a reduction in mean body weight was observed in both study arms, although greater reductions were observed with semaglutide than with placebo. The estimated mean change in body weight (%) from baseline to Week 52 was −13.3% in the semaglutide group compared with −2.6% in the placebo group. Superiority of semaglutide over placebo was demonstrated by an ETD of −10.7 %-points (95% CI: −11.9, −9.4; p<0.001)
- Secondary estimand (hypothetical estimand): As with the primary estimand, a reduction in mean body weight was observed in both study arms at Week 52, although greater reductions were observed with semaglutide than with placebo. For the semaglutide group, the estimated mean change in body weight (%) from baseline to Week 52 was –15.1% vs –2.4% in the placebo group. The ETD was –12.7 %-points (95% CI: –13.9, –11.5) in favour of semaglutide.

2.6.2.2.1.2. Change in KCCQ CCS

The KCCQ is a standardised 23-item, self-administered instrument that quantifies heart failure symptoms (frequency, severity, and recent change), physical limitation, QoL, and social limitation. Scores are transformed to a range of 0 to 100 in which higher scores reflect better health status.

- Primary estimand (treatment policy estimand): In both treatment arms, there was an increase in the KCCQ CSS from baseline to Week 52, however, the increase was greater in the semaglutide group than in the placebo group. The estimated mean change in the KCCQ CSS from baseline to Week 52 was 16.6 points in the semaglutide group vs 8.7 points in the placebo group. Superiority of semaglutide over placebo was demonstrated by an ETD of 7.8 points (95% CI: 4.8, 10.9; p<0.001)
- Secondary estimand (hypothetical estimand): As with the primary estimand, a greater increase in the KCCQ CSS was observed with semaglutide than with placebo. The estimated mean change in the KCCQ CSS from baseline to Week 52 was 19.1 points in the semaglutide group compared with 10.3 points in the placebo group. The ETD was 8.8 points (95% CI: 5.9, 11.7) in favour of semaglutide.

2.6.2.2.2. STEP-HFpEF DM

2.6.2.2.2.1. Change in body weight

- Primary estimand (treatment policy estimand): At Week 52, a reduction in mean body weight was observed in both study arms, although greater reductions were observed with semaglutide than with placebo. The estimated mean change in body weight (%) from baseline to Week 52 was −9.8% in the semaglutide group compared with −3.4% in the placebo group. Superiority of semaglutide over placebo was demonstrated by an ETD of −6.4 %-points (95% CI: −7.6, −5.2; p<0.0001)
- Secondary estimand (hypothetical estimand): As with the primary estimand, a reduction in mean body weight was observed in both study arms at Week 52, although greater reductions were observed with semaglutide than with

placebo. For the semaglutide group, the estimated mean change in body weight (%) from baseline to Week 52 was –11.0% vs –3.1% in the placebo group, resulting in a statistically significant ETD of –7.9 % -points (95% CI: –9.0, –6.8; p[redacted]) in favour of semaglutide.

2.6.2.2.2.2. Change in KCCQ CCS

- Primary estimand (treatment policy estimand): In both treatment arms, there was an increase in the KCCQ CSS from baseline to Week 52, however, the increase was greater in the semaglutide group than in the placebo group. The estimated mean change in the KCCQ CSS from baseline to Week 52 was 13.7 points in the semaglutide group vs 6.4 points in the placebo group. Superiority of semaglutide over placebo was demonstrated by an ETD of 7.3 points (95% CI: 4.1, 10.4; p<0.0001) .

- Secondary estimand (hypothetical estimand): As with the primary estimand, a greater increase in the KCCQ CSS was observed with semaglutide than with placebo. The estimated mean change in the KCCQ CSS from baseline to Week 52 was 16.6 points in the semaglutide group compared with 7.9 points in the placebo group, resulting in a statistically significant ETD of 8.6 points (95% CI: 5.6, 11.6; p[redacted]) in favour of semaglutide.

2.6.2.3 CVD risk-related secondary outcomes

Similarly to SELECT, changes in hsCRP, SBP and DBP were investigated as secondary endpoints in both STEP-HFpEF and STEP-HFpEF DM. As observed in SELECT (Section 2.6.1.4.3), treatment with semaglutide resulted in greater decreases in SBP, DBP and hsCRP than placebo. Primary and secondary estimands were applied to quantify the average change in hsCRP and SBP; results for the primary estimand are presented here, and results for the secondary estimand can be found in Appendix K.

2.6.2.3.1. STEP-HFpEF

From baseline to Week 52, the geometric mean hsCRP decreased with semaglutide and to a lesser extent with placebo. The estimated ratio to baseline at Week 52 was 0.56 for semaglutide vs 0.93 with placebo. The mean hsCRP percentage change

from baseline to Week 52 was significantly lower with semaglutide (−43.5%) than with placebo (−7.3%), with an ETD of [redacted]% (95% CI: [redacted]; p[redacted]) in favour of semaglutide.

At baseline, the mean SBP was 132.2 mmHg for the total population and was similar between the two treatment groups. The estimated treatment change in mean SBP from baseline to Week 52 was −4.9 mmHg with semaglutide and −2.0 mmHg with placebo, resulting in an ETD of −2.9 mmHg (95% CI: −5.8, 0.1) in favour of semaglutide.

At baseline, mean DBP was 78.3 mmHg for the total population and was similar between the two treatment groups. The changes in mean DBP from baseline to Week 52 was slightly higher with semaglutide (−1.4 mmHg) than with placebo (−1.3 mmHg).

2.6.2.3.2. STEP-HFpEF DM

From baseline to Week 52, the geometric mean hsCRP decreased with semaglutide and to a lesser extent with placebo. The estimated ratio to baseline at Week 52 was 0.58 for semaglutide vs 0.87 with placebo. The mean hsCRP percentage change from baseline to Week 52 was significantly greater with semaglutide (−42.0%) than with placebo (−12.8%), with a statistically significant ETD of [redacted]% (95% CI: [redacted]; p[redacted]) in favour of semaglutide.

At baseline, the mean SBP was 133.8 mmHg for the total population and was similar between the two treatment groups. The estimated treatment change in mean SBP from baseline to Week 52 was −4.2 mmHg with semaglutide and −1.7 mmHg with placebo, resulting in an ETD of −2.5 mmHg (95% CI: −5.3, 0.3) in favour of semaglutide.

At baseline, mean DBP was 77.3 mmHg for the total population and was similar across the two treatment groups. The changes in mean DBP from baseline to Week 52 were [redacted] with semaglutide ([redacted] mmHg) than with placebo ([redacted] mmHg).

2.6.2.4 Exploratory endpoints

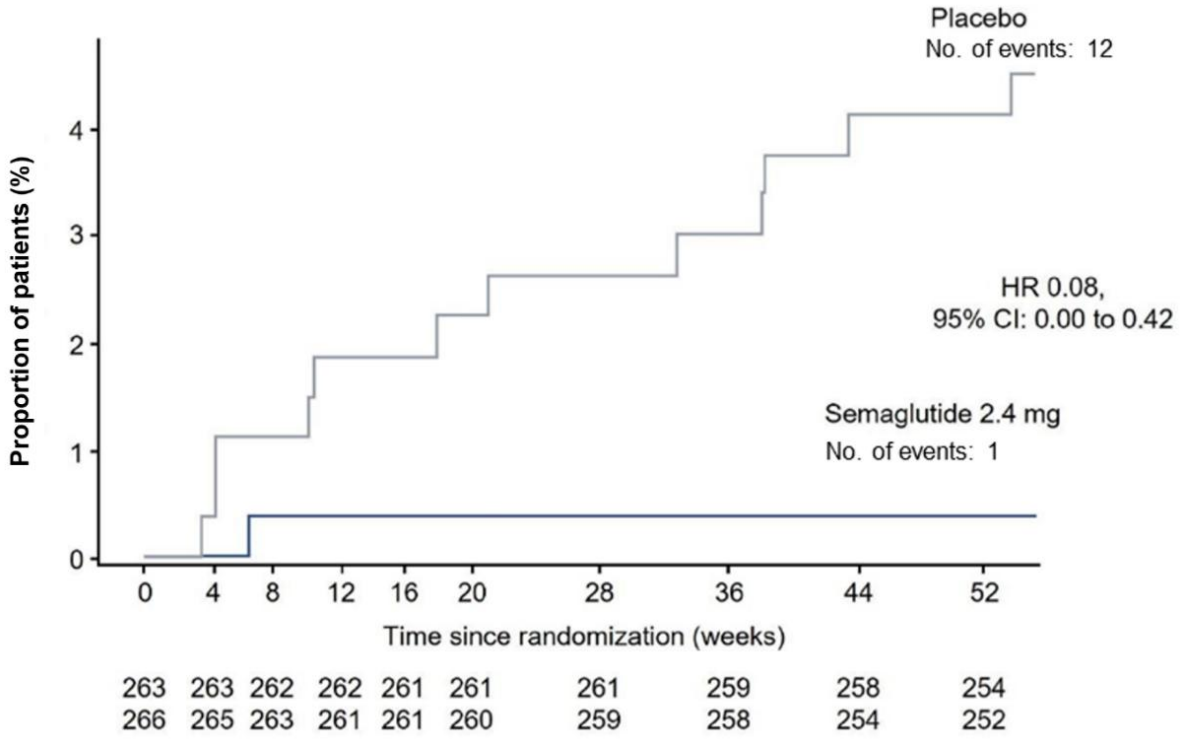
2.6.2.4.1. Time to first HF event

One of the exploratory objectives of STEP-HFpEF and STEP-HFpEF DM was to investigate the effects of semaglutide on HF outcomes, by measuring time to first HF event (adjudicated events of HF hospitalisations or urgent visits requiring intravenous therapy) from baseline to Week 57. Similar to what was observed in SELECT (Section 2.6.1.3.2), the risk of experiencing an HF event was lower with semaglutide than with placebo, in both STEP-HFpEF and STEP-HFpEF DM.

2.6.2.4.1.1. STEP-HFpEF

In the semaglutide group, one participant had an adjudicated event of hospitalisation for HF or an urgent visit, compared with 12 participants in the placebo group (HR: 0.08; 95% CI: 0.00, 0.42) (107). The cumulative incidence plot of time from randomisation to first HF event is illustrated in Figure 17.

Figure 17: Cumulative incidence plot of time from randomisation to first HF event

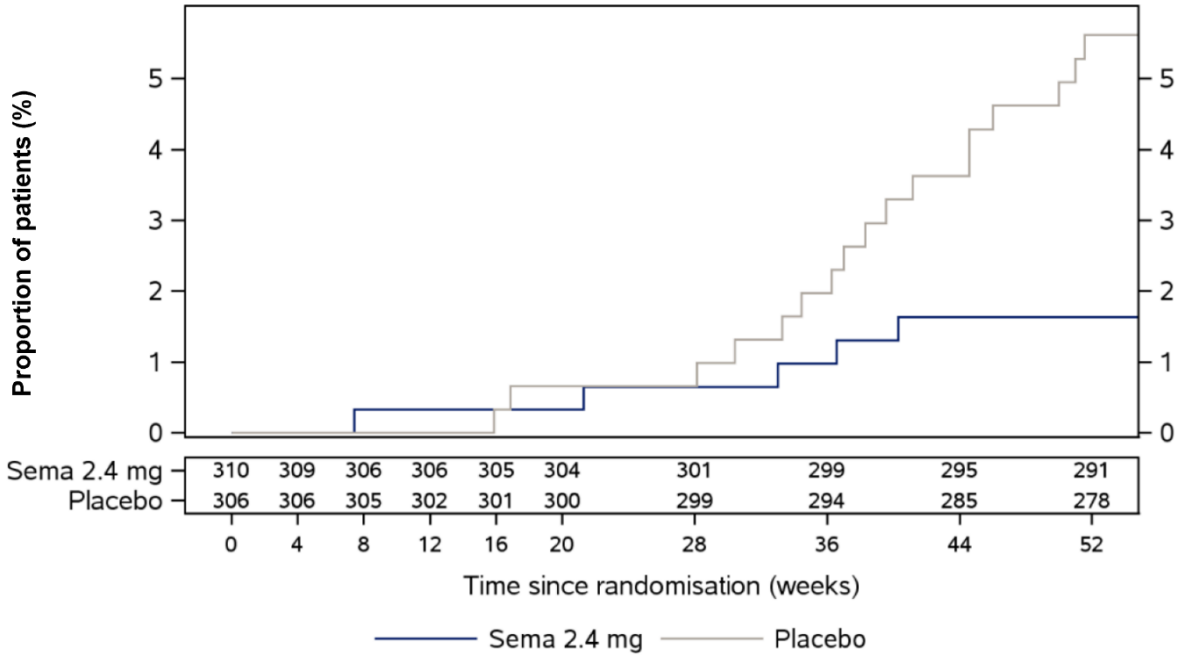


Source: Kosiborod 2023 appendix (107).
Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio.

2.6.2.4.1.2. STEP-HFpEF DM

At Week 57, seven participants had experienced eight HF events in the semaglutide group vs 18 participants who had experienced 23 HF events in the placebo group (Figure 18), resulting in an estimated HR of 0.40 (95% CI: 0.15, 0.92).

Figure 18: Time from randomisation to first EAC-confirmed heart failure event - cumulative incidence plot



Source: Kosiborod 2024 appendix (108)
Abbreviations: CI, confidence interval; CTR, clinical trial report; EAC, event adjudication committee; HF, heart failure; HR, hazard ratio; sema, semaglutide.

2.6.2.4.2. Change in NT-proBNP from baseline to Week 52

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a biomarker of myocardial strain and HF. In STEP-HFpEF and STEP-HFpEF DM, treatment with semaglutide resulted in a greater decrease in NT-proBNP levels than with placebo. Although changes in NT-proBNP were not measured in SELECT, it is a relevant outcome to report in this submission as it is a marker of CV health.

2.6.2.4.2.1. STEP-HFpEF

At baseline, geometric mean NT-proBNP was [redacted] pg/ml across the total trial population and was similar between the two treatment groups. The ratio to baseline changes in mean NT-proBNP from baseline to Week 52 were [redacted] and [redacted] with semaglutide and placebo, respectively. The estimated treatment change in mean

NT-proBNP was −20.90% with semaglutide and −5.31% with placebo, resulting in a statistically significant (CIs did not cross zero) ETD of [redacted]% (95% CI: [redacted]).

2.6.2.4.2.2. STEP-HFpEF DM

Similar to what was observed in STEP-HFpEF, treatment with semaglutide resulted in a greater decrease in NT-proBNP levels than with placebo. At baseline, geometric mean NT-proBNP was [redacted] pg/ml across the total trial population and was similar between the two treatment groups. The ratio to baseline changes in mean NT-proBNP from baseline to Week 52 were [redacted] and [redacted] with semaglutide and placebo, respectively. The estimated treatment change in mean NT-proBNP was −23.20% with semaglutide and −4.58% with placebo, resulting in a statistically significant (CIs did not cross zero) ETD of [redacted]% (95% CI: [redacted]).

2.6.3 Other studies of semaglutide with CV outcomes

SELECT was the first CVOT of semaglutide conducted in people with eCVD and BMI ≥27 kg/m^2, without T2D, but it was based on a body of evidence collected in previous studies, presented in Appendix J. Across all studies, there were statistically significant and clinically important improvements in CV risk factors (such as hsCRP and blood pressure) with semaglutide vs placebo. The evidence collected in those previous studies is not presented here as primary or supporting evidence, since the indications, populations studied, semaglutide doses and/or primary outcomes differ from those in the decision problem; however, a brief overview of studies where Time to first occurrence of MACE was a primary or key secondary endpoint is presented below.

The SUSTAIN-6 RCT (NCT01720446) was excluded from the clinical SLR as it used a lower dose of semaglutide, but is included in the Wegovy® SmPC as supportive evidence for the effectiveness of semaglutide in preventing MACE (28). In SUSTAIN-6, people with insufficiently controlled T2D and at high risk of CV events (irrespective of baseline BMI) were randomised to either semaglutide s.c. 0.5 mg or 1.0 mg once-weekly, or placebo. The non-inferiority margin was 1.8 for the upper boundary of the 95% CI of the HR. Treatment with semaglutide reduced the rate of MACE vs placebo by 26% (HR: 0.74, 95% CI: 0.58, 0.95; p<0.001 for non-inferiority).

This was mainly driven by a significant 39% decrease in the rate of non-fatal stroke (HR: 0.61, 95% CI: 0.38, 0.99; p=0.04) and a non-significant 26% decrease in non-fatal MI (HR: 0.74, 95% CI: 0.51, 1.08; p=0.12) (109).

The CV benefits of the oral formulation of semaglutide was investigated in the PIONEER 6 RCT (NCT02692716). In PIONEER 6, people with T2D and at high risk of CV events (irrespective of baseline BMI) were randomised to either once-daily oral semaglutide (target dose: 14 mg) or placebo (126). As in SUSTAIN-6, the non-inferiority margin was 1.8 for the upper boundary of the 95% CI of the HR. Treatment with semaglutide reduced the rate of MACE vs placebo by 21% (HR: 0.79, 95% CI: 0.57, 1.11; p<0.001 for non-inferiority).

The latest data on the CV benefits of semaglutide come from the FLOW RCT (NCT03819153), where s.c. semaglutide (1.0 mg weekly) significantly reduced the risk of MACE vs placebo (HR: 0.82; 95% CI: 0.68, 0.98; p=0.029) in people with CKD and T2D (127), and from the SOUL RCT (NCT03914326), where oral semaglutide demonstrated a statistically significant and superior reduction in MACE of 14% (HR: 0.86; 95% CI: 0.77, 0.96; p=0.006) vs placebo in people with T2D and eCVD and/or CKD (128).

2.7 Subsequent treatments used in the relevant studies

In SELECT, data on subsequent treatments were not collected. At the end of the trial, treatment with semaglutide could be continued at the discretion of the Investigator.

2.8 Subgroup analysis

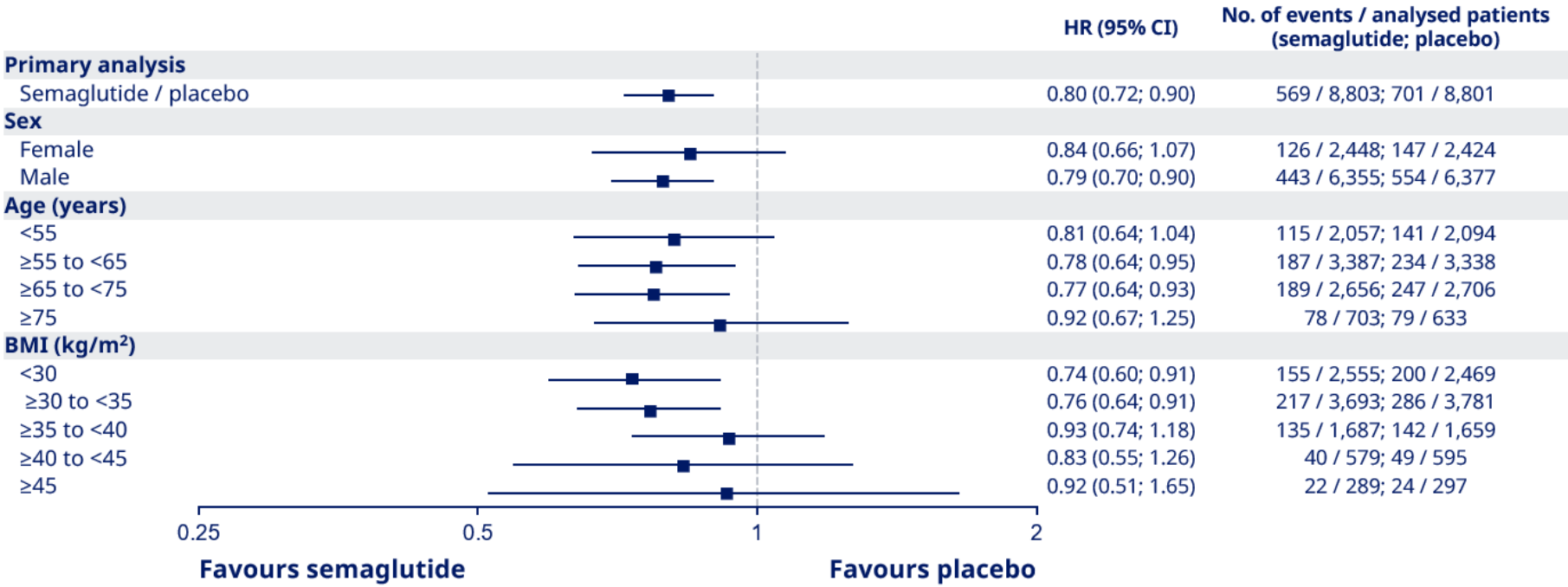
Subgroup analyses from SELECT are presented in this section; subgroup analyses from STEP-HFpEF and STEP-HFpEF DM are presented in Appendix C.

In SELECT, the consistency in the treatment effect for the primary endpoint was explored by predefined subpopulation analyses based on baseline information (age, sex, BMI; baseline CVD, HF status, eGFR, HbA1c; region, race, and ethnicity). Results of the subpopulation analyses were consistent with the results from the primary analysis, with point estimates of HR below 1 indicating the consistent beneficial effect of semaglutide vs placebo across all subpopulations (Figure 19,

Figure 20 and Figure 21), as confirmed by the MHRA in their UK Public Assessment Report (129).

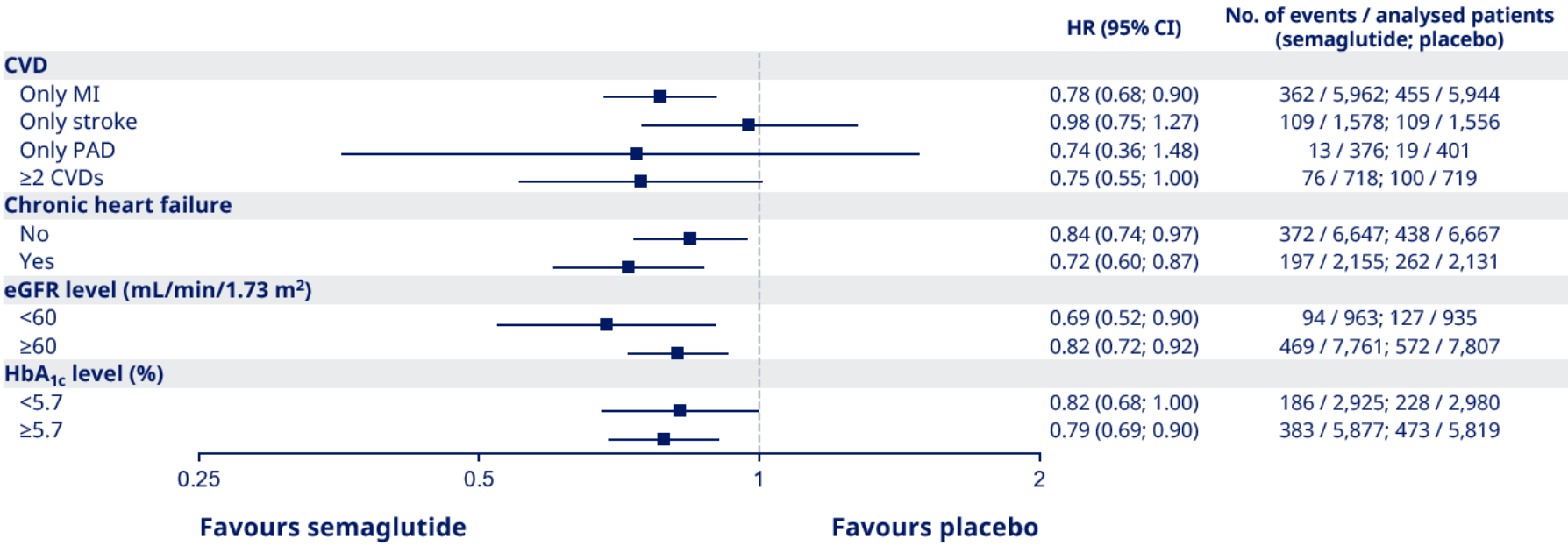
Some wide CIs were noted in the following subgroups, indicating a degree of uncertainty with regards to treatment effect: Female; Age (<55 and ≥75 subpopulations); BMI (≥35 to <40, ≥40 to 45 and ≥45 subpopulations); Baseline CVD (Only stroke and Only PAD subpopulations); Region (North America and Other subpopulations); Race (Black or African American and Other subpopulations); and Hispanic/Latino. However, some of the wide CIs may be due to small participant numbers in the following subpopulations (each representing <5% of the total trial population): BMI ≥45; Only PAD; and Black or African American and Other subpopulations. Overall, subgroup analyses from the primary endpoint supported results of the primary analysis, and consistent results were seen across all subpopulations investigated.

Figure 19: Forest plot of time from randomisation to first EAC-confirmed MACE, statistical subpopulation analyses for baseline sex, age, BMI (FAS – in trial)



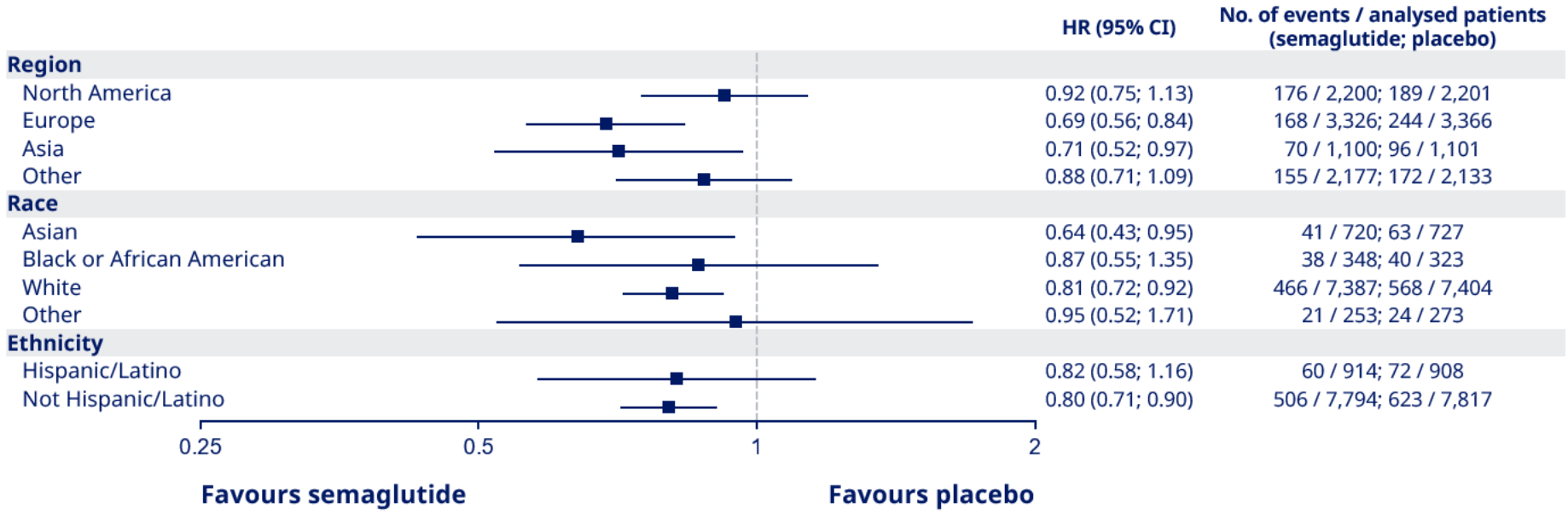
Source: Adapted from Lincoff 2023 appendix (44).
Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; EAC, event adjudication committee; FAS, full analysis set; HR, hazard ratio; MACE, major adverse cardiovascular event.

Figure 20: Forest plot of time from randomisation to first EAC-confirmed MACE, statistical subpopulation analyses for baseline CVD, chronic heart failure, eGFR level, and HbA1c level (FAS – in trial)



Source: Adapted from Lincoff 2023 appendix (44).
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; EAC, event adjudication committee; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HbA1c, glycated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; PAD, peripheral arterial disease.

Figure 21: Forest plot of time from randomisation to first EAC-confirmed MACE, statistical subpopulation analyses for region, race, and ethnicity (FAS – in trial)



Source: Adapted from Lincoff 2023 appendix (44).
Abbreviations: CI, confidence interval; EAC, event adjudication committee; FAS, full analysis set; HR, hazard ratio; MACE, major adverse cardiovascular event.

2.9 Meta-analysis

As SELECT was a head-to-head study of semaglutide vs comparator (SoC covering the management of CV risk factors including medical treatment and healthy lifestyle counselling), Novo Nordisk has not conducted a meta-analysis as part of this appraisal.

Novo Nordisk is aware of a number of recently published meta-analyses and in addition, several studies which included a meta-analysis were flagged for review during the SLR screening process. Of the reviewed published meta-analyses, none were considered to be relevant to the decision problem outlined in the scope, and none were considered to provide estimates on the effects of semaglutide in people with eCVD and living with overweight or obesity, that were more robust than SELECT. This is because the published meta-analyses varied in the trials that were included, meaning there was heterogeneity across the published meta-analyses in terms of study populations (baseline CV risk, people with and without T2D), interventions and comparators (GLP-1 agonists of any kind; specific GLP-1 agonists such as semaglutide; oral and/or subcutaneous administration, dose differences) and outcomes analysed. Additionally, across the published meta-analyses the SELECT trial was routinely identified as the largest and only CVOT which aligned directly with the decision problem for this submission, i.e. the trial used the 2.4 mg dose of semaglutide, included only participants with eCVD, and was designed to measure the effect of semaglutide on MACE and other CV outcomes.

This is illustrated in one SLR and meta-analysis exploring the effect of semaglutide on CV outcomes (130), which included the following five trials: SELECT, STEP-HFpEF, STEP-HFpEF DM, SUSTAIN-6, and PIONEER 6. As noted in Section 2.6.3, although Time to first MACE was a reported outcome, the SUSTAIN-6 and PIONEER 6 studies are not relevant as both employed doses of semaglutide that fall outside the scope of the current submission (1 mg subcutaneous and 14 mg oral semaglutide, respectively; these doses are indicated for insufficiently controlled T2D, which would be subject to specific T2D pathways). SELECT, which provides the evidence for the present submission, was the largest trial included in the meta-analysis; it was the highest weighted study in any relevant analysis, and pooled data were very similar to data from SELECT when considered alone (Table 25).

The SELECT trial is therefore considered to be the most appropriate evidence source for this appraisal with published meta-analyses further highlighting and supporting the use of SELECT as the key evidence for this submission.

Table 25: Results of the Cleto meta-analysis and SELECT for CV outcomes

Outcome	SELECT (44)		Cleto meta-analysis (130)						
	RR	CI	Pooled results†		S.c. semaglutide‡		Oral semaglutide		p-value¶
			RR	CI	RR	CI	RR	CI	
Death from CV causes	0.85	0.71, 1.01	0.83	0.71, 0.98	0.87	0.74, 1.02	0.50	0.27, 0.93	0.09
Death from any cause	0.81	0.71, 0.93	0.79	0.70, 0.89	0.81	0.72, 0.92	0.51	0.31, 0.84	0.08
Hospitalisation or urgent medical visit for HF	0.79	0.60, 1.03	0.77	0.55, 1.08	0.61	0.31, 1.22	0.88	0.49, 1.57	0.44
Unstable angina leading to hospitalisation	0.87	0.67, 1.13	0.97	0.79, 1.19	0.94	0.77, 1.16	1.57	0.61, 4.05	0.30
Non-fatal MI	0.72	0.61, 0.85	0.76	0.66, 0.88	0.73	0.63, 0.85	1.19	0.74, 1.91	0.05
Non-fatal stroke	0.93	0.74, 1.15	0.86	0.71, 1.04	0.87	0.71, 1.05	0.75	0.35, 1.58	0.72
CR	0.77	0.68, 0.87	0.76	0.69, 0.85	0.76	0.69, 0.85	–	–	–§
HF hospitalisation on participants with HFpEF	_††	_††	0.26	0.12, 0.57	0.26	0.12, 0.57	–	–	–§

†Pooled results for: semaglutide s.c. 1 mg; semaglutide s.c. 2.4 mg; oral semaglutide 14 mg; ‡Pooled results for: semaglutide s.c. 1 mg; semaglutide s.c. 2.4 mg; ¶p-value of comparison between s.c. semaglutide and oral semaglutide; §It was not possible to perform a test because only studies that used s.c. semaglutide evaluated this outcome; ††HF hospitalisation in participants with HFpEF was not an endpoint in SELECT.
Abbreviations: CI, confidence interval; CR, coronary revascularisation; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction; RR, relative risk; s.c., subcutaneous.

2.10 Indirect and mixed treatment comparisons

As SELECT was a placebo-controlled, head-to-head study of semaglutide + SoC vs SoC alone, and no other studies relevant to the scope were identified in the SLR, no indirect or mixed treatment comparison was required.

2.11 Adverse reactions

The key safety data from SELECT are presented in Section 2.11.1, with additional data provided in Appendix D. A brief overview of safety for STEP-HFpEF and STEP-HFpEF DM is presented in Section 2.11.2, with key safety data presented in Appendix D.

2.11.1 SELECT

2.11.1.1 Treatment exposure

In total, [redacted] participants were exposed to treatment. The median on-treatment observation time was [redacted] for the semaglutide group and [redacted] for the placebo group.

2.11.1.2 Adverse events

2.11.1.3 All adverse events

Overall, the AEs reported in the trial were as expected for the enrolled trial population and the trial product. An overview of all AEs with onset during the in-trial period is provided in Appendix D.

2.11.1.4 Serious adverse events and deaths

The proportion of participants with serious adverse events (SAE) (including events with fatal outcome) with onset during the in-trial observation period was significantly lower with semaglutide than with placebo (33.4% vs 36.4% of participants, p<0.001; Table 26). Most reported SAEs were of severe or moderate severity; SAEs of severe intensity were reported in [redacted]% of participants in the semaglutide group compared with [redacted]% with placebo. According to investigator assessment, most SAEs were judged as unlikely to be related to trial product, both with semaglutide and placebo. Most SAEs were resolved at the end of the trial.

As described in Section 2.6.1.3.3, 375 participants in the semaglutide group and 458 in the placebo group died during the in-trial observation period, based on EAC-determined day of death. However, based on an investigator-led analysis, [redacted] participants in the semaglutide group and [redacted] in the placebo group had an SAE with a fatal outcome with onset during the in-trial observation period. The difference between the EAC and investigator evaluations can be due to the EAC-determined date of death deviating from the onset date of the fatal SAE provided by the investigator, resulting in a slightly different number of deaths during the in-trial period. Furthermore, discrepancies may exist between the EAC and the investigator evaluations with respect to the causative event leading to a fatal outcome.

Table 26: Overview of SAEs (FAS – in trial)

	Semaglutide N=8,803 n (%)†	**Placebo N=8,801 n (%)†**	**p-value**
SAEs	2,941 (33.4)	3,204 (36.4)	<0.001
Severity			
Severe	[redacted]	[redacted]	–
Moderate	[redacted]	[redacted]	–
Mild	[redacted]	[redacted]	–
Relationship to trial product‡			
Probable	[redacted]	[redacted]	–
Possible	[redacted]	[redacted]	–
Unlikely	[redacted]	[redacted]	–
Outcome			
Recovered	[redacted]	[redacted]	–
Not recovered	[redacted]	[redacted]	–
Fatal	[redacted]	[redacted]	–
Recovered with sequelae	[redacted]	[redacted]	–
Recovering	[redacted]	[redacted]	–
Unknown	[redacted]	[redacted]	–
SAEs leading to permanent treatment discontinuation	[redacted]	[redacted]	–

Source: Lincoff 2023 (44), SELECT final CTR (112).
†Number of participants with at least one event; ‡As judged by the investigator.
Abbreviations: CTR, clinical trial report; FAS, full analysis set; SAE, serious adverse event.

2.11.1.5 Serious adverse events by system organ class

Serious adverse events were most frequently reported in the system organ class (SOC) of cardiac disorders and infections and infestations, both with semaglutide and placebo. Notably, the proportion of participants reporting SAEs within these SOCs were lower with semaglutide than placebo. The proportion of participants reporting SAEs within the SOC of gastrointestinal (GI) disorders was similar in the semaglutide and placebo groups The most frequently reported SAEs, occurring in ≥2% of participants, are listed in Table 27.

Table 27: Most frequent SAEs by SOC in ≥2% of participants (FAS – in trial)

	Semaglutide N=8,803 n (%)†	Placebo N=8,801 n (%)†	p-value
Cardiac disorders	1,008 (11.5)	1,184 (13.5)	<0.001
Infections and infestations	624 (7.1)	738 (8.4)	0.001
Nervous system disorders	444 (5.0)	496 (5.6)	0.08
Surgical and medical procedures	433 (4.9)	548 (6.2)	<0.001
Neoplasms benign, malignant, and unspecified	405 (4.6)	402 (4.6)	0.94
Gastrointestinal disorders	342 (3.9)	323 (3.7)	0.48
Injury, poisoning, and procedural complications	305 (3.5)	313 (3.6)	0.74
General disorders and administration-site conditions	273 (3.1)	316 (3.6)	0.07
Musculoskeletal and connective tissue disorders	236 (2.7)	254 (2.9)	0.41
Vascular disorders	231 (2.6)	259 (2.9)	0.20
Renal and urinary disorders	192 (2.2)	198 (2.2)	0.76
Respiratory, thoracic, and mediastinal disorders	180 (2.0)	276 (3.1)	<0.001

Source: Lincoff 2023 (44).
†Number of participants with at least one event.
Abbreviations: FAS, full analysis set; SAE, serious adverse event; SOC, system organ class.

2.11.1.6 Adverse events leading to treatment discontinuation

The proportion of participants with AEs leading to permanent discontinuation of trial product was higher with semaglutide than with placebo (16.6% vs 8.2%), and this was predominantly driven by AEs in the SOCs of GI disorders (semaglutide: 10.0%;

placebo: 2.0%) (Table 28). The majority of AEs leading to permanent trial product discontinuation were mild or moderate.

Table 28: Adverse events leading to permanent discontinuation of trial product in ≥1% of participants (FAS – in trial)

	Semaglutide N=8,803 n (%)†	Placebo N=8,801 n (%)†	p-value
AEs leading to permanent discontinuation of trial product	1,461 (16.6)	718 (8.2)	<0.001
Severity			
Mild	[redacted]	[redacted]	–
Moderate	[redacted]	[redacted]	–
Severe	[redacted]	[redacted]	–
AEs by SOC			
Gastrointestinal disorders	880 (10.0)	172 (2.0)	<0.001
Nervous system disorders	124 (1.4)	92 (1.0)	0.03
Metabolism and nutrition disorders	108 (1.2)	27 (0.3)	<0.001
General disorders and administration-site conditions	105 (1.2)	47 (0.5)	<0.001
Neoplasms benign, malignant, and unspecified	80 (0.9)	105 (1.2)	0.07
Infections and infestations	75 (0.9)	84 (1.0)	0.47

Source: Lincoff 2023 (44), SELECT final CTR (112).
†Number of participants with at least one event.
Abbreviations: AE, adverse event; CTR, clinical trial report; FAS, full analysis set; SOC, system organ class.

2.11.2 STEP-HFpEF and STEP-HFpEF DM

In both STEP-HFpEF and STEP-HFpEF DM, the safety and tolerability profile of semaglutide was in line with what was previously reported, and no new safety concerns were identified. During the treatment period[b], semaglutide was associated with a significantly lower rate of SAEs than placebo (STEP-HFpEF: semaglutide 13.3% vs placebo 26.7%, p<0.001; STEP-HFpEF DM: semaglutide 17.7% vs placebo 28.8%, p=0.002), which was mainly driven by the SOCs of Cardiac

[b] Period from the date of the first administration of semaglutide or placebo to the date of last administration, excluding potential intervals during which semaglutide or placebo was not being received (i.e. two or more consecutive missed doses).

disorders and Infections or infestations (107, 108). The types and frequencies of AEs were in line with the known safety profile of GLP-1 RAs. Safety data for both trials are presented in Appendix D.

2.12 Ongoing studies

The long-term effects of semaglutide in people with eCVD and BMI ≥27 kg/m^2 are currently being investigated in SELECT-LIFE (NCT04972721), discussed further in Section 2.13 (131). While a read out is expected in late 2025 (interim data cutoff), the study is not due to complete until 2033, and is a survey-based study only, with no trial product provided. Ongoing clinical trials of semaglutide with estimated completion dates beyond 12 months of this submission are listed in Appendix J.

2.13 Interpretation of clinical effectiveness and safety evidence

Scientific evidence

SELECT recruited people at high risk of secondary CV events, who had eCVD and a BMI ≥27 kg/m^2, and benefitted from a large sample size (17,000+). SELECT confirmed the superiority of semaglutide for the primary endpoint of time to first EAC-confirmed MACE (comprising CV death, non-fatal MI, and non-fatal stroke) over placebo, with a significant reduction in the risk of MACE vs placebo (HR: 0.80; 95% CI: 0.72, 0.90; p<0.0001). Both semaglutide and placebo were administered on top of evidence-based SoC, which included management of CV risk factors through optimisation of treatment with medication, and individualised healthy lifestyle counselling. Semaglutide also showed a benefit in the confirmatory secondary endpoints, with a numerical reduction in the risk of CV death, occurrence of an HF composite endpoint and all-cause death vs placebo.

The emergence of between-group difference in CVD incidence early in the trial, as shown by the early separation of the curves shortly after trial initiation (Section 2.6.1.2) suggests more rapid semaglutide-induced physiological changes beyond the magnitude of body weight loss; this is supported by the pre-specified analysis by Deanfield et al, 2024 reporting on the relationship between baseline weight measures, early change in weight and MACE outcomes, which found that the magnitude of the treatment effect with semaglutide on the primary endpoint was independent of the extent of weight loss (110). Altogether, the data indicate that

people with BMI ≥27 kg/m^2 may derive CV benefit from semaglutide, even before they start losing weight, and irrespective of how much weight they lose.

Furthermore, semaglutide showed clinically relevant improvements in a broad range of pre-specified cardiometabolic risk factors (3), including blood pressure, lipid profile, hsCRP, glucose metabolism and kidney function (2). SELECT was an outcomes, not a mechanistic, trial, therefore the mechanisms of cardiovascular protection with semaglutide remain speculative. However, it is known that semaglutide selectively binds to and activates GLP-1 receptors (40), which are expressed throughout the body (30). The multiple sites of action of semaglutide, the consistent effects on cardiometabolic risk factors, and the consistent CV benefit seen across the primary and confirmatory secondary endpoints all support the hypothesis that clinical benefit is achieved through multiple interrelated pathways, and not just through weight loss alone (44).

The CV benefits observed with semaglutide in the whole study were supported by subgroup analyses, which showed directionally similar effects on MACE among all prespecified participant subgroups, supporting a consistent treatment effect and clinical benefit across all patient subpopulations.

Safety findings were consistent with previous trials with semaglutide, confirming the well-established safety and tolerability profile of semaglutide. Notably, there were significantly fewer SAEs in the SOC of Cardiac disorders in the semaglutide group than in the placebo group (11.5% vs 13.5%, p<0.001), demonstrating once again the CV benefits of semaglutide added to SoC vs SoC alone. No new safety concerns were identified during the long-term follow-up of participants in SELECT (median in-trial observation period of [redacted], with total observation time of 29,283 patient-years for semaglutide).

Commentary on scientific evidence/protocol and clinical practice

***Strengths*:** SELECT evaluated semaglutide on top of SoC vs SoC alone. The SoC in the trial included management of CV risk factors and individualised healthy lifestyle counselling, but no specific lifestyle intervention: this is in contrast to weight management trials such as the STEP programme (presented in Appendix J), where counselling was done by a dietician or a similar qualified healthcare professional

every 4th week via visits/phone contacts, and participants were required to record their food intake and physical activity daily in order to assist and evaluate their lifestyle intervention (132). The SoC in SELECT is representative of UK guidelines, and clinical practice (as confirmed by UK clinicians) which recommend patients should be given advice about lifestyle changes, including diet and physical exercise, but without specific intervention goals as part of CV risk management (87, 88, 95, 115). People who have suffered an MI should be given advice on and offered a cardiac rehabilitation programme, as described in Section 1.3.4 (87).

In SELECT, people with diabetes at baseline were excluded to eliminate any confounding effect that a diabetes diagnosis could have on future CV risk (112); the beneficial CV effects of semaglutide had previously been demonstrated in people with insufficiently controlled T2D in the SUSTAIN-6 trial, where semaglutide reduced the rate of MACE vs placebo by 26% (HR: 0.74, 95% CI: 0.58, 0.95) (109). Notably, a clinical expert remarked that although SELECT did not include people with T2D, the benefit for people with eCVD, overweight or obesity and T2D was likely to be greater than the benefit for people without T2D (115). Taken together, the positive outcomes from SELECT and SUSTAIN-6 show that the CV benefits of semaglutide are applicable to a broad population that includes people with eCVD and with BMI ≥27 kg/m^2, with or without T2D, which is reflected in the semaglutide licence (28).

Notably, the strength and relevance of the clinical evidence from SELECT has been internationally recognised, with the ESC recommending semaglutide in patients with CCS and BMI >27 kg/m^2 to reduce CV mortality, MI, or stroke and the US Food and Drug Administration (FDA) approving semaglutide to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal MI, or non-fatal stroke) in adults with eCVD and either obesity or overweight (29, 133).

Limitations: In SELECT, the superiority hypothesis was tested for all confirmatory endpoints via a hierarchical testing scheme (Section 2.4.3). The testing procedure was stopped the first time an analysis failed to confirm superiority of the endpoint in question. This means that, because the confirmatory endpoint of time to CV death did not meet statistical significance, superiority was not measured for the other confirmatory endpoints. However, the robustness of the primary endpoint results was supported by the results from Time to first event analyses of other composite CV

endpoints, such as Expanded MACE and All-cause death, non-fatal MI or non-fatal stroke, which both showed a substantial benefit with semaglutide vs placebo ($p<0.0001$ [two-sided p-value for test of no difference] for both endpoints – Table 14).

As described in Section 2.6.1.7, it is likely the COVID-19 pandemic impacted some of the mortality outcomes in SELECT (122). However, the trial was able to complete despite the pandemic, and while the competing risk of COVID was a likely contributor to the convergence of the survival curves for CV deaths, the rate of non-CV death was lower with semaglutide than with placebo, including in participants with reported cases of COVID-19 (122), which highlights the mortality benefit seen with semaglutide across supportive and confirmatory secondary endpoints (Sections 2.6.1.2.1 and 2.6.1.3).

Clinical feedback

Clinical experts consulted at the advisory board conducted by Novo Nordisk have stated that the population in SELECT is broadly representative of patients attending cardiology clinics in the UK and that even though the majority (70%) were male, the findings were also applicable to women (95). Additional clinical expert opinion confirmed that overall, there was no significant difference between the SELECT population and the UK population who have had a CV event, and that semaglutide could be prescribed in cardiovascular clinics, although cardiologists could also communicate with GPs to initiate semaglutide, based on SELECT data (78). Another clinical expert consulted as part of this submission noted that a key benefit of SELECT was its very large sample size, and that study generalisability should not be a concern (115). Notably, although only 5.3% of the participants included in the FAS were from the UK, this still represents a large sample size (933 participants, Section 2.3.1).

Clinical experts (advisory board and individual interviews) were impressed with the 20% reduction of MACEs in a population of 17,000+, especially in participants who were receiving guideline-recommended secondary prevention therapy, and by the reduction in blood pressure (95, 115). There was a consensus that the data from SELECT supported the use of semaglutide to mitigate residual CV risk in those at high-risk. Another clinical expert commented that event rates in the placebo arm of

SELECT were significant (MACE rate of 10% at 4 years), despite reasonably well-controlled risk factors (78): approximately [redacted]% of participants were receiving CV medication at randomisation (Section 2.3.3) and baseline blood pressures were within the normal range (SBP ~131 mmHg and DBP ~79 mmHg, Section 2.6.1.4.3).

Innovation

As described in Section 1.3.5, most CVOTs in obesity have been inconclusive, with several trials being terminated prematurely and others failing to show superiority or efficacy of the trial drug (100, 103, 134-137). To date, SELECT is the first and only Phase 3 study demonstrating improved cardiovascular outcomes with a GLP-1 RA vs placebo in people without T2D, and this has been applied to a population at high risk of recurrent CV events. The consistent CV benefits observed in the semaglutide group support the role of semaglutide as a CVD-modifying agent.

Conclusion

Despite CV mortality rates having decreased over the past decades, CVD remains the second most common cause of death in the UK, despite advances in treatment in the acute CV event setting, and in the long-term management of risk factors. Alarmingly, rates of premature mortality due to CVD have increased in the past few years, partially due to an increase of risk factors such as obesity and hypertension. While more people now survive MI and stroke, they remain at high risk of experiencing subsequent CV events, and of increased mortality.

Data from SELECT support the addition of semaglutide to the existing pathway of care, where it could significantly benefit the growing population of people with eCVD and BMI ≥27 kg/m^2, by reducing the risk of subsequent CV events and by its positive impact on risk factors such as blood pressure, lipid profile, hsCRP, glucose metabolism, kidney function and excess weight. Additionally, semaglutide has a well-known, favourable safety profile which has been evidenced in clinical practice, where it is used extensively. This is particularly important as several anti-obesity drugs investigated in CVOTs had to be terminated due to safety concerns. Furthermore, the average duration of follow-up in SELECT was over 3 years, which supports its use as a long-term CVD therapy, as part of effective residual risk management.

3 Cost effectiveness

The cost-effectiveness of semaglutide to reduce the risk of major CV events in adults with eCVD and living with overweight or obesity was estimated to be £14,702 per quality-adjusted life year (QALY) gained, compared with established clinical management.

- No cost-effectiveness study with a UK perspective addressing the cost-effectiveness of semaglutide to reduce the risk of MACE in adults with eCVD and living with obesity or overweight was identified, therefore a de novo UK economic analysis was conducted, based on a validated model structure used in a study with a US perspective (138)
- This analysis was conducted using a state-transition model, states were: non-fatal MI, non-fatal stroke, non-fatal hospitalisation for heart failure (HHF), non-fatal hospitalisation for unstable angina (HUA), non-fatal coronary revascularisation (CR), CV death, non-CV death, and T2D
- Event incidence was estimated using parametric survival equations derived from SELECT
- Base utility was defined according to patient age, sex and the presence of CVD. Utility decrements were applied for: acute CV events; post-CV event health states; CKD states, presence of T2D, AEs of treatment and BMI. Costs were informed by reference costs and published literature
- The addition of semaglutide to the established clinical management was associated with [redacted] incremental costs, [redacted] incremental QALYs, and [redacted] life-years per patient, resulting in an incremental cost-effectiveness ratio (ICER) of £14,702 per QALY gained.

The cost-effectiveness model was robust to reasonable variation.

- The one-way sensitivity analysis (OWSA) suggested that the model was stable, with ICERs below £20,000/QALY for the analyses performed
- Scenario and subgroup analyses were conducted: all resulted in ICERs below £20,000/QALY. Scenarios resulting in lower ICERs than the base case included treatment of a UK population with eCVD (£11,072/QALY), people with chronic heart failure (£12,684/QALY) and people with chronic kidney disease (£11,961/QALY).
- The probabilistic sensitivity analysis (PSA) resulted in an ICER of £14,832/QALY, very similar to the deterministic base case. At a £20,000 WTP threshold, approximately 90% of samples found semaglutide to be cost-effective; at a £30,000 WTP threshold, this rose to more than 99%.

In conclusion, an economic analysis closely modelled on direct evidence from SELECT found the cost-effectiveness of semaglutide for the prevention of MACE to be within the range usually considered acceptable by NICE.

3.1 Published cost-effectiveness studies

An SLR (comprising a de novo SLR conducted in September 2024 and an SLR update performed in May 2025) did not identify any cost-effectiveness studies that report the cost-effectiveness of semaglutide for the reduction of MACE in adults with eCVD and BMI ≥27 kg/m2 in England. However, the model structure has already been validated in one peer-reviewed study identified that used the same model structure with a US perspective (138).

The methodology and findings of the systematic review are described in Appendix E.

The review identified seven publications referring to six cost-effectiveness studies of semaglutide 2.4 mg used for the prevention of MACE. These studies were conducted in the US, Canada and Australia (138-144). Five of the six studies estimated utility gain, all five found semaglutide to improve QALYs; estimated incremental cost-effectiveness ratios (ICERs) were sensitive to the acquisition cost of semaglutide. A pragmatic review of recent NICE guidance was conducted.

NICE guidance reported several models assessing the cost-effectiveness of interventions to reduce the risk of CV events in people with eCVD (Table 29). None of these models considered semaglutide as an intervention, and none focused on adults with eCVD and BMI ≥27 kg/m^2.

NICE TA875 assessed semaglutide for weight management in people living with obesity. However, the economic evaluation conducted as part of TA875 is not relevant to this submission: the current appraisal addresses a distinct population with different treatment goals and uses direct evidence of the effect of semaglutide on MACE, which was not available at the time of TA875.

3.2 Economic analysis

No existing cost-effectiveness study was identified that uses the SELECT data to evaluate the cost-effectiveness of semaglutide for the reduction of MACE in adults with eCVD and BMI ≥27 kg/m^2 in England. Therefore, a de novo UK economic analysis was conducted to inform this appraisal.

3.2.1 Model overview

The model structure was designed to compare a single treatment arm (semaglutide in addition to established clinical management) against a single control arm (established clinical management), aligning to the validated model structure reported in McEwan et al, 2025 (138). The model was developed as a cohort-level, state transition model. Event incidence was estimated using parametric survival equations fitted to data from SELECT.

Previous models developed to assess the cost-effectiveness of managing CVD, weight loss and obesity have included both patient-level simulations and state transition/semi-Markov approaches. Patient-level simulations have significant runtime requirements and can be computationally burdensome. A state transition approach was chosen to allow patient costs and outcomes to be estimated across their entire lifetime without the computational demands of a patient-level simulation.

3.2.2 Patient population

The base case of the economic analysis considers the population from SELECT where participants were 45 years of age or older, had a BMI ≥27 kg/m^2 and had eCVD defined as previous MI, previous stroke, or symptomatic PAD (44, 112). The SELECT population is described in Section 2.3.5.

SELECT excluded people with CV events in the preceding 60 days, and people with a diagnosis of diabetes (T1D or T2D – history of gestational diabetes was allowed). The licence does not contain these exclusions: people with with diabetes fall within the licensed indication and decision problem. Therefore, in addition to the base case, scenario analyses were conducted exploring cost-effectiveness in people with different levels of risk, with recent CV events and those with diabetes (See Section 3.11.3).

3.2.3 Model structure

This analysis was conducted using a state-transition model, in line with prior NICE technical appraisals and guidance for prevention of CVD (19, 88, 145, 146). Similar to previous technical appraisals and cost-effectiveness analyses on interventions for CVD (19, 145), event incidence was estimated using parametric survival equations

derived from SELECT. Treatment-dependent outcomes are modelled according to survival extrapolations for the first modelled event incidence by treatment arm. The modelled endpoints are:

- Non-fatal MI
- Non-fatal stroke
- Non-fatal hospitalisation for heart failure (HHF)
- Non-fatal hospitalisation for unstable angina (HUA)
- Non-fatal coronary revascularisation (CR)
- CV death
- Non-CV death
- T2D.

Subsequent event risks are estimated using the same per cycle event risks. The value of treatment is also captured via modelled differences in:

- AEs
- Progression of CKD
- Weight gain/loss.

All patients have eCVD at baseline and enter the model in the “established CVD” state. Patients may remain in this state or experience an acute CV event and progress to one of five post-event states: Post-MI, Post-stroke, Post-CR, Post-HHF or Post-HUA.

Patients who experience a second CV event in the model return to the same state if they experience the same acute event (e.g. a patient in the “Post-MI” state who experiences a further MI remains in the “Post-MI” state) or progress to one of 10 CV states for patients who have experienced two different modelled events (e.g. a patient in the “Post-MI” state who experiences a stroke moves to the “Post-MI & Stroke” state). Patients who have experienced two different CV events in the model remain at risk of further CV events, but do not change state again until they die.

Death, which is split into CV-related and non-CV-related death, can occur from any health state. The model tracks the number of patients receiving treatment, and change in mean BMI; however, these parameters do not impact health states related to CV events. No stopping rule or maximum treatment duration is assumed for semaglutide. Patients treated with semaglutide are at risk of discontinuing onto established clinical management alone, where they are subject to event incidences associated with the comparator arm.

The model considers costs and utilities associated with: CV events; CV and non-CV death; time spent in the post-CV event states for patients who have experienced one and two CV events within the model; different CKD categories; varying diabetes status (normal, prediabetes, and T2D); age; treatment status; AEs and BMI.

The model aimed for an acceptable balance between thoroughness and complexity. Simplifications that were made include:

- For patients experiencing a third or subsequent different modelled event, acute costs and utility loss are considered, but patients return to their previous heath state, so post-event states costs and utilities remain the same as they were after the second modelled event
- The model does not estimate acute cost and utility separately for patients with three (or more) modelled events compared with a second modelled event
- Outcomes and costs do not vary according to an individual's CV morbidity (MI, stroke or other) before model entry; the average for each arm is used
- Separate modules track CV events, CKD and T2D, so potential interactions are not fully captured.

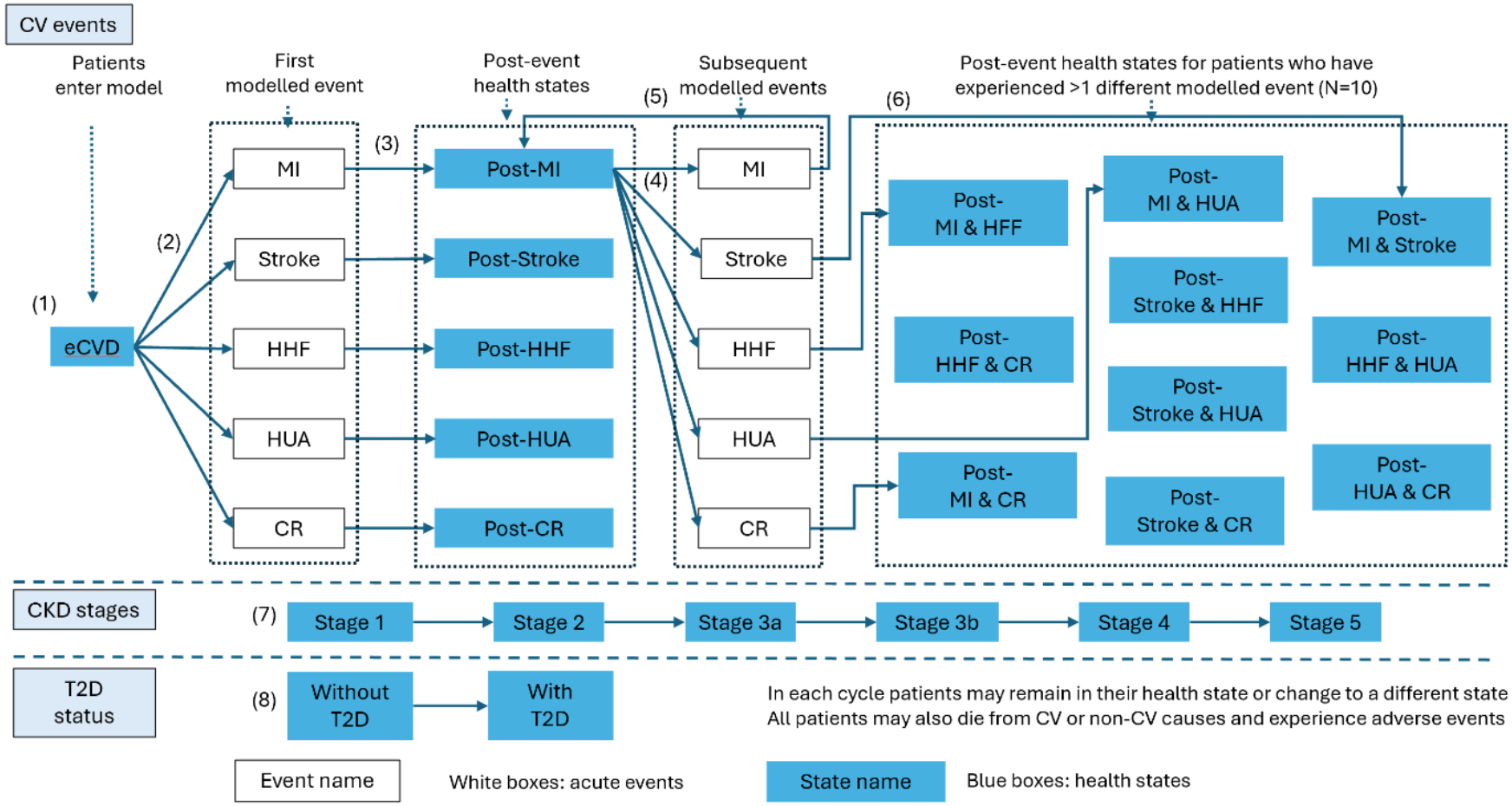
The structure of other similar models is discussed in Table 29 – the analysis presented here is more complex than some other NICE evaluations.

The model employs a four-week cycle length with half-cycle correction applied. The cycle length of four weeks provides reasonable trade-off between model granularity and runtime, and to align with the treatment titration schedule for semaglutide.

To reflect the chronic and progressive nature of CVD, the maximum age in the model was effectively assumed to be a lifetime horizon, in line with the technology assessment guidelines outlined by NICE. For the SELECT population, which had a mean age of 61.6 years, this was assumed to be 40 years. All costs and health outcomes were discounted at 3.5%, in line with the NICE technology assessment guidance (147).

The structure of the model is summarised in Figure 22.

Figure 22: Model flow diagram



(1) Patients enter the model with eCVD; (2) Patients are at risk of a first modelled event; (3) Patients who survive an event enter a post-event health state; (4) Patients are at risk of subsequent events. Transitions are shown for patients with MI as a first modelled event: similar risks exist for other post-event health states; (5) Patients who experience the same event (e.g. 2nd MI) return to the post-event health state; (6) Patients who experience a different event (e.g. a stroke after an MI) enter a post-event health state for patients with >1 modelled event. Patients have ongoing risk of further events (transitions not shown); (7) Patient CKD status and (8) patient T2D status are tracked separately.

Abbreviations: CKD, chronic kidney disease; CR, coronary revascularisation; CV, cardiovascular; eCVD, established cardiovascular disease; HHF, hospitalisation for heart failure; HUA, hospitalisation for unstable angina; MI, myocardial infarction; T2D, type 2 diabetes.

3.2.4 Comparison with previous NICE technology evaluations

Semaglutide is the first GLP-1 RA that has been shown to significantly reduce the risk of major CV events in people with eCVD and BMI ≥27 kg/m^2, a population that has high morbidity and mortality rates. As a result, no previous NICE guidance has addressed the use of a GLP-1 RA to reduce CV risk in this population. Therefore, other CVD guidance from NICE was reviewed to inform the model structure. This included NICE guidance that considered the prevention of CV events in people with eCVD, which was based on direct evidence of CV outcomes, and was conducted or updated in the last 5 years (since 2019). Guidance that considered specific subpopulations (e.g. HF) or where the evidence base consisted only of trials using surrogate markers was considered less helpful. These criteria were met by two NICE clinical guidelines (Acute coronary syndromes – NG185 (87), and CV risk reduction – NG238 (88)) and two TAs (Icosapent ethyl in people with raised triglycerides – TA805 (19) and Rivaroxaban in people with coronary or PAD – TA607 (145)). In addition, the eligibility criteria were expanded to include recent guidelines where secondary prevention was modelled as a long-term event (Hypertension in adults – NG136 (146)).

All evaluations were based on state transition models considering MACEs and their sequelae. Reported evaluations consistently obtained unit costs from NHS reference costs, supplemented by published sources. Utility values were most often estimated from EQ-5D data from the Health Survey for England, also supplemented by published sources.

Table 29: Features of the economic analysis

Evaluations and Guidance	TA805: Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides (19)	NG136: Hypertension in adults: diagnosis and management (146)	NG185: Acute coronary syndromes (87)	NG238: Cardiovascular disease: risk assessment and reduction, including lipid modification (88)	TA607: Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease (145)	This submission	
						Chosen Values	**Justification**
Model structure	State transition model	State transition model	State transition model	State transition model	State transition model	State transition model	Aligns with approach in existing evaluations
Health states considered	**Initial state:** History of CVD – coronary artery disease, MI, stroke, carotid/peripheral artery disease **Acute events:** First CV event, Second CV event, 3+ CV event **Subsequent states:** Post-first CV event, post second CV event, post 3+ CV event **Absorbing state(s):** Death (CV or other)	**Initial state:** Event free **Acute events**: HF, TIA, Stroke, MI, Angina (stable and unstable) **Subsequent states:** A tunnel state (post-event) is specified for each CV event. **Absorbing state(s):** Death (CV and non-CV)	**Initial state:** History of CVD – MI and unstable angina **Acute events:** Stroke, MI reinfarction, major bleed, minor bleed, all-cause mortality **Subsequent states:** No further event, stroke; reinfarction, post-stroke, post-reinfarction **Absorbing state:** Death (CV or non-CV)	**Initial state:** History of CVD – MI, stroke, unstable angina, CR, PAD **Acute events:** UA admission, elective CR, non-coronary revascularisation, new elective CR, MI, stroke, TIA **Subsequent states:** Post TIA, post UA, post PAD, post elective CR, post MI, post stroke **Absorbing state(s):**	**Initial state:** History of CVD – coronary or PAD **Acute events:** MI, IS, ICH **Subsequent states:** Post-MI, post-IS, post-ICH **Absorbing state(s):** Death	**Initial state:** History of CVD – MI, stroke, symptomatic PAD **Acute events:** MI, Stroke, HUA, HHF, CR **Subsequent states:** Post MI, post stroke, post HUA, post HF, post CR & post 2 events combined **Absorbing state(s):** Death (CV and non-CV)	Consideration of acute events, subsequent states and CV & non-CV death follows previous evaluations Inclusion of MI, stroke, UA and CR similar to NICE models Including HF, CKD, T2D, and combined states allow greater granularity of costing and utility assessment

Evaluations and Guidance	TA805: Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides (19)	NG136: Hypertension in adults: diagnosis and management (146)	NG185: Acute coronary syndromes (87)	NG238: Cardiovascular disease: risk assessment and reduction, including lipid modification (88)	TA607: Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease (145)	This submission	
				Death (CV and non-CV)			
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime	Aligns with approach in existing evaluations
Patient population	Adults on statin therapy with elevated triglycerides who are at high risk of CV events (matched to trial entry criteria)	Adults with primary stage 1 hypertension who do not have target organ damage, eCVD, renal disease or diabetes. Patient groups were defined according to 10-year QRISK cardiovascular risk levels in increments of 5%	People with STEMI undergoing PCI and people with unstable angina/non-STEMI undergoing PCI	Adults with eCVD on lipid modification treatment. 30 cholesterol /gender sub-groups were identified/ modelled	Adults with stable atherosclerotic vascular disease	Adults with eCVD (prior MI, prior stroke or symptomatic PAD) and BMI ≥27 kg/m^2	Base-case population matched to SELECT

Evaluations and Guidance	TA805: Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides (19)	NG136: Hypertension in adults: diagnosis and management (146)	NG185: Acute coronary syndromes (87)	NG238: Cardiovascular disease: risk assessment and reduction, including lipid modification (88)	TA607: Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease (145)	This submission	
Intervention	Icosapent ethyl (Vazkepa®) in combination with a stable dose of statins with or without ezetimibe	Antihypertensive drug treatment (including ACE inhibitor, calcium channel blocker and diuretic)	DAPT – Aspirin plus clopidogrel/ prasugrel/ ticagrelor	Interventions defined according to established pathways: highest tolerated intensity of statin; ezetimibe + statin; injectable therapy (inclisiran or PCSK9 inhibitors)	Rivaroxaban twice daily + aspirin once daily	Semaglutide plus established clinical management	Intervention in line with the scope and decision problem
Comparators	Established clinical management consisting of a stable dose of statins with or without ezetimibe	No antihypertensive drug treatment	SoC based on audit data from 2017/18 – clopidogrel, prasugrel, ticagrelor	SoC	Aspirin 100 mg once daily	Established clinical management (without semaglutide)	Comparator as in SELECT, final scope and current practice in NHS
Source of utilities	NICE CG181 Baseline utility Stevanovic 2016 (secondary prevention); O'Reilly 2011 (primary prevention)	Health Survey for England 2014 NICE CG181 Peasgood 2009 NICE AKI guideline	NICE TA236 PLATO health economic subgroup analysis Amin 2016	Bespoke analysis of Health Survey for England 2017 NICE CG181	Health utilities estimated from the COMPASS trial (148)	Health Survey for England 2017 SLR of relevant literature	In line with previous guidance

Evaluations and Guidance	TA805: Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides (19)	NG136: Hypertension in adults: diagnosis and management (146)	NG185: Acute coronary syndromes (87)	NG238: Cardiovascular disease: risk assessment and reduction, including lipid modification (88)	TA607: Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease (145)	This submission	
Source of costs	Event costs: NHS Reference Costs Other: Danese 2016	NHS reference costs 2016-2017 CVD-related costs: Danese 2016; Xu et al 2016 – SSNAP project	NHS reference cost 2017/18 CVD-related costs: Danese 2016; Xu 2018	CVD-related costs: NHS Reference Costs (2019-2020) Others: PSSRU 2020/2021; Zhou et al 2023; Danese 2016; Walker 2016	NHS Reference Costs Health event and follow-up care cost:	CVD-related costs: NHS England National Cost Collection data Other: Alva 2015; Georghiou 2014; Hex 2012; Willis 2021	In line with previous guidance

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; CR, coronary revascularisation; CV(D), cardiovascular (disease); DAPT, dual antiplatelet therapy; HF, heart failure; HHF, hospitalisation for heart failure; HUA, hospitalisation for unstable angina; ICH, intracerebral haemorrhage; IS, ischaemic stroke; MI, myocardial infarction; NG, national guideline; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; (N)STEMI, (non-)ST elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; PSSRU, Personal Social Services Research Unit; SLR, systematic literature review; SoC, standard of care; SSNAP, Sentinel Stroke National Audit Programme; T2D, type 2 diabetes; TA, technology appraisal; TIA, transient ischaemic attack; UA, unstable angina.

3.2.5 Intervention technology and comparators

The intervention is semaglutide in addition to established clinical management for CV risk reduction. The comparator (SoC) is the established clinical management for CV risk reduction without semaglutide. In SELECT, investigators were encouraged to follow evidence-based recommendations in their choice of medical management of CV risk factors. Clinical feedback has confirmed that the usage of concomitant medications in SELECT reflected what was observed in the real world (78). The approach to the use of concomitant medications, and advice on diet and physical exercise is described in Section 2.3.4.

The target dose for semaglutide in the model is 2.4 mg once weekly, as per the SmPC and decision problem. The titration schedule and dose achieved in the model reflect dosing in SELECT; additional information on dosing can be found in Section 2.3.3.

Treatment discontinuation probabilities for semaglutide were estimated using SELECT data (Section 2.6.1.1). The median time from treatment initiation to discontinuation (defined as no dose administered for 35 days) was [redacted], which yielded a discontinuation rate of [redacted]% per cycle. No stopping rule or maximum treatment duration was assumed.

3.3 Clinical parameters and variables

Baseline demographics

The modelled population baseline characteristics were reflective of the total SELECT population with key baseline characteristics provided in Table 30.

Table 30: Baseline demographic inputs

Demographic	Mean	SE	Source
Mean age, years	61.6	0.016	Lingvay 2023 (120)
Male, %	72.3	0.034†	
Mean BMI, kg/m^2	33.3	0.009	
T2D at baseline, %	0.00	0.000	
Prediabetes at baseline, %	66.4	13.28†	
Proportion in each CKD stage, %‡			
Stage 1 (eGFR ≥90 ml/min/1.73 m^2)	[redacted]	[redacted]	
Stage 2 (eGFR 60–89 ml/min/1.73 m^2)	[redacted]	[redacted]	

Demographic	Mean	SE	Source
Stage ≥3a (eGFR ≤59 ml/min/1.73 m^2)	[redacted]	[redacted]	SELECT (data on file) (149)

†Univariate or multivariate Beta distribution as appropriate; ‡Share calculated as % of all participants with a reported eGFR category.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; SE, standard error; T2D, type 2 diabetes.

Time to event analysis

The risk of non-fatal events (MI, stroke, HHF, HUA, CR and the development of T2D), CV death and non-CV death were predicted by parametric survival extrapolations, derived from patient data in SELECT (44). The SELECT data pertaining to each non-fatal event were used to fit survival models to the best fitting functions for parametric distributions, in line with the methodology set out by the NICE Decision Support Unit (150).

The survival models were based on the intention-to-treat principle and included all unique participants who underwent randomisation regardless of adherence to semaglutide or placebo. Outcomes were measured across a maximum follow-up time from randomisation to 56 months.

For non-fatal events, death of any cause was considered a competing event. For CV and non-CV death, the other mortality outcome was considered a competing event. The following functional forms for the parametric survival distributions were considered: Exponential, Weibull, Gompertz, Log-logistic, Log-normal, Gamma and Generalised gamma.

An assessment of accelerated failure time (AFT) and proportional hazards (PH) assumptions was carried out to determine whether PH/AFT models were suitable, or whether single-arm models per treatment arm were required.

The best fitting distribution was selected based on examination of extrapolated cumulative incidence function (CIF) curves, goodness-of-fit statistics, a comparison of extrapolated smoothed hazard plots with real-world data, and an assessment of clinical validity by clinical experts. Appendix Q reports the survival analysis in detail.

Table 31: Survival model selection per outcome

Outcome	Type of modelling	Distribution	Rationale for selection
Non-fatal MI	PH/AFT	Exponential	• Distribution with best fit to trial data • Best alignment to clinician expectation and long-term hazard trajectory from CPRD
Non-fatal stroke	PH/AFT	Exponential	• Distribution with best fit to trial data • Best alignment to clinician expectation and long-term hazard trajectory from CPRD
Non-fatal HHF	Individual models per arm	Weibull	• Distribution with good fit to trial data • Increasing hazard in long term aligned with clinician expectation and long-term hazard trajectory from CPRD • Based on visual inspection proportional hazards was deemed implausible
Non-fatal HUA	Individual models per arm	Weibull	• Distribution with good fit to trial data • Aligned with clinical expectation and available data from CPRD • Simplest of several distributions with similar performance • Individual models preferred due to crossing log-cumulative hazard
Non-fatal CR	PH/AFT	Weibull	• One of several distributions with good fit to trial data • Projection was best aligned with clinical expectation and CPRD • Simplest of several models with similar performance
CV death	PH/AFT	Gompertz	• Only distribution to reflect CPRD and clinical expectation of increasing long run mortality
Non-CV death	PH/AFT	Gompertz	• Only distribution to reflect CPRD and clinical expectation of increasing long run mortality

Abbreviations: AFT, Accelerated Failure Time; CPRD, Clinical Practice Research Datalink; CR, coronary revascularisation; CV, cardiovascular; HHF, hospitalisation for heart failure; HUA, hospitalisation for unstable angina; MI, myocardial infarction; PH, proportional hazards.

Patient event risk was independent of prior CV events experienced, reflecting a cohort already at high risk due to the presence of eCVD at baseline. Results from the deterministic sensitivity analysis (DSA) suggest that the model is not sensitive to including a different HR for subsequent events.

3.3.1 Diabetes status

Presence of T2D at baseline was an exclusion criterion of SELECT and therefore the percentage of the cohort with T2D at baseline was 0%. However, 66.4% of the cohort had prediabetes at baseline, indicating a credible risk of progression to T2D. Figure 10 in Section 2.6.1.4.2 shows the incidence of T2D (first occurrence of HbA1c ≥6.5%, indicating T2D development) during the trial period. In the model, the risk of progression to T2D was estimated via independent survival model fitted to an exponential distribution in line with the methodology described as per CV events.

The increased risk of incurring a CV event in those who develop T2D was captured via event-specific HRs (Table 32). These risks are applied only after the trial period to avoid double-counting events already observed in the trial (151, 152).

Table 32: Increased CV risk HR for people with T2D

Event	Mean	SE	Source
MI†	2.04	0.148	de Jong 2020 (152)
Stroke	1.67	0.136	
HHF‡	1.20	0.028	
HUA‡	1.20	0.028	
CR‡	1.20	0.028	
CV death‡	1.20	0.028	
Non-CV death	1.00	–	Assumption§

†For MI, the reported HRs are 2.33 for female and 1.81 for male. For stroke, the reported HRs are 1.88 for female and 1.51 for male. These values are weighted based on the proportion of diabetic females in the UK (44%) (153); ‡For HHF, HUA, CR and CV death, the HR for CV events from de Jong 2020 is assumed; §Non-CV death HR assumed as 1.
Abbreviations: CR, coronary revascularisation; CV, cardiovascular; HHF, hospitalisation for heart failure; HR, hazard ratio; HUA, hospitalisation for unstable angina; MI, myocardial infarction; SE, standard error; T2D, type 2 diabetes.

Results from the DSA suggest that the model is not sensitive to including different HRs for people with T2D.

3.3.2 Body mass

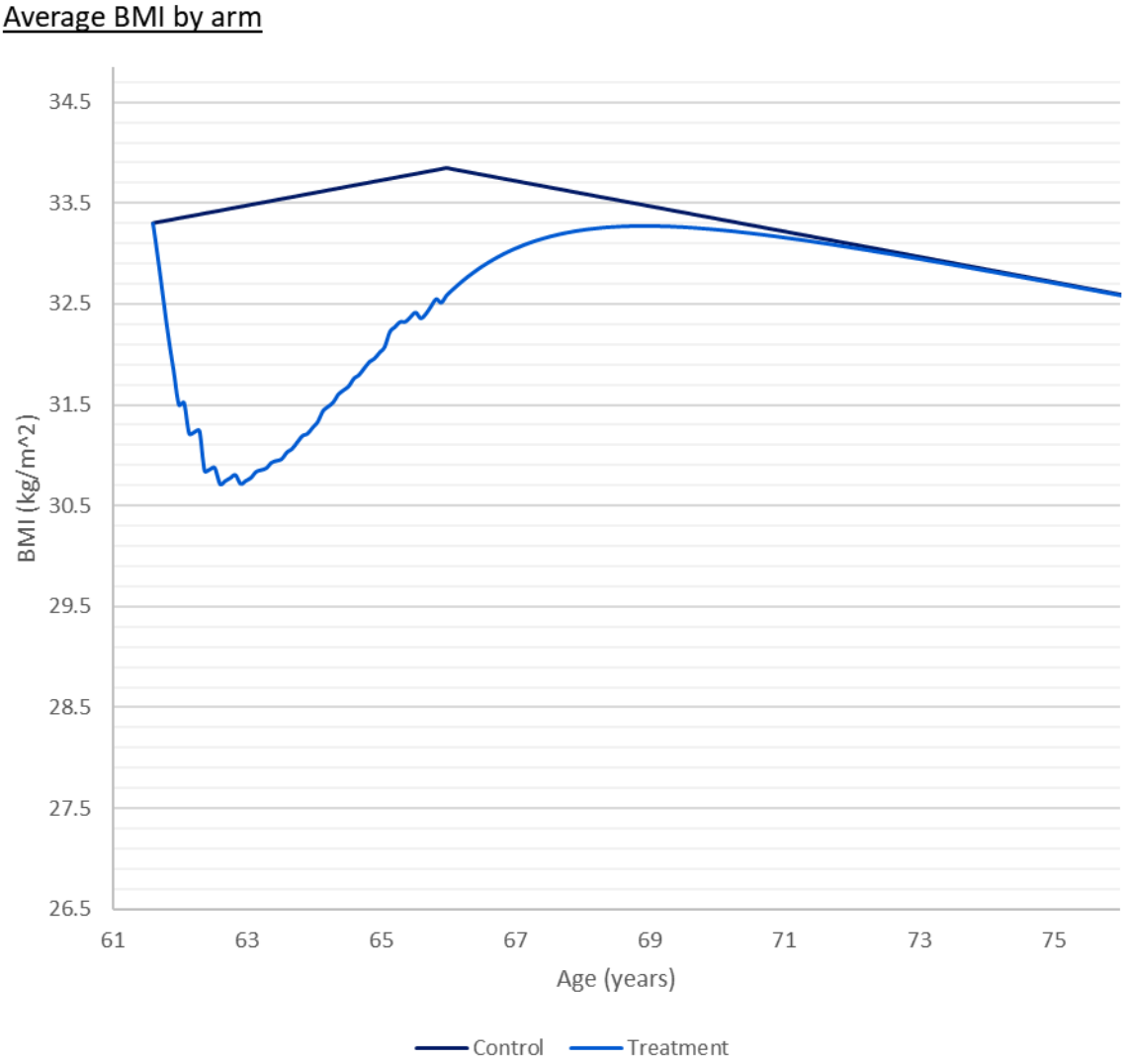
In SELECT, participants in the semaglutide arm experienced a greater decrease in body mass than participants in the placebo arm at Week 104, with an ETD of 8.51% (Section 2.6.1.4.4).

In the model, the body mass of people receiving SoC only follows a path defined by natural history. People experience a weight gain of 0.106 kg/m^2 per year until the age of 66, after which their BMI declines at the same rate of 0.106kg/m^2 per year. This assumption aligns with NICE's preferred inputs in TA875 (154).

In SELECT, participants in the semaglutide arm experienced weight loss of 8.51% by Week 104 relative to SoC. In the model, weight change in people on semaglutide is based on the weight change difference between people on semaglutide + SoC and people on SoC only in SELECT (112). Weight thereafter follows natural history, with the effect that the treatment benefit is maintained while patients remain on therapy, aligned with the assumptions accepted within TA1026 (155). Once people discontinue treatment, they lose treatment benefit over time, until after 2 years body weight returns to that of the control arm. Those who discontinue have body weight equal to the control group thereafter. The average BMI across ages for both arms are presented in Figure 23.

As SELECT directly measured rates of CV events, BMI change is not modelled to have an additional impact on outcomes. In SELECT, CV benefit was independent of the extent of weight loss (see Section 2.6.1.6.1).

Figure 23: BMI projection



Treatment: semaglutide in addition to established clinical management; Control: established clinical management without semaglutide.
Abbreviations: BMI, body mass index.

3.3.3 Chronic kidney disease

In line with the decision problem, the model tracks kidney function over time. Six eGFR-defined CKD stages (1–5, including stages 3a and 3b) were incorporated in line with Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (156). At baseline, patients were distributed across CKD stages 1 to 3 (Table 30). To help reduce the number of model input states all people with eGFR <60 ml/min/1.73 m^2 start the model in stage 3a.

CKD progression over time was informed by observed eGFR trajectories from SELECT. To reduce complexity, the only CKD transitions included in each model

cycle are progression from one CKD state to the next most severe state. The possibilities that patients may deteriorate by more than one state in a single cycle or that CKD state may improve are not included. This will understate the complexity of individual patient experiences; however, at the cohort level the model is able to reflect average rates of CKD progression. Rates of transition between eGFR states varied by treatment received (Table 33), reflecting the significant impact of semaglutide on kidney function observed in SELECT (Section 2.6.1.4.1).

Annual eGFR decline for the placebo and semaglutide arms are aligned to SELECT data by default. Due to limited incidence of transitions to severe stages of CKD in SELECT, annual declines are used to estimate a per cycle transition probability for patients on and off treatment. The equation below illustrates how the transition probability is calculated:

$$P(transition) = \frac{eGFR\ decline * cyclic\ adjustment}{\max(\text{eGFR level}) - \min(\text{eGFR level})}$$

Where P (transition) is the probability of transitioning to the next CKD stage, eGFR decline is the annual rate of eGFR decline, cyclic adjustment is the adjustment made for the probability estimate to fit the model cycle length. max(eGFR level) is the maximum rate of eGFR in the respective CKD category the probability is estimating an exit from, and min(eGFR level) is the minimum rate of eGFR in the respective CKD category.

Detailed consideration of end-stage renal disease (ESRD) and kidney replacement therapies, such as dialysis or kidney transplantation, was not included in this analysis. Very few patients in the model reach CKD stage 5, so any inaccuracy is expected to be minor. CKD state influences utility and cost but does not impact CV event risk.

Table 33: CKD Per cycle transition probabilities

Per cycle probability	Mean	SE†	Source
Placebo			
Stage 1 to 2	[redacted]	[redacted]	SELECT (data on file) (157)
Stage 2 to 3a	[redacted]	[redacted]	
Stage 3a to 3b	[redacted]	[redacted]	

Per cycle probability	Mean	SE†	Source
Stage 3b to 4	[redacted]	[redacted]	
Stage 4 to 5	[redacted]	[redacted]	
Semaglutide			
Stage 1 to 2	[redacted]	[redacted]	SELECT (data on file) (157)
Stage 2 to 3a	[redacted]	[redacted]	
Stage 3a to 3b	[redacted]	[redacted]	
Stage 3b to 4	[redacted]	[redacted]	
Stage 4 to 5	[redacted]	[redacted]	

†SE estimated as 20% of mean.
Abbreviations: CKD, chronic kidney disease; SE, standard error.

3.3.4 Adverse events

SAEs occurring in >1% of participants in at least one arm of SELECT were accounted for in the analysis. Because GI disorders are a known and common AE of GLP-1 RAs (158), SAEs of the GI system that occurred on 10 or more occasions in either arm were also included. The SAEs meeting these criteria, number of events, and per cycle event frequency are listed in Table 34. After patients discontinue semaglutide they experience the AE risk associated with established clinical management.

Table 34: Adverse event probability (per cycle) for patients on semaglutide in addition to established clinical management and established clinical management alone

	Semaglutide in addition to established clinical management		Established clinical management		Source
Adverse events	**Incidence (per cycle)**	**SE**	**Incidence (per cycle)**	**SE**	
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	SELECT CTR (112), SELECT data on file (159)
Non-cardiac chest pain	[redacted]	[redacted]	[redacted]	[redacted]	
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	
Inguinal hernia	[redacted]	[redacted]	[redacted]	[redacted]	
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	
GI haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	

	Semaglutide in addition to established clinical management		Established clinical management		Source
Upper GI haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	
Gastritis	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CTR, clinical trial report; GI, gastrointestinal; SE, standard error.

3.4 Measurement and valuation of health effects

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

Although EQ-5D data were collected in SELECT, they have not been used within the model. The key benefit of semaglutide in this indication is the prevention of MACEs and their consequences. These events are uncommon, and the timing is unpredictable. HRQoL data collection in the trial was at predetermined intervals aligned with trial visits, and hence unlikely to capture participants at the time they experience major events.

3.4.2 Mapping

Not applicable.

3.4.3 HRQoL studies

A systematic review of literature informing HRQoL in people with eCVD and overweight or obesity was performed to inform this appraisal (see Appendix F). Findings from the SLR and the rationale for the choice of utility estimates for the evaluation are discussed in the sub-sections below. In addition to the SLR, a pragmatic review of relevant models and other sources was conducted to inform model inputs not fully addressed by the SLR.

3.4.4 HRQoL data used in the cost-effectiveness analysis

To estimate utility in the economic model the following approach was taken:

- Base utility was defined according to patient age and the presence of CVD
- A utility decrement was determined for post-CV event health states
- A further utility decrement was calculated if an acute CV event occurred

- Utility impacts were calculated for CKD state, presence of diabetes, AEs of treatment and BMI.

The following sections provide further details on the calculations and sources used. Values used are reported in Table 35.

Base utilities

The model uses baseline utility values for a UK population of appropriate age and sex without CVD (Ara and Brazier, 2010 (160)). A health state disutility associated with eCVD was then applied to all patients based on the data from Luah et al, 2024 (161). Luah uses EQ-5D-5L data from the Health Survey for England, a large and representative data source used in several previous NICE appraisals (See Table 29). Health profiles obtained from survey responses were mapped to utilities using the validated crosswalk by van Hout et al, 2012 (162), a methodology previously recommended by NICE (163).

Health state disutilities

State-specific disutility was applied to patients in the post-CV event health states (e.g. a disutility associated with long-term health decrement after a stroke). Patients in the post two-CV event states experience both relevant disutilities.

The SLR identified numerous studies reporting disutility associated with CV events. The study selected for the model was Lewis et al, 2014 (82). The participants in this study had a mean age of 64.8 years (mean age in SELECT: 61.6 years) and all had eCVD. Medical history was well characterised as this is a secondary publication of a large interventional trial. This study administered the EQ-5D to participants with a recent MI and reported change in utility in those with recurrent MI, stroke and HF. Results were reported using the UK EQ-5D scoring algorithm. Importantly for the model, this study provided a consistent set of estimates of disutility observed after MI, stroke and HF in people with eCVD: we anticipated that the model would be more sensitive to these long-term estimates than to the utility impact of acute events. Limitations include the population not being limited to people with obesity and overweight.

Disutilities associated with acute CV events

Patients who experience an acute CV event in the model – MI, stroke, HHF, HUA or CR – experience a one-off utility loss, implemented in the cycle in which the CV event occurs. No single study was identified that consistently estimated acute utility loss for this situation, so a pragmatic review of literature from the SLR and other economic models was conducted, with evidence from large representative studies using EQ-5D and from previous NICE appraisals being preferred. Studies reporting utility loss over a period of more or less than one model cycle were adjusted so the appropriate QALY loss could be implemented as a single disutility in the cycle in which the event occurred.

Other

A disutility related to the proportion of the population with T2D is applied in each model cycle (e.g. if 50% of the population have T2D in a particular cycle, then 50% of this disutility will be applied). This utility was derived from Luah et al, 2024, the same source as for the baseline value (161).

A disutility related to CKD stage is applied to the proportion of the population in each CKD stage. This utility was taken from Jesky et al, 2016 (164), a UK-based EQ-5D source reporting utility decrement in a population with CKD.

The impact of the AEs of treatment was accounted for by applying an estimated event specific disutility to the per cycle incidence of each AE (Ara and Wailoo, 2011 (165)). These events are extremely heterogeneous; various sources were used with EQ-5D studies and more recent studies that were included in previous NICE appraisals preferred. Adverse events may persist for more than one model cycle: however in the model the total QALY loss was implemented as a single disutility in the cycle in which the event began. Studies reporting utility loss over a period of more or less than one model cycle were adjusted accordingly.

A weight related disutility is applied based on mean BMI in each cycle. This was derived from a UK general population study using recent data from the Health Survey for England (161), with coefficients fitted to the SELECT population.

The model combines disutilities in an additive manner; this allows disutility associated with different morbidities (e.g. CKD and also T2D) to be included without a proliferation of health states. The model structure does allow to identify individuals with two separate CV events; a scenario analysis exploring a multiplicative approach to considering CV health state utilities was conducted.

Table 35: Summary of disutility values for cost-effectiveness analysis

	Parameter	Mean disutility	SE	Source
Health states disutility	eCVD	0.0369	0.01400	Luah 2024 (161)
	Post MI	0.0600	0.0257	Lewis 2014 (82)
	Post stroke	0.1800	0.0213	
	Post HHF	0.0500	0.0072	
	Post HUA	0.0500	0.0072	
	Post CR	0.0500	0.0072	
Cardiovascular event disutility	MI	0.1612	0.0005	NICE TA494 (166)
	Stroke	0.1828	0.0006	
	HHF	0.1167	0.0144	Sullivan 2011 (167)
	Unstable angina	0.0854	0.1340	
	CR	0.0844	0.0327	Baron 2017 (168)
Disutility associated with comorbidities	T2D	0.0315	0.01930	Luah 2024 (161)
	CKD stage 1	0.0000	0.15306	Jesky 2016 (164)
	CKD stage 2	0.0000	0.15306‡	
	CKD stage 3a	0.0500	0.15306‡	
	CKD stage 3b	0.0500	0.15306‡	
	CKD stage 4	0.1100	0.19388‡	
	CKD stage 5	0.1200	0.19388‡	
Treatment-related adverse event disutility	Pneumonia	0.0080	0.0031	Delgleize 2016 (169)
	Non-cardiac chest pain	0.1130	0.0590	McCarty 2022 (170)
	Acute kidney injury	0.0100	0.0020‡	Tafazzoli 2023 (171)
	Inguinal hernia	0.1160	0.0232‡	NICE TA83 (172), McIntosh 2001 (173)
	Diarrhoea	0.0125	0.0025‡	NICE TA875 (154),TA494 (166)

	Parameter	Mean disutility	SE	Source
	GI haemorrhage	0.0910	0.3240	Keng 2022 (174)
	Vomiting	0.0125	0.0025‡	NICE TA875 (154), TA494 (166)
	Abdominal pain	0.0700	0.0700	NICE TA378 (175)
	Upper respiratory disease	0.1500	0.0300‡	Kelly 2023 (176)
	Gastritis†	0.0125	0.0025‡	NICE TA875 (154), TA494 (166)
BMI calculations	Parameter	Mean disutility or parameter value	SE	Source
BMI (male)	BMI	–0.0014	0.0007	Luah 2024 (161)
	BMI squared	–0.0003	0.0001	
	BMI cubic	1.05E-05	7.21E-06	
	BMI centring	27.7000	2.2580	
	BMI calculated at minimum	48.8500	–	
	BMI calculated at maximum	25.6000	–	
	Utility calculated at minimum	0.8836	–	
	Utility calculated at maximum	0.9496	–	
	Reported constant	0.9481	0.0077	
	Calculated constant	–0.00152	–	
BMI (female)	BMI	–0.0035	0.0005	Luah 2024 (161)
	BMI squared	–0.0003	0.0001	
	BMI cubic	8.50E-06	2.89E-06	
	BMI centring	27.8000	2.5100	
	BMI calculated at minimum	56.1700	–	
	BMI calculated at maximum	22.9600	–	
	Utility calculated at minimum	0.8014	–	
	Utility calculated at maximum	0.9193	–	

	Parameter	Mean disutility	SE	Source
	Reported constant	0.9104	0.0077	
	Calculated constant	–0.090	–	

†Severe GI event associated with a utility decrement of 0.05 that persisted for a 1-week duration. It is assumed the event duration is within the modelled cycle; ‡SE assumed to be 20% of mean.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CR, coronary revascularisation; eCVD, established cardiovascular disease; GI, gastrointestinal; HHF, hospitalisation for heart failure; HUA, hospitalisation for unstable angina; MI, myocardial infarction; T2D, type 2 diabetes.

3.5 Cost and healthcare resource use identification, measurement and valuation

A systematic review of published costs and healthcare resource identification, measurement and valuation data in people with eCVD and overweight or obesity was conducted and results are reported in Appendix G.

In line with previous appraisals, the preferred unit cost input for acute events was obtained from the latest available NHS National Cost Collection data (177).

Published costs were inflated from the original price base to 2025 costs using the National Health Service Cost Index from Personal Social Services Research Unit (178).

3.5.1 Intervention and comparators' costs and resource use

The cost of the intervention reflects the dose-specific drug acquisition costs and number of people expected to be on each dose in each model cycle. People use lower doses of semaglutide during the titration phase, aiming to reach the full dose by Week 16. Based on data derived from SELECT, not all participants reached the target dose of semaglutide 2.4 mg, as discussed in Section 2.6.1.1. In the model, a proportion of people are predicted to remain on each dose based on data derived from SELECT. These proportions of people, reported in Table 36, are based on observations from Week 20 to Week 230 in SELECT, where participants were still titrating up their doses upon entering the trial up to Week 20 and low number of participants remain from Week 230 onwards, leading to unstable proportion estimates.

The NHS price of semaglutide (1.7 mg and 2.4 mg) is subject to a confidential Commercial Access Agreement (CAA).

Table 36: Intervention cost inputs

Cost inputs	Parameter	Proportion of people on dose (SE)†	Cost per week	Source
Cost of semaglutide treatment	0.24 mg dose‡	[redacted]	£18.31	Novo Nordisk
	0.5 mg dose	[redacted]	£18.31	Novo Nordisk
	1.0 mg dose	[redacted]	£18.31	Novo Nordisk
	1.7 mg dose	[redacted]	£[redacted]	Novo Nordisk
	2.4 mg dose	[redacted]	£[redacted]	Novo Nordisk

†SE assumed based on assuming a binary distribution with $SE = \sqrt{(p)(1-p)/n}$ where p is the probability of patient receiving the given dose and n is the number of observations (17,604) in SELECT. These SEs are then used to estimate an approximate multivariate beta distribution so that all proportions sum to 100%; ‡As reported in Ryan et al, 2020 (179) participants in SELECT received a 0.24 mg dose, while people in clinical practice receive 0.25 mg. For this model the two doses are assumed to be interchangeable, with the 0.25 mg costed.
Abbreviations: SE, standard error.

In line with NICE guideline NG28 (180), initiation of a GLP-1 RA was assumed to require an average of two 20-minute nurse consultations. As semaglutide can be initiated in secondary or in primary care, the average of inpatient and outpatient nursing costs was used.

Table 37: Administration cost of semaglutide

Cost inputs	Parameter	Mean (£) (SE)	Source
Cost of semaglutide admin-istration	Weekly cost, first cycle only	9.21 (1.84)	Inpatient: 2 x 20-minute appointments with a band 6 or band 7 nurse (180) Outpatient: 2 x 20-minute appointments with a GP practice nurse Average of inpatient and outpatient nursing cost used, for a per-patient cost of £36.83 (178) Cost assumed to be incurred over the first cycle (4 weeks); £36.83 was divided by 4 to generate a weekly cost of £9.21.

Abbreviations: GP, general practitioner; SE, standard error.

Semaglutide is expected to be used in addition to SoC for the prevention of CV events. The model does not contain a separate cost for comparator therapy. Costs of SoC for the prevention of CV events are included in the health state costs for eCVD and for people who have experienced MACEs.

3.5.2 Health-state unit costs and resource use

All people incur a per-cycle maintenance cost associated with eCVD.

People experiencing a new event incur an acute cost and post event costs in later cycles. All individuals in the model continue to experience the cost of eCVD after additional CV events. The model has the ability to include separate post-event cost increases but this is not used in the base case. To avoid double counting, people in subsequent health states incur the higher of the maintenance costs associated with CV events experienced.

A relevant study identified from the SLR was Danese et al, 2016, which reported the cost of initial and recurrent CV events (13). Danese et al allowed Novo Nordisk to reflect the higher cost of managing recurrent events, compared with the average cost considered by reference costs. Estimates from Danese were also used in numerous prior NICE guidance including TA805, NG136, NG185 and NG238. An alternative approach using reference costs alone is reported in the scenario analysis.

Additional costs for T2D onset, CKD progression, and AEs are also included. Further details on the calculation of the weighted eCVD maintenance cost and base-case event costs are reported in Appendix M and Appendix N, respectively.

Table 38: Health state cost inputs

Cost inputs	Parameter	Mean (£) (SE)	Source
Health state costs (per cycle)	eCVD	126.74 (25.35)	Weighted eCVD maintenance cost (See Appendix M for sources and calculations)
Base-case event costs (per event)	MI	3,902.63 (780.53)	NHS National Cost Collection data (EB10A, EB10B, EB10C, EB10D, EB10E), inflated in line with Danese 2016 (Appendix P)
	Stroke	5,709.99 (1,142.00)	NHS National Cost Collection data (weighted average of AA35A, AA35B, AA35C, AA35D, AA35E, AA35F), inflated in line with Danese 2016 (Appendix P)
	HHF	4,484.93 (896.99)	NHS National Cost Collection data (weighted average of EB03A, EB03B, EB03C, EB03D, EB03E), inflated in line with Danese 2016 (Appendix P)

Cost inputs	Parameter	Mean (£) (SE)	Source
	HUA	1,633.79 (326.76)	NHS National Cost Collection data (weighted average of EB13A, EB13B, EB13C, EB13D), inflated in line with Danese 2016 (Appendix P)
	CR	7,529.67 (1,505.93)	NHS National Cost Collection data (weighted average of ED22A, ED22B, ED2C, ED23A, ED23B, ED23C, ED26A, ED26B, ED26C, ED27A, ED27B, ED27C, ED28A, ED28B, ED28C, EY40A, EY40B, EY40C, EY40D, EY41A, EY41B, EY41C, EY41D, EY44A, EY44B, EY44C, EY44D), inflated in line with Danese 2016 (Appendix P)
Fatal event costs (per event)	CV death	2,068.03 (413.61)	Alva 2015 (181)
	Non-CV death (base case)	0.00 (0.00)	Assumption

Abbreviations: CR, coronary revascularisation; CV, cardiovascular; eCVD, established cardiovascular disease; HHF, hospitalisation for heart failure; HUA, hospitalisation for unstable angina; MI, myocardial infarction; NHS, National Health Service.

3.5.3 Adverse event unit costs and resource use

All AE-related costs were obtained from the NHS reference unit costs (177). A one-off per event cost is applied in the cycle when the event occurs given that most of these events are typically acute, and chronic AEs are very rare (28). Further details on the calculation of the AE-related costs are reported in Appendix O.

Table 39: AE-related cost inputs, initial cycle only

Cost inputs	Parameter	Mean (£) (SE) †	Source
AE-related costs	Pneumonia	2,661.2 (532.24)	NHS National Cost Collection data (weighted average of DZ11K, DZ11L, DZ11M, DZ11N, DZ11P, DZ11Q, DZ11R, DZ11S, DZ11T, DZ11U, DZ11V, DZ23H, DZ23J, DZ23K, DZ23L, DZ23M, DZ23N)
	Non-cardiac chest pain	534.11 (106.82)	NHS National Cost Collection data (weighted average of EB12A, EB12B, EB12C)
	Acute kidney injury	2,732.54 (546.51)	NHS National Cost Collection data (weighted average of LA07H, LA07J, LA07K, LA07L, LA07M, LA07N, LA07P)
	Inguinal hernia	5,440.18 (1,088.04)	NHS National Cost Collection data (weighted average of FF62A, FF62B, FF62C, FF62D, FF62E, FF62F)
	Diarrhoea	161.26 (32.25)	NHS National Cost Collection data (WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C, WF02D)
	GI haemorrhage	1,936.35 (387.27)	NHS National Cost Collection data (weighted average of FD03A, FD03B, FD03C, FD03D, FD03E, FD03F, FD03G, FD03H)
	Vomiting	161.26 (32.25)	NHS National Cost Collection data (WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C, WF02D)
	Abdominal pain	737.56 (147.51)	NHS National Cost Collection data (weighted average of FD05A, FD05B)
	Upper GI haemorrhage	1,936.35 (387.27)	NHS National Cost Collection data (weighted average of FD03A, FD03B, FD03C, FD03D, FD03E, FD03F, FD03G, FD03H)
	Gastritis	2,047.77 (409.55)	NHS National Cost Collection data (weighted average of FD10A, FD10B, FD10C, FD10D, FD10E, FD10F, FD10G, FD10H, FD10J, FD10K, FD10L, FD10M)

†SE is assumed to be 20% of mean.
Abbreviations: AE, adverse event; GI, gastrointestinal; SE, standard error.

3.5.4 Miscellaneous unit costs and resource use

Additional costs related to the progression to T2D, and progression of CKD are included in the model. T2D costs include all T2D-related costs for treating a patient with T2D, including acute events such as amputations, and exclude T2D-related CVD and CKD costs to avoid double counting. Costs for managing CKD vary by disease stage.

Table 40: T2D and CKD progression cost inputs

Cost inputs	Parameter	Mean (£) (SE)	Source
T2D and CKD progression costs, per cycle	T2D	55.35 (11.07)	Alva 2015 (181)
	CKD stage 1	17.62 (3.52)	TA358 (182)
	CKD stage 2	17.62 (3.52)	
	CKD stage 3a	147.19 (29.44)	
	CKD stage 3b	147.19 (29.44)	
	CKD stage 4	344.12 (68.82)	
	CKD stage 5	536.90 (107.38)	

Abbreviations: CKD, chronic kidney disease; SE, standard error; T2D, type 2 diabetes.

3.6 Severity

Not applicable.

3.7 Uncertainty

Not applicable.

3.8 Managed access proposal

Not applicable.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

The CV event risks were obtained from SELECT as detailed in Sections 2.6.1.2 and 2.6.1.3. Other base-case analysis inputs are summarised in Table 41.

Table 41: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	SE (Distribution)	Reference to section in submission
Time horizon (maximum age) (years)	100 (lifetime)	–	3.2 Economic analysis
Mean age (years)	61.6	0.016 (Normal)	3.3 Clinical parameters and variables Table 30
Proportion of male (%)	72.3	0.034 (Beta)	
Mean BMI (kg/m^2)	33.3	0.009 (Normal)	
Prediabetes at baseline (%)	66.4	13.28 (Beta)	
Proportion in each CKD stage, %			
Stage 1 (eGFR ≥90 ml/min/1.73 m^2)	[redacted]	[redacted] (Beta)	3.3 Clinical parameters and

Variable	Value (reference to appropriate table or figure in submission)	SE (Distribution)	Reference to section in submission
Stage 2 (eGFR 60–89 ml/min/1.73 m^2)	[redacted]	[redacted] (Beta)	variables Table 30
Stage 3a (eGFR ≤59 ml/min/1.73 m^2)	[redacted]	[redacted] (Beta)	
CKD Markov Transition probabilities (placebo), per cycle			
Stage 1 to 2	[redacted]	[redacted] (Beta)	3.3 Clinical parameters and variables Table 33
Stage 2 to 3a	[redacted]	[redacted] (Beta)	
Stage 3a to 3b	[redacted]	[redacted] (Beta)	
Stage 3b to 4	[redacted]	[redacted] (Beta)	
Stage 4 to 5	[redacted]	[redacted] (Beta)	
CKD Markov Transition probabilities (semaglutide), per cycle			
Stage 1 to 2	[redacted]	[redacted] (Beta)	3.3 Clinical parameters and variables Table 33
Stage 2 to 3a	[redacted]	[redacted] (Beta)	
Stage 3a to 3b	[redacted]	[redacted] (Beta)	
Stage 3b to 4	[redacted]	[redacted] (Beta)	
Stage 4 to 5	[redacted]	[redacted] (Beta)	
AE probability (placebo), per cycle			
Pneumonia	[redacted]	[redacted] (Beta)	3.3 Clinical parameters and variables Table 34
Non-cardiac chest pain	[redacted]	[redacted] (Beta)	
Acute kidney injury	[redacted]	[redacted] (Beta)	
Inguinal hernia	[redacted]	[redacted] (Beta)	
Diarrhoea	[redacted]	[redacted] (Beta)	
GI haemorrhage	[redacted]	[redacted] (Beta)	
Vomiting	[redacted]	[redacted] (Beta)	
Abdominal pain	[redacted]	[redacted] (Beta)	
Upper GI haemorrhage	[redacted]	[redacted] (Beta)	
Gastritis	[redacted]	[redacted] (Beta)	
AE probability (semaglutide), per cycle			
Pneumonia	[redacted]	[redacted] (Beta)	3.3 Clinical parameters and variables Table 34
Non-cardiac chest pain	[redacted]	[redacted] (Beta)	
Acute kidney injury	[redacted]	[redacted] (Beta)	
Inguinal hernia	[redacted]	[redacted] (Beta)	
Diarrhoea	[redacted]	[redacted] (Beta)	
GI haemorrhage	[redacted]	[redacted] (Beta)	
Vomiting	[redacted]	[redacted] (Beta)	
Abdominal pain	[redacted]	[redacted] (Beta)	
Upper GI haemorrhage	[redacted]	[redacted] (Beta)	
Gastritis	[redacted]	[redacted] (Beta)	

Variable	Value (reference to appropriate table or figure in submission)	SE (Distribution)	Reference to section in submission
Discontinuation probability, per cycle			
Discontinuation, per cycle (%)	[redacted]	[redacted] (Beta)	3.2.5 Intervention technology and comparators
Health state disutilities			
eCVD	0.0369	0.01400 (Beta)	3.3 Clinical parameters and variables Table 35
Post MI	0.0368	0.02570 (Beta)	
Post stroke	0.0349	0.02130 (Beta)	
Post HHF	0.0247	0.00720 (Beta)	
Post HUA	0.0247	0.00720 (Beta)	
Post CR	0.0860	0.0335 (Beta)	
Cardiovascular event disutility			
MI	0.1612	0.00048 (Beta)	3.3 Clinical parameters and variables Table 35
Stroke	0.1828	0.00059 (Beta)	
HHF	0.1167	0.01440 (Beta)	
Unstable angina	0.0854	0.13400 (Beta)	
CR	0.0841	0.03265 (Beta)	
Disutility associated with comorbidities			
T2D	0.0315	0.01930 (Beta)	3.3 Clinical parameters and variables Table 35
CKD stage 1	0.0000	0.15306 (Beta)	
CKD stage 2	0.0000	0.15306 (Beta)	
CKD stage 3a	0.0500	0.15306 (Beta)	
CKD stage 3b	0.0500	0.15306 (Beta)	
CKD stage 4	0.1100	0.19388 (Beta)	
CKD stage 5	0.1200	0.19388 (Beta)	
Treatment-related AE disutility			
Pneumonia	0.0080	0.0031 (Normal)	3.3 Clinical parameters and variables Table 35
Non-cardiac chest pain	0.1130	0.0590 (Normal)	
Acute kidney injury	0.0100	0.0020 (Normal)	
Inguinal hernia	0.1160	0.0232 (Normal)	
Diarrhoea	0.0125	0.0025 (Normal)	
GI haemorrhage	0.0910	0.3240 (Normal)	
Vomiting	0.0125	0.0025 (Normal)	
Abdominal pain	0.0700	0.0700 (Normal)	
Upper respiratory disease	0.1500	0.0300 (Normal)	
Gastritis	0.0125	0.0025 (Normal)	

Variable	Value (reference to appropriate table or figure in submission)	SE (Distribution)	Reference to section in submission
BMI utility values (male)			
BMI	–0.0014	0.0007 (Normal)	3.3 Clinical parameters and variables Table 35
BMI squared	–0.0003	0.0001 (Normal)	
BMI cubic	1.05E-05	7.21E-06 (Normal)	
BMI centring	27.7000	2.2580 (Normal)	
Reported constant	0.9481	0.0077 (Normal)	
Calculated constant	–0.00152	–	
BMI utility values (female)			
BMI	–0.0035	0.0005 (Normal)	3.3 Clinical parameters and variables Table 35
BMI squared	–0.0003	0.0001 (Normal)	
BMI cubic	8.50E-06	2.89E-06 (Normal)	
BMI centring	27.8000	2.5100 (Normal)	
Reported constant	0.9104	0.0077 (Normal)	
Calculated constant	–0.090	–	
Proportion of people on each semaglutide dose			
0.24 mg dose‡	4.69%	0.16% (Beta)	3.5 Cost and healthcare resource use identification, measurement and valuation Table 36
0.5 mg dose	4.98%	0.16% (Beta)	
1.0 mg dose	6.56%	0.19% (Beta)	
1.7 mg dose	7.40%	0.20% (Beta)	
2.4 mg dose	76.37%	0.32% (Beta)	
Cost of semaglutide, per week			
0.24 mg dose‡	£18.31	N/A	3.5 Cost and healthcare resource use identification, measurement and valuation Table 36
0.5 mg dose	£18.31	N/A	
1.0 mg dose	£18.31	N/A	
1.7 mg dose	£[redacted]	N/A	
2.4 mg dose	£[redacted]	N/A	
Administration cost (per week, first cycle)	£9.21	1.84	
Health state costs, per cycle			
eCVD	£126.74	£25.35 (Gamma)	3.5 Cost and healthcare resource use identification, measurement and valuation Table 38
Base case event costs, per event			

Variable	Value (reference to appropriate table or figure in submission)	SE (Distribution)	Reference to section in submission
MI	£3,902.63	£780.53 (Gamma)	3.5 Cost and healthcare resource use identification, measurement and valuation Table 38
Stroke	£5,709.99	£1,142.00 (Gamma)	
HHF	£4,484.93	£896.99 (Gamma)	
HUA	£1,633.79	£326.76 (Gamma)	
CR	£7,529.67	£1,505.93 (Gamma)	
Fatal event costs, per event			
CV death	£2,068.03	£413.61 (Gamma)	3.5 Cost and healthcare resource use identification, measurement and valuation Table 38
Non-CV death (base case)	0	0	
AE-related costs, initial cycle only			
Pneumonia	£2,661.20	£532.24 (Gamma)	3.5 Cost and healthcare resource use identification, measurement and valuation Table 39
Non-cardiac chest pain	£534.11	£106.82 (Gamma)	
Acute kidney injury	£2,732.54	£546.51 (Gamma)	
Inguinal hernia	£5,440.18	£1,088.04 (Gamma)	
Diarrhoea	£161.26	£32.25 (Gamma)	
GI haemorrhage	£1,936.35	£387.27 (Gamma)	
Vomiting	£161.26	£32.25 (Gamma)	
Abdominal pain	£737.56	£147.51 (Gamma)	
Upper GI haemorrhage	£1,936.35	£387.27 (Gamma)	
Gastritis	£2,047.77	£409.55 (Gamma)	
T2D and CKD progression costs			
T2D	£55.35	£11.07 (Gamma)	3.5 Cost and healthcare resource use identification, measurement and valuation Table 40
CKD stage 1	£17.62	£3.52 (Gamma)	
CKD stage 2	£17.62	£3.52 (Gamma)	
CKD stage 3a	£147.19	£29.44 (Gamma)	
CKD stage 3b	£147.19	£29.44 (Gamma)	
CKD stage 4	£344.12	£68.82 (Gamma)	
CKD stage 5	£536.90	£107.38 (Gamma)	

Abbreviations: AE, adverse event; BMI, body mass index; CKD, chronic kidney disease; CR, coronary revascularisation; CV, cardiovascular; eCVD, established cardiovascular disease; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HHF, hospitalisation for heart failure; HUA, hospitalisation for unstable angina; MI, myocardial infarction; N/A, not applicable; SE, standard error; T2D, type 2 diabetes.

3.9.2 Summary of assumptions

Table 42: Summary of assumptions in the economic model

Assumption	Justification	Resulting uncertainty and mitigation
The model structure captures the main costs and effects of the intervention and comparator. The model considers CV and non-CV mortality, MI, stroke, HUA, HHF, CKD, T2D, CR, CKD, BMI and AEs. Additional states consider people who have experienced one or two different modelled events. Utility and cost are estimated based on health states and events	The scope included the following endpoints: MACE avoided (including CV death, non-fatal MI, and non-fatal stroke), all-cause death, HF events, worsening kidney function, development of T2D, body weight, AEs of treatment and HRQoL. Revascularisation events were included in the model as these are important costs in CVD and were also captured in SELECT. Health states for people who have experienced two different acute events adds granularity. The model structure is broadly consistent with – although more complex than some – other evaluations of CVD prevention (Table 29).	The model does not consider other benefits of weight loss such as impact on sleep apnoea (183), musculoskeletal diseases such as osteoarthritis (184) and gout (185), and respiratory diseases such as asthma (186)and COPD (187) as well as several types of cancer. In the SELECT population, 14% of participants had sleep apnoea, 24% had knee and/or hip osteoarthritis, around 15% had asthma and/or COPD, and approximately 9% had gout (112). The model does not consider other benefits of semaglutide, such as its impact on MASH (188). These limitations mean the model most likely understates benefit and overestimates the ICER. The model does not reflect increasing severity in people with multiple or repeated events. This is likely to underestimate benefits and therefore overstates the ICER, but the inaccuracy should be small.
The model separately considers CV events, CKD and T2D	The number of health states is already large, therefore introducing a large number of states combining CKD, CV events and T2D would render the model intractable.	The model is not able to consider combined risk (e.g. higher risk of CVD in people with CKD): this will likely underestimate the benefit of effective therapy and overstate the ICER. The model is not able to consider multiplicative utilities across different

Assumption	Justification	Resulting uncertainty and mitigation
		modules: this will likely overestimate the benefit of effective therapy and understate the ICER. The overall impact on the ICER is not known. DSA of the individual parameters suggests the impact on the ICER is likely to be small.
The SELECT population is representative of the decision problem	The SELECT population meets the criteria of the decision problem. SELECT is the only study designed and powered to detect the effectiveness of semaglutide in preventing MACE.	SELECT may understate CV risk in a UK population: participants in SELECT were younger and used more SoC medications than a CPRD cohort who met similar inclusion criteria. Some people with eCVD in the real-world UK population would not meet entry criteria for SELECT – e.g. people with recent CV events (>60 days) and those with T2D. Scenario analyses were conducted by applying efficacy from SELECT to baseline risk for people with T2D, people with recent CV events and people identified from a real-world UK cohort based on the CPRD analysis (68)
The treatment effect in SELECT can be generalised to the UK population	Novo Nordisk believes that the endpoints of SELECT – notably risk reduction in MACE – is the most robust available estimate of the likely impact of semaglutide in the population defined in the decision problem. The MHRA granted semaglutide a licence for "established CVD" which refers to SELECT and the T2D outcomes study SUSTAIN-6. Novo Nordisk infers that the MHRA believes	Sensitivity analyses explore the implications of plausible variation on the effectiveness of semaglutide.

Assumption	Justification	Resulting uncertainty and mitigation
	the evidence is sufficient to show acceptable risk-benefit in UK use.	
Survival analysis modelling of the SELECT population is representative of the likely benefits of semaglutide in UK practice	Survival analysis was conducted according to NICE DSU technical support document 14: Survival analysis for economic evaluations alongside clinical trials, extrapolation with patient level data (150). A similar approach was taken in TA805 (19), the most recent TA where patient level data from a CVOT was available. Distributions chosen were informed by both goodness of fit to the trial data and plausibility of long-term extrapolation	Scenario analysis explores alternative methods of extrapolating risk, including use of joint distributions and alternative risk profiles
EQ-5D values from the Health Survey for England (39) and utilities from published literature appropriately describe utility in this population	The Health Survey for England is a large and representative survey. The survey uses the EQ-5D, the instrument preferred by NICE. The search to identify other utility measures was systematic. Utility measures in the trial were not considered suitable for modelling as explained in Section 3.4. This approach is consistent with other evaluations including NICE guidelines NG136 (146) and NG238 (88).	Sensitivity analysis explores the impact of individual utility values on the ICER. Scenario analyses explored alternative methods of assessing utility.

Assumption	Justification	Resulting uncertainty and mitigation
NHS Reference costs appropriately describe cost in this population	This approach is consistent with other evaluations including NICE guidelines NG136 (146) and NG238 (88) Where clearly relevant reference costs were not available, a systematic search was undertaken.	Reference costs are not in general specific to people with eCVD, who may have greater severity of disease and require more intensive management. This limitation means the model likely understates the costs of treatment in this population and overestimates the ICER.

Abbreviations: AE, adverse event; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DSA, deterministic sensitivity analysis; DSU, Decision Support Unit; HHF, hospitalisation for heart failure; HRQoL, health-related quality of life; HUA, hospitalisation for unstable angina; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event; MASH, metabolic dysfunction-associated steatohepatitis; MHRA, Medicines and Healthcare products Regulatory Agency; MI, myocardial infarction; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SoC, standard of care; T2D, type 2 diabetes; TA, technology appraisal; UK, United Kingdom.

3.10 Base-case results

3.10.1 Base-case incremental cost-effectiveness analysis results

The discounted base-case incremental cost-effectiveness results are reported in Table 43. The addition of semaglutide to the established clinical management was associated with £[redacted] incremental costs, [redacted] incremental QALYs, and 0.16 life-years per patient, resulting in an ICER of £14,702 per QALY.

Table 43: Discounted base-case deterministic results (per patient)

Technologies	Total costs (£)	Total LYG	Total QALYs
Semaglutide in addition to established clinical management	[redacted]	10.24	[redacted]
Established clinical management	27,843	10.08	7.20
Incremental costs (£)	[redacted]		
Incremental LYG	0.16		
Incremental QALYs	[redacted]		
ICER (£/QALY)	14,702		
NHB at £20,000 (£)	[redacted]		
NHB at £30,000 (£)	[redacted]		

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALY, quality-adjusted life year.

The disaggregated discounted base-case results are reported in Table 44. Per patient, the largest cost increase associated with semaglutide was the cost of treatment. The largest cost offsets were reductions in costs of managing T2D and CKD as well as CV events. Semaglutide was associated with an increase in CVD maintenance cost, reflecting longer time alive in the semaglutide arm.

Table 44: Disaggregated base-case deterministic cost results (per patient)

	Semaglutide in addition to established clinical management	Established clinical management	Incremental
Management costs			
Treatment costs	[redacted]	£0	[redacted]
CVD maintenance costs	[redacted]	£16,659	[redacted]
Clinical event costs			
MI (non-fatal)	[redacted]	£533	[redacted]
Stroke (non-fatal)	[redacted]	£372	[redacted]

	Semaglutide in addition to established clinical management	Established clinical management	Incremental
HF (non-fatal)	[redacted]	£211	[redacted]
Unstable angina (non-fatal)	[redacted]	£66	[redacted]
CR (non-fatal)	[redacted]	£1,525	[redacted]
CV Mortality	[redacted]	£813	[redacted]
Adverse events	[redacted]	£346	[redacted]
T2D	[redacted]	£1,555	[redacted]
CKD (all stages)	[redacted]	£5,763	[redacted]
Total cost	[redacted]	**£27,843**	[redacted]

Abbreviations: CKD, chronic kidney disease; CR, coronary revascularisation; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; MI, myocardial infarction; T2D, type 2 diabetes.

Table 45: Disaggregated base case deterministic QALY results (per patient)

	Semaglutide in addition to established clinical management	Established clinical management	Incremental
Health state/maintenance			
eCVD	[redacted]	5.907	[redacted]
MI	[redacted]	0.400	[redacted]
Stroke	[redacted]	0.157	[redacted]
HF	[redacted]	0.138	[redacted]
Unstable angina	[redacted]	0.126	[redacted]
CR	[redacted]	0.682	[redacted]
Multiple events	[redacted]	0.239	[redacted]
Non-fatal events			
CV events	[redacted]	–0.060	[redacted]
BMI	[redacted]	–0.226	[redacted]
AEs	[redacted]	–0.001	[redacted]
T2D	[redacted]	–0.068	[redacted]
CKD (all stages)	[redacted]	–0.100	[redacted]
Total QALYs	[redacted]	**7.196**	[redacted]

Abbreviations: AE, adverse event; BMI, body mass index; CKD, chronic kidney disease; CR, coronary revascularisation; CV, cardiovascular; eCVD, established cardiovascular disease; HF, heart failure; MI, myocardial infarction; QALY, quality-adjusted life year; T2D, type 2 diabetes.

The largest cost difference is the cost of treatment, followed by an increase in maintenance costs, reflecting longer life expectancy in the semaglutide arm. Cost offsets include reductions in the cost of managing acute CV events, CKD and T2D.

All people in both arms of the model receive CV prevention therapies appropriate to high-risk individuals as part of their usual care. Costs of ongoing management of diabetes and CKD do however differ between arms to reflect higher rates of T2D emergence and CKD deterioration shown in the usual care arm.

The largest component of the QALY difference between arms occurs due to people remaining longer in the eCVD state, with smaller differences due to BMI, CKD, T2D and acute events. Longer stay in the eCVD state for those receiving semaglutide reflects the difference between arms in time to major CV events found in the trial.

The clinical outcomes predicted by the model and the disaggregated results of the base-case incremental cost effectiveness analysis are detailed in Appendix H.

To reduce run time, the deterministic base case was used as the basis of one-way scenario and subgroup analyses. The ICER estimates for the deterministic and probabilistic base cases are very similar.

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted. The model inputs were sampled from distributions around the means of input parameters and, for survival equations, covariance matrices. Section 3.9 describes uncertainty measures and distributions used. A total of 1,000 PSA iterations were found to be sufficient to yield a stable estimate of the mean model results.

The PSA cost-effectiveness results are reported in Table 46. The mean incremental results were also plotted in a cost-effectiveness plane (CEP) (Figure 24), cost-effectiveness acceptability curve (CEAC) (Figure 25), and cost-effectiveness acceptability frontier (CEAF) (Figure 26).

The PSA resulted in an ICER of £14,832/QALY, very similar to the deterministic base case of £14,702/QALY.

Table 46: Base case probabilistic results (per patient)

Technologies	Total costs (£)	Total LYG	Total QALYs
Semaglutide in addition to established clinical management	[redacted]	10.23	[redacted]
Established clinical management	28,109	10.06	7.14
Incremental costs (£)	[redacted]		
Incremental LYG	0.165		
Incremental QALYs	[redacted]		
ICER incremental (£/QALY)	14,832		
NHB at £20,000 (£)	[redacted]		
NHB at £30,000 (£)	[redacted]		

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALY, quality-adjusted life year.

All PSA simulation outputs fall in the north-east quadrant of the CEP, indicating the addition of semaglutide leads to both increased QALYs and increased costs (Figure 24). At a £20,000 willingness-to-pay (WTP) threshold, approximately 90% of samples found the addition of semaglutide to be cost-effective compared with established clinical management. At a £30,000 WTP threshold, more than 99% of samples found the addition of semaglutide to be cost-effective compared with established clinical management (Figure 25). At a WTP higher than ~£15,000, the likelihood of semaglutide being cost-effective is greater than that of established clinical management (Figure 26).

Figure 24: CEP illustrating the distribution of probabilistic results of the analysis

Abbreviations: CEP, cost-effectiveness plane; QALY, quality-adjusted life year; WTP, willingness-to-pay.

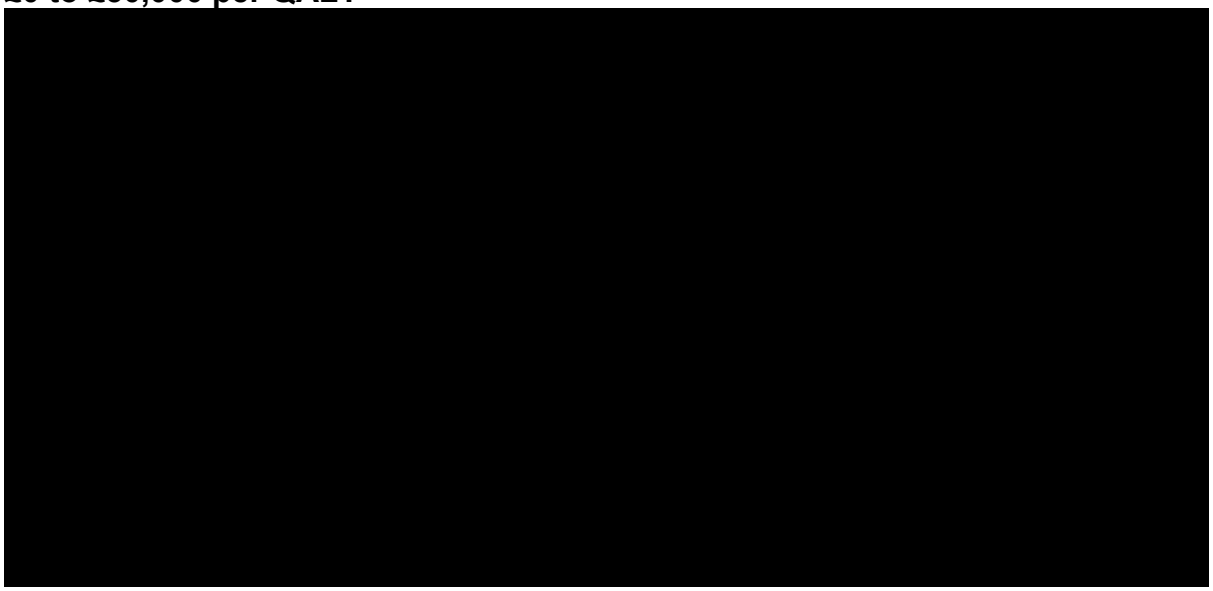
Figure 25: CEAC of semaglutide in addition to established clinical management and established clinical management across a WTP threshold of £0 to £50,000 per QALY

Legend:

- Semaglutide with established clinical management
- Established clinical management

Abbreviations: CEAC, cost-effectiveness acceptability curve; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 26: CEAF of semaglutide in addition to established clinical management and established clinical management across a willingness-to-pay threshold of £0 to £50,000 per QALY



Legend:

- Semaglutide with established clinical management
- Established clinical management

Abbreviations: CEAF, cost-effectiveness acceptability frontier; QALY, quality-adjusted life year; WTP, willingness-to-pay.

3.11.2 Deterministic sensitivity analysis

A one-way DSA was performed. Individual parameters were varied according to appropriate ranges to assess the impact of each input on base case outcomes to assess key drivers of cost-effectiveness. The ranges were obtained or derived from literature in the first instance. Where the standard error was not available to calculate the range, it was assumed to be 20% of the mean value. The one-way sensitivity analysis (OWSA) results of the top 20 most sensitive parameters are reported in Table 47 and presented in a tornado diagram (Figure 27). Based on the OWSA results, the model was most sensitive to assumptions relating to utility for BMI, treatment effect on CV death and the transition probabilities around CKD.

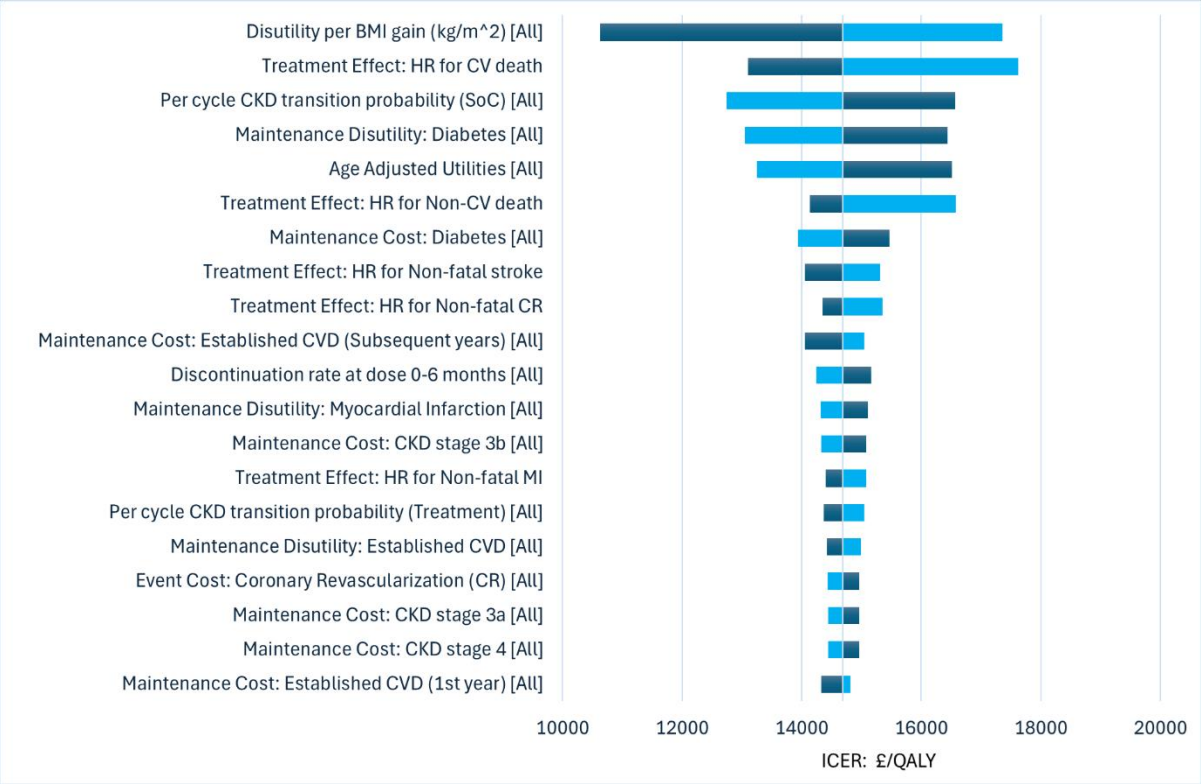
Table 47: OWSA results

Parameter Name [Applicable arm]	ICER using parameter lower bound (£/QALY)	ICER using parameter upper bound (£/QALY)
Base-case ICER	£14,702	
Disutility per BMI gain (kg/m^2) [All]	£17,361	£10,633
Treatment Effect: HR for CV death	£13,099	£17,620

Parameter Name [Applicable arm]	ICER using parameter lower bound (£/QALY)	ICER using parameter upper bound (£/QALY)
Per cycle CKD transition probability (SoC) [All]	£16,570	£12,738
Maintenance Disutility: Diabetes [All]	£16,437	£13,048
Age Adjusted Utilities [All]	£16,518	£13,246
Treatment Effect: HR for Non-CV death	£14,134	£16,572
Maintenance Cost: Diabetes [All]	£15,468	£13,935
Treatment Effect: HR for Non-fatal stroke	£14,056	£15,311
Treatment Effect: HR for Non-fatal CR	£14,349	£15,347
Maintenance Cost: Established CVD (Subsequent years) [All]	£14,052	£15,046
Discontinuation rate at dose 0-6 months [All]	£15,165	£14,238
Maintenance Disutility: Myocardial Infarction [All]	£15,111	£14,314
Maintenance Cost: CKD stage 3b [All]	£15,080	£14,323
Treatment Effect: HR for Non-fatal MI	£14,400	£15,078
Per cycle CKD transition probability (Treatment) [All]	£14,367	£15,043
Maintenance Disutility: Established CVD [All]	£14,425	£14,989
Event Cost: Coronary Revascularization (CR) [All]	£14,966	£14,438
Maintenance Cost: CKD stage 3a [All]	£14,962	£14,441
Maintenance Cost: CKD stage 4 [All]	£14,957	£14,446
Maintenance Cost: Established CVD (1st year) [All]	£14,329	£14,811

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CR, coronary revascularisation; CV(D), cardiovascular (disease); HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

Figure 27: Tornado diagram – ICERs for semaglutide in addition to established clinical management compared to established clinical management in one way sensitivity analyses



Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CR, coronary revascularisation; CV(D), cardiovascular (disease); HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

3.11.3 Scenario analyses

Scenario analyses were conducted to explore the uncertainty around the model assumptions. A list summarising the scenarios explored in the analysis and the rationale for conducting each scenario analysis is shown in Table 48. None of the scenarios explored resulted in an ICER above £20,000/QALY (Section 3.11.3.2).

Table 48: List of scenarios explored

No.	Scenario	Justification
1-4	Patient risk of MACE (CV death, non-fatal MI and stroke, CR, HUA and HHF) in control arm set to 20%; 30%; 40%; 50% (scenarios 1–4, respectively)	The base case model predicts 34.2 MACE events per 100 patients in the usual care arm. In these scenarios, total MACE event risk in the control arm was varied; the HR for each endpoint was as observed in SELECT. A similar approach was taken in the NICE Guideline on Hypertension (NG136 (146)) to explore the impact of varying baseline risk on cost-effectiveness
5	People with T2D	The risk of major CV events for a population with diabetes was estimated to be 22% higher than in SELECT. This increase in risk was estimated by comparing the 10-year risk using the SMART-REACH risk calculator (94) for a CPRD population with eCVD, with and without diabetes (68). The HR for each endpoint was as observed in SELECT. In this scenario the costs of developing diabetes are removed
6	UK eCVD prevalent population	Cost-effectiveness was estimated for an NHS cohort with eCVD identified from the CPRD analysis. This cohort is described in Section 3.11.3.1
7	UK eCVD incident population	Cost-effectiveness was estimated for an NHS cohort hospitalised for eCVD in the previous 12 months, identified from CPRD and HES data. This cohort is described in Section 3.11.3.1
8	Real world discontinuation rates	In this scenario, discontinuation rates per cycle were set at 4.5%. This gives a median duration of 1.2 years of treatment, which is the same median persistence reported in a CPRD study on 589 patients receiving a first prescription for a GLP-1 RA in the UK (median persistence: 426 days, 95% CI: 384, 476 days) (189)
In scenarios 9–11, alternative approaches to extrapolating efficacy were considered. Multiple functional forms were fitted to the trial data and preferred functional forms are presented in the base case. An additional survival analysis is presented in Appendix Q		

No.	Scenario	Justification
9	Efficacy extrapolation based on the best fitting proportional hazard model	A proportional hazard approach, in which the best fitting proportional hazard model was selected for each endpoint
10	Efficacy extrapolation based on a single hazard model	A single hazard model in which the HR for MACE (SELECT primary endpoint) was applied to each component of MACE (MI, stroke and CV mortality), using the functional form that gave the lowest cumulative error in the SMART-REACH extrapolation
11	Efficacy extrapolation based on a trial data model	In place of parametric extrapolations, fitted trial AJ plots were used to model CV events, to simulate a cohort with complete follow-up over 4 years
12	Multiplicative utility combination for CV events	An alternative utility assumption was tested. Instead of calculating utility in an additive approach, a multiplicative approach was tested in this scenario
13	Alternative CV cost approach	The average cost of CV events was taken from NHS average costs, without adjusting for higher severity of events in people with eCVD
14	Cost for non-CV death	The cost of non-CV death was set at zero in the base case (in line with the NICE Reference Case). This scenario assumes the cost of non-CV death to be £7,157 based on the study by Georghiou and Bardsley, 2014 (190)
15–16	Discount rates	Two scenario analyses assuming discounted rates for both health outcomes and costs at 0% and 5% were performed

Abbreviations: AJ, Aalen-Johansen; CI, confidence interval; CPRD, Clinical Practice Research Datalink; CR, coronary revascularisation; CV, cardiovascular; eCVD, established cardiovascular disease; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HES, Hospital Episode Statistics; HHF, hospitalisation for heart failure; HR, hazard ratio; HUA, hospitalisation for unstable angina; MACE, major adverse cardiovascular event; MI, myocardial infarction; T2D, type 2 diabetes.

3.11.3.1 Scenarios 6 and 7: Cost-effectiveness in UK eCVD population

A cohort ("UK eCVD prevalent population") was identified from the CPRD data, comprising those who had a confirmed diagnosis of eCVD (MI, stroke or PAD), were living with obesity or had a BMI of ≥27kg/m^2, were over the age of 18 and had no recorded evidence of diabetes. Those who had received GLP-1 drugs were excluded, as were those with insufficient data. A total of 141,642 people were identified who met these criteria. The cohort was followed up for three years (the approximate duration of treatment in SELECT). Rates of non-fatal MI, non-fatal stroke, HHF, hospitalisation for ACS, CR and all-cause mortality were identified from records in the CPRD linked to Hospital Episode Statistics (HES) and the Office for National Statistics (ONS).

A second cohort ("UK eCVD incident population") was identified, comprising those who met the above criteria and who had been hospitalised for a CV event (MI, stroke or PAD) in the year prior to index. The cohort was followed up for six years, to explore change in risk over time.

Characteristics of the SELECT and CPRD populations, and their corresponding CV event rates used in the model are shown in Table 49 and Table 50, respectively.

Table 49: Characteristics of SELECT and UK eCVD populations

	SELECT†	UK eCVD prevalent	UK eCVD incident
Age (mean, years)	61.60	[redacted]	[redacted]
Proportion Male (%)	72.30	[redacted]	[redacted]
BMI (mean, kg/m^2)	33.30	[redacted]	[redacted]
People with eGFR <60 ml/min/1.73 m^2 (%)	10.80	[redacted]	[redacted]
People with eGFR 60–90 ml/min/1.73 m^2 (%)	48.70	[redacted]	[redacted]
People with eGFR >90 ml/min/1.73 m^2 (%)	40.50	[redacted]	[redacted]
People with prediabetes (%)	66.40	[redacted]	[redacted]

†SELECT characteristics from Lincoff 2023 (44); ‡Mean of 9.9 years since first MACE; ¶Based on reported IQR [redacted]% of patients have eGFR <61.5 ml/min/1.73m^2 and [redacted]% have eGFR >90.0 ml/min/1.73m^2; §Prediabetes was present in [redacted]% of patients with recorded HbA1c.
Abbreviations: BMI, body mass index; eCVD, established cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; IQR, interquartile range; MACE, major adverse cardiovascular event.

The UK eCVD prevalent population was older than the SELECT population, had a lower BMI and a higher frequency of CKD. The UK eCVD incident population also had a lower BMI and a higher frequency of CKD, but was of a similar age to the SELECT population.

Table 50: Rates of CV events in SELECT and UK eCVD populations

	SELECT	UK eCVD prevalent	UK eCVD incident	
	Annual event rate†	Annual event rate	Annual event rate, Year 1‡	Annual event rate, Years 2+
MI	0.011	[redacted]	[redacted]	[redacted]
Stroke	0.005	[redacted]	[redacted]	[redacted]
HF	0.004	[redacted]	[redacted]	[redacted]
Unstable angina	0.005	[redacted]	[redacted]	[redacted]
CR	0.023	[redacted]	[redacted]	[redacted]
Incident T2D	0.011	[redacted]	[redacted]	[redacted]
All-cause mortality	0.011	[redacted]	[redacted]	[redacted]

†SELECT event rates from usual care arm of base-case model, Year 1; ‡People who had a hospitalised CV event (MI, stroke or PAD) in the 12 months before index.
Abbreviations: CR, coronary revascularisation; CV, cardiovascular; eCVD, established cardiovascular disease; HF, heart failure; MI, myocardial infarction; PAD, peripheral arterial disease; T2D, type 2 diabetes.

Rates of CV events and mortality were in general higher in the UK eCVD prevalent population than in SELECT; in particular, rates of hospitalisation for HF were much higher. However, rates of CR were lower than in SELECT.

In the UK eCVD incident population, rates of CV events and mortality were increased in the first year after a hospitalised CV event; event rates in subsequent years were more similar to the rates in the UK eCVD prevalent population.

The model was run with demographics and placebo event rates adjusted to match the UK eCVD populations. The HR for CV events was as observed in SELECT.

3.11.3.2 Scenario analyses results

The summary results for all scenario analyses are presented in Table 51.

Table 51: Scenario analyses results

Scenario	Scenario description	Incremental cost (£) per patient	Incremental QALY per patient	ICER (£/QALY)
Base case		[redacted]	[redacted]	14,702
1	People with 20% risk of MACE	[redacted]	[redacted]	15,907
2	People with 30% risk of MACE	[redacted]	[redacted]	15,017
3	People with 40% risk of MACE	[redacted]	[redacted]	14,309
4	People with 50% risk of MACE	[redacted]	[redacted]	13,721
5	People with T2D	[redacted]	[redacted]	16,340
6	UK eCVD prevalent population	[redacted]	[redacted]	11,072
7	UK eCVD incident population	[redacted]	[redacted]	10,851
8	Real world discontinuation rates of 4.5% per month	[redacted]	[redacted]	8,505
9	Efficacy extrapolation based on the best fitting proportional hazard model	[redacted]	[redacted]	14,675
10	Efficacy extrapolation based on a single hazard model	[redacted]	[redacted]	13,952
11	Efficacy extrapolation based on a trial data model	[redacted]	[redacted]	14,524
12	Multiplicative utility combination for CV events	[redacted]	[redacted]	14,897
13	Alternative CV cost approach	[redacted]	[redacted]	14,954
14	Cost for non-CV death	[redacted]	[redacted]	14,647
15	Discount rate for costs and benefits at 0%	[redacted]	[redacted]	12,021
16	Discount rate for costs and benefits at 5%	[redacted]	[redacted]	16,666

MACE defined as CV death, non-fatal MI and non-fatal stroke.
Abbreviations: CV, cardiovascular; eCVD, established cardiovascular disease; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; QALY, quality-adjusted life year.

The scenario analysis suggests that cost-effectiveness is robust when the rate of CV events is varied (scenarios 1–5). Cost-effectiveness was improved when considering a UK cohort with eCVD taken from the CPRD analysis (scenario 6); the unmet need was especially high and cost-effectiveness was also improved in a population who had experienced a hospitalised CV event in the previous year (scenario 7). Applying higher discontinuation rates to reflect RWE also resulted in a lower ICER (scenario 8). The model was not very sensitive to alternative methodologies for survival analysis (scenarios 9–11), or cost and utility calculation (scenarios 12–14). The

ICER varied when discount rates were changed, reflecting benefits that occur over a longer time period than treatment costs (scenarios 15–16).

3.12 Subgroup analysis

3.12.1 Subgroups considered

Cost-effectiveness was estimated for subgroups of SELECT, identified in the decision problem. Subgroups presented are:

- People with BMI ≥35 kg/m^2 (n=5,106)
- People with previous MI (n=11,908)
- People with previous stroke (n=3,135)
- People with symptomatic PAD (n=777)
- People with HF (n=4,286)
- People with CKD, here defined as eGFR <60 mL/min/1.73 m^2 (n=1,898).

A further 8% of participants in SELECT met two or more eligibility criteria (e.g. prior stroke and prior MI) – these participants were not included in the diagnosis-specific subgroups above and are not considered further here.

Predefined subpopulation analyses of SELECT considered baseline information (age, sex, BMI; baseline CVD, HF status, eGFR, HbA1c; region, race, and ethnicity). Results for the primary endpoint in predefined subgroups are reported in Section 2.8. Novo Nordisk suggests that the cost-effectiveness estimates for subgroups should be interpreted with caution, considering the lower precision when estimating results for smaller patient groups.

3.12.2 Methodology

ICERs were estimated using subgroup-specific event rates and an estimated subgroup-specific treatment effect, as follows.

Demographic data including age, gender, BMI and prevalence of prediabetes, CKD and HF were extracted from SELECT for each subgroup and input to the economic model (120, 149).

Rates of major CV events in the placebo arm in SELECT were extracted for each subgroup. Events considered were: non-fatal MI, non-fatal stroke, HHF, HUA, CR, and CV and non-CV mortality (191). The placebo arm of the model was calibrated so that, when run with a 3.3-year time horizon, events predicted by the placebo arm of the model closely matched those that occurred in each subgroup in the placebo arm of SELECT.

Hazard ratios for each major CV event in SELECT were determined for each subgroup and input to the model (191). If fewer than 10 events occurred in either arm of any subgroup, a subgroup-specific HR was not calculated and the HR from the whole study population was used instead.

3.12.3 Results

Event rates for non-fatal MI, non-fatal stroke, and for CV and non-CV mortality for each subgroup are shown in Figure 28. Compared with the whole population, these major CV events were more common in people with HF and in people with eGFR <60 mL/min/1.73 m^2. Event rates were not notably elevated for people with BMI ≥35 kg/m^2. A similar pattern was observed for other major CV events (data not shown).

Hazard ratios for each subgroup are shown in Table 52. HRs were not calculated for a subgroup if the number of events in either arm was <10, instead the model used the whole population HR for that endpoint. When comparing with the whole population, the majority of the calculated HRs were lower for people with eGFR<60 and for people with HF. Other subgroups ratios did not show a clear pattern of difference (either higher or lower) when compared with the whole population. Confidence limits around HRs for subgroups were wider than for the whole population, and for each endpoint all subgroup CIs overlapped.

Figure 28: Event rates, SELECT, subgroups – Placebo arm

Source: Data on file, Novo Nordisk (191).
Abbreviations: BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; MI, myocardial infraction; NF, non-fatal; PBO, placebo.

Cost-effectiveness ratios for each subgroup are shown in Table 52. Compared with the whole population, the ICER was lower in people with HF and people with eGFR <60, reflecting higher event rates in these subgroups. None of the ICER estimates exceeded £20,000 (Table 53).

Table 52: Subgroup analyses – hazard ratios

Subgroup	Non-fatal AMI	Non-fatal stroke	HHF	HUA	CR	CV death	All death[a]
Whole population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI ≥35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR<60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N/A - hazard ratios not calculated as number of events in either arm was <10
a Model uses non-CV mortality, calculated as all mortality less CV mortality.
Abbreviations: BMI, body mass index; CR, coronary revascularisation; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalisation for heart failure; HUA, hospitalisation for unstable angina; MI, myocardial infarction; PAD, peripheral arterial disease

Table 53: Subgroup analyses – cost-effectiveness results

Population considered	ICER (£/QALY)
Whole population	£14,702
People with BMI ≥35	£18,751
People with previous myocardial infarction	£14,758
People with previous stroke	£16,773
People with symptomatic peripheral arterial disease	£16,092
People with heart failure	£12,684
People with eGFR<60	£11,961

Subgroup specific demographics, placebo event rates and treatment effects implemented. See text for fuller explanation

The exploratory subgroup analyses suggests that treatment in all the specific subgroups listed in the final scope would be considered cost effective at a WTP

threshold of £20,000. The analyses suggest additional benefit in people with HF and those with eGFR <60 mL/min/1.73m^2, due to higher event rates and lower point estimates for HRs, when compared with the whole population. These findings should be interpreted with caution in light of limited sample size and overlapping CIs.

3.13 Benefits not captured in the QALY calculation

Semaglutide offers a number of benefits not fully reflected in the QALY gain in this economic model.

As shown in the STEP-HFpEF and STEP-HFpEF DM studies (Section 2.6.2), use of semaglutide in people with HFpEF quickly results in clinically and statistically significant benefits in quality of life, as measured by the improvement in the KCCQ disease-specific HRQoL instrument. These benefits are not captured in the model.

People with eCVD and living with overweight or obesity have an elevated risk of a wide range of health conditions, including musculoskeletal diseases (e.g. osteoarthritis), GI diseases, sleep apnoea, and several cancers. Sustained and significant weight loss with semaglutide can be expected to result in additional benefits by modifying these complications. In SELECT, participants in the semaglutide arm lost weight in comparison to those in the placebo arm. The impact of weight loss on modifying complications of obesity has not been fully reflected in the QALY gain.

3.14 Validation

Computational accuracy

Computational validation was conducted by senior health economists, both within and outside of the core modelling team. Major spreadsheet calculations and Visual Basic for Application (VBA) subroutines were reviewed and assessed to verify their accuracy and ensure proper functionality. Survival equations were internally validated to ensure correct implementation. Internal validation was conducted to assess whether outputs from the health economic model were consistent with the data sources used to inform model development, in this case SELECT. The choice of survival curves was justified as reported in Section 3.3.

A further technical review of the NICE submission version of the model (pre-final) was conducted by a UK health economics agency experienced in preparing material for review by NICE. The model inputs, settings and reporting were updated following the review.

Comparison to trial data

A modelled 4-year follow-up period was compared against trial event incidence estimates. For some events, particularly HHF, CV death and non-CV death, observed event rates varied over time. An Aalen-Johansen (AJ) plot was used to model these events, extended to simulate a cohort with complete follow-up over 4 years. Lifetable capping was removed during the trial period.

The trial validation rates for both semaglutide and placebo treatment arms are reported in Table 54. The moderately low model error rates suggest that the model achieves a close match to events observed in the trial over this time period.

Table 54: Trial validation of modelled AJ plots compared against actual trial outcomes observed in the SELECT trial

Clinical event	Modelled AJ plot event rate	Observed trial event rate	Absolute model error	Model error, %
Semaglutide arm				
MI	7.96	8.10	–0.14	–1.72
Stroke	5.19	5.30	–0.11	–2.17
HHF	3.46	3.33	0.13	3.83
HUA	3.54	3.75	–0.21	–6.00
CR	16.10	16.65	–0.55	–3.44
CV death	7.85	7.62	0.23	2.96
Non-CV death	5.31	5.19	0.12	2.27
Established clinical management arm				
MI	10.89	11.27	–0.38	–3.53
Stroke	5.42	5.72	–0.30	–5.51
HHF	4.37	4.22	0.16	3.56
HUA	4.16	4.29	–0.13	–3.18
CR	21.21	21.71	–0.50	–2.36
CV death	9.52	9.00	0.52	5.47
Non-CV death	6.58	6.73	–0.15	–2.30

Abbreviations: AJ, Aalen-Johansen; CR, coronary revascularisation; CV, cardiovascular; HHF, hospitalisation for heart failure; HUA, hospitalisation for unstable angina; MI, myocardial infarction.

Comparison between HRs observed in SELECT and UK general practice was part of the curve selection process described in Section 3.3.

Comparison with UK general practice

A UK cohort meeting similar criteria to SELECT was identified from the CPRD, as described in Section 3.11.3. People in the prevalent eCVD population were older than the SELECT cohort, with higher rates of HHF and CV events, and lower rates of CR. People with eCVD and a recent hospitalisation for MI, stroke or PAD were similar in age to the SELECT population but had a much higher rate of CV events in the first year after a prior CV event.

3.15 Interpretation and conclusions of the economic evidence

Over a lifetime horizon, people with eCVD and overweight or obesity receiving semaglutide in addition to established clinical management were estimated to accrue [redacted] QALYs at a cost of £[redacted]. People receiving established clinical management accrued 7.20 QALY at a cost of £27,843. The base-case ICER was £14,702 per QALY.

Scenario analysis results fell within an acceptable ICER range across variation in model inputs, including baseline risk and plausible changes in cost and utility inputs. Cost-effectiveness improved when HRs from the trial were applied to populations with a higher baseline risk level, particularly people with CKD, people with HF, and a UK CPRD cohort, including those at increased risk of events during the 12 months after a CV event.

The DSA shows the impact on the ICER of plausible variation in input parameters relating to several benefits of semaglutide shown in SELECT, including efficacy preventing MACE, and the rate of transition through CKD health states. Findings were also influenced by the impact of BMI on utility, and the utility and costs associated with long-term management of diabetes. None of these analyses resulted in an ICER that exceeded £20,000/QALY.

The PSA found a high probability of semaglutide being cost-effective in WTP ranges consistent with usual NICE decision-making thresholds. Results from the uncertainty analyses generally gave results that fall below £20,000/QALY.

A separate scenario explored cost-effectiveness in people with T2D. People with T2D are included within the license and decision problem, but were not included in SELECT: the SUSTAIN-6 trial had already shown that semaglutide reduced the risk of MACE in a population with T2D at high risk of CV events (Section 2.6.3; HR for MACE of 0.74 for semaglutide up to 1.0 mg once weekly, relative to placebo in addition to SoC). The scenario analysis suggests that cost-effectiveness in people with eCVD, BMI ≥27 kg/m^2 and T2D is similar to that in the SELECT population.

In SELECT, persistence on therapy was high, despite some initial drop-outs during titration, when the most common GLP-1 RA side effects first occur. In UK practice, however, maintaining persistence on therapy remains a significant challenge for achieving CV risk reduction. To achieve the full benefits of semaglutide people need to remain on treatment; the symptomatic benefit of weight loss could encourage greater persistence on therapy compared with other CV prevention drugs. A scenario analysis suggested cost-effectiveness was improved under higher real world discontinuation rates, although the QALY gain was smaller as people remained on therapy for a shorter time.

In conclusion, this economic analysis found the cost-effectiveness of semaglutide for the prevention of MACE to be within the range usually considered acceptable by NICE. Semaglutide offers a new route to further reductions in CV events in a high-risk population, that can be cost-effective when delivered in addition to SoC in people with eCVD and BMI ≥27 kg/m^2.

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Appendices

- Appendix A: Summary of product characteristics (SmPC) and UK public assessment report
- Appendix B: Identification, selection and synthesis of clinical evidence
- Appendix C: Subgroup analysis
- Appendix D: Adverse reactions
- Appendix E: Published cost-effectiveness studies
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and living with overweight or obesity [ID6441]

Summary of Information for Patients (SIP)

12th August 2025

File name	Version	Contains confidential information	Date
ID6441 semaglutide_CV prevention_obesity_SIP	6.0	No	12th August 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Generic: semaglutide Brand name: Wegovy®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Semaglutide is intended to be used in addition to a reduced-calorie diet and increased physical activity to reduce the risk of major adverse cardiovascular (CV) events (cardiovascular death, non-fatal heart attack, or non-fatal stroke) in adults who have already had a heart attack, a stroke or have peripheral arterial disease (PAD) (collectively described as having established cardiovascular disease [eCVD]) and live with either overweight or obesity (body mass index [BMI] ≥27 kg/m^2).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Wegovy® has a UK marketing authorisation from the MHRA (granted in July 2024): https://www.gov.uk/government/news/mhra-approves-glp-1-receptor-agonist-semaglutide-to-reduce-risk-of-serious-heart-problems-in-obese-or-overweight-adults

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

- Corporate sponsorship for 2025 (Jan–Dec) of the Primary Care Cardiovascular Society (PCCS). £10,000 is being provided to support the PCCS to carry out its mission to support, educate and empower primary care to deliver high quality holistic care to those with or at risk of cardiovascular disease
- Corporate sponsorship (April 2025 – March 2026) of the British Cardiovascular Society (BCS). £24,000 is being provided to support the BCS to enhance research, treatment, education, and patient care, benefiting clinicians, researchers and the broader cardiovascular community
- Corporate sponsorship for (May 2025 – April 2026) of the UK Kidney Association (UKKA). £10,000 is being provided to support the UKKA's activities
- Sponsorship of Kidney Care UK's Bloody Amazing Kidneys campaign. £25,000 is being provided to Kidney Care UK to support delivery of their chronic kidney disease awareness campaign

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Cardiovascular disease (CVD) is a general term used to describe a group of serious, chronic conditions affecting the heart and blood vessels (1) (Company submission, Section 1.3.1). This includes:

- Coronary heart disease (CHD): coronary arteries (blood vessels supplying oxygen to the heart muscle) become narrowed by fatty material within their walls. Over time, the fatty material (called atheroma) can build up inside the coronary arteries. If a piece of atheroma breaks off, a blood clot forms, which can block the coronary artery and cut off the supply of blood and oxygen to the heart, resulting in a heart attack (also called a myocardial infarction) (2)
- Cerebrovascular disease: a group of diseases that affects blood circulation to the brain, which can result in strokes. There are three main types of stroke: ischaemic (when a blockage cuts off the blood supply to part of the brain, killing brain cells), haemorrhagic (due to bleeding in or around

the brain, damaging brain cells) and transient ischaemic attack (TIA; also known as a "mini-stroke", when symptoms only last a short time) (3)

- Peripheral arterial disease (PAD): a disease of blood vessels supplying the arms and legs. In PAD, arteries become narrowed by a build-up of fatty material within their walls (4). The narrowing of the arteries results in reduced blood flow to the legs. Milder cases of PAD can cause leg pain when walking; in more severe cases, PAD can result in gangrene (death of body tissues due to loss of blood supply) and even amputation. PAD also increases the risk of heart attack and stroke (5, 6).

People who have already experienced a heart attack, a stroke or have a diagnosis of PAD are referred to here as having eCVD, as described in section 1b.

Many factors increase the risk of CVD, including diabetes, high blood pressure, high cholesterol, smoking and living with overweight and obesity (7). While obesity can contribute to some of those risk factors (diabetes, high blood pressure, and high cholesterol), it also has direct negative effects on heart function, and increases the risk of developing CVD and the risk of death from CVD (8).

Despite conventional treatment to manage risk factors, people who have experienced a CV event are at a very high risk of experiencing another event, which may be more severe and debilitating than the first one; they also face an increased risk of death compared with people who have never had a CV event (9-13) (Company Submission, Section 1.3.3.1).

In the United Kingdom (UK), around 1.4 million people (2.2% of the population) have survived a heart attack, just under 1.2 million (1.9%) have had a stroke or TIA, and just over 350,000 (0.6%) have PAD (7, 14) (Company Submission, Section 1.3.2). CVD is the second most common cause of death in the UK, with over 174,000 deaths a year (15), and the biggest cause of death in people under 75 years old (16). In people living with overweight or obesity, CVD is a leading cause of death and disability (17).

CV events can have significant, long-term impacts on quality of life (QoL) (18) (Company Submission, Section 1.3.3.2). In the UK, strokes are the single biggest cause of severe disability (7), and up to 30% of people who have had a heart attack will go on to develop heart failure; symptoms of heart failure such as shortness of breath, tiredness, and ankle swelling all significantly impact an individual's QoL (19, 20). The QoL burden on patients with very high CV risk can be particularly heavy, and if they experience multiple CV events this may lead to further deterioration in QoL (21).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

People are diagnosed with eCVD after they have had a heart attack, a stroke or a diagnosis of PAD. Patients with eCVD will need to be on life-long medication to reduce the risk of experiencing another CV event (or a first CV event, if they have PAD).

BMI is a measurement that works out if a person is overweight or obese by using their height and their weight. Your GP can calculate your BMI, but people can also use an online tool such as the NHS health assessment tool:

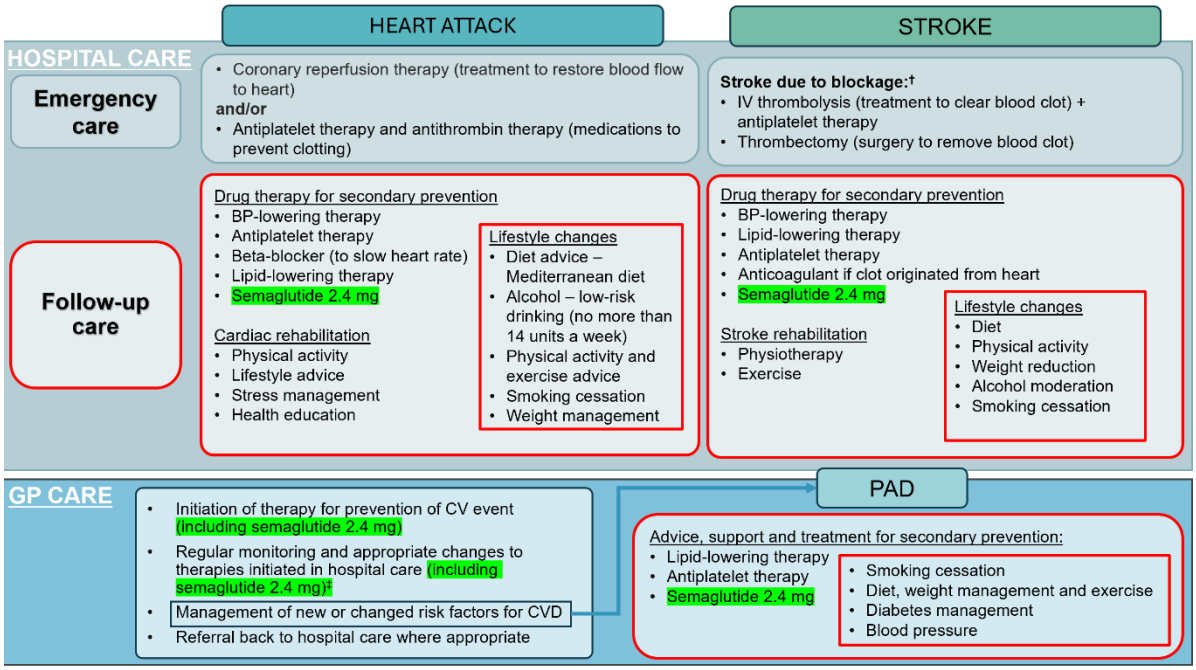
https://www.nhs.uk/health-assessment-tools/calculate-your-body-mass-index/calculate-bmi-for-adults

No additional diagnostic tests will be required with semaglutide.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed: • What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP. • Please also consider: o if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data. o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.
People with eCVD are at high risk of experiencing a CV event, either because they have already had one or more events or because they have PAD. Therefore, they are given treatment and advice to reduce that risk: this is called secondary prevention. There are guidelines available from the National Institute for Health and Care Excellence (NICE), the Stroke Association and the European Society of Cardiology (ESC) for the secondary prevention of CV events (11, 22-26); details of the guidelines are available in Section 4a – Further information. There are similarities between the guidelines: for example, people with eCVD should be given lipid-lowering medication, most often statins, to help lower their levels of cholesterol and triglycerides (a type of fat found in fat cells). People will also be advised on lifestyle modifications to reduce their risk of CV event, such as healthy eating, exercising, losing weight and stopping smoking. People may also be given medication to lower their blood pressure and/or medication to prevent the blood from clotting (known as anticoagulant, antiplatelet and/or antithrombin therapy). The ESC guidelines for the prevention of CVD state that anti-obesity medications with protective CV effects may be considered for risk reduction (11), and additional ESC guidelines for the treatment of chronic CHD state that semaglutide should be considered in non-diabetic patients with CHD and who are living with overweight or obesity (BMI >27 kg/m^2) to reduce the risk of death from CVD, heart attack, or stroke (26). Figure 1 is an overview of the treatment pathways for the secondary prevention of CV events depending on whether people have had a heart attack, a stroke or have PAD (please refer to Section 1.3.6, Figure 2 in the Company submission for a detailed description of the treatment pathways). The existing treatment pathways include both drug therapies and non-drug therapies/interventions; semaglutide does not replace any of these existing therapies, it is given as an additional treatment for the secondary prevention of CV events (Please see Section 3b for further details).

Figure 1: Future anticipated treatment pathway for the secondary prevention of CV events



†Details of treatment for other types of stroke are available from the National Clinical Guideline for Stroke (25); ‡For CV indication only.
Abbreviations: BP, blood pressure; CV, cardiovascular; CVD, cardiovascular; IV, intravenous; PAD, peripheral arterial disease; UK, United Kingdom.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

No PBE has been collected.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities. If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.
Semaglutide belongs to a class of medicines called glucagon-like peptide-1 receptor agonists (GLP-1-RA). They are similar to the natural hormone GLP-1, which helps to regulate blood sugar levels, cardiovascular function and food intake (27). Semaglutide reduces blood sugar levels, decreases appetite and leads to weight loss; semaglutide has also been shown to have beneficial effects on the CV system by decreasing blood pressure, reducing levels of cholesterol and triglycerides, and by reducing inflammation (which can contribute to CVD) in the body (28-30) (Company Submission, Section 1.2, Table 2).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.
Semaglutide is expected to be used in addition to standard of care medication for the secondary prevention of CV events such as statins and blood pressure-lowering medication. Because semaglutide works in a different way to these other CV medications, patients will need to keep taking their other medications as well as semaglutide. Semaglutide has been used for many years in patients with type 2 diabetes, and therefore any risk of interference with the effect of other medicines is well understood.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Semaglutide is administered once a week via an injection under the skin (called a “subcutaneous” injection). The injection can be self-administered or given by a carer, or someone else. People starting semaglutide will follow a fixed dose escalation scheme, meaning they will start at the lowest dose (0.25 mg) for 4 weeks, then move on to a higher dose for another 4 weeks (0.5 mg, then 1.0 mg, then 1.7 mg), until the maintenance dose – the ongoing dose required to maintain a desired drug concentration in the body – of 2.4 mg is reached (31).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The main clinical trial providing evidence for semaglutide in the secondary prevention of CV events is the completed Phase 3 trial called SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity). In SELECT, patients received semaglutide 2.4 mg subcutaneously once weekly, the same dose being assessed by NICE, or a matching dummy medicine (called a placebo) (Company submission, Section 2.3.1).

SELECT (NCT03574597)

The SELECT trial was a multinational, multicentre, randomised, double-blind, placebo-controlled study with sites in America, Asia, Australia and Europe (including the UK), which completed in June 2023. A total of 17,604 patients participated in SELECT. People could take part in the trial if they:

- Were aged ≥45 years at the time of signing the informed consent form
- Had a BMI ≥27 kg/m^2
- Had eCVD as evidenced by at least one of the following:
    - Prior heart attack
    - Prior stroke (ischaemic or haemorrhagic)
    - Symptomatic PAD.

People could not take part if they:

- Had experienced a heart attack, stroke, or had been hospitalised for unstable angina (severe chest pain caused by reduced blood flow to the heart) or TIA within 60 days prior to the day of screening
- Were presently classified as having Class IV heart failure (as per the New York Heart Association [NYHA] classification)
- Had levels of glycated haemoglobin (HbA1c) ≥48 mmol/mol (6.5%) (indicative of type 2 diabetes)
- Had a history of type 1 or type 2 diabetes (history of gestational diabetes was allowed)
- Had had treatment with glucose-lowering agent(s) or GLP-1 RA within 90 days before screening.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Efficacy evidence from the SELECT trial (Company submission, Section 2.6.1)

Risk of experiencing a CV event and death

In SELECT , patients in the semaglutide group had a 20% lower risk of experiencing a major CV event such as a heart attack, stroke or CVD-related death compared with those in the placebo group (Company Submission, Section 2.6.1.2). Additionally, patients on semaglutide had an 18% lower risk of experiencing a heart failure event (defined as hospitalisation or urgent visit due to heart failure – Section 2.6.1.3.2) and a 19% lower risk of dying from any cause than those on placebo (Company Submission, Section 2.6.1.3.3).

Benefits on CV risk factors

Treatment with semaglutide also resulted in improvements in blood pressure, cholesterol and triglyceride levels compared with placebo (Company Submission, Section 2.6.1.4.3). Furthermore, patients on semaglutide had a 22% lower risk of experiencing a deterioration in kidney function than those on placebo (Company Submission, Section 2.6.1.4.1). Patients in the semaglutide group had a 73% lower risk of developing type 2 diabetes, and a 67% lower risk of developing prediabetes than those on placebo (Company Submission, Section 2.6.1.4.2).

Efficacy evidence from additional analyses of SELECT data (Company Submission, Section 2.6.1.6)

While patients on semaglutide lost more weight than those on placebo (average weight loss 9.39% vs 0.88%), additional analyses of SELECT data showed that the beneficial effects of semaglutide on CV risk started before patients began losing weight, and were demonstrated regardless of how much weight patients had lost: in the semaglutide group, patients who had lost <5% of their body weight saw a similar reduction in risk of experiencing a CV event as those who had lost >5% of their body weight (32, 33).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the SELECT trial, QoL was measured using two different measures:

- The EQ-5D-5L, a questionnaire consisting of 2 pages:
    - The EQ-5D descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate their health state by ticking the box next to the most appropriate statement in each of the five dimensions (EQ-5D-5L index score range: 0–1)
    - The EQ visual analogue scale (EQ VAS) records the patient's self-rated health on a vertical scale where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement.

  For both descriptive system and VAS, a **higher** score indicates **better** self-reported health status.

- The weight-related signs and symptoms measure (WRSSM): A questionnaire designed to assess symptoms commonly associated with overweight and obesity. The WRSSM was used as a supplement to the EQ-5D-5L, as the latter is not designed to capture changes in QoL specifically

related to living with overweight and obesity. The WRSSM total scores range from 0 to 4, with **higher** scores reflecting **worse** symptoms.

The questionnaires were completed by patients at baseline (start of trial), Week 20, Week 52 and thereafter every 52 weeks, until the end of trial.

Results (Company submission, Section 2.6.1.4.5)

There were more improvements in QoL in the semaglutide group than in the placebo group:

- At baseline, the average score on the VAS was 77.15 in both the semaglutide and placebo groups. At Year 2 (Week 104), this had increased by an average of 2.52 points in the semaglutide group, compared with 0.92 points in the placebo group
- At baseline, the average EQ-5D-5L index score was 0.88 in both the semaglutide and placebo groups. At Year 2, this had increased by an average of 0.01 point in the semaglutide group, whereas it decreased by 0.01 point in the placebo group
- At baseline, the average WRSSM score was 1.12 and 1.13 for the semaglutide group and the placebo group, respectively. At Year 2, the WRSSM score had decreased by 0.26 point in the semaglutide group, compared with a 0.12 point decrease in the placebo group, corresponding to a greater improvement in the semaglutide group.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Side effects occur with all drugs, however not everyone will experience them.

There are side effects associated with semaglutide use but based on safety data from the SELECT trial and from other clinical trials, semaglutide is generally well tolerated by most people.
The most common side effects (frequency ≥1/10 patients) with semaglutide are: gastrointestinal disorders (vomiting, diarrhoea, constipation, nausea and abdominal pain), headache, and fatigue (31). These are mainly seen in the dose-escalation period, when patients are adjusting to increasing doses of semaglutide. However, most side-effects are temporary and manageable. Strategies for managing nausea in the dose escalation period include, but are not limited to: eating smaller meals, avoiding fatty or fried food and to stop eating when full.

In the SELECT trial (Company Submission, Section 2.11.1.2), side effects that caused patients to stop taking semaglutide or placebo permanently (known as permanent discontinuation) occurred in 16.6% of patients in the semaglutide group and 8.2% in the placebo group. The most common type of side-effects that led to permanent discontinuation of treatment were gastrointestinal disorders (10.0% of patients in the semaglutide group and 2.0% of patients in the placebo group) (34).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

• Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments. • Please include benefits related to the mode of action, effectiveness, safety and mode of administration

• The key benefits of treatment with semaglutide are:
  o A 20% reduction in the risk of experiencing a recurrent CV event or dying from CVD compared with placebo
  o Improvement in factors known to increase the risk of CV events, including blood pressure, lipids, body weight, diabetes, and kidney function compared with placebo
• Semaglutide needs to be taken only once a week, and can be self-administered
• Semaglutide is known to be well tolerated by most people, as shown by the data from the SELECT trial, but also by what has been observed in people who have been taking it for weight management (semaglutide is recommended by NICE for managing overweight and obesity (35)).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response: • Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers? • Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration • What is the impact of any disadvantages highlighted compared with current treatments.
• Some people might not be able to self-inject due to fear of needles, in which case semaglutide would have to be administered by someone else • Some people may experience side-effects of semaglutide treatment, predominantly affecting the gastrointestinal system. However, those side-effects are usually temporary and manageable

3i) Value and economic considerations

Introduction for patients: Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model. In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on: • The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the health economic model reflects the condition (Company Submission, Sections 3.2.3 and 3.15)

The company presented NICE with an economic model. The economic model is a simplified representation of the real world (36) and is used to predict the costs and consequences (life expectancy and QoL), of using semaglutide over a lifetime in people with eCVD and living with overweight or obesity, compared with current standard of care treatments. The model in this submission considers the main events that were measured in the SELECT trial including heart attacks, strokes and death due to CVD and to other causes. The model also considered other benefits shown in the SELECT trial including effects on kidney function, risk of developing diabetes and body weight.

In the SELECT trial, semaglutide reduced the risk of experiencing a CV event and of dying from CVD, therefore the economic model estimates that taking semaglutide will extend patients' life expectancy and also improve their QoL.

Modelling how much a treatment extends life (Company Submission, Section 3.2.1)

The SELECT trial evaluated several years of treatment with semaglutide but did not follow up patients for long enough to show all the consequences of preventing major CV events. The model uses mathematical extrapolation (a prediction of future values based on available data) to estimate how the benefits shown in the SELECT trial would affect long-term life expectancy.

Modelling how much a treatment improves QoL (Company Submission, Section 3.4.4)

The model estimates whether preventing major CV events and other benefits would improve patients' QoL in the future, and by how much. The model also takes into consideration how side-effects of treatment with semaglutide may impact the patients' QoL.

Modelling how the costs of treatment differ with the new treatment (Company Submission, Section 3.10)

Semaglutide is an additional treatment and is not intended to replace any of the current treatments. Therefore, there will be an additional cost to the NHS to provide semaglutide. However, because semaglutide will reduce the number of heart attacks and strokes, there will be a reduction in costs for treating these events. Reducing the number of heart attacks and strokes will also mean NHS resources, such a hospital beds, can be used to treat other patients.

The company's economic model considers the different types of costs involved and describes the balance between extra costs and savings.

Uncertainty (Company Submission, Section 3.11)

All economic modelling is associated with uncertainty. There are uncertainties about which groups of patients benefit the most from semaglutide, how long patients will continue taking the treatment, and whether the treatment should be started by a specialist or a GP. All these uncertainties affect whether NICE will see semaglutide as offering good value for money.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Innovation (Company Submission, Section 2.13)

To date, semaglutide is the first GLP1-RA to have demonstrated improved CV outcomes in a clinical trial, compared with placebo, in patients without type 2 diabetes. Semaglutide and some other, but not all, GLP1-RAs are currently used for weight management, but as described in section 3e, the SELECT data show that the beneficial effects of semaglutide on CV risk reduction were observed even in patients who lost <5% body weight. This supports the theory that semaglutide has direct beneficial effects on the CV system, thereby reducing the risk of CV events (32).

QALY benefits not captured in the QALY calculation (Company Submission, Section 3.13)

Semaglutide offers a number of benefits that are not fully reflected in the economic model.

Patients with heart failure and preserved ejection fraction (HFpEF) are a subgroup of patients with eCVD who have poor QoL and are at high risk of severe health issues. In a separate study, the use of semaglutide resulted in clinically significant benefits in QoL in patients with HFpEF (37). However, data from that study were not used in the economic model, to avoid double counting of the overall QoL benefit in the QALY calculation; therefore, the benefits of semaglutide in patients with eCVD and HFpEF have not been captured.

Living with overweight or obesity is associated with a wide range of health conditions including, but not limited to, osteoarthritis, gastrointestinal diseases, sleep apnoea, and several cancers. Sustained and significant weight loss with semaglutide can be expected to result in additional benefits by reducing these complications. The impact of these benefits is not fully reflected in the economic model as the model focuses mostly on CV events.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? 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

Find more general information about the Equality Act and equalities issues here

First, CVD disproportionately affects disadvantaged populations, widening existing health inequalities (8) (Company Submission, Section 1.4). People living in England's most deprived areas are almost four times more likely to die prematurely from CVD than those in the least deprived (38, 39).

Secondly, there is a known and acknowledged elevated CV risk in people of South Asian or sub-Saharan African ethnic origin (40). In the UK, people of South Asian ethnicities have an increased risk of CHD, heart failure and hypertension, compared with people of White European origin (41). In England, data from the King's Fund have shown that the Black population has higher rates of CVD (42).

Thirdly, there are gender inequalities with regards to the frequency of CVD, prognosis and specific disease characteristics. Men are almost twice as likely to develop CHD than women, but women have higher mortality rates and worse prognosis after CV events (43, 44); women are often underdiagnosed for heart attacks, with the result that they do not always get the same timely interventions as men (45). In PAD, the

outcomes in women tend to be worse than in men, mainly because women have smaller arteries, and they are more likely to develop complications than men (46).

Finally, people with severe mental illness have a 53% higher risk of developing CVD and a 85% higher risk of dying from CVD than the general population (47).

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Information relating to semaglutide

- Main publication on the SELECT clinical trial: https://www.nejm.org/doi/full/10.1056/NEJMoa2307563

Information relating to cardiovascular disease

- British Heart Foundation: https://www.bhf.org.uk/
- The Stroke Association: https://www.stroke.org.uk/

Guidelines including recommendations for the prevention of CV events:

- NICE:
    - Acute coronary syndromes. NICE guideline [NG185]: for people who have had a heart attack https://www.nice.org.uk/guidance/ng185
    - Peripheral arterial disease: diagnosis and management. Clinical guideline [CG147] https://www.nice.org.uk/guidance/cg147
    - Cardiovascular disease: risk assessment and reduction, including lipid modification. NICE guideline [NG238] https://www.nice.org.uk/guidance/ng238
- The Stroke Association. National Clinical Guideline for Stroke: https://www.stroke.org.uk/professionals/resources-professionals/national-clinical-guideline-stroke
- ESC:
    - 2021 Guidelines on cardiovascular disease prevention in clinical practice: https://academic.oup.com/eurheartj/article/42/34/3227/6358713
    - 2024 Guidelines for the management of chronic coronary syndromes: for people who have had a heart attack or have angina https://academic.oup.com/eurheartj/article/45/36/3415/7743115

Information relating to BMI:

- NHS website: https://www.nhs.uk/health-assessment-tools/calculate-your-body-mass-index/calculate-bmi-for-adults

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Angina: Chest pain due to reduced blood flow to the heart. The most common type is Stable angina, which tends to happen when the heart works harder, lasts for less than 5 minutes and improves with medication or rest. Unstable angina is more severe, lasts longer and can happen even when resting.

Body mass index (BMI): A measurement that works out if a person has a healthy weight by using their height and their weight. For most people, a BMI of 18.5–24.9 indicates a healthy weight. A BMI of 25–29.9 indicates overweight and 30 or higher indicates obesity.

Cardiovascular disease (CVD): A group of diseases that affect the heart and/or blood vessels.

Cholesterol: A type of fat that is produced in the liver but is also found in some foods. It is carried around the body to the cells that need it by proteins in the blood. The combined cholesterol and protein molecule is called a lipoprotein, of which there are two types:

- **High-density lipoproteins or HDL** is known as 'good' cholesterol. It gets rid of the 'bad' cholesterol from the blood by taking cholesterol that is not needed back to the liver, where it is broken down and removed from the body
- **Non-high-density lipoproteins or non-HDL** is known as 'bad' cholesterol. Too much non-HDL leads to a build-up of fatty deposits inside the walls of the blood vessels.

Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. They are carefully designed, reviewed, and completed, and need to be approved before they can start.

Efficacy: The measurement of a medicine's desired effect under ideal conditions, such as in a clinical trial.

EQ-5D-5L: A questionnaire used to measure changes in an individual's quality of life. The questionnaire assesses five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Gangrene: A serious condition where the loss of blood supply causes body tissues to die. It can affect any part of the body but typically starts in the toes, feet, fingers and hands.

Lipids: Fatty molecules, such as cholesterol and triglycerides, that perform various functions in the body.

Maintenance dose: The ongoing dosage of a medication required to maintain a desired steady-state drug concentration in the body.

Medicines and Healthcare products Regulatory Agency (MHRA): An agency that regulates medicines and medical devices in the UK.

National Institute for Health and Care Excellence (NICE): An independent organisation set up by the Government to decide which drugs and treatments are available on the NHS in England.

Phase 3 clinical trial: A trial that compares a new treatment with the current standard treatment for a disease, or with a placebo (dummy drug).

Quality-adjusted life year (QALY): A measure of disease burden that includes the length and quality of life.

Quality of life (QoL): A measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living.

Randomised: People taking part in a trial are allocated at random to one of two groups; in SELECT, people were allocated to receive either semaglutide or placebo.

Subcutaneous: Giving medicines through a needle inserted under the skin.

Triglycerides: A type of fat found in fat cells which can contribute to narrowed arteries.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and living with overweight or obesity [ID6441]

Clarification questions

September 2025

File name	Version	Contains confidential information	Date
ID6441 semaglutide CV prevention_EAG clarification questions_answers_[REDACTED]	1.0	No (redacted)	September 2025

Section A: Clarification on effectiveness data

SELECT trial

A1. Please provide the rationale for excluding the following people from the SELECT trial: those who had had a myocardial infarction, stroke, or hospitalisation for unstable angina or transient ischaemic attack within the past 60 days prior to the day of screening (company submission [CS], Table 8).

The design of cardiovascular outcome trials (CVOTs) follows global standards and excluding patients with recent major adverse cardiovascular events (MACE) is common practice, as demonstrated in several other past and ongoing CVOTs, including SUSTAIN-6 (NCT01720446), MARITIME-CV (NCT07037433), TRIUMPH-Outcomes (NCT06383390), and SURMOUNT-MMO (NCT05556512).

The rationale for excluding participants with recent cardiovascular (CV) events is that they may be at a higher risk of complications that are not preventable or modifiable by the study drug, potentially leading to spurious findings. Specifically, recent occurrences of myocardial infarction (MI), stroke, or unstable angina could confound the results, as these participants may face fluctuations in CV health that could affect the trial's outcome measures. By eliminating these confounding factors, a more accurate assessment of the efficacy and safety of the intervention being studied (i.e. semaglutide 2.4 mg vs placebo) can be achieved.

Ensuring the homogeneity of the study population was deemed crucial for reducing variability in trial results, thereby enhancing the interpretability and comparability of outcomes, and allowing treatment effect to be isolated more easily. Furthermore, including participants with recent CV events complicates the determination of primary and secondary endpoints related to these outcomes. For example, it can be challenging to discern whether an adverse event (AE) is a result of the intervention or a continuation of prior CV issues, or if it is a complication following a recent intervention, such as suboptimal stenting after revascularisation.

Please note that the exclusion of participants with recent CV events is not reflected in the semaglutide label for CV risk reduction, which is indicated “as an adjunct to a reduced-calorie diet and increased physical activity to reduce the risk of major

adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight (BMI ≥27 kg/m^2)" (1).

A2. In the protocol (available as a supplement to the Lincoff 2023 SELECT trial publication (2)), it is specified that the receipt of healthy lifestyle counselling will be documented in the electronic case report form. Please provide the numbers and proportions of participants in the SELECT trial semaglutide and placebo arms who received this counselling.

A baseline of lifestyle advice on healthy diet, smoking cessation and physical activity were provided and taken up by almost all participants in both arms. This represents the standard of care in the UK (and globally) for this population (as confirmed by clinician interviews and at the advisory board conducted by the company in March 2024 (3, 4)). As part of the SELECT trial participants in both groups were offered leaflets providing this healthy lifestyle advice, which were included as part of the original reference pack (Data on file subfolder) provided with the CS. The SELECT additional outputs report (data on file provided in new reference pack (5)) shows that over 99.9% of SELECT participants in both arms received the leaflets, as captured in the participants' eCRF. Clinicians at the advisory board confirmed that the healthy lifestyle advice received by participants in SELECT was similar to that received in UK practice (3).

A3. Priority question. Please provide Schoenfeld residual plots, Grambsch-Therneau test results and log-log plots for the following outcomes:

- **First event adjudicated committee (EAC)-confirmed major adverse cardiac event (MACE) (CS, Table 12)**
- **EAC-confirmed cardiovascular death (CS, Table 15)** (if not provided in CS, Appendix Q)
- **First EAC-confirmed composite heart failure outcome (CS, Table 16)**
- **EAC-confirmed all-cause death (CS, Table 17)**

In the SELECT additional outputs report (5), Figures 3 to 6 and 14 to 17 show the log-log and residual plots, respectively, for first EAC-confirmed MACE, EAC-

confirmed CV death (results for CV death were also available in Appendix Q of the CS, however they have now been updated with a spline-based smoother), first EAC-confirmed composite heart failure (HF) and EAC-confirmed all-cause death; [redacted]

[redacted] and the estimated HRs and confidence intervals (CI) from the clinical study report (CSR) provide reliable information about the treatment effects in SELECT. Furthermore, the prespecified statistical test for superiority does not rely on an assumption of proportionality.

A4. To better understand the methodological rigor behind the August 2015 protocol amendment that elevated the heart failure composite endpoint to a confirmatory secondary outcome, please provide the following:

1. The specific protocol amendment document detailing the new testing hierarchy
2. Any statistical power or alpha-spending simulations conducted to justify the addition of a new confirmatory endpoint
3. Documentation (e.g., steering committee minutes) detailing the rationale for the change, confirming it was driven solely by external trial data and not by any internal blinded or unblinded data review.

Please note that, as discussed at a clarification meeting with the EAG, the company's response is focussed on the SELECT protocol.

1. The latest versions of the protocol (v7.0 – 09 February 2022) and statistical analysis plan (SAP; v3.0 – 22 April 2022) contain the specific amendment pertaining to the update of the hierarchy. As noted by the EAG in question A2, the protocol is available from the supplementary material of Lincoff et al, 2023, as is the SAP. Both documents are available in the original reference pack with the CS (Lincoff 2023 pdf), but are included in the new reference pack for convenience.

2. SELECT was only powered for the primary endpoint. For the confirmatory secondary endpoints a testing hierarchy was used, therefore there were no specific considerations on alpha-split. The same alpha spending function was used for the composite HF endpoint, as for the other confirmatory secondary endpoints. The boundaries for HR significance for the HF composite endpoint were discussed at the SELECT steering committee held in January 2022 (6).

3. [redacted]

A5. Results reported by Scirica 2024 (10) show that, compared with placebo, semaglutide reduced COVID-19 deaths (43 vs 65; hazard ratio [HR]: 0.66; 95% confidence interval [CI]: 0.44 to 0.96). Please provide a clinical rationale to explain why semaglutide had this effect.

Although the SELECT protocol was amended in order to collect data regarding COVID-19 outcomes in light of the pandemic, the overall trial and the post-hoc analysis by Scirica et al, 2024 were both event-driven and were not designed as mechanistic studies. Scirica et al concluded that “The mechanism by which semaglutide is associated with lower CV or non-CV mortality is unknown”.

There are some data within the published literature which postulate potential mechanisms of action for the reduction in mortality observed with semaglutide vs placebo. The cluster of differentiation 147 (CD147) receptor, a highly glycosylated Type 1 transmembrane glycoprotein of the immunoglobulin superfamily and

prominent matrix metalloproteinase (MMP) inducer, is one of several receptors for the SARS-CoV-2 spike protein that mediate viral infection of host cells and may be downregulated by the GLP-1 agonists. CD147 expression has been noted to be upregulated in a cohort of patients with acute COVID-19 infection with increased disease severity and poorer prognosis. Furthermore, in the critical care setting, hyperglycaemia may be associated with worse outcomes, suggesting that therapies such as semaglutide, that can control blood glucose with a reduced risk of hypoglycaemia, may be beneficial. In cases of sepsis, GLP-1 agonists can further regulate the immune response, downregulating inflammatory factors associated with vascular homeostasis and platelet adhesion, with potentially protective effects on organ function. Potentially favourable influences on cardiac biomarkers in patients with milder COVID-19 pneumonia, which are not explained by a reduction in systemic blood pressure (a known effect of GLP-1 agonist therapy) have also been observed in studies of other GLP-RAs (11).

Other trials

A6. Changes in mean diastolic blood pressure between baseline and Week 52 observed in the STEP-HFpEF and STEP-HFpEF DM trials are reported in the CS (CS, p96); however, the estimated treatment differences and 95% confidence intervals (CI) are not provided. If available, please provide these data.

In STEP-HFpEF, the estimated treatment change in mean DBP from baseline to Week 52 was [redacted] mmHg with semaglutide and [redacted] mmHg with placebo, resulting in an estimated treatment difference (ETD) of [redacted] mmHg (95% CI: [redacted]) [redacted] (Table 18 of additional outputs (5)).

In STEP-HFpEF DM, the estimated treatment change in mean DBP from baseline to Week 52 was [redacted] mmHg with semaglutide and [redacted] mmHg with placebo, resulting in an ETD of [redacted] mmHg (95% CI: [redacted]) [redacted] (Table 19 of additional outputs (5)).

Clinical Practice Research Datalink (CPRD) analysis

A7. Priority question. Please provide patient numbers and baseline characteristics data in a format similar to CS, Table 10 (CS, Section 2.3.5) for the Clinical Practice Research Datalink (CPRD) "SELECT-like population".

Patient numbers and baseline characteristics from the CPRD analysis are shown in Table 1, next to the SELECT participants characteristics (taken from Table 10 in the CS).Please note, some baseline characteristics were not identifiable for all patients in the CPRD, introducing risk of bias, and data may not have been entered exactly at the index date. Therefore, caution should be exercised when comparing data points where the CPRD has high rates of unreported data.

Table 1: Baseline demographic and clinical characteristics – FAS

	Semaglutide (N=8,803)	**Placebo (N=8,801)**	**CPRD Dataset (N=141,642)**
Age, years, mean (SD)	61.6 (8.9)	61.6 (8.8)	[redacted]
Age group, years, n (%)			
<55	2,057 (23.4)	2,094 (23.8)	[redacted]
55 to <65	3,387 (38.5)	3,338 (37.9)	[redacted]
65 to <75	2,656 (30.2)	2,706 (30.7)	[redacted]
≥75	703 (8.0)	663 (7.5)	[redacted]
Sex, n (%)			
Female	2,448 (27.8)	2,424 (27.5)	[redacted]
Male	6,355 (72.2)	6,377 (72.5)	[redacted]
Region, n (%)			
Asia	1,100 (12.5)	1,101 (12.5)	[redacted]
Europe	3,326 (37.8)	3,366 (38.2)	[redacted]
North America	2,200 (25.0)	2,201 (25.0)	[redacted]
Other	2,177 (24.7)	2,133 (24.2)	[redacted]
Race or ethnicity, n (%)			
White	7,387 (83.9)	7,404 (84.1)	[redacted]
Asian	720 (8.2)	727 (8.3)	[redacted]
Black or African American	348 (4.0)	323 (3.7)	[redacted]

	Semaglutide (N=8,803)	Placebo (N=8,801)	CPRD Dataset (N=141,642)
Other	227 (2.9)	247 (3.1)	[redacted]
Hispanic or Latino	914 (10.4)	908 (10.3)	[redacted]
Not reported	95 (1.1)	76 (0.9)	[redacted]
Body weight, kg, mean (SD)	96.5 (17.5)	96.8 (17.8)	[redacted]
NR	–	–	[redacted]
BMI, kg/m^2, mean (SD)	33.3 (5.0)	33.4 (5.0)	[redacted]
BMI, kg/m^2, n (%)			
27 to <30	2,555 (29.0)	2,469 (28.1)	[redacted]
30 to <35	3,693 (42.0)	3,781 (43.0)	[redacted]
35 to <40	1,687 (19.2)	1,659 (18.9)	[redacted]
40 to <45	579 (6.6)	595 (6.8)	[redacted]
≥45	289 (3.3)	297 (3.4)	[redacted]
NR	–	–	[redacted]
Waist circumference, cm, mean (SD)	111.3 (13.1)	111.4 (13.1)	[redacted]
NR	–	–	[redacted]
HbA1c, %, mean (SD)	5.78 (0.34)	5.78 (0.33)	
<5.7%	2,925 (33.2)	2,980 (33.9)	[redacted]
≥5.7%	5,877 (66.8)	5,879 (66.1)	[redacted]
NR	1 (<0.1)	2 (<0.1)	[redacted]
Median high-sensitivity CRP level (IQR) – mg/l	1.87 (0.89–4.18)	1.80 (0.86–4.06)	[redacted]
CV inclusion criteria			
Only MI	5,962 (67.7)	5,944 (67.5)	[redacted]
Only stroke	1,578 (17.9)	1,556 (17.7)	[redacted]
Only PAD	376 (4.3)	401 (4.6)	[redacted]
Two or more inclusion criteria	718 (8.2)	719 (8.2)	[redacted]
Other[†]	181 (2.1)	193 (2.2)	[redacted]

	Semaglutide (N=8,803)	Placebo (N=8,801)	CPRD Dataset (N=141,642)
Chronic heart failure, n (%)			
Yes	2,155 (24.5)	2,131 (24.2)	[redacted]
No	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]
Subclass			[redacted]
HFpEF	[redacted]	[redacted]	[redacted]
HFrEF	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]
eGFR, ml/min/1.73 m^2, mean (SD)	82.4 (17.5)	82.5 (17.3)	[redacted]
NR	–	–	[redacted]
Median lipid level (IQR) – mg/dl			[redacted]
Total cholesterol	153 (131–182)	153 (131–183)	[redacted]
NR, n (%)			[redacted]
HDL cholesterol	44 (37–52)	44 (37–52)	[redacted]
NR, n (%)			[redacted]
LDL cholesterol	78 (61–102)	78 (61–102)	[redacted]
NR, n (%)			[redacted]
Triglycerides	134 (99–188)	135 (100–190)	[redacted]
NR, n (%)			[redacted]
Mean systolic blood pressure (SD) – mmHg	131.0 (15.6)	130.9 (15.3)	[redacted]
NR, n (%)			[redacted]
Mean diastolic blood pressure (SD) – mmHg	79.4 (10.0)	79.2 (9.9)	[redacted]
NR, n (%)			[redacted]
Pulse – beats/min	68.9 (10.6)	68.6 (10.7)	[redacted]

	Semaglutide (N=8,803)	Placebo (N=8,801)	CPRD Dataset (N=141,642)
NR, n (%)			[redacted]

Source: Lincoff 2023 including appendix (2), SELECT CSR (12), Data on file – additional CPRD analysis data (13).
†This category included participants where it is unknown if they fulfilled only one or several criteria and participants who were randomised in error and did not fulfil any criteria.
Abbreviations: CRP, C-reactive protein; CTR, clinical trial report; CV, cardiovascular; FAS, full analysis set; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; NR, not reported; PAD, peripheral arterial disease; SD, standard deviation.

Generalisability of SELECT trial

A8. If possible, please provide:

- The number and proportion of SELECT trial participants (in-trial population) who experienced each MACE (both as a first- and any-event) and who died from cardiovascular disease

Table 1 of the additional outputs report (5) shows the number of SELECT participants who experienced EAC-confirmed MACE and who died from EAC-confirmed CV death (broken down into CV death components of cardiovascular death and death from undetermined causes, and presented by component of first EAC-confirmed MACE). Table 2 further depicts how many participants died of EAC-confirmed CV death after experiencing an EAC-confirmed MI or stroke.

- UK SELECT trial participants results for time from randomisation to first EAC-confirmed MACE endpoint in a forest plot, similar to the results presented in CS, Figure 21.

Figures 10 to 12 in the additional outputs report (5) show results for the SELECT UK population, and Figures 7 to 9 results for the SELECT Europe population, which were additionally provided to support results of the SELECT UK population due to low number of events. Results for some subgroups in the SELECT UK overview could not be presented due to no reported events in either treatment group. There is no indication of heterogeneity between groups, and results are aligned with results in the overall trial population.

Section B: Clarification on cost effectiveness data

B1. Priority question. STEP-1 trial extension data show that, for some outcomes, following treatment discontinuation, the benefit of treatment with semaglutide reduces over time. The EAG highlights that treatment-effect waning has been implemented in the model for progression to type 2 diabetes. Please adapt the company model so that it includes the ability to apply treatment-effect waning for all other affected outcomes. Please implement the treatment-effect waning in a way that allows the EAG to change (i) the time point that treatment-effect waning starts, (ii) the duration of treatment-effect waning and (iii) the type of curve used to model treatment-effect waning. Please also identify the company's preferred approach to treatment-effect waning.

The company cost-effectiveness model has been adapted to provide the additional functionality requested by the EAG. This response describes the approach taken to treatment-effect waning in the model; existing functionality to amend waning; new functionality prepared in response to EAG comments; waning in the STEP-1 trial extension data, and the company's preferred approach and sensitivity analyses around treatment-effect waning.

Approach to treatment-effect waning in CS

Major CV events, T2D and mortality

This section describes the approach taken for: Non-fatal MI, Non-fatal stroke, Non-fatal hospitalisation for heart failure (HHF), Non-fatal hospitalisation for unstable angina (HUA), Non-fatal coronary revascularisation (CR), incidence of type 2 diabetes (T2D), CV death and Non-CV death.

For these endpoints, the survival analysis estimated per cycle event rates using a whole arm estimand. Event rates reflect allocated therapy, and so the event rates for the semaglutide arm reflect both patients on therapy and those who had discontinued during the trial.

For the duration of the median trial follow-up (3.3 years) SELECT provides direct evidence, so the event rates from the survival analysis are used for the whole population in the semaglutide and established clinical management arms.

After median trial follow-up has passed, additional patients discontinue, so the treatment policy estimand no longer reflects the portion of patients receiving semaglutide. After 3.3 years, only patients who continue to be treated with semaglutide experience the event rate for the semaglutide arm. Patients who have discontinued semaglutide experience the event rate for the established clinical management arm. Thus, any benefit of semaglutide in reducing CV events, mortality, and T2D progression is lost upon discontinuation.

Chronic kidney disease (CKD) progression

Change in eGFR between baseline and Week 104 was a secondary endpoint in the trial. As eGFR is a continuous endpoint, this was not suitable for inclusion in the survival analysis of time to event variables. To inform the economic model, change in eGFR in each arm was transformed to estimate risk of progression between CKD categories, as described in the company submission. The analysis of eGFR compared patients who continue to be treated with semaglutide against patients receiving established clinical management alone, referred to as the trial product estimand.

In all cycles, patients who continue to be treated with semaglutide experience the CKD progression rate for semaglutide. Patients who discontinue semaglutide experience the CKD progression rate for established clinical management. Thus any benefit of semaglutide in reducing risk of CKD progression is lost upon discontinuation.

Body mass index (BMI)

In the model patients who remain on semaglutide treatment experience BMI benefit. BMI benefit is calculated as the difference between arms in the percentage change in BMI from baseline, taken from the SELECT trial. Patients who discontinue receive partial BMI benefit in the first year and the second year after discontinuation. In the first year after discontinuation they receive 2/3^{rds} (67%) of the benefit of semaglutide

treatment and in the second year they experience 1/3rd (33%) of the benefit. The model assumes that BMI in discontinued patients rebounds to equal that in the established clinical management arm after two years, in line with TA1026 (14).

Benefits after discontinuation

After discontinuation of semaglutide and loss of effect, cost and utility in the semaglutide arm do not immediately return to equal established clinical management, due to the long term consequences of events that occurred while receiving semaglutide therapy. A similar approach, where CV events result in acute cost and utility impact followed by lasting sequelae, is taken in other models, such as NG238 (15).

Existing treatment-effect waning functionality in the model

The company's submitted cost-effectiveness model already has the following functionality:

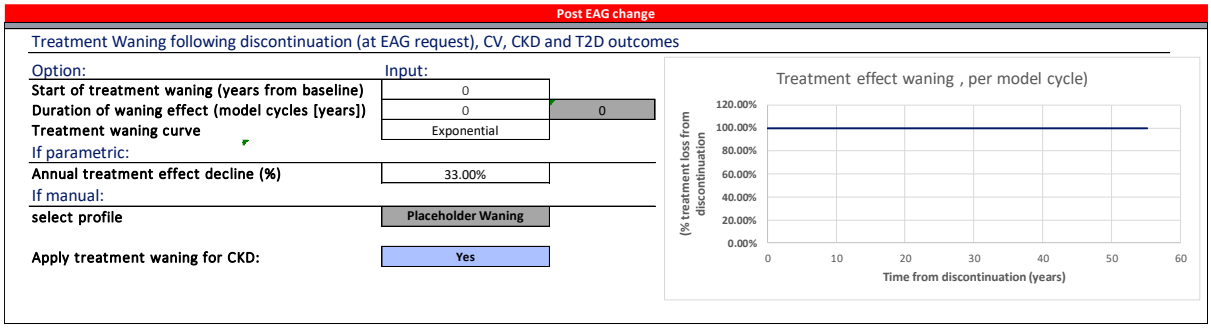
Cell label and location	Effect of change	Comment
BMI treatment effect adjustment < 1 year since discontinued [Page lists and figures: cell AF57]	Sets the % of BMI treatment effect that is maintained in the first year after discontinuation	Partly addresses EAG request
1-2 years discontinued [Page lists and figures: cell AF58]	Sets the % of BMI treatment effect that is maintained in the second year after discontinuation	

Abbreviations: BMI, body mass index; EAG, external assessment group.

The model assumes that BMI returns to control level over time, with partial benefit in Year 1 and Year 2 after discontinuation.

New functionality requested by the EAG

Additional functionality has been added to the model control page, illustrated below.



The following cells may be altered by the user:

Cell label and location	Effect of change	Comment
Start of treatment waning [Cell E113]	Sets the time from baseline when treatment waning occurs	To address EAG request B1 (i) for CV ,T2D and mortality
Duration of waning effect (model cycles [years]) [Cell E114]	Sets the time horizon over which waning occurs in model cycles after discontinuation After this time horizon is reached treatment effect is lost	To address EAG request B1 (ii) for CV, T2D and mortality
Treatment waning curve [Cell E115]	Allows the user to choose between exponential, linear or manual entry of waning rate Manual waning rates can be added in rows 11708 onwards in the sheet “Manual extrapolations”	To address EAG request B1 (iii) for CV, T2D and mortality
If parametric: Annual treatment effect decline (%) [Cell E117]	Allows the user to enter annual % waning for exponential or linear waning assumption	
If manual: Select profile [Cell: E119]	Allows the user to select manual inputs from the sheet “Manual extrapolations”	
Apply treatment waning for CKD	Yes/no box to select whether waning effect also applied to CKD benefit	To include CKD endpoint in waning

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; EAG, external assessment group, ITT, intention-to-treat; T2D, type 2 diabetes.

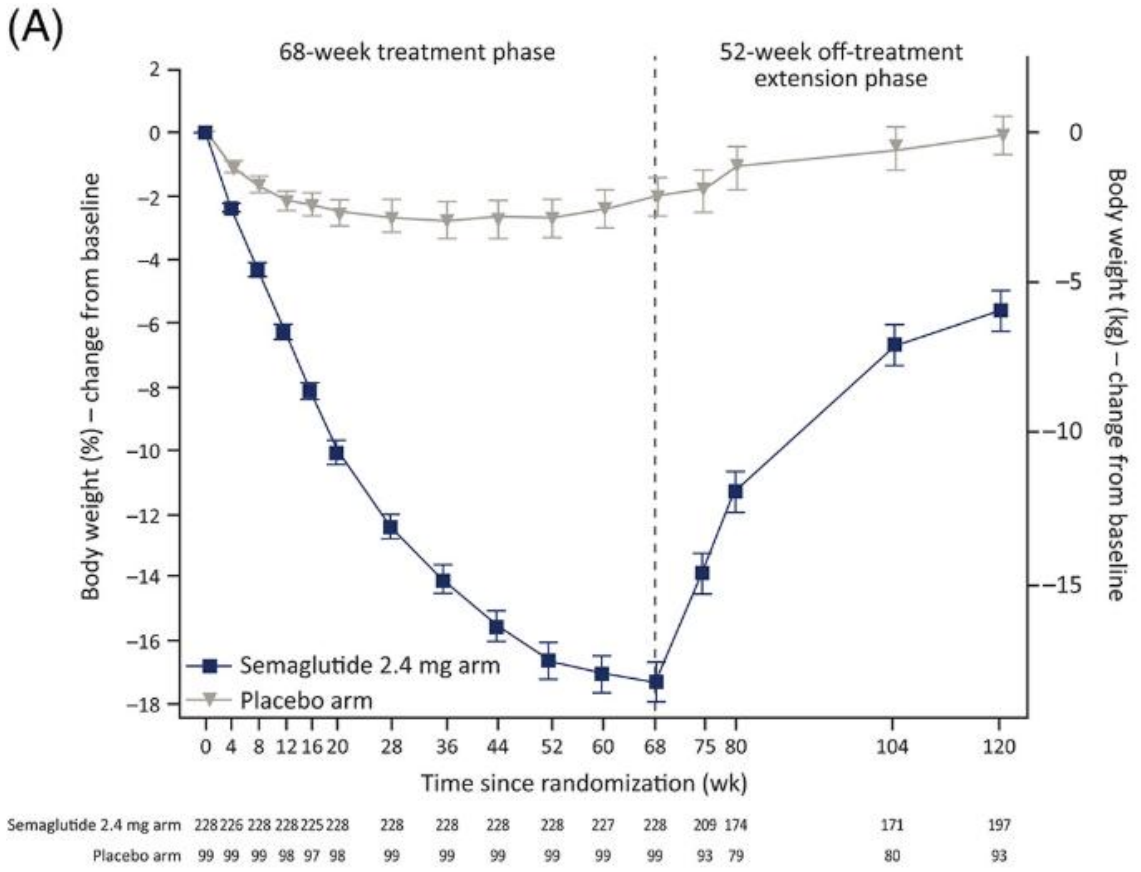
An additional figure shows the % of treatment effect waning modelled in each cycle from discontinuation, for the assumptions entered.

STEP 1 trial extension data

STEP 1 (NCT03548935) randomised 1,961 adults with a BMI ≥ 30 kg/m^2 (or ≥ 27 kg/m^2 with ≥1 weight-related co-morbidity) without diabetes to 68 weeks of once-weekly subcutaneous semaglutide 2.4 mg (including 16 weeks of dose escalation) or placebo, as an adjunct to diet and physical activity counselling. At Week 68, treatments (including lifestyle counselling) were discontinued. An off-treatment extension assessed for a further year a representative subset of 327 participants, who had completed 68 weeks of treatment. From Week 0 to Week 68, mean weight loss was 17.3% (standard deviation [SD]: 9.3%) with semaglutide and 2.0% (SD: 6.1%) with placebo. Following treatment withdrawal, semaglutide and placebo participants regained 11.6 (SD: 7.7) and 1.9 (SD: 4.8) percentage points of lost weight, respectively, by Week 120, resulting in net losses of 5.6% (SD: 8.9%) and 0.1% (SD: 5.8%), respectively, from Week 0 to Week 120. Cardiometabolic improvements seen from Week 0 to Week 68 with semaglutide reverted towards baseline at Week 120 for most variables (16).

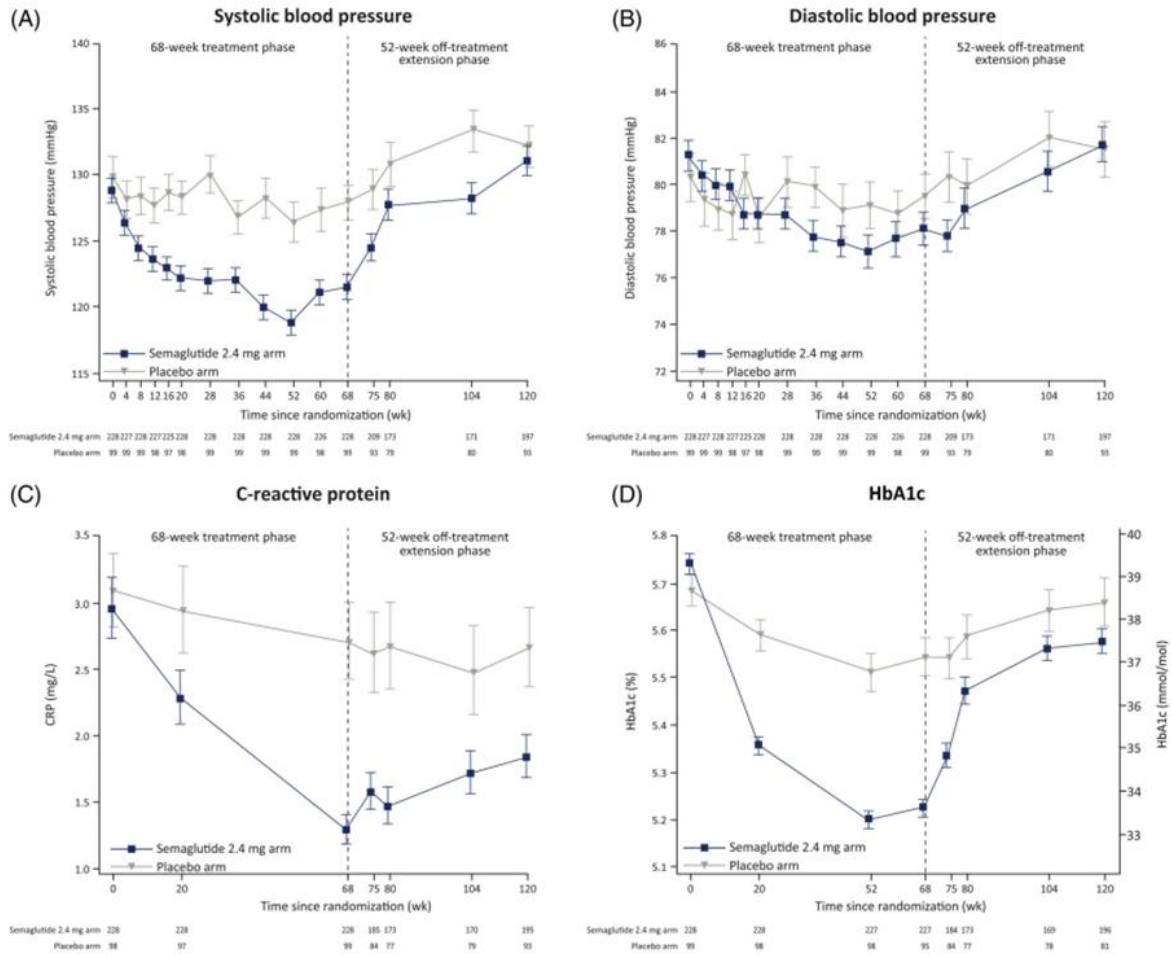
The change in BMI over time in the STEP-1 extension population is shown in Figure 1. Figure 2 shows other selected endpoints from the same publication (Wilding et al, 2022 (16)).

Figure 1: Change from baseline in body weight by week for all participants in the extension study



Reproduced from Wilding 2022, Figure 1 (A) (16).

Figure 2: Change from baseline for selected parameters, all participants in the extension study



Reproduced from Wilding 2022 , Figure 2 (16).
A, Systolic blood pressure, B, Diastolic blood pressure, C, C-reactive protein, and D, HbA1c by week. Data are observed means (± standard error) for the extension analysis set from the in-trial period; for C-reactive protein, standard error was calculated on the logarithmic scale and back-transformed to the linear scale. The dashed vertical line at week 68 indicates the end of the main phase and start of the off-treatment extension phase. Numbers shown in the lower panels are participants contributing to the mean.
Abbreviations: CRP, C-reactive protein; HbA1c, glycated haemoglobin.

The company, noting that these analyses are exploratory, interprets these data as showing:

- After 68 weeks in the study, patients on semaglutide had experienced a weight change of –15.3% compared with placebo (weight change from baseline of –17.3% less –2.0% = –15.3%)

- 52 weeks after discontinuation, patients who had received 68 weeks of semaglutide experienced a weight change of –5.5% compared with placebo (weight change from baseline of –5.6% less –0.1% = –5.5%)
- Visual inspection of Figure 1 (A) from Wilding et al, 2022 (16) suggests that weight regain in the semaglutide-treated patients was fastest in the first 12 weeks after discontinuation and slowed thereafter.
- Visual inspection of Figure 2 from the same publication suggests a broadly similar pattern of rebound in selected other factors associated with risk of CV events.

The company believes that the base-case assumption in the model of 2/3^{rds} of weight benefit in the first year after discontinuation, 1/3rd benefit in the second year and none thereafter are a reasonable extrapolation from these data, given that:

- The average of the weight benefit at the start and end of the first year after discontinuation is 10.4% ((15.5% + 5.3%)/2), which is around 2/3^{rds} of weight benefit on treatment (15.3%)
- Weight had not returned to control group levels one year after discontinuation and the study suggests that weight regain slowed over time. The company suggests that at least one further year of partial benefit, at a lower level than 2/3^{rds} is a reasonable extrapolation of the data from Wilding et al, 2022.
- As data are uncertain a simple assumption was preferred and a value of 1/3rd was chosen.

The STEP-1 and SELECT studies differed in terms of objectives, populations studied, baseline characteristics and change in BMI observed. However the company is not aware of other more relevant data to inform treatment waning in the model.

Company's preferred approach to treatment-effect waning and new sensitivity analysis

The company's base case submission reflects the following waning settings (Table 2).

Table 2: Waning assumptions in submitted company model

Cell label and location	Value aligned to company submission	Comment
Start of treatment waning	0	No benefit on CV events after discontinuation
Duration of waning effect (model cycles)	0	No benefit on CV events after treatment
Treatment waning curve	N/A	N/A as waning is instantaneous
If parametric: Annual treatment effect decline (%)	N/A	
If manual: Select profile	N/A	
Apply treatment waning for CKD	No	Assumes no effect on CKD events after discontinuation during or after the trial period
BMI treatment effect adjustment		Patients return to control levels of BMI over 2 years after discontinuation
<1 year since discontinued	67%	
1-2 year since discontinuation	33%	

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; N/A, not applicable.

Sensitivity analyses have been performed using the new waning settings, shown in Table 3. These analyses suggest that the model is not very sensitive to changes in assumptions about waning of BMI effect. Introducing treatment waning for CV and CKD benefits reduces the ICER compared the submitted model.

Table 3: Scenario analyses around waning assumptions – alternative treatment-effect waning settings and resulting ICERs

	BMI treatment effect adjustment		Start of treatment waning	Duration of waning effect (model cycles)	Treatment waning curve	If parametric	If manual	Apply treatment waning for CKD	ICER (£ per QALY gained)
	< 1 year since discon-tinuation	1-2 year since discon-tinuation				Annual treatment effect decline (%)	Select profile		
Base case	67%	33%	0	0	N/A	N/A	N/A	No	£14,702
Waning applied to CV & CKD benefits	67%	33%	0	**39**	**Linear**	**33%**	**N/A**	**Yes**	£12,203
Exponential waning at 33% per year over 5 years	67%	33%	0	**65**	**Exponential**	**33%**	**N/A**	**Yes**	£11,105
More rapid BMI waning	**50%**	**25%**	0	0	N/A	N/A	N/A	No	£14,845
Slower BMI waning	**75%**	**50%**	0	0	N/A	N/A	N/A	No	£14,562

Interpretation of the individual treatment-effect waning settings is provided in the text above. **Bold** text indicates inputs that differ from the base case in the company-submitted model.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALY, quality-adjusted life year.

B2. Priority question. Average cost per patient per cycle is higher for patients receiving semaglutide and established clinical management versus clinical management alone for the first few years after beginning treatment, after which patients receiving semaglutide and established clinical management have a lower per cycle cost than patients receiving clinical management only (CS, Appendix H, Figure 1). Please explain this model outcome.

The company thanks the EAG for highlighting this discrepancy. There is an error in Figure 1 from Appendix H: when the semaglutide arm costs were extracted to generate this figure, one cost component (T2D management) was omitted. A corrected figure (Figure 3) is shown below. This error did not affect costs used to calculate the ICER, which is unchanged.

Figure 3: Per cycle average cost per patient for semaglutide with established clinical management, and established clinical management

Legend:
Semaglutide with established clinical management
Established clinical management

Table 5 in Appendix A shows per-cycle costs divided into components and the difference between arms in each component for the first 150 cycles of the model.

The semaglutide arm is initially associated with higher costs of treatment, partly offset by lower costs of CV events, AEs, CKD and T2D. Some years later, after

many patients have discontinued semaglutide, differences in treatment costs and acute CV events are much smaller. Costs of CKD and T2D however remain lower in the semaglutide arm, eventually leading to slightly lower average cost in the semaglutide arm than the established clinical management arm.

While on treatment, fewer patients in the semaglutide arm than in the established clinical management arm develop T2D or experience CKD progression. In the model, patients who develop T2D or experience progression of CKD do not experience subsequent regression. So, differences in T2D status and CKD that occur during treatment are maintained later, and the model reflects the ongoing cost of treating these chronic conditions.

Late in the model, differences between arms also exist in the maintenance and AE costs, reflecting higher overall survival in the semaglutide arm, a consequence of fewer fatal events while on treatment earlier in the model.

Section C: Textual clarification and additional points

C1. Priority question. Please provide the SUSTAIN trial statistical analysis plan.

The statistical analysis plan for SUSTAIN-6 is available at:

https://www.nejm.org/doi/suppl/10.1056/NEJMoa1607141/suppl_file/nejmoa1607141_protocol.pdf

As noted in our answer to Question A4, the SAP for SELECT is included in the reference pack, but can also be accessed here:

https://www.nejm.org/doi/suppl/10.1056/NEJMoa2307563/suppl_file/nejmoa2307563_protocol.pdf

C2. Priority question. Please clarify that our understanding of the number and cause of deaths is correct (see Table 1)

Table 1: Number and causes of events

Cause of death	Semaglutide (N=8,803) n (%)	Placebo (N=8,801) N (%)	Hazard ratio (95% confidence interval)	p-value	Source in company submission
All-cause	375 (4.3)	458 (5.2)	0.81 (0.71, 0.93)	Not tested	Table 17
Cardiovascular (CV)	223 (2.5)	262 (3.0)	0.85 (0.71, 1.01)	[redacted]	Table 15
Non-CV	[redacted]	[redacted]	-	-	Table 17

The figures above are correct. In Table 15 of the CS, "EAC-confirmed CV death" (2nd row in above table) includes "undetermined cause of death", as per footnote on page 69 of CS, which explains that in SELECT, deaths of undetermined cause were presumed to be CV deaths. Please see further detail in answer to question C3 below about the use of "CV" and "cardiovascular" in the CSR vs in the CS.

C3. Priority question. Please clarify whether the deaths described as "CV death" and "undetermined cause of death" in CS, Table 17 are all cardiovascular deaths (as in the SELECT clinical trial report, Tables 11-14).

In the SELECT CSR, a distinction is made between "CV death" (including both "cardiovascular death" and "death of undetermined causes") and "cardiovascular death" (written out fully). The former is also the definition for confirmatory endpoints. The CS used the abbreviation "CV" for "cardiovascular" throughout, therefore the distinction between "CV death" and "cardiovascular death", e.g. in Tables 15 and 17 of the CS, was not as clear as in the SELECT CSR. Analyses of CV death in the economic evaluation are also aligned to the CSR definition of "EAC-confirmed CV death".

Please note that further details on Deaths of undetermined cause are provided in Section 11.2.3 of the SELECT CSR.

C4. Priority question. Please clarify whether all the data reported in CS, Table 14, are correct. The endpoints are all described in the table heading as the first occurrence of these events. However, these data appear to be the data presented in the clinical trial report, Table 11-4, 11-6 and 11-19 (all events) rather than Tables 11-5, 11-7 and 11-20 (first events).

The data presented in Table 14 of the CS (shown below) align with Table 2 "Time to first event efficacy endpoints" from the Lincoff et al, 2023 publication, with p-values taken from the CSR tables listed in the additional column below (in blue) as these were not reported in the Lincoff et al, 2023 publication. These are the correct data and are aligned with the definition of confirmatory endpoints, which for e.g. non-fatal MI is "Time from randomisation to first EAC-confirmed non-fatal MI" (CSR Table 14.2.64; reference tables for other confirmatory endpoints are available in Table 14 below, in blue). The number of participants in Table 14 would thus correspond to the number of participants experiencing a specific EAC-confirmed outcome (shown in Tables 11-4, 11-6, 11-19, which display an overview of all EAC-confirmed events which occur). Please be aware there could be a difference in number of events due to participants potentially experiencing multiple events of the same type (e.g. more than one stroke), where total number of events in Tables 11-4, 11-6, 11-19 are displayed under 'E'. The number of events in Table 14 would match the number of

participants, due to only accounting for the first event each participant experienced of that type.

Tables 11-5, 11-7, 11-20, on the other hand, present an overview of first EAC-confirmed events when summarised as components of composite outcomes, where only the first event in the composite is accounted for. So if, for example, a participant experienced a non-fatal MI followed by a non-fatal stroke, only the first event (in this case, a non-fatal MI) would contribute to analyses of first EAC-confirmed expanded MACE and be counted in Table 11-7.

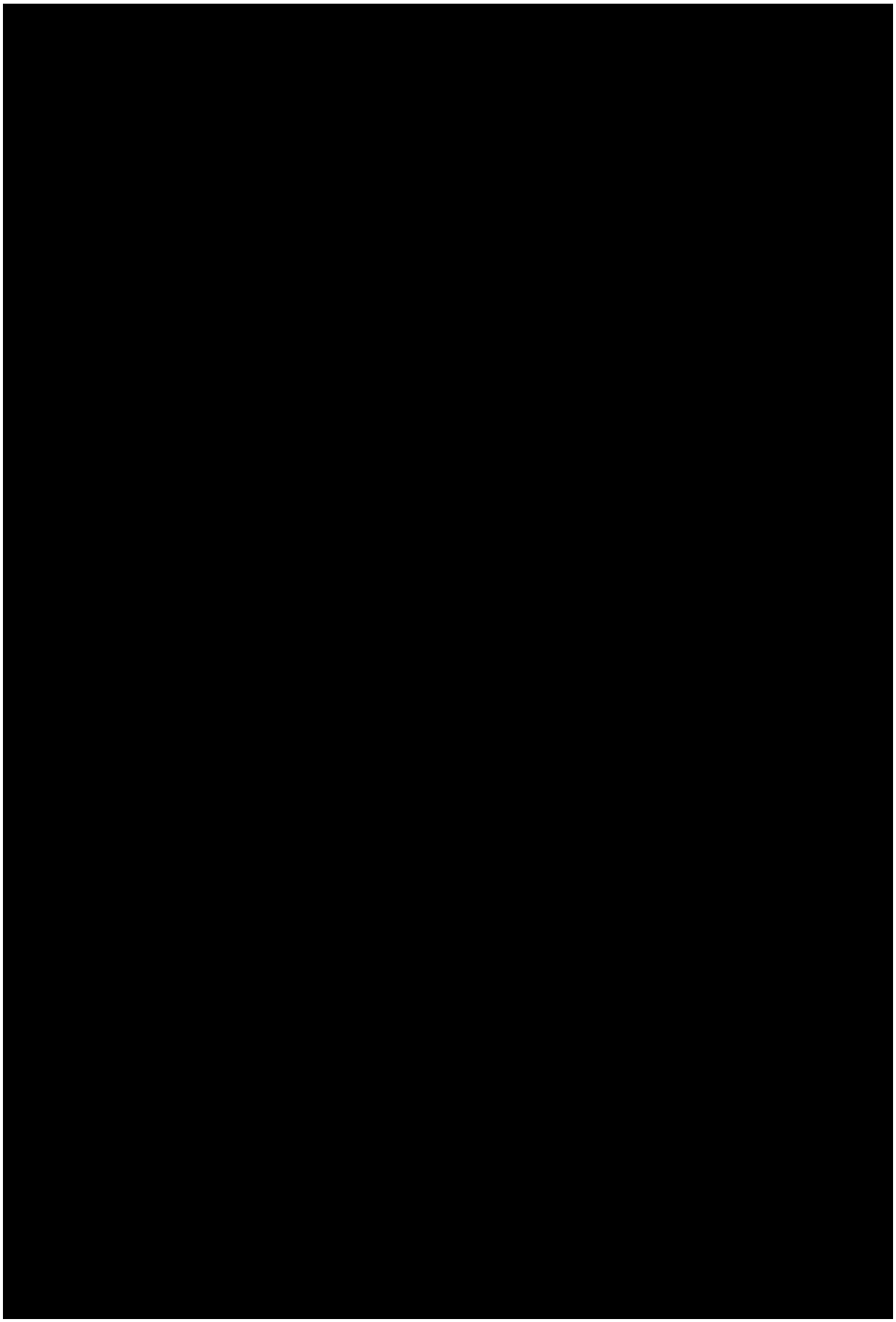
Table 14, CS: First occurrence of EAC-confirmed events (FAS – in trial)

	Semaglutide (N=8,803) n (%)	Placebo (N=8,801) n (%)	Hazard ratio (95% CI)	p-value†	Table in CSR
Expanded MACE‡	873 (9.9)	1,074 (12.2)	0.80 (0.73, 0.87)	[redacted]	14.2.55
All-cause death, non-fatal MI, or non-fatal stroke	710 (8.1)	877 (10.0)	0.80 (0.72, 0.88)	[redacted]	14.2.61
Non-fatal MI	234 (2.7)	322 (3.7)	0.72 (0.61, 0.85)	[redacted]	14.2.64
Non-fatal stroke	154 (1.7)	165 (1.9)	0.93 (0.74, 1.15)	[redacted]	14.2.70
CR	473 (5.4)	608 (6.9)	0.77 (0.68, 0.87)	[redacted]	14.2.76
Hospitalisation for unstable angina	109 (1.2)	124 (1.4)	0.87 (0.67, 1.13)	[redacted]	14.2.79
HF hospitalisation or urgent HF visit	97 (1.1)	122 (1.4)	0.79 (0.60, 1.03)	[redacted]	14.2.82

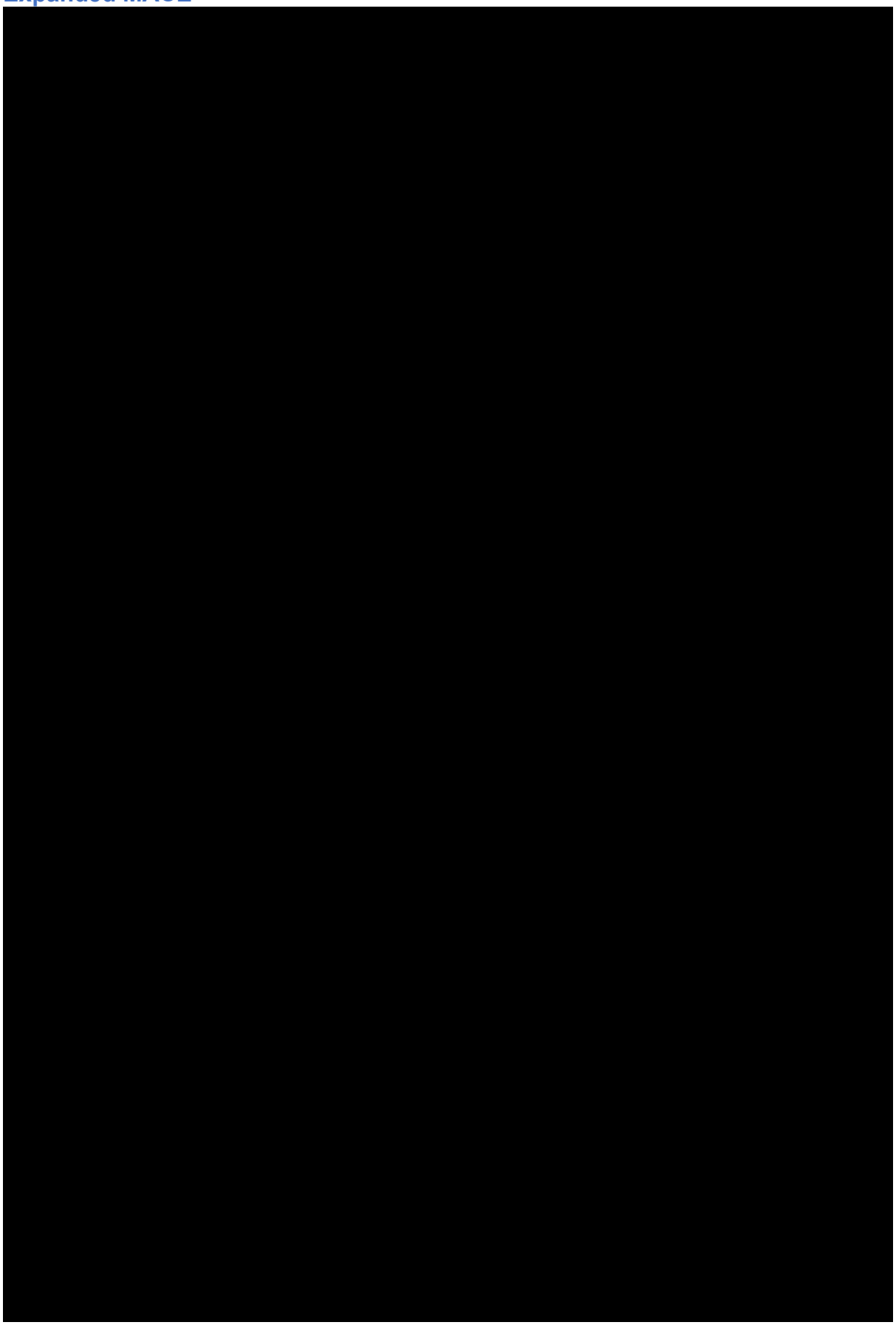
Source: Lincoff 2023 (2), SELECT CSR (12).
†Two-sided p-value for test of no difference; ‡The Expanded MACE outcome included CV death, non-fatal MI, non-fatal stroke, CR, or unstable angina requiring hospitalisation.
Abbreviations: CI, confidence interval; CR, coronary revascularisation; CTR, clinical trial report; CV, cardiovascular; EAC, event adjudication committee; FAS, full analysis set; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; N, number of participants; %, number of participants experiencing at least one event.

The relevant tables from the CSR are presented below for ease of reference and comparison.

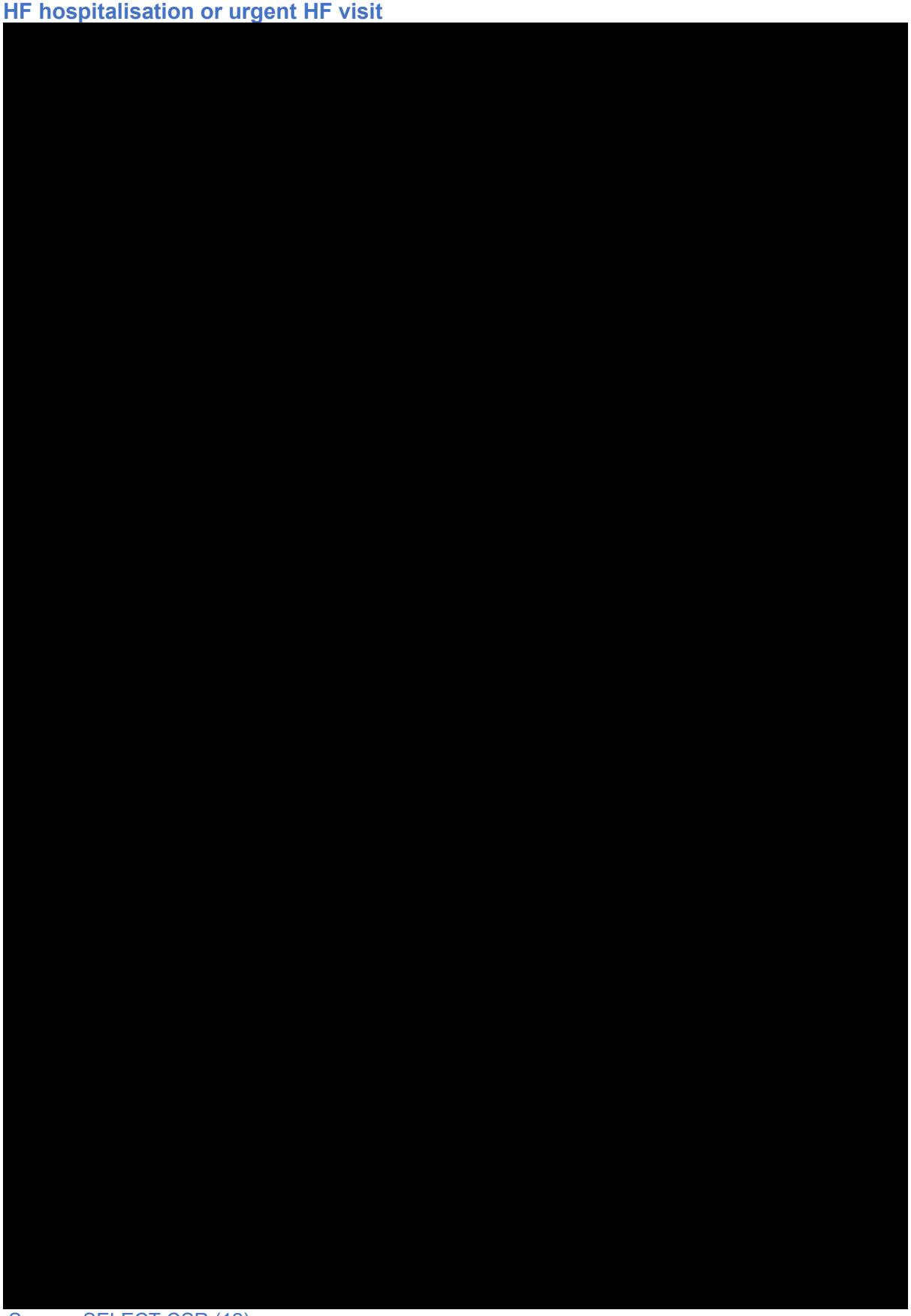
All-cause death, non-fatal MI, or non-fatal stroke



Expanded MACE



HF hospitalisation or urgent HF visit



Source: SELECT CSR (12).

C5. Priority question. Please clarify why the CPRD data reported in CS, Appendix Q, Table 2 appear to differ to data reported in CS, Section 2.3.5 (e.g., the proportions of patients with a history of myocardial infarction or stroke).

The main differences between the data presented in Appendix Q and Section 2.3.5 of the CS are outlined in Table 4 below. The key differences are:

- Index dates
- Appendix Q considers patients aged ≥45 years, whereas Section 2.3.5 of the CS considers patients aged ≥18 years
- The exclusion criteria of anyone with an MI, stroke, hospitalisation for unstable angina or TIA within 60 days prior to index was not applied to the data presented in Section 2.3.5 of the CS
- For the baseline characteristics presented in Section 2.3.5, patients who received semaglutide or any other GLP-1 RAs during the follow-up were included.

Table 4: CPRD data characteristics

	Appendix Q	Section 2.3.5, CS
HEOR project aim	To inform the choice of parametric distribution for survival modelling for use in the SELECT CEM	To understand the incidence, prevalence, and event rates of a SELECT-like population in UK real-world data
Index date	**04/10/2008**	**01/01/2017**
Inclusion criteria	• At least 1 years' worth of registration data • Sex recorded as male or female • Aged **≥45** years at index • BMI ≥27 at index • Have eCVD, defined as a history of at least one of the following: MI; stroke (ischemic or haemorrhagic stroke); or PAD as evidenced by a PAD diagnosis or ABI <0.85	• At least 1 years' worth of registration data • Sex recorded as male or female • Aged **≥18** years at index • BMI ≥27 at index • Have eCVD, defined as a history of at least one of the following: MI; stroke (ischemic or haemorrhagic stroke); or PAD as evidenced by a PAD diagnosis or ABI <0.85
Exclusion criteria	• **Any of the following: MI, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within the past 60 days prior to index** • Classified as being in NYHA Class IV HF at index • HbA1c ≥48 mmol/mol (6.5%) based on most recent recording at index • History of T1D or T2D (history of gestational diabetes was allowed and was not excluded) • Treatment with diabetes drugs or GLP-1 RAs within 90 days before index • History or presence of chronic pancreatitis. • Presence of acute pancreatitis within the past 180 days prior to index • ESRD • Presence of history of malignant neoplasms within the past 5 years prior to index	• Classified as being in NYHA Class IV HF at index • HbA1c ≥ 48 mmol/mol (6.5%) based on most recent recording at index • History of T1D or T2D (history of gestational diabetes was allowed and was not excluded) • Treatment with diabetes drugs or GLP-1 RAs within 90 days before index • History or presence of chronic pancreatitis. • Presence of acute pancreatitis within the past 180 days prior to index • ESRD • Presence of history of malignant neoplasms within the past 5 years prior to index

	Appendix Q	Section 2.3.5, CS
	• **Received semaglutide during the follow-up period**	

The key differences between the 2 datasets are in **bold.**

Abbreviations: ABI, ankle-brachial index; BMI, body mass index; CEM, cost-effectiveness model; eCVD, established cardiovascular disease; ESRD, end-stage renal disease;HbA1c, glycated haemoglobin; HF, heart failure; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral arterial disease; T1D, type 1 diabetes; T2D, type 2 diabetes.

Regarding the proportions of patients with a history of MI or stroke, the additional difference between Section 2.3.5 of the CS and Appendix Q (Table 2) is that in Section 2.3.5 patients with an MI **only** or a stroke **only** are included, whereas in Table 2**, all** patients who have had an MI (including those who have also had a stroke or have PAD) or a stroke (including those who have also had an MI or have PAD) are presented.

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Appendix A

Table 5: Expect cost per cycle, semaglutide arm (£ per patient, discounted)

Cycle	Study treatment	Maintenance	CV events	CKD	T2D	AEs	Total
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cycle	Study treatment	Maintenance	CV events	CKD	T2D	AEs	Total
37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event, CKD, chronic kidney disease; CV, cardiovascular; T2D, type 2 diabetes.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity [ID6441]

Professional organisation submission

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	HEART UK – The Cholesterol Charity
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** or No A specialist in the treatment of people with this condition? **Yes** or No A specialist in the clinical evidence base for this condition or technology? Yes or **No** Other (please specify):
5a. Brief description of the organisation (including who funds it).	We are the only charity to cover all lipids. We provide support and education to patients, carers and healthcare professionals. We produce lipid guidelines where there are none. Our name is an acronym HEART UK stands for Hyperlipidaemia Education and Atherosclerosis Research Trust UK. Our funds are from traditional fundraising sources, such as Marathons and donations. We also work with corporate organisations such as fundraising corporates such as iCollectClothes, also food, diagnostic and pharmaceutical companies.

5b. 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.**	Yes, for our annual scientific conference. **Amgen Uk Ltd - £53,900** Conference - £24,500 Lp(A) Taskfirce - £29,400 **BHR Pharmaceuticals Ltd - £4,500** Conference - £4,500 **Chiesi Ltd - £16,500** Conference - £16,500 **Daiichi Sankyo Europe GmbH - £450** Project Work - £450 **Daiichi Sankyo UK Ltd - £108,122.35** Conference - £29,000 CVD - £30,000 Project Work - £898.35 Changemaker - £48,224 **LINC Medical Systems Ltd - £4,500** Conference - £4,500 **Merck Sharp & Dohme Ltd - £4,500** Conference - £4,500

	Novartis Pharmaceuticals UK Ltd - £90,500 Conference - £15,100 CVD - £30,000 Lp(A) Taskforce - £15,400 Changemaker - £30,000 **NovoNordisk - £8,500** Conference - £8,500 **Richmond Pharmacology - £3,000** Project Work - £3,000 **Sanofi - £24,500** Conference - £24,500 **Ultragenyx UK Ltd - £35,200** Conference - £25,000 Homoztgous Community FH - £10,200 **Verve Therapeutics - £25,000** Conference - £4,500 Project Work - £20,500 **Menarini - £20,000** Changemaker - £20,000

	Grand Total - £399,172.35
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 reduce cardiovascular risk and events in people with existing cardiovascular disease who are already on established treatment. This is an added benefit treatment in order to reduce the risk further.
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.)	The treatment appears to have an effect on progression of atherosclerosis and stability of plaques in people who are already on established treatment. This is an add on treatment and won't replace existing treatment. Adding this treatment in will add benefit to the patient and their family by adding additional option to give them a better quality of life with further risk reduction.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Whilst managing CVD has a lot of treatment options, not one option suits all, therefore the more treatments available the better the outcome for the population. Accessibility is really important with this treatment and it being available across the country is important. We would encourage this treatment to be available regardless of lipid levels.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	The lipid management pathway is followed and some areas have developed their own pathways based on the national pathway. There are also other treatments available such as aspirin and other anticoagulants/antiplatelets, beta blockers, ace inhibitors as well as lipid lowering therapy.
9a. Are any clinical guidelines used in the	NG238, ACS

treatment of the condition, and if so, which?	
9b. 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 pathways of care are well defined.
9c. What impact would the technology have on the current pathway of care?	Not much as it will just be an add in so a slight adjustment only, but a bigger impact on the patient and their families to reduce risk and worry further.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes the treatment would be used.
10a. How does healthcare resource use differ between the technology and current care?	It's an add on and unlikely to change what is currently done.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This is capable of being delivered as an add on through primary care.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	These need to be kept in a fridge and as a self-injected treatment will need a training video or something similar. Also sharps disposal infrastructure will be required.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes it is an added reduction of CVD risk, which will not just bring clinical benefit but also more peace of mind to the patient and their families.
11a. Do you expect the technology to increase length of life more than current care?	We believe this must have a contribution to adding to a patients length of life by helping reduce the risk of major CVD adverse events, alongside the treatment they are already on.
11b. Do you expect the technology to increase health-related quality of life more than current care?	We believe this must have a contribution to a patients quality of life by helping reduce the risk of major CVD adverse events, alongside the treatment they are already on.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	People with injections phobia. Note, there is a caution for women who are taking oral contraceptive and oral HRT that this drug may cause the oral contraceptive and HRT to be less effective.

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	As above, it being an injection. Also there are some side effects may be difficult so engaging with the patient around this will be important on how to manage them, especially as the treatment gets up titrated.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Unsure of any rules or additional testing.
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 does rely on the patient taking their existing treatment as well as this add on treatment and also following a healthy diet and lifestyle. Also making sure all other CVD risk factors are well controlled.
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?	It is innovative as it targets something different to other CVD treatments. It certainly appears to reduce CVD risk which will give benefit to the patient and their families, which largely can't be quantified.
16a. Is the technology a 'step-change' in the management of the condition?	It is an add on so it may not be a 'step change' but it will bring a lot of benefit to the patient and the pressure on the health system as the CVD risk is reduced.

16b. Does the use of the technology address any particular unmet need of the patient population?	It will help patients reduce their weight and obesity is a significant problem amongst the population (26% of adults in 2021 were obese which is a risk factor for CVD).
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?	The common side effects include nausea and gastro effects which can be unpleasant, but this can be managed by up-titrating the dose gradually for patients so they can tolerate the treatment. Education on diet and lifestyle is also important – HEART UK's Cholesterol SMART could be signposted as this covers a CVD healthy diet and lifestyle. Injection site reaction is also common, but this is the same for most injectable treatments.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	It was a worldwide trial for people with established CVD and a BMI of at least 27 kg/m_2 There were also improvements in CVD risk, blood pressure and lipids.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	There is improvement in a range of CVD risk factors, including BP, BMI, HbA1c. BP and BMI are risk factors included in CVD risk prediction in primary prevention
18d. 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?	Important to look at the convincing evidence of benefit on cardiovascular, mortality and kidney outcomes in other risk groups such as patients with type 2 diabetes where there is a lot of data e.g. Meta-analysis of eight trials comprising 60 080 patients GLP-1 receptor agonists reduced MACE by 14% (HR 0·86 [95% CI 0·80-0·93]; p<0·0001), with no significant heterogeneity across GLP-1 receptor agonist structural homology or eight other examined subgroups (all $p_{interaction}$≥0·14). GLP-1 receptor agonists reduced all-cause mortality by 12% (HR 0·88 [95% CI 0·82-0·94]; p=0·0001), hospital admission for heart failure by 11% (HR 0·89 [95% CI 0·82-0·98]; p=0·013), and the composite kidney outcome by 21% (HR 0·79 [95% CI 0·73-0·87]; p<0·0001), with no increase in risk of severe hypoglycaemia, retinopathy, or pancreatic adverse effects. Lancet Diabetes Endocrinol 2021 Oct;9(10):653-662
20. How do data on real-world experience compare with the trial data?	Very similar effects

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Patients from more disadvantaged groups tend to have higher BMIs and higher risk of CVD. Such individuals should be considered a higher priority group
21b. Consider whether these issues are different from issues with current care and why.	There is an even greater need in patients from more disadvantaged groups because of their increased risk of higher BMIs and CVD

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• This would be a beneficial add on treatment to reduce CVD risk in the population with established CVD • This will support people to reduce their weight, which will help reduce wider risk factors • We would support the treatment of be available as part of a CVD pathway, with support to manage the side effects and have a healthy diet and lifestyle • •

Thank you for your time.

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

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The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - **YES** or NO

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity [ID6441]

Patient Organisation Submission

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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].

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- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Kidney Care UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Care UK is the UK's leading kidney patient support charity providing advice, support and financial assistance to thousands every year. It is not a membership organisation, but it is in touch with thousands of kidney patients through its direct patient services (eg advocacy, counselling, facebook support group, patient grants), social media channels, telephone helpline and website.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information and views represented in this submission has been gathered through a range of sources: Kidney Care UK advocacy services and Facebook support group, the views of Kidney Care Staff who are kidney patients, our Patient Advisory Group. We have also run regular surveys to explore the current challenges kidney patients are facing as well as the annual Patient Reported Experience Measures survey which reports on how kidney patients feel about their experience of care.

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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?	Many cases of CKD are mild or moderate and risks can be managed by patients and their GPs without ever visiting a hospital. However, for people with CKD that progresses and requires specialist input from the renal team it can be extremely serious and require life changing treatment. A diagnosis of CKD has huge implications for a person's quality of life. Challenges include the stress of coming to terms with a diagnosis of an incurable, progressive condition, as well as difficult decisions about treatment options and the strain of adjusting to new treatments. Many patients must also adhere to strict medication regimes and dietary restrictions. Symptoms include debilitating fatigue, significant pain, itching, swelling, restless leg syndrome, muscle cramps and sleep problems. People's capacity to stay in work, maintain relationships and quality of life can be severely compromised. There are almost 30,000 people receiving dialysis in the UK,[i] many of whom spend four hours a day, three days a week, every week, at hospital. Fiona Loud, our policy director and a kidney patient, explains "dialysis meant drinking just 500 ml of fluid a day, an almost impossible diet where chocolate, coffee, bananas, cheese, and so many others things are banned or restricted. And you must spend 5 or 6 hours in a hospital 3 days a week, with 2 big needles plunged into your arm, connected to a machine. And all this gives you just 10% of your normal kidney function, and you probably feel even sicker after treatment than you did before, your blood pressure has dropped way down and you may be bleeding from where those great big needles were for a long time. You may be too weak to walk and you are likely to be depressed and out of work. You have a day off, and then it all starts again…and again….and again." Kidney transplant, while not a cure, is the best form of treatment for kidney disease. However there are more people waiting for a transplant than there are available organs and people from Black and Minority Ethnic communities have to wait considerably longer than people from White British backgrounds. Kidney transplants from deceased donors last on average 15-20 years and 20-25 years from a living donor, although some longer and some less.[ii] Kidney patients may therefore face returning to dialysis if their kidney fails. Unsurprisingly, CKD can take a huge toll on the mental health and emotional wellbeing of patients and service levels do not meet demand (see our recent report Left to get on with it). Nearly half of in-centre haemodialysis patients experience some form of distress[iii] and up to 1 in 3 kidney patients will experience depression at some point. This in turn exacerbates physical ill health and a person's ability to manage their condition. Symptoms of depression in people with early stage kidney disease

	increases their risk of progressing to end-stage renal disease (requiring dialysis or a transplant) and death.[iv,v] In transplant patients, depressive symptoms have been shown to increase the risk of death by 65%.[vi] A carer's role will depend partly on the individual's stage of kidney disease, their symptoms (eg fatigue), comorbidities and the treatment they receive. Roles can include helping with activities of daily living and mobility, transportation, personal care, and support with treatment, for example adhering to the medication regime and also with dialysis (for example if the person has dialysis at home). As well as the physical demands of caring, it can be emotional challenging as the carer and the person with kidney disease come to terms with the change in role and the impact of a life changing diagnosis. Caregiving demands in managing dialysis has proved to be taxing on the physical, social and emotional health of informal caregivers.[vii,viii] People with CKD are also living with the risk of cardiovascular events. This risk is already significantly higher in patients with early CKD stages (CKD stages 1–3) compared with the general population, and patients with advanced CKD stages (CKD stages 4–5) have a greatly elevated risk. Cardiovascular rather than end-stage kidney disease (CKD stage 5) is the leading cause of death in people with CKD. Cardiovascular mortality accounts for 40% to 50% of all deaths in patients with CKD 4 and 5, compared with 26% in people with normal kidney function (Jankowski, 2021)

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 most recent Patient Related Experience Measures found that overall patients rate the overall experience of the service provided by their renal unit highly.[ix] People who progress to kidney failure often find the burden of treatment is very significant. As described above, many patients can find living with four-hour dialysis sessions plus travel time, three times a week every week, as well as the stringent fluid and dietary restrictions, very challenging. Receiving a kidney transplant, although not a cure, can make a huge different to the health and quality of life of a person with kidney disease. People fortunate enough to receive a kidney transplant will also need to follow certain restrictions on their diet and lifestyle, as well as being on medication for the rest of their lives. In the case of deceased donations, transplant comes with the emotional burden of knowing the donor has lost their life. Decisions regarding accepting a living donation can also be emotionally challenging. There are relatively new medications that can slow decline in kidney function and reduce risk of cardiovascular mortality and morbidity. These have been welcomed by patients, although the roll out of these treatments has been variable around the country.
8. Is there an unmet need for patients with this condition?	There is no cure for chronic kidney disease and limited options for medications that can slow or prevent decline in kidney function, although lifestyle, diet and treatments for problems linked with kidney disease such as high blood pressure are important. Progress in developing new pharmaceutical treatments has been extremely slow.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	People with CKD are excited about the growing evidence suggesting GLP-1 medications may be beneficial for people living with CKD and obesity. It is extremely daunting to face a future of severe kidney disease with its huge burden of symptoms and the potential need to start lifelong kidney replacement. Therefore, studies which indicate that a new medication may play a role in reducing the risk of kidney disease worsening are always welcomed by people living with the burden of CKD. People with CKD are more likely to die from cardiovascular events than kidney failure, so treatments that may reduce this risk are extremely important and valuable to patients. In addition, obesity impacts both the development and progression of kidney disease and can be a barrier to kidney care. Therefore, drugs which help people lose weight are also of great interest. There has been significant discussion regarding the weight loss drugs on our patient support forums (questions about weight loss drugs are currently one of the most common on our closed facebook group of over 14,200 people with CKD), with hugely variable experience in terms of whether people with CKD can access the weight loss drugs on the NHS. A high BMI can be a barrier to access to the transplant list. Often, people with CKD have tried for many years to lose weight but found it extremely challenging and are therefore interested to see how the weight loss drugs may add to diet and lifestyle interventions.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	There is concern among kidney patients regarding any potential side effects of the technology**.**

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 from lower socio-economic groups are more likely to develop CKD and progress faster towards kidney failure. People from Black, Asian and minority ethnic populations are more likely to progress towards kidney failure. Therefore, people from these groups may benefit more from a treatment which can slow the decline of kidney function.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There is growing awareness of the potential benefits of this technology for people CKD but variation in NHS access around the UK. Therefore, some people are paying privately for treatment. This is leading to a situation where people who cannot afford to buy privately have poorer access to the treatments, as well as safety concerns if people do not discuss the treatments open and honestly with their kidney doctor.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Chronic kidney disease can have a hugely negative impact on quality of life, with a range of debilitating symptoms that can impact on many aspects of life and wellbeing. • It is currently incurable although pharmaceutical options for delaying progression and reducing CVD risk have emerged over recent years. Treatments for kidney failure very burdensome with access to the gold standard treatment of kidney transplant limited • This treatment provides hope through the provision of another option for slowing CKD progression and reducing CVD risk • People with CKD are also excited about treatments that treat obesity and therefore support kidney health and, for some, potentially offer a route to accessing the transplant list • Drug treatments such semaglutide must be accompanied by information and support about dietary, exercise and lifestyle interventions that can help in weight loss, management of CVD complications and delaying progression of kidney disease • Patients must be supported to report side effects as the ongoing monitoring and evaluation of adverse events is important (including where they have paid for the drug privately).

Thank you for your time.

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[i] UK Renal Registry, 2020, UK Renal Registry 22nd Annual Report – data to 31/12/2018, Bristol, UK. Available from: renal.org/audit-research/annual-report

[ii] NHSBT, 2021, Comparison of deceased donor and living donor kidney transplantations, NHSBT, accessed 260521 < https://www.nhsbt.nhs.uk/organ-transplantation/kidney/receiving-a-kidney/deceased-donor-kidney-transplant/>

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[vii] Belasco AG, Sesso R. Burden and quality of life of caregivers for hemodialysis patients. Am J Kidney Dis. 2002;39(4):805–12.

[viii] Tong A, Sainsbury P, Craig JC. Support interventions for caregivers of people with chronic kidney disease: a systematic review. Nephrol Dial Transplant. 2008;23(12):3960–5

[ix] Kidney Care UK and the Renal Association, 2021, Patient Reported Experience of Kidney Care in the UK 2019, Available at: file:///C:/Users/Samantha/Downloads/2019_Kidney_PREM_report.pdf

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity [ID6441]

Patient Organisation Submission

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].

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- Your response should not be longer than 10 pages.

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About you

1.Your name	[redacted]
2. Name of organisation	Kidney Research UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the country's leading kidney research charity. We fund and promote research into kidney disease and related topics; bring together patients and researchers in networks and clinical study groups; campaign for the adoption of best practice in the NHS and improve pathways and health outcomes for kidney patients. Our latest annual report 2023/24 shows the majority of our income is from donations, gifts, and legacies. The remainder is from trusts, partnerships, investments, trading, and government funding. We are not a membership organisation but have an extensive supporter base and a significant number of active volunteers, many of whom are kidney patients.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No

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?	We have included quotes from a person with lived experience.

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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?	*"I had to take ill-health retirement aged 50." – Person on kidney dialysis and living with overweight / obesity* Living with kidney disease, cardiovascular disease (CVD) and overweight/obesity can be physically and emotionally exhausting. Many patients experience daily breathlessness, fatigue, and limited mobility, which can impact their independence, confidence, and mental health. The constant fear of a heart attack or stroke creates anxiety, while managing medications, lifestyle changes, and comorbidities like diabetes adds complexity and stress. For carers, the burden can be equally challenging. They often juggle emotional support with practical tasks – managing dialysis if dialysing from home, transporting their loved one to hospital if in-centre dialysis, managing appointments, medications, and dietary needs – while watching their loved one struggle with a chronic, life-threatening condition. This can lead to caregiver fatigue, poor mental health, and social isolation. **People living with kidney disease** Semaglutide is associated with changes in multiple biomarkers of cardiovascular risk, including blood pressure, waist circumference, glycaemic control, nephropathy, and levels of lipids and C-reactive protein. These biomarkers are also closely associated with chronic kidney disease (CKD). [Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes | New England Journal of Medicine] People living with chronic kidney disease (CKD) are an under-served and under-recognised patient population in the UK. Kidney disease costs the UK economy more than £7 billion a year; these costs could rise to £13.9 billion by 2033 if we don't do more now to prevent the onset and progression of CKD. And, growing numbers of people are at risk of kidney disease due to increased cases of diabetes, heart disease, high blood pressure and obesity. [Kidney disease: A UK public health emergency 2023 Economics-of-Kidney-Disease-summary-report_accessible.pdf] In addition to the physical and emotional impact of CKD on individuals, there is also a significant financial impact. According to a recent ONS (Office for National Statistics) study, CKD causes the second-highest total loss of earnings for individuals for five years following hospital diagnosis (£14,721) and reduces the probability of their employment by 9.4 percentage points [Impact of health conditions requiring hospitalisation on earnings, employment and benefits receipt, England - Office for National Statistics]. Cardiovascular events are more likely to occur with albuminuria present (and hence the presence of CKD) and less likely to occur if albuminuria is reduced [De Zeeuw D, et al. Circulation 2004;110:921–927. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy - PubMed (Post hoc analysis of RENAAL trial)] We would therefore like to focus our submission on the subgroup of patients living with overweight / obesity who are diagnosed with CKD in addition to CVD. Of these, patients with kidney failure who require dialysis and are on the waiting list for a kidney transplant could benefit most from semaglutide therapy.

	These patients have a complex CVD risk profile. According to USRDS (United States Renal Data System) Annual Data Reports, CVD is the major cause of morbidity and mortality in patients on haemodialysis (HD). [Cardiovascular disease in dialysis patients - PMC]. In this population, mortality due to CVD is 20 times higher than in the general population and the majority of maintenance HD patients have CVD. [Cardiovascular disease in dialysis patients - PMC]. Thus, a significant patient population affected by obesity or overweight and existing or potential cardiovascular disease stands to gain from semaglutide's dual benefits of weight reduction and cardiovascular protection. Patients living with obesity, CVD and CKD are caught in a vicious cycle. They may not be eligible for transplant without losing weight but are not able to lose weight due to the demands of being on dialysis. A person living with kidney disease told us: *"I was told I needed to lose weight before I could be listed for a transplant. I tried to lose weight, but I had no energy to exercise [while on dialysis].* *"I'm on dialysis 3 days a week which takes 7-8 hours each time and then I just sleep. I feel so drained all the time.* *"When you're on dialysis you have to eat when you can, and salads and soups aren't allowed because of diet and fluid restrictions.* *"I was prescribed mounjaro and it worked phenomenally well. I've lost 5 stone and am now talking to my consultant about going on the transplant list. If I could have a transplant I would get my life back again.* *"Weight loss drugs should be available to everyone on dialysis if they need to lose weight."* In addition, people living with overweight / obesity who may be considering becoming a living kidney donor would benefit from semaglutide therapy to help them lose weight and so become eligible to donate. With the increasing number of medications available, the treatment of obesity with anti-obesity medications may increase the pool of potential donors and enhance donor safety [Antiobesity pharmacotherapy to facilitate living kidney donation]. Dialysis costs the NHS approximately £34,000 per person per year. [Kidney disease: A UK public health emergency 2023 Economics-of-Kidney-Disease-summary-report_accessible.pdf]. This compares to costs of around £17,000 during the first year of care following a kidney transplant with annual costs of £5,000 for every subsequent year (mainly for immunosuppressive drugs) (data from 2009). [Microsoft Word - Adult Kidney Transplant Service PUB130217]

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	For people with CKD who are on hemodialysis (HD), living with overweight or obesity may limit their access to kidney transplantation whilst increasing the risk of complications and mortality post transplantation. GLP-1RAs, such as semaglutide, could provide a pharmacological alternative to bariatric surgeries for these HD patients. A published case study, for example, reported a reduction of 9 kg in a patient's body weight (BMI 42 kg/m^2) after nine months of semaglutide treatment enabling her to be considered for a kidney transplant. (REF: Semaglutide for treatment of obesity in hemodialysis patients waiting for a kidney transplant: new hope? - PMC) Another study [Semaglutide in patients with kidney failure and obesity undergoing dialysis and wishing to be transplanted: A prospective, observational, open-label study - Vanek - 2024 - Diabetes, Obesity and Metabolism - Wiley Online Library] found that semaglutide resulted in significant reductions in weight and BMI in people living with obesity undergoing dialysis whilst maintaining an acceptable side effect profile that was comparable to that of the non-dialysis population.
8. Is there an unmet need for patients with this condition?	There is a significant unmet need for people with CKD and cardiovascular disease who are also living with overweight or obesity. While treatments for CVD are well-established, the coexisting challenge of obesity is often under-addressed. Many people struggle to access effective, sustainable weight management support within the NHS, and pharmacological options like semaglutide have only recently become available. There is a lack of integrated, multidisciplinary care that tackles CKD, cardiovascular risk and obesity holistically. People frequently need more personalised, long-term support that combines medical therapy, lifestyle interventions, psychological input, and education. Addressing this gap could improve outcomes and quality of life significantly.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	In general, patients and carers view semaglutide as a promising advance with several key advantages. Many appreciate the dual benefit: it not only supports substantial and sustained weight loss but also reduces the risk of major cardiovascular events. This dual action is particularly meaningful for those living with both cardiovascular disease and obesity, where traditional treatments often address only one aspect. The once-weekly injection is generally seen as convenient and manageable, improving adherence. People have reported feeling more in control of their health, with improvements in energy, mobility, and confidence. Carers have reported reduced caregiving burden as patients become more independent and stable. As the person with lived experience noted above, due to the gruelling schedule of dialysis, many people are not able to exercise and face severe restrictions on food and drink. The option of pharmacological interventions could therefore be a game changer for this population.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	In general, patients and carers acknowledge several disadvantages of semaglutide. Some people experience side effects such as nausea, vomiting, or gastrointestinal discomfort, especially during the early stages of treatment, which can affect their quality of life and willingness to continue. The injectable form, although weekly, may be off-putting for those uncomfortable with needles or who have difficulty self-administering medication. Access and availability through the NHS can also be a concern, with some people facing delays or uncertainty around eligibility. Carers sometimes worry about the long-term safety of newer medications and may feel anxious about managing potential side effects or supporting adherence to treatment.

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.	Certain groups of people may benefit more or less from semaglutide for preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity: **Groups who may benefit more:** • **People with coexisting CKD who are unable to go on the transplant waiting list due to living with overweight or obesity:** These people would benefit from weight reduction in order to be placed on the waiting list. • **People with coexisting type 2 diabetes:** These individuals often see dual benefits in both cardiovascular risk reduction and improved glycaemic control. • **People with severe obesity (BMI >35):** This group may experience more pronounced weight loss, which can lead to improved mobility, reduced cardiovascular strain, and better quality of life. • **Those with prior cardiovascular events:** These people are at higher baseline risk, so the absolute risk reduction with semaglutide may be greater. • **Motivated patients with support systems:** People with strong family/carer support and motivation to change lifestyle habits may adhere better and gain more from the treatment. **Groups who may benefit less:** • **People with significant gastrointestinal conditions:** Due to the drug's GI side effects, those with pre-existing issues like gastroparesis may tolerate it poorly. • **People with needle phobia or cognitive impairment:** They may struggle with self-injection or consistent use, reducing effectiveness. Personalised assessment is crucial to maximise benefits and minimise risks.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are several potential equality issues that should be considered when evaluating access to, and the use of, semaglutide for people with cardiovascular disease and overweight or obesity: **1. Socioeconomic Inequality** • People from lower-income backgrounds often have higher rates of obesity, CVD and CKD but may face greater barriers to accessing new treatments. • Lifestyle interventions and follow-up support (e.g. dieticians, exercise programmes) are not always equitably available, especially in deprived areas. **2. Ethnic Disparities** • Certain ethnic groups (e.g. South Asian and Black communities) are at higher risk for cardiovascular disease at lower BMI thresholds yet may be underrepresented in clinical trials and underdiagnosed or undertreated in practice. • BMI-based criteria for treatment eligibility may not account for ethnic variations in risk. **3. Language and Health Literacy** • Understanding how to use semaglutide safely and effectively requires clear communication. People with limited English proficiency or lower health literacy may struggle to access, understand, or adhere to treatment plans. **4. Disability and Cognitive Impairment** • People with physical or cognitive impairments may have difficulty with self-injection or recognising side effects, requiring carer support or adapted services. **5. Gender/Sex Differences** • Women may face delays in diagnosis and referral for cardiovascular care and may be under-treated despite similar risk profiles. Addressing these issues through inclusive eligibility criteria, accessible patient education, and equitable service delivery is essential to avoid widening health inequalities.

Other issues

13. Are there any other issues that you would like the committee to consider?	Several additional issues may be important for the committee to consider when evaluating semaglutide for preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity: **1. Long-term sustainability and adherence** • While semaglutide shows strong short- to medium-term benefits, data on long-term use, discontinuation effects, and sustained cardiovascular protection after stopping the drug remain limited. Clear guidance on duration of therapy is needed. **2. Integration into existing care pathways** • There should be clarity on how semaglutide will be integrated into current cardiovascular and weight management services, particularly across primary and secondary care. Fragmented pathways could limit uptake and effectiveness. **3. Cost-effectiveness and prioritisation** • As demand is likely to be high, it's important to ensure the NHS can afford widespread use without compromising access for other high-risk patients. Stratification tools may be needed to prioritise those at greatest benefit. **4. Psychological impact** • For some patients, starting pharmacological treatment for weight loss may carry stigma or emotional burden. Others may view it as a last resort. Psychological support should be considered as part of holistic care. **5. Real-world data collection** • Continued monitoring and collection of real-world data on outcomes, side effects, adherence, and health inequalities will be essential to inform future guidance and optimise implementation. Ensuring equitable, safe, and effective use of semaglutide will require coordinated planning, multidisciplinary input, and robust follow-up structures.

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Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• People living with chronic kidney disease are an under-served and under-recognised patient population. More must be done to prevent the cost of kidney disease from overwhelming the NHS. • Semaglutide is associated with changes in multiple biomarkers that are also closely associated with chronic kidney disease. • People living with overweight / obesity, who have CVD, are on dialysis and waiting for a kidney transplant form a significant population who would benefit greatly from semaglutide therapy. Such treatment could mean considerable cost savings for the NHS over the long term. • Integrated, multidisciplinary care that tackles CKD, CVD and obesity holistically is urgently needed. •

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Single Technology Appraisal

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity [ID6441]

Patient Organisation Submission

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- Your response should not be longer than 10 pages.

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About you

1.Your name	[redacted]
2. Name of organisation	Pumping Marvellous Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Pumping Marvellous Foundation is the UK's Patient led Heart Failure Charity. It helps people to live well with heart failure and advocates for patients at local, regional, national and global level. It has worked with NICE for over 10 years and has been involved in all heart failure STA's, Guideline and QS work. It does not have any formalised member structure – it has over 40 patient educators who are expert patients, 15 recognised heart failure experts on its clinical advisory committee and 9 Trustees. It has a diverse funding approach from NHSE, ICB's, Life Science Grant Funding and charity fundraising events etc The CEO and a Senior Patient Educator and Trustee sit on NHSE's Heart Failure Expert Board
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	No funding has been received from the company bringing the treatments to NICE. See the link here to your funders page - https://pumpingmarvellous.org/fundraising/partnerships-and-funders/ And our quarterly report here https://pumpingmarvellous.org/wp-content/uploads/2025/07/Updated-PMF-Quarterly-Report.pdf

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?	**We have large patient and carer communities which we regularly poll along with our patient educators who are patients themselves. We have over one million interactions every year within our communities. Obesity is a significant topic and consistently topic in the community.**

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?	We are the UK's heart failure charity. A diagnosis of heart failure carries many co-morbidities which includes obesity. Heart failure also causes severe symptoms which in many cases prevents people from leading a healthy lifestyle, like breathlessness, fatigue and oedema. This means they are, in many cases incapable of exercise leading to a sedentary lifestyle, brought on by symptoms.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**They may or may not know the access or have access to local services. Although readily marketed in health settings and online, NHS campaigns about health lifestyles don't seem to be helping. People need clarity around GLP-1's of all types regarding access and safety. Access to existing services is variable and short termism. There is a not a broad brush that suits all.**
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**Patients tell us that (private or prescribed by the NHS) that the technology in the vast majority has a huge impact on there lives. They lose weight, there comorbidities (T2D Hypertension Lipds) are better controlled in their regular blood tests. They report that the weight loss is an enabler to a better quality of life.**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Mainly some people report challenging GI side effects, however this needs to be unpicked. Access and cost.

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.	Nothing other than what has been mentioned above.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Equality of access including local prescribing.

Other issues

13. Are there any other issues that you would like the committee to consider?	We understand the cost implication issues however we need to view this technology differently as it's wide implementation could have significant, multiple domain, population heath impact. A conundrum that needs to be driven by clinical appropriateness.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Effective treatment • Challenging access • Value to patients • Improvement in QOL • Cost

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity [ID6441]

Professional organisation submission

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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- 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	British & Irish Association of Stroke Physicians
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British and Irish Association of Stroke Physicians (BIASP), formerly known as BASP (British Association of Stroke Physicians), was founded in 1999 with the overarching goal of promoting stroke medicine within Great Britain. In parallel to the major developments and improvements in the care of people with stroke or at risk of stroke over the past decades, BIASP evolved into an organisation that has provided leadership in advancing clinical standards, promoting research and improving training across the United Kingdom and the Republic of Ireland. BIASP is run by its executive committee and subcommittees consisting of members who are stroke physicians with a dedication to advancing stroke medicine across all aspects of the specialty. They are elected by the BIASP membership and meet regularly to ensure progress is made towards achieving BIASP's strategic objectives. Funding comes from membership only.
5b. 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.**	No

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 lose weight and prevent CVDs - including strokes and TIAs
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.)	20-30% relative risk reduction of the risk of CVD including strokes and TIAs
8. 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?

9. How is the condition currently treated in the NHS?	Variable, primary vs secondary care, lifestyle vs medications
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	For overweight and obesity, we use the Overview | Overweight and obesity management | Guidance | NICE For stroke, we use the National-Clinical-Guideline-for-Stroke-2023.pdf
9b. 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.)	Significant variations amongst professionals
9c. What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example,	

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Possibly. Weight optimisation can be difficult for some stroke patients as their function is affected and they find it difficult to exercise.
11a. Do you expect the technology to increase length of life more than current care?	
11b. Do you expect the technology to increase health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes, for some stroke patients whose function is significantly affected and they find it difficult to exercise to lose weight.

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.)	Easier for patients but the exact risk vs benefit balance to be determined. Cost effectiveness to be determined
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
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?	

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
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	For patients whose function is significantly affected and they find it difficult to exercise to lose weight.
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?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	

18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• This is an important topic for NICE to evaluate as a single technology appraisal (STA) • Other international guidance by the ESC or AHA should be considered • Please clarify if this TA includes people with diabetes or not, with justifications • Special mention for stroke patients who are disabled may find it difficult to exercise to lose weight • Special mention for other disadvantaged groups such as older, frailer, or those with learning disability

Thank you for your time.

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Single Technology Appraisal

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity [ID6441]

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About you

1. Your name	[redacted]
2. Name of organisation	British Obesity and metabolic specialist society
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. 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.**	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	

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.)	Secondary prevention of cardiovascular disease in people with obesity and established CVD
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.)	Relative risk reduction of 10% in MACE
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, because the rates of CVD continue to be high in people with obesity

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Through standard CVD interventions, but not GLP-1 based treatments
9a. Are any clinical guidelines used in the	Yes, NICE and from CVD societies

treatment of the condition, and if so, which?	
9b. 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 CVD pathway is well defined, but not the obesity pathway. This is the reason that this medication should be used predominantly in CVD pathways.
9c. What impact would the technology have on the current pathway of care?	Addition of semaglutide to medications like statins that have prognostic benefit in CVD. CVD services should be trained to include this medication in their pathways, but that should not be that challenging.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No, these medications are currently being used predominantly in obesity pathways.
10a. How does healthcare resource use differ between the technology and current care?	As above
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary prevention as delivered by both secondary and primary care
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	HCP training and some basic support by MDT members (dietitians and nurses mostly)

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Based on the SELECT trial we expect a 20% reduction in MACE
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. 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?	The treatment should be given to people who meet the eligibility criteria of the SELECT trial

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	It will require some additional resource and training. A lot of this can be supported by digital technologies

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	no
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?	yes
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
16a. Is the technology a 'step-change' in the management of the condition?	yes

16b. Does the use of the technology address any particular unmet need of the patient population?	Reduction in CVD
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?	These can be managed well by MDTs following appropriate training with digital technologies supporting this.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	20% reduction in MACE which is independent of initial BMI or weight loss
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	no
18d. Are there any adverse effects that were not apparent in clinical	Yes, but they are very well known

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. How do data on real-world experience compare with the trial data?	This is not known yet

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
21b. Consider whether these issues are different from issues with current care and why.	No

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	The proposed wok by NICE is important and well designed. There is a plan to study subpopulations based on their starting BMI. This will not be useful because the response to the SELECT trial was independent of initial BMI. We suggest that this subgroup is removed from the pre-defined subgroup analyses

Thank you for your time.

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Your privacy

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About you

1. Your name	[redacted]
2. Name of organisation	**Royal College of General Practitioners**
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? No A specialist in the clinical evidence base for this condition or technology? No
5a. Brief description of the organisation (including who funds it).	The Royal College of General Practitioners (RCGP) is the UK's professional membership body for general practitioners. The College is committed to improving patient care, clinical standards, and GP training. It is a registered charity, primarily funded by membership fees, grants, educational activities, and professional events.
5b. 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.**	No
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 main aim of treatment is to reduce the risk of major adverse cardiovascular events (MACE) in individuals with established CVD who also live with overweight or obesity. This includes reducing the likelihood of events such as MI, stroke, and CV death, while also improving overall metabolic health and supporting sustained weight loss.
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.)	A clinically significant response would be a meaningful reduction in cardiovascular events (e.g., >20% relative risk reduction in MACE), accompanied by sustained weight loss of at least 5–10% of baseline body weight, improvements in blood pressure, glycaemic control, and lipid profile. In primary care, improvements in functional capacity and quality of life - particularly where obesity contributes to multimorbidity - are also key markers of success.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Despite the well-established link between obesity and CVD, there are few effective and sustainable treatment options available in primary care. Lifestyle interventions are important but often insufficient on their own for those at high CV risk. There is also limited access to multidisciplinary weight management services. Semaglutide offers a potential option to fill this treatment gap by addressing both weight and CV risk through a pharmacological approach.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Patients with CVD and obesity are typically managed with a combination of lifestyle advice, pharmacotherapy for cardiovascular risk factors (e.g. antihypertensives, statins), and support for weight management. In primary care, GPs provide brief interventions and may refer patients to tier 2 or 3 weight management services, which vary significantly by region and often oversubscribed.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. NICE guidelines on obesity (CG189), cardiovascular disease prevention (CG181), and the newer guidelines for pharmacological interventions in obesity (NG224) are commonly referenced. Additionally, SIGN, ESC, and EASO guidelines are sometimes used in more specialist settings.
9b. 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 is variability across NHS. While pathways are theoretically tiered (tiers 1-4), in practice, access to higher-tier weight management services is limited and often inequitable. There is variation in referral thresholds, availability, and regional commissioning policies, which can create disparities in care.
9c. What impact would the technology have on the current pathway of care?	Semaglutide could provide an effective pharmacological option in primary care settings for people with established CVD and obesity. It may reduce the need for referrals to higher-tier services or complement these services when combined with lifestyle and behavioural interventions. It could also shift the management of obesity from being seen as predominantly lifestyle-based to a more medicalised, long-term risk-reduction strategy.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Semaglutide is already used in NHS settings for type 2 diabetes and weight management (under different criteria). However, for cardiovascular prevention in patients with obesity, this represents a novel indication. Its use will align partially with existing care but would expand pharmacological options available in primary care to address both obesity and cardiovascular risk.
10a. How does healthcare resource use differ between the technology and current care?	Current care relies heavily on lifestyle advice and long-term management of comorbidities such as hypertension, hyperlipidaemia, and diabetes. Introducing semaglutide may increase short-term prescribing costs and require initial training and monitoring. However, it may reduce long-term healthcare utilisation by preventing cardiovascular events, delaying complications, and reducing medication burden across multiple domains (e.g., antihypertensives, insulin, statins).
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology could be used in primary care, especially for patients already under GP care for cardiovascular disease. It may also be used in specialist weight management or cardiometabolic clinics for complex cases or for initiation and titration before shared care agreements in general practice.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training for primary care clinicians and pharmacists on prescribing, eligibility, and monitoring • Clear clinical protocols and inclusion criteria • Digital or manual systems to support follow-up and outcome tracking • Patient education resources

	Infrastructure costs are likely modest, as semaglutide is already used in other indications.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Semaglutide has the potential to reduce cardiovascular events and improve weight-related comorbidities, which current care often fails to achieve sustainably through lifestyle interventions alone.
11a. Do you expect the technology to increase length of life more than current care?	Yes. Particularly in individuals with established CVD. Evidence suggests that reducing cardiovascular events through GLP-1 receptor agonists can lead to increased survival.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. Improvements in weight, blood pressure, glycaemic control, and physical function can lead to better mobility, lower medication burden, and improved mental health -all of which enhance quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology is likely most effective in people with established CVD and class II or III obesity. It may be less appropriate in individuals with a history of pancreatitis, severe gastrointestinal conditions, or those with contraindications to GLP-1 receptor agonists. Adherence may also be lower in populations with needle phobia unless oral formulations become available

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.)	Semaglutide is generally well tolerated and easy to administer once weekly via subcutaneous injection. While this may be a barrier for some patients (e.g., those with needle phobia), many find the once-weekly dosing acceptable and preferable to daily medications. There is a need for initial counselling and training on administration. Monitoring for gastrointestinal side effects and weight loss progress is needed, but this can be integrated into routine reviews in primary care or supported remotely. No significant concomitant treatments are required beyond standard cardiovascular risk management.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. It is likely that clear eligibility criteria will be required (e.g. established CVD and a specific BMI threshold). Formal stopping rules- such as achieving a minimum percentage weight loss by a defined time point (e.g. 5% by 6 months)- may be necessary to ensure clinical and cost-effectiveness. Periodic weight and cardiovascular risk monitoring would be standard practice.

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?	Yes. Improvements in self-esteem, physical functioning, ability to work or care for family, and reductions in weight-related stigma are important and may not be fully captured in QALY modelling. Reduced polypharmacy and medication burden can also enhance wellbeing.
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. Semaglutide represents a step-change in managing obesity not just as a lifestyle issue but as a treatable chronic disease with cardiometabolic consequences. It provides GPs with an evidence-based pharmacological tool that addresses both obesity and cardiovascular risk, potentially shifting the clinical paradigm.
16a. Is the technology a 'step-change' in the management of the condition?	Yes. It redefines obesity and cardiovascular risk management in primary care and offers a new treatment avenue for patients previously limited to lifestyle advice and non-specific support.
16b. Does the use of the technology address any	Yes.

particular unmet need of the patient population?	It provides an evidence-based treatment option for people with obesity and CVD who often have limited or no access to structured tier 3 services or face long waits for specialist care.
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?	The most common adverse effects (nausea, vomiting, diarrhoea) are usually transient and manageable. They may require dose titration and patient support but rarely lead to discontinuation. Long-term tolerability is generally good, and these side effects are outweighed by the potential benefits in appropriate patients.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Broadly, yes. Trials such as SELECT included patients with established cardiovascular disease and BMI thresholds relevant to UK populations. However, real-world implementation will involve a more diverse range of patients and healthcare settings.
18a. If not, how could the results be extrapolated to the UK setting?	Results can be extrapolated with minor caution, taking into account the UK's primary care-led management of chronic disease and variability in access to weight management services.

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Yes. Key outcomes such as cardiovascular event rates, weight loss, and quality-of-life measures were included. Additional functional and psychological outcomes could enhance future evaluations.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes. Cardiovascular event reduction and sustained weight loss are strong predictors of long-term health benefits.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No major unexpected adverse events have been identified in routine use to date, though ongoing pharmacovigilance is important, especially regarding rare events such as pancreatitis.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Real-world data from NHS specialist weight management services and anecdotal reports from GPs using semaglutide for other indications suggest high acceptability and notable improvements in multimorbidity, but these are not yet fully published.
20. How do data on real-world experience	Real-world data generally align with trial outcomes in terms of weight loss and tolerability. Adherence rates may be slightly lower, and patient selection is broader, but overall effectiveness remains strong in motivated patients.

compare with the trial data?	

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes. People from deprived backgrounds and ethnic minority groups are disproportionately affected by obesity and CVD but may face greater barriers to access new treatments. Ensuring equity in prescribing and education will be important. People with learning difficulties, severe mental illness, or language barriers may also need tailored support.
21b. Consider whether these issues are different from issues with current care and why.	Current care often already fails to meet the needs of these populations due to inconsistent access to tiered services and under-resourcing of primary care. If not carefully implemented, new technologies like semaglutide may exacerbate inequalities unless clear equity-focused commissioning is applied.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• There is a significant unmet need in primary care for effective treatment options for patients with obesity and established cardiovascular disease. • Semaglutide offers a clinically effective pharmacological approach that reduces cardiovascular events and supports weight loss, addressing both conditions simultaneously. • Its use in primary care could shift the paradigm from reactive to proactive cardiometabolic risk management. • While implementation requires investment in training and systems, it has the potential to reduce long-term healthcare costs and improve patient outcomes. • Equity in access and prescribing will be essential to avoid widening existing health inequalities

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Your privacy

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Additional Submission Responses

9. How is the condition currently treated in the NHS?

Content to be inserted...

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?

Content to be inserted...

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?

Content to be inserted...

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?

Content to be inserted...

13. Will the technology be easier or more difficult to use...

Content to be inserted...

14. Will any rules (informal or formal) be used to start or stop treatment with the technology?

Content to be inserted...

15. Do you consider that the use of the technology will result in any substantial health-related benefits...

Content to be inserted...

16. Do you consider the technology to be innovative...

Content to be inserted...

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?

Content to be inserted...

18. Do the clinical trials on the technology reflect current UK clinical practice?

Content to be inserted...

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?

Content to be inserted...

20. How do data on real-world experience compare with the trial data?

Content to be inserted...

21a. Are there any potential equality issues...

Content to be inserted...

22. In up to 5 bullet points, please summarise the key messages of your submission.

Content to be inserted...

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NHS organisation submission (ICBs and NHS England)

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- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England

3. Job title or position	[redacted]
4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? **No** Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? **No** Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? **No** An expert in treating the condition for which NICE is considering this technology? **No** An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? **No** Other (please specify): **The responsible commissioners for the relevant care pathways are ICBs. NHS England has collated information from several clinical experts to inform this evidence submission to NICE.**
5a. Brief description of the organisation (including who funds it).	NHS England leads the NHS in England to deliver high-quality services. We work with the wider NHS, national partner organisations and other key stakeholders to optimise outcomes and patient experience through expert clinical leadership, the use of digital technology, research and innovation, and the delivery of value for money and increased productivity and efficiency for all. The establishment of integrated care boards within integrated care systems, which are made up of public services that provide health and care, means that NHS England is changing the way it works to best support and

	empower local system partners to deliver on their responsibilities. We work with, and support, regional and ICB leadership teams in the commissioning of high-quality services. Our NHS England Operating Framework sets out how we are supporting systems and providers to lead locally to improve the health of the population, improve the quality of patient care, tackle inequalities and deliver care more efficiently. It describes our six longer-term aims: 1. Longer healthy life expectancy. 2. Excellent quality, safety and outcomes. 3. Excellent access and experience. 4. Equity of healthy life expectancy, quality, safety, outcomes, access and experience. 5. Value for taxpayers' money. 6. Support to society, the economy and environment.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The proposed use of semaglutide would need to be incorporated into the care pathways described in the following guidelines: - stroke rehabilitation (NG236); - acute coronary syndrome (NG185); and - peripheral arterial disease: diagnosis and management (CG147).
7. 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 is no universally accepted definition of established cardiovascular disease. To ensure clarity about the eligible population, please consider including the trial definition in section 1.1 of the technology appraisal guidance: "prior myocardial infarction, prior stroke, or symptomatic peripheral arterial disease, as distinct from a history of angina or transient ischaemic attack". Further definition of symptomatic peripheral arterial disease would be useful: what degree of symptomatic? If semaglutide is not considered cost-effective in the full licensed population, please consider subgroups defined by cardiovascular risk factors alongside BMI.
8. What impact would the technology have on the current pathway of care?	Please consider the stroke rehabilitation (NG236), acute coronary syndrome (NG185), and peripheral arterial disease (CG147) pathways in addition to the lipid pathway referred to in the scope.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	All elements of the pathway fall within ICB commissioning responsibilities.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Semaglutide is not expected to require new services outside of existing clinical pathways, but existing services may require additional capacity, especially prescribing capacity.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity [ID6441]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR172247

Completed using list prices 16 October 2025
Updated using list prices 4 November 2025
Updated using CAA prices 5 December 2025
Updated after correcting for errors 16 January 2026

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

External Assessment Group (EAG) Report

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity [ID6441]

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Date completed: 16 October 2025 using list prices; updated 4 November following factual accuracy check and confidential information check and updated using commercial access agreement prices 5 December 2025 and 16 January 2026 (after correcting minor typographical errors)

Source of funding: This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number NIHR172247.

Declared competing interests of the authors: Professor Carel le Roux has received consultancy fees, reimbursement for conference attendance and fees for speaking from the sponsor, Novo Nordisk. Professor le Roux is co-owner of a clinic providing clinical obesity care. There are no other completing interests to declare.

Acknowledgements: The authors would like to thank: Professor Alex Miras (Clinical Professor of Medicine, Ulster University) and Dr Shazli Azmi (Consultant Diabetes and Endocrinology, Manchester University Hospital NHS Foundation Trust) who provided feedback on a draft version of the report, Marty Chaplin who reviewed and provided feedback on draft versions of the clinical and statistical sections of the report, Sam Bryning who quality checked cost-effectiveness results and Vincy Huang who reviewed and provided feedback on a draft version of the report and contributed to finalising the report.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Fleeman N, Mahon J, Beale S, Hill R, Stainthorpe, A Dundar Y, Marsden A, le Roux C. Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity [ID6441]: A Single Technology Appraisal. Liverpool Reviews and Implementation Group, 2025.

Contributions of authors: Please refer to the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals.

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Carel le Roux	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CHD	coronary heart disease
CKD	chronic kidney disease
CPRD	Clinical Practice Research Datalink
CS	company submission
CV	cardiovascular
CVD	cardiovascular disease
CVOTs	cardiovascular outcome trials
DPB	diastolic blood pressure
EAC	event adjudication committee
EAG	External Assessment Group
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQol-5 Dimensions
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
eCVD	established cardiovascular disease
EAG	External Assessment Group
ETD	estimated treatment difference
ETR	estimated treatment ratio
FAS	full analysis set
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	glycated haemoglobin
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
hsCRP	high-sensitivity C-reactive protein
ICER	incremental cost-effectiveness ratio
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire clinical summary score
K-M	Kaplan Meier
MACE	major adverse cardiovascular event
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
mmHg	millimetres of mercury
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
PAD	peripheral arterial disease
QALY	quality-adjusted life year
SAE	serious adverse event
SBP	systolic blood pressure
T1D	type 1 diabetes
T2D	type 2 diabetes
UK	United Kingdom

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG'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 economic model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of EAG's key issues

An overview of the EAG's key issues is presented in Table A.

Table A Summary of the EAG's key issues

ID6441	Summary of issue	Impact on results	Report sections
Issue 1	The SELECT trial excluded patients with diabetes at baseline	Unknown	2.3.2.1, 3.2.2, 3.3.7, 3.7, 4.2.3, 5.1.2.2 (Scenario analysis 5) and 5.5
Issue 2	The SELECT trial excluded patients with recent CV events	Unknown	2.3.2.2, 3.2.2,3.7,4.2.3, 5.1.2.2 (Scenario analysis 7) and 5.5
Issue 3	Generalisability of the SELECT trial to NHS practice	Low	3.2.3.2, 3.3.3.1, 3.7, 5.1.2.2 (Scenario analysis 6) and 5.5
Issue 4	The costs of semaglutide are uncertain	Unknown	4.2.7.1
Issue 5	The company included non-statistically significant results in the economic model	Medium	3.3.2.1, 4.2.5, 5.2.2, and 5.2.3 (R1)
Issue 6	The company unnecessarily adjusted CV risk in the model at the end of the SELECT trial period by diabetes status and whether patients were still receiving semaglutide treatment	Large	4.2.5, 5.2.2 and 5.2.3 (R2 and R3)

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the removal of CV events that were not statistically significantly different in

the SELECT trial and the removal of CV event hazard modifiers for diabetes and stopping semaglutide treatment.

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.

Overall, the technology is modelled to affect QALYs by:

- reducing non-fatal CV events
- increasing survival.

Overall, the technology is modelled to affect costs by:

- increasing treatment costs for people with eCVD
- reducing CV events.

The modelling assumptions that have the greatest effect on the ICER are:

- the reduction in CV events assumed for people treated with semaglutide
- the underlying CV risk of the eCVD population
- the semaglutide discontinuation rate.

1.3 EAG's key issues

The EAG's key issues are summarised in the tables in Sections 1.3.1 to 1.3.6.

1.3.1 Issue 1 The SELECT trial excluded patients with diabetes

Report sections	2.3.2.1, 3.2.2, 3.3.7, 3.7, 4.2.3, 5.1.2.2 (Scenario analysis 5) and 5.5
Description of issue and why the EAG has identified it as important	The SELECT trial excluded patients with diabetes (T1D or T2D). These patients are not excluded from the indication for semaglutide for adults with eCVD who are overweight or obese (BMI ≥27 kg/m^2). The company presented results from analyses of secondary endpoints and safety and tolerability data from the STEP-HFpEF DM trial MACE endpoints in four CVOTs. The company conducted a cost effectiveness scenario analysis by applying SELECT trial efficacy data to baseline risk for people with T2D in the CPRD population. The results suggest patients with T2D benefit from treatment with semaglutide. However: • patients in the STEP-HFpEF DM trial had HF but were not required to have a previous CV event • patients in the four CVOTs received different doses of semaglutide and/or mode of administration, were not required to have BMI ≥27 kg/m^2 and were not required to have had a previous CV event • the cost effectiveness scenario analysis may be biased since efficacy results based on the trial population are modelled to the CPRD population which has patient characteristics that differ to the trial.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	The company scenario analysis would suggest that the cost effectiveness of semaglutide in a T2D population would be similar to the cost effectiveness in a non-diabetic population. However, this is based on an assumption that semaglutide is similarly effective at reducing CV risk in a T2D population and non-diabetic population.
Could any additional evidence or analyses be provided to resolve this key issue?	No. The EAG considers the results presented by the company from the STEP-HFpEF DM trial, four CVOTs and cost effectiveness scenario analyses to be the best available evidence, despite the limitations of this evidence. The EAG highlights evidence is lacking for patients with T1D as these patients are typically excluded from CV trials.

BMI=body mass index; CV=cardiovascular; CVOTs=cardiovascular outcome trials; eCVD=established cardiovascular disease; MACE= major adverse cardiovascular event; T1D=type 1 diabetes; T2D=type 2 diabetes

1.3.2 Issue 2 The SELECT trial excluded patients with recent CV events

Report sections	2.3.2.2, 3.2.2,3.7,4.2.3, 5.1.2.2 (Scenario analysis 7) and 5.5
Description of issue and why the EAG has identified it as important	The SELECT trial excluded patients with recent CV events (within past 60 days prior to the day of screening). These patients are not excluded from the indication for semaglutide for adults with eCVD who are overweight or obese (BMI ≥27 kg/m^2). The company explained that: • the design of CVOTs follows global standards and excluding patients with recent MACE is common practice • including participants with recent CV events may confound and complicate the determination of primary and secondary endpoints related to these outcomes. The company conducted a cost effectiveness scenario analysis by applying SELECT trial efficacy data to baseline risk for people with recent CV events in the CPRD population. The cost effectiveness scenario analysis may be biased since efficacy results based on the trial population are modelled to the CPRD population which has patient characteristics that differ to the trial.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	The company scenario analysis of an incident eCVD population suggest that the cost effectiveness of semaglutide would be similar to the cost effectiveness in a prevalent eCVD population. However, this is based on an assumption that semaglutide is similarly effective regardless of the length of time from the initial CV event.
Could any additional evidence or analyses be provided to resolve this key issue?	No. The EAG considers the cost effectiveness scenario analyses to be the best available evidence, despite the limitations of this evidence.

BMI=body mass index; CPRD=Clinical Practice Research Datalink; CV=cardiovascular; CVOTs=cardiovascular outcome trials; eCVD=established cardiovascular disease; MACE= major adverse cardiovascular event

1.3.3 Issue 3 Generalisability of the SELECT trial to NHS practice

Report section	3.2.3.2, 3.3.3.1, 3.7, 5.1.2.2 (Scenario analysis 6) and 5.5
Description of issue and why the EAG has identified it as important	There were differences in baseline age, MI, stroke and PAD events in the SELECT trial compared with a "SELECT-like" population from real world data of NHS practice in England (CPRD analysis). This could result in differences in treatment effects in a UK population to that reported in the SELECT trial FAS population. The company conducted a cost effectiveness scenario analysis by applying SELECT trial efficacy data to baseline risk for people in the CPRD population.
What alternative approach has the EAG suggested?	The EAG considered the SELECT trial subgroup results for MACE by age, MI, stroke and PAD events at baseline as well as results for MACE for the Europe and the UK SELECT trial subgroups (requested at clarification).
What is the expected effect on the cost-effectiveness estimates?	The company scenario analysis of a prevalent eCVD population that had characteristics in line with characteristics seen in NHS practice suggest that the cost effectiveness of semaglutide would be similar to the cost effectiveness in the company base case.
Could any additional evidence or analyses be provided to resolve this key issue?	No. SELECT trial subgroup results considered by the EAG show treatment effects that are mostly at least equal to overall trial FAS population.

CPRD=Clinical Practice Research Datalink; eCVD=established cardiovascular disease; FAS=full analysis set; MACE= major adverse cardiovascular event; MI=myocardial infarction; PAD=peripheral arterial disease

1.3.4 Issue 4 The costs of semaglutide are uncertain

Report section	4.2.7.1
Description of issue and why the EAG has identified it as important	The costs of semaglutide are dependent on treatment discontinuation, which is modelled by the company at a constant rate of [redacted] per cycle throughout the modelled time horizon for patients on all dose levels, calculated from median time to treatment discontinuation ([redacted]) in the SELECT trial. It is unclear how well this constant discontinuation rate reflects semaglutide discontinuation over the whole of the SELECT trial time horizon and whether this discontinuation rate would continue after the end of the SELECT trial time horizon. If the modelled discontinuation is different to that seen in the SELECT trial, this could mean the costs of semaglutide treatment in the model are biased.
What alternative approach has the EAG suggested?	The EAG considers it would have been informative for the company to have shown the modelled time on treatment for patients receiving semaglutide compared to that seen for patients receiving semaglutide in the SELECT trial.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
Could any additional evidence or analyses be provided to resolve this key issue?	Yes. The company could provide evidence on modelled time on treatment versus time on treatment for patients in the SELECT trial.

1.3.5 Issue 5 The company included non-statistically significant results in the economic model

Report section	3.3.2.1, 4.2.5, 5.2.2, and 5.2.3 (R1)
Description of issue and why the EAG has identified it as important	The company included CV events in the economic model where no statistically significant differences were observed between patients treated with semaglutide and standard of care in the SELECT trial. Inclusion of non-statistically significant CV events in the model means that the ICER per QALY gained for semaglutide may have been underestimated.
What alternative approach has the EAG suggested?	The EAG has only modelled CV events where a statistically significant difference was observed in the SELECT trial.
What is the expected effect on the cost-effectiveness estimates?	Including only statistically significant differences in CV events increased the ICER per QALY gain for semaglutide.
Could any additional evidence or analyses be provided to resolve this key issue?	No.

CV=cardiovascular; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year

1.3.6 Issue 6 The company unnecessarily adjusted CV risk in the model at the end of the SELECT trial period by diabetes status and whether patients were still receiving semaglutide treatment

Report section	4.2.5, 5.2.2 and 5.2.3 (R2 and R3)
Description of issue and why the EAG has identified it as important	The company adjusted the risk of CV events in the economic model at the end of the SELECT trial period based upon whether patients have developed diabetes and/or are still receiving treatment with semaglutide. The EAG considers that it was unnecessary to adjust the risk of CV events at the end of the SELECT trial period.
What alternative approach has the EAG suggested?	The EAG has removed the CV risk adjustments for developing diabetes and stopping treatment with semaglutide.
What is the expected effect on the cost-effectiveness estimates?	The EAG amendment reduces the ICER per QALY gained.
Could any additional evidence or analyses be provided to resolve this key issue?	No.

CV=cardiovascular; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year

1.4 Secondary issues identified by the EAG

Secondary issues identified by the EAG are presented in the table in Section 1.4.

1.4.1 Issue 7 The company included AE costs and AE utility losses in the economic model

Report section	4.2.7.4, 5.2.2 and 5.2.3 (R5)
Description of issue and why the EAG has identified it as important	The company included AE rates from the placebo arm of the SELECT trial, which the EAG considers to be unusual. Further, there was not a statistically significant difference in the majority of SAE rates between semaglutide and placebo in the SELECT trial.
What alternative approach has the EAG suggested?	The EAG has removed AE costs and AE disutilities from the economic model.
What is the expected effect on the cost-effectiveness estimates?	The EAG amendment increases the ICER per QALY gained.
Could any additional evidence or analyses be provided to resolve this key issue?	No.

AE-adverse event; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; SAE=serious adverse event

1.5 Company's modelling errors identified by the EAG

The EAG identified one algorithmic error that affected QALY estimates of the economic model if the time horizon was shortened (Section 5.2.1). This error was corrected by the EAG but did not affect base case results or any of the sensitivity or scenario analyses undertaken by the company.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table B Summary of EAG's preferred assumptions and deterministic ICERs, semaglutide versus established clinical management (CAA price for semaglutide)

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base case	[redacted]	[redacted]	£14,702
Key issue 5: Only modelled CV events where hazard rates were statistically significantly different for patients treated with semaglutide or placebo in the SELECT trial	[redacted]	[redacted]	£20,071
Key issue 6: Diabetes is not included as a CV event risk modifier	[redacted]	[redacted]	£16,238
Key issue 6: Semaglutide treatment discontinuation does not remove the benefit of semaglutide in reducing CV event risk	[redacted]	[redacted]	£6,442
Key issue 7: AE costs and AE utility losses were not included in the economic model.	[redacted]	[redacted]	£14,730
EAG's preferred base-case deterministic	[redacted]	[redacted]	£9,110
EAG's preferred base-case probabilistic	[redacted]	[redacted]	£9,189

AE=adverse event; CAA=commercial access agreement; CV=cardiovascular

1.7 Outline of confidential comparator or subsequent treatment prices

At the request of NICE, the CAA price for semaglutide have been used in all analyses.

2 BACKGROUND

This External Assessment Group (EAG) report presents the EAG critique of the company submission (CS) for semaglutide (Wegovy®) for preventing major cardiovascular (CV) events in people with cardiovascular disease (CVD) and with overweight or obesity.

2.1 Critique of the company's description of underlying health problem

The company provided a description of CVD in the CS (summary box, p12) and Section 1.1, Sections 1.3.1 to 1.3.3 and Section 1.3.5). As highlighted by the company:

- CVD is a general term used to describe a group of serious, chronic conditions affecting the heart and blood vessels, including coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease (PAD)[1] (CS, p12, p20)
- CVD is the second most common cause of death and biggest cause of premature disability in people with overweight or obesity in the UK[2] (CS, p12, p25)
- CVD can lead to severe acute events such as myocardial infarction (MI) and strokes (CS, p12)
- CV events lead to significant chronic impairments in quality of life caused by long-lasting functional impairments and psychosocial limitations[3] (CS, p12, p28).

The CS focused on the prevention of major CV events in people with established CVD (eCVD) and overweight or obesity where eCVD is defined (CS, p20) as at least one of the following: prior MI, prior stroke or symptomatic PAD. This is the definition of eCVD used to define the eligible population in the SELECT trial,[4] the primary source of evidence in the CS. The company highlighted:

- most people (70%)[5] survive an MI, however MI survivors are at high risk of experiencing a subsequent MI or other CV event[6] and/or develop heart failure (HF); MI remains the most common cause of HF (CS, p24)
- most people survive a stroke (proportion not cited) but recovery is prolonged and most people remain disabled or experience neurological deficits[7] (CS, p22)
- most people with PAD (proportion not cited) have co-existence of cerebrovascular disease or CHD, which also increases the mortality rate, due to a higher risk of MI and stroke[8-10] (CS, p22)
- the highest risk of subsequent CV events for people with eCVD is in the 12 months following the first event, decreasing thereafter[11-14] (CS, p12, p24, p41)
- people with a raised BMI[15,16] and/or diabetes[17] are over-represented in eCVD (CS, p24).

EAG comment

The EAG considers the company's description of the underlying health problem in the CS is relevant and in line with current biomedical understanding of CVD.

2.2 Critique of the company's overview of current service provision

The company presented an overview of current service provision in the CS, Sections 1.4 to 1.6. The company identified eight guidelines[18-25] including three NICE guidelines[18,19,22] relevant to the secondary prevention of CV events (CS, Table 4). Common elements across guidelines include lipid modification therapy (using statins), antiplatelet therapies and lifestyle changes (such as diet, physical activity and weight management). CV medications are indicated along with lifestyle changes (including advice on diet and physical exercise).

The company highlighted (CS, p31) that there is not one standardised pathway for the secondary prevention of CV events. Care pathways include primary and secondary care, formal cardiac rehabilitation programmes, cardiology outpatient clinics as well as lipid management and hypertension services. These services support people to manage risks to reduce future CV events, improve or support function and improve outcomes.

A CVD risk reduction pathway without semaglutide is presented in CS Figure 1. The company's proposed treatment pathway, with the inclusion of semaglutide, is presented in CS Figure 2. The company highlighted (CS, p42) that semaglutide would not displace any of the current treatments for secondary prevention of CV events.

EAG comment

The EAG considers that the company's overview of current service provision is an accurate description of NHS practice.

2.3 Critique of the company's definition of decision problem

A summary of the final scope issued by NICE and the decision problem addressed by the company is presented in Table 1. Additional EAG comment is provided in Sections 2.3.1 to 2.4.

Table 1 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
Intervention	Semaglutide (Wegovy®)	As per scope	The intervention in this appraisal is specific to semaglutide marketed as Wegovy® not Ozempic® or Rybelsus® (which are both used in clinical practice for T2D). The intervention was provided in addition to SoC. The intervention considered in the CS aligns with the intervention in the final scope issued by NICE. See Section 2.3.1 for more information.
Population	Adults with eCVD (previous myocardial infarction, stroke or symptomatic peripheral arterial disease) and a BMI of at least 27 kg/m^2	As per scope	The SELECT trial excluded some patients with eCVD who would be eligible for treatment according to the indication for CV risk reduction for people with eCVD (CS, Table 8), namely: • people with diabetes (HbA1c ≥48 mmol/mol) at screening • people who had a recent CV event (within past 60 days prior to the day of screening). The company attempted to address these evidence gaps from other sources of evidence. See Section 2.3.2 for more information.
Subgroups	If the evidence allows the following subgroups will be considered: • People with BMI > 35	Clinical effectiveness: As per scope, except for subgroups according to calculated baseline risk of CV events (baseline risk of CV events was not calculated for individuals	The company used the SELECT trial data to assess subgroup effects (CS, Section 2.8). The EAG requested additional subgroup

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
	• People with previous myocardial infarction • People with previous stroke • People with symptomatic peripheral arterial disease • People with HF • People with chronic kidney disease • Subgroups according to calculated baseline risk of CV events	in SELECT and the study did not report findings stratified by risk) Cost effectiveness: As per scope (subgroups according to calculated baseline risk of CV events is addressed through scenario analyses in the economic model)	analyses for SELECT trial UK patients (for the SELECT trial primary endpoint).
Comparator(s)	Established clinical management for the prevention of CV events without semaglutide	As per scope	The comparator was provided in addition to SoC. The comparator considered in the CS aligns with the comparator described in the final scope issued by NICE.
Outcomes	The outcome measures to be considered include: • Heart function • Non-fatal stroke • Non-fatal myocardial infarction • Symptoms of HF • Hospitalisation for HF • All-cause hospitalisation • Mortality • CV mortality • Kidney function • Development of diabetes • Treatment discontinuation	As per scope, except for “heart function”. The clinical studies identified and included in the CS did not include formal measures of heart function (such as ejection fraction) as outcomes	The outcomes presented in the CS align with the outcomes listed in the final scope issued by NICE. The SELECT trial primary endpoint was time from randomisation to first occurrence of MACE, a composite endpoint consisting of CV death, non-fatal MI, or non-fatal stroke. Clinical advice to the EAG is that all endpoints reported in the SELECT trial and CS provide evidence for outcomes relevant to NHS practice.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
	• Health-related quality of life • Adverse effects of treatment		
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 and cost of biosimilar and generic products should be taken into account.	As per scope	Economic analysis in the CS is per the NICE reference case. The company generated cost effectiveness results using the CAA price for semaglutide. At the request of NICE, the EAG generated cost effectiveness results using the list prices (for the results of the analyses included in initial EAG reports submitted to NICE) and then again using the CAA prices (which were used for the results of analyses presented in this report).

BMI=body mass index; CAA=commercial access agreement; CV=cardiovascular; CVD=cardiovascular disease; eCVD=established cardiovascular disease; HF=heart failure; MI=myocardial infarction; UK=United Kingdom

2.3.1 Intervention

Full information about the intervention being appraised in this STA is presented in the CS (CS, Table 2). In summary:

- semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) administered by subcutaneous injection once at any time of the day, with or without meals
- the relevant indication for semaglutide for this STA is Wegovy® "as an adjunct to a reduced-calorie diet and increased physical activity to reduce the risk of major adverse CV events (CV death, non-fatal myocardial infarction, or non-fatal stroke) in adults with eCVD and either obesity or overweight (BMI ≥27 kg/m^2)"[26]
- in order to reduce the likelihood of gastrointestinal symptoms, semaglutide should be escalated over a 16-week period to a maintenance dose of 2.4mg once weekly; dose escalations occur after 4 weeks of semaglutide at 0.24 mg, followed by 0.5 mg, 1.0 mg, 1.7 mg and finally 2.4 mg at Week 16.

EAG comment

The EAG highlights that the intervention in this appraisal is specific to semaglutide marketed as Wegovy® (subcutaneous semaglutide 2.4mg once weekly) not Ozempic® (subcutaneous semaglutide indicated for insufficiently controlled type 2 diabetes [T2D] and with a different dose escalation and maintenance dose) or Rybelsus® (once daily oral semaglutide indicated for insufficiently controlled T2D).

The EAG notes that semaglutide, marketed as Wegovy®, is currently recommended by NICE (TA875[27]) for weight management and is provided within a specialist weight management service providing multidisciplinary management of overweight or obesity. In this appraisal, semaglutide is positioned as an intervention to prevent major adverse CV events (MACE) for people with eCVD and is expected to be provided within the context of secondary prevention for CVD, as described in Section 2.2.

The EAG notes that in NICE guidance TA875, people eligible for treatment must be overweight or obese with ≥1 weight-related comorbidity. Overweight or obesity is more conservatively defined in TA875 (BMI ≥35.0 kg/m^2 or 30 kg/m^2 to 34.9 kg/m^2 if a person meets criteria outlined in NG246[28]) than in the SELECT trial and indication for eCVD (BMI ≥ 27 kg/m^2).

The primary source of evidence presented in the CS is the SELECT trial,[4] a large (N=17,604) phase 3, double-blind, placebo-controlled, global, multicentre randomised controlled trial (RCT). Evidence from this trial also informed the semaglutide marketing authorisation[26] application which the Medicines and Healthcare products Regulatory Agency (MHRA) approved in July 2024 under its accelerated International Recognition

Procedure.[29]

The EAG also highlights that in TA875, it is recommended that semaglutide is used for a maximum of 2 years. As an intervention to prevent MACE for people with eCVD, there are no stopping rules in the SELECT trial nor has the company implemented a stopping rule in the economic model for this STA; this aligns with clinical advice to the company and EAG regarding expected NHS practice for semaglutide for preventing major CV events in people with eCVD.

2.3.2 Population

The population in the primary source of evidence (the SELECT trial) excluded some people who would be eligible for treatment according to the indication for semaglutide for CV risk reduction for people with eCVD, namely:

- people who had a recent CV event (within past 60 days prior to the day of screening)
- people with diabetes (HbA1c ≥48 mmol/mol) at screening.

EAG comment

The company attempted to address these evidence gaps from other sources of evidence (see Sections 2.3.2.1 to 2.3.2.2).

2.3.2.1 People with diabetes at screening

Supportive evidence[30,31] of clinical effectiveness is provided by the company from the STEP-HFpEF DM[31] trial for people with HF with preserved ejection fraction (HFpEF) and with T2D.

EAG comment

The primary objective of the STEP-HFpEF DM[31] trial was to reduce symptoms and physical limitations associated with HF with preserved ejection fraction (HFpEF) and obesity and to improve exercise function, and this trial did not include MACE as an endpoint. Therefore, the company also presented evidence from four CV outcome trials (CVOTs)[32-35] in which patients had T2D (see Section 3.3.7). However, it should be noted that patients with type 1 diabetes (T1D) were excluded and T2D patients were not required to have BMI ≥27 kg/m^2 or have had previous CV events. Patients in these trials also received Ozempic® or Rybelsus® and not Wegovy®.

The EAG further notes that it is stated in the MHRA Public Assessment Report[36] that, as trials of “semaglutide in diabetic patients (with a large proportion overweight or

obesity) have also provided evidence of beneficial effects … it is reasonable to not specifically mention non-diabetic patients in the indication." Furthermore, the EAG also notes that for the economic analyses, scenario analysis was conducted by applying SELECT trial efficacy data to baseline risk of people with T2D in a real-world UK cohort, the Clinical Practice Research Datalink (CPRD) (see Section 4.2.3 and 5.1.2.2 [Table 14, Scenario 5]).

2.3.2.2 People who had a recent CV event

In response to clarification question A1, the company highlighted that exclusion of participants with recent CV events is not reflected in the indication for semaglutide for CV risk reduction for people with eCVD. The company explained that patients with recent CV events were excluded from the SELECT trial because:

- the design of CVOTs follows global standards and excluding patients with recent MACE is common practice
- including participants with recent CV events may confound and complicate the determination of primary and secondary endpoints related to these outcomes.

EAG comment

The EAG considers the explanation to be reasonable. The EAG also notes that for the economic analyses, scenario analysis was conducted by applying SELECT trial efficacy data to baseline risk for people with recent CV events in a real-world UK cohort, the CPRD) (see Section 4.2.3 and 5.1.2.2 [Table 14, Scenario 7]).

2.4 Special considerations including issues related to equity or equality

The company highlighted (CS, p44) that CVD disproportionately affects already disadvantaged populations, widening existing health inequalities[15] including:

- people experiencing socioeconomic deprivation[37]
- people of South Asian or sub-Saharan African ethnic origin[38,39]
- people with experience of severe mental illness.[40]

In addition, men are almost twice as likely to develop CHD than women but women are often underdiagnosed for MIs and women often have worse outcomes than men.[10,37,41,42]

EAG comment

The EAG considers this description to be relevant, sufficiently referenced and to align with current biomedical and sociobiological understanding. The EAG notes that the

company has not made specific claims in relation to semaglutide addressing these inequalities other than offering an addition to CVD prevention pathways. Clinical advice to the EAG is that access to high quality care including lifestyle management and rehabilitation programmes may also be subject to inequalities. For example, over 50% of those indicated for cardiac rehabilitation do not access programmes.[43] It is possible that the potential of semaglutide to reduce risk of CV events may not be subject to the same accessibility and maintenance challenges given it could be provided in combination with a relatively low level of supportive advice on diet and physical activity.[44]

3 CLINICAL EFFECTIVENESS

This section includes a summary and critique of the clinical effectiveness evidence included in the CS. Section 3.1 focuses on the company's review methods. Sections 3.2 and 3.3 include a critique of the included studies and clinical effectiveness analyses. Sections 3.4 to 3.5 highlight why the company did not present any indirect comparisons. Additional work carried out by the EAG is presented in Section 3.6. Section 3.7 contains the EAG's clinical effectiveness conclusions.

3.1 Critique of the methods of review

As stated in the CS (Section 2.1), the objective of the company's systematic literature review (SLR) was to identify efficacy, safety, and health-related quality of life data from clinical trials investigating semaglutide 2.4mg for the treatment of adults (≥18 years) with eCVD and either overweight or obesity (BMI≥27 kg/m^2).

EAG comment

The company's SLR searches were comprehensive and were updated <6 months before the company's evidence submission to NICE (initially conducted the SLR search on 18 September 2023 with an update on 7 May 2025). An assessment of the extent to which the company's SLR was conducted in accordance with the EAG's in-house systematic review checklist is summarised in Table 2. The EAG considers that the company's SLR methods were appropriate.

Table 2 EAG appraisal of the company's SLR methods (clinical effectiveness)

Review process	EAG response	EAG comment
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix B, Table 8
Were appropriate sources searched?	Yes	See CS Appendix B (B.1, B.1.1, B.1.2) An appropriate range of biomedical databases were searched; handsearching of conference proceedings, HTA submissions and clinical trial registries was conducted.
Was the timespan of the searches appropriate?	Yes	See CS Appendix B.1 and B.1.1. Relevant databases were searched from inception. The May 2025 searches updated an original SLR. Sufficient time overlap with original searches was included in the updated searches.
Were appropriate search terms used?	Yes	See CS, Appendix B.1 Table 1, Table 2 to Table 4, and Table 5 to Table 7 for original

Review process	EAG response	EAG comment
		and updated SLR search strategies.
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix B.1.3, Table 8 Limiting the search to RCTs is considered appropriate.
Was study selection applied by two or more reviewers independently?	Yes	See CS, Appendix B.1.4
Was data extracted by two or more reviewers independently?	Partly	See CS, Appendix B.1.5 One reviewer extracted data and these data were checked by a second reviewer.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	See CS, Appendix B.1.6, Table 12 Quality assessment was based on criteria presented in the NICE process and methods guide [PMG24] guide,[45] but with the omission of an item on whether conflicts of interest had been presented. The primary SELECT trial publication (Lincoff 2023[4]) includes authors' declarations of interest.
Was the quality assessment conducted by two or more reviewers independently?	Partly	See CS, Appendix B.1.6 One reviewer quality assessed the included trials, and these assessments were checked by a second reviewer.
Were attempts to synthesise evidence appropriate?	Yes	See CS, Sections 2.9 and 2.10 A single trial (SELECT) is the most relevant source of evidence and that combining data from other studies would not reduce uncertainty as there is also considerable heterogeneity across other studies (including population, intervention and outcomes assessed). Adverse effects are reported from three semaglutide RCTs (see CS, Section 2.11).

BMI=Body Mass Index; CVD=cardiovascular disease; ITC=Indirect Treatment Comparison; RCTs=randomised controlled trials; SLR=Systematic Literature Review
Source: LRiG in-house checklist

3.2 Critique of the methods of the trials of the technology of interest

3.2.1 Trials included in the review

The company's SLR identified 30 records relating to three unique phase 3 RCTs:[4,30,31]

- 21 records reported SELECT trial data (primary trial publication: Lincoff 2023[4])
- 7 records reported STEP-HFpEF trial data (primary trial publication: Kosiborod 2023[30])
- 3 records reported STEP-HFpEF DM trial data (primary trial publication: Kosiborod 2024[31]).

Data from the SELECT trial form the primary source of clinical effectiveness evidence in the CS since the included population aligned with that specified in the final scope

issued by NICE. All patients had had a previous CV event. The primary objective of the trial was to reduce MACE. SELECT trial data were also used to inform the choice of clinical parameters in the economic model.

The STEP-HFpEF and STEP-HFpEF DM trials did not include patients with a BMI <30kg/m^2. The primary objective of the intervention (semaglutide) in these two trials was to reduce symptoms and physical limitations associated with HFpEF and to improve exercise function, not to reduce CV events. Hence these trials did not include MACE (or components of MACE) as primary or secondary endpoints. Data from the STEP-HFpEF and STEP-HFpEF DM trials are therefore presented in the CS as supportive evidence.

In addition to the three clinical trials, the company presented information from a Clinical Practice Research Datalink (CPRD) analysis[46] as well as four other CVOTs[32-35] which were excluded from the SLR. The CPRD was included to enable comparison of SELECT trial characteristics with real-world data from England (see Section 3.2.3.2) and also to inform the selection of the distributions used in the company economic analyses (see Sections 4.2.3 and 4.2.5). The company stated that the four CVOTs[32-35] were excluded from the SLR because "...the indications, populations studied, semaglutide doses and/or primary outcomes differ from those in the decision problem" (CS, p48). However, these trials did measure MACE for patients with T2D (see Section 3.3.7).

EAG comment

The EAG agrees with the company that the most relevant trial for addressing the company's decision problem is the SELECT trial which had important differences in terms of trial and patient characteristics to the STEP-HFpEF and STEP-HFpEF DM trials and, consequently, concomitant medication (see Sections 3.2.2 to 3.2.4). The EAG highlights that the SELECT trial is also a substantially larger trial (N=17,604) than the STEP-HFpEF and STEP-HFpEF DM trials (N=529 and N=616, respectively).

Evidence from the four CVOTs provides evidence of the impact of semaglutide (both subcutaneous and oral) on MACE for patients with T2D, albeit these patients were not required to have BMI ≥27 kg/m^2 or have had previous CV events and they also received different doses/modes of administration of semaglutide.

3.2.2 Trial characteristics

Key characteristics of the trials are presented in Table 3.

In all three trials, patients received standard of care as well as semaglutide or placebo. The company highlighted (CS, p113) that unlike in the STEP-HFpEF and STEP-HFpEF DM trials, standard of care in the SELECT trial "included management of CV risk factors [including concomitant medications (see Section 3.2.4)] and individualised healthy lifestyle counselling, but no specific lifestyle intervention". The company described (CS, p55) that in the SELECT trial, leaflets providing healthy lifestyle advice were offered to patients consistent with existing local standard of care (related to diet, physical exercise, smoking and alcohol consumption) for adults with eCVD and BMI ≥27 kg/m^2. Uptake of leaflets offered to all patients in both arms of the SELECT trial was 99.9% (response to clarification question A2).

EAG comment

Clinical advice to the company[47] and the EAG is that the absence of a specific lifestyle intervention is representative of NHS practice. Clinical advice to the EAG is that NHS patients are given information (including leaflets) and counselled by a member of a multidisciplinary team. Clinical advice to the EAG is that this is the same approach as used in the SELECT trial.

It is not known whether the intensity and uptake of counselling in the SELECT trial differed between individual participants and if this influenced outcomes. However, the trial's double-blind design and similar baseline characteristics between arms (see Section 3.2.3) is expected to ensure that any variation was balanced across treatment arms.

Similarly, it is unclear to what extent patients followed a reduced calorie diet and increased physical activity and how this may have impacted trial outcomes. However, there is no reason to suggest there were systematic differences between trial arms that could have biased results

The EAG highlights that given all patients in the STEP-HFpEF and STEP-HFpEF DM trials had HF, some patients would likely have had a previous CV event. However, data on prior CV events was not reported in these trials. Although the STEP-HFpEF and STEP-HFpEF DM trials excluded patients with a BMI <30kg/m^2, patients with a BMI ≥30kg/m^2 would be eligible for treatment with semaglutide for preventing major CV events. However, as previously highlighted (Sections 2.3.2.1 and 3.2.1), the primary objective of the STEP-HFpEF and STEP-HFpEF DM trials was not to reduce CV events and MACE was therefore not an endpoint in these trials.

Table 3 Trials included in the company's SLR

	SELECT	STEP-HFpEF	STEP-HFpEF DM
Role in this evaluation	Primary source of clinical effectiveness evidence	Supportive evidence	Supportive evidence
Study aim	To reduce the risk of MACE	To reduce symptoms and physical limitations and to improve exercise function	To reduce symptoms and physical limitations and to improve exercise function
Study type	Randomised, double-blind, placebo-controlled, multinational, multi-centre trial	Randomised, double-blind, placebo-controlled, multinational, multi-centre trial	Randomised, double-blind, placebo-controlled, multinational, multi-centre trial
Patient group	People with BMI ≥27 kg/m^2 aged ≥45 years with eCVD (≥1 prior MI, prior stroke or symptomatic PAD)	Adult patients aged ≥18 years with HFpEF and a BMI of ≥30 kg/m2 but no history of diabetes	Adult patients aged ≥18 years with HFpEF and a BMI of ≥30 kg/m2 and T2D

Key inclusion criteria	• Adults aged ≥45 years at the time of signing informed consent
	• BMI ≥27kg/m^2
	• Established CVD as evidenced by at least one of the following:
	  ○ prior MI
	  ○ prior stroke (ischaemic or haemorrhagic)
	  ○ symptomatic PAD
		• Persons aged ≥18 years with a LVEF of ≥45
		• BMI ≥30kg/m^2
		• Class II, III, or IV HF (NYHA)
		• KCCQ-CSS <90 points
		• 6-minute walk distance of at least 100m
		• At least one of the following findings:
		  ○ elevated left ventricular filling pressures
		  ○ elevated natriuretic peptide levels plus echocardiographic abnormalities
		  ○ hospitalisation for HF in the 12 months before screening plus ongoing treatment with diuretics or echocardiographic abnormalities
			• Persons aged ≥18 years with a LVEF of ≥45
			• BMI ≥30kg/m^2
			• Class II, III, or IV HF (NYHA)
			• KCCQ-CSS <90 points
			• 6-minute walk distance of at least 100m
			• At least one of the following findings:
			  ○ elevated left ventricular filling pressures
			  ○ elevated natriuretic peptide levels plus echocardiographic abnormalities
			  ○ hospitalisation for HF in the 12 months before screening plus ongoing treatment with diuretics or echocardiographic abnormalities
			• Participants were required to have received a diagnosis of T2D at least 90 days before screening and to have a glycated haemoglobin level of ≤10%

	SELECT	STEP-HFpEF	STEP-HFpEF DM
Key exclusion criteria	• MI, stroke, or hospitalisation for unstable angina or TIA within past 60 days prior to the day of screening • Presently classified as class IV HF (NYHA) • HbA1c ≥48 mmol/mol (6.5%) as measured by the central laboratory at screening • History of T1D or T2D (history of gestational diabetes was allowed) • Treatment with glucose-lowering agent(s) or GLP-1 RA within 90 days before screening	• Patient-reported change in body weight of >5kg within 90 days before screening • History of diabetes (glycated hemoglobin level of ≥6.5% based on medical record data within 3 months before screening or on a local laboratory value at the time of screening; patients were also excluded if they had a known medical history of diabetes)	• Patient-reported change in body weight of >5kg within 90 days before screening • History of T1D • Use of a GLP-1 RA within 90 days before screening • Uncontrolled diabetic retinopathy
Intervention	SC semaglutide, up to target dose of target dose of 2.4mg once-weekly plus SoC (n=8803)	SC semaglutide at a dose of 2.4mg once weekly plus SoC (n=263)	SC semaglutide at a dose of 2.4mg once weekly plus SoC (n=310)
Comparator	Placebo plus SoC (n=8801)	Placebo plus SoC (n=266)	Placebo plus SoC (n=306)
Duration	Event driven, with trial closure occurring when the targeted number (≥1225) of primary endpoint events was reached, median follow-up of [redacted] months	Endpoints evaluated after 52 weeks	Endpoints evaluated after 52 weeks
Dates	October 2018 to June 2023	March 2021 to March 2022	June 2021 to August 2022
Location	804 sites in 41 countries (including the UK)	96 sites in 13 countries (including the UK)	108 sites in 16 countries (including the UK)
Primary endpoint	Time from randomisation to first occurrence of MACE (composite endpoint consisting of CV death, non-fatal MI, or non-fatal stroke)	Change from baseline in the KCCQ-CSS and the change in body weight (dual primary outcome)	Change from baseline in the KCCQ-CSS and the change in body weight (dual primary outcome)
Note		MACE endpoint was not a prespecified outcome in the study	MACE endpoint was not a prespecified outcome in the study

BMI=body mass index; CV=cardiovascular; CVD=cardiovascular disease; GLP-1 RA= glucagon-like peptide-1 receptor agonist; HbA1c=glycated haemoglobin; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire clinical summary score; LVEF=left ventricular ejection fraction; MACE=major adverse CV event; MHRA=Medicines and Healthcare products Regulatory Agency; MI=myocardial infarction; NYHA=New York Heart Association; PAD=peripheral arterial disease; SC=subcutaneous; SoC=standard of care; SLR=systematic literature review; T1D=type 1 diabetes; T2D=type 2 diabetes; TIA=transient ischaemic attack
Source: CS, Sections 2.3.1 to 2.3.3 and 2.6.1.2, Appendix B, Appendix J, Kosiborod 2023;[30] Kosiborod 2024[31]

3.2.3 Patient characteristics

3.2.3.1 Comparison of SELECT, STEP-HFpEF and STEP-HFpEF DM trial patient characteristics

SELECT trial baseline characteristics are presented by the company in the CS (Table 10) and are reported to be well balanced between treatment arms (CS, Section 2.3.5).

EAG comment

The EAG agrees with the company that patient characteristics were well balanced between treatment arms in the SELECT trial. However, the EAG highlights there are baseline characteristics that may affect the generalisability of the SELECT trial results to patients treated in England and Wales (Section 3.2.3.2).

3.2.3.2 Comparison of SELECT trial patient characteristics with real-world data

The company compared data with a "SELECT-like" population of NHS patients from a CPRD analysis (CS, Section 1.3.2.1). Patients in the "SELECT-like" CPRD population were aged ≥18 years (as opposed to ≥45 years in the SELECT trial, see response to clarification question C5). The CPRD eligibility criteria were detailed in the company response to clarification question C5 (Table 4). The company highlighted some differences in baseline characteristics (CS, Section 2.3.5) and provided additional baseline characteristics in response to clarification question A8.

EAG comment

Baseline characteristics that were similar between the SELECT trial and CPRD "SELECT-like" population are summarised by the EAG in Appendix 1 (Section 7.1), Table 20, while those that differed are summarised in Appendix 1 (Section 7.1), Table 21.

Similarities were identified between the populations by the EAG in terms of:

- the proportions of patients recorded as male and female
- mean body weight (however, the proportion of patients with BMI ≥27 to <30 kg/m^2 was notably higher in the CPRD "SELECT-like" population [[redacted]%] than the SELECT trial population [28.5%])
- the proportions of patients with HbA1c levels <5.7% and ≥5.7%
- the proportions of patients with two or more CV events (non-fatal MI, stroke or PAD); however, the proportions of patients with only one non-fatal MI, stroke or PAD differed, as described below)
- the proportions of patients with chronic HF

- median estimated glomerular filtration rate (eGFR) levels
- median lipid levels (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides)
- mean systolic blood pressure and mean diastolic blood pressure
- mean heart rate.

The following differences were highlighted by the company and the EAG:

- SELECT trial patients had eCVD for a shorter time (median time from qualifying CV event to randomisation was [redacted] years) than CPRD patients (people in the CPRD cohort had experienced their first CV event between [redacted] years prior to inclusion in the database); reflecting this difference, the SELECT trial patients were younger (mean 61.6 years) than CPRD patients (mean [redacted] years)
- in terms of CV inclusion criteria (non-fatal MI, stroke or PAD):
    - the proportion of SELECT trial patients who had only one MI event was greater (67.7%) than the CPRD "SELECT-like" population ([redacted]%)
    - the proportion of SELECT trial patients who had only one stroke event was smaller (17.9%) than the CPRD "SELECT-like" population ([redacted]%)
    - the proportion of SELECT trial patients who had only one PAD event was smaller (4.2%) than the CPRD "SELECT-like" population ([redacted]%).

Nonetheless, the company reported (CS, Section 2.3.5) that clinical advice it received[47,48] was that, overall, the SELECT trial population was broadly representative of UK patients with eCVD.

Clinical advice to the EAG agrees with the clinical advice received by the company that the SELECT trial patients are broadly similar to patients seen in the UK. However, given differences in age and previous CV events, the EAG requested that the company provide MACE results for UK patients enrolled in the SELECT trial (n=933 from 42 UK sites, of which 37 sites were in England and 1 site was in Wales); these results are presented in Section 3.3.3.

3.2.4 Concomitant medication

The company highlighted that SELECT trial investigators were encouraged to optimise treatment with medications affecting CV risk in accordance with treatment guidelines or local clinical practice (CS, Section 2.3.4).

EAG comment

Clinical feedback to the company confirmed that the usage of concomitant medications in the SELECT trial reflected real world[48] usage (CS, Section 3.2). As shown in Appendix 2, Section 7.2, Table 22, a high proportion (>[redacted]%) of SELECT trial patients

received CV medications, lipid-lowering drugs and platelet aggregation inhibitors. Clinical advice to the EAG is that the concomitant medications reflect NHS practice.

3.2.5 Quality assessment

The three included RCTs were assessed for risk of bias by the company (CS, Appendix B.5, see Appendix 3, Section 7.3, Table 23).

EAG comment

The EAG agrees with the company that, overall, all three trials were clearly reported, with a low risk of bias. However, the EAG notes that some AEs (e.g., gastrointestinal AEs) are well recognised AEs associated with semaglutide and other GLP-1 receptor agonists, meaning participants and investigators may have been able to infer treatment allocation despite double-blinding. Such awareness could have influenced self-reporting of non-serious events, adherence to other therapies, and even clinical decision-making around investigations or hospitalisations. Although endpoints were adjudicated by a blinded committee, functional unblinding could still bias secondary endpoints, tolerability assessments, and health-related quality of life outcomes.

3.2.6 Statistical approach adopted for the analysis of results

The company presented the statistical approach adopted for the primary source of evidence, the SELECT trial, in the CS, Section 2.4 and the SELECT CTR (section 9.7).[49]

The primary estimand for all objectives was an intention-to-treat estimand, evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment or any changes to background medication. This estimand was addressed using full analysis set (FAS) and the in-trial observation period. The in-trial observation period was defined as the period from date of randomisation to one of the following dates, whichever came first: i) date of follow-up visit, ii) date when participant withdrew consent, iii) date of last contact with participant lost to follow-up, iv) date of death. The in-trial observation period covered the time from randomisation to the last day of the trial, regardless of treatment adherence.

A secondary estimand for primary and confirmatory secondary endpoints, as well as body weight evaluated the effect of the randomised treatment intervention in all randomised participants had they remained on their randomised treatment for the entire trial. The estimand was addressed using the overall trial FAS population and the first on-treatment observation period. The first on-treatment observation period was

defined as the on-treatment observation period (the sum of all time points in the in-trial period where a participant had taken trial product within the previous five weeks) until first time being off treatment for >35 days. The on-treatment observation period for a participant could therefore consist of several time intervals with gaps between, if treatment had been paused for >35 consecutive days.

The end of trial occurred when the follow-up visit of the last participant, which took place 7 weeks after end of treatment, was completed.

EAG comment

The EAG considers that the SELECT trial design (large [N=17,604], multicentre, double-blind, randomised, placebo-controlled, event-driven superiority trial) minimises bias and provides high internal validity. Further, as described by Lincoff 2023,[4] trial completion was high: vital status was available for 99.6% of patients who completed the trial (defined as having died or attended the final trial visit), and >95% of patients contributed to the primary endpoint analysis. This low loss-to-follow-up minimises attrition bias and strengthens the validity of the primary endpoint analysis.

Generally, the EAG considers that the company used appropriate statistical methods to analyse SELECT trial data (see Sections 3.2.6.1 to 3.2.6.4).

3.2.6.1 Cox proportional hazards

Cox proportional hazard (PH) models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for time-to event endpoints.

EAG comment

The EAG highlights that the Cox PH model is only an appropriate method if the PH assumption holds, i.e., if the event hazards associated with the intervention and comparator data are proportional over time. The EAG therefore asked the company to provide Schoenfeld residual plots, Grambsch-Therneau test results and log-log plots for the following key SELECT trial efficacy endpoints:

- time from randomisation to first occurrence of event adjudication committee (EAC)-confirmed MACE
- time from randomisation to EAC-confirmed CV death
- time from randomisation to first EAC-confirmed composite HF outcome
- time from randomisation to EAC-confirmed all-cause death.

The EAG agrees with the company (response to clarification question A3) that

[redacted]. The EAG therefore agrees with the company that [redacted] and that the estimated HRs and CI provide reliable information about the treatment effect for these endpoints.

3.2.6.2 Hierarchical testing

The SELECT trial was only powered for the primary endpoint. This was defined as time from randomisation to the first occurrence of the composite MACE endpoint (CV death, non-fatal MI, or non-fatal stroke). For the confirmatory secondary endpoints, the company applied a hierarchical testing strategy to control Type I error, requiring each endpoint in a pre-specified sequence to achieve significance before the next could be formally assessed. In SELECT, the order was:

- time from randomisation to EAC-confirmed CV death
- time from randomisation to first EAC-confirmed composite HF outcome
- time from randomisation to EAC-confirmed all-cause death.

EAG comment

The EAG highlights that where a result in the hierarchy is not statistically significant, subsequent results cannot be considered statistically significant and should only be regarded as hypothesis generating.

3.2.6.3 Protocol change to include HF

The original SELECT trial design did not include the composite HF outcome in the hierarchical testing strategy; this was added later via a protocol amendment.

EAG comment

The EAG asked the company to provide details about this protocol change (clarification question A4). The company explained that the composite HF outcome was elevated on the basis of biological plausibility and external data alone. The change was approved by the trial steering committee and the company categorically confirmed that no unblinded data were discussed at steering committee meetings and that neither unblinded nor blinded SELECT trial data influenced the decision to elevate this endpoint. The EAG considers that while the amendment was appropriately implemented and clearly reported, the post hoc nature of the amendment means the result for the elevated endpoint should be interpreted with more caution than endpoints that were pre-specified to be part of the hierarchy at trial initiation.

3.2.6.4 Large number of endpoints

The SELECT trial specified a large number of secondary and exploratory endpoints, ranging from individual MACE components and composite endpoints to endpoints measuring weight, biomarkers, quality of life measures, and adverse events of special interest (AESIs).

EAG comment

The EAG considers that while this breadth reflects the wide-ranging potential benefits of semaglutide, it also raises concerns about statistical multiplicity and interpretability. Only a small subset of endpoints was included in the hierarchical testing strategy, meaning that most secondary endpoints were analysed without formal control of Type I error. These results should be considered as hypothesis-generating rather than confirmatory.

3.3 Critique of the results of the trials of the technology of interest

3.3.1 Dose intensity and treatment duration

The company reported (CS, Section 2.11.1.1) that [redacted] SELECT trial participants were exposed to treatment with semaglutide. The median on-treatment observation time was [redacted] for the semaglutide arm and [redacted] for the placebo arm.

The company reported (CS, Section 2.6.1.1) that in the SELECT trial, approximately [redacted]% and 77% of patients on-treatment were receiving the planned 2.4mg dose of semaglutide after 16 weeks and 104 weeks, respectively. The median time from treatment initiation to discontinuation (i.e., the on-treatment observation period until first time being off treatment for over 35 days), was [redacted] months.

EAG comment

The EAG notes that in the STEP-HFpEF and STEP-HFpEF DM trials, [redacted]% and [redacted]% patients, respectively, were receiving the planned 2.4mg dose of semaglutide after 52 weeks.

Overall, the results from all three trials suggest that most patients who receive semaglutide were able to tolerate the 2.4mg dose.

3.3.2 Efficacy results

3.3.2.1 SELECT trial FAS efficacy results

The company has presented results from analyses of the overall trial FAS population data (CS, Section 2.6.1). The company focussed on the analysis of the primary estimand. Data are presented for the primary endpoint, confirmatory secondary endpoints and supportive secondary endpoints. The analyses of secondary estimand data are reported for the primary endpoint and confirmatory secondary endpoints (CS, Section 2.6.1.2 and CS, Appendix K), namely:

- MACE and time from randomisation to first occurrence of EAC-confirmed MACE
- EAC-confirmed CV death and time from randomisation to CV death
- first EAC-confirmed composite HF outcome and time from randomisation to first occurrence of EAC-confirmed composite HF outcome
- EAC-confirmed all-cause death and time from randomisation to EAC-confirmed all-cause death.

The company highlighted that the SELECT trial met its primary endpoint, showing a statistically significant reduction in MACE incidence among patients treated with semaglutide versus placebo. As the between-arm difference with respect to CV death (the first confirmatory secondary endpoint) was not statistically significant, superiority testing was not performed for the remaining confirmatory secondary endpoints from the hierarchical testing procedure.

The company highlighted that coronavirus disease 2019 (COVID-19) may have contributed to the lack of a statistically significant difference for confirmed CV death. The company highlighted (CS, 2.6.1.7) that the competing risk of non-CV death (which prevents the occurrence of CV death) combined with the lower rates of non-CV death in the semaglutide arm may have resulted in the unanticipated convergence of survival curves for CV death (CS, Figure 6). The curves were observed to converge from 24 months to approximately 36 months after randomisation which corresponds to the most severe periods of the COVID-19 pandemic (March 2020 to March 2022). Results reported by Scirica 2024[50] show that, compared with placebo, semaglutide reduced COVID-19 deaths (43 vs 65; HR=0.66; 95% CI: 0.44 to 0.96).

EAG comment

Clinical advice to the EAG agrees that COVID-19 may have contributed to the lack of a statistically significant difference for confirmed CV death.

The EAG observes that curves also converged around the same time with regard to first EAC-confirmed composite HF outcome (CS, Figure 7). The company offered no explanation for why these curves converged.

Except for confirmed CV death, which was a confirmatory secondary endpoint, all endpoints that informed the economic model were supportive secondary endpoints, including expanded MACE. This endpoint comprised five endpoints (CV death, non-fatal MI, non-fatal stroke, coronary revascularisation and hospitalisation for unstable angina). These individual endpoints were used to populate the economic model

The EAG observes CIs were suggestive of a statistically significant difference (based on the CIs around the effect sizes reported) favouring semaglutide versus placebo for the following endpoints used to inform the economic model:

- all-cause death (which indirectly informed the economic model; non-CV deaths [all-cause deaths minus CV deaths] were used in the economic model)
- non-fatal MI
- coronary revascularisation
- development of diabetes (HbA1c ≥48 mmol/mol [6.5%])
- change in body weight from baseline.

For the following endpoints that informed the economic model, the CIs were suggestive of results that were not statistically significant:

- confirmed CV death
- non-fatal stroke
- hospitalisation for unstable angina
- HF hospitalisation or urgent HF visit.

However, as highlighted by the EAG in Section 3.2.6.4, because all secondary endpoints were not powered to detect statistically significant differences or corrected for multiplicity, the widths of the CIs should not be used to infer definitive treatment effects.

Regarding the secondary estimand (on-treatment period), the EAG observes that event rates were lower (in both arms) but HRs were similar to the results reported for the primary estimand.

Exploratory endpoints (primary estimand) are also reported in the CS (Section 2.6.1.5) but are not considered in the EAG report. A summary of the key efficacy results (primary estimand) presented in the CS is provided in Table 4.

Table 4 SELECT trial endpoint results at Week 104 (primary estimand, FAS – in-trial)

Endpoint	Semaglutide (n=8803)	Placebo (n=8801)	Effect (95% CI)	p-value	Source
First EAC-confirmed MACE, n (%)	569 (6.5)	701 (8.0)	HR=0.80 (0.72 to 0.90)	<0.0001	CS, Table 12
CV death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 12
Non-fatal MI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 12
Non-fatal stroke, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 12
Confirmatory secondary endpoints					
Confirmed CV death, n (%)	223 (2.5)	262 (3.0)	HR=0.85 (0.71 to 1.01)	[redacted]	CS, Table 15
First occurrence of a composite HF endpoint, n (%)	300 (3.4)	361 (4.1)	HR=0.82 (0.71 to 0.96)	NA[a]	CS, Table 16
CV death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 16
HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 16
HF hospitalisation or urgent HF visit, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 16
Urgent HF visit, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 16
All cause death, n (%)	375 (4.3)	458 (5.2)	HR=0.81 (0.71 to 0.93)	NA[a]	CS, Table 17
Non-CV death, n (%)	[redacted]	[redacted]	[redacted][b]	[redacted]	CS, Table 17[b]
Supportive secondary endpoints					
Expanded MACE, n (%)	873 (9.9)	1074 (12.2)	HR=0.80 (0.73 to 0.87)	[redacted]	CS, Table 14
CV death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CTR,[49] Table 11-19
Non-fatal MI, n (%)	234 (2.7)	322 (3.7)	HR=0.72 (0.61 to 0.85)	[redacted]	CS, Table 14
Non-fatal stroke, n (%)	154 (1.7)	165 (1.9)	HR=0.93 (0.74 to 1.15)	[redacted]	CS, Table 14
Coronary revascularisation, n (%)	473 (5.4)	608 (6.9)	HR=0.77 (0.68 to 0.87)	[redacted]	CS, Table 14
Hospitalisation for unstable angina, n (%)	109 (1.2)	124 (1.4)	HR=0.87 (0.67 to 1.13)	[redacted]	CS, Table 14

Endpoint	Semaglutide (n=8803)	Placebo (n=8801)	Effect (95% CI)	p-value	Source
All-cause death, non-fatal MI, or non-fatal stroke, n (%)	710 (8.1)	877 (10.0)	HR=0.80 (0.72 to 0.88)	[redacted]	CS, Table 14
HF hospitalisation or urgent HF visit, n (%)	97 (1.1)	122 (1.4)	HR=0.79 (0.60 to 1.03)	[redacted]	CS, Table 14
Composite nephropathy event, n (%)	155 (1.8)	198 (2.2)	HR=0.78 (0.63 to 0.96)	[redacted]	CS, Table 18
Persistent macroalbuminuria	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 18
Persistent reduction in eGFR	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 18
Onset of persistent eGFR <15 ml/min/1.73 m^2	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 18
Initiation of chronic RRT	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 18
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 18
HbA1c ≥48 mmol/mol [6.5%], n (%) [c]	306 (3.5)	1059 (12.0)	HR=0.27 (0.24 to 0.31)	[redacted]	CS, page 78
HbA1c ≥39 mmol/mol [5.7%], n (%) [d]	623 (21.3)	1501 (50.4)	HR=0.33 (0.30 to 0.36)	[redacted]	CS, page 79
hsCRP ratio to baseline	[redacted]	[redacted]	ETR=0.62 to (0.60 to 0.64)	[redacted]	CS, Table 21
SBP change from baseline, mmHg	−3.82	−0.51	ETD=−3.31 (−3.75 to −2.88)	[redacted]	CS, Table 21
DBP change from baseline, mmHg	−1.02	−0.47	ETD=−0.55 (−0.83 to −0.27)	[redacted]	CS, Table 21
Pulse change from baseline, bpm	3.79	0.69	ETD=3.10 (2.80 to 3.39)	[redacted]	CS, Table 21
Body weight change from baseline, %	−9.39	−0.88	ETD=−8.51 (−8.75 to −8.27)	[redacted]	CS, Table 22
Waist circumference change from baseline, cm	−7.56	−1.03	ETD=−6.53 (−6.79 to −6.27)	[redacted]	CS, Table 22

Endpoints shaded and in bold are used in the economic model; the company highlighted (CS, Table 6 footnote) that the economic model uses a different nephropathy outcome and instead tracks chronic kidney disease stage (1–5).

[a] Superiority of semaglutide vs placebo for time from randomisation to first composite HF endpoint was not tested as per the pre-specified hierarchical testing scheme – described in Table 11

[b] HR reported by Scirica 2024[50]

[c] Patients who underwent randomisation in error and had a baseline HbA1c level ≥48 mmol/mol [6.5%] were excluded from this analysis; 8800 patients in the semaglutide arm and 8797 patients in the placebo arm were included

[d] HbA1c level ≥39 mmol/mol [5.7%] was assessed in a time-to-first-event analysis only among patients whose HbA1c level was <5.7% at baseline screening; 2925 patients in the semaglutide arm and 2980 patients in the placebo arm were included

CI=confidence interval; CS=company submission; CTR=clinical trial report; CV=cardiovascular; DBP=diastolic blood pressure; EAC=event adjudication committee; ETD=estimated treatment difference; ETR=estimated treatment ratio; FAS=full analysis set; HF=heart failure; HR=hazard ratio; hsCRP=high-sensitivity C-reactive protein; MACE=major adverse CV event; MI=myocardial infarction; SBP=systolic blood pressure

3.3.2.2 STEP-HFpEF and STEP-HFpEF DM trials efficacy results

The STEP-HFpEF and STEP-HFpEF DM trials both aimed to reduce symptoms and physical limitations associated with HFpEF and obesity and to improve exercise function. The company reported that the STEP-HFpEF and STEP-HFpEF DM trials both met their dual primary endpoints, showing a statistically significant reduction in body weight and increase in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ CSS) between baseline and the end of treatment (Week 52) (CS, Section 2.6.2.2). The company also highlighted (CS, Section 2.6.2.4.2) that treatment with semaglutide resulted in a greater decrease in N-terminal pro-brain natriuretic peptide (NT-proBNP, a biomarker of myocardial strain and HF) levels than treatment with placebo.

While the STEP-HFpEF and STEP-HFpEF DM trials did not measure MACE, results are presented for the following endpoints that are relevant to this appraisal:

- HF hospitalisation or urgent HF visit
- hsCRP ratio to baseline
- change in SBP from baseline
- change in DPB from baseline
- change in body weight, from baseline.

EAG comment

A summary of the key STEP-HFpEF and STEP-HFpEF DM trial efficacy results presented in the CS, alongside the results for the same SELECT trial endpoints, is presented by the EAG in Appendix 4, Section 7.4. Table 24. The EAG considers that the results suggest that, compared with placebo, semaglutide leads to broadly similar improvements in these endpoints in these slightly different populations to the SELECT trial (importantly, patients were not required to have had a previous CV event in the STEP-HFpEF and STEP-HFpEF DM trials).

3.3.3 Subgroup analyses

3.3.3.1 SELECT trial subgroup results

SELECT trial subgroup analysis results are presented in CS, Section 2.8. In the SELECT trial, the consistency in the treatment effect for MACE was explored by carrying out predefined subpopulation analyses based on baseline information (age, sex, BMI, baseline CVD, HF status, eGFR, HbA1c, region, race, and ethnicity). The company reported that results of the subpopulation analyses (shown in CS, Figure 19 to Figure 21) were consistent with results from the primary analysis of the overall trial

FAS population data (HR=0.80 [95% CI: 0.72 to 0.90]). However, wide CIs were observed for some subgroups, meaning not all results were statistically significant.

EAG comment

In terms of characteristics identified by the company and EAG as differing between the SELECT trial and the "SELECT-like" CPRD population:

- the HRs for MACE by age group were consistent with the HR for the overall trial FAS population; CIs were widest in the ≥75 years age group where there were the fewest numbers of events/numbers of patients (n/N):
    - age<55 years: HR=0.81 (95% CI: 0.64 to 1.04); n/N=115/2057 (5.6%) vs 141/2094 (6.7%)
    - age ≥55 years to <65 years: HR=0.78 (95% CI: 0.64 to 0.95); n/N=187/3387 (5.5%) vs 234/3338 (7.0%)
    - age 65 to <75 years: HR=0.77 (95% CI: 0.64 to 0.93); n/N=189/2656 (7.1%) vs 247/2706 (9.1%)
    - ≥75 years: HR=0.92 (95% CI: 0.67 to 1.25); n/N=78/703 (11.1%) vs 79/633 (12.5%)
- the HRs for MACE by baseline CVD showed a HR close to 1 for patients who had only had a stroke at baseline; this subgroup had the fewest numbers of patients and events and the 95% CI for the HR was wide:
    - only MI: HR=0.78 (95% CI: 0.68 to 0.90); n/N=362/5962 (6.1%) vs 455/5944 (7.7%)
    - only stroke: HR=0.98 (95% CI: 0.75 to 1.27); n/N=109/1578 (6.9%) vs 109/1556 (7.0%)
    - only PAD: HR=0.74 (95% CI: 0.36 to 1.48); n/N=13/376 (3.5%) vs 19/401 (4.7%)
    - two or more CV events: HR=0.75 (95% CI: 0.55 to 1.00); n/N=76/718 (10.6%) vs 100/719 (13.9%)

The EAG agrees with the company that wide confidence intervals may occur due to small numbers of patients and small numbers of events in some subgroups.

Given SELECT trial patients had differences in baseline characteristics to the "SELECT-like" CPRD population, being younger with more patients with only a stroke event and fewer with only an MI or PAD event, the EAG requested subgroup analyses for the SELECT trial UK population (clarification question A8). In response to clarification, the company presented MACE subgroup results for Europe and the UK; these show:

- Europe subpopulation: a similar HR ([redacted]) to the overall trial FAS population;
- UK subpopulation: a similar HR ([redacted]) to the overall European subpopulation and the overall trial FAS population.

Overall, the subgroup results for age, baseline CV risk, Europe and the UK show treatment effects that, except for patients aged ≥75 years and patients who had only had one prior stroke, are at least equal to those for the overall trial FAS population.

3.3.3.2 ***STEP-HFpEF and STEP-HFpEF DM trials efficacy results***

The company considered (CS, Appendix C.2) that it was not possible to conduct subgroup analyses using STEP-HFpEF and STEP-HFpEF DM trial data, "due to their small sample size and limited power for such analyses". Therefore, it was prespecified that subgroup analyses for the dual primary outcomes (changes in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score [KCCQ-CSS] and body weight from baseline to Week 52) were carried out using the pooled dataset of STEP-HFpEF and STEP-HFpEF DM trials.

EAG comment

The EAG considers that the pooled dataset results were largely consistent across all subgroups for both endpoints.

3.3.4 Additional pre-specified analyses

The company reported (CS, Section 2.6.1.6) the results of two pre-specified analyses of SELECT trial data: the association of weight loss and MACE (Deanfield 2024,[51] reported in CS, Table 24) and time-to onset of benefit of semaglutide on MACE (Plutzky 2025[52] shown in Figure 16), as follows:

- by Week 20, 62% of semaglutide and 10% of placebo participants had lost ≥5% of their body weight; the reduction in the MACE rates by semaglutide versus placebo was similar in participants who lost ≥5% and those who lost <5% or gained weight (HR=0.67; 95% CI: 0.52 to 0.87 and HR=0.85, 95% CI: 0.72 to 1.00, respectively; interaction p-value >0.10 between weight loss subgroups)
- the first sustained, statistically significant effect (HR and upper CI below 1) was observed within 3 months of randomisation, with an overall HR of 0.62 (95% CI: 0.41 to 0.93) for those first 3 months.

The company considered (CS, p91) that results from these two analyses show that the magnitude of the treatment effect of semaglutide on the primary endpoint (MACE) was independent of the extent of weight loss (<5% and ≥5% at Week 20) and the CV benefits of semaglutide were first observed early in the trial.

EAG comment

The EAG note that as highlighted at the 32nd European Congress on Obesity 2025[53] that that while benefits were observed regardless of weight loss within the first 6

months prior to receiving the target dose of 2.4mg semaglutide, they also continued to accrue over time once the 2.4mg dose had been reached. Clinical advice to the EAG agrees with the company that the results suggest that the benefit of treatment with semaglutide in terms of MACE may be observed early and is not driven by weight loss. For this reason, clinical advice to the EAG is that patients should receive semaglutide at the maximum dose (up to 2.4mg) that the patient can tolerate.

3.3.5 Patient reported outcomes

Improvements in quality of life as measured by patient reported outcomes (PROs) were observed in the SELECT trial (CS, Section 2.6.1.4.5) and STEP-HFpEF and STEP-HFpEF DM trials (CS, Section 2.6.2.2).

EAG comment

The EAG notes that SELECT, STEP-HFpEF or STEP-HFpEF DM trials PRO data were not used to populate the economic model (see also Section 4.2.6). The results from analyses of PROs reported in the CS and STEP-HFpEF or STEP-HFpEF DM clinical trial reports (CTRs)[54,55] are summarised in Appendix 5, Section 7.5.

3.3.6 Safety and tolerability

As explained in the CS, Appendix D, because the safety profile of semaglutide is well characterised, a targeted approach was adopted with regard to the collection of AEs in the SELECT, STEP-HFpEF and STEP-HFpEF DM trials, i.e., in all countries prespecified AEs were systematically collected whereas in some countries, both prespecified AEs and all other AEs were collected due to local requirements. Systematically collected AEs in all countries included:

- all serious adverse events (SAEs) with a non-fatal or fatal outcome
- selected pre-defined categories of AEs regardless of seriousness
- AEs leading to permanent discontinuation of trial product
- AEs in scope for additional data collection via a specific event form (AESIs)
- AEs for adjudication.

Non-serious AEs not fulfilling one or more of the above listed criteria were not systematically collected. However, in some countries all AEs were collected due to local requirements.

EAG comment

AE data are reported in the CS, Section 2.11 and CS, Appendix D. In summary, in the SELECT trial, over 104 weeks, and the STEP-HFpEF and STEP-HFpEF DM trials, over 52 weeks:

- semaglutide was associated with a statistically significantly lower rate of SAEs than placebo:
    - SELECT: semaglutide 33.4% vs placebo 36.4% in, p<0.001
    - STEP-HFpEF: semaglutide 13.3% vs placebo 26.7%, p<0.001
    - STEP-HFpEF DM: semaglutide 17.7% vs placebo 28.8%, p=0.002
- the company highlighted that the difference in SAEs was mainly driven by the system organ classes of cardiac disorders and infections or infestations, which were reported by more patients in the placebo arm:
    - cardiac disorders:
        - SELECT: semaglutide 11.5% vs placebo 13.5%, p<0.001
        - STEP-HFpEF: semaglutide 2.7% vs placebo 11.3%, p<0.001
        - STEP-HFpEF DM: semaglutide 6.1% vs placebo 13.1%, p=0.004
    - infections and infestations:
        - SELECT: semaglutide 7.1% vs placebo 8.4%, p=0.001
        - STEP-HFpEF: semaglutide 1.5% vs placebo 6.4%, p=0.006
        - STEP-HFpEF DM: semaglutide 3.9% vs placebo 8.8%, p=0.01
- The most common AESIs were COVID-19-related events, as follows:
    - SELECT: semaglutide 23.9% vs placebo 24.4%, p=0.46
    - STEP-HFpEF: semaglutide [redacted]% vs placebo [redacted]%
    - STEP-HFpEF DM: semaglutide [redacted]% vs placebo [redacted]%
- AEs leading to permanent discontinuation of trial product were more common in the semaglutide arm than the placebo arm:
    - SELECT: semaglutide 16.6% vs placebo 8.2%, p<0.001
    - STEP-HFpEF: semaglutide 13.3% vs placebo 5.3%
    - STEP-HFpEF DM: semaglutide 10.6% vs placebo 8.2%
- the most common AEs leading to permanent discontinuation of trial product by system organ class were gastrointestinal disorders, as follows:
    - SELECT: semaglutide 10.0% vs 2.0% placebo, p<0.001
    - STEP-HFpEF: semaglutide 9.5% vs placebo 2.6%
    - STEP-HFpEF DM: semaglutide 6.5% vs placebo 2.9%.

The EAG observes that there were proportionately more SAEs and COVID-19 events in both arms of the SELECT trial than reported for the equivalent arms of the STEP-HFpEF and STEP-HFpEF DM trials. Clinical advice to the EAG is that may be a result of the additional 52 weeks of follow-up in the SELECT trial. In addition, clinical advice to the EAG is that the SELECT trial was conducted in many regions of the world where

the COVID-19 burden was higher when compared to the countries where HFpEF and STEP-HFpEF DM trials were conducted. The increase in incidence of AEs leading to permanent treatment discontinuation in the SELECT trial compared with the STEP-HFpEF and STEP-HFpEF DM trials, was less marked.

The EAG considers that while systematically recording only certain AEs reduces a trial's data collection and reporting burden, it also limits the completeness of the safety profile. Nonetheless, the EAG agrees with the company (CS, Sections 2.11.1.3 and 2.11.2) that overall, the safety and tolerability profile of semaglutide is in line with previously reported data in the HFpEF and STEP-HFpEF DM trials and no new safety concerns were identified.

3.3.7 Trials of semaglutide that have included people with diabetes and which have reported MACE

Since patients with diabetes were excluded from the SELECT trial and since the STEP-HFpEF DM trial did not measure MACE, the company also referred to four CVOTs[32-35] of semaglutide that included patients with T2D and where MACE was a primary or key secondary endpoint (CS, Section 2.6.3). The company highlighted that the evidence collected in these trials is not presented in the CS as primary or supporting evidence since the indications, populations, semaglutide doses and/or primary endpoints differ from those described in the decision problem. However, the MACE results are nonetheless reported in the CS (Section 2.6.3). Key trial characteristics and MACE results are presented in Table 5.

EAG comment

The EAG notes that two of the CVOTs (SUSTAIN-6 and PIONEER-6) are included in the Wegovy® SmPC as supportive evidence for the effectiveness of semaglutide in preventing MACE. However, the EAG highlights that the semaglutide in these trials are marketed as Ozempic® and Rybelsus® respectively). Furthermore, there were no inclusion eligibility criteria relating to BMI or previous CV events for any of these four CVOTs in which patients with T1D were excluded. The EAG agrees that these trials are therefore not directly relevant to the decision problem. Nevertheless, the efficacy results suggest semaglutide reduces the incidence of MACE in populations of patients with diabetes. The EAG notes the HRs for the first occurrence of MACE are all similar to the SELECT trial HR (HR=0.80; 95% CI: 0.72 to 0.90).

Clinical advice to the EAG is that these results suggest that the exclusion of patients with diabetes from the SELECT trial is not a major limitation and that, if recommended

by NICE, semaglutide could be used for preventing MACE in people with CVD and overweight or obesity, with or without diabetes.

Table 5 Trials that enrolled patients with diabetes and which included a MACE (or similar) endpoint

	SUSTAIN-6	PIONEER-6	FLOW	SOUL
Study type	Randomised, double-blind, placebo-controlled, multinational, multi-centre trial	Randomised, double-blind, placebo-controlled, multinational, multi-centre trial	Randomised, double-blind, placebo-controlled, multinational, multi-centre trial	Randomised, double-blind, placebo-controlled, multinational, multi-centre trial
Patient group	People with insufficiently controlled T2D and at high risk of CV events (irrespective of baseline BMI)	People with T2D and at high risk of CV events (irrespective of baseline BMI)	People with CKD and T2D (irrespective of baseline BMI)	People with T2D and eCVD and/or CKD (irrespective of baseline BMI)
Intervention	SC semaglutide 0.5mg or 1.0mg (n=1648)	Oral semaglutide, up to target dose of 14mg (n=1591)	SC semaglutide 1.0mg (n=1767)	Oral semaglutide, up to target dose of 14mg (n=4825)
Comparator	Placebo (n=1649)	Oral placebo (n=1592)	Placebo (n=1766)	Oral placebo (n=4825)
Duration	Event-driven trial, median observation time of 2.1 years	Event-driven trial, median time in the trial of 15.9 months	Event-driven trial, median participant follow-up of 3.4 years	Event driven trial, median follow-up of 49.5 months
Dates	February to December 2013	January to August 2017	June 2019 to May 2021	June 2019 to March 2021
Location	229 sites in 20 countries (including the UK)	214 sites in 21 countries (including the UK)	387 sites in 28 countries (including the UK)	444 sites in 33 countries (including the UK)
Note	Non-inferiority trial. The non-inferiority margin for the first occurrence of MACE was 1.8 for the upper boundary of the 95% CI of the HR	Non-inferiority trial. The non-inferiority margin for the first occurrence of MACE was 1.8 for the upper boundary of the 95% CI of the HR	Superiority trial. First occurrence of MACE was a secondary endpoint (primary endpoint was major kidney disease events)	Superiority trial. First occurrence of MACE was primary endpoint
MACE	HR=0.74, 95% CI=0.58 to 0.95; p<0.001 for non-inferiority	HR=0.79, 95% CI=0.57 to 1.11; p<0.001 for non-inferiority	HR=0.82; 95% CI=0.68 to 0.98; p=0.029	HR=0.86; 95% CI=0.77 to 0.96; p=0.006

BMI=body mass index; CI=confidence interval; CKD=chronic kidney disease; CV=cardiovascular, eCVD=established CV disease; HR=hazard ratio; MACE=major adverse CV event; SC=subcutaneous; T2D=type 2 diabetes; UK-United Kingdom
Source: CS, Section 2.6.3 and published papers,[32-35]

3.3.8 Meta-analyses

The company identified nine publications reporting pooled analyses (CS, Section 2.1). As described in the CS (CS, Section 2.9), none of these publications were considered by the company to be relevant to the decision problem or to be more robust than SELECT trial data. This is because the company considered there was heterogeneity across the published meta-analyses in terms of study populations (baseline CV risk, people with and without diabetes), interventions (oral and/or subcutaneous administration, dose differences) and comparators and endpoints analysed. Therefore, the company did not conduct a meta-analysis. However, the company presented results from one meta-analysis, reported by Cleto 2025,[56] which included data from the following five trials: SELECT, STEP-HFpEF, STEP-HFpEF DM, SUSTAIN-6, and PIONEER 6 (CS, Table 25).

Results from the Cleto 2025 meta-analysis are presented in the CS (Table 25) for the following SELECT trial endpoints:

- CV death
- all-cause death
- hospitalisation or urgent medical visit for HF
- unstable angina leading to hospitalisation
- non-fatal MI
- non-fatal stroke
- coronary revascularisation.

EAG comment

The results were similar to those reported for the SELECT trial. The EAG also highlights that the number of patients in the SELECT trial exceeded the total number of patients in the STEP-HFpEF, STEP-HFpEF DM, SUSTAIN-6, and PIONEER-6 trials combined and therefore it would be surprising if results were not similar to SELECT trial results.

The EAG agrees with the company that meta-analyses of these studies are subject to heterogeneity and that the evidence from the SELECT trial is more relevant to this appraisal than any pooled analysis.

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

The company considered (CS, Section 2.10) that since no other trials of semaglutide versus placebo (in which both arms which contained standard of care) relevant to the scope issued by NICE were identified no indirect treatment comparison or multiple treatment comparison was required.

EAG comment

The EAG agrees with the company that there were no relevant trials to include in an indirect treatment comparison or multiple treatment comparison.

3.5 Critique of the indirect comparison or multiple treatment comparison

No indirect comparison or multiple treatment comparison was conducted as none was required.

3.6 Additional work on clinical effectiveness done by the EAG

For information, the EAG extracted additional information not included in the CS about the 4 CVOTs in Section 3.3.7, Table 5. The EAG also extracted and summarised EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) results reported in the STEP-HFpEF and STEP-HFpEF DM trials that were also reported in the SELECT trial (Appendix 5), Section 7.5. The EAG did not conduct any additional clinical effectiveness analyses.

3.7 Conclusions of the clinical effectiveness section

The company SLR identified three relevant trials (the SELECT, STEP-HFpEF and STEP-HFpEF DM trials); of these, the SELECT trial was the most relevant in terms of population and endpoints. The primary objective of the SELECT trial was to demonstrate that, compared to placebo, semaglutide lowers the incidence of MACE when added to standard of care in people with eCVD and BMI ≥27 kg/m^2. Key strengths of the SELECT trial was its large sample size (N=17,604) and low risk of bias.

The SELECT trial was powered only for its primary endpoint: time from randomisation to the first occurrence of the composite MACE outcome. For confirmatory secondary outcomes, a hierarchical testing strategy was used to control Type I error. Although there was a statistically significant reduction in MACE among patients treated with semaglutide versus placebo, as the between-arm difference for the first confirmatory secondary endpoint (CV death) was not statistically significant, superiority testing was

not performed for the remaining two confirmatory secondary endpoints (HF composite and all-cause death). Nonetheless, SELECT trial results suggest there were improvements in secondary endpoints.

Subgroup results by age, previous CV event and for the Europe and UK SELECT trial populations show benefits in terms of MACE that are mostly at least equivalent to those for the overall trial FAS population. Pre-specified analyses suggested benefits with semaglutide were observed within the first 3 months of treatment and were observed in patients who lost <5% of their body weight, or gained weight, by Week 20.

Semaglutide also resulted in modest improvements in quality of life in the SELECT trial and safety and tolerability findings were consistent with previous trials of semaglutide, including those reported in the STEP-HFpEF and STEP-HFpEF DM trials.

Overall, the evidence provided in the CS largely reflects the final scope issued by NICE and company decision problem. However, there is no evidence from the SELECT trial for people with diabetes (HbA1c ≥48 mmol/mol) at screening or people who had a recent CV event (within past 60 days prior to the day of screening).

Evidence for people with T2D from the STEP-HFpEF DM trial supports improvements versus placebo for HF hospitalisation or urgent HF visit, hsCRP ratio to baseline and change in SBP, DPB or body weight from baseline. Evidence from four CVOTs found improvements in MACE for people with T2D but with different eligibility criteria and semaglutide doses/modes of administration (Ozempic® or Rybelsus®) to the indication for CV risk reduction for people with eCVD (Wegovy®). However, patients were not required to have had previous CV events prior to trial entry in any of the trials other than the SELECT trial.

There are no trials of people with T1D or patients who had a recent CV event (within past 60 days prior to the day of screening).

4 COST EFFECTIVENESS

This section presents a summary and critique of the cost-effectiveness evidence included in the CS. Section 4.1 focuses on the company's review of the cost-effectiveness evidence and Section 4.2 covers the company's economic evaluation. The two key components of the cost-effectiveness evidence presented in the CS are (i) a SLR of the cost effectiveness literature and (ii) a report of the company economic evaluation. The company has provided an electronic copy of their economic model, developed in Microsoft® Excel.

4.1 Critique of the review of cost-effectiveness evidence

The company conducted an SLR to identify and appraise evidence relevant to the decision problem on:

- cost effectiveness (CS, Appendix E)
- health-related quality life (HRQoL) utilities (CS, Appendix F)
- healthcare resource use (HCRU) and cost data (CS, Appendix G).

Details of the company's SLR methods and results are presented in the CS (Appendix E for cost effectiveness, Appendix F for HRQoL and Appendix G for cost and health care resource).

The population considered in the economic SLR was adults with eCVD and BMI ≥27 kg/m^2. The population and intervention terms used in the economic SLR searches aligned with the clinical SLR. These incorporated a combination of relevant index terms (Emtree, MeSH) and free-text keywords and were limited to English language. Validated study design filters were used with adjustments to increase sensitivity. All search strategies were reviewed by an Information Scientist (from SCHARR) according to the PRESS search peer review statement.

The company initially conducted the SLR search on 18 September 2023 with an update on 7 May 2025. Bibliographic databases included Embase, MEDLINE, Econlit and legacy CRD databases (which have not been updated since 2016). These were supplemented with searching of conference proceedings, economic databases and registries (CEA Registry, EconPapers [within RePEc), EQ-5D website, INAHTA HTA Database), clinical trial registries and handsearching of reference lists.

The SLR identified 6 cost-effectiveness studies of semaglutide (2.4 mg) used for the prevention of MACE (CS, Appendix E Section E.2.1). The cost effectiveness studies were developed for Australia, Canada or USA. None of the identified studies were for

the UK. The company used the Drummond 1996 quality checklist[57] to quality assess three of the six included cost effectiveness studies (CS, Appendix E.3, Table 15), justifying this as only McEwan 2025,[58] Zomer 2024[59] and Rennert-May 2025[60]were available as published manuscripts with sufficient detail to permit quality assessment. (see CS, Appendix E Section E.3).

A further 31 studies reported HRQoL with 4 of these reporting utility values for CV events in UK participants with established CVD (CS, Appendix F Section F.2.2) and 39 studies reporting HCRU and cost data (CS, Appendix G Section G.2.2).

EAG comment

Assessment of the extent to which the company's SLRs were conducted in accordance with the EAG's in-house systematic review checklist is summarised in Table 6.

The EAG considers the methods used to conduct the company's SLR of cost effectiveness evidence, HRQoL and HCRU studies were of a good standard.

The quality assessment of cost effectiveness studies was limited for three of the six included studies since three studies were only available in unpublished sources as conference poster presentations and a report of health technology assessment submission. The EAG assessment indicates that none of the cost effectiveness studies from SLR were used in the company's de novo economic model. The EAG consider the SLR is limited to describing the economics evidence base and justifying development of a de novo economic model.

No quality assessment was conducted for HRQoL and HCRU and cost data studies.

Table 6 EAG appraisal of the company's SLR methods (economics reviews)

Review process	EAG response	EAG comment
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Section 3.1 and Appendices E.1.3, F.1.3 and G.1.3.
Were appropriate sources searched?	Yes	See CS, Appendices E.1.1, F.1.1 and G.1.1.
Was the timespan of the searches appropriate?	Yes	See CS, Appendices E.1.1.1, F.1.1.1 and G.1.1.1
Were appropriate search terms used?	Yes	See CS, Appendices E.1.2 (Tables 2 to 8), F.1.2 (Tables 2 to 8) and G.1.2 (Tables 2 to 8)
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendices E.1.2 (Table 9), F.1.2 (Table 9) and G.1.2 (Table 9)
Was study selection applied by two or more reviewers independently?	Yes	See CS, Appendices E.1.4.2, F.1.4.2 and G.1.4.2
Was data extracted by two or more reviewers independently?	Yes	See CS, Appendices E.1.5, F.1.5 and G.1.5. One reviewer extracted data which were checked by a second independent reviewer.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Partly	See CS, Appendix E.2.3, Table The company used the Drummond quality checklist for included economic evaluations only. No quality assessments were provided HRQoL and HCRU studies.
Was the quality assessment conducted by two or more reviewers independently?	Yes	See CS, Appendices E.3, F.1.6 and G.1.6. Quality assessment conducted for included economic evaluations only.
Were attempts to synthesise evidence appropriate?	Yes	The CS summarised economic data in tables and narratively

HRQoL=health-related quality of life; HCRU=healthcare resource use; SLR=systematic literature review
Source: LRiG in-house checklist

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

Table 7 NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	QALYs were appropriately used to reflect patient health benefits.
Perspective on costs	NHS and Personal Social Services	The analysis adopted the NHS and PSS perspective, which is appropriate for the decision problem.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company produced a cost-utility analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A lifetime horizon was used (40 years) which is considered long enough to capture all relevant costs and outcomes for the population included in this decision problem.
Synthesis of evidence on health effects	Based on systematic review	The company identified all relevant efficacy studies for semaglutide in the relevant population
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.	Health effects were expressed in QALYs with utility values from studies that used the EQ-5D
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	HRQoL was reported directly by patients in the studies providing utility data
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	HRQoL was valued using UK population valuation sets for the EQ-5D in studies providing utility data
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	Additional QALYs had equal weight for all patients
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	Costs were derived from UK based sources but were incorrectly calculated
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discounting of 3.5% per annum was applied to costs and benefits

EQ-5D=EuroQol-5 Dimensions; PSS=Personal Social Services; QALY=quality-adjusted life year

4.2.2 Model structure

The company developed a de novo cohort-based state-transition Markov model to evaluate the cost effectiveness of semaglutide for reducing the risk of major CV events in adults with eCVD and overweight or obesity. Patients enter the economic model in the eCVD state without T2D, having previously experienced a major non-fatal CV event. In each model cycle, patients in the eCVD health state may remain in this state or transition to a post-event health state following a first modelled acute non-fatal CV event, or a fatal event. Non-fatal CV events included in the economic model are MI, stroke, hospitalisation for HF (HHF), hospitalisation for unstable angina (HUA) and coronary revascularisation (CR). Fatal events included in the economic model are CV death and non-CV death.

Patients in the non-fatal post-event health states are then at risk of further non-fatal or death events in subsequent model cycles. Patients experiencing a subsequent modelled event of the same type as their first modelled event remain in the same health state. Patients who experience a subsequent modelled event of a different type to their first modelled event transition to a new health state. For instance, a patient who experiences a first modelled MI event transitions into the Post-MI health state. If that patient then goes on to experience a subsequent modelled MI, they remain in the Post-MI health state. A patient who experiences a first modelled MI event who then goes on to experience a stroke moves first to the Post-MI health state and then into the Post-MI & Stroke health state. The order in which events occur is not tracked, so the Post MI & Stroke health state includes patients who experienced an MI followed by a stroke and patients who experienced a stroke followed by an MI. Following a subsequent modelled CV event, patients remain at risk of further CV events but remain in the same health state until death or the end of the economic model time horizon. Patients are at risk of CV and non-CV death from each of the non-fatal health states.

The proportion of patients with diabetes and with chronic kidney disease (CKD) Stages 1-5 are estimated in each model cycle along with average BMI for the cohort. The evolution of these cohort baseline characteristics is separate from the CV health states and their values do not influence the modelled risk of experiencing a non-fatal CV event or CV death.

The economic model cycle length is 4 weeks and includes a half-cycle correction. The time horizon is 40 years (lifetime). The economic model perspective is the NHS and personal social services.

The economic model structure is summarised in Figure 1.

EAG comment

The EAG is satisfied that the economic model structure is suitable to address the decision problem.

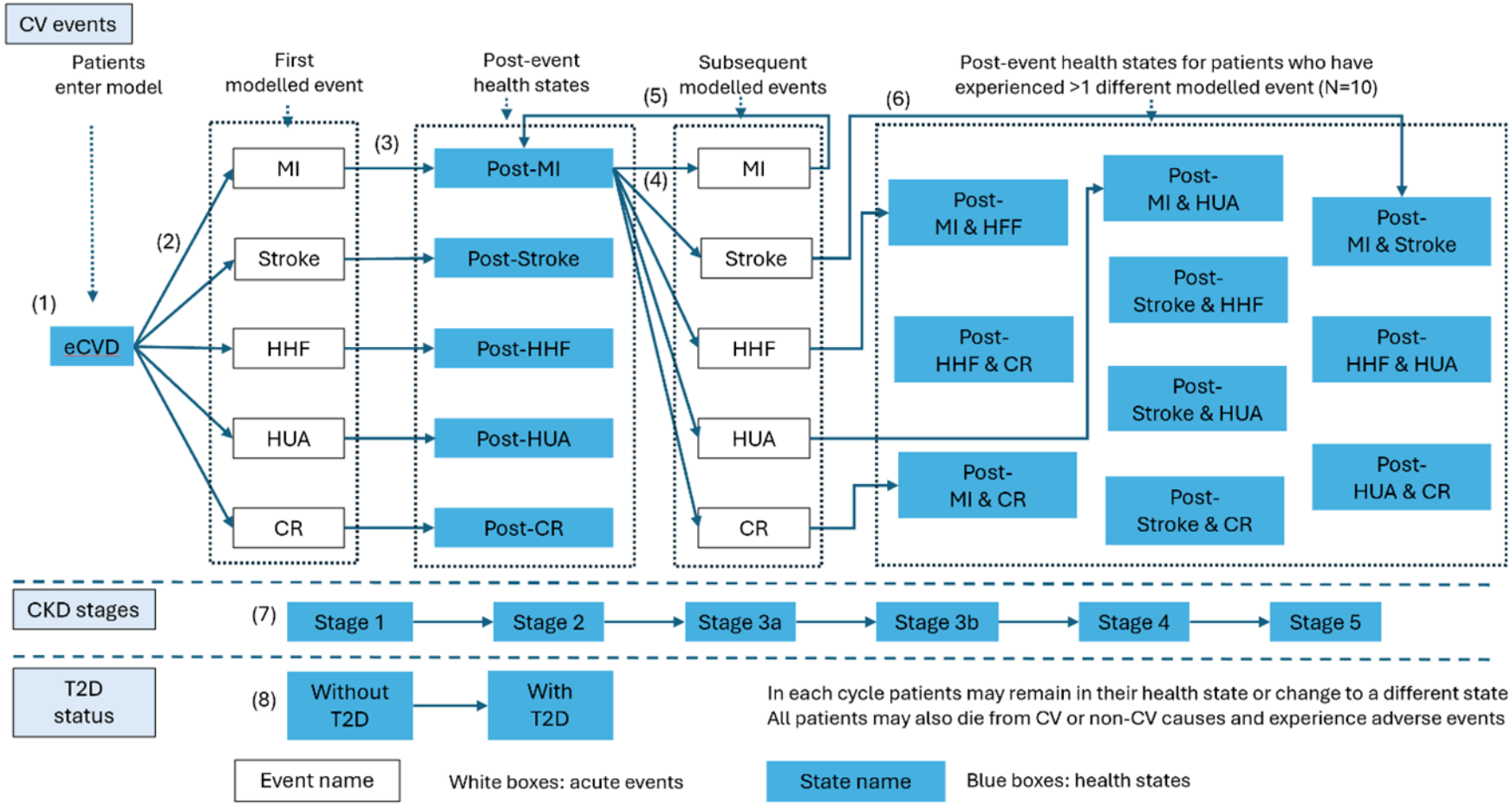


Figure 1 Economic model structure

Source: CS, Figure 22

4.2.3 Population

The modelled patient population is adult patients with overweight and obesity and eCVD, defined as previous MI, previous stroke, or symptomatic PAD. Baseline characteristics in the economic model were derived from the literature and from the SELECT trial (Table 8).

The base case population mirrors the population from the SELECT trial and therefore excludes people with (T1D or T2D) and those who have had a CV event in the previous 60 days. The company noted that the licence does not include these exclusions, and it has presented scenario analyses that consider people with T2D and recent CV events, as well as people with different levels of risk.

Table 8 Economic model baseline characteristics (SELECT trial)

Economic model parameter	Mean Value (Cycle 0)	Source
Mean age, years	61.6	Lingvay 2023[61]
Male, %	72.3	Lingvay 2023[61]
Mean BMI, kg/m^2	33.3	Lingvay 2023[61]
T2D at baseline, %	0.00	Lingvay 2023[61]
Prediabetes at baseline, %	66.4	Lingvay 2023[61]
Stage 1 (eGFR ≥90 ml/min/1.73 m^2)	[redacted]	Data on file[62]
Stage 2 (eGFR 60–89 ml/min/1.73 m^2)	[redacted]	Data on file[62]
Stage ≥3a (eGFR ≤59 ml/min/1.73 m^2)	[redacted]	Data on file[62]

BMI=body mass index; eGFR=estimated glomerular filtration rate; T2D=type 2 diabetes

EAG comment

The EAG highlights that the population in the SELECT trial are younger than the matched CPRD population with a shorter time since their first CV event (see Section 3.2.3.2). Furthermore, the SELECT trial excludes patients with diabetes at baseline and patients with recent CV events (within past 60 days prior to the day of screening) (see Section 2.3.2.2). The company have produced scenario analyses to explore the impact on cost effectiveness results if a population more in line with the CPRD population was modelled for people with T2D, a UK eCVD prevalent population and a UK eCVD incident population in which efficacy data from the SELECT trial were used (see CS, Table 48 and CS Section 3.11.3.1 for information). The HR for CV events was as observed in SELECT. The EAG cautions that bias may be introduced when efficacy results based on a trial population are modelled to another population which has patient characteristics that differ to the trial. Therefore, the results of the scenario analyses should be interpreted with caution.

4.2.4 Interventions and comparators

The economic model compares the cost-effectiveness of semaglutide in addition to established clinical management for CV risk reduction versus established clinical management for CV risk reduction alone. Established clinical management includes the use of concomitant medications, and advice on diet and physical exercise.

The target dose for semaglutide in the economic model is 2.4mg once weekly, although not all patients achieve this dose. The maximum dose distribution is reached after four cycles and this distribution is maintained throughout the economic model time horizon. The dosing titration schedule and proportion of patients receiving each dose is shown in Table 9.

Table 9 Modelled semaglutide dose titration schedule

Cycle	0.24mg	0.5mg	1.0mg	1.7mg	2.4mg
[redacted]					

Source: Economic model

EAG comment

The EAG is satisfied that the semaglutide dose distribution from the SELECT trial is appropriate to use in the economic model.

4.2.5 Treatment effectiveness and extrapolation

The company used parametric survival models to estimate the risk of non-fatal CV events (MI, stroke, HHF, HUA and CR), CV death and non-CV death to inform transitions between modelled health states. The risk estimates are the same for first and subsequent modelled events, and do not depend on the timing or type of previous events. Parametric survival models for all survival outcomes were fitted to Kaplan Meier (K-M) data from the SELECT trial adjusted for competing risks. Survival models were chosen based upon an assessment of goodness of fit statistics, proportional hazards, clinical advice and long-term hazard profiles from CPRD data matched to the SELECT trial population.

For non-fatal CV events, all-cause death was considered to be a competing event. For fatal events, death from the alternative cause was considered to be a competing event. Base case distributions for each event are given in the CS, Table 31.

The company assumed that since 66.4% of patients in the SELECT trial had prediabetes (HbA1c ≥5.7%) at baseline, the cohort was at risk of developing T2D. The company used an exponential distribution fitted to SELECT trial K-M data to estimate the probability of the cohort developing T2D in each model cycle. The risk of each non-fatal CV event and fatal event was adjusted by an HR for the proportion of patients considered to have T2D in each model cycle. The HRs were applied after the trial period (3.3 years) to avoid double counting. The increased CV risk HRs are given in the CS, Table 32.

The company has modelled the effect of semaglutide treatment on weight loss via BMI, with patients losing treatment benefit over time once treatment is discontinued (CS, Figure 23). Patient BMI for treatment with standard of care was assumed to increase by 0.106kg/m^2 every year until the age of 66 years, after which it was assumed to decrease by 0.106kg/m^2 every year in line with the committee's preferred assumption in TA875. Average BMI for patients treated with semaglutide was calculated using the relative difference in weight from the treatment arm versus the control arm from the SELECT trial. The company has assumed that body weight in the treated cohort will equal that in the untreated cohort two years after treatment discontinuation. Change in BMI is not linked in the economic model to the risk of CV or death events.

Changes in kidney function in the overall cohort is tracked in the economic model. Patients start in eGFR-defined CKD stages 1 to 3a according to the proportions at baseline in the SELECT trial and are modelled to either remain in that stage or progress to the next most severe stage in each model cycle. Patients in the economic model are not permitted to progress more than one stage per cycle and were not permitted to improve. Constant transition probabilities were assumed between any two given states based on data from the SELECT trial (CS, Table 33). Change in CKD stage is not linked in the economic model to the risk of CV or death events.

At the end of the trial period in the economic model, the company has assumed that patients no longer on treatment with semaglutide or who stop treatment after that point receive no further benefit and have the same risk of CV events as patients receiving established clinical management.

At clarification, the EAG requested the company modify the economic model to allow the effect of treatment waning to be explored (clarification question B1). The company considered that waning was already in effect in the economic model, as patients who stopped treatment with semaglutide at or after the end of the trial period received no

benefit in terms of reduction in risk of CV events and BMI also rebounded in line with what had been seen in the SELECT and other trials. However, they also produced scenarios whereby waning occurred in patients who stopped treatment as opposed to an instant loss in efficacy. As these scenarios effectively improved the efficacy of semaglutide compared to the company base case, they also showed reduced ICERs for semaglutide.

EAG comment

The EAG considers that the company approach to distribution selection for modelling second and subsequent CV events in the economic model was robust and produced distribution choices that produce CV event rates over the first 4.6 years that closely match the CV events seen in the SELECT trial.

The EAG disagrees with the company approach of adjusting the CV event rates by rates of diabetes after the end of the trial period. The CV event rates projected and used in the economic model are based upon HbA1c and diabetes rates experienced during the SELECT trial and therefore represent risks for a population with fluctuating rates of HbA1c and increasing rates of diabetes over the SELECT trial period. Any impact from diabetes rates on event rates should therefore be captured in the distributions chosen by the company.

Similarly, the EAG disagrees with the company approach to adjusting the CV event rates by the discontinuation rate of semaglutide after the end of the trial period. As is the case with the diabetes rate, the curve selection chosen by the company is based upon SELECT trial data that reflects patient outcomes for a population where a proportion has discontinued semaglutide by the end of follow up. As such, the SELECT trial CV events and curves selected to match those events already reflect discontinuation from semaglutide and there is no need to adjust these curves for discontinuation in the economic model. Such an approach is supported by evidence from the SELECT trial that the MACE hazard ratio for patients treated with semaglutide converged over the trial period with no indication that it was increasing despite half the trial population having stopped treatment over the trial time horizon (Figure 2).

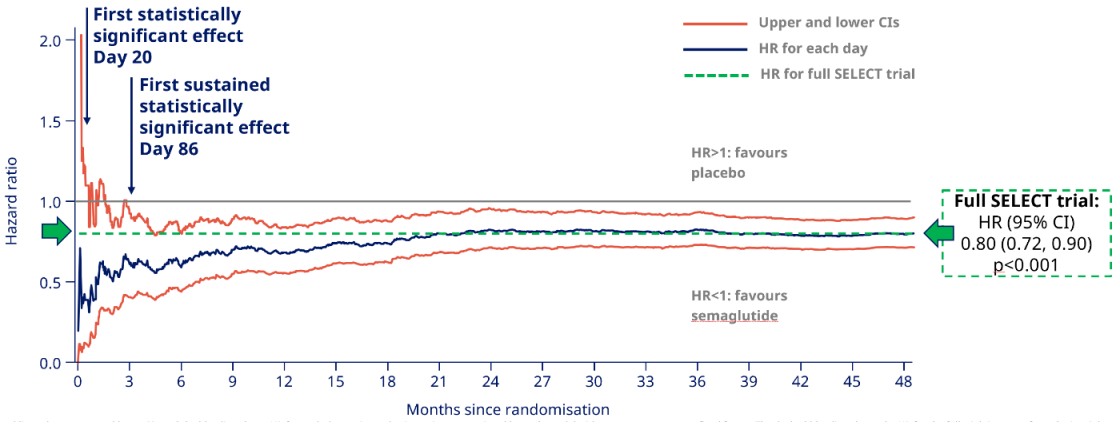


Figure 2 Daily HR for MACE calculation

Source: CS Figure 16
HR=hazard ratio; MACE=major adverse cardiovascular event

The EAG has therefore removed the end of trial adjustments to CV event rates for diabetes and stopping semaglutide in the economic model.

The EAG has also removed from the economic model the following CV events as they were not statistically significantly different for patients treated with semaglutide or placebo in the SELECT trial:

- Confirmed CV death
- Non-fatal stroke
- Hospitalisation for unstable angina
- HF hospitalisation or urgent HF visit.

4.2.6 Health-related quality of life

Health state and event utility values were calculated by applying disutilities to an age- and sex-adjusted general UK population without CVD.[63] Although EQ-5D was collected in the SELECT trial, the company considered it unsuitable for use in the economic model because it was thought unlikely to have captured the full effect of CV events on quality of life due to lack of events and the timing of EQ-5D collection. Instead, cycle disutilities for the post-CV event health states, comorbidities (CKD and T2D) and mean BMI, and event disutilties for CV events and AEs were derived from the literature (CS, Table 35). Disutilities are included in an additive manner so that disutilities in any given model cycle can be combined.

EAG comment

The EAG is satisfied with the utility values chosen by the company and how they have been incorporated into the economic model. Utility decrements for CKD and diabetes may already be partly incorporated into the age-related decrements applied in the

economic model, so there may be some double counting of decrements in the economic model, but the EAG considers this would have a minor impact on economic model results.

4.2.7 Resources and costs

4.2.7.1 Drug acquisition costs

Modelled semaglutide acquisition cost per cycle is calculated as the proportion of people alive and on treatment in a given cycle multiplied by the weekly cost of a semaglutide dose multiplied by four. The weekly cost of semaglutide depends on the proportion of patients receiving a given dose (CS, Table 36). The company has assumed that the cohort will titrate up to their maximum dose over the initial five model cycles (Table 9) and that this distribution of maximum doses will remain constant from cycle five onwards. Treatment discontinuation is included at a constant rate of [redacted] per cycle throughout the modelled time horizon for patients on all dose levels, calculated from median time to treatment discontinuation ([redacted]) in the SELECT trial. The base case does not include a treatment stopping rule.

EAG comment

The EAG considers it would have been informative for the company to have shown the modelled time on treatment for patients receiving semaglutide compared to that seen for patients receiving semaglutide in the SELECT trial. In the absence of this comparison, uncertainty exists on the true costs of semaglutide treatment, although the EAG notes that the discontinuation rate does align with median time on treatment in the trial.

4.2.7.2 Drug administration costs

An administration cost for semaglutide treatment is included in the first cycle to represent the cost of patient education (CS, Table 37). Modelled semaglutide administration costs were zero from the second model cycle onwards.

EAG comment

The EAG is satisfied with the administration costs of semaglutide in the economic model.

4.2.7.3 Health-state and event-related unit costs and resource use

All non-fatal health states include a baseline cost of £126.74 per cycle to represent the cost of maintenance for eCVD and these health-state maintenance costs do not

change according to first or subsequent non-fatal CV events. One-off event costs are applied for each non-fatal CV event in the cycle the event occurs, which differ according to the type of event (CS, Table 38). A one-off cost is applied for CV death but non-CV death incurs no costs in the economic model.

EAG comment

The EAG is satisfied with the costs used in the economic model for eCVD.

The EAG considers that the costs used for CV events in the economic model have been estimated incorrectly. NHS Cost Calculator data[64] does not differentiate between first and subsequent event and so cannot be used as an estimate of the cost of the first event. Further, the company has used the percentage increase between first and second event between months 7 to 36 from the Danese 2016 study[65] to inflate the first event cost estimated from the NHS Cost Calculator to estimate the second event cost. It is unclear to the EAG why the costs between months 1 to 6, which would more accurately reflect the acute costs estimated from the NHS Cost Calculator were not used.

The EAG considers that given the Danese 2016 study, which uses CPRD data to establish costs,[65] provided robust estimates of second CV events to the NHS that this can be used directly to estimate the costs of second (and subsequent) CV events. The Danese 2016 study has the advantage over NHS Cost Calculator data in that it not only includes cost to discharge of the event but also the immediate follow up visits and any treatment directly related to treating the event over the first six months (which the EAG considers could still be considered 'acute'). As such the EAG has used the costs from the Danese 2016 study for second and subsequent CV events, inflated to 2024 prices using the NHS Cost Inflation Index (Source PSSRU 2024[66]). The costs used by the company and preferred by the EAG are shown in Table 10.

Table 10 Costs of subsequent events – company base case and EAG preferred

Description	Cost in model	Cost in Danese 2016	Danese 2016 cost inflated to 2024 values (EAG preferred)
Myocardial infarction	£3,902.63	£4301.01	£5451.05
Stroke	£5,709.99	£4572.28	£5794.85
Heart failure	£4,484.93	£3460.91	£4386.31
Hospitalisation for unstable angina	£1,633.79	£2489.48	£3155.14
Coronary revascularisation	£7,529.67	£5823.12	£7380.15

4.2.7.4 AE-related unit costs and resource use

A one-off cost per AE event is included in the first model cycle. The mean cost of each AE event is given in Table 39 of the CS.

EAG comment

The EAG considers it to be unusual that AE rates were included from the placebo arm of the trial for the current standard of care arm of the economic model and ordinarily would not include placebo AEs in an economic model. The SELECT trial showed a statistically significant difference in SAEs in favour of patients treated with semaglutide but the absolute difference was small and most of the individual SAEs were not statistically significant. As such, the EAG has removed AEs from the economic model. The EAG notes this makes minimal difference to cost effectiveness results.

4.2.7.5 Costs of T2D and CKD progression

The cost of a T2D or CKD progression event is included in the cycle the event occurs. The cost of T2D and CKD progression events are given in Table 40 of the CS.

EAG comment

The EAG is satisfied with how the costs of T2D and CKD were identified and included in the economic model.

5 COST-EFFECTIVENESS RESULTS

Section 5.1 summarises the company's cost-effectiveness results, Section 5.2 presents the EAG's additional work and preferred assumptions, and section 5.3 explores decision modifiers including the company's and EAG's preferred QALY weighting for severity. Section 5.4 highlights commercial access agreement (CAA) prices for semaglutide have been used and there are no other treatment costs in the model. Section 5.5 contains the EAG's cost effectiveness conclusions.

5.1 Company's cost-effectiveness results

5.1.1 Company's base case

Deterministic base-case results from the company economic model are presented in Table 11 and probabilistic results are shown in Table 12. A disease severity modifier of 1.0 was applied by the company. Results are taken from the economic model presented at the clarification stage.

Table 11 Company's deterministic base-case cost-effectiveness results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Established clinical management alone	£27,843	7.196	-	-	-
Semaglutide in addition to established clinical management	[redacted]	[redacted]	[redacted]	[redacted]	£14,702

The company considered a disease severity modifier of 1.0 is appropriate
ICER=incremental cost effectiveness ratio, QALY=quality adjusted life years
Source: Company economic model

Table 12 Company's probabilistic base-case cost-effectiveness results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Established clinical management alone	£28,109	7.149	-	-	-
Semaglutide in addition to established clinical management	[redacted]	[redacted]	[redacted]	[redacted]	£14,832

The company considered a disease severity modifier of 1.0 is appropriate
ICER=incremental cost effectiveness ratio, QALY=quality adjusted life years
Source: Company economic model

5.1.2 Company's sensitivity and scenario analyses

5.1.2.1 Deterministic sensitivity analyses

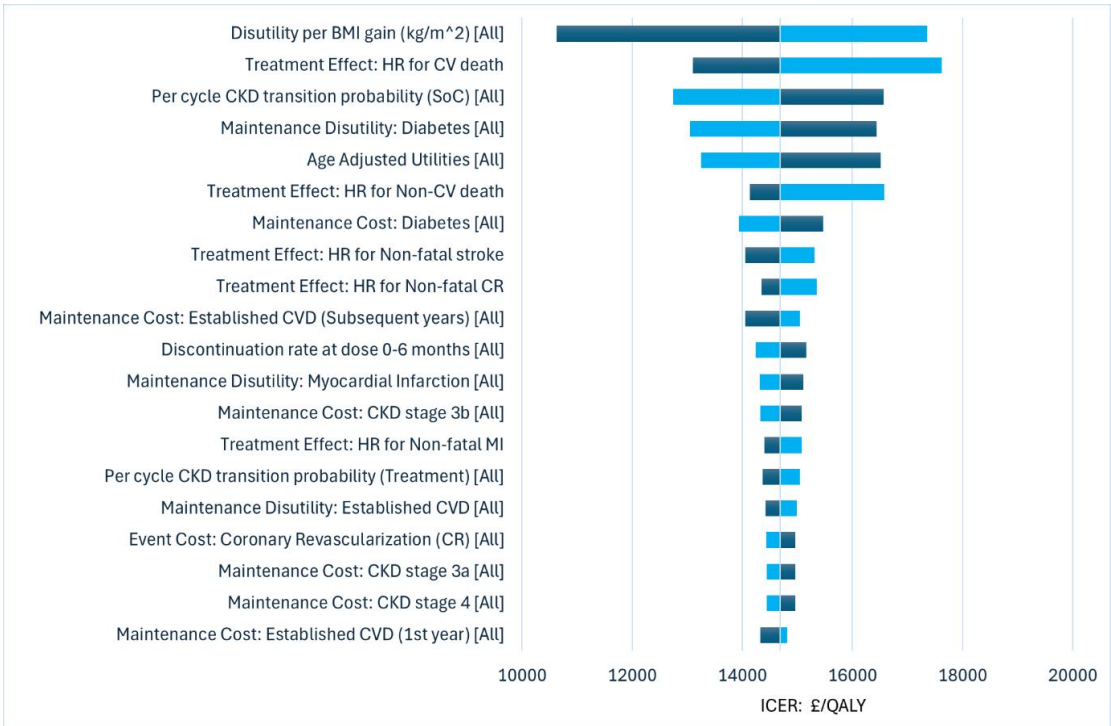
The company undertook a deterministic one-way sensitivity analysis (OWSA) by varying individual parameters. The top ten parameters with the biggest individual impact on the ICER are shown in Table 13 and Figure 3. Based on the results of the OWSA, the economic model was most sensitive to assumptions relating to utility values (BMI disutility, diabetes maintenance disutility and age-adjusted utilities), CKD transition probability and non-CV mortality rates.

Table 13 One-way sensitivity analysis results

Name [Applicable Arm]	Lower ICER	Upper ICER
Disutility per BMI gain (kg/m^2) [All]	£17,361	£10,633
Treatment Effect: HR for CV death	£13,099	£17,620
Per cycle CKD transition probability (SoC) [All]	£16,570	£12,738
Maintenance Disutility: Diabetes [All]	£16,437	£13,048
Age Adjusted Utilities [All]	£16,518	£13,246
Treatment Effect: HR for non-CV death	£14,134	£16,572
Maintenance Cost: Diabetes [All]	£15,468	£13,935
Treatment Effect: HR for non-fatal stroke	£14,056	£15,311
Treatment Effect: HR for non-fatal CR	£14,349	£15,347
Maintenance Cost: Established CVD (Subsequent years) [All]	£14,052	£15,046

The company considered a disease severity modifier of 1.0 is appropriate
BMI=body mass index, CKD=chronic kidney disease; CR=coronary revascularisation; eCVD=established cardiovascular disease; CV=cardiovascular; T2D=type 2 diabetes; HR=hazard ratio; ICER=incremental cost effectiveness ratio; MACE=Major Adverse Cardiovascular Events;
Source: CS, Table 47

Figure 3 Company base case one-way sensitivity analysis tornado diagram



The company considered a disease severity modifier of 1.0 is appropriate
Source: CS, Figure 27

5.1.2.2 Scenario analyses

The company carried out 16 scenario analyses (Table 14). These included scenarios 5 to 7 which related to issues with the population identified by the EAG (Section 2.3.2).

Table 14 Company scenario analyses results

Scenario	Scenario description	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
0	Base case	[redacted]	[redacted]	£14,702
1	People with 20% risk of MACE	[redacted]	[redacted]	£15,907
2	People with 30% risk of MACE	[redacted]	[redacted]	£15,017
3	People with 40% risk of MACE	[redacted]	[redacted]	£14,309
4	People with 50% risk of MACE	[redacted]	[redacted]	£13,721
5	People with T2D	[redacted]	[redacted]	£16,340
6	UK eCVD prevalent population	[redacted]	[redacted]	£11,072
7	UK eCVD incident population	[redacted]	[redacted]	£10,851
8	Real world discontinuation rates of 4.5% per month	[redacted]	[redacted]	£8,505
9	Efficacy extrapolation based on the best fitting proportional hazard model	[redacted]	[redacted]	£14,675
10	Efficacy extrapolation based on a single hazard model	[redacted]	[redacted]	£13,952
11	Efficacy extrapolation based on a trial data model	[redacted]	[redacted]	£14,524
12	Multiplicative utility combination for CV events	[redacted]	[redacted]	£14,897
13	Alternative CV cost approach	[redacted]	[redacted]	£14,954
14	Cost for non-CV death	[redacted]	[redacted]	£14,647
15	Discount rate for costs and benefits at 0%	[redacted]	[redacted]	£12,021
16	Discount rate for costs and benefits at 5%	[redacted]	[redacted]	£16,666

The company considered a disease severity modifier of 1.0 is appropriate
eCVD=established cardiovascular disease, CV= cardiovascular, T2D=type 2 diabetes, MACE=Major Adverse Cardiovascular Events, ICER=incremental cost effectiveness ratio, QALY=quality adjusted life years
Source: Values updated from economic model, based on CS, Table 51

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

The EAG conducted model validation and verification in the following areas:

- cross-checking of parameter values against their original data sources, where data were available
- assessment of consistency between the executable model, the descriptions provided in the CS, and the company's clarification response
- cell-by-cell checks to ensure the accuracy and integrity of model programming
- assessment of whether the model outputs were consistent with the model inputs and key outcomes from the trials and what clinical expert advice to the EAG would expect based upon outcomes from the SELECT trial
- reproduction of the base-case results, PSA, DSAs, and scenario analyses presented in the CS using the company's executable model.

The EAG is satisfied following these checks that the economic model results accurately represent the assumptions and parameter values specified by the company in the CS and/or at clarification. One algorithmic error was identified that affected QALY estimates of the model if the time horizon was shortened. This error was corrected by the EAG but did not affect base case results or any of the sensitivity or scenario analyses undertaken by the company.

Details of EAG revisions to the company cost effectiveness model are presented in Appendix 6 (Section 7.6).

5.2.2 EAG's exploratory analyses using company's base case

The EAG's individual revisions are summarised in Table 15 with the impact of each revision on the company base case provided in Table 16.

Probabilistic results would be expected to be almost identical given the similarity of the of the company base case deterministic and probabilistic results.

Table 15 Summary of EAG's exploratory analyses using company's base case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1	Included different CV event risks for events where the hazard rates were not statistically significantly different for patients treated with semaglutide or placebo in the SELECT trial.	Only modelled CV events where hazard rates were statistically significantly different for patients treated with semaglutide or placebo in the SELECT trial.	The lack of a statistically significant difference in hazard rates for a CV event between semaglutide and placebo in the SELECT trial means there is no robust statistical evidence to support modelling a different hazard rate for those events for patients treated with semaglutide or current standard of care.	4.2.5
2	Diabetes is included as a CV event risk modifier 3.3 years into the model time horizon.	Diabetes is not included as a CV event risk modifier.	The impact of differential diabetes rates on risk of CV event between patients treated with semaglutide or standard of care should have been captured within the SELECT trial with extrapolations beyond the trial time horizon being implicitly based upon how diabetes rates in patients treated with semaglutide or standard of care affected CV risk.	4.2.5
3	Semaglutide treatment discontinuation removes the benefit of semaglutide in reducing CV event risk 3.3 years into the model time horizon.	Semaglutide treatment discontinuation does not remove the benefit of semaglutide in reducing CV event risk.	The impact of treatment discontinuation on risk of CV event for patients treated with semaglutide should have been captured within the SELECT trial with extrapolations beyond the trial time horizon being implicitly based upon how discontinuation was impacting semaglutide efficacy in reducing CV risk.	4.2.5

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
4	Costs of subsequent CV events based on NHS Cost Calculator data inflated by evidence from Danese 2016.	Costs of subsequent CV events taken directly from Danese 2016 and inflated by the NHS Cost Inflation Index.	The company approach was overcomplicated and was not clearly identifying costs of second and subsequent CV events.	4.2.7
5	AE costs and AE utility losses were included in the model.	AE costs and AE utility losses were not included in the model	There was not a statistically significant difference in the majority of SAE rates between semaglutide and placebo in the SELECT trial.	4.2.7

AE=adverse event, CV=cardiovascular

Table 16 Results of EAG's exploratory analyses using company's base case

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs	ICER £/ QALY
1	Only modelled CV events where hazard rates were statistically significantly different for patients treated with semaglutide or placebo in the SELECT trial	[redacted]	[redacted]	£20,071
2	Diabetes is not included as a CV event risk modifier	[redacted]	[redacted]	£16,238
3	Semaglutide treatment discontinuation does not remove the benefit of semaglutide in reducing CV event risk	[redacted]	[redacted]	£6,442
4	Costs of subsequent CV events taken directly from Danese 2016 and inflated by the NHS Cost Inflation Index	[redacted]	[redacted]	£14,566
5	Adverse event costs and utility losses were not included in the economic model	[redacted]	[redacted]	£14,730

The EAG considers a disease severity modifier of 1.0 is appropriate
CV=cardiovascular, ICER=incremental cost effectiveness ratio, QALY=quality adjusted life years

5.2.3 EAG's preferred assumptions

The EAG's deterministic base case results are presented in Table 17 with probabilistic base case results in Table 18. Scenario analysis results for patients with T2D, for a UK eCVD prevalent population and a UK eCVD incident population are presented in Table 19.

Table 17 Deterministic results using EAG's preferred model assumptions

Analysis	Semaglutide		Established clinical management		Incremental		Deterministic ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Company base case	[redacted]	[redacted]	£27,843	7.196	[redacted]	[redacted]	£14,702
R1: Only modelled CV events where hazard rates were statistically significantly different for patients treated with semaglutide or placebo in the SELECT trial	[redacted]	[redacted]	£27,843	7.196	[redacted]	[redacted]	£20,071
R2: Diabetes is not included as a CV event risk modifier	[redacted]	[redacted]	£27,883	7.270	[redacted]	[redacted]	£16,238
R3: Semaglutide treatment discontinuation does not remove the benefit of semaglutide in reducing CV event risk	[redacted]	[redacted]	£27,843	7.196	[redacted]	[redacted]	£6,442
R4: Costs of subsequent CV events taken directly from Danese 2016 and inflated by the NHC Cost Inflation Index	[redacted]	[redacted]	£28,087	7.196	[redacted]	[redacted]	£14,566
R5: Adverse event costs and utility losses were not included in the economic model	[redacted]	[redacted]	£27,497	7.196	[redacted]	[redacted]	£14,730
EAG base case (R1-R5)	[redacted]	[redacted]	£27,742	7.271	[redacted]	[redacted]	£9,110

The EAG considers a disease severity modifier of 1.0 is appropriate
CV=cardiovascular, ICER=incremental cost effectiveness ratio, QALY=quality adjusted life years

Table 18 Probabilistic results using EAG's preferred model assumptions

Analysis	Semaglutide		Established clinical management		Incremental		Probabilistic ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Company base case	[redacted]	[redacted]	£28,109	7.141	[redacted]	[redacted]	£14,832
EAG base case	[redacted]	[redacted]	£27,902	7.226	[redacted]	[redacted]	£9,189

The EAG considers a disease severity modifier of 1.0 is appropriate
ICER=incremental cost effectiveness ratio, QALY=quality adjusted life years

Table 19 Scenario analyses of T2D, prevalent and incident populations using EAG base case (deterministic)

Scenario	Scenario description	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
0	EAG Base case	[redacted]	[redacted]	£9,110
5	People with T2D	[redacted]	[redacted]	£9,268
6	UK eCVD prevalent population	[redacted]	[redacted]	£10,382
7	UK eCVD incident population	[redacted]	[redacted]	£9,700

The EAG considers a disease severity modifier of 1.0 is appropriate
eCVD=established cardiovascular disease, T2D=type 2 diabetes, ICER=incremental cost effectiveness ratio, QALY=quality adjusted life years

5.3 Decision modifiers

5.3.1 QALY weighting for severity

The company did not consider that a severity modifier should be applied. The EAG considers a disease severity modifier of 1.0 is appropriate.

5.3.2 Uncaptured benefits

The company highlighted a number of benefits of treating the target population with semaglutide that they considered were not captured in the cost-effectiveness analysis (CS, Section 3.13):

- quality of life benefits from the use of semaglutide in people with HFpEF
- reduction in the risk of a range of health conditions (e.g. osteoarthritis, GI diseases, sleep apnoea, and several cancers) from the reduced weight achieved for patients treated with semaglutide.

EAG comment

The EAG agrees that these benefits are possible with treatment with semaglutide in the target population and would reduce the ICER per QALY gained for semaglutide.

The EAG considers that there are other uncaptured benefits not stated by the company or discussed in the CS or where the analysis is likely to be conservative:

- The HR for MACE in the SELECT trial was more favourable compared to placebo in the UK population as opposed to the overall trial FAS population (the results for the overall trial FAS population were used in the cost-effectiveness analysis). The SELECT trial therefore provides evidence that suggests that semaglutide may be more clinically effective (and therefore more cost effective) in a UK population than has been modelled by the company.
- The risk of all second CV events is substantially higher in the first six months after the first event than after the first six months. Provided CV event hazard ratios for patients treated with semaglutide seen in the SELECT trial were applicable to patients treated earlier after a first CV event than has been modelled by the company (i.e., in an incident population), semaglutide may be more cost-effective than in the company base case (as the company base case showed in the incident CPRD population).
- Impact on costs and quality of life with third and subsequent CV events may be more severe than the second CV event but no additional loss in quality of life or higher costs have been assumed for the third and subsequent CV events.
- The impact on caregiver quality of life, particularly for people affected by stroke, has not been captured.

5.3.3 Health inequalities

The company has presented information (CS, Section 1.4, see also EAG report Section 2.7) to suggest that CVD tends to disproportionally impact:

- people experiencing socioeconomic deprivation
- people of South Asian or sub-Saharan African ethnic origin
- men more than women, but women have worse outcomes than men
- people with experience of severe mental illness.

EAG comment

The EAG considers the evidence presented by the company supports a conclusion that differing CVD rates and outcomes for the populations outlined above will be a driver of health inequalities. Effective prevention of second and subsequent CV events may therefore reduce health inequalities.

5.4 Confidential comparator and subsequent treatment prices

CAA prices for semaglutide have been used. There are no other treatment costs in the model.

5.5 Conclusions of the cost-effectiveness section

The base case analyses provided by the company in their submission and at clarification do not provide evidence of the cost effectiveness of semaglutide for the full population specified in the final scope issued by NICE. The base case analyses explicitly excludes patients with diabetes at the time of the initial CV event (i.e., at screening) and is based upon SELECT trial data that excluded patients with recent CV events (within past 60 days prior to the day of screening). A scenario analysis did explore the potential cost effectiveness in a T2D population but required an assumption that semaglutide is equally effective in reducing CV events in T2D and non-diabetic populations. The company undertook a scenario analysis for an incident population but again this required an assumption semaglutide is equally effective regardless of the length of time from the first CV event.

The company analysis was unnecessarily complex in how some costs were calculated and adjustments to CV hazards after the end of the SELECT trial time horizon were included. However, these complexities also made the analysis potentially more conservative than simpler approaches adopted by the EAG.

The EAG considers that semaglutide has the potential to have an ICER below £20,000 per QALY gained in the population modelled by the company although some uncertainties remain about the overall cost of semaglutide treatment and the long-term efficacy of treatment. If the semaglutide discontinuation rate modelled by the company does not reflect the SELECT trial (and patients are on treatment longer than modelled)

and long-term efficacy is worse than modelled by the company or EAG than this would increase the ICER. However, there are likely benefits of semaglutide that have not been included in the analysis, perhaps most notably the impact of weight loss on non CV, diabetes or CKD health outcomes.

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7 APPENDICES

7.1 Appendix 1: Comparison of SELECT trial and CPRD "SELECT-like" patient characteristics

Table 20: Baseline characteristics that were similar in the SELECT trial to the "SELECT-like" population from the CPRD

Characteristic	SELECT trial			CPRD "SELECT-like" population
	Semaglutide (n=8803)	Placebo (n=8801)	All FAS (N=17,604)	N=141,642
Sex, n (%)				
Female	2448 (27.8)	2424 (27.5)	4872 (27.7)	[redacted]
Male	6355 (72.2)	6377 (72.5)	12,732 (72.3)	[redacted]
Body weight, kg, mean (SD)	96.5 (17.5)	96.8 (17.8)	[redacted]	[redacted]
HbA1c, n (%)				
<5.7%	2925 (33.2)	2980 (33.9)	5905 (33.5)	[redacted][a]
≥5.7%	5877 (66.8)	5879 (66.1)	11,756 (66.8)	[redacted][a]
CV inclusion criteria				
Two or more inclusion criteria	718 (8.2)	719 (8.2)	1437 (8.2)	[redacted]
Chronic HF, n (%)	2155 (24.5)	2131 (24.2)	4286 (24.3)	[redacted]
eGFR, ml/min/1.73 m2, mean (SD)	82.4 (17.5)	82.5 (17.3)	[redacted]	[redacted][b]
Median lipid level (IQR) –mg/dl				
Total cholesterol	153 (131–182)	153 (131–183)	[redacted]	[redacted][c]
HDL cholesterol	44 (37–52)	44 (37–52)	[redacted]	[redacted][d]
LDL cholesterol	78 (61–102)	78 (61–102)	[redacted]	[redacted][e]
Triglycerides	134 (99–188)	135 (100–190)	[redacted]	[redacted][f]
Mean systolic blood pressure (SD) – mmHg	131.0 (15.6)	130.9 (15.3)	131.0 [redacted]	[redacted][g]
Mean diastolic blood pressure (SD) – mmHg	79.4 (10.0)	79.2 (9.9)	79.3 [redacted]	[redacted][h]
Pulse – beats/min	68.9 (10.6)	68.6 (10.7)	68.8 [redacted]	[redacted][i]

[a]Excludes not reported (n=[redacted]), hence N=[redacted]
[b]Excludes not reported (n=[redacted]), hence N=[redacted]
[c]Excludes not reported (n=[redacted]), hence N=[redacted]
[d]Excludes not reported (n=[redacted]), hence N=[redacted]
[e]Excludes not reported (n=[redacted]), hence N=[redacted]
[f]Excludes not reported (n=[redacted]), hence N=[redacted]
[g]Excludes not reported (n=[redacted]), hence N=[redacted]
[h]Excludes not reported (n=[redacted]), hence N=[redacted]
[i]Excludes not reported (n=[redacted]), hence N=[redacted]

CV=cardiovascular; eGFR=estimated glomerular filtration rate; HbA1=glycated haemoglobin; HDL=high density lipoprotein; HF=heart failure; IQR=interquartile range; LDL=low density lipoprotein; mmHg=millimetres of mercury; SD=standard deviation

Source: Response to clarification question A7, Table 1, SELECT trial CTR,[49] Table 10-5, Table 10-9, Table 10-12

Table 21: Baseline characteristics that differed in the SELECT trial to the "SELECT-like" population from the CPRD

Characteristic	SELECT trial			CPRD "SELECT-like" population
	Semaglutide (n=8803)	Placebo (n=8801)	All FAS (N=17,604)	N=141,642
Age, years, mean (SD)	61.6 (8.9)	61.6 (8.8)	61.6 [redacted]	[redacted]
Age group, n (%)				
<55 years	2057 (23.4)	2094 (23.8)	4151 (23.6)	[redacted]
55 to <65 years	3387 (38.5)	3338 (37.9)	6725 (38.2)	[redacted]
65 to <75 years	2656 (30.2)	2706 (30.7)	5362 (30.5)	[redacted]
≥75 years	703 (8.0)	663 (7.5)	1366 (7.8)	[redacted]
Race/ethnicity, n (%)				
White	7387 (83.9)	7404 (84.1)	14,791 (84.0)	[redacted][a]
Asian	720 (8.2)	727 (8.3)	1447 (8.2)	[redacted][a]
Black/African American	348 (4.0)	323 (3.7)	671 (3.8)	[redacted][a]
Other	227 (2.9)	247 (3.1)	474 (2.7)	[redacted][a]
Hispanic or Latino	914 (10.4)	908 (10.3)	1822 (10.3)	[redacted][a]
BMI, n (%)				
27 to <30 kg/m^2	2555 (29.0)	2469 (28.1)	5024 (28.5)	[redacted][b]
30 to <35 kg/m^2	3693 (42.0)	3781 (43.0)	7474 (42.5)	[redacted][b]
35 to <40 kg/m^2	1687 (19.2)	1659 (18.9)	3346 (19.0)	[redacted][b]
40 to <45 kg/m^2	579 (6.6)	595 (6.8)	1173 (6.7)	[redacted][b]
≥45 kg/m^2	289 (3.3)	297 (3.4)	586 (3.3)	[redacted][b]
CV inclusion criteria				
Only MI	5962 (67.7)	5944 (67.5)	11,906 (67.6)	[redacted]
Only stroke	1578 (17.9)	1556 (17.7)	3134 (17.8)	[redacted]
Only PAD	376 (4.3)	401 (4.6)	777 (4.4)	[redacted]

[a]Excludes not reported (n=[redacted]), hence N=[redacted]
[b]Excludes not reported (n=[redacted]), hence N=[redacted]
SD=standard deviation, CV=cardiovascular, CPRD= Clinical Practice Research Datalink, BMI=body mass index, MI=myocardial infarction, PAD=peripheral arterial disease
Source: Response to clarification question A7, Table 1, SELECT trial CTR,[49] Table 10-2

7.2 Appendix 2: Concomitant medications in the SELECT, STEP-HFpEF and STEP-HFpEF DM trials

Table 22 Concomitant CV-related medication ongoing at randomisation (FAS populations)

Medication	SELECT		STEP HFpEF		STEP HFpEF DM	
	Semaglutide (n=8803)	Placebo (n=8801)	Semaglutide (n=263)	Placebo (n=266)	Semaglutide (n=310)	Placebo (n=306)
CV medications, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta blockers, n (%)	6182 (70.2)	6175 (70.2)	201 (76.4)	217 (81.6)	257 (82.9)	253 (82.7)
ACE inhibitors, n (%)	3963 (45.0)	3966 (45.1)	[redacted]	[redacted]	[redacted]	[redacted]
Angiotensin receptor blockers, n (%)	2618 (29.7)	2569 (29.2)	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blockers, n (%)	2407 (27.3)	2331 (26.5)	[redacted]	[redacted]	[redacted]	[redacted]
ARNI, n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lipid-lowering drugs, n (%)	7928 (90.1)	7929 (90.1)	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics, n (%)	[redacted]	[redacted]	207 (78.7)	220 (82.7	246 (79.4)	252 (82.4)
Platelet aggregation inhibitors, n (%)†	7612 (86.5)	7569 (86.0)	74 (28.1)	74 (27.8)	126 (40.6)	133 (43.5)
Anti-thrombotic medications, n (%)	1086 (12.3)	1150 (13.1)	[redacted]	[redacted]	[redacted]	[redacted]
Anti-arrhythmic agents, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-angina agents, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Includes aspirin and P2Y12 inhibitors
ACE=Angiotensin-Converting Enzyme; ARNI=Angiotensin Receptor-Neprilysin Inhibitor; CV=cardiovascular; FAS=full analysis set
Source: CS, Table 9; Kosiborod 2023[30] and STEP-HFpEF CTR[55] (Table 49); Kosiborod 2024[31] and STEP-HFpEF DM CTR[54] (Tables 4-6) and STEP-HFpEF CTR[55] (Table 49); Kosiborod 2024[31] and STEP-HFpEF DM CTR[54] (Tables 4-6)

7.3 Appendix 3: Quality assessment of included trials

Table 23: Quality assessment of RCTs using the NICE 7-item checklist for RCTs

Question	SELECT	STEP-HFpEF	STEP-HFpEF DM
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Partially (see text below table)	Partially (see text below table)
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in dropouts between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
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	Yes	Yes

RCT=randomised controlled trial
Source: CS, Appendix B.5, Table 12

The company identified the following minor differences in baseline characteristics (semaglutide versus placebo):

- STEP-HFpEF trial: the proportions of patients with NYHA functional class III or IV HF (30.4% vs 37.2%), the proportions of patients receiving concomitant beta blockers (76.4% vs 81.6%) and the median levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (414.4 pg/ml vs 499.8 pg/ml)
- STEP-HFpEF DM trial: the proportions of female patients (41.3% vs 47.4%), White patients (81.0% vs 87.6%) and patients with hypertension (88.6% vs 82.3%).

7.4 Appendix 4: Endpoints that can be compared across trials

Table 24 Comparison of endpoints reported in the SELECT trial that were also reported in the STEP-HFpEF and STEP-HFpEF DM trials

Endpoint	SELECT (104 weeks)				STEP-HFpEF (52 weeks)				STEP-HFpEF DM (52 weeks)				Source in CS
	SEM n=8803	PBO n=8801	Effect (95% CI)	p-value	SEM n=263	PBO n=266	Effect (95% CI)	p-value	SEM n=310	PBO n=306	Effect (95% CI)	p-value	
HF hospitalisation or urgent HF visit, n (%)	97 (1.1)	122 (1.4)	HR= 0.79 (0.60 to 1.03)	[redacted]	1 (0.4)	12 (4.5)	HR= 0.08 (0.00 to 0.42)	–	7 (2.3)	18 (5.9)	HR= 0.40 (0.15 to 0.92)	–	Table 14 pp 97-98 Figures 17-18
hsCRP ratio to baseline	[redacted]	[redacted]	ETR= 0.62 to (0.60 to 0.64)	[redacted]	0.56	0.93	ETD= [redacted]	[redacted]	0.58	0.87	ETD= [redacted]% [redacted]	[redacted]	Table 21 Sections 2.6.2.3.1 + 2.6.2.3.2
SBP, change from baseline, mmHg	−3.82	−0.51	ETD= −3.31 (−3.75 to −2.88)	[redacted]	−4.9	−2.0	ETD= −2.9 (−5.8 to 0.1)	–	−4.2	−1.7	ETD= −2.5 (−5.3 to 0.3)	–	Table 21 Sections 2.6.2.3.1 + 2.6.2.3.2
DBP, change from baseline, mmHg	−1.02	−0.47	ETD= −0.55 (−0.83 to −0.27)	[redacted]	[redacted]	[redacted]	[redacted]	–	[redacted]	[redacted]	[redacted]	–	Table 21 Sections 2.6.2.3.1 + 2.6.2.3.2 CQ A6
Body weight, change from baseline, %	−9.39	−0.88	ETD= −8.51 (−8.75 to −8.27)	[redacted]	−13.3	−2.6	ETD= −10.7- (−11.9 to −9.4)	<0.001	−9.8	−3.4	ETD= −6.4 (−7.6 to −5.2)	<0.0001	Table 22 Section 2.6.2.2

Note: Data in shaded cells taken from response to clarification question A6 (see also Table 18 of additional outputs[67]) which differ to the data reported in the CS, Section 2.6.2.3.1 and 2.6.2.3.2

CS=company submission; DPB=diastolic blood pressure; ETD=estimated treatment difference; ETR=estimated treatment ratio; HF=heart failure; hsCRP=high-sensitivity C-reactive protein; PBO=placebo; SEM=semaglutide; SBP=systolic blood pressure

7.5 Appendix 5: Quality of life results

7.5.1 SELECT trial quality of life results

The company highlighted (CS, p75) that in the SELECT trial, semaglutide led to improved EQ-5D-5L and EQ-5D-VAS scores versus placebo (a higher score from 0 to 1 and 0 to 100, respectively, indicates better health status). Semaglutide also resulted in improved weight-related signs and symptoms measure (WRSSM) scores versus placebo (lower scores from 0 to 4 indicate improved symptoms).

The EAG agrees that semaglutide resulted in improved PROs compared with placebo (see Table 25). However, the EAG also notes that, it was highlighted in the company's advisory board minutes[47] that [redacted].

Table 25 SELECT trial PROs at Week 104 reported in the CS (primary estimand, FAS – in-trial)

Endpoint	Semaglutide (n=8803)	Placebo (n=8801)	ETD (95% CI)	p-value
Change in EQ-5D-5L index	0.01	−0.01	0.01 (0.01 to 0.02)	[redacted]
Change in EQ-5D-5L VAS	2.52	0.92	1.60 (1.16 to 2.04)	[redacted]
Change in WRSSM	[redacted]	[redacted]	[redacted]	[redacted]

EQ-5D 5L=EuroQol 5-Dimension, 5 Level, VAS=visual analogue scale, WRSSM=weight-related signs and symptoms measure
Source: CS, Section 2.6.1.4.5

7.5.2 STEP-HFpEF and STEP-HFpEF DM trials quality of life results

Quality of life was reported using the KCCQ-CSS co-primary endpoint in the STEP-HFpEF and STEP-HFpEF DM trials (CS, Sections 2.6.2.2.1.2 and 2.6.2.2.2.2). Superiority of semaglutide over placebo was demonstrated by an estimated treatment difference (ETD) of 7.8 points (95% CI: 4.8 to 10.9; p<0.001) and an ETD of 7.3 points (95% CI: 4.1 to 10.4; p<0.0001), respectively. Results from an analysis of EQ-5D-5L and EQ-5D-VAS scores are presented in the CTRs and summarised in Table 26. The results show [redacted].

Table 26 STEP-HFpEF trial and STEP-HFpEF DM trial PROs at Week 52

Endpoint	STEP-HFpEF		STEP-HFpEF DM	
	Semaglutide (n=263)	Placebo (n=266)	Semaglutide (n=310)	Placebo (n=306)
Change in EQ-5D-5L index	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D-5L VAS	[redacted]	[redacted]	[redacted]	[redacted]

EQ-5D 5L=EuroQol 5-Dimension, 5 Level, VAS=visual analogue scale
Source: STEP-HFpEF CTR, Section 5.1.2.4 and STEP-HFpEF DM CTR, Section 5.1.2.4

7.6 Appendix 6: EAG revisions to the company model

All revisions have been applied to the company model provided at clarification.

EAG revision	Implementation instructions
Set up EAG revision switches	Insert sheet 'EAG revisions' Set cell B3="EAG_R1" Set cell C3="Only statistically significant results" Name cell D3 ="EAG_R1"
R1) Only statistically significant results	In sheet 'EAG revisions' Set cell D3 = 1 In Sheet "Treatment Trace" Set Cell CG13= IF(EAG_R1=1,'ControlTrace'!CG13,IF($CS13=1,0,IF(OR(Control03RiskEquationManual12NonFatalStroke_00=INDEX(Manual02NonFatalStroke02AlternativeExtrapolations,1),$C13>$CJ$9),IF(OR(EXACT(AX14,0),EXACT(AX13,0),EXACT(BF14,0),EXACT(BF13,0)),0,1-EXP(-(-LN(AX14/AX13)*(1-$S12+$S12*IF($C13>$CI$2,CG$7,1))*CG$4*$CE13+(-LN(BF14/BF13))*(1-$S12+$S12*IF($C13>$CI$2,CG$7,1))*CG$4*(1-$CE13)))),IF(OR(EXACT(BN14,0),EXACT(BN13,0),EXACT(BV14,0),EXACT(BV13,0)),0,1-EXP(-(-LN(BN14/BN13)*(1-$S12+$S12*CG$7)*CG$4*$CE13+(-LN(BV14/BV13))*(1-$S12+$S12*CG$7)*CG$4*(1-$CE13))))))) Copy Cell CG13 Paste to range CG13:CI733 Set Cell CK13= IF(EAG_R1=1,'ControlTrace'!CK13,IF(OR(INDEX(LifeTables01Male,MIN(ROUND($K13,0),101))=1,INDEX(LifeTables02Female,MIN(ROUND($K13,0),101))=1,$K13>=101),0,IF(OR(Control03RiskEquationManual16CVdeath_00=INDEX(Manual06CVdeath02AlternativeExtrapolations,1),$C13>$CJ$9),IF(OR(EXACT(BB14,0),EXACT(BB13,0),EXACT(BJ14,0),EXACT(BJ13,0)),0,1-EXP(-(-LN(BB14/BB13)*(1-$S12+$S12*IF($C13>$CI$2,CK$7,1))*CK$4*$CE13+(-LN(BJ14/BJ13))*(1-$S12+$S12*IF($C13>$CI$2,CK$7,1))*CK$4*(1-$CE13)))),IF(OR(EXACT(BR14,0),EXACT(BR13,0),EXACT(BZ14,0),EXACT(BZ13,0)),0,1-EXP(-(-LN(BR14/BR13)*(1-$S12+$S12*IF($C13>$CI$2,CK$7,1))*CK$4*$CE13+(-LN(BZ14/BZ13))*(1-$S12+$S12*IF($C13>$CI$2,CK$7,1))*CK$4*(1-$CE13))))))) Copy Cell CK13 Paste to rangeCK13:CK733

EAG revision	Implementation instructions
R2) Diabetes not included as a CV event risk modifier	In Sheet “Model Control” Enter ‘Advanced clinical inputs’ menu Select tab ‘In trial period’ Set mean of ‘remove diabetes HRs’ to ‘40’ Press ‘save as new’ and save as ‘EAG R2’ Press ‘Load’
R3) Semaglutide treatment discontinuation does not remove the benefit of semaglutide in reducing CV event risk	In Sheet “Model Control” Enter ‘Advanced clinical inputs’ menu Select tab ‘In trial period’ Set mean of ‘whole arm treatment effect’ to ‘40’ Press ‘save as new’ and save as ‘EAG R3’ Press ‘Load’
R4) Costs of subsequent CV events taken directly from Danese 2016 and inflated by the NHC Cost Inflation Index	In Sheet “Model Control” Enter ‘Cost profile’ menu Select tab ‘Event costs’ Set mean of ‘myocardial infarction’ to ‘5451.05’ Set mean of ‘Stroke’ to ‘5794.85’ Set mean of ‘hospitalisation for heart failure to ‘4386.31’ Set mean of ‘unstable angina’ to ‘3155.14’ Set mean of ‘coronary revasculisation’ to ‘7380.15’ Press ‘save as new’ and save as ‘EAG R4’ Press ‘Load’
R5) Adverse event costs and utility losses were not included in the model	In Sheet “Model Control” Enter ‘Safety profile’ menu Select ‘No AEs’ Press ‘Load’

EAG revision	Implementation instructions
R6) EAG base case	In sheet ‘EAG revisions’ Set cell D3 = 1 In Sheet “Model Control” Enter ‘Advanced clinical inputs’ menu Select tab ‘In trial period’ Set mean of ‘remove diabetes HRs’ to ‘40’ Set mean of ‘whole arm treatment effect’ to ‘40’ Press ‘save as new’ and save as ‘EAG base case’ Press ‘Load’ Enter ‘Cost profile’ menu Select cost profile ‘EAG R4’ Press ‘load’ Enter ‘Safety profile’ menu Select ‘No AEs’ Press ‘Load’

Single Technology Appraisal

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and living with overweight or obesity [ID6441]

EAG report – factual accuracy check and confidential information check

EAG response (5 December 2025)

Contents

Issue 1 **High Priority: The confidential price should be used in the cost-effectiveness analysis, and the current lack of confidential marking in the EAG report allows back calculation of confidential price**

The company considers that removing the list price and using the confidential price in the cost effectiveness analysis to be high priority. In addition, whether the list price or confidential price is used, confidential marking of cost-effectiveness results and outputs throughout the EAG report is required to prevent back calculation of the confidential price. **For results using the list price, all outputs including the ICERs should be redacted.**

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, page 14, page 19, page 65 The EAG states "At the request of NICE, list prices have been used in all analyses" In EAG report the company and EAG cost-effectiveness results are presented based on the list price (section 1.6, section 5.1 and section 5.2).	Please amend "At the request of NICE, list prices have been used in all analyses" To "There is no PAS in place for semaglutide (Wegovy®). Instead, a confidential CAA between Novo Nordisk and NHS England exists for semaglutide (Wegovy®), allowing the NHS to procure semaglutide	The price of Wegovy® used in the cost-effectiveness analysis should be the current net price values (e.g. £[redacted] per pack for the 2.4mg dose), not the list price values as currently applied. [redacted] This means that the current EAG cost-effectiveness results substantially underestimate	The EAG was originally advised by NICE to use list prices for semaglutide in all analyses and was advised that the use of list prices did not need to be confidential (original EAG report, 16 October 2025). Following advice from NICE, the EAG submitted an updated report using list prices but with the confidential marking requested by

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	[redacted] The 1.7 mg and 2.4 mg presentations of semaglutide (Wegovy®) are provided to the NHS at a [redacted], respectively, and this price has been included in the economic analysis of this submission." Please re-run the cost-effectiveness analyses using the confidential price and also update the confidential markings in the results section as outlined in the "incorrect confidentiality marking" section of this document.	the cost-effectiveness of semaglutide. It is important to ensure that the current net price remains confidential in all documentation until such a time that price confidentiality is formally removed. The use of the list price in the EAG report, when paired with the results reported in the CS allows back calculation of the confidential discount used in the CS.	the company (4 November 2025). The EAG has now updated the EAG report using only CAA prices (5 December 2025). All relevant data has been marked as confidential as requested by the company.

Abbreviations: CAA, commercial access arrangement; CS, company submission; EAG, External Assessment Group; NICE, National Institute of Health and Care Excellence; PAS, patient access scheme.

Issue 2 Inclusion of AE rates from placebo arm of the trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG reports, page 64, section 4.2.7.4, EAG comment The EAG states *"EAG considers it to be unusual that AE rates were included from the placebo arm of the trial"*	Please amend "EAG considers it to be unusual that AE rates were included from the placebo arm of the trial" To The CS considered AE rates from both the semaglutide and placebo arms of the SELECT trial.	The NICE STA user guide (1) recommends that adverse reactions in controlled trials are reported for each group. This allows the incremental impact of therapy to be identified. The company interprets AEs in the placebo arm as being associated with usual care that these patients receive rather than with the inactive placebo given as part of the trial. As shown in EAG exploratory analysis R5 this has a very small impact on results.	This is not a factual inaccuracy and, as the company states, a matter of interpretation. The EAG analysis was exploratory in nature. No change made.

Abbreviations: AE, adverse events; CS, company submission; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; STA, single technology appraisal.

Issue 3 High priority: Include SELECT trial primary endpoint in base case model and exploratory analyses R1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG key issue 5: sections 1.1 & 1.3, also 3.3.2.1, 4.2.5, 5.2.2, and 5.2.3 (R1) EAG states "The company included CV events in the economic model where no statistically significant differences were observed" (1.3.5) EAG scenarios and preferred base case assume equal risk of non-fatal stroke and confirmed CV death between arms on grounds that "they were not statistically significantly different for patients treated with semaglutide or placebo in the SELECT trial" (4.2.5) Section 1.3.5 states that "Inclusion of non-statistically significant CV events in the model means that the ICER	1. Amend EAG exploratory analyses R1 and base case model to include the SELECT trial primary endpoint, a hazard ratio of 0.80 (95% CI: 0.72, 0.90; p<0.0001) for all MACE endpoints: non-fatal MI, non-fatal stroke and confirmed CV death. 2. Amend section 1.3.5 to state that "Exclusion of non-statistically significant CV events in the EAG model will introduce a bias that overestimates the ICER per QALY gained for semaglutide but is a more conservative interpretation of the SELECT trial data. The CS follows guidance in the NICE manual (4.7.12) that uncertain parameters should be included in cost-effectiveness analysis, not excluded (2).	1. The EAG approach aims to include endpoints with 95% CIs suggestive of significant difference between arms, subject to comment about multiple endpoints and type I error. The approach in the EAG exploratory analyses R1 and base case model however does not reflect the significant benefit shown in MACE – it includes benefit for part of MACE only, non-fatal MI. This is not consistent with EAG's stated approach, as benefit in the model no longer reflects a statistically significant benefit shown in the trial – in this case the primary endpoint. The proposed amendment allows EAG to test a more	This is not a factual inaccuracy. The company model does not model a composite endpoint but rather multiple endpoints from the SELECT trial, all modelled individually (i.e., not with a single HR of 0.8 applied to each endpoint for patients treated with semaglutide). The benefit shown in MACE exists in the model after the EAG amendment as statistically significant endpoints are still modelled. Modelling of non-statistically significant trial results is a matter of interpretation of

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
per QALY gained for semaglutide may have been underestimated.”		conservative interpretation of CIs while still reflecting the statistically significant primary endpoint of the SELECT trial. 2. The unbiased estimate of benefit is the point estimate from the trial. Using a non-statistically significant point estimate does not introduce directional bias, so stating that the ICER is “underestimated” is incorrect. Not using a point estimate that is known to favour the intervention does introduce directional change – it increases the ICER – hence the EAG approach introduces bias. As noted by EAG, this issue has a medium impact on results.	evidence, not a factual inaccuracy.

Abbreviations: CI, confidence interval; CV, cardiovascular; EAG, External Assessment Group; ICER, incremental cost effectiveness ratio; MACE, major adverse cardiovascular event; QALY, quality adjusted life year.

Issue 4 Inaccuracies in wording

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13 Table B, column 1, row 3 The EAG states *"Key issue 4: Costs of subsequent CV events taken directly from Danese 2016 (3) and inflated by the NHS Cost Inflation Index"* EAG challenges company cost inputs as incorrect and data retrieval from Danese et al as unclear.	No amendment proposed.	The company acknowledges that there was an error in the CS and the EAG approach is reasonable. The company notes that the impact of the EAG change is very small.	No change to EAG report necessary.
Page 7, section 1.1, page 11, section 1.3.6 and page 13, section 1.6	Please correct table B (page 13) to reflect that key issue 4 relates to cost of semaglutide (as noted in section 1.1 and 1.3.6).	For clarity and accuracy	Thank you for highlighting this inconsistency. Revision 4 (R4) which does not relate to a key issue in the summary was inadvertently included

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG has attributed costs of subsequent CV events to key issue 4.			in Table B in error. The EAG has not made any revisions in relation to key issue 4. R4, which was mislabelled as key issue 4, has been removed from Table B.
Page 20 Section 2.3.1, EAG comment The EAG states *"The EAG highlights that the intervention in this appraisal is specific to semaglutide marketed as Wegovy® not Ozempic® (subcutaneous semaglutide used in clinical practice for type 2 diabetes [T2D]) or Rybelus® (oral semaglutide used in clinical practice for T2D)."* There is a lack of clarity that the specific difference in the marketed versions of	Please amend The EAG highlights that the intervention in this appraisal is specific to semaglutide marketed as Wegovy® not Ozempic® (subcutaneous semaglutide used in clinical practice for type 2 diabetes [T2D]) or Rybelsus® (oral semaglutide used in clinical practice for T2D). To The EAG highlights that the intervention in this appraisal is specific to semaglutide marketed as Wegovy® (subcutaneous semaglutide, 2.4mg once weekly) not Ozempic®	Additional details provide accuracy and clarity that both route of administration and dose differences are relevant considerations.	Thank you for highlighting this. Text amended in EAG report for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
semaglutide relate to both route of administration and dose.	(subcutaneous semaglutide, indicated for insufficiently controlled type 2 diabetes [T2D] and with different dose escalation schedule and maintenance dose) or Rybelsus® (once daily oral semaglutide tablets indicated for insufficiently controlled T2D).		
Page 27 Section 3.2.2, EAG comment The EAG states *"It is unclear whether counselling in the SELECT trial differed in intensity or uptake between arms and if this influenced outcomes. However, this may not have resulted in systematic bias between arms due to the trial's double-blind design and similar baseline characteristics"* The company are concerned that the wording used when	Please amend "It is unclear whether counselling in the SELECT trial differed in intensity or uptake between arms and if this influenced outcomes. However, this may not have resulted in systematic bias between arms due to the trial's double-blind design and similar baseline characteristics" To "It is not known whether the intensity and uptake of counselling in the SELECT trial differed between individual participants, however the trial's double-blind design and similar baseline characteristics between arms	The language used "…may not have resulted in systematic bias…" implies that there were differences between the arms however there is no suggestion that this was the case. The company proposes the wording is changed to avoid risk of misinterpretation/over interpretation.	Thank you for highlighting this. Text amended in EAG report for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
discussion the counselling provided in the SELECT trial may be open to misinterpretation.	is expected to ensure that any variation was balanced across treatment arms.”		
Page 29, table 3, column 2 and 3 The EAG states *“MACE endpoint not measured in the study”*	Please amend “MACE endpoint not measured in the study” To “MACE endpoint was not a prespecified outcome in the study”	Corrected for accuracy.	Thank you for highlighting this. Table text amended in EAG report for accuracy.
EAG report, page 38, table 4 Incorrect p value for confirmed secondary endpoint ‘Confirmed CV death’	Please amend [redacted] To [redacted]	Corrected to align with p value reported in table 15 of CS	Thank you for highlighting this. Table text amended in EAG report for accuracy.
EAG report, page 38, table 4 Incorrect source reference for confirmatory secondary endpoint ‘All cause death’	Please amend CS, table 15 and 17 To CS, table 17	Corrected for accuracy	Thank you for highlighting this. Table text amended in EAG report for accuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 61 Section 4.2.6, EAG Comment The EAG states *"Utility decrements for CV events, CKD and diabetes may already be partly incorporated into the age-related decrements…"*	Please amend "Utility decrements for CV events, CKD and diabetes…" To "Utility decrements for CKD and diabetes…"	It is unclear how the use of CVD free general population utilities results in double counting from CV events, since presumably all patients experiencing a CV event also has CVD, and was thus not included in the CVD-free utility. The company therefore suggests removing CV events.	Thank you for highlighting this. The sentence has been changed in line with the company suggestion
EAG report, page 69 Section 5.2.1, EAG comment The EAG states *"Details of EAG revisions to the company cost comparison model are presented in Appendix 6"* Incorrect classification of company economic model as a cost comparison model	Please amend "Details of EAG revisions to the company cost comparison model are presented in Appendix 6" To "Details of EAG revisions to the company cost effectiveness model are presented in Appendix 6"	Correction of company economic model type for accuracy	Thank you for highlighting this. Text amended in EAG report for accuracy.

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; EAG, External Assessment Group; T2D, type 2 diabetes

Issue 5 Minor typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 11 Section 1.3.3, column 2, row 4 Duplicate word	Please amend "…characteristics seen in NHS practice suggest that suggest that the cost effectiveness…" To "…characteristics seen in NHS practice that suggest that the cost effectiveness…"	Deletion of duplicate word for clarity and readability	Thank you for highlighting this. Text amended in EAG report.
Page 20 Section 2.3.1, EAG comment Spelling of Rybelsus® is incorrect	Please amend Rybelus® To Rybelsus®	Correction of spelling of drug name for accuracy	Thank you for highlighting this. Text amended in EAG report for accuracy.
Page 21 Section 2.3.2.1, EAG comment	Please amend Rybelus® To Rybelsus®	Correction of spelling of drug name for accuracy	Thank you for highlighting this. Text amended in EAG report for accuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Spelling of Rybelsus® is incorrect			
Page 27 Section 3.2.2, line 2 Duplicate word	Please amend "…that unlike in the the STEP-HFpEF and STEP-HFpEF DM trials…" To "…that unlike in the STEP-HFpEF and STEP-HFpEF DM trials…"	Deletion of duplicate word for clarity and readability	Thank you for highlighting this. Text amended in EAG report.
Page 36 Section 3.3.2.1, EAG comment Incomplete/missing word	Please amend "The EAG observes that curves also converged around the same time with regard to first EAC-confirmed composite HF out…" To "The EAG observes that curves also converged around the same time with regard to first EAC-confirmed composite HF outcome…"	Correction for clarity	Thank you for highlighting this. Text amended in EAG report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, page 42 Section 3.3.4, EAG comment Spelling of 'weight'	Please amend "…were observed regardless of wight loss within the first …" To "…were observed regardless of weight loss within the first …"	Correction for clarity	Thank you for highlighting this. Text amended in EAG report.
EAG report, page 45 Section 3.3.7, EAG comment Spelling of Rybelsus® is incorrect	Please amend Rybelus® To Rybelsus®	Correction of spelling of drug name for accuracy	Thank you for highlighting this. Text amended in EAG report.
EAG report, page 49 Section 3.7 Spelling of Rybelsus® is incorrect	Please amend Rybelus® To Rybelsus®	Correction of spelling of drug name for accuracy	Thank you for highlighting this. Text amended in EAG report.
EAG report, page 50 Section 4.1, paragraph 3	Please amend "…have not been updated since 2026)."	Correction of date for accuracy	Thank you for highlighting this. Text

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incorrect date cited for last legacy database update.	To "…have not been updated since 2016).		amended in EAG report.
EAG report, page 54 Section 4.2.2, paragraph 1 Typographical error in outcome abbreviation	Please amend "…hospitalisation for HF (HHH)…" To "…hospitalisation for HF (HHF)…"	Correction of abbreviation for accuracy	Thank you for highlighting this. Text amended in EAG report.
EAG report, page 63 Section 4.2.7.3, EAG comment Space between words to be added	Please amend "…second CV events to the NHSthat this can…" To "…second CV events to the NHS that this can…"	Correction for readability	Thank you for highlighting this. Text amended in EAG report.
EAG report, page 74, table 19	Please amend	Correction for accuracy	Thank you for highlighting this. Text

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incorrect table number, update table reference	"Table 18 Scenario analyses of T2D, prevalent and incident populations using EAG base case (deterministic)" To "Table 19 Scenario analyses of T2D, prevalent and incident populations using EAG base case (deterministic)"		amended in EAG report. List of tables also corrected in the EAG report.

Abbreviations: EAG, External Assessment Group; HHF, hospitalisation for heart failure; NHS, National Health Service; T2D, type 2 diabetes

Incorrect confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report, page 31 Missing CiC marking	The median time from qualifying CV event to randomisation for the SELECT trial is not currently in the public domain and is considered commercially sensitive information.	Please add CiC marking as follows: • SELECT trial patients had eCVD for a shorter time (median time from qualifying CV event to randomisation was [redacted] years)	CiC marking added to the EAG report.
EAG report, page 34, section 3.2.6.3	Unnecessary confidential marking of clarification response detail.	Please remove CiC marking and replace with "…the composite HF outcome was elevated on the basis of biological plausibility and external data alone. The change was approved by the trial steering committee and the company categorically confirmed that no unblinded data were discussed at steering committee meetings and that neither unblinded nor blinded SELECT trial data influenced the decision to elevate this endpoint."	CiC marking removed from the EAG report.
EAG report, page 35, section 3.3.1, EAG comment	Missing CiC marking. Details of the patients receiving the planned 2.4mg dose of	Please add CiC marking as follows:	CiC marking added to the EAG report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	semaglutide in the STEP-HFpEF and STEP-HFpEF DM trials are not in the public domain and have been taken from Confidential Data on File references provided by the company and therefore should be marked CiC and redacted.	"The EAG notes that in the STEP-HFpEF and STEP-HFpEF DM trials, [redacted]% and [redacted]% patients, respectively, were receiving the planned 2.4mg dose of semaglutide after 52 weeks."	
EAG report, page 38-39, table 4 Unnecessary CiC marking applied throughout table	The following primary outcomes have been published and do not require CiC marking • first reported MACE	Please remove CiC marking to align with CS, table 12. See **Appendix 1**, Table 1 for details	There was a formatting issue with this table which resulted in all table text being marked as CiC. The CiC marking has been corrected in the EAG report by inserting the corrected EAG table provided by the company.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report, page 38-39, table 4 Unnecessary CiC marking applied throughout table	The proportions and hazard ratios for the following supportive secondary endpoints have been published and do not require CiC marking • Expanded MACE • Non-fatal MI • Non-fatal stroke • Coronary revascularisation • Hospitalisation for unstable angina • All-cause death, non-fatal MI or non-fatal stroke • HF hospitalisation or urgent HF visit	Please remove CiC marking to align with CS, table 14. See **Appendix 1**, Table 1 for details	There was a formatting issue with this table which resulted in all table text being marked as CiC. The CiC marking has been corrected in the EAG report by inserting the corrected EAG table provided by the company.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	Please note that the • The outcome CV death remains CiC in its entirety as this has not been made available publicly • P-values for all outcomes remain CiC as they have not been published publicly		
EAG report, page 38-39, table 4 Unnecessary CiC marking applied	The proportions and hazard ratios for the following confirmatory secondary endpoints have been published and do not require CiC marking • Confirmed CV death	Please remove CiC marking in line with table 15 in the CS See **Appendix 1**, Table 1 for details	There was a formatting issue with this table which resulted in all table text being marked as CiC. The CiC marking has been corrected in the EAG report by

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
throughout table	Please note the p-value remains CiC.		inserting the corrected EAG table provided by the company.
EAG report, page 38-39, table 4 Unnecessary CiC marking applied throughout table	The proportions and hazard ratios for the following confirmatory secondary endpoints have been published and do not require CiC marking • First occurrence of a composite HF endpoint	Please remove CiC marking in line with table 16 in the CS See **Appendix 1**, Table 1 for details	There was a formatting issue with this table which resulted in all table text being marked as CiC. The CiC marking has been corrected in the EAG report by inserting the corrected EAG table provided by the company.
EAG report, page 38-39, table 4	The proportions and hazard ratios for the following confirmatory secondary endpoints	Please remove CiC marking in line with table 17 in the CS See **Appendix 1**, Table 1 for details	There was a formatting issue with this table which resulted in all table text being

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Unnecessary CiC marking applied throughout table	have been published and do not require CiC marking • All cause death		marked as CiC. The CiC marking has been corrected in the EAG report by inserting the corrected EAG table provided by the company.
EAG report, page 38-39, table 4 Unnecessary CiC marking applied throughout table	The proportions and hazard ratios for the following supportive secondary endpoints have been published and do not require CiC marking • Composite nephropathy event Please note that the p-value for this outcome remains CiC.	Please remove CiC marking in line with table 18 in the CS See **Appendix 1**, Table 1 for details	There was a formatting issue with this table which resulted in all table text being marked as CiC. The CiC marking has been corrected in the EAG report by inserting the corrected EAG table provided by the company.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report, page 38-39, table 4 Unnecessary CiC marking applied throughout table	The proportions and hazard ratios for the following supportive secondary endpoints have been published and do not require CiC marking • HbA1c≥48 mmol/mol [6.5%] • HbA1c≥39 mmol/mol [5.7%]	Please remove CiC marking in line with text on pages 78 and 79 in the CS See **Appendix 1**, Table 1 for details	There was a formatting issue with this table which resulted in all table text being marked as CiC. The CiC marking has been corrected in the EAG report by inserting the corrected EAG table provided by the company.
EAG report, page 38-39, table 4 Unnecessary CiC marking applied throughout table	The estimates and CIs for the following supportive secondary endpoints have been published and do not require CiC marking • hsCRP ratio to baseline	Please remove CiC marking in line with table 21 in the CS See **Appendix 1**, Table 1 for details	There was a formatting issue with this table which resulted in all table text being marked as CiC. The CiC marking has been corrected in the EAG report by

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	• SBP change from baseline, mmHg • DBP change from baseline, mmHg • Pulse change from baseline, bpm Please not that all other data related to these outcomes remains CiC		inserting the corrected EAG table provided by the company.
EAG report, page 38-39, table 4 Unnecessary CiC marking applied throughout table	The estimates and CIs for the following supportive secondary endpoints have been published and do not require CiC marking • Body weight change from baseline	Please remove CiC marking in line with table 22 in the CS See **Appendix 1**, Table 1 for details	There was a formatting issue with this table which resulted in all table text being marked as CiC. The CiC marking has been corrected in the EAG report by

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	• Waist circumference change from baseline Please not that all other data related to these outcomes remains CiC		inserting the corrected EAG table provided by the company.
EAG report, page 42 Section 3.3.3.2 Highlighting of section number	Please amend "3.3.3.2…" To "3.3.3.2"	Highlighting of section number not required	CiC marking removed from the EAG report.
EAG report, page 44, section 3.3.6 Missing CiC marking	COVID-19 related AESI results for STEP-HFpEF and STEP-HFpEF DM have been taken from CS Appendix D figure 1 and figure 2 respectively. These	Please add CiC marking as follows: The most common AESIs were COVID-19-related events, as follows: • SELECT: semaglutide 23.9% vs placebo 24.4%, p=0.46 • STEP-HFpEF: semaglutide [redacted]% vs placebo [redacted]%	CiC marking added to the EAG report.

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG response</th></tr>
<tr><td></td><td>figures are CiC as not all data within have been published. Therefore COVID-19 related AESIs should be marked CiC</td><td>• STEP-HFpEF DM: semaglutide [redacted]% vs placebo [redacted]%</td><td></td></tr>
<tr><td>EAG report, page 63, table 10

Unnecessary CiC marking</td><td>Data in table 10 has been taken from published sources and does not require CiC marking</td><td>Please remove CiC marking in table 10</td><td>There was a formatting issue with this table which resulted in all table text being marked as CiC. The CiC marking has been removed from the EAG report.</td></tr>
<tr><td>EAG report, page 65, table 11

Missing CiC marking</td><td>The unredacted results based on the list or confidential price should be redacted. This is because in combination with unredacted ICERs in the CS allows back calculation of the</td><td>Please add CiC marking to table 11

<table><tr><th></th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr><tr><td>Established clinical management</td><td>£27,843</td><td>7.196</td><td>-</td><td>-</td><td>-</td></tr></table></td><td>CiC marking as requested by the company was added to the updated EAG report using list prices (4 November 2025). The EAG has now</td></tr>
</table>

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG response</th></tr>
<tr><td></td><td>confidential price. Therefore,
total costs for semaglutide arm
total QALYs for semaglutide arm
incremental costs
incremental QALYs
ICER (where an ICER is based on list price)
all need to have CiC marking added.</td><td><table><tr><td>alone</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Semaglutide in addition to established clinical management</td><td>£[redacted]</td><td>[redacted]</td><td>£[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>submitted a report using only CAA prices with all relevant confidential marking applied (5 December 2025).</td></tr>
<tr><td>EAG report, page 65, table 12

Missing CiC marking</td><td>The unredacted results based on the list or confidential price should be redacted. This is because in combination with unredacted ICERs in</td><td>Please add CiC marking to table 12<table><tr><th></th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr><tr><td>Established clinical management</td><td>£28,154</td><td>7.149</td><td>-</td><td>-</td><td>-</td></tr></table></td><td>CiC marking as requested by the company was added to the updated EAG report using list prices (4</td></tr>
</table>

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	the CS allows back calculation of the confidential price. Therefore, • total costs for semaglutide arm • total QALYs for semaglutide arm • incremental costs • incremental QALYs • ICER (where an ICER is based on list price) all need to have CiC marking added.	alone | | | | | | Semaglutide in addition to established clinical management | £[redacted] | [redacted] | £[redacted] | [redacted] | £[redacted]	November 2025). The EAG has now submitted a report using only CAA prices with all relevant confidential marking applied (5 December 2025).
EAG report, page 66, table 13	The unredacted results based on the list price should be redacted. This is because in	Please add CiC marking to table 13, all data points	CiC marking as requested by the company was added to the

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Missing CiC marking	combination with unredacted ICERs in the CS allows back calculation of the confidential price.		updated EAG report using list prices (4 November 2025). The EAG has now submitted a report using only CAA prices with all relevant confidential marking applied (5 December 2025).
EAG report, page 67, figure 3 Missing CiC marking	The unredacted results based on the list should be redacted. This is because in combination with unredacted ICERs in the CS allows back calculation of the confidential price.	Please add CiC marking to figure 3	CiC marking as requested by the company was added to the updated EAG report using list prices (4 November 2025). The EAG has now submitted a report using only CAA prices with all relevant

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
			confidential marking applied (5 December 2025).
EAG report, page 68, table 14 Missing CiC marking	The unredacted results based on the list or confidential price should be redacted. This is because in combination with unredacted ICERs in the CS allows back calculation of the confidential price. Therefore, • incremental costs • incremental QALYs • ICER (where an ICER is based on list price)	Please ass CiC marking to table 14.	CiC marking as requested by the company was added to the updated EAG report using list prices (4 November 2025). The EAG has now submitted a report using only CAA prices with all relevant confidential marking applied (5 December 2025).

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report, page 71, table 16 Missing CiC marking	The unredacted results based on the list or confidential price should be redacted. This is because in combination with unredacted ICERs in the CS allows back calculation of the confidential price, therefore the • incremental costs • incremental QALYs • ICER (where an ICER is based on list price) should have CiC marking applied.	Please add CiC marking to table 16, column 2 (Incremental costs), column 3 (incremental QALYs) and column 4 (ICERs/QALY) all data points.	CiC marking as requested by the company was added to the updated EAG report using list prices (4 November 2025). The EAG has now submitted a report using only CAA prices with all relevant confidential marking applied (5 December 2025).

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report, page 73, table 17 Missing CiC marking	The unredacted results based on the list or confidential price should be redacted. This is because in combination with unredacted ICERs in the CS allows back calculation of the confidential price., therefore the • costs for semaglutide arm • QALYs for semaglutide arm • incremental costs • incremental QALYs • ICER (where an ICER is based on list price)	Please add CiC marking to table 17, • column 2 (costs), • column 3 (QALYs), • column 6 (incremental costs), • column 7 (incremental QALYs) • column 8 (Deterministic ICER)	CiC marking as requested by the company was added to the updated EAG report using list prices (4 November 2025). The EAG has now submitted a report using only CAA prices with all relevant confidential marking applied (5 December 2025).

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	columns should have CiC marking applied.		
EAG report, page 74, table 19 Scenario analyses of T2D, prevalent and incident populations using EAG base case (deterministic) (currently labelled table 18 Scenario analyses of T2D, prevalent and incident populations using EAG base case (deterministic))	The unredacted results based on the list or confidential price should be redacted. This is because in combination with unredacted ICERs in the CS allows back calculation of the confidential price, therefore the • incremental costs • incremental QALYs • ICER (where an ICER is based on list price) columns should have CiC marking applied.	Please add CiC marking to table 19, column 3 (incremental costs), column 4 (incremental QALYs), and column 5 (ICER) all data points.	CiC marking as requested by the company was added to the updated EAG report using list prices (4 November 2025). The EAG has now submitted a report using only CAA prices with all relevant confidential marking applied (5 December 2025).

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Missing CiC marking			
EAG Report, Appendix 1, table 20 Baseline characteristics that were similar in the SELECT trial to the “SELECT-like” population from the CPRD And Table 21 Baseline characteristics that differed in the SELECT trial to the “SELECT-like” population	All FAS data taken from the SELECT clinical trial report should be marked CiC as it is not in the public domain and is considered commercially sensitive	Please add CiC marking to the ‘All FAS’ column of table 20 Baseline characteristics that were similar in the SELECT trial to the “SELECT-like” population from the CPRD	The data that was not marked as CiC was calculated by the EAG from data provided in the previous two columns which was not marked as CiC. No changes made to the EAG report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
from the CPRD (note these are currently labelled table 19 and table 20 in EAG report due to earlier table being mislabelled) Missing CiC marking			
EAG report, Appendix 2, table 22 Concomitant CV-related medication ongoing at randomisation	The STEP HFPEF DM concomitant medication details for • Angiotensin receptor blockers • Calcium channel blockers	Please add CiC marking to the data for outcomes • Angiotensin receptor blockers • Calcium channel blockers	CiC marking added to the EAG report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
(FAS populations) (note this is currently labelled table 21 in EAG report due to earlier table being mislabelled) Missing CiC marking	Are not reported in Kosibord 2024 (4) and therefore should be marked CiC		
EAG report, Appendix 7.5 Unnecessary CiC marking	Only the p-values for the outcomes • EQ-5D-5L index • EQ-5D-5L VAS data in table 24 Need to be marked CiC.	Please remove CiC marking in columns 1 to 3 for the EQ-5D-5L outcomes	CiC marking added to the EAG report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	Please note, all data relating to WRSSM should remain CiC		

Abbreviations: CiC, commercial in confidence; CI, confidence interval; CPRD, clinical practice research datalink; CS, company submission; FAS, full analysis set; EAG, External Assessment Group; HFpEF, heart failure with preserved ejection fraction; hsCRP, high-sensitivity C-reactive protein; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; NHS(E), National Health Service (England); WRSSM, weight-related signs and symptoms measure

References

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Appendix 1

Table 1 Corrections to CiC marking in table 4 of EAG report

Endpoint	Semaglutide (n=8803)	Placebo (n=8801)	Effect (95% CI)	p-value	Source
First EAC-confirmed MACE, n (%)	569 (6.5)	701 (8.0)	HR=0.80 (0.72 to 0.90)	<0.0001	CS, Table 12
CV death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 12
Non-fatal MI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 12
Non-fatal stroke, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 12
Confirmatory secondary endpoints					
Confirmed CV death, n (%)	223 (2.5)	262 (3.0)	HR=0.85 (0.71 to 1.01)	[redacted]	CS, Table 15
First occurrence of a composite HF endpoint, n (%)	300 (3.4)	361 (4.1)	HR=0.82 (0.71 to 0.96)	NA[a]	CS, Table 16
CV death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 16
HF, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 16
HF hospitalisation or urgent HF visit, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 16
Urgent HF visit, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 16
All cause death, n (%)	375 (4.3)	458 (5.2)	HR=0.81 (0.71 to 0.93)	NA[a]	CS, Tables 15 and 17
Non-CV death, n (%)	[redacted]	[redacted]	[redacted][b]	[redacted]	CS, Table 17[b]
Supportive secondary endpoints					
Expanded MACE, n (%)	873 (9.9)	1074 (12.2)	HR=0.80 (0.73 to 0.87)	[redacted]	CS, Table 14
CV death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	CTR,(5) Table 11-19
Non-fatal MI, n (%)	234 (2.7)	322 (3.7)	HR=0.72 (0.61 to 0.85)	[redacted]	CS, Table 14
Non-fatal stroke, n (%)	154 (1.7)	165 (1.9)	HR=0.93 (0.74 to 1.15)	[redacted]	CS, Table 14
Coronary revascularisation, n (%)	473 (5.4)	608 (6.9)	HR=0.77 (0.68 to 0.87)	[redacted]	CS, Table 14

Endpoint	Semaglutide (n=8803)	Placebo (n=8801)	Effect (95% CI)	p-value	Source
Hospitalisation for unstable angina, n (%)	109 (1.2)	124 (1.4)	HR=0.87 (0.67 to 1.13)	[redacted]	CS, Table 14
All-cause death, non-fatal MI, or non-fatal stroke, n (%)	710 (8.1)	877 (10.0)	HR=0.80 (0.72 to 0.88)	[redacted]	CS, Table 14
HF hospitalisation or urgent HF visit, n (%)	97 (1.1)	122 (1.4)	HR=0.79 (0.60 to 1.03)	[redacted]	CS, Table 14
Composite nephropathy event, n (%)	155 (1.8)	198 (2.2)	HR=0.78 (0.63 to 0.96)	[redacted]	CS, Table 18
Persistent macroalbuminuria	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 18
Persistent reduction in eGFR	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 18
Onset of persistent eGFR <15 ml/min/1.73 m^2	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 18
Initiation of chronic RRT	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 18
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	CS, Table 18
HbA1c ≥48 mmol/mol [6.5%], n (%) [c]	306 (3.5)	1059 (12.0)	HR=0.27 (0.24 to 0.31)	[redacted]	CS, page 78
HbA1c ≥39 mmol/mol [5.7%], n (%) [d]	623 (21.3)	1501 (50.4)	HR=0.33 (0.30 to 0.36)	[redacted]	CS, page 79
hsCRP ratio to baseline	[redacted]	[redacted]	ETR=0.62 to (0.60 to 0.64)	[redacted]	CS, Table 21
SBP change from baseline, mmHg	−3.82	−0.51	ETD=−3.31 (−3.75 to −2.88)	[redacted]	CS, Table 21
DBP change from baseline, mmHg	−1.02	−0.47	ETD=−0.55 (−0.83 to −0.27)	[redacted]	CS, Table 21
Pulse change from baseline, bpm	3.79	0.69	ETD=3.10 (2.80 to 3.39)	[redacted]	CS, Table 21
Body weight change from baseline, %	−9.39	−0.88	ETD=−8.51 (−8.75 to −8.27)	[redacted]	CS, Table 22
Waist circumference change from baseline, cm	−7.56	−1.03	ETD=−6.53 (−6.79 to −6.27)	[redacted]	CS, Table 22

Single Technology Appraisal

Semaglutide for preventing major cardiovascular events in people with cardiovascular disease and living with overweight or obesity [ID6441]

EAG report – factual accuracy check and confidential information check – EAG response (16 January 2026)

Issue 1 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Updated EAG report, Section 5.2.3, page 72: wrong table numbers and minor typographical error	Please change "The EAG's deterministic base case results are presented in Tabel 16 with probabilistic base case results in Table 17. Scenario analysis results for patients with T2D, for a UK eCVD prevalent population and a UK eCVD incident population are presented in Table 18" to "The EAG's deterministic base case results are presented in Tab**le 17** with probabilistic base case results in Table **18**. Scenario analysis results for patients with T2D, for a UK eCVD prevalent population and a UK eCVD incident population are presented in Table **19**"	Correction for accuracy	Thank you for highlighting these errors. Changes made as suggested.

Issue 2 Incorrect CiC marking

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Updated EAG report, Table 11, page 65 Incorrect CiC marking	Please remove CiC marking from the ICER (£14,702)	ICERs should be unmarked	Thank you for highlighting this error. Change made as requested.