NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Liraglutide for managing overweight and obesity [ID740]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Liraglutide for managing overweight and obesity [ID740]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from **Novo Nordisk**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Hoop UK (Obesity UK)
   b. Obesity Group of the British Dietetic Association
   c. Royal College of Physicians

4. **Expert personal perspectives** from:
   a. Prof. Carel le Roux, Consultant in Metabolic Medicine and Obesity – clinical expert nominated by Novo Nordisk
   b. Lucy Perrow, Clinical Lead Weight Management Dietitian – clinical expert nominated by The British Dietetic Association
   c. Dr Abd Tahrani, Honorary Consultant Endocrinologist and Senior Lecturer in Metabolic Endocrinology and Obesity Medicine – clinical expert, nominated by Novo Nordisk
   d. Sarah Le Brocq – patient expert, nominated by Hoop UK (*see submission from Hoop UK)*

5. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

6. **Evidence Review Group – factual accuracy check**

<u>Post-technical engagement documents:</u>

7. **Technical engagement response from Novo Nordisk**
   a. Response form
   b. Appendices
   c. Appendix 2 – revised price analyses

8. **Technical engagement responses from experts:**
   a. Prof. Carel Le Roux – clinical expert, nominated by Novo Nordisk

9. **Final Technical Report**

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10. Evidence Review Group critique of company response to technical engagement prepared by Kleijnen Systematic Reviews

** Please note that this document was produced after the first committee meeting*

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Liraglutide 3.0mg in the management of overweight and obesity (ID740)

Document B

Company evidence submission

June 2019

File name	Version	Contains confidential information	Date
ID740_Lira3.0mg_DocB_Evidence Submission_redacted.docx	1.0	Yes	June 2019

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List of abbreviations

ACE	Angiotensin Converting Enzyme
AE	Adverse Events
ACS	Acute Coronary Syndrome
ADA	American Diabetes Association
AHI	Apnoea-Hypopnea Index
AMI	Acute Myocardial Infarction
BMI	Body Mass Index
BMJ	British Medical Journal
BOCF	Baseline Observation Carried Forward
BOMSS	British Obesity & Metabolic Surgery Society
CEAC	Cost-Effectiveness Acceptability Curve
CHD	Coronary Heart Disease
CPAP	Continuous Positive Airway Pressure
CTR	Clinical Trial Results
CVD	Cardiovascular Disease
CVOT	Cardiovascular Outcomes Trial
DPP	Diabetes Prevention Programme
DPP-4	Dipeptidyl Peptidase-4
EMA	European Medicines Agency
EOT	End of Trial
EPAR	European Public Assessment Report
ERG	Evidence Review Group
ETD	Estimated Treatment Difference
FAS	Full Analysis Set
FFA	Free Fatty Acids
FPG	Fasting Plasma Glucose
GBP	Pound Sterling
GLP-1	Glucagon-Like Peptide-1
GPRD	General Practice Research Datalink
HDL	High-Density Lipoproteins
HRG	Healthcare Resource Group
HRQoL	Health-Related Quality of Life
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IHD	Ischaemic Heart Disease
IWQOL	The Impact of Weight on Quality of Life Questionnaire

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LDL	Low-Density Lipoproteins
LEADER	Liraglutide And Cardiovascular Outcomes in Type 2 Diabetes
LOCF	Last Observation Carried Forward
LYs	Life Years
LYG	Life Years Gained
MI-ME	Multiple-imputation for measurement error
MIMS	Monthly Index of Medical Specialities
NEP	Neutral Endopeptidase
NGT	Normal Glucose Tolerance
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIH-AARP	National Institutes of Health-American Association of Retired Persons
OAD	Oral Anti-diabetic Drug
OGTT	Oral Glucose Tolerance Test
OSA	Obstructive Sleep Apnoea
PAS	Patient Access Scheme
PHQ-9	Patient Health Questionnaire-9
PRO	Patient Reported Outcome
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PYO	Person Years of Observation
QALY	Quality-Adjusted Life Year
RPP	Resting pulse
SAS	Safety Analysis Set
SC	Subcutaneous
SBP	Systolic Blood Pressure
SLR	Systematic Literature Review
SMQ	Standard Medical Query
SOC	System Organ Classes
STA	Single Technology Appraisal
TEAE	Treatment Emergent Adverse Events
TIA	Transient Ischaemic Attack
TRIM	Treatment Related Impact Measure
UKPDS	United Kingdom Prospective Diabetes Study
VLDL	Very Low-Density Lipoproteins
WAMC	Weight Assessment and Management Clinics
WAP	Weight Action Programme
WHO	World Health Organization

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

B.1.1. Decision problem

The population defined in the final scope is consistent with the current European Medicines Agency (EMA) indication:

Liraglutide 3.0mg (Saxenda®) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial body mass index (BMI) of:

- ≥30 kg/m^2 (obesity); or
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity such as dysglycemia (prediabetes or type 2 diabetes), hypertension, dyslipidaemia or obstructive sleep apnoea.

As part of the EMA licence, a stopping rule is applied to 'non-responders' of liraglutide 3.0mg, where treatment should be discontinued after 12 weeks on the 3.0mg/day maintenance dose if patients have not lost 5% of their initial body weight. Patients that lose equal to or more than 5% of their initial body weight are classified as 'early responders' (Table 1).

This submission will focus on a subpopulation of the EMA licence which are patients with:

- BMI ≥35 kg/m^2 (obesity class II and above) with
    - Non-diabetic hyperglycaemia (prediabetes) at high risk of type 2 diabetes which is defined as having either:
        - fasting plasma glucose level of 5.5–6.9 mmol/L; or
        - HbA_{1c} of 6.0-6.4% (42 – 47 mmol/mol) aligned with National Institute for Health and Care Excellence (NICE) guidelines (1); and

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- High risk of cardiovascular disease (CVD) aligned with the NICE guidelines and expert opinion:
  - Total cholesterol >5 mmol/L; or
  - High-density lipoprotein (HDL) <40 mg/dL for men and <50 mg/dL for women(2); or
  - Systolic blood pressure >140 mmHg (3).[1]

The subpopulation defined above will subsequently be referred to as 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD'. The treatment setting for these patients would be in a specialist tier 3 weight assessment and management clinic (WAMC) service, offering lifestyle modification advice, pharmacotherapy, psychological treatment as well as assessing patients for bariatric surgery (4). Based on NICE clinical guidelines, patients with obesity should be referred to a specialist tier 3 service when conventional treatment options (including treatment with orlistat) have not been successful (5).

The submission focuses on part of the marketing authorisation because this patient population would benefit the most from treatment with liraglutide 3.0mg in United Kingdom (UK) clinical practice:

- Obesity is associated with a significant number of complications (6-10). Thus, weight loss and chronic weight management in a population at high risk of developing these complications, such as type 2 diabetes and CVD are likely to have the greatest gains in terms of risk reduction, quality of life and life expectancy.

[1] High risk CVD was developed in combination with expert opinion and NICE clinical guidelines. NICE CG181 Cardiovascular disease: risk assessment and reduction, including lipid modification recommends to use the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to the age of 84 years. However the QRISK2 risk assessment tool was not a suitable method for identifying high risk patients from the liraglutide 3.0mg clinical trial as not all the parameters required for QRISK2 were collected in the clinical trial for example QRISK2 calculates risk on an individual patient basis using data such as patient age, gender, postcode and smoking status. Systolic blood pressure, total cholesterol and HDL values are however components of QRISK2 and were collected in the clinical trial. Clinical expert opinion was used to determine suitable levels for these three parameters which could then be used to identify high CVD risk patients from the clinical trial for subgroup analysis. The levels for cholesterol and HDL are also referred to in the lipid panel which is referenced in CG181.

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- This subpopulation is also the focus for the National Health Service (NHS) due to the continued prioritisation and investment in the Diabetes Prevention Programme (DPP) which aims to deliver evidence-based behavioural interventions for individuals with prediabetes (11):
    - The NHS DPP eligibility criteria recommend individuals with a BMI >40 kg/m^2, or BMI >35 kg/m^2 plus comorbidities (such as prediabetes) to be referred to a specialist tier 3 WAMC.
- The NICE guidelines for cardiovascular risk management (CG 181) recommend, offering advice and support for people who are overweight or obese and are at high risk of CVD (12).

- This subpopulation of patients has limited treatment options as they have failed treatment in tier 2 and may be unwilling or unable to undergo bariatric surgery.

Treatment in this easily identifiable subpopulation also optimises the cost-effectiveness of liraglutide 3.0mg.

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Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope

Population	Adults who have a BMI of;
	• ≥30 kg/m^2 (obesity) or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity
		Adult patients with:
		• BMI ≥35 kg/m^2 with
		  • prediabetes, and
		  • high risk of cardiovascular disease
			This subpopulation of patients would benefit the most from liraglutide 3.0mg in UK clinical practice, and therefore optimises cost effectiveness.

Comparator(s)	• Standard management without liraglutide 3.0mg • Orlistat (prescription dose) • Bariatric surgery	Standard management without liraglutide 3.0mg	The only relevant comparator in this submission is standard management without pharmacotherapy. The reason for omitting orlistat as a comparator is 2-fold: firstly, orlistat is currently recommended as a treatment option in primary care in a much wider population than is proposed for liraglutide 3.0mg and as such would be used earlier in the treatment pathway (tier 2). Secondly, the use of orlistat is currently limited in clinical practice; this is supported by Section 3.4 of the final appraisal determination for naltrexone–bupropion (TA494), where it is stated that clinical experts and consultees reported that standard management (diet and lifestyle interventions) is the only relevant comparator because orlistat is not often used in clinical practice. This is due to undesirable side effects leading to poor adherence and weight loss outcomes. As a result, most patients do not want to take it or stop treatment after a short time. Based on this, the committee concluded that standard

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			management was the main comparator in the appraisal. Liraglutide 3.0mg is intended for use in patients who have been referred to a specialist tier 3 service where conventional treatments such as orlistat have been unsuccessful earlier in the clinical pathway. For patients where bariatric surgery would be an appropriate option and this is acceptable to the patient, this would be a relevant treatment alternative according to the NICE clinical guideline (CG 189) (13). Bariatric surgery has already been demonstrated as a cost-effective treatment option for a selected group of patients. Liraglutide 3.0mg would not be a direct replacement for bariatric surgery, however, it could be suitable for a group of patients who are unwilling or unable to undergo surgery. As noted by the clinical expert in TA494 bariatric surgery is highly effective but only a small proportion (around 0.1% of those eligible for bariatric surgery) receive surgery. For this reason, bariatric surgery is not included as a comparator but will be included as a downstream event for a proportion of patients in the health-economic model in both treatment arms.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • BMI • Weight loss • Percentage body fat • Waist circumference • Incidence of type 2 diabetes • Cardiovascular events • Idiopathic intracranial hypertension • Non-alcoholic fatty liver disease • Mortality • Adverse effects of treatment • Health-related quality of life.	The outcome measures included in the clinical studies for liraglutide 3.0mg include: • BMI • Weight loss (change from baseline %, kg) • Waist circumference • Incidence of type 2 diabetes and impact on glycaemia (i.e., HbA_{1c}, fasting plasma glucose) • Changes in CV risk markers including lipid parameters (total cholesterol and high-density lipoprotein) and systolic blood pressure • Adverse effects of treatment • Health-related quality of life The outcomes measures in the economic model include • Mortality/life expectancy • Health-related quality of life • Cumulative incidence of acute Cardiovascular events including stroke, transient ischaemic attack, myocardial infarction and angina	Outcomes listed in the scope which are not included in this submission are: 1) Percentage body fat was not collected in the clinical trial programme, nor is it routinely collected in the UK clinical practice. Section 1.2.2 of NICE clinical guidelines 189, suggests using BMI as a practical estimate of adiposity in adults. In Section 1.2.6 it also does not recommend/ endorse the routine use of the bioimpedance for measurement of the body fat percentage or as means of diagnosing overweight or obesity (13). This is also supported in Section 5.1.3 of the NICE Evidence Review for clinical guideline 43, which states there is a weak association between BMI and percentage adiposity: "Adiposity is defined as the amount of body fat expressed as either the absolute fat mass (in kilograms) or as the percentage of total body mass. Absolute adiposity is highly correlated with body mass, but percentage adiposity is relatively uncorrelated with body mass" (14). 2) Idiopathic intracranial hypertension was not collected as part of the clinical trial and therefore data are lacking on this outcome. 3) Non-alcoholic fatty liver disease: It is unknown what proportion of patients in the liraglutide 3.0mg clinical studies could be classified as also having non-alcoholic fatty

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			liver disease as liver biopsies were not taken as part of the study protocol. Therefore, there is no information to assess this outcome. It should be noted that patients with impaired liver function (defined as ALAT ≥2.5 times upper limit of normal) were excluded from the liraglutide 3.0mg clinical trials.

Subgroups to be considered	If the evidence allows, the following subgroups will be considered. These include:
	• people with obesity-related complications;
	• people with type 2 diabetes;
	• people with serious mental illness;
	• people with a BMI ≥35 kg/m^2 who have prediabetes and a high risk of cardiovascular disease and are in specialist tier 3 services.
		As noted in Section B.1.1 above, the company submission only considers adults patients with:
		• BMI ≥35 kg/m^2 with
		  • Prediabetes, and
		  • High risk of cardiovascular disease
			People with severe mental illness were excluded from the clinical studies for liraglutide 3.0mg and hence there is little evidence to inform clinical and cost-effectiveness evaluations in this subgroup of patients. Adjustment for BMI according to ethnicity has not been explicitly evaluated within this submission but Novo Nordisk sees no reason not to follow NICE's Public Health guidance (PH46) (15), BMI: preventing ill health and premature death in black, Asian and other minority ethnic groups.

Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers. EQ-5D is preferred.	Baseline utility values in the model were derived from an analysis of the 2003 Health Survey for England data, which used EQ-5D in a large UK population (16).	HRQoL inputs used in the economic model were based on a large UK population-based

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			study as it has demonstrated a robust association between BMI and utility (16). The applied method is important for the economic model for two reasons: 1) It allowed the separation of the effects of comorbidities from a pure effect related to increased weight; 2) In the model, a health-related quality of life decrement specific to each obesity complication health state could be applied separately. Trial-based patient-derived SF-36 data have previously been mapped to EQ-5D as reported by Kolotkin et al., 2017 (17), however, this analysis did not incorporate the stopping rule, nor did it have the benefits noted above.

ALAT: Alanine aminotransferase; CV: Cardiovascular; HRQoL, Health-Related Quality of Life; NICE: National Institute for Health and Care Excellence; UK, United Kingdom

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B.1.2. Description of the technology being appraised

Appendix C includes the summary of product characteristics and the European public assessment report for liraglutide 3.0mg in the treatment of overweight and obesity (Table 2).

Table 2: Technology being appraised

UK approved name and brand name	Liraglutide 3.0mg (Saxenda®)
Mechanism of action	Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) analogue with 97% amino acid sequence homology to endogenous human GLP-1 (7-37). GLP-1 is a physiological regulator of appetite and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. Endogenous GLP-1 has a half-life of 1.5–2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase 4 (DPP-4) and neutral endopeptidases (NEP). Like endogenous GLP-1s, liraglutide binds to and activates the GLP-1 receptor, a cell-surface receptor coupled to adenylyl cyclase activation through the stimulatory G-protein, Gs, in pancreatic beta-cells. Unlike native GLP-1s, liraglutide is both stable against metabolic degradation by both peptidases and has a reduced renal clearance thereby increasing the plasma half-life to 13 hours after subcutaneous (SC) administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding, and stability against metabolic degradation by DPP-4 and NEP. Liraglutide regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and reducing prospective food consumption.
Marketing authorisation/CE mark status	EMA marketing authorisation for liraglutide 3.0mg (Saxenda®) was granted in April 2015.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Liraglutide 3.0mg is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial BMI of: • ≥30 kg/m^2 or • ≥27 kg/m^2 or <30 kg/m^2 in the presence of at least one weight-related comorbidity such as dysglycemia (prediabetes or type 2 diabetes

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	mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea Treatment with liraglutide 3.0mg should be discontinued after 12 weeks on the maintenance dose of 3.0mg/day if patients have not lost at least 5% of their initial body weight. NB. Liraglutide (Victoza®), approved in June 2009, is licensed at lower maintenance doses (1.2mg and 1.8mg) for treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, as monotherapy when metformin is inappropriate due to intolerance or contraindications, or with other medicinal products for the treatment of diabetes.
Method of administration and dosage	Liraglutide 3.0mg is for SC use only. It is administered once daily at any time, independent of meals. It is preferable that liraglutide 3.0mg is injected at the same time every day. The starting dose is 0.6mg once daily. The dose should be increased to 3.0mg daily in increments of 0.6mg with at least one week intervals. Daily doses higher than 3.0mg are not recommended.
Additional tests or investigations	No additional tests or investigations are required.
List price and average cost of a course of treatment	List price of a pack of 5 prefilled pens (18mg/3ml) = £196.20. The equates to £2.18 per mg. During the titration phase 42mg of liraglutide is used to titrate to 3.0mg daily over a 4 week period costing £91.56. From then onwards the maintenance dose of 3.0mg costs £6.54 per day and £196.20 per 30 days therapy. The economic model assumes 2 years of treatment. The annual cost in the 1st year of treatment is £2,289.00 and £2,380.56 in the 2nd year.
Patient access scheme (if applicable)	The documentation for a simple discount scheme was submitted to the Patient Access Scheme Liaison Unit at NICE on 17th May 2019. The proposed Patient access scheme (PAS) price = £[redacted] per pack of 5 prefilled pens (18mg/3ml) equal to a discount of [redacted]%. The annual cost in the 1st year of treatment is £[redacted] and £[redacted] in the 2nd year.

DPP-4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide-1; NEP: neutral endopeptidases; SC: subcutaneous

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

B.1.3.2. Disease overview

Epidemiology and risk factors

Obesity is considered a chronic disease by the American Medical Association (18) and the UK Royal College of Physicians (19), requiring holistic long-term management (20, 21) using appropriate interventions. It is defined by the World Health Organization (WHO) as an abnormal or excessive fat accumulation that may impair health (22). It is classified as a BMI of ≥30 kg/m^2. Obesity can be further classified into Obesity Class I (BMI 30 kg/m^2 to <35 kg/m^2), Obesity Class II (BMI 35 kg/m^2 to <40 kg/m^2) and Obesity Class III (BMI 40+ kg/m^2) (22). Obesity is a complex and multifactorial disease which is influenced by genetic, physiological, environmental, and psychological factors (23-28).

In 2016, the global prevalence was estimated to be 11% for men and 15% for women, equating to over 600 million adults living with obesity worldwide (22, 29). In the UK, obesity rates doubled between 1993 and 2011, from 13% to 24% in men and from 16% to 26% in women (13). In England, an estimated 40% of men and 32% of women are overweight and a further 27% of men and 30% of women have obesity as of 2017 (30).

Currently, among adults with obesity, seven out of every ten are classified as having Class I obesity (BMI 30-34.9 kg/m^2), two out of these ten have Class II obesity (BMI 35-39.9 kg/m^2) and one out of ten have Class III or morbid obesity (BMI >40 kg/m^2) (31). The prevalence of obesity is highest in people aged 55-64 years, while those aged between 16-24 years have the lowest prevalence (32).

Developed and sustained obesity may involve central pathophysiological mechanisms such as impaired brain circuit regulation and neuroendocrine hormone dysfunction. Peripheral hormonal signals released from the gastrointestinal (GI) tract (ghrelin, peptide tyrosine (PYY), GLP-1, and cholecystokinin), pancreas (insulin), and adipose tissue (leptin)

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constitute a key component in the gut-brain axis-mediated control of appetite, energy expenditure, and obesity. These hormones and peptides alter appetite and eating behaviours by acting on hypothalamic and brainstem nuclei (33).

There are also genetic factors, epigenetics, and developmental biology relevant to energy balance control that contribute to the pathophysiological mechanisms underlying obesity (34).

It is the multifactorial nature of the disease which adds to the challenging nature of this condition. It is the interaction between multiple factors that is largely contributing to the growing obesity epidemic (35). Some of these factors include:

- Physiological – Excess weight results when calories consumed exceed calories expended. However, this positive energy balance leads to the storage of additional and unnecessary adipose tissue, macrophage recruitment and to complex adaptive changes in the adipocytes and in the levels circulating hormones that mediate appetite and satiety, leptin and ghrelin (36, 37).
- Psychological – Stress and psychological disorders are linked to overeating and can contribute to the development of obesity. Individuals that suffer from psychological disorders (e.g. depression and anxiety) may have more difficulty controlling their consumption of food, exercising sufficiently and maintaining a healthy weight (38).
- Genetics – Some people are genetically predisposed to developing obesity. A number of genome-wide association studies have identified obesity susceptible loci associated with BMI and waist circumference (39). Studies have also suggested that 40-70% of the variation in BMI in the population is due to genetic factors, and it is believed that many different genes contribute to this effect (40, 41).
- Socioeconomic – Education, income and occupational status can influence one's chance of developing obesity. Studies have shown that in countries with a Western-type lifestyle, such as the UK, socially disadvantaged groups are more often affected by obesity than are comparatively better-off groups (42, 43).

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- Environmental – Many aspects of our environment have changed over the past couple of decades. Advances in technology have led to a reduction in physical activity, instead replaced by increased screen time due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization. Busy lifestyles, the increased accessibility of energy-dense food that is high in fat and the decline in its relative price have resulted in greater exposure to oversized food portions and more processed foods owing to an increase in calories consumed (44, 45).
- Medical – Some diseases might contribute to weight gain and to patients developing obesity, including Cushing's syndrome and underactive thyroid gland. There are also certain medicines, including some corticosteroids and antidepressants, which can contribute to weight gain (46-49).

Due to its multifactorial nature, obesity is a complex, chronic disease with pathophysiological mechanisms resulting in appetite dysregulation and hormonal dysfunction.

Clinical burden of disease

Obesity is associated with a marked decrease in life expectancy. Studies have shown that obesity in adulthood is associated with a decrease in life expectancy of approximately 6 – 13 years (50-52). In the UK, obesity contributes to more than 30,000 deaths each year or 6% of all deaths (53).

Obesity is also associated with an increase in all-cause mortality when compared with normal weight individuals. In a systematic review and meta-analysis of 97 studies including more than 2.88 million individuals and 270,000 deaths, obesity was associated with an 18% increase in all-cause mortality when compared with normal weight individuals (BMI of 18.5 to ≤25 kg/m^2). Risk increased with increasing severity of the disease, rising to a 29% increase for a BMI of ≥35 kg/m^2 (54). A population-based cohort study of 3.6 million adults in the UK using data from the Clinical Practice Research Datalink also found an

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association between BMI and mortality. Compared with individuals of healthy weight (BMI 18.5–24.9 kg/m^2), life expectancy from age 40 years was 4.2 years shorter in obese (BMI ≥30.0 kg/m^2) men and 3.5 years shorter in obese women (55). Aune *et al.,* 2016 found a dose-response relationship between BMI and mortality with a BMI of 35 kg/m^2, 40 kg/m^2 and 45 kg/m^2 having a relative risk of all-cause mortality of 1.29, 1.74 and 2.49 respectively (56).

A Clinical Practice Research Datalink (CPRD)/Hospital Episode Statistics (HES) study was recently undertaken to measure the association between different BMI categories and the risk of obesity-related outcomes (57). The study population was a large UK population-representative cohort of patients who visit UK general practice clinics. Patients included in this study were 18 years or older, had a baseline BMI measurement of 18.5–45.0 kg/m^2 between the years 2000 and 2010, and had been registered in the CPRD database for at least 3 years before the index date. Median age and BMI at baseline were 51 years and 26.5 kg/m^2, respectively, and 43% of the study population were male. The population was stratified into groups according to baseline BMI. Individuals with a BMI of 18.5–24.9 kg/m^2 were considered normal weight and used as the reference group. Of the baseline comorbidities examined, the most common across all BMI groups were hypertension (22.8%), asthma (13.1%), osteoarthritis (10.2%), dyslipidaemia (9.7%) and type 2 diabetes (5.2%). The prevalence of each outcome was greater in higher BMI classes than in groups with lower BMI. The results from this study showed that higher BMI classes were associated with a higher risk of a wide range of serious diseases and outcomes, including cardiovascular events. The highest risk increase associated with higher BMI categories was observed for sleep apnoea and type 2 diabetes, followed by heart failure and hypertension.

Many people with obesity have also been shown to experience a lower health-related quality of life (HRQoL). Living with obesity can have a significant psychological impact as a result of social stigmatisation, exclusion and isolation, low self-esteem and low quality of life (53). Studies have demonstrated that adults with obesity had significantly reduced

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physical component scores of the SF-36 questionnaire (–2.54 points for Class I; –3.91 for Class II; –9.72 for Class III; all p<0.001) and mental component scores was significantly reduced among adults with Class III obesity (-1.75; p=0.031) (58).

Obesity has been directly linked to numerous complications including, but not limited to, prediabetes and type 2 diabetes, cardiovascular disease (high blood pressure, stroke and heart attack), osteoarthritis, and certain types of cancer, as well as psychological and psychiatric morbidities (13). The prevalence of obesity-related complications generally increases with BMI (59). Weight loss, even moderate can lead to significant improvements in glycaemic status, blood pressure, triglycerides, and HDL cholesterol (60).

Although obesity is generally perceived as a disease, obesity is not commonly treated as such given a divergence in perceptions and attitudes that potentially hinder better management, as highlighted by the National ACTION Study which found an inconsistent understanding of the impact of obesity and need for both self-directed and medical management (61).

Economic burden of disease

There is a significant financial burden, through both increased total direct healthcare costs and indirect costs, associated with obesity (62, 63). A significant portion of this burden is driven by the associated comorbidities (type 2 diabetes, coronary heart disease, stroke, cancer, and osteoarthritis etc.), which impose substantial medical costs from their treatment (64). In the UK, the cost of obesity to society and the economy was estimated to almost £16 billion in 2007 and is estimated to increase to approximately £50 billion in 2050 if obesity rates continue to rise (13). The total cost to the NHS specifically is estimated to be £6.1 billion in 2014/15 and is projected to reach £9.7 billion by 2050 (53).

The impact of obesity and cardiovascular risk status on healthcare utilisation in the UK has recently been studied in a large retrospective UK population-representative CPRD database study (65). Another recent analysis of the CPRD database assessed resource

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use utilisation for different BMI categories and different cardiovascular event risk levels. The study differentiates between 3 levels of cardiovascular event risk: low, high, and established CVD. For all cardiovascular risk levels, a higher BMI is generally associated with higher resource use. Individuals with BMI ≥40 kg/m^2 have the greatest number of general practitioner contacts, prescriptions and hospital admissions. Patients with established CVD had the greatest utilisation of all components of healthcare resources, followed by high then low risk. Patients with established CVD carried the highest costs of all 3 categories, across all BMI levels. The findings of this study highlight the importance of effective obesity management and treatment of CVD risk factors in containing the economic burden of obesity and its complications.

B.1.3.2 Current standard of care

NICE guidelines

Treatment of people with obesity is often complex, and a wide range of services can be involved. Given that the population being discussed in this submission are those with a BMI ≥35 kg/m^2, prediabetes and a high risk of CVD and eligible for treatment for weight management in tier 3 setting, it is pertinent to consider all NICE guidelines relevant to these conditions. In the key NICE guidelines (presented in Table 3), lifestyle modification forms a key pillar on which additional interventions are added (1, 2, 13). This indicates the importance of addressing obesity first to prevent the downstream clinical and economic consequences of its associated comorbidities.

Table 3: Key NICE clinical guidelines

NICE Clinical Guidelines
Obesity: identification, assessment and management (CG189)
Type 2 diabetes: prevention in people at high risk (PH38)
Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181)

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The NICE guidelines (CG189) for obesity, the British Obesity & Metabolic Surgery Society (BOMSS) commissioning guide and NHS England's report on Joined up clinical pathways in obesity all recommend a four-tiered approach to weight management (see Figure 1) (4, 13, 66). Different tiers of weight management services cover different activities. Definitions vary locally, but usually tier 1 covers universal services (such as health promotion or primary care); tier 2 covers lifestyle interventions; tier 3 covers specialist weight management services; and tier 4 covers bariatric surgery (67).

In tier 1 services, lifestyle interventions in the form of diet and exercise are considered the standard of care and the foundation of all further interventions. At this stage, it is important that patients receive sufficient guidance and education so that they are equipped with sufficient knowledge to set realistic and achievable physical activity goals and to reduce their calorie intake while accommodating their own individual approach and food preference.

In tier 2 services, diet and exercise advice is continued in a primary care setting. Interventions may also include pharmacotherapy in appropriate clinical circumstances. Orlistat is the only NICE recommended pharmacological intervention for the treatment of obesity currently available in the UK and should only be prescribed as part of an overall plan for managing obesity in adults who meet one of the following criteria:

- A BMI of ≥28 kg/m^2 with associated risk factors such as type 2 diabetes, hypertension, or hypercholesterolaemia.
- A BMI of ≥30 kg/m^2.

As per the license, treatment with orlistat should only continue beyond 3 months if the patient has demonstrated a loss of at least 5% of their initial body weight from baseline. However, due to its adverse events (AEs) profile, causing unpleasant and socially unacceptable side effects, orlistat prescriptions are declining and some patients are not willing to take it (68).

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According to NICE CG189, patients should be considered for referral to a specialist tier 3 service WAMC if:

- the underlying causes of being overweight or obese needs to be assessed;
- the person has complex disease states or needs that cannot be managed adequately in tier 2 (for example, the additional support needs of people with learning disabilities);
- conventional treatment has been unsuccessful;
- drug treatment is being considered for a person with a BMI of more than 50 kg/m^2;
- specialist interventions (such as a very-low-calorie diet) may be needed;
- surgery is being considered.

Tier 4 referral is considered appropriate when a patient with obesity is eligible for bariatric surgery. Bariatric surgery should only be considered for adults who fulfil all of the criteria below:

- They have a BMI of 40 kg/m^2 or more, or between 35 kg/m^2 and 40 kg/m^2 and other significant diseases (for example, type 2 diabetes or high blood pressure) that could be improved if they lost weight.
- All appropriate non-surgical measures have been tried but the person has not achieved or maintained adequate, clinically beneficial weight loss.
- The person has been receiving or will receive intensive management in a tier 3 service.
- The person is generally fit for anaesthesia and surgery.
- The person commits to the need for long-term follow-up.

It is important to note that tier 3 assessment and weight management interventions should be provided prior to being referred for bariatric surgery in tier 4. Given that not all patients eligible for bariatric surgery go on to have it, additional treatment options, which aid weight management, should be made available for patients with obesity in tier 3.

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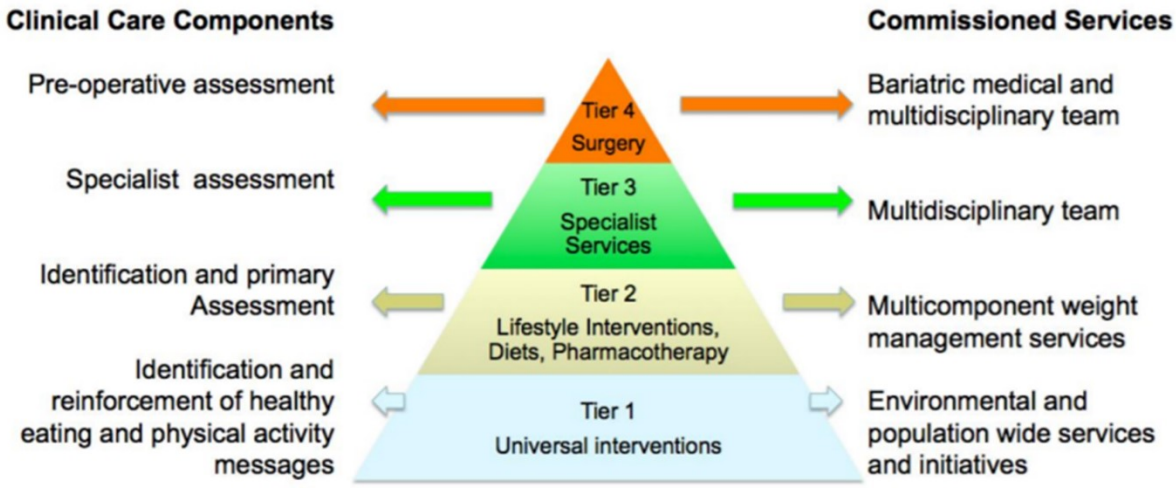
British Obesity & Metabolic Surgery Society (BOMSS) guidelines

In NICE clinical guideline 189, NICE has stated that the BOMSS commissioning guide, Figure 1, will be taken into account when defining the tiered structure for obesity management in clinical practice (69). Figure 1 summarises the tiered model of NHS services for the treatment of obesity in the UK as proposed by clinical experts in obesity and summarised by BOMSS (4). The tiers are defined according to the terminology from the previous Department of Health best practice guidance for tier 2 services (70). It is assumed that this model of obesity care will characterise the standard of care for the treatment of obesity given that, as part of the consultation process in 2018, NICE has agreed to align with this model in the upcoming update to CG189 (13).

Figure 1: Tiered model of obesity services according to BOMSS guidance (2014)



Referral to tier 3 setting is recommended for patients with a BMI >40 kg/m^2 or a BMI ≥35 kg/m^2 with comorbidities, such as hypertension, obstructive sleep apnoea (OSA), benign intracranial hypertension, functional disability, infertility and depression if specialist advice is needed regarding overall patient management. In this setting, patients with obesity undergo initial specialist assessment and are offered specialist diets, psychological treatment, and pharmacotherapy.

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Currently, patients should be assessed and managed in a tier 3 WAMC prior to being recommended for bariatric surgery in tier 4 which is only provided to compliant patients who demonstrate behavioural changes with diet and exercise. Specialist assessment can typically take months prior to referral to surgery. During this time, clinically meaningful weight loss may be achieved without the need or wish for referral for surgery. After bariatric surgery, tier 4 services will follow-up patients at regular intervals for a minimum of 2 years.

Unmet need

In addition to diet and exercise, pharmacotherapy may be an appropriate treatment option for some patients. Currently, the only NICE recommended pharmacological option available to patients with obesity is orlistat (13). However, orlistat is not commonly prescribed due to efficacy and tolerability issues (68). This is also reflected in prescription cost analysis data that shows patients treated with orlistat halved from 2011 to 2016 (12, 68). Additionally, secondary care use of pharmacotherapy appears to be much lower compared to overall NHS prescribing, suggesting high use in primary care (tier 2). Therefore there are no pharmacotherapy options are available in tier 3.

Three other pharmacotherapies, sibutramine (Reductil®), rimonabant (Acomplia®), and naltrexone–bupropion (Mysimba®), were referred to NICE for appraisal in 2002, 2007, and 2017, respectively. The rimonabant and sibutramine technology appraisals were withdrawn following the withdrawal of their marketing authorisations due to safety concerns (71, 72). Naltrexone–bupropion did not obtain a positive recommendation from NICE due to considerable uncertainty around the true incremental cost-effectiveness ratio (ICER), along with a very large patient population and long-term treatment leading to a potentially high impact on NHS resources. It was suspected unlikely to be cost-effective.

For patients who are unsuccessful on pharmacotherapy (orlistat) as an adjunct to diet and exercise in tier 2 and are referred to specialist tier 3 services, there is currently no further pharmacological treatment options available, as an adjunct to diet and exercise. Therefore, additional treatment options are needed for these patients.

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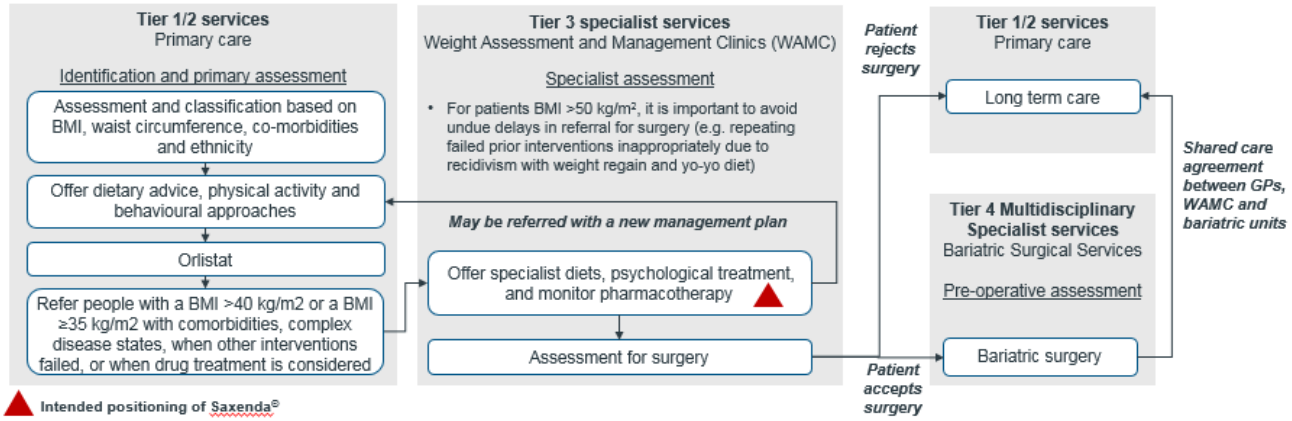
Liraglutide 3.0mg and positioning in current treatment pathway

Liraglutide 3.0mg (Saxenda®) is a human glucagon-like peptide-1 (GLP-1) analogue, which acts as a GLP-1 receptor agonist (GLP-1 RA) administered by SC injection. It is a physiological regulator of appetite and calorie intake and regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and reducing prospective food consumption. In patients with obesity and prediabetes, liraglutide 3.0mg has demonstrated greater weight reduction and more patients achieving ≥5% weight loss. Alongside benefits in weight reduction and delay in the onset of type 2 diabetes it also has cardiovascular benefits, such as reduction in systolic blood pressure (SBP) versus no pharmacotherapy in combination with diet and exercise (73).

Providing liraglutide 3.0mg as an adjunct treatment option in a specialist tier 3 service addresses a critical need for patients when conventional treatment options are not appropriate or unsuccessful. Therefore, the proposed positioning of liraglutide 3.0mg falls within the current NHS treatment pathway, summarised in Figure 2.

Figure 2: Placement of liraglutide 3.0mg in the NHS tiered services pathway for weight management



Source: Figure adapted based on the NICE and BOMSS guidelines (4, 13)

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B.1.4. Equality considerations

It is stated in the decision problem that no equality issues have been identified in relation to the use of liraglutide 3.0mg. To the contrary, liraglutide 3.0mg is likely to promote equality of opportunity and assist people with particular protected characteristics and with additional characteristics for consideration (socioeconomic status) for the reasons set out below, a number of which were also raised in the Equality Impact Assessment dated 10 April 2019 (74):

1. The effects associated with obesity may amount to impairment such that these effects can be considered a disability under the Equality Act 2010 in certain circumstances (75). This means that liraglutide 3.0mg can assist certain people considered to have a disability, protected under the Equality Act 2010.

2. The indications for liraglutide 3.0mg include a lower initial BMI threshold for patients with at least one weight-related comorbidity such as prediabetes or type 2 diabetes (≥27 kg/m^2 or <30 kg/m^2 as detailed in Section A.4 below). Some ethnic groups have been found to be at increased risk of comorbidities such as prediabetes or type 2 diabetes at a lower BMI when compared with the larger population. This is reflected by NICE Public Health guideline (PH 46) recommends using a lower BMI threshold for preventing type 2 diabetes among Asian, black African and African-Caribbean populations (15). This may mean that liraglutide 3.0mg may be of greater assistance to people in these minority ethnic groups, protected under the race element of the Equality Act 2010.

3. Socioeconomic status has an influence on the incidence and the impact of obesity (42, 43). A higher prevalence of obesity has been found in people of lower socioeconomic status. For example, a WHO report published in 2014, found that "significant socioeconomic, gender and ethnic inequities in obesity exist in Europe" and "socioeconomic inequities in obesity in Europe are widening and the gradient is becoming steeper" (76). Consequently, as an adjunct treatment option for obesity, liraglutide 3.0mg

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may have a positive differential impact on this portion of the population, thereby promoting equality of opportunity.

4. Further, there is also evidence to suggest that obesity results in inequity in access to other treatments. For example, according to a report by the Royal College of Surgeons, 31% of Clinical Commissioning Groups have at least one mandatory policy on BMI level and weight management, adversely affecting access by overweight or obese patients to routine surgery such as hip and knee replacements (77). As an adjunct treatment option for obesity, by assisting in lowering BMI levels and accordingly, allowing patients to meet BMI thresholds, liraglutide 3.0mg may reduce this inequity in access to other medical treatments.

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B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.1.1. Clinical trials with liraglutide 3.0mg (Saxenda®)

The clinical development programme for liraglutide 3.0mg was designed to assess its efficacy and safety on weight loss and comorbidities associated with obesity.

The clinical development programme for liraglutide 3.0mg for weight management comprises the completed trials listed below. For ongoing trials, please refer to Section B.2.11.

Five Phase 1 trials:

- **Trial 3630 (NCT00978393)**: Clinical pharmacology trial in adults with obesity.
- **Trial 3967 (NCT01789086)**: Clinical pharmacology trial in adolescents with obesity conducted after the Phase 3 programme in adults.
- **Trial 4162 (NCT02207348)**: Clinical pharmacology trial conducted to investigate the bioequivalence between SC administration of liraglutide with the FlexPen® and the PDS290 pen-injectors.
- **Trial 4181 (NCT02696148)**: Clinical pharmacology trial conducted to assess safety, tolerability, pharmacokinetics and pharmacodynamics of liraglutide 3.0mg in paediatric patients with obesity.
- **Trial 4192 (NCT02717858)**: Clinical pharmacology trial conducted to assess the effects of liraglutide on gallbladder emptying in subjects with overweight or obesity.

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One Phase 2 trial:

- **Trial 1807 (NCT00422058)**: Phase 2 dose-finding trial in adult patients with obesity or overweight (without type 2 diabetes). 564 patients were randomised in a 1:1:1:1:1:1 manner to receive one of four doses of liraglutide (1.2, 1.8, 2.4 or 3.0mg once daily), or placebo (once daily) or orlistat (120 mg three times daily). The main trial was of 20 weeks duration with an extension period of 84 weeks. Of the 92 patients in the liraglutide 3.0mg group, only 31 patients had prediabetes at baseline. Although these patients may overlap with the intended target population in this submission, Trial 1807 is not considered relevant for the decision problem as it was a dose-finding study in a low number of patients and therefore not adequately powered to measure long-term efficacy in the target population. The main findings were published in Astrup *et al*., 2009 (78) and Astrup *et al*., 2012 (79).

Four confirmatory Phase 3a trials - SCALE (Satiety and Clinical Adiposity – Liraglutide Evidence):

- **Trial 1839; SCALE obesity and prediabetes (NCT01272219):** Investigated the long-term efficacy of liraglutide 3.0mg in adult patients with obesity. The main trial was 56 weeks in duration and included patients with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2 plus comorbidities) both with and without prediabetes (n=3,731 patients in total). In addition, the trial had a pre-planned 2-year extension period for patients with prediabetes at screening (2,254 patients in total) to evaluate the effect of liraglutide 3.0mg on the onset of type 2 diabetes for a total of 3 years.

The main findings of Trial 1839 were published in Pi-Sunyer *et al.*, 2015 (80) and Le Roux *et al.*, 2017 (81). For the purposes of the decision problem under consideration in this submission, a *post-hoc* analysis from the SCALE obesity and prediabetes trial provides the

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key evidence base for liraglutide 3.0mg, as it included patients who are representative of the target population in scope (i.e. patients with BMI ≥35 kg/m^2 and prediabetes and high risk of CVD). Details of methods and design of Trial 1839 are provided in Section B.2.3. As the decision problem relates to patients with prediabetes, the following sections will focus on patients that were part of the full 3-year assessment (i.e. patients with prediabetes at screening).

- **Trial 1922; SCALE diabetes (NCT01272232):** Investigated the efficacy and safety of liraglutide 3.0mg in inducing long-term weight loss in 846 patients with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) and diabetes treated with one to three oral antidiabetics. The main findings were published in Davies *et al*, 2015 (82).
    - Trial 1922 did not include patients with prediabetes and is therefore not considered relevant for the decision problem.

- **Trial 3970; SCALE sleep apnoea (NCT01557166):** Investigated the efficacy and safety of liraglutide 3.0mg in reducing the severity of OSA in 359 patients with obesity (BMI ≥30 kg/m^2) and moderate or severe OSA. The main findings were published in Blackman *et al*, 2016 (83).
    - Trial 3970 had a short duration (32 weeks) and did not assess prediabetes status. The trial is therefore not considered relevant for the decision problem.

- **Trial 1923; SCALE maintenance (NCT00781937):** Investigated the efficacy and safety of liraglutide 3.0mg to maintain a weight loss of at least 5 % achieved by a low-calorie (1,200−1,400 kcal) diet- and increased physical activity - during a run-in period in 422 patients with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) without diabetes. The main findings were published in Wadden *et al.*, 2013 (84).

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- Only a small proportion of the patients in Trial 1923 had prediabetes. Moreover evidence synthesis with these patients was not possible due to the different study designs.

Phase 3b trials:

The following two Phase 3b trials included few patients with prediabetes, the comparator in Trial 4274 did not reflect the standard practice and patients with type 2 diabetes were included in Trial 4272. These studies are therefore not considered relevant for the decision problem:

- **Trial 4274; SCALE IBT (NCT02963935):** Maximising weight loss in adult patients with obesity receiving intensive behaviour therapy.
- **Trial 4272; SCALE Insulin (NCT02963922):** Weight management in insulin-treated patients with type 2 diabetes. The trial is currently under reporting.

B.2.2. List of relevant clinical effectiveness evidence

Clinical effectiveness evidence was provided by Trial 1839 (i.e. patients with prediabetes at screening/baseline) (Table 4).

Table 4: Clinical effectiveness evidence - Trial 1839

Study	Trial 1839 - SCALE obesity and prediabetes
Trial design	Randomised, double-blind (investigators and patients were blinded during the full trial duration; Novo Nordisk was unblinded after 1year), placebo-controlled, parallel group, multicentre, multinational clinical trial. The 56-week period of the trial evaluated the efficacy and safety of liraglutide 3.0mg for weight management in individuals with and without prediabetes (1-year part). From week 56, individuals with prediabetes at screening continued on treatment for a further 2 years, with a 12-week off treatment follow-up period. The information hereafter refers to the 3-year study.
Population	Patients with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with comorbidities, diagnosed with prediabetes at screening.
Intervention	Once daily administration of liraglutide 3.0mg (in addition to a 500 kcal/day deficit diet and at least 150 minutes of physical activity per week).

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<table>
<tr><th>Study</th><th colspan="5">Trial 1839 - SCALE obesity and prediabetes</th></tr>
<tr><td>Comparator</td><td colspan="5">Once daily administration of placebo (in addition to a 500 kcal/day deficit diet and at least 150 minutes of physical activity per week).</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>X</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>X</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the economic model</td><td colspan="5">The economic model is based on data from the 3-year part of Trial 1839, as this trial included patients which are representative for the patient population in scope for this submission (i.e. patients with BMI ≥35 kg/m^2, prediabetes and high risk of CVD).</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">Outcomes listed below are from the 3-year part of the trial
[Outcomes that are incorporated into the model are marked in bold]
• Fasting body weight (%, kg), mean change from baseline to week 160
• Change from baseline to week 160 in waist circumference
• Change from baseline to week 160 in BMI
• Proportion of patients losing ≥5% of baseline fasting body weight (5% responders) at week 160
• Proportion of patients losing >10% of baseline fasting body weight (10% responders) at week 160
• Change from baseline to week 160 in systolic blood pressure
• Relative change from baseline to week 160 in HDL and total cholesterol
• Change from baseline to week 160 in HbA$_{1c}$
• Adverse effects</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">Secondary efficacy endpoints:
• Change from baseline to week 160 in excess body weight
• Proportion of patients with type 2 diabetes at week 160
• Proportion of patients with normoglycemia at week 160
• Change from baseline to week 160 in FPG, fasting insulin at week 160 and fasting C-peptide at week 160
• Change from baseline to week 160 in FPG, fasting insulin at week 160 and fasting C-peptide at week 160</td></tr>
</table>

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Study	Trial 1839 - SCALE obesity and prediabetes
	• Homeostasis model assessment – beta-cell function (HOMA-B) and Homeostasis model assessment – insulin resistance (HOMA-IR) evaluated at week 160 • Relative change from baseline to week 160 in LDL, VLDL, triglycerides and FFA • Change from baseline to week 160 in diastolic blood pressure • Relative change from baseline to week 160 in hsCRP, adiponectin and fibrinogen; PAI-1 at week 160) • Relative change from baseline to week 160 in LDL, VLDL, triglycerides, total cholesterol and free fatty acids (FFA) • Relative change from baseline to week 160 in urinary albumin-to-creatinine ratio (UACR) • Change from baseline to week 160 in PRO assessed by IWQoL-Lite and SF-36 • Treatment related impact measure (TRIm)-Weight at week 160 • Proportions of patients with change from baseline to week 160 in antihypertensive drugs, lipid lowering drugs and oral anti-diabetic drugs • Secondary efficacy endpoints in the 12-week observational follow-up period: • Proportion of patients with type 2 diabetes at week 172 evaluated as the time to onset of type 2 diabetes until week 172 as well as by using logistic regression • Fasting body weight (%, kg), mean change from baseline to week 172 • Waist circumference, change from baseline to week 172 • FPG, change from baseline to week 172 • Vital signs (systolic and diastolic blood pressure), change from baseline to week 172 • UACR, relative change from baseline to week 172 • Safety endpoints: • Mental health assessed by the C-SSRS and PHQ-9 • Hypoglycaemic episodes • Haematology and biochemistry including amylase, lipase and calcitonin • Formation of anti-liraglutide antibodies • Resting pulse and RPP (vital signs)

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Study	Trial 1839 - SCALE obesity and prediabetes
	• Physical examination (CV system, respiratory system, abdomen, central and peripheral nervous system, musculoskeletal system and the thyroid gland) • ECGs

C-SSRS: Columbia-Suicide Severity Rating Scale; CVD: cardiovascular disease; CV: cardiovascular; ECGs: electrocardiography; FFA: free fatty acids; FPG: fasting plasma glucose; HDL: high-density lipoprotein; HOMA -B: homeostasis model assessment – beta-cell function; HOMA-IR: homeostasis model assessment – insulin resistance; hsCRP: high sensitivity C-reactive protein; LDL: low-density ipoprotein; PAI-1: plasminogen activator inhibitor-1; RPP: rate pressure product; TRIm: treatment related impact measure; UACR: urinary albumin-to-creatinine ratio; VLDL: very low-density lipoprotein

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

B.2.3.1. Summary of Trial 1839 methodology

Trial 1839 was a randomised, double-blind (investigators and patients were blinded during the full trial; Novo Nordisk was unblinded after one year), placebo-controlled, parallel group, multicentre, multinational trial in patients with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with comorbidities. Study participants were randomised two to one to receive liraglutide 3.0mg (n=2,487) or placebo (n=1,244) as an adjunct to diet and exercise and stratified according to prediabetes status (according to American Diabetes Association [ADA] 2010 criteria) at screening (85). The trial design is illustrated in Figure 3.

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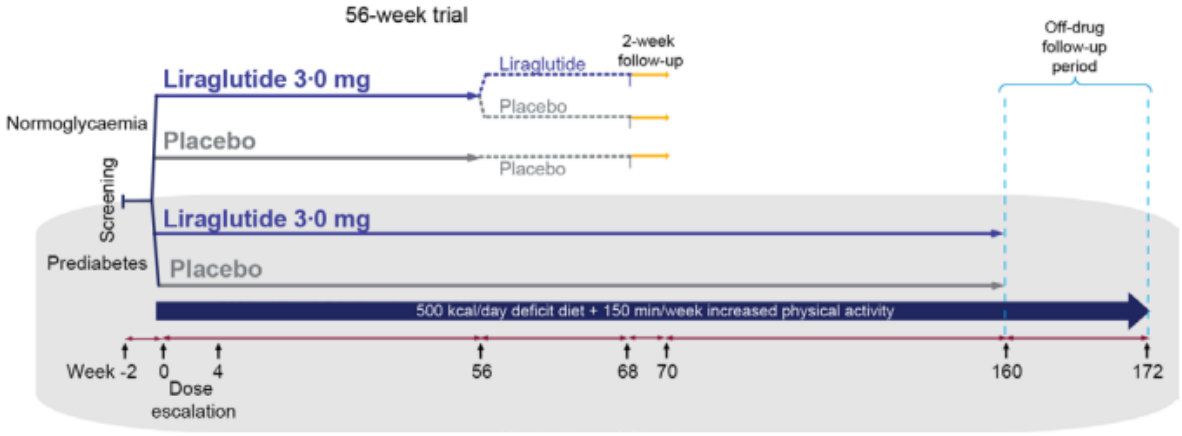
Figure 3: Trial design - SCALE– obesity and prediabetes (Trial 1839)



1-year part (n=3,731 patients)

The initial 56 weeks of the trial included both patients with and without prediabetes. Dose escalation in weekly increments of 0.6mg of liraglutide up to 3.0mg once daily was applied during the first 4 weeks of treatment. For patients without prediabetes at screening, the initial 56 weeks were followed by a 12-week re-randomised treatment period (patients in the liraglutide 3.0mg group either continued on liraglutide 3.0mg or switched to placebo whereas patients in the placebo group remained on placebo) and a 2-week follow-up period. The primary results from the 1-year part of Trial 1839 were published in Pi-Sunyer *et al*., 2015 (80).

3-year assessment - patients with prediabetes (n=2,254 patients)

Following the 1-year part (including both subjects with and without prediabetes), the trial had a 2-year extension period for patients with prediabetes at the screening. Thus, patients with prediabetes at screening received either liraglutide 3.0mg or placebo as an adjunct to diet and exercise for 160 weeks, followed by a 12-week off-drug/placebo observational follow-up period, for a total trial duration of 172 weeks. Patients consented to the 3-year assessment at randomisation. The primary results from the 3-year assessment of Trial 1839 were published in le Roux *et al*., 2017 (81).

Company evidence submission for liraglutide 3.0mg in the management of overweight and obesity (ID740)

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As the decision problem relates to patients with prediabetes, the data presented in the following sections (Section B.2.3.2 Demographics and baseline characteristics in Trial 1839 onwards) will focus on the 3-year assessment of the trial which included patients with prediabetes at the screening.

A summary of the methodology of SCALE– obesity and prediabetes (Trial 1839) is provided in Table 5.

Table 5: Summary of methodology – SCALE – obesity and prediabetes (Trial 1839)

Location	The trial was conducted at 191 sites in 27 countries in Europe, North America, South America, Asia, Africa, and Australia. In the UK, 112 randomised patients at eight sites participated.
Trial design	Randomised, double-blind, placebo-controlled trial with randomisation of patients to either 56 or 160 weeks of treatment based on prediabetes status at the screening.
Trial inclusion criteria	Adults aged 18 years or older with stable body weight and a body mass index (BMI) of at least 30 kg/m², or at least 27 kg/m² with treated or untreated comorbidities (dyslipidaemia, or hypertension, or both) were enrolled in the trial. Patients were stratified according to BMI (≥30 kg/m^2 or <30 kg/m^2) and prediabetes status. To be eligible for stratification as having prediabetes, patients had to meet one of the following criteria based on the ADA 2010 (86) guidance: • HbA_{1c} 5.7%−6.4% both inclusive, or • Fasting plasma glucose (FPG) ≥5.6 mmol/L and ≤6.9 mmol/L, or • Two hours post-challenge (oral glucose tolerance test [OGTT]) plasma glucose (PG) ≥7.8 mmol/L and ≤11.0 mmol/L. Key exclusion criteria were: type 1 or type 2 diabetes, medications causing significant weight gain or loss, bariatric surgery, history of pancreatitis, major depressive or other severe psychiatric disorders, and family or personal history of multiple endocrine neoplasia Type 2 or familial medullary thyroid carcinoma.
Trial drug	Liraglutide 3.0mg or placebo was administered once daily by subcutaneous (SC) injections with the FlexPen® either in the abdomen, thigh or upper arm. Injections could be done at any

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	time of day irrespective of meals. In order to reduce the level of side effects, patients followed a fixed dose escalation in weekly increments of 0.6mg liraglutide. If patients did not tolerate an increase in dose during dose escalation, the investigator had the option to individualise the dose escalation with a total delay of up to 7 days. All patients had to be at the target dose of 3.0mg by 35 days after randomisation.
Permitted and disallowed concomitant medication	Medications causing significant weight gain or loss were disallowed.
Primary outcomes	The primary endpoint in the 3-year assessment of the trial was: Proportion of patients with onset of type 2 diabetes at week 160 among patients with prediabetes at baseline - evaluated as the time to onset of type 2 diabetes.
Other outcomes used in the economic model	The outcomes listed below were included in the economic model: • % weight loss vs. baseline at 6 months (28 weeks), 1 year (56 weeks), 2 years (104 weeks), and 3 years (160 weeks) • Change in systolic blood pressure (mmHg, positive = increase) vs. baseline at 6 months, 1 year, 2 year and 3 years • Change in serum lipids (total cholesterol, HDL) vs baseline at 6 months, 1 year, 2 year and 3 years • Change in HbA_{1c} vs. baseline at 6 months, 1 year, 2 year and 3 years • % reversing from prediabetes to NGT at 3 months, 1 year and 2 years • Proportion not achieving 5% weight loss after 16 weeks (i.e. after 4 weeks titration and 12 weeks on maintenance dose) The analyses used in the economic modelling were performed *post-hoc* (see Section B.2.7.2 for further details).
Pre-planned subgroups	Pre-planned subgroup analyses from the 3-year assessment of the trial were performed to investigate whether baseline BMI (in four categories) had any effect on changes in body weight or HbA_{1c}.

ADA: American Diabetes Association; FPG: Fasting plasma glucose; HDL: High-density lipoprotein; OGTT: oral glucose tolerance test; PG: plasma glucose; NGT: Normal glucose tolerance; SC: Subcutaneous; UK: United Kingdom

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B.2.3.2 Demographics and baseline characteristics in Trial 1839

Demographics and baseline characteristics for all randomised patients are summarised in Table 6. Overall, the liraglutide 3.0mg and the placebo groups were well matched with respect to demographics and baseline characteristics. The average age of all randomised patients was 47.5 years and 76.0% of patients were women.

Table 6: Demographic and baseline characteristics (means) - randomised patients – Trial 1839

	Liraglutide 3.0mg (N=1,505)	Placebo (N=749)	Total (N=2,254)
Age (years)	47.5 (11.7)	47.3 (11.8)	47.5 (11.7)
Height (m)	1.66 (0.09)	1.66 (0.09)	1.66 (0.09)
Fasting body weight (kg)	107.5 (21.6)	107.9 (21.8)	107.6 (21.6)
BMI (kg/m^2)	38.8 (6.4)	39.0 (6.3)	38.8 (6.4)
HbA_{1c} (%)	5.8 (0.3)	5.7 (0.3)	5.7 (0.3)
Fasting plasma glucose (mmol/L)	5.5 (0.6)	5.5 (0.5)	5.5 (0.6)
Sex			
Female (%)	75.8%	76.5%	76.0%
Male (%)	24.2%	23.5%	24.0%
Race			
White	83.5%	83.8%	83.6%
Black or African American	9.7%	9.5%	9.6%
Asian	5.0%	5.2%	5.1%
Other[a]	1.9%	1.5%	1.7%
Smoker status			
Current smoker	14.4%	16.6%	15.1%
Never smoked	58.9%	57.7%	58.5%
Previous smoker	26.7%	25.8%	26.4%
History of CV disease (SMQ search)[b]			

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	Liraglutide 3.0mg (N=1,505)	Placebo (N=749)	Total (N=2,254)
Yes	12.7%	13.2%	12.9%
No	87.3%	86.8%	87.1%
Dyslipidaemia[b]			
Yes	33.2%	33.2%	33.2%
No	66.8%	66.8%	66.8%
Hypertension[b]			
Yes	42.2%	41.7%	21.0%
No	57.8%	58.3%	79.0%

[a] including “American Indian or Alaska Native”, “Native Hawaiian or other Pacific Islander” or “Other”;
[b] History of CV disease was based on an SMQ search of the medical history including Ischaemic heart disease, Cardiac failure, Central nervous system haemorrhages, Cerebrovascular conditions and Embolic and thrombotic events. Dyslipidaemia was found by SMQ search of the medical history. Hypertension was found by SMQ search of the medical history.
Values for continuous variables are means. Values in parentheses are standard deviations; CV: cardiovascular; N: number of patients; SMQ: standard medical query
Cross-reference: Trial 1839 Clinical trial results (CTR) (3-year part) Table 3-3

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

B.2.4.1. Overview of analyses

Analysis sets

All efficacy analyses used data from the full analysis set from Trial 1839; i.e. including patients with prediabetes at screening, which included all patients who underwent randomisation and received at least one dose of a study drug and had at least one assessment after baseline. The safety analysis set included all patients who were exposed to at least one dose of the study drug.

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Imputation methods

In the original analyses, missing values were imputed using the last observation carried forward (LOCF) for post-baseline measurements. The results obtained using this method are included in the Trial 1839 CTR, the publications and the European SmPC (Appendix C) (80, 81).

For the economic modelling, a number of *post-hoc* analyses were conducted for patients in Trial 1839 matching the target population in scope for this submission. The *post-hoc* analyses have been conducted using three different imputation methods:

a) LOCF;

b) Baseline observation carried forward (BOCF);

c) Multiple imputations based on the McEvoy (ME) approach (ME-MI approach): This was used to handle missing data for patients on treatment at the time of the visit the estimation is done for (i.e. week 28, 56, 104 or 160) (87). For patients off treatment at the specific visit, the ME approach cannot be generally applied, since patients that discontinue treatment during the extension part of the trial, were not asked to come back for assessments at later visits. Therefore, for patients off treatment at the visit, single imputation is done by extrapolating from the last available observation and until the time of the visit. Extrapolation is based on change estimates from the 12-week follow-up period (following the 3-year assessment of Trial 1839) without treatment. If single imputed values cross baseline values, baseline values are used.

The European license for liraglutide 3.0mg for obesity is based on calculations where missing data is handled by LOCF. Therefore, the results from the *post-hoc* analyses that are used for the base case in the economic modelling are also based on LOCF. For the sensitivity analyses in the economic modelling, results from the *post-hoc* analyses using BOCF and ME-MI approach are applied to test the impact of using different imputation methods on the cost-effectiveness results.

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Definition of prediabetes

In the planned analyses included in Trial 1839, patients were defined as having prediabetes according to the ADA 2010 criteria. In the *post-hoc* analyses performed for the purposes of this submission, patients were defined as having prediabetes if they fulfilled the criteria provided by NICE for high risk of type 2 diabetes in addition to the original ADA criteria (88), presented below in Table 7. The ADA and NICE criteria, however, do not overlap completely; patients with fasting plasma glucose (FPG) ≥5.5 and <5.6 mmol/L would be considered prediabetic according to the NICE criteria but were not included in Trial 1839, as they did not meet the ADA criteria. With the exception of these patients, the population in the subgroup analyses otherwise complies fully with the NICE criteria.

Table 7: Prediabetes Definitions

Definition	Source
HbA_{1c} 5.7−6.4% both inclusive; or FPG ≥5.6 mmol/L and ≤6.9 mmol/L; or 2-hour post-challenge (OGTT) PG ≥7.8 mmol/L and ≤11.0 mmol/L	ADA
HbA_{1c} 6.0−6.4% both inclusive; or FPG ≥5.5 mmol/L and ≤6.9 mmol/L	NICE
HbA_{1c} 5.7−6.4% both inclusive; or FPG ≥5.6 mmol/L and ≤6.9 mmol/L	Trial 1839

FPG: fasting plasma glucose; ADA: American Diabetes Association; NICE: National Institute for Health and Care Excellence

Subgroup analyses

The *post-hoc* analysis used for the economic modelling was performed to obtain comparative evidence for the target subgroup; patients with BMI ≥35 kg/m^2, prediabetes, high risk of CVD. In addition to defining the target subgroup, data presented focus on "Early responders" which denote patients achieving at least 5% weight loss at week 16 (i.e. after 4 weeks titration and 12 weeks on the maintenance dose of the drug) in accordance with the stopping rule as per the European license for liraglutide 3.0mg (see Appendix C).

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As described in Section B.1.1. The definition for high risk of CVD was based on fulfilling at least one of the following criteria:

- Total cholesterol >5 mmol/L
- SBP >140 mmHg
- HDL <1.0 mmol/L (<40 mg/dL) for men and <1.3 mmol/L (<50 mg/dL) for women.

A summary of the objectives and associated statistical analysis methods adopted in Trial 1839 are presented in Table 8.

Table 8: Summary of statistical analyses - Trial 1839

Objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Primary To investigate the long-term efficacy of liraglutide 3.0mg in delaying the onset of type 2 diabetes in obese patients with prediabetes and in overweight patients with prediabetes and treated or untreated comorbidities (dyslipidaemia and/or hypertension) *Secondary* To investigate the long-term efficacy of liraglutide 3.0mg versus placebo on cardiovascular risk markers such as blood pressure, lipids, glucose parameters, UACR, as well as	*Planned analyses* The primary endpoint of the 3-year assessment of the trial was analysed using a Weibull model, using methods for the analysis of interval-censored time-to-event data. The Weibull model included treatment, sex, and baseline BMI stratum as fixed-effects, and baseline fasting glucose value as a covariate. Mean changes in continuous endpoints were analysed using an analysis of covariance and categorical changes for dichotomous endpoints using logistic regression. *Post-hoc* analyses Mean changes from baseline in continuous endpoints were for each	Sample size of 2,400 patients assigned to receive liraglutide and 1,200 assigned to receive placebo was estimated to provide more than 99% power to detect a between group difference in the three co-primary efficacy endpoints of the main 56-week trial and also sufficient power in the primary endpoint of the 3-year assessment of the trial. The power for the first co-primary endpoint (weight change) was calculated using a two-sided Student's t-test at a 5% significance level. The power for the	*Planned analyses* In the original analyses, missing values were imputed using LOCF for post-baseline measurements. *Post-hoc* analyses In the *post-hoc* analyses, missing values were imputed using: LOCF (used as the base case for the economic model), BOCF and ME-MI approach.

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Objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
effects on quality of life and PROs.	visit estimated using analysis of covariance with treatment and sex as factors and baseline value as covariate. Glycaemic status was summarised for each visit.	categorical co-primary endpoints was calculated using a two-sided chi-square test, also at a 5% significance level.	

BOCF: baseline observation carried forward; LOCF: last observation carried forward; MI-ME: multiple-imputation for measurement error; PRO: patient reported outcome; UACR: urinary albumin-to-creatinine ratio

B.2.4.2 Participant flow

A total of 2,254 prediabetic patients were randomised to receive either liraglutide 3.0mg or placebo as an adjunct to diet and exercise in Trial 1839. There were 1,505 patients in the liraglutide 3.0mg group and 749 in the placebo group. A larger proportion of patients in the liraglutide 3.0mg group discontinued treatment due to AEs (mostly gastrointestinal in nature) than in the placebo group over the first 16 weeks of treatment, while post week 16 more patients discontinued diet and exercise. The participant flow for Trial 1839 is presented in Appendix D.

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

A summary of the quality assessment for Trial 1839 is shown in Table 9. The complete quality assessment for Trial 1839 is provided in Appendix D.

In summary, Trial 1839 was conducted in accordance with ICH Good Clinical Practice (89), and therefore the investigators were required to have been trained according to these standards. Training of the investigators in the protocol was carried out through training sessions and/or investigator meetings, to ensure compliance and standardise performance across the trial. All principal investigators provided written commitment to comply with

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Good Clinical Practice and conduct the trial according to the protocol, prior to participation in the trial.

The trial was monitored by the sponsor by means of on-site visits, telephone calls, and regular inspection of the electronic case report form with sufficient frequency to verify the following: subject enrolment; compliance with the protocol; the completeness and accuracy of data entered in the database system by verification against original source documents; compliance in the use of trial product; drug accountability; and recording of AEs.

All trials are thought to reflect routine clinical practice in England regarding population, comparator choice, treatment administration and outcomes assessed. Outcome assessments were conducted in accordance with the trial validated methodology.

Table 9: Quality assessment results – SCALE– obesity and prediabetes (Trial 1839)

SCALE– obesity and prediabetes (Trial 1839)	
	Grade (Yes/No/Not clear/NA)
Was randomisation carried out appropriately?	Yes - Performed using a funder-provided telephone or web-based system
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes - There were no noteworthy differences in baseline characteristics or medical history
Were the care providers, participants and outcome assessors blind to the treatment allocation?	Yes - Participants & investigators were masked to treatment allocation during the entire trial[a]
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes - The rate of discontinuation was higher for liraglutide 3.0mg over the first 12 weeks due to adverse events, after which the rate of discontinuation increased at a higher rate with placebo due to ineffective therapy (see Table 21)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No

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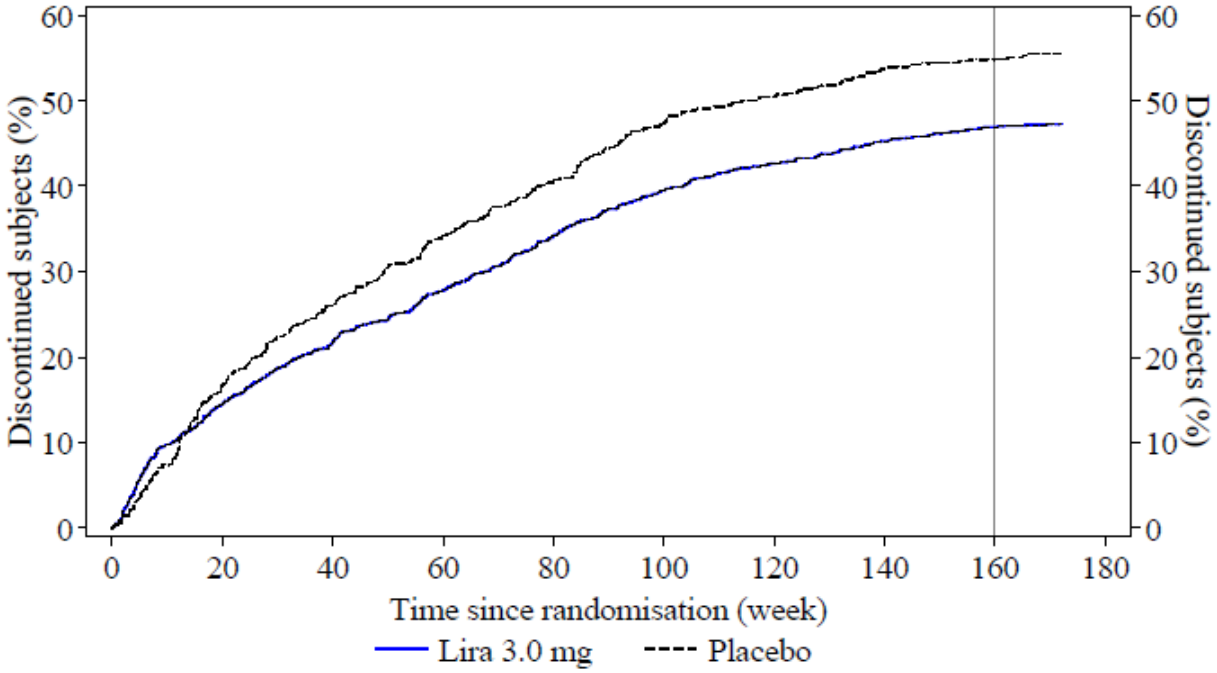
SCALE– obesity and prediabetes (Trial 1839)	
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No - The pre-specified efficacy analyses used data from the full analysis set of all randomised individuals who received at least one treatment dose and had at least one post-baseline assessment[b]

[a] Patients and investigators were blinded to treatment allocation during the entire trial (160 weeks plus the 12-week off-drug follow-up period), whereas Novo Nordisk were blinded to treatment allocation during the 1-year assessment of the trial.
[b] A modified intention to treat (mITT) was used, since it was a requirement that patients were exposed to at least one dose of trial product and had at least one assessment after baseline.

Figure 4: Time to discontinuation during the entire trial (0 to 172 weeks) - all reasons



Cross-reference: EOT Table 14.1.6

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B.2.6. Clinical effectiveness results of the relevant trials

As described in the following sections, Trial 1839 (including patients with prediabetes at screening) demonstrated the efficacy of liraglutide 3.0mg (as an adjunct to diet and exercise) in inducing and maintaining weight loss as well as in delaying the onset of type 2 diabetes in patients with prediabetes at the screening. The results from Trial 1839 together with the rest of the clinical development programme provide clear evidence of the clinical benefits of liraglutide 3.0mg as an adjunct to diet and exercise for weight management in adult patients with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with comorbidities.

Relevant efficacy results from the planned analyses included in the CTR Trial 1839 are presented in Section B.2.6.1. *Post-hoc* subgroup analyses based on data from Trial 1839 which are used to inform the economic model are presented in Section B.2.7.2.

Supportive evidence on cardiovascular and long-term safety from the other three Phase 3a trials and the cardiovascular outcomes from the LEADER trial studying liraglutide 1.8mg is presented in Section B.2.10.2.

B.2.6.1. Trial 1839

The outcomes from the planned analyses which are relevant for the economic modelling are summarised in Table 10 for continuous variables (except for lipids which are presented in Section B.2.6.10) and Table 11 for categorical variables. Further details regarding the differences between the parameters shown in the two tables are presented in Section B.2.6.2.

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Table 10: Change from baseline to week 160 in relevant continuous variables used in the economic modelling – Trial 1839 - LOCF

	Liraglutide 3.0mg	Placebo	ETD [95% CI] liraglutide 3.0mg - placebo
Fasting body weight (%)	-6.14 (7.34)	-1.89 (6.27)	-4.32 [-4.94; -3.70]
BMI (kg/m^2)	-2.37	-0.73	-1.69 [-1.93; -1.44]
HbA_{1c} (%)	-0.35 (0.32)	-0.14 (0.34)	-0.21 [-0.24; -0.18]
Systolic blood pressure (mmHg)	-3.19 (13.00)	-0.53 (13.73)	-2.80 [-3.81; -1.79]

Values in parentheses are standard deviations. ETD: estimated treatment difference; CI: confidence interval
Cross-reference: Trial 1839 CTR Tables 11-7, 11-8, 11-13, 11-14, 11-15, 11-22, 11-23, 11-30, 11-31 and EOT Table 14.2.115

Table 11: Proportions at week 160 in relevant categorical variables – Trial 1839

	Liraglutide 3.0mg	Placebo
Glycaemic status (Observed proportions)		
Normoglycemic	970 (65.9%)	268 (36.3%)
Prediabetes	460 (31.3%)	405 (54.9%)
Transient type 2 diabetes	16 (1.1%)	19 (2.6%)
Confirmed type 2 diabetes	26 (1.8%)	46 (6.2%)
Weight responders (LOCF)		
Responders (at least 5% reduction in body weight)*	49.61%	23.40%
Responders (at least 10% reduction in body weight)*	24.37%	9.45%

* after 4 weeks titration and 12 weeks of treatment on the maintenance dose. “Transient type 2 diabetes” and “Confirmed type 2 diabetes” were defined as: if for two consecutive samples at least one of the following is fulfilled for both samples then the subject has confirmed type 2 diabetes: FPG ≥126 mg/dL / HbA_{1c} ≥6.5%/2hr post-challenge (OGTT) plasma glucose ≥200 mg/dL; If “a positive” was not confirmed by the following test, then it was classified as transient type 2 diabetes; LOCF: last observation carried forward

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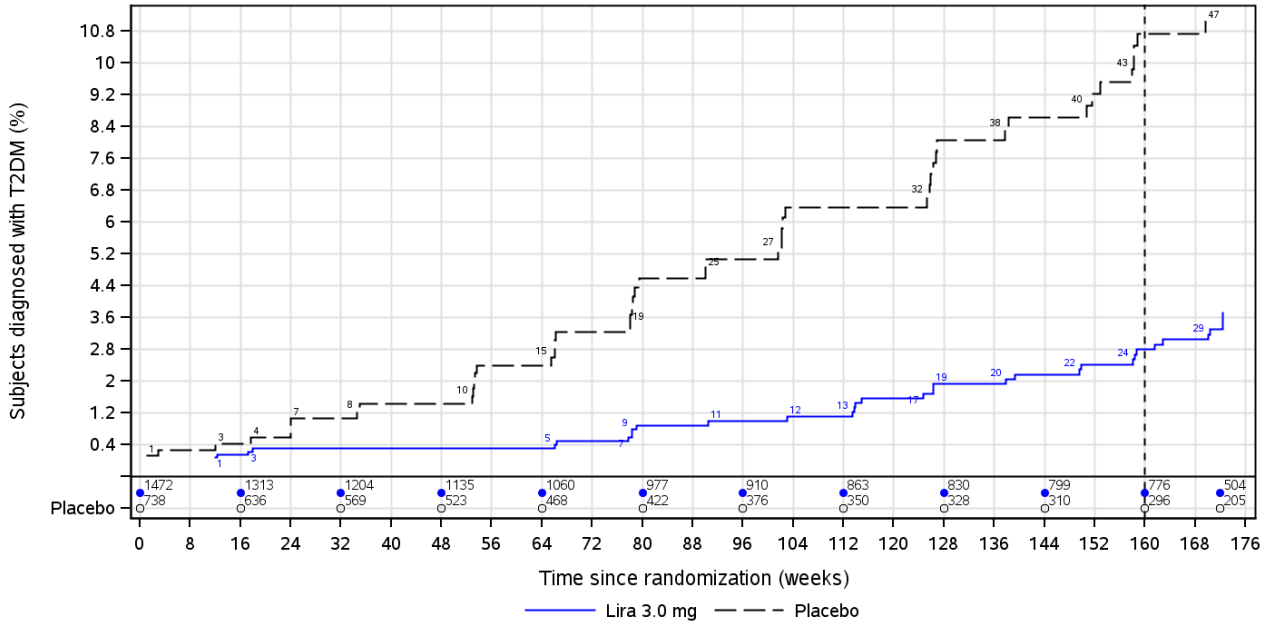
B.2.6.2. Time to onset of type 2 diabetes in Trial 1839

The primary endpoint for the 3-year assessment of the trial was the proportion of patients with onset of type 2 diabetes at week 160 among patients with prediabetes at baseline - evaluated as the time to onset of type 2 diabetes. For glycaemic status at week 160, please see Table 11.

At week 160, 26 patients treated with liraglutide 3.0mg and 46 patients treated with placebo had developed type 2 diabetes corresponding to an observed annualised type 2 diabetes incidence rate of 0.8 and 3.2 events per 100 years of exposure, respectively.

The Kaplan-Meier plot of time to onset of type 2 diabetes from 0 to 172 weeks, showing the accumulated number of patients with type 2 diabetes, is presented in Figure 5 Note that the Kaplan-Meier plot accounts for censoring of the data (e.g. accounts for patients who drop out of the trial).

Figure 5: Time to onset of type 2 diabetes (0 to 172 weeks) Kaplan-Meier curve



Numbers in the figure corresponds to the accumulated number of diagnosed patients. Numbers in the lower panel are the numbers of patients with a measurement at the given time.
Cross-reference: Trial 1839 CTR Figure 11-1

The primary endpoint was evaluated in a time-to-event analysis applying a Weibull model.

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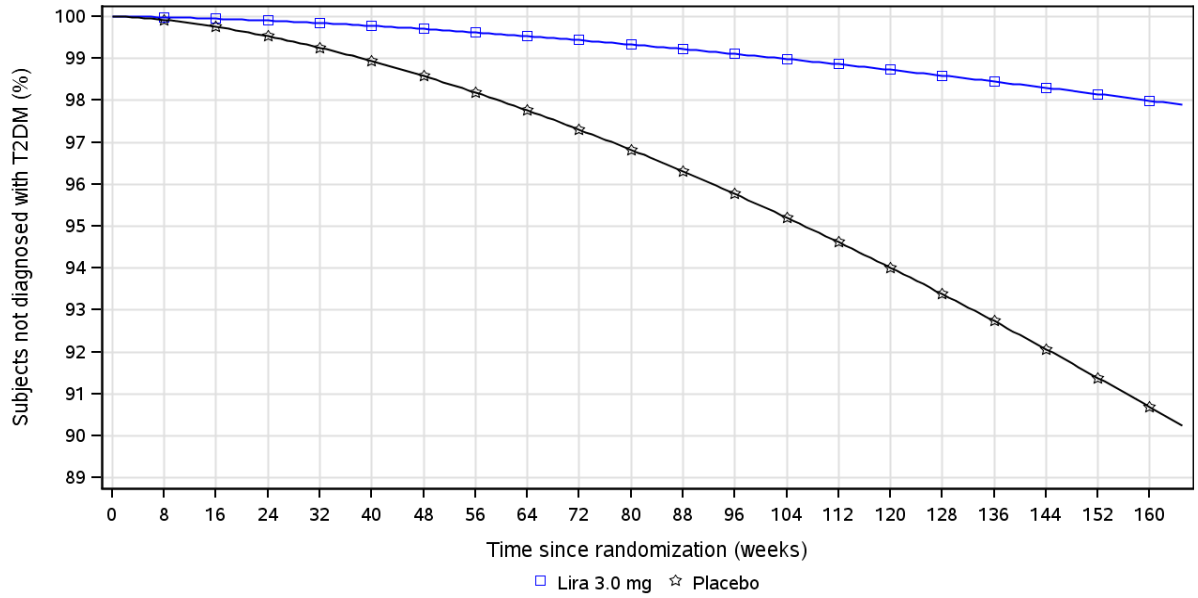
The estimated time to onset of type 2 diabetes for subjects treated with liraglutide 3.0mg was 2.681 times longer, [1.856, 3.872] 95% CI, p<0.0001, than for subjects treated with placebo (Table 12 and Figure 6). The corresponding estimated treatment hazard ratio (liraglutide 3.0mg/placebo) was 0.207, showing that the risk of developing type 2 diabetes within the 3-year period for patients treated with liraglutide was reduced by approximately 80% compared with placebo (Table 12).

Figure 6: Time to onset of type 2 diabetes up to 160 weeks of treatment - estimated diabetes-free time



Note: The time of onset of type 2 diabetes occurs in between the first of the two required registrations of elevated HbA_{1c}, FPG or 2h OGTT plasma glucose, and the diabetes assessment visit prior to the first registration. The estimated diabetes-free time is based on an analysis of time to onset of type 2 diabetes analysed in a Weibull model that includes treatment, sex and BMI stratification factors as fixed factors and baseline FPG as a covariate. Cross-reference: EOT Figure 14.2.7

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Table 12: Time to onset of type 2 diabetes up to 160 weeks of treatment - Weibull analysis – LOCF

	Number of events	Estimate
Liraglutide 3.0mg (N=1,472)	26	
Placebo (N=738)	46	
Treatment estimate (Lira 3.0mg/placebo)		2.681 [1.856, 3.872] 95% CI, p<0.0001
Treatment hazard ratio (Lira 3.0mg/placebo)		0.207

N: number of patients; Lira: liraglutide;
The time of onset type 2 diabetes occurred in between the first of the two required registrations of elevated HbA_{1c}, Fasting Plasma Glucose or 2-hour oral glucose tolerance test plasma glucose, and the diabetes assessment visit prior to the first registration. The endpoint was analysed in a Weibull model that includes treatment, sex and BMI stratification factor as fixed factors and baseline FPG as a covariate. The treatment estimate is the factor that the time-to-event is multiplied with for liraglutide 3.0mg compared to placebo.
Cross-reference: Trial 1839 CTR Table 11-2

B.2.6.3. Fasting body weight in Trial 1839

The relative change in mean fasting body weight (%) by week 0 from baseline to week 172 is shown in Figure 7. At baseline (week 0) mean fasting body weight was 107.64kg for patients treated with liraglutide 3.0mg and 107.96kg for patients treated with placebo. At the end of treatment (week 160), patients treated with liraglutide 3.0mg had lost 7.09% (observed value) (LOCF: 6.14%) of their baseline fasting body weight corresponding to 7.53kg (LOCF: 6.51kg), and patients treated with placebo had lost 2.69% (LOCF: 1.89%) corresponding to 2.84kg (LOCF: 2.03 kg).

The relative change from baseline to week 160 in fasting body weight (%) showed a statistically significantly greater weight loss with liraglutide 3.0mg than with placebo, with an estimated treatment difference of -4.32% [-4.94, -3.70] 95% CI, p<0.0001 corresponding to -4.57kg [-4.94, -3.70] 95%CI, p<0.0001.

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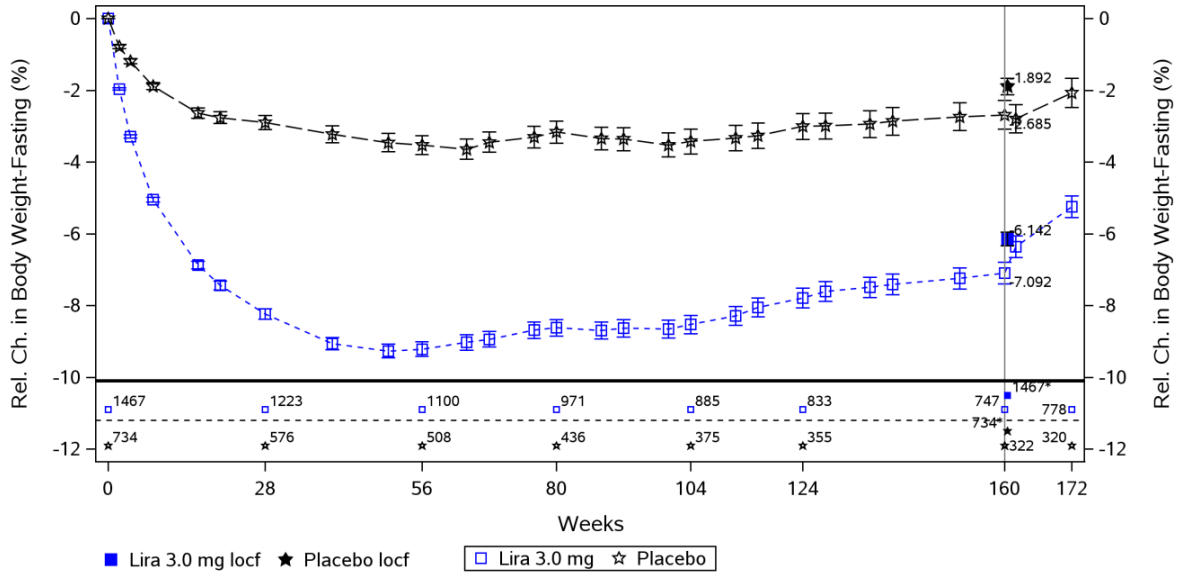
Figure 7: Fasting body weight - relative change (%) from baseline over time (0 to 172 weeks)



Numbers in the lower panel are the numbers of patients with a measurement at the given time.
Cross-reference: Trial 1839 CTR Figure 11-4

B.2.6.4. Body mass index in Trial 1839

Change in mean BMI over time (0-172 weeks) is shown in Figure 8. At baseline, mean BMI values were similar in the liraglutide 3.0mg (38.79 kg/m^2) and placebo (38.99 kg/m^2) groups. At the end of treatment (week 160), a reduction in BMI of -2.73 kg/m^2 (observed value) (LOCF: -2.37 kg/m^2) was seen with liraglutide 3.0mg compared with -1.03 kg/m^2 (LOCF: -0.73 kg/m^2) with placebo. The corresponding statistical analysis of change from baseline to week 160 in BMI showed a statistically significantly greater reduction with liraglutide 3.0mg than with placebo, with an estimated treatment difference of -1.69 kg/m^2 [-1.93, -1.44] 95% CI, p<0.0001.

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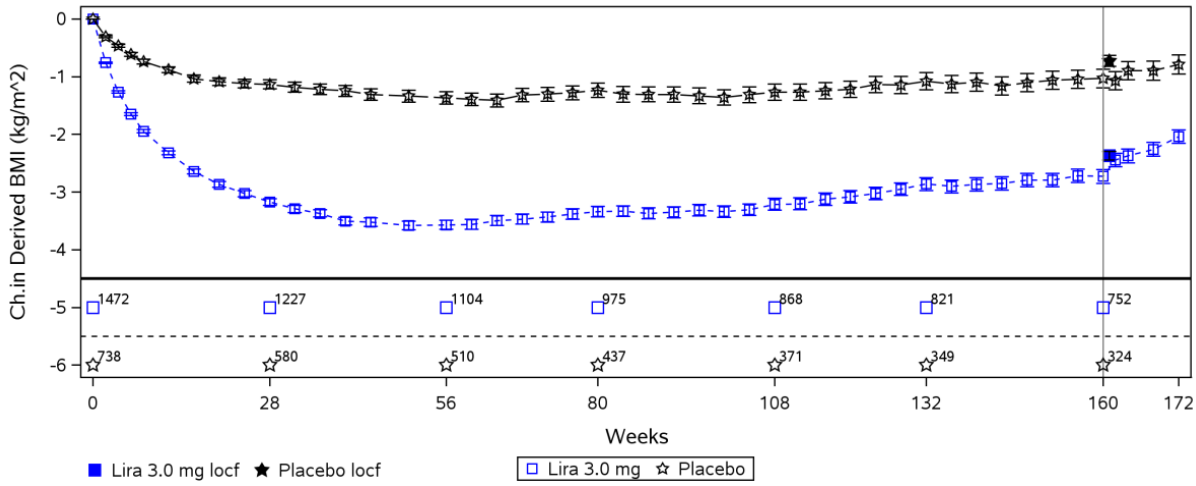
Figure 8: BMI (kg/m^2) - change from baseline over time (0 to 172 weeks)



Numbers in the lower panel are the numbers of patients with a measurement at the given time.
Cross-reference: Trial 1839 CTR Figure 11-15

B.2.6.5. Proportion of patients losing ≥5% of baseline fasting body weight in Trial 1839

At the end of treatment (week 160), the percentage of patients losing ≥5% of baseline fasting body weight was 56.8% (observed value) (LOCF: 49.6%) with liraglutide 3.0mg and 31.7% (LOCF: 23.7%) with placebo.

The corresponding statistical analysis of patients losing ≥5% of baseline fasting body weight after 160 weeks of treatment is shown in Table 13. The likelihood of achieving a weight loss of ≥5% of baseline fasting body weight was statistically significantly higher with liraglutide 3.0mg than with placebo, with an estimated treatment odds ratio of 3.223 [2.637, 3.940] 95% CI, p<0.0001.

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Table 13: Patients losing ≥5% of baseline fasting body weight after 160 weeks of treatment - logistic regression - LOCF

	Liraglutide 3.0mg (N=1,467)	Placebo (N= 734)	Liraglutide 3.0mg/Placebo
Frequencies	49.61%	23.70%	
Odds	0.984	0.305	
Treatment odds ratio			3.223 [2.637, 3.940] 95% CI, p<0.0001

N: number of patients contributing to analysis; LOCF: last observation carried forward. The binary endpoint is analysed in a logistic regression model using a logit link. The model includes treatment, country, sex, and baseline BMI stratum as fixed factors, and the baseline value as covariate
Cross-reference: Trial 1839 CTR Table 11-10

B.2.6.6. Proportion of patients losing ≥10% of baseline fasting body weight in Trial 1839

At the end of treatment (week 160), 31.3% (observed value) (LOCF: 24.8%) of patients with liraglutide 3.0mg and 15.2% (LOCF: 9.9%) of patients with placebo had lost >10% of fasting baseline body weight.

The corresponding statistical analysis of the proportion of patients losing >10% of fasting body weight after 160 weeks of treatment is shown in Table 14. The likelihood of achieving a weight loss of >10% of baseline fasting body weight was statistically significantly higher with liraglutide 3.0mg than with placebo, with an estimated treatment odds ratio of 3.086 [2.350, 4.052] 95% CI, p<0.0001.

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Table 14: Patients losing ≥10% of baseline fasting body weight after 160 weeks of treatment - logistic regression - LOCF

	Liraglutide 3.0mg (N=1,467)	Placebo (N= 734)	Liraglutide 3.0mg/Placebo
Frequencies	24.37%	9.45%	
Odds	0.322	0.104	
Treatment odds ratio			3.086 [2.350, 4.052] 95% CI, p<0.0001

N: number of patients contributing to analysis; LOCF: last observation carried forward
The binary endpoint is analysed in a logistic regression model using a logit link. The model includes treatment, country, sex, and baseline BMI stratum as fixed factors, and the baseline value as covariate
Cross-reference: Trial 1839 CTR Table 11-11

B.2.6.7. Waist circumference in Trial 1839

Change in mean waist circumference over time (0-172 weeks) is shown in Figure 9. At baseline, the mean waist circumferences were similar in the liraglutide 3.0mg (116.64 cm) and placebo (116.74 cm) groups (cross-reference: Trial 1839 CTR, EOT Table 14.2.96). At the end of treatment (week 160), a reduction in waist circumference of -7.98 cm (observed value) (LOCF: -6.87 cm) was seen with liraglutide 3.0mg compared with -3.90 cm (LOCF: -3.37 cm) with placebo.

The corresponding statistical analysis of change from baseline to week 160 in waist circumference showed a statistically significantly greater reduction with liraglutide 3.0mg than with placebo, with an estimated treatment difference of -3.53 cm [-4.23, -2.83] 95% CI, p<0.0001.

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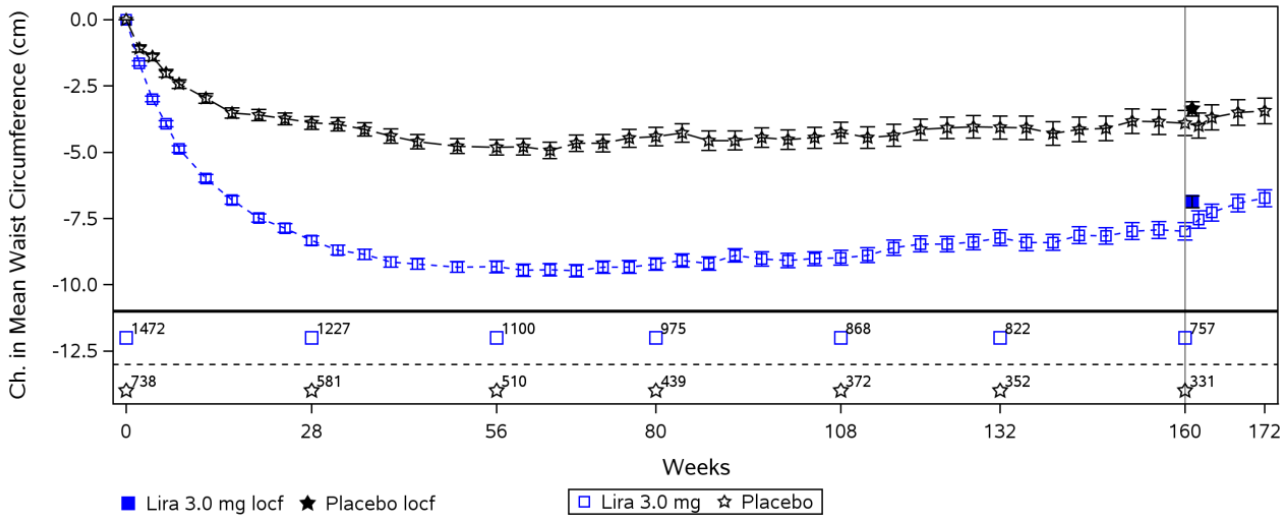
Figure 9: Waist circumference (cm) - change from baseline over time (0 to 172 weeks)



Cross-reference: Trial 1839 CTR Figure 11-14

B.2.6.8. HbA$_{1c}$ in Trial 1839

Change in mean HbA$_{1c}$ over time (weeks 0-172) is shown in Figure 10 At baseline, mean HbA$_{1c}$ levels were similar in the liraglutide 3.0mg (5.75%) and placebo groups (5.74%). Shortly after treatment initiation, HbA$_{1c}$ decreased with liraglutide 3.0mg, and during the entire treatment period, the levels were lower with liraglutide 3.0mg than with placebo. At week 160, the change from baseline was -0.41% (observed value) (LOCF -0.35%) with liraglutide 3.0mg and -0.19% (LOCF -0.14%) with placebo.

The corresponding statistical analysis of change from baseline to week 160 in HbA$_{1c}$ showed a statistically significantly greater reduction in HbA$_{1c}$ with liraglutide 3.0mg than with placebo, with an estimated treatment difference of -0.21% [-0.24, -0.18] 95% CI, p<0.0001.

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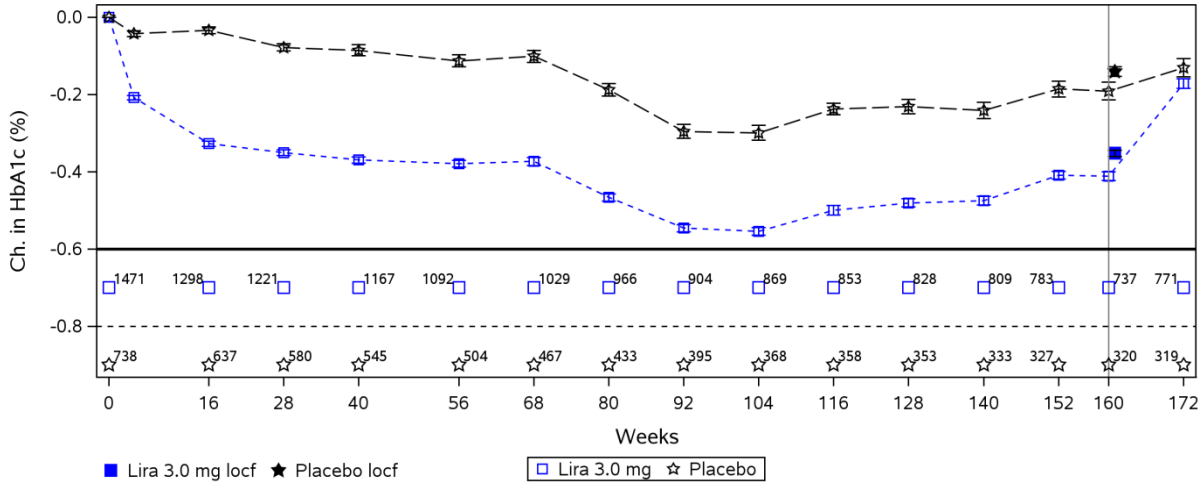
Figure 10: HbA_{1c} (%) - change from baseline over time (0 to 172 weeks)



Cross-reference: Trial 1839 CTR Figure 11-18

B.2.6.9. Systolic blood pressure in Trial 1839

Change in mean SBP over time (0 to 172 weeks) is shown in Figure 11. At baseline, mean SBP was similar in the liraglutide 3.0mg (124.80 mmHg) and placebo (125.01 mmHg) groups. Immediately after treatment initiation, SBP decreased in both treatment groups, more pronounced with liraglutide 3.0mg than with placebo. At the end of treatment (week 160), the mean change from baseline in SBP was -3.72 mmHg (observed value) (LOCF: -3.19 mmHg) in the liraglutide 3.0mg group and -1.33 mmHg (LOCF: -0.53 mmHg) in the placebo group.

The corresponding statistical analysis of change from baseline to week 160 in SBP showed a statistically significantly greater decrease with liraglutide 3.0mg than with placebo, with an estimated treatment difference in SBP of -2.80 mmHg [-3.81, -1.79] 95% CI, p<0.0001.

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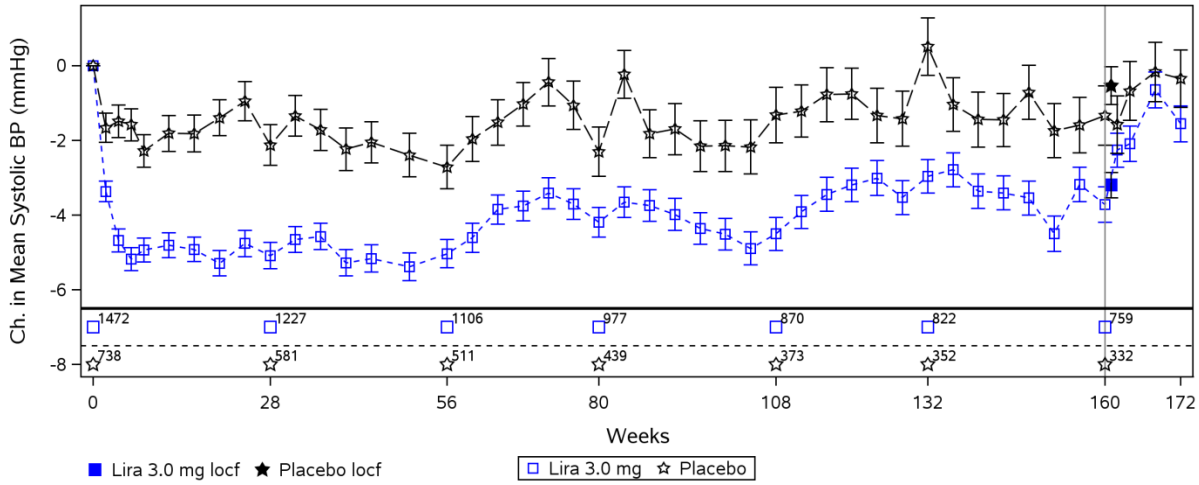
Figure 11: SBP (mmHg) - change from baseline over time (0 to 172 weeks)



Cross-reference: Trial 1839 CTR Figure 11-36

B.2.6.10. Lipid parameters in Trial 1839

HDL

At baseline, HDL levels were the same in both groups: 1.30 mmol/L (50.05 mg/dL) in the liraglutide 3.0mg group and 1.30 mmol/L (50.09 mg/dL) in the placebo group (Table 15). During the 160 weeks treatment period, HDL increased in both treatment groups. At the end of treatment (week 160), the geometric mean of the relative change in HDL was increased with 6.78% (observed value) (LOCF: 4.89%) in the liraglutide 3.0mg group and with 6.86% (LOCF: 4.04%) in the placebo group (Table 15).

Total cholesterol

At baseline, total cholesterol levels were similar in both groups: 4.99 mmol/L in the liraglutide 3.0mg group and 5.09 mmol/L in the placebo group (Table 15). During the 160 weeks of treatment, the levels decreased in both treatment groups compared to baseline values, with some fluctuations over time. At the end of treatment (week 160), the geometric

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mean of relative change from baseline in total cholesterol was decreased with -2.21% (LOCF: -2.62%) in the liraglutide 3.0mg group and with -1.38% (LOCF: -1.60%) in the placebo group (Table 15).

Table 15: HDL and total cholesterol from baseline to week 160 – LOCF

	Liraglutide 3.0mg			Placebo		
	Baseline [a]	**Week 160[a]**	**Change, %[b]**	**Baseline [a]**	**Week 160[a]**	**Change, %[b]**
HDL(mmol/L)	1.30	1.37	4.89	1.30	1.35	4.04
Total cholesterol (mmol/L)	4.99	4.87	-2.62	5.09	5.02	-1.60

HDL: high-density lipoproteins; LOCF: last observation carried forward
[a] Geometric mean; [b] Change is calculated as 'geometric mean of relative change from baseline' -100, where 'relative change from baseline' = (Week 160/baseline) *100%. Cross-reference: Trial 1839 Table 11-38

B.2.6.11. Patient reported outcomes

HRQoL was assessed during the 1839 trial using three different questionnaires (90): IWQoL-Lite (91), SF-36 (version 2.0) (92-94), and TRIM-Weight (95). Results for SF-36 are presented below.

At baseline, the SF-36 scores were similar for each of the eight domains in addition to the two overall scores in the liraglutide 3.0mg and placebo groups. Overall physical scores were 47.28 and 46.57, respectively, and overall mental health scores were 53.90 and 54.00, respectively (cross-reference: Trial 1839 CTR, EOT Table 14.2.376). At the end of treatment (week 160), the estimated mean change from baseline on all domains were greater with liraglutide 3.0mg than with placebo. The improvements in general health score, vitality score, physical functioning score and mental health score were statistically significant (Figure 12). Overall, treatment with liraglutide 3.0mg, plus diet and exercise, over three years is associated with improvements in HRQoL in patients with obesity or overweight with comorbidity vs. placebo.

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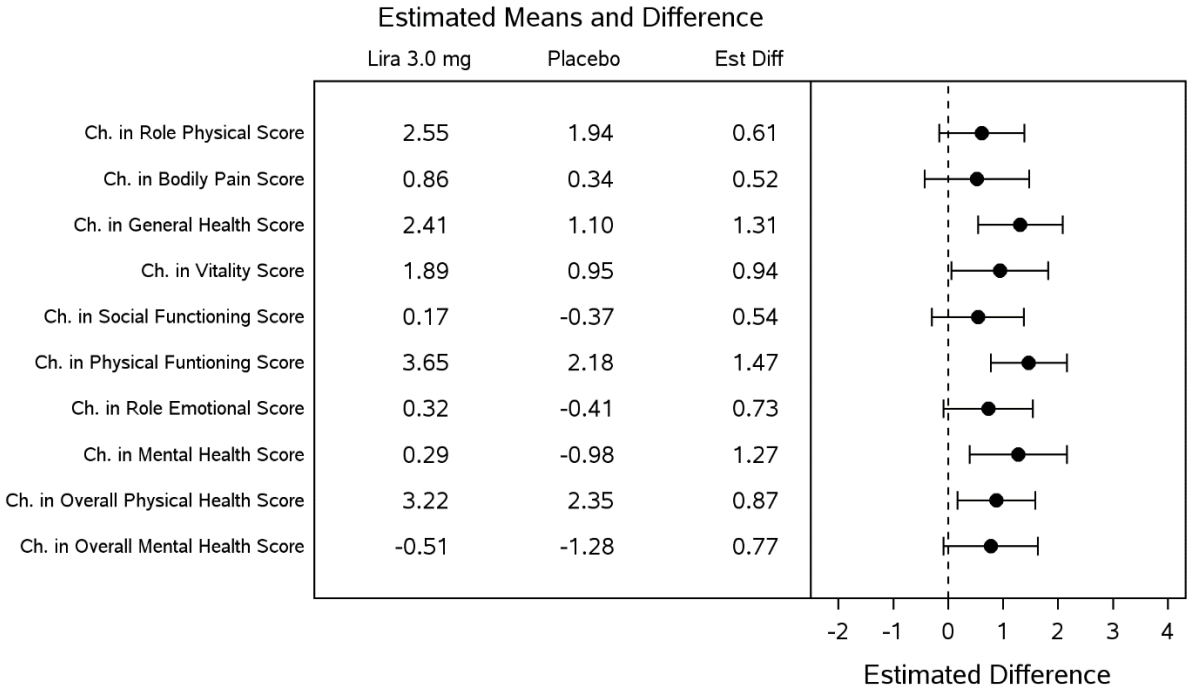
Figure 12: SF-36 scores change - statistical analyses after 160 weeks treatment



Cross-reference: Trial 1839 CTR Figure 11-55

B.2.7. Supportive evidence on effectiveness

B.2.7.1. Weight loss across Phase 3a trials

The three Phase 3a trials besides Trial 1839 (see Section B.2.1) provided results which were in line with Trial 1839 both in terms of efficacy and safety. The estimated treatment differences in weight loss for liraglutide 3.0mg vs. placebo ranged from -4.0% to -6.1% (compared to -4.3% in Trial 1839) (Table 16).

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Table 16: Body weight (%) change from baseline in the liraglutide 3.0mg phase 3a trials

Trial	Liraglutide 3.0mg	Placebo	ETD [95% CI] liraglutide 3.0mg-placebo
Trial 1839 (81)	-6.1	-1.9	-4.3 [-4.9; -3.7]
Trial 1922 (82) SCALE Diabetes	-6.0	-2.0	-4.0 [-5.1; -2.9]
Trial 3970 (83) SCALE Sleep Apnoea	-5.7	-1.6	-4.2 [-5.2; -3.1]
Trial 1923 (84) SCALE Maintenance	-6.2	-0.2	-6.1 [-7.5; -4.6]

ETD: estimated treatment difference

B.2.7.2. Post-hoc subgroup analyses used to inform the economic model

A *post-hoc* subgroup analysis of the results from Trial 1839 including patients with prediabetes at the screening was performed to inform the economic model using LOCF, BOCF or ME-MI analyses (Appendix E; see Section B.2.4.1 for an overview of the analyses). The results presented focus on patients with BMI ≥35 kg/m^2, prediabetes and high risk of CVD, as this is the population considered in this submission and can be compared with the originally planned analysis (presented in Section B.2.6). Results for the additional subgroup analyses are available in Appendix E. In the economic modelling, results for early responders are included as this is the strongest predictor of later and overall response. The definition of early response was defined according to the stopping rule stated in the marketing authorisation.

Demographics and baseline characteristics

Of the 2,254 total randomised patients in Trial 1839, 1,021 patients had BMI ≥35 kg/m^2, and prediabetes at baseline.

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Of the 1,021 patients with BMI ≥35 kg/m^2, and prediabetes, 800 patients fulfilled one or more criteria for high risk of CVD. Of the 1,021 patients with BMI ≥35 kg/m^2, high risk of diabetes and prediabetes:

- 47.7% of patients fulfilled the criterion of total cholesterol >5 mmol/L
- 13.5% of patients fulfilled the criterion of SBP >140 mmHg
- 43.7% of patients fulfilled the criterion of <1.0 mmol/L (<40 mg/dL) for men and <1.3 mmol/L (<50 mg/dL) for women

Table 17: Patients with BMI ≥35 kg/m^2, prediabetes, and fulfilling one or more criteria for high risk of CVD

Criterion	Liraglutide 3.0mg (N=676)	Placebo (N=345)	Total (N=1,021)
Total cholesterol >5 mmol/L (N, [%])	315 (46.6%)	172 (49.9%)	487 (47.7%)
Systolic blood pressure >140 mmHg (N, [%])	94 (13.9%)	44 (12.8%)	138 (13.5%)
HDL <40 mg/dL[a] (men) / <50 mg/dL[b] (women) (N, [%])	304 (45.0%)	142 (41.2%)	446 (43.7%)

[a] ~1.034 mmol/L; [b] ~1.293 mmol/L
N: number of patients; %: percentage of patients within the treatment group; HDL: high-density lipoproteins; CVD: cardiovascular disease. Cross-reference: Appendix E, Tables 1 and 2

Demographics and baseline characteristics for patients with a BMI ≥35 kg/m^2, prediabetes and high risk of CVD are presented in Table 18 (and for the other subgroups in Appendix E). Note that since not all patients fulfilled each criterion, the mean values for all patients included in the *post-hoc* analyses are below the cut-off values. Mean BMI was higher in the *post-hoc* analyses compared to the planned analyses which was expected due to the BMI cut-off of ≥35 kg/m^2. Besides BMI, there were no apparent differences when comparing baseline characteristics of patients in the *post-hoc* analyses with baselines characteristics of all patients in Trial 1839.

All baseline characteristics of the patients included in the economic model are described in Section B.3.2Economic analysis.

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Table 18: Demographics and baseline characteristics for patients with BMI ≥35 kg/m^2, prediabetes and high risk of CVD

Number of patients in subgroup	**800**
Age (years)	48.2 (11.2)
Height (m)	1.66 (0.09)
BMI (kg/m^2)	41.7 (5.3)
Waist circumference (cm)	122.3 (13.1)
Sex	
Female	75.8%
Male	24.3%
HbA_{1c} (%) (mean)	5.8
Total cholesterol (mg/dL) (mean)	200.6[a] (37.3)
HDL cholesterol (mg/dL) (mean)	48.7[b] (13.2)
Triglycerides (mg/dL) (mean)	158.7 (75.9)
Triglycerides at baseline >150 mg/dL	
No	54.0%
Yes	46.0%
Systolic blood pressure (mmHg) (mean)	127.2 (13.6)
Smoker status	
Current smoker	15.0%
Previous smoker	28.5%
Never smoked	56.5%
History of CV disease	
Yes	11.0%
On antihypertensive medication	
No	54.8%
Yes	45.3%

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Number of patients in subgroup	800
On lipid lowering medication	
No	83.0%
Yes	17.0%

[a] ~5.195 mmol/L; [b] ~1.262 mmol/L
Values for continuous variables are means. Values in parentheses are standard deviations; History of CV disease was based on an SMQ search of the medical history including Ischaemic heart disease, Cardiac failure, Central nervous system haemorrhages, Cerebrovascular conditions and Embolic and thrombotic events.
CVD: cardiovascular disease; HDL: high-density lipoproteins; SMQ: standard medical query
Cross-reference: Appendix E, Table 1

B.2.7.3. Clinical effectiveness for patients with BMI ≥35 kg/m^2, prediabetes and high risk of CVD in Trial 1839

Change in body weight, waist circumference, blood pressure, lipids, HbA_{1c} and glycaemic status

Change from baseline in outcomes relevant for the decision problem is presented in Table 19 and Table 20 for patients with BMI ≥35 kg/m^2, prediabetes and high risk of CVD. Results are presented for LOCF, as this is used for the base case in economic modelling.

Overall, fasting body weight, blood pressure, total cholesterol and HbA_{1c} were reduced throughout the trial when compared to baseline in both treatment groups, whereas HDL was increased in both treatment groups (Table 19). The changes from baseline were greater in the liraglutide 3.0mg group compared to the placebo group.

Please note that % weight loss is presented here, whereas the % change in BMI is included in the economic model. This has no implications as the % weight change is equal to % change in BMI for adults, since they have a constant height.

For glycaemic status throughout the trial, a higher proportion of patients receiving liraglutide 3.0mg achieved normoglycemia compared to patients receiving placebo

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(Table 20). Conversely, a lower proportion of patients receiving liraglutide 3.0mg were confirmed to have developed type 2 diabetes compared to patients receiving a placebo.

Thus, the results in patients with a BMI ≥35 kg/m^2, prediabetes and high risk of CVD were in line with the originally planned analyses in all patients in Trial 1839.

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Table 19: Change from baseline in relevant continuous variables - patients with BMI ≥35 kg/m^2, prediabetes and high risk of CVD – LOCF

	Liraglutide 3.0mg				Placebo			
Week	28	56	104	160	28	56	104	160
Relative change in fasting body weight (%-point)	-7.30 (4.73)	-7.88 (6.06)	-6.90 (6.55)	-5.92 (6.79)	-2.43 (4.73)	-2.48 (6.06)	-2.07 (6.55)	-1.65 (6.79)
Change in waist circumference (cm)	-7.82 (6.12)	-8.61 (6.97)	-7.77 (7.51)	-6.95 (8.09)	-3.59 (6.12)	-4.13 (6.97)	-3.57 (7.51)	-3.44 (8.09)
Change in SBP (mmHg)	-6.08 (11.05)	-6.68 (10.87)	-5.73 (11.12)	-4.09 (11.69)	-1.70 (11.05)	-1.76 (10.87)	-1.72 (11.12)	-1.09 (11.69)
Change in HDL cholesterol (mg/dL)	0.03 (6.70)	1.68 (7.42)	2.46 (7.82)	3.13 (8.88)	00.20 (6.70)	0.80 (7.42)	1.52 (7.82)	2.22 (8.88)
Change in total cholesterol (mg/dL)	-8.74 (25.28)	-6.58 (25.92)	-9.54 (29.09)	-7.38 (27.70)	-3.85 (25.31)	-6.10 (25.95)	-7.01 (29.12)	-4.15 (27.73)
Change in HbA_{1c} (%-point)	-0.36 (0.23)	-0.38 (0.26)	-0.49 (0.32)	-0.39 (0.32)	-0.08 (0.23)	-0.09 (0.26)	-0.19 (0.32)	-0.13 (0.32)

Values in parenthesis are standard deviations
CVD: cardiovascular disease; LOCF: last observation carried forward; SBP: systolic blood pressure; HDL: high-density lipoproteins
Cross-reference: Appendix E, Tables 9, 21, 33, 45, 57 and 69

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Table 20: Glycaemic status over time for patients with BMI ≥35 kg/m^2 and prediabetes and high risk of CVD - LOCF

	Liraglutide 3.0mg (N=531)					Placebo (N=271)				
Week	16	28	56	104	160	16	28	56	104	160
Normoglycaemic (N, [%])	413 (77.9)	406 (76.6)	400 (75.5)	386 (72.8)	360 (67.9)	81 (30.0)	97 (35.9)	95 (35.2)	111 (41.1)	104 (38.5)
High risk of diabetes (N, [%])	114 (21.5)	121 (22.8)	121 (22.8)	134 (25.2)	149 (28.1)	183 (67.5)	162 (60.0)	160 (59.3)	134 (49.6)	135 (50)
Transient type 2 diabetes (N, [%])	2 (0.4)	1 (0.2)	7 (1.3)	6 (1.1)	8 (1.5)	5 (1.8)	9 (3.3)	8 (3.0)	9 (3.3)	9 (3.3)
Confirmed type 2 diabetes (N, [%])	1 (0.2)	2 (0.4)	2 (0.4)	4 (0.8)	13 (2.4)	1 (0.4)	2 (0.7)	7 (2.6)	16 (5.9)	22 (8.1)

High risk of diabetes is according to NICE definition; “Transient type 2 diabetes” and “Confirmed type 2 diabetes” were defined as: if for two consecutive samples at least one of the following is fulfilled for both samples then the subject has confirmed type 2 diabetes: FPG ≥126 mg/dL/HbA_{1c} ≥6.5%/2 hr post-challenge (OGTT) plasma glucose ≥200 mg/dL; If “a positive” was not confirmed by the following test, then it was classified as transient type 2 diabetes.
N: number of patients; %: percentage of patients; CVD: cardiovascular disease; LOCF: last observation carried forward
Cross-reference: Appendix E, Table 64

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Early responders

Demographics and baseline characteristics for patients with BMI ≥35 kg/m^2, prediabetes and high risk of CVD were similar for early responders (i.e. patients achieving at least 5% weight loss after 4 weeks titration and 12 weeks of treatment on the maintenance dose) and all patients in this subgroup (Appendix E, Table 1). A higher proportion of patients receiving liraglutide 3.0mg compared to placebo met the definition of an early responder (Table 21). As expected, early responders showed better outcomes for all endpoints compared to all patients with BMI ≥35 kg/m^2, prediabetes and high risk of CVD (Table 22 and Table 23). This is in line with results for all patients in Trial 1839 (96). The waist circumference parameter is not provided for the early responders because it was not applied in the health-economic model and therefore was not included in the post-hoc analysis. It is, however, provided in Appendix E.

Table 21: Early response status for patients with BMI ≥35 kg/m^2 and prediabetes and high risk of CVD

Early responder (Yes/No)	Liraglutide 3.0mg (N=531)	Placebo (N=271)
Yes	314 (59.9%)	55 (20.3%)
No	156 (29.4%)	179 (66.1%)
Unknown	61 (11.5%)	37 (13.7%)

CVD: cardiovascular disease
Cross-reference: Appendix E, Table 2

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Table 22: Change from baseline in relevant continuous variables - early responders with BMI ≥35 kg/m^2, prediabetes and high risk of CVD – LOCF

	Liraglutide 3.0mg				Placebo			
Week	28	56	104	160	28	56	104	160
Relative change in fasting body weight (%-point)	-9.96 (4.04)	-10.91 (5.81)	-9.46 (6.68)	-8.02 (7.27)	-9.15 (4.05)	-8.82 (5.82)	-8.07 (6.68)	-7.29 (7.28)
Change in waist circumference (cm)	-10.03 (5.73)	-11.17 (6.64)	-11.17 (6.64)	-8.56 (8.41)	-9.57 (5.75)	-10.16 (6.65)	-8.76 (7.64)	-8.90 (8.43)
Change in SBP (mmHg)	-6.22 (10.94)	-7.58 (10.26)	-6.21 (11.21)	-4.08 (11.01)	-3.59 (10.94)	-3.53 (10.26)	-3.89 (11.21)	-1.82 (11.02)
Change in HDL cholesterol (mg/dL)	0.88 (6.42)	2.80 (7.20)	3.53 (7.81)	4.42 (9.03)	1.44 (6.42)	1.85 (7.20)	3.75 (7.82)	4.35 (9.03)
Change in total cholesterol (mg/dL)	-6.80 (25.57)	-3.84 (25.87)	-6.41 (28.10)	-4.49 (27.21)	-0.72 (25.64)	-5.43 (25.94)	-2.54 (28.18)	1.80 (27.29)
Change in HbA_{1c} (%-point)	-0.43 (0.22)	-0.45 (0.24)	-0.59 (0.27)	-0.46 (0.27)	-0.21 (0.22)	-0.26 (0.24)	-0.39 (0.27)	-0.29 (0.27)

Data is presented as the mean (SD). CVD: cardiovascular disease; LOCF: last observation carried forward

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Table 23: Glycaemic status over time for early responders with BMI ≥35 kg/m2, prediabetes and high risk of CVD – LOCF

	Liraglutide 3.0mg (N=314)					Placebo (N=55)				
Week	16	28	56	104	160	16	28	56	104	160
Normoglycemic (N, [%])	256 (81.5)	264 (84.1)	255 (81.2)	238 (75.8)	223 (71.0)	22 (40.0)	21 (38.2)	29 (52.7)	31 (56.4)	25 (45.5)
High risk of diabetes (N, [%])	56 (17.8)	50 (15.9)	54 (17.2)	72 (22.9)	84 (26.8)	32 (58.2)	34 (61.8)	25 (45.5)	22 (40.0)	27 (49.1)
Transient type 2 diabetes (N, [%])	2 (0.6)	0 (0)	5 (1.6)	3 (1.0)	4 (1.3)	1 (1.8)	0 (0)	1 (1.8)	1 (1.8)	2 (3.6)
Confirmed type 2 diabetes (N, [%])	0 (0)	0 (0)	0 (0)	1 (0.3)	3 (1.0)	0 (0)	0 (0)	0 (0)	1 (1.8)	1 (1.8)

CVD: cardiovascular disease; LOCF: last observation carried forward

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B.2.8. Meta-analysis

Not applicable.

B.2.9. Indirect and mixed treatment comparisons

Not applicable.

B.2.10. Adverse events

B.2.10.1. Trial 1839 (including patients with and without prediabetes at screening)

A summary of treatment emergent adverse events (TEAEs) in the 3-year assessment (week 0 to 162) of Trial 1839 is provided in Table 24. Liraglutide 3.0mg was generally well tolerated in patients with prediabetes and obesity or overweight with comorbidities over the 3-year treatment period.

The proportion of patients with TEAEs and the rate of TEAEs were higher with liraglutide 3.0mg (94.7% and 489.6 events per 100 person years of observation [PYO]) than with placebo (89.4% and 431.9 events per 100 PYO), primarily during the first year of treatment. This treatment difference was mainly driven by higher proportions of patients treated with liraglutide 3.0mg having events within the system organ classes (SOC): ‘gastrointestinal disorders’, ‘general disorders and administration site reactions’, ‘metabolism and nutrition disorders’, ‘investigations’ and ‘hepatobiliary disorders’ compared to patients treated with placebo. In both treatment groups, the majority of AEs were mild or moderate in severity. The majority of the patients reporting TEAEs had recovered or were recovering at the end of the trial. The majority of TEAEs reported with both treatments were assessed as unlikely related to the trial products by the investigators. TEAEs assessed as possibly or probably related to trial products were reported by higher proportions of patients and at higher rates with liraglutide 3.0mg (probable: 47.8%, 60.5 events per 100 PYO; possible: 61.5%, 91.7 events per 100 PYO) compared to placebo (probable: 22.9%, 19.0 events per 100 PYO; possible: 42.3%, 58.3 events per 100 PYO) (Table 24).

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Table 24: Summary of treatment emergent adverse events (TEAE) - Trial 1839 (week 0 to 162)

	Liraglutide 3.0mg				Placebo			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Number of patients	1,501				747			
Years of observation time	3,218.9				1,470.2			
Events	1,421	94.7	15,759	489.6	668	89.4	6,350	431.9
Serious adverse events	227	15.1	350	10.9	96	12.9	143	9.7
Severity								
Severe	311	20.7	558	17.3	115	15.4	186	12.7
Moderate	1,025	68.3	4,788	148.7	449	60.1	1,913	130.1
Mild	1,324	88.2	10,410	323.4	623	83.4	4,248	288.9
Missing	3	0.2	3	0.1	2	0.3	3	0.2
Relationship to investigational product								
Probable	717	47.8	1,947	60.5	171	22.9	279	19.0
Possible	923	61.5	2,951	91.7	316	42.3	857	58.3
Unlikely	1,274	84.9	10,797	335.4	634	84.9	5,166	351.4
Missing	55	3.7	64	2.0	38	5.1	48	3.3
Outcome								
Recovered	1,401	93.3	13,550	421.0	646	86.5	5,251	357.2
Fatal	2	0.1	3	0.1	2	0.3	2	0.1
Recovering	71	4.7	117	3.6	43	5.8	51	3.5
Recovered with sequelae	6	0.4	6	0.2	1	0.1	1	<0.1
Not recovered	753	50.2	2,012	62.5	372	49.8	1,013	68.9
Unknown	49	3.3	71	2.2	23	3.1	32	2.2
Leading to withdrawal	199	13.3	287	8.9	46	6.2	66	4.5

A treatment emergent adverse event is defined as an event that has onset date on or after the first day of randomised treatment and no later than 14 days after the last day of randomised treatment.
N: number of patients; %: percentage of patients; E: number of events, R: event rate per 100 years of observation time; TEAE: treatment emergent adverse event.
Cross-reference: CTR (extension part) Table 12-2

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Gastrointestinal disorders were the most common TEAEs assessed related to trial products in both treatment groups. The proportion of patients with gastrointestinal TEAEs and the corresponding rate of events assessed as related to treatment by the investigators were higher with liraglutide 3.0mg (60.2%, 82.7 events per 100 PYO) than with placebo (30.5%, 32.3 events per 100 PYO). The most common 'gastrointestinal disorders' assessed related to the trial product by the investigators were nausea, diarrhoea, constipation and vomiting. The majority of the gastrointestinal events occurred at the beginning of the trial when the liraglutide dose was increased from 0.6mg to 3.0mg (for nausea as an example, see Figure 13). After approximately 8 weeks, the onset of new gastrointestinal events decreased, indicating that patients gradually developed a tolerance towards the product.

Permanent treatment discontinuation due to TEAEs was observed in a higher proportion of patients in the liraglutide 3.0mg group than in the placebo group. The most frequently reported TEAEs leading to permanent treatment discontinuation during the treatment period in either group were within the SOCs 'gastrointestinal disorders' (~59% of TEAEs leading to discontinuation in the liraglutide 3.0mg group), 'general disorders and administration site conditions', 'nervous system disorders', 'investigations', 'neoplasms benign, malignant and unspecified (including cysts and polyps)' and 'psychiatric disorders'.

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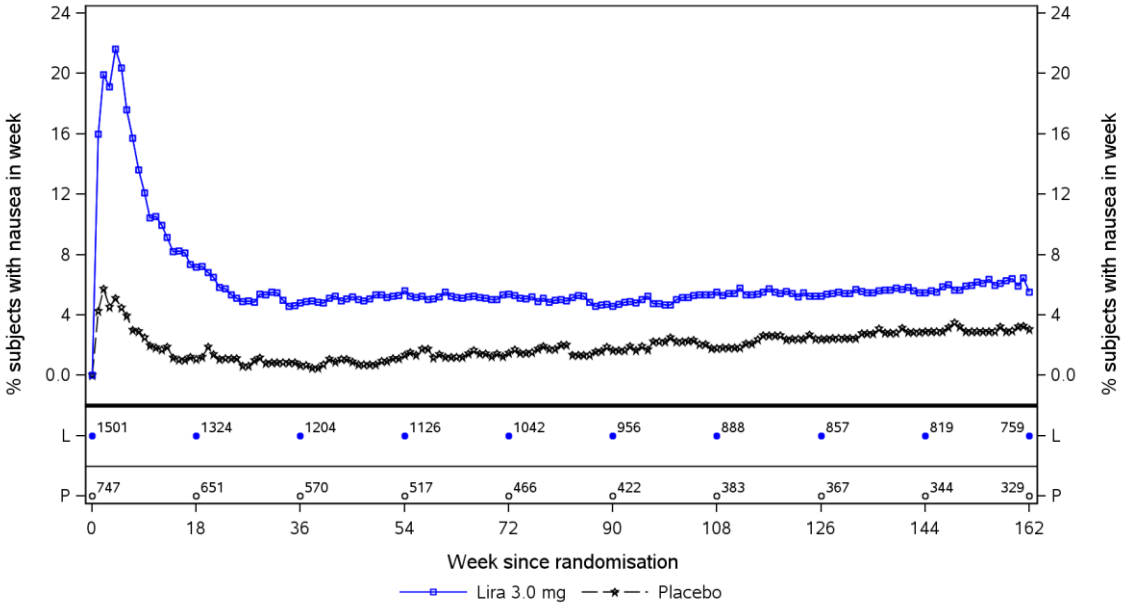
Figure 13: Proportions of subjects with nausea over time (0 to 162 weeks)



L: Number of subjects at risk in Lira 3.0 mg arm. P: Number of subjects at risk in Placebo arm |MedDRA version 15.1
Output presents data for subjects with pre-diabetes at baseline and includes 6 subjects who did not have pre-diabetes at baseline, but participated in the extension period of the trial.

Cross-reference: Trial 1839 CTR Figure 12-6

The most common AEs by preferred term (≥5% in at least one of the treatment groups) are presented in Figure 14. Gastrointestinal disorders including nausea, diarrhoea, constipation, vomiting, dyspepsia, abdominal pain and upper abdominal pain as well as gastroesophageal reflux disease, eructation and flatulence were among the most commonly reported AEs with liraglutide 3.0mg and reported at higher frequencies and rates than with placebo. Hypoglycaemia, decreased appetite, fatigue, dizziness, lipase increased, and gastroenteritis were also more commonly reported with liraglutide 3.0mg than with placebo.

Of the TEAEs of hypoglycaemia (reported spontaneously or at FPG or OGTT visits), none were serious, and the majority of events in both treatment groups were classified as mild (having no important symptoms) or moderate (marked symptoms with moderate interference with subject's daily activities) in severity. Of the spontaneously reported TEAEs of hypoglycaemia (which are most relevant for regular practice), the rate of events was; liraglutide 3.0mg: 3.3% of subjects, 1.9 events per 100 PYO and placebo: 1.9% of subjects, 1.3 events per 100 PYO.

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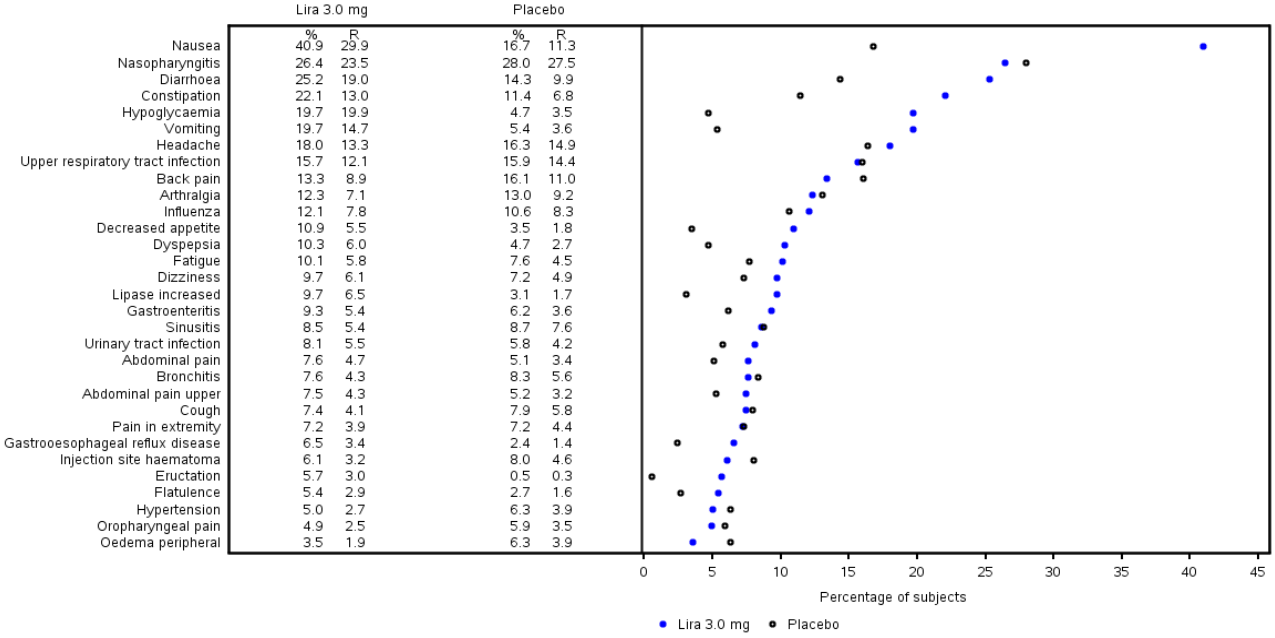
Figure 14: Most frequent treatment emergent adverse events [≥5%] - Trial 1839 (week 0 to 162)



%: Percentage of patients; R: Event rate per 100 years; Lira: liraglutide
Cross-reference: CTR (extension part) Figure 12-2

B.2.10.2. Supportive evidence on cardiovascular and long-term safety

Meta-analysis on cardiovascular safety

The cardiovascular safety of liraglutide 3.0mg was evaluated *post-hoc* using data from a total of 5,908 patients from the four Phase 3a trials and the Phase 2 trial (see Section B.2.1.1) (97).

The primary analysis compared the incidence of cardiovascular events for the approved weight management dose of liraglutide 3.0mg compared to a pooled comparator group (placebo or orlistat). The hazard ratio for the primary analysis was 0.42 [95% CI: 0.17, 1.08]. In Trial 1839, which represented approximately 80% of total person years, the hazard ratio was 0.70 [95% CI: 0.20, 2.50].

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The LEADER trial (NCT01179048; EX2211-3748)

No cardiovascular outcomes trial (CVOT) has been performed with liraglutide 3.0mg as it was agreed with health authorities in the major regions (including the EMA) to base the evaluation of cardiovascular safety on the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) performed for Victoza® (liraglutide 1.8mg). The LEADER trial is considered supportive for this submission, as it provides evidence for the cardiovascular and long-term safety of liraglutide.

The LEADER trial was a CVOT comparing liraglutide 1.8mg and placebo in patients with type 2 diabetes and at least one cardiovascular coexisting condition (i.e., high cardiovascular risk). A total of 9,340 patients were randomised into the trial of whom the majority received randomised treatment for a period of 3 to 5 years enabling assessment of long-term safety and efficacy. The safety data obtained in the LEADER trial has been included in the SmPC for liraglutide 3.0mg (Appendix C). Liraglutide 1.8mg significantly reduced the rate of major adverse cardiovascular events (primary endpoint) vs. placebo (3.41 vs. 3.90 per 100 patient years of observation in the liraglutide 1.8mg and placebo groups, respectively) with a risk reduction of 13%, HR 0.87, [0.78, 0.97] 95% CI (p=0.005). The primary results from the LEADER trial were published in Marso *et al*., 2016 (98).

B.2.10.3. Safety conclusion

Liraglutide 3.0mg treatment was generally safe and well tolerated in patients with obesity or overweight patients with comorbidities.

The overall proportion of patients with AEs, and the rate of AEs, was higher with liraglutide 3.0mg than with placebo. This difference was mainly driven by a higher proportion of patients reporting gastrointestinal-related events with liraglutide 3.0mg than with placebo, but also due to imbalances in reporting frequencies of events in the SOCs ‘general disorders and administration site disorders’, ‘metabolism and nutrition disorders’ and ‘investigations’. In both treatment groups, the majority of AEs

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were mild or moderate in severity. The majority of the patients reporting TEAEs had recovered or were recovering at the end of the trial.

The events considered to be related to liraglutide 3.0mg were primarily events related to gastrointestinal disorders such as nausea, diarrhoea, constipation and vomiting, which are common and well-known transient side effects of liraglutide. Gastrointestinal events were also the primary reason for AE withdrawal in the liraglutide 3.0mg group. The majority of the gastrointestinal events occurred in the beginning of the trial when the liraglutide dose was increased from 0.6mg to 3.0mg. After approximately 8 weeks, onset of new gastrointestinal events decreased, indicating that patients gradually developed a tolerance towards liraglutide.

The safety profile in other trials in the liraglutide 3.0mg programme is consistent with Trial 1839 (please refer to the European SmPC (Appendix C) for further details). In addition, long-term safety is supported by a meta-analysis using data from a total of 5,908 patients from the four Phase 3a trials and the Phase 2 trial as well as the LEADER CVOT, which was consistent with the overall clinical safety profile of liraglutide.

B.2.11. Ongoing studies

Two trials with liraglutide 3.0mg sponsored by Novo Nordisk are currently ongoing.

Trial 4180 (Phase 3b) (NCT02918279): Efficacy and safety of liraglutide in adolescent patients with obesity (results expected Q4 2019).

Trial 4179 (Phase 3b) (NCT02527200): Effect of liraglutide for weight management in paediatric patients with Prader-Willi Syndrome (results expected Q4 2020).

The Saxenda® in Obesity Services (STRIVE) study (ClinicalTrials.gov Identifier: NCT03036800) is an investigator sponsored study by the University of Leicester with Novo Nordisk as a collaborator. The protocol is expected to be published by July 2019. The study is currently ongoing and estimated to be completed in Q1 2021. Some participants in the study may have prediabetes and therefore overlap with the

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population relevant for the decision problem. The study is a 2-year, parallel, two-group, open-label, real-world randomised controlled trial in 375 patients with severe and complex obesity who are referred to a tier 3 or equivalent specialist weight management/obesity service. Participants will be randomised to receive 1) obesity-specialist care, or 2) obesity-specialist care plus targeted use of liraglutide 3.0mg with pre-specified stopping rules for treatment. The aim of the study is to compare the effectiveness, budget impact, and cost-effectiveness between the two groups in a real-world setting among otherwise largely unselected patients.

B.2.12. Innovation

Previously, NHS available pharmacotherapy options for obesity and weight management have all had an unfavourable adverse event profile that was sufficiently serious to prevent patients from continuing treatment and for some the marketing authorisation was withdrawn. Poor tolerability of previous pharmacotherapy has therefore resulted in their poor effectiveness and declining use in clinical practice (68).

Liraglutide 3.0mg, however, has a good safety and tolerability profile and therefore provides an effective pharmacotherapeutic option for obesity and weight management for the NHS. As it is the first GLP-1 indicated for obesity and weight management, liraglutide 3.0mg is first in its class for this therapy area, while offering the added benefits of reducing the risk of type 2 diabetes and preventing CVD events.

The ability of liraglutide 3.0mg to act on satiety to enable weight loss makes it is more likely that additional interventions that promote better behavioural and lifestyle activities can be put in place that ensure a more successful long-term weight loss or maintenance of weight loss.

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B.2.13. Interpretation of clinical effectiveness and safety evidence

In Trial 1839, long-term treatment with liraglutide 3.0mg as an adjunct to diet and exercise led to improvements in glycaemic status, a clinically meaningful weight loss as well as improvements in comorbidity markers for patients with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with comorbidities, diagnosed with prediabetes at screening.

The risk of developing type 2 diabetes for patients treated with liraglutide 3.0mg was reduced by approximately 80% compared with placebo after 160 weeks. 66% of patients in the liraglutide 3.0mg group reverted to normoglycemia compared to 36% in the placebo group after 160 weeks.

The relative change from baseline to week 160 in fasting body weight (%) showed a statistically significantly greater weight loss with liraglutide 3.0mg (6.14%) than with placebo (1.89%), resulting in an estimated treatment difference in relative change of -4.32% [-4.94, -3.70] 95% CI, p<0.0001.

BMI, waist circumference, HbA_{1c} and SBP were also significantly reduced in the liraglutide group compared to placebo.

The results from *post-hoc* analyses in patients with BMI ≥35 kg/m^2, prediabetes and high risk of CVD were in line with the originally planned analyses in all patients in Trial 1839.

The clinical benefits in Trial 1839 were balanced by liraglutide 3.0mg treatment being generally safe and well tolerated in patients with obesity or overweight patients with comorbidities. The overall proportion of patients with AEs, and the rate of AEs was higher with liraglutide 3.0mg than with placebo. This difference was mainly driven by gastrointestinal-related events which are common and well-known transient side effects of liraglutide. Gastrointestinal events were also the primary reason for AE withdrawal in the liraglutide 3.0mg group. The majority of the gastrointestinal events occurred in the beginning of the trial when the liraglutide dose was increased from 0.6mg to 3.0mg. After approximately eight weeks, the onset of new gastrointestinal

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events decreased, indicating that patients gradually developed a tolerance towards the product. In both treatment groups, the majority of AEs were mild or moderate in severity. The majority of the patients reporting TEAEs had recovered or were recovering at the end of the trial.

The conclusions from Trial 1839 were consistent with the other Phase 3a trials with liraglutide 3.0mg. Cardiovascular and long-term safety of liraglutide 3.0mg is furthermore supported by a meta-analysis using data from a total of 5,908 patients from the four Phase 3a trials and the Phase 2 trial as well as the LEADER CVOT.

The clinical outcomes for liraglutide 3.0mg presented in this submission are from a controlled setting, lending them to both a high level of internal and external validity increasing the likelihood of generalisability to an NHS specialist setting in England. As the clinical data was obtained in compliance with international guidelines in a broad patient population, including patients from eight sites in the UK, the clinical outcomes observed are regarded as being representative of UK clinical practice.

In conclusion, the data presented demonstrate the clinical benefits of liraglutide 3.0mg in patients with BMI ≥35 kg/m^2, prediabetes and high risk of CVD, supporting the use of liraglutide 3.0mg in a population of obese patients with a high disease burden.

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B.3. Cost-effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) of cost-effectiveness studies in obesity was conducted in August 2018. Further details on the SLR are provided in Appendix G. None of the studies identified in the review precisely met the definition of the target population for the present submission, being obese with BMI ≥35 kg/m^2, prediabetes and at high risk of cardiovascular disease (CVD), nor were any subgroup analyses in this population published. Further, orlistat and bariatric surgery, which were identified as treatments in a number of these studies, were not included as the comparators in this submission. This was because orlistat is intended for use in a tier 2 setting, while liraglutide 3.0mg is intended for use in specialist tier 3 services. Also, orlistat is used in a limited number of patients in actual clinical practice due to undesirable side effects and consequently low adherence. Bariatric surgery was not considered a direct comparator either. Rather, it was modelled as rescue therapy, and applied to both liraglutide 3.0mg and diet and exercise based on an annual incidence rate and minimum weight eligibility criteria. Surgery was not considered a direct comparator to liraglutide 3.0mg because only a very small proportion of the eligible patients would actually receive surgery in practice. Hence, liraglutide 3.0mg was considered a treatment option in patients who are unwilling or unable to receive surgery.

In summary, a total of six published cost-effectiveness analyses which reported results from the UK NHS perspective were identified and reviewed (Table 25). Of the reviewed studies, one was a piggy-pack cost-effectiveness analysis conducted alongside a clinical trial (99); all other published cost-effectiveness analyses involved some degree of modelling to estimate treatment effect on costs and health outcomes. Cohort, state-transition modelling was used in three of the published cost-effectiveness studies (100-102), while the remaining two studies used simple decision analyses based on a 1- year and 5-year time horizon (103, 104).

With the exception of one study published in 2005 (104) and a piggy-back trial analysis (99) - both conducted on a 1-year time-frame analysis - all of the reviewed

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cost-effectiveness analyses modelled long-term consequences of type 2 diabetes and CVD in obese patients, the association between obesity, onset of type 2 diabetes and cardiovascular disease risk being thus well established in the health-economic literature herein reviewed (105). One study modelled the association of BMI with colon cancer (102). The methods used to extrapolate short term changes in BMI to onset of complications differed across studies. For example, Ara *et al*., 2007 (103, 106) used the Framingham risk model to calculate incidence of CVD as a function of BMI. Later, the same authors published a de novo analysis informed by a set of newly developed risk models (101); the models were developed on a random sample of adults with data from the General Practice Research Datalink (GPRD) (n=100,000). Risk models were developed for: onset of type 2 diabetes, incidence of acute myocardial infarction (AMI), stroke and death from any cause as function of BMI, age, gender, smoking status, aspirin, insulin, statin and blood pressure treatment, for type 2 diabetes and non-type 2 diabetes cohorts. A natural disease progression model of the BMI trajectory was also estimated by the authors (101) on the GPRD data.

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Table 25: Summary list of published cost-effectiveness studies

Study, Year	Summary of model	Patient population	Results
Foxcroft *et al.*, 2005 (104)	Decision tree with costs and QALYs assigned to orlistat and placebo responders (assumed zero costs and QALYs in non-responders); the analysis time horizon was 1 year; there was no extrapolation of clinical benefits; assumed a utility gain of 0.017 per unit decrease in BMI (107); considered costs of obesity pharmacotherapy and GP visits from published NHS tariffs.	Orlistat and placebo responders defined according to NICE or EMA criteria for treatment response	Results NICE definition of response/100 responders: QALY gains: orlistat: 1.498; placebo: 0.567 QALYs Total costs: orlistat £22,744 ICER: £24,431/QALY gained (SA: £10,856 - £77,197)
Ara *et al.,* 2007 (103), supplemented with data from Warren et al. 2004 (106)	Decision tree analysis on treatment response pathway over 12 months with sibutramine or placebo, followed by a period of up to 5 years natural history weight regain of 1 kg/year; incidence of CHD calculated on trial, patient-level data with Framingham risk model (108) and type 2 diabetes onset using estimates of Colditz et al (109) and Sjostrom et al (110); utility multiplier for CHD of 0.85; assuming diabetes increases mortality by RR 1.33 (111) and decreases utility by 0.95; applies a utility gain of 0.00297 per kg lost with sibutramine and 0.00472 gain per kg lost with placebo (unpublished data from SAT trial); assumes 1 GP visit in patients with adverse events; CHD and type 2 diabetes costs sourced from literature.	Obese individuals free of complications at baseline, mean age 42 years, mean BMI 32.7 kg/m^2, 80% females	Results of UK analysis: total QALYs not reported; incremental QALYs sibutramine /1,000 patients 48.5; Incremental costs sibutramine / 1,000 patients €572,449; ICER: €11,811 per QALY gained (SA: €7,637- €22,701)
Ara *et al.,* 2011 (100) poster only available	Markov, cohort model comparing orlistat with standard of care; obesity complications modelled: first/ recurrent AMI and stroke, type 2 diabetes; a natural history BMI model was developed on patient-level data (n=100,000) from the GPRD. BMI was linked to onset of cardiovascular disease, type 2 diabetes and all-cause mortality via risk regression models developed in the same GPRD data; incidence of subsequent cardiovascular events	Overweight and obese patients treated in primary care	Total costs and QALYs not available from the abstract; ICER: orlistat £1,665 per QALY gained vs. placebo

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Study, Year	Summary of model	Patient population	Results
	estimated based on the Nottingham Heart Attack register and the South London Stroke register. The authors developed a model for BMI and HRQoL using EQ-5D data controlling for age and comorbidities.		
Ara *et al.,* 2012 (101)	State-transition Markov model comparing diet and exercise plus one of the following: no active treatment (placebo), orlistat 120mg X3/day, sibutramine 15mg/day, rimonabant 20mg/day. Obesity complications considered: first/ recurrent AMI and stroke, type 2 diabetes; analyses were conducted on a lifetime horizon; BMI effectiveness data from a mixed treatment comparison applied at 3, 6 and 12 months for 1 year; post active treatment BMI, assumed to return to baseline values linearly over 3 years; post treatment and weight regain period, a natural disease model was developed with data from the GPRD; transition probabilities to obesity complications (first AMI, and stroke, type 2 diabetes and all-cause mortality) were estimated based on time-to-event models developed on the GPRD dataset, for type 2 diabetes and non-type 2 diabetes; BMI, age, gender, use of aspirin, statins and BP treatment were the predictive variables; recurrent CV risk was derived on the Nottingham Heart Attack Register and the South London Stroke Register.	Obese individuals with mean BMI 34.92 kg/m^2, average age 45.5 years, 33.2% having type 2 diabetes at baseline	Results of lifetime analysis: total discounted QALYs: placebo: 5.128; orlistat: 15.303; rimonabant: 15.317; sibutramine 10 mg: 15.376; sibutramine 15 mg: 15.418. Total discounted costs: placebo: £2,806, orlistat: £3,097; rimonabant: £3,478; sibutramine 10 mg: £3,011; sibutramine 15 mg: £2,967 ICER results vs. placebo: orlistat £1,665 /QALY; rimonabant £3,553 /QALY; sibutramine 10mg: £827 /QALY; sibutramine 15mg: £557 /QALY gained
Lewis *et al.,* 2014 (102)	Cohort model comparing LighterLife Total, a very low-calorie diet, with: no treatment and other weight management interventions in BMI ≥30 kg/m^2 or with no treatment, gastric banding or gastric bypass in BMI ≥40 kg/m^2; obesity complications modelled: type 2 diabetes, CHD and colon cancer. Transition probabilities estimated using continuous BMI-dependent trend lines fitted on	Separate analyses were conducted for: obese (BMI ≥30 kg/m^2) and morbidly obese (BMI ≥40 kg/m^2)	Subgroup BMI ≥30 kg/m^2: ICERs vs. no treatment: Slimming World £5,613/QALY; Counterweight £2,618/QALY; Weight Watchers dominant; LighterLife Total £12,585/QALY;

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Study, Year	Summary of model	Patient population	Results
	incidence data from the literature: type 2 diabetes onset (112), CHD (112), colon cancer (113, 114). Weight reductions were applied at 12 months; post 12 months, treatment-specific BMI increase was assumed per year until BMI reached the natural history disease model of no treatment whereby weight increased at a rate of 0.16 kg/m^2 per year (101). HRQoL was modelled as function of BMI (115).		subgroup BMI ≥40 kg/m^2: LighterLife Total £4,356/QALY; gastric banding £20,505/QALY; gastric bypass £10,627/QALY
McRobbie *et al.,* 2016 (99)	Cost-effectiveness analysis conducted alongside a 1-year clinical trial comparing Weight Action Programme (n=116) with nurse-led weight management (standard care, n=63). No modelling was conducted.	WAP arm (n=221): 35 kg/m^2, 10% heart disease, 10% type 2 diabetes; nurse-management (n=109): 35.7 kg/m^2, 6% heart; 8% type 2 diabetes	Total QALYs WAP 0.404; total QALY nurse-led weight management 0.389; ICER of £7,742 per QALY

AMI: acute myocardial infarction; BP: blood pressure; CHD: coronary heart disease; CV: cardiovascular; GP: general practitioner; GPRD: General Practice Research Datalink; HRQoL: health-related quality of life; ICER, incremental cost-effectiveness ratio; NHS: National Health Services; QALYs, quality-adjusted life years; WAP: Weight Action Programme

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B.3.2 Economic analysis

The cost-effectiveness analysis conducted for this submission utilises a state-transition Markov, cohort model, programmed in MS Excel® with minimal coding in Visual Basic. Obesity-related complications were modelled as health states or events with an impact on the estimated costs and quality-adjusted life years (QALYs) projections. The choice of complications to be modelled was based on the following considerations:

1) A known and demonstrated increase in the risk of the respective complication with obesity;
2) Information available to estimate the relation between levels of BMI and the risk of complication;
3) Whether or not the respective complication was expected to significantly affect total costs of care and quality of life in the affected individuals.

As such, the year 2000 report of the WHO ranked nineteen debilitating health problems according to their association with obesity as: greatly increased risk (relative risk much higher than 3), moderately increased risk (relative risk 2-3) or slightly increased risk (relative risk 1-2) (105). Non-insulin dependent type 2 diabetes, sleep apnoea, gallbladder disease, dyslipidaemia, insulin resistance and breathlessness “greatly” increased in risk with obesity according to 2000 WHO report. Coronary heart disease, hypertension, osteoarthritis (knees) and hyperuricaemia and gout were considered to moderately increase in risk with obesity. Cancer - breast cancer in post-menopausal women, endometrial cancer, colon cancer - were considered among complications at slightly increased risk with obesity. Further on this, a recent study conducted on the CPRD GOLD database in the UK, and linked with data from the HES, showed that “individuals with a BMI of 40.0–45.0 kg/m^2 were at particularly high risk of sleep apnoea (hazard ratio [95% CI]: 21.9 [20.6–23.3]) and type 2 diabetes (hazard ratio [95% CI]: 12.4 [12.1–12.7])” compared to a reference BMI group of 18.5–24.9 kg/m^2 (57).

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Based on this evidence, type 2 diabetes, sleep apnoea, coronary heart disease and osteoarthritis of the knees were included in the base case analysis of the present submission report, being strongly or moderately increased in risk by obesity and having an important impact on costs and quality of life. Hypertension and dyslipidaemia were considered complicating risk factors, i.e. increasing the risk of the previously mentioned complications, but without an important, immediate impact on costs or quality of life. These conditions were thus included as comorbidities in the base case analysis. The three types of cancer, post-menopausal breast, post-menopausal endometrial, and colorectal cancer were considered in scenario analyses given their increase in risk with obesity was considered “slight” in the WHO report.

The model is not singular in the obesity complications considered. As shown before, all of the reviewed cost-effectiveness analyses, conducted over a time horizon beyond one year, extrapolated the consequences of obesity on type 2 diabetes onset and incidence of cardiovascular disease.

However, several elements in the design of the present model were new. Firstly, no previous study considered prediabetes, along with cardiovascular risk, a complicating risk factor of obesity. The choice was justified by the mentioned findings of the WHO report, and those of the CPRD study (57), as well as those of other epidemiological studies (116, 117) whereby prediabetes precludes and increases the risk of type 2 diabetes onset. Predicting type 2 diabetes onset in patients with prediabetes - in lack of a specific risk model - was done by calibrating a published type 2 diabetes risk model, the QDiabetes (116) to account for elevated blood-glucose levels in prediabetic cohorts, whereby the haemoglobin A_{1c} (HbA_{1c}) parameter was set equal to 42 mmol/mol (HbA_{1c} %-points 6) in prediabetes states, and 35 mmol/mol (HbA_{1c} %-points 5.4) in normal glucose tolerance health states.

Secondly, this analysis was the first to account for the additional costs and HRQoL consequences of sleep apnoea in the context of obesity modelling. The inclusion of sleep apnoea was justified by the findings of the WHO report and those of the

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CPRD-HES study (57) whereby the risk of sleep apnoea in individuals with a BMI of 40.0-45.0 kg/m^2 was 21.9 times greater (95% CI: 20.6–23.3) than in individuals with a reference BMI of 18.5–24.9 kg/m^2.

Lastly, this was the first analysis to explore costs and quality of life consequences of the additional burden posed by knee osteoarthritis, as well as certain types of cancer (cancers considered in scenario analyses) known to increase in incidence in patients with obesity, such as colorectal cancer, post-menopausal breast and post-menopausal endometrial cancer (105).

The present analysis builds extensively upon previous published work in obesity modelling with regards to: the use of risk prediction models to link treatment effects with long-term outcomes (101-103) as well as assumptions with regards to weight regain post treatment and the natural history BMI trajectory over time (101), respectively the work published by Ara et al., 2012 (101) who have estimated an annual increase in BMI of 0.145 kg/m^2 (males) and 0.175 kg/m^2 (females) in absence of treatment. The model does not, however, utilise the four risk prediction models for all-cause mortality, onset of type 2 diabetes, incidence of MI and stroke developed by the same authors since the time-to-event analysis for onset of type 2 diabetes conducted by Ara et al., 2012 could not accommodate a calibration of the risk in prediabetic cohorts. Further, the present model includes additional, treatment-modifiable risk factors not considered by Ara et al., 2012 such as SBP, total and HDL cholesterol.

B.3.2.1 Model perspective

This analysis was conducted from the perspective of the NHS and Personal and Social Services in England and Wales in line with the NICE reference case (118). All costs are reported in pounds sterling (2018) and updated using hospital and community health services (HCHS) (119). Costs, QALYs and life years (LYs) were discounted at an annual rate of 3.5% in base case analyses and at rates of 0% or 6% as a scenario analysis.

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B.3.2.2 Patient population

The target population for the economic evaluation comprised a subgroup of the liraglutide 3.0mg licensed indication based on a post-hoc analysis of the SCALE 1839 obesity and prediabetes trial population (73), defined as adult patients with:

- BMI ≥35kg/m^2;
- prediabetes, defined as a HbA_{1c} level of 42–47 mmol/mol (6.0–6.4%) or a fasting plasma glucose (FPG) level of 5.5–6.9 mmol/L; and
- high risk of cardiovascular disease, defined as either of the following: (A) total cholesterol >5mmol/L, or (B) SBP >140 mmHg, or (C) HDL <1.0 mmol/L for men and <1.3 mmol/L for women.

Further details on the relevance and applicability of this subpopulation to UK clinical practice and to the current decision problem are given in Section B.1.1.

B.3.2.3 Model structure

Analyses were conducted utilising a simple and transparent state-transition, Markov, cohort model developed in MS Excel®. The clinical effectiveness of the intervention and comparator was introduced in the model through changes in BMI and cardio-metabolic risk factors, namely SBP, HDL cholesterol, and total cholesterol. These intermediate endpoints were used in risk equations or risk look-up tables to calculate transition probabilities, guiding the progression of the cohort through the model and to estimate the incidence of fatal and non-fatal events. In addition, treatment-specific probabilities of temporarily reverting prediabetes to a normal glucose tolerance state were also directly sourced from a subgroup *post-hoc* analysis of the SCALE 1839 obesity and prediabetes (Section 2.7.2). The risk prediction models and risk look-up tables were substantiated and selected based on a SLR (120) and after consultations with clinical experts in the field of obesity (Appendix O).

State-transition models have been previously used in obesity modelling (100-102). Additionally, state-transition models are widely used in modelling of diabetes and cardiovascular disease (121), which is appropriate given the nature of the condition characterised by recurrent risks. A state-transition model evaluated as a patient-level simulation would have been considered as an alternative to the cohort analysis

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approach as applied here given the ability of this method to more accurately capture any additional heterogeneity between patients that would be difficult to capture with a cohort analysis approach. However, as the target population for this submission is relatively homogenous (all patients have prediabetes at baseline, and BMI ≥ 35kg/m^2), a microsimulation analysis was not deemed necessary as it was unlikely to add much value to the decision problem, while at the same time adding significant computational burden and additional data requirements to populate the model.

A cycle length of three months has been defined for the first year, to allow for incorporation of the stopping rule in liraglutide 3.0mg SmPC and to incorporate efficacy evaluation endpoints at week 28 and week 56 in SCALE. Annual cycles were implemented after the first year and were half cycle corrected.

A forty-year time horizon was defined in base case analyses to incorporate all costs and outcomes associated with weight loss as this was considered the point at which most patients would have reached the average life expectancy in the UK. For the few patients living beyond this time horizon (i.e., approximately 30%), any residual costs and benefits for diet and exercise with or without liraglutide 3.0mg were expected to be heavily discounted and thus have a negligible impact on the cost-effectiveness results. Alternative shorter time horizons were, however, assessed for their impact on the results.

Figure 15 below illustrates the structure of the model, health states and possible transitions between these health states.

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Figure 15: Markov model schematic

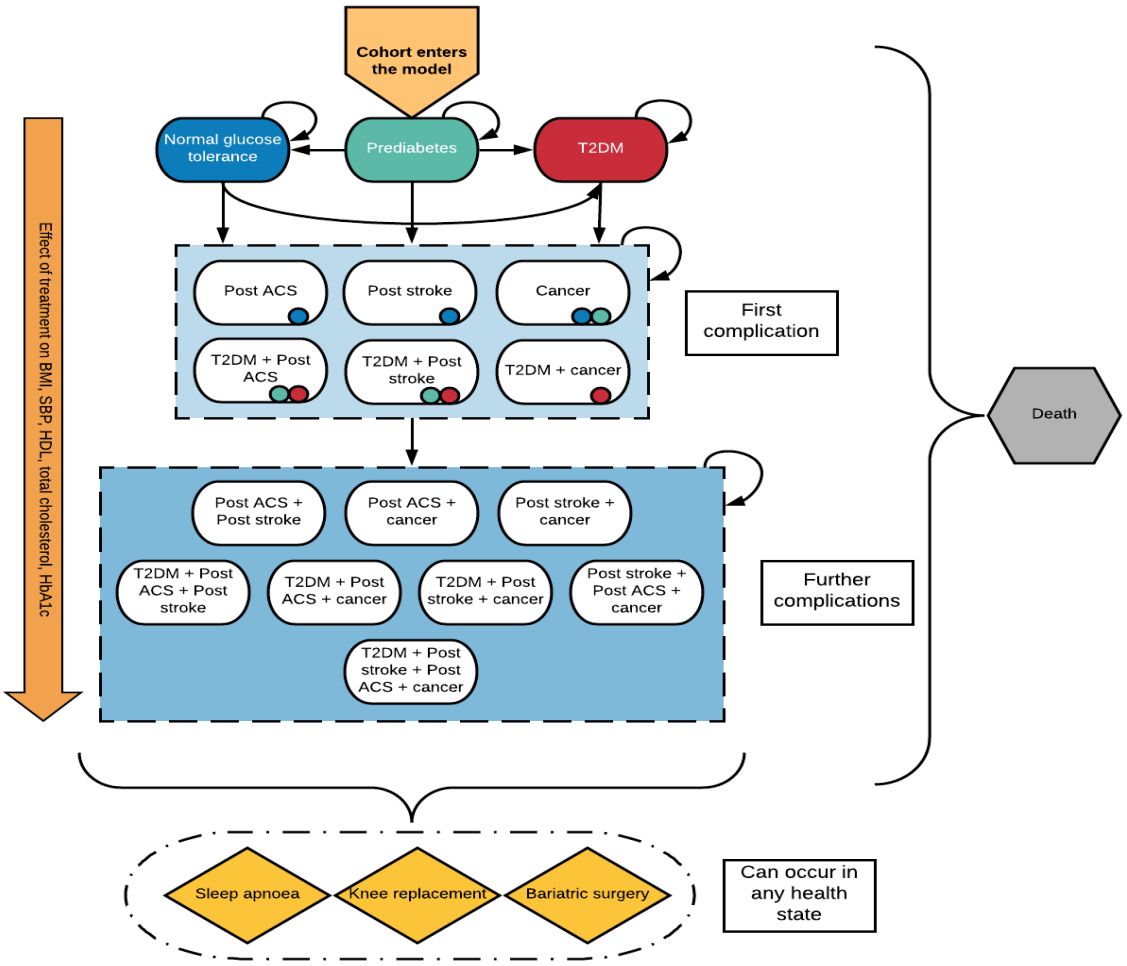

Figure notes: coloured dots in health states encompassing first complications denote possible originating health states (e.g. green colour-coding denotes patients with prediabetes); cancer state was not included in the base case analysis, only in scenario analyses. ACS: acute coronary syndrome; HDL: high-density lipoprotein; T2DM: type 2 diabetes.

Briefly, patients enter the model with prediabetes, having a BMI ≥35 kg/m^2, deemed at high risk of cardiovascular disease (CVD), and hence eligible for initiating treatment with liraglutide 3.0mg or diet and exercise (comparator arm) in specialist tier 3 services.

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In the next cycle, a proportion of the cohort can either revert to a normal glucose tolerance state if treatment is effective in reverting prediabetes (i.e. probability of prediabetes reversal >0%), remain in the prediabetes health state, develop type 2 diabetes, experience a cardiovascular event: myocardial infarction (MI), angina, or stroke, and move to a post-acute coronary syndrome (ACS) or post stroke plus type 2 diabetes, or have cancer in scenario analyses. Note that after an MI, angina or stroke event, prediabetes patients can only move to a post ACS plus type 2 diabetes or a post stroke plus type 2 diabetes state. This was a simplifying assumption as otherwise the number of health states would have increased from 18 to 32 states, making the model difficult to handle and affecting its transparency. This simplifying assumption was also necessary as current cardiovascular risk equations in non-type 2 diabetes do not allow incorporation of an additional risk for prediabetic cohorts (122, 123), albeit an increase in cardiovascular risk with prediabetes is well established (124).

Within each cycle, a proportion of the cohort has sleep apnoea (defined in relation to the level of BMI in cycle), can have a knee replacement surgery, or be eligible and undergo bariatric surgery independent of the treatment received (from year 2 onwards), or die. The risk of death is assigned dependent of the mortality associated with events (fatal MI, angina, stroke, knee replacement, or bariatric surgery) or of the mortality of the underlying diseases (cancer, type 2 diabetes, post ACS and/or post stroke) as well as dependent of the age and gender-specific general population mortality.

Transitions between health states and rates of events are determined by the level of five physiological parameters in each cycle: BMI, SBP, total and HDL cholesterol, and HbA_{1c} once type 2 diabetes develops, via published risk prediction models or risk look-up tables. Treatments can alter the level of four of the five physiological parameters: BMI, SBP, total and HDL cholesterol. HbA_{1c} was considered as a risk factor only after the cohort develops type 2 diabetes. Presence or absence of prediabetes itself was included as a risk predictor in the risk equations for type 2 diabetes onset, whilst presence or absence of type 2 diabetes determined the choice

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of cardiovascular risk prediction models. Hence, no further effect of liraglutide 3.0mg on HbA_{1c} was implemented to avoid double counting, given a direct effect of liraglutide 3.0mg on prediabetes reversal is modelled, as described further. Treatment efficacy was therefore indirectly linked to obesity complications, via modelled levels in physiological parameters which affect the risk of complications. Smoking and triglyceride levels do not change with treatment or time over the time horizon of the analysis.

In the base case analysis, treatment with liraglutide 3.0mg was assumed to be maintained for two years (responders only). Non-responders were assumed to remain on diet and exercise, and were hence applied the full analysis set efficacy with diet and exercise, i.e. placebo arm in SCALE 1839 obesity and prediabetes. This assumption was in line with the demonstrated maintenance of the treatment benefit in liraglutide 3.0mg SCALE program (73) and was also validated by clinical experts in the field of obesity (Appendix N). Non-responders to liraglutide discontinued treatment after the first cycle (3 months), based on the stopping rule included in the licence, and their disease pathway was entirely modelled on efficacy in the comparator, diet and exercise arm, in base case analyses (i.e. liraglutide 3.0mg efficacy is never applied to non-responders). Post two years of treatment, physiological parameter values in liraglutide 3.0mg responders were assumed to return to their baseline values at a constant annual rate of 33% (i.e. waning of treatment effect), in line with previously published evidence (101). A rate of 33%, 67% and 100% was applied at start of years 1, 2 and 3 following treatment discontinuation. Beyond the of treatment effect period, a natural disease pathway was modelled whereby the BMI in all patients was assumed to increase at an annual rate of 0.1447 kg/m^2 in men and 0.1747 kg/m^2 in women (101). In the base case analysis, diet and exercise was maintained in all the patients who discontinued liraglutide 3.0mg treatment (including liraglutide non-responders and post liraglutide treatment discontinuation in responders) to reflect clinical practice in the UK, which maintains diet and exercise as a core ongoing component of weight management. This approach was validated with clinical experts in the field of obesity (Appendix O). Additionally, a small proportion of patients become eligible for bariatric surgery each

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year (starting from year 2), and the levels of the physiological parameters change further, corresponding to the efficacy of surgery. The rate of surgery was defined in the model with respect to the annual incidence of bariatric surgeries performed in England and Wales, and eligibility criteria on minimum BMI (35 kg/m^2) , and maximum age (5, 13, 125), and thus was not specific to the treatment received.

A summary of methods for the health-economic analysis, in comparison with other analyses in obesity submitted to NICE is provided in Table 26 below. Orlistat (TA22) (126) is now part of NICE clinical guideline CG189, and thus it has been included in the summary of previous appraisals. It should be noted that although included in the summary table, sibutramine and rimonabant have now been withdrawn from the market (71, 72).

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Table 26: Summary features of the economic analysis

	Previous appraisals				Current appraisal	
Factor	**TA494 (Naltrexone-bupropion)**	**TA144 (Rimonabant)***	**TA22 (Orlistat)**	**TA31 (Sibutramine)***	**TA [ID740] (Liraglutide 3.0mg)**	**Justification**
Time horizon	Lifetime	Lifetime (60 years)	Not available	Lifetime	Lifetime (40 years)	As per the NICE reference case for modelling chronic conditions such as obesity
Extrapolation of treatment effect	Weight regain begins immediately after a patient discontinues all treatment. Weight is regained linearly over a 3-year period**	Treatment effect is assumed to wane over a 12-month period following treatment discontinuation	Treatment effect is assumed to wane over 26 months following end of treatment	Treatment effect is assumed to wane over 33 months following end of treatment	Treatment effect is assumed to wane in a linear fashion within three years following treatment discontinuation at a rate of 33%, 67% and 100% applied in years 1, 2 and 3 following discontinuation	This assumption is in line with Ara *et al*., 2012 (101) and was the preferred assumption by the ERG in TA494
Source of HRQoL data	The utility scores were taken from a published Public Health England analysis of weight loss interventions by Copley et al. (127)	Health Survey of England for age-specific utilities and Currie *et al*. for the disutilities	Health Survey for England data on utility gained per kilogram lost	Not available	Baseline utility was derived from Søltoft *et al*., 2009 (16). Health state disutilities were sourced from Søltoft *et al*., 2009 and	Søltoft *et al.,* 2009 uses data from the Health Survey for England with a sample size over 14,000 people and good representation of the English adult

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	Previous appraisals				Current appraisal	
Factor	**TA494 (Naltrexone-bupropion)**	**TA144 (Rimonabant)***	**TA22 (Orlistat)**	**TA31 (Sibutramine)***	**TA [ID740] (Liraglutide 3.0mg)**	**Justification**
					Sullivan *et al*., 2011 (16, 128). Event disutilities were sourced from Campbell *et al*., 2010, Søltoft *et al*., 2009 and Sullivan *et al*., 2011 (16, 128, 129).	population. Utility was assessed using EQ-5D and adjusted for confounding factors including five obesity-related morbidities thus, utilities applied at baseline are free of any additional effects of obesity-related comorbidities allowing the separation of the effects of comorbidities from a pure effect related to increased weight.
Measure of health effects	QALYs	QALYs	QALYs	QALYs	QALYs	NA
Source of drug acquisition costs	Not available	British National Formulary	Not available	Not available	Novo Nordisk	NA

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	Previous appraisals				Current appraisal	
Factor	**TA494 (Naltrexone-bupropion)**	**TA144 (Rimonabant)***	**TA22 (Orlistat)**	**TA31 (Sibutramine)***	**TA [ID740] (Liraglutide 3.0mg)**	**Justification**
Perspective	NHS/PSS	NHS/PSS	Not available.	NHS/PSS	NHS/PSS	NA
Discounting	3.5% for costs and benefits	3.5% for costs and benefits	Not available.	6% for costs and 1.5% for benefits	3.5% for costs and benefits	NA

*Rimonabant (EMA, 2009) and sibutramine (EMA, 2010) have been withdrawn from the market (71, 72); **The ERG criticised the manufacturers implementation of weight regain in the model (TA494).

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B.3.2.4 Intervention technology and comparators

The intervention considered in the model is liraglutide 3.0mg in combination with diet and exercise, which is compared to diet and exercise without pharmacological treatment. These regimens were chosen to be consistent with UK clinical practice and the decision problem and this is supported by evidence from the SCALE 1839 obesity and prediabetes study.

- Consistent with the current standard of care in specialist tier 3 services (130), diet and exercise consist of:
  - Dietary and physical activity counselling (either group or individual sessions);
  - Hypocaloric diet (e.g. reduce calorie intake by 500 calories per day);
  - Increased physical activity.
- Liraglutide 3.0mg in combination with diet and exercise consists of:
  - Diet and exercise as defined above and liraglutide 3.0mg daily.

Daily injection of liraglutide 3.0mg has a starting titration dose of 0.6mg daily which is escalated to a recommended maintenance dose of 3.0mg daily. The titration dose should be escalated to the 3.0mg maintenance dose in increments of 0.6mg with at least 1-week intervals to improve gastrointestinal tolerability. Treatment should be discontinued after 12 weeks on the 3.0mg daily dose if patients have not lost at least 5% of their initial body weight.

Bariatric surgery is available in England as part of tier 4 specialist weight loss services. Given the placement of liraglutide 3.0mg in tier 3 specialist services, bariatric surgery was included in the model as a rescue treatment following the failure of interventions provided in tier 3.

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B.3.3 Clinical parameters and variables

B.3.3.1 Parameters relating to baseline cohort characteristics

The characteristics of the model population at baseline were sourced from a *post-hoc* analysis of the SCALE 1839 clinical trial subset of patients matching the patient population considered in this technology appraisal, see Section B.3.2.2 Patient population. Values entered in the model are illustrated in Table 27 below.

Table 27: Baseline cohort characteristics

Characteristic	Model input Mean (SD)	Input in UK units, where applicable
Age (years)	48.2 (11.2)	NA
BMI (kg/m^2)	41.7 (5.3)	
Height (m)	1.66 (0.1)	
Systolic blood pressure (mmHg)	127.2 (13.6)	
Total cholesterol (mg/dL)	200.6 (37.3)	5.2 mmol/mol
HDL cholesterol (mg/dL)	48.7 (13.2)	1.3 mmol/mol
Triglyceride level ≥150 mg/dL (%)	46.0 (NR)	NA
Smokers (%)	15.0 (NR)	
Females (%)	75.8 (NR)	
Patients on lipid lowering drugs (%)	17.0 (NR)	
Patients on antihypertensive medication (%)	45.3 (NR)	
Patients with prediabetes (%)	100.0 (NR)	

NA, not applicable; NR: not reported; SD: standard deviation

B.3.3.2 Parameters relating to treatment efficacy and safety

Treatment efficacy was propagated in the model via six efficacy parameters, as follows:

1) **Treatment response** – denotes the proportion of liraglutide 3.0mg patients who achieve ≥5% weight loss after 12 weeks of treatment at maintenance dose and continue liraglutide 3.0mg for two years (base case). A stopping rule

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parameter was applied in the model denoting the proportion of non-responders, i.e. proportion of patients who do NOT achieve the mentioned target weight loss and who discontinue liraglutide 3.0mg at start of cycle 2. The stopping rule does not apply to diet and exercise arm in base case analyses, as weight management with diet and exercise was assumed to continue throughout the treatment period. All efficacy parameters applied after the stopping rule (i.e. weight change, SBP change etc.) were sourced from a responder analysis for liraglutide 3.0mg responders and from the full analysis set (FAS) of the placebo arm in SCALE 1839 for liraglutide 3.0mg non-responders and for all patients on diet and exercise arm (Table 28).

2) **Temporary prediabetes reversal** – denotes the proportion of patients who temporarily revert to a normal glucose tolerance state until weight is fully regained. It is applied once in the model, at the start of cycle 2; the parameter is sourced from week 56 glycaemic status results in SCALE 1839 and is calculated as one minus the proportion of patients with prediabetes at week 56 divided by the total population at risk. The proportion reverting to normal glucose tolerance remains in this state until weight returns to its baseline value, hence both over the treatment and over waning of treatment effect periods. Onset of type 2 diabetes in both normal glucose tolerance and prediabetes states was based on the model risk prediction and not on SCALE 1839.
3) **Percent weight loss** – represents the percentage reduction in weight versus baseline as measured in the SCALE obesity and prediabetes at weeks 28, 56, 104 and 160 with liraglutide 3.0mg and diet and exercise; the efficacy observed at week 28 in SCALE was applied half way through the observed time in the model, i.e. at the start of cycle 2; the efficacy observed at week 56 was applied at start of cycle 4; the efficacy observed at week 104 was applied at the start of cycle 5 (i.e. start of year 2 in the model); the efficacy observed at week 160 was only applied in analyses where liraglutide 3.0mg treatment was maintained beyond 2 years (not base case), at start of cycle 6 (i.e. start of year 3 in the model); treatment effects were therefore applied at the start of

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the model cycle corresponding to each timepoint of efficacy assessment in SCALE.

4) **Change in SBP** – represents the absolute change in SBP (mmHg) vs. baseline observed in liraglutide SCALE obesity and prediabetes study with liraglutide 3.0mg and diet and exercise at weeks 28, 56, 104, and 160 and was applied at the same time points in the model as described above for weight loss.
5) **Change in total cholesterol** – represents the absolute change in total cholesterol (mg/dl) vs. baseline observed in liraglutide SCALE obesity and prediabetes study with liraglutide 3.0mg and diet and exercise at weeks 28, 56, 104, and 160 and was applied at the same time points as described above for weight loss.
6) **Change in HDL cholesterol** - represents the absolute change in HDL cholesterol (mg/dl) vs. baseline observed in liraglutide SCALE obesity and prediabetes study with liraglutide 3.0mg and diet and exercise at weeks 28, 56, 104, and 160 and was applied at the same time points as described above for weight loss.

Note: HbA_{1c} was not a treatment efficacy parameter. HbA_{1c} becomes a relevant parameter (i.e. determining transition probabilities) only for the proportion of the cohort which develops type 2 diabetes over time and was maintained at a constant level of 7.5% throughout the analysis time horizon (in base case analyses). A variation of HbA1c upon type 2 diabetes onset to 6.5% or 8.0% was tested in scenario analyses.

The levels of the physiological parameters, BMI, SBP, total cholesterol, HDL cholesterol and HbA_{1c} (in type 2 diabetes) in the cycle further determine the transition probabilities to the modelled health states and the incidence of the modelled events every cycle, including fatal events. BMI level in each cycle also determined the BMI-specific utility in the model.

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Table 28 below illustrates treatment efficacy parameters applied in the model base case settings using the LOCF for missing data where diet and exercise were considered standard management in all patients post liraglutide 3.0mg treatment discontinuation. Scenario analyses explored the effect of assuming a fixed treatment duration for diet and exercise, by setting discontinuation to no treatment (efficacy data inputs for this analysis are illustrated in Appendix L).

Table 28: Treatment efficacy parameters applied in base case economic analysis taken from SCALE 1839 obesity and prediabetes study

Model parameter	Liraglutide 3.0mg responders[(1)] Mean (SD)	Liraglutide 3.0mg non-responders[(2)] Mean (SD)	Diet and exercise[(3)] Mean (SD)
Probability of not achieving ≥5% weight loss vs. baseline at week 16 in SCALE (12 weeks on 3.0mg)	155/(155+314) (33.05%)		N/A
Probability of prediabetes reversal at week 56 in SCALE	1- 54/314 (82.80%)	(40.74%)	1- 160/270 (40.74%)
Weight loss (%-reduction) vs. baseline			
Start of cycle 2	-9.96% (4.04%)	-2.43% (4.73%)	-2.43% (4.73%)
Start of cycle 4	-10.91% (5.81%)	-2.48% (6.06%)	-2.48% (6.06%)
Start of cycle 5 (start year of 2)	-9.46% (6.68%)	-2.07% (6.55%)	-2.07% (6.55%)
Start of cycle 6 (start year of 3)*	-8.02% (7.27%)	-1.65% (6.79%)	-1.65% (6.79%)
Change in SBP (mmHg) vs baseline			
Start of cycle 2	-6.22 (10.94)	-1.70 (11.05)	-1.70 (11.05)
Start of cycle 4	-7.58 (10.26)	-1.76 (10.87)	-1.76 (10.87)
Start of cycle 5 (start year of 2)	-6.21 (11.21)	-1.72 (11.12)	-1.72 (11.12)
Start of cycle 6 (start year of 3)*	-4.08 (11.01)	-1.09 (11.69)	-1.09 (11.69)
Change in total cholesterol (mg/dl)			
Start of cycle 2	-6.80 (25.57)	-3.85 (25.31)	-3.85 (25.31)
Start of cycle 4	-3.84 (25.87)	-6.10 (25.95)	-6.10 (25.95)
Start of cycle 5 (start year of 2)	-6.41 (28.10)	-7.01 (29.12)	-7.01 (29.12)
Start of cycle 6 (start year of 3)*	-4.49 (27.21)	-4.15 (27.73)	-4.15 (27.73)

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Model parameter	Liraglutide 3.0mg responders[(1)] Mean (SD)	Liraglutide 3.0mg non-responders[(2)] Mean (SD)	Diet and exercise[(3)] Mean (SD)
Change in HDL cholesterol (mg/dl)			
Start of cycle 2	0.88 (6.42)	0.20 (6.70)	0.20 (6.70)
Start of cycle 4	2.80 (7.20)	0.80 (7.42)	0.80 (7.42)
Start of cycle 5 (start year of 2)	3.53 (7.81)	1.52 (7.82)	1.52 (7.82)
Start of cycle 6 (start year of 3)*	4.42 (9.03)	2.22 (8.88)	2.22 (8.88)

*not applied in base case analysis; (1): liraglutide 3.0mg responder analysis; (2): assumed equal to diet and exercise arm; (3): full analysis set efficacy with placebo; HDL: High-density lipoprotein; SBP: systolic blood pressure; SD: standard deviation

Non-responder rates in the model were calculated as the number of subjects not achieving ≥5% weight loss at week 16 in SCALE 1839 divided by the total number of patients with known response status (i.e. number of responders plus non-responders), as for some subjects the response status was unknown at week 16 (11.5% on liraglutide 3.0mg and 13.7% on placebo). This effectively assumed that subjects with unknown response status would have the same response rate as those with known status.

Treatment related AEs were not considered in the present analysis. As reported by Pi-Sunyer et al., 2015 (131), common AEs with liraglutide 3.0mg in SCALE obesity and prediabetes included gastrointestinal events and hypoglycaemia (see Section B.2.10). These were however transient and mild in nature, thus not expected to have a significant impact on patient quality of life, henceforth not accounted for in the economic analysis.

Bariatric surgery was considered a possible event in both the liraglutide 3.0mg and diet and exercise arms. Starting from cycle 5 of the model (start of year 2), a proportion of patients becomes eligible for bariatric surgery at a rate of 1.15% annually (the proportion is given by the annual incidence of bariatric surgery in the UK, which considers the availability of this service and patients' willingness to undergo surgery) (5). Two additional eligibility criteria were defined, aligned with UK clinical practice: minimum BMI eligibility was set to 35 kg/m^2 (13), and maximum age eligibility was 57 years (125). The efficacy by type of bariatric surgery was sourced

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from the literature and was weighted to an average according to the distribution of surgeries performed in the UK (activity data from the UK National schedule of reference costs 2017/2018) further details on bariatric surgery efficacy are provided in Appendix L.

B.3.3.3 Disease pathway post treatment

Post treatment period, all physiological parameters – BMI, SBP, total and HDL cholesterol - were assumed to return to their baseline values (i.e. waning of treatment effect) at a constant annual rate of 33% (i.e. waning of treatment effect). This assumption is similar to the approach preferred by the ERG in TA494 and was validated by a clinical expert in obesity (Appendix O.1.). Alternative scenario analyses were defined whereby physiological parameters returned to their baseline value immediately after treatment stop, over one or three years after treatment stop, or, by assuming their values after the waning period returned to a value on the natural disease trajectory instead of the value at baseline.

In the post treatment and waning period, the BMI of the modelled cohort was assumed to increase at an annual rate of 0.1447 kg/m^2 in men and 0.1747 kg/m^2 in women, corresponding to a natural history of BMI progression estimated by Ara *et al.,* 2012 based on the GPRD study (101). A natural increase in weight of 1 kg per year (corresponding to a 0.3629 kg/m^2 annual increase in BMI) is available in the model as an alternative to the GPRD weight increase. This was based on advice from a clinical expert in the UK (Appendix O) and mentioned in the NICE clinical guidelines 43 for obesity management (132). Additionally, the model assumed the natural increase in weight to occur only up to the age of 68 years after which BMI would level-off, in line with advice received from a clinical expert in the UK (Appendix O.1.1). The maximum age until weight increased was tested in one-way sensitivity analyses with +/- 2 years.

All other physiological parameter values (i.e. SBP, total and HDL cholesterol) were maintained constant throughout the time horizon at the level post treatment and post waning period. It was assumed that patients remained on their standard blood pressure and lipid lowering medication and therefore the levels of these parameters

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do not change significantly over time. Also, the model assumed that once patients develop type 2 diabetes, their HbA_{1c} value remained constant at 7.5%-points (base case analysis; tested in scenario analyses) throughout the time horizon of the analysis. This was a simplifying assumption since beta-cell function is expected to deteriorate and HbA_{1c} to increase over time (133). However, a constant HbA_{1c} was a modelling simplification as the present health-economic analyses were not intended to model type 2 diabetes; also, in type 2 diabetes modelling, it is often assumed that patients intensify their diabetes treatment to maintain a relatively constant HbA_{1c} over life. Figure 16, Figure 17, Figure 18, and Figure 19 illustrate the progression of physiological parameters over time with and without the additional effect of bariatric surgery.

Figure 16: BMI trajectories over time (base case analysis)

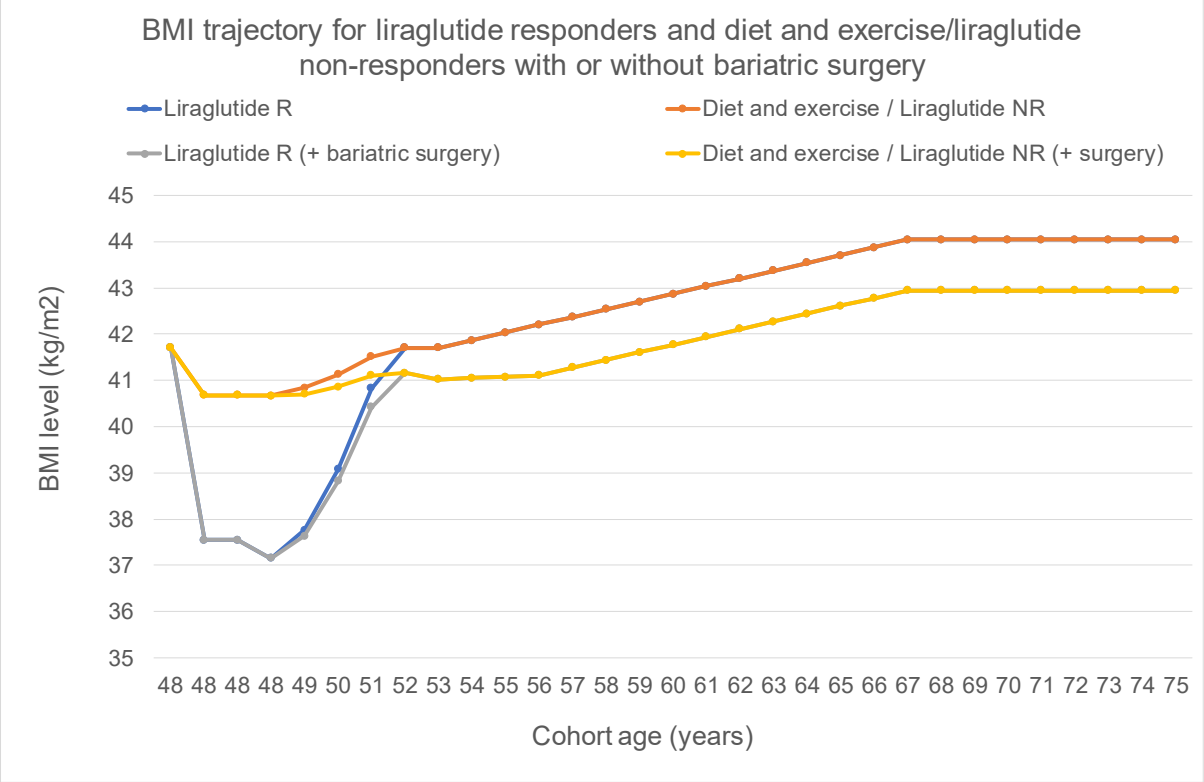

Figure notes: all patients on diet and exercise and all liraglutide non-responders follow the same parameter trajectory; the total efficacy in liraglutide 3.0mg arm is the weighted average of liraglutide responders and non-responder efficacy. NR: non-responder; R: responder.

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Figure 17: SBP trajectories over time (base case analysis)

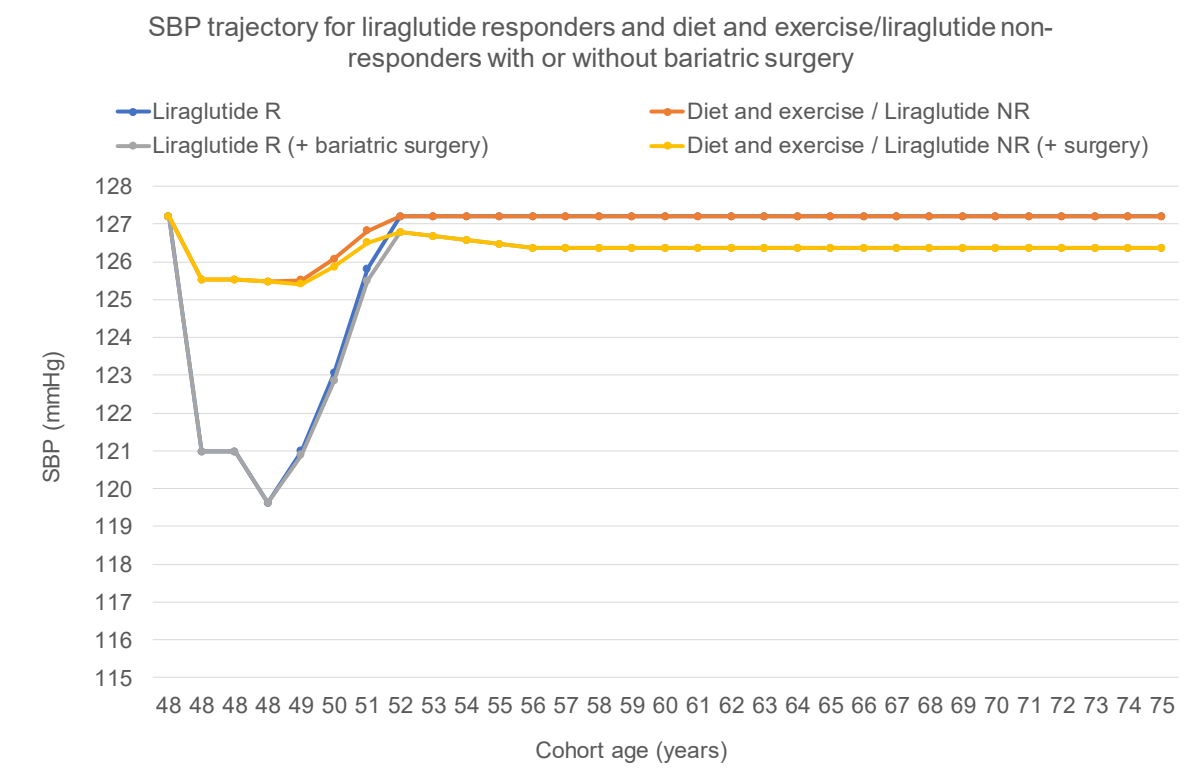

Figure notes: all patients on diet and exercise and all liraglutide non-responders follow the same parameter trajectory; the total efficacy in liraglutide 3.0mg arm is the weighted average of liraglutide responders and non-responder efficacy. NR: non-responder; R: responder; SBP: systolic blood pressure.

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Figure 18: Total cholesterol trajectories over time (base case analysis)

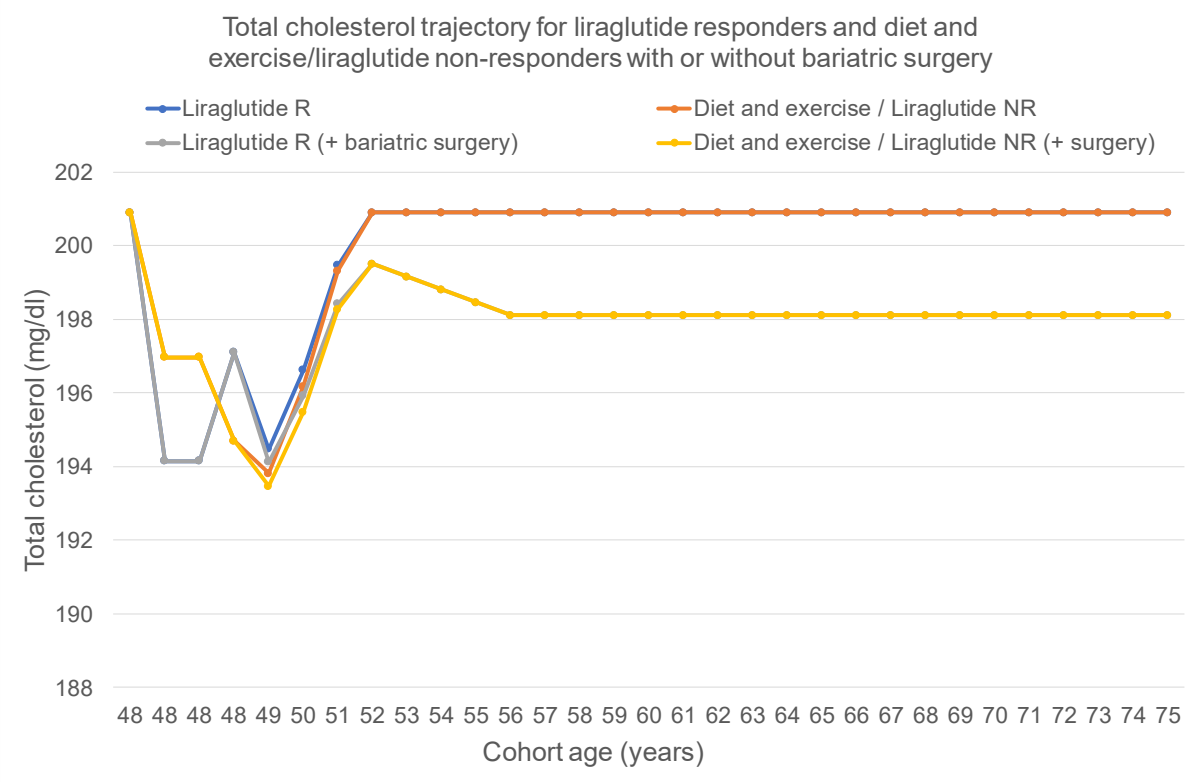

Figure note: all patients on diet and exercise and all liraglutide non-responders follow the same parameter trajectory; the total efficacy in liraglutide 3.0mg arm is the weighted average of liraglutide responders and non-responder efficacy. NR: non-responder; R: responder.

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Figure 19: HDL cholesterol trajectories over time (base case analysis)

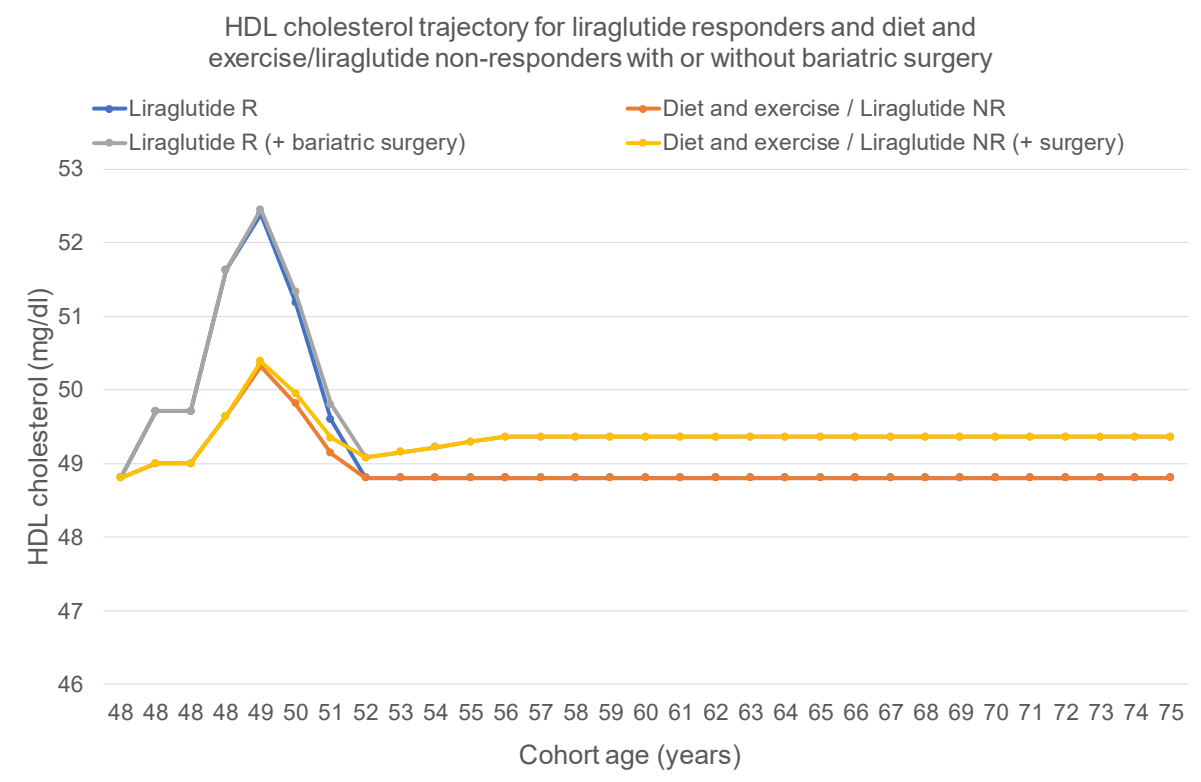

Figure note: all patients on diet and exercise and all liraglutide non-responders follow the same parameter trajectory; the total efficacy in liraglutide 3.0mg arm is the weighted average of liraglutide responders and non-responder efficacy. HDL: high-density lipoprotein; NR: non-responder; R: responder

B.3.3.4 Extrapolation of clinical efficacy parameters to disease outcomes

A systematic review of the literature was conducted in 2017 to validate the link between obesity and complications modelled and further update or identify sources to inform transition probabilities (120).

Onset of type 2 diabetes

To link treatment efficacy parameters with the onset of type 2 diabetes and thus predict the occurrence of type 2 diabetes in the model, a published risk prediction model, the QDiabetes-2018 model C (116), was used.

Several risk prediction models were available in the literature (120), including one developed specifically in obese individuals by Ara et al., 2012 (101). The QDiabetes risk model was preferred as being the most validated risk score in European

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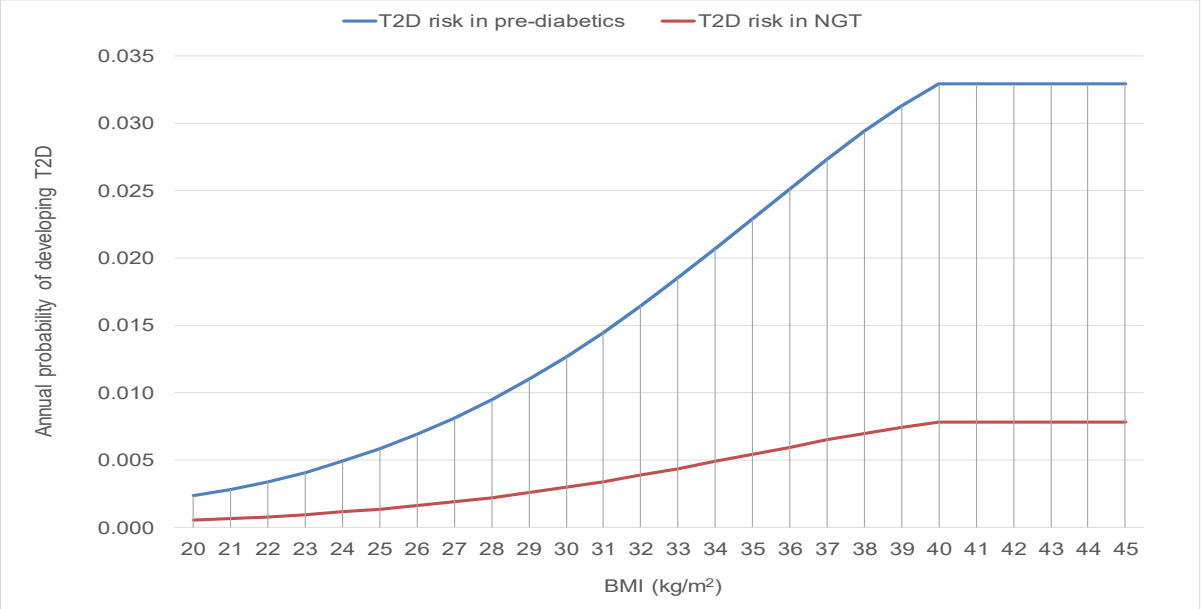
populations, allowing 10-years prediction of risks and including BMI and HbA_{1c} as predictive variables. The HbA_{1c} parameter was used to model the higher risk of type 2 diabetes in prediabetes, by setting its value to 42 mmol/mol (HbA_{1c} %-points: 6), the HbA_{1c} parameter was set to 35 mmol/mol (corresponding to HbA_{1c} %-points: 5.4) in patients who reverted to normal glucose tolerance.

Figure 20 illustrates the association between BMI and incidence of type 2 diabetes in normal glucose tolerant and in prediabetes patients. The full specifications of the risk equation are available in the source paper (116).

Figure 20: Annual probabilities of type 2 diabetes onset by BMI level



NGT: normal glucose tolerance; T2D: type 2 diabetes.

Several assumptions were applied to the modelling of type 2 diabetes as follows. Type 2 diabetes occurs when prediabetic or normal glucose tolerant patients develop type 2 diabetes, as well as when prediabetic patients experience a cardiovascular event (stroke, including transient ischaemic attack, MI or angina). This assumption was made to limit the number of possible health state combinations (see Section B.3.2.3 Model structure).

Type 2 diabetes is associated with additional mortality, an annual pharmacy cost of treatment and an annual health state cost (encompassing costs of treating microvascular complications) as well as a utility decrement. For prediabetes, the

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model assigns the average cost of the NHS DPP per participant per year, but no utility decrement.

Also, no microvascular complications, known to be associated with type 2 diabetes (e.g. end-stage renal disease, diabetic foot complications), were explicitly accounted for in the modelling analysis as doing so would have substantially increased the number of health states. However, the costs and quality of life decrements related to diabetes microvascular complications were incorporated in the type 2 diabetes health state cost, and disutility associated with type 2 diabetes, respectively. As such, by avoiding type 2 diabetes, an obesity intervention would also avoid the costs and quality of life losses of type 2 diabetes microvascular complications.

Finally, it should be noted an important limitation of the QDiabetes risk model which is insensitive to changes in BMI levels beyond 40 kg/m^2, i.e. same risk of type 2 diabetes applies at any BMI level of 40 kg/m^2 and above. Conservatively, no attempt was made to alter this limitation and/or to extrapolate the increase in risk on type 2 diabetes onset beyond the observed 40 kg/m^2 level in QDiabetes.

Sleep apnoea

The proportion of the cohort having sleep apnoea depends on the BMI level in the cycle. The prevalence of sleep apnoea by BMI level was sourced from the Sleep Heart Study (134). This study found that the prevalence of sleep apnoea as defined according to Apnoea-Hypopnea Index (AHI) ≥15 is 13% at BMI levels between 24.4-28.0 kg/m^2 (irrespective of gender). The reported odds corresponded to one standard deviation (SD) increment in BMI was 1.6 kg/m^2 (1.45, 1.76). This study was identified in a SLR (120) and was preferred to other studies available as it was the largest in sample size (n=5,615) and it provided sufficient data to calculate a prevalence rate per unit BMI. It was also preferred to other studies as it investigated the prevalence of moderate-to-severe sleep apnoea (AHI ≥15), given that in the present health-economic analysis, sleep apnoea was assigned a hospital cost for continuous positive airway pressure treatment. The BMI-prevalence table used in the model is illustrated in Appendix M.

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Throughout the time horizon, the proportion of the cohort having sleep apnoea may reside in any non-dead health state (i.e. sleep apnoea co-occurs with any obesity complication including prediabetes at baseline). This was possible as sleep apnoea was assumed not to influence the progression to and from other health states or events. Sleep apnoea was given a utility decrement (applied each cycle for the proportion of the cohort with sleep apnoea) and a treatment cost. Sleep apnoea did not affect mortality in the model.

Cardiovascular events

Cardiovascular events considered in the model encompass: MI, angina and stroke, including transient ischaemic attacks (TIA). Different risk prediction models were used to estimate transition and event probabilities for first and second cardiovascular events and for patients with normal glucose tolerance, prediabetes and for patients with type 2 diabetes. The risk prediction models were identified following a systematic review of the literature (120) and were selected based on their applicability and relevance to the UK population, as well as precedence to whether BMI and other treatment-effect variables were indicated as predictors of risk.

The QRisk3 equation was used to predict the risk of first cardiovascular event in prediabetes and normal glucose tolerance states (122). The outcome of interest in QRisk3 was a composite of cardiovascular disease risk, including coronary heart disease, ischaemic stroke, or TIA. The composite outcome predicted by QRisk3 had to be calibrated to account separately for individual events in the model: MI, angina, stroke and TIA. The distributions by type of event used in the present analysis are illustrated in Table 29. As for type 2 diabetes onset, QRisk3 is sensitive to changes in BMI (i.e. different risk applies to different BMI levels) up to 40 kg/m^2. Conservatively, no attempt was made to overcome this limitation.

The Framingham Recurring Coronary Heart Disease risk model (135) was used to predict recurrent cardiovascular events in normal glucose tolerance states. The outcome of the prediction model was two year risk of subsequent CHD (including mostly hospitalised events consisting of MI, coronary insufficiency, angina pectoris,

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and sudden and non-sudden coronary death). CHD events do not include stroke; hence the Framingham algorithm was up-adjusted to predict total CVD, including stroke events, based on the proportions of CHD to total CVD as exhibited in Table 29, after which the composite risk was partitioned into individual events based on proportions in Table 29.

Neither of the above studies quantify the risk of cardiovascular outcomes in prediabetic populations specifically. Consequently: the risk of first cardiovascular event in prediabetic patients was assumed to be identical to normal glucose tolerance; the risk of a recurrent cardiovascular event in prediabetics was assumed identical to the risk of recurrent cardiovascular events in type 2 diabetics.

The UKPDS82 risk model (outcome model 2) (136) was used to predict first and recurrent cardiovascular events after onset of type 2 diabetes. Individual risk models were available for the outcomes: first ischaemic heart disease (IHD) considered angina herein, first MI and first stroke, recurrent MI and recurrent stroke. There was no model to predict recurrent angina, hence, the estimated risk for recurrent events (MI and stroke) was adjusted based on the proportions of MI and stroke of total CVD exhibited in Table 29 .

Table 29: Clinical inputs for calibration of composite cardiovascular endpoints

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

Table notes (1): calculated as proportion of initial: MI, sudden and non-sudden CHD of total CHD (excl. coronary insufficiency) in D'Agostino 2000 (135) for males and females then multiplied with the proportion of CHD (excl. coronary insufficiency) of total CHD plus stroke from D'Agostino 2008 (123); (2): calculated as proportion of initial angina of total CHD (excl. coronary insufficiency) in D'Agostino 2000 (135) for males and females then multiplied with the proportion of CHD (excl. coronary insufficiency) of total CHD plus stroke from D'Agostino 2008 (123); (3): calculated as the proportion of strokes out of total CHD and strokes in D'Agostino 2008 (123); (4): calculated as proportion of TIA in total strokes from Wolf et al., 1991 (137) in males and females.

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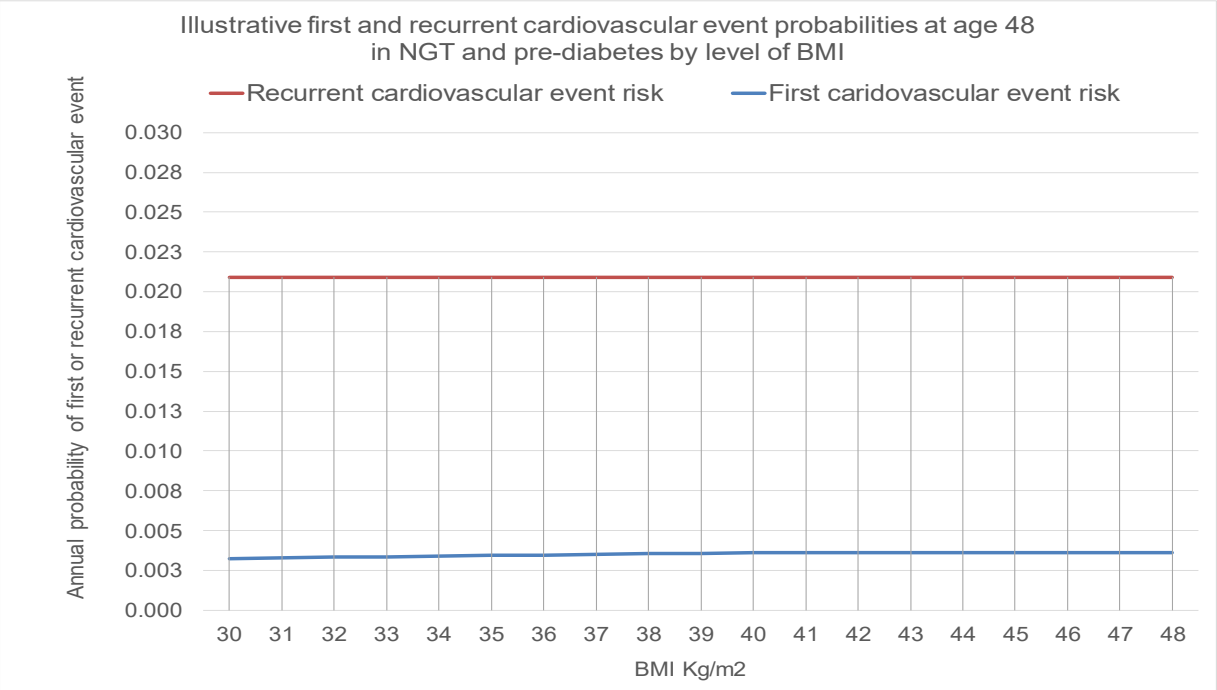
Further details on the risk equations are given in Appendix M. The graphs in Figure 20 and Figure 21 illustrate the BMI-cardiovascular probabilities applied in model for a cohort aged 48 years.

Figure 21: Annual probability of a first and recurrent cardiovascular events in NGT by BMI



Source: QRisk3; Figure notes: NGT: normal glucose tolerance

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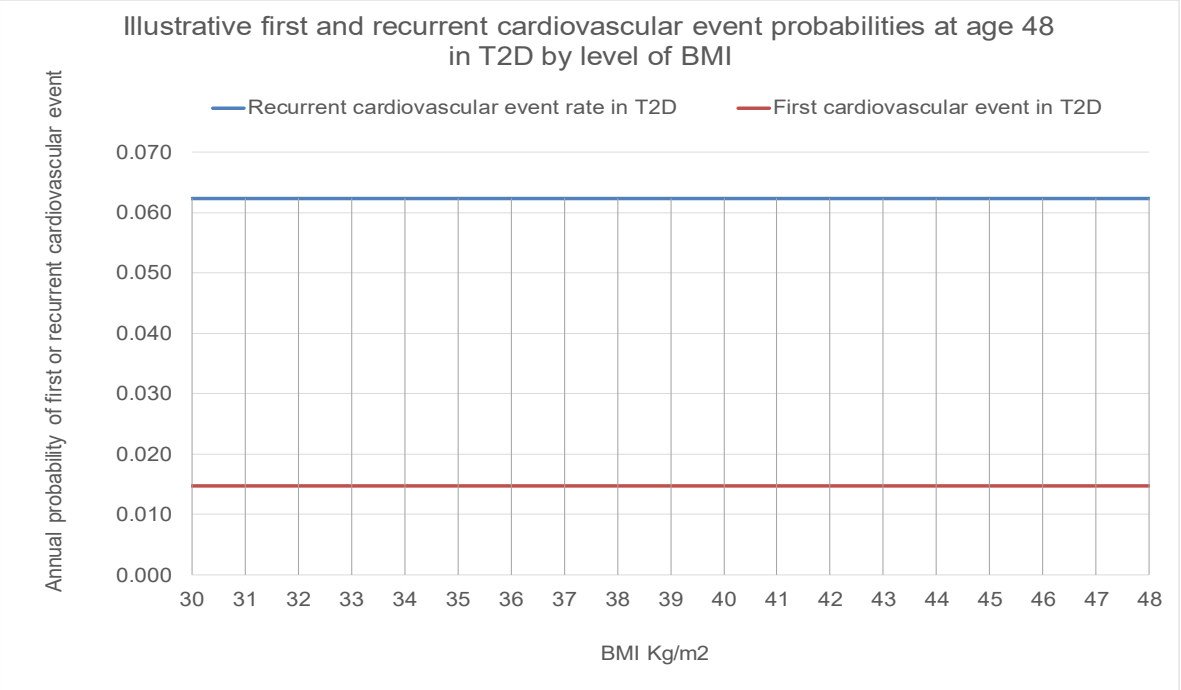
Figure 22: Annual probability of first and recurrent cardiovascular event in type 2 diabetes



Source: Qdiabetes 2016

Knee replacement

Knee replacement was considered an event in the model, to simplify the structure. Consequently, the associated disutility (applied once-off in the model when the event occurs) was multiplied by a factor of 3 to account for the time spent in a debilitating state prior to the knee replacement surgery. This assumption was validated with a clinical expert in the field of obesity (see Appendix O). A one-off cost was applied in the model, encompassing the cost of surgery. The cost of managing osteoarthritis before surgery (e.g. analgesics) was considered negligible and not accounted for in the model. Each knee replacement surgery was associated with a risk of death in the model (138).

The annual incidence of knee replacement surgeries in the reference BMI group (20-22.5 kg/m^2) for ages <65 years and ≥65 years was sourced from the study of Wendelboe et al., 2003, reporting figures of 0.053% and 0.12%, respectively (139). The study provided granular data on the association between BMI and incidence of knee surgeries by 2.5 BMI-unit steps for observed BMI levels between 17.50 and

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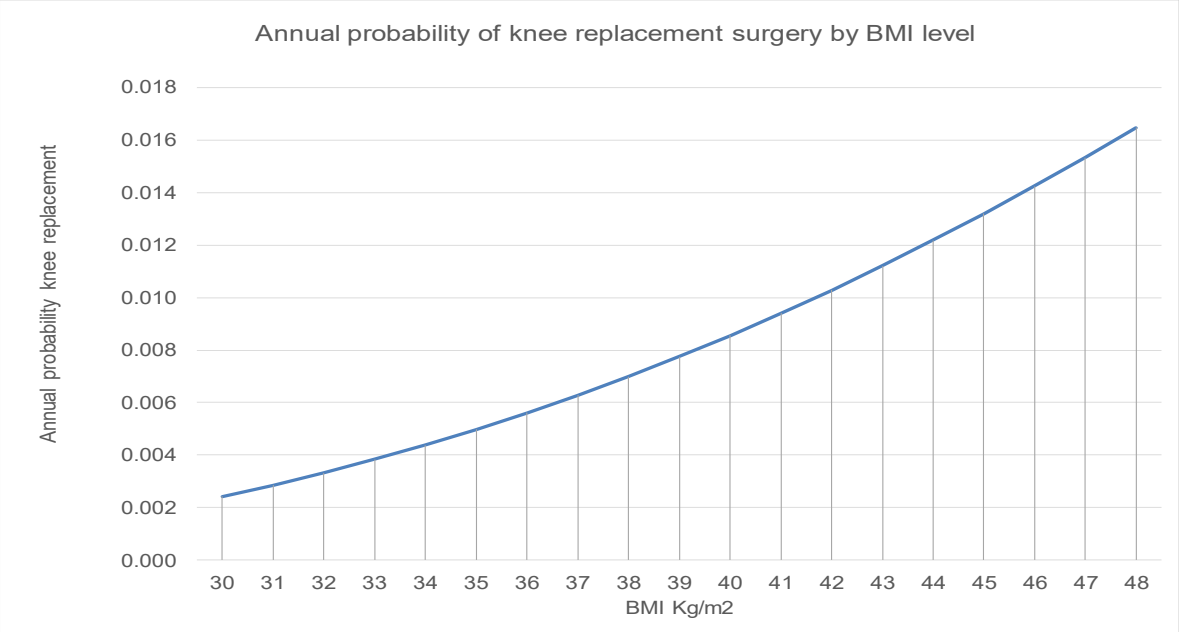
42.49 kg/m^2 was hence preferred to other studies available in the literature. To derive a continuous function of the BMI - risk of knee replacement, and to extrapolate the association beyond the observed 42.49 kg/m^2 BMI in the study, a second-order polynomial trend was fitted to the calculated probabilities. Separate trend lines were fitted for males and females aged 64 years or lower, and above 65 years. Figure 23 illustrates the incidence rate applied corresponding to an average age of the cohort of 48 years. The fitted polynomial trend functions are illustrated in Table 30.

Figure 23: Annual probability of knee replacement surgery by level of BMI



Source: Wendelboe *et al.,* 2003

Table 30: BMI-dependent risk functions for knee osteoarthritis

Patient group	BMI-dependent function for knee osteoarthritis
Males aged <65 years	0.00002 * 〖BMI〗^(2) - 0.00095 * BMI + 0.01149
Males aged ≥65 years	0.00005 * 〖BMI〗^(2) - 0.00213 * BMI + 0.02582
Females aged <65 years	0.00002 * 〖BMI〗^(2) - 0.00082 * BMI + 0.00847
Females aged ≥65 years	0.00005 * 〖BMI〗^(2) - 0.00185 *BMI + 0.01902

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Cancer (applied in scenario analyses)

Several studies and SLRs were identified reporting a measure of association between colon, post-menopausal breast and post-menopausal endometrial cancer with obesity (120). A SLR and meta-analysis was used to inform the association between post-menopausal breast and endometrial cancer (140). The authors found a positive association with a 5 kg/m^2 increase in BMI and post-menopausal breast cancer with a Relative Risk (RR) of 1.09 [1.04-1.14] 95%CI for European and Australian women, and a positive association with a 5 kg/m^2 increase in BMI and endometrial cancer with a RR of 3.04 [2.31-4.01] 95%CI for BMI levels greater than 28 kg/m^2. The baseline/reference incidence of colorectal cancer was sourced from a population-based study of the US National Institute of Health (NIH-AARP) Diet and Health Study (141) while the additional risk with increasing BMI was sourced from a meta-analysis of Schlesinger et al. who have shown an increase in colorectal cancer risk with 4% per each 5 kg increase in weight compared to the reference group. The baseline and hazard/relative ratios by BMI level reported in these studies were used to derive continuous functions for the risk of cancer occurrence by BMI.

Figure 24-26 illustrates the annual probability of each cancer type by BMI level at an average age of 48 years (weighted by the proportion of males and females in the modelled cohort).

In the model, the incidence of each cancer type was modelled according to probabilities described above. A cancer type specific mortality risk was applied in the year of cancer onset. Post onset, the proportion of the cohort moved into a generic health state encompassing all cancer types as a simplifying model assumption. A generic cost and HRQoL decrement were thereafter applied encompassing possible cancer recurrences and the costs and HRQoL associated with recurrences, as well as the additional mortality.

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Figure 24: Annual probability of post-menopausal breast cancer

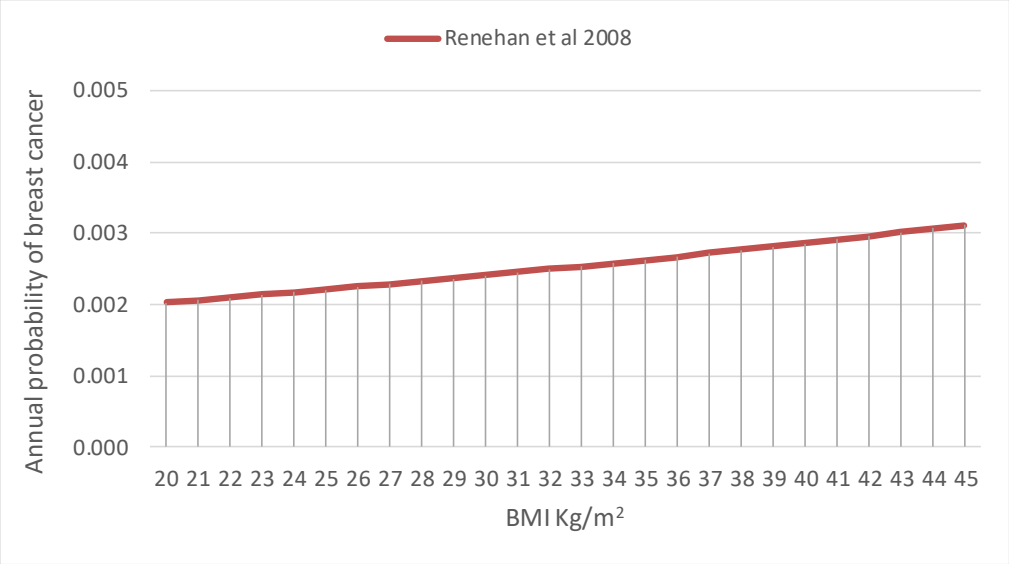

Figure 25: Annual probability of post-menopausal endometrial cancer

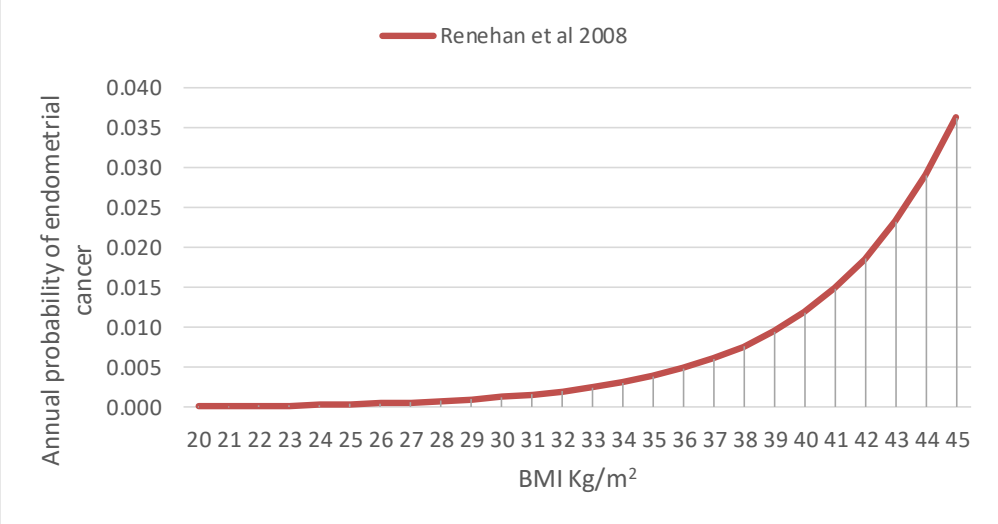

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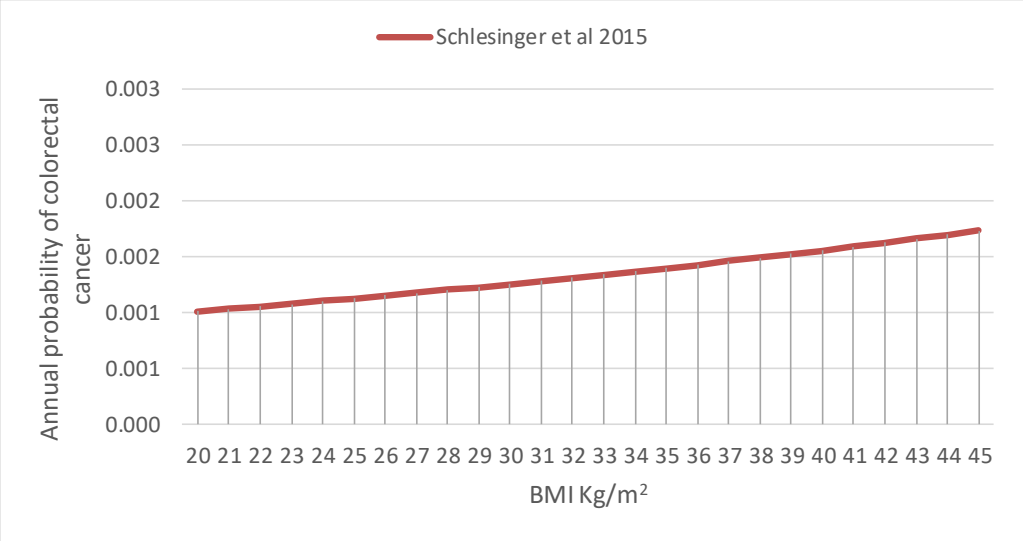
Figure 26: Annual probability of obesity-associated colorectal cancer



Mortality

Death in the model can be attributable to events and health states. For example, in each cycle, a proportion of the cohort will experience an MI; 30.48% of all MI events will be fatal; the proportion of the cohort experiencing a non-fatal MI event will have an increased risk of death in the years following the event. For this, the general population mortality (142) was multiplied with the RR of death post ACS (RR: 1.3 (143)). If a stroke event occurred following the non-fatal MI, 22.86% of stroke events were assumed to be fatal in the year they have occurred. In the cycles/years following a non-fatal stroke, the age and gender mortality were multiplied by a RR of 2.0, reflective of the additional mortality in years following both ACS and stroke events. Indeed Brammas et al. (2013) observed the 1-year mortality of MI complicated by ischaemic stroke to be almost twice as high when compared with MI without stroke: - 36.5% vs 18.3% without stroke (144). If the respective proportion of the cohort also developed type 2 diabetes, the RR of death post ACS and post stroke were multiplied with the age and gender-specific general population mortality plus the general population mortality attributable to type 2 diabetes sourced from UK life tables by selected cause of death (Appendix M). Event case-fatalities and adjustments to the general population mortality applied in the model are illustrated in Table 31 below.

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Table 31: Death probabilities of events and health states

Model parameter	Applied in year of disease onset	Source	Applied in years post onset*	Source
Bariatric surgery	Prob: 0. 07%	(145)	-	-
MI	Prob: 30.48%	(146)	RR: 1.30	(143)
Angina	Prob: 30.48%	(146)	RR: 1.30	(143)
Stroke	Prob: 22.86%	(146)	RR: 2.00	(144)
Knee replacement	Prob: 0.30%	(138, 147)	-	-

Table notes: (1) weighted average males 32% and females 30%; (2) weighted average males 17.1% and females 24.7%;. MI: myocardial infarction; prob: probability of event being fatal. RR: relative risk; *relative risks are applied to the age and gender-specific annual probabilities of mortality

In scenario analyses considering cancer, death probabilities in the year of cancer onset were cancer type specific. In the following years, a generic probability of cancer was applied (as a simplifying assumption and encompassing the risk of recurrent fatal cancers). This probability replaces the gender and age-adjusted UK general population mortality and is added to the annual probabilities of death in case of co-occurring type 2 diabetes, post ACS or post stroke states.

Table 32: Death probabilities of cancer states applied in scenario analysis

Model parameter	Applied in year of disease onset	Source	Applied in years post onset	Source
Colon cancer	Prob: 27.84%	(147)	Prob: 3.45%	(147)
Post-menopausal breast cancer	Prob: 4.08%	(147)		
Post-menopausal endometrial cancer	Prob: 10.20%	(147)		

Table 33 provides an overview of the sources applied to populate the risk equations for the obesity-related complications considered in the model, with those in bold indicating the sources applied in the base case.

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Table 33: Summary of all risk equations applied in the model

Obesity complications (bold indicates inclusion in base case)	Source for risk equation (bold indicates chosen source for base case and/or scenario analysis)	Justification for base case source
Risk of type 2 diabetes onset in NGT patients	**QDiabetes-2018 Model C (UK):** Hippisley-Cox J, Coupland C. Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study. BMJ. 2017;359. Alternative: Framingham Offspring Study: Wilson et al. Prediction of Incident Diabetes Mellitus in Middle-aged Adults: The Framingham Offspring Study, Archives of Internal Medicine 2007	The QDiabetes risk model was preferred as being the most validated risk score in a UK population, allowing 10 years prediction of risk including prediction of risk in patients with prediabetes (122).
Risk of type 2 diabetes onset in patients with prediabetes	**QDiabetes-2018 Model C (UK) adjusted to reflect a higher risk of diabetes by setting the HbA_{1c} parameter equal 42 mmol/mol (6 %-points) then held constant over time until diabetes development http://www.qdiabetes.org/index.php:** Hippisley-Cox J, Coupland C. Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study. BMJ. 2017;359. Alternative: Framingham Offspring Study adjusted to reflect a higher risk of diabetes by setting the FG 100-126 mg/dL parameter equal to 1 (parameter is 0 for normal glucose tolerance patients): Wilson et al. Prediction of Incident Diabetes Mellitus in Middle-aged Adults: The Framingham Offspring Study, Archives of Internal Medicine 2007	
Risk of CVD in primary prevention in NGT and prediabetic patients	**QRisk3 (UK) https://qrisk.org/:** Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017;357:j2099. Framingham Heart Study: D'Agostino, Vasan, Pencina, Wolf, Cobain, Massaro, Kannel. 'A General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study'. 2008;11:478-86.	The QRisk3 equation was used to predict the risk of first cardiovascular event in prediabetes and normal glucose tolerance states and was chosen because it contains UK cohort and as such is being used in UK.

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Obesity complications (bold indicates inclusion in base case)	Source for risk equation (bold indicates chosen source for base case and/or scenario analysis)	Justification for base case source
Risk of CVD in secondary prevention in NGT patients	**Framingham Recurrent Coronary Heart Disease (US):** D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H, Wilson PW, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham study. American heart journal. 2000;139(2 Pt 1):272-81.	The Framingham Recurring Coronary Heart Disease risk model was used to predict recurrent cardiovascular events (135).
Risk of CVD in primary prevention in patients with type 2 diabetes	**UKPDS82 (UK):** Hayes A, Leal J, Gray A, Holman R, Clarke P. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia. 2013;56(9):1925-33. Alternative 1: QRisk3: Hippisley-Cox et al. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017 Alternative 2: Swedish NDR: Cederholm J, Eeg-Olofsson, Eliasson B, Zethelius B, Nilsson PM, Gudbjörnsdottir S, Risk Prediction of Cardiovascular Disease in Type 2 Diabetes A risk equation from the Swedish National Diabetes Register, Diabetes Care. 2008 October; 31(10): 2038–2043	The UKPDS 82 risk model (outcome model 2) was used, as it is a UK study and able to predict both first and recurrent cardiovascular events after the onset of type 2 diabetes (136).
Risk of CVD in secondary prevention in patients with type 2 diabetes	**UKPDS82 (UK):** Hayes A, Leal J, Gray A, Holman R, Clarke P. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia. 2013;56(9):1925-33. Alternative: Framingham Recurrent Coronary Heart Disease (US): D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H, Wilson	The UKPDS 82 risk model (outcome model 2) was used, as it is a UK study and able to predict both first and recurrent cardiovascular events

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Obesity complications (bold indicates inclusion in base case)	Source for risk equation (bold indicates chosen source for base case and/or scenario analysis)	Justification for base case source
	PW, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham study. American heart journal. 2000;139(2 Pt 1):272-81.	after the onset of type 2 diabetes (136).
Risk of knee replacement	**Incidence in reference BMI group and per unit increase from calculated:** Wendelboe *et al.* Relationships between body mass indices and surgical replacements of knee and hip joints. Am J Prev Med. 2003 Nov;25(4):290-5.	
Obstructive sleep apnoea prevalence	**Prevalence by BMI level from the Sleep Heart Study:** Young, T., et al. 2002. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Archives of internal medicine, 162(8)	
Risk of colorectal cancer	*Incidence in reference BMI group:* **US National Institutes of Health (NIH) AARP Diet and Health Study:** Adams *et al.* Body mass and colorectal cancer risk in the NIH-AARP cohort. Am J Epidemiol. 2007 Jul 1;166(1):36-45. *Risk adjustment by BMI level:* **Meta-analysis:** Schlesinger, S., Lieb, W., Koch, M., Fedirko, V., Dahm, C.C., Pischon, T., Nöthlings, U., Boeing, H. and Aleksandrova, K., 2015. Body weight gain and risk of colorectal cancer: a systematic review and meta-analysis of observational studies. Obesity Reviews, 16(7), pp.607-619 Alternative: Incidence in reference BMI group AND risk adjustment by BMI: US National Institutes of Health (NIH) AARP Diet and Health Study: Adams *et al.* Body mass and colorectal cancer risk in the NIH-AARP cohort. Am J Epidemiol. 2007 Jul 1;166(1):36-45.	Meta-analyses and systematic review were preferred over individual studies.
Risk of endometrial cancer in post-menopausal women	**Incidence in the reference BMI group and per unit BMI increase calculated from:** Renehan et al. Body mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. The Lancet, 2008; 371(9612), pp.569-578 Alternative: Million Women Study: Yang TY, Cairns BJ, Allen N, Sweetland S, Reeves GK, Beral V; Million Women Study, Post-menopausal	Meta-analyses and systematic review were preferred over individual studies.

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Obesity complications (bold indicates inclusion in base case)	Source for risk equation (bold indicates chosen source for base case and/or scenario analysis)	Justification for base case source
	endometrial cancer risk and body size in early life and middle age: prospective cohort study, Br J Cancer. 2012 Jun 26;107(1):169-75.	
Risk of breast cancer in post-menopausal women	**Incidence in the reference BMI group and per unit increase calculated from:** Renehan *et al.* Body mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. The Lancet, 2008; 371(9612), pp.569-578 Alternative: Ahn J, Schatzkin A, Lacey JV Jr, Albanes D, Ballard-Barbash R, Adams KF, Kipnis V, Mouw T, Hollenbeck AR, Leitzmann MF Adiposity, adult weight change, and post-menopausal breast cancer risk Arch Intern Med. 2007 Oct 22;167(19):2091-102. '- Study conducted on 99,039 post-menopausal women in the US National Institutes of Health–AARP Diet and Health Study	Meta-analyses and systematic review were preferred over individual studies.

NGT: normal glucose tolerance; CVD: cardiovascular disease

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B.3.4 Measurement and valuation of health effects

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

As mentioned in Section B.2.6.11, HRQoL was assessed in some participants enrolled in the SCALE obesity and prediabetes trial by means of the obesity-specific IWQoL-Lite questionnaire, as well as the SF-36 health survey. A study by Kolotkin *et al*., 2017 (17) reported on the improvements in HRQoL over three years with liraglutide 3.0mg compared to diet and exercise. This study found that liraglutide 3.0mg, plus diet and exercise, was shown to be associated with long-term improvements in HRQoL versus diet and exercise.

Although mapping from SF-36 to EQ-5D was carried out, Kolotkin *et al*., 2017 it did not incorporate the stopping rule and the results could not be used across the full time horizon of the model. For these reasons, trial-specific utility data was not applied in this analysis, and therefore alternative literature-based sources for utilities were applied.

B.3.4.2 Mapping

As stated above, no mapping was carried out for the purposes of informing health state utilities for the current analysis.

B.3.4.3 Health-related quality of life studies

A SLR was conducted to identify relevant HRQoL data for obese patients with BMI ≥35 kg/m^2 from published sources to inform the health state utilities applied within the economic model. Data presented in economic evaluations, utility elicitation studies, published models, randomised controlled trials, validation studies, mapped values studies and technology assessments were eligible for inclusion in the review.

Searches were conducted and retrieved 901 records originally, 795 records after removing duplications. After these studies were assessed for relevance, 126 records were eligible for review. Forty-two records were retrieved for data extraction, which covered 26 individual studies. Findings from the SLR demonstrated the lack of comprehensive published utility data. The findings of the SLR were not used in the Company evidence submission for liraglutide 3.0mg in the management of overweight and obesity (ID740)

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base case analysis. HRQoL inputs used in the base case were instead based on a large UK population-based study that has demonstrated a robust association between BMI and utility, which is described in more detail in section B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis. Detailed information on the HRQoL literature review and included studies is provided in Appendix H.

B.3.4.4 Adverse events

Pi-Sunyer *et al*., 2015 reported AEs from the SCALE obesity and prediabetes trial that occurred in greater than or equal to 5% of the patients in each arm, i.e. common AEs, and those which were classed as serious AEs (SAEs) and occurred in greater than or equal to 0.2% of the patients in each arm (131). Common AEs reported included gastrointestinal events and hypoglycaemia (see Section B.2.10), the latter of which was routinely recorded, irrespective of symptoms, as part of biochemical measurements taken during the oral glucose tolerance test and/or visits where fasting plasma glucose was measured. Common AEs were transient and considered to be mild in nature, thus having a minimal impact on patient quality of life and therefore not considered in the analysis.

As adverse reactions were not considered in this analysis, no amendments to HRQoL were made based on this.

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

Baseline utility values in the model were derived from an analysis of the 2003 Health Survey for England data, a large UK population-based study (16) and were dependent on age and BMI level. The baseline utility values were then adjusted for HRQoL decrements associated with obesity-related complications e.g. type 2 diabetes, MI, stroke etc. Health state and event utility decrements were then applied to the BMI and age-dependent baseline utilities.

Derivation of baseline, BMI and age-dependent utilities

Baseline utility values were estimated using a two-step process:

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1. Elicitation of BMI-dependent utility values
2. Application of age-specific coefficients.

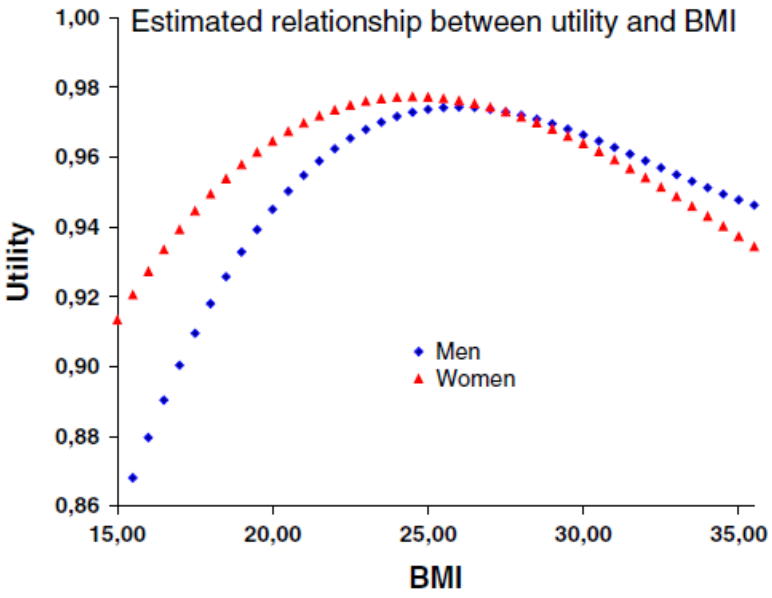
Søltoft *et al*., 2009 (16), analysed EQ-5D responses of 14,416 UK individuals aged ≥18 years in the 2003 Health Survey for England in relation to BMI utilising multiple linear regressions. The authors presented an adjusted analysis by the presence of obesity complications (type 2 diabetes, heart, respiratory, musculoskeletal problems and cancer) and age; thus, the baseline, age and BMI-dependent utilities could be applied in the model free of additional effects of obesity complications.

This is important for the economic model for two reasons:

1) it allows a separation of the effects of complications from the pure effect of increased weight; and
2) it permits HRQoL decrement to be specific to each obesity complication..

Figure 27 below illustrates the relationship between BMI and EQ-5D scores after controlling for confounding factors in Søltoft *et al*., 2009.

Figure 27: Estimated relationship between utility and BMI (Søltoft *et al*., 2009)



Source: Søltoft *et al.,* 2009 (16)

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Søltoft *et al.*, 2009 presented the coefficients for a third-order polynomial function on EQ-5D utilities and BMI. However, the results of the regression analysis were presented with four decimals points and, upon implementation in the model, it was noted that the third-order polynomial function could not be estimated with precision using these coefficients (i.e. no sufficient decimals were presented for the coefficients of BMI^3). Thus, a re-estimation of the polynomial functions was needed based on digitized values from the figure above. The re-estimated coefficients are shown in the table below, next to the ones presented by Søltoft *et al.*, 2009. The re-estimated EQ-5D utilities are illustrated in Figure 28 below.

Table 34: Re-estimated polynomial function for EQ-5D utilities over BMI ranges between 15-35 kg/m^2

Parameter	Re-estimated coefficient for males	Coefficient reported by Søltoft et al.	Re-estimated coefficient for females	Coefficient reported by Søltoft et al.
BMI^3	0.00003	0.0000	0.00002	0.0000
BMI^2	-0.0032	-0.0032	-0.0018	-0.0018
BMI	0.0986	0.0990	0.0570	0.0572
Constant	-0.0206	-0.0228	0.4018	0.4010

Note: Squared and cubed terms reflect the non-linearity of BMI disutility

An important limitation of this study was that EQ-5D utilities were available up to a BMI level of 35 kg/m^2. Beyond this level, a logarithmic extrapolation of EQ-5D utilities presented by Søltoft *et al.*, 2009 was conducted, as a function of BMI. The estimated coefficients of the logarithmic function are shown in the table below, separately for males and females.

Table 35: Coefficients logarithmic function for EQ-5D utilities corresponding to BMI levels above 35 kg/m^2

Parameter	Males	Females
BMI	-0.105431	-0.147297
Constant	1.323834	1.462846

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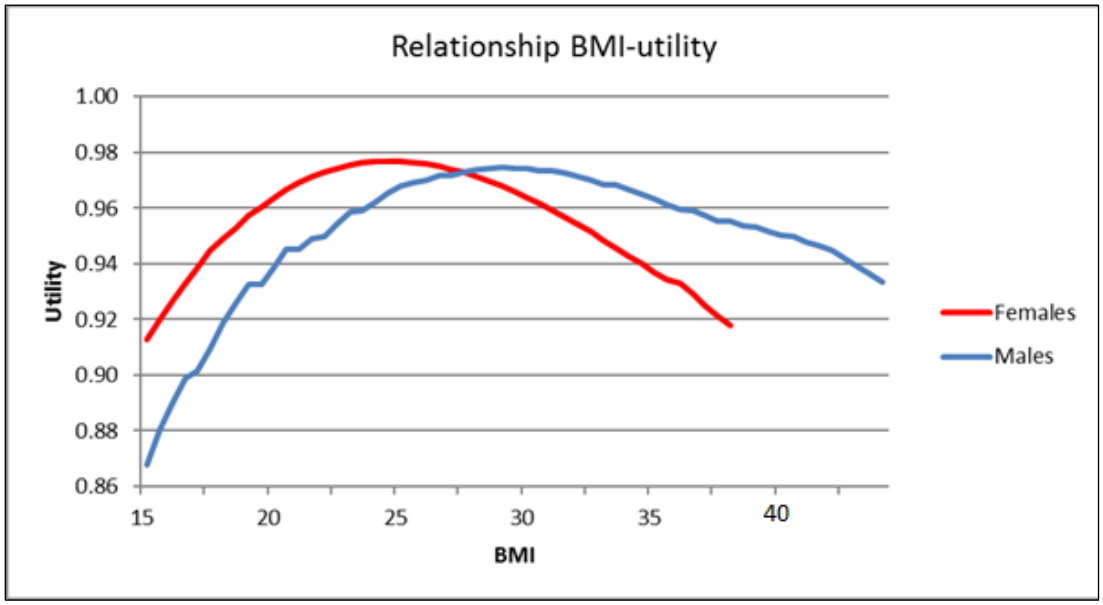
Figure 28: Re-estimated utility curves



Finally, BMI-dependent utility values obtained based on the Søltoft *et al*., 2009 polynomial model were adjusted by age using age-specific HRQoL coefficients reported in the same publication. The coefficients are reported in Table 36.

Table 36: Coefficients to adjust BMI-dependent baseline utility as a function of age from Søltoft *et al*., 2009

Age	Derived coefficient by age, men	Derived coefficient by age, women
18–24	0.0287	0.0055
25-34	0	0
35–44	-0.0028	-0.0213
45–54	-0.0081	-0.0336
55–64	-0.043	-0.0425
65–74	-0.0223	-0.0619
≥75	-0.0565	-0.0754

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Derivation of health state utility values

HRQoL data is included in the model in the form of disutilities. Table 37 reports the disutilities applied to the baseline utility, as reported above, to derive the HRQoL of the cohort given possible complications.

In addition to short term decrements associated with acute events, long-term absolute HRQoL decrements associated with each obesity-related complication are considered in the model (Table 37). HRQoL decrements are derived from the literature and are subtracted from age, gender and BMI-dependent baseline utility values at each cycle to derive health state utility values. Long-term utility decrements associated with obesity-related complications adjust baseline utility for all future cycles, whereas short term utility decrements associated with acute events apply in the cycle in which the event occurs. To account for HRQoL impact associated with severe musculoskeletal disorders, the model includes a disutility applied in the year a knee replacement surgery occurs. The disutility is applied once, to the event, and is multiplied with a factor of three to account for three years of living with a chronic, debilitating condition prior to surgery.

Table 37: HRQoL decrements applied to baseline utility to derive health state utility values

Health state disutility	Utility decrement	95% confidence interval	Reference	Justification
Type 2 diabetes	-0.037	N/A	Søltoft et al., 2009. Table 3 p. 1296 (16). Decrements provided by sex were weighted by the proportion of males and females in the modelled cohort.	Based on the association between type 2 diabetes and HRQoL
Post ACS	-0.037	-0.087 to 0.014	Sullivan et al., 2011 'Catalogue of EQ-5D Scores for the United Kingdom'. Supplementary data. ICD-9 412 old myocardial infarct. (128)	Post ACS HRQoL is based on the ICD-9 code for the Old myocardial infarction
Post stroke	-0.035	-0.077 to 0.007	Sullivan et al., 2011 'Catalogue of EQ-5D Scores for the United	Post stroke HRQoL is based on the ICD-9 code for the

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Health state disutility	Utility decrement	95% confidence interval	Reference	Justification
			Kingdom'. Supplementary data. ICD-9 433 precerebral occlusion. (128)	Occlusion and stenosis of precerebral arteries
Cancer	-0.078	N/A	Søltoft et al., 2009. Table 3 p. 1296 (16) Decrements provided by sex were weighted by the proportion of males and females in the modelled cohort.	Based on the association between cancer and HRQoL

*excluding acute disutility
ACS, acute coronary syndrome; N/A, not available

Table 38: HRQoL decrements applied to baseline utility to derive event utility values

Event disutility	Utility decrement	95% confidence interval	Reference	Justification
Bariatric surgery	-0.184	N/A	Campbell *et al.,* 2010. Table 1. p. 176 (129), and Jansen and Szende. 2014, Table 3.6 p. 30 (148)	Average of initial procedure-related decrement for laparoscopic adjustable gastric banding and laparoscopic Roux-en-Y gastric bypass, adjusted by UK population norm.
Knee replacement	-0.194	N/A	Søltoft *et al.,* 2009. Table 3 p. 1296 (16) Decrements provided by sex were weighted by the proportion of males and females in the modelled cohort.	Based on the association between musculoskeletal problems and HRQoL
ACS	-0.063	-0.088 to -0.037	Sullivan *et al.,* 2011. 'Catalogue of EQ-5D Scores for the United Kingdom'. Supplementary data. ICD-9 410 Acute Myocardial Infarct (128)	ACS HRQoL is based on the ICD-9 code for the Acute myocardial infarction

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Event disutility	Utility decrement	95% confidence interval	Reference	Justification
Stroke	-0.117	-0.141 to -0.093	Sullivan *et al.,* 2011. 'Catalogue of EQ-5D Scores for the United Kingdom'. Supplementary data. ICD-9 436 Cva (128)	Stroke HRQoL is based on the ICD-9 code for the Acute, but ill-defined, cerebrovascular disease
TIA	-0.033	-0.077 to 0.011	Sullivan *et al.,* 2011. 'Catalogue of EQ-5D Scores for the United Kingdom'. Supplementary data. ICD-9 435 Transient Cereb Ischemia (128)	TIA HRQoL is based on the ICD-9 code for the Transient cerebral ischemia
Obstructive sleep apnoea	-0.038	N/A	Søltoft *et al.,* 2009. Table 3. Assumed equal to respiratory problems p. 1296 (16). Decrements provided by sex were weighted by the proportion of males and females in the modelled cohort.	Based on the association between obesity and respiratory problems (which were assumed to reflect obstructive sleep apnoea)

*excluding acute disutility
ACS: acute coronary syndrome; HRQoL: Health-Related Quality of Life; N/A: not available; TIA: transient ischaemic attack

When health states combine two or more obesity complications, the HRQoL decrement associated with every single complication is summed together and the total is then subtracted from the baseline utility. For example, in the health state 'type 2 diabetes + Post ACS', the total HRQoL decrement subtracted from the baseline utility is equal to the sum of the HRQoL decrement for type 2 diabetes and the HRQoL decrement for post ACS. This is a limitation of the current model since it has been shown in the literature that the effect of multiple comorbidities on the HRQoL of a patient is less than the sum of the HRQoL decrement associated with each comorbidity, however Gough *et al*., 2009 (149) concluded that the HRQoL decrements associated with type 2 diabetes and obesity showed no significant

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interaction and thus could be assumed to be additive. Nevertheless, HRQoL decrements associated with each potential combination of obesity complications included in the model are not reported in the literature. The current approach was therefore seen as the most appropriate solution to account for the HRQoL impact of obesity complications in a transparent way without underestimating the associated severe humanistic burden.

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

Appendix I outlines the SLR to search for studies reporting cost and healthcare resource data for the treatment of patients with obesity in the UK. Three studies located in the literature search were from the UK perspective (150-152). Information extracted was not found to be relevant for the current economic analysis as they did not focus on the patient population or treatments identified as relevant to the decision problem, and thus were not utilised (see Appendix G and I).

Cost and healthcare resource use in this analysis

The model considers the following costs:

- Obesity treatment costs;
- Other pharmacy costs (i.e. the cost of blood pressure treatments and type 2 diabetes medication);
- Long-term costs of obesity-related complications (health state costs);
- Acute costs of obesity-related complications (event costs).

B.3.5.1 Intervention and comparators' costs and resource use

Treatment costs included in the model consist of drug acquisition costs and obesity monitoring costs. The drug acquisition cost of treatment with liraglutide 3.0mg is included in the model based on dose as per product marketing authorisation and a PAS price. Liraglutide 3.0mg treatment involves a titration phase and a maintenance phase. The titration phase starts at treatment initiation and lasts for four weeks,

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during which the dose is increased each week, until maintenance dose of 3.0mg per day is achieved. The applied dosage regimen is shown in Table 39.

Table 39: Liraglutide dosing regimen

	Dose
Titration phase	Week 1: 0.6mg/day Week 2: 1.2mg/day Week 3: 1.8mg/day Week 4: 2.4mg/day
Maintenance phase	From week 5 onwards: 3.0mg/day

The total liraglutide 3.0mg treatment cost per cycle is calculated by multiplying the cost per milligram by the dose in milligram required in a given cycle (3-month cycles in the first year and annual cycles from the second year onwards), to which the cost of needles is added. In the liraglutide 3.0mg arm, the first cycle of the analysis accounts for the drug cost of 16 weeks (4 weeks titration and 12 weeks of maintenance dose) of treatment, to accurately capture the drug acquisition costs of liraglutide 3.0mg.

The cost of obesity monitoring is defined as the cost of all routine visits, examinations and diet and exercise advice which is required for the management of an adult patient with obesity. The obesity monitoring cost is included per year; however, it is readjusted to fit the 3-month cycles in the first year of the simulation. The cost of obesity monitoring comprises specialist visits, assumed to correspond to specialist tier 3 service visits, nurse visits and a blood test. The cost of obesity monitoring is applied to both the comparator and intervention.

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Table 40: Obesity treatment costs

	Cost (£)	Comment	Source
Liraglutide 3.0mg	£[redacted]	Cost per pack of 5 pens at 18mg/3ml	Novo Nordisk, data on file (153)
Diet & exercise	£130.83	Annual non-pharmacological cost comprising monitoring visits (specialist and nurse visits) and a blood test.	Curtis and Burns, 2017, Ara *et al*., 2012 and NHS Reference Costs 2017/18 (101, 119, 154)
Cost of needles	£5.94	Cost per pack. 100 needles.	MIMS (155)

Other pharmacy costs are accounted for in the model in the form of the annual cost of blood pressure treatment and the annual cost of treating type 2 diabetes. A summary of other pharmacy costs is included in Table 41 .

Table 41: Other pharmacy costs

	Cost (£)	Comment	Source
Annual blood pressure treatment	£33.72	Simple average annual cost of treatment with enalapril 5mg, lisinopril 10mg, perindopril 4mg and ramipril 2.5mg.	British National Formulary (156)
Annual cost of type 2 diabetes medication	£316.76	Combined cost of type 1 and type 2 diabetes, assuming the cost of treatment is similar.	Calculation based on NHS Digital (157)

B.3.5.2 Health state unit costs and resource use

Separate health state costs are applied in the model for the first year in a given health state and subsequent years in that health state. Where a health state is entered following an event, e.g. stroke, the health state cost does not include the cost of the event, which is accounted for separately.

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Annual cost of obesity-related complications includes costs associated with monitoring and treating a given disease and are used in the model to define health states costs. The only exception is type 2 diabetes, where the cost of pharmacological treatment is taken into account separately. In addition, states encompassing type 2 diabetes are attributed to a higher cost to account for the prevalence of microvascular complications.

Given the complexity of the model, cancer health states (progression free survival, partial or complete relapse, local or distal metastases *et cetera*) are not considered in detail. To account for possible future cancer recurrence, an average follow-up cost of cancer is included in the model.

The costs of health states including multiple obesity complications are calculated by summing the costs associated with each condition. Health state costs for the first and subsequent years are presented in Table 42.

Table 42: Cost of obesity-related complications

Obesity-related complication	Annual cost (£)	Comment	Source	Justification
Type 2 diabetes microvascular complications costs	£468	The cost associated with microvascular complications e.g. eye complications, nephropathy and diabetic foot. It does not include the cost of medication, which is taken into account separately.	Calculation based on Morgan *et al.*, 2010 (158, 159)	Mean cost of microvascular complications in type 2 diabetes per person per year.
Prediabetes	£55	Increased monitoring associated with higher than normal HbA_{1c}	NHS England (160)	Average cost of the National Diabetes Prevention Programme per participant per year
Colon cancer, 1st year	£19,404	Including treatment, monitoring, hospitalisation	Laudicella *et al.*, 2016 (161)	Average incident cost per colon cancer patient

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Obesity-related complication	Annual cost (£)	Comment	Source	Justification
Post-menopausal breast cancer, 1st year	£12,503	Including treatment, monitoring, hospitalisation	Laudicella *et al*., 2016 (161)	Average incident cost per breast cancer patient
Post-menopausal endometrial cancer, 1st year	£4,839	Including treatment, monitoring, hospitalisation	Pennington *et al*., 2016 (162)	Mean annual cost of treatment for endometrial cancer
Cancer treatment follow-up years	£2,512	The same annual follow-up cost was assumed for all types of cancer included in the analysis and accounts for the fact that cancer follow-up cost will decrease with time. Applied from 2nd year from event onwards.	Laudicella *et al*., 2016 and Pennington *et al*., 2016 (161, 162)	The average of follow-up costs calculated for colon, post-menopausal breast and post-menopausal endometrial cancers
Angina, 1st year	£573	Excluding acute event cost. Inflated from 2004 prices.	Ward *et al*., 2007 (163)	The average monitoring and medication costs for patients with angina in line with Ward *et al*., 2007
Myocardial infarction (MI), 1st year	£3,523	Excluding acute event cost. Inflated from 2004 prices.	Ward *et al*., 2007 (163)	Average health state costs estimated by aggregating the resources consumed by each patient in line with Ward *et al*., 2007
Stroke, 1st year	£6,120	Excluding acute event cost. Inflated from 2004 prices.	Ward *et al*., 2007 (163)	Based on the weighted distribution of strokes and costs associated with mild, moderate and severe stroke in line with Ward *et al*., 2007
TIA, 1st year	£1,385	Excluding acute event cost. Inflated from 2004 prices.	Ward *et al*., 2007 (163)	Monitoring and medication costs patients receive following the event in line with Ward *et al*., 2007

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Obesity-related complication	Annual cost (£)	Comment	Source	Justification
ACS, from 2nd year from event onwards	£223	Inflated from 2004 prices.	Ward *et al*., 2007 (163)	Assumed to be average of MI and angina
Stroke, from 2nd year from event onwards	£2,815	Inflated from 2004 prices.	Ward *et al*., 2007 (163)	Based on the weighted distribution of strokes and costs associated with mild, moderate and severe stroke in in line with Ward *et al*., 2007
Sleep apnoea	£869	Cost of treated sleep apnoea applied to the proportion of the cohort with sleep apnoea in each year	National schedule of reference costs 2017/18 (154)	Assumed to correspond to sleep disorders affecting breathing. Weighted average of HRG codes DZ18.

MI: Myocardial infarction; TIA: Transient Ischaemic Attack

Acute event unit costs

The model includes the one-off cost of obesity-related acute events: angina, MI, stroke, TIA, knee replacement and bariatric surgery. The cost of obesity-related acute events represents the economic burden associated with managing the patient at the moment when the acute event occurs. In the case of knee replacement, the cost associated with pre-surgery visits/examinations and post-surgery follow-up is also applied. For each acute event, the cost of fatal and non-fatal events is accounted for separately in the model.

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Table 43: Cost of obesity-related acute events

Acute episode	Cost (£)	Comment	Source
Angina, fatal and non-fatal	£1,466	Cost of managing and treating a fatal acute angina event. This includes hospitalisation. Assumed equal to non-fatal angina.	National schedule of reference costs 2017/18 (154)
MI, fatal and non-fatal	£2,265	Cost of managing and treating a fatal MI. This includes hospitalisation. Assumed equal to non-fatal MI.	National schedule of reference costs 2017/18 (154)
Stroke, fatal and non-fatal	£4,351	Cost of managing and treating a fatal stroke. This includes hospitalisation. Assumed equal to non-fatal stroke.	National schedule of reference costs 2017/18 (154)
TIA	£1,945	Cost of managing and treating a TIA. This includes hospitalisation.	National schedule of reference costs 2017/18 (154)
Knee replacement, fatal and non-fatal	£6,251	Average cost of pre-surgery visit/examination, surgical intervention and post-surgery follow-up. For the cohort dying, the cost of pulmonary embolism can be used as a proxy for fatal knee replacement. Assumed equal to non-fatal knee replacement.	National schedule of reference costs 2017/18 (154)

MI: Myocardial infarction; TIA: Transient Ischaemic Attack

For bariatric surgery, the average procedure cost is calculated as the weighted average cost of the three types of procedure: gastric bypass (50.69%), laparoscopic banding (17.85%) and sleeve gastrectomy (31.46%), based on the proportion of each type of surgery in the model, calculated based on the NHS Reference Costs 2017/18 and shown in Appendix L (154). As a known and described complication of bariatric surgical procedures (164), the cost of leaks is used as a proxy for bariatric surgery related complications (130) and is included in the model as an average across all patients, i.e., already weighted by the incidence of complications.

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Table 44: Cost of bariatric surgery

Costs	Cost (£)	Comment	Source
Preoperative management	£1,024	Cost of required management of patients before bariatric surgery, including: visits, examinations and other interventions	Gulliford *et al*. 2017. Table 1. Preoperative weight management. Tier 3 weight management program (130)
Gastric bypass procedure	£5,184	Total HRGs	National schedule of reference costs 2017/2018 (154)
Laparoscopic banding procedure	£3,076	Total HRGs	National schedule of reference costs 2017/2018 (154)
Sleeve gastrectomy procedure	£4,823	Total HRGs	National schedule of reference costs 2017/2018 (154)
Post-operative follow-up	£875	Cost of post-operative visits and examinations	Gulliford *et al*. 2017. Table 1. Post-operative review (130)
Surgery related complications	£3,158	Cost of leaks weighted by the incidence. Converted to GBP and inflated from 2015 prices	Borisenko *et al*., 2018 (165)
Total cost of bariatric surgery	£9,753	Sum of preoperative management, procedure, post-operative follow-up and complication costs	Calculation

HRG: Healthcare Resource Group

B.3.5.3 Adverse reaction unit costs and resource use

As explained in Section B.3.4.4 Adverse events, AEs were not included in the analysis.

B.3.5.4 Miscellaneous unit costs and resource use

Not applicable.

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B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

Table 45: Summary of baseline cohort characteristics applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: 95% CI (distribution)
Age	48.2	47.42 to 48.98 (gamma)
BMI (kg/m^2)	41.7	41.33 to 42.07 (gamma)
Height (m)	1.66	1.65 to 1.67 (gamma)
Systolic blood pressure (mmHg)	127.2	126.26 to 128.14 (gamma)
Total cholesterol (mg/dL)	200.6	198.02 to 203.18 (gamma)
HDL cholesterol (mg/dL)	48.7	47.79 to 49.61 (gamma)
Average HbA_{1c} from type 2 diabetes onset (%-points)	7.5	6.5 to 8.5 (gamma)
Triglyceride level ≥150 mg/dL (%)	46.0	42.6 to 49.5 (beta)
Smokers (%)	15.0	12.6 to 17.6 (beta)
Females (%)	75.8	72.8 to 78.7 (beta)
Patients on lipid lowering drugs (%)	17.0	13.7 to 20.6 (beta)
Patients on antihypertensive medication (%)	45.3	45.3 to 45.3 (beta)
Patients with prediabetes (%)	100.0	No variation

See Section B.3.3.1 Parameters relating to baseline cohort characteristics
HDL: high-density lipoprotein

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Table 46: Summary of epidemiological inputs applied in the economic model

Variable	Value		Measurement of uncertainty and distribution: 95% CI (distribution)		Reference to section in submission
	Liraglutide 3.0mg	Diet & exercise	Liraglutide 3.0mg	Diet & exercise	
Natural weight increases per year (kg)	0.46		0.35 to 0.58 (gamma)		See section B.3.3.3 Disease pathway post treatment
Maximum age until which weight increases (years)	68		66 to 70 (gamma)		
Weight loss at 6 months (%)	-9.96	-2.43	-10.41 to -9.51 (normal)	-3.00 to -1.86 (normal)	See section B.3.3.2 Parameters relating to treatment efficacy and safety
Weight loss at 1 year (%)	-10.91	-2.48	-11.55 to -10.27 (normal)	-3.21 to -1.75 (normal)	
Weight loss at 2 years (%)	-9.46	-2.07	-10.20 to -8.72 (normal)	-2.85 to -1.29 (normal)	
Weight loss at 3 years[a] (%)	-8.02	-1.65	-8.83 to -7.21 (normal)	-2.46 to -0.84 (normal)	
Change in SBP at 6 months (mmHg)	-6.22	-1.70	-7.43 to -5.01 (normal)	-3.02 to -0.38 (normal)	
Change in SBP at 1 year (mmHg)	-7.58	-1.76	-8.71 to -6.45 (normal)	-3.06 to -0.46 (normal)	
Change in SBP at 2 years (mmHg)	-6.21	-1.72	-7.45 to -4.97 (normal)	-3.05 to -0.39 (normal)	
Change in SBP at 3 years[a] (mmHg)	-4.08	-1.09	-5.30 to -2.86 (normal)	-2.48 to 0.30 (normal)	
Change in total cholesterol at 6 months (mg/dL)	-6.80	-3.85	-9.69 to -3.91 (normal)	-7.20 to -0.50 (normal)	
Change in total cholesterol at 1 year (mg/dL)	-3.84	-6.10	-6.74 to -0.94 (normal)	-9.51 to -2.69 (normal)	
Change in total cholesterol at 2 years (mg/dL)	-6.41	-7.01	-9.56 to -3.26 (normal)	-10.84 to -3.18 (normal)	

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Variable	Value		Measurement of uncertainty and distribution: 95% CI (distribution)		Reference to section in submission
	Liraglutide 3.0mg	Diet & exercise	Liraglutide 3.0mg	Diet & exercise	
Change in total cholesterol at 3 years[a] (mg/dL)	-4.49	-4.15	-7.54 to -1.44 (normal)	-7.80 to -0.50 (normal)	
Change in HDL cholesterol at 6 months (mg/dL)	0.88	0.20	0.15 to 1.61 (normal)	-0.69 to 1.09 (normal)	
Change in HDL cholesterol at 1 year (mg/dL)	2.80	0.80	1.99 to 3.61 (normal)	-0.18 to 1.78 (normal)	
Change in HDL cholesterol at 2 years (mg/dL)	3.53	1.52	2.65 to 4.41 (normal)	0.49 to 2.55 (normal)	
Change in HDL cholesterol at 3 years[a] (mg/dL)	4.42	2.22	3.41 to 5.43 (normal)	1.05 to 3.39 (normal)	
Patients reverting from prediabetes to normal glucose tolerance (%)	82.80	40.74	79.09 to 86.23 (beta)	34.95 to 46.66 (beta)	
Proportion of patients not achieving stopping rule criteria following 12 weeks on maintenance dose	0.33	0.76	0.29 to 0.37 (beta)	0.71 to 0.81 (beta)	
Treatment duration (years)	2.0	2.0	Variability assessed in a scenario analysis		See section B.3.2.3 Model structure

[a] These values were applied in sensitivity analyses, where treatment duration equals 3 years
HDL: high-density lipoprotein; SBP: systolic blood pressure

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Table 47: Summary of epidemiological inputs applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Proportion CVD events which are MI	0.331	0.331 to 0.331 (Dirichlet)	See section B.3.3.3 Disease pathway post treatment
Case fatality MI /death within event year	0.305	0.167 to 0.463 (beta)	
Proportion CVD events which are angina	0.402	0.402 to 0.402 (Dirichlet)	
Case fatality angina /death within event year	0.305	0.167 to 0.463 (beta)	
Proportion CVD events which are stroke	0.267	0.267 to 0.267 (Dirichlet)	
Case fatality stroke /death within event year	0.229	0.127 to 0.350 (beta)	
Proportion of strokes events which are TIA	0.219	0.122 to 0.334 (beta)	
Case fatality knee replacement	0.003	0.002 to 0.005 (beta)	
Colon cancer fatality (year 1)	0.278	0.153 to 0.424 (beta)	
Breast cancer fatality (year 1)	0.041	0.023 to 0.063 (beta)	
Endometrial cancer fatality (year 1)	0.102	0.058 to 0.157 (beta)	
Cancer fatality (year 2+)	0.034	0.025 to 0.067 (beta)	
Relative risk of death after ACS	1.300	0.98 to 1.63 (gamma)	
Relative risk of death after stroke	2.000	1.50 to 2.50 (gamma)	

ACS: Acute Coronary Syndrome; CVD: Cardiovascular Disease; MI: Myocardial Infarction; TIA: Transient Ischaemic Attack

Table 48: Summary of cost input data applied in the economic model

Variable	Cost (£)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Liraglutide - Price per pack (prefilled pens of 18mg/3ml)	£[redacted]	Not applicable	See section B.3.5.1 Intervention and comparators' costs and resource use
Cost needles per annum	£22	Not applicable	
Monitoring costs obesity, annual (cost of D&E)	£131	£98 to £164 (gamma)	
Blood pressure treatment (most used ACE inhibitor), annual	£34	£25 to £42 (gamma)	

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Variable	Cost (£)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Annual type 2 diabetes medication cost	£317	£238 to £396 (gamma)	
Type 2 diabetes microvascular complications costs	£468	£351 to £584 (gamma)	
Prediabetes cost	£55	£41 to £69 (gamma)	
Cancer treatment colon, 1st year cost	£19,404	£14,553 to £24,255 (gamma)	
Cancer treatment breast, 1st year cost	£12,503	£9,377 to £15,628 (gamma)	
Cancer treatment endometrial, 1st year cost	£4,839	£3,629 to £6,048 (gamma)	
Cancer treatment, follow-up year	£2,512	£1,884 to £3,140 (gamma)	
MI 1st year cost, excl. acute event cost	£3,523	£2,642 to £4404 (gamma)	
Angina 1st year, excl. acute event cost	£573	£429 to £716 (gamma)	
Post ACS (average MI and angina following year)	£223	£167 to £278 (gamma)	
Stroke 1st year, excl. acute event cost	£6,120	£4,590 to £7,649 (gamma)	
TIA 1st year, excl. acute event cost	£1,385	£1,038 to £1,731 (gamma)	
Post stroke (average stroke and TIA following year)	£2,815	£2,111 to £3,518 (gamma)	
Sleep apnoea cost (annual CPAP treatment)	£869	£652 to £1,086 (gamma)	
MI non-fatal event cost	£2,265	£1,699 to £2,832 (gamma)	See section B.3.5.1 Intervention and comparators' costs and resource use
MI fatal event cost (cost within 30 days after event)	£2,265	£1,699 to £2,832 (gamma)	
Angina non-fatal event cost	£1,466	£1,100 to £1,833 (gamma)	
Angina fatal event cost (cost within 30 days after event)	£1,466	£1,100 to £1,833 (gamma)	
Stroke non-fatal event cost	£4,351	£3,263 to £5,439 (gamma)	
Stroke fatal event cost (cost within 30 days after event)	£4,351	£3,263 to £5,439 (gamma)	
TIA event	£1,945	£1,458 to £2,431 (gamma)	
Bariatric surgery, preoperative management	£1,024	£768 to £1,280 (gamma)	

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Variable	Cost (£)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Gastric bypass procedure	£5,184	£3,888 to £6,480 (gamma)	
Laparoscopic banding procedure	£3,076	£2,307 to £3,844 (gamma)	
Sleeve gastrectomy procedure	£4,830	£3,622 to £6,037 (gamma)	
Bariatric surgery, post-operative follow-up	£875	£656 to £1,094 (gamma)	
Bariatric surgery, complications (leaks)	£3,158	£2,369 to £3,948 (gamma)	
Bariatric surgery, TOTAL non-fatal	£9,753	£7,315 to £12,192 (gamma)	
Bariatric surgery, TOTAL fatal	£9,753	£7,315 to £12,192 (gamma)	
Knee replacement, non-fatal	£6,251	£4,688 to £7,813 (gamma)	
Knee, fatal	£6,251	£4,688 to £7,813 (gamma)	

ACE: Angiotensin Converting Enzyme; ACS: Acute Coronary Syndrome; MI: Myocardial Infarction; TIA: Transient Ischaemic Attack

Table 49: Summary of utility decrements applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Health state disutilities			
Type 2 diabetes	-0.0374	-0.047 to -0.028 (beta)	See section B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis
Post ACS	-0.0368	-0.062 to -0.011 (beta)	
Sleep apnoea	-0.0385	-0.048 to -0.029 (beta)	
Cancer	-0.0778	-0.097 to -0.058 (beta)	
Post stroke	-0.0349	-0.056 to -0.014 (beta)	
Event disutilities			
Bariatric Surgery	-0.184	-0.184 to -0.184 (beta)	See section B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis
ACS	-0.063	-0.076 to -0.049 (beta)	
Musculoskeletal	-0.194	-0.243 to -0.146 (beta)	
Stroke	-0.117	-0.129 to -0.105 (beta)	
TIA	-0.033	-0.055 to -0.011 (beta)	
Knee replacement*	-0.194	-0.146 to -0.243 (beta)	

*multiplied with number of years spent in severe osteoarthritis before surgery
ACS: Acute Coronary Syndrome; TIA: Transient Ischaemic Attack

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Table 50: Miscellaneous inputs

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Age at menopause	50	50.15 to 50.25 (gamma)	See section B.3.2.3 Model structure
Bariatric surgery criteria - minimum BMI	35	35 to 47 (gamma)	See Appendix L
Incidence of bariatric surgery per year	0.0115	0.006 to 0.0178 (beta)	
Maximum age for bariatric surgery (years)	57	55 to 59 (gamma)	
Time with osteoarthritis before knee replacement surgery (years)	3	0 to 5 (beta)	See section B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

B.3.6.2 Base case assumptions

The assumptions applied in the base case are provided in Table 51.

Table 51: Base case model assumptions

Model Input and cross-reference	Source/assumption	Justification
Treatment duration, 2 years	Treatment with liraglutide 3.0mg was assumed to be maintained for two years	Despite the availability of clinical trial data for up to three years of follow-up with liraglutide 3.0mg, a two year treatment duration was assumed in the base case analysis, in line with the results of a UK physicians' survey (see Appendix N) which suggested an average treatment duration of 1-2 years. This assumption is however recognised to be associated with a certain degree of uncertainty and was therefore tested in scenario analyses encompassing one or alternatively three years treatment

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		duration, assuming each time equal duration for liraglutide 3.0mg and diet and exercise.
Waning of initial treatment effect	Post treatment duration, the initial weight loss, as well as all changes in: SBP, total and HDL cholesterol were assumed to return to their baseline values (i.e. waning of treatment effect) at a constant annual rate of 33.33%, i.e. 33.33% of the initial loss was applied in year 1 post treatment, 66.66% applied in year 2, and applied 100% in year 3. This is done in the same manner in both liraglutide 3.0mg and diet and exercise arm.	The application of a constant rate of 33.33% per year following treatment cessation is in line with Ara *et al*., 2012 (101) which assumed BMI returned to baseline value at 3 years after treatment cessation in a linear fashion.
Natural progression of weight post treatment and post waning of treatment effect: 0.46 kg increase per year, until cohort reaches 68 years	Following the initial treatment duration and treatment effect waning period, a weight increase of 0.46 kg per year occurs, in line with a natural progression of weight. This annual weight increase was applied until an average age of 68 years. The maximum age until weight increased was varied in one-way sensitivity analyses to a plausible range of ±2 years.	Natural weight increase over time was a common assumption in obesity models, including Ara *et al*., 2012 (101), Heitmann 1999 and in previous NICE clinical guidelines (CG43). In line with advice received from a clinical expert in the field of obesity (see Appendix O), weight ceases to increase around the age of 68 years coinciding with an age-related decline in muscular mass called sarcopenia.
Progression of systolic blood pressure, total cholesterol and HDL cholesterol post treatment and post	Post treatment and waning of treatment effect, systolic blood pressure, total cholesterol, and HDL cholesterol were assumed	Although SBP, total and HDL cholesterol are also associated with natural progression, for reasons of simplicity, the model only accounted for evolution based on treatment effect. The cohort returns to baseline value,

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waning of treatment effect periods	constant for the remainder of the time horizon.	corresponding to the average in the cohort, which is then maintained over the entire time horizon of the model when treatment is discontinued. However, as the cohort is assumed to remain treated with antihypertensive medications, and accrues the cost of this, it is plausible to assume the averages would remain stable.
Temporary reversal of prediabetes to a normal glucose tolerance state, maintenance of the glucose status effect over time and risk of type 2 diabetes in prediabetes vs. normal glucose tolerance	All patients initiated the model in a prediabetes state and were assigned a higher risk of developing type 2 diabetes (vs. normo-glucose tolerant patients) by modification of the glycaemic status parameter in the corresponding type 2 diabetes risk equations. In line with changes in glycaemic status observed in study 1839 (baseline to week 56) and applied in the model in cycle 2, a proportion of patients in both liraglutide 3.0mg and diet and exercise arm temporarily reverted to a normal glycaemic status whereby a lower risk of type 2 diabetes was applied. All patients reverting to normal glucose tolerance were assumed to return to a prediabetes status at the end of the treatment effect waning period, assuming glycaemic status be correlated with weight loss. For simplicity, there was no	According to published risk equations (116, 166), patients with prediabetes have a higher risk of developing type 2 diabetes than those with normal glucose tolerance. Changes in glycaemic status observed at week 56 were applied in the model starting from cycle 2. In line with clinical expert opinion (see Appendix N) and with results of study 1839 with diet and exercise, prediabetes reversal was assumed to be a consequence of the initial weight loss and thus applied in the model to occur on the same time, albeit glycaemic status being measured later-on in the clinical study. Consequently, the loss of temporary normo-glycaemia was also assumed to occur at the same time with the complete loss of the initial weight loss benefit. Recognising the uncertainty around these assumptions, several scenario analyses were conducted one of which assumed an immediate loss of treatment effect as well as immediate loss of

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	waning of the glycaemic status, and all patients returned to prediabetes in the year weight was regained to 100% of the baseline weight.	normo-glycaemic status after treatment stop.
Treatment discontinuation	The proportion of liraglutide 3.0mg patients who do not achieve ≥5% weight loss (vs. baseline) as well as all liraglutide 3.0mg responders post liraglutide treatment were assumed to remain on a diet and exercise program for the rest of the analysis time horizon. This assumption was varied in a scenario analysis whereby all non-responders (including diet and exercise non-responders) as well as all responders at the end of the treatment period discontinued to receive no treatment. No treatment benefit was applied to non-responders, albeit the initial cost of treatment (4 weeks titration and 12 weeks maintenance for liraglutide 3.0mg) was. Rather, weight started to increase from cycle 2 of the model.	Diet and exercise was considered an integral part of the treatment of all individuals with obesity, regardless of any pharmacological or surgical intervention co-administered, as validated via a physician survey (Appendix N). Given, some patients may still discontinue any kind of weight management program, this assumption was tested in a scenario analysis, whereby all patients were assumed to receive no treatment upon treatment discontinuation, and to follow a natural disease progression pathway (i.e. weight increase pathway) as simulated in the no treatment arm of the model.
Treatment efficacy and costs applied to liraglutide 3.0mg non-responders	Patients not responding to liraglutide 3.0mg (response defined as ≥5% weight loss vs. baseline) were assumed to discontinue treatment with liraglutide 3.0mg in cycle 2 of the model and remain on diet and exercise	This stopping rule was aligned to liraglutide 3.0mg SmPC (Appendix C).

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	treatment throughout the rest of the analysis. The full analysis set efficacy with diet and exercise (placebo arm in trial 1938) was applied to this proportion of the liraglutide 3.0mg cohort, this proportion of the cohort being thus modelled in mirror to the diet and exercise arm. Despite liraglutide 3.0mg efficacy not being applied to these patients, the cost of liraglutide 3.0mg over 4 weeks of titration and 12 weeks of maintenance dose was applied.	
Retreatment following treatment discontinuation	Following liraglutide 3.0mg treatment stop, it was assumed that there would not be any repeated course of treatment with liraglutide 3.0mg. Rather, patients were assumed to continue a lifetime weight management with diet and exercise.	Diet and exercise was considered an integral part of the treatment for all obese individuals as validated by a physician survey (Appendix N). Further, no published clinical data was available to provide evidence with regards to a “stop and re-start” type of weight management, for either liraglutide 3.0mg or diet and exercise.
Incidence of bariatric surgery, 1.15% per year	Bariatric surgery was included in the model as an event occurring in both treatment arms. Bariatric surgery does not occur in the first year of treatment.	Bariatric surgery is available in England as part of tier 4 specialist weight loss services. Given the placement of liraglutide 3.0mg in tier 3 specialist services, bariatric surgery was included in the model as a rescue treatment following failure of interventions provided in tier 3. Thus, patients in both arms can receive bariatric surgery at all times (except the first year when treatment with liraglutide 3.0mg is initiated). Its occurrence depends however upon a minimum BMI eligibility criterion (which can be

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		reached sooner in the less effective treatment arm) and a maximum age at which patients would be eligible for surgery (which was applied at the same time to both treatment arms).
Waning of treatment effect following bariatric surgery	Following bariatric surgery, a treatment effect waning was assumed, equal to the annual natural weight regain of 0.46 kg. This waning of treatment effect was different from the one applied to diet and exercise or liraglutide 3.0mg, as there, weight (and other physiological parameter values) returned to their baseline values before the natural, annual weight increase was applied. No waning of bariatric surgery effect on systolic blood pressure, total and HDL cholesterol was applied.	In line with Sjostrom *et al.* (167), whereby weight was regained following all types of bariatric surgeries over the 20 years follow-up, but never returned to its baseline value, and with Ara *et al*. for the natural weight regain. As for diet and exercise and liraglutide 3.0mg, the cohort was assumed to remain on antihypertensive and lipids-lowering medication for the remainder of the analysis time horizon, thus systolic blood pressure, total and HDL cholesterol were assumed not to change over time. This was a simplifying assumption due to lack of robust data to model their long-term progression in the target population.
Type 2 diabetes microvascular complications	Type 2 diabetes microvascular complications were not explicitly modelled as health states or events in the model. Rather, type 2 diabetes health state cost and disutility encompass the possible consequences of microvascular complications on the costs of care and patients HRQoL.	This was a simplifying assumption given the current model was intended to evaluate treatments in obesity, and not type 2 diabetes, and that the addition of other, chronic health states, such as chronic kidney disease, may have increased the number of health states two-three times.

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Application of acute and health state disutilities	Acute event and health state disutilities are assumed to be additive.	Assumption. Given existing evidence base is inconclusive and further research is required, as per NICE DSU 12 (168).
Application of acute and health state costs	Acute event costs and health state costs are assumed to be additive.	In line with Ara *et al*., 2012 (101)

HDL: High-density lipoprotein; HRQoL: Health-Related Quality of Life; NICE: National Institute for Health and Care Excellence; SBP: systolic blood pressure

B.3.7 Base case results

B.3.7.1 Base case cost-effectiveness analysis results

Total costs in the base case analysis were higher with liraglutide 3.0mg compared with diet and exercise, respectively £20,988 vs. £19,419, resulting in an additional cost of £1,568 with liraglutide 3.0mg. Liraglutide 3.0mg was associated with higher total health benefits of 18.584 LYs and 15.336 QALYs, compared with total 18.496 LYs and 15.216 QALYs for diet and exercise, respectively, or an additional 0.085 LYs and additional 0.116 QALYs for liraglutide 3.0mg. The incremental results for costs and health effects indicate that treatment with liraglutide 3.0mg was associated with an ICER of £13,059 per QALY gained compared with treatment with diet & exercise. Results are presented in Table 52.

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Table 52: Base case results based on PAS price

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,988	18.584	15.336	£13,059
Diet & exercise	£19,419	18.496	15.216	
Incremental	£1,568	0.088	0.120	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to account for multivariate and stochastic uncertainty in the model. One thousand simulations were run. The results are presented as the probability of being cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 per QALY.

PSA was conducted to simultaneously take into account the uncertainty associated with parameter values. The implementation of PSA involved assigning specific parametric distributions and repeatedly sampling mean parameter values. No data on the covariance structure between parameters was available, hence parameter correlation could not be implemented in the PSA. Sampling was based on parameter distribution around the mean estimate at a 95% confidence interval, constructed using reported standard errors where available. A default margin of error of 25% around the mean estimate was applied where standard errors of the mean were not available/ not reported.

The mean probabilistic ICER was £13,623 per QALY gained, 95% CI (£10,014 - £19,209 per QALY gained) and 99% CI (£8,899 - £22,312 per QALY gained). The ICER scatter plot (Figure 29) showed some degree of uncertainty with regards to both additional costs and QALY gains with liraglutide 3.0mg. However, all ICERs fell within the North-West quadrant showing no uncertainty with regards to the existence of additional benefits as well as no uncertainty with regards to liraglutide 3.0mg being

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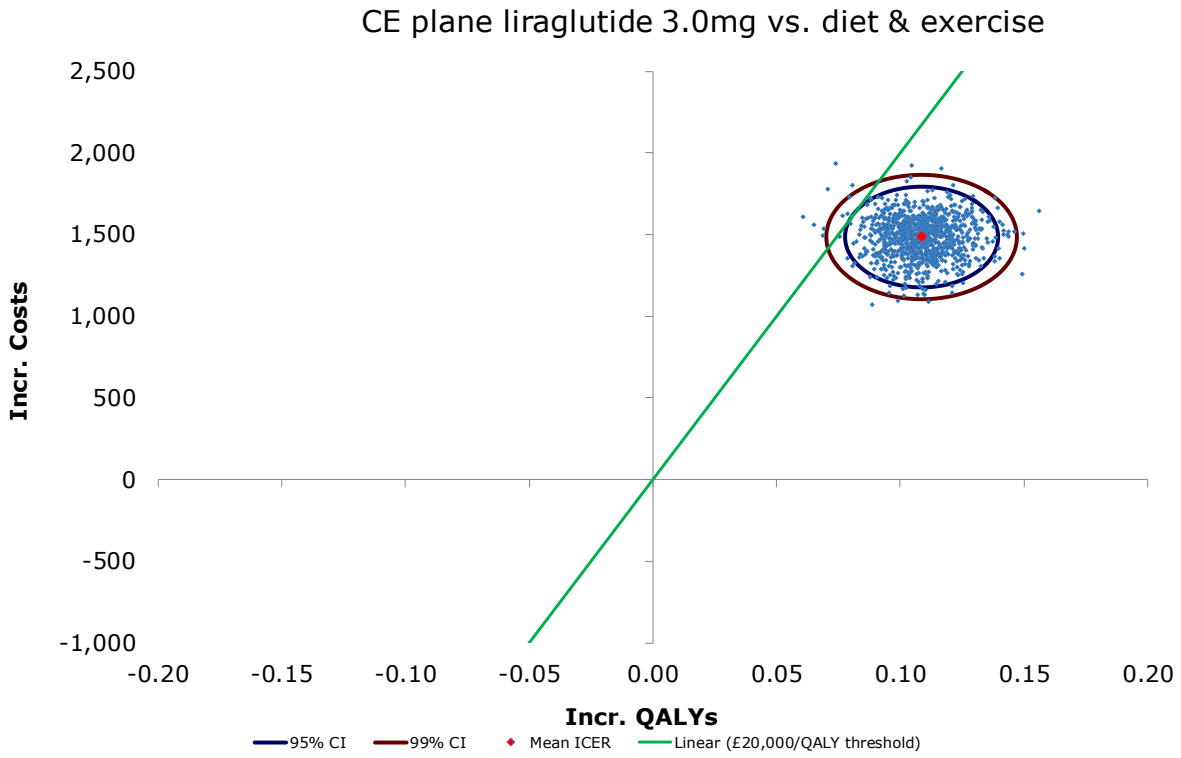
more costly than diet and exercise, under the current modelling framework, parameter uncertainty and analysis assumptions.

Figure 29: Cost-effectiveness plane



QALYs: quality-adjusted life years

The cost-effectiveness acceptability curve (CEAC), (Figure 30), shows that liraglutide 3.0mg is likely to be considered cost-effective in 99% of cases, under a threshold of £20,000 per QALY and in 100% of cases under an acceptability threshold of £30,000 per QALY.

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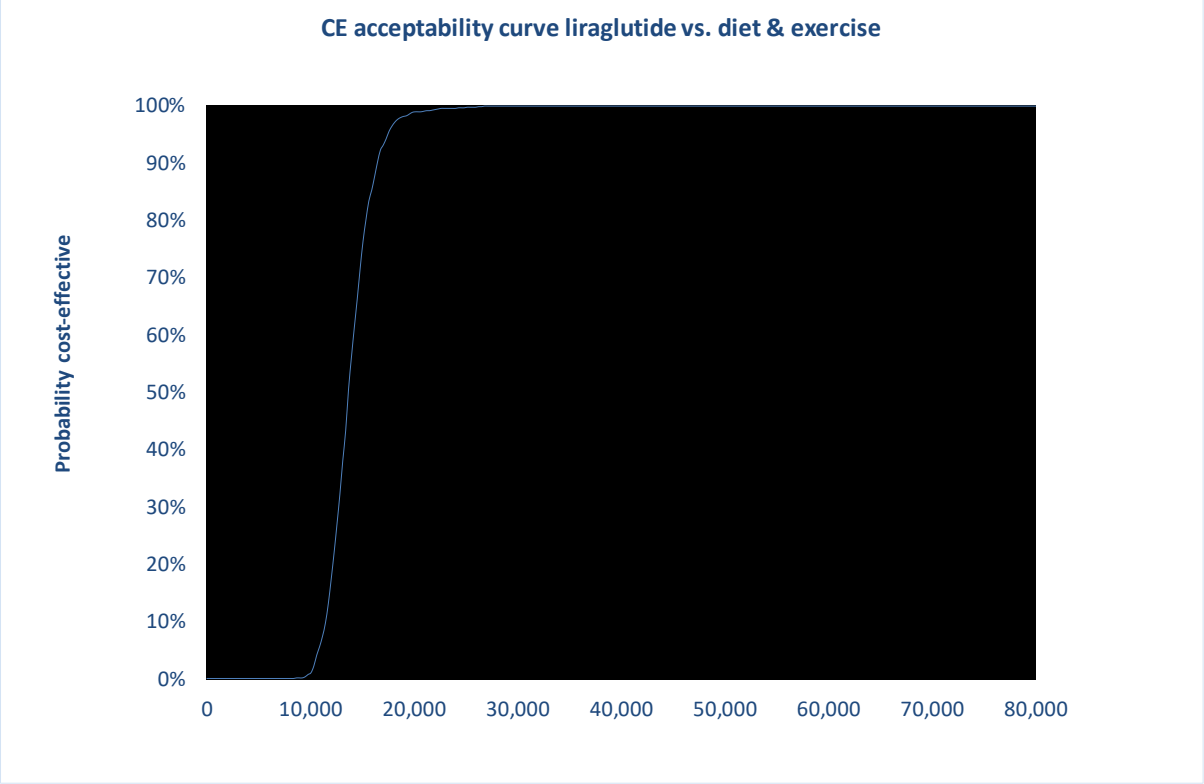
Figure 30: Cost-effectiveness acceptability curve



B.3.8.2 Deterministic sensitivity analysis

To assess the uncertainty around the base case estimates, deterministic sensitivity analyses have been performed. Confidence intervals were constructed using reported standard errors of the mean (SEM) where these were available, or by calculating a margin of error of 25% around the mean estimate where standard errors were not available or not reported, then applying the formulae to construct 95% confidence intervals (e.g. for a normal distribution, upper CI = mean+1.96*SEM; lower CI = mean-1.96*SEM or, where SEM was not reported, upper CI = mean + 25%*mean; lower CI = mean-25%*mean).

Table 53 illustrates the results of the deterministic sensitivity analyses, with the ten most significant drivers listed from top to bottom. Figure 31 provides a graphical representation of these results. The top three drivers of results were found to be the proportion of patients on diet and exercise who (temporarily) revert from prediabetes to normal glucose tolerance following treatment, the proportion of patients on

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liraglutide 3.0mg who temporarily revert from prediabetes to normal glucose tolerance, and weight reduction at the start of year 2 with diet and exercise. Neither of these scenarios had a substantial impact on the results and ICERs remained below the £20,000 per QALY acceptability threshold. The (temporary) reversal of prediabetes (in both arms) appeared to be the efficacy parameter with highest impact on the results. This is expected as the parameter affects the progression to type 2 diabetes in the model which in turn affects total costs of care, LYs and QALY estimates, as well as the risk of cardiovascular events in the model (i.e. higher risks apply for type 2 diabetes). The third parameter with impact on results was the weight reduction at the start of year 2 with diet and exercise, given a higher uncertainty was associated with this parameter (based on the SEM reported in the trial) as well as the importance of BMI changes on all model outcomes. The fourth highest driver of the results was the parameter encompassing the value of glycaemic control (HbA_{1c}) upon type 2 diabetes onset. This was also expected given HbA_{1c} was the main clinical parameter driving cardiovascular outcomes once patients transition to type 2 diabetes (and no longer BMI, due to limitations in risk equations discussed before). Thus, a lower HbA_{1c} upon type 2 diabetes onset would lower total cardiovascular outcomes per arm, and also the incremental benefits of treatment with liraglutide 3.0mg in postponing progression to type 2 diabetes. The opposite was true at a higher HbA_{1c} level upon type 2 diabetes onset.

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Table 53: Deterministic sensitivity analyses results

	Variation (SD or ±25%)		ICER (£/QALY)	
Parameter	**Low**	**High**	**Low**	**High**
Base case			£13,059	
D&E: Prop. reverting from prediabetes to NGT (%)	34.95%	46.66%	£10,573	£16,119
Liraglutide: Prop. reverting from prediabetes to NGT (%)	79.09%	86.23%	£13,935	£12,376
D&E: Weight reduction at 2 years (%)	-1.29%	-2.85%	£12,220	£13,242
HbA_{1c} after type 2 diabetes onset (%)	6.50%	8.50%	£13,785	£12,344
Proportion of smokers (%)	12.61%	17.56%	£13,160	£13,645
Baseline BMI (kg/m^2)	41.333	42.067	£13,182	£12,481
Liraglutide: Weight reduction at 2 years (%)	-8.72%	-10.20%	£13,578	£12,831
Case fatality rate of stroke (%)	12.70%	34.96%	£12,728	£13,474
Case fatality rate of angina (%)	16.71%	46.34%	£12,848	£13,445
Annual cost of prediabetes (£)	£41	£69	£13,427	£12,690

ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

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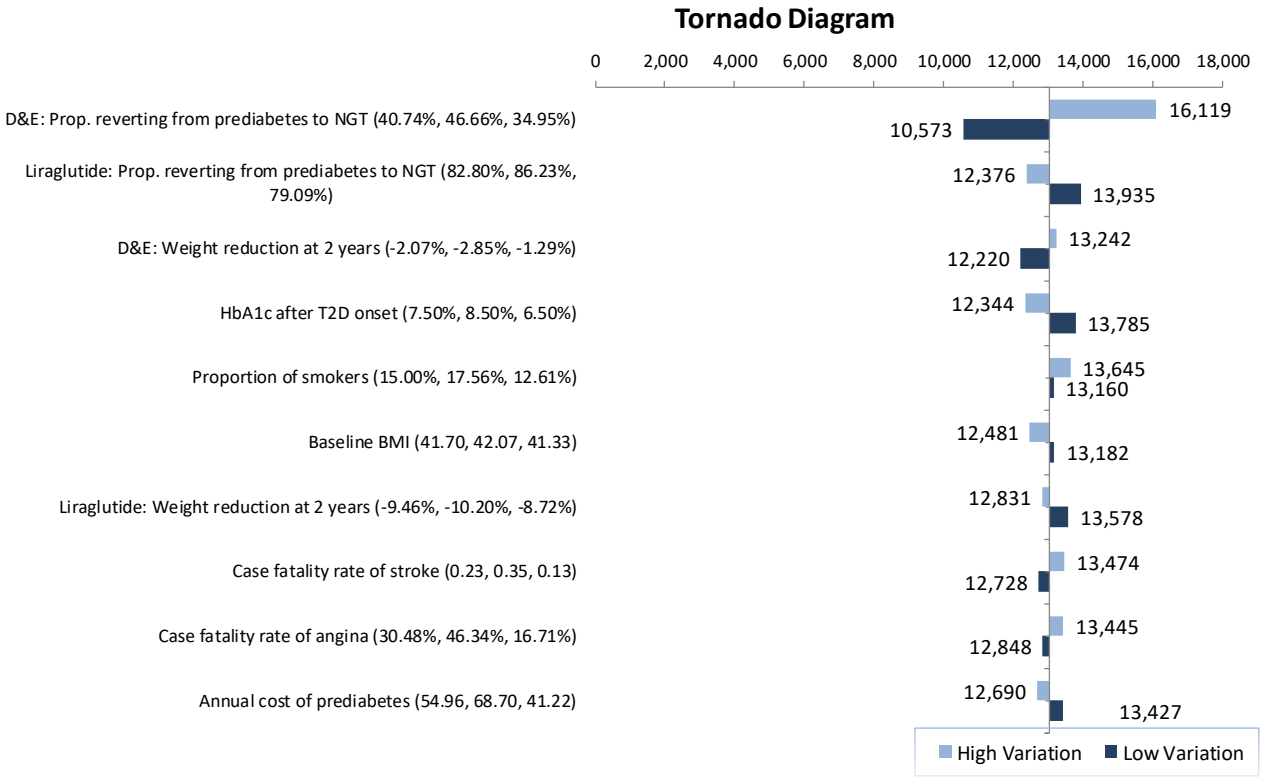
Figure 31: Tornado Diagram



T2D: Type 2 diabetes

B.3.8.3 Scenario analyses

The table below summarises scenario analyses conducted to explore uncertainty around the structural assumptions used in the analysis. Results are presented in separate tables thereafter.

Table 54: Key scenario analyses

Model settings	Base case	Scenario analysis	Justification
Discount rates	3.5% discount rate applied to costs and benefits	The discount rates for both costs and health outcomes were varied at 0% and 6%	To show the impact on results of a 0% or 6% discounting
Time horizon	40 years	5, 10, 20 and 30 years	Shorter time horizons were modelled to test the impact on costs and outcomes over time

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Model settings	Base case	Scenario analysis	Justification
Complications considered	Type 2 diabetes, ACS, stroke, sleep apnoea, knee replacement	Exclusion of all complications and then one by one re-inclusion of each complication considered in the base case analysis	To illustrate the incremental impact of: BMI on QALY, type 2 diabetes, cardiovascular disease (both ACS and stroke), sleep apnoea and knee replacement
Inclusion of cancers with known relationship with obesity and variation of baseline age to 50 years	Cancers not included, baseline age 48 years	Cancers included and mean baseline age 50 years	To evaluate the cost-effectiveness of liraglutide 3.0mg compared with diet and exercise when cancer complications of obesity are considered in the analysis, in the population at risk (i.e. population of menopausal age)
Inclusion of cancers with known relationship with obesity, no variation of the baseline age	Cancers not included	Cancers included	To evaluate the cost-effectiveness of liraglutide 3.0mg compared with diet and exercise when cancer complications of obesity are considered in the analysis, without specific considerations on the population at risk
Treatment duration	2 years	1 year and 3 years	A one year treatment duration for both liraglutide 3.0mg and diet and exercise was tested in line with Ganguly *et al*., 2018 (169), the treatment duration implemented by Ara *et al*., 2012 (101), and as indicated by responses to the physician survey which indicated an average treatment duration in obesity of 1-2 years (see Appendix N). A three year treatment duration was tested in line with the maximum duration of the SCALE obesity and prediabetes trial (73)
Waning of treatment effect	Treatment effect wanes linearly at an annual rate of	Treatment effect is lost: immediately after treatment stop, one year or	To test the impact of varying assumptions around the maintenance of initial treatment effect

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Model settings	Base case	Scenario analysis	Justification
	33.33% post treatment period	three years post treatment period	
Cohort treated with liraglutide 3.0mg or with diet and exercise discontinue to no treatment (non-responders and responders post treatment duration), and physiological parameter values return to a value simulated by the no treatment arm at the end of treatment and treatment effect waning periods	Liraglutide 3.0mg non-responders and liraglutide 3.0mg responders post treatment duration discontinue to diet and exercise, diet and exercise treatment continues throughout the analysis time horizon for all patients initiating the model on diet and exercise (i.e. no responder analysis applied in diet and exercise arm)	Stopping rule applies to both liraglutide 3.0mg and diet and exercise. Non-responders and responders post treatment period discontinue to no treatment for the rest of the analysis time horizon. The values of the physiological parameters return to a value on the natural progression simulated by no treatment at the end of treatment and waning periods	To test the impact of assuming all patients receive no further treatment upon early discontinuation (due to non-response) or post treatment period (for initial responders). Effectively, the model applies responder efficacy to both liraglutide 3.0mg and diet and exercise responders and no efficacy to non-responders. To test the impact of patients returning to the weight associated with natural progression following treatment discontinuation and treatment effect waning period
No high risk of CVD	Modelled cohort is defined as having high risk of CVD based on SBP, total cholesterol or HDL being elevated	The modelled cohort is not defined as high risk of CVD	To demonstrate the cost-effectiveness of liraglutide 3.0mg in patients not at high risk of CVD; a new efficacy dataset was applied based on the study population defined as prediabetes without the criteria for high risk of CVD
High risk values for SBP, total cholesterol and HDL	Modelled cohort is at high risk of CVD based on at least one of SBP, total cholesterol or HDL	Modelled cohort is at high risk of CVD based on all three of these parameters. 1. SBP: 140.8 mmHg 2. Total cholesterol: 238.3 mg/dL 3. HDL: 62.0 mg/dL	To demonstrate the cost-effectiveness of liraglutide 3.0mg in these patients

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Model settings	Base case	Scenario analysis	Justification
Imputation method applied to account for missing trial data	Last Observation Carried Forward (LOCF)	Baseline Observation Carried Forward (BOCF) and multiple-imputation for measurement error (MI-ME) statistical modelling	Alternative imputation methods to account for missing data have been tested
Bariatric surgery	Include	Exclude	To test the impact of excluding bariatric surgery as a rescue therapy on cost-effectiveness results
Bariatric surgery criteria - minimum BMI	BMI 35 kg/m^2	BMI 47 kg/m^2	To test the impact of using the actual average BMI level at which patients receive bariatric surgery in the UK, as the BMI level where bariatric surgery is applied in the model
Incidence of bariatric surgery per year	1.15%	0.57%	The NICE costing report on implementing CG189, produced in 2014, states that the current incidence of bariatric surgery in patients with recent onset of type 2 diabetes with a BMI of 35 kg/m^2 and over is 0.57%, with future incidence expected to double to 1.15% in these patients (5)

ACS: Acute Coronary Syndrome; BOCF: Baseline observation carried forward; CVD: Cardiovascular Disease; HDL: High-density lipoprotein; LOCF: Last observation carried forward; MI-ME: Multiple-imputation for measurement error; NICE: National Institute for Health and Care Excellence; SBP: Systolic blood pressure; QALY: Quality-adjusted life year

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Table 55: Costs, LYs and QALYs discounted at 6%

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£15,463	14.063	11.714	£19,949
Diet & exercise	£13,780	14.012	11.630	
Incremental	£1,683	0.051	0.084	

ICER: incremental cost-effectiveness ratio; LY: Life years; LYG: life years gained; QALYs: quality-adjusted life years

Table 56: Costs, LYs and QALYs discounted at 0%

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£36,759	30.659	24.888	£5,563
Diet & exercise	£35,470	30.450	24.656	
Incremental	£1,289	0.209	0.232	

ICER: incremental cost-effectiveness ratio; LY: Life years; LYG: life years gained; QALYs: quality-adjusted life years

The analysis results were sensitive to changes in discounting rates, showing these to have an important impact on results. This was expected, given the additional treatment costs with liraglutide 3.0mg are accrued within the first 2 years, while the additional benefits occur further on in the analysis, and are discounted more. Hence, a lower discount rate lowers the ICER substantially, while a higher discount rate (vs. base case) increases the ICER. Nevertheless, the scenario ICER was below the acceptable threshold of £20,000 per QALY gained.

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Table 57: Five-year time horizon

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£5,428	4.640	4.014	£62,825
Diet & exercise	£3,380	4.639	3.982	
Incremental	£2,048	0.001	0.033	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 58: Ten-year time horizon

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£8,562	8.452	7.233	£44,844
Diet & exercise	£6,680	8.446	7.191	
Incremental	£1,882	0.005	0.042	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 59: Twenty-year time horizon

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£14,132	13.967	11.758	£24,264
Diet & exercise	£12,472	13.939	11.689	
Incremental	£1,660	0.028	0.068	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

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Table 60: Thirty-year time horizon

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£18,682	17.177	14.263	£16,015
Diet & exercise	£17,109	17.116	14.165	
Incremental	£1,573	0.061	0.098	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Scenarios around the time horizon of the cost-effectiveness analyses showed significant uncertainty around the estimated ICER, generating ICERs much above the acceptable thresholds of £30,000 (when time horizon was set to 5, 10 years), and above £20,000 when time horizon was set to 20 years. This was expected given treatment benefits accrue later in life while the full costs of treatment with liraglutide 3.0mg occur in the first 2 years. While these results demonstrate that the model produces results in line with expectations, the results for time horizons of 5 and 10 years are not helpful for decision-making as they are too short to capture all important differences in costs and outcomes, hence deviating from NICE's recommendation to model time horizons "sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared" (118).

Table 61: Exclusion of all complications (impact of BMI on QALYs only)

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£4,066	19.858	17.242	£113,041
Diet & exercise	£1,982	19.858	17.223	
Incremental	£2,085	0.000	0.018	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

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Table 62: Inclusion of type 2 diabetes and BMI impact on QALY

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£8,133	19.850	17.037	£104,836
Diet & exercise	£5,989	19.850	17.017	
Incremental	£2,144	0.000	0.020	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 63: Inclusion of cardiovascular disease, type 2 diabetes, BMI impact on QALY

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£10,653	18.593	15.882	£15,151
Diet & exercise	£8,939	18.506	15.769	
Incremental	£1,714	0.088	0.113	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 64: Inclusion of sleep apnoea in addition to complications above

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£19,350	18.593	15.498	£13,208
Diet & exercise	£17,775	18.506	15.379	
Incremental	£1,575	0.088	0.119	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

The four scenario analyses presented above showed that the most important drivers of liraglutide 3.0mg cost-effectiveness compared with diet and exercise were the cumulative impact of a delay in type 2 diabetes onset and the avoidance of cardiovascular disease. If these two complications were not to be considered, the

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model showed little contribution of the BMI impact on HRQoL (when considered solely, i.e. ICER much above acceptable thresholds), and the same was true when type 2 diabetes was considered without cardiovascular complications. This was expected given the interdependency between type 2 diabetes and cardiovascular risks. Finally, the addition of sleep apnoea had some impact on the results, but not of the same magnitude. ICERs decreased from £15,151 per QALY to £13,208 per QALY gain when considering sleep apnoea and to £13,059 per QALY gain (base case) when considering knee replacement (i.e., base case ICER with all complications included).

Table 65: Inclusion of cancers with relationship with obesity baseline age 50 years

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£25,778	17.335	14.116	£11,438
Diet & exercise	£24,193	17.224	13.977	
Incremental	£1,585	0.111	0.139	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 66: Inclusion of cancers with relationship with obesity baseline age 48 years

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£25,866	17.821	14.570	£15,330
Diet & exercise	£24,175	17.740	14.459	
Incremental	£1,691	0.081	0.110	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

The two scenario analyses presented above show the impact on ICERs should the avoidance of colorectal, post-menopausal breast and post-menopausal endometrial

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cancers be considered as consequences of better weight management. The first analysis was conducted in a high risk population (76% women of menopausal age), while the second analysis was conducted in the base case patient population. Conducting the analysis in a high risk group showed significant impact on the results, with the scenario ICER going down to £11,438 per QALY gain. This was due to the immediate effect of liraglutide 3.0mg in reducing the risk of these three cancers; the risk reduction was mediated entirely by changes in weight compared to diet and exercise. In the second scenario, the effect on the ICER was no longer noted and this was in part because the initial effect of liraglutide 3.0mg on weight had already been partially lost by the time the cohort reached menopausal age, and secondly, because of a competing risk effect: explicitly modelling cancers decreased the life expectancy of the cohort, diminishing the long-term benefits seen with liraglutide 3.0mg in delaying the onset of type 2 diabetes and avoiding cardiovascular events.

Table 67: Treatment duration of one year

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,066	18.567	15.290	£6,220
Diet & exercise	£19,455	18.490	15.192	
Incremental	£611	0.078	0.098	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

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Table 68: Treatment duration of three years

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,697	18.599	15.386	£18,350
Diet & exercise	£19,166	18.502	15.248	
Incremental	£2,530	0.097	0.138	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

As expected, in the one year treatment duration scenario total and incremental costs were lower with liraglutide 3.0mg, while these increased vs. base case in the three year treatment duration. Treatment duration also affected total and incremental QALYs, with higher total and incremental QALYs in the three year treatment duration. However, the estimated ICER decreased in the one year treatment duration and increased in the three year treatment duration as the effect on health outcomes takes place gradually though the analysis time horizon (and is discounted to a higher extent) while costs occur in the first years (and are less discounted).

Table 69: Immediate loss of treatment effect (i.e. no waning of treatment benefit)

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,517	18.555	15.261	£20,723
Diet & exercise	£19,701	18.486	15.174	
Incremental	£1,815	0.070	0.088	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

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Table 70: Waning of treatment effect applied over one year post treatment stop

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,182	18.573	15.311	£14,802
Diet & exercise	£19,534	18.492	15.199	
Incremental	£1,648	0.081	0.111	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 71: Waning of treatment effect applied over three years post treatment

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,330	18.606	15.413	£8,535
Diet & exercise	£18,998	18.506	15.257	
Incremental	£1,332	0.100	0.156	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Scenarios around the duration of maintenance of the initial treatment benefit had some impact on the results; however, ICERs remained below the willingness-to-pay threshold of £30,000 per QALY gain, and the ICER was only £723 per QALY gain above the £20,000 threshold in an extreme scenario whereby all treatment benefits including weight loss, reversal of prediabetes, and changes on other physiological parameters (SBP, total and HDL cholesterol) would be lost immediately after treatment stop (i.e. no treatment effect waning period). This scenario is unlikely given part of the initial treatment benefits have been demonstrated to be maintained beyond treatment with liraglutide (see Section B.2.6).

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Table 72: All patients discontinue to no treatment and physiological parameters return to a value on the natural progression following treatment

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£22,699	18.511	15.127	£2,482
Diet & exercise	£22,067	18.340	14.872	
Incremental	£632	0.171	0.254	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Discontinuation to no treatment results in higher total costs overall, total projected LY and total QALYs in both arms as patients are worse-off. Indeed, a higher BMI is projected in both arms, as BMI wanes more rapidly in absence of treatment, returning to a value on the natural progression of the disease – for initial responders, while no weight, blood pressure or cholesterol-lowering benefits are assigned to non-responders. Incrementally, treatment with liraglutide 3.0mg results in a much lower ICER compared with the base case, due to a higher responder rate compared with diet and exercise (i.e. 67% vs. 24%) and thus a higher proportion of patients benefiting from treatment.

Table 73: Not high risk of CVD

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,934	18.631	15.382	£14,300
Diet & exercise	£19,315	18.550	15.268	
Incremental	£1,618	0.081	0.113	

CVD: Cardiovascular Disease; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

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The glycaemic effect (i.e. reversal of prediabetes) noted in the population not considered high risk of cardiovascular events was less strong with liraglutide 3.0mg compared with diet and exercise when compared with the base case population (i.e. BMI>35, prediabetic and at high risk of cardiovascular disease). Prediabetes reversal being a key driver of liraglutide efficacy, the projected ICER was £1,241 per QALY gain higher than in the base case analysis.

Table 74: Increased SBP, total cholesterol and HDL

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,099	18.459	15.228	£11,695
Diet & exercise	£19,558	18.359	15.096	
Incremental	£1,541	0.100	0.132	

HDL: High-density lipoproteins; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SBP: Systolic Blood pressure

A higher SBP, total cholesterol and HDL cholesterol assigned at baseline (without further changes to efficacy parameters) resulted in a population at higher risk of developing cardiovascular disease, and treatment with liraglutide 3.0mg thus resulting in incrementally higher savings and incrementally higher quality of life, with an ICER £1,364 per QALY gain lower than in the base case analysis.

Table 75: BOCF data imputation method

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,275	18.552	15.295	£9,050
Diet & exercise	£19,932	18.437	15.147	
Incremental	£1,343	0.115	0.148	

BOCF: Baseline observation carried forward; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

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Table 76: MI-ME data imputation method

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,050	18.583	15.330	£13,387
Diet & exercise	£19,463	18.495	15.211	
Incremental	£1,587	0.088	0.119	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; MI-ME: multiple-imputation for measurement error; QALYs: quality-adjusted life years

The two analyses of alternative imputation methods showed relatively little impact on the results. However, these scenarios provide little additional information. Given all subjects in SCALE 1839 had prediabetes at baseline, the BOCF method would assign more patients to prediabetes at the timepoint of glycaemic status assessment (week 56) in the arm with higher discontinuation. Thus, carrying forward the baseline observation for missing glycaemic status, results can be expected to be biased against diet and exercise (placebo arm in SCALE 1839) where a higher discontinuation was observed at week 56 (see patient flow in Appendix D). Conversely, the MI-ME method could not be implemented for the endpoint glycaemic status at week 56, the model applying prediabetes reversal rates based on LOCF, hence there were no important differences in the results versus base case.

Table 77: Exclude bariatric surgery from the model

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,137	18.557	15.231	£12,950
Diet & exercise	£19,571	18.468	15.110	
Incremental	£1,566	0.089	0.121	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

The exclusion of bariatric surgery led to a slightly lower ICER vs. base case as, in base case, patients on diet and exercise received more surgeries because they qualified sooner having a higher BMI than with liraglutide 3.0mg and had thus better

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health outcomes at lower costs with surgery. The difference in the ICER was however very small, of approximately £110 per QALY gain.

Table 78: Bariatric surgery criteria - minimum BMI 47 kg/m^2

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,137	18.557	15.231	£12,950
Diet & exercise	£19,571	18.468	15.110	
Incremental	£1,566	0.089	0.121	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Increasing the minimum BMI for bariatric surgery to 47 kg/m^2 which is the average weight at which patients actually receive surgery in the UK had the same impact with excluding bariatric surgery from the analysis given as patients would no longer be eligible for surgery in the model.

Table 79: Incidence of bariatric surgery per year of 0.57%

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,851	18.569	15.291	£12,990
Diet & exercise	£19,284	18.481	15.171	
Incremental	£1,567	0.088	0.121	

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

As for the two above analyses, lowering the incidence of bariatric surgery decreased the base case ICER, but the impact was minor, i.e. ICER was £69 per QALY gain.

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B.3.8.4 Summary of sensitivity analyses results

By far, the main drivers of liraglutide 3.0mg benefits were the avoidance or delay of type 2 diabetes onset and cardiovascular disease. Further, as the benefits of avoiding these complications are accrued over time, while the additional treatment costs are accrued in the first years, the model was highly sensitive to shorter analysis time horizons and discounting rates. It is, however, unlikely that such benefits would not be seen with liraglutide 3.0mg, given the already proven weight and glycaemic status effect seen with liraglutide in SCALE 1839. Moreover, all long-term obesity health-economic analyses identified in the literature simulated the impact of weight management interventions on avoiding and delaying these two interlinked complications. The model was robust to all other parameters varied in one-way sensitivity and scenario analyses, showing little uncertainty with regards to liraglutide 3.0mg cost-effectiveness in this indication.

B.3.9 Subgroup analysis

The analyses performed above represent a small subgroup of the licensed indication for liraglutide 3.0mg therefore no further subgroup analyses were conducted.

B.3.10 Validation

B.3.10.1 Technical QC

A check of internal validity was performed by the model developers using a quality control process. This involved checks on the selection and results of different modelling options, calculation spot checks, cross checks against source data and extreme value scenarios to check if the model behaved logically (see Appendix O for the details of quality checks performed by the model developers).

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

- Top down tests. This involved systematic variation of the model input parameters to establish whether changes in inputs results in predictable

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changes in the model outputs. These tests were designed to identify failures in model logic or material computation errors

- Model internal functionality (e.g. testing of all key model parameters, extreme value testing). The following aspects of the spreadsheet were identified as key areas for detailed checking: Markov traces; translation of drug prices, complications and resource use into state costs
- Internal consistency. Accuracy of input data. This was checked by comparing the model inputs in Excel against the data sources referenced

Overall, the validation identified no major issues with the computational accuracy of the model. A number of small inaccuracies were identified and rectified.

B.3.10.2 External dependent validation

A dependent validation was conducted by an external agency, independent from the one who developed the model and wrote the present submission report. The dependent validation consisted of comparing model predictions to data from the same studies that were used to build the model. The methods and results of this validation are presented in (170).

B.3.10.3 Cross validation

A cross validation was conducted by comparing the results of the present model with predictions of a different, published cost-effectiveness model in obesity. The model published by Ara *et al.*, (101) was selected, due to its comprehensive nature and relevance to the UK setting. The present model was populated with baseline clinical and demographic characteristics, costs and utility inputs described in the Ara et al. where available and supplemented with data from relevant published literature. The full methods and results of this cross validation are presented in (171).

B.3.11 Interpretation and conclusions of economic evidence

Base case deterministic results suggest that liraglutide 3.0mg is associated with an ICER of £13,059 when compared with diet & exercise for the treatment of UK patients with a BMI of ≥35 kg/m^2, prediabetes and high risk of CVD. The PSA results

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indicate that liraglutide 3.0mg is 99% likely to be cost-effective at a willingness-to-pay threshold of £20,000 per QALY and 100% likely to be cost-effective at a willingness-to-pay threshold of £30,000 per QALY, with a mean ICER of £13,682. Deterministic sensitivity analysis results demonstrate that the main drivers of liraglutide 3.0mg cost-effectiveness were the avoidance or delay of type 2 diabetes onset and cardiovascular disease. Further, as the benefits of avoiding these complications are accrued over time, while the additional treatment costs are accrued in the first years, the model was highly sensitive to shorter analysis time horizons and discounting rates. The model was, however, robust to all other parameters varied in one-way sensitivity and scenario analyses, showing little uncertainty with regards to liraglutide 3.0mg cost-effectiveness in this indication.

Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

As stated above, the economic SLR (Appendix G) demonstrated that there are no published economic evaluations considering treatment with liraglutide 3.0mg and diet and exercise in a population strictly defined as patients with obesity, prediabetes and high risk of CVD, the target patient population of this submission. Only the study by Ara *et al.*, 2012 (101) provided scenario analysis results that facilitated a comparison of the modelled costs and health effects for diet and exercise as an external validity check, which is discussed above in section B.3.10.

Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?

The results of the economic analysis are relevant to people with obesity who are referred to a specialist tier 3 weight management setting, which is recommended for patients with a BMI >40 kg/m^2 or a BMI ≥35 kg/m^2 with comorbidities and is aligned with the patient population considered in the decision problem (4).

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How relevant (generalisable) is the analysis to clinical practice in England?

The results from this study are derived from patients treated in a randomised clinical study setting, which may not always reflect the real-world clinical setting in daily practice in England. However, the baseline characteristics and outcomes reported from patients in the clinical study that provided the model inputs were similar to UK practice, which has been validated based on UK clinical expert opinion. Furthermore, the comparator in the SCALE obesity and prediabetes trial falls largely in line with the definition of standard management observed in UK clinical practice. At each of the 8 UK sites in the clinical study, patients received diet counselling, were put on a hypocaloric diet (under the guidance of a qualified dietitian) and expected to undertake physical activity, which is aligned with the standard of care provided by specialist tier 3 weight management services.

What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Obesity is a complex condition which affects an individual's immediate quality of life and increases the risk of certain conditions which themselves impact life expectancy and quality of life. Understanding the impact that sustained weight loss has on health-related benefits is highly complex as obesity has been associated with over 236 obesity-related complications (172). By necessity the economic model in this submission is a simplification of the impact obesity has on quality-adjusted life year calculations; but importantly an attempt has been made to quantify the impact of three different types of cancer not normally attempted in previous economic models (101). The model applied in this economic assessment has however been built with the intention of capturing, not only the costs and benefits directly associated with the treatment of obesity, but also the impact that this has on the numerous complications associated with obesity. To this end, the model captures the most relevant costs and benefits attributable to weight loss management in terms of its impact on the reversal and/or prevention of obesity-related complications.

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There are a few limitations to this current modelling approach that should be considered. In order to keep the model complexity to a minimum, a number of simplifying assumptions have been made.

A further limitation is the absence of longer-term data to model what happens when patients stop treatment (i.e., waning of treatment effect). This limitation is common to other models/treatments in obesity and is hence explored for its impact on the results by means of a scenario analysis with immediate loss of treatment effect. The results of this scenario showed some influence with an ICER just above £20,000. However, this is an extreme scenario which is unlikely in practice given part of the initial treatment benefits have been demonstrated to be maintained beyond treatment with liraglutide 3.0mg (see Section B.2.6).

Finally, mortality and costs in the model have not been adjusted by BMI and therefore, may be potentially underestimated.

What further analyses could be carried out to enhance the robustness or completeness of the results?

The model currently does not adjust mortality according to BMI. Instead, the modelled mortality is largely driven by the risk equations and event-related mortality. Adjusting for BMI-associated mortality would enhance the accuracy of the modelled life expectancy. However, by not adjusting for BMI, the results presented can be considered conservative since making this adjustment would be expected to increase the modelled benefits of liraglutide 3.0mg through the treatment effect BMI reduction.

Notwithstanding the limitations mentioned above, based on the currently available evidence the results shown here demonstrate that with a high degree of certainty, liraglutide 3.0mg is a clinically and cost-effective alternative to diet and exercise in patients with BMI ≥35 kg/m^2, prediabetes and high risk of CVD.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Liraglutide for managing overweight and obesity [ID740]

Clarification questions

August 2019

File name	Version	Contains confidential information	Date
ID740_Lira3.0mg_ERG_questions_NoACIC v3.0	3.0	No	16th August 2019

Notes for company

Highlighting in the template

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To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

LITERATURE SEARCHES

A1. Please clarify the date on which database searches were conducted for cost-effectiveness studies (Appendix G).

Company response:

The searches were conducted on 04.09.2018 for the clinical data, 10.09.2018 for the Quality of Life data and 11.10.2018 for the economic data.

A2. Please confirm which host was used to search EconLit and NHS EED for the cost-effectiveness searches (Appendix G). The CS states that searches 'were carried out simultaneously as one combined search using Ovid'. However, the EconLit/NHS EED searches are not the same as those used for MEDLINE and Embase.

Company response:

All of the searches were conducted through Ovid.

A3. Please confirm the total number of records found by the cost-effectiveness searches. The PRISMA diagram (Appendix G; Figure 3) states 1,997 records were found, however the total number of records documented in the strategies is 1,996. Additionally, some database results appear to be missing from this section of the flow diagram.

Company response:

The total number of records should indeed be 1,997 as 1 record was identified in a search of the following database:

EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews - Health Technology Assessment 4th Quarter 2016

Table 1: Total number of records by the cost-effectiveness searches

#	Searches	Results
1	exp Obesity/ or exp Obesity, Morbid/	11649
2	exp Weight reduction/	5384
3	exp Overweight/	13026
4	("adipose tissue hyperplasia" or adipositas or adiposity or "fat overload syndrome" or obese or obesitas or obesity).ti,ab,kw.	28778
5	(obes* or "body mass ind*" or adipos* or overweight or "overweight" or "overload syndrom*" or overeat* or "over eat*" or overfeed* or "over feed*" or overfed or "over fed" or "weight cycling" or ((weight or fat) adj3 (gain* or reduc* or los* or maint* or decreas* or watch* or control*)) or "skinfold thickness" or bodyweight or "body weight").mp	89938
6	or/1-5	90074
7	liraglutide/	464
8	(liraglutide or "nn 2211" or nn2211 or "nnc 90 1170" or "nnc901170" or Saxenda).mp.	1183
9	tetrahydrolipstatin.mp.	148
10	(alli or orlipastat or orlistat or "ro 18 0647" or "ro 180647" or ro180647 or tetrahydrolipstatin or xenical).mp.	530
11	or/7-10	1690
12	diet/	6146
13	exercise/	13541
14	12 and 13	1079
15	6 and 11 and 14	1

A4. Please provide details of which 'other sources' were searched to provide the additional two records listed in the PRISMA diagram in Appendix G; Figure 3.

Clarification questions

Company response:

Two additional records were identified through review of references of systematic literature review publications, provided below. The studies were carried over to review and data extraction.

1. Jennings A, Hughes CA, Kumaravel B, Bachmann MO, Steel N, Capehorn M, et al. Evaluation of a multidisciplinary Tier 3 weight management service for adults with morbid obesity, or obesity and comorbidities, based in primary care. Clinical obesity. 2014;4(5):254-66.

2. Lewis L, Taylor M, Broom J, Johnston KL. The cost-effectiveness of the LighterLife weight management programme as an intervention for obesity in England. Clin Obes. 2014;4(3):180-8.

POPULATION

A5. Priority question: According to the CS, this submission focuses on a subpopulation of the technology's marketing authorisation in people with 'BMI ≥35 kg/m2, prediabetes and high risk of CVD' (Table 1, CS, document B). It is also stated in Table 1 that 'Liraglutide 3.0mg is intended for use in patients who have been referred to a specialist tier 3 service where conventional treatments such as orlistat have been unsuccessful earlier in the clinical pathway' and 'it could be suitable for a group of patients who are unwilling or unable to undergo surgery'.

A. Could the company please clarify the precise nature of the index population i.e. is it only those with a BMI ≥35 kg/m2, prediabetes and high risk of CVD or is it a smaller subgroup of patients with a BMI ≥35 kg/m2, prediabetes and high risk of CVD and who have also failed on orlistat and/or are unwilling/unable to undergo bariatric surgery?
B. If the index population is only those with a BMI ≥35 kg/m2, prediabetes and high risk of CVD i.e. it includes patients who have not already experienced orlistat or who might be willing and able to undergo bariatric surgery then could the company please include both orlistat and bariatric surgery as

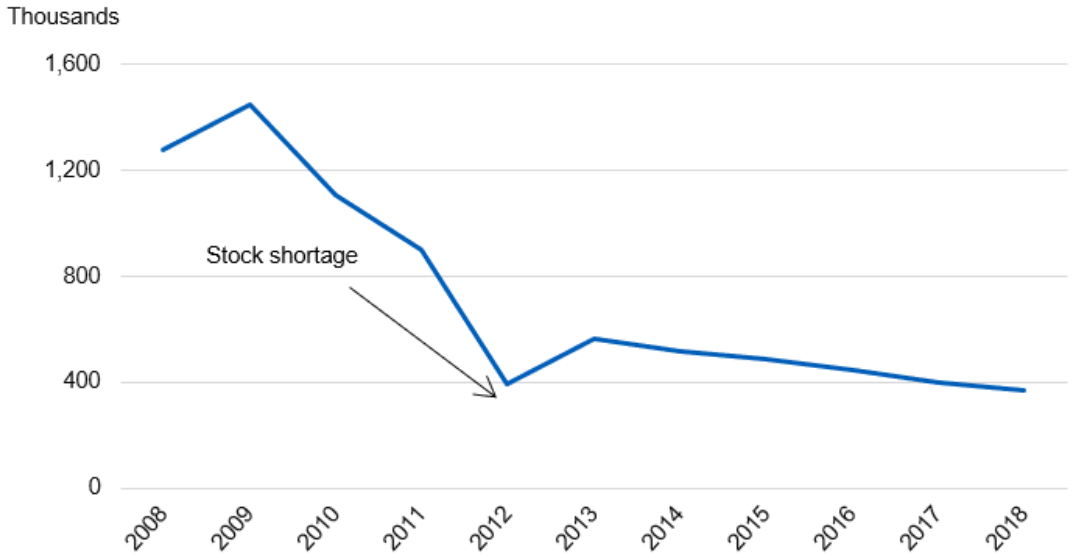
comparators in the clinical effectiveness sections and in the cost-effectiveness sections?

Company response:

A. The index population for the company submission (CS) is patients with a 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD'.

B. In this submission we have not considered orlistat as a relevant comparator. This is partly because orlistat is currently recommended in primary care in a much wider patient population than the one defined in the CS and partly due to the evidence of its limited clinical use in real life. As demonstrated in Figure 1 below, prescribing of anti-obesity medication is declining, demonstrated by the continued downward trend since 2009 (NHS Digital, 2019). In 2018, 371,000 items were prescribed for the treatment of obesity in primary care.

Figure 1: Anti-obesity medication prescribed per year (NHS Digital, 2019)



The index population (BMI ≥35 kg/m^2, prediabetes and high risk of CVD) are likely to have failed orlistat or be unwilling to take it. This is also supported by Section 3.4 of the final appraisal determination for naltrexone–bupropion (TA494), where it is stated that clinical experts and consultees reported that standard management (diet and

lifestyle interventions) is the only relevant comparator because orlistat is not often used in clinical practice (NICE TA494, 2017). This is due to undesirable side effects leading to poor adherence and weight loss outcomes. As a result, most patients do not want to take it or stop treatment after a short time. Based on this, the committee concluded that standard management was the main comparator in the appraisal.

We do not anticipate that liraglutide 3.0mg will be a direct replacement for bariatric surgery. Bariatric surgery has already been demonstrated as a cost-effective treatment option for a selected group of patients. However, as noted by the clinical expert in TA494 bariatric surgery is highly effective but only a small proportion (around 0.1% of those eligible for bariatric surgery) receive surgery. Bariatric surgery is however included in the economic model as a downstream event.

A6. It is also stated that "The treatment setting for these patients would be in a specialist tier 3 weight assessment and management clinic (WAMC) service, offering lifestyle modification advice, pharmacotherapy, psychological treatment as well as assessing patients for bariatric surgery" (CS, Document B, page 10). However, NICE Clinical Guideline 189 states that "Currently, tier 3 services are not comprehensively available across the country so funding may be needed to set up or expand the services" (Costing report: Obesity Implementing the NICE guideline on obesity (CG189),[1] November 2014, page 6).

A. Please clarify how the intervention can be delivered in areas where tier 3 services are not available.
B. According to NICE guidelines,[2] individuals can be considered for Tier 3 services if they have complex disease states, do any of the trial participants fit this description? If so, please provide details.

Company responses:

A. The Costing report from NICE CG 189 (obesity) from November 2014 noted '*Currently, tier 3 services are not comprehensively available across the country*

so funding may be needed to set up or expand the services' (NICE, 2014). The finding is not quantified but at the time and subsequently the effective commissioning and indeed provision of tier 3 services has remained a policy priority for NHS England. In more recent reviews attempting to map the provision of tier 3 services across England, a report issued by the All-Party Parliamentary Group for Obesity stated that 19.7% of CCGs state they do not commission a tier 3 service. However, this information needs to be coupled with Freedom of Information data from Local Authorities that suggests some of the above gaps in tier 3 service provision reported by CCGs may be covered by services commissioned directly through Local Authorities. An RCP commissioned assessment on National mapping of weight management services reports that Local Authorities may be responsible for 42% of all tier 3 services across England (Royal College of Physicians, 2015).

More broadly, it is also clear that from a policy perspective NHS England has maintained Obesity and prevention of Type 2 Diabetes as a priority within the recently published Long-term Plan and indeed the LTP implementation plan. The latter confirms an additional targeted funding for 2020/21 and 2021/22 for an enhanced weight management support offer for those with a BMI of 30+ with Type 2 diabetes or hypertension and enhanced Tier 3 services for people with more severe obesity and comorbidities. NHS England has also focussed on expanding the provision of Tier 3 weight management services within the 'Getting It Right First Time' (GIRFT) programme. It is understood that the Endocrinology workstream has included questions regarding the provision of tier 3 services as part of the assessments of all NHS Trusts across England. If during these assessments, the NHS Trust states that no tier 3 weight management service is commissioned, the assessment will make a recommendation as part of the final report, that such a service is established. No data is yet available from this GRIFT work stream.

B. On reviewing the relevant NICE guidelines mentioned, there is an example of a complex disease state cited, but not a definition. It may be possible to run a post hoc analysis across the trial participants if a clear, defined criteria for complex disease can be established in addition to that as already defined by the index

population. This would be contingent on data relevant to the definition of complex disease state having been collected within the trial. The example cited in the NICE guideline of a complex disease state mentions '*the additional support needs of people with learning disabilities*' (NICE, 2014), due to the nature of clinical trial design it would likely limit the scope of participation of such patients and therefore limit the value in further post hoc analysis. Further to the aforementioned NICE guideline criteria for referral to tier 3 services, NHS England has subsequently issued guidance regarding the Eligibility Criteria: NHS Diabetes Prevention Programme and Weight Management Services (NHS England, 2016). This guidance refers to tier 3 weight management services being suitable for people with complex obesity and within this description it specifically supports the eligibility of people with BMI >35 kg/m^2 plus non-diabetic hyperglycaemia and co-morbidities, in alignment with the proposed index population within the CS (see section 7.2 in NHS England, 2016).

COMPARATOR

A7. The comparator in the company submission is described as 'standard management without liraglutide 3.0mg'. Please define standard management. Please clarify whether this was the same across all sites in Trial 1839; and, if not, please explain what the differences were.

Company response:

In trial 1839 'standard management without liraglutide 3.0mg' refers to counselling on life-style modification according to the study protocol, which means that patients received both dietary counselling and physical activity encouragement. Standard management was the same across all sites, except for the qualification of dieticians, which were based on local/national standards. Specific details of standard management can be found in our response to question A11.

Clarification questions

INCLUDED TRIALS

A8. Priority question: Do any of the other Liraglutide trials (other than Trial 1839), include patients in the index population (as specified in your response to question A5) or according to the criteria: 'BMI ≥35 kg/m2, prediabetes and high risk of CVD' patients? If so, please specify which trials, how many patients with these characteristics were included in each arm and please provide all relevant outcomes for these patients**.**

Company response:

Trial 1839 is the most significant evidence base for our submission, as it contained 800 patients who met the criteria of BMI ≥35 kg/m^2, prediabetes and high risk of CVD. It also has the longest duration of all the trials and reflects standard practice in the UK. It thus forms the best available evidence base for decision making in the index population.

There are four trials sponsored by Novo Nordisk, investigating liraglutide 3.0mg: SCALE Sleep Apnoea (trial 3970), SCALE maintenance (trial 1923), SCALE Intensive Behavioural Therapy (IBT) (trial 4274) and the Phase 2 dose-finding trial (trial 1807). The number of patients relating to the index population is outlined below. Due to the small patient numbers, differences in study design, heterogeneity of the study population and treatment duration we do not believe these data will help inform decisions regarding the use of liraglutide 3.0mg for the treatment of obesity in the index population.

The Phase 2 trial 1807 is described in response to question A9.

SCALE sleep apnoea (trial 3970) required patients to have moderate to severe sleep apnoea for participation but not managed on the standard treatment, Continuous Positive Airway Pressure (CPAP). The trial had a different treatment period of only 32 weeks (compared to trial 1839 with a treatment period of 52 weeks and a further 104 week follow-up) and the placebo arm of the trial does not reflect UK clinical

practice for patients with sleep apnoea. We have analysed SCALE sleep apnoea to find the number of mild to moderate sleep apnoea patients fulfilling the index population. The number of patients fulfilling these criteria is shown below in Table 2.

Table 2: Patients fulfilling the index population criteria in SCALE sleep apnoea

SCALE sleep apnoea (trial 3970)		
Subgroup/number of subjects	Lira 3.0 mg	Placebo
BMI ≥35 kg/m^2, prediabetes and high risk of CVD	49	45

SCALE maintenance (trial 1923) included patients who lost ≥5% of initial body weight during a variable length (4-12 weeks) low-calorie diet run-in period. The number of patients fulfilling the criteria BMI ≥35 kg/m^2, prediabetes and high risk of CVD is shown below in Table 3.

Table 3: Patients fulfilling the index population criteria in SCALE maintenance

SCALE maintenance (trial 1923)		
Subgroup/number of subjects	Lira 3.0 mg	Placebo
BMI ≥35 kg/m^2, prediabetes and high risk of CVD	51	48

Similarly, SCALE Intensive Behavioural Therapy, IBT (trial 4274), also had few subjects that fit the index population (Table 4). This trial was a single-site, randomised, open-label, parallel-group study conducted in primary care in the United States.

Table 4: Patients fulfilling the index population criteria in SCALE IBT

SCALE IBT (trial 4274)		
Subgroup/number of subjects	Lira 3.0 mg	Placebo
BMI ≥35 kg/m^2, prediabetes and high risk of CVD	38	26

A9. Priority question: Trial 1807 (NCT00422058) is a Phase 2 dose-finding trial in adult patients with obesity or overweight (without type 2 diabetes). 564 patients were randomised in a 1:1:1:1:1:1 manner to receive one of four doses of liraglutide (1.2, 1.8, 2.4 or 3.0mg once daily), or placebo (once daily) or orlistat (120 mg three times

daily). This trial was of 20 weeks duration with an extension period of 84 weeks. Please provide data for the index population (as specified in your response to question A5) or the 'BMI ≥35 kg/m2, prediabetes and high risk of CVD'-subgroup for placebo, liraglutide 3mg and orlistat, for the outcomes reported in the following tables from Astrup 2009[3]:

- Table 2 (changes in bodyweight, waist circumference blood pressure and prediabetes status from randomisation to week 20)
- Table 4 (safety data at week 20) and Table 5 (Adverse events with an incidence of 10% or more in any treatment group at week 20)
- the same data at 104 weeks.

Please also provide the full Clinical Study Report for Trial 1807.

Company response:

Very few patients in the Phase 2 dose finding trial (trial 1807), matched the index population (Table 5). In addition the trial duration was only 32 weeks.

Table 5: Patients fulfilling the index population criteria in Phase II dose-finding study

Phase II dose-finding study (1807)			
Subgroup/number of subjects	Lira 3.0 mg	Placebo	Orlistat
BMI ≥35 kg/m^2, prediabetes and high risk of CVD	13	16	10

The full Clinical Study Report is provided as requested. However, the Clinical trial Report does not report outcomes for the index population.

TRIAL 1839

A10. Priority question: Please provide the full Clinical Study Report for Trial 1839. Please also ensure that data are included on all outcomes and baseline

Clarification questions

characteristics for the ‘BMI ≥35 kg/m2, prediabetes and high risk of CVD subgroup’ (see also questions A14 and A16 for specifics).

Company response:

The full Clinical Study Report for Trial 1839 has been provided as PDF files. All outcomes for the index population (BMI ≥35 kg/m^2, prediabetes and high risk of CVD subgroup) not included in Appendix E of the CS, are submitted as ‘Appendix E: Post hoc analysis – Supplementary data 1’ as a PDF file.

A11. Please provide full details of the diet (500 kcal/day deficit diet) and exercise (at least 150 minutes of physical activity per week) in both arms and any additional tier 3 weight management/obesity services patients received in both arms. Please explain whether adherence to diet and exercise regimes was monitored in both arms; and if so, please provide the results by treatment arm for the index population.

Please also explain how long participants had to engage in diet and exercise programs prior to commencing pharmacotherapy.

Company response:

In trial 1839, all patients received standardised counselling on life-style modification according to the study protocol in both treatment arms. This meant that patients received both dietary counselling and physical activity encouragement.

Diet

Diet counselling was administered by a qualified dietician according to local standards and delegated by the Principal investigator of the site. Subjects were put on a hypo-caloric diet based on their total energy expenditure (TEE), stratified on age and gender. An energy deficit was calculated for each subject by subtracting 500kcal/day from the TEE estimate to produce the final target value. The TEE was calculated by multiplying the estimated basal metabolic rate (BMR) (see table 6 below) with a physical activity level (PAL) value of 1.3, i.e. TEE (kcal/day) = BMR x

1.3. This calculation was based on the 2004 equations by the WHO (World Health Organisation, 2004).

Table 6: Equations for estimating BMR, kcal/day (World Health Organisation, 2004)

Sex	Age	BMR (kcal/day)
Males	18-30 years	15.057 x actual weight in kg + 692.2
	31-60 years	11.472 x actual weight in kg + 873.1
	>60 years	11.711 x actual weight in kg + 587.7
Females	18-30 years	14.818 x actual weight in kg + 486.6
	31-60 years	8.126 x actual weight in kg + 845.6
	>60 years	9.082 x actual weight in kg + 658.5

A diet was recommended based on a maximum energy source of 30% from fat, approximately 20% from protein, and 50% from carbohydrates. The hypo-caloric diet was continued after randomisation and throughout the treatment period.

Adherence to the visit schedule was a recommendation as counselling could be done either in a group or individually at the dietician's discretion. For the purpose of diet counselling, all subjects were instructed by dieticians to keep a 3-day food diary. This food diary was used by the dietician to assess compliance with the prescribed diet. This was handed out at visit 2, 5, 7, 9, 11, 13, 16 and 19a.

Exercise

Subjects were also encouraged to increase and/or maintain their physical activity levels to around 150 minutes per week. Subjects were asked if they performed less than half an hour, between half an hour and 1 hour, or more than 1 hour of physical activity per day at weeks 0, 8, 16, 24, 32, 49, 56 and, for the re-randomised treatment period, 64. An increase in physical activity was re-enforced by use of pedometers provided per protocol at visit 3 (baseline/randomisation) and encouraged at each visit.

Adherence and existence of pre-trial requirements

Compliance to diet and physical activity was assessed at visits 3, 6c, 8, 10, 12, 14,

Clarification questions

17 and 20a, in both treatment arms. Whether or not the patient was in compliance with the prescribed diet was at the discretion of the dietician after review of the food diary.

Data collected in Trial 1839 included an assessment of whether the patients complied with dietary & physical activity advice as judged by the dietician. These are shown in table 7 and 8 respectively. It should be noted that the assessments by dieticians may be subject to bias as patients who lose weight may be judged as more compliant than those who do not.

Table 7: Adherence to dietary advice in the index population

Adherence to dietary advice				
	Liraglutide 3.0mg		**Placebo**	
	N	**%**	**N**	**%**
Week 16	480		237	
Generally followed diet directions	228	43	79	29.3
Almost followed diet direction	192	36.2	112	41.5
Did not follow diet directions	50	9.4	44	16.3
Unknown	10	1.9	2	0.7
Not applicable	0	0	0	0
Week 56	412		197	
Generally followed diet directions	159	30	48	17.8
Almost followed diet direction	156	29.4	90	33.3
Did not follow diet directions	73	13.8	38	14.1
Unknown	21	4	20	7.4
Not applicable	3	0.6	1	0.4
Week 104	412		135	
Generally followed diet directions	111	20.9	39	14.4
Almost followed diet direction	145	27.4	62	23
Did not follow diet directions	61	11.5	33	12.2
Unknown	10	1.9	1	0.4
Not applicable	0	0	0	0
Week 160	295		125	
Generally followed diet directions	103	19.4	34	12.6
Almost followed diet direction	118	22.3	52	19.3
Did not follow diet directions	56	10.6	33	12.2
Unknown	18	3.4	6	2.2
Not applicable	0	0	0	0

Clarification questions

Table 8: Adherence to physical activity advice in the index population

Adherence to physical activity advice				
	Lira		Placebo	
	N	%	N	%
Week 0	530		270	
More than one hour per day	64	12.1	26	9.6
Between half and one hour per day	156	29.4	87	32.2
Less than half an hour per day	309	58.3	157	58.1
Unknown	1	0.2	0	0
Week 16	525		263	
More than one hour per day	72	13.6	23	8.5
Between half and one hour per day	189	35.7	120	44.4
Less than half an hour per day	240	45.3	113	41.9
Unknown	24	4.5	7	2.6
Week 56	525		263	
More than one hour per day	72	13.6	21	7.8
Between half and one hour per day	199	37.5	100	37
Less than half an hour per day	206	38.9	107	39.6
Unknown	48	9.1	35	13
Week 104	525		263	
More than one hour per day	58	10.9	25	9.3
Between half and one hour per day	164	30.9	90	33.3
Less than half an hour per day	246	46.4	111	41.1
Unknown	57	10.8	37	13.7
Week 160	525		263	
More than one hour per day	59	11.1	21	7.8
Between half and one hour per day	141	26.6	71	26.3
Less than half an hour per day	258	48.7	129	47.8
Unknown	67	12.6	42	15.6

The eligibility criteria for trial 1839 stated that subjects needed to have had a stable weight and lifestyle for 3 months. The relevant sections are:

- Inclusion criteria 3: stable body weight (less than 5kg self-reported change during the previous 3 months).
- Exclusion criteria 11: Diet attempts using herbal supplements or over-the-counter medications within 3 months before screening visit 1.
- Exclusion criteria 12: Current participation in an organised weight reduction programme (or within the last 3 months) and/or are currently using or have used within 3 months before screening visit 1: pramlintide, sibutramine, orlistat, zonisamide, topiramate, phenteremine, or metformin (either by prescription or as part of a clinical trial).

Clarification questions

A12. Priority question: The evidence within this submission is based on a subgroup of Trial 1839 – SCALE obesity and prediabetes (NCT01272219); i.e. the 'BMI ≥35 kg/m2, prediabetes and high risk of CVD' subgroup. Does this subgroup in the trial fulfil all criteria for this subgroup as specified in the CS i.e. with a 'BMI ≥35 kg/m2, prediabetes and high risk of CVD' or is it a smaller subgroup of patients with a 'BMI ≥35 kg/m2, prediabetes and high risk of CVD' and who have also either failed on orlistat or are unwilling/unable to undergo bariatric surgery? If there were patients included in Trial 1839 who have not failed on orlistat (or for whom this is not known), then please provide the number of patients in each arm in each of the three populations (FAS (N=2254), the 'BMI ≥35 kg/m2, prediabetes and high risk of CVD'-subgroup (N=800) and the (BMI ≥35 kg/m2'-subgroup (N=1021)) who have previously received orlistat. Please also provide the number of patients in each arms in each of the three populations who have failed on orlistat (please also provide a definition of 'failure on orlistat').

Company response:

Data on previous treatment with orlistat, or any other anti-obesity pharmacotherapy was not collected in the study. Trial 1839 had the following exclusion criteria: *Current participation in an organised diet reduction program (or within the last 3 months) and /or are currently using or have used within three months before Screening visit 1: pramlintide, sibutramine, orlistat, zonisamide, topiramate, phenteremine, or metformin (either by prescription or as part of a clinical trial)*.

Therefore, patients taking orlistat therapy within 3 months of study start were excluded from the study. As part of expert advice, we are submitting the comments by lead investigator in the trial Professor Carel le Roux to comment on orlistat, he commented "*The use of orlistat in current practice is very low for several of reasons:*

A. *The drug is more than 20 years old thus most patients with obesity would have had a trial of orlistat by their GPs at some point in their lives as it was the only obesity drug available to GPs in the NHS. Thus, by the time they come to Tier 3 they would have tried and failed orlistat.*

Clarification questions

B. *Doctors in Tier 3 have little success with orlistat as all those patients that would have responded to the medication when their GPs prescribed it won't be referred to Tier 3, thus there is an acquisition bias.*
C. *Most patients and doctors don't like the mechanism of action of orlistat and hence there is a low level of enthusiasm to retry the drug if patients have already failed.*

A13. Please provide the number of patients from the UK in each arm of the 'BMI ≥35 kg/m2, prediabetes and high risk of CVD' subgroup. Please provide information regarding where within the UK tier 3 services have been received by Trial 1839 participants.

Company response:

The total number of patients from the UK in Trial 1839 with 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD' subgroup was 41. Of these 29 patients were randomised to liraglutide 3.0mg and 12 were randomised to placebo. The following eight UK study sites were part of Trial 1839: Western Infirmary (Scotland), University of Aintree, University Hospitals of Coventry and Warwickshire NHS Trust, Hull Royal Infirmary, Charing Cross Hospital, Luton & Dunstable Hospital – Centre for Obesity Research, Morriston Hospital (Wales) and Guys Hospital. All eight study sites are specialist Tier 3 services in the UK.

A14. Priority question: In Table 6 (CS, page 42) baseline characteristics are presented for the FAS-population and in Table 18 (CS, page 66) baseline characteristics are presented for the 'BMI ≥35 kg/m2, prediabetes and high risk of CVD'-subgroup. Please present the data for all baseline characteristics listed in both tables by treatment arm, for the FAS population (N=2254), for the BMI ≥35 kg/m2'-subgroup (N=1021) and for the 'BMI ≥35 kg/m2, prediabetes and high risk of CVD'-subgroup (N=800).

Clarification questions

Company response:

The baseline characteristics for the FAS population by treatment arm can be found in the CS (Table 6, page 42). Baseline characteristics by treatment arm for the BMI ≥35 kg/m^{2}'-subgroup (N=1021) and for the 'BMI ≥35 kg/m^{2}, prediabetes and high risk of CVD'-subgroup (N=800) can be found in Tables 9 and 10 respectively.

Table 9: Baseline characteristics by treatment arm for the BMI ≥35 kg/m^{2} and prediabetes (N=1,021)

	Liraglutide 3.0mg (N=676)	Placebo (N=345)	Total (N=1,021)
Age (years)	48.1 (11.4)	48.6 (11.3)	48.3 (11.4)
Height (m)	1.66 (0.09)	1.67 (0.09)	1.67 (0.09)
Fasting body weight (kg)	115.8 (20.3)	116.4 (20.1)	116.0 (20.2)
BMI (kg/m^{2})	41.7 (5.6)	41.7 (5.2)	41.7 (5.5)
HbA_{1c} (%)	5.8 (0.4)	5.8 (0.3)	5.8 (0.3)
Fasting plasma glucose (mmol/L)	5.7 (0.6)	5.6 (0.5)	5.7 (0.6)
Sex			
Female (%)	74.7%	75.7%	75.0%
Male (%)	25.3%	24.3%	25.0%
Race			
White	84.8%	84.3%	84.6%
Black or African American	10.2%	10.7%	10.4%
Asian	3.1%	2.9%	3.0%
Other[a]	1.8%	2.0%	2.0%
Smoker status			
Current smoker	13.5%	13.6%	13.5%
Never smoked	56.2%	60.3%	57.6%
Previous smoker	30.3%	26.1%	28.9%
History of CV disease (SMQ search)[b]			
Yes	14.2%	15.7%	14.7%
No	85.8%	84.3%	85.3%
Dyslipidaemia[b]			
Yes	33.9%	35.7%	34.5%
No	66.1%	64.3%	65.5%
Hypertension[b]			
Yes	47.2%	49.0%	47.8%
No	52.8%	51.0%	52.2%

Clarification questions

a including “American Indian or Alaska Native”, “Native Hawaiian or other Pacific Islander” or “Other”;
b History of CV disease was based on an SMQ search of the medical history including Ischaemic heart disease, Cardiac failure, Central nervous system haemorrhages, Cerebrovascular conditions and Embolic and thrombotic events. Dyslipidaemia was found by SMQ search of the medical history. Hypertension was found by SMQ search of the medical history.
Values for continuous variables are means. Values in parentheses are standard deviations; CV: cardiovascular; N: number of patients; SMQ: standard medical query

Table 10: Baseline characteristics by treatment arm for the BMI ≥35 kg/m^2, prediabetes and high risk of CVD (N=800)

	Liraglutide 3.0mg (N=530)	Placebo (N=270)	Total (N=800)
Age (years)	48.1 (11.3)	48.2 (11.1)	48.2 (11.2)
Height (m)	1.66 (0.09)	1.67 (0.09)	1.67 (0.09)
Fasting body weight (kg)	115.6 (19.8)	116.5 (19.8)	115.9 (19.8)
BMI (kg/m^2)	41.7 (5.4)	41.9 (5.3)	41.7 (5.3)
HbA_{1c} (%)	5.8 (0.3)	5.8 (0.3)	5.8 (0.3)
Fasting plasma glucose (mmol/L)	5.7 (0.6)	5.6 (0.5)	5.7 (0.6)
Sex			
Female (%)	75.7%	75.9%	75.8%
Male (%)	24.3%	24.1%	24.3%
Race			
White	86.2%	84.1%	85.5%
Black or African American	8.2%	10.0%	9.3%
Asian	3.6%	3.7%	3.6%
Other[a]	1.4%	2.3%	1.6%
Smoker status			
Current smoker	15.7%	13.7%	15.0%
Never smoked	55.1%	59.3%	56.5%
Previous smoker	29.2%	27.0%	28.5%
History of CV disease (SMQ search)[b]			
Yes	12.5%	15.2%	13.4%
No	87.5%	84.8%	86.6%
Dyslipidaemia[b]			
Yes	33.6%	34.8%	34.0%
No	66.4%	65.2%	66.0%
Hypertension[b]			
Yes	48.5%	48.9%	48.6%
No	51.5%	51.1%	51.4%

a including “American Indian or Alaska Native”, “Native Hawaiian or other Pacific Islander” or “Other”;
b History of CV disease was based on an SMQ search of the medical history including Ischaemic heart disease, Cardiac failure, Central nervous system haemorrhages, Cerebrovascular conditions and Embolic and thrombotic events. Dyslipidaemia was found by SMQ search of the medical history. Hypertension was found by SMQ search

Clarification questions

of the medical history.
Values for continuous variables are means. Values in parentheses are standard deviations; CV: cardiovascular; N: number of patients; SMQ: standard medical query

A15. Priority question: On page 36 of the CS, it is stated that the comparator is: "Once daily administration of placebo (in addition to a 500 kcal/day deficit diet and at least 150 minutes of physical activity per week)". However, the relevant population in the CS is described as 'BMI ≥35 kg/m2, prediabetes and high risk of CVD' and that "this subpopulation should be treated in a specialist tier 3 service, offering specialist services including specialist dietary advice, pharmaco-therapy, psychological support as well as assessing patients for bariatric surgery" (CS, Document A, page 9).

A. Please clarify whether the patients in the comparator arm received all specialist tier 3 services.
B. If not, please comment on the implications of this difference with UK clinical practice and please explain whether the effectiveness of liraglutide in Trial 1839 will be different when offered in combination with TIER 3 UK clinical practice (compared with control in combination with TIER 3 UK clinical practice)?
C. Given the variety of countries included in clinical trial 1839 and the fact that diets were only restricted to a reduced calorie intake of 500 calories per day (and not, e.g. based on specific proportions of macronutrients), please justify that the diets used in the trial are representative for the UK population.

Company responses:

A. Trial 1839 was a double-blind study conducted in 191 clinical research sites in 27 countries in Europe, North America, South America, Asia, Africa and Australia. Patients in the comparator arm (placebo injection) and the active arm (liraglutide 3.0mg injection) all received the same standard management as described in A11, this is representative of a tier 3 service. As specialist tier 3 services are unique to the UK, only those patients in the UK would have been treated in these centres. However, study sites outside of the UK are representative of tier 3

services.

B. The difference between the effectiveness of liraglutide 3.0mg in a specialist tier 3 centre in the UK and those in the clinical trial is expected to be minimal, as both are specialist centres for weight management. Professor Carel le Roux, who is the lead investigator in the SCALE Diabetes and Prediabetes trial (le Roux, et al., 2017) advised the company that '*Standard management for obesity across the world deliver similar results'*. He also referred to two recent real-world publications in Canada (Wharton, 2019) and Abu Dhabi (Suliman, 2019) showing similar results to the phase 3 liraglutide 3.0mg clinical trial programme (SCALE). The company recommends that patients should be treated with liraglutide 3.0mg in specialist tier 3 services to enable patients to access specialist services including dietary advice.

C. The response to question A11 gives the specific details of standard management in Trial 1839, including the reduced calories intake and recommended macronutrient energy (approximately 30% from fat, 20% from protein and 50% carbohydrate). We believe this is representative of a Tier 3 standard management service in the UK.

A16. Priority question: For the main trial (Trial 1839) please provide the data for all outcomes for the 'BMI ≥35 kg/m2, prediabetes and high risk of CVD' subgroup (N=800) and for the 'BMI ≥35 kg/m2'-subgroup (N=1021) for each treatment arm; including 'treatment discontinuation due to adverse events (before and after the stopping rule (i.e. after 12 weeks))' and '% change in BMI'. Please also provide the between group effect sizes and 95% CIs for all outcomes. Please provide data using all three methods of analyses (LOCF, BOCF and ME-MI) for up to 3-years follow-up. Specifically:

A. In Table 19 (CS, page 69), the company presents results for weight loss and waist circumference for the 'BMI ≥35 kg/m2, prediabetes and high risk of CVD'-subgroup. Please provide data in the same format for all other outcomes mentioned in Table 1 (CS, page 14); i.e. BMI, Incidence of type 2 diabetes,

Cardiovascular events, Mortality, Adverse effects of treatment, and Health-related quality of life (SF-36). Please provide all results (as above plus Weight loss and Waist circumference) also using BCOF and ME-MI methods. Please also provide these data for 'treatment discontinuation due to adverse events (before and after the stopping rule (i.e. after 12 weeks))'. Please also provide the between group effect sizes and 95% CIs for all outcomes

B. In Table 24 (CS, page 75) a summary of TEAEs are presented from Trial 1839 (week 0 to 162) for the FAS. Please provide the same data for the two subgroups (the 'BMI ≥35 kg/m2, prediabetes and high risk of CVD'-subgroup (N=800) and the (BMI ≥35 kg/m2'-subgroup (N=1021)).
C. Please provide a full list of individual AEs and SAEs (e.g. all AEs experienced by more than 5% of patients in either arm, and all SAEs in >0.2% of patients – see Table 3 in Pi-Sunyer 2015[4]) for the three populations (FAS (N=2254), the 'BMI ≥35 kg/m2, prediabetes and high risk of CVD'-subgroup (N=800) and the (BMI ≥35 kg/m2'-subgroup (N=1021)). Please present these data by treatment arm.

Company responses:

A. Further statistical analyses are presented in 'Appendix E: Post hoc analysis – Supplementary data 1', submitted in PDF. Table 11 below details were the different analyses can be found.

Table 11: Additional data requests location

	Relevant tables in Appendix E: Post hoc subgroup analysis - Supplementary data 1
BMI	11-16
Incidence of type 2 diabetes	Reported in Appendix E in CS, Tables 75-76
Cardiovascular events	3-6
Mortality	7-10

Clarification questions

Health-related quality of life (SF-36)	17-22
Body weight	23-28
Waist circumference	29-34
Systolic blood pressure	35-40
HDL Cholesterol	41-46
Total cholesterol	47-52
HbA1c (%)	53-58
Summary of treatment emergent adverse events	59-68
Discontinuation due to adverse events before and after stopping rule	69-70

B. A summary of Treatment-Emergent Adverse Events (TEAEs) are presented below in Table 12 and 13 for the two requested populations.

Clarification questions

Table 12: Treatment-Emergent Adverse Events (TEAEs) for the subgroup BMI ≥35 kg/m^2 and prediabetes (N=1021).

	Liraglutide 3.0mg				Placebo			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Number of patients	676				345			
Years of observation time	1502.9				681.6			
Events	652	96.4	7554	502.6	308	89.3	2704	396.7
Serious adverse events	106	15.7	185	12.3	49	14.2	76	11.1
Severity								
Severe	157	23.2	294	19.6	55	15.9	98	14.4
Moderate	476	70.4	2415	160.7	212	61.4	825	121.0
Mild	612	90.5	4845	322.4	291	84.3	1780	261.1
Missing	0	-	-	-	1	0.3	1	0.1
Relationship to investigational product								
Probable	305	45.1	872	58.0	73	21.2	113	16.6
Possible	433	64.1	1376	91.6	147	42.6	355	52.1
Unlikely	590	87.3	5278	351.2	294	85.2	2210	324.2
Missing	23	3.4	28	1.9	22	6.4	26	3.8
Outcome								
Recovered	640	94.7	6373	424.0	302	87.5	2211	324.4
Fatal	0	-	-	-	1	0.3	1	0.1
Recovering	38	5.6	51	3.4	16	4.6	18	2.6
Recovered with sequelae	4	0.6	4	0.3	0	-	-	-
Not recovered	27	4.0	41	2.7	11	3.2	15	2.2
Unknown	-	-	-	-	-	-	-	-
Leading to withdrawal	85	12.6	-	-	15	4.3	-	-

Clarification questions

Table 13: Treatment-Emergent Adverse Events (TEAEs) for the subgroup BMI ≥35 kg/m^2, prediabetes and high risk of CVD (N=800).

	Liraglutide 3.0mg				Placebo			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Number of patients	530				270			
Years of observation time	1170.8				528.9			
Events	512	96.6	5794	494.9	240	88.9	2065	390.5
Serious adverse events	82	15.5	142	12.1	37	13.7	59	11.2
Severity								
Severe	119	22.5	240	20.5	43	15.9	68	12.9
Moderate	370	69.8	1876	160.2	165	61.1	630	119.1
Mild	476	89.8	3678	314.1	227	84.1	1367	258.5
Missing	-	-	-	-	-	-	-	-
Relationship to investigational product								
Probable	228	43.0	648	55.3	58	21.5	92	17.4
Possible	339	64.0	1086	92.8	110	40.7	287	54.3
Unlikely	460	86.8	4038	344.9	228	84.4	1667	315.2
Missing	17	3.2	22	1.9	17	6.3	19	3.6
Outcome								
Recovered	502	94.7	4923	420.5	236	87.4	1681	317.9
Fatal	0	-	-	-	1	0.4	1.	0.2
Recovering	25	4.7	33	2.8	15	5.6	17	3.2
Recovered with sequelae	2	0.4	2	0.2	0	-	-	-
Not recovered	281	53.0	807	68.9	131	48.5	356	67.3
Unknown	18	3.4	29	2.5	7	2.6	10	1.9
Leading to withdrawal	62	11.7	-	-	13	4.8	-	-

C. A full list of AEs and SAEs can be found in ‘Appendix E: Post hoc analysis – Supplementary data 2’, in PDF format.

Clarification questions

A17. It is mentioned in the company submission (CS, page 9) that "As part of the EMA licence, a stopping rule is applied to 'non-responders' of liraglutide 3.0mg, where treatment should be discontinued after 12 weeks on the 3.0mg/day maintenance dose if patients have not lost 5% of their initial body weight." However, Trial 1839 did not include a stopping rule. Please explain how this affects the representativeness and applicability of Trial 1839 for the UK.

Company response:

The stopping rule is part of the EMA licence and is common to all other licenced anti-obesity medicines (including those now discontinued due to safety concerns) and therefore we do not see any issues with representativeness of Trial 1839 for the UK.

Early response to treatment (defined as ≥5% weight loss) is clinically useful to identify individuals who would achieve clinically meaningful weight loss at 56 weeks (Fujioka, et al., 2016). By stopping drug therapy early in patients unlikely to achieve clinical benefit, clinicians can minimise drug exposure, improve the benefit:risk ratio for the patient (Apovian, et al., 2015), and use health resources more effectively. Early weight loss, whether through lifestyle (Stotland & Larocque, 2005) (Handjieva-Darlenska, et al., 2010) (Unick, et al., 2015) or pharmacotherapy (Rissanen, et al., 2003) (Fujioka, et al., 2016) (Finer, et al., 2006) (Smith, et al., 2014), is a good predictor of long-term weight loss.

Although a threshold of 5% weight loss after 12 weeks on full-dose treatment is the general criterion for stopping anti-obesity medication, variability across types of anti-obesity medications exists (Rebello, et al., 2016). In addition, EMA and FDA sometimes apply different stopping rules, which is also the case for liraglutide 3.0mg (FDA guidance is 4% weight loss after 12 weeks on full-dose) (FDA, 2014). A consequence of this is that the appropriate stopping rule cannot be identified pre-licence and thus not incorporated in the design of Phase 3a studies.

As the stopping rule was not part of Trial 1839, the outcomes of those patients failing to meet the stopping rule and who would therefore in clinical practice discontinue therapy is unknown. As noted below in question A18, treatment efficacy for non-

responders was modelled using data from the placebo arm as efficacy. We asked Professor Carel le Roux to comment on the stopping rule, he commented '*The stopping rule is very important to doctors as it helps us stop the medication when it doesn't work. This way we avoid the side effects of the medications in patients who do not benefit. The fact that we can tell so early after we started the medication is a real advantage'.*

A18. Priority question: In the cost-effectiveness model, treatment efficacy in liraglutide non-responders was modelled using data from the placebo arm as efficacy data post non-response and liraglutide discontinuation, i.e. in line with the stopping rule, was not obtained in the trial (See also question B6). It is most probable that patients who do not respond in the liraglutide arm are quite different to those who enter the trial and who are randomised to either arm, including the placebo arm. It is also plausible that such patients might have outcomes that are not only worse than those of responders in the liraglutide arm, but also than those in the placebo arm, which are an average of both responders and non-responders in that arm. Indeed, a better proxy for non-responder outcomes in clinical practice is likely to be those from non-responders in the trial, either those from the liraglutide arm or the placebo arm. Please provide a comparison of all outcomes including change in fasting body weight, BMI, HbA1c and SBP of responders and non-responders at week 16 and over time separately in the liraglutide arm and in the placebo arm.

Company response:

Tables 14 and 15 illustrate the outcomes for fasting body weight, BMI, HbA_{1c} and SBP for early responders and non-responders (and total) for each treatment arm in the index population. Analyses of all outcomes can be found in 'Supplementary data – Early responder and non-responder outcomes' as a PDF file.

Clarification questions

Table 14: Outcomes for the liraglutide 3.0mg treatment arm split in early responders and non-responders for the index population

Liraglutide 3.0mg treatment arm															
	Early responders (N=314) LS Mean (SE)					**Non-responders (N=216)** LS Mean (SE)					**Total (N=530)** LS Mean (SE)				
Week	16	28	56	104	160	16	28	56	104	160	16	28	56	104	160
Relative change in fasting body weight (%-point)	-8.50 (0.15)	-9.96 (0.23)	-10.91 (5.81)	-9.46 (6.68)	-8.02 (7.27)	-3.06 (0.14)	-3.45 (0.19)	-3.50 (0.28)	-3.23 (0.34)	-2.93 (0.36)	-6.27 (0.16)	-7.30 (0.21)	-7.88 (0.26)	-6.90 (0.29)	-5.92 (0.30)
Relative change in BMI (%)	-8.49 (0.15)	-9.95 (0.23)	-10.88 (0.33)	-9.44 (0.38)	-7.97 (0.41)	-3.14 (0.14)	-3.52 (0.19)	-3.61 (0.28)	-3.36 (0.34)	-3.12 (0.36)	-6.30 (0.16)	-7.32 (0.21)	-7.91 (0.26)	-6.95 (0.28)	-5.97 (0.30)
Change in HbA_{1c} (%-point)	-0.39 (0.01)	-0.43 (0.01)	-0.45 (0.01)	-0.59 (0.02)	-0.46 (0.02)	-0.27 (0.01)	-0.27 (0.02)	-0.27 (0.02)	-0.35 (0.01)	-0.28 (0.01)	-0.34 (0.01)	-0.36 (0.01)	-0.38 (0.01)	-0.49 (0.01)	-0.39 (0.01)
Change in SBP (mmHg)	-7.11 (0.57)	-6.22 (0.62)	-7.58 (0.58)	-6.21 (0.63)	-4.08 (0.62)	-4.35 (0.75)	-5.90 (0.75)	-5.40 (0.77)	-5.10 (0.75)	-4.18 (0.84)	-5.95 (0.46)	-6.08 (0.48)	-6.68 (0.47)	-5.73 (0.48)	-4.09 (0.51)

Table 15: Outcomes for the placebo treatment arm split in early responders and non-responders for the index population

Placebo treatment arm															
	Early responders (N=55) LS Mean (SE)					**Non-responders (N=215)** LS Mean (SE)					**Total (N=270)** LS Mean (SE)				
Week	16	28	56	104	160	16	28	56	104	160	16	28	56	104	160
Relative change in fasting body weight (%-point)	-8.40 (0.37)	-9.15 (0.55)	-8.82 (0.78)	-8.07 (0.90)	-7.29 (0.98)	-0.81 (0.14)	-0.68 (0.19)	-0.81 (0.28)	-0.48 (0.34)	-0.13 (0.36)	-2.38 (0.22)	-2.43 (0.29)	-2.48 (0.37)	-2.07 (0.40)	-1.65 (0.41)
Relative change in BMI (%)	-8.40 (0.37)	-9.07 (0.55)	-8.73 (0.79)	-7.92 (0.91)	-7.08 (0.99)	-0.81 (0.14)	-0.69 (0.19)	-0.81 (0.28)	-0.45 (0.34)	-0.08 (0.36)	-2.37 (0.22)	-2.41 (0.29)	-2.44 (0.37)	-2.00 (0.40)	-1.54 (0.41)
Change in HbA_{1c} (%-point)	-0.17 (0.03)	-0.21 (0.03)	-0.26 (0.03)	-0.39 (0.04)	-0.29 (0.04)	-0.02 (0.01)	-0.05 (0.02)	-0.05 (0.02)	-0.13 (0.02)	-0.09 (0.02)	-0.05 (0.01)	-0.08 (0.01)	-0.09 (0.02)	-0.19 (0.02)	-0.13 (0.02)
Change in SBP (mmHg)	-6.26 (1.35)	-3.59 (1.47)	-3.53 (1.38)	-3.89 (1.51)	-1.82 (1.49)	-0.13 (0.75)	-1.20 (0.76)	-1.28 (0.77)	-1.08 (0.75)	-0.84 (0.84)	-1.46 (0.65)	-1.70 (0.67)	-1.76 (0.66)	-1.72 (0.68)	-1.09 (0.71)

Section B: Clarification on cost-effectiveness data

Intervention and comparator

B1. Priority question: In the base case analysis, treatment with liraglutide 3.0mg was assumed to be maintained for two years (responders only).

1. From Figure 4 and Table 24 in the CS, it appears as if treatment discontinuation did occur after the initial 16 weeks. Please explain why no treatment discontinuation (e.g. due to adverse events or loss of efficacy) was included in the model during this period (besides the stopping rule as per the European licence).

2. Please provide a scenario analysis (and the accompanying model) in which treatment discontinuation is included during the two-year treatment period in the model. Please use similar assumptions for patients that discontinue treatment as used for non-responders. In addition, alternative scenarios may be added in which alternative assumptions are explored.

3. The treatment duration of 2 years is considered uncertain in CS Table 51. Please justify the plausibility of this assumption, for UK clinical practice, considering that based on CS Figure 4 more than half of the patients did not discontinue liraglutide after 3 year.

4. Please provide a scenario analysis (and the accompanying model) in which parametric survival models for treatment discontinuation are incorporated, estimated using the Trial 1839 data (see for instance CS Figure 4), consistent with NICE TSD 14. Please remove the fixed treatment duration (e.g. of 2 years) in this analysis and extrapolate treatment discontinuation based on the parametric survival model.

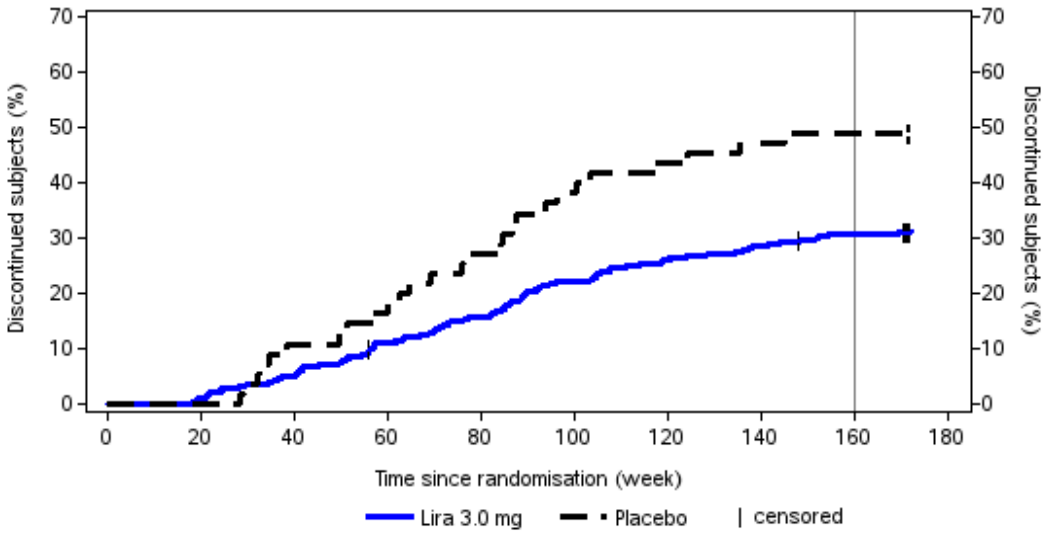
Company responses:

1. Treatment discontinuation is incorporated into the model by incorporating the stopping rule at 16 weeks. This is in line with other models including Ara et al

(Ara, et al., 2012) and effectively assumes that the stopping rule encapsulates the majority of discontinuation due to adverse events or loss of efficacy from liraglutide 3mg (an assertion which is corroborated by the Real World Evidence explained further in B1.3 below). Moreover, the impact of missing observations on outcomes was incorporated and evaluated via alternative imputation methods.

2. A scenario analysis was conducted whereby additional discontinuation (due to any reason) was incorporated per cycle (starting from cycle 3 and up to the maximum treatment duration of two years defined in the CS base case) in liraglutide early responders. Patients who discontinued treatment in cycle 2 due to non-response or other reasons were assumed to immediately loose the initial treatment benefit of liraglutide and continue treatment with diet and exercise. No discontinuation was applied in the diet and exercise arm, assuming diet and exercise would be continued lifelong. Patients who discontinued treatment from cycle 3 onwards (after 6 months of treatment) were assumed to gradually lose their initial liraglutide benefit according to the catch-up rate defined in the CS base case, after which, the values of their physiological parameters returned to baseline. Equally, the additional proportion of patients reverting to a normal glucose tolerance state with liraglutide (vs. diet and exercise) returned to a prediabetes state after liraglutide 3.0mg discontinuation and catch-up period.
   The per-cycle probability of discontinuation was sourced from an analysis of time to discontinuation in early liraglutide responders (Figure 2) and was applied additionally to the stopping rule discontinuation used in the CS base case (reflective of liraglutide 3.0mg marketing authorisation). The results of this analysis showed an increase in ICER with £7,761 per QALY (Table 16) compared with the revised CS base case (Table 54).

Figure 2: Time to discontinuation (weeks) in 0 to 172 weeks for the early responders in the index population



Subjects were off-drug in the observational follow-up period (weeks 160 to 172).
Subjects 428017 and 102025, both in Lira arm, are censored in weeks 57 and 149 resp. due to missing date and reason resp. of discontinuation.
High risk of CVD at baseline is determined by Total cholesterol > 5mmol/L or Systolic Blood Pressure > 140 mmHg or HDL < 40 mg/dL for men and < 50 mg/dL for women.
Early response status is determined by at least 5% loss of baseline weight at week 16.

nn8022/nn8022-exploratory/heewe017
02AUG2019:12:32:08 - f_dicont.sas/f_dicont_respo_39.png

Table 16: Scenario treatment discontinuation during the two-year treatment period

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0 mg	£21,650	18.467	15.191	£16,857
Diet & exercise	£20,270	18.417	15.109	
Incremental	£1,379	0.049	0.082	

3. Roughly half the patients in study 1839 persisted on therapy (both liraglutide 3.0mg and placebo) until the planned end of the study period (160 weeks plus 12 weeks off treatment follow-up). This 3 year treatment duration is longer than would be expected in clinical practise both in the UK and elsewhere. Evidence from a real-world study in the United States (Ganguly, et al., 2018), showed despite liraglutide 3.0mg having the highest persistence rate compared to four other anti-obesity pharmacotherapies, persistence at 15 months was only

26.6%. In relation to early discontinuation, the study also showed that the highest drop-outs occurred within the first 3 months, and up to 6 months, after which the drop-out rate was rather small (approximately 2% between 12 and 15 months). The authors believe this may have been due to some patients having unrealistic expectations of weight loss medication benefits and become discouraged early in therapy if results are not sufficiently immediate or dramatic.

Furthermore, in a systematic review of cost effectiveness studies in obesity (Ara, et al., 2012) commented 'the duration of treatment modelled was generally one-year'. A two-year treatment duration was assumed as the most plausible assumption in line with the results of a UK physicians' survey (see Appendix N of CS) which suggested an average treatment duration of 1-2 years. This assumption is however recognised to be associated with a degree of uncertainty and was therefore tested in scenario analyses encompassing one or alternatively three years treatment duration, assuming each time equal duration for liraglutide 3.0mg and diet and exercise.

4. NICE TSD 14 provides recommendations on how survival analysis should be undertaken (Latimer, 2013). Following a review of the survival analyses included in NICE TA's of metastatic and/or advanced cancer interventions, it provides recommendations for how survival analysis can be undertaken more systematically and guidance on how extrapolations should be assessed based on their internal and external validity. The document explains how the extrapolation approach should be undertaken and mentions it is particularly important to justify the plausibility of the extrapolated portion of any survival model chosen. It is our view, and which is corroborated by clinical opinion (see Appendix N in CS), that treatment with liraglutide 3.0mg will not continue beyond the period observed in trial 1839, and that in clinical practise, treatment will continue for a maximum of 1-2 years for responders. It is on this basis that we do not believe that extrapolation of treatment duration beyond that observed in the trial will have any plausibility. For this reason, we have chosen 2 years of treatment for responders in our base case, and that the impact of treatment for 1 and 3 years on outcomes are assessed in scenario analyses.

Nonetheless, an exploratory analysis was conducted whereby the time-to-discontinuation in liraglutide early responders (as illustrated in Figure 2 above) was extrapolated using different distributions in the parametric survival model. In this analysis, the observed time-to-discontinuation was applied for the first 3 years of modelling analysis after which a log-normal parametric model was selected. The log-normal model resulted as the best fit according to the Bayesian Information Criterion (BIC) and the second best fit according to the Akaike Information Criterion (AIC).

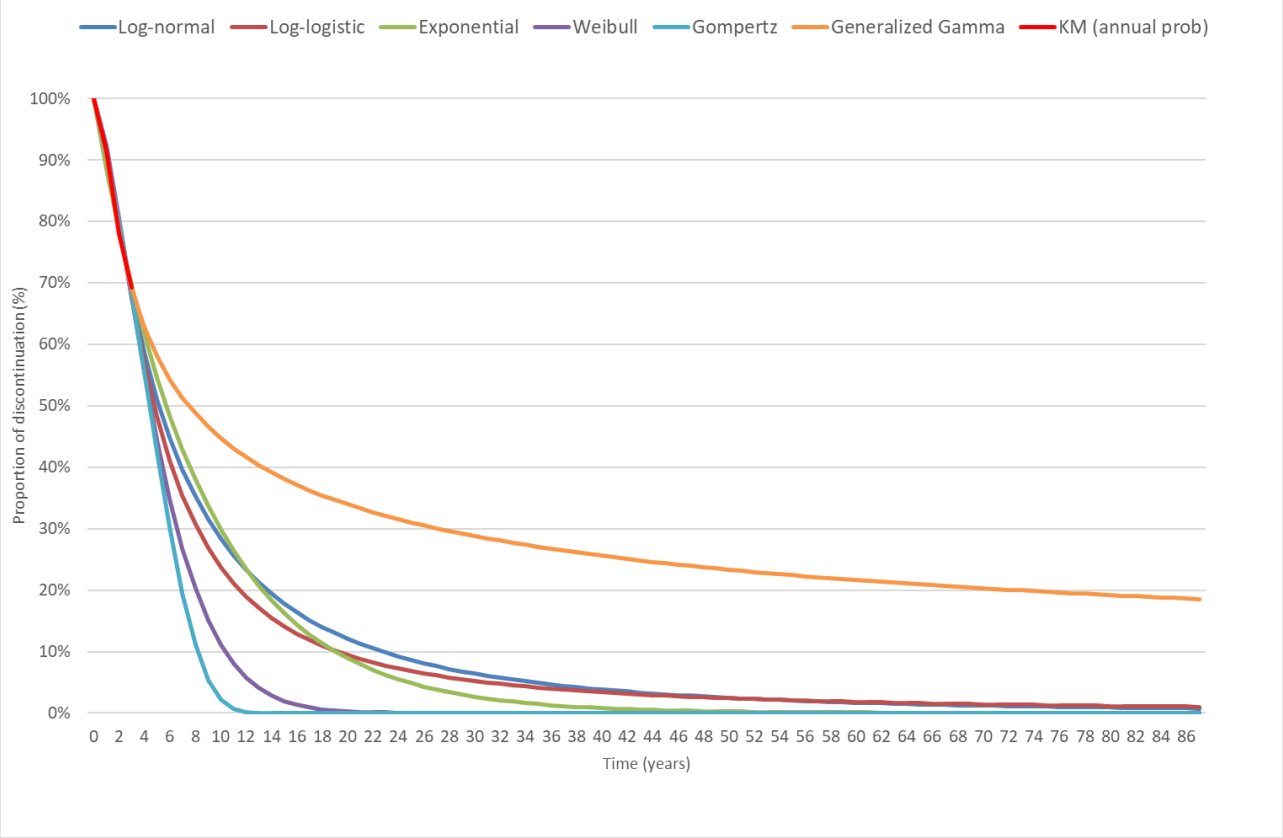
Table 17: Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC)

Distribution	BIC	AIC
Log-normal	**494.66**	487.16
Generalized Gamma	495.76	**484.51**
Log-logistic	500.32	492.82
Weibull	503.13	495.64
Exponential	508.91	505.16
Gompertz	511.03	503.53
Log-normal	494.66	487.16

Table note: The values in bold signal the lowest value for each criterion

The best fit according to the AIC criterion was a Generalized Gamma model; however the time-to-discontinuation extrapolation using a Generalized Gamma distribution showed patients continuing treatment up to 24 years which is highly implausible given real-world evidence on treatment duration (Ganguly, et al., 2018) (Wharton, 2019), as can be observed in Figure 3.

Figure 3: Time to discontinuation extrapolations using parametric survival functions



Several assumptions with regards to the continuation of treatment benefit had to be taken to perform the requested analysis. Patients continuing liraglutide 3.0mg treatment were assumed to maintain the LOCF efficacy observed at week 160 for as long as they remained on treatment; consistently, patients on diet and exercise were assumed to maintain the LOCF efficacy with placebo at week 160 for the entire time-horizon of the analysis. The additional proportion of patients reverting to a normal glucose tolerance state with liraglutide (vs. diet and exercise) returned to a prediabetes state after liraglutide 3.0mg discontinuation and catch-up period. As in scenario B1.2, patients who discontinued treatment in cycle 2 due to non-response or other reasons were assumed to immediately lose the initial treatment benefit of liraglutide 3.0mg and continue treatment with diet and exercise. No discontinuation was applied in the diet and exercise arm. Patients who discontinued liraglutide 3.0mg from cycle 3 onwards (after 6 months of treatment) were assumed to gradually lose their initial benefit according to the catch-up rate defined in the CS base case,

after which, the values of their physiological parameters returned to the corresponding values in the diet and exercise arm of the model. Results of this scenario are shown in the table below.

We consider this analysis as fully exploratory, given the high uncertainly with regards to both the continuation of treatment beyond 3 years and to the assumptions around efficacy of liraglutide 3.0mg and diet and exercise beyond the observed trial duration.

Table 18: Extrapolated treatment discontinuation, using parametric survival models

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0 mg	£20,101	18.625	15.594	£19,157
Diet & exercise	£17,505	18.544	15.458	
Incremental	£2,596	0.081	0.135	

B2. Priority question: As mentioned in A5, in the CS liraglutide is compared to standard management (a reduced calorie diet and increased physical activity). Contrary to the final scope issued by NICE, orlistat and bariatric surgery were not considered as comparators in the cost effectiveness model.

1. Please include orlistat as a comparator in the cost-effectiveness model.
2. Please include bariatric surgery as a comparator in the cost-effectiveness model.

Company response:

As noted earlier in response to question A5, orlistat and bariatric surgery are not considered relevant comparators for the index population (BMI ≥35kg/m^2, prediabetes and high risk of CVD).

Population

B3. Please justify that the baseline cohort characteristics used in the model are representative of the UK population with the target condition as specified in the CS (e.g., an average height of 1.66m).

Company response:

We believe patients in Trial 1839, specifically the subgroup we have identified, are representative of those typically seen in a tier 3 setting in the UK. Trial 1839 included 112 patients from 8 sites in the UK (see Table 5, CS), 41 of which fitted the criteria of the index population. A recent review corroborates our assertion. Alkharaiji et al. 2018 performed a systematic review of Tier 3 specialist weight management services in the UK (Alkharaiji, et al., 2018). The authors summarised the baseline characteristics of the 19 studies identified (where data was available) shown below. Table 18 compares the baseline characteristics of Trial 1839 all patients, Trial 1839 the index population (BMI ≥35 kg/m^2, prediabetes and high-risk CVD) and Alkharaiji et al. As can be seen from Table 18, the baseline characteristics from the three populations are similar with the notable difference being HbA1c which is higher in Alkharaiji et al. reflecting this cohort included patients with a diagnosis of type 2 diabetes. NB. Average height is not given in Alkharaiji et al. 2018 to allow comparison.

Table 18: Representativeness of baseline cohort characteristics

	1839 all patients	**1839 subgroup**	**Alkharaiji et al. 2018**
Mean age (years)	47.5	48.2	49.2
BMI (kg/m^2)	38.8	41.7	42.54
Weight (kg)	107.6	114.9	117.88
Waist circumference (cm)	116.6	122.3	126.9
HbA1c (%) (mmol/mol)	5.7% 38.8	5.8 % 39.9	7.5% 58.8

Fasting blood sugar (mmol/L)	5.5	5.7	5.44
Cholesterol (mmol/L)	5.0 in lira 3.0mg 5.1 in placebo	5.02	5.09
SBP (mmHg)	124.8 in lira 3.0mg 125.0 in placebo	126.4	134.7

Model structure

B4. Priority question: Given the model structure and that the clinical effectiveness of the intervention and comparator was introduced in the model through changes in BMI and cardio-metabolic risk factors, namely SBP, HDL cholesterol, and total cholesterol, please discuss the risk of double counting (e.g. due to cost and benefits are assumed to be additive whereas in reality they might be multiplicative) and justify why this is not an issue.

Company response:

In instances where the risk of events or the transitions between health states are predicted via multifactorial cardio-metabolic parameters and BMI (e.g. risk of type 2 diabetes, risk of CVD), the model uses published, validated risk equations whereby each parameter independently predicts the outcome of interest. For outcomes where no multifactorial risk equation was available (e.g. risk of knee replacement), BMI was the only predictor of risk. There was no additional effect of BMI on mortality, other than the one accounted for via the projected fatal events in the model.

Further, the health-economic analysis used a disease-free (baseline) utility function from Søltoft et al. (Søltoft, et al., 2009) adjusted for the presence of the following complications: cardiovascular, type 2 diabetes, respiratory, musculoskeletal problems and cancer (please also refer to our response on B16). Following an event or progression to a more debilitating heath-state, the baseline utility was adjusted

with condition-specific utility decrements (disutilities). All utility decrements used in the CS base case represent marginal disutilities substantiated via regression analyses of either Søltoft et al. or Sullivan et al. (Sullivan, et al., 2011), controlling for presence of complications. Indeed, the marginal disutilities reported by Sullivan et al. were obtained via a regression analysis of 135 ICD-9 chronic conditions, including type 2 diabetes, cardiovascular disease, cancer, and osteoarthritis. As such, we believe that the utility estimates are not double-counted in the base case analyses presented.

Finally, some marginal double-counting of chronic cardiovascular disease costs (e.g. secondary prevention medication such as diuretics, calcium channel blockers, angiotensin II receptor blockers, statins etc.) may have occurred when patients experienced different, multiple cardiovascular events in the model (e.g. stroke and ACS). However, given these medications are relatively inexpensive, and that only a minority of patients experience ACS and stroke in the model (at the end of the analysis time-horizon 1.47% and 1.57% of the liraglutide 3.0mg and diet and exercise cohorts respectively were in a health state encompassing both stroke and ACS event history), the effects of this double-counting on costs will be negligible.

B5. As stated in the CS, in the model, type 2 diabetes occurs when prediabetic or normal glucose tolerant patients develop type 2 diabetes, as well as when prediabetic patients experience a stroke or ACS event. This will overestimate the rate of development of Type 2 diabetes. It is also not a conservative approach given the higher chance of stroke or ACS event in the comparator arm and the accompanied consequences. Please provide a scenario analysis (and the accompanying model) assuming that prediabetic patients do not automatically develop Type 2 diabetes due to experiencing a stroke or ACS event.

Company response:

In preparing a response to this question we identified an inconsistency in the model (see end of document for further details). Using a revised version[1] of the model with the inconsistency amended (see accompanying model), a scenario analysis was conducted assuming prediabetic patients do not automatically develop type 2 diabetes after ACS or stroke. Results are outlined below.

Table 19: Scenario prediabetic patients do not develop type 2 diabetes after ACS or stroke

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,129	18.610	15.347	£26,026
Diet & exercise	£19,372	18.580	15.279	
Incremental	£1,757	0.031	0.068	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

We believe that this scenario provides an unfair representation of liraglutide 3.0mg benefits in the target population given the higher risk of cardiovascular disease in this population cannot be represented in the model in absence of a specific risk equation.

Numerous studies have demonstrated the increased risk of cardiovascular disease and cardiovascular death in prediabetes (Khaw, et al., 2004) (Bonora, et al., 2003) (Kernan, et al., 2005) (Rijkelijkhuizen, et al., 2007) (Smith, et al., 2002) including two systematic literature reviews and meta-analyses (Cavero-Redondo, et al., 2017) (Huang, et al., 2016). One such study conducted in the UK, the EPIC Norfolk study, showed a 1.36 (95% CI: 1.28-1.46) increase in risk of coronary heart disease, 1.30 (95% CI: 1.22-1.38) increase in risk of cardiovascular disease and 1.29 (95% CI: 1.20-1.40) increase in all-cause mortality with each 1%-point increase in HbA1c when compared with normal glucose concentrations (HbA1c <5%) in males. The corresponding values for females were 1.37 (95% CI: 1.26-1.49), 1.33 (95% CI:

[1] The revised version of the model is only used to respond to questions B5, B6 and B15. The responses to questions B1.2 and B1.4 will also use the revise version of the model. All other results presented in this response were generated using the CS model (June 2019).

1.24-1.42) and 1.28 (95% CI: 1.17-1.41) for coronary heart disease, cardiovascular disease and all-cause mortality risk, respectively, after controlling for age (Khaw, et al., 2004).

Additionally, it should be noted that cardiovascular disease risk and the benefits of liraglutide 3.0mg treatment on cardiovascular outcomes are most likely under-represented in the CS base case analyses. In patients with prediabetes and normal glucose tolerance, where QRisk3 equation was used, cardiovascular outcomes are not affected by changes in BMI values above 40kg/m^2 given the range of BMI values in QRisk3 was restricted to 20-40 kg/m^2 (Hippisley-Cox, et al., 2017). Conservatively, no extrapolation of cardiovascular risk beyond 40kg/m^2 BMI was applied in the CS base case model, although liraglutide efficacy was observed precisely around this cut-off point. Namely, liraglutide 3.0mg reduced baseline weight from 41.7 kg/m^2 to 37.15 kg/m^2 in the first year of treatment. Similarly, the risk of type 2 diabetes development does not increase beyond BMI values of 40kg/m^2 when QDiabetes equation is used (CS base case analyses) as BMI was restricted to values between the 20-40 kg/m^2 in QDiabetes (Hippisley-Cox, et al., 2009). For these reasons, we believe that neither cardiovascular risks nor type 2 diabetes risks and risk-reductions are overestimated in the CS base case analyses when assuming prediabetic patients develop type 2 following a stroke or ACS event.

Effectiveness

B6. Priority question: Treatment efficacy in liraglutide non-responders was modelled using data from the placebo arm as efficacy data post non-response and liraglutide discontinuation, i.e. in line with the stopping rule, was not obtained in the trial.

1. Please justify the assumption that efficacy in non-responders and placebo patients is equal and discuss the implications of alternatives, including the use of placebo arm non-responder data and of the liraglutide non-responder data obtained in the trial.

2. Please provide scenario analyses (and the accompanying models) in which the liraglutide non-responder efficacy is modelled using I.) only data of non-responders in the placebo arm and II.) using the liraglutide non-responder data as collected in the trial, i.e. not adhering to the stopping rule.

Company responses:

Please see the response to question A18 for a comparison of outcomes for the responders, non-responders and total at week 16 and over time in each treatment arm.

1. Assuming the same efficacy as placebo for liraglutide 3.0mg non-responders implies that a biological effect has a greater influence on patient outcomes than a psychological effect. This is supported by clinical expert advice from Professor Carel le Roux, who commented, "*Patients who do not respond to liraglutide are biologically different to those that do respond. Unfortunately, we are not yet in a position to identify the biological difference prior to starting the medication. There are no psychological differences between responders and non-responders, neither are there any differences in internal or external motivation. Thus, unfortunately there is no blood test or questionnaire that can tell responder and non-responders apart prior to starting the medication. The best we can do is give a trial of therapy for 16 weeks and then make a determination. The benefit of this approach is that both the positive and negative predictive value of >5% weight loss at 16 weeks is sufficient to be of significant clinical value."* Hence the most plausible assumption for non-responders to liraglutide 3.0mg is to assume the same efficacy as placebo in the trial, as patients would continue with standard management (diet and lifestyle interventions).

2. Table 20 shows the efficacy inputs applied in the CS base case, and the two requested scenario analyses for non-responders.

Table 20: Efficacy in liraglutide 3.0mg non-responders

Model Parameter	CS base case inputs placebo FAS	Scenario inputs Placebo non-responders	Scenario inputs Liraglutide non-responders
	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)
Probability prediabetes reversal week 56 in SCALE	40.74% (2.99%)	37.21% (3.30%) [1-135/215]	68.98% (3.15%) [1-67/216]
Weight loss (%-reduction) vs. baseline			
Model cycle 2	-2.43% (0.29%)	-0.69% (0.19%)	-3.52% (0.19%)
Model cycle 4	-2.48% (0.37%)	-0.81% (0.28%)	-3.61% (0.28%)
Model cycle 5 (year 2 efficacy)	-2.07% (0.40%)	-0.45% (0.34%)	-3.36% (0.34%)
Change in SBP (mmHg) vs. baseline			
Model cycle 2	-1.70 (0.67)	-1.20 (0.76)	-5.90 (0.76)
Model cycle 4	-1.76 (0.66)	-1.28 (0.77)	-5.40 (0.77)
Model cycle 5 (year 2 efficacy)	-1.72 (0.68)	-1.08 (0.75)	-5.10 (0.75)
Change in total cholesterol (mg/dl)			
Model cycle 2	-3.85 (1.71)	-5.87 (1.94)	-11.63 (2.08)
Model cycle 4	-6.10 (1.74)	-7.28 (2.01)	-11.13 (2.16)
Model cycle 5 (year 2 efficacy)	-7.01 (1.95)	-9.51 (2.33)	-14.82 (2.50)
Change in HDL cholesterol (mg/dl)			
Model cycle 2	0.20 (0.45)	-0.32 (0.54)	-1.56 (0.58)
Model cycle 4	0.80 (0.50)	0.33 (0.58)	-0.47 (0.62)
Model cycle 5 (year 2 efficacy)	1.52 (0.52)	0.70 (0.59)	0.36 (0.63)

Table 21 shows the results of a scenario where non-responders to liraglutide 3.0mg are assumed to have the same efficacy as the non-responders in the placebo arm of SCALE prediabetes (trial 1839). As expected the ICER increases to £10,185/QALY compared to the revised base case of £9,096/QALY (Table 54)[2].

[2] The revised version of the model is only used to respond to questions B5, B6 and B15. The responses to questions B1.2 and B1.4 will also use the revise version of the model. All other results presented in this response were generated using the CS model (June 2019).

Table 21: Scenario using placebo non-responder efficacy

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,679	18.520	15.248	£10,185
Diet & exercise	£20,270	18.417	15.109	
Incremental	£1,408	0.102	0.138	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 22 shows the results of a scenario where non-responders to liraglutide 3.0mg are assumed to continue with therapy (i.e. not adhering to the stopping rule) and therefore have the efficacy of non-responders receiving liraglutide 3.0mg. This scenario analysis lowers the ICER to £5,615/QALY as the cost of liraglutide is not included for non-responders. We have therefore also included the cost of liraglutide in non-responders in a scenario analysis (Table 23), however it should be noted that this scenario contradicts the marketing authorisation for liraglutide 3.0mg which includes a stopping rule.

Table 22: Scenario using liraglutide non-responder efficacy

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,320	18.558	15.296	£5,615
Diet & exercise	£20,270	18.417	15.109	
Incremental	£1,049	0.141	0.187	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 23: Scenario using liraglutide non-responder efficacy and including 2-year treatment costs for liraglutide non-responders

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£22,251	18.558	15.296	£10,603
Diet & exercise	£20,270	18.417	15.109	
Incremental	£1,981	0.141	0.187	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B7. Priority question: For the prediction of the complications included in the model structure (CS Figure 15), various risk equations are used. CS Table 33 very helpfully summarises these risk equations. Although justifications are provided in CS Table 33 (as well as the preceding text), it is not completely clear to the ERG whether the most appropriate risk equations are selected in the base-case.

1. Please describe the methodology used to systematically identify the risk equations for the complications incorporated in the economic model.

2. Please describe the criteria used to subsequently select the risk equations for the complications incorporated in the economic model.

3. Please provide expert opinion used (if applicable) to assess the results of the preceding steps (i.e. both the identification and selection of the risk equations).

4. Please provide scenario analyses (and the accompanying model) incorporating alternative risk equations (e.g. those reported in CS Table 33)

5. Please justify that the risk equation selected was (in some instances) dependent on type 2 diabetes status. For instance, for the primary cardiovascular event UKPDS82 and QRisk3 were used for patients with and without type 2 diabetes.

6. Please justify whether the selection of different risk equations, depending on type 2 diabetes status results in differences induced solely by the use of different risk equations (i.e. differences between the selected risk equations that are unrelated to type 2 diabetes status). Please elaborate on the likely impact of this on the estimated results, separately for the complications incorporated in the economic model.

Company responses:

1. Multiple structured reviews have been conducted since the early development of the model. The most recent review was a systematic review undertaken by ScHARR to identify studies that would be the most appropriate for a UK population and from a UK Health Technology Assessment perspective. The full methods and results of this systematic review were shared as part of the reference pack (Holmes, 2017).

   Briefly, searches were conducted by including search terms related to 9 obesity complications and their etiology. Searches were conducted in September 2016 for the previous 10 years.

   The databases searched included:

   a. MEDLINE, MEDLINE In-Process and E-Pub ahead of print (OvidSP)

   b. Embase (OvidSP)

   c. The Cochrane Library (Wiley) including the Cochrane Database of Systematic Reviews, NHS Economic Evaluations Database (NHS EED), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL) and the Health Technology Assessment Database (HTA), and Econlit (OvidSP). More details on the search strategy and results are available in Holmes et al., 2017.

   d. Reference lists of included studies and any relevant reviews identified were checked for any further relevant references, and relevant conference

proceedings (including the Association for Study of Obesity (ASO) and the European Association for the Study of Obesity (EASO)) were searched for the past two years to identify any recent or ongoing and yet unpublished research.

Studies were included if they investigated a link between any index of weight loss or weight gain and the risk of developing obesity related complications. These could be reported as relative risks, odds ratios, and incidence of disease as well as risk prediction models or risk equations. If systematic reviews were available, they were given precedence over all other studies. The methodological quality of systematic reviews was assessed using the "Assessing the Methodological Quality of Systematic Reviews" (AMSTAR) tool. Any studies and/or risk equations recommended by The National Institute for Health and Care Excellence (NICE) took precedence over any other study.

2. To select the risk equations for the complications incorporated in the economic model and in the CS base case analyses, the following criteria were considered:

    a. Studies and/or risk equations recommended by The National Institute for Health and Care Excellence (NICE) as to best reflect the pathway of the underlying disease (e.g. cardiovascular disease in type 2 diabetes) in relation to known pathophysiological parameters (i.e. primarily BMI, SBP and cholesterol levels and HbA1c in type 2 diabetes);

    b. Studies conducted in the target population, if available (obese, with prediabetes) with or without complications included in the model which may substantially affect the risk of other, co-occurring complications (e.g. presence of type 2 diabetes for cardiovascular disease risk);

    c. Studies which allowed incorporation of a multifactorial effect, primarily BMI, but also SBP, cholesterol and HbA1c in type 2 diabetes (i.e. multifactorial risk equations were preferred to simple risk adjustments in relation to BMI only);

    d. Studies conducted in a population within UK practices;

e. Meta-analyses or systematic literature reviews were preferred to individual studies;

f. The sample size of the investigated population, follow-up duration and publication year.

3. Expert opinion to assess the results of the identification and selection of the risk equations was not sought given the systematic review was performed by an external agency, i.e., ScHARR. However, the model outcomes were presented and discussed with a clinical expert in the field of obesity (CS Appendix O) and were further validated via an independent external validation (HEOR Ltd., June 2019).
4. Results using the Framingham Offspring Study (Wilson, et al., 2007) are presented in the table below. This equation was not selected in the CS base case as the underlying population was mainly of American origin. Also, the risk model only included BMI values between 20 - 30 kg/m^2, thus the additional risk with BMI above the cut-off point of 30 kg/m^2 cannot be captured. Indeed, the projected incidence of type 2 diabetes was lower, thus total costs were lower in each arm; total LYG and total QALYs were higher in each arm, compared with the CS base case (ICER £13,059/QALY, Table 53) when using QDiabetes (Hippisley-Cox, et al., 2009).

Table 24: Analysis using Framingham Offspring Study

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0 mg	£19,141	18.72	15.54	£9,536
Diet & exercise	£17,770	18.61	15.39	
Incremental	£1,371	0.11	0.14	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Results of an alternative risk equation for primary cardiovascular prevention in normal glucose tolerance and prediabetes using the Framingham Heart Study (D'Agostino, et al., 2008) are presented below. This study was not considered in the CS base case as it was conducted in an American population; it also did not include

cholesterol as a predictor of risk and was much older compared with the risk model included in the CS base case, respectively QRisk3 (Hippisley-Cox, et al., 2017).

Table 25: Analysis using Framingham Heart Study in primary prevention normal glucose tolerance and prediabetes

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0 mg	£21,316	18.28	15.07	£13,867
Diet & exercise	£19,704	18.20	14.95	
Incremental	£1,613	0.08	0.12	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Results of alternative risk equations for primary and secondary cardiovascular prevention after type 2 diabetes development using the QRisk3 (Hippisley-Cox, et al., 2017), the Swedish NDR (Cederholm, et al., 2008) and Framingham Recurrent CHD (D'Agostino, et al., 2000), respectively, are presented below.

QRisk3 was estimated on a sample of patients followed in general practices in England. Most patients did not have type 2 diabetes at baseline (1.5% and 1.2% of males and females had type 2 diabetes) and the risk equation was intended as a cardiovascular risk prediction model in the general population (Hippisley-Cox, et al., 2017). As such, the main predictor of risk of complications in type 2 diabetes, HbA_{1c}, was not included in the model. Instead, the equation included a categorical variable (yes, no) for presence of type 2 diabetes. The Swedish NDR risk equation was estimated on a type 2 diabetes population in Sweden, with likely a different risk profile compared with the British population (Wennerholm, et al., 2017). Similarly, the Framingham Recurrent CHD was estimated on a North American population and HbA_{1c} was not included as a risk predictor.

For these reasons, we believe that neither of these three equations, QRisk3, Swedish NDR and Framingham Recurrent CHD would fully reflect the cardiovascular disease burden in the British population with type 2 diabetes.

Table 26: Analysis using QRisk3 in primary prevention type 2 diabetes

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0 mg	£20,914	18.64	15.38	£17,530
Diet & exercise	£19,249	18.57	15.29	
Incremental	£1,665	0.06	0.09	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 27: Analysis using Swedish NDR in primary prevention type 2 diabetes

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0 mg	£20,533	18.94	15.65	£24,911
Diet & exercise	£18,732	18.90	15.58	
Incremental	£1,801	0.04	0.07	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 28: Analysis using Framingham Recurrent CHD in secondary prevention type 2 diabetes

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0 mg	£21,080	18.68	15.41	£15,770
Diet & exercise	£19,545	18.62	15.31	
Incremental	£1,535	0.06	0.10	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

All the analyses illustrated above can be conducted by selecting the respective risk equation from the ‘Controls’ tab drop-down menu of the submitted model (e.g. control “Risk equation selection of T2DM:”), hence no scenario model is submitted to accompany this question.

5. Type 2 diabetes is an important determinant of cardiovascular risk. Ignoring the presence of type 2 diabetes would unjustifiably underestimate the additional

burden of diabetes on cardiovascular outcomes. The UKPDS82 was preferred over QRisk3 when estimating cardiovascular outcomes in type 2 diabetes as it was derived primarily in type 2 diabetes patients (i.e. all subjects had type 2 diabetes at baseline, compared with QRisk3 where less than 2% of the population did). Moreover, UKPDS82 has been NICE's preferred healthcare analysis tool to evaluate new interventions in diabetes (NICE, 2015).

6. Whilst there are differences resulting from the risk equations used, the differences are primarily related to diabetes status. Contrary to the ERG's suggestion, the risk of cardiovascular complications is related to type 2 diabetes status, as already discussed above and further elaborated below. We believe that our choice of risk equation in our base case analysis in the CS best reflects the population under consideration and the impact of complications on outcome. The impact of alternative risk equations on the estimated results has been illustrated in point 4 above.

    a. When estimating first cardiovascular events in type 2 diabetes using UKPDS82 (company BC analyses) the difference in cardiovascular risk (vs. first cardiovascular events in non-type 2 diabetes) is expected to be mostly due to type 2 diabetes status. Differences may also arise due to other factors which may well be related to type 2 diabetes (e.g. differences in type 2 patients' characteristics at baseline such as diabetes duration, level of glycaemic control, history of other complications etc. but not reported by Hippisley-Cox, (2017) and therefore impossible to evaluate) or other factors possibly unrelated to type 2 diabetes.
    b. When estimating first cardiovascular events in type 2 diabetes using QRisk3 (alternative scenario; results presented above) the difference in cardiovascular risk (vs. primary cardiovascular risk in non-type 2 diabetes) can be entirely attributed to type 2 diabetes status as the parameter for presence or absence of type 2 diabetes was set to 0 (in non-type 2 diabetes), and 1 (after type 2 diabetes onset in the model).
    c. When estimating first cardiovascular events in type 2 diabetes using the Swedish NDR (alternative scenario; results presented above) the difference in cardiovascular risk (vs. primary cardiovascular risk in non-

type 2 diabetes) is believed to be mostly due to type 2 diabetes status however, other differences e.g. due to a different cardiovascular risk profile in the Swedish population may play a role (as explained in point 4 above).

B8. Priority question: On multiple occasion in the CS, it is mentioned that risk equations are calibrated/(up-)adjusted.

1. Please justify the need to calibrate/(up-)adjust the risk equations if applicable (separately per risk equation).

2. Please describe the methodology used to calibrate/(up-)adjust the risk equations if applicable (separately per risk equation).

3. Please describe the methodology used to assess the validity of the calibration/(up-)adjustment of the risk equations if applicable (separately per risk equation). Moreover, please provide the results of this validity assessment.

Company responses:

Risk equations were calibrated (adjusted) whenever the observed study endpoint did not entirely match the endpoint considered in the model as described in Table 29 below. The validity of the calibration was assessed via an external independent validation of the model, as described in the HEOR Ltd. external independent validation report (HEOR Ltd., June 2019) submitted together with this document.

Table 29: Summary of risk equation calibration techniques

Risk equation	Justification	Methodology
QRisk3 (UK) (Hippisley-Cox, et al., 2017)	QRisk was used in the CS analyses to estimate cardiovascular events in normal glucose tolerance and prediabetes. The outcome measure in the QRisk3 study was cardiovascular disease, defined as a composite outcome of coronary heart disease, ischaemic stroke, or transient ischaemic attack (Hippisley-Cox, et al., 2017). Given different costs, utility decrements and case-fatality estimates are applied in the model for each of the included events, the composite risk was split (calibrated) into individual cardiovascular endpoint risks using the distribution of events for MI, angina, stroke and transient ischaemic attack reported in the CS Table 29.	Each cycle, an individual cardiovascular endpoint risk was calculated by applying the following proportions to the composite risk predicted by QRisk3 in the model: 33.1%, 40.2%, 26.7% and 21.8% for MI, angina, stroke with TIA and TIA out of stroke respectivelly (CS Table 29).

Framingham Heart Study (D'Agostino, et al., 2008)	Is available in the model but has not been used in the CS analyses. The outcome measure in Framingham Heart Study was composite of cardiovascular disease outcomes including: coronary heart disease (coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (including ischemic stroke, hemorrhagic stoke, and transient ischemic attack), peripheral artery disease (intermittent claudication), and heart failure. Given, the economic model does not consider the following outcomes: coronary insufficiency, peripheral artery disease and heart failure, not considered to increase in risk with weight, or likely to generate double counting of costs and QALYs (heart failure), the composite endpoint was down-adjusted to exclude these endpoints, and then was split into individual endpoints using the distribution of events reported in the CS Table 29.	Each cycle, the composite endpoint predicted with Framingham Heart Study was divided (down-adjusted) by 86.71% (70.8% coronary heart disease excluding insufficiency plus 15.9% stroke, out of total CVD) and 81.30% (57.5% coraonary heart disease excl. insufficiency plus 23.9% stroke, out of total CVD) for males and females respectivelly to exclude endpoints not included in the economic model (D'Agostino, et al., 2008) Then, per cycle, an individual cardiovascular endpoint risk was calculated by applying the following proportions to the composite risk: 33.1%, 40.2%, 26.7% and 21.8% for MI, angina, stroke with TIA and TIA out of stroke respectivelly (CS Table 29).
Framingham Recurrent Coronary Heart Disease (D'Agostino, et al., 2000)	Used in base case analyses to predict the risk of recurrent cardiovascular events in normal glucose tolerance and prediabetes. The outcome measure in Framingham Recurrent was coronary heart disease (including mostly hospitalized events consisting of myocardial infarction, coronary insufficiency, angina pectoris, and sudden and non-sudden coronary death) (D'Agostino, et al., 2000). Given, no risk equation was available to predict recurrent stroke events, the Framingham Recurrent risk was up-	Firstly, the per cycle risk predicted by Framingham Recurrent was up-adjusted (divided) by the proportion of MI (33.1%) plus angina (40.2%) events out of total cardiovascular disease CS Table 29. Next, the composite CVD risk as such calculated, was split into individual endpoints following the approach described above for

	adjusted to allow prediction of a composite endpoint including recurrent stroke.	QRisk3 and using the distribution of events reported in the CS Table 29.
UKPDS82 (Hayes, et al., 2013)	In UKPDS82, separate risk models were estimated for: primary MI, primary angina, primary stroke, secondary MI and secondary stroke. As there was no risk equation to predict recurrent angina events, the predicted risk for secondary events had to be up-adjusted to include secondary angina. For consistency with the rest of the risk equations, and in order not to add extra complexity to the Markov traces also the risk of primary events was summed and then divided using the distribution of individual endpoints in CS Table 29.	Per cycle, the risk of recurrent stroke and recurrent MI as predicted by the UKPDS82 were summed, to give a total risk of recurrent CVD, which was then divided (up-adjusted) by the proportion of MI (33.1%) and stroke (26.7%) in total CVD. The risk of primary MI, primary angina and primary stroke as predicted by UKPDS82 was summed to give a composite CVD endpoint risk and then divided by the proportion of the individual endpoints as reported in the CS Table 29.
Swedish NDR (Cederholm, et al., 2008)	The outcome measure in the Swedish NDR was first incident of composite cardiovascular disease, including fatal ischemic heart disease or sudden cardiac death, nonfatal myocardial infarction, unstable angina, percutaneous coronary intervention and/or coronary artery bypass grafting and fatal or nonfatal stroke. The composite outcome predicted by the Swedish NDR function had to be split into invidivual cardivascular endpoints to allow consideration of specific costs, disutilities and mortality.	Each cycle, an individual cardiovascular endpoint risk was calculated by applying the following proportions to the composite cardiovascular risk predicted by the Swedish NDR model: 33.1%, 40.2%, 26.7% and 21.8% for MI, angina, stroke with TIA and TIA out of stroke respectivelly (CS Table 29).

QRisk3 in type 2 diabetes (Hippisley-Cox, et al., 2017)	As described above for QRisk in normal glucose tolerance.	As described above In adition, a value of 1 was assigned to the categorical variable b_type 2 diabetes, to reflect the higher risk in this population.
QDiabetes (Hippisley-Cox, et al., 2009)	The QDiabetes Model C implemented in the model provides an estimate of the risk of type 2 diabetes incidence. The risk equation has HbA1c (mmol/mol) as a continuous risk-variable. Given, in the model HbA1c is taken into account only after type 2 diabetes development to avoid double-counting of the temporary prediabetes reversal, the QDiabetes risk model was calibrated i.e. a fixed HbA1c value was entered in the equation when the risk function was applied in normal glucose tolerant patients (HbA1c = 35 mmol/mol) and separately in prediabetics (HbA1c = 42 mmol/mol).	Fixed value assigned to the HbA1c parameter in QDiabetes: HbA1c = 35 mmol/mol when type 2 diabetes was predicted in normal glucose tolerance and HbA1c = 42 mmol/l when type 2 diabetes risk was predicted for prediabetics.
Framingham Offspring Study (Wilson, et al., 2007)	The Framingham Offspring Study predicts the risk of type 2 diabetes development and has not been used in the analyses presented in the CS. The risk model includes a categorical variable for fasting glucose if this is between the ranges 100-126 mg/dL (yes/no).	To assign a specific risk in normal glucose tolerant and prediabetic patients, the fasting glucose parameter was set to 0 when applied in normal glucose tolerant and to 1 when applied in prediabetics.

B9. Priority question: CS Table 31 (as well as the preceding text) provides an overview of the death probabilities. It is not clear to the ERG whether the most appropriate evidence is used to inform these death probabilities.

1. Please describe the methodology used to systematically identify the evidence used to inform the death probabilities in the economic model.

2. Please describe the criteria used to subsequently select the evidence used to inform the death probabilities in the economic model.

3. Please provide expert opinion used (if applicable) to assess the results of the preceding steps (i.e. both the identification and selection of the evidence used to inform the death probabilities).

4. Please provide scenario analyses (and the accompanying model) incorporating alternative evidence used to inform the death probabilities.

Company response:

1. A systematic search of death probabilities in the model was not conducted, as death was considered not to be directly linked to the intervention nor to the efficacy data in the model. Hence, a systematic search for evidence that would inform death probabilities was not deemed necessary.

2. The following criteria were considered when selecting death probabilities to inform the model:

    a. For all death probabilities or risk-ratios, the aim was to select those studies which reported, to the extent possible, an adjusted mortality, which would account only for the additional mortality associated with the complication in scope, in order to avoid double-counting.

    b. Next, for case fatalities associated with cardiovascular events (MI, stroke, angina), the aim was to select studies which reported mortality within the first year after the event, to capture pre-hospital, in-hospital, and post-discharge mortality altogether.

c. Finally, studies had to report mortality in the UK population, to the extent to which this was available.

3. Expert opinion was not sought for validation of the source for event-specific death rates.

4. To identify alternative evidence to inform the death probabilities in the model, pragmatic searches were conducted on PubMed and Google Scholar using combinations of the following search terms: acute coronary syndromes, stroke, diabetes, mortality, case-fatality, United Kingdom. Additionally, the QResearch publications database was accessed to identify studies on cardiovascular mortality (QResearch, 2019). A selection of studies was made using the criteria described on point 2 above to the extent possible, looking to identify mortality estimates adjusted for presence of complications separately accounted for in the model. The alternative mortality inputs identified and used to conduct the requested scenario are shown in Table 30 below. The impact of using these alternative estimates is illustrated in Table 31 below.

Table 30: Alternative death probabilities/risk-ratios for scenario analysis

Model parameter	CS base case parameter value	Alternative parameter value	Calculations alternative value	Reference alternative value
Case fatality MI (% of events)	30.48%	23.20%	Calculated as sum of death probabilities before hospital and within first year after event	(Taylor, et al., 2007)
Case fatality angina (% of events)	30.48%	23.20%		
Case fatality stroke (% of events)	22.86%	16.83%	Weighted average for males (11.30%) and females (18.60%)	(Lee, et al., 2011)
Diabetes mortality (HR applied to general population* probability of death)	Age-adjusted mortality ICD10 E10-E14 (Office for National	1.82	Calculated by multiplying HR associated with diabetes complications** and their occurrence	(Saleh, et al., 2012)

Model parameter	CS base case parameter value	Alternative parameter value	Calculations alternative value	Reference alternative value
	Statistics, 2018)			
Case fatality knee replacement	0.30%	0.70%	n/a	(Gerlier, et al., 2010)
Death after ACS (RR applied to general population mortality)	1.30	1.33	Adjusted HR, previous MI	(Saleh, et al., 2012)
Death after stroke (RR applied to general population mortality)	2.00	1.26	Adjusted HR, previous stroke	(Saleh, et al., 2012)
Case fatality bariatric surgery	0.07%	0.25%	n/a	(Sjostrom, 2013)

*General population death probabilities in the model have been adjusted to exclude deaths due to causes considered in the model separately when event or progression to health-state occurs (by subtracting the corresponding probability according to ICD10 codes from the general-population mortality by cause of death ; **HRs for mortality due to diabetes complications not accounted for otherwise in the model, weighted by the prevalence of the respective complications in the subgroup "patients with type 2 diabetes on oral treatment n=5,051) reported by Saleh et al (2012) : 1-point increase in HbA1c in the modelled type 2 diabetes cohort (HbA1c 7.5%) versus reference HbA1c assumed 5.9%-points HR: 1.04; renal insufficiency HR: 1.51 (prevalence: 0.80%); peripheral artery disease HR: 1.46 (prevalence: 4.30%); dialysis HR: 1.85 (prevalence: 0.20%); retinopathy HR: 1.25 (prevalence: 24.30%); amputation HR: 1.47 (prevalence: 0.90%).

Table 31: Scenario alternative sources for death probabilities

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,292	18.528	15.287	£13,446
Diet & exercise	£19,850	18.461	15.180	
Incremental	£1,442	0.067	0.107	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B10. Priority question: In CS B.3.2.2 it is implied that to calculate non-responder rates, patients with unknown response status at week 16 are excluded. This is effectively a complete case analysis, assuming that if the response status is missing, it is missing completely at random. This assumption seems unlikely to the ERG, for instance given patients with AE withdrawal might be more likely to have missing response status.

1. Please recalculate the non-responder rates while assuming that patients with missing response status are non-responders.

2. Please provide a scenario analysis (and the accompanying model) incorporating these recalculated non-responder rates.

Company responses:

The recalculated non-responder rate with liraglutide 3.0mg, assuming patients with missing response status are non-responders is 40.8%. The results of the scenario incorporating the recalculated rate are presented in the table below.

Table 32: Scenario recalculated non-responder rate

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,865	18.574	15.323	£13,599
Diet & exercise	£19,419	18.496	15.216	
Incremental	£1,445	0.106	0.106	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B11. Temporary prediabetes reversal at 56 weeks is 82.8% and 40.74% for diet and exercise with and without liraglutide respectively (see CS Table 28).

1. The abovementioned 56 weeks temporary prediabetes reversal probabilities are applied in model cycle 2 (as described in CS section B.3.2.3). Please justify that 56 weeks probabilities are applied in cycle 2 (i.e. between 3 and 6 months).

2. Please provide a scenario analysis (and the accompanying models) in which the 56 weeks temporary prediabetes reversal probabilities are applied in model cycle 4.

Company response:

Prediabetes reversal is a direct and immediate consequence of weight loss. This justifies the application of a prediabetes reversal probability as early as cycle 2 in the model, contrary to the requested scenario above.

Indeed, the calculated reversal probabilities based on glycemic status assessed at week 28 in SCALE were 84.1% and 40.0% for diet and exercise with and without liraglutide 3.0mg respectively and were comparable to those calculated in the CS base case based on glycemic status at week 56 (82.8% and 40.74% respectively for diet and exercise with and without liraglutide 3.0mg). This indeed justifies the application of a temporary prediabetes reversal in the model in cycle 2, rather than in cycle 4 as suggested. A scenario analysis was conducted and is presented below illustrating the application of prediabetes reversal in cycle 2 based on glycemic status assessed at week 28, to match the trial timepoint assessment of this outcome.

Table 33: Scenario analysis applying prediabetes reversal in cycle 2 based on efficacy reported at week 28 in SCALE

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,985	18.585	15.337	£12,458
Diet & exercise	£19,442	18.494	15.213	
Incremental	£1,543	0.091	0.124	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B12. Once patients develop type 2 diabetes, their HbA1c value is assumed to remain constant at 7.5%-points. Please provide evidence to justify the HbA1c value of 7.5%-points.

Company response:

NICE guideline (NG28) – Type 2 diabetes in adults (NICE, 2015), recommend 'For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, support the person to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, support the person to aim for an HbA1c level of 53 mmol/mol (7.0%). In adults with type 2 diabetes, if HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher. Given NICE advocates three different target HbA1c levels we looked to the National Diabetes Audit 2017-18 Report (NHS Digital, 2019)which uses the upper value of 58 mmol/mol (7.5%) to measure whether patients meet treatment target. According to the National Diabetes Audit 2017-18, only 65.8% of people with type 2 diabetes met the upper treatment target for HbA1c therefore we performed sensitivity analysis varying the 7.5 % value (Table 53, page 160 of company submission). Reducing the HbAc1 value to 6.5% increased the ICER, from £13,059 (base case) to £13,785, while increasing the HbA1c value to 8.5% decreased the ICER to £12,344, suggesting the assumption does not have a marked impact on results.

B13. "Natural progression of weight post-treatment and post-waning of treatment effect: 0.46 kg increase per year, until cohort reaches 68 years" (CS Table 51). This assumption (weight increase stops at age 68 year) appears inconsistent with TA494 and Ara et al., (2012).[5]

1. Please justify this inconsistency and provide a scenario analysis (and the accompanying model) while relaxing this assumption by assuming that weight increases indefinitely.

2. Please compare the weight increase of 0.46 kg per year with the weight increase as used by Ara et al., (2012).[5]

Company responses:

1. The base case analyses presented in the CS assumed that weight increases up to a maximum age, rather than lifetime, in consideration of the loss of skeletal muscle mass and strength, as a result of aging (sarcopenia). Indeed, in the physicians' survey (CS Appendix N) experts claimed that on average, patients' weight increases until the age of 65.7 years, thus less than considered in the CS base case. Consequently, a +/- 2 years variation on the maximum age until weight increases was tested in one-way sensitivity analyses; this variation had a marginal impact on results (low variation ICER £13,005/QALY; high variation ICER £13,070/QALY). The results of a scenario analysis assuming weight increases indefinitely is shown in the table below.

Table 34: Scenario weight increases indefinitely

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,306	18.584	15.299	£13,173
Diet & exercise	£19,732	18.496	15.180	
Incremental	£1,574	0.088	0.119	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

2. The natural progression of weight used by Ara et al. (Ara, et al., 2012) was 0.1447 kg/m^2 in non-diabetic males and 0.1747 kg/m^2 in non-diabetic females (Ara et al. Table 25 Input parameters). Given the starting cohort is non-diabetic, these exact same values were used in the CS base case to construct a weighted average annual increase in weight 0.1674 kg/m^2 for males (24%) and females (76%) and was applied as such in the model. The value reported in the 'Cohort Inputs'J144 and the CS (0.46 kg weight increase per year) represents the weighted average annual weight increase as calculated above (0.1674 kg/m^2) converted in kg by division with the square of the average height of the cohort (1.66 m).

B14. In contrast with BMI, SBP, total and HDL cholesterol are assumed constant over time (after the treatment waning period) while these patient characteristics are associated with natural progression (as mentioned in CS Table 51).

1. Please elaborate on the potential impact of this simplifying assumption on the estimated results.

2. Please provide a scenario analysis (and the accompanying model) incorporating natural progression of SBP, total and HDL cholesterol (e.g. by linking these patient characteristics to the natural progression of BMI).

Company response:

1. Relaxing this assumption (i.e. assuming a change in SBP, total and HDL cholesterol over time) could be expected to slightly modify (increase or decrease) the total projected incidence of complications in the model. The impact is however expected to be small given these parameters may increase (e.g. SBP is known to increase with age) but equally decrease (e.g. resulting from initiation or intensification of primary and/or secondary cardiovascular prevention therapies). Indeed, in The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC), SBP was observed to slightly increase on average over 30 years from 114.5 to 122.4 mmHg in the intervention arm, and from 114.6 to 121.8 mmHg in the control arm. Total cholesterol decreased from 177.1 to 174.8 mg/dl and from 175.7 to 172.1 mg/dl in the intervention and control arms respectively over the same period. HDL cholesterol increased from 50.8 to 61.9 mg/dl and from 50.3 to 61.5 mg/dl respectively in the intervention and control arms. At the same time, the proportion of people living with obesity (BMI ≥30 kg/m^2) in the cohort increased from 1.3 and 1.9% at baseline to 36.1 and 33% at 30 years for the intervention and control, respectively (Nathan, 2014). Given these changes would affect both arms of the model in the same way, the impact on the incremental results is expected to be minor.

2. A scenario analysis was conducted with the model applying the above annualized changes post treatment and catch-up period in the model, and assuming constant change over time (Table 35). Cost-effectiveness results of this scenario are illustrated in

3. **Table** 36 below.

Table 35: Changes in SBP, total and HDL cholesterol assumed in scenario analysis

Parameter	Change observed in DCCT/EDIC control	Annual change applied in model (by division with 30)
SBP (mmHg)	7.20 mmHg	0.24 mmHg
Total cholesterol (mg/dl)	-3.6 mg/dl	-0.12 mg/dl
HDL cholesterol (mg/dl)	11.20 mg/dl	0.37 mg/dl

Table 36: Scenario: changes in SBP, total and HDL cholesterol

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,967	18.608	15.357	£13,068
Diet & exercise	£19,400	18.521	15.237	
Incremental	£1,567	0.087	0.120	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Adverse events

B15. The submitted economic model incorporates more granularity than the identified economic evaluations (CS B.3.1), in terms of complications reflected in the model structure. However, despite this granularity, the company did not reflect adverse events. This was justified by stating that this is not expected to have a significant impact on the patients' quality of life. Nevertheless, CS Table 24 indicates that liraglutide has a substantial higher proportion of severe adverse events compared with placebo (20.7% vs 15.4%). Thus, this simplification is unlikely to be conservative. Moreover, for liraglutide adverse events led to withdrawal of 199 of

1,501 patients (13.3%) indicating that the impact on patients is not negligible. Also, occurrence of adverse events likely impacts costs.

1. Please provide a scenario analysis (and the accompanying model) incorporating the impact of adverse event on both quality of life and costs. Ideally all relevant adverse events are incorporated but minimally gastrointestinal events and hypoglycaemia should be reflected.

2. Please clarify how withdrawal due to adverse events is reflected in the economic model.

Company response:

1. A scenario analysis was conducted to evaluate the impact of gastrointestinal adverse events (AEs) and hypoglycaemia on both quality of life and costs. Non-severe gastrointestinal AEs were assumed to have no impact on either costs or quality of life. However as previous models in diabetes have included an impact on quality of life and costs for both non-severe and severe hypoglycaemia, we have followed the same approach (Vega-Hernandez, et al., 2017). The adverse event rates used in the model are shown in Table 37. The proportion of severe gastrointestinal AEs was calculated from the overall SCALE prediabetes safety set in the liraglutide arm (incremental to placebo) and was applied per cycle to the rate of all gastrointestinal AEs observed in the index population. In line with the efficacy data in the CS base case, cycle 1 probabilities were calculated from the safety-set of the index population, whilst for cycles 2 onwards, the early responder analysis set was used for liraglutide 3.0mg and the safety set was used for diet and exercise (placebo).

Table 37: Event rates per 100 patient-years

	Liraglutide 3.0mg	Placebo	Liraglutide 3.0mg	Placebo	Incr.
	Rate/100 pt-years		Per cycle probability		
Non-severe hypoglycaemia					
Week 0-16[1]	3.8	0.0	0.009	0.000	0.009
Week 17-56[2]	15.6	2.5	0.038	0.009	0.029
Week 57-108[2]	16.9	10.1	0.156	0.056	0.100
Week 109-162[2]	23.1	3.3	0.206	0.044	0.162
Severe hypoglycaemia					
Week 0-16[1]	0.0	0.0	0.000	0.000	0.000
Week 17-56[2]	0.4	0.0	0.001	0.000	0.001
Week 57-108[2]	0.0	0.0	0.000	0.000	0.000
Week 109-162[2]	0.0	0.0	0.000	0.000	0.000
All gastrointestinal AEs					
Week 0-16[1]	501.6	162.1	0.715	0.333	0.381
Week 17-28[2]	110.2	85.9	0.241	0.104	0.137
Week 29-40[2]	90.3	42.0	0.202	0.096	0.106
Week 41-56[2]	49.4	47.3	0.116	0.093	0.024
Week 57-108[2]	72.6	50.5	0.516	0.264	0.253
Week 109-162[2]	54.8	13.0	0.422	0.172	0.250
Ratio severe GI to all GI events[3]	4.7/124.4	1.4/62.4	N/A	N/A	3.3/62.0 (5%*)
Severe gastrointestinal AEs					
Week 0-16[4]	N/A	N/A	N/A	N/A	0.020
Week 17-28[4]	N/A	N/A	N/A	N/A	0.007
Week 29-40[4]	N/A	N/A	N/A	N/A	0.006
Week 41-56[4]	N/A	N/A	N/A	N/A	0.001
Week 57-108[4]	N/A	N/A	N/A	N/A	0.013
Week 109-162[4]	N/A	N/A	N/A	N/A	0.013

Table notes: (1) safety set index population; (2) early responders index population; (3) Overall safety analysis set in SCALE prediabetes (trial 1839); (4) calculated as the rate of all GI events in index population (safety set for week 0-16 and early responders for weeks 17-162) multiplied by the

proportion of severe GI events of total GI events in the overall safety analysis set of SCALE prediabetes (trial 1839); * proportion of severe GI events of total GI events.

Table 38 and 39 detail the quality of life impact (disutility) and costs assumed for each AE respectively.

Table 38: Event disutilities

	Mean	Upper	Lower	Comment /reference
Non-severe hypoglycaemia	-0.014	-0.018	-0.010	(Beaudet, 2014)
Severe hypoglycaemia	-0.047	-0.059	-0.035	(Beaudet, 2014)
Severe gastrointestinal	-0.001	-0.001	-0.001	-0.05 decrement applied for one week (NICE, 2017)

Table 39: Costs of adverse events

	Mean	Upper	Lower	Comment /reference
Non-severe hypoglycaemia	£3.16	3.95	2.37	(Chubb, 2015)
Severe hypoglycaemia	£427	533.75	320.25	(Evans, 2018)
Severe gastrointestinal event	£149	186.25	111.75	Service code 301: Gastroenterology (NHS, 2018)

For consistency with models in diabetes a cost and disutility has been included for non-severe hypoglycaemia, however these are likely to be an over estimate of the impact of non-severe hypoglycaemia. Non-severe hypoglycaemic events in Trial 1839 were mainly recorded via laboratory tests at visits and not spontaneously reported by patients, hence few symptoms were experienced by patients. In addition, the cost for non-severe hypoglycaemia reported in Chubb, 2015 is a study in patients with diabetes and the cost of non-severe hypoglycaemia is mainly attributed to additional self-monitoring of blood glucose (Chubb, 2015). As patients in Trial 1839 did not have diabetes they did not self-monitor their blood glucose, therefore this cost is likely to be an over estimate.

Result shown in Table 40 demonstrate the incorporation of the costs and quality of life impact of severe and non-severe hypoglycaemic and severe gastrointestinal adverse events. Table 41 shows the impact of incorporating severe gastrointestinal AEs and severe hypoglycaemic events in the model. Both analyses show the inclusion of AEs in the model have little impact the ICER (revised model ICER of £9,096/QALY)[3].

Table 40: Scenario analyses results including costs and disutilities for severe gastro-intestinal AEs and all (severe and non-severe) hypoglycaemia

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,613	18.524	15.255	£9,216
Diet & exercise	£20,270	18.417	15.109	
Incremental	£1,342	0.106	0.146	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 41: Scenario analyses results incl. disutilities and costs for severe gastrointestinal AEs and severe hypoglycaemia

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,613	18.524	15.256	£9,142
Diet & exercise	£20,270	18.417	15.109	
Incremental	£1,342	0.106	0.147	

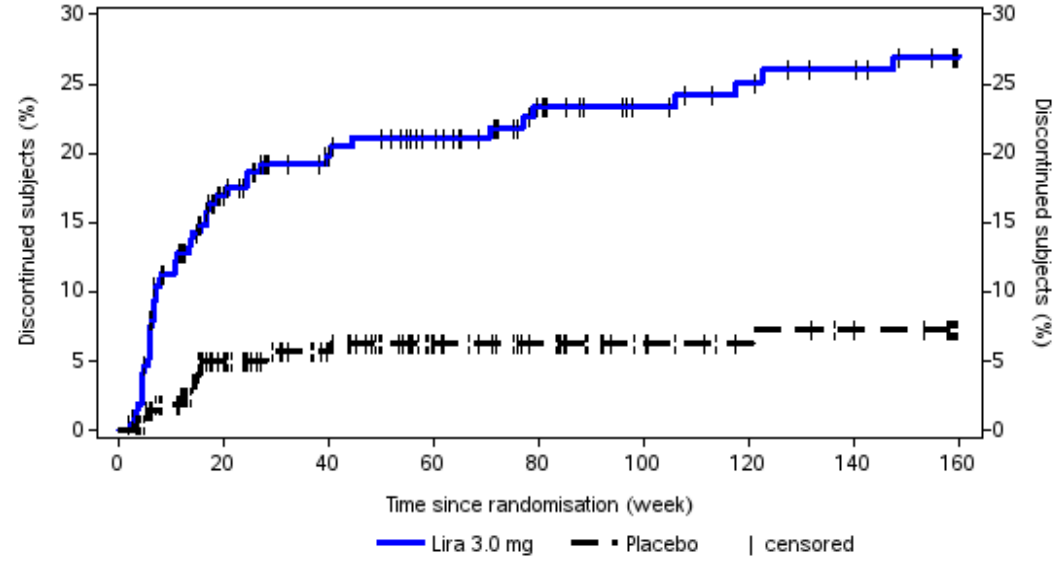
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

2. Withdrawal due to adverse events is captured in the model solely via the 16 week stopping rule. This is supported by the higher discontinuation due to AEs

[3] The revised version of the model is only used to respond to questions B5, B6 and B15. The responses to questions B1.2 and B1.4 will also use the revise version of the model. All other results presented in this response were generated using the CS model (June 2019).

in liraglutide non-responders (Figure 4) compared to liraglutide early responders (Figure 5) observed in the first weeks of treatment. As illustrated below patients who respond to treatment with liraglutide 3.0mg are much less likely to discontinue due to adverse events.

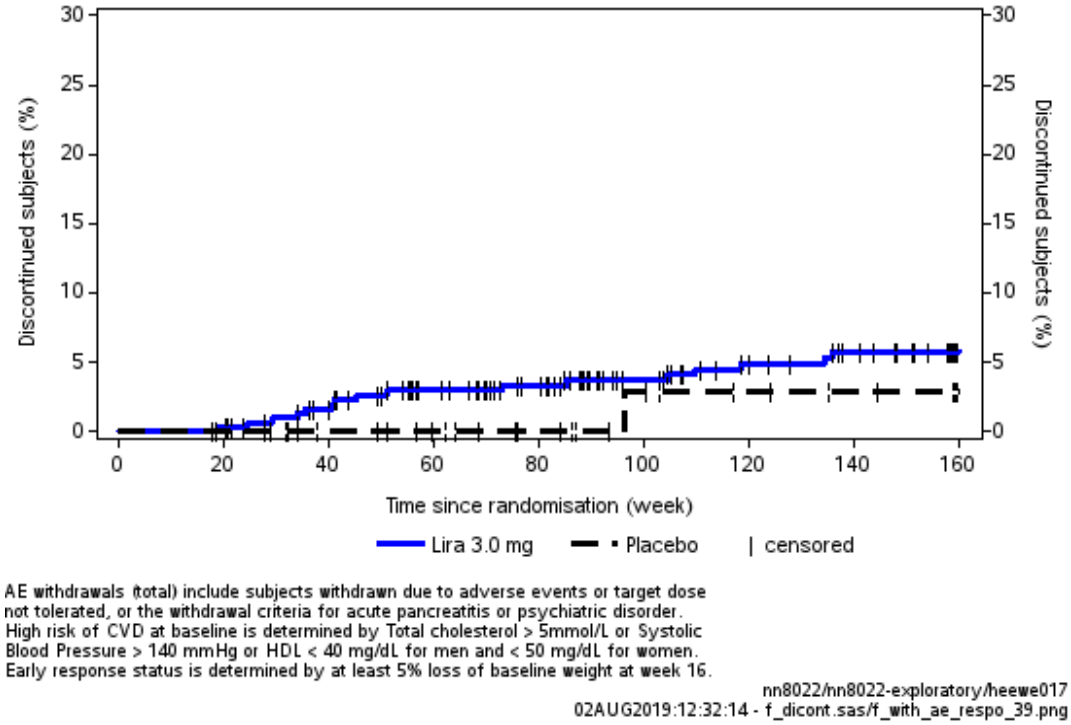
Figure 4: Time to discontinuation (weeks) where primary reason for withdrawal is adverse event in the index population liraglutide 3.0mg non-responders



AE withdrawals (total) include subjects withdrawn due to adverse events or target dose not tolerated, or the withdrawal criteria for acute pancreatitis or psychiatric disorder.
High risk of CVD at baseline is determined by Total cholesterol > 5mmol/L or Systolic Blood Pressure > 140 mmHg or HDL < 40 mg/dL for men and < 50 mg/dL for women.
Early response status is determined by at least 5% loss of baseline weight at week 16.

nn8022/nn8022-exploratory/heewe017
02AUG2019:12:32:15 - f_dicont.sas/f_with_ae_non_resp_39.png

Figure 5: Time to discontinuation (weeks) where primary reason for withdrawal is adverse event in the index population liraglutide 3.0mg early responders



Quality of life

B16. Priority question: As stated in the CS, when health states combine two or more obesity complications, the HRQoL decrement associated with every single complication is summed together and the total is then subtracted from the baseline utility. The reference provided in the CS does not fully justify this assumption (i.e. it does not consider all obesity complications incorporated in the model structure) and it is likely that the utility decrements are not necessarily additive. Please provide a scenario analysis (and the accompanying model) wherein the utility decrements are adjusted to be multiplicative (instead of additive).

Company responses:

The study used to inform the baseline utility in the modelling analyses presented in the CS (Søltoft, et al., 2009) provided estimates for EQ-5D, BMI-dependent utilities, adjusted for the presence of the following obesity complications: type 2 diabetes, heart and circulatory problems, respiratory problems, musculoskeletal problems and cancer. In the model, a utility decrement was applied for the following complications:

type 2 diabetes, ACS, stroke and TIA, sleep apnoea, knee replacement and bariatric surgery. Therefore, the only event considered in the model and not controlled for in the Søltoft et al. was bariatric surgery. This is however likely to have only a minor (if any) impact on HRQOL given the low incidence of bariatric surgery in the model (1.15% per year).

The disutilities applied for events and complications in the model were sourced from either the regression coefficients published in the same Søltoft et al. study (disutilities for: type 2 diabetes, sleep apnoea, cancer, knee replacement) or from regression coefficients of the EQ-5D Scores Catalogue for the United Kingdom published by Sullivan et al. (Sullivan, et al., 2011) (disutilities for: cardiovascular events and chronic cardiovascular health states). The later study was used to have a more granular representation of the disutilities per type of cardiovascular event or health state. Indeed, also in Sullivan et al. the regression coefficients represented the 'marginal disutility' of each condition controlling for covariates, including 135 chronic conditions (overweight and obesity included), age, gender, ethnicity, income, education and presence of two or more complications concomitantly.

Conservatively, the marginal impact of having two or more chronic conditions concomitantly, as estimated in the regression analysis of Sullivan et al. 2011 were not taken into account, although they could have been in e.g. health states post ACS and post stroke. Therefore, we believe that both the baseline utility and disutilities applied in the CS base case were sourced from studies where all modelled conditions co-occurred, and were controlled for, therefore it is reasonable to assume the utility decrements applied are additive.

B17. Table 34 of the CS presents the re-estimated polynomial function for EQ-5D utilities over BMI ranges between 15-35 kg/m2. Please justify why all re-estimated coefficients were used instead of using only the re-estimated third-order polynomial BMI coefficient in combination with the original coefficients as reported by Søltoft et al. 2009.[6]

Company responses:

In absence of the BMI cubic effect i.e. third-order polynomial coefficient, we attempted to replicate as close as possible the BMI-dependent, adjusted utility functions presented in the original paper (See Figure 1 of Søltoft et al. 2009). Using the re-estimated third-order polynomial BMI coefficient in combination with the original coefficients as reported by Søltoft et al. 2009 would have produced visually lower baseline utilities compared with the original ones presented in Søltoft et al. 2009, Figure 1. An example of the re-estimated utilities and their relationship with BMI in females using the original coefficients for BMI and BMI2 in comparison with the same using the fully re-estimated polynomial function used in the CS is illustrated in the left-hand figure below (Figure 6), which is then compared with the original curve from Søltoft et al. 2009 on the right. It can be noted that at the reference BMI level (25 kg/m^2) as well as at BMI 35 kg/m^2 (red lines crossing the graphs below) the fully re-estimated polynomial function (blue curve on the left-hand side figure below) coincides with the red curve (on the right-hand side figure below) representing baseline utilities for females in Søltoft et al., while the orange curve on the left-hand side figure representing the re-estimated cubic effect is below the original estimated at both points. The coefficients of the re-estimated utility function had to be thus considered collectively.

Figure 6: Re-estimated baseline utilities

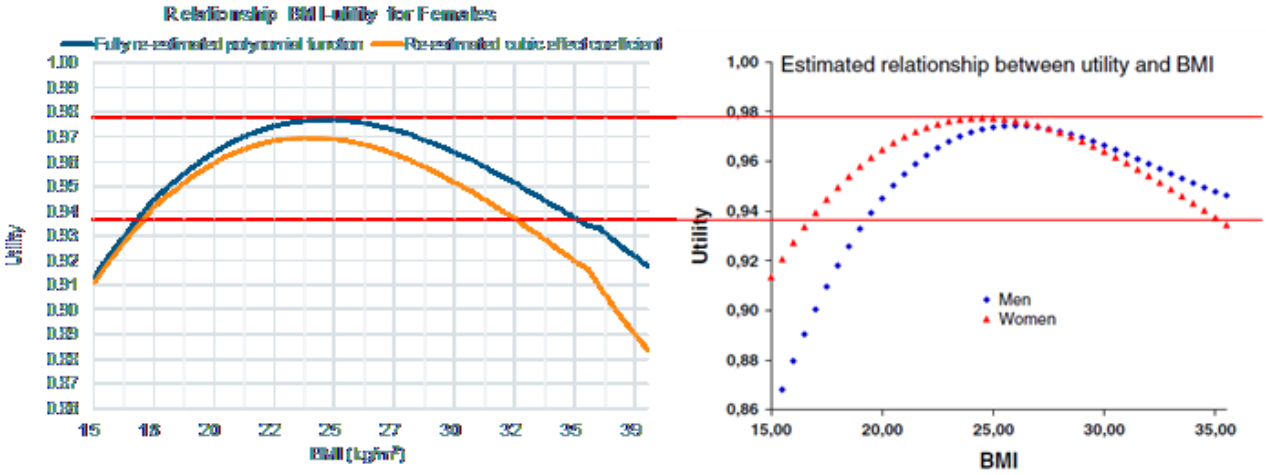


Fig. 1 Estimated relationship between BMI and EQ-5D score after controlling for confounding factors

B18. Utility (decrements) were derived from an analysis of the 2003 Health Survey for England data. However, as mentioned in the CS, quality of life was empirically assessed in clinical trial 1839 and a mapping from SF-36 to EQ-5D was carried out by Kolotkin et al., 2017.[7] Given that these utilities were derived from the target population and trial 1839 serves as the main source of evidence for the model, please add a scenario analysis in which utility are derived from the trial (e.g. using the individual patient data from trial 1839 to estimate the coefficients reported in CS Table 34). If possible and the amount of data permits, also add a scenario in which utility decrements are derived from the trial.

Company response:

The results of a scenario analysis whereby the coefficients of the baseline, BMI, age and gender-dependent utility function was estimated using individual patient data from SCALE prediabetes and obesity are shown in Table 42 below. The methods and full results of this analysis will be reported in a stand-alone technical report which is currently being prepared and can be shared with the ERG at the end of August 2019 once it is finalised, if required.

In brief, coefficients demonstrating the relationship between utility values at baseline and BMI at baseline were computed using the individual patient level data from

SCALE by means of multiple linear regression analyses, controlling for demographic and clinical parameters.

The response variable was the baseline utility score. To allow comparisons with the methods applied in the CS base case, the predictors included in the model were selected to align with those implemented by Søltoft et al., 2009, where available in the SCALE trial dataset. The model included covariates for age group (18–24, 25–34, 35–44, 45–54, 55–64, 65–74 and ≥75 years), smoking Status (Never Smoked vs Previously Smoker vs Current Smoker), BMI (at baseline and at analysis visits), BMI quadratic and BMI cubic and Heart and circulatory problems (excluding hypertension) (Yes vs No) and hypertension (Yes vs No).

Due to a significant difference between genders for many parameters, separate models for males and females were conducted.

Tables 42 and 43 provide the results of the regression analysis. The direction of the relationship between utility and the model predictors in the analysis using the individual patient level data from SCALE was in line with the results reported by Søltoft et al., 2009, although significant results were observed in that study. The not statistically significant results observed in our study are likely due to the smaller sample size, and multiple comorbidities in the study population, which was predominantly overweight and obese. The Søltoft et al., 2009 study included more than 14,000 participants, and about 67.8% of the men and 54.0% of the women were overweight or obese (BMI ≥25 kg/m^2).

The coefficients presented here were then applied within the model as a scenario analysis by replacing those sourced from Søltoft et al. 2009, the results of which are presented in Table 44. The results applying the coefficients based on the SCALE trial demonstrates a very comparable ICER (small reduction of £70) which supports the results of both analyses.

Table 42: Regression model on EQ-5D for males

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

Bold indicates statistically significant results.

Table 43: Regression model on EQ-5D for females

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

Bold indicated statistically significant results.

Table 44: Scenario: baseline utilities from SCALE

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,988	18.584	16.021	£12,989
Diet & exercise	£19,419	18.496	15.901	
Incremental	£1,568	0.088	0.121	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

An analysis incorporating modelled health-state or events disutilities derived from SCALE could not be conducted as subjects studied in the trial did not present with a high level of morbidity either at baseline or during the follow-up of the study.

B19. The disutility for knee-replacement is multiplied by three, assuming a duration before knee surgery of three years. Please provide evidence for 1) this duration of three years; 2) that the disutility is constant over time and; 3) the impact of this multiplication assumption (e.g. by multiplying it by one in a scenario analysis).

Company response:

In a health-economic analysis of symptomatic knee cartilage lesions, Gerlier et al. 2010 used a time between development of osteoarthritis and total knee replacement of five years (Gerlier, et al., 2010). It is likely that the disutility experienced by patients during this time is not linear. By applying a disutility for 3 instead of 5 years, it is assumed that the first years are less affected by the condition, compared with the last. Applying a constant disutility over three years was therefore a simplifying assumption, given, in the model, patients experience knee replacement each cycle and that considering a non-linear disutility, different in each year preceding the knee replacement would be impractical. The impact of this multiplication assumption when assuming a one-year impact is illustrated in Table 45 below.

Table 45: Scenario assessing impact of applying 1-year disutility for osteoarthritis before knee replacement

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,988	18.584	15.439	£13,117
Diet & exercise	£19,419	18.496	15.320	
Incremental	£1,568	0.088	0.120	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Costs

B20. Costs for diet & exercise were derived from existing literature and based on annual non-pharmacological cost comprising monitoring visits (specialist and nurse visits) and a blood test. It is unclear to what extend these costs are representative for tier 3 services. Please elaborate and justify that these costs are applicable to tier 3 treatment costs and provide scenario analyses (and the accompanying model) when appropriate.

Company response:

The cost of diet and exercise reflects the cost of obesity weight management and monitoring, which comprises specialist visits, assumed to correspond to specialist tier 3 service visits, nurse visits and a blood test. The physician survey, conducted in October and November of 2018 (see Appendix N of CS), elicited the frequency of annual number of blood tests, as well as GP, nurse, dietitian and specialist consultations expected for tier 3 obesity weight management. The table below compares the current model assumptions with those derived from the survey, in terms of annual frequency of visit and annual cost of diet and exercise.

Table 46: Resource use and costs for diet and exercise

	Physician survey frequency	Currently modelled frequency
GP consultation	2	0
Nurse consultation	4	8
Dietitian consultation	3	0
Specialist consultation	2	4
Blood test	2	1
Annual cost	£353.60	£130.83

A scenario analysis has been conducted to test the impact of this, results can be found in the table below. As demonstrated, this generates an absolute increase in costs in each arm but results in no change to the incremental difference seen in base case analysis, thus producing no change to the base case ICER (Table 53), given the cost of diet and exercise is applied equally in both arms (i.e. receive diet and exercise along with liraglutide 3.0mg treatment, and remain on diet and exercise following liraglutide 3.0mg treatment stop).

Table 47: Scenario analysis incorporating alternative diet and exercise costs

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,425	18.584	15.336	£13,059
Diet & exercise	£19,857	18.496	15.216	
Incremental	£1,568	0.088	0.120	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Sensitivity/scenario analyses

B21. Probabilistic sensitivity analysis (PSA) was performed by running 1,000 simulations. Given the complexity and data requirements of the model, it is likely that 1,000 is insufficient to provide stable results. Please illustrate that the PSA results are stable and increase the number of simulations used for the PSA whenever appropriate.

Company response:

Following the approach suggested by Hatswell et al. (Hatswell, et al., 2018), a mean and 95% CI for the incremental net monetary benefit (INMB) resulting from 1,000 PSA iterations simulated with the model was calculated, considering a willingness to pay threshold of £20,000. The resulting mean (95% CI) INMB was £709 (95% CI: £42 - £1,503). According to the same authors, if the CI of the INMB does not contain zero, the number of simulations *"may be considered sufficient […] as the adoption decision would be unlikely to change should an increased number of simulations be performed."*

Additionally, a convergence graph for incremental ICERs has been generated increasing the number of simulations up to 10,000. These are illustrated in the figures below suggesting that convergence is achieved at 1,000 simulations. Based on the INMB approach described above, and the visual inspection of the 10,000 iterations convergence graph, we believe that 1,000 simulations can be considered sufficient in this case, and that increasing the number of simulations would add little value, while increasing the computational time for generating PSA results with the model. Acceptability curves also showed the proportion of simulations likely to be considered cost-effective under a £20,000 per QALY threshold are the same when running 1,000 simulations (Figure 8) and when running 10,000 simulations (Figure 9), at 98% and 98% respectively.

Figure 7: ICER Convergence Graph

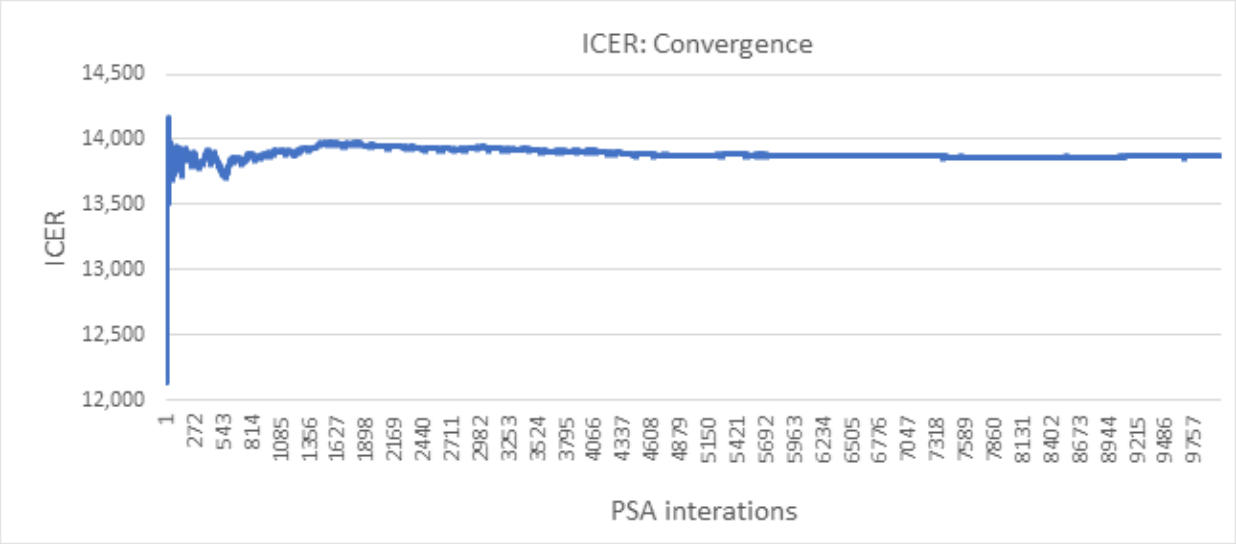


Figure 8: CEAC Under 1,000 simulations

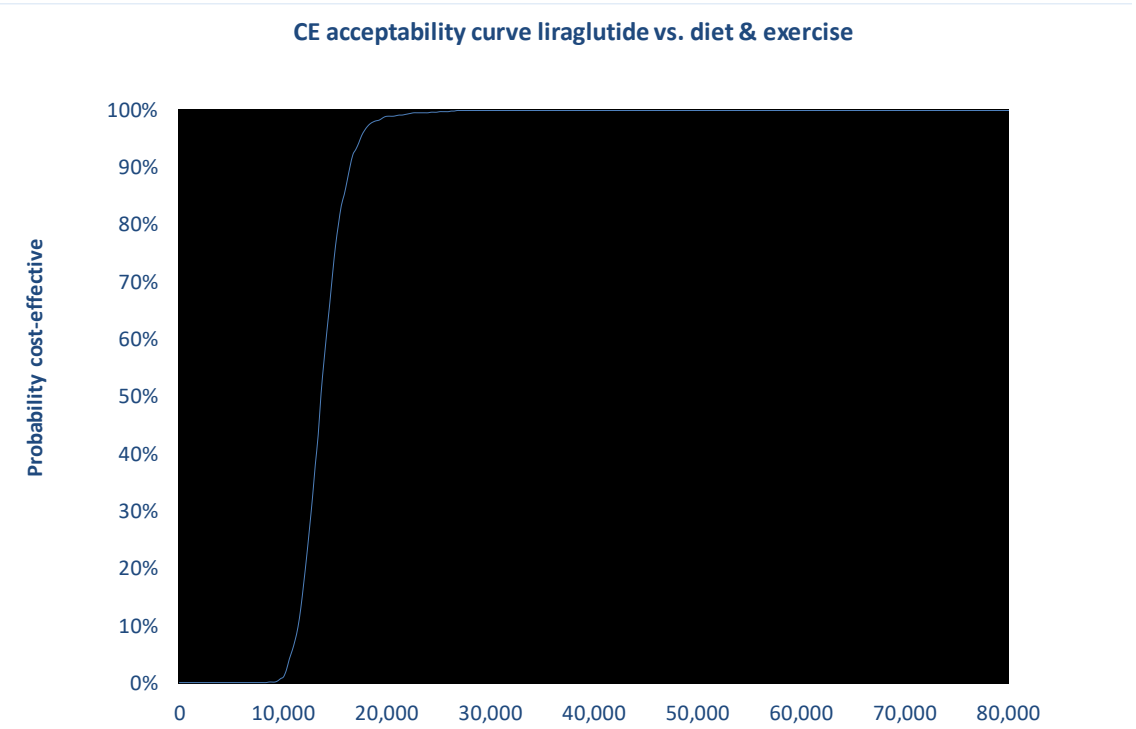
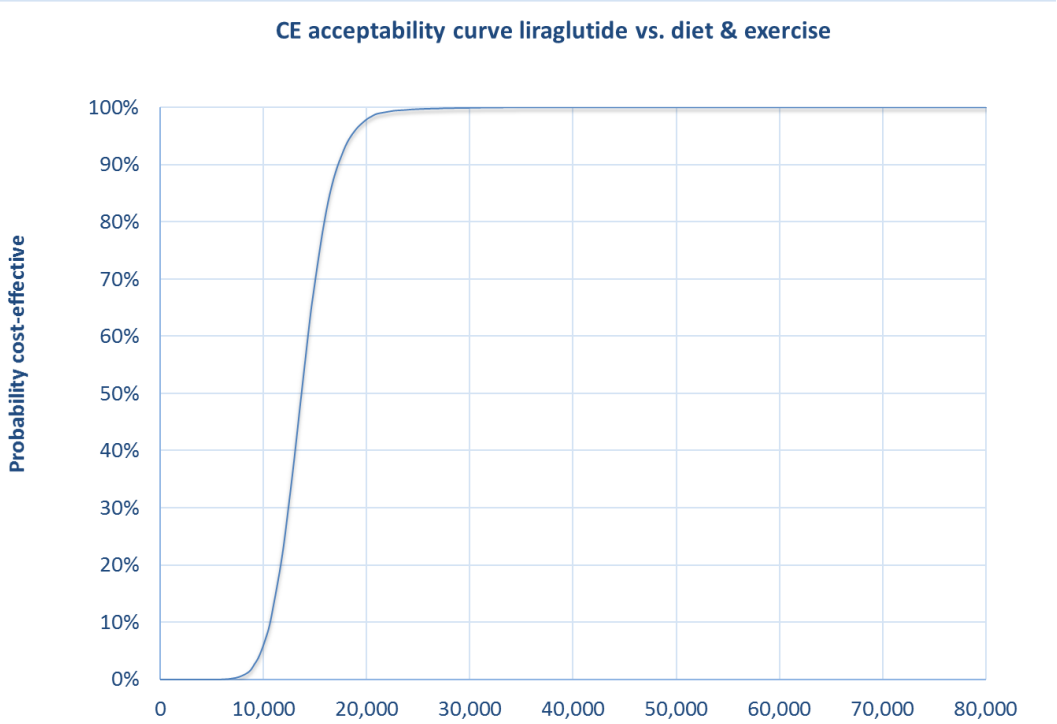


Figure 9: CEAC Under 10,000 simulations



Validation

B22. Priority question: The submitted economic model is not self-explanatory (particularly the Markov worksheets; e.g. “Markov Lira”). Please provide a manual explaining: 1) what the numerical values in the cells represent and; 2) for the calculations, what the purpose of the calculations is as well as the underlying inputs and assumptions. The explanations can be grouped for numerical values representing similar aspects or similar calculations.

Company response:

Table 48: Explanations provided for Markov sheet “Markov Lira”

Reference for section	Numerical values represent	Purpose of calculation
Rows #9-25	Per cycle values of the parameters which change over time and which affect the risk of events and transitions between health states	While patients remain on treatment, baseline values are adjusted with the treatment effects; beyond treatment duration (i.e. xlontreatment_lira=1), if the parameters are set to return to their baseline values (ret_bas=0), a catch-up rate is applied until baseline is reached, if parameters are set to return to a

Reference for section	Numerical values represent	Purpose of calculation
		value on the natural progression, the catch-up is calculated to the value of the parameter either in the diet and exercise arm (if discontinuation is set to diet) or to the no treatment arm (if discontinuation set to no treatment)
Rows #26-77	Per cycle risk of events (cardiovascular, type 2 diabetes onset etc.) as determined by alternative risk equations available in the model. The actual risk of event used in the model (dependent of the choice for the risk equation) is shown on the lines labelled “live in model” (e.g. row #32)	In each row, the risk equation functions determining the risk of events or transition between health states are written. Risk function coefficients are linked to sheet 'Risk eq 1'!
Rows #79	Per cycle baseline utility applied in the model	The utility functions for baseline utility are picked up from rows #79-82 columns #BI onwards depending on choice of utility method
Rows #80	Per cycle baseline utility adjusted for age	Baseline utility is adjusted with the age-dependent decrements
Rows #81-104	Per cycle and per health state utility applied in the model	Baseline utilities are adjusted with utility decrements per health state
Rows #107-130	Markov trace for patients remaining on liraglutide 3.0mg treatment after week 16 (i.e. liraglutide 3.0mg early responders)	Calculation of proportion of patients in cycle in each health state, by multiplying the proportion of patients in each health state in the previous cycle with the cycle-dependent transition probabilities to the new health state from rows #520-1093, and subtracting mortality occurring in cycle
Row #133	Proportion of cohort remaining on liraglutide after week 16 with sleep apnoea	Calculation of sleep apnoea prevalence as function of BMI
Rows #136-158	Markov trace for patients stopping liraglutide (due to non-response status at week 16), and continuing diet and exercise	Model picks-up the proportion of the cohort in each health state, per cycle from either the Markov D&E or Markov NoTx, depending on whether the proportion of non-responders discontinue to diet and exercise or no treatment
Row #161	Prevalence of sleep apnoea in cohort discontinuing liraglutide (due to non-response) to diet or to no treatment	Model picks-up the prevalence of sleep apnoea from either the Markov D&E or Markov NoTx, depending on whether the proportion of non-responders discontinue to diet and exercise or no treatment
Rows #164-186	Markov trace for all patients initiating liraglutide (i.e. weighted	Calculation of weighted average proportion of patients in health state for responders and non-

Reference for section	Numerical values represent	Purpose of calculation
	average between early responders and non-responders)	responders to liraglutide; a cycle correction is applied from cycle 5 onwards
Rows #191-198	Proportion of patients with complications in each cycle	Sum of proportions calculated in Rows #164-186 by health state
Rows #201-223	Per cycle costs by health state and proportion of patients in health state for patients continuing liraglutide treatment	The proportion of patients on liraglutide is multiplied with the costs per health state; a cycle correction is applied from cycle 5 onwards
Rows #226-248	Per cycle costs by health state and proportion of patients in health state for patients discontinuing liraglutide	Model picks-up the cost per health state from Markov D&E or Markov NoTx, depending on whether the proportion of non-responders discontinue to diet and exercise or no treatment
Rows #251-275	Per cycle costs by health state and proportion of patients in health state for all patients initiating liraglutide (i.e. weighted average between early responders and non-responders discontinuing to diet and exercise)	Calculation of weighted costs for patients in health state for responders and non-responders to liraglutide
Row #279, 280	Per cycle total, discounted costs	Application of discounting rate
Rows #282-304	Per cycle QALYs by health state and proportion of patients in health state for patients continuing liraglutide treatment	The proportion of patients on liraglutide is multiplied with the utility per health state; a cycle correction is applied from cycle 5 onwards
Rows #307-329	Per cycle QALYs by health state and proportion of patients in health state for patients discontinuing liraglutide	Model picks-up the utility per health state from Markov D&E or Markov NoTx, depending on whether the proportion of non-responders discontinue to diet and exercise or no treatment
Rows #332-354	Per cycle QALYs by health state and proportion of patients in health state for all patients initiating liraglutide (i.e. weighted average between early responders and non-responders discontinuing to diet and exercise)	Calculation of weighted utilities for patients in health state for responders and non-responders to liraglutide
Rows #360, 361	Per cycle total, discounted QALYs	Application of discounting rate
Rows #363-385	Per cycle, per health-state life-years	Equal to the proportion of patients alive in each health state

Reference for section	Numerical values represent	Purpose of calculation
Rows #390-393	Total, per cycle, discounted life-years	Application of discounting rate
Rows #395-431	Per cycle number of events for patients remaining on liraglutide (rows #395-405), discontinuing (rows #408-418) and weighted average for all patients initiating liraglutide (rows #421-431)	Calculation of number of events in each state; the number of events is calculated by multiplying the proportion of patients in each health state in the previous cycle, by the corresponding cycle risk of events; and adjustment (division by 4) is made to the risk in cycles of 3-months duration; fatal and non-fatal events are calculated separately.
Rows #434-470	Per cycle cost of events for patients remaining on liraglutide (rows #434-444), discontinuing (rows #447-457) and weighted average for all patients initiating liraglutide (rows #460-470)	Multiplication of the number of events with the cost per event
Rows #474,475	Per cycle, total, discounted cost of events	Application of discounting rate
Rows #477-513	Per cycle disutilities for events occurring in cycle: patients remaining on liraglutide (rows #477-487), discontinuing (rows #490-500) and weighted average for all patients initiating liraglutide (rows #503-513)	Multiplication of the number of events with the disutility per event
Rows #517,518	Per cycle, total, discounted disutilities for events	Application of discounting rate
Rows #520-1093	Per cycle transition probabilities from each health state of the model to each health state of the model	Calculation of transition probabilities from each health-state to each health state of the model; e.g. for the transition from no complication to type 2 diabetes row #621, if type 2 diabetes is included in the model, the cycle probability of type 2 diabetes is defined as the risk of type 2 diabetes development in normal glucose tolerance (row #62) transformed in a 3-month or 12-months probability using the formulae 1-exp(-r*t); whereby r is the per cycle risk and t is time taking value ¼ for 3-month probability or 1 for 1-year probability
Rows #1095-1117	Per cycle and per health state probability of death	Model picks-up the health-state and age-specific probability of death from the Mortality Inputs tab
Rows #1121-1123	Illustration of BMI values for cohort remaining on liraglutide (early responders), discontinuing (non-responders), and weighted average	Model picks-up BMI for responders on liraglutide and non-responders discontinuing to diet or no treatment

Reference for section	Numerical values represent	Purpose of calculation
	– values are not used in the model engine	
Section # AT520 to BR1093	Costs by health state and by year in which transition to health-state occurs	e.g. in row #721 col. BB and BC the first-year cost following an MI/angina (excl. event cost) is applied when patients transition from any health state free of ACS history to the health state post ACS; in row #729 the year 2+ cost post ACS is applied for patients remaining in a post ACS state

B23. Priority question: CS Appendix O.1.1 provides questions asked during the expert validation meeting. However, the responses to these questions are not provided. Please provide the responses to the questions presented in CS Appendix O.1.1.

Company response:

The minutes of the meeting for the model validation have been provided as part of this response as a PDF (ID740_Lira3.0mg_Model_validation_minutes).

B24. The HEOR technical reports[8, 9] considering cross-validation and external validation are very informative.

1. Could the company provide the HEOR technical reports considering verification (i.e. internal validity) and face validity if available?

2. In supplementary Table 2 of the external validation report, the observed and predicted RR for CVD and mortality seems inconsistent. Please provide an explanation for these differences and elaborate on the implications of these differences.

3. In addition to the external validation provided in the HEOR technical report,[9] please provide, for different time points, the proportion of patients (both predicted and observed) that have experienced the following events for both the intervention and control:

a. Bariatric surgery,
b. Non-fatal MI
c. Fatal MI
d. Non-fatal stroke
e. Fatal stroke
f. Non-fatal angina
g. Fatal angina
h. TIA
i. CV death
j. Composite Events

4. Please provide an external independent validation (i.e. using sources that were not used to build the model) using the items mentioned in the preceding sub-question.

Company responses:

1. The internal validity of the model was performed by the developers of the model. A checklist and results of this review were provided in the CS Appendix O, "Summary of the model quality control". The face-validity of the model was considered part of the clinical expert validation; the details of this validation were provided in the CS Appendix O "KOL Validation".

2. When preparing a response to this question, we noted an inconsistency in the HEOR Ltd. external dependent validation report supplementary Table 2. Namely, the columns "Intervention" and "Control" for the Framingham and QRisk3 studies should have been labelled "Females" and respectively "Males". For the two validations against the UKPDS model the columns are labelled correctly. We apologise for this inconsistency. We would like to note as well that the objective of the external dependent validation was to assess the correspondence of the model predictions to actual event data as observed in the published studies informing the model development. The intention was to analyse the total incidence of events predicted with the model at different time points, rather than incrementally

between treatment arms. A validation of differences between arms (i.e. predicted RR) was not within the scope, given such an attempt would face significant limitations. Firstly, the progression of the physiological parameters (e.g. BMI, SBP) was not always available for the follow-up duration of the study, and different data sources and assumptions had to be taken. In addition, the interventions evaluated in the studies informing the model development were very different from the weight-loss interventions evaluated by the obesity model. For example, the UKPDS80 SU-INS was a comparison between intensive blood glucose management with either sulfonylurea or insulin and conventional therapy (primarily with diet). It was not in the scope of the validation to replicate the efficacy of these treatments on the modelled physiological parameter.

3. Given the very low numbers of events in the trial, comparisons between observed and predicted events are unfounded. In the index population (BMI ≥35 kg/m^2, prediabetes and high risk of CVD) only 1 fatal event occurred (cardio-respiratory arrest), which was in the placebo group. In addition, the years of observation time were different in the observed vs. the predicted, and thus the proportion of patients with events should not be compared directly. Rather, the event rates (i.e. events divided by the years of observation-time) should be compared.
   The observed event rates for the index population in SCALE prediabetes (trial 1839) are shown in Table 49 and the predicted event rates over 1-3 years from the model are shown in Table 50-52. Please note that we present the event rate for ‘unstable angina’ as ‘non-fatal angina’ was not specifically collected in the trial.

Table 49: Observed proportion of patients in the index population from Trial 1839 having experienced specific events as requested by the ERG

Trial 1839: Index population, week 0-172 (observed)								
	Liraglutide				**Placebo**			
No. subjects	530				170			
Years of observation time	1170.82				528.86			
	N	%	E	R	N	%	E	R
Bariatric surgery	-	-	-	-	-	-	-	-
Non-fatal MI	0	0.0	0	0.0	0	0.0	0	0.0
Fatal MI	0	0.0	0	0.0	0	0.0	0	0.0
Non-fatal stroke	0	0.0	0	0.0	0	0.0	0	0.0
Fatal stroke	0	0.0	0	0.0	0	0.0	0	0.0
Unstable angina	1	0.2	1	0.09	0	0.0	0	0.0
Fatal angina	0	0.0	0	0.0	0	0.0	0	0.0
TIA	1	0.2	1	0.09	0	0.0	0	0.0
CV death	0	0.0	0	0.0	0	0.0	0	0.0
Composite events (MACE: CV death, non-fatal MI and non-fatal stroke)	0	0.0	0	0.0	0	0.0	0	0.0

More details on the cardiovascular adverse events in the index population are given in Appendix E: Post hoc analysis – Supplementary data 1.

Table 50: Predicted proportion of patients from the model having experienced specific events as requested by the ERG in a 1-year time horizon

Model (predicted): 1-year horizon with cohort of 1,000 patients								
	Liraglutide				**Placebo**			
No. subjects	1,000				1,000			
Years of observation time	2,987				2,987			
	N*	%	E	R	N*	%	E	R
Bariatric surgery	-	-	-	-	-	-	-	-
Non-fatal MI	N/A	0.07%	0.68	0.001	N/A	0.07%	0.73	0.001
Fatal MI	N/A	0.03%	0.30	0.000	N/A	0.03%	0.32	0.000
Non-fatal stroke	N/A	0.05%	0.48	0.000	N/A	0.05%	0.51	0.001
Fatal stroke	N/A	0.01%	0.14	0.000	N/A	0.02%	0.15	0.000
Non-fatal angina	N/A	0.08%	0.83	0.001	N/A	0.09%	0.89	0.001
Fatal angina	N/A	0.04%	0.36	0.000	N/A	0.04%	0.39	0.000
TIA	N/A	0.01%	0.13	0.000	N/A	0.01%	0.14	0.000
CV death	N/A	0.08%	0.80	0.001	N/A	0.09%	0.86	0.001
Composite events	N/A	0.20%	1.960	0.002	N/A	0.21%	2.103	0.002

* Number of patients with events (N) cannot be calculated from the model, as this is a cohort model, i.e. it is not possible to distinguish whether multiple events occurred in the same patient

Table 51: Predicted proportion of patients from the model having experienced specific events as requested by the ERG in a 2-year time horizon

Model (predicted): 2-year horizon with cohort of 1,000 patients								
	Liraglutide				**Placebo**			
No. subjects	1,000				1,000			
Years of observation time	2,987				2,987			
	N*	%	E	R	N*	%	E	R
Bariatric surgery	N/A	1.15%	11.47	0.006	N/A	1.15%	11.47	0.006
Non-fatal MI	N/A	0.17%	1.67	0.001	N/A	0.18%	1.81	0.001
Fatal MI	N/A	0.07%	0.73	0.000	N/A	0.08%	0.79	0.000
Non-fatal stroke	N/A	0.12%	1.17	0.001	N/A	0.13%	1.26	0.001
Fatal stroke	N/A	0.03%	0.35	0.000	N/A	0.04%	0.37	0.000
Non-fatal angina	N/A	0.20%	2.03	0.001	N/A	0.22%	2.19	0.001
Fatal angina	N/A	0.09%	0.89	0.000	N/A	0.10%	0.96	0.000
TIA	N/A	0.03%	0.33	0.000	N/A	0.04%	0.35	0.000
CV death	N/A	0.20%	1.97	0.001	N/A	0.21%	2.13	0.001
Composite events	N/A	0.48%	4.808	0.002	N/A	0.52%	5.193	0.003

* Number of patients with events (N) cannot be calculated from the model, as this is a cohort model, i.e. it is not possible to distinguish whether multiple events occurred in the same patient

Table 52: Predicted proportion of patients from the model having experienced specific events as requested the ERG in a 3-year time horizon

Model (predicted): 3-year horizon with cohort of 1,000 patients								
	Liraglutide				**Placebo**			
No. subjects	1,000				1,000			
Years of observation time	2,987				2,987			
	N*	%	E	R	N*	%	E	R
Bariatric surgery	N/A	2.29%	22.91	0.008	N/A	2.29%	22.91	0.008
Non-fatal MI	N/A	0.28%	2.84	0.001	N/A	0.31%	3.09	0.001
Fatal MI	N/A	0.12%	1.25	0.000	N/A	0.14%	1.35	0.000
Non-fatal stroke	N/A	0.20%	1.98	0.001	N/A	0.22%	2.16	0.001
Fatal stroke	N/A	0.06%	0.59	0.000	N/A	0.06%	0.64	0.000
Non-fatal angina	N/A	0.35%	3.45	0.001	N/A	0.38%	3.75	0.001
Fatal angina	N/A	0.15%	1.51	0.001	N/A	0.16%	1.64	0.001
TIA	N/A	0.06%	0.55	0.000	N/A	0.06%	0.60	0.000
CV death	N/A	0.33%	3.35	0.001	N/A	0.36%	3.64	0.001
Composite events	N/A	0.82%	8.18	0.003	N/A	0.89%	8.88	0.003

* Number of patients with events (N) cannot be calculated from the model, as this is a cohort model, i.e. it is not possible to distinguish whether multiple events occurred in the same patient

4. An external independent validation report performed by HEOR Ltd has been provided.

B25. The ERG identified some inconsistencies, please clarify and/or correct these inconsistencies if applicable

1. The deterministic scenario analyses related to treatment duration and waning of treatment effect (i.e. CS Tables 67-71) are expected to affect the results for liraglutide only (i.e. not the costs and QALYs for Diet & exercise) compared with the base-case results presented in Table 52. However, the costs and QALYs for Diet & exercise are also affected in these scenario analyses.

2. The value (54.5%) in 'Early responders'!F61 is not consistent with the value reported in CS Table 28 (40.7%) nor consistent with 'Cohort Inputs'!J337 (40.7%).

3. CS Table 21 indicates 156 non-responders while 155 non-responders are reported in CS Table 28 as well as the economic model ('Stopping rules'!F15)

Company responses:

1. In the deterministic scenario analyses related to treatment duration and waning of treatment effect costs and QALYs for diet and exercise are expected to change for several reasons. Firstly, in the treatment duration analyses (CS Tables 67, 77) both liraglutide 3.0mg and diet and exercise treatment duration were varied concomitantly. Although all patients in the model remain on diet and exercise over the entire time horizon, i.e. treatment duration with diet and exercise was lifelong, the treatment duration parameter in the diet and exercise arm affects the number of cycles over which the SCALE obesity and prediabetes placebo-efficacy was applied. In other words, patients stay on diet and exercise lifelong, but placebo efficacy is applied only for the treatment duration specified, after which, consistently with the liraglutide 3.0mg plus diet and exercise arm, patients are assumed to return to their baseline values during the catch-up period, and then progress according to the natural disease pathway simulated by the model. In the same way, varying the waning of treatment effect parameter (CS Tables 69-71) affects the duration over which patients remain in a temporary normal glucose tolerance state after the initial prediabetes reversal, in both arms.

2. The value (54.5%) in 'Early responders'!F61 represents the calculated proportion of patients reverting to normal glucose tolerance state in SCALE placebo responders. The value reported in the CS Table 28 (40.7%) and in 'Cohort Inputs'!J337 (40.7%) represents the proportion of patients reverting to normal glucose tolerance state in the full analysis set on placebo in SCALE (BMI ≥35 kg/m2, high risk of diabetes, high risk of CVD). In the base case analysis, the model applies the full-analysis set efficacy with placebo from SCALE (40.7%), as reported in the CS Table 28 and in 'Cohort Inputs'!J337. The value 54.5% in 'Early responders'!F61 is therefore not used in the CS base case.

3. There were 155 liraglutide 3.0mg subjects who did not achieve an early response status at week 16, therefore the value (156) reported in the CS Table 21 is wrong and we apologise for the inconvenience. The value reported in the CS Table 28 and economic model are correct.

Revised base case model

As described above, in preparing a response to question B5, an inconsistency was identified in the model. In summary, this related to:

- The calculation of type 2 diabetes risk after prediabetes reversal - the model applied a lower risk of type 2 diabetes onset post temporary reversal of prediabetes, whilst this should have been equal the risk of type 2 diabetes development in all prediabetic patients
- The adjustment to account for the shorter cycle length in the first year of the model had been applied twice
- There was a typographical error in the formulae to calculate of the number of MI events per cycle for liraglutide 3.0mg and comparator

Whilst the original CS base case model has been used in most scenario analyses presented in this document, we kindly request that NICE and the ERG consider the revised base case model for any further analyses and presentation to the appraisal committee henceforth. As noted earlier the revised model has been used in responses to questions B5, B6 and B15.

The impact of updating the model to address these issues on the base case ICER is illustrated below in Table 53 and 54.

Table 53: Original base case ICER

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,988	18.584	15.336	£13,059
Diet & exercise	£19,419	18.496	15.216	
Incremental	£1,568	0.088	0.120	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 54: Revised base case ICER

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,606	18.524	15.256	£9,096
Diet & exercise	£20,270	18.417	15.109	
Incremental	£1,336	0.106	0.147	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Liraglutide for managing overweight and obesity

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.

Information on completing this submission

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	HOOP UK (Obesity UK)
3. Job title or position	Director of Obesity UK
4a. Brief description of the organisation (including who funds it). How many members does it have?	Obesity UK is a charity, it is funded by fundraising and has been supported by pharmaceutical companies, one of which being Novo Nordisk. We have over 17,000 members
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Through our members online support groups.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with obesity is a constant struggle, life is very restrictive. There are huge amounts of stigma faced by people living with obesity. Access to treatment and weight management services are sporadic across the UK and it is very much a postcode lottery. GP's have very limited training in obesity and some are nervous to bring up the conversation around obesity as a result.
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 only treatments currently available on the NHS currently are Orlistat, and bariatric surgery.
8. Is there an unmet need for patients with this condition?	There are no medications that focus on the biological or physiological causes of obesity. We know from the Foresight Report that there are over 100 different factors why someone is living with obesity, so we need medications addressing some of these. We know from bariatric surgery how successful modifying the gut hormones can be, so more medications focusing on this would be helpful.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	They are happy that another treatment option could become available.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Injectable device
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 with a BMI of 30 or above. People living with obesity and co morbidities These groups have limited treatment options currently and are at greater risk.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No
Other issues	
13. Are there any other issues that you would like the committee to consider?	
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.]	

if there are none delete highlighted rows and renumber below	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- People living with obesity face stigma on a daily basis
- Weight management services are sporadic and it is a postcode lottery
- More treatment options are required, especially those working on the physiology
-
-

Thank you for your time.

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

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Professional organisation submission

Liraglutide for managing overweight and obesity

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Obesity Group of the British Dietetic Association**

3. Job title or position	**Senior Lecturer in Nutrition, Kingston University**
4. Are you (please tick all that apply):	**X**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The Obesity Group is a specialist group of the national professional organisation for dietitians, the British Dietetic Association. We are dietitians with a special interest in obesity prevention and management in adults and children. We are a membership organisation so receive funding from the annual fee for our members. We sometimes receive funding from organisations also involved in treatment of obesity (e.g. slimming organisations), usually in association with study days which we organise and run for the profession and other healthcare professionals.**
5b. 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	The overall aim of treatment is to achieve clinically significant benefits. In those still gaining weight. To stop or reduce the rate of weight gain is important. For those whose weight is stable, achieving weight loss which will bring about improvements to weight-related clinical conditions would be a primary aim. Any treatment should result in the patient feeling better than they did at the start of the treatment and that is not

mobility, to cure the condition, or prevent progression or disability.)	just about weight, but also quality of life, quality of diet, ability to be active and to participate in activities of daily living. For each patient individual treatment goals will be set. These may include the following: to regularise eating patterns in those with erratic eating behaviours, to improve the overall quality of the diet, to achieve patient own identified goals (which may relate to specific activities, to physical activity, to quality of life), to improve levels of physical activity and quality of life.
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.)	In those still gaining weight, an initial aim is to stop weight gain. In those with BMI of 25-35kg/m^2, 5-10% weight loss is associated with clinically significant benefits. Greater weight loss may be required in those with higher initial BMI (e.g. 15-20% weight loss in those with BMI of >35kg/m^2). These levels of weight loss are clinically meaningful and achievable.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, undoubtedly so. Long-term support and follow-up have been shown to improve outcomes of this complex progressive long-term disease but this is not easy to achieve within primary and secondary care resources. Specialist services are limited across the country and inequity to access is a result of this. Specific subgroups within the population may be less likely to access services for a variety of personal, cultural or other reasons (e.g. men, BAME groups, those with mental health conditions, those from lower socioeconomic groups); often these same subgroups have greater need for treatment. All treatments are based on the same principles; changing dietary and activity behaviours with additional adjunct therapy as required (currently limited to Orlistat, which is not acceptable to many). Bariatric surgery is difficult to access, complex and not suitable for everyone; it has also very limited availability compared with the numbers who are eligible for it. Furthermore, it should also be noted that currently there is only one pharmacological agent that is recommended for use within the UK for weight loss, namely Orlistat. This medication, although it can be clinically effective, is rarely prescribed due to unpleasant and socially unacceptable side effects which affect adherence. Therefore, there is a high unmet need at the present time for additional pharmacological

	treatments to fill the gap between traditional lifestyle treatment and bariatric surgery. Liraglutide would present a welcome addition.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	It depends on the resources within the local area and the extent to which it is recognised as a priority. Prevention and population-based prevention activities take place within the community, delivered by a range of healthcare and exercise professionals (Tier 1). Tier 2 represents community based treatment services delivered by dietitians or exercise professionals, while Tier 3 services are based in primary and secondary care and involves a multidisciplinary team; both tiers focus on diet, activity and behaviour change to bring about a reduction in energy intake relative to requirements resulting in weight loss. Tier 4 specialist services are hospital based and usually focus on bariatric surgery. Pharmacotherapy is used as an adjunct to treatment in Tiers 2 and 3; failed pharmacotherapy is one of the indications for Tier 4 treatment.
● Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, a variety of clinical guidelines are used including NICE CG189, SIGN 115. In addition many services develop their own local guidance (clinical guidelines and obesity care pathways), which are usually based on national guidance as well as local provision.
● 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.)	While a pathway of care may be defined it is putting it into practice that may vary. Variation in access to services varies across the country depending on local provision and the extent to which obesity is recognised as a local priority. Access in particular to Tier 3 and 4 services is inequitable which is often related to social determinants such as access to healthcare, socioeconomic status and the environment.

● What impact would the technology have on the current pathway of care?	It would add an additional treatment option to those already available. This could have a positive impact on those individuals who do not wish to use Orlistat but would benefit from a pharmacological to assist with their weight loss goals. As mentioned the issue will be whether local areas take up this option. We suggest a risk: benefit analysis comparing Orlistat, Liraglutide and Metformin is carried out (we suggest the addition of Metformin as although it is not a weight reduction drug *per se*, is the drug of choice for those with obesity and type 2 diabetes and is widely used).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is likely to be offered in Tiers 2 and 3 as an alternative to Orlistat. In addition, there could be a place for use as an adjunct with those that have responded poorly after bariatric surgery, recent data has shown that the addition of Liraglutide can help to reduce both weight and improve glycaemic control (GRAVITAS trial results recently reported in the Lancet Diabetes & Endocrinology).
● How does healthcare resource use differ between the technology and current care?	The only pharmacological alternative is Orlistat which is taken orally. Liraglutide requires an injection, so differs in that way. In addition, the cost of the technology is greater than current available pharmacological treatment, and this may affect access and willingness to prescribe at a local level. Both Liraglutide and Orlistat require ongoing support with diet and lifestyle changes to facilitate weight loss and maintenance of lower weight in those who have lost weight.
● In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tiers 2 and 3 are most likely; will require at least initial healthcare administration as an injection is required, and patients will need initial support with this.
● What investment is needed to introduce the technology? (For	Training of healthcare staff; inclusion of the treatment within existing care pathways; updating of clinical guidance; ensuring access to the treatment. Patients will need to be trained to self-administer the injection.

example, for facilities, equipment, or training.)	Ongoing support with lifestyle and dietary changes, although this is also the case with Orlistat so does not represent an additional cost. Liraglutide is more expensive than Orlistat, but may be more acceptable to some patients. Compared with the costs of treating obesity-related co-morbidities in those not treated, Liraglutide is likely to be cost effective.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Clinical trials with Liraglutide resulted in greater weight loss compared with placebo, and a greater proportion of those treated with Liraglutide achieved 5% and 10% weight loss than those treated with placebo. Weight losses are typically between 4-6kg. Obesity-related co-morbidities also improved (pre-diabetes, obstructive sleep apnoea & type 2 diabetes). In addition, there is evidence that Liraglutide has cardiovascular benefits.
● Do you expect the technology to increase length of life more than current care?	It has the potential to do so within a package of care which includes ongoing support with dietary and lifestyle changes, improved physical activity and long-term monitoring. It is likely to do so by improving obesity-related co-morbidities associated with increased morbidity and mortality (e.g. type 2 diabetes). However weight regain has been shown to occur after stopping treatment so long-term efficacious support needs to be in place.
● Do you expect the technology to increase health-related quality of life more than current care?	Clinical trials have demonstrated a greater potential for weight loss with Liraglutide than placebo or other treatments for obesity, with the exception of bariatric surgery. Therefore it has the potential to improve health-related quality of life to a greater degree than alternatives (with the exception of bariatric surgery).
12. Are there any groups of people for whom the technology would be more or	It has been shown to be more effective in those with type 2 diabetes, prediabetes and increased cardiovascular risk; and there may be benefits for those with mental health conditions. It may be more effective in groups of the population at increased risk of these conditions (e.g. those of Asian origin and type 2 diabetes); however these groups have been under-represented in clinical trials to date. In addition, those groups for whom Liraglutide is contraindicated (such as those with pancreatitis or alcoholism), will not be able to access it. We would recommend using Liraglutide with caution in some groups such as those

less effective (or appropriate) than the general population?	with certain mental health conditions/in long-term residential setting due to the training involved with administration and possible contraindications with other medications. .
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.)	It is administered by injection, which some patients may find more difficult or less acceptable. Nausea and gastrointestinal symptoms were the most common side effect reported within the clinical trials. When used alongside sulphonylureas with patients who have Type 2 Diabetes, the risk of hypoglycaemia will need to be monitored.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Additional testing may be needed in those of Asian ethnicities as they are a high risk group who have been under-represented in the clinical trials to date.

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?	There may be additional benefit in subgroups who were excluded from the clinical trials, and this may not be included within QALY improvement calculations (e.g. severe mental health conditions).
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?	From clinical trials it appears to be more effective than alternative non-surgical treatments for obesity.

● Is the technology a 'step-change' in the management of the condition?	In the sense that it offers a viable option for those who are unwilling or unable to tolerate Orlistat, who may benefit from the higher weight loss possible with Liraglutide and potentially in subgroups who may benefit more (e.g. those with prediabetes, type 2 diabetes, cardiovascular disease).
● Does the use of the technology address any particular unmet need of the patient population?	There is a dearth of pharmacological options for those with obesity, and this treatment potentially offers a non-surgical alternative to what is already available.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Gastrointestinal symptoms including nausea were the most common side effects identified within the clinical trials. Pulse rate was also raised. Dropout rates from the trials were higher in treatment compared with placebo groups, so discontinuation of the treatment may be an issue, and weight regain after discontinuation has been shown.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Some clinical trials included UK centres. Trials included counselling on diet and activity, encouraging a reduction of calorie intake (e.g. 500 kcal reduction) and an increase in activity levels (e.g. 150mins/week). These both represent standard approaches within UK practice. However dietary guidance varies with different approaches to energy intake reduction (e.g. use of very low energy diets), format of diets (e.g. use of liquid or solid food replacement products, often within a low or very low energy dietary approach), and macronutrient composition (e.g. low carbohydrate dietary approaches). There is not a single standard of UK

	practice, although all should include advocacy for reduction on calorie intake through dietary change and increase in energy expenditure through activity. In practice what this looks like varies widely. In addition, support and frequency and type of follow up in clinical trials may vary from what is available within clinical practice.
● If not, how could the results be extrapolated to the UK setting?	
● What, in your view, are the most important outcomes, and were they measured in the trials?	Changes to body weight, weight loss from baseline, % achieving 5% and 10% weight loss, changes to co-morbidity markers (e.g. glycosylated haemoglobin, heart rate, systolic and diastolic blood pressure), incidence of adverse effects. These are commonly measured in clinical practice. In addition within trials of specific subgroups markers of co-morbidities were measured (e.g. microvascular complications in those with type 2 diabetes) and the cardiovascular benefits.
● If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No comment.
● Are there any adverse effects that were not apparent in clinical trials	No comment.

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 comment.
20. How do data on real-world experience compare with the trial data?	Those taking part in clinical trials are not necessarily representative of those seen in clinical practice. The relatively high dropout rates in those treated with Liraglutide may be of concern in this regard, since those taking part in clinical trials may be more motivated individuals.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not other than those already identified.
21b. Consider whether these issues are different from issues with current care and why.	N/a.

Key messages	
24. In up to 5 bullet points, please summarise the key messages of your submission. ● Liraglutide treatment has been shown to result in greater weight loss than current alternative non-surgical treatments for obesity. ● It is not clear what long-term monitoring and support would be needed for those taking liraglutide. ● It is unclear what is needed for those who achieve 5% weight loss within 12 weeks of treatment. ● High risk groups such as those of Asian descent may benefit more from the treatment but have not been adequately represented within clinical trials. ● There is a high unmet need at the present time for additional pharmacological treatments to fill the gap between traditional lifestyle treatment and bariatric surgery. Liraglutide would present a welcome addition treatment in helping people living with obesity tackle this disease.	

Thank you for your time.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Physicians (RCP)**

3. Job title or position	**RCP registrar**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Royal College of Physicians, London, charitable trust that supports physicians in the UK including clinical education and research**
5b. 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,	Weight loss in patients with obesity or overweight leading to improvements in obesity related health conditions (cardiovascular problems, type 2 diabetes mellitus, high blood pressure functional status, fertility, mental health, fatty liver etc) as well as quality of life, mobility and mortality. In addition, in patients without Type 2 diabetes, weight loss result in reduction in the risk of developing future Type 2 diabetes.

or prevent progression or disability.)	
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.)	5% reduction in body weight is recognised and proven scientifically as a clinically significant weight loss leading to health benefits
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, obesity is a significant issue with 60% of the population living with obesity or overweight. Living with obesity has significant health and wellbeing effects on patients. Currently there is unmet need in regard to obesity pharmacotherapy in the UK with only orlistat available at present in the NHS. Orlistat has limited effectiveness and is often not tolerated by patients. Access to other management option in Tier 2, 3 or 4 settings is limited in some parts of the UK, further limiting treatment options for obesity. More pharmacotherapy options to treat these patients are badly needed.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	In the UK the only pharmacotherapy currently available is orlistat which can be prescribed in primary or secondary care. There are also Tier 2 services (such as referral to a health trainer or commercial weight loss programme), but the coverage of these services across the UK is patchy so not accessible to all patients. Similarly, patients for whom Tier 2 has been unsuccessful and for certain BMI ranges (as per NICE guidance) can be referred to specialist weight management clinics (Tier 3) and for some for consideration of bariatric surgery (Tier 4). Similarly to Tier 2 services these are patchy across the UK, again limiting access. Patients with a BMI>50 can be referred for consideration of bariatric surgery as a first line treatment while those with a recent diagnosis of type 2 diabetes mellitus (in last 10 years) can be referred

	for bariatric surgery at a lower BMI range (>30). Please see NICE CG189 for details of BMI ranges –these have been adopted by most CCGs and NHS trusts. Overall the provision of obesity treatment across England is poor with many areas have no access to tier 2, 3 or 4 and weight management services/ bariatric surgery not commissioned in many areas of England
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Clinical guidance in adult patients: • NICE CG189, PH53 and QS127 and QS111 • NICE PH 42, PH 46 • Specific treatments for obesity: NICE TA494, IPG569, IPG471, IPG432
• 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 Tiers of care for obesity are well defined and care pathways in the clinical guidance are well defined. This treatment would fit into the existing care pathway as an alternative pharmacotherapy treatment option. However, as mentioned earlier the coverage of services across the UK is not consistent so for some areas the care pathway may not be clear to all clinicians, in particular those in primary care.
• What impact would the technology have on the current pathway of care?	This treatment would fit into the existing care pathway as an alternative and more effective pharmacotherapy treatment option. If available it would likely lead to more patients being able to be managed in primary care in the long term. This treatment will fill a gap between what can be achieved with lifestyle interventions and orlistat on one hand and bariatric surgery on the other.
10. Will the technology be used (or is it already used) in	Yes, because there is a treatment need and there are many patients would benefit from the treatment. In addition, many healthcare professionals are used to using liraglutide as it is already used at lower doses in the management of patients with type 2 diabetes mellitus.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	If available it would likely lead to more patients being able to be managed in primary care in the long term. In addition, it will allow to improve the weight loss efficacy achieved in Tier 3 weight management services and will aid patients who need weight loss to receive other treatments (such as needing to lose weight before receiving fertility treatment or joint replacement).
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment would be initiated in specialist weight management or endocrinology clinics (in secondary care or community setting), but can be continued in primary care on a long term basis after the patient is established on treatment and achieved good early response to treatment
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This treatment is already used for patients with type 2 diabetes mellitus so clinicians and nurses are familiar with its use for that purpose as well as safety issues with its use. Some training updates for clinicians would be needed for use in the management of obesity in terms of indications and the necessary responses that are needed to continue treatment. This would be secondary care and primary care clinicians including nursing staff and other allied health professionals managing patients with obesity.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase	Liraglutide in the field of Type 2 diabetes has been shown to reduce mortality and reduce the risk of cardiovascular disease and chronic kidney disease.

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, because this treatment result in weight loss, a drop in blood pressure, and reduction in the risk of Type 2 diabetes, cardiovascular disease, mortality and chronic kidney disease.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology would be indicated for people with obesity or overweight as indicated in the license Early weight loss responses predict longer weight loss outcomes; but there are no pre-treatment predictors of weight loss.
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	Liraglutide is an injectable treatment. However, the use of liraglutide will not add extra complexity because as we said above, healthcare professionals are familiar with this treatment for patients with Type 2 diabetes.

treatments needed, additional clinical requirements, factors 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?	Yes, clear rule already exists. They are based on weight measurement. No additional testing is needed.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Possibly, there might be a favourable impact on employment in some patients in which obesity contribute to their unemployment.

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, currently this technology will fill a gap between orlistat and lifestyle interventions on one hand and bariatric surgery on the other.
• Is the technology a 'step-change' in the management of the condition?	Yes, this technology would be a significant change in how patients with obesity can be treated since it will provide healthcare professionals with a proven clinically effective pharmacotherapy option to offer to patients.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, the lack of pharmacotherapy options available in the UK. Also this treatment would help with unmet needs of those who live in areas with poor coverage of obesity services.
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 main side effect is nausea that usually settles over time and the vast majority of patients will continue the treatment; < 6% of patients will stop treatment due to nausea. Other side effects are rare. The drug is injectable, but despite that patients are happy to inject due to the metabolic and mental health benefits of weight loss.

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes, the trial measured the important outcomes such as weight loss, impact on obesity related complications (including type 2 diabetes and obstructive sleep apnoea for example) and quality of life.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	The drug is not available in the NHS in England except in one trust. I (Abd Tahrani) and others have used it privately. The results obtained in the private sector are more impressive and exceeded the weight loss benefits observed in the clinical trial.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	This technology is currently available if privately funded. Therefore availability on the NHS would reduce this current inequality in access to treatments for obesity in the UK.
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Effective
- Fills an important treatment gap
- Safe
- Has a wide range of health benefits beyond weight loss
- Healthcare professionals already familiar with using liraglutide as a treatment

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Liraglutide for managing overweight and obesity [ID740]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Imperial College London, Faculty of Medicine, Department of Medicine**
3. Job title or position	**Consultant in Metabolic Medicine and Obesity**

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. 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 objective is to prevent the onset of type 2 diabetes by sustained weight loss and improvement of pancreatic function. Secondarily this will also improve quality of life and lower the risk of other obesity complications.
8. 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 prevention of a patient developing type 2 diabetes and sustaining weight loss of at least 10% over 1 year.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	• For some patients, new pharmacological treatment will be appropriate in addition to diet and exercise. Most patients have already tried orlistat as per NICE guideline (CG 189 'Obesity: identification, assessment and management'). Those who were successful have continued the treatment but for the majority orlistat does not provide a sustained weight loss response. For these patients who were unsuccessful with orlistat and who are referred into a tier 3 service, there is currently no available pharmacological treatment option. Bariatric surgery is a highly effective treatment and those patients interested and eligible for the treatment under the NICE guideline should be offered surgery. However, there are many patients who do not want to consider a surgical treatment or who are not eligible for a surgical treatment. Additional pharmacological treatment options would be welcomed for those who were unsuccessful with orlistat and who cannot have or do not want bariatric surgery.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	• People living with obesity are for the most part treated in primary care by general practitioners who have already tried diet and exercise and/or orlistat therapies. • Patients who are interested are referred into a specialist tier 3 service (referral is recommended for patients with a BMI >40 kg/m^2 or a BMI ≥35 kg/m^2 with comorbidities) if specialist advice is needed. In a tier 3 service, patients are assessed and offered multidisciplinary therapy. • Patients who are interested in surgical options are also assessed in tier 3 for eligibility for bariatric surgery, which takes place in tier 4 services. The majority of patients in tier 3 services are either not eligible or willing to undergo bariatric surgery.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	• The CG 189 'Obesity: identification, assessment and management' is the main guidance for management of obesity. This guideline does not reflect the state-of-the art in obesity treatment at present and is due to be updated.
• 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 NHS model for treating obesity (tiered services from tier 1 to tier 4) provides a guidance for the clinical pathway of care. However, as it is stated in the CG 189, tier 3 services are not covering all of England leading to inequality in access to treatment. Professionals across the NHS agree that more treatment options are required. The infrastructure exists to provide any new treatments in a sensible way to optimise clinical and cost effectiveness.
• What impact would the technology have on the current pathway of care?	• Liraglutide 3.0mg would be made available for patients who are at very high risk of developing type 2 diabetes and have obesity. The patients are referred in to a tier 3 service and allow the multidisciplinary teams to offer a pharmacological treatment option in addition to existing treatment options. This will make it possible for clinicians to identify those patients at highest risk of obesity who have tried and failed lifestyle approaches, orlistat and who are not eligible

	or do not want bariatric surgery. Making liraglutide 3.0mg available to this subgroup will reduce the development of type 2 diabetes, improve weight loss related outcomes for patients and give healthcare professional an important extra tool in the treatment of obesity.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	• As described above, orlistat is the only pharmacological treatment recommended by NICE, but many patients do not respond to orlistat. Liraglutide 3.0mg will thus be third line to be considered for those who did not respond to lifestyle treatment alone or lifestyle combined with orlistat.
• How does healthcare resource use differ between the technology and current care?	• Tier 3 services are multidisciplinary and introducing liraglutide 3.0mg as a third line treatment (after lifestyle and orlistat) will not lead to a difference in healthcare resource use provided it is focussed on treating those patients at highest risk of type 2 diabetes because of their obesity.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	• Liraglutide 3.0mg will be most appropriately placed in a tier 3 setting as part of a multidisciplinary treatment offering.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	• No additional investment will be needed to introduce liraglutide 3.0mg. However, as noted above, existing tier 3 services do not cover all of England.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	• Yes, because the treatment will be focussed on those patients who have failed diet, exercise and or orlistat. Thus, significant healthcare benefits can be provided in a very cost-effective manner.
• Do you expect the technology to increase length of life more than current care?	• At present a meta-analysis of the randomised controlled trial evidence suggest a trend towards a reduction in major adverse cardiovascular events (MACE), but the studies were underpowered. A major 17500 patient clinical trial with a newer generation agent is currently on-going but will only report after 2026.

• Do you expect the technology to increase health-related quality of life more than current care?	• Yes, as this has been established in the clinical trials of liraglutide 3.0mg.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• Patients with a very high risk of developing type 2 diabetes and obesity are the subgroup who may benefit clinically the most from liraglutide 3.0mg, while this is also the group where the medication is the most cost effective.
The use of the technology	
14. 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.)	• The technology is a daily subcutaneous injection, therefore not all patients would be willing to accept this. Diet and exercise would remain a key component of therapy. The medication is used in a lower dose for the treatment of hyperglycaemia in patients with type 2 diabetes. All general practitioners and most hospital consultants are thus familiar with the technology at a lower dose for glycaemic control as it is now more than a decade old.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• The licence for the technology already includes a stopping rule, which would need to be followed. The value of the stopping rule is that patients who do not lose 5% of their weight after 12 weeks on liraglutide 3.0mg are very unlikely to respond at any time during prolonger treatment. Thus, these patients may only develop side effects without experiencing much benefit. On the other hand, those patients who do achieve 5% weight loss after 12 weeks on liraglutide 3.0mg are “biological responders” and usually go on to lose more than 10% weight after 1 year. Thus, the stopping rule protects those that don’t respond and identify those that do respond to allow them to benefit most.

16. 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?	• Obesity is a highly complex condition which has an impact on many different complications. Obesity may also worsen other unrelated conditions, such as asthma and arthritis. It would be impossible to incorporate all aspects of the disease in the QALY calculation. Patients however now talk about “non-scalable victories” when they refer to the ability to get on an aeroplane without being offered an extension seat belt, or when they are allowed to go with their children on an amusement park ride which they have previously been asked not to attempt because of a weight limit. These impacts on patients’ lives also contribute to significant improvements in quality of life as it reduces weight stigma.
17. 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?	• There are a large number of patients who have not been able to sustain long term weight loss with lifestyle treatment and or orlistat. For the subgroup of these patients who are at very high risk of developing type 2 diabetes, liraglutide 3.0mg will have a significant and substantial impact on health-related benefits as it will reduce the risk of developing diabetes by an additional 80% while also improving quality of life.
• Is the technology a ‘step-change’ in the management of the condition?	• As a third line choice, liraglutide 3.0mg should be considered when treatment with lifestyle and or orlistat has been unsuccessful and bariatric surgery is not appropriate or unwanted.
• Does the use of the technology address any particular unmet need of the patient population?	• Liraglutide 3.0mg offers an effective prevention strategy for type 2 diabetes and provide sustained weight loss.
18. 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 main side effects of liraglutide 3.0mg are gastrointestinal and can be reduced by appropriate titration and are usually transient.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	• Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	• Prevention of type 2 diabetes and sustained weight loss are important outcomes measured in the clinical trials. Improvement in quality of life was also evident from the clinical trial programme.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	• Diabetes incidence and weight loss were measured as well as quality of life. Surrogate markers for cardiovascular risk were measured and provided the pilot data for a major 17500 patient clinical trial of a new generation agent to test a reduction in cardiovascular death.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	• No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	• I am currently one of the lead investigators for the Saxenda in Obesity Services (STRIVE Study), which is expected to be completed in January 2021. NCT03036800.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of	• No

NICE technology appraisal guidance [TA494]	
22. How do data on real-world experience compare with the trial data?	• In my experience, results in clinical practise are similar to the trial data. We have published the largest real-world evidence study with liraglutide 3.0mg in 2092 patients treated in the Imperial College London Diabetes Centre and showed our outcomes were comparable with the randomised clinical trials. • Suliman M, Buckley A, Al Tikriti A, Tan T, le Roux CW, Lessan N, Barakat M. Routine clinical use of liraglutide 3 mg for the treatment of obesity: Outcomes in non-surgical and bariatric surgery patients. Diabetes Obes Metab. 2019 Jun;21(6):1498-1501. doi: 10.1111/dom.13672.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	• No equality issues identified - there is currently no medical treatment available for these patients, so liraglutide 3.0mg is likely to promote equal opportunity for treatment.
23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24.	1. Is the group identified in the company submission (that is people with a BMI ≥35 kg/m2, pre-diabetes, and high risk of cardiovascular disease) reasonable and identifiable? **Yes, the population is reasonable and easily identifiable (I was consulted during the company discussions on the patient population).**

	2. Would liraglutide be provided within a Tier 3 service? Given that not all CCGs commission a Tier 3 service, where would liraglutide be given in the case where there is no Tier 3 service commissioned? **It would be appropriate to make liraglutide 3.0mg available in tier 3 services where specialist support is available as part of a multidisciplinary team. The availability may further support the case for the establishment of more tier 3 services. Wherever specialist support is available outside of tier 3, liraglutide 3.0mg may also be an option.** 3. Would liraglutide be considered an alternative option in clinical practice for those who are unable/ unwilling to have orlistat? **Yes, liraglutide 3.0mg could be considered a third line option after lifestyle and orlistat treatment and for those not eligible or who do not want bariatric surgery.** 4. Would liraglutide be considered an alternative option in clinical practice for those who are unable/ unwilling to have bariatric surgery? **Yes, liraglutide 3.0mg could be considered a third line option after lifestyle and orlistat treatment and for those not eligible or who do not want bariatric surgery.** 5. What drop-out pattern would we expect to see in practice? i.e. would most people discontinue liraglutide within the first 3 or 6 months or would you continue to see discontinuations after 6 months? **The licence includes a stopping rule at 12 weeks of full dose, which means that 33% of patients must stop then. Clinical practice from across Europe suggested that the majority of patient will discontinue within the first three months of treatment. In randomized controlled clinical trial only 33% of patients achieve more than 10% weight loss at 1 year. These patients stand to benefit the most. In clinical practice most patients who lose less than 10% bodyweight do not perceive injecting themselves every day as worthwhile while those who lose more than 10% body weight perceive significant value.**

	6. Treatment with liraglutide 3.0mg should be discontinued after 12 weeks on the maintenance dose of 3.0mg/day if patients have not lost at least 5% of their initial body weight. Would a treatment stopping rule be implementable in clinical practice? **Yes, the stopping rule is easily implemented and is common for anti-obesity medications. The stopping rule also has real clinical value as it protects those patients who do not respond to the drug from the side effects. Thus, a large number of education programmes are in place to teach clinicians to stop the medication if patients don't benefit. This was a major problem with previous obesity medications and in part contributing to the withdrawal of sibutramine and rimonabant.** 7. Treatment with liraglutide 3.0mg should be discontinued after two years how implementable is this stopping Rule? **Further stopping rules could be easily implemented as has been the case with orlistat.**

Key messages

- 25. In up to 5 bullet points, please summarise the key messages of your statement.
- Obesity is a chronic disease requiring multiple types of interventions, including lifestyle pharmacotherapy and bariatric surgery.
- Liraglutide 3.0mg is an effective treatment with an established safety profile, shown in randomised controlled trials and confirmed in real-world studies.
- Patients with prediabetes and a BMI >35 kg/m^2 at high risk of cardiovascular disease represent the target population for which treatment with liraglutide 3.0mg would be most beneficial as a third line agent after lifestyle and or orlistat.
- Liraglutide 3.0mg can provide a pharmacological treatment for patients with a high unmet need.
- Tier 3 services will need to be supported to expand in order to treat the current obesity epidemic with clinically effective and cost-effective treatments.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Liraglutide for managing overweight and obesity [ID740]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Dietetic Association and Central London Community Healthcare Trust**
3. Job title or position	**Clinical Lead Weight Management dietitian**

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? X☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	X☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	X☐ yes
The aim of treatment for this condition	

7. 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 obesity in people with BMI over 30/kg/m2 and stop development or progression of associated diseases such as type 2 diabetes.
8. 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.)	Reduction of weight by 5% in 6 months – although I think measuring just weight and BMI is very difficult as there could be so many measures e.g. HbA1c, improvement in lifestyle choices,
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – Definitely!
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Lifestyles changes, drug therapy – Orlistat or bariatric surgery.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes NICE CG189
• 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.)	I think obesity is still something that clinicians in this area are still trying to find the best treatment. It is very difficult to treat as there are so many factors that need to be taken into consideration, from social, ethnicity, economic, lifestyle, media, food production, family history. So ones size does not fit all in treating it.
• What impact would the technology have on the current pathway of care?	I think the use of Liraglutide would be another tool for helping teat people with obesity.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Liraglutide is currently used in diabetes but would be used for weight management. I believe it is currently used in private practices for weight management but not in the NHS.

• How does healthcare resource use differ between the technology and current care?	We would need additional people such as dietitians to be able to prescribe it.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist weight management clinics alongside lifestyle changes by a tier 3 weight management services
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This is an expensive drug, so I think criteria need to be managed well. I think it would require the need for more trained people to be able to prescribe it.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – I think with the right support of a tier 3 weight management team with could be used as an alternative to bariatric surgery.
• Do you expect the technology to increase length of life more than current care?	Yes

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I am not sure if it would be suited for people with learning disabilities and mental health on obesogenic medications.
The use of the technology	
14. 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	Yes – it would require more specialists to prescribe and administer the drug. As I said I think they would need to be alongside lifestyle changes to prevent patients cycling losing weight and regaining and then using the drug again.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	If no weight loss within 12 weeks then it should be stopped
16. 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 – if weight loss is sustained can have huge impact on QOL
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes as only 1 other medication to help with obesity and weight loss.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes – obesity treatment other than surgery is very limited to lifestyle and behaviour changes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Self injecting can affect quality of life in some people
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Not for use within obese population in the NHS
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Weight loss
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not sure
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA494]	No
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	It is an expensive drug currently only avilable to those that can afford it. I think cost should be considered when considering this availability on the NHS.

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24.	1. Is the group identified in the company submission (that is people with a BMI ≥35 kg/m2, pre-diabetes, and high risk of cardiovascular disease) reasonable and identifiable? Yes 2. Would liraglutide be provided within a Tier 3 service? Given that not all CCGs commission a Tier 3 service, where would liraglutide be given in the case where there is no Tier 3 service commissioned? I would recommend CCG's commission a tier 3 service, as this would be the best environment for this drug to be administered. 3. Would liraglutide be considered an alternative option in clinical practice for those who are unable/ unwilling to have orlistat? Potentially yes 4. Would liraglutide be considered an alternative option in clinical practice for those who are unable/ unwilling to have bariatric surgery? Yes 5. What drop-out pattern would we expect to see in practice? i.e. would most people discontinue liraglutide within the first 3 or 6 months or would you continue to see discontinuations after 6 months? I think if no weight loss after 3 months it should be discontinued regardless of drop out.

	6. Treatment with liraglutide 3.0mg should be discontinued after 12 weeks on the maintenance dose of 3.0mg/day if patients have not lost at least 5% of their initial body weight. Would a treatment stopping rule be implementable in clinical practice? Yes if monitored correctly within a tier 3 service, such as orlistat should be. Treatment with liraglutide 3.0mg should be discontinued after two years how implementable is this stopping Rule? Yes – with monitoring this should be implementable.

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Liraglutide would benefit obese individuals as part of pathway or alternative to bariatric surgery
- It should be administered and monitored within a tier 3 weight management service
- It should only be supplied alongside dietary and lifestyle changes – not as a stand alone treatment
- If no weight loss after 12 weeks it should be stopped
- As it is an expensive drug it should be closely monitored

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About you	
1. Your name	[redacted]
2. Name of organisation	**University of Birmingham and University Hospitals Birmingham NHS Foundation Trust**
3. Job title or position	**Honorary Consultant Endocrinologist and Senior Lecturer in Metabolic Endocrinology and Obesity Medicine. I am also a trustee of ASO UK.**

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	

7. 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 burden of obesity on patients, carers, the NHS and the wider economy is huge. The main aim of this treatment is to reduce the burden of obesity by causing weight loss in patients with obesity or overweight leading to improvements in obesity related complications such as cardiovascular disease, type 2 diabetes mellitus, hypertension (high blood pressure), impaired functional status, subfertility, mental health disorders and fatty liver amongst others as well as improvements in quality of life, mobility and mortality. In addition, in patients without Type 2 diabetes, weight loss result in reduction in the risk of developing future Type 2 diabetes. In patients with Type 2 diabetes, weight loss resulted in reduction in diabetes-related complications.
8. 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 exact cut off will depend on the outcome of interest. However, overall, 5% reduction in body weight is proven scientifically as a clinically significant weight loss leading to health benefits especially in glucose metabolism.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, the prevalence of overweight and obesity in the UK is 60% and the prevalence of obesity is just under 30%. The burden of obesity on patients, carers, the NHS and the wider economy is huge. Currently there are two modalities for obesity treatment available in the UK. Lifestyle interventions which usually produce around 5% weight loss that is not sustained in the majority of patients (weight regain occur in 80% of patients), and bariatric surgery, which results in 25% weight loss that is sustained for about 20 years based on the data from the Swedish Obese Subjects (SOS) study. Although bariatric surgery is currently the most effective treatment modality available, not all patients want to undergo surgery and there is a post code lottery in the availability of bariatric surgical services in England and the UK. Similarly, access to medical weight management services and lifestyle interventions is also subject to post code lottery in England and the UK. Hence, there is a big unmet need in the care for people of obesity between lifestyle interventions and bariatric surgery which can be filled by pharmacotherapy. In addition, there are many patients that are

	denied treatment in the NHS due to their obesity (for example knee replacement, transplant surgery, fertility treatment, hernia operations…etc) and they are not offered any alternative or support to be able to lose the weight to get the other procedure or treatment that they need. Currently, only orlistat available in the NHS. Orlistat has limited effectiveness and is often not tolerated by patients. More pharmacotherapy options to treat these patients are badly needed and several pharmacological agents available and in development showing increasing efficacy in terms of weight loss.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	In the UK the only pharmacotherapy currently available is orlistat which can be prescribed in primary or secondary care. There are also Tier 2 services (such as referral to a health trainer or commercial weight loss programme), but the coverage of these services across the UK is patchy so not accessible to all patients. Similarly, patients for whom Tier 2 has been unsuccessful and for certain BMI ranges (as per NICE guidance) can be referred to specialist weight management clinics (Tier 3) and for some for consideration of bariatric surgery (Tier 4). Similarly to Tier 2 services these are patchy across the UK, again limiting access. Patients with a BMI>50 can be referred for consideration of bariatric surgery as a first line treatment while those with a recent diagnosis of type 2 diabetes mellitus (in last 10 years) can be referred for bariatric surgery at a lower BMI range (>30). Please see NICE CG189 for details. Overall the provision of obesity treatment across England is poor with many areas have no access to tier 2, 3 or 4 and weight management services/ bariatric surgery not commissioned in many areas of England.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Clinical guidance in adult patients: NICE CG189, PH53 and QS127 and QS111 NICE PH 42, PH 46 Specific treatments for obesity: NICE TA494, IPG569, IPG471, IPG432
• Is the pathway of care well defined? Does it vary or are there	The Tiers of care for obesity are well defined and care pathways in the clinical guidance are well defined. This treatment would fit into the existing care pathway as an alternative pharmacotherapy treatment option.

differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	However, as mentioned earlier the coverage of services across the UK is not consistent so for many areas the care pathway may not be clear to all clinicians, in particular those in primary care
• What impact would the technology have on the current pathway of care?	This treatment would fit into the existing care pathway as an alternative and more effective pharmacotherapy treatment option. If available it would likely lead to more patients being able to be managed in primary care in the long term. This treatment will fill a gap between what can be achieved with lifestyle interventions and orlistat on one hand and bariatric surgery on the other.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, because there is a treatment need and there are many patients would benefit from the treatment. In addition, many HCPs are used to use liraglutide as it is already used at lower doses in the management of patients with type 2 diabetes mellitus.
• How does healthcare resource use differ between the technology and current care?	If Saxenda to become available, many more patients with obesity who are currently treated within the current tiers system will be able to achieve their treatment targets and achieve significant weight loss in excess of 5% and in many cases more than 10% weight loss. If available it could also lead to more patients being able to be managed in primary care in the long term. In addition, it will aid patients who need weight loss to receive other treatments (as detailed above) to actually get the treatment they need.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The answer to this question will depends on the target population of the treatment. Also, the answer depends on how restricted the treatment is going to be. Theoretically, the drug can be used in primary care as most GPs will be familiar with liraglutide as a treatment to Type 2 diabetes. However, realistically, and targeting specific population, then the best approach will be for the treatment to be initiated in specialist weight management (i.e. tier 3) or endocrinology clinics (in secondary care or community setting), and then continued in primary care after the patient is established on treatment and achieved good early response to treatment (as per the license for Saxenda regarding early stopping rules in non-responders)

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This is likely to be minimal as the drug (at a lower dose) is already used for patients with type 2 diabetes mellitus so clinicians and nurses are familiar with its use for that purpose as well as safety issues with its use. Some training to HCPs might be needed in order to make sure that HCPs (especially prescribing HCPs) are aware of the licensed indications (BMI cut offs) and the stopping rule regarding earl responders vs non responders.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, without a doubt, for the majority of patients.
• Do you expect the technology to increase length of life more than current care?	Yes, for two reasons. 1. Liraglutide has been shown to reduce mortality and the risk of cardiovascular disease and chronic kidney disease in patients with Type 2 diabetes; 2. Weight loss is associated with reduced mortality
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, because this treatment results in significant weight loss, improvement in blood pressure, and reduction in the risk of Type 2 diabetes and possibly it will reduce cardiovascular disease, mortality and chronic kidney disease as shown in patients with Type 2 diabetes
13. Are there any groups of people for whom the technology would be more or	This technology would be indicated for people with obesity or overweight as indicated in the license (the exact BMI cut off will depends on the presence or absence of obesity complications as per license). Early weight loss predicts longer weight loss outcomes (as indicated in the license); but there are no pre-treatment predictors of post-treatment weight loss.

less effective (or appropriate) than the general population?	
The use of the technology	
14. 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.)	The use of liraglutide will not add extra complexity because as we said above, HCPs are familiar with this treatment for patients with Type 2 diabetes.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Yes, clear rule already exist in the license and it is based on percentage weight loss. No additional testing needed.

Do these include any additional testing?	
16. 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?	Possibly yes, there might be a favourable impact on employment in some patients in which obesity contribute to their unemployment. We see this effect in patients who had bariatric surgery
17. 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, currently this technology will fill a gap between orlistat and lifestyle interventions on one hand and bariatric surgery on the other
• Is the technology a 'step-change' in the	Yes

management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Yes the lack of pharmacotherapy options available in the UK. Also would help with unmet needs of those who live in areas with poor coverage of obesity services
18. 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 main side effect is nausea (24.7%, 14.7% and 5.5% at weeks 4, 8 and 56 respectively).Nausea usually settles over time and the vast majority of patients will continue the treatment; < 6% of patients will stop treatment due to nausea. Other side effects are rare. The drug is injectable, but despite that patients are happy to inject due to the metabolic and mental health benefits of weight loss
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes, the trials measured the most important outcomes. The trials assessed the impact of Saxenda on weight, obesity-related complications and quality of life.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the	No, I have checked Pubmed for new clinical trials and found none in regards to Naltrexone–bupropion (which TA494 was about)

publication of NICE technology appraisal guidance [TA494]	
22. How do data on real-world experience compare with the trial data?	Saxenda is not available on the NHS except in one NHS Trust; so data from real life in the UK are limited. Recent real-world data from Spain has been published (Gorgojo-Martinez JJ et al. *Int J Clin Pract* 2019; doi: 10.1111/ijcp.13399. [Epub ahead of print https://onlinelibrary.wiley.com/doi/abs/10.1111/ijcp.13399).This data showed weight loss in real-world comparable to what was achieved in the SCALE trials. The data also showed greater weight loss with Saxenda compared to orlistat, but this data was real-world and not randomised. This real-world data also showed that saxenda resulted in the expected improvements in blood pressure, lipids and glucose levels. In addition, Saxenda is used privately discussing with colleagues they are reporting weight losses exceeding those reported in the SCALE trials which I also observed in the patients that I treated privately
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	This technology is currently available if privately funded. Therefore availability on the NHS would reduce this current inequality in access to treatments for obesity in the UK.

23b. Consider whether these issues are different from issues with current care and why.	Current care inequalities are related to the post code lottery of services availability. But with Saxenda the inequalities is due to the availability of this treatment mainly in the private sector.
Topic-specific questions	
24.	1. Is the group identified in the company submission (that is people with a BMI ≥35 kg/m2, pre-diabetes, and high risk of cardiovascular disease) reasonable and identifiable? It is reasonable and identifiable as these criteria fit with the referral criteria to tier 3 weight management services. Hence, these patients are easily identifiable in Tier 3 Weight management services. In areas where no tier 3 services are commissioned then these patients will need to be identified from primary care and the electronic records in primary have information about BMI, diabetes and CVD risk well documented. 2. Would liraglutide be provided within a Tier 3 service? Given that not all CCGs commission a Tier 3 service, where would liraglutide be given in the case where there is no Tier 3 service commissioned? As mentioned in my response above, the target population is easily identifiable in tier 3 services and the HCPs in these services would be already familiar with the use of GLP-1 receptor agonists and liraglutide. In areas where tier 3 services are not commissioned then the options are that Saxenda can be either be given via the local Endocrinology services as the Endocrinologists will be familiar with using GLP-1 receptor agonists and liraglutide or via a local primary care physician with interest in diabetes as such GP will be also familiar with GLP-1 receptor agonists and liraglutide.

	3. Would liraglutide be considered an alternative option in clinical practice for those who are unable/ unwilling to have orlistat? It can be an alternative to orlistat in those who are unable/unwilling to use orlistat or in those who orlistat did not achieve enough weigh loss. But Saxenda can also be used as the first line agent and not necessary after orlistat considering the likely greater efficacy of Saxenda (although this is not based on head-to-head RCT but shown in network meta-analysis https://jamanetwork.com/journals/jama/fullarticle/2528211). 4. Would liraglutide be considered an alternative option in clinical practice for those who are unable/ unwilling to have bariatric surgery? Yes 5. What drop-out pattern would we expect to see in practice? i.e. would most people discontinue liraglutide within the first 3 or 6 months or would you continue to see discontinuations after 6 months? I expect most dropouts to takeplace in the first 3 months, with may be a little up to 6 months but very little thereafter. In private practice I am seeing little drop outs but when they occur then they occur within the first few weeks. 6. Treatment with liraglutide 3.0mg should be discontinued after 12 weeks on the maintenance dose of 3.0mg/day if patients have not lost at least 5% of their initial body weight. Would a treatment stopping rule be implementable in clinical practice? Yes, it should be implemented because it maximises the benefits of using the drug. Those who do not lose the 5% by 12 weeks, still don't achieve an average 5% weight loss at 56 weeks. But

	those who achieve 5% weight loss by 12 weeks they achieve 10.8% weight loss on average by 56 weeks (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5129670/) 7. Treatment with liraglutide 3.0mg should be discontinued after two years how implementable is this stopping Rule? It will be implementable of this is how the services are commissioned. However, it may not be easy to convince patients to stop a treatment that is working for them. But these rules (including the stopping rule) need to be explained clearly to patients before the treatment is initiated and patients expectations should be managed appropriately.

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Effective
- Safe and well tolerated
- It addresses an important treatment gap
- It has benefits on obesity-related complication and quality of life
- HCPs are already familiar with the drug (at lower doses)

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Erasmus School of Health Policy & Management

Maastricht University

Liraglutide for managing overweight and obesity

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 17/09/2019

Source of funding: This report was commissioned by the NIHR HTA Programme as project number STA 12/82/75.

Declared competing interests of the authors
None.

Acknowledgements
None.

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This report should be referenced as follows:
Riemsma R, Ramaekers B, Petersohn S, Chalker A, Swift S, Armstrong N, Buksnys T, Wijnen B, Worthy G, Stirk L, Joore MA, Kleijnen J. Liraglutide for managing overweight and obesity: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2019.

Contributions of authors
Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Svenja Petersohn, Ben Wijnen, Titas Buksnys and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Annette Chalker and Stephanie Swift acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ADA	American Diabetes Association
AE	Adverse events
AHI	Apnoea-hypopnea index
AIC	Akaike information criterion
AMI	Acute myocardial infarction
BI	Budget impact
BIC	Bayesian information criterion
BMI	Body mass index
BMJ	British Medical Journal
BOCF	Baseline observation carried forward
BOMSS	British Obesity & Metabolic Surgery Society
BSC	Best supportive care
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHD	Coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPAP	Continuous positive airway pressure
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CTR	Clinical trial results
CVD	Cardiovascular disease
CVOT	Cardiovascular outcomes trial
DPP	Diabetes Prevention Programme
DPP-4	Dipeptidyl peptidase-4
EMA	European Medicines Agency
EOT	End of trial
EPAR	European Public Assessment Report
EQ-5D	European quality of life-5 dimensions
ERG	Evidence review group
ETD	Estimated treatment difference
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FDA	Food and Drug Administration
FFA	Free fatty acids
FPG	Fasting plasma glucose
GBP	Pound sterling
GLP-1	Glucagon-like peptide-1
GPRD	General practice research datalink
HDL	High-density lipoproteins
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HRU	Healthcare resource use
HTA	Health technology assessment
IC	Indirect comparison
ICD	International statistical classification of diseases and related health problems

ICER	Incremental cost effectiveness ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IHD	Ischaemic heart disease
ITT	Intention to treat
IWQOL	The impact of weight on quality of life questionnaire
KSR	Kleijnen Systematic Reviews
LDL	Low-density lipoproteins
LEADER	Liraglutide and cardiovascular outcomes in type 2 diabetes
LOCF	Last observation carried forward
LYs	Life years
LYG	Life years gained
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MI-ME	Multiple-imputation for measurement error
MIMS	Monthly index of medical specialities
MTC	Mixed treatment comparison
NA	Not applicable
NEP	Neutral endopeptidase
NGT	Normal glucose tolerance
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIH-AARP	National Institutes of Health-American Association of Retired Persons
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
OAD	Oral anti-diabetic drug
OGTT	Oral glucose tolerance test
OR	Odds ratio
OS	Overall survival
OSA	Obstructive sleep apnoea
PAS	Patient access scheme
PHQ-9	Patient health questionnaire-9
PICOS	Population – intervention - comparators - outcomes- study
PRESS	Peer review of electronic search strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PYO	Person years of observation
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RPP	Resting pulse
RR	Relative risk; risk ratio
SAE	Serious adverse events
SAS	Safety analysis set
SC	Subcutaneous
ScHARR	School of Health and Related Research
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SHTAC	Southampton Health Technology Assessments Centre
SIGN	Scottish Intercollegiate Guidelines Network

SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SMQ	Standard medical query
SOC	System organ classes
STA	Single technology appraisal
TA	Technology assessment
TEAE	Treatment emergent adverse events
TIA	Transient ischaemic attack
TRIM	Treatment related impact measure
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
UMC	University Medical Centre
USA	United States of America
VLDL	Very low-density lipoproteins
WAMC	Weight assessment and management clinics
WAP	Weight action programme
WHO	World Health Organization
WTP	Willingness-to-pay

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population defined in the scope is: 'Adults who have a BMI of ≥ 30 kg/m^2 (obese) or ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity.' This population is consistent with the current European Medicines Agency (EMA) indication for liraglutide: 'Liraglutide 3.0mg (Saxenda®) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial body mass index (BMI) of: ≥30 kg/m^2 (obesity); or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity such as dysglycemia (prediabetes or type 2 diabetes), hypertension, dyslipidaemia or obstructive sleep apnoea'. However, the population addressed in the CS is limited to 'Adult patients with: BMI ≥35 kg/m^2 with prediabetes, and high risk of cardiovascular disease' (the index population).

In addition, the company stated that liraglutide 3.0mg is intended for use in patients who have been referred to a specialist tier 3 service where conventional treatments such as orlistat have been unsuccessful earlier in the clinical pathway. However, no data have been provided specifically for patients who have previously failed on orlistat (see Section 3.3 of this report).

The intervention is liraglutide 3.0mg, which is in line with the scope. According to the license, liraglutide 3.0mg should be discontinued after 12 weeks on the maintenance dose of 3.0mg/day if patients have not lost at least 5% of their initial body weight. However, this stopping rule was not applied in Trial 1839, which represents the only study providing evidence to inform the decision problem.

The comparators mentioned in the scope are standard management without liraglutide (including a reduced calorie diet and increased physical activity), orlistat (prescription dose), and bariatric surgery. According to the company, standard management without pharmacotherapy is the only relevant comparator in this appraisal. The company stated that liraglutide 3.0mg is intended for use in patients who have been referred to a specialist tier 3 service where conventional treatments such as orlistat have been unsuccessful earlier in the clinical pathway. However, it was not clear how many patients in Trial 1839 have indeed failed on orlistat, as these data were not collected in the trial.

1.2 Summary of clinical effectiveness evidence submitted by the company

A single set of searches was undertaken to identify clinical effectiveness and adverse events data. The company submission (CS) and response to clarification provided sufficient details for the Evidence Review Group (ERG) to appraise the literature searches. A good range of database and conference proceedings were searched, but additional grey literature resources and reference checking could have been useful. Additional synonyms, greater use of Medical Subject Headings (MeSH) in the MEDLINE searches, more complete study design filters and the removal of the English language limit could mitigate against loss of recall.

The company submission focusses on a post-hoc analysis from one trial: the SCALE obesity and prediabetes trial (Trial 1839). Trial 1839 was a randomised, double-blind (investigators and patients were blinded during the full trial; the sponsors, Novo Nordisk, were unblinded after one year), placebo-controlled, parallel group, multicentre, multinational trial in patients who were obese (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with comorbidities. Study participants were randomised two to one to receive liraglutide 3.0mg (n=2,487) or placebo (n=1,244) as an adjunct to diet and exercise and stratified according to prediabetes status (according to American Diabetes Association [ADA] 2010 criteria) at screening. The trial was conducted in 27 countries in Europe, North America, South America, Asia,

Africa, and Australia. In the UK, 112 randomised patients participated at eight sites. The primary endpoint in the three-year assessment of the trial was: 'Proportion of patients with onset of type 2 diabetes at week 160 among patients with prediabetes at baseline - evaluated as the time to onset of type 2 diabetes'.

Since the population in the CS was limited to 'Adult patients with: BMI ≥35 kg/m^2 with prediabetes, and high risk of cardiovascular disease', the company performed a post-hoc analysis of Trial 1839, including 800 patients (liraglutide: n=530, placebo: n=270). Results in terms of weight-related outcomes significantly favoured liraglutide when compared with placebo (BMI (percentage change from baseline to 160 weeks, Last Observation Carried Forward (LOCF)): estimated treatment difference (ETD) = -4.43 (95% CI: -5.43 to -3.43); weight loss (%): ETD = -4.28 (-5.28 to -3.28); waist circumference (cm): ETD = -3.52 (-4.71 to -2.33)). Likewise, there were significantly fewer confirmed type 2 diabetes cases with liraglutide than with placebo (odds ratio (OR) = 0.28 (0.14 to 0.57)). Cardiovascular adverse events, mortality and health-related quality of life (SF-36, general health) showed no significant differences between groups (OR = 0.94 (0.64 to 1.40), OR = 0.17 (0.01 to 4.17) and ETD = 1.61 (0.25 to 2.97), respectively). However, significantly more patients discontinued treatment due to adverse events in the liraglutide group than in the placebo group (OR = 2.62 (1.41 to 4.85)). Nearly all of these discontinuations happened after week 16.

Outcomes used in the economic model showed significant effects favouring liraglutide for number of patients achieving at least 5% weight loss after 16 weeks (OR = 5.68 (4.03 to 8.01), reduction in systolic blood pressure (SBP) (ETD = -3.01 (-4.72 to -1.29) and HbA_{1c} (ETD = -0.25 (-0.30 to -0.21)). Cholesterol results showed no significant differences between groups (Total: ETD = 0.91 (-0.52 to 2.34) and High-Density Lipoproteins (HDL): ETD = -3.23 (-7.70 to 1.24)).

The most frequent adverse events in the index population were nausea (41% for liraglutide 3.0mg versus 14% for placebo), nasopharyngitis (28% vs. 27%), diarrhoea (26% vs. 12%), constipation (20% vs. 10%), vomiting (18% vs. 5%), headache (18% vs. 16%) and upper respiratory tract infection (17% vs. 16%). The company did not provide a statistical comparative analysis of these data, but numerically, the frequency of nausea, diarrhoea, constipation and vomiting appeared higher for liraglutide 3.0mg versus placebo.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The population in the CS was not the same as the population in the NICE final scope. The company limited the population to 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD', 'because this subpopulation of patients would benefit the most from liraglutide 3.0mg in UK clinical practice, and therefore optimises cost effectiveness' (CS, Table 1, page 12). As a consequence, the company used data from a post-hoc analysis of Trial 1839 including only a subgroup of patients for this appraisal.

The intervention is in line with the scope. However, according to the license for liraglutide 3.0mg, liraglutide should be discontinued after 12 weeks on the maintenance dose of 3.0mg/day if patients have not lost at least 5% of their initial body weight. However, this stopping rule was not applied in Trial 1839. It is not clear how this discrepancy influenced results.

The description of the comparators in the NICE scope was as follows: Standard management without liraglutide (including a reduced calorie diet and increased physical activity), orlistat (prescription dose), and bariatric surgery. The company claimed that standard management without pharmacotherapy is the only relevant comparator in this submission. In addition, the company stated that liraglutide 3.0mg is intended for use in patients who have been referred to a specialist tier 3 service where conventional

treatments such as orlistat have been unsuccessful earlier in the clinical pathway. However, data on previous treatment with orlistat, or any other anti-obesity pharmacotherapy, were not collected in Trial 1839. Therefore, no evidence for this specific population (i.e. those who have failed on orlistat) have been presented in the CS. Furthermore, bariatric surgery would almost certainly represent an appropriate comparator for some patients with BMI ≥35 kg/m^2 and other significant disease (i.e. the population presented in the CS) who have been or will be referred to a specialist tier 3 service (see NICE Clinical Guideline 189: Obesity: identification, assessment and management).

Trial 1839 was a good quality randomised controlled trial. The ERG has no concerns with the trial design and the trial methods. However, the company's choice to focus on a post-hoc subgroup analysis is a concern as it means that the CS is based on a smaller sample of only 35% of the whole trial population (n=800). This means that the analyses no longer have sufficient statistical power to detect statistically significant differences between the treatment groups and the two groups may not be comparable at baseline as the randomisation was not stratified for this particular subgroup.

1.4 Summary of cost effectiveness evidence submitted by the company

A single search was undertaken for cost effectiveness, costs and healthcare resource studies, and a separate search was conducted for HRQoL data. The CS provided sufficient details for the ERG to appraise the searches. A good range of databases were searched, but additional grey literature resources may have been useful. Additional synonyms, greater use of MeSH in the MEDLINE searches, more complete study design filters and the removal of the English language limit could mitigate against loss of recall.

The model adopted the perspective of the National Health Service (NHS) and Personal and Social Services (PSS) in England and Wales. The model time horizon was 40 years, at the end of which approximately 30% of the patients in the model were still alive. A cycle length of three months was defined for the first year, to allow for incorporation of the liraglutide 3.0mg stopping rule. Annual cycles were implemented after the first year and were half cycle corrected. All costs and health gains were discounted at a rate of 3.5% per year.

The target population for the economic evaluation comprised of a subgroup of the licensed indication based on a post-hoc analysis of the Trial 1839 study population, defined as adult patients with: BMI ≥35kg/m^2, prediabetes and high risk of cardiovascular disease. This is in line with the final scope issued by NICE and the EMA licence although both documents considered a broader population.

The intervention consisted of a daily injection of liraglutide 3.0mg by the patient in combination with diet and exercise (in line with the final scope issued by NICE and the EMA licence). Dose escalation in weekly increments of 0.6mg of liraglutide up to 3.0mg once daily was applied during the first four weeks of treatment. Treatment should be discontinued after 12 weeks on the 3.0mg daily dose if patients have not lost at least 5% of their initial body weight. The maximum treatment period for responders was assumed to be two years.

Liraglutide 3.0mg daily with diet and exercise was compared to diet and exercise alone. Diet and exercise were assumed to be consistent with the current standard of care in specialist tier 3 services. Other comparators listed in the final scope (i.e. orlistat and bariatric surgery) were not included as comparators in the economic model.

The company developed a cohort state transition model using Microsoft Excel®. In the base-case analysis, the model consisted of 10 health states, i.e. normal glucose tolerance, prediabetes, type 2 diabetes (T2DM), post-acute coronary syndrome (ACS) with normal glucose tolerance, post-stroke with

normal glucose tolerance, post stroke & post ACS with normal glucose tolerance, post ACS with T2DM, post-stroke with T2DM, post stroke & post ACS with T2DM, and death. In scenario analyses, cancer was added as complication in patients with normal glucose tolerance or T2DM, which lead to eight additional health states. Treatment related adverse events were not considered in the economic model.

Transitions between health states were based on the estimation of T2DM status, CV events (primary and secondary) using risk models as well as death probabilities. Additionally, probabilities calculated for knee replacement, sleep apnoea and bariatric surgery were incorporated. The relative treatment effectiveness was estimated through changes in the BMI, SBP, total and HDL cholesterol parameters in the risk models. In contrast, HbA_{1c} was not a treatment dependent parameter as it is assumed only to be dependent on T2DM by setting its value to HbA_{1c} %-points of 7.5%, 6.0% and 5.4% for T2DM patients, prediabetes patients and patients with normal glucose tolerance respectively.

Health state utility values were sourced from published literature and were dependent on BMI and the occurrence of events (ACS, stroke, TIA, bariatric surgery, knee replacement and obstructive sleep apnoea).

The costs included in the model were acquisition and administration costs of obesity treatment, pharmacy costs (blood pressure and T2DM medications), and costs of obesity-related complications. Unit prices were based on the NHS reference prices, British National Formulary (BNF), the Monthly Index of Medical Specialities (MIMS) and literature sources.

In the revised (probabilistic) company base-case liraglutide is more expensive (£1,336) and more effective (0.106 QALYs gained) than diet and exercise, resulting in an ICER of £9,096.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG is concerned that relevant references were potentially missed by the systematic literature reviews (SLRs) and noticed a lack of clarity regarding the identification of cost and resource use and HRQoL evidence used in the company submission.

The model time horizon of 40 years (cohort age at model start was 48 years) resulted in a significant proportion of patients alive at the end of the model time horizon. Unfortunately, the functionality of the submitted economic model did not allow for selecting a longer time horizon.

The ERG considers the model structure is appropriate to reflect this condition and treatment pathway. The ERG's main concerns regarding the model structure relate to the assumption that prediabetic patients automatically develop T2DM after experiencing a cardiovascular (CV) event. The ERG believes that this overestimates the rate of development of T2DM as well as the treatment effect for liraglutide 3.0mg.

Inconsistent with the scope, the company did not include orlistat and bariatric surgery as direct comparators in the model. If it is the case, as the company argues, that orlistat is not a comparator because patients will have failed or were unwilling to take orlistat then this needs to be explicitly recognised in the index population. However, this brings into question the applicability of Trial 1839, where the extent to which patients fulfil these criteria is unclear. The ERG believes that for consistency with the final scope both should have been incorporated.

The company assumed no treatment discontinuation (e.g. due to adverse events or loss of efficacy) besides the stopping rule for liraglutide 3.0mg (as per the European Medicine Agency licence) after the initial 12 weeks (in case of no response) and the assumption that patients would stop liraglutide 3.0mg

after two years (regardless of response). Assumptions related to discontinuation have a relatively large impact on the estimated cost effectiveness. Unfortunately, due to the substantially delayed clarification response from the company, the ERG was not able to incorporate discontinuation scenarios into their ERG base-case.

Related to treatment effectiveness, the main concerns of the ERG include the selection of risk models that are different for patients with and without T2DM and the calculation of responder probabilities while assuming missing values to be missing completely at random. Another concern is the assumption that liraglutide 3.0mg non-responders would have the same effectiveness as the placebo arm in Trial 1839 given that non-responders to liraglutide 3.0mg continued to take liraglutide in Trial 1839.

After a substantial delay, the company submitted scenario analyses in response to clarification question B15, indicating that including adverse events would only have a minimal impact on the cost effectiveness.

The ERG would have preferred to use Trial 1839 data to estimate the health state utility values dependent on BMI (instead of using values from published literature). In its clarification responses, the company provided a scenario analysis using mapped BMI-dependent utilities based on Trial 1839. This scenario indicated that the impact of using an alternative source to estimate BMI-dependent utilities is expected to be minimal.

The assumption that patients temporarily reverted to normal glucose tolerance do not receive monitoring seems to be unlikely given their history of prediabetes, their remaining obesity and increased risk for developing T2DM and CV events. An underestimation of costs for normal glucose tolerance patients is likely not to be conservative. Therefore, the ERG explored the impact of adding monitoring costs equal to those of patients with prediabetes in a scenario analysis.

To support the validity of the economic model, the company provided multiple reports (produced by external bodies) examining the cross validity as well as external validity. The ERG found these reports to be informative and helpful in assessing the validity of the submission. It is however unclear to what extend the conclusions drawn from the assessments also apply to the revised base-case where the company corrected several errors. In addition, in response to clarification question B24, the company provided a comparison of modelled and observed CV event rates. The ERG is concerned that this comparison is suggestive of an overestimation of CV events in the model. However, this comparison is subject to uncertainty given the low number of events observed in Trial 1839.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

A good range of databases were searched and the searches were well documented making them transparent and reproducible.

Trial 1839 was a good quality randomised controlled trial. The ERG has no concerns with the trial design and the trial methods.

1.6.2 Weaknesses and areas of uncertainty

A limited range of synonyms, use of EMTREE indexing terms in MEDLINE searches, inappropriate study design filters and an English language limit mean that relevant records may have been missed by the searches. Further grey literature searches and additional resources would have made the searches more comprehensive.

The post-hoc subgroup analysis is a concern as it means that the CS is based on a smaller sample of only 35% of the whole trial population. This means that the analyses no longer have sufficient statistical power to detect statistically significant differences between the treatment groups and the two groups may not be comparable at baseline as the randomisation was not stratified for this particular subgroup.

No evidence has been submitted for a comparison of liraglutide with orlistat or bariatric surgery. The company stated that liraglutide 3.0mg is intended for use in patients who have been referred to a specialist tier 3 service where conventional treatments such as orlistat have been unsuccessful earlier in the clinical pathway. However, it was not clear how many patients in Trial 1839 have indeed failed on orlistat, as these data were not collected in the trial.

In addition to the abovementioned areas of uncertainty (particularly the lacking comparisons with orlistat and bariatric surgery), additional assumptions that likely impact the cost effectiveness relate to the development of T2DM for prediabetic patients, liraglutide discontinuation, liraglutide treatment duration, waning of liraglutide effectiveness as well as the treatment effectiveness for liraglutide non-responders.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

In the revised (probabilistic) company base-case liraglutide is more expensive (£1,336) and more effective (0.106 QALYs gained) than diet and exercise, resulting in an ICER of £9,096. The ERG has incorporated various adjustments to the company base-case this resulted in the (probabilistic) ERG base-case with a corresponding ICER of £13,805 per QALY gained when assuming that prediabetic patients automatically develop T2DM with a CV event. When removing the simplifying assumption that prediabetic patients automatically develop T2DM with a CV event, this resulted in a (probabilistic) ICER of £31,782 per QALY gained. The ERG is concerned that the company's base-case assumptions (i.e. that prediabetic patients automatically develop T2DM after ACS or stroke) overestimates the T2DM incidence as well as the treatment effect for liraglutide 3.0mg. On the other hand, the ERG acknowledges that removing this assumption (as implemented by the company), probably results in an underestimated T2DM incidence as well as treatment effect for liraglutide 3.0mg. Other factors that had a noticeable impact on the ICERs were assumptions related to the modelling of effectiveness for liraglutide non-responders (not observed in Trial 1839), liraglutide discontinuation, liraglutide treatment duration and waning of liraglutide effectiveness (all explored by the company). Moreover, other assumptions and/or parameters that might have individually a minimal impact on the estimated cost effectiveness potentially have, when all combined, a considerable impact. However, the company's substantially delayed clarification responses and the complexity of the economic model hampered the ERG in performing its analyses. Most importantly, due to delayed clarification responses, the ERG was not able to include alternative assumptions into the ERG base-case. These assumptions related to treatment discontinuation (e.g. incorporating treatment discontinuation throughout the model time horizon and relaxing the assumption of a maximum liraglutide treatment duration of two years) and to treatment effectiveness for liraglutide non-responder (e.g. assuming equal to the effectiveness of non-responders on diet and exercise). The scenarios submitted in the company's delayed clarification response letter indicated that the ICER could substantially increase when using alternative assumptions for these issues.

In conclusion, the ERG analyses indicate that the cost effectiveness of liraglutide versus diet and exercise ranges between £13,805 per QALY and £31,782 per QALY gained. However, the cost effectiveness of liraglutide is likely impacted by assumptions related to the development of T2DM for prediabetic patients, liraglutide discontinuation, liraglutide treatment duration, waning of liraglutide

effectiveness as well as the treatment effectiveness for liraglutide non-responders. Moreover, the exclusion of comparators listed in the scope can be regarded as an additional source of uncertainty.

2. BACKGROUND

2.1 Critique of company's description of underlying health problem.

The company submission (CS) emphasises the classification of obesity as a chronic disease by organisations such as the American Medical Association (AMA) and the UK Royal College of Physicians.[1] However, it is often not treated as such due to perceptions and attitudes that can hinder obesity managment.[1, 2] Obesity is classified as a condition in which the body mass index (BMI) is of ≥30 kg/m^2.[1] Further classifications distinguish Obesity Class I, with a BMI of 30-35 kg/m^2, Class II, with a BMI of 35-40 kg/m^2, and Class III, with a BMI of >40 kg/m^2.[3]

According to the CS, obesity rates have doubled in the United Kingdom (UK) for men, from 13% to 24%, and for women, from 16% to 26%.[1, 4] In England, 27% of men and 30% of women are reported to be obese.[1, 5] The CS notes the prevalence of obesity to be highest among people between the ages of 55-64 years.[1, 5, 6]

The CS highlights the association between obesity and an increase in all-cause mortality when compared to individuals with a normal weight.[1] This risk is noted to increase as obesity severity increased.[1, 7] When compared with healthy weight individuals, life expectancy from age 40 was 4.2 years shorter in obese men and 3.5 years shorter in obese women.[1, 7] The CS emphasises the link between obesity and complications such as hypertension, asthma, osteoarthritis, dyslipidaemia, and type II diabetes, as well as a lower health-related quality of life (HRQoL).[1] The company noted obese adults scored lower on the physical component scores of the SF-36 questionnaire with -2.54 points for Class I, -3.91 points for Class II, and -9.72 points for Class III.[1, 8] Class III obesity also noted significantly reduced mental component scores.[1, 8]

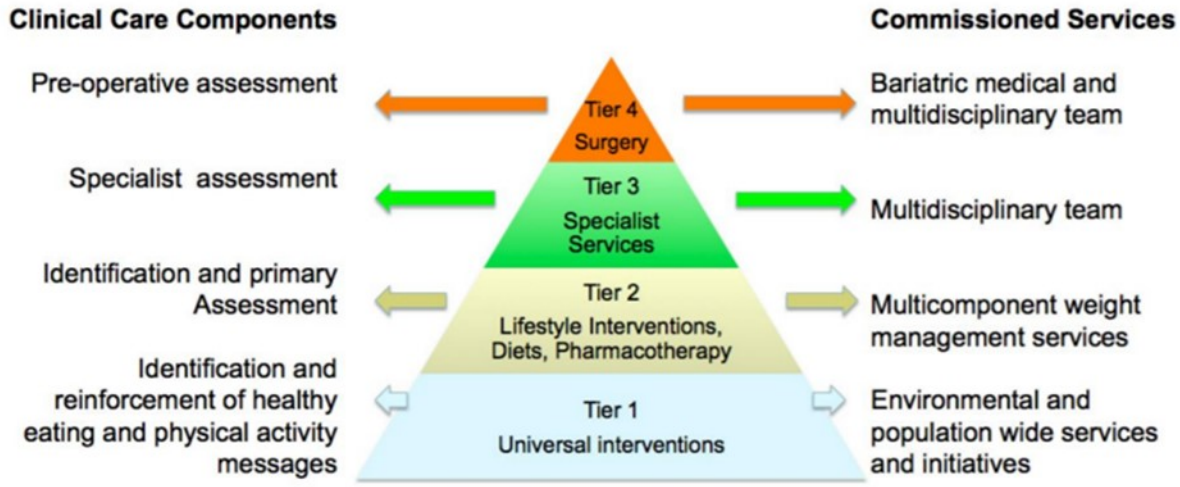
The company also emphasises the economic burden of obesity through direct and associated indirect costs.[1, 9, 10] The CS highlights the cost of obesity, within the UK, reached an estimated cost of £16 billion in 2007 and projected future costs to be upwards of £50 billion in 2050.[1, 11] The CS presented findings from the Clinical Practice Research Datalink (CPRD) database which assessed the utilisation of resources stratified by the different BMI classifications and the levels of cardiovascular-event risk, such as low, high, and established cardiovascular disease (CVD).[1] The findings note observed for all cardiovascular risk levels, a higher BMI was typically affiliated with a higher usage of resources, particularly among patients with established CVD.[1]

Due to the multifactorial nature of obesity, treatment plans can be complex and include a range of treatment plans across four service tiers. According to existing NICE guidelines, lifestyle modifications should be used as a primary method to address obesity, allowing for additional interventions to be supplementary.[1, 4, 12, 13] The CS notes that pharmacotherapy may be a treatment option for some patients.[1] At present, the main pharmacological treatment method for obesity is orlistat. Pharmacotherapy is not available at the tier 3 service level, in which specialist services are provided and is the level of focus for the CS.[1] The ERG noted an ambiguity with this presentation and wanted clarification regarding an appropriate identification of the index population. This clarification was needed to address whether the index population had already completed a course of drug therapy with orlistat. In the response to clarification [14], the company states that the index population are likely to have failed orlistat or have been unwilling to take it. The ERG wanted further clarification regarding the provision of services when tier 3 services were unavailable. The company addressed this by noting that this finding is not officially quantified at this time. However, according to a report issued by the All-Party Parliamentary Group for Obesity, 19.7% of clinical commissioning groups (CCGs) state that they do not commission a tier 3-level services.

2.2 Critique of company's overview of current service provision

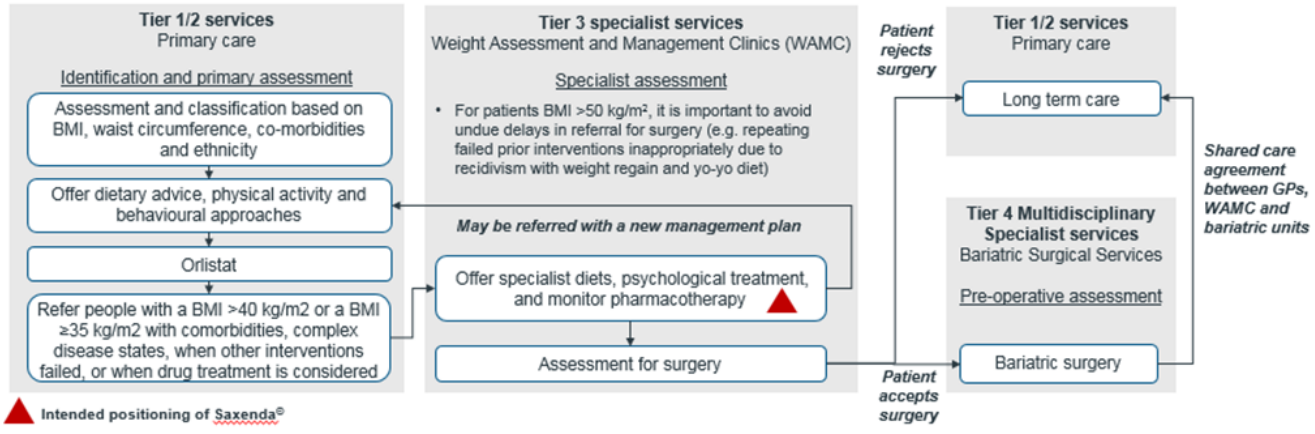
Figure 2.1 highlights the tiered model of obesity services according to the British Obesity & Metabolic Surgery Society (BOMSS) guidance.[1] Meanwhile, Figure 2.2 shows the proposed placement of 3.0mg of liraglutide in the NHS tiered services pathway for weight management. In the proposed pathway, the CS specified liraglutide as being incorporated into a tier 3 specialist services.[15]

Figure 2.1: Tiered model of obesity services according to the British Obesity & Metabolic Surgery Society (BOMSS) guidance



Source: Cs, Section B.1.3.2.[1]

Figure 2.2: Placement of liraglutide 3.0mg in the NHS tiered services pathway for weight management



Source: CS, Section B.1.3.2.[1]

BMI = body mass index; GP = general practitioner; kg = kilogram; m = meter; mg = milligram; NHS = National Health Services; WAMC = weight assessment and management clinics

The CS emphasises the NICE recommendation of utilising the BOMSS commissioning guide (see Figure 2.1) when defining a tiered structure for the management of obesity.[1] This summarises the model used by the NHS regarding the treatment of obesity in the UK. According to this tiered model, patients with a BMI >40 kg/m^2 or with a BMI ≥35 kg/m^2 and comorbidities such as hypertension, are recommended for referral to tier 3 services.[1] This level of service provides patients with an initial specialist assessment, specialised diets, psychological treatment, and pharmacotherapy.[1] In particular,

the tier 3 level service is intended for patients for whom conventional treatments have been unsuccessful, before seeking tier 4 services, which include bariatric surgery.

The company presents the positioning of liraglutide in the NHS tiered services pathway for weight management in Figure 2.2. The CS notes Figure 2.2 is adapted based on NICE and BOMSS guidelines.[1] According to the CS, NICE has one pharmacological option for treating patients with obesity which is orlistat, in addition to diet and exercise.[1] The ERG enquired about the potential suitability of orlistat as a comparator in the present submission. However, the company states orlistat is used earlier in the treatment pathway, during tier 2 services, and claims that standard management without pharmacotherapy is the only relevant comparator. The company also notes the limited use of orlistat in clinical practice.[14] According to the company in their response to clarification, orlistat is not often used in clinical practice due to the experience of undesirable side effects, which impacts patients from wanting to take orlistat or ceasing treatment after a short period.[14] This can negatively impact overall weight loss outcomes for patients. The ERG also noted the appropriateness of bariatric surgery as a relevant comparator for liraglutide, due to it being an alternative treatment according to the NICE clinical guidelines that is already acceptable to patients (CG189).[4] The ERG notes that liraglutide would not be a replacement for bariatric surgery, however, it could be an option for patients who are unwilling or ineligible candidates for surgery. Due to the small number of people who are able to receive bariatric surgery, this is not included as a comparator by the company. The company refer to clinical experts and consultees who stated that diet and lifestyle interventions are considered standard management for obesity and are therefore the only relevant comparator in this appraisal. However, the ERG believes orlistat and bariatric surgery could be used as comparators in some patients who are eligible for liraglutide (see also Section 3.3 of this report).

The ERG also noted the company focused on a subpopulation of patients rather than the broader population identified by NICE. The broader population included adults who have a BMI ≥30 kg/m^2, which is a parameter for obesity, or adults who meet the classification for being overweight, with a BMI ≥27 kg/m^2 to <30 kg/m^2 and are in the presence of at least one weight-related comorbidity.[16] The focused population of the CS is adult patients with a BMI ≥35 kg/m^2 who had pre-diabetes and a high risk of cardiovascular disease. The company states that this specific population would benefit more from liraglutide within clinical practice than the broader overweight and obese populations. In the current CS, no other subgroups have been considered.

The company presents outcomes that are within the NICE scope. However, the ERG noted that most of the outcomes are reported for the intention-to-treat population in Trial 1839.[14] The focused population, as outlined in the CS, is meant to be patients with BMI ≥35 kg/m^2, prediabetes, and are at a high risk of cardiovascular disease. The only outcomes reported for this population in the CS, were noted to be weight loss, waist circumference and incidence of type 2 diabetes.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	Adults who have a BMI of; • ≥30 kg/m^2 (obesity) or • ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity	Adult patients with: • BMI ≥35 kg/m^2 with pre-diabetes, and high risk of cardiovascular disease	This subpopulation of patients would benefit the most from liraglutide 3.0mg in UK clinical practice, and therefore optimises cost effectiveness.	The NICE scope and the UK marketing authorisation for liraglutide describe the population as Adults who have a BMI of; • ≥ 30 kg/m^2 (obese) or • ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity. However, the CS only focusses on a sub-population of patients: • BMI ≥35 kg/m^2 with pre-diabetes, and high risk of cardiovascular disease.
Intervention	Liraglutide 3.0mg	Liraglutide 3.0mg	NA	In line with NICE scope.
Comparator(s)	• Standard management without liraglutide 3.0mg • Orlistat (prescription dose) • Bariatric surgery	Standard management without liraglutide 3.0mg	The only relevant comparator in this submission is standard management without pharmacotherapy. The reason for omitting orlistat as a comparator is two-fold: firstly, orlistat is currently recommended as a treatment option in primary care in a much wider population than is proposed for liraglutide 3.0mg and as such would be used earlier in the treatment pathway (tier 2). Secondly, the use of orlistat is currently limited in clinical practice; this	The company claims that standard management without pharmacotherapy is the only relevant comparator in this submission. The company claims that orlistat is used earlier in the treatment pathway (tier 2), while liraglutide 3.0mg is

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
			is supported by Section 3.4 of the final appraisal determination for naltrexone–bupropion (TA494), where it is stated that clinical experts and consultees reported that standard management (diet and lifestyle interventions) is the only relevant comparator because orlistat is not often used in clinical practice. This is due to undesirable side effects leading to poor adherence and weight loss outcomes. As a result, most patients do not want to take it or stop treatment after a short time. Based on this, the committee concluded that standard management was the main comparator in the appraisal. Liraglutide 3.0mg is intended for use in patients who have been referred to a specialist tier 3 service where conventional treatments such as orlistat have been unsuccessful earlier in the clinical pathway. For patients where bariatric surgery would be an appropriate option and this is acceptable to the patient, this would be a relevant treatment alternative according to the NICE clinical guideline (CG 189) [17]. Bariatric surgery has already been demonstrated as a cost-effective treatment option for a selected group of patients. Liraglutide 3.0mg would not be a direct replacement for bariatric surgery, however, it could be suitable for a group of patients who are unwilling or unable to undergo surgery. As noted by the clinical expert in TA494 bariatric surgery is highly effective but only a small proportion	intended for use in patients who have been referred to a specialist tier 3 service where conventional treatments such as orlistat have been unsuccessful earlier in the clinical pathway. However, orlistat and bariatric surgery could be relevant comparators in some patients eligible for liraglutide.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
			(around 0.1% of those eligible for bariatric surgery) receive surgery. For this reason, bariatric surgery is not included as a comparator but will be included as a downstream event for a proportion of patients in the health-economic model in both treatment arms.	
Outcomes	The outcome measures to be considered include: • BMI • Weight loss • Percentage body fat • Waist circumference • Incidence of type 2 diabetes • Cardiovascular events • Idiopathic intracranial hypertension • Non-alcoholic fatty liver disease • Mortality • Adverse effects of treatment • Health-related quality of life.	The outcome measures included in the clinical studies for liraglutide 3.0mg include: • BMI • Weight loss (change from baseline %, kg) • Waist circumference • Incidence of type 2 diabetes and impact on glycaemia (i.e., HbA_{1c}, fasting plasma glucose) • Changes in CV risk markers including lipid parameters (total cholesterol and high-density lipoprotein) and systolic blood pressure • Adverse effects of treatment • Health-related quality of life	Outcomes listed in the scope which are not included in this submission are: 1) Percentage body fat was not collected in the clinical trial programme, nor is it routinely collected in the UK clinical practice. Section 1.2.2 of NICE clinical guidelines 189, suggests using BMI as a practical estimate of adiposity in adults. In Section 1.2.6 it also does not recommend/endorse the routine use of the bioimpedance for measurement of the body fat percentage or as means of diagnosing overweight or obesity[4]. This is also supported in Section 5.1.3 of the NICE Evidence Review for clinical guideline 43, which states there is a weak association between BMI and percentage adiposity: 'Adiposity is defined as the amount of body fat expressed as either the absolute fat mass (in kilograms) or as the percentage of total body mass. Absolute adiposity is highly correlated with body mass, but percentage adiposity is relatively uncorrelated with body mass'.[18] 2) Idiopathic intracranial hypertension was not collected as part of the clinical trial and therefore data are lacking on this outcome.	The outcomes reported are in line with the NICE scope. However, most outcomes are only reported for the ITT population in Trial 1839; while the company claims the CS focusses on 'patients with BMI ≥35 kg/m^2, prediabetes, high risk of CVD'. For this population only three outcomes are reported in the CS: weight loss (change from baseline %, kg), waist circumference and incidence of type 2 diabetes.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
		The outcomes measures in the economic model include • Mortality/life expectancy • Health-related quality of life • Cumulative incidence of acute cardiovascular events including stroke, transient ischaemic attack, myocardial infarction and angina	3) Non-alcoholic fatty liver disease: It is unknown what proportion of patients in the liraglutide 3.0mg clinical studies could be classified as also having non-alcoholic fatty liver disease as liver biopsies were not taken as part of the study protocol. Therefore, there is no information to assess this outcome. It should be noted that patients with impaired liver function (defined as ALAT ≥2.5 times upper limit of normal) were excluded from the liraglutide 3.0mg clinical trials.	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered. These include: • people with obesity-related complications; • people with type 2 diabetes; • people with serious mental illness; • people with a BMI ≥35 kg/m^2 who have prediabetes and a high risk of cardiovascular disease and are in specialist tier 3 services.	As noted in Section B.1.1 (of the CS), the company submission only considers adults patients with: • BMI ≥35 kg/m^2 with • Prediabetes, and • High risk of cardiovascular disease	People with severe mental illness were excluded from the clinical studies for liraglutide 3.0mg and hence there is little evidence to inform clinical and cost-effectiveness evaluations in this subgroup of patients. Adjustment for BMI according to ethnicity has not been explicitly evaluated within this submission but Novo Nordisk sees no reason not to follow NICE's Public Health guidance (PH46),[19] BMI: preventing ill health and premature death in black, Asian and other minority ethnic groups.	The CS only focusses on 'patients with BMI ≥35 kg/m^2, prediabetes, high risk of CVD'. No other subgroup data are reported.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers. EQ-5D is preferred.	Baseline utility values in the model were derived from an analysis of the 2003 Health Survey for England data, which used EQ-5D in a large UK population.[20]	HRQoL inputs used in the economic model were based on a large UK population-based study as it has demonstrated a robust association between BMI and utility.[20] The applied method is important for the economic model for two reasons: 1) It allowed the separation of the effects of comorbidities from a pure effect related to increased weight; 2) In the model, a health-related quality of life decrement specific to each obesity complication health state could be applied separately. Trial-based patient-derived SF-36 data have previously been mapped to EQ-5D as reported by Kolotkin et al., 2017,[21] however, this analysis did not incorporate the stopping rule, nor did it have the benefits noted above.	The approach used to estimate HRQOL inputs for the economic model was considered reasonable. The main concerns of the ERG relate to the risk of double-counting due to the use of multiple HRQoL sources and an additive disutility approach and the implementation of some of the adverse event related disutility values. Additionally, available HRQOL data from the Trial 1839 were not used in the company base-case. However, the scenario analyses provided by the company in response to clarification question B18 (based on mapped BMI-dependent utilities measured during Trial 1839) showed similar results as the company base-case.

Source: CS, Table 1, pages 12-16.

ALAT = Alanine aminotransferase; CV = Cardiovascular; HRQoL = Health-Related Quality of Life; NICE = National Institute for Health and Care Excellence; UK = United Kingdom.

3.1 Population

The population defined in the scope is: Adults who have a BMI of ≥ 30 kg/m^2 (obese) or ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity.[16] The population in the CS is limited to 'Adult patients with: BMI ≥35 kg/m^2 with prediabetes, and high risk of cardiovascular disease'.[1]

The population defined in the final scope is consistent with the current European Medicines Agency (EMA) indication for liraglutide: 'Liraglutide 3.0mg (Saxenda®) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial body mass index (BMI) of: ≥30 kg/m^2 (obesity); or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity such as dysglycemia (prediabetes or type 2 diabetes), hypertension, dyslipidaemia or obstructive sleep apnoea.'.[22]

As part of the EMA licence, a stopping rule is applied to 'non-responders' of liraglutide 3.0mg, where treatment should be discontinued after 12 weeks on the 3.0mg/day maintenance dose if patients have not lost 5% of their initial body weight. Patients that lose equal to or more than 5% of their initial body weight are classified as 'early responders'.

The company submission focusses on a subpopulation of the EMA licence which are patients with:

- BMI ≥35 kg/m^2 (obesity class II and above) with
  - Non-diabetic hyperglycaemia (prediabetes) at high risk of type 2 diabetes which is defined as having either:
    - fasting plasma glucose level of 5.5–6.9 mmol/L; or
    - HbA_{1c} of 6.0-6.4% (42 – 47 mmol/mol) aligned with National Institute for Health and Care Excellence (NICE) guidelines;[12] and
  - High risk of cardiovascular disease (CVD) aligned with the NICE guidelines and expert opinion:
    - Total cholesterol >5 mmol/L; or
    - High-density lipoprotein (HDL) <40 mg/dL for men and <50 mg/dL for women;[13] or
    - Systolic blood pressure >140 mmHg.[23]

The subpopulation defined above will subsequently be referred to as 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD'. The treatment setting for these patients would be in a specialist tier 3 weight assessment and management clinic (WAMC) service, offering lifestyle modification advice, pharmacotherapy, psychological treatment as well as assessing patients for bariatric surgery.[24]

ERG comment: The company limited the population to 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD', 'because this subpopulation of patients would benefit the most from liraglutide 3.0mg in UK clinical practice, and therefore optimises cost effectiveness' (CS, Table 1, page 12).[1] Although effectiveness data from Trial 1839 are presented for the full ITT population, which is largely in line with the population described in the NICE scope, the economic analysis is focussed on a narrower population of patients with 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD'.

3.2 Intervention

The intervention (liraglutide) is in line with the scope.

Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) analogue with 97% amino acid sequence homology to endogenous human GLP-1 (7-37). GLP-1 is a physiological regulator of appetite

and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding, and stability against metabolic degradation by DPP-4 and Neutral Endopeptidase (NEP). Liraglutide regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and reducing prospective food consumption.

EMA marketing authorisation for liraglutide 3.0mg (Saxenda®) was granted in April 2015.

Liraglutide 3.0mg is for subcutaneous (SC) use only. It is administered once daily at any time, independent of meals. It is preferable that liraglutide 3.0mg is injected at the same time every day. The starting dose is 0.6mg once daily. The dose should be increased to 3.0mg daily in increments of 0.6mg with at least one week intervals. Daily doses higher than 3.0mg are not recommended. Treatment with liraglutide 3.0mg should be discontinued after 12 weeks on the maintenance dose of 3.0mg/day if patients have not lost at least 5% of their initial body weight.

No additional tests or investigations are required.

ERG comment: As mentioned, according to the license for liraglutide 3.0mg, it should be discontinued after 12 weeks on the maintenance dose of 3.0mg/day if patients have not lost at least 5% of their initial body weight. However, this stopping rule was not applied in Trial 1839. It is not clear how this discrepancy influenced results, but it is possible that the effectiveness of liraglutide is overestimated in Trial 1839 (assuming that liraglutide is more effective than placebo, even in patients achieving less than 5% weight loss at 16 weeks).

3.3 Comparators

The description of the comparators in the NICE scope is as follows: Standard management without liraglutide (including a reduced calorie diet and increased physical activity), orlistat (prescription dose), and bariatric surgery.

The company claims that standard management without pharmacotherapy is the only relevant comparator in this submission.

The company provides the following two reasons for omitting orlistat as a comparator:

1. orlistat is currently recommended as a treatment option in primary care in a much wider population than is proposed for liraglutide 3.0mg and as such would be used earlier in the treatment pathway (tier 2).
2. the use of orlistat is currently limited in clinical practice.

In addition, the company states that liraglutide 3.0mg is intended for use in patients who have been referred to a specialist tier 3 service where conventional treatments such as orlistat have been unsuccessful earlier in the clinical pathway.

Regarding bariatric surgery the company states that 'For patients where bariatric surgery would be an appropriate option and this is acceptable to the patient, this would be a relevant treatment alternative according to the NICE clinical guideline (CG 189).[4] Bariatric surgery has already been demonstrated as a cost-effective treatment option for a selected group of patients. Liraglutide 3.0mg would not be a direct replacement for bariatric surgery, however, it could be suitable for a group of patients who are unwilling or unable to undergo surgery.'[1]

Regarding 'standard management without liraglutide (including a reduced calorie diet and increased physical activity)', all patients received standardised counselling on life-style modification according to the study protocol in both treatment arms.[14] This meant that patients received both dietary counselling and physical activity encouragement. Compliance to diet and physical activity was assessed in both treatment arms. These data were provided to NICE as part of the response to clarification by 13 August 2019.

ERG comment: Regarding orlistat, it is not clear whether all patients in Trial 1839 have indeed failed on orlistat. In fact, in their response to the clarification letter (Question A12), the company state that 'data on previous treatment with orlistat, or any other anti-obesity pharmacotherapy was not collected in the study'.[14] This means orlistat could be a relevant comparator in some patients eligible for liraglutide. Regarding bariatric surgery, the company states that liraglutide 'could be suitable for a group of patients who are unwilling or unable to undergo surgery'.[1] This means that bariatric surgery is a relevant comparator for patients who are willing or able to undergo surgery. Therefore, bariatric surgery could also be a relevant comparator in some patients eligible for liraglutide.

In conclusion, the two comparators omitted by the company may be relevant comparators in some patients, and for the one comparator included in the CS (standard management) adherence is not clear.

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- BMI
- weight loss
- percentage body fat
- waist circumference
- incidence of type 2 diabetes
- cardiovascular events
- idiopathic intracranial hypertension
- non-alcoholic fatty liver disease
- mortality
- adverse effects of treatment
- health-related quality of life.

ERG comment: Most of these outcome measures are reported in the CS, but only for the full ITT population in Trial 1839. For the 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD' population, which is the focus of the CS and the economic evaluation, the company only presents data for weight loss, waist circumference and incidence of type 2 diabetes in the clinical effectiveness chapter of the CS.

3.5 Other relevant factors

The company claims liraglutide is innovative in that 'it is the first GLP-1 indicated for obesity and weight management, liraglutide 3.0mg is first in its class for this therapy area, while offering the added benefits of reducing the risk of type 2 diabetes and preventing CVD events'.[1]

The company has submitted a Patient Access Scheme (PAS) for a simple discount to the Department of Health on 17 May 2019. The proposed PAS price is equal to a discount of [redacted].

End-of-life criteria are not applicable for this appraisal.

The company claims that there are several equality issues that need to be taken in to account in this appraisal. In the first place, liraglutide 3.0mg can assist certain people considered to have a disability;

secondly, liraglutide 3.0mg may be of greater assistance to people in specific minority ethnic groups; and thirdly, liraglutide 3.0mg may have a positive differential impact on people of lower socioeconomic status, thereby promoting equality of opportunity; and fourthly, by assisting in lowering BMI levels and accordingly, allowing patients to meet BMI thresholds, liraglutide 3.0mg may reduce inequity in access to other medical treatments (CS, Section B.1.4, pages 30-31).[1]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D.1.1 of the CS details a systematic search performed to identify studies assessing the efficacy, safety, and tolerability outcomes associated with pharmacological interventions for the treatment of obesity in patients with body mass index (BMI) ≥35 kg/m^2, prediabetic conditions and a high cardiovascular disease (CVD) risk. Searches were limited to studies published in English from 1976 to 4 September 2018. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

	Resource	Host/Source	Date Range	Date searched
Electronic Databases	Medline	Ovid SP	1976-4/9/18	4/09/18
	Medline In-Process			
	Embase			
	Cochrane CENTRAL			
Conference Proceedings	ECO	Ovid SP	2016-2018	
	The Obesity Society – Obesity Week			
	BOMSS			
	IFSO			
	UKCO	Hand searched		
	EASD			
	ENDO			

ECO = European Conference on Obesity; BOMSS = British Obesity & Metabolic Surgery Society; IFSO = International Federation for the Surgery of Obesity and Metabolic Disorders; UKCO = UK Congress on Obesity; EASD = European Association for the Study of Diabetes; ENDO = Endocrine Society.

ERG comments:

- No additional searches were conducted to identify data on adverse events or indirect comparisons. While the searches outlined may have retrieved some relevant information in these areas, the addition of a trials filter may have resulted in relevant references being missed. Guidance by the Centre for Reviews and Dissemination (CRD)[25] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed.
- A single search appears to have been conducted across Embase and CENTRAL. While some additional MEDLINE (MeSH) indexing terms are included in the MEDLINE obesity facet, this is not the case for the rest of the searches. Although mapping between indexing terms does take place within OvidSP, the extensive use of EMTREE indexing may mean that MeSH terms were not included in the search. Potentially relevant records in MEDLINE and CENTRAL may therefore have been missed.
- All facets of the search were limited, with few synonyms being employed. Additional search terms (free-text and subject indexing terms) could have been included to increase the sensitivity of the search strategies.

- Lines #30/#31 of the MEDLINE strategy, and lines #25/#26 of the Embase strategy were included in order to remove references relating to bariatric surgery, sibutramine and rimonabant. This could unintentionally also remove relevant references from the results sets.
- A limited trials filter, containing only EMTREE indexing terms and including no free-text terms was used. This means potentially relevant references could have been missed by the searches of these databases, particularly on databases indexed with MeSH subject headings such as MEDLINE and CENTRAL.
- The trials filter used in CENTRAL is unnecessary, as CENTRAL is a trials database. The use of this filter means that potentially relevant references could have been missed by the searches.
- Limiting the MEDLINE and Embase clinical effectiveness searches to English language only studies may have introduced language bias. Current best practice states that 'Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication'.[26]
- Limited additional searching was conducted, and this was restricted to searches for conference proceedings. Other useful sources of information may have included trials registers, relevant organisations, company databases and web resources.
- Best practice outlined in the Cochrane handbook states that 'Reference lists in other reviews, guidelines, included (and excluded) studies and other related articles should be searched for additional studies'.[27] No reference checking was reported for this SLR.

4.1.2 Inclusion criteria

The systematic review is not described in the main body of the CS. In document B of the CS, the company only describes liraglutide trials and concludes that the results of a post-hoc analysis of Trial 1839 using only a subgroup of patients (the 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD' population) are used for this appraisal.

As described in Appendix D of the CS, a systematic review was performed to identify studies assessing the efficacy, safety, and tolerability outcomes associated with pharmacological interventions for the treatment of obesity in patients with Body Mass Index (BMI) ≥35 kg/m^2, prediabetic conditions and a high Cardiovascular Disease (CVD) risk. The eligibility criteria used in the search strategy for relevant studies are presented in Table 4.2.

Table 4.2: Eligibility criteria used in search strategy for relevant studies

Inclusion criteria	
Population	Adult patients with BMI ≥35 kg/m^2 and prediabetes and high CVD risk, as defined by: Prediabetes: • NICE definition: fasting plasma glucose level of 5.5–6.9 mmoL/l or HbA_{1c} level of 42–47 mmoL/mol (6.0–6.4%); • ADA definition: HbA_{1c} level of 39–47 mmoL/mol (5.7–6.4%); • Any other definition applied in the publication. High risk of CVD: • Total cholesterol > 5mmoL/L, or • Systolic Blood Pressure >140 mmHg, or • HDL < 1.0 mmoL/L for men and < 1.3 for women mmoL/L, or • Or any other definition applied in the publication.

Interventions/ Comparators	Trials containing interventions, one or more of: • Liraglutide injection 3.0mg (Saxenda) • Orlistat (Xenical, Alli) Compared to one or more of: • Liraglutide injection 3.0mg • Orlistat • Placebo • Usual care (commonly diet and exercise, which may or may not also include behavioural modification components)
Outcomes	Any outcomes
Study design	RCTs Systematic reviews and meta-analyses of RCTs
Limits	The searches were limited to human studies published in the English language No time limit was applied
Exclusion Criteria	
Population	Below 18 years of age or a population that does not include the target patient group or a population that overlaps but does not provide the results as a subgroup specifically for the target population of interest.
Interventions/ Comparators	Does not include any of the interventions, or Does not report listed comparisons
Outcomes	No outcomes reported, for example study protocols
Study Design	In vitro studies Preclinical studies Comments, letters, editorials Case reports, case series Reviews Uncontrolled studies
Source: Appendix D, Table 4, pages 10-11 of the CS ADA = American Diabetes Association; BMI = Body Mass Index; CVD = Cardiovascular Disease; HbA_{1c} = haemoglobin A_{1c}; HDL = High-Density Lipoproteins; mmoL/l = millimoles per litre; NICE = National Institute for Health and Care Excellence RCT = Randomised Controlled Trial.	

ERG comment: The methods used to select relevant studies for inclusion were not clearly described; however, it appeared that only a single reviewer was involved in study selection, meaning reviewer error and bias could not be ruled out, and relevant publications may have been missed.

As can be seen from the inclusion criteria reported in Table 4.2, the company only searched for studies in the population they defined (BMI ≥35 kg/m^2, prediabetes and high risk of CVD), i.e. not in the population defined in the scope (which is in line with the license indication for liraglutide). Specifically, they did not search for the broader population of adult patients with a BMI ≥30 kg/m^2, which was detailed in the scope. The searches resulted in 120 full-text publications which were assessed for eligibility; 98 of these were excluded (most often because the population was out of scope, n=79), and

22 publications were included. In the 22 included publications, orlistat was evaluated three times and liraglutide 19 times. The orlistat studies were subsequently removed 'for reasons stated in the Decision Problem' according to the company.[1] As discussed in Section 3.3 of this report, we do not agree with the company's decision to remove orlistat as a relevant comparator. The remaining 19 of the 22 studies identified described Trial 1839, i.e. the obesity and prediabetes study that examined the safety and efficacy of liraglutide 3.0mg.

To explore the issue with orlistat in more detail, the ERG confirmed that orlistat was initially included as a comparator in the systematic review. Indeed, orlistat was included as a named drug in the search strategies and studies reporting on orlistat were included at the screening stage. However, these studies were ultimately excluded from the final clinical effectiveness synthesis, based on the company's reasons stated in the decision problem. As described in the paragraph above, the ERG does not agree with this decision.

Bariatric surgery was not included as a comparator in the company's PICOS (population, intervention, comparators, outcome study design) for the systematic review, which was not in line with the scope. The company justified this by reporting that they did not expect this comparator would appear in the scope; and that they were not positioning liraglutide as a replacement for bariatric surgery. Consequently, the company did not perform update searches to include bariatric surgery as a comparator once the scope had been defined. As detailed in Section 1.3, the ERG does not agree with this decision.

As detailed in Table 4.2, the company PICOS indicated that any outcome should be included; however, six records were excluded during full-text screening due to 'outcomes out of scope': Bjorner et al, Kolotkin et al (A), Kolotkin et al- (B), Kolotkin et al (C), Kolotkin et al (D), von Scholten et al. (See CS, Table 5 of Appendix D, Section D.1.1.8).[1] These full-text records appeared to report relevant outcomes (HRQoL, including physical component subscales; weight loss; kidney function). A further 150 records were excluded for the same reason ('outcomes out of scope') at the earlier title and abstract screening stage. The exclusion of these studies on the basis of outcome was not further explained or clarified. This implied that several relevant studies may have been missed.

4.1.3 Critique of data extraction

Data extraction was performed by two reviewers – one reviewer extracted the data and a second reviewer checked it. Any discrepancies were resolved by the intervention of a third reviewer. This was considered adequate.

4.1.4 Quality assessment

Study quality was assessed using seven criteria: 1) randomisation, 2) allocation concealment, 3) similarity of prognostic factors between groups at baseline, 4) blinding of care providers, participants and outcome assessors to treatment allocation, 5) unexpected imbalances or drop-outs between groups, 6) selective reporting and 7) the inclusion of an ITT analysis. While it was not clear if this represented a validated quality assessment tool, most of the criteria recommended by Cochrane for the assessment of quality in randomised controlled trials appeared to be presented.[28] Of note, while question #2, which addressed whether allocation concealment was adequate, was answered as a 'yes', no information was provided to support this statement, and no information regarding allocation concealment could be identified by the ERG in either of the key Trial 1839 publications.[29, 30] Similarly, while question #4, which addressed whether care providers, participants or outcome assessors were blinded to treatment allocation, was answered as a 'yes', it was unclear who was involved in the outcome assessment (i.e. investigators or funders), and therefore the ERG felt it was possible that unmasking the funders to treatment allocation at week 56 may have biased outcome assessments.

4.1.5 Evidence synthesis

Since only one liraglutide study was included, no evidence synthesis of liraglutide studies was performed.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Included studies

The company submission focusses on a post-hoc analysis from the SCALE obesity and prediabetes trial (Trial 1839). However, key study information presented in the CS, such as baseline characteristics and most results, are reported for the full ITT population in Trial 1839. Therefore, we asked the company to clarify the precise nature of the index population (Clarification question A5A) and to provide full baseline characteristics, results and adverse events for this subpopulation (Clarification question A16).[14]

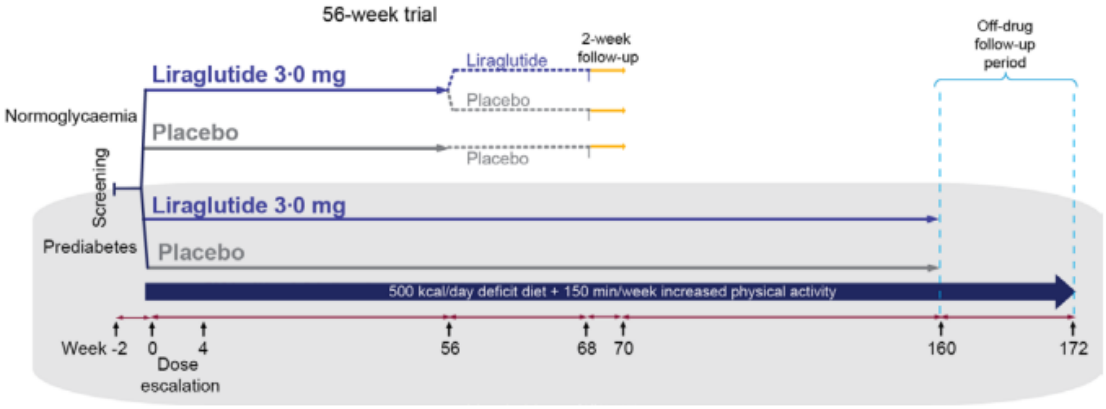
Studies that examined the safety and efficacy of orlistat were excluded by the company. There are two potential studies that might allow a comparison with orlistat. First, there is Trial 1807, a Phase 2 dose-finding trial in adult patients with obesity or overweight (without type 2 diabetes). 564 patients were randomised in a 1:1:1:1:1:1 manner to receive one of four doses of liraglutide (1.2, 1.8, 2.4 or 3.0mg once daily), or placebo (once daily) or orlistat (120 mg three times daily). This trial was of 20 weeks duration with an extension period of 84 weeks. The head-to-head comparison of liraglutide 3.0mg once daily vs orlistat (120 mg three times daily) may provide relevant information for the committee about the relative effectiveness and safety of liraglutide compared to orlistat in a population similar to that described in the NICE scope. We asked the company to provide data from this trial for the index population (Clarification question A9).[14] However, the company only provided numbers of patients in each arm (liraglutide 3.0mg: 13; orlistat: 10; and placebo: 16).

Secondly, there is the XENDOS study,[31] a four-year, double-blind, prospective study, including 3,305 patients randomised to lifestyle changes plus either orlistat 120 mg or placebo, three times daily. Participants had a BMI ≥30 kg/m^2 and normal (79%) or impaired (21%) glucose tolerance (IGT). Primary endpoints were time to onset of type 2 diabetes and change in body weight. The impaired IGT subgroup from the XENDOS study is more comparable to (though not the same) as the 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD' population in Trial 1839. Despite the fact that this comparison relies on an indirect comparison of two trials with slightly different populations and control arms, the comparison of liraglutide vs. orlistat in a population more like the index population in the submission might still be of interest to the committee. However, as the company has clearly stated that liraglutide is intended for use in patients who have been referred to a specialist tier 3 service where conventional treatments such as orlistat have been unsuccessful earlier in the clinical pathway, we will not perform this comparison.

4.2.2 Methodology of included studies

Trial 1839 was a randomised, double-blind (investigators and patients were blinded during the full trial; the sponsors, Novo Nordisk, were unblinded after one year), placebo-controlled, parallel group, multicentre, multinational trial in patients with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with comorbidities. Study participants were randomised two to one to receive liraglutide 3.0mg (n=2,487) or placebo (n=1,244) as an adjunct to diet and exercise and stratified according to prediabetes status (according to American Diabetes Association [ADA] 2010 criteria) at screening.[32] The trial design is illustrated in Figure 4.1.

Figure 4.1: Trial design - SCALE– obesity and prediabetes (Trial 1839)



Source: CS, Figure 3, page 39.

One-year part (n=3,731 patients)

The initial 56 weeks of the trial included both patients with and without prediabetes. Dose escalation in weekly increments of 0.6mg of liraglutide up to 3.0mg once daily was applied during the first four weeks of treatment. For patients without prediabetes at screening, the initial 56 weeks were followed by a 12-week re-randomised treatment period (patients in the liraglutide 3.0mg group either continued on liraglutide 3.0mg or switched to placebo whereas patients in the placebo group remained on placebo) and a two-week follow-up period. The primary results from the one-year part of Trial 1839 were published in Pi-Sunyer et al., 2015.[30]

Three-year assessment - patients with prediabetes (n=2,254 patients)

Following the one-year part (including both patients with and without prediabetes), the trial had a two-year extension period for patients with prediabetes at the screening. Thus, patients with prediabetes at screening received either liraglutide 3.0mg or placebo as an adjunct to diet and exercise for 160 weeks, followed by a 12-week off-drug/placebo observational follow-up period, for a total trial duration of 172 weeks. Patients consented to the three-year assessment at randomisation. The primary results from the three-year assessment of Trial 1839 were published in le Roux et al., 2017.[29]

A summary of the methodology of SCALE– obesity and prediabetes (Trial 1839) is provided in Table 4.3.

Table 4.3: Summary of methodology – SCALE – obesity and prediabetes (Trial 1839)

Location	The trial was conducted at 191 sites in 27 countries in Europe, North America, South America, Asia, Africa, and Australia. In the UK, 112 randomised patients participated at eight sites.
Trial design	Randomised, double-blind, placebo-controlled trial with randomisation of patients to either 56 or 160 weeks of treatment based on prediabetes status at the screening.
Trial inclusion criteria	Adults aged 18 years or older with stable body weight and a body mass index (BMI) of at least 30 kg/m², or at least 27 kg/m² with treated or untreated comorbidities (dyslipidaemia, or hypertension, or both) were enrolled in the trial. Patients were stratified according to BMI (≥30 kg/m^2 or <30 kg/m^2) and prediabetes status. To be eligible for stratification as having prediabetes, patients had to meet one of the following criteria based on the ADA 2010.[32] guidance:

	• HbA_{1c} 5.7%−6.4% both inclusive, or • Fasting plasma glucose (FPG) ≥5.6 mmol/L and ≤6.9 mmol/L, or • Two hours post-challenge (oral glucose tolerance test [OGTT]) plasma glucose (PG) ≥7.8 mmol/L and ≤11.0 mmol/L. Key exclusion criteria were: type 1 or type 2 diabetes, medications causing significant weight gain or loss, bariatric surgery, history of pancreatitis, major depressive or other severe psychiatric disorders, and family or personal history of multiple endocrine neoplasia Type 2 or familial medullary thyroid carcinoma.
Trial drug	Liraglutide 3.0mg or placebo was administered once daily by subcutaneous (SC) injections with the FlexPen® either in the abdomen, thigh or upper arm. Injections could be done at any time of day irrespective of meals. In order to reduce the level of side effects, patients followed a fixed dose escalation in weekly increments of 0.6mg liraglutide. If patients did not tolerate an increase in dose during dose escalation, the investigator had the option to individualise the dose escalation with a total delay of up to 7 days. All patients had to be at the target dose of 3.0mg by 35 days after randomisation.
Permitted and disallowed concomitant medication	Medications causing significant weight gain or loss were disallowed.
Primary outcomes	The primary endpoint in the 3-year assessment of the trial was: Proportion of patients with onset of type 2 diabetes at week 160 among patients with prediabetes at baseline - evaluated as the time to onset of type 2 diabetes.
Other outcomes used in the economic model	The outcomes listed below were included in the economic model: • % weight loss vs. baseline at 6 months (28 weeks), 1 year (56 weeks), 2 years (104 weeks), and 3 years (160 weeks) • Change in systolic blood pressure (mmHg, positive = increase) vs. baseline at 6 months, 1 year, 2 year and 3 years • Change in serum lipids (total cholesterol, HDL) vs baseline at 6 months, 1 year, 2 year and 3 years • Change in HbA_{1c} vs. baseline at 6 months, 1 year, 2 year and 3 years • % reversing from prediabetes to NGT at 3 months, 1 year and 2 years • Proportion not achieving 5% weight loss after 16 weeks (i.e. after 4 weeks titration and 12 weeks on maintenance dose) The analyses used in the economic modelling were performed *post-hoc* (see Section B.2.7.2 of the CS for further details).
Pre-planned subgroups	Pre-planned subgroup analyses from the 3-year assessment of the trial were performed to investigate whether baseline BMI (in four categories) had any effect on changes in body weight or HbA_{1c}.
ADA = American Diabetes Association; FPG = Fasting plasma glucose; HDL = High-density lipoprotein; OGTT = oral glucose tolerance test; PG = plasma glucose; NGT = Normal glucose tolerance; SC = Subcutaneous; UK = United Kingdom	

ERG comment: Trial 1839 is a good quality randomised controlled trial. The ERG has no concerns with the trial design and the trial methods. However, the company's choice to focus on a post-hoc subgroup analysis is a concern as it means that the CS is based on a smaller sample of only 35% of the whole trial population. This means that the analyses no longer have sufficient statistical power to detect

statistically significant differences between the treatment groups and the two groups may not be comparable at baseline as the randomisation was not stratified for this particular subgroup.

4.2.3 Baseline characteristics

Demographics and baseline characteristics for all randomised patients and for 'patients with a BMI ≥35 kg/m^2, prediabetes and high risk of CVD' are summarised in Table 4.4. The average age of all randomised patients was 47.5 years compared to 48.2 years in the index population and 76.0% of patients were women compared to 75.8% in the index population. Mean BMI was higher in the post-hoc analyses (index population) compared to the planned analyses (full ITT population) which was expected due to the BMI cut-off of ≥35 kg/m^2.

Table 4.4: Demographic and baseline characteristics (means, SD) - randomised patients – Trial 1839

	Full trial population			**Subgroup used in CS**		
	Liraglutide 3.0mg (N=1,505)	**Placebo (N=749)**	**Total (N=2,254)**	**Liraglutide 3.0mg (N=530)**	**Placebo (N=270)**	**Total (N=800)**
Age (years)	47.5 (11.7)	47.3 (11.8)	47.5 (11.7)	48.1 (11.3)	48.2 (11.1)	48.2 (11.2)
Height (m)	1.66 (0.09)	1.66 (0.09)	1.66 (0.09)	1.66 (0.09)	1.67 (0.09)	1.67 (0.09)
Fasting body weight (kg)	107.5 (21.6)	107.9 (21.8)	107.6 (21.6)	115.6 (19.8)	116.5 (19.8)	115.9 (19.8)
BMI (kg/m^2)	38.8 (6.4)	39.0 (6.3)	38.8 (6.4)	41.7 (5.4)	41.9 (5.3)	41.7 (5.3)
HbA_{1c} (%)	5.8 (0.3)	5.7 (0.3)	5.7 (0.3)	5.8 (0.3)	5.8 (0.3)	5.8 (0.3)
Fasting plasma glucose (mmol/L)	5.5 (0.6)	5.5 (0.5)	5.5 (0.6)	5.7 (0.6)	5.6 (0.5)	5.7 (0.6)
Gender						
Female (%)	75.8%	76.5%	76.0%	75.7%	75.9%	75.8%
Male (%)	24.2%	23.5%	24.0%	24.3%	24.1%	24.3%
Race						
White	83.5%	83.8%	83.6%	86.2%	84.1%	85.5%
Black or African American	9.7%	9.5%	9.6%	8.2%	10.0%	9.3%
Asian	5.0%	5.2%	5.1%	3.6%	3.7%	3.6%
Other[a]	1.9%	1.5%	1.7%	1.4%	2.3%	1.6%
Smoker status						
Current smoker	14.4%	16.6%	15.1%	15.7%	13.7%	15.0%
Never smoked	58.9%	57.7%	58.5%	55.1%	59.3%	56.5%
Previous smoker	26.7%	25.8%	26.4%	29.2%	27.0%	28.5%
History of CV disease (SMQ search)[b]						
Yes	12.7%	13.2%	12.9%	12.5%	15.2%	13.4%
No	87.3%	86.8%	87.1%	87.5%	84.8%	86.6%
Dyslipidaemia[b]						

	Full trial population			Subgroup used in CS		
	Liraglutide 3.0mg (N=1,505)	**Placebo (N=749)**	**Total (N=2,254)**	**Liraglutide 3.0mg (N=530)**	**Placebo (N=270)**	**Total (N=800)**
Yes	33.2%	33.2%	33.2%	33.6%	34.8%	34.0%
No	66.8%	66.8%	66.8%	66.4%	65.2%	66.0%
Hypertension[b,c]						
Yes	42.2%	41.7%	42.0%	48.5%	48.9%	48.6%
No	57.8%	58.3%	58.0%	51.5%	51.1%	51.4%

Source: CS, Table 6, page 41; Table 18, page 66; Appendix E and Response to Clarification letter (Question A14).
CV = cardiovascular; N = number of patients; SMQ = standard medical query.
[a] including 'American Indian or Alaska Native', 'Native Hawaiian or other Pacific Islander' or 'Other';
[b] History of CV disease was based on an SMQ search of the medical history including Ischaemic heart disease, Cardiac failure, Central nervous system haemorrhages, Cerebrovascular conditions and Embolic and thrombotic events. Dyslipidaemia was found by SMQ search of the medical history. Hypertension was found by SMQ search of the medical history.
[c] For the 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD' subgroup this was described as 'On antihypertensive medication'.
Values for continuous variables are means. Values in parentheses are standard deviations;

ERG comment: As expected, BMI, was higher when comparing baseline characteristics of patients in the post-hoc analyses with baselines characteristics of all patients in Trial 1839. In addition, patients in the post-hoc analyses were slightly older, had higher fasting body weight, higher HbA_{1c} and fasting plasma glucose and patients in the post-hoc analyses had more often hypertension (48.6%) than all patients in Trial 1839 (42.0%).

The total number of patients from the UK in Trial 1839 with 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD' subgroup was 41. Of these, 29 patients were randomised to liraglutide 3.0mg and 12 were randomised to placebo. Eight UK study sites took part in Trial 1839; all eight study sites provide specialist tier 3 services in the UK.

4.2.4 Statistical analyses

The company states that 'All efficacy analyses used data from the full analysis set from Trial 1839; i.e. including patients with prediabetes at screening, which included all patients who underwent randomisation and received at least one dose of a study drug and had at least one assessment after baseline. The safety analysis set included all patients who were exposed to at least one dose of the study drug.' (CS, Section 2.4.1, page 43).[1] However, the analyses that are relevant for the submission are based on a subgroup of patients in Trial 1839, i.e. 'patients with a BMI ≥35 kg/m^2, prediabetes and high risk of CVD'. Therefore, data relevant for the submission are based on post-hoc subgroup analyses.

Imputation methods

In the original analyses, missing values were imputed using the last observation carried forward (LOCF) for post-baseline measurements. The results obtained using this method are included in the Trial 1839 clinical trial results (CTR),[33] the trial publications[29, 30] and the European SmPC.[34]

For the economic modelling, a number of post-hoc analyses were conducted for patients in Trial 1839 matching the target population in scope for this submission. The post-hoc analyses have been conducted using three different imputation methods:

a) LOCF;
b) Baseline observation carried forward (BOCF);
c) Multiple imputations based on the McEvoy (ME) approach (MI-ME approach): This was used to handle missing data for patients on treatment at the time of the visit the estimation is done for (i.e. week 28, 56, 104 or 160).[35] For patients off treatment at the specific visit, the ME approach cannot be generally applied, since patients that discontinue treatment during the extension part of the trial, were not asked to come back for assessments at later visits. Therefore, for patients off treatment at the visit, single imputation is done by extrapolating from the last available observation and until the time of the visit. Extrapolation is based on change estimates from the 12-week follow-up period (following the three-year assessment of Trial 1839) without treatment. If single imputed values cross baseline values, baseline values are used.

The European license for liraglutide 3.0mg for obesity is based on calculations where missing data is handled by LOCF. Therefore, the results from the post-hoc analyses that are used for the base case in the economic modelling are also based on LOCF. For the sensitivity analyses in the economic modelling, results from the post-hoc analyses using BOCF and MI-ME approach are applied to test the impact of using different imputation methods on the cost-effectiveness results.

Definition of prediabetes

In the planned analyses included in Trial 1839, patients were defined as having prediabetes according to the ADA 2010 criteria. In the post-hoc analyses performed for the purposes of this submission, patients were defined as having prediabetes if they fulfilled the criteria provided by NICE for high risk of type 2 diabetes in addition to the original ADA criteria,[32] presented below in Table 4.5. The ADA and NICE criteria, however, do not overlap completely; patients with fasting plasma glucose (FPG) ≥5.5 and <5.6 mmol/L would be considered prediabetic according to the NICE criteria but were not included in Trial 1839, as they did not meet the ADA criteria. With the exception of these patients, the population in the subgroup analyses otherwise complies fully with the NICE criteria.

Table 4.5: Prediabetes definitions

Definition	Source
HbA_{1c} 5.7−6.4% both inclusive; or FPG ≥5.6 mmol/L and ≤6.9 mmol/L; or 2-hour post-challenge (OGTT) PG ≥7.8 mmol/L and ≤11.0 mmol/L	ADA
HbA_{1c} 6.0−6.4% both inclusive; or FPG ≥5.5 mmol/L and ≤6.9 mmol/L	NICE
HbA_{1c} 5.7−6.4% both inclusive; or FPG ≥5.6 mmol/L and ≤6.9 mmol/L	Trial 1839

Source: CS, Table 7, page 45.
FPG = fasting plasma glucose; ADA = American Diabetes Association; NICE = National Institute for Health and Care Excellence.

ERG comment: Trial 1839 criteria differ from the NICE criteria in that patients with HbA_{1c} 5.7−6.0% are considered prediabetic in the trial but not by NICE; and patients with FPG ≥5.5 mmol/L and <5.6 mmol/L are considered prediabetic in the trial but not by NICE.

In the post-hoc subgroup analyses and in the economic model, the population was defined as adult patients with: 1) BMI ≥35kg/m^2; 2) prediabetes, defined as a HbA_{1c} level of 42–47 mmol/mol (6.0–6.4%) or a fasting plasma glucose (FPG) level of 5.5–6.9 mmol/L; and 3) high risk of cardiovascular

disease, defined as either of the following: (A) total cholesterol >5mmol/L, or (B) SBP >140 mmHg, or (C) HDL <1.0 mmol/L for men and <1.3 mmol/L for women.[16]

In addition, the company presented data for 'Early responders' which were defined as patients achieving at least 5% weight loss at week 16 (i.e. after four weeks titration and 12 weeks on the maintenance dose of the drug), Since the stopping rule was not applied in Trial 1839, this was the company's attempt to bring the data in line with the stopping rule as per the European license for liraglutide 3.0mg. Patients achieving less than 5% weight loss at 16-weeks in Trial 1839 should have stopped using liraglutide but all patients with prediabetes used liraglutide for 160 weeks (unless they discontinued for any reason during the trial; see Figure 4.2 of this report). It is not clear how this discrepancy influenced results, but it is possible that the effectiveness of liraglutide is overestimated in Trial 1839 (assuming that liraglutide is more effective than placebo, even in patients achieving less than 5% weight loss at 16-weeks). The ERG feels that the effectiveness of liraglutide should be based on all patients who receive liraglutide, including those who achieve less than 5% weight loss at 16-weeks. Therefore, the data for 'early responders' alone will be ignored in this report.

A summary of the objectives and associated statistical analysis methods adopted in Trial 1839 are presented in Table 4.6.

Table 4.6: Summary of statistical analyses - Trial 1839

Objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Primary To investigate the long-term efficacy of liraglutide 3.0mg in delaying the onset of type 2 diabetes in obese patients with prediabetes and in overweight patients with prediabetes and treated or untreated comorbidities (dyslipidaemia and/or hypertension) Secondary To investigate the long-term efficacy of liraglutide 3.0mg versus placebo on cardiovascular risk markers such as blood pressure, lipids, glucose parameters, UACR, as well as effects on quality of life and PROs.	<u>Planned analyses</u> The primary endpoint of the 3-year assessment of the trial was analysed using a Weibull model, using methods for the analysis of interval-censored time-to-event data. The Weibull model included treatment, sex, and baseline BMI stratum as fixed-effects, and baseline fasting glucose value as a covariate. Mean changes in continuous endpoints were analysed using an analysis of covariance and categorical changes for dichotomous endpoints using logistic regression. <u>Post-hoc analyses</u> Mean changes from baseline in continuous endpoints were for each visit estimated using analysis of covariance with treatment and sex as factors and baseline value as covariate. Glycaemic status was summarised for each visit.	Sample size of 2,400 patients assigned to receive liraglutide and 1,200 assigned to receive placebo was estimated to provide more than 99% power to detect a between group difference in the three co-primary efficacy endpoints of the main 56-week trial and also sufficient power in the primary endpoint of the 3-year assessment of the trial. The power for the first co-primary endpoint (weight change) was calculated using a two-sided Student's t-test at a 5% significance level. The power for the categorical co-primary endpoints was calculated using a two-sided chi-square test, also at a 5% significance level.	<u>Planned analyses</u> In the original analyses, missing values were imputed using LOCF for post-baseline measurements. <u>Post-hoc analyses</u> In the post-hoc analyses, missing values were imputed using: LOCF (used as the base case for the economic model), BOCF and MI-ME approach.

Source: CS, Table 8, pages 46-47.
BOCF = baseline observation carried forward; LOCF = last observation carried forward; MI-ME = multiple-imputation for measurement error; PRO = patient reported outcome; UACR = urinary albumin-to-creatinine ratio

4.2.5 Results

Only three of the outcomes specified in the NICE scope have been reported in the CS specifically for 'patients with a BMI ≥35 kg/m^2, prediabetes and high risk of CVD': weight loss, waist circumference, and incidence of type 2 diabetes (CS, Table 19 and 20, pages 69-70).[1] We asked the company to provide the other results as part of the clarification letter (Response to clarification, Question A16).[14]

The company used three different methods to deal with missing data (see Section 4.2.4 in this report). The European license for liraglutide 3.0mg for obesity is based on calculations where missing data is handled by LOCF. In addition, the results from the post-hoc analyses that are used for the base case in the economic modelling are also based on LOCF. Therefore, we will present results based on LOCF in this section (Table 4.7). Results from the post-hoc analyses using BOCF and MI-ME approaches are reported in Appendix 2 (See Tables A2.1 and A2.2 of this report) of this report.

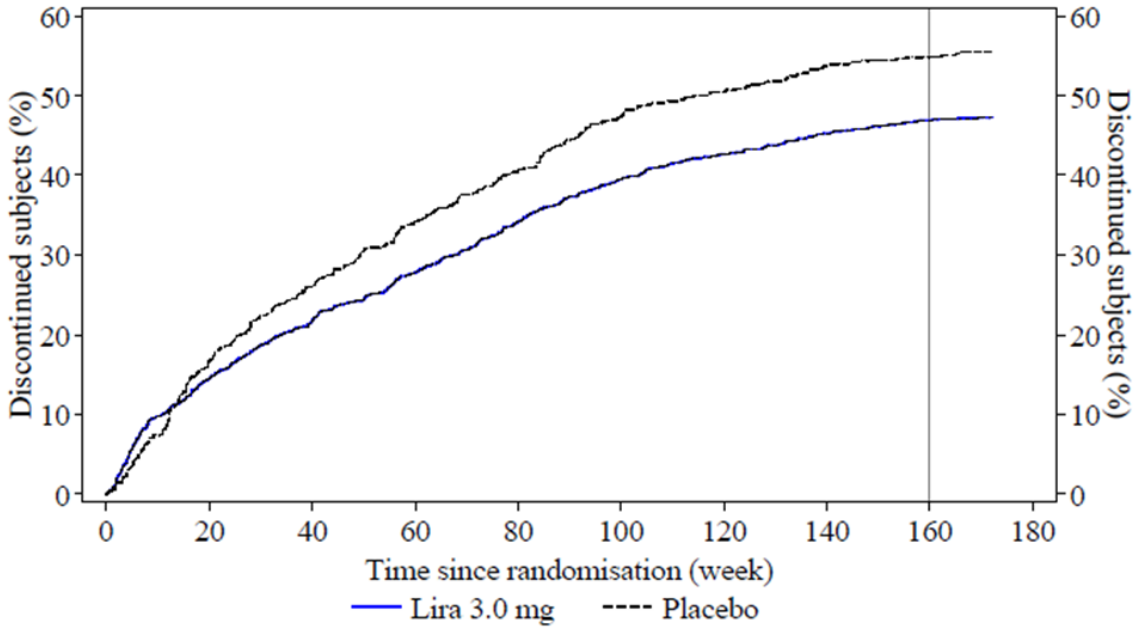
Table 4.7: Main outcomes as specified in the NICE scope for 'patients with a BMI ≥35 kg/m^2, prediabetes and high risk of CVD' (Change between baseline and week 160 (LOCF)).

Outcome	Liraglutide (n=530)	Placebo (n=270)	Estimated treatment difference, liraglutide vs. placebo (95% CI)†
Body weight-related outcomes, change from baseline to week 160 (LS Mean (SE))			
Body-mass index (%)	-5.97 (0.30)	-1.54 (0.41)	-4.43 [-5.43; -3.43]
Weight loss (%)	-5.92 (0.30)	-1.65 (0.41)	-4.28 [-5.28; -3.28]
Percentage body fat	Not assessed		
Waist circumference (cm)	-6.95 (0.35)	-3.44 (0.49)	-3.52 [-4.71; -2.33]
Other NICE specified outcomes			
Confirmed type 2 diabetes (n/N, %)	13/530 (2.4%)	22/270 (8.1%)	OR: 0.28 [0.14, 0.57]
Cardiovascular adverse events (week 162; n/N, %)	86/530 (16.2%)	46/270 (17.0%)	OR: 0.94 [0.64, 1.40]
Idiopathic intracranial hypertension	Not assessed		
Non-alcoholic fatty liver disease	Not assessed		
Mortality (0 to 162 weeks)	0/530 (0%)	1/270 (0.4%)	OR: 0.17 [0.01, 4.17]
Health-related quality of life – SF-36 General Health; Change from baseline at week 160 (N, LS Mean (SE))	2.67 (0.40)	1.05 (0.57)	1.61 [0.25; 2.97]
Discontinuations (n/N (%))			
Discontinued due to AE	62/530 (11.7%)	13/270 (4.8%)	OR: 2.62 [1.41, 4.85]
Discontinued due to AE after week 16	60/530 (11.3%)	13/270 (4.8%)	OR: 2.52 [1.36, 4.68]
Discontinued due to AE before week 16	2/530 (0.4)	0/270 (0%)	OR: 2.56 [0.12, 53.49]
Other outcomes used in the economic model			
5% responder rate (n/N, %)‡	314/530 (59.2%)	55/270 (20.4%)	OR: 5.68 [4.03, 8.01]
Other outcomes used in the economic model, change from baseline to week 160 (LS Mean (SE))			
SBP (reduction in mmHg)	-4.09 (0.51)	-1.09 (0.71)	-3.01 [-4.72; -1.29]
HDL cholesterol (reduction in mg/dl)	3.13 (0.42)	2.22 (0.60)	0.91 [-0.52; 2.34]
Total cholesterol (reduction in mg/dl)	-7.38 (1.31)	-4.15 (1.86)	-3.23 [-7.70; 1.24]
HbA_{1c}	-0.39 (0.01)	-0.13 (0.02)	-0.25 [-0.30; -0.21]

Source: CS, Table 20-21, page 70-71; Response to Clarification Letter, Appendix E (Supplementary data 1).
AE = Adverse event; HDL = High density lipoprotein; LOCF = last observation carried forward; OR = Odds Ratio; SBP = Systolic blood pressure; SE = standard error.
† Estimated treatment differences are from an analysis of covariance with data from the full-analysis set, with last-observation-carried-forward (LOCF) imputation. The full-analysis set comprised patients who underwent randomization, were exposed to at least one treatment dose, and had at least one assessment after baseline (69 patients were excluded from the full-analysis set: 61 owing to lack of an assessment and 8 owing to no exposure). The safety-analysis set included all patients who were randomly assigned to a study group and had exposure to a study drug.
‡ patients achieving at least 5% weight loss after 4 weeks titration and 12 weeks of treatment on the maintenance dose.

ERG comment: As can be seen from Table 4.7, results for 'patients with a BMI ≥35 kg/m^2, prediabetes and high risk of CVD' in terms of weight-related outcomes significantly favoured liraglutide when compared with placebo. Likewise, there were significantly fewer confirmed type 2 diabetes cases with liraglutide than with placebo. Cardiovascular adverse events, mortality and health-related quality of life (SF-36, General Health) showed no significant differences between groups. However, significantly more patients discontinued treatment due to adverse events in the liraglutide group than in the placebo group. Nearly all of these discontinuations happened after week 16. In the CS, the company presents time to discontinuation during the entire trial (0 to 172 weeks) for all reasons in the full trial population (see Figure 4.2).

Figure 4.2: Time to discontinuation during the entire trial (0 to 172 weeks) - all reasons (Trial 1839, full trial population)



Source: CS, Figure 4, page 49.

This figure shows that approximately 50% of patients in both arms have discontinued at week 172 and that discontinuations can happen during the full length of the trial (not only at 16 weeks).

Outcomes used in the economic model show significant effects favouring liraglutide for patients achieving at least 5% weight loss after 16 weeks, reduction in systolic blood pressure (SBP) and HbA_{1c}. Cholesterol results showed no significant differences between groups.

4.2.6 Adverse events

The index population included 530 patients who were randomised to the liraglutide 3.0mg group, while 270 patients were randomised to the placebo group. The full trial population included 2,481 patients who were randomised to the liraglutide 3.0mg group, while 1,242 patients were randomised to the placebo group. According to the CS, the reported proportion of patients in the broader population with treatment emergent adverse events (TEAEs) within the three-year assessment was higher within the liraglutide group (94.7%) than the placebo group (89.4%).[15]

The most common adverse events among the liraglutide 3.0mg group and the placebo group in the index population were related to gastrointestinal symptoms, in particular nausea, diarrhoea and constipation (Table 4.8). This was the same for the broad population (See Table A2.3 of this report). Of the serious adverse events (SAE) amongst the index population, for the liraglutide 3.0mg group the most common events were cholelithiasis and osteoarthritis (Table 4.8). Meanwhile, for the placebo group, the most common SAE were cholelithiasis and back pain (Table 4.8). This was the same for the broad population (See Table A2.3 in Appendix 2 of this report).

Comparing adverse events in the index population (Table 4.8 below) with AEs in the ITT population (Table A2.3 in Appendix 2), it seems that AEs are generally higher in the index population.

Table 4.8: Adverse events and serious adverse events (index population)*

Event	Liraglutide (n=530)			Placebo (n=270)		
	No. of patients (%)	No. of events	Event rate per 100 exposure-years	No. of patients (%)	No. of events	Event rate per 100 exposure-years
AEs in ≥5% of patients						
Nausea	219 (41.3)	359	30.7	39 (14.4)	48	9.1
Diarrhoea	140 (26.4)	228	19.5	33 (12.2)	41	7.8
Constipation	107 (20.2)	136	11.6	28 (10.4)	33	6.2
Vomiting	97 (18.3)	158	13.5	14 (5.2)	19	3.6
Dyspepsia	56 (10.6)	72	6.1	13 (4.8)	14	2.6
Upper abdominal pain	36 (6.8)	51	4.4	12 (4.4)	14	2.6
Abdominal pain	42 (7.9)	55	4.7	14 (5.2)	18	3.4
Nasopharyngitis	149 (28.1)	274	23.4	73 (27)	143	27.0
Upper respiratory tract infection	89 (16.8)	141	12.0	44 (16.3)	69	13.0
Sinusitis	48 (9.1)	69	5.9	22 (8.1)	40	7.6
Influenza	62 (11.7)	82	7.0	28 (10.4)	41	7.8
Headache	96 (18.1)	152	13.0	44 (16.3)	64	12.1
Dizziness	43 (8.1)	54	4.6	18 (6.7)	20	3.8
Decreased appetite	62 (11.7)	67	5.7	5 (1.9)	6	1.1
Back pain	78 (14.7)	119	10.2	40 (14.8)	49	9.3
Arthralgia	74 (14)	91	7.8	34 (12.6)	48	9.1
Fatigue	49 (9.2)	61	5.2	19 (7.0)	21	4.0

Event	Liraglutide (n=530)			Placebo (n=270)		
	No. of patients (%)	No. of events	Event rate per 100 exposure-years	No. of patients (%)	No. of events	Event rate per 100 exposure-years
Injection-site hematoma	32 (6.0)	35	3.0	14 (5.2)	14	2.6
SAEs in ≥0.2% of patients						
Cholelithiasis	8 (1.5)	8	0.7	3 (1.1)	3	0.6
Cholecystitis acute	3 (0.6)	3	0.3	0	-	-
Osteoarthritis	8 (1.5)	10	0.9	1 (0.4)	2	0.4
Intervertebral disc protrusion	NR	NR	NR	NR	NR	NR
Pancreatitis acute†	NR	NR	NR	NR	NR	NR
Cholecystitis	3 (0.6)	3	0.3	0	-	-
Breast cancer	2 (0.4)	2	0.2	0	-	-
Back pain	1 (0.2)	1	0.1	3 (1.1)	3	0.6
Uterine leiomyoma	2 (0.4)	2	0.2	0	-	-
Cellulitis	1 (0.2)	1	0.1	2 (0.7)	2	0.4
Gastroesophageal reflux disease	NR	NR	NR	NR	NR	NR
Bronchitis	NR	NR	NR	NR	NR	NR
Bladder prolapse	NR	NR	NR	NR	NR	NR
Chest pain	0	-	-	1 (0.4)	1	0.2

Source: Response to Clarification Letter, Appendix E (Supplementary data 1): Tables 65 and 68, pages 127 and 134.
AE = adverse events; NR = not reported; SAE = serious adverse events
* Treatment emergent adverse events experienced by ≥5% of patients with BMI >=35, High risk of Diabetes and high risk of CVD; From week 0 to week 162 in Trial 1839 (safety analysis set); and treatment emergent serious adverse events experienced by >=0.2% of patients with BMI >=35, High risk of Diabetes and high risk of CVD.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company only included data from a post-hoc subgroup analysis of Trial 1839, including 'Adult patients with: BMI ≥35 kg/m^2 with prediabetes, and high risk of cardiovascular disease'; the index population. In the clarification letter (Question A8), we asked the company whether any of the other liraglutide trials (other than Trial 1839) included patients in the index population (patients with BMI ≥35 kg/m^2, prediabetes and high risk of CVD), and to specify which trials, how many patients with these characteristics were included in each arm and to provide all relevant outcomes for these patients. The company responded that 'Trial 1839 is the most significant evidence base for our submission, as it contained 800 patients who met the criteria of BMI ≥35 kg/m^2, prediabetes and high risk of CVD. It also has the longest duration of all the trials and reflects standard practice in the UK. It thus forms the best available evidence base for decision making in the index population.'.[14]

In addition, the company stated that there are four other trials sponsored by Novo Nordisk, which investigated liraglutide 3.0mg and included patients in the index population: SCALE Sleep Apnoea

(Trial 3970), SCALE maintenance (Trial 1923), SCALE Intensive Behavioural Therapy (IBT) (Trial 4274) and the Phase 2 dose-finding trial (Trial 1807). The company provided the number of patients relating to the index population in each of these trails (see Table 4.9 below), but did not provide any outcome data from these trials.

Table 4.9: Patients fulfilling the index population criteria in four trials

Index population N / Total N	**Liraglutide 3.0mg**	**Placebo**
Phase II dose-finding study (Trial 1807)*	13/93	16/98
SCALE sleep apnoea (Trial 3970)	49/180	45/179
SCALE maintenance (Trial 1923)	51/212	48/210
SCALE IBT (Trial 4274)	38/142	26/140
Source: Response to Clarification, Question A8. Index population: BMI ≥35 kg/m^2, prediabetes and high risk of CVD In Trial 1807, 10/95 patients fulfilling the index population criteria were randomised to orlistat.		

ERG comment: As the company provided no data for these patients, the ERG was unable to compare results from these trials with the data from Trial 1839.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company did not perform any meta-analyses (See CS, Section B.2.8) or indirect comparisons (See CS, Section B.2.9).

4.5 Additional work on clinical effectiveness undertaken by the ERG

No further additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

Searches were well documented making them transparent and reproducible. A limited range of synonyms, the use of EMTREE indexing terms in MEDLINE searches, inappropriate study design filters and an English language limit mean that relevant records may have been missed by the searches.

The company submission focusses on a post-hoc analysis from one trial: the SCALE obesity and prediabetes trial (Trial 1839). Trial 1839 was a randomised, double-blind (investigators and patients were blinded during the full trial; the sponsors, Novo Nordisk, were unblinded after one year), placebo-controlled, parallel group, multicentre, multinational trial in patients who were obese (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with comorbidities. Study participants were randomised two to one to receive liraglutide 3.0mg (n=2,487) or placebo (n=1,244) as an adjunct to diet and exercise and stratified according to prediabetes status (according to American Diabetes Association [ADA] 2010 criteria) at screening. The trial was conducted in 27 countries in Europe, North America, South America, Asia, Africa, and Australia. In the UK, 112 randomised patients participated at eight sites. The primary endpoint in the three-year assessment of the trial was: 'Proportion of patients with onset of type 2 diabetes at week 160 among patients with prediabetes at baseline - evaluated as the time to onset of type 2 diabetes.'[1]

The population in the CS is limited to 'Adult patients with: BMI ≥35 kg/m^2 with prediabetes, and high risk of cardiovascular disease'. Therefore, the company performed a post-hoc analysis of Trial 1839, including 800 patients (liraglutide: n=530, placebo: n=270). Results in terms of weight-related outcomes significantly favoured liraglutide when compared with placebo (BMI (percentage change from baseline to 160 weeks, LOCF): estimated treatment difference (ETD) = -4.43 (95% CI: -5.43 to -3.43); weight loss (%): ETD = -4.28 (-5.28 to -3.28); waist circumference (cm): ETD = -3.52 (-4.71 to

-2.33)). Likewise, there were significantly fewer confirmed type 2 diabetes cases with liraglutide than with placebo (OR = 0.28 (0.14 to 0.57)). Cardiovascular adverse events, mortality and health-related quality of life (SF-36, General Health) showed no significant differences between groups (OR = 0.94 (0.64 to 1.40), OR = 0.17 (0.01 to 4.17) and ETD = 1.61 (0.25 to 2.97), respectively). However, significantly more patients discontinued treatment due to adverse events in the liraglutide group than in the placebo group (OR = 2.62 (1.41 to 4.85)). Nearly all of these discontinuations happened after week 16.

Outcomes used in the economic model showed significant effects favouring liraglutide for the achievement of at least 5% weight loss after 16 weeks (OR = 5.68 (4.03 to 8.01), reduction in systolic blood pressure (SBP) (ETD = -3.01 (-4.72 to -1.29) and HbA_{1c} (ETD = -0.25 (-0.30 to -0.21)). Cholesterol results showed no significant differences between groups (Total: ETD = 0.91 (-0.52 to 2.34) and HDL: ETD = -3.23 (-7.70 to 1.24)).

The most frequent adverse events in the index population were nausea (41% for liraglutide 3.0mg versus 14% for placebo), nasopharyngitis (28% vs. 27%), diarrhoea (26% vs. 12%), constipation (20% vs. 10%), vomiting (18% vs. 5%), headache (18% vs. 16%) and upper respiratory tract infection (17% vs. 16%). The company did not provide a statistical comparative analysis of this data, but numerically, the frequency of nausea, diarrhoea, constipation and vomiting appeared higher for liraglutide 3.0mg versus placebo.

The population in the CS is not the same as the population in the NICE final scope. The company limited the population to 'BMI ≥35 kg/m^2, prediabetes and high risk of CVD', 'because this subpopulation of patients would benefit the most from liraglutide 3.0mg in UK clinical practice, and therefore optimises cost effectiveness' (CS, Table 1, page 12).[1] As a consequence, the company used data from a post-hoc analysis of Trial 1839 including only a subgroup of patients for this appraisal.

The intervention is in line with the scope. However, according to the license for liraglutide 3.0mg, liraglutide should be discontinued after 12 weeks on the maintenance dose of 3.0mg/day if patients have not lost at least 5% of their initial body weight. However, this stopping rule was not applied in Trial 1839. It is not clear how this discrepancy influenced results.

The description of the comparators in the NICE scope is as follows: Standard management without liraglutide (including a reduced calorie diet and increased physical activity), orlistat (prescription dose), and bariatric surgery. The company claims that standard management without pharmacotherapy is the only relevant comparator in this submission. In addition, the company states that liraglutide 3.0mg is intended for use in patients who have been referred to a specialist tier 3 service where conventional treatments such as orlistat have been unsuccessful earlier in the clinical pathway. However, data on previous treatment with orlistat, or any other anti-obesity pharmacotherapy, was not collected in the Trial 1839. Therefore, no evidence for this specific population (those who have failed on orlistat) has been presented in the CS. Further, bariatric surgery would almost certainly represent an appropriate comparator for some patients with BMI ≥35 kg/m^2 and other significant disease (i.e. the population presented in the CS) who have been or will be referred to a specialist tier 3 service (see NICE Clinical Guideline 189: Obesity: identification, assessment and management[4]).

Trial 1839 is a good quality randomised controlled trial. The ERG has no concerns with the trial design and the trial methods. However, the company's choice to focus on a post-hoc subgroup analysis is a concern as it means that the CS is based on a smaller sample of only 35% of the whole trial population. This means that the analyses no longer have sufficient statistical power to detect statistically significant

differences between the treatment groups and the two groups may not be comparable at baseline as the randomisation was not stratified for this particular subgroup.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

Appendix G of the CS details systematic searches of the literature used to identify cost effectiveness costs and healthcare resource studies. Searches were limited to studies published in English, with a date limit of 15 years. A summary of the sources searched is provided in Table 5.1.

Table 5.1: Data sources for the cost effectiveness systematic review (as reported in CS)

	Resource*	Host/Source	Date Range	Date searched
Electronic Databases	Medline	Ovid	2003-2018 Week 41	11/10/18
	Medline In-Process			
	Embase			
	EconLit		1886-Sept 2018	
	NHS EED	EBM Reviews via Ovid	1st Quarter 2016	
Conference Proceedings	ISPOR	Ovid	Not reported	

ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NHS EED = NHS Economic Evaluation Database.
*Searches of the following databases were also conducted, but only reported in the Company's response to clarification questions: EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews - Health Technology Assessment 4th Quarter 2016.

Appendix H of the CS details systematic searches of the literature used to identify health-related quality of life data reported directly for adult obese patients. Section H.1.1 reports that searches were limited to studies published in English with a date limit of 10 years, however a 15 year date range was included in the search strategies. A summary of the sources searched is provided in Table 5.2.

Table 5.2: Data sources for the HRQoL systematic review (as reported in CS)

	Resource	Host/Source	Date Range	Date searched*
Electronic Databases	Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Medline Daily, Medline and Versions	Ovid SP	2003-23/10/18	24/10/18
	Embase			
	EconLit		2003-18/10/18	
	NHS EED			

	DARE	EBM Reviews via Ovid	1st Quarter 2016	
Other resources	HERC	Not stated	Not stated	
	CEA Registry	Website	Not stated	

CEA = Cost effectiveness analysis; DARE = Database of Abstracts of Reviews of Effects; HERC = Health Economic Research Centre; NHS EED = NHS Economic Evaluation Database.
* The date reported for these searches in the Company's response to clarification questions was 10/09/18, however as the date range searched was given as 2003-23/10/18, the ERG presumes this is incorrect.

ERG comments:

- Similar searches appear to have been conducted across the MEDLINE and Embase databases for both cost effectiveness and HRQoL searches. Although mapping between indexing terms does take place within OvidSP, the extensive use of EMTREE indexing within the searches may mean that relevant MeSH terms were omitted. Potentially relevant records in MEDLINE may therefore not have been retrieved.
- The cost and HRQoL study design filters used are extensive, containing a wide range of search terms, but the MEDLINE strategy contains EMTREE rather than MeSH subject indexing terms. The cost effectiveness MEDLINE strategy, for example, shows many lines with 0 hits for EMTREE terms, but the MeSH term 'Costs and Cost Analysis/' has not been included.
- All facets of the searches were limited, with few synonyms being employed. Additional search terms (free-text and subject indexing terms) could have been included to greatly increase the sensitivity of the strategies.
- Use of search terms across strategies was inconsistent. For example, a broader range of synonyms for obesity was included in the cost effectiveness Econlit and NHS EED strategies, but omitted from the other searches. A limited number of terms for diet and exercise were included in the MEDLINE and Embase strategies, but omitted from the Econlit and NHS EED cost effectiveness searches.
- Limiting the MEDLINE and Embase searches to English language only may have introduced language bias. Current best practice states that 'Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication'.[26]
- Limited additional searching was conducted, and this was restricted to a search for ISPOR conference proceedings within Ovid for the cost-effectiveness searches, and to HERC and the CEA Registry for HRQoL data. Other useful sources of information may have included relevant organisations, company databases and web resources.
- Best practice outlined in the Cochrane handbook states that 'Reference lists in other reviews, guidelines, included (and excluded) studies and other related articles should be searched for additional studies'.[27] No reference checking was reported for this SLR, however the Company's response to clarification questions stated that 'Two additional records were identified through review of references of systematic literature review publications'. [14]

5.1.2 Inclusion/exclusion criteria used in the study selection

Two systematic literature reviews (SLRs) were performed with the objectives to identify and select relevant 1) cost effectiveness analysis (CEA) studies and costs and healthcare resource use studies in obesity (CS Appendix G[36]), 2) health-related quality of life (HRQoL) evidence for adult obese patients (CS Appendix H[36]).

In- and exclusion criteria for the review on cost effectiveness, and costs and resource use studies are presented in Table 5.3.

Table 5.3: Eligibility criteria for the systematic literature reviews

PICOS	Inclusion criteria	Exclusion criteria
Patient population	Adult patients with BMI ≥35 kg/m^2	Below 18 years of age or a population that does not include the target patient group or a population that overlaps but does not provide the results as a subgroup specifically for the target population of interest.
Intervention	Either one: - Liraglutide injection 3.0mg - Orlistat - Usual care (diet and exercise, which may or may not include behaviour modification component)	
Comparator	Either one: - Liraglutide injection 3.0mg - Orlistat - Usual care (diet and exercise, which may or may not include behaviour modification component)	
Outcomes(s) 1 (Published economic evaluations)	- Incremental cost effectiveness ratios - Health benefits (total and incremental)	
Outcomes(s) 2 (Utility studies)	Reported utility (to include (dis)utility of obesity by means of any validated preference-based questionnaire)	
Outcomes(s) 3 (Cost/resource use studies)	- Health state costs (total and incremental) - Medical costs itemised per cost component (direct, indirect; total and incremental) - Resource use associated with treatment of obesity and related comorbidities	

PICOS	Inclusion criteria	Exclusion criteria
	like diabetes, CV disorders etc. - Societal impact (direct and indirect non-medical costs)	
Study design 1 (Cost effectiveness analysis studies)	- Cost benefit analysis - Cost effectiveness analysis - Cost minimisation analysis - Cost utility analysis - Cost consequence analysis - SLRs of economic evaluations	- Non-systematic reviews - Letters - Comment articles
Study design 2 (Utility studies)	- Utility validation or elicitation exercises, including mapping algorithms - Economic evaluations using utility measures gathered during the studies - Other studies using validated preference-based questionnaires	- Non-systematic reviews, letters, comment or editorials - Studies not reporting adequate methodology or extractable data
Study design 3 (Cost/resource use studies)	- Costing analysis - Cost of illness study - Budget impact analysis - Resource use study	- Non-systematic reviews - Letters - Comment articles
Source: CS Appendix G[36] BMI = body-mass-index; CV = cardiovascular; SLRs = systematic literature reviews		

ERG comment: In general the ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies, however the English language restriction, the time restriction (15 year restriction for cost effectiveness and 10 year restriction for utility studies) as well as the UK restriction (unclear how this is implemented) might have resulted in relevant references being missed.

5.1.3 Included/excluded studies in the cost effectiveness review

The cost effectiveness and cost and resource use SLR yielded five full publications and one conference abstract on cost effectiveness of long-term consequences of type 2 diabetes (T2DM) and cardiovascular disease (CVD) in obese patients from the United Kingdom (UK) NHS perspective. Five of these cost effectiveness analyses included some modelling methods. The SLR also yielded three studies on healthcare cost and resource use in the UK. The HRQoL SLR yielded 26 unique HRQoL studies, of which one reported EuroQoL-5-Dimensions (EQ-5D) utilities.

ERG comment: The rationales for excluding CE studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

5.1.4 Conclusions of the cost effectiveness review

None of the HRQoL studies were deemed consistent with the NICE reference case and appropriate to inform the decision problem as the patient population was not aligned with the target population, neither were the identified resource use and cost studies found informative for the decision problem.

ERG comment: The ERG is concerned that relevant references were potentially missed by the SLRs (see Section 5.1.2) and noticed a lack of clarity regarding the identification of cost and resource use and HRQoL evidence used in the company submission (see also the literature referred to in Sections 5.2.8 and 5.2.9). The company considered none of the publications identified in the SLR appropriate for the CEA model but used a number of publications in their economic model. It is thus unclear how this evidence used was identified and the ERG is concerned that essential publications, such as the publications informing most utilities and disutilities,[20, 37] were missed by the SLRs.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.4: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	Markov cohort state-transition model	In line with previous models build for diabetes or CVD	Section B.3.2.3
States and events	Prediabetes, normal glucose tolerance, T2DM; First complication: post ACS, post stroke; separate health states with and without T2DM Further complications: post ACS and stroke, separate health states with and without T2DM; and death. A scenario analysis modelled cancer as a complication using additional health states.	The health states/events to be modelled were chosen as they were a known complication of obesity, information was available to model the relation between BMI and the complication, and the complication was expected to significantly affect total costs of care and quality of life.	Sections B.3.2 and B.3.2.3
Comparators	Liraglutide 3.0mg in combination with diet and exercise, compared to diet and exercise without pharmacological treatment. A stopping rule applied to treatment with liraglutide 3.0mg, non-responders (less than 5% weight loss after 12 weeks of treatment) discontinued treatment while responders were assumed to maintain treatment for two years.	Consistent with UK clinical practice and the decision problem, and supported by evidence from the obesity and prediabetes study (Trial 1839)	Section B.3.2.4

	Approach	Source/Justification	Signpost (location in CS)
Population	Patients with a BMI ≥35kg/m^2, prediabetes, high risk of cardiovascular disease	Reflective of a subgroup of the obesity and prediabetes study (Trial 1839). The population is a subgroup of the population described in the NICE scope, it was selected due to the high CV risk which determines a large expected benefit from weight reduction.	Section B.3.2.2 and B.1.1.
Treatment effectiveness	The clinical effectiveness was modelled through treatment-dependent changes in BMI and cardio-metabolic risk factors, (SBP, HDL cholesterol, and total cholesterol), which were used in risk models to calculate transition probabilities. Moreover, treatment-specific probabilities of temporarily reverting prediabetes to a normal glucose tolerance state were used.	Changes in BMI and cardio-metabolic risk factors, (SBP, HDL cholesterol, and total cholesterol) were informed by Trial 1839. The risk models used to predict events were the QDiabetes-2018 model C[38] for the onset of type 2 diabetes, the QRisk3 equation,[39] the Framingham Recurring Coronary Heart Disease risk model [40] and the UKPDS82 risk model[41] for cardiovascular events.	Sections B.3.2.3, B.3.3.2 and B.3.3.4
Adverse events	Adverse events (AEs) were not considered in this analysis	AEs in Trial 1839 were transient and mild in nature, thus having a minimal impact	Section B.3.4.4
Health related QoL	'Prediabetes' and 'Normal glucose tolerance' health state EQ-5D estimates were calculated independently for each treatment arm in each cycle based on BMI and age. All other health state utilities were computed based on the BMI- and age-dependent utilities and one or more complication-specific disutility. Short term utility decrements associated with acute complication events were applied in the cycle in which the event occurred.	The BMI- and age-dependent EQ-5D estimates used were obtained from Søltoft et al., 2009.[20] Complication-specific disutilities were obtained from Søltoft et al., 2009[20] and Sullivan et al., 2011.[37] The one-off disutilities for acute events were obtained from Sullivan et al., 2011,[37] Campbell et al., 2010.,[42] Jansen and Szende,[43] and Søltoft et al., 2009.[20]	Section B.3.4
Resource utilisation and costs	The costs included in the model were acquisition and administration costs of obesity treatment, pharmacy costs (blood pressure and T2DM medications) and	Resource use was largely informed from the literature. Unit prices were based on the National Health Service (NHS) reference prices, British National Formulary	Section B.3.5

	Approach	Source/Justification	Signpost (location in CS)
	long-term and acute costs of obesity-related complications.	(BNF), the Monthly Index of Medical Specialities (MIMS) and literature sources.	
Discount rates	Discount of 3.5% for utilities and costs.	As per NICE reference case	Section B.3.2.1
Subgroups	No subgroup analysis was performed	As per NICE final scope	Section B.3.2.2
Sensitivity analysis	Both DSA and PSA were performed as well as scenario analyses	As per NICE reference case	Sections B.3.8
ACS = acute coronary syndrome; BMI = body-mass-index; CV = cardiovascular; CVD = cardiovascular disease = DSA = deterministic sensitivity analysis; EQ-5D = EuroQoL-5-Dimensions questionnaire; HDL = High density lipoprotein; NICE; National Institute for Health and Care Excellence; PSA = probabilistic sensitivity analysis; SBP = Systolic blood pressure; T2DM = type 2 diabetes; UK = United Kingdom			

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.5: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Partly	The population is a subgroup of the population described in the NICE scope.
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	Partly	Relevant comparators are missing: orlistat and bariatric surgery
Type of economic evaluation	Cost utility analysis	Yes	As per NICE reference case
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	As per NICE reference case
Perspective on outcomes	All health effects on individuals	Yes	As per NICE reference case
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	As per NICE reference case
Synthesis of evidence in outcomes	Systematic review (SLR)	Yes	As per NICE reference case
Measure of health effects	Quality adjusted life years (QALYs)	Yes	As per NICE reference case

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Yes	As per NICE reference case
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Yes	As per NICE reference case
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	As per NICE reference case
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	As per NICE reference case
Sensitivity analysis	Probabilistic modelling	Yes	As per NICE reference case
NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review			

5.2.2 Model structure

The company developed a cohort state transition model using Microsoft Excel®. In the base-case analysis, the model consisted of 10 health states, i.e. normal glucose tolerance, prediabetes, type 2 diabetes (T2DM), post-acute coronary syndrome (ACS) with normal glucose tolerance, post-stroke with normal glucose tolerance, post stroke & post ACS with normal glucose tolerance, post ACS with T2DM, post-stroke with T2DM, post stroke & post ACS with T2DM, and death (Figure 5.1). In scenario analyses, cancer was added as complication in patients with normal glucose tolerance or T2DM, which lead to eight additional health states.

Patients entered the model with prediabetes. In the next cycle, a proportion of the cohort could either revert to a normal glucose tolerance state, remain in the prediabetes health state, develop T2DM, or experience a fatal or non-fatal cardiovascular (CV) event which meant they moved to post ACS or post stroke (with or without T2DM), or died. Prediabetes patients experiencing ACS or a stroke could only move to post ACS plus T2DM or a post stroke plus T2DM (i.e. once prediabetes patients developed a CV event, they were assumed to develop T2DM as well). Within each alive health state, patients were at risk of sleep apnoea (defined in relation to the level of BMI in cycle), a knee replacement surgery, or (from year 2 onwards and if BMI $\geq$35 kg/m^2 with maximum age of 57 year) bariatric surgery independent of the treatment received. Mortality in the model could be attributable to events (i.e., due to bariatric surgery, myocardial infarction (MI), angina, stroke, or knee replacement) and health state specific mortality (i.e., background mortality and excess mortality due to the presence of T2DM and/or CV-events).

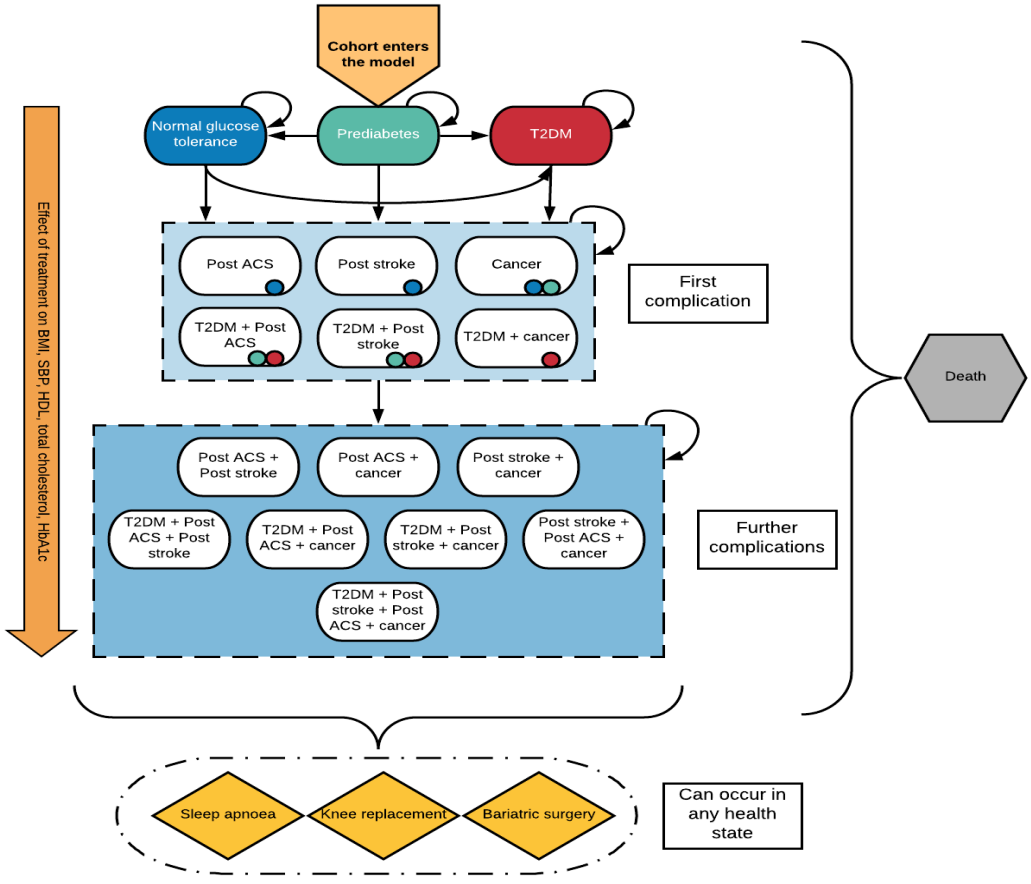
The clinical effectiveness of treatment was introduced in the model through changes in BMI (determined through percentage reduction in weight; assuming an average height of 1.66m in the cohort), SBP (reduction in mmHg per cycle), total cholesterol (reduction in mg/dl per cycle), and HDL

cholesterol (reduction in mg/dl per cycle). These intermediate endpoints were used to calculate transition probabilities, guiding the progression of the cohort through the model (e.g., from prediabetes to T2DM) and to estimate the incidence of fatal and non-fatal events (e.g. CV events).

In agreement with the EMA license, treatment was assumed to be discontinued after 12 weeks on the 3.0mg daily dose if patients did not respond to treatment (i.e. have not lost at least 5% of their initial body weight). Hence, non-responders to liraglutide discontinued treatment after the first cycle (three months). Non-responders were assumed to remain on diet and exercise. The company assumed the effectiveness of diet and exercise, i.e. placebo arm in Trial 1839 for liraglutide non-responders. Responders remained on liraglutide treatment for two years (or until death) after which a treatment effect waning period of three years was assumed.

A cycle length of three months was defined for the first year, to allow for incorporation of the stopping rule in liraglutide 3.0mg and to incorporate efficacy evaluation endpoints at week 28 and week 56 in Trial 1839. Annual cycles were implemented after the first year and were half cycle corrected upon a total time horizon of 40 years.

Figure 5.1 Model structure



Source: Based on Figure 15 of the CS [1]
ACS = acute coronary syndrome; HDL = high-density lipoprotein; T2DM = type 2 diabetes.
Note: coloured dots in health states encompassing first complications denote possible originating health states (e.g. green colour-coding denotes patients with prediabetes); cancer state was not included in the base-case analysis, only in scenario analyses.

ERG comment: The main concerns of the ERG relate to: a) the assumption that prediabetic patients automatically develop T2DM after experiencing a CV event and; b) the use of a cohort state transition model.

a) As stated in the CS, in the company's base case analysis, T2DM occurs when prediabetic or normal glucose tolerant patients develop T2DM, as well as when prediabetic patients experience a CV event. The ERG is concerned that this assumption overestimates the rate of development of T2DM, and hence the treatment effect for liraglutide 3.0mg. In response to clarification question B5, the company provided a scenario assuming that prediabetic patients do not automatically develop T2DM after ACS or stroke, which increased the ICER substantially to £26,026 per QALY gained. The ERG incorporated this scenario provided by the company, in the ERG analyses. The ERG acknowledges that this scenario is likely to underestimate the T2DM incidence as well as the treatment effect for liraglutide 3.0mg.
b) The use of a cohort state transition model might be debatable as previous assessments (e.g. naltrexone–bupropion for managing overweight and obesity; TA494) used individual patient models. According to NICE DSU Technical support document 15, individual patient models are indicated amongst others to reflect patient heterogeneity and non-linear relations. However, according the company, an individual patient model was not deemed necessary as the target population is assumed to be relatively homogenous. Although individual patient models can be preferred in case of relatively limited heterogeneity (to model non-linear relations), the ERG believes that it was reasonable to use a cohort state transition model.

5.2.3 Population

Liraglutide has a marketing authorisation in the UK as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial BMI of ≥30 kg/m² (obese), or ≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or T2DM), hypertension, dyslipidaemia or obstructive sleep apnoea.[16]

The target population for the economic evaluation comprised of a subgroup of the licensed indication based on a post-hoc analysis of the Trial 1839 study population,[1], referred to as the index population and defined as adult patients with: 1) BMI ≥35kg/m^2; 2) prediabetes, defined as a HbA_{1c} level of 42–47 mmol/mol (6.0–6.4%) or a fasting plasma glucose (FPG) level of 5.5–6.9 mmol/L; and 3) high risk of cardiovascular disease, defined as either of the following: (A) total cholesterol >5mmol/L, or (B) SBP >140 mmHg, or (C) HDL <1.0 mmol/L for men and <1.3 mmol/L for women.[16] This is in line with the final scope issued by NICE and the EMA licence although both documents consider a broader population (i.e. '≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity' not further specified).

The characteristics of the model population at baseline were sourced from a post-hoc analysis of a subset of patients of Trial 1839 (see Table 5.6).

Table 5.6: Key baseline patient characteristics as applied in the CS base-case model based on patient-level data of Trial 1839

Characteristic	Model input Mean (SD)	Input in UK units, where applicable
Age (years)	48.2 (11.2)	NA
BMI (kg/m^2)	41.7 (5.3)	
Height (m)	1.66 (0.1)	

Characteristic	Model input Mean (SD)	Input in UK units, where applicable
Systolic blood pressure (mmHg)	127.2 (13.6)	
Total cholesterol (mg/dL)	200.6 (37.3)	5.2 mmol/mol
HDL cholesterol (mg/dL)	48.7 (13.2)	1.3 mmol/mol
Triglyceride level ≥150 mg/dL (%)	46.0 (NR)	NA
Smokers (%)	15.0 (NR)	
Females (%)	75.8 (NR)	
Patients on lipid lowering drugs (%)	17.0 (NR)	
Patients on antihypertensive medication (%)	45.3 (NR)	
Patients with prediabetes (%)	100.0 (NR)	
Source: Based on Table 27 of the CS[1]; BMI = body-mass-index		

ERG comment: The main concerns of the ERG relate to: a) the extent to which the population characteristics are representative for the UK population, b) the fact that effectiveness data does not match the index population.

a) Given that the evidence used in the model was not solely based on results from the UK population, the ERG asked the company to justify whether the trial population was representative for the UK population. The justification provided on this issue by the company in response to clarification question B3 seems reasonable to the ERG supporting the representativeness of the baseline patient characteristics used in the model for the UK population.

b) The ERG asked the company to clarify the precise nature of the index population (i.e. is it only those with a BMI ≥35 kg/m^2, prediabetes and high risk of CVD or is it a smaller subgroup of patients with a BMI ≥35 kg/m^2, prediabetes and high risk of CVD and who have also failed on orlistat and/or are unwilling/unable to undergo bariatric surgery). In response to clarification question A5 (and B2), the company stated that the index population of the CS is likely to have failed orlistat or be unwilling to take it. However, having failed orlistat or be unwilling to take is not necessarily in line with the population in Trial 1839. Hence, it is unclear to the ERG whether the results of the trial can be generalised beyond this population (e.g., to patients who failed or are unwilling to take orlistat).

5.2.4 Interventions and comparators

The company stated that the treatment setting for these patients would be a specialist tier 3 weight assessment and management clinic service, offering lifestyle modification advice, pharmacotherapy, psychological treatment as well as assessing patients for bariatric surgery. This is in line with the final scope issued by NICE (although the tier is not explicitly specified in the scoping document).[16]

The intervention consists of daily injection of liraglutide 3.0mg by the patient in combination with diet and exercise and has a starting titration dose of 0.6mg daily which is escalated to the recommended maintenance dose of 3.0mg daily. The titration dose should be escalated to the 3.0mg maintenance dose in increments of 0.6mg with at least one-week intervals to improve gastrointestinal tolerability. This is in line with the final scope issued by NICE and the EMA licence. [1, 16, 44] Treatment should be discontinued after 12 weeks on the 3.0mg daily dose if patients have not lost at least 5% of their initial body weight. In the CS, the base-case analysis utilises the maintenance dose of 3.0mg daily and only included the costs of titration in the first cycle (i.e. the treatment costs of four weeks titration of

liraglutide and 12 weeks maintenance dose). Treatment period for responders was assumed to be two years.[1] The company stated that this assumption was in line with the demonstrated maintenance of the treatment benefit in Trial 1839 and was also validated by clinical experts in the field of obesity [1, 29].

In the CS, liraglutide 3.0mg daily with diet and exercise was compared to diet and exercise alone. Diet and exercise was assumed to be consistent with the current standard of care in specialist tier 3 services which included: dietary and physical activity counselling (either group or individual sessions); hypocaloric diet (e.g. reduced calorie intake by 500 calories per day); and increased physical activity.[1]

The company assumed that, although orlistat is issued in the final scope by NICE as a relevant comparator, it was deemed not relevant for the submission as it is recommended earlier in the treatment pathway (tier 2). Furthermore, bariatric surgery was included as a downstream event only (and not as a direct comparator) as the company stated that liraglutide 3.0mg would not be a direct replacement for bariatric surgery but it could be suitable for a group of patients who are unwilling or unable to undergo surgery. The company emphasised that bariatric surgery is highly effective but only a small proportion (assumed to be 1.15% based on annual incidence of bariatric surgery in the UK) receives surgery.[1]

ERG comment: The main concerns of the ERG relate to exclusion of orlistat and bariatric surgery as direct comparators in the model. Both the exclusion of orlistat and bariatric surgery as direct comparators in the CS are not in line with the final scope issued by NICE.[16]

In response to clarification question A5 and B2 the company argues that orlistat was not considered a relevant comparator as orlistat is currently recommended in primary care in a much wider patient population than the one defined in the CS. Furthermore, the company refers to a previous NICE technology appraisal in which the appraisal committee decided not to consider orlistat as a relevant comparator. Regarding bariatric surgery, the company states that they 'do not anticipate that liraglutide 3.0mg will be a direct replacement for bariatric surgery. Bariatric surgery has already been demonstrated as a cost-effective treatment option for a selected group of patients'.[1] Nevertheless, the ERG believes that orlistat and bariatric surgery could be relevant comparators in some patients eligible for liraglutide (see Section 3.3) and for consistency with the final scope both should have been incorporated. Indeed, if they are deemed to be not relevant then the index population of the decision problem needs to recognise this explicitly, e.g. by stating that it only applies to patients who failed or are unwilling to take orlistat.

5.2.5 Perspective, time horizon and discounting

The analysis takes an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits, with a 40-year time horizon (cohort starting age: 48 year).[1]

ERG comment: Although the ERG prefers a lifetime time horizon, the ERG agrees that a 40-year time horizon is likely to have captured the main part of the difference in costs and effects between the treatment options, and that, in this case, a time horizon shorter than lifetime is likely to be conservative. However, as also stated in the CS, approximately 30% of patients are still alive in the model at the end of the time horizon.[1] The model did not allow the ERG to increase the time horizon but the impact of this shorter time horizon (40 years as opposed to life time) is likely to be conservative given that a longer time horizon would likely increase the incremental QALYs and most of the costs occur in the first cycles of the model.

5.2.6 Treatment effectiveness and extrapolation

Transitions between health states were based on the estimation of T2DM status, CV events (primary and secondary) using risk models as well as death probabilities (probabilities for cancer were only added

in scenario analyses). Moreover, a once-only transition was used to incorporate the proportion of patients reversing from prediabetes to normal glucose tolerance based on Trial 1839 data. Probabilities calculated for knee replacement, sleep apnoea and bariatric surgery were incorporated (e.g. through the impact of bariatric surgery on BMI and by impacting mortality). The relative treatment effectiveness was estimated through changes in the BMI, SBP, total and HDL cholesterol parameters in the risk models. In contrast, HbA_{1c} was not a treatment dependent parameter as it is assumed only to be dependent on T2DM status.

This section starts with an overview of the different risk models used to estimate the abovementioned transition probabilities. Subsequently, parameters used as input parameters for these risk models (particularly those used to estimate relative treatment effectiveness) are described.

This section focussed on treatment effectiveness (parameters) as implemented in the CS base-case, thus the estimation of probabilities related to cancer (scenario analysis only) is not considered. See CS section B.3.3.4 for more details regarding the estimation of cancer probabilities.

Estimation of responder status

Responder status (≥5% weight loss versus baseline) after 12 weeks of treatment with liraglutide 3.0mg, based on Trial 1839, was estimated to be 67% (314/469). This calculation was based on the complete cases, assuming that if the response status is missing, it is missing completely at random. As mentioned in Section 5.2.2, liraglutide 3.0mg treatment was assumed to be discontinued after 12 weeks for non-responders while responders remained on liraglutide treatment for two years (or until death). For liraglutide non-responders, effectiveness was assumed to be equal to that for diet and exercise (from the start of the model), while liraglutide 3.0mg effectiveness (estimated based on the responder subgroup) was assumed for responders.

Estimation of T2DM status

Patients have prediabetes at the start of the model and can subsequently develop type T2DM, revert to normal glucose tolerance or remain prediabetic. A once-only transition was used to incorporate the proportion of patients reversing from prediabetes to normal glucose tolerance in the model. This was based on the week 56 proportion in Trial 1839 (82.8% and 40.7% for liraglutide 3.0mg (responders) and diet and exercise (responders and non-responders combined) respectively) and applied in cycle 2 (month 3 to 6). Patients that reversed from prediabetes to normal glucose tolerance were assumed to transit back to prediabetes once their weight returns to the baseline value.

Onset of T2DM (from either normal glucose tolerance or prediabetes) was estimated using the QDiabetes-2018 C risk model.[38] This model was preferred by the company (over for instance the Framingham Offspring risk model[45]) as it stated that this was the most validated risk score in European populations. The increased risk for prediabetes patients (compared to normal glucose tolerance patients) was incorporated by assuming a HbA_{1c} of 42 mmol/mol for prediabetes patients and 35 mmol/mol for normal glucose tolerance patients. In addition, for prediabetes patients, onset of T2DM was assumed whenever a CV event occurred (for normal glucose tolerance patients this was not assumed).

Estimation of primary and secondary CV events

CV events considered in the model were: MI, angina and stroke (including Transient Ischemic Attack (TIA)). After occurrence of a CV event (estimated using a composite endpoint), the company assumed a fixed distribution for the different types of CV events (i.e. MI, angina, stroke, TIA), see Table 5.7.

The QRisk3 model[39] (calibrated) was used to predict primary CV events for normal glucose tolerance and prediabetes patients while the UKPDS82 risk model[41] (outcome model 2; adjusted to include

angina) was used for T2DM patients. The company stated that risk models to estimate the probability of primary CV events were selected based on their applicability and relevance to the UK population, as well as precedence to whether BMI and other treatment-effect variables were indicated as predictors of risk.

Probabilities for secondary CV events were estimated using the Framingham Recurring Coronary Heart Disease risk model[40] (adjusted to include stroke) for normal glucose patients while the abovementioned UKPDS82 risk model[41] (outcome model 2; adjusted to include angina) was used for T2DM patients. For prediabetes patients the same risk was assumed as for T2DM patients due to a lack of data.

Table 5.7: Distribution of CV events

Event	Fatal/non-fatal	Proportion
MI	fatal	10.1%
	non-fatal	23.0%
Angina	fatal	12.3%
	non-fatal	27.9%
Stroke / TIA[a]	fatal	6.1%
	non-fatal	20.6%

Source: obtained from the economic model submitted by the company
[a)] It is assumed that the proportion of TIA events of total strokes is 21.9%

Estimation of mortality

Age and gender dependent mortality (UK lifetables from the Office for National Statistic[46]) was used to inform mortality for patients (retrieving specific mortality data for patients with and without T2DM). After patients experienced ACS and/or stroke additional relative risks for mortality of 1.3[47] and 2.0[48] were respectively applied for the remaining duration of the patients' life. Additionally, increased mortality probabilities were applied in the year after onset of an MI, angina, stroke and knee replacement as well as after bariatric surgery (see CS Table 31).

Estimation of knee replacement, sleep apnoea and bariatric surgery

Knee replacement

The proportion of patients with knee replacement was estimated conditional on BMI, age and gender using the study of Wendelboe et al., 2003.[49]

Sleep apnoea

The proportion of patients with moderate-to-severe sleep apnoea (AHI≥15) was estimated conditional on BMI using the Sleep Heart Study.[50] This source was identified in a systematic review and was preferred based on its sample size (n=5,615).

Bariatric surgery

Bariatric surgery (either gastric banding [18%], gastric bypass [51%] or sleeve gastrectomy [31%][51]) was included as a rescue treatment. Starting from cycle 5 of the model (start of year 2), bariatric surgery was considered a possible event for both liraglutide 3.0mg and diet and exercise. Based on availability of bariatric surgery and patients' willingness to undergo this service in the UK, the annual bariatric surgery incidence was estimated to be 1.15%[11] for eligible patients (i.e. BMI ≥35 kg/m^2 and maximum age of 57 year). One year after bariatric surgery the following outcomes were assumed to change

(assumed equal for gastric banding, gastric bypass and sleeve gastrectomy), which impacted the risk models:

- Weight – decreased by 28.3%
- SBP – decreased by 9.04 mmHg
- Total cholesterol – decreased by 30.31 mg/dl
- HDL cholesterol – increased by 6.09 mg/dl
- HbA_{1c} – decreased by 2.2%

See CS Appendix L for further details on bariatric surgery.

Estimation of relative treatment effectiveness

As described in Section 5.2.2 the relative treatment effect of liraglutide 3.0mg or diet and exercise was introduced in the model through changes in BMI (by percentage reduction in weight per cycle), SBP (reduction in mmHg per cycle), total cholesterol (reduction in mg/dl per cycle), and HDL cholesterol (reduction in mg/dl per cycle). HbA_{1c} was not a treatment dependent parameter as it is assumed only to be dependent on T2DM by setting its value to HbA_{1c} percentage points of 7.5%, 6.0% and 5.4% for T2DM patients, prediabetes patients and patients with normal glucose tolerance respectively. Table 5.8 provides an overview of these parameters as used in the risk models to estimate T2DM and CV events.

Table 5.8: Relative treatment effectiveness parameters used to estimate T2DM and CVD

	Qdiabetes	QRisk3	UKPDS82	Framingham recurrent coronary heart disease
Used to estimate	**T2DM (normal glucose and prediabetes)**	**Primary CV event (normal glucose and prediabetes)**	**Primary CV event (T2DM)** **Secondary CV event (prediabetes and T2DM)**	**Secondary CV event (normal glucose)**
BMI	X	X		
SBP		X	X	X
Total cholesterol		X		X
HDL cholesterol		X	X	X
HbA_{1c}			X	
Source: obtained from the economic model submitted by the company				

Differences in weight loss, SBP, total cholesterol and HDL cholesterol between liraglutide 3.0mg and diet and exercise up to two years were based on Trial 1839 (see CS Table 28).[1] After the two-year treatment period, these parameters were assumed to return to their baseline values (i.e. waning of treatment effect) at a constant annual rate of 33%. Subsequently, after all parameters returned to the baseline values (i.e. post-treatment waning), BMI was assumed to increase annually by 0.1447 kg/m^2 in men and 0.1747 kg/m^2 in women based on the GPRD study.[52] The BMI increase was assumed to stop at the age of 68 year based on expert opinion.

ERG comment: The main concerns of the ERG relate to: a) the identification of risk models; b) selection of risk models that are different for patients with and without T2DM; c) calibration/(up-)adjustment of risk models; d) the identification and selection of mortality probabilities; e) calculation of responder probability using complete cases only; f) applying 56 weeks temporary prediabetes reversal probabilities in model cycle 2 (month 3 to 6); g) BMI was assumed to stop increasing after the age of 68 year; h) SBP, total cholesterol and HDL cholesterol were assumed constant over time (after the treatment waning period); i) the assumptions made for liraglutide 3.0mg non-responders; j) use of HbA_{1c} percentage points of 7.5% for T2DM patients; k) the lack of treatment discontinuation in the model between 12 weeks in liraglutide 3.0mg and two years and; l) the estimate used for annual incidence of bariatric surgery.

a) The ERG was concerned about the systematic identification of the various risk models. However, based on the detailed response from the company on clarification question B7, the company's approach to identify the various models seems reasonable.
b) The company uses different risk models to estimate CV events (both primary and secondary) dependent on the T2DM status. As highlighted in a recent review of prediabetes decision models, using different risk models dependent on T2DM status might 'introduce bias in terms of rates of disease progression when these are dependent on the study and the population informing the model rather than on the stage of disease'[53]. Consistently, the company acknowledges (clarification response B7[14]) that differences might arise due to factors unrelated to T2DM. Therefore, the ERG prefers to use the same risk models to estimate primary and secondary CV events for patients with and without T2DM. In the ERG base-case, QRisk3 is used to estimate primary CV events and Framingham recurrent coronary heart disease is used to estimate secondary CV events.
c) The calibration and (up-)adjustments applied to the risk models were not clear to the ERG based on the CS. However, based on the explanations provided by the company in response to clarification question B8,[14] the adjustments to the risk models seem acceptable.
d) The company clarified (clarification response B9[14]) that no systematic search was conducted to identify mortality probabilities. Nor did the company obtain expert opinion to validate the sources used for mortality probabilities. The company justified its approach by stating that the mortality probabilities were neither directly linked to liraglutide 3.0mg nor to the effectiveness data in the model. The ERG believes that mortality probabilities are indirectly linked to the relative benefits of liraglutide 3.0mg and hence sources should be carefully selected and justified. However, the company provided a scenario analysis, with alternative mortality probabilities, indicating that the impact of these mortality parameters is unlikely to be very influential.
e) In the CS calculation of (non-)responder probabilities (CS Table 28), patients with unknown response status after 12 weeks of treatment with liraglutide 3.0mg are excluded. This corresponds to a complete case analysis, assuming that if the response status is missing, it is missing completely at random. This assumption seems unlikely to the ERG, for instance patients with withdrawal due to adverse events might be more likely to have missing response status. Therefore, the responder probabilities for the ERG base-case are recalculated (based on clarification response B10[14]) assuming non-response if the response status is missing. This resulted in a responder probability of 59% (314/530) instead of 67% (314/469).
f) The company applied the temporary prediabetes reversal probabilities, using 56 weeks Trial 1839 data, in model cycle 2 (month 3 to 6). The company justified this (clarification response B11) by stating that prediabetes reversal is a direct and immediate consequence of weight loss,

providing 28 weeks Trial 1839 data to support this statement. Despite the inconsistency in timing between the model and Trial 1839 data, this justification seems reasonable to the ERG.

g) In response to clarification question B13, the company stated that the assumption that BMI stops increasing after the age of 68 year is supported by expert opinion. Moreover, the company provided a scenario analysis assuming weight increases indefinitely indicating that the impact of this assumption is likely to be minimal.

h) After the treatment waning period, BMI is modelled over time using the natural progression of weight (up to the age of 68 year). In contrast, SBP, total cholesterol and HDL cholesterol were assumed constant over time. The company provided a scenario analysis (clarification response B14) relaxing this assumption and assuming time dependent SBP, total cholesterol and HDL cholesterol. This scenario indicated that the likely impact of assuming constant SBP, total cholesterol and HDL cholesterol (over time), on the incremental results, is minimal.

i) Treatment effectiveness for liraglutide non-responders was modelled using data from the placebo arm as effectiveness data post non-response and liraglutide discontinuation, i.e. in line with the stopping rule, was not obtained in Trial 1839. The ERG believes that this assumption is debatable, as liraglutide non-responders are likely a selected population that potentially has worse treatment effectiveness than the overall placebo group. If it is assumed that liraglutide non-responders have no treatment benefit from liraglutide, then assuming equal treatment effectiveness as for placebo non-responders might be more appropriate. This was explored by the company in response to clarification question B6,[14] indicating that this alternative assumption would increase the ICER by approximately £1,100. The ERG would have preferred to incorporate this scenario in its base-case; however, this was not feasible given the substantial delay before the company provided this scenario analysis.

j) Ideally, glycaemic deterioration should be modelled as a continuum.[53] Nevertheless, the ERG believes it is a reasonable assumption to model glycaemic deterioration with a constant value (HbA_{1c} percentage points of 7.5%, 6.0% and 5.4% for T2DM patients, prediabetes patients and patients with normal glucose tolerance respectively) given the explanation provided by the company in response to clarification question B12 as well as the scenarios provided which indicated that the ICER would only increase/decrease by ~£700 for HbA_{1c} percentage points of 6.5% and 8.5% in TD2M respectively.

k) In the base-case, no treatment discontinuation (e.g. due to adverse events or loss of efficacy) was included in the model besides the stopping rule for liraglutide 3.0mg (as per the European Medicine Agency licence) after the initial 12 weeks on liraglutide 3.0mg and the assumption that patient would stop liraglutide 3.0mg after two years. In response to clarification question B1 the company argued that 'the highest drop-outs occurred within the first 3 months, and up to 6 months, after which the drop-out rate was rather small (approximately 2% between 12 and 15 months)'.[14] However, from Figure 4 in the CS it appears that discontinuation (also) occurs gradually over time (as opposed to (only) a steep decrease in discontinuation after six months as argued by the company).[1] In response to clarification question B1, the company provided two scenario analyses in which additional discontinuation rates per cycle were included, starting from cycle 3 up to the maximum treatment duration of two years: 1) using per cycle discontinuation probabilities as observed in the SCALE 1839 study; 2) using a scenario in which the observed time-to-discontinuation was applied for the first three years after which a log-normal parametric model was used. In the latter scenario, the fixed treatment duration of two years was removed from the model and treatment duration was extrapolated based on the parametric survival model. Both scenarios resulted in considerably higher ICERs (£16,857 per QALY gained and £19,157 per QALY gained). However, due to the substantially delayed

response from the company, the ERG was not able to incorporate these discontinuation scenarios in its analyses.

l) The incidence rate of bariatric surgery was based on the annual incidence of bariatric surgery in the UK in patients with a BMI of <35.[11] As the average BMI of the cohort in the model was 41.7, the incidence rate might be underestimated. Given the ERG does not have another plausible estimate and changing this parameter is not influential (see CS Table 79), the ERG believes the assumptions made by the company, regarding incidence rate of bariatric surgery, are reasonable.

5.2.7 Adverse events

Treatment related adverse events were not considered in the economic model.

ERG comment: The company justified the exclusion of adverse events by stating that it is not expected that adverse events would have a significant impact on the patients' quality of life. Nevertheless, CS Table 24 indicates that the inclusion of liraglutide resulted in a substantial higher proportion of severe adverse events (20.7% versus 15.4%), while for the index population this was 15.5% versus 13.7%.[1] Thus, this simplification is unlikely to be conservative. Moreover, for liraglutide adverse events led to withdrawal in 199 of 1,501 patients (13.3%) indicating that the impact on patients is not negligible, similarly for the index population adverse events led to withdrawal 62 out of 530 patients (11.7%). Also, occurrence of adverse events likely impacts costs. Therefore, the ERG believes that excluding adverse events is likely not conservative and adds to the uncertainty of the estimated results. After a substantial delay, the company submitted scenario analyses in response to clarification question B15,[14] indicating that including adverse events would increase the ICER by approximately £100.

5.2.8 Health-related quality of life

The utility values were obtained from the literature for all health states as the company stated that HRQoL data of Trial 1839 did not align with the NICE reference case. Moreover, the treatment-dependent HRQoL data from Trial 1839 (Medical Outcomes Study 36-Item Short-From Health Survey, Impact of Weight on Quality of Life-Lite and Treatment Related Impact Measure-Weight questionnaires data) did not incorporate the stopping rule, whereby the company concluded that liraglutide 3.0mg HRQoL data could not be used for the period following the stopping rule.

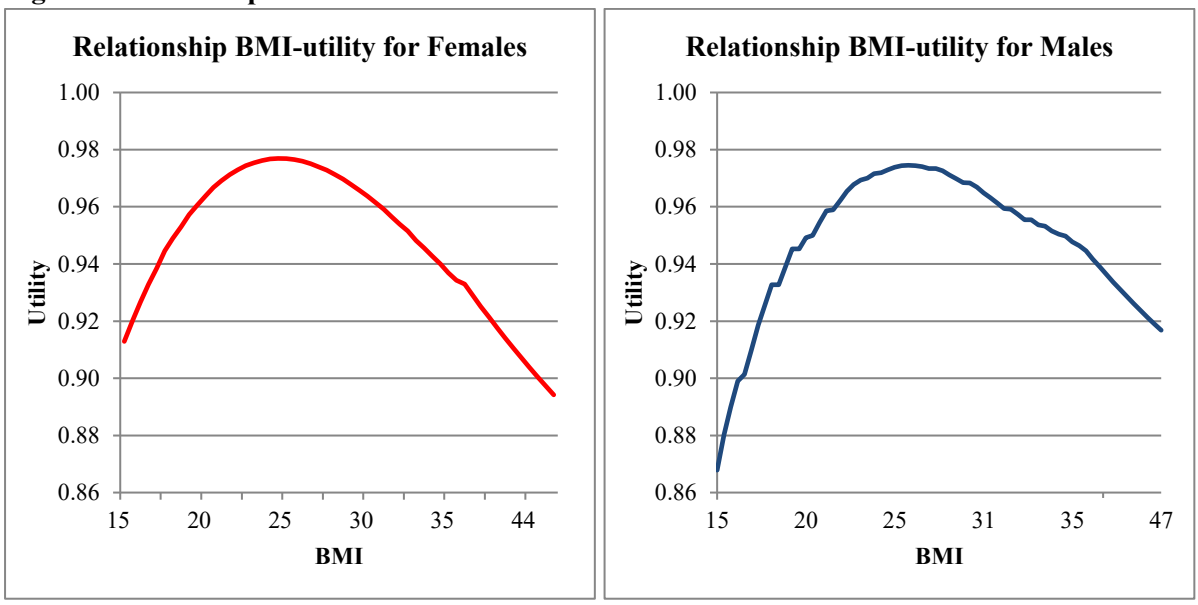
Health-related quality of life data identified in the review

According to the CS, the SLR identified 26 studies. The company considered none of these to be consistent with the NICE reference case and to be appropriate for the CEA model.

Prediabetes health state utility values

To obtain utility values for the prediabetes health state, data from a study reporting UK EQ-5D utilities by BMI level were digitised (Søltoft et al., 2009[20]) (Table 36 in CS[1]). The resulting estimated utility values were dependent on age, gender as well as BMI and consequently also treatment-dependent due to the BMI-dependency. Figure 5.2 shows the BMI-dependent utilities for males and females.

Figure 5.2: BMI-dependent utilities



Source: Based on the CS model.[1]
BMI = body-mass-index.

Normal glucose tolerance health state utility values

The health state utility of normal glucose tolerance was assumed equal to the prediabetes health state utility.

T2DM, CV event and sleep apnoea health state utility values

Utility decrements reflecting the impact of T2DM and CV events were obtained from the literature and applied to the age, gender and BMI-dependent prediabetes health state utility. Multiple disutilities were applied in health states with multiple conditions (e.g. post ACS with T2DM), i.e. assuming that disutilities were additive. A summary of all utility decrements used is provided in Table 5.9. A proportion of all patients was assumed to have obstructive sleep apnoea (OSA), which was associated with a utility decrement as well.

One-off utility decrements of acute events

Utility decrements associated with acute events (ACS, stroke, TIA, bariatric surgery and knee replacement) were applied once in the cycle in which the event occurred. The decrement of knee replacement was multiplied by three to reflect the assumption that patients undergoing knee replacement live with a chronic, debilitating condition prior to surgery for three years. An overview of the decrements is provided in Table 5.9.

Table 5.9: Long-term and one-off utility decrements

	Utility decrement (95% CI)	Reference	Justification
Utility decrements for type 2 diabetes and obesity-related complication health states			
Type 2 diabetes	-0.037 (N/A)	Søltoft et al., 2009[20]	Based on the association between T2DM and HRQoL
Post ACS	-0.037 (-0.087 to 0.014)	Sullivan et al., 2011[37]	Post ACS HRQoL is based on the ICD-9

	Utility decrement (95% CI)	Reference	Justification
			code for the Old myocardial infarction
Post stroke	-0.035 (-0.077 to 0.007)	Sullivan et al., 2011[37]	Post stroke HRQoL is based on the ICD-9 code for the Occlusion and stenosis of precerebral arteries
Cancer (scenario analyses only)	-0.078 (N/A)	Søltoft et al., 2009[20]	Based on the association between cancer and HRQoL
Acute event utility decrements			
ACS	-0.063 (-0.088 to -0.037)	Sullivan et al., 2011[37]	ACS HRQoL is based on the ICD-9 code for the Acute myocardial infarction
Stroke	-0.117 (-0.141 to -0.093)	Sullivan et al., 2011[37]	Stroke HRQoL is based on the ICD-9 code for the Acute, but ill-defined, cerebrovascular disease
TIA	-0.033 (-0.077 to 0.011)	Sullivan et al., 2011[37]	TIA HRQoL is based on the ICD-9 code for the Transient cerebral ischemia
Bariatric surgery	-0.184 (N/A)	Campbell et al., 2010,[42] and Jansen and Szende[43]	Average of initial procedure-related decrement for laparoscopic adjustable gastric banding and laparoscopic Roux-en-Y gastric bypass, adjusted by UK population norm.
Knee replacement	-0.194 (N/A)	Søltoft et al., 2009[20]	Based on the association between musculoskeletal problems and HRQoL
Obstructive sleep apnoea	-0.038 (N/A)	Søltoft et al., 2009[20]	Based on the association between obesity and respiratory problems (which were assumed to reflect obstructive sleep apnoea)

Source: Based on Table 37 and Table 38 of the CS.[1]

ACS = acute coronary syndrome; CI = confidence interval; HRQoL = health-related quality of life; N/A = not available; T2DM = type 2 diabetes; TIA = transient ischemic attack

Adverse event related disutility values
Adverse events were not considered in the analysis. ERG comments on the absence of AEs can be found in Section 5.2.7.

ERG comment: The main concerns of the ERG relate to: a) data used for the estimation of BMI-dependent utilities, b) the risk of double-counting due to the use of multiple HRQoL sources and an additive disutility approach, c) the knee replacement and obstructive sleep apnoea disutilities.

a) The BMI-dependent utilities informing all health state utilities were obtained from the literature by digitising and re-estimating data. Moreover, the estimated HRQoL values was based on a study population that only included patients with BMI values up to 35. The company extrapolated the data from this study to estimate utility values for BMI values above 35. The ERG was concerned that given the inclusion criteria of the Trial 1839 index population was a BMI >35, the assumed relationship between BMI and HRQoL in the extrapolation may bias the results in unknown degree and direction. In response to clarification question B18 the company provided results based on mapped BMI-dependent utilities measured in Trial 1839. In this analysis the number of QALYs was increased in both arms and the ICER was reduced by £70.[14]

b) Multiple sources were used to inform the utility of health states and disutility of events. Moreover, the impact of multiple obesity complications on HRQoL were assumed to be additive, i.e. disutilities were added up in health states reflecting multiple obesity complications. The ERG was concerned this approach would lead to double-counting. The company argues in response to clarification question B4 and B16[14] that all disutilities used were marginal disutilities adjusted for the effects of all other events modelled except for bariatric surgery, taken from Søltoft et al. and Sullivan et al.. [20, 37] The company concluded that the health state utility estimates are therefore not double-counted and an additive approach would be reasonable.[14] The ERG indeed considers the risk for double-counting to be small and implemented a scenario analysis using disutilities from Sullivan et al.[37] when available to replace disutilities from other sources (see Table 5.10).

Table 5.10: Alternative utility decrements

	CS utility decrement	Alternative utility decrement from Sullivan et al.[37]	Description
Type 2 diabetes health state utility decrement	-0.037	-0.062	Utility decrement of diabetes mellitus without complications
Acute event utility decrements			
Bariatric surgery	-0.184	-	CS utility decrement used
Knee replacement	-0.194	-0.099	Utility decrement of non-traumatic joint disorder
Obstructive sleep apnoea	-0.038	-0.037	Utility decrement of other respiratory system diseases
T2DM = type 2 diabetes			

c) The ERG questions whether the disutilities of knee replacement and of OSA, reflected by the disutilities of musculoskeletal problems and of respiratory problems, respectively, may be

overestimated. The disutility of OSA was higher than or equal to disutilities of some CV events, while the disutility of knee replacement of 0.194 was multiplied by three to reflect the assumption that undergoing knee replacement entails a HRQoL loss lasting an extended period of three years. The ERG explored the impact of these disutilities in a scenario analysis by setting both disutilities to zero.

5.2.9 Resources and costs

The costs included in the model were acquisition and administration costs of obesity treatment, pharmacy costs (blood pressure and T2DM medications), and costs of obesity-related complications.

Unit prices were based on the National Health Service (NHS) reference prices, British National Formulary (BNF), the Monthly Index of Medical Specialities (MIMS) and literature sources.[51, 54-64]

Resource use and costs data identified in the review

According to the CS, the SLR identified three studies reporting UK relevant resource use and cost information. However, it was argued that none of these studies were found to contain relevant information for this economic evaluation due to discrepancies in the patient population and treatments used.

Obesity treatment costs

Costs of obesity treatment with liraglutide included acquisition costs and administration cost i.e. cost of needles (Table 5.11). The price per pack of five pens of 18mg/3ml liraglutide each was [redacted],[65] this includes a simple discount/patient access scheme (PAS) of [redacted]. Administration costs were £0.06 per injection. Annual total treatment costs in the maintenance phase following the titration phase were [redacted]. Diet and exercise treatment did not have acquisition and administration cost but incurred costs of monitoring visits (specialist and nurse visits, and a blood test [52, 55]), the annual costs were £130.83.[51] A BMI-dependent proportion of patients was assumed to have OSA,[50] which was associated with cyclic costs of £869.[51]

Liraglutide treatment was initiated with a titration phase. The starting dose of 0.6mg/day was increased weekly over a period of four weeks to reach the maintenance dose of 3.0mg/day (CS Table 39[1]). The total cost of liraglutide treatment in the first 16 weeks of treatment (four weeks titration period and 12 weeks maintenance dose of 3.0mg/day), i.e. up to the stopping rule, were therefore [redacted].

Table 5.11: Treatment costs with PAS

Item	Description	Costs	References	Frequency
Cost components				
Liraglutide 3.0mg treatment	Acquisition cost per mg	[redacted]	Novo Nordisk, data on file[65]	
	Cost per administration / needle	£0.06	MIMS[54]	daily
Diet and exercise treatment	Specialist visit (10 min.)	£18.00	Curtis et al., 2017[55]	4 per year
	Nurse visit (15 min.)	£7.00	Curtis et al., 2017[55] Ara et al., 2012[52]	8 per year
	Blood test (10 min.)	£2.83	Price: NHS National schedule of reference costs[51] Frequency: Ara et al., 2012[52]	1 per year
Source: Based on Table 40 of the CS and the economic model[1]				

Health state and event costs

Pharmacy costs and long-term costs of obesity-related complications were included in the health state costs. Blood pressure treatment was assumed to entail treatment with enalapril 5mg, lisinopril 10mg, perindopril 4mg or ramipril 2.5mg and amounted to annual costs of £33.72.[56] These were applied to 45.3% of patients in all health states in line with the proportion of patients using antihypertensive drugs in Trial 1839.[66]

Prediabetes health state costs

The health state costs of prediabetes were £55, reflecting increased monitoring associated with higher than normal HbA_{1c}. The annual cost was informed by the average cost of participants of the National Diabetes Prevention Programme.[57]

Normal glucose tolerance health state costs

Only costs of blood pressure treatment and costs of OSA treatment were applied.

T2DM health state costs

T2DM medication costs were based on the cost of type 1 and type 2 diabetes and amounted to an annual cost of £317.[58] Moreover, cost associated with microvascular complications e.g. eye complications, nephropathy and diabetic foot, were added with an annual cost of £468.[61]

Health state costs of obesity-related complications

Different health state costs applied in the first year in a obesity-related complication health state and the subsequent years in that health state, these are summarised in Table 42 of the CS.[1] In health states including multiple complications, the costs of the individual complications were added up. For health

states entered following an acute event (e.g. ACS), additional costs relating to the event applied, as these were not included in the health state costs.

Acute event costs

Event costs were applied upon the occurrence of angina, MI, stroke, TIA, knee replacement and bariatric surgery, to reflect the costs of managing the acute health event. These costs are summarized in Table 43 of the CS.[1] This includes resource use relating to preparation of the intervention and follow-up care in the case of knee replacement. Costs were informed by NHS reference costs.[51]

The costs of bariatric surgery were calculated as a weighted average of the costs of gastric bypass (50.7%), laparoscopic banding (17.9%) and sleeve gastrectomy (31.5%), based on the incidence of these surgeries reported by the NHS and NHS reference costs.[51] Additionally, the costs of preoperative and post-operative management[59] and of complications of bariatric surgery, approximated by the cost of leaks,[60] were reflected in the event costs.

Adverse event related costs

Costs of adverse events were not considered in the analysis (see also Section 5.2.7 of this report).

ERG comment: The main concerns of the ERG relate to: a) the lack of adjustment of costs of bariatric surgery complications for the incidence of these events, b) the lack of monitoring costs in patients reverted to normal glucose tolerance, c) the application of microvascular diabetes complication costs from T2DM onset onwards, d) the costs of diet and exercise treatment, e) potential double-counting of costs, and f) the lack of transparency regarding the costs used.

a) The ERG identified an error in the calculation of costs relating to complications of bariatric surgery. These costs, reflected by the cost of leaks, were applied to 100% of bariatric surgery patients, i.e. were not adjusted for the incidence of complications. The ERG corrected the mistake by correcting the complication costs assuming 5.95% of bariatric surgery patients would have serious complications, based on the incidence of hernia- and cholecystectomy-related reoperations reported in Borisenko et al.[60]
b) The ERG considers the assumption that patients temporarily reverted to normal glucose tolerance do not receive monitoring to be unlikely given their history of prediabetes, their remaining obesity and increased risk for developing T2DM and CV events. An underestimation of costs in normal glucose tolerance patients would likely not be conservative. The ERG explores the impact of adding monitoring costs equal to those of patients with prediabetes in a scenario analysis.
c) The costs of microvascular T2DM complications were applied from onset of diabetes onwards. The ERG considers this assumption unlikely given that microvascular T2DM complications have a delayed onset compared to T2DM onset. An overestimation of costs with T2DM is likely not conservative. The ERG explored the impact of a reduction of microvascular T2DM complication costs by 50% in a scenario analysis.
d) The ERG was concerned that the costs of diet and exercise treatment (monitoring visits by specialists and nurses, blood test) may not be representative of treatment provided in tier three. In their response to clarification question B20, the company stated that a physician survey indicated that the GP visits, consultations with nurses, dieticians, specialists and blood tests would be representative of tier three services and elicited the assumed frequency of these.[14] The company used these data in a scenario analysis which showed increased total costs but no change in incremental costs or in the ICER.[14] The ERG therefore concludes that the representativeness of treatment cost with diet and exercise to tier three services may be uncertain, however, this does not affect the cost effectiveness results.

e) As acknowledged by the company in response to clarification question B4 [14], it is likely that some double-counting occurred between the costs of different chronic cardiovascular disease. This pertains to a small proportion of patients and was considered not influential; it was therefore not further explored by the ERG.

f) The ERG would like to comment that they encountered some difficulties in assessing the modelled cost and resource use as many costs were informed by sources that were not directly based on the most recent NHS reference prices but instead based on publications using dated NHS reference prices without providing details on the tariffs used. Although the costs used seem reasonable, the ERG was not able to validate all costs items leaving some uncertainty related to the costs used and how reflective these are of current NHS costs.

5.2.10 Cost effectiveness results

In the deterministic base-case analysis, total QALYs gained were larger for liraglutide compared to diet and exercise (0.120 QALYs gained). Total costs were also higher for liraglutide (£1,568). The difference in incremental costs mainly resulted from higher treatment costs. The deterministic incremental cost effectiveness ratio (ICER) amounted to £13,059 per QALY gained (Table 5.12).

Table 5.12: Company's base-case results (deterministic)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Deterministic					
Liraglutide	£20,988	15.336	--	--	--
Diet and exercise	£19,419	15.216	£1,568	0.12	£13,059
Source: Based on Table 52 of the CS[1]					

Revised base-case submitted by the company

The company provided a revision of the original submission and economic model accompanying the clarification letter (see Table 5.13). The company clarified that this was done to incorporate the following inconsistencies that were identified in the clarification phase: 1) the calculation of T2DM risk after prediabetes reversal - the model applied a lower risk of T2DM onset post temporary reversal of prediabetes, 2) the adjustment to account for the shorter cycle length in the first year of the model had been applied twice, 3) There was a typographical error in the formulae to calculate of the number of MI events per cycle for liraglutide 3.0mg and comparator.

Table 5.13: Company's revised base-case results (deterministic)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Deterministic					
Liraglutide	£21,606	15.256			
Diet and exercise	£20,270	15.109	£1,336	0.147	£9,096
Source: Based on the revised model provided by the company in their clarification response					

5.2.11 Sensitivity analyses

The company performed and presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) in order to show the uncertainty surrounding the CS base-case results.

Compared with the deterministic results, the PSA with 1,000 iterations showed a slightly increased ICER (£13,623; 95%CI: £10,014 - £19,209) (see Table 5.14). The PSA included parameters used to determine treatment effects (e.g. percentage weight loss per cycle, change in SBP, etc.), cohort characteristics (e.g. age, BMI, weight, etc.), treatment discontinuation rates, bariatric surgery related inputs (e.g., efficacy estimates, types of bariatric surgery, etc.) and epidemiological inputs (e.g., proportion CV events which are MI, case fatality knee replacement, etc.). The cost effectiveness acceptability curve in the model showed that liraglutide approximately had a 99% and 100% probability of being cost effective at a willingness to pay (WTP) threshold of £20,000 and £30,000 respectively (see Figure 30 of CS [1]).

Table 5.14: Company's PSA results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Probabilistic					
Liraglutide	£21,395	15.317	--	--	--
Diet and exercise	£19,913	15.207	£1,482	0.11	£13,531
Source: Based on the CS[1] and model provided by the company					

The company conducted DSAs by varying model parameters related to, e.g., the probability of reverting to normal glucose tolerance, weight reduction at two years, and baseline BMI, between upper and lower values based on the literature or a specified range (e.g. +/- 25% around the mean estimate). The top three drivers of results were found to be the proportion of patients on diet and exercise who revert from prediabetes to normal glucose tolerance following treatment, the proportion of patients on liraglutide 3.0mg who (temporarily) revert from prediabetes to normal glucose tolerance, and weight reduction at the start of year 2 with diet and exercise (see Table 5.15).

Table 5.15: Deterministic sensitivity analyses results

	Variation (SD or ±25%)		ICER (£/QALY)	
Parameter	**Low**	**High**	**Low**	**High**
Base-case			£13,059	
D&E: Prop. reverting from prediabetes to NGT (%)	34.95%	46.66%	£10,573	£16,119
Liraglutide: Prop. reverting from prediabetes to NGT (%)	79.09%	86.23%	£13,935	£12,376
D&E: Weight reduction at 2 years (%)	-1.29%	-2.85%	£12,220	£13,242
HbA_{1c} after type 2 diabetes onset (%)	6.50%	8.50%	£13,785	£12,344
Proportion of smokers (%)	12.61%	17.56%	£13,160	£13,645
Baseline BMI (kg/m^2)	41.333	42.067	£13,182	£12,481
Liraglutide: Weight reduction at 2 years (%)	-8.72%	-10.20%	£13,578	£12,831
Case fatality rate of stroke (%)	12.70%	34.96%	£12,728	£13,474
Case fatality rate of angina (%)	16.71%	46.34%	£12,848	£13,445
Annual cost of prediabetes (£)	£41	£69	£13,427	£12,690
Source: Based on Table 53 of the CS[1] BMI = Body Mass index, D&E = Diet and exercise, NGT = normal glucose tolerance				

Scenario analyses

The company conducted several scenario analyses (see Table 5.16). The main drivers of liraglutide 3.0mg benefits were the avoidance or delay of T2DM onset and cardiovascular disease. The three most influential scenarios that increased the ICER were the exclusion of all complications (impact of BMI on QALYs only; ICER: £113,041 per QALY); inclusion of T2DM diabetes and BMI impact on QALY only (so excluding CV events; ICER: £104,836 per QALY gained); and a five-year time horizon (ICER: £62,825 per QALY gained). The three most influential scenarios that decreased the ICER were: treatment duration of one year assuming costs and effects for one year only (ICER: £6,220 per QALY gained); discount rate of 0% (ICER: £5,563 per QALY gained); and all patients discontinue to no treatment and returning to weight based on natural progression at the end of the catch-up period (ICER: £2,482 per QALY gained).

Table 5.16: Overview results of scenario analyses

	Incremental costs (£) (Lira – DE)	Incremental QALYs (Lira – DE)	ICER (£/QALY)
Scenario			
Exclusion of all complications (impact of BMI on QALYs only)	£ 2,085	0.018	£ 113,041
Inclusion of T2DM and BMI impact on QALY	£ 2,144	0.02	£ 104,836
Five-year time horizon	£ 2,048	0.033	£ 62,825
Ten-year time horizon	£ 1,882	0.042	£ 44,844
Twenty-year time horizon	£ 1,660	0.068	£ 24,264
Immediate loss of treatment effect (i.e. no waning of treatment benefit)	£ 1,815	0.088	£ 20,723
Discount rate of 6%	£ 1,683	0.084	£ 19,949
Treatment duration of three years	£ 2,530	0.138	£ 18,350
Thirty-year time horizon	£ 1,573	0.098	£ 16,015
Inclusion of cancers with relationship with obesity baseline age 48 years	£ 1,691	0.11	£ 15,330
Inclusion of cardiovascular disease, T2DM, BMI impact on QALY	£ 1,714	0.113	£ 15,151
Waning of treatment effect applied over one year post treatment stop	£ 1,648	0.111	£ 14,802
Not high risk of CVD	£ 1,618	0.113	£ 14,300
MI-ME data imputation method	£ 1,587	0.119	£ 13,387
Inclusion of sleep apnoea in addition to complications above	£ 1,575	0.119	£ 13,208
Incidence of bariatric surgery per year of 0.57%	£ 1,567	0.121	£ 12,990
Exclude bariatric surgery from the model	£ 1,566	0.121	£ 12,950
Bariatric surgery criteria - minimum BMI 47 kg/m^2	£ 1,566	0.121	£ 12,950
Increased SBP, total cholesterol and HDL	£ 1,541	0.132	£ 11,695
Inclusion of cancers with relationship with obesity baseline age 50 years	£ 1,585	0.139	£ 11,438
BOCF data imputation method	£ 1,343	0.148	£ 9,050

	Incremental costs (£) (Lira – DE)	Incremental QALYs (Lira – DE)	ICER (£/QALY)
Scenario			
Waning of treatment effect applied over three years post treatment	£ 1,332	0.156	£ 8,535
Treatment duration of one year	£ 611	0.098	£ 6,220
Discount rate of 0%	£ 1,289	0.232	£ 5,563
All patients discontinue to no treatment and physiological parameters return to a value on the natural progression following treatment	£ 632	0.254	£ 2,482

Source: Based on Table 55 to Table 79 of the CS[1]
BMI = Body Mass index, BOCF: Baseline observation carried forward, CVD = Cardiovascular disease, D&E = Diet and exercise, NGT = normal glucose tolerance, QALY = Quality-adjusted life years, T2DM = Type 2 diabetes mellitus

ERG comment: Although the company provided most of the additional requested scenario analyses or adjustments to their base-case, some requested analyses were not provided or with a substantial delay (of ≥2 weeks). The company did not provide an analysis (either a scenario or in their base-case analysis) in which orlistat and bariatric surgery were included as separate comparators which was requested by the ERG in clarification question B2.[14]

In clarification question B16,[14] the ERG requested the company to provide a scenario analysis (and the accompanying model) where the utility decrements were adjusted to be multiplicative (instead of additive). The company stated however that 'both the baseline utility and disutilities applied in the CS base-case were sourced from studies where all modelled conditions co-occurred, and were controlled for, therefore it is reasonable to assume the utility decrements applied are additive'[14] and hence did not provide the requested analysis.

5.2.12 Model validation and face validity check

The company undertook efforts to validate the cost effectiveness model and the cost effectiveness estimates for intervention and control. The company reports a clinical expert was consulted to validate model assumptions.

An internal validity check included a comparison of input data with the data sources, and the variation of model inputs to assess if changes in results were in line with expectations, including the assessment of the visual basic code. The company reports a number of small inaccuracies were identified and rectified.

A cross validation comparing the LYs, total costs, QALYs and ICER of the health economic model to those of a published UK-relevant cost effectiveness model by Ara et. al[52] on obesity was conducted by a third party. For this comparison, baseline clinical characteristics, costs and utilities of the published cost effectiveness study were entered into the health economic model. The health economic model overestimated LYs (range 30.0-30.5 vs. 32.18-32.19), QALYs (range 15.13-15.42 vs. 15.67-15.83) and costs (range £2,806-£3,097 vs. £3,244-£4,368) in all treatment arms and produced higher ICERs (lowest ICER sibutramine 15mg £557, highest ICER rimonabant £3,553 vs. lowest ICER sibutramine 15mg and 10mg (effectiveness assumed equal) both £6,622, highest ICER rimonabant £7,230).[67] According to the third party, this may (partly) be explained by a difference in time horizon, which was not reported

for the reference model, a decision-making process would lead to the same conclusions based on either model.[52]

An external validation comparing model predictions to data from the studies that were used to build the model was conducted by a third party, assessing goodness of fit measured by the R^2.[68] The endpoints assessed were CV events (MI, stroke, angina), mortality, T2DM incidence and OSA. The reported R^2s were reasonably high (range 0.927-0.984 for CV events, 0.979 for T2DM, 100% correspondence for OSA). The company concluded the models had been implemented correctly without substantial error. A small underestimation of CV events was observed especially in higher risk profile patients. It is concluded that the overall underestimation of CV events may affect the cost effectiveness results conservatively as less events modelled may entail that less events can be prevented by the intervention.[68] A formal face validity check or a validation against data not used to build the prediction models was not conducted.

ERG comment: The main concerns of the ERG relate to: a) the face validity check, b) the applicability of the HEOR reports to the revised base-case, c) the external validation of event rates predicted by the model against event rates observed in Trial 1839, d) the errors identified by the ERG and the company.

a) The ERG was concerned about the lack of detail in the reporting of the face validity check with a clinical expert. In response to clarification question B23,[14] the company provided a summary of the model validation meeting in form of a list of topics discussed and conclusions drawn from the expert responses.[14] The ERG found this information to be helpful.
b) The ERG found the HEOR reports to be informative and helpful in assessing the validity of the submission. It is however unclear in how far the conclusions drawn from the assessments also apply to the revised base-case where the company corrected several errors (related to 1) the calculation of T2DM risk after prediabetes reversal; 2) incorrect application of the cycle length correction and; 3) typographical error in the formulae to calculate of the number of MI events, see also Section 5.2.10.
c) The ERG is concerned that the validation exercises submitted by the company in response to clarification question B24[14] is suggestive of an overestimation of CV events in the model. The provided comparison of CV event rates modelled with event rates observed in the population of Trial 1839 shows that the number of CV events modelled may be overestimated. However, this comparison is subject to uncertainty given the low number of events observed in Trial 1839. An overestimation of events is unlikely to be conservative.
d) Several errors in the coding have been identified by the ERG and the company during the assessment of this submission. See the above-mentioned errors that are corrected in the company's revised base-case as well as the errors fixed by the ERG (see fixing errors in Section 5.3). Although these errors were corrected, given the complexity of the model and the time available, the ERG is unable to guarantee that there are no remaining errors in the economic model.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations in section 5.2, the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[69]):

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)

- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Fixing error

1. Costs of leaks (related to bariatric surgery) are not weighted for incidence (Section 5.2.9).
   The ERG corrected the costs of leaks.

Fixing violations

2. The calculation of proportion of responders assumed missing response values to be missing completely at random (Section 5.2.6).
   The ERG recalculated the proportion of responders assuming patients with missing response values to be non-responders.

Matters of judgment

3. After a CV event, the company assumed that prediabetic patients automatically develop T2DM as well (Section 5.2.2).
   The ERG assumed that prediabetic patients do not automatically develop T2DM.
4. Different risk models are selected for patients with and without T2DM (Section 5.2.6).
   The ERG used QRisk3 and Framingham recurrent coronary heart disease to estimate primary and secondary CV events respectively.

Table 6.1 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the (deterministic) ERG base-case. The 'fixing error' adjustments were combined and the other ERG analyses were performed also incorporating these 'fixing error' adjustments given the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues. All ERG analyses are conditional on the company's revised base-case.

5.3.1 ERG base-case results

The ERG base-case consisted of an ICER range, reflecting the uncertainty related to the assumption that prediabetic patients automatically develop T2DM with a CV event. The probabilistic ERG base-case indicated that when assuming that prediabetic patients automatically develop T2DM with a CV event, liraglutide would become cost effective at an ICER of £13,805 per QALY gained (corresponding probabilities for liraglutide being cost effective were 98% and 100% at thresholds of £20,000 and £30,000 per QALY gained respectively). When removing the simplifying assumption that prediabetic patients automatically develop T2DM with a CV event, this increased to £31,782 per QALY gained (corresponding probabilities for liraglutide being cost effective were 0% and 38% at thresholds of £20,000 and £30,000 per QALY gained respectively).

5.3.2 Additional exploratory analyses performed based on the ERG base-case

Additional sensitivity analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. These were all performed using the ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event. Results are presented in Table 6.3.

Exploratory analyses using the ERG base-case:

1. Alternative utilities (retrieved from Sullivan et al.[37]) are used (Section 5.2.8)
2. Disutilities for knee replacement and obstructive sleep apnoea are set to 0 (Section 5.2.8)
3. Monitoring costs are applied to patients reverted to normal glucose tolerance, equal to the monitoring costs of prediabetic patients (Section 5.2.9)

4. Costs of microvascular complications are halved (Section 5.2.9)

5.3.3 Subgroup analyses performed based on the ERG base-case

No subgroup analyses were performed.

5.4 Conclusions of the cost effectiveness section

The ERG is concerned that relevant references were potentially missed by the SLRs and noticed a lack of clarity regarding the identification of cost and resource use and HRQoL evidence used in the company submission. The company considered none of the publications identified in the SLR appropriate for the CEA model but used a number of publications in their economic model. It is thus unclear how this evidence used was identified.

The company developed a de novo model. The ERG considers that the model structure is appropriate to reflect this condition and treatment pathway. The economic model described in the CS is considered by the ERG to partly meet the NICE reference case. The main deviation from the NICE reference case was that the comparators considered in the scope were not fully considered. The ERG believes that for consistency with the final scope, orlistat and bariatric surgery should have been incorporated as comparators.

In the revised (probabilistic) company base-case liraglutide 3.0mg is more expensive (£1,336) and more effective (0.106 QALYs gained) than diet and exercise, resulting in an ICER of £9,096. The ERG has incorporated various adjustments to the company base-case this resulted in the (probabilistic) ERG base-case with a corresponding ICER of £13,805 per QALY gained when assuming that prediabetic patients automatically develop T2DM with a CV event. When removing the simplifying assumption that prediabetic patients automatically develop T2DM with a CV event, this resulted in an (probabilistic) ICER of £31,782 per QALY gained. The ERG is concerned that the company's base-case assumptions (i.e. that prediabetic patients automatically develop T2DM after ACS or stroke) overestimates the T2DM incidence as well as the treatment effect for liraglutide 3.0mg. On the other hand, the ERG acknowledges that removing this assumption (as implemented by the company), probably results in an underestimated T2DM incidence as well as treatment effect for liraglutide 3.0mg. Other factors that had a noticeable impact on the ICERs were assumptions related to the modelling of effectiveness for liraglutide non-responders (not observed in Trial 1839), liraglutide discontinuation, liraglutide treatment duration and waning of liraglutide effectiveness (all explored by the company). Moreover, other assumptions and/or parameters that might have individually a minimal impact on the estimated cost effectiveness potentially have, when all combined, a considerable impact. However, the company's substantially delayed clarification responses and the complexity of the economic model hampered the ERG in performing its analyses. Most importantly, due to delayed clarification responses, the ERG was not able to include alternative assumptions into the ERG base-case. These assumptions related to treatment discontinuation (e.g. incorporating treatment discontinuation throughout the model time horizon and relaxing the assumption of a maximum liraglutide treatment duration of two years) and to treatment effectiveness for liraglutide non-responder (e.g. assuming equal to the effectiveness of non-responders on diet and exercise). The scenarios submitted in the company's delayed clarification response letter indicated that the ICER could substantially increase when using alternative assumptions for these issues.

In conclusion, the ERG analyses indicate that the cost effectiveness of liraglutide versus diet and exercise ranges between £13,805 per QALY and £31,782 per QALY gained. However, the cost effectiveness of liraglutide is likely impacted by assumptions related to the development of T2DM for prediabetic patients, liraglutide discontinuation, liraglutide treatment duration, waning of liraglutide

effectiveness as well as the treatment effectiveness for liraglutide non-responders. Moreover, the exclusion of comparators listed in the scope can be regarded as an additional source of uncertainty.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Analyses undertaken by the ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. All ERG analyses are performed conditional on the company's revised base-case. Table 6.1 shows how individual changes impact the deterministic results plus the combined effect of all changes simultaneously. The probabilistic results for the ERG base-case are provided in Table 6.2. The exploratory scenario analyses are presented in Table 6.3 (probabilistic), these are all conditional on the ERG base-case that assumes prediabetic patients automatically develop T2DM with a CV event. The analyses numbers in Tables 6.1 and 6.3 correspond to the numbers reported in Section 5.3. The submitted model file contains technical details on the analyses performed by the ERG (e.g. the 'ERG' sheet provides an overview of the cells that were altered for each adjustment).

Table 6.1: Deterministic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base-case (original CS)					
Liraglutide	£20,988	15.336			
Diet and exercise	£19,419	15.216	£1,568	0.120	£13,059
Company base-case (revised) – used as starting point for all ERG analyses					
Liraglutide	£21,606	15.256			
Diet and exercise	£20,270	15.109	£1,336	0.147	£9,096
Fixing error (ERG analysis 1)					
Liraglutide	£21,375	15.256			
Diet and exercise	£20,040	15.109	£1,336	0.147	£9,095
Fixing error + assuming patients with missing response values to be non-responders (ERG analyses 1 + 2)					
Liraglutide	£21,279	15.239			
Diet and exercise	£20,040	15.109	£1,239	0.130	£9,537
Fixing error + assumed that prediabetic patients do not automatically develop T2DM (ERG analyses 1 + 4)					
Liraglutide	£20,898	15.347			
Diet and exercise	£19,141	15.279	£1,757	0.068	£26,025
Fixing error + same risk models (ERG analyses 1 + 3)					
Liraglutide	£21,357	15.381			
Diet and exercise	£19,945	15.282	£1,412	0.099	£14,251
ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event (ERG analyses 1, 2, 4)					
Liraglutide	£21,252	15.370			
Diet and exercise	£19,945	15.282	£1,307	0.088	£14,906
ERG base-case assuming prediabetic patients do not automatically develop T2DM with a CV event (ERG analyses 1-4)					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Liraglutide	£20,827	15.421			
Diet and exercise	£19,215	15.369	£1,613	0.051	£31,456

Table 6.2: Probabilistic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event (ERG analyses 1, 2, 4)					
Liraglutide	£21,631	15.296			
Diet and exercise	£20,363	15.204	£1,268	0.092	£13,805
ERG base-case assuming prediabetic patients do not automatically develop T2DM with a CV event (ERG analyses 1-4)					
Liraglutide	£21,395	15.357			
Diet and exercise	£19,913	15.306	£1,616	0.051	£31,782

Table 6.3: Probabilistic scenario analyses conditional on ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG scenario 1: Alternative disutilities based on Sullivan					
Liraglutide	£21,725	15.255			
Diet and exercise	£20,455	15.153	£1,270	0.103	£12,348
ERG scenario 2: Disutilities of knee replacement and of obstructive sleep apnoea set to 0					
Liraglutide	£21,696	15.832			
Diet and exercise	£20,428	15.747	£1,267	0.085	£14,966
ERG scenario 3: Monitoring costs in normal glucose tolerance health states = monitoring costs with prediabetes					
Liraglutide	£22,144	15.302			
Diet and exercise	£20,699	15.211	£1,446	0.092	£15,762
ERG scenario 4: Costs of microvascular complications reduced by 50%					
Liraglutide	£20,440	15.298			
Diet and exercise	£19,055	15.206	£1,384	0.092	£15,074

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Appendix 1: ERG search strategies

Additional limitations of the CS searches not covered in the main body of the report:

- Line #1 of the MEDLINE clinical effectiveness search incorrectly searches for 'exp mrbid obesity/' rather than 'exp morbid obesity/'
- ISPOR proceedings are included in Embase, rather than MEDLINE, as stated in Appendix G; p.32.
- There were some irregularities in the reporting of the number of retrieved records for all databases in the HRQoL searches, e.g. the MEDLINE search in Appendix H; p.59 gives the number of retrieved records as 2,216,256, whereas the actual number of records found by the search was 236.

Appendix 2: Additional results and adverse events tables

Table A2.1: Main outcomes as specified in the NICE scope for 'patients with a BMI ≥35 kg/m^2, prediabetes and high risk of CVD' (change between baseline and week 160 (BOCF).*

Outcome	Liraglutide (n=530)	Placebo (n=270)	Estimated treatment difference, liraglutide vs. placebo (95% CI)†
Body weight-related outcomes, change from baseline to week 160 (LS Mean (SE))			
Body-mass index (%)	-3.47 (0.27)	-1.00 (0.37)	-2.47 [-3.37; -1.57]
Weight loss (%)	-3.45 (0.27)	-1.01 (0.38)	-2.44 [-3.34; -1.54]
Percentage body fat	Not assessed		
Waist circumference (cm)	-4.11 (0.31)	-1.72 (0.44)	-2.39 [-3.45; -1.32]
Other NICE specified outcomes			
Confirmed type 2 diabetes (n/N, %)	3/530 (0.6%)	2/270 (0.7%)	NR
Cardiovascular adverse events (week 162; n/N, %)	86/530 (16.2%)	46/270 (17.0%)	NR
Idiopathic intracranial hypertension	Not assessed		
Non-alcoholic fatty liver disease	Not assessed		
Mortality (0 to 162 weeks)	0/530 (0%)	1/270 (0.4%)	NR
Health-related quality of life – SF-36 General Health; Change from baseline at week 160 (N, LS Mean (SE))	1.41 (0.28)	0.33 (0.40)	1.08 [0.12; 2.04]
Discontinuations (n/N (%))			
Discontinued due to AE	62/530 (11.7%)	13/270 (4.8%)	NR
Discontinued due to AE after week 16	60/530 (11.3%)	13/270 (4.8%)	NR
Discontinued due to AE before week 16	2/530 (0.4)	0/270 (0%)	
Other outcomes used in the economic model			
5% responder rate (n/N, %)‡	314/530 (59.2%)	55/270 (20.4%)	OR: 5.68 [4.03, 8.01]
Other outcomes used in the economic model, change from baseline to week 160 (LS Mean (SE))			
SBP (reduction in mmHg)	-2.07 (0.41)	-1.09 (0.58)	-0.98 [-2.38; 0.41]
HDL cholesterol (reduction in mg/dl)	1.96 (0.30)	1.45 (0.42)	0.51 [-0.51; 1.53]
Total cholesterol (reduction in mg/dl)	-4.03 (0.91)	-0.29 (1.28)	-3.73 [-6.81; -0.65]
HbA_{1c}	-0.22 (0.01)	-0.07 (0.02)	-0.15 [-0.19; -0.11]

Source: Response to Clarification Letter, Appendix E (Supplementary data 1).
AE = Adverse event; BOCF = best observation carried forward; HDL = High density lipoprotein; SBP = Systolic blood pressure; SE = standard error.
† Estimated treatment differences are from an analysis of covariance with data from the full-analysis set, with best-observation-carried-forward (BOCF) imputation. The full-analysis set comprised patients who underwent randomization, were exposed to at least one treatment dose, and had at least one assessment after baseline (69 patients were excluded from the full-analysis set: 61 owing to lack of an assessment and 8 owing to no exposure). The safety-analysis set included all patients who were randomly assigned to a study group and had exposure to a study drug.
‡ patients achieving at least 5% weight loss after 4 weeks titration and 12 weeks of treatment on the maintenance dose.

Table A2.2: Main outcomes as specified in the NICE scope for 'patients with a BMI ≥35 kg/m², prediabetes and high risk of CVD' (change between baseline and week 160 (MI-ME).*

Outcome	Liraglutide (n=530)	Placebo (n=270)	Estimated treatment difference, liraglutide vs. placebo (95% CI)†
Body weight-related outcomes, change from baseline to week 160 (MI-ME, LS Mean (SE))			
Body-mass index (%)	-3.99 (0.29)	-0.70 (0.40)	-3.28 [-4.25; -2.32]
Weight loss (%)	-3.94 (0.29)	-0.77 (0.40)	-3.17 [-4.14; -2.20]
Percentage body fat	Not assessed		
Waist circumference (cm)	-4.99 (0.34)	-2.36 (0.48)	-2.64 [-3.79; -1.48]
Other NICE specified outcomes			
Confirmed type 2 diabetes (n/N, %)	Not reported		
Cardiovascular adverse events (week 162; n/N, %)	86/530 (16.2%)	46/270 (17.0%)	NR
Idiopathic intracranial hypertension	Not assessed		
Non-alcoholic fatty liver disease	Not assessed		
Mortality (0 to 162 weeks)	0/530 (0%)	1/270 (0.4%)	NR
Health-related quality of life – SF-36 General Health; Change from baseline at week 160 (LS Mean (SE))	2.22 (0.35)	0.99 (0.49)	1.23 [0.06; 2.41]
Discontinuations (n/N (%))			
Discontinued due to AE	62/530 (11.7%)	13/270 (4.8%)	NR
Discontinued due to AE after week 16	60/530 (11.3%)	13/270 (4.8%)	NR
Discontinued due to AE before week 16	2/530 (0.4)	0/270 (0%)	
Other outcomes used in the economic model			
5% responder rate (n/N, %)‡	314/530 (59.2%)	55/270 (20.4%)	OR: 5.68 [4.03, 8.01]
Other outcomes used in the economic model, change from baseline to week 160 (MI-ME, LS Mean (SE))			
SBP (reduction in mmHg)	-1.19 (0.47)	1.19 (0.66)	-2.39 [-3.97; -0.81]
HDL cholesterol (reduction in mg/dl)	3.09 (0.35)	1.19 (0.49)	1.90 [0.72; 3.08]
Total cholesterol (reduction in mg/dl)	-2.40 (1.07)	-4.83 (1.50)	2.43 [-1.19; 6.05]
HbA_{1c}	-0.23 (0.01)	-0.05 (0.02)	-0.18 [-0.22; -0.13]

Source: Response to Clarification Letter, Appendix E (Supplementary data 1).
AE = Adverse event; HDL = High density lipoprotein; MI-ME = multiple-imputation for measurement error; SBP = Systolic blood pressure; SE = standard error.
† Estimated treatment differences are from an analysis of covariance with data from the full-analysis set, with multiple-imputation for measurement error (MI-ME) imputation. The full-analysis set comprised patients who underwent randomization, were exposed to at least one treatment dose, and had at least one assessment after baseline (69 patients were excluded from the full-analysis set: 61 owing to lack of an assessment and 8 owing to no exposure). The safety-analysis set included all patients who were randomly assigned to a study group and had exposure to a study drug.
‡ patients achieving at least 5% weight loss after 4 weeks titration and 12 weeks of treatment on the maintenance dose.

Table A2.3: Adverse events and serious adverse events (full trial population).*

Event	Liraglutide (n=2,481)			Placebo (n=1,242)		
	No. of patients (%)	No. of events	Event rate per 100 exposure-years	No. of patients (%)	No. of events	Event rate per 100 exposure-years
AEs in ≥5% of patients	**1992 (80.3)**	**7191**	**321.8**	**786 (63.3)**	**2068**	**193.7**
Nausea	1040 (41.9)	1579	36.7	201 (16.2)	259	13.1
Diarrhoea	583 (23.5)	917	21.3	153 (12.3)	200	10.1
Constipation	528 (21.3)	661	15.4	126 (10.1)	147	7.4
Vomiting	474 (19.1)	742	17.3	64 (5.2)	82	4.2
Dyspepsia	260 (10.5)	317	7.4	48 (3.9)	55	2.8
Upper abdominal pain	175 (7.1)	223	5.2	59 (4.8)	69	3.5
Abdominal pain	176 (7.1)	232	5.4	55 (4.4)	72	3.6
Nasopharyngitis	569 (22.9)	994	23.1	307 (24.7)	534	27.1
Upper respiratory tract infection	316 (12.7)	479	11.1	164 (13.2)	265	13.4
Sinusitis	197 (7.9)	251	5.8	95 (7.6)	149	7.6
Influenza	234 (9.4)	316	7.3	102 (8.2)	153	7.8
Headache	392 (15.8)	589	13.7	182 (14.7)	299	15.2
Dizziness	208 (8.4)	270	6.3	74 (6.0)	93	4.7
Decreased appetite	270 (10.9)	290	6.7	43 (3.5)	45	2.3
Back pain	270 (10.9)	370	8.6	159 (12.8)	206	10.4
Arthralgia	224 (9.0)	274	6.4	120 (9.7)	165	8.4
Fatigue	228 (9.2)	275	6.4	84 (6.8)	97	4.9
Injection-site hematoma	129 (5.2)	141	3.3	82 (6.6)	89	4.5
SAEs in ≥0.2% of patients						
Cholelithiasis	31 (1.2)	32	0.7	7 (0.6)	7	0.4
Cholecystitis acute	13 (0.5)	13	0.3	1 (0.1)	1	0.1
Osteoarthritis	12 (0.5)	14	0.3	5 (0.4)	6	0.3
Intervertebral disc protrusion	7 (0.3)	7	0.2	1 (0.1)	1	0.1
Pancreatitis acute†	NR	NR	NR	NR	NR	NR
Cholecystitis	8 (0.3)	8	0.2	0	-	-
Breast cancer	2 (0.3)	2	0.1	2 (0.6)	2	0.3
Back pain	4 (0.2)	4	0.1	4 (0.3)	4	0.2
Uterine leiomyoma						
Cellulitis	3 (0.1)	3	0.1	3 (0.2)	3	0.2
Gastroesophageal reflux disease	44 (6.5)	50	3.3	10 (2.9)	11	1.6
Bronchitis	0	-	-	1 (0.3)	1	0.1

Event	Liraglutide (n=2,481)			Placebo (n=1,242)		
	No. of patients (%)	No. of events	Event rate per 100 exposure-years	No. of patients (%)	No. of events	Event rate per 100 exposure-years
Bladder prolapse	1 (0.1)	1	0.1	1 (0.3)	1	0.1
Chest pain	0	-	-	1 (0.4)	1	0.2

Source: Response to Clarification Letter, Appendix E (Supplementary Data 1): Tables 63 and 66, pages 123 and 129.
AE = adverse events; NR = not reported; SAE = serious adverse event
* Treatment emergent adverse events experienced by ≥5% of patients with BMI >=35, High risk of Diabetes and high risk of CVD; From week 0 to week 162 in Trial 1839 (safety analysis set); and treatment emergent serious adverse events experienced by >=0.2% of patients with BMI >=35, High risk of Diabetes and high risk of CVD.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Liraglutide for managing overweight and obesity [ID740]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **12pm on Monday 9 September 2019** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

General Comments

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In numerous places the ERG report refers to a "*substantially delayed clarification response from the company"* (page 15 onwards). At the clarification telephone call on 22nd July 2019, the company explained that given the number of ERG questions some of which required new statistical analyses of clinical trial data and substantial reprogramming to the model the company could not response to all questions in the given 10-day response period. The company submitted a response to 17 of the 18 clinical questions and 21 of the 25 economic questions within 10 days as agreed, the full response to all questions was submitted a further 10 working days later. The project manager at NICE has been informed of the timeline for the delayed response.	Change "*substantially delayed clarification response"* to "*agreed delayed clarification response"*.	The phrase substantially delayed response implies there was no agreement between the company, NICE and the ERG on the response to questions.	Not a factual error, responses to several questions were substantially delayed.

Issue 1 Normal glucose *in*tolerance stated several times

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 13 (paragraph 8), page 14 (paragraph 1) and page 55 (paragraph 1). The term normal glucose intolerance state is mentioned several times. This is a factual inaccuracy as the correct term should be *normal glucose tolerance*, while glucose intolerance is denoted by prediabetes.	Replace the term *normal glucose intolerance* with *normal glucose tolerance* (8 incidences in total).	Typographical error – no impact.	This has been amended.

Issue 2 Omission of reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 20 (paragraph 2). The ERG report states '*According to the company in their response to clarification, orlistat is not often used in clinical practice due to the experience of undesirable side effects, which impacts patients from wanting to take orlistat or ceasing treatment after a short period,*' this statement is referenced to the company submission (ref 14). However, the comment should be referenced to the NICE TA 494 - Naltrexone–	A reference to TA494 should be added in addition to the company response (ref 14).	Primary reference sources should be used (as have been used elsewhere in the report). The reference implies that the company is the only reference source for the statement however originate to text within NICE TA 494.	Reference 14 is the response to clarification, which is the correct reference for this statement.

bupropion for managing overweight and obesity, as this is the primary source for the comment.			

Issue 3 Missing outcomes in submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 23, Table 3.1. The ERG comment on page 23 states "*For this population only two outcomes are reported in the CS: weight loss (change from baseline %, kg) and waist circumference."* Values for change in systolic blood pressure, HDL and total cholesterol and HbA_{1c} in the index population can be found in Table 19 of the company submission.	The sentence "*However, most outcomes are only reported for the ITT population in Trial 1839; while the company claims the CS focusses on 'patients with BMI ≥35 kg/m^2, prediabetes, high risk of CVD'. For this population only two outcomes are reported in the CS: weight loss (change from baseline %, kg) and waist circumference.*" should be removed.	The values were reported in the company submission (Table 19).	We were referring to the outcomes listed in the NICE scope. The only outcomes reported for the index population in the CS, were weight loss, waist circumference and incidence of type 2 diabetes. We have amended the sentence in Table 3.1 to: For this population only three outcomes are reported in the CS: weight loss (change from baseline %, kg), waist circumference and incidence of type 2 diabetes.

Issue 4 Reference list checking in other reviews and guidelines

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 31 (paragraph 6). The ERG state that "*No reference*	Clarification - no amendment needed.		Thank you.

checking was reported for this SLR". We would like to clarify that reference lists of these SLRs and meta-analyses were reviewed. Please accept our apologies this should have been clearer in the PICOS (table 4 of Appendix D).			

Issue 5 Synonym use in SLR search strategies

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 49, Section 5.1.1. Section 5.1.1, page 49, the ERG state: "*Use of search terms across strategies was inconsistent. For example, a broader range of synonyms for obesity was included in the cost effectiveness Econlit and NHS EED strategies, but omitted from the other searches. A limited number of terms for diet and exercise were included in the MEDLINE and Embase strategies, but omitted from the Econlit and NHS EED cost effectiveness searches.*" However, the indication search terms used for Econlit and NHS EED are aligned with the search engine fields possible within these	Please clarify this statement. Suggested revision: "*Use of search terms across strategies was inconsistent due to the need to be more specific in larger databases where an unmanageable number of hits would like be retrieved (i.e., Medline and Embase) and less specific in smaller databases that have a more narrow focus and a more sensitive strategy would be necessary (i.e., EconLit and NHS EED).*"	The synonyms used were used as per the need of different databases, as such there was little risk of missing relevant sources in NHS EED and Econlit.	Not a factual error.

databases. Further, the intervention was not included in the EconLit and NHS EED database search as these are more narrow, focused databases, whereas Medline and Embase are much larger in scope requiring more specific search strategies to narrow the search results to answer the research question.			

Issue 6 Use of validated quality assessment tool in the clinical effectiveness SLR

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 33, section 4.1.4. Section 4.1.4. page 33, the ERG states that there was lack of clarity on a validated quality assessment tool in clinical effectiveness SLR: "*While it was not clear if this represented a validated quality assessment tool, most of the criteria recommended by Cochrane for the assessment of quality in randomised controlled trials appeared to be presented*." However, the standard quality checklist recommended by NICE in the guidelines manual was provided and used for the quality appraisal presented in Appendix	No amendment needed, please accept our apologies for the lack of clarity.		Thank you.

D, section D.1.3, Table 7.			

Issue 7 HDL and total cholesterol change from baseline

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 41, Table 4.7; page 88, Table A2.1 and page 89, Table A2.2. Values for change from baseline HDL cholesterol and total cholesterol are given the wrong way around.	Amend the data within the tables to align with the data provided in CS chapter B.3 (i.e. switch headings for total cholesterol and HDL cholesterol around).	The data is not correctly aligned with the CS.	This has been amended.

Issue 8 Description of health states and events

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 52, Table 5.4. In addition to the states and events mentioned in the table (second row) the impact on costs and health outcomes of knee replacement surgeries, sleep apnoea and bariatric surgery were explored in the CS base case.	It is suggested to add the following to the description of states and events provided in table 5.4, column 2, row 3: "*sleep apnoea health-state, co-occurring in function of BMI with any of the other health states; knee replacement surgery considered an event which may occur at any point in time, and has an associated mortality; bariatric surgery, considered an event which can occur in both intervention and comparator arm in function of a given annual incidence, minimum BMI criteria and maximum age for eligibility*."	To provide a complete description of health states and events in the model which have an impact on costs and quality of life.	Not a factual error.

Issue 9 Clarification on duration of Liraglutide 3.0mg treatment at assessment of non-responder status

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 52, Table 5.4. It is stated that the stopping rule applied to liraglutide 3.0mg non-responders is applied after 12 weeks of treatment. The statement is imprecise in the sense that, in SCALE weight loss was evaluated after 16 weeks of treatment (i.e. 4 weeks titration followed by 12 weeks maintenance). In the model, the cost of liraglutide 3.0mg titration (4 weeks) and maintenance (12 weeks) were both considered, henceforth, 16 weeks of treatment in total.	It is proposed to rephrase the statement related to the stopping rule as "less than 5% weight loss <u>after 16 weeks of treatment, i.e. 4 weeks titration and 12 weeks at maintenance</u>."	To clarify the duration of liraglutide 3.0mg treatment at the timepoint of non-response efficacy assessment.	Not a factual error.

Issue 10 Clarification on model structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 55 (paragraph 2). The ERG mentions excess mortality due to presence of prediabetes, T2DM, and/or CV	Remove the reference to prediabetes excess mortality and rephrase the sentence "*…(i.e., background mortality and excess mortality due to the presence of ~~prediabetes,~~ T2DM, and/or*	To clarify which health states in the model were attributed excess mortality.	This has been amended.

events. While it is true that excess mortality was considered for health states encompassing T2DM, ACS, stroke and cancer, as well as for fatal events (MI, angina, stroke, knee-replacement surgery, bariatric surgery), no excess mortality was attributed to the prediabetes state. As such, for patients in a prediabetes state the general population (background) mortality was applied.	*CV-events).”*		

Issue 11 Clarification on scenario assuming patients with prediabetes do not automatically develop T2DM after ACS or stroke

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 57 (Paragraph 2). The ERG acknowledges that the scenario assuming patients with prediabetes do not automatically develop T2DM after ACS or stroke is likely to underestimate the T2DM incidence as well as the treatment effect for liraglutide 3.0mg. However, cardiovascular events are also likely to be underestimated by such an approach.	It is suggested to rephrase to: “*[..] this scenario is likely to underestimate T2DM incidence, cardiovascular event incidence as well as the treatment effect for liraglutide 3.0mg.*”	To clarify the risks that are being underestimated in the scenario.	Not a factual error.

Issue 12 Clarification on risk equations used (and alternative equations) to simulate the occurrence of T2DM

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 60 (Paragraph 6). The report states the QDiabetes-2018 C risk model was preferred by the company (over for instance the Framingham Recurring Coronary Heart Disease risk model). This is a factual inaccuracy as the Framingham Recurring Coronary Heart Disease estimates the risk of recurrent heart disease, this should be the Framingham Offspring risk model.	Is suggested to rephrase to "QDiabetes-2018 C risk model was preferred by the company (over for instance the Framingham Offspring risk model)."	Clarify risk equations available in the model for T2DM onset.	This has been amended.

Issue 13 Clarification on relative treatment effectiveness parameters used to estimate T2DM and CVD

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 62 (Table 5.8). BMI is listed as a treatment efficacy parameter influencing primary and secondary CV events in T2DM (based on UKPDS82 risk model). This is a factual inaccuracy as neither of the CV endpoints included in the economic model (angina, MI, stroke) are influenced by changes in BMI. Whilst BMI is a risk factor in the UKPDS82 model for congestive heart failure, this	In Table 5.8, remove "X" mark in column 4, row 3 corresponding to BMI.	Changes in BMI do not influence the risk of CV events in T2DM.	This has been amended.

outcome is not considered in the submitted economic model.			
Page 62 (Table 5.8). BMI is listed as a treatment efficacy parameter influencing secondary CV events in normal glucose tolerance (based on Framingham recurrent coronary heart disease). This is a factual inaccuracy as Framingham recurrent coronary heart disease includes the following independent predictors of risk: "age, ln (total cholesterol/HDL), ln (SBP), diabetes, smoker.	In Table 5.8, remove "X" mark in column 5, row 3 corresponding to BMI; add "X" mark in column 5, rows 5 and 6 corresponding to total and HDL cholesterol.	Changes in BMI do not influence the risk of recurrent CV events in normal glucose tolerance, but the ratio total/HDL cholesterol does.	This has been amended.
Page 62 (Table 5.8). HbA_{1c} is listed as a relative treatment effectiveness parameter is a factual inaccuracy. As noted in the paragraph above, while HbA_{1c} is an independent predictor of risk in the UKPDS82 model, HbA_{1c} is not a relative treatment effect parameter as changes on HbA_{1c} with liraglutide 3.0mg and diet and exercise were not modelled.	In Table 5.8, is suggested to remove row 7 altogether, corresponding to HbA_{1c}.	Treatment-specific changes in HbA_{1c} do not influence the estimation of CV risks in T2DM.	Not a factual error.

Issue 14 Correction of event disutilities in 3-month cycles

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 69 (Paragraph 2). The report refers to an error in the	The model should not be corrected by dividing the disutilities of acute events in the first 4	The ERG did not identify an error in the calculation of disutilities of acute	The analyses have been re-run and results have been

calculation of disutilities of acute events during the first four cycles of the model which use a cycle length of three months. We believe this is not an error and the model should not be corrected. Event disutilities represent a once-off loss in quality of life and are therefore applied only once in the model when the event occurs. Therefore, the adjustment performed by the ERG would underestimate the impact on quality of life of events 4 times, if corrected for cycle length.	cycles (which use a cycle length of three months).	events during the first four cycles, we believe these are calculated correctly. Dividing event disutilities by 4 to account for shorter cycle length would have the effect reduce to 1/4th the impact of events given events affect HRQOL only in the cycle when they occur.	amended.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Liraglutide for managing overweight and obesity [ID740]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm, Thursday 14 November 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

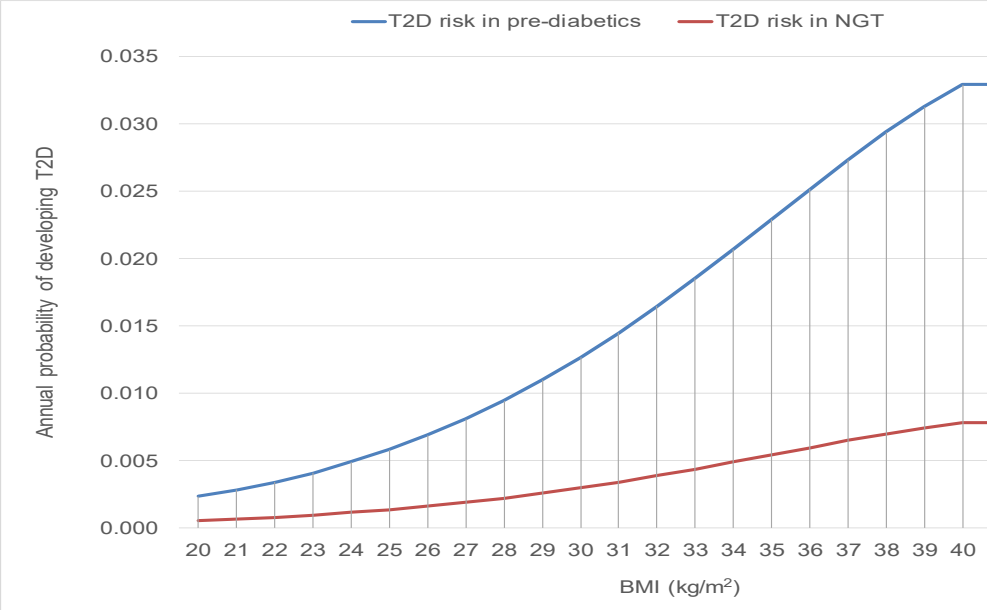
Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Anne Schou**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novo Nordisk Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Is the population defined in the company submission generalisable and clearly justified?	
Is the group identified in the company submission (that is people with a BMI ≥35 kg/m2, with pre-diabetes, and high risk of cardiovascular disease) identifiable and sufficiently justified?	The population is easily identifiable as the measures used to identify people with BMI ≥35 kg/m^2, with prediabetes, and high risk of cardiovascular disease are routinely measured in clinical practice. We believe this subgroup is sufficiently justified. This subgroup is at a higher risk of developing long term complications including type 2 diabetes and cardiovascular disease which affects life expectancy and quality of life as well as healthcare costs, therefore represents the patients most likely to benefit from treatment and optimises the cost-effectiveness. We have defined this subgroup based on advice from clinical experts and NICE (Office for Market Access). This subgroup is also the focus for the NHS in the Diabetes Prevention Programme (DPP) and NICE guidelines for cardiovascular risk management (CG 181).
Is the group identified in the company submission more likely to benefit from liraglutide than other populations, if so how and why?	The criteria for the index population identifies a subgroup of patients at a higher risk of obesity-related complications i.e. type 2 diabetes and CV events. People with prediabetes have an increased probability of developing type 2 diabetes, versus patients with normal glucose

	tolerance, which increases with increasing BMI (Figure 20 of CS) making prediabetes patients more likely to benefit from a reduction in risk in developing type 2 diabetes. **Figure 20 of CS: Annual probabilities of type 2 diabetes onset by BMI level**  NGT: normal glucose tolerance; T2D: type 2 diabetes. Source Qdiabetes. Physiological parameters such as BMI, systolic blood pressure, total cholesterol and HDL values are all components of the QRISK2 risk assessment which identifies a population at higher risk of CVD, and therefore more likely to benefit from a risk reduction.
Would liraglutide be provided within a Tier 3 service? Given that not all CCGs commission a Tier 3 service, how would people in those areas access liraglutide?	Liraglutide 3.0mg should be provided within a Tier 3 service or an equivalent specialist-led weight management service for CCGs that do not commission a Tier 3 service.

<table>
<tr><th colspan="2">Issue 2: The submission is based on a post-hoc subgroup</th></tr>
<tr><td>How reliable is the subgroup analysis and is it acceptable for decision making?</td><td>We believe the subgroup analysis is reliable and acceptable for decision making. The subgroup analysis is based on 800 patients (530 of which were randomised to liraglutide 3.0mg). Prediabetes was a pre-specified stratification at baseline in the trial 1839. The efficacy results from Trial 1839 in the prediabetes population (n=2,254) and in the index population (n=800) were similar as demonstrated in the summary table below (Table 1).

Table 1: Change from baseline to week 160 in efficacy outcomes for the whole trial population (prediabetes at baseline, n= 2,254) and the index population (with prediabetes, BMI ≥35 kg/m^2 and high risk of cardiovascular disease, n=800) – Trial 1839 - LOCF
<table>
<tr><th></th><th colspan="2">Liraglutide 3.0mg</th><th colspan="2">Placebo</th></tr>
<tr><th></th><th>Prediabetes at baseline</th><th>Index population</th><th>Prediabetes at baseline</th><th>Index population</th></tr>
<tr><td>Fasting body weight (%)</td><td>-6.14
(7.34)</td><td>-5.92
(6.79)</td><td>-1.89
(6.27)</td><td>-1.65
(6.79)</td></tr>
<tr><td>HbA_{1c} (%)</td><td>-0.35
(0.32)</td><td>-0.39
(0.32)</td><td>-0.14
(0.34)</td><td>-0.13
(0.32)</td></tr>
<tr><td>Waist circumference (cm)</td><td>-6.87</td><td>-6.95
(8.09)</td><td>-3.90</td><td>-3.44
(8.09)</td></tr>
<tr><td>Systolic blood pressure (mmHg)</td><td>-3.19
(13.00)</td><td>-4.09
(11.69)</td><td>-0.53
(13.73)</td><td>-1.09
(11.69)</td></tr>
</table>
Values in parentheses are standard deviations.</td></tr>
<tr><td>Should the treatment benefit be derived from the full ITT population (the full clinical trial results) or the index population?</td><td>The analysis should be based on the index population, reflecting where liraglutide 3.0mg would be used in clinical practice.</td></tr>
</table>

Given that the 12-week stopping rule was not applied in Trial 1839, can the results of Trial 1839 be generalisable to the intended UK population?	We believe that the results of trial 1839 are generalisable to the intended UK population. The stopping rule was not included in the trial, as stopping rules can only be assessed after trials have been completed and the non-responder population identified. The stopping rule is part of the license for liraglutide 3.0mg, hence needs to be incorporated into the evaluation as it will be applied in UK clinical practice.
Issue 3: Can orlistat and bariatric surgery be excluded as comparators?	
If liraglutide were approved for use in the NHS would it be considered as an option for someone likely to be treated with orlistat?	As mentioned in our CS, the reason for omitting orlistat as a comparator is 2-fold: 1. Orlistat is currently recommended as a treatment option in primary care in a much wider population than is proposed for liraglutide 3.0mg and as such would be used earlier in the treatment pathway (tier 2). 2. The use of orlistat is currently limited and declining, supported by Section 3.4 of the final appraisal determination for naltrexone-bupropion (TA494) where the committee concluded that standard management was the main comparator in the appraisal.
If liraglutide were approved for use in the NHS would it be considered as an option for someone likely to be recommended for bariatric surgery? Is the limited use of orlistat in clinical practice sufficient justification to exclude it as a comparator?	Liraglutide 3.0mg would not be a direct replacement for bariatric surgery. Bariatric surgery has already been demonstrated as a cost-effective treatment option in Tier 4 services for a selected group of patients. For patients where bariatric surgery would be an appropriate option, and this is acceptable to the patient, this should be the preferred option according to NICE clinical guideline CG 189.
Would bariatric surgery be offered to people with people with a BMI ≥35 kg/m2, pre-diabetes, and high risk of cardiovascular disease?	As noted above according to NICE Clinical Guidelines (CG189) these patients could be eligible for bariatric surgery. However, only around 0.1% of those eligible for bariatric surgery receive it (NICE TA494). Liraglutide 3.0mg could be suitable for a group of patients who are unwilling or unable to undergo surgery. These patients currently have no other treatment options.
Issue 4: Assumptions related to treatment discontinuation	

<table>
<tr>
<td>What drop-out pattern would we expect to see in practice? Would most people discontinue liraglutide within the first 3 or 6 months or would you continue to see discontinuations after 6 months?</td>
<td>We have no data that describes treatment discontinuation patterns for liraglutide 3.0mg in clinical practice in the UK.

Following discussions during technical engagement, we provide a revised base case which incorporates treatment discontinuation using per cycle discontinuation probabilities as observed in Trial 1839 (see Appendix 1 and Table 2).

Table 2: Revised company base case
<table>
<tr><th>Technologies</th><th>Costs (£)</th><th>LYG</th><th>QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>Liraglutide 3.0mg</td><td>£21,040</td><td>18.547</td><td>15.271</td><td rowspan="3">£19,935</td></tr>
<tr><td>Diet & exercise</td><td>£19,780</td><td>18.514</td><td>15.208</td></tr>
<tr><td>Incremental</td><td>£1,260</td><td>0.033</td><td>0.063</td></tr>
</table>
Incorporating cost of bariatric surgery (ERG 1), assuming patients with missing response values to be non-responders (ERG 2) and per cycle treatment discontinuation up to 2 years

As noted in the CS, a physician survey (Questions 16 Appendix N) reported that most patients would be expected to have discontinued treatment after 2 years. This justifies our base case assumption of a maximum treatment duration of 2 years. However, based on the data from trial 1839 we have evaluated the impact of a 1- and 3-year maximum treatment duration which results in a deterministic ICER of £14,375 and £23,170, respectively (see Appendix 1).</td>
</tr>
<tr>
<td>How likely is it that patients will receive liraglutide until they are not achieving clinical benefit (i.e. maintaining an initial loss of 5% body weight)?</td>
<td>We anticipate patients will continue to receive liraglutide 3.0mg whilst they are achieving clinical benefit and it is acceptable to the patient to stay on treatment.</td>
</tr>
<tr>
<td colspan="2">Issue 5: Implementation of treatment stopping rules</td>
</tr>
</table>

Given that the treatment stopping rules (all non-responder patients with pre-diabetes) and (after two years of treatment) were not implemented in the trial, what is the rationale for stopping treatment with liraglutide after 2 years?	The rationale for the maximum treatment duration of 2 years is based on the availability of data from trial 1839 and a physician survey as explained under Issue 4. In accordance with the license for liraglutide 3.0mg patients will discontinue therapy if they fail to achieve ≥5% weight loss after 12 weeks of treatment.
Would a treatment stopping rule be implementable in clinical practice?	A stopping rule is easily implementable in clinical practice and has been previously used for other anti-obesity therapies, including orlistat, and the now withdrawn rimonabant and sibutramine.
Does clinical experience of rates and degree of weight regain match the assumptions in the modelling?	We sought clinical expert advice on the rates and degree of weight regain and used an approach to be consistent with other published models and the preferred assumptions of the committee/ERG that evaluated Naltrexone-bupropion for managing overweight and obesity in 2017 (TA494).
Issue 6: The assumption that pre-diabetic patients automatically develop type 2 diabetes after a cardiovascular event	
Is the company's simplifying assumption that all people (who have a BMI ≥35 kg/m2, pre-diabetes, and high risk of cardiovascular disease) develop type 2 diabetes following a cardiovascular event unreasonable?	The company maintains that the approach taken is reasonable, we also present a scenario analysis with an alternative approach. There are no risk equations that estimate risk of second and subsequent CV events specifically for patients with prediabetes. A rapid review of the literature identified two systematic reviews that reported increasing risk of CV disease and death in people with prediabetes[1, 2]. The approach taken in the model gives patients with prediabetes who have CV events elevated risk of subsequent events, at the same level as patients who have diabetes. A scenario analysis of the company's revised base case explored an alternative approach where risk of subsequent events is reduced to the level of patients who do not have diabetes, this increases the base case ICER from £19,935 to £21,474 (see Table 3).

<table>
<tr><td></td><td>
Table 3: Revised cost-effectiveness results - No automatic development of type 2 diabetes post CV event (Issue 6)
<table>
<tr><th>Technologies</th><th>Costs (£)</th><th>LYG</th><th>QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td colspan="5">Revised base case</td></tr>
<tr><td>Liraglutide 3.0mg</td><td>£21,040</td><td>18.547</td><td>15.271</td><td rowspan="3">£19,935</td></tr>
<tr><td>Diet & exercise</td><td>£19,780</td><td>18.514</td><td>15.208</td></tr>
<tr><td>Incremental</td><td>£1,260</td><td>0.033</td><td>0.063</td></tr>
<tr><td colspan="5">Scenario analysis – No automatic development of type 2 diabetes post CV event (Issue 6)</td></tr>
<tr><td>Liraglutide 3.0mg</td><td>£20,404</td><td>18.648</td><td>15.379</td><td rowspan="3">£21,474</td></tr>
<tr><td>Diet & exercise</td><td>£19,131</td><td>18.619</td><td>15.320</td></tr>
<tr><td>Incremental</td><td>£1,273</td><td>0.029</td><td>0.059</td></tr>
</table>
</td></tr>
<tr><td>What proportion of people (who have a BMI ≥35 kg/m2, pre-diabetes, and high risk of cardiovascular disease) are likely to have a diagnosis of type 2 diabetes following a CVD event?</td><td>We identified no direct evidence specific to this population. Our rapid review of the literature identified two systematic reviews showing that patients with prediabetes who have a CV event are at elevated risk of subsequent events. As described above this approach is intended to act as a proxy for the increased risk of subsequent events in patients with prediabetes who experience a CV event.</td></tr>
<tr><td colspan="2">Issue 7: The assumption that liraglutide 3.0mg non-responders would have the same effectiveness as the placebo arm in Trial 1839 (A non-responder is someone with less than 5% weight loss after 12 weeks of treatment)</td></tr>
<tr><td>Which is a better proxy in the economic model of the treatment effect for liraglutide non-responders the treatment effect for the overall placebo (diet and</td><td>We believe response to liraglutide 3.0mg is biologically determined. The most plausible assumption for non-responders would be to adopt the same efficacy as placebo in the trial, as patients would continue with standard management of diet and lifestyle interventions. Our revised base case (Appendix 1) assumes non-responders have the same efficacy as placebo (as per our</td></tr>
</table>

<table>
<tr>
<td>exercise) group in the trial or the treatment effect for the placebo non-responders in the trial?</td>
<td>original CS). Table 4 presents a scenario analysis showing the impact of assuming these patients have the same efficacy as placebo non-responders.

Table 4: Revised cost-effectiveness – including liraglutide 3.0mg non-responder efficacy have the same efficacy as placebo non-responders (Issue 7)
<table>
<tr><th>Technologies</th><th>Costs (£)</th><th>LYG</th><th>QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td colspan="5">Revised base case</td></tr>
<tr><td>Liraglutide 3.0mg</td><td>£21,040</td><td>18.547</td><td>15.271</td><td rowspan="3">£19,935</td></tr>
<tr><td>Diet & exercise</td><td>£19,780</td><td>18.514</td><td>15.208</td></tr>
<tr><td>Incremental</td><td>£1,260</td><td>0.033</td><td>0.063</td></tr>
<tr><td colspan="5">Scenario analysis where liraglutide 3.0mg non-responders have the same efficacy as placebo non-responders</td></tr>
<tr><td>Liraglutide 3.0mg</td><td>£21,107</td><td>18.545</td><td>15.264</td><td rowspan="3">£23,772</td></tr>
<tr><td>Diet & exercise</td><td>£19,780</td><td>18.514</td><td>15.208</td></tr>
<tr><td>Incremental</td><td>£1,328</td><td>0.031</td><td>0.056</td></tr>
</table>
</td>
</tr>
<tr>
<td>Would the modelled liraglutide non-responders be likely to have worse outcomes than the whole placebo group in the trial?</td>
<td>We are unaware of any evidence to suggest liraglutide non-responders would have worse outcomes than the whole placebo group in the trial.</td>
</tr>
<tr>
<td>Should the effectiveness of liraglutide should be based on all patients who receive liraglutide, including those who achieve less than 5% weight loss at 16-weeks?</td>
<td>Patients who achieve less than 5% weight loss at 16 weeks will discontinue therapy in accordance with the license. The effectiveness of liraglutide 3.0mg should be based on those treated within license.</td>
</tr>
</table>

References

[1] Cavero-Redondo, I. et al., 2017. Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis.. *BMJ Open,* 7(7)(Jul 31), p. e015949.

[2] Huang, Y. et al., 2016. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis.. *BMJ,* Issue Nov 23, p. 355:i5953.

APPENDIX 1

Liraglutide 3.0mg for managing overweight and obesity

Technical Engagement Response

Summary of technical Engagement and ERG Report Issues

Technical Engagement report		Incorporated into analyses
Issue 1	Is the population defined in the CS generalisable and clearly justified?	NA
Issue 2	The submission is based on a post-hoc subgroup	Analyses are based on the post-hoc subgroup
Issue 3	Can orlistat and bariatric surgery be excluded as comparators?	Diet and exercise is the only comparator
Issue 4	Assumptions related to treatment discontinuation	Per cycle discontinuation has been included in revised company base case (Table I)
Issue 5	Implementation of treatment stopping rules	The licensed stopping rule (≥ 5% weight loss at 12 weeks) and a maximum treatment duration are included in analyses as per original base case
Issue 6	The assumption that pre-diabetes patients automatically develop type 2 diabetes after a CV event	Included in revised company base case, alternative approach included as scenario analysis (Table J)
Issue 7	The assumption that liraglutide 3.0mg non-responders would have the same effectiveness as the placebo arm in Trial 1839	Included in revised company base case, alternative approach included as scenario analysis (Table K)
ERG Report		
ERG 1	Correction of cost of leaks related to bariatric surgery	Included in revised company base case (Table I)
ERG 2	Calculation of proportion of non-responders. ERG preference is to assume patients with a missing response are non-responders	We have accepted the assumption that patients with a missing value for response are non-responders and included this in our revised company base case (Table I)
ERG 3	Same as Issue 6	Not included in revised company base case but included as a scenario analysis (Table J)
ERG 4	The use of different risk models for patients with and without type 2 diabetes	Not included in revised company base case but included as scenario analyses (Table L)

Table A: Summary of revised cost effectiveness analyses

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Revised Company Base Case – incorporating Issue 4, Issue 5, ERG 1 and ERG 2					
Liraglutide	£21,040	15.271			
Diet and exercise	£19,780	15.208	£1,260	0.063	£19,935
Scenario Analysis - Updated company base case + Issue 6 - No automatic development of T2D post CV event					
Liraglutide	£20,404	15.379			
Diet and exercise	£19,131	15.32	£1,273	0.059	£21,474
Scenario Analysis - Updated company base case + Issue 7 – The assumption that liraglutide 3.0mg non-responders would have the same effectiveness as placebo non-responders in Trial 1839 (non-responder's assumption)					
Liraglutide	£21,107	15.264			
Diet and exercise	£19,780	15.208	£1,328	0.056	£23,772
Scenario Analysis - Updated company base case + selection of risk models QRISK3 + Framingham in Type 2 diabetes					
Liraglutide	£21,139	15.381			
Diet and exercise	£19,882	15.329	£1,257	0.052	£23,990
Scenario Analysis - Updated company base case + combined Issue 6 and Issue 7					
Liraglutide	£20,471	15.372			
Diet and exercise	£19,131	15.320	£1,340	0.052	£25,657
Scenario Analysis - Updated company base case + Issue 6 and alternative risk models					
Liraglutide	£20,464	15.447			
Diet and exercise	£19,190	15.397	£1,274	0.050	£25,452
Scenario Analysis - Updated company base case + Issues 6, Issue 7 and alternative risk models					
Liraglutide	£20,531	15.440			
Diet and exercise	£19,190	15.397	£1,340	0.044	£30,804

1. Introduction

In the ERG report which reviews the company submission (CS) and economic model for the Technology Appraisal - Liraglutide for managing overweight and obesity (ID740), the ERG comment they were unable to implement all '*assumptions and/or parameters that might have individually a minimal impact on the estimated cost effectiveness potentially have, when all combined, a considerable impact'.* In an effort to allow assumptions and scenarios to be evaluated more easily in one model, we initiated further work to permit this.

1.1. Update 1: Modelling of prediabetes reversal

The re-programming and update of the model identified a legacy issue with the way in which prediabetes reversal had been modelled. The obesity model was originally developed to model outcomes for a mixed population with prediabetes and/or normal glucose tolerance and/or type 2 diabetes. In the original obesity model, which was based on the mixed population, it was not technically possible to distinguish patients who initiated the model in NGT from those who transitioned to "no complication" following prediabetes reversal efficacy. Therefore, the original obesity model contained both of these patient groups within the "no complication" state and applied an average risk for developing diabetes (average for prediabetes and NGT) after the treatment duration and catch-up period.

The CS focused on a subpopulation of patients who (as described previously) had a BMI ≥35 kg/m^2, with prediabetes, and high risk of cardiovascular disease. As 100% of patients had prediabetes at baseline, the programming of the original model has the following consequences:

a) The calculated average risk (described above) did not reflect the risk of diabetes development in patients with prediabetes, once these patients returned to prediabetes after treatment and catch-up period. This issue was identified as a consequence of ERG question B5 and adjusted in response to ERG questions which revised the base case ICER from £13,059 to £9,096 (page 97 of company response to ERG questions). However, the implementation to fix this issue was incomplete.

b) Keeping the cohort with baseline prediabetes beyond treatment and catch-up in the "no complication" state as per the original model assumes that patients with prediabetes at baseline, who never reversed to NGT, develop diabetes post a cardiovascular event (i.e. patients move from "prediabetes" state to "T2D plus ACS/stroke" state after an ACS or stroke event). Yet, this assumption does not apply to patients in the "no complication" state, and as such, not to patients with baseline prediabetes who return to prediabetes after treatment and catch-up. Consequently, the original model programming needed to be further modified by making all patients with temporary prediabetes reversal transition from "no complication" back to "prediabetes" state after treatment and catch-up period.

The results tables below illustrate the impact of this update to the originally submitted base case cost-effectiveness results in an iterative manner:

Table B: Base case cost-effectiveness submitted in CS

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,988	18.584	15.336	£13,059
Diet & exercise	£19,419	18.496	15.216	
Incremental	£1,568	0.088	0.120	

Table C: Updated cost-effectiveness submitted during ERG questions

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,606	18.524	15.256	£9,096
Diet & exercise	£20,270	18.417	15.109	
Incremental	£1,336	0.106	0.147	

Table D: Updated cost-effectiveness after update 1

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£22,555	18.399	15.129	£18,261
Diet & exercise	£20,831	18.344	15.034	
Incremental	£1,725	0.055	0.094	

1.2.Update 2: Cardiovascular risk applied in prediabetes

In the CS with the original model, the risk of cardiovascular disease in people with prediabetes is not as conservative as initially described in the submission, i.e. based on CVD risk in NGT using QRisk3. The submitted model uses a simple average of CVD risk specific to NGT and to diabetes, calculated as:

CVD risk in "prediabetes" = [QRisk3 (for NGT) + UKPDS82 (for T2D)] /2

to define the transition from "prediabetes" to "T2D + post ACS/stroke".

Calculating the number of cardiovascular events (in prediabetes) as well as the transition from "prediabetes" to "T2D + post ACS/stroke", the CVD risk in NGT based on QRisk3 needs to be applied, as described in the CS. The change has the following impact on the cost-effectiveness results:

Table E: Updated cost-effectiveness incorporating update 1 & 2

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,790	18.538	15.275	£22,313
Diet & exercise	£19,996	18.497	15.195	
Incremental	£1,794	0.042	0.080	

1.3. Quality check of updated base case model

Following updates 1 and 2 above, a systematic model review and quality assessment was undertaken by two independent modellers to ensure no further issues were present in the model. The tests performed and proposed resolution are available in a separate report (Quality Check Report - Obesity Model v1.0 18OCT2019). Two minor programming issues were identified: one that impacted the base case results slightly (see **Table F**), and another which marginally impacted the results when incorporating adverse events in the model (ICER decreased by £6).

Table F: Updated cost-effectiveness following quality check

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,804	18.555	15.288	£22,458
Diet & exercise	£20,011	18.514	15.208	
Incremental	£1,793	0.041	0.080	

2. Presentation of updated cost effectiveness results and company revised base case

Considering the critical appraisal by the ERG and remaining areas of uncertainty described in the NICE Technical Report, we present a revised base case (incorporating the updates described above) which better reflects the preferred assumptions of the NICE Technical team in order to support the committee in reaching a decision regarding the cost effectiveness of liraglutide 3.0mg in the index population.

2.1. ERG Report – ERG analysis 1 – Cost of Bariatric Surgery

We accept the correction of calculation of bariatric surgery cost and incorporate it into our revised base case (see **Table G**).

Table G: Revised cost-effectiveness – incorporating the ERG preferred cost of bariatric surgery (ERG analysis 1)

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,573	18.555	15.288	**£22,456**
Diet & exercise	£19,780	18.514	15.208	
Incremental	£1,793	0.041	0.080	

2.2. ERG Report – ERG analysis 2 – Assuming patients with missing response values to be non-responders (ERG analyses 1+2)

We are happy to incorporate the ERG suggestion that patients with missing values would more likely be non-responders than missing at random, although note it is not an issue raised in the technical engagement report.

Table H: Revised cost-effectiveness – incorporating cost of bariatric surgery and assuming patients with missing response values to be non-responders (ERG analyses 1+2)

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,424	18.550	15.278	**£23,269**
Diet & exercise	£19,780	18.514	15.208	
Incremental	£1,644	0.036	0.071	

2.3. Technical Report – Issue 4 – Assumptions related to treatment discontinuation

In the original CS model a simplifying assumption was made that patients only discontinue treatment via the stopping rule and after the maximum treatment duration. We are happy to accept the ERG and NICE technical team's preferred scenario using per cycle discontinuation probabilities as observed in Trial 1839. Incorporation of this assumption yields a deterministic ICER of £19,935 (see **Table I**).

Table I: Revised company base case - incorporating cost of bariatric surgery, assuming patients with missing response values to be non-responders (ERG analyses 1+2) and per cycle treatment discontinuation up to 2 years (Issue 4)

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	**£21,040**	**18.547**	**15.271**	**£19,935**
Diet & exercise	**£19,780**	**18.514**	**15.208**	
Incremental	**£1,260**	**0.033**	**0.063**	

2.4. Scenario analyses

2.4.1. Issue 6 (ERG 3) No automatic development of T2D post CV event

A scenario analysis removing the assumption that patients with prediabetes automatically develop type 2 diabetes after a cardiovascular event is shown in **Table J**. The total costs per arm decrease as consequence of lower CVD and lower type 2 diabetes whilst total LYG and total QALYs per arm increase versus the updated company base case. However, the impact on the ICER is small.

Table J: Scenario analysis – Issue 6 - incorporating the assumption that prediabetes patients do not develop type 2 diabetes after a CV event

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,404	18.648	15.379	**£21,474**
Diet & exercise	£19,131	18.619	15.320	
Incremental	£1,273	0.029	0.059	

2.4.2. Issue 7 – Liraglutide non-responders have the efficacy of placebo non-responders

A scenario analysis with the assumption that liraglutide 3.0mg non-responders would have the same effectiveness as placebo non-responders in Trial 1839 (non-responder's assumption) is shown in **Table K**). There is a slight decrease in projected LY and QALY

in liraglutide arm as consequence of lower treatment benefits along with a slight increase in total costs, (no change for diet and exercise arm) compared with update company base case.

Table K: Scenario analysis – Issue 7 - incorporating the assumption that liraglutide 3.0mg non-responders have the same efficacy as placebo non-responders

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,107	18.545	15.264	**£23,772**
Diet & exercise	£19,780	18.514	15.208	
Incremental	£1,328	0.031	0.056	

2.4.3. Other issues – Selection of risk models QRISK3 and Framingham in Type 2 diabetes

In the CS the UKPDS 82 risk model was used to predict cardiovascular risk in patients with type 2 diabetes, however the ERG stated a preference for using QRISK3 and Framingham in type 2 diabetes patients.

The UKPDS82 is preferred over QRisk3 when estimating cardiovascular outcomes in type 2 diabetes as it was derived primarily in type 2 diabetes patients (i.e. all subjects had type 2 diabetes at baseline, compared with QRisk3 where less than 2% of the population did). Moreover, UKPDS82 has been NICE's preferred healthcare analysis tool to evaluate new interventions in diabetes. QRisk3 was estimated on a sample of patients followed in general practices in England. Most patients did not have type 2 diabetes at baseline and the risk equation was intended as a cardiovascular risk prediction model in the general population (Hippisley-Cox, et al., 2017 ref 122 in CS). Also, the main predictor of risk of complications in type 2 diabetes, HbA1c, was not included in the model. Instead, the equation included a categorical variable (yes, no) for presence of type 2 diabetes.

UKPDS82 is also preferred over Framingham Recurrent CHD as the later was estimated on a North American population and HbA1c was not included as a risk predictor.

However, scenario analyses have been performed as shown in **Table L**, using QRISK3 for the prediction of a first CV event in type 2 diabetes, Framingham for the risk of recurrent CV events and the two risk models together.

Table L: Scenario analyses – Selection of risk models

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
QRISK3 for prediction of first CV event in type 2 diabetes				
Liraglutide 3.0mg	£21,073	18.582	15.300	**£22,424**
Diet & exercise	£19,810	18.557	15.244	
Incremental	£1,262	0.025	0.056	
Framingham for prediction of recurrent CV event in type 2 diabetes				
Liraglutide 3.0mg	£21,115	18.655	15.356	**£21,373**
Diet & exercise	£19,861	18.628	15.297	
Incremental	£1,254	0.027	0.059	
QRISK3 and Framingham for prediction of CV events in Type 2 diabetes				
Liraglutide 3.0mg	£21,139	18.685	15.381	**£23,990**
Diet & exercise	£19,882	18.665	15.329	
Incremental	£1,257	0.020	0.052	

2.4.4. Cumulative impact of alternative scenario analyses

The cumulative impact of the different issues raised in the technical engagement and ERG report are presented in **Table M**.

Table M: Scenario analyses combining issues (deterministic)

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Revised company base case plus Issues 6 and Issue 7				
Liraglutide 3.0mg	£20,471	18.647	15.372	**£25,657**
Diet & exercise	£19,131	18.619	15.320	
Incremental	£1,340	0.027	0.052	
Revised company base case plus Issue 6 and selection of risk models QRISK3 & Framingham in Type 2 diabetes				
Liraglutide 3.0mg	£20,464	18.733	15.447	**£25,452**
Diet & exercise	£19,190	18.714	15.397	
Incremental	£1,274	0.018	0.050	
Revised company base case plus Issue 6, Issue 7 and selection of risk models QRISK3 & Framingham in Type 2 diabetes				
Liraglutide 3.0mg	£20,531	18.731	15.440	**£30,804**

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Revised company base case plus Issues 6 and Issue 7				
Diet & exercise	£19,190	18.714	15.397	
Incremental	£1,340	0.017	0.044	

2.4.5. Probabilistic revised company base case

Probabilistic results for the revised cost effectiveness analyses are presented in

Table N.

Table N: Probabilistic revised company base case and cumulative scenario analyses

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Probabilistic revised company base case				
Liraglutide 3.0mg	£21,503	18.536	15.261	**£20,502**
Diet & exercise	£20,265	18.507	15.201	
Incremental	£1,238	0.030	0.060	
Probabilistic revised company base case plus Issue 6 & Issue 7				
Liraglutide 3.0mg	£20,801	18.599	15.337	**£25,455**
Diet & exercise	£19,490	18.574	15.286	
Incremental	£1,310	0.026	0.051	
Probabilistic revised company base case plus Issue 6 and selection of risk models QRISK3 & Framingham in Type 2 diabetes				
Liraglutide 3.0mg	£20,892	18.655	15.384	**£24,901**
Diet & exercise	£19,634	18.636	15.333	
Incremental	£1,258	0.019	0.051	
Probabilistic revised company base case plus Issue 6, Issues 7 and selection of risk models QRISK3 & Framingham in Type 2 diabetes				
Liraglutide 3.0mg	£20,908	18.648	15.369	**£29,529**
Diet & exercise	£19,595	18.630	15.324	
Incremental	£1,314	0.018	0.044	

2.4.6. Revised company base case with maximum treatment duration of 1 and 3 years

Further scenario analyses have been performed testing a maximum treatment duration of 1 and 3 years (**Table O**).

Table O: Revised company base case with maximum treatment duration of 1 and 3 years

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Revised company base case & maximum treatment duration 1 year				
Liraglutide 3.0mg	£20,628	18.530	15.229	**£14,375**
Diet & exercise	£19,877	18.501	15.177	
Incremental	£750	0.028	0.052	
Revised company base case & maximum treatment duration 3 years				
Liraglutide 3.0mg	£21,094	18.561	15.316	**£23,170**
Diet & exercise	£19,466	18.525	15.246	
Incremental	£1,628	0.036	0.070	

We would be happy to provide additional scenario analyses should these be helpful to the ERG and committee.

3. Factual accuracy

In section 1.5 (pages 4-5) of the technical report the text states '*Cardiovascular adverse events, mortality and health-related quality of life (SF-36, General Health) showed no significant differences between groups*', however as noted in the CS (section B.2.6.11 Patient reported outcomes) for SF-36 at the end of treatment (week 160), the estimated mean change from baseline on all domains were greater with liraglutide 3.0mg than with placebo. The improvements in general health score, vitality score, physical functioning score and mental health score were statistically significant (Kolotkin et al Ref 90 in CS). HRQoL (SF-36, General Health) was also analysed in the post-hoc analysis subgroup for the index population and found similar results, see Appendix E: Post hoc subgroup analysis – Supplementary data, (page 34).

In their report (page 15) the ERG questions the assumption that patients who temporarily revert to NGT do not receive monitoring given their history of prediabetes, their remaining obesity and increased risk of developing type 2 diabetes and CV events. It should be noted that the annual non-pharmacological cost of diet and exercise still applied to these patients (£130.83, Table 40 page 137 of CS) and it is only the cost of prediabetes (£55 Table 42, page 138) that is removed.

APPENDIX 2 – Revised Price Analyses

Liraglutide 3.0mg for managing overweight and obesity (ID740)

Following discussion with NHS England Novo Nordisk has provisionally agreed a revised price through a commercial arrangement. The new pack price is [redacted] per pack of 5 prefilled pens [18mg/3ml]. This document provides the company revised ICERs which were submitted in response to Technical Engagement incorporating this revised price.

Summary of Technical Engagement and ERG Report Issues

Technical Engagement report		Incorporated into analyses
Issue 1	Is the population defined in the CS generalisable and clearly justified?	NA
Issue 2	The submission is based on a post-hoc subgroup	Analyses are based on the post-hoc subgroup
Issue 3	Can orlistat and bariatric surgery be excluded as comparators?	Diet and exercise is the only comparator
Issue 4	Assumptions related to treatment discontinuation	Per cycle discontinuation has been included in revised company base case (Table D)
Issue 5	Implementation of treatment stopping rules	The licensed stopping rule (≥5% weight loss at 12 weeks) and a maximum treatment duration are included in analyses as per original base case
Issue 6	The assumption that pre-diabetes patients automatically develop type 2 diabetes after a CV event	Included in revised company base case, alternative approach included as scenario analysis (Table E)
Issue 7	The assumption that liraglutide 3.0mg non-responders would have the same effectiveness as the placebo arm in Trial 1839	Included in revised company base case, alternative approach included as scenario analysis (Table F)
ERG Report		
ERG 1	Correction of cost of leaks related to bariatric surgery	Included in revised company base case (Table D)
ERG 2	Calculation of proportion of non-responders. ERG preference is to assume patients with a missing response are non-responders	We have accepted the assumption that patients with a missing value for response are non-responders and included this in our revised company base case (Table D)
ERG 3	Same as Issue 6	Not included in revised company base case but included as a scenario analysis (Table E)
ERG 4	The use of different risk models for patients with and without type 2 diabetes	Not included in revised company base case but included as scenario analyses (Table G)

Table A: Summary of revised cost effectiveness analyses (new pack price [redacted])

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Revised Company Base Case – incorporating Issue 4, Issue 5, ERG 1 and ERG 2					
Liraglutide	£20,867	15.271			
Diet and exercise	£19,780	15.208	£1,087	0.063	£17,194
Scenario Analysis - Updated company base case + Issue 6 - No automatic development of T2D post CV event					
Liraglutide	£20,231	15.379			
Diet and exercise	£19,131	15.320	£1,100	0.059	£18,552
Scenario Analysis - Updated company base case + Issue 7 – The assumption that liraglutide 3.0mg non-responders would have the same effectiveness as placebo non-responders in Trial 1839 (non-responder's assumption)					
Liraglutide	£20,934	15.264			
Diet and exercise	£19,780	15.208	£1,154	0.056	£20,670
Scenario Analysis - Updated company base case + selection of risk models QRISK3 + Framingham in Type 2 diabetes					
Liraglutide	£20,966	15.381			
Diet and exercise	£19,882	15.329	£1,084	0.052	£20,684
Scenario Analysis - Updated company base case + combined Issue 6 and Issue 7					
Liraglutide	£20,298	15.372			
Diet and exercise	£19,131	15.320	£1,167	0.052	£22,340
Scenario Analysis - Updated company base case + Issue 6 and alternative risk models					
Liraglutide	£20,291	15.447			
Diet and exercise	£19,190	15.397	£1,100	0.050	£21,989
Scenario Analysis - Updated company base case + Issues 6, Issue 7 and alternative risk models					
Liraglutide	£20,357	15.440			
Diet and exercise	£19,190	15.397	£1,167	0.044	£26,821

Presentation of updated cost effectiveness results and company revised base case with new price

Following the same structure as Appendix 1, this document provides a summary of analyses with the new price agreed with NHS England.

ERG Report – ERG analysis 1 – Cost of Bariatric Surgery

We accept the correction of calculation of bariatric surgery cost and incorporate it into our revised base case (see **Table B**).

Table B: Revised cost-effectiveness – incorporating the ERG preferred cost of bariatric surgery (ERG analysis 1)

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,337	18.555	15.288	**£19,504**
Diet & exercise	£19,780	18.514	15.208	
Incremental	£1,557	0.041	0.080	

ERG Report – ERG analysis 2 – Assuming patients with missing response values to be non-responders (ERG analyses 1+2)

We are happy to incorporate the ERG suggestion that patients with missing values would more likely be non-responders than missing at random, although note it is not an issue raised in the technical engagement report.

Table C: Revised cost-effectiveness – incorporating cost of bariatric surgery and assuming patients with missing response values to be non-responders (ERG analyses 1+2)

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£21,210	18.550	15.278	**£20,236**
Diet & exercise	£19,780	18.514	15.208	
Incremental	£1,430	0.036	0.071	

Technical Report – Issue 4 – Assumptions related to treatment discontinuation

In the original CS model, a simplifying assumption was made that patients only discontinue treatment via the stopping rule and after the maximum treatment duration. We are happy to accept the ERG and NICE technical team's preferred scenario using per cycle discontinuation probabilities as observed in Trial 1839 (see **Table D**).

Table D: Revised company base case - incorporating cost of bariatric surgery, assuming patients with missing response values to be non-responders (ERG analyses 1+2) and per cycle treatment discontinuation up to 2 years (Issue 4)

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	**£20,867**	**18.547**	**15.271**	**£17,194**
Diet & exercise	**£19,780**	**18.514**	**15.208**	
Incremental	**£1,087**	**0.033**	**0.063**	

Scenario analyses

Issue 6 (ERG 3) No automatic development of T2D post CV event

A scenario analysis removing the assumption that patients with prediabetes automatically develop type 2 diabetes after a cardiovascular event is shown in **Table E**.

Table E: Scenario analysis – Issue 6 - incorporating the assumption that prediabetes patients do not develop type 2 diabetes after a CV event

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,231	18.648	15.379	**£18,552**
Diet & exercise	£19,131	18.619	15.320	
Incremental	£1,100	0.029	0.059	

Issue 7 – Liraglutide non-responders have the efficacy of placebo non-responders

A scenario analysis with the assumption that liraglutide 3.0mg non-responders would have the same effectiveness as placebo non-responders in Trial 1839 (non-responder's assumption) is shown in **Table F**.

Table F: Scenario analysis – Issue 7 - incorporating the assumption that liraglutide 3.0mg non-responders have the same efficacy as placebo non-responders

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	£20,934	18.545	15.264	**£20,670**
Diet & exercise	£19,780	18.514	15.208	
Incremental	£1,154	0.031	0.056	

Other issues – Selection of risk models QRISK3 and Framingham in Type 2 diabetes

In the CS the UKPDS 82 risk model was used to predict cardiovascular risk in patients with type 2 diabetes, however the ERG stated a preference for using QRISK3 and Framingham in type 2 diabetes patients.

Scenario analyses have been performed as shown in **Table G**, using QRISK3 for the prediction of a first CV event in type 2 diabetes, Framingham for the risk of recurrent CV events and the two risk models together.

Table G: Scenario analyses – Selection of risk models

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
QRISK3 for prediction of first CV event in type 2 diabetes				
Liraglutide 3.0mg	£20,899	18.582	15.300	**£19,347**
Diet & exercise	£19,810	18.557	15.244	
Incremental	£1,089	0.025	0.056	
Framingham for prediction of recurrent CV event in type 2 diabetes				
Liraglutide 3.0mg	£20,941	18.655	15.356	**£18,420**
Diet & exercise	£19,861	18.628	15.297	
Incremental	£1,081	0.027	0.059	
QRISK3 and Framingham for prediction of CV events in Type 2 diabetes				
Liraglutide 3.0mg	£20,966	18.685	15.381	**£20,684**
Diet & exercise	£19,882	18.665	15.329	
Incremental	£1,084	0.020	0.052	

Cumulative impact of alternative scenario analyses

The cumulative impact of the different issues raised in the technical engagement and ERG report are presented in **Table H**.

Table H: Scenario analyses combining issues (deterministic)

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Revised company base case plus Issues 6 and Issue 7				
Liraglutide 3.0mg	£20,298	18.647	15.372	**£22,340**
Diet & exercise	£19,131	18.619	15.320	
Incremental	£1,167	0.027	0.052	
Revised company base case plus Issue 6 and selection of risk models QRISK3 & Framingham in Type 2 diabetes				
Liraglutide 3.0mg	£20,291	18.733	15.447	**£21,989**
Diet & exercise	£19,190	18.714	15.397	
Incremental	£1,100	0.018	0.050	
Revised company base case plus Issue 6, Issue 7 and selection of risk models QRISK3 & Framingham in Type 2 diabetes				
Liraglutide 3.0mg	£20,357	18.731	15.440	**£26,821**
Diet & exercise	£19,190	18.714	15.397	
Incremental	£1,167	0.017	0.044	

Probabilistic revised company base case

Probabilistic results for the revised cost effectiveness analyses are presented in **Table I**.

Table I: Probabilistic revised company base case and cumulative scenario analyses

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Probabilistic revised company base case				
Liraglutide 3.0mg	£21,218	18.537	15.265	**£17,631**
Diet & exercise	£20,151	18.507	15.205	
Incremental	£1,067	0.030	0.061	
Probabilistic revised company base case plus Issue 6 & Issue 7				
Liraglutide 3.0mg	£20,682	18.604	15.339	**£22,363**
Diet & exercise	£19,545	18.579	15.288	
Incremental	£1,138	0.025	0.051	
Probabilistic revised company base case plus Issue 6 and selection of risk models QRISK3 & Framingham in Type 2 diabetes				
Liraglutide 3.0mg	£20,708	18.645	15.379	**£21,412**
Diet & exercise	£19,629	18.626	15.329	
Incremental	£1,079	0.019	0.050	
Probabilistic revised company base case plus Issue 6, Issues 7 and selection of risk models QRISK3 & Framingham in Type 2 diabetes				
Liraglutide 3.0mg	£20,673	18.651	15.378	**£25,884**
Diet & exercise	£19,529	18.634	15.334	
Incremental	£1,144	0.017	0.044	

Revised company base case with maximum treatment duration of 1 and 3 years

Further scenario analyses have been performed testing a maximum treatment duration of 1 and 3 years (**Table J**).

Table J: Revised company base case with maximum treatment duration of 1 and 3 years

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Revised company base case & maximum treatment duration 1 year				
Liraglutide 3.0mg	£20,516	18.530	15.229	**£12,230**
Diet & exercise	£19,877	18.501	15.177	
Incremental	£638	0.028	0.052	
Revised company base case & maximum treatment duration 3 years				
Liraglutide 3.0mg	£20,876	18.561	15.316	**£20,063**
Diet & exercise	£19,466	18.525	15.246	
Incremental	£1,410	0.036	0.070	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Liraglutide for managing overweight and obesity [ID740]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm, Thursday 14 November 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Professor Carel le Roux**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Imperial College London**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Is the population defined in the company submission generalisable and clearly justified?	
Is the group identified in the company submission (that is people with a BMI ≥35 kg/m2, with pre-diabetes, and high risk of cardiovascular disease) identifiable and sufficiently justified?	At Imperial College London we were one of the largest recruiting sites internationally for the SCALE Obesity and Prediabetes study. The patients in our centre behaved the same as regards all the outcomes and side effects as was shown in the New England Journal of Medicine and the subsequent Lancet papers. We went on to conduct a real-world evidence study at Imperial College London Diabetes Centre and confirmed in our publication that liraglutide 3mg gave the same results in clinical practice compared to what we saw in the clinical trials (Diabetes Obes Metab. 2019 Jun;21(6):1498-1501). In my own clinical practice our clinical audit data show that prescribing liraglutide 3mg privately also deliver the same outcomes and side effects as shown in the clinical trials. The group of patients with a BMI>35, prediabetes and at high cardiovascular risk is easily identifiable in clinical practice given the clinical biochemistry we do as part of usual clinical care. This group of patients are also often the ones that seek help or are referred for help to obesity services. Thus, they are easily identifiable and focussing treatment on them is clinically justified.
Is the group identified in the company submission more likely to benefit from liraglutide than other populations, if so how and why?	The proposed group are at the highest risk of developing type 2 diabetes and the subsequent complications of diabetes. The randomized controlled trial evidence and real-world evidence suggest they respond as well as any other group to liraglutide 3mg, but they stand to benefit more as regards absolute risk reduction of developing type 2 diabetes.
Would liraglutide be provided within a Tier 3 service? Given that not all CCGs commission a Tier 3 service, how would people in those areas access liraglutide?	Liraglutide 3.0mg will be most appropriately placed in a tier 3 setting as part of a multidisciplinary treatment offering. Where tier 3 isn't available, I am aware of specialist (endocrinologists) are taking referrals for weight management and this can also be a suitable place for use of liraglutide 3mg. The availability of such an effective treatment may also encourage service development in

	more CCGs thus bringing more benefit to the wider population of patients with a BMI>35, prediabetes and high cardiovascular risk.
Issue 2: The submission is based on a post-hoc subgroup	
How reliable is the subgroup analysis and is it acceptable for decision making?	
Should the treatment benefit be derived from the full ITT population (the full clinical trial results) or the index population?	
Given that the 12-week stopping rule was not applied in Trial 1839, can the results of Trial 1839 be generalisable to the intended UK population?	Yes, the trial results should still be considered generalisable to the intended UK population. If a stopping rule was implemented within the large RCT then the weight loss of those patients that exceeded 5% weight loss at 12 weeks on maintenance dose would have exceeded 10% on average (Obesity (Silver Spring). 2016 Nov; 24(11): 2278–2288). Thus, the overall trial results are generalisable even if they may be a little conservative.
Issue 3: Can orlistat and bariatric surgery be excluded as comparators?	
If liraglutide were approved for use in the NHS would it be considered as an option for someone likely to be treated with orlistat?	Standard clinical practice in the NHS relies on the existing NICE guidelines which support the use of orlistat as well as bariatric surgery. In the case where liraglutide 3mg will be approved by NICE it is likely to be used as a third line agent in those patients a) who did not respond or could not tolerate orlistat or b) who were not eligible or did not want bariatric surgery. Thus, liraglutide is likely only to be used when orlistat and bariatric surgery are not options. Thus, neither orlistat nor bariatric surgery are comparators in clinical practice.
If liraglutide were approved for use in the NHS would it be considered as an option for someone likely to be recommended for bariatric surgery? Is the limited use of orlistat in clinical practice sufficient justification to exclude it as a comparator?	
Would bariatric surgery be offered to people with people with a BMI ≥35 kg/m2, pre-diabetes, and high risk of cardiovascular disease?	Bariatric surgery has NICE approval to treat patients a BMI ≥35 kg/m^2, pre-diabetes, and high risk of cardiovascular disease. If these patients want surgery and are eligible for surgery on technical grounds, then they should have surgery for the reasons articulated in the previous NICE

	guidelines. For those patients who do not want surgery or cannot have surgery, liraglutide 3mg may be an effective alternative option.
Issue 4: Assumptions related to treatment discontinuation	
What drop-out pattern would we expect to see in practice? Would most people discontinue liraglutide within the first 3 or 6 months or would you continue to see discontinuations after 6 months?	The clinical experience of good multidisciplinary obesity clinics across the world that have used liraglutide 3mg is consistent as regards patient compliance. Patients do not like to inject themselves every day or a prolonged period but are prepared to use a subcutaneous injection of liraglutide 3mg to ascertain whether they are likely to respond as regards improvements in symptoms of obesity (hunger and lack of satiation), weight loss and complications of obesity (development of type 2 diabetes). If patients do not have a sufficient response within 3 months (weight loss of more than 5%), then most patients will discontinue the treatment. Clinically it appears that most patients perceive value only if they exceed 10% weight loss at one year (25-35% of all patients) and it is often only these patients that are prepared to continue with the treatment. There is another group who lose more than 15% of their weight (14-20% of all patients) who experience such benefit from the treatment that they never wish to discontinue the treatment. In summary, the majority of patients will discontinue the treatment before 6 months, but those who lose more than 10% of their body weight are likely to want to continue the treatment longer. This latter group is also the cohort that stand to benefit most, while patients who don't lose much weight don't have as much benefit but yet may have the same number of side effects. Thus, it is correct that they discontinue the treatment if they don't have good biological response.
How likely is it that patients will receive liraglutide until they are not achieving clinical benefit (i.e. maintaining an initial loss of 5% body weight)?	The original submission to NICE followed the EMA stopping rule (5% weight loss at 12 weeks on maintenance dose) and then assumed that all remaining patients continues therapy for 2 years. It is reasonable to assume that some patients discontinue throughout the 2 years. This is a very likely clinical scenario because patients often do not experience clinical value or major improvements in quality of life unless 10% weight loss is achieved. Thus, the effort of taking a daily injection often exceed the value of having less than 10% weight loss. It is relatively rare in clinical practice to find patients who remain enthusiastic about a daily injection if they only lose 5% weight. Compliance improves in patients who have a more substantive biological response and lose more than 10% weight. This is clinically appropriate as most of the medical benefits of weight loss (improvements in cardiovascular events, sleep apnoea, fertility and fatty liver disease) only become evident after 10% weight loss.

	When liraglutide 3mg is stopped as per licence, after 12 weeks on maintenance dose when patients do not achieve 5% weight loss it results in approximately 30% of patients receiving the medication for this period without very significant weight loss. This is usually acceptable to patients as they understand that effectively the initial 12-16 week period represents a “diagnostic phase” where we have to determine whether they biologically respond to the treatment. Thus, if they don’t respond we discontinue the treatment.
Issue 5: Implementation of treatment stopping rules	
Given that the treatment stopping rules (all non-responder patients with pre-diabetes) and (after two years of treatment) were not implemented in the trial, what is the rationale for stopping treatment with liraglutide after 2 years?	It is a reasonable question whether it is appropriate to have a maximum treatment duration of 2 years. We only have data up to 3 years and therefore 3 years is the maximum that can be used for modelling. In an ideal world it would be preferable if a mechanism can be created where patients who lose more than 15% weight at 2 years are allowed to continue with the treatment in the long term. Such a very significant weight loss would have profound medical and quality of life benefits, while the relatively small number of patients achieving this weight loss would limit the budget impact of such a decision. However, given a choice between not having the medication available or having it available for the patients with a BMI>35, prediabetes and high cardiovascular risk for 2 years, I would opt for the latter.
Would a treatment stopping rule be implementable in clinical practice?	Yes, the stopping rule for patients that do not achieve 5% weight loss at 3 months is part of usual care for the last decade as we applied the same rule for treatments such as orlistat, sibutramine and rimonabant. Thus, it will not be difficult to apply the same rule to liraglutide 3mg. Clinically we use a further efficacy stopping rule at one year of 10% weight loss or other significant clinical benefit assessed by individual treatment targets, but this is based on data showing that most complications of obesity only improve after double digit weight loss.
Does clinical experience of rates and degree of weight regain match the assumptions in the modelling?	At Imperial College London we were one of the largest recruiting sites internationally for the SCALE Obesity and Prediabetes study. The patients in our centre behaved the same as regards all the outcomes and side effects as was shown in the New England Journal of Medicine and the subsequent Lancet papers. We went on to conduct a real-world evidence study at Imperial College London Diabetes Centre and confirmed in our publication that liraglutide 3mg gave the same results in clinical practice compared to what we saw in the clinical trials (Diabetes Obes

	Metab. 2019 Jun;21(6):1498-1501). In my own clinical practice our clinical audit data show that prescribing liraglutide 3mg privately also deliver the same outcomes and side effects as shown in the clinical trials. The same is also true for weight regain after treatment is discontinued. It is often the case that some patients who experience rapid weight regain after discontinuation of liraglutide 3mg opt to have bariatric surgery as a tool to achieve weight loss maintenance. This is appropriate. These discussions can also be had with patients at an earlier stage if we know treatment will be discontinued at 2 years to allow appropriate planning and referral for surgery. Most patients will however not consider surgery and lifestyle measures can be implemented to attenuate weight regain, albeit that success varies.
Issue 6: The assumption that pre-diabetic patients automatically develop type 2 diabetes after a cardiovascular event	
Is the company's simplifying assumption that all people (who have a BMI ≥35 kg/m2, pre-diabetes, and high risk of cardiovascular disease) develop type 2 diabetes following a cardiovascular event unreasonable?	The assumption is not unreasonable but unfortunately, there is no definitive data to base assumptions on for patients with prediabetes who have a cardiovascular event. The modelling used shows people with prediabetes have a higher risk of CV events and a higher risk of developing type 2 diabetes. There are no risk equations for what happens with a person with prediabetes once they have a CV event. Therefore, the model will have to assume either A) patients with prediabetes who have a CV event go on to develop type 2 diabetes to allow the model to adopt the same risks as someone with type 2 diabetes, or B) that patients with prediabetes who have a CV event go into a health state where they have no history of prediabetes and therefore have the same risk of a normal glucose tolerant person with a CV event. It would be reasonable to hypothesise that the truth lies somewhere in between A) and B), but closer to A).
What proportion of people (who have a BMI ≥35 kg/m2, pre-diabetes, and high risk of cardiovascular disease) are likely to have a diagnosis of type 2 diabetes following a CVD event?	Unfortunately, there is no definitive to base assumptions on for patients with prediabetes who have a cardiovascular event, but it is a clinical sound assumption to model increased risk of type 2 diabetes following a CVD event.
Issue 7: The assumption that liraglutide 3.0mg non-responders would have the same effectiveness as the placebo arm in Trial 1839 (A non-responder is someone with less than 5% weight loss after 12 weeks of treatment)	

Which is a better proxy in the economic model of the treatment effect for liraglutide non-responders the treatment effect for the overall placebo (diet and exercise) group in the trial or the treatment effect for the placebo non-responders in the trial?	A patient who does not have a weight loss response of more than 5% at 12 weeks on maintenance dose of liraglutide 3.0mg does not go on to develop a weight loss response to the medication thereafter. Thus, in the clinical trials and clinical practice these patients have very few of the weight loss dependent benefits. Liraglutide 3mg have a weight loss independent action on the pancreas to facilitate optimal insulin secretion in the context of a meal. The weight loss in the liraglutide 3mg non-responders and the weight loss of the placebo arm is similar, and I would not expect worse outcomes for the liraglutide non-responders compared to the placebo group. It is thus reasonable to assume that the changes in quality of life for the liraglutide 3mg non-responders and the patients on the placebo arm may be similar, even if the liraglutide 3mg non-responders have weight loss independent benefits such as improved glycaemia, blood pressure and inflammation.
Would the modelled liraglutide non-responders be likely to have worse outcomes than the whole placebo group in the trial?	
Should the effectiveness of liraglutide should be based on all patients who receive liraglutide, including those who achieve less than 5% weight loss at 16-weeks?	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft technical report

Liraglutide for managing overweight and obesity

This document is the draft post-engagement technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee. A draft version of this technical report was sent out for technical engagement between 18th October 2019 and 14th November 2019. The draft report included a list of issues that have an impact on the uncertainty of the company's estimates of clinical or cost-effectiveness. The aim of the engagement was to seek feedback from consultees and commentators on these issues to help inform the technical team's favoured modelling assumptions.

The aim of the post-engagement version of the technical report is to:

- Summarise the feedback that was received on the issues that were identified originally
- Explain how the feedback has or has not been helpful in resolving areas of uncertainty

Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission

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- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

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1. Topic background

1.1 Disease background

Overweight and obesity is a chronic condition characterised by increased body fat. People who are overweight or obese are at an increased risk of developing cardiovascular disease, type 2 diabetes, atherosclerosis (the presence of fatty deposits in the arteries), hypertension and dyslipidaemia (abnormal levels of fats in the blood). Other conditions associated with obesity are non-alcoholic fatty liver disease, non-diabetic hyperglycaemia, subfertility, osteoarthritis, obstructive sleep apnoea and idiopathic intracranial hypertension. The most common method for measuring obesity is body mass index (BMI) which is calculated as the ratio of weight to height squared. Overweight is typically defined by a BMI of 25 kg/m^2 to <30 kg/m^2 and obesity by a BMI of 30 kg/m^2 or more. BMI scores of 30 kg/m^2 to <35 kg/m^2 are defined as Obesity class I, scores of 35 kg/m^2 to <40kg/m^2 as Obesity class II and scores of ≥40 kg/m^2 as Obesity class III. Some ethnic groups may be at increased risk of some ill health conditions at lower BMI than people of European family origin.

In England, an estimated 26% of adults are obese and a further 35% are overweight. Around 10% of obese adults are morbidly obese, with a BMI of 40 and above. People aged 55 to 64 years are the most likely to be obese, while people aged 16 to 24 years are the least likely. The percentage of adults overweight or obese in England rose from 53% in 1993 to 61% in 2016.

1.2 Treatment pathway

Standard management of overweight and obesity includes dietary and lifestyle advice, behaviour modification, pharmacological treatments and surgical intervention. Specialist multi-disciplinary weight management interventions (known as Tier 3 interventions) are also used in current practice. Tier 3 interventions include dietary, lifestyle and behaviour modification with or without drug therapy. These interventions can be delivered in either primary or secondary care. NICE clinical guideline 189 ‘Obesity: identification, assessment and management’ recommends

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that drug therapy with orlistat should only be considered after dietary, physical activity and behavioural approaches have been started and evaluated.

It recommends orlistat for the management of obesity in people with a BMI of 30 kg/m^2 or more, and in people with a BMI of 28 kg/m^2 or more and significant comorbidities. If dietary and lifestyle advice, behaviour modification and drug treatments are unsuccessful, the NICE clinical guideline recommends bariatric surgery for people with a BMI of:

- 40 kg/m^2 or more,
- between 35 kg/m^2 and 40 kg/m^2 with significant comorbidities,
- between 30 kg/m^2 and < 35 kg/m^2 and with recent-onset of type 2 diabetes (surgery can be considered for people of Asian family origin who have recent-onset type 2 diabetes at a lower BMI than other populations).

The NICE final scope defined the population as adults who have a BMI of ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity or ≥ 30 kg/m^2 (obese). The scope defined the relevant comparators as standard management without liraglutide (including a reduced-calorie diet and increased physical activity), orlistat (prescription dose), or bariatric surgery. In its evidence submission, the company positioned liraglutide as a treatment option for adults with a BMI ≥ 35 kg/m^2 with pre-diabetes and a high risk of cardiovascular disease who have been referred to a specialist Tier 3 service where conventional treatments such as orlistat have been unsuccessful earlier in the clinical pathway.

1.3 The technology

Liraglutide (Saxenda, Novo Nordisk Limited) is a glucagon-like peptide-1 (GLP-1) analogue produced by recombinant DNA technology in saccharomyces cerevisiae. It is administered by subcutaneous injection.

Liraglutide has a marketing authorisation in the UK as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial BMI of ≥30 kg/m² (obese), or ≥27 kg/m² to <30 kg/m² (overweight) in

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the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

The list price of liraglutide (Saxenda) is £196.20 for 5 x 6 mg/ml 3ml pre-filled pens.

The price of liraglutide (Saxenda) under the commercial access agreement is [redacted] for 5 x 6 mg/ml 3ml pre-filled pens. The commercial access agreement is confidential. [redacted]

1.4 Decision problem

	Final scope issued by NICE	Evidence used in the model
Population	Adults who have a BMI of; • ≥ 30 kg/m^2 (obese) or • ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity	Adults who have a BMI of • ≥35 kg/m^2; • pre-diabetes, and • high risk of cardiovascular disease
Intervention	Liraglutide	Liraglutide
Comparator	Standard management without liraglutide Orlistat (prescription dose) Bariatric surgery	Standard management without pharmacotherapy
Outcome	• BMI • weight loss • percentage body fat • waist circumference • incidence of type 2 diabetes • cardiovascular events • idiopathic intracranial hypertension • non-alcoholic fatty liver disease • mortality • adverse effects of treatment • health-related quality of life.	• BMI • weight loss • waist circumference • incidence of type 2 diabetes • cardiovascular events • mortality • adverse effects of treatment • health-related quality of life.

1.5 Clinical evidence

The company identified one multi-centre, placebo-controlled randomised control trial (RCT) in people who were obese (BMI ≥ 30 kg/m^2) or overweight ≥27 kg/m² with comorbidities the SCALE obesity and pre-diabetes (Trial 1839). Participants were randomised 2 to 1 to receive liraglutide 3.0 mg (n=2,487) or placebo (n=1,244) as an

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adjunct to diet and exercise and stratified according to pre-diabetes status. The trial was conducted across 191 sites in 27 countries in Europe, North America, South America, Asia, Africa and Australia. Eight of these sites were based in the UK and these recruited a combined 112 participants. The primary outcome of Trial 1839 was: the proportion of patients with onset of type 2 diabetes at week 160 among patients with pre-diabetes at baseline.

Since the company submission was limited to people with a BMI ≥ 35 kg/m^2 with pre-diabetes and a high risk of cardiovascular disease, the company performed a post-hoc analysis of the trial. The post-hoc analysis included 800 participants, 35% of the initial trial population, where n=530 received liraglutide and n=270 received placebo.

Trial design	Randomised, double-blind, placebo-controlled trial with randomisation of patients to either 56 or 160 weeks of treatment based on prediabetes status at the screening.
Trial inclusion criteria	Adults aged 18 years or older with stable body weight and a body mass index (BMI) of at least 30 kg/m², or at least 27 kg/m² with treated or untreated comorbidities (dyslipidaemia, or hypertension, or both) were enrolled in the trial. Patients were stratified according to BMI (≥30 kg/m^2 or <30 kg/m^2) and prediabetes status. To be eligible for stratification as having prediabetes, patients had to meet one of the following criteria based on the ADA 2010 (86) guidance: • HbA_{1c} 5.7%−6.4% both inclusive, or • Fasting plasma glucose (FPG) ≥5.6 mmol/L and ≤6.9 mmol/L, or • Two hours post-challenge (oral glucose tolerance test [OGTT]) plasma glucose (PG) ≥7.8 mmol/L and ≤11.0 mmol/L.
Trial drug	Liraglutide 3.0mg or placebo was administered once daily by subcutaneous (SC) injections in either in the abdomen, thigh or upper arm. Injections could be done at any time of day irrespective of meals. In order to reduce the level of side effects, patients followed a fixed dose escalation in weekly increments of 0.6mg liraglutide.
Comparators	Diet and exercise
Primary outcomes	Proportion of patients with onset of type 2 diabetes at week 160 among patients with prediabetes at baseline - evaluated as the time to onset of type 2 diabetes.

Index population	A subgroup of Trial 1839 with: 1) BMI ≥35 kg/m^2; 2) pre-diabetes, defined as a HbA1c level of 42 to 47 mmol/mol (6.0 to 6.4%) or a fasting plasma glucose (FPG) level of 5.5 to 6.9 mmol/L; and 3) high risk of cardiovascular disease, defined as either of the following: (A) total cholesterol >5 mmol/L, or (B) SBP >140 mmHg, or (C) HDL <1.0 mmol/L for men and <1.3 mmol/L for women.

1.6 Key trial results

Three of the outcomes specified in the NICE scope have been reported in the CS specifically for 'patients with a BMI ≥35 kg/m^2, pre-diabetes and high risk of CVD':

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weight loss, waist circumference, and incidence of type 2 diabetes which will be referred to as the index population. In the original analyses, missing values were imputed using last observation carried forward (LOCF) for post-baseline measurements. The company used 3 different methods to deal with missing data in the post-hoc analyses. Weight-related outcomes significantly favoured liraglutide when compared with placebo. Likewise, there were significantly fewer confirmed type 2 diabetes cases with liraglutide than with placebo. Cardiovascular adverse events, mortality and health-related quality of life (SF-36, General Health) showed no significant differences between groups. However, significantly more patients discontinued treatment due to adverse events in the liraglutide group than in the placebo group. Nearly all of these discontinuations happened after week 16.

Table 0.1 (from ERG report): Main outcomes as specified in the NICE scope for 'patients with a BMI ≥35 kg/m^2, pre-diabetes and high risk of CVD' (Change between baseline and week 160 (LOCF)).

Outcome	Liraglutide (n=530)	Placebo (n=270)	Estimated treatment difference, liraglutide vs. placebo (95% CI)†
Body weight-related outcomes, change from baseline to week 160 (LS Mean (SE))			
Body-mass index (%)	-5.97 (0.30)	-1.54 (0.41)	-4.43 [-5.43; -3.43]
Weight loss (%)	-5.92 (0.30)	-1.65 (0.41)	-4.28 [-5.28; -3.28]
Percentage body fat	Not assessed		
Waist circumference (cm)	-6.95 (0.35)	-3.44 (0.49)	-3.52 [-4.71; -2.33]
Other NICE specified outcomes			
Confirmed type 2 diabetes (n/N, %)	13/530 (2.4%)	22/270 (8.1%)	OR: 0.28 [0.14, 0.57]
Cardiovascular adverse events (week 162; n/N, %)	86/530 (16.2%)	46/270 (17.0%)	OR: 0.94 [0.64, 1.40]
Idiopathic intracranial hypertension	Not assessed		
Non-alcoholic fatty liver disease	Not assessed		
Mortality (0 to 162 weeks)	0/530 (0%)	1/270 (0.4%)	OR: 0.17 [0.01, 4.17]
Health-related quality of life – SF-36 General Health; Change from baseline at week 160 (N, LS Mean (SE))	2.67 (0.40)	1.05 (0.57)	1.61 [0.25; 2.97]
Discontinuations (n/N (%))			
Discontinued due to AE	62/530 (11.7%)	13/270 (4.8%)	OR: 2.62 [1.41, 4.85]
Discontinued due to AE after week 16	60/530 (11.3%)	13/270 (4.8%)	OR: 2.52 [1.36, 4.68]
Discontinued due to AE before week 16	2/530 (0.4)	0/270 (0%)	OR: 2.56 [0.12, 53.49]
Other outcomes used in the economic model			

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5% responder rate (n/N, %)‡	314/530 (59.2%)	55/270 (20.4%)	OR: 5.68 [4.03, 8.01]
Other outcomes used in the economic model, change from baseline to week 160 (LS Mean (SE))			
SBP (reduction in mmHg)	-4.09 (0.51)	-1.09 (0.71)	-3.01 [-4.72; -1.29]
HDL cholesterol (reduction in mg/dl)	3.13 (0.42)	2.22 (0.60)	0.91 [-0.52; 2.34]
Total cholesterol (reduction in mg/dl)	-7.38 (1.31)	-4.15 (1.86)	-3.23 [-7.70; 1.24]
HbA_{1c}	-0.39 (0.01)	-0.13 (0.02)	-0.25 [-0.30; -0.21]

Source: CS, Table 20-21, page 70-71; Response to Clarification Letter, Appendix E (Supplementary data 1).
AE = Adverse event; HDL = High-density lipoprotein; LOCF = last observation carried forward; OR = Odds Ratio; SBP = Systolic blood pressure; SE = standard error.
† Estimated treatment differences are from an analysis of covariance with data from the full-analysis set, with last-observation-carried-forward (LOCF) imputation. The full-analysis set comprised patients who underwent randomisation, were exposed to at least one treatment dose, and had at least one assessment after baseline (69 patients were excluded from the full-analysis set: 61 owing to lack of an assessment and 8 owing to no exposure). The safety-analysis set included all patients who were randomly assigned to a study group and had exposure to a study drug.
‡ patients achieving at least 5% weight loss after 4 weeks titration and 12 weeks of treatment on the maintenance dose.

1.7 Model structure

The company's economic model is a cohort state transition model. The model includes 10 health states: normal glucose tolerance, pre-diabetes, type 2 diabetes, post-acute coronary syndrome (ACS) with normal glucose intolerance, post-stroke with normal glucose intolerance, post-stroke & post ACS with normal glucose intolerance, post ACS with type 2 diabetes, post-stroke with type 2 diabetes, post-stroke and post ACS with type 2 diabetes, and death.

Patients entered the model with pre-diabetes. In the next cycle, a proportion of the cohort could either revert to a normal glucose tolerance state, remain in the pre-diabetes health state, develop type 2 diabetes, or experience a fatal or non-fatal CV event which meant they moved to post ACS or post-stroke (with or without type 2 diabetes), or died. Pre-diabetes patients experiencing ACS or a stroke could only move to post ACS plus type 2 diabetes or a post-stroke plus type 2 diabetes (once pre-diabetes patients developed a CV event, they were assumed to develop type 2 diabetes as well). Within each alive health state, patients were at risk of sleep apnoea (defined in relation to the level of BMI in cycle), a knee replacement surgery, or (from year 2 onwards and if BMI ≥ 35 kg/m^2 with maximum age of 57 years) bariatric surgery independent of the treatment received. Mortality in the model could be attributable to events (due to bariatric surgery, myocardial infarction (MI), angina,

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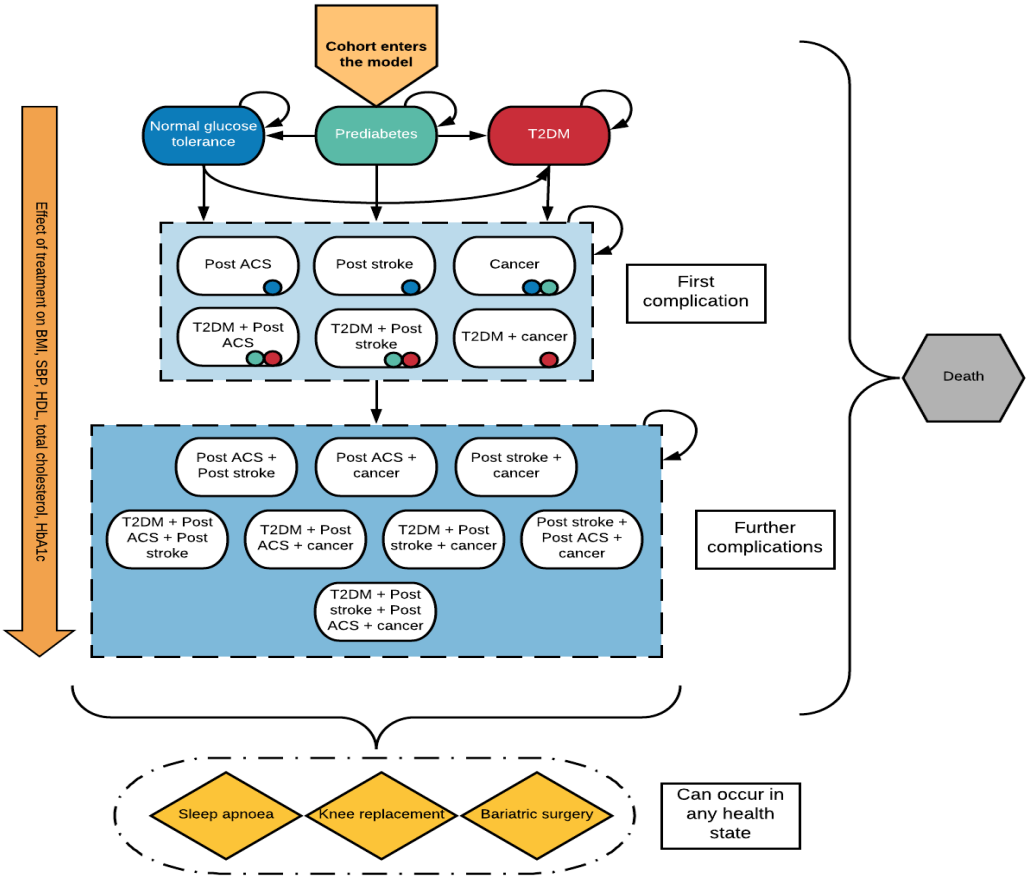
stroke, or knee replacement) and health state specific mortality (background mortality and excess mortality due to the presence of type 2 diabetes, and/or CV events).



Source: Taken from the ERG report and based on Figure 15 of the CS [1]
ACS = acute coronary syndrome; HDL = high-density lipoprotein; T2DM = type 2 diabetes.
Note: coloured dots in health states encompassing first complications denote possible originating health states (e.g. green colour-coding denotes patients with pre-diabetes); cancer state was not included in the base-case analysis, only in scenario analyses.

1.8 Key model assumptions

The company made several assumptions in the design of its economic model. Key model assumptions are listed below:

- **Population:** The target population for the economic evaluation comprised a subgroup of the licensed indication based on a post-hoc analysis of the Trial

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1839 study population, referred to by the ERG as the index population and defined as adult patients with: 1) BMI ≥35 kg/m^2; 2) pre-diabetes, defined as a HbA1c level of 42 to 47 mmol/mol (6.0 to 6.4%) or a fasting plasma glucose (FPG) level of 5.5 to 6.9 mmol/L; and 3) high risk of cardiovascular disease, defined as either of the following: (A) total cholesterol >5 mmol/L, or (B) SBP >140 mmHg, or (C) HDL <1.0 mmol/L for men and <1.3 mmol/L for women. The final scope issued by NICE and the EMA marketing authorisation includes a broader population (≥ 30 kg/m^2 [obese] or ≥ 27 kg/m^2 to < 30 kg/m^2 [overweight] in the presence of at least one weight-related comorbidity').

- **Intervention:** The intervention consists of a self-administered daily injection of liraglutide 3.0 mg in combination with diet and exercise and has a starting titration dose of 0.6 mg daily which is escalated to the recommended maintenance dose of 3.0 mg daily.

- **Perspective, time horizon and discounting:** The analysis takes an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits, with a 40-year time horizon (cohort starting age: 48 year).

- **Treatment effectiveness and extrapolation:** Transitions between health states were based on the estimation of T2DM status, CV events (primary and secondary) using risk models as well as death probabilities (probabilities for cancer were only added in scenario analyses). Moreover, a once-only transition was used to incorporate the proportion of patients reversing from pre-diabetes to normal glucose tolerance based on Trial 1839 data. The relative treatment effectiveness was estimated through changes in the BMI, SBP, total and HDL cholesterol parameters in the risk models. Patients were assumed to have stopped treatment at 2 years and regain their baseline weight over the next 3 years but not return to the expected higher weight.

- **Adverse events:** Treatment related adverse events were not considered in the economic model.

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- **Health-related quality of life:** The utility values were obtained from the literature for all health states as the company stated that health-related quality of life (HRQoL) data from Trial 1839 did not align with the NICE reference case.

- **Resources and costs:** The costs included in the model were acquisition and administration costs of obesity treatment, pharmacy costs (blood pressure and T2DM medications), and costs of obesity-related complications.

- In the revised (probabilistic) company base-case liraglutide is more expensive (£1,087) and more effective (0.063 QALYs gained) than diet and exercise, resulting in an incremental cost-effectiveness ratio (ICER) of £17,194.

  The ERG analyses indicate that the cost-effectiveness of liraglutide versus diet and exercise ranges between £11,475 per QALY and £27,313 per QALY gained. Some assumptions and/or parameters that might have individually a minimal impact on the estimated cost-effectiveness potentially have, when all combined, a considerable impact.

1.9 Overview of how quality-adjusted life years accrue in the model

Multiple sources were used to inform the utility of health states and disutility of events. Moreover, the impact of multiple obesity complications on HRQoL were assumed to be additive, that is, disutilities were added up in health states reflecting multiple obesity complications.

2. Summary of the draft technical report

After technical engagement, the technical team has collated the comments received and, if relevant, updated the judgement made by the technical ream and rationale. The issues that were considered at technical engagement are described in detail in section 3 below, along with the feedback that was received. The following table summarises the current status of each issue in terms of the technical team's view on the level of outstanding uncertainty

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Issue title, number and issue status following engagement	Response to consultation	Technical team judgement after engagement
Issue 1 – Is the population defined in the company submission clearly justified? **Agreed**	According to the company and clinical experts, the population is clearly justified. The group is easily identifiable and most likely to benefit from liraglutide.	The technical team understand that the subgroup is clearly identifiable and that these measures are taken routinely in clinical practice. The technical team also understand that this population are likely to benefit more than the population given in the scope.
Issue 2 – The submission is based on a post-hoc subgroup **Agreed**	The clinical experts and the company state that the subgroup is acceptable for decision making. The ERG maintains that the post-hoc subgroup is a concern because the baseline characteristics may not be comparable, and the analyses no longer have sufficient statistical power.	The technical team maintain that post-hoc subgroup analyses will not be as reliable as those based on the intention to treat population; however, the technical team considers the post-hoc analysis suitable for decision making if this is where liraglutide will be used in clinical practice.
Issue 3 – Can orlistat and bariatric surgery be excluded as comparators? **For discussion**	The company and clinical experts state that orlistat and bariatric surgery are not suitable comparators in most patients. Orlistat would be used earlier in the treatment pathway and liraglutide would only be offered to those who are not eligible or do not want bariatric surgery.	The technical team acknowledges that orlistat and bariatric surgery may not be suitable comparators for some people, that is in those who have failed orlistat and in people who are not eligible for bariatric surgery or don't want bariatric surgery. However, there is a small group in whom these would be suitable comparators.

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Issue 4 – Assumptions related to treatment discontinuation **For discussion**	Most people that do not have a sufficient response within 3 months (weight loss of more than 5%), will discontinue. The company quoted a physician survey which reported that most patients would be expected to have discontinued treatment after 2 years. The ERG maintain that assumptions related to discontinuation have a relatively large impact on the estimated cost-effectiveness and that discontinuation occurs gradually over time, as opposed to only a steep decrease in discontinuation after 6 months.	The Technical team's preferred approach is using per cycle discontinuation probabilities as observed in Trial 1839.
Issue 5 - Implementation of treatment stopping rules **For discussion**	Company and clinical experts – treatment stopping rules are implementable in clinical practice. The company's rationale for maximum treatment duration of 2 years is based on the data from the trial and a physician survey. The ERG were concerned that the EMA stopping rule was not applied in the trial and the rationale for a maximum liraglutide treatment duration of 2 years was unclear.	A 2-year stopping rule appears reasonable based on clinical expert opinion and trial data, however it is difficult to know whether this would be implemented in practice. Continued treatment for longer than 2 years would increase the ICER.

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Issue 6 - The assumption that pre-diabetic patients automatically develop type 2 diabetes after a cardiovascular event **For discussion**	There is not data on the incidence of T2DM following a CV event in people with pre-diabetes. The company assumption may result in an overestimate of T2DM incidence and thus improved cost-effectiveness however, removing this assumption would result in an underestimate of T2DM incidence and reduced cost-effectiveness.	The technical team understands that there is no definitive data to determine the proportion of people who would develop type 2 diabetes. The true value is likely to lie within the two extremes of £11,475 (all develop type 2 diabetes) and £27,313 (none develop type 2 diabetes) per QALY gained.
Issue 7 - The assumption that liraglutide 3.0mg non-responders would have the same effectiveness as the placebo arm in Trial 1839 (A non-responder is someone with less than 5% weight loss after 12 weeks of treatment) **For discussion**	The company and the clinical experts state that this is a reasonable assumption. The ERG maintain that non-responders are likely a selected population that potentially has worse treatment effectiveness than the overall placebo group.	The technical team understand that there are good arguments for using both the placebo group and the placebo non-responders to model liraglutide non-responders however, the more conservative method would be to use placebo non-responders.

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2.1 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The company's submission is based on only 35% of the population of Trial 1839
- According to the license for liraglutide 3.0mg, liraglutide should be discontinued after 12 weeks on the maintenance dose of 3.0mg/day if patients have not lost at least 5% of their initial body weight. However, this stopping rule was not applied in Trial 1839.

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2.2 The cost-effectiveness results include a commercial arrangement (commercial access agreement) for liraglutide.

2.3 Taking these aspects into account, the technical team's preferred assumptions result in an ICER of £11,475 to £27,313 per QALY gained (see section 4: Issues for information, Table 1: Technical team's preferred assumptions).

2.4 The company states that liraglutide is innovative in that "it is the first GLP-1 indicated for obesity and weight management, liraglutide 3.0 mg is first in its class for this therapy area, while offering the added benefits of reducing the risk of type 2 diabetes and preventing CVD events".

2.5 The company states that liraglutide 3.0 mg can assist certain people considered to have a disability; liraglutide 3.0 mg may be of greater assistance to people in specific minority ethnic groups; liraglutide 3.0 mg may have a positive differential impact on people of lower socioeconomic status, thereby promoting equality of opportunity; and, by assisting in lowering BMI levels and accordingly, allowing patients to meet BMI thresholds, liraglutide 3.0 mg may reduce inequity in access to other medical treatments.

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3. Key issues for consideration

Issue 1 – Is the population defined in the company submission clearly justified? – Agreed

Background/description of issue	- The NICE scope and the UK marketing authorisation for liraglutide describe the population as adults who have a BMI of; • ≥ 30 kg/m^2 (obese) or • ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity. - However, the company submission only focuses on a sub-population of the EMA licensed population: • BMI ≥35 kg/m^2 with pre-diabetes, and high risk of cardiovascular disease. The company's selected population. The full trial population included 2,481 patients who were randomised to the liraglutide 3.0mg group, while 1,242 patients were randomised to the placebo group. The company submission is based on a smaller sample of only 35% of the whole trial population. - **The company** states that their selected population would benefit most from liraglutide, and therefore optimises cost-effectiveness. - **The ERG** states that the population in the CS was not the same as the population in the NICE final scope. Clarity is also required on the positioning of liraglutide on the **treatment pathway**. - The **company** stated that liraglutide 3.0mg is intended for use in patients who have been referred to a specialist Tier 3 service where conventional treatments such as orlistat have been unsuccessful earlier in the clinical pathway. - The **ERG** wanted further clarification regarding the provision of services when Tier 3 services were unavailable. The company addressed this by noting that this finding is not officially quantified at this time. However, according to a report issued by the All-Party Parliamentary Group for Obesity, 19.7% of clinical commissioning groups (CCGs) state that they do not commission Tier 3-level services.
Why this issue is important	The company submission focuses on a sub-population of the EMA licensed population and it's not clear whether the selected population (index population) reflects the population who would be treated in the NHS. Given that not all CCGs commission a tier 3 obesity service, there may be an issue regarding equity of access.

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Questions for engagement	1. Is the group identified in the company submission (that is people with a BMI ≥35 kg/m^{2,} with pre-diabetes, and high risk of cardiovascular disease) identifiable and sufficiently justified? 2. Is the group identified in the company submission more likely to benefit from liraglutide than other populations, if so how and why? 3. Would liraglutide be provided within a Tier 3 service? Given that not all CCGs commission a Tier 3 service, how would people in those areas access liraglutide?
Technical team preliminary judgement and rationale	The technical team agrees that people at the highest risk of adverse consequences of obesity would benefit most from effective treatment. It would welcome clinical opinion about whether the population defined in the company submission are more likely to benefit from liraglutide than other populations including those covered by the marketing authorisation. The technical team require further clarity on why the index population was selected.
Summary of comments	Both the company and the clinical experts agreed that the subgroup is clearly identifiable. The company and the clinical experts believe the subgroup is sufficiently justified because they are at a higher risk of developing type 2 diabetes and cardiovascular disease, therefore represents the patients most likely to benefit from treatment and optimises the cost-effectiveness.
Technical team judgement after engagement	The technical team understand that the subgroup is clearly identifiable and that these measures are taken routinely in clinical practice. The technical team also understand that this population are likely to benefit more than the population given in the scope.

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Issue 2 – The submission is based on a post-hoc subgroup – Agreed

Background/description of issue	- The **company** submission focuses on a sub-population of the EMA licensed population: people with BMI ≥35 kg/m^2 with pre-diabetes, and high risk of cardiovascular disease. This is referred to as the index population and included 530 patients who received liraglutide 3.0mg, while 270 patients received placebo. The full trial population included 2,481 patients who were randomised to the liraglutide 3.0mg group, while 1,242 patients were randomised to the placebo group. The company submission is based on a smaller sample of only 35% of the whole trial population. Consequently, the analysis may not have enough statistical power. The **ERG** state that while Trial 1839 was a good quality randomised controlled trial and there were no concerns with the trial design or methods, the company's choice to focus on a post-hoc subgroup analysis is a concern because the baseline characteristics of the subgroup may not be comparable, and that the CS is based on a smaller sample of only 35% of the whole trial meaning that the analyses no longer have sufficient statistical power to detect statistically significant differences between the treatment groups.
Why this issue is important	Although effectiveness data from Trial 1839 are presented for the full intention to treat (ITT) population, which is largely in line with the population described in the NICE scope, the economic analysis is focused on a narrower population of patients with 'BMI ≥35 kg/m^2, pre-diabetes and high risk of CVD'.
Questions for engagement	1. How reliable is the subgroup analysis and is it acceptable for decision making? 2. Should the treatment benefit be derived from the full ITT population (the full clinical trial results) or the index population? 3. Given that the 12-week stopping rule was not applied in Trial 1839, can the results of Trial 1839 be generalisable to the intended UK population?
Technical team preliminary judgement and rationale	The technical team is aware that estimates of treatment effectiveness based on subgroup data are not as reliable as those based on the intention to treat population of the trial.

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Summary of comments

Clinical experts

The clinical experts believe the trial results are generalisable to the intended UK population.

Company

The subgroup analysis is reliable and acceptable for decision making. The subgroup analysis is based on 800 patients (530 of which were randomised to liraglutide 3.0mg). Prediabetes was a pre-specified stratification at baseline in the trial 1839. The efficacy results from Trial 1839 in the prediabetes population (n=2,254) and in the index population (n=800) were similar as demonstrated in the summary table below (Table 2).

Table 2: Change from baseline to week 160 in efficacy outcomes for the whole trial population (prediabetes at baseline, n= 2,254) and the index population (with prediabetes, BMI ≥35 kg/m^2 and high risk of cardiovascular disease, n=800) – Trial 1839 - LOCF

	Liraglutide 3.0mg		Placebo	
	Prediabetes at baseline	Index population	Prediabetes at baseline	Index population
Fasting body weight (%)	-6.14 (7.34)	-5.92 (6.79)	-1.89 (6.27)	-1.65 (6.79)
HbA_{1c} (%)	-0.35 (0.32)	-0.39 (0.32)	-0.14 (0.34)	-0.13 (0.32)
Waist circumference (cm)	-6.87	-6.95 (8.09)	-3.90	-3.44 (8.09)
Systolic blood pressure (mmHg)	-3.19 (13.00)	-4.09 (11.69)	-0.53 (13.73)	-1.09 (11.69)

Values in parentheses are standard deviations.

The analysis should be based on the index population, reflecting where liraglutide would be used in clinical practice.
The results of Trial 1839 are generalisable to the intended UK population.

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	The stopping rule was not included in the trial, as stopping rules can only be assessed after trials have been completed and the non-responder population identified. The stopping rule is part of the license for liraglutide 3.0mg, hence needs to be incorporated into the evaluation as it will be applied in UK clinical practice.
Technical team judgement after engagement	The technical team maintain that post-hoc subgroup analyses will not be as reliable as those based on the intention to treat population; however, the technical team considers the post-hoc analysis suitable for decision making if this is where liraglutide will be used in clinical practice.

Issue 3 – Exclusion of orlistat and bariatric surgery as comparators – FOR DISCUSSION

Background/description of issue	- The only comparator in the company submission is standard management without pharmacotherapy. The comparators in the scope included orlistat and bariatric surgery. **The company** - The reasons for omitting bariatric surgery as a comparator were: • liraglutide 3.0mg would not be a direct replacement for bariatric surgery, however, it could be suitable for a group of patients who are unwilling or unable to undergo surgery, • only a small proportion (around 0.1% of those eligible for bariatric surgery) receive surgery. For this reason, bariatric surgery was not included as a comparator but was included as a downstream event for a proportion of patients in the health-economic model in both treatment arms. - The company also notes the limited use of orlistat in clinical practice. According to the company in their response to clarification, orlistat is not often used in clinical practice due to the experience of undesirable side effects, which impacts patients from wanting to take orlistat or ceasing treatment after a short period. This can negatively impact overall weight loss outcomes for patients. The company refer to clinical experts and consultees who stated that diet and lifestyle interventions are considered standard management for obesity and are therefore the only relevant comparator in this appraisal. **The ERG** - If it is the case that orlistat is not a comparator because patients will have failed or were unwilling to take orlistat then this should have been explicitly recognised in the index population of Trial 1839 (see Issue 1 on generalisability). The extent to which participants fulfilled these criteria was unclear, thus bringing into question the applicability of Trial 1839.

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	- The ERG enquired about the potential suitability of orlistat as a comparator in the present submission. However, the company states orlistat is used earlier in the treatment pathway, during Tier 2 services, and claims that standard management without pharmacotherapy is the only relevant comparator. - The ERG also noted the appropriateness of bariatric surgery as a relevant comparator for liraglutide, due to it being an alternative treatment according to the NICE clinical guidelines (CG189). - The ERG notes that liraglutide would not be a replacement for bariatric surgery, however, it could be an option for patients who are unwilling or ineligible candidates for surgery. Due to the small number of people who can receive bariatric surgery, this is not included as a comparator by the company. The ERG believes orlistat and bariatric surgery could be used as comparators in some patients who are eligible for liraglutide.
Why this issue is important	The company submission does not include all comparators considered relevant in the scope. If orlistat and bariatric surgery are suitable alternatives at this stage in the treatment pathway then this omission could result in an overestimate of the efficacy of liraglutide.
Questions for engagement	1. If liraglutide were approved for use in the NHS would it be considered as an option for someone likely to be treated with orlistat? 2. If liraglutide were approved for use in the NHS would it be considered as an option for someone likely to be recommended for bariatric surgery? Is the limited use of orlistat in clinical practice sufficient justification to exclude it as a comparator? 3. Would bariatric surgery be offered to people with people with a BMI ≥35 kg/m^2, pre-diabetes, and high risk of cardiovascular disease?
Technical team preliminary judgement and rationale	The technical team believes that orlistat and bariatric surgery would be relevant comparator for at least some of the people who would be candidates for liraglutide according to the company submission, but also accepts that these options might not be acceptable for others.

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Summary of comments	**Clinical experts** Liraglutide would probably be used as a third line agent in people a) who did not respond or could not tolerate orlistat or b) who were not eligible or did not want bariatric surgery. Liraglutide is likely only to be used when orlistat and bariatric surgery are not options. Thus, neither orlistat nor bariatric surgery are comparators in clinical practice. Bariatric surgery has NICE approval to treat patients a BMI ≥35 kg/m^2, pre-diabetes, and high risk of cardiovascular disease. If these patients want surgery and are eligible for surgery on technical grounds, then they should have surgery for the reasons articulated in the previous NICE guidelines. For those patients who do not want surgery or cannot have surgery, liraglutide 3mg may be an effective alternative option. **Company** Orlistat is currently recommended as a treatment option in primary care in a much wider population than is proposed for liraglutide and as such would be used earlier in the treatment pathway (tier 2). The use of orlistat is currently limited and declining, supported by Section 3.4 of the final appraisal determination for naltrexone-bupropion (TA494) where the committee concluded that standard management was the main comparator in the appraisal. Liraglutide would not be a direct replacement for bariatric surgery. For patients where bariatric surgery would be an appropriate option, and this is acceptable to the patient, this should be the preferred option.
Technical team judgement after engagement	The technical team acknowledges that orlistat and bariatric surgery may not be suitable comparators for some people, that is in those who have failed orlistat and in people who are not eligible for bariatric surgery or don't want bariatric surgery. However, there is a small group in whom these would be suitable comparators.

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Issue 4 – Assumptions related to treatment discontinuation – FOR DISCUSSION

Background/description of issue	- The **company** assumed no treatment discontinuation (for example, due to adverse events or loss of efficacy) besides the stopping rule for liraglutide 3.0mg (as per the European Medicine Agency licence) after the initial 12 weeks (in case of no response) and the assumption that patients would stop liraglutide 3.0mg after 2 years (regardless of response). - The company stated that adverse events would not have a significant impact on quality of life and therefore did not include the impact of adverse events in the model. **The ERG** - Assumptions related to discontinuation have a relatively large impact on the estimated cost-effectiveness. - In response to a clarification question the company argued that 'the highest dropouts occurred within the first 3 months, and up to 6 months, after which the drop-out rate was small (approximately 2% between 12 and 15 months)'. - However, from Figure 4.2 in the ERG report, Time to discontinuation during the entire trial (0 to 172 weeks) for all reasons (Trial 1839, full trial population, see **Appendix 1**) in the company submission it appears that discontinuation also occurs gradually over time, as opposed to only a steep decrease in discontinuation after 6 months as argued by the company. - The company provided 2 scenario analyses in which additional discontinuation rates per cycle were included, starting from cycle 3 up to the maximum treatment duration of 2 years: 1) using per cycle discontinuation probabilities as observed in Trial 1839 study; 2) using a scenario in which the observed time-to-discontinuation was applied for the first 3 years after which a log-normal parametric model was used. In the latter scenario, the fixed treatment duration of 2 years was removed from the model and treatment duration was extrapolated based on the parametric survival model. Both scenarios resulted in considerably higher ICERs.
Why this issue is important	Exclusion of discontinuation scenarios and adverse events from the economic model is likely to result in an overestimate of the cost-effectiveness of liraglutide. Having scenarios incorporating treatment discontinuation throughout the model time horizon and relaxing the assumption of a maximum liraglutide treatment duration of 2 years would enable a more robust assessment of the impact of the uncertainty around these parameters.

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Questions for engagement	1. What drop-out pattern would we expect to see in practice? Would most people discontinue liraglutide within the first 3 or 6 months or would you continue to see discontinuations after 6 months? 2. How likely is it that patients will receive liraglutide until they are not achieving clinical benefit (that is, maintaining an initial loss of 5% body weight)?
Technical team preliminary judgement and rationale	The Technical team prefer discontinuation scenarios using per cycle discontinuation probabilities as observed in Trial 1839 as well as scenarios incorporating treatment discontinuation throughout the model time horizon.

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Summary of comments

Clinical experts

Patients do not like to inject themselves every day or a prolonged period but are prepared to use a subcutaneous injection of liraglutide to ascertain whether they are likely to respond as regards improvements in symptoms of obesity. If patients do not have a sufficient response within 3 months (weight loss of more than 5%), then most patients will discontinue the treatment. Clinically it appears that most patients perceive value only if they exceed 10% weight loss at one year (25-35% of all patients) and it is often only these patients that are prepared to continue with the treatment.

The majority of patients will discontinue the treatment before 6 months, but those who lose more than 10% of their body weight are likely to want to continue the treatment longer. This latter group is also the cohort that stand to benefit most, while patients who don't lose much weight don't have as much benefit but may have the same number of side effects. Thus, it is correct that they discontinue the treatment if they don't have good biological response.

It is reasonable to assume that some patients discontinue throughout the 2 years. This is a very likely clinical scenario because patients often do not experience clinical value or major improvements in quality of life unless 10% weight loss is achieved.

Company

In the original CS model, a simplifying assumption was made that patients only discontinue treatment via the stopping rule and after the maximum treatment duration. We are happy to accept the ERG and NICE technical team's preferred scenario using per cycle discontinuation probabilities as observed in Trial 1839 (see Table D).

Table C: Revised company base case - incorporating cost of bariatric surgery, assuming patients with missing response values to be non-responders (ERG analyses 1+2) and per cycle treatment discontinuation up to 2 years (Issue 4)

Technologies	Costs (£)	LYG	QALYs	ICER (£/QALY)
Liraglutide 3.0mg	**£20,867**	**18.547**	**15.271**	**£17,194**
Diet & exercise	**£19,780**	**18.514**	**15.208**	
Incremental	**£1,087**	**0.033**	**0.063**	

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	A physician survey (Questions 16 Appendix N) reported that most patients would be expected to have discontinued treatment after 2 years. This justifies our base case assumption of a maximum treatment duration of 2 years.
Technical team judgement after engagement	The Technical team's preferred approach is using per cycle discontinuation probabilities as observed in Trial 1839.

Issue 5 – Implementation of two treatment stopping rules – FOR DISCUSSION

Background/description of issue	**The treatment stopping rules were not implemented in the Trial 1839** - As part of the EMA licence, a stopping rule is applied to 'non-responders' of liraglutide 3.0mg, where treatment should be discontinued after 12 weeks on the 3.0mg/day maintenance dose if patients have not lost 5% of their initial body weight. However, this stopping rule was not applied in Trial 1839. Patients achieving less than 5% weight loss at 16-weeks (after 4 weeks titration and 12 weeks on the maintenance dose of the drug) in Trial 1839 should have stopped using liraglutide but all patients with pre-diabetes used liraglutide for 160 weeks (unless they discontinued for any reason during the trial; see Appendix 1). It is not clear how this discrepancy influenced results. - The company model assumes that all patients stop treatment at 2 years. The maximum treatment duration stopping rule (Appendix 1) shows that at 160 weeks of the clinical trial over 50% of patients were still on treatment therefore, the rationale for a maximum liraglutide treatment duration of two-years in unclear. Therefore, there is a discrepancy in the clinical trial around the stopping rules for non-responders and treatment duration. - The company model assumes that after two years, patients will stop treatment and gradually regain weight over the next three years back to their baseline weight (not to the projected higher weight they would be if they had never taken liraglutide), and that they would not be re-treated with liraglutide.
Why this issue is important	There is a discrepancy in the clinical trial around the stopping rules for non-responders and treatment duration versus the stopping rules according to the licence and how it will be implemented in clinical practice and uncertainty on the impact on the analysis. Having scenarios varying the assumption of a maximum liraglutide treatment duration would enable a more robust assessment of the impact of the uncertainty around these parameters. The assumptions related to rate and extent of weight regain after two years treatment, and no retreatment assumptions are inherent in the model but are not based on trial data.

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Questions for engagement	1. Given that the treatment stopping rules (all non-responder patients with pre-diabetes) and (after two years of treatment) were not implemented in the trial, what is the rationale for stopping treatment with liraglutide after 2 years? 2. Would a treatment stopping rule be implementable in clinical practice? 3. Does clinical experience of rates and degree of weight regain match the assumptions in the modelling?
Technical team preliminary judgement and rationale	The Technical team notes that the estimates of cost effectiveness that have been presented are based on an assumption that only responders continue on treatment, and all patients stop treatment at two years. There is no such requirement to stop treatment after a particular time in the marketing authorisation. As the estimates of cost effectiveness are based on this assumption, any recommendation for liraglutide would include a stipulation that treatment duration should be capped at 2 years.

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Summary of comments	**Clinical experts** It would be preferable if patients who lose more than 15% weight at 2 years are allowed to continue with the treatment in the long term. Such a very significant weight loss would have profound medical and quality of life benefits, while the relatively small number of patients achieving this weight loss would limit the budget impact of such a decision. The stopping rule for patients that do not achieve 5% weight loss at 3 months is part of usual care for the last decade as we applied the same rule for treatments such as orlistat, sibutramine and rimonabant. It would not be difficult to apply the same rule to liraglutide 3mg. Clinically we use a further efficacy stopping rule at one year of 10% weight loss or other significant clinical benefit assessed by individual treatment targets, but this is based on data showing that most complications of obesity only improve after double digit weight loss. Some patients who experience rapid weight regain after discontinuation of liraglutide opt to have bariatric surgery. This is appropriate. These discussions can also be had with patients at an earlier stage if we know treatment will be discontinued at 2 years to allow appropriate planning and referral for surgery. Most patients will however not consider surgery and lifestyle measures can be implemented to attenuate weight regain, albeit that success varies. **Company** The rationale for the maximum treatment duration of 2 years was based on the availability of data from trial 1839 and a physician survey as explained under Issue 4. A stopping rule is easily implementable in clinical practice and has been previously used for other anti-obesity therapies, including orlistat, and the now withdrawn rimonabant and sibutramine. The rates and degree of weight regain are based on clinical expert advice and the approach used was consistent with other published models and the preferred assumptions of the committee/ERG that evaluated Naltrexone-bupropion for managing overweight and obesity in 2017 (TA494).
Technical team judgement after engagement	A 2-year stopping rule appears reasonable based on clinical expert opinion and trial data, however it is difficult to know whether this would be implemented in practice. Continued treatment for longer than 2 years would increase the ICER.

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Issue 6 – The assumption that pre-diabetic patients automatically develop type 2 diabetes after a cardiovascular event – FOR DISCUSSION

Background/description of issue	**The company** - The company assumed in the model that all people with pre-diabetes who experienced a CVD event progressed to type 2 diabetes. **The ERG** - The ERG was concerned that the company's base-case assumption that pre-diabetic patients automatically develop type 2 diabetes after a cardiovascular event overestimates the incidence of type 2 diabetes as well as the treatment effect for liraglutide 3.0 mg. - The ERG also acknowledged that removing this assumption would probably result in an underestimated type 2 diabetes incidence as well as treatment effect for liraglutide 3.0mg.
Why this issue is important	The company's assumption (that all people with pre-diabetes who experienced a CVD event progressed to type 2 diabetes) could result in an overestimate of the treatment effect but removing the assumption completely (that is, assuming that all people with pre-diabetes who experience a CVD event do not progress to type 2 diabetes) could result in an underestimate of the treatment effect. A more reasonable estimate is likely to lie within the extremes of these arguments based on the number of people who develop type 2 diabetes following a CVD event. When removing the simplifying assumption that pre-diabetic patients automatically develop type 2 diabetes (that is, no patients with pre-diabetes develop type 2 diabetes) with a CV event, this resulted in a (probabilistic) ICER of £27,313 per QALY gained.
Questions for engagement	1. Is the company's simplifying assumption that all people (who have a BMI ≥35 kg/m^2, pre-diabetes, and high risk of cardiovascular disease) develop type 2 diabetes following a cardiovascular event unreasonable? 2. What proportion of people (who have a BMI ≥35 kg/m^2, pre-diabetes, and high risk of cardiovascular disease) are likely to have a diagnosis of type 2 diabetes following a CVD event?
Technical team preliminary judgement and rationale	The technical team is not persuaded that it is reasonable to assume that all people with a BMI ≥35 kg/m^2, pre-diabetes, and high risk of cardiovascular disease who have a cardiovascular event develop type 2 diabetes.

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Summary of comments	**Clinical experts** There is no definitive data to base assumptions on for patients with prediabetes who have a cardiovascular event. The modelling used shows people with prediabetes have a higher risk of CV events and a higher risk of developing type 2 diabetes. There are no risk equations for what happens with a person with prediabetes once they have a CV event. The model would have to assume either A) patients with prediabetes who have a CV event go on to develop type 2 diabetes to allow the model to adopt the same risks as someone with type 2 diabetes, or B) that patients with prediabetes who have a CV event go into a health state where they have no history of prediabetes and therefore have the same risk of a normal glucose tolerant person with a CV event. The truth lies somewhere in between A) and B), but closer to A). **Company** The company maintains that the approach taken is reasonable. They presented an alternative approach in response to technical engagement, but this approach related to CV outcomes rather than the development of type 2 diabetes.
Technical team judgement after engagement	The technical team understands that there is no definitive data to determine the proportion of people who would develop type 2 diabetes. The true value is likely to lie within the two extremes of £11,475 (all develop type 2 diabetes) and £27,313 (none develop type 2 diabetes) per QALY gained.

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Issue 7 – The assumption that liraglutide 3.0mg non-responders would have the same effectiveness as the placebo arm in Trial 1839 (non-responder's assumption) – FOR DISCUSSION

Background/description of issue	For liraglutide non-responders, effectiveness was assumed to be the same as diet and exercise. A non-responder is someone with less than 5% weight loss after 12 weeks of treatment. **The company** - The company defined non-responders to liraglutide as those who discontinued treatment after the first cycle (3 months), based on the licence stopping rule. - Treatment effectiveness for liraglutide non-responders was modelled using data from the placebo arm as effectiveness data post non-response and post liraglutide discontinuation were not available. - In addition, the company presented data for 'Early responders' which were defined as patients achieving at least 5% weight loss at week 16, that is (after 4 weeks titration and 12 weeks on the maintenance dose of the drug). Since the stopping rule was not applied in Trial 1839, this was the company's attempt to bring the data in line with the stopping rule as per the European license for liraglutide 3.0mg. Patients achieving less than 5% weight loss at 16-weeks in Trial 1839 should have stopped using liraglutide but all patients with pre-diabetes used liraglutide for 160 weeks (unless they discontinued for any reason during the trial; see Appendix 1). It is not clear how this discrepancy influenced results, but it is possible that the effectiveness of liraglutide is overestimated in Trial 1839 (assuming that liraglutide is more effective than placebo, even in patients achieving less than 5% weight loss at 16-weeks). The ERG feels that the effectiveness of liraglutide

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	should be based on all patients who receive liraglutide, including those who achieve less than 5% weight loss at 16-weeks. Therefore, the data for 'early responders' alone was ignored in the ERG report **The ERG** - The ERG believes that the non-responder's assumption is debatable, as liraglutide non-responders are likely a selected population that potentially has worse treatment effectiveness than the overall placebo group. - The ERG's preferred assumption is that liraglutide non-responders have the same treatment effectiveness as placebo non-responders. - This was explored by the company in response to a clarification question indicating that this alternative assumption would increase the ICER. - The ERG would have preferred to incorporate this scenario in its base-case; however, this was not feasible given the delay before the company provided this scenario analysis.
Why this issue is important	The assumption that liraglutide non-responders would experience the same treatment effectiveness as the placebo arm could result in an overestimate of the cost-effectiveness of liraglutide if these people are more likely to have worse outcomes than the placebo group as a whole.
Questions for engagement	1. Which is a better proxy in the economic model of the treatment effect for liraglutide non-responders: the treatment effect for the overall placebo (diet and exercise) group in the trial or the treatment effect for the placebo non-responders in the trial? 2. Would the modelled liraglutide non-responders be likely to have worse outcomes than the whole placebo group in the trial? 3. Should the effectiveness of liraglutide be based on all patients who receive liraglutide, including those who achieve less than 5% weight loss at 16-weeks?
Technical team preliminary judgement and rationale	The technical team is not persuaded that liraglutide non-responders would experience the same treatment effect as an unselected population on diet and exercise. Therefore, the company's base case ICER is an underestimate.

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<table>
<tr>
<td>Summary of comments</td>
<td>
Clinical experts
The weight loss in the liraglutide non-responders and the weight loss of the placebo arm is similar. You would not expect worse outcomes for the liraglutide non-responders compared to the placebo group.
Company
Response to liraglutide is biologically determined. The most plausible assumption for non-responders would be to adopt the same efficacy as placebo in the trial, as patients would continue with standard management of diet and lifestyle interventions.

A scenario analysis with the assumption that liraglutide 3.0mg non-responders would have the same effectiveness as placebo non-responders in Trial 1839 (non-responder's assumption) is shown in Table F.

Table D: Scenario analysis – Issue 7 - incorporating the assumption that liraglutide 3.0mg non-responders have the same efficacy as placebo non-responders
<table>
<tr><th>Technologies</th><th>Costs (£)</th><th>LYG</th><th>QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>Liraglutide 3.0mg</td><td>£20,934</td><td>18.545</td><td>15.264</td><td rowspan="3">£20,670</td></tr>
<tr><td>Diet & exercise</td><td>£19,780</td><td>18.514</td><td>15.208</td></tr>
<tr><td>Incremental</td><td>£1,154</td><td>0.031</td><td>0.056</td></tr>
</table>

The company were unaware of any evidence to suggest liraglutide non-responders would have worse outcomes than the whole placebo group in the trial.
Patients who achieve less than 5% weight loss at 16 weeks will discontinue therapy in accordance with the license. The effectiveness of liraglutide should be based on those treated within license.
</td>
</tr>
<tr>
<td>Technical team judgement after engagement</td>
<td>The technical team understand that there are good arguments for using both the placebo group and the placebo non-responders to model liraglutide non-responders however, the more conservative method would be to use placebo non-responders.</td>
</tr>
</table>

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4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: ERG preferred assumptions and impact on the cost-effectiveness estimate

Table 1 (from revised ERG base-case): Deterministic and probabilistic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event (deterministic)					
Liraglutide	£21,038	15.370			
Diet & exercise	£19,945	15.282	£1,093	0.088	£12,462
ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event (probabilistic)					
Liraglutide	£21,505	15.290			
Diet & exercise	£20,449	15.198	£1,056	0.092	£11,475
ERG base-case assuming prediabetic patients do not automatically develop T2DM with a CV event (deterministic)					
Liraglutide	£20,613	15.421			
Diet & exercise	£19,215	15.369	£1,398	0.051	£27,276
ERG base-case assuming prediabetic patients do not automatically develop T2DM with a CV event (probabilistic)					
Liraglutide	£21,395	15.356			
Diet & exercise	£19,913	15.305	£1,395	0.051	£27,313

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Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
The company submission only focuses on a sub-population of the EMA licensed population	The ERG asked the company to clarify whether the population had failed on orlistat and/or were unwilling to/unable to undergo bariatric surgery. The company said that this was likely. However, this was not a criteria for inclusion in trial 1839.	Cost-effectiveness estimates are likely to be optimistic.
Adverse events	Treatment related adverse events were not considered in the economic model. The company justified the exclusion of adverse events by stating that it is not expected that adverse events would have a significant impact on the patients' quality of life. The inclusion of liraglutide resulted in a higher proportion of severe adverse events (20.7% versus 15.4%), while for the index population this was 15.5% versus 13.7%. Liraglutide adverse events led to withdrawal in 199 of 1,501 patients (13.3%) indicating that the impact on patients is not negligible, and for the index population adverse events led to withdrawal in 62 out of 530 patients (11.7%). Occurrence of adverse events likely impacts costs. Therefore, the ERG believes that excluding adverse events is likely not conservative and adds to the uncertainty of the estimated results.	The company submitted scenario analyses indicating that including adverse events would increase the ICER.
Exclusion of orlistat and bariatric surgery as comparators	Orlistat and bariatric surgery were not included as direct comparators.	Cost-effectiveness estimates are likely to be optimistic.

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Table 3: Other issues for information

Issue	Comments
Selection of risk models	The company used different risk models to estimate CV events dependent on the type 2 diabetes status. The ERG stated that using different risk models dependent on type 2 diabetes status might 'introduce bias in terms of rates of disease progression when these are dependent on the study and the population informing the model rather than on the stage of disease'. The company acknowledged that differences might arise due to factors unrelated to type 2 diabetes. Therefore, the ERG preferred to use the same risk models to estimate CV events for patients with and without type 2 diabetes. In the ERG base-case, QRisk3 (a cardiovascular risk prediction model) was used to estimate primary CV events and Framingham recurrent coronary heart disease is used to estimate secondary CV events.
HRQoL source	The approach used to estimate HRQoL inputs for the economic model was considered reasonable by the ERG. The main concerns of the ERG relate to the risk of double-counting due to the use of multiple HRQoL sources and an additive disutility approach and the implementation of some of the adverse event related disutility values. Available HRQoL data from the Trial 1839 were not used in the company base-case. However, the scenario analyses provided by the company showed similar results to the company base-case.
Calculation of (non-) responder probabilities using complete cases only	The company's calculation of (non-)responder probabilities, patients with unknown response status after 12 weeks of treatment with liraglutide 3.0mg are excluded. The ERG stated that this corresponds to a complete case analysis, assuming that if the response status is missing, it is missing completely at random. The ERG said that this seemed unlikely as, for instance, patients with withdrawal due to adverse events might be more likely to have missing response status. Therefore, the responder probabilities for the ERG base-case were recalculated assuming non-response if the response status is missing. This resulted in a responder probability of 59% (314/530) instead of 67% (314/469). Assuming all those with missing response status are missing completely at random could result in an overestimate of the cost-effectiveness of liraglutide.
Definition of pre-diabetes differs	In the planned analyses included in Trial 1839, patients were defined as having pre-diabetes according to the (American Diabetes Association) ADA 2010 criteria. In the post-hoc analyses performed for the purposes of this submission; patients were defined as having pre-diabetes if they fulfilled the criteria provided by NICE for high risk of type 2 diabetes in addition to the original ADA criteria. The ADA and NICE criteria, however, do not overlap completely; patients with fasting plasma glucose (FPG) ≥5.5 and <5.6 mmol/L would be considered pre-diabetic according to the NICE criteria but were not included in Trial 1839, as they did not meet the ADA criteria. With the exception of these patients, the population in the subgroup analyses otherwise complies fully with the NICE criteria.

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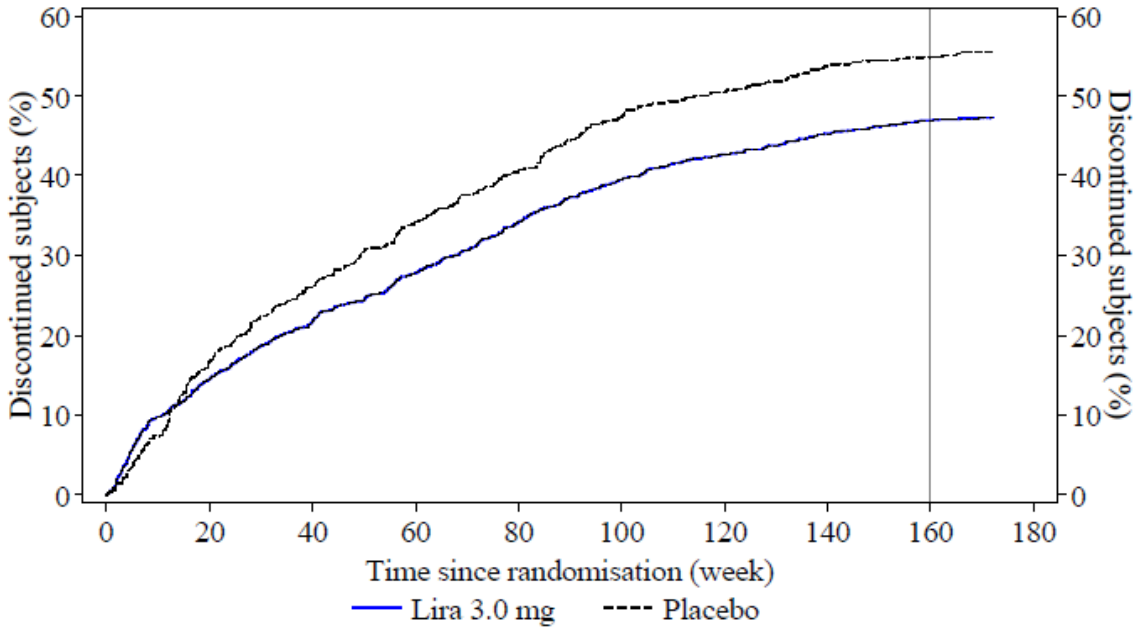
Appendix 1

Figure 0.1 (in ERG report): Time to discontinuation during the entire trial (0 to 172 weeks) - all reasons (Trial 1839, full trial population)



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Issue date: September 2019

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Validating the changes made by the company in the revised economic model

In Appendix 1 of the Company's technical engagement response, the company indicated that it updated the modelling of prediabetes reversal (update 1) as well as the cardiovascular risk applied for prediabetes (update 2). Update 1 was already partly included in the economic model submitted by the company during the clarification phase (as well as the original ERG base-case). According to Tables C and E in the Appendix, including the most recent updates increases the ICER from £9,096 per QALY gained (company base-case submitted during clarification phase) to £22,313 per QALY gained (company base-case submitted during clarification phase + updates 1 and 2). This increased slightly to £22,458 per QALY gained after correcting two minor programming issues identified during the quality check of the updated model.

After the first appraisal committee meeting, the ERG received the revised economic model. This revised economic model included a 'change log' ("Log of changes" worksheet in model version 9) describing in total 8 changes. After clarification (received mid December 2019), the company indicated that changes #1 and #2 relate to updates 1 and 2 described in Appendix 1 of the Company's technical engagement response. It was clarified that changes #3 to #6 relate to the quality review and fixes implemented as a result, and #7 and #8 were implemented as requested by NICE. However, after considering the revised economic model, the ERG noted that the model also included multiple changes/ adjustments that were not described in the change log. The company indicated that indeed only reverting back updates 1 and 2 would not allow to reproduce the results submitted in the original company submission (clarifications received mid and end December 2019) due to other changes that were implemented. This includes the changes that were described in the "log of changes from v7.0" according to the company (not shared with the ERG), the changes highlighted above (shared with the ERG) as well as potential other adjustments the ERG is not aware of.

Assuming that the other changes (other than those shared with the ERG) did not (notably) impact the results compared with the version used for the ERG report (economic model received during clarification phase), changes #1 and #2 were considered in more detail by the ERG:

- Change #1: all patients return to "prediabetes" state after treatment stop (update 1b described in Appendix 1 of the Company's technical engagement response).

  This consisted of the following adjustments: (a) all patients transition from "normal glucose tolerance" to "prediabetes" in cycle 8 i.e. the reversal from "prediabetes" to "normal glucose tolerance" is undone after year 5. (b) The T2DM risk for "normal glucose tolerance" patients is calculated based on normal glucose tolerance risk scores only (i.e. no longer using prediabetes risks after year 5).

- Change #2: modification of risk of CVD in cohort with "prediabetes" (update 2 described in Appendix 1 of the Company's technical engagement response).

  This consisted of adjusting the probability of having a CVD in the "prediabetes" health state. Previously this CVD probability was estimated using the average probability for "normal glucose tolerance" and T2DM patients. Currently (after implementing change #2), this CVD probability was estimated using the probability for "normal glucose tolerance" only (i.e. assuming the CVD probability for the "prediabetes" health state is equal to the probability for the "normal glucose tolerance" health state).

The ERG believes the technical implementation of both changes is correct and agrees with the implementation of change #1. The implementation of change #2 however encompasses a matter a judgement, i.e. whether the CVD probability for prediabetes patients should be assumed equal to the probability for normal glucose tolerance patients or whether it should be the average probability of normal glucose tolerance and T2DM patients. The ERG believes that the assumption as implemented with change #2 is reasonable.

ERG base-case with liraglutide revised PAS price and revised economic model

The ERG performed its analyses (Tables 1 and 2 for deterministic and probabilistic results) based on the liraglutide revised PAS price (i.e. [redacted] per pack of 5 prefilled pens of 18mg/3ml each; equating to [redacted] per mg) as well as the revised company model (received by the ERG after first appraisal committee meeting).

The analyses performed by the ERG include several scenarios that were implemented in the revised economic model with the revised PAS. ERG scenarios 1 and 2 are consistent with the ERG base-case as reported the in ERG report. The difference between ERG scenario 1 and the most recent company base-case are: (1) the use of different risk models to estimate CV events (for patients with T2DM) and (2) fixed treatment duration of 2 year in combination with the early stopping rule). ERG scenario 2, is identical to ERG scenario 1 but in contrast, assumes prediabetic patients do not automatically develop T2DM with a CV event. ERG scenarios 3 to 5 correspond to assumptions/ changes that were mentioned in the ERG report, but could not be explored/ incorporated in the original ERG base-case. The impact of these assumptions on the results (when compared to ERG scenario 1) range from little (ERG scenario 5) to more prominent (ERG scenarios 3 and 4). When ERG scenarios 2 to 5 would be combined the ICER would increase substantially as illustrated by scenario 6. Moreover, ERG scenario 7 provides the results of a combination of scenarios conditional on assuming that prediabetic patients do not automatically develop T2DM with a CV event (ERG scenarios 1, 3 to 5). Based on these results, the cost effectiveness of liraglutide likely depends on the preferred assumptions.

Related to the results presented in Tables 1 and 2, the face validity of these results (produced using available options in the revised model submitted by the company) can be questioned. For instance, it is unclear why the results for diet & exercise are different for ERG scenario 1 and ERG scenario 4. The difference between these scenario consists of assumptions related to liraglutide discontinuation. Therefore, it would be expected that only the liraglutide results would differ between ERG scenario 1 and ERG scenario 4. Also for ERG scenarios 6 and 7, the ERG expected that the ICER would increase compared with ERG scenarios 1 to 5, however, the plausibility of the magnitude of change is unclear (particularly when considering the differences in incremental QALYs).

Table 1: ERG base-case (deterministic) based on the liraglutide revised PAS price and revised economic model

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
1) ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event*					
Liraglutide	£21,309	15.387			
Diet & exercise	£19,882	15.329	£1,427	0.059	£24,242
2) ERG base-case assuming prediabetic patients do not automatically develop T2DM with a CV event					
Liraglutide	£20,634	15.453			
Diet & exercise	£19,190	15.397	£1,444	0.056	£25,632
3) ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + liraglutide non-responders have diet & exercise non-responder effectiveness					
Liraglutide	£21,375	15.381			
Diet & exercise	£19,882	15.329	£1,493	0.052	£28,531
4) ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + liraglutide discontinuation extrapolated (log-normal distribution)					
Liraglutide	£18,634	15.746			
Diet & exercise	£16,757	15.680	£1,877	0.066	£28,511
5) ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + include disutility and costs of adverse events (liraglutide arm)					
Liraglutide	£21,315	15.386			
Diet & exercise	£19,882	15.329	£1,433	0.058	£24,783
6) ERG base-case assuming prediabetic patients do not automatically develop T2DM with a CV event + liraglutide non-responders have diet & exercise non-responder effectiveness + liraglutide discontinuation extrapolated (log-normal distribution) + include disutility and costs of adverse events (liraglutide arm)					
Liraglutide	£18,456	15.751			
Diet & exercise	£16,334	15.721	£2,122	0.029	£72,159
7) ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + liraglutide non-responders have diet & exercise non-responder effectiveness + liraglutide discontinuation extrapolated (log-normal distribution) + include disutility and costs of adverse events (liraglutide arm)					
Liraglutide	£18,866	15.712			
Diet & exercise	£16,757	15.680	£2,110	0.031	£67,078

*This is the ERG base-case using the assumptions as described in the ERG report but applied using the revised liraglutide PAS price and the revised economic model. Differences compared with company's revised base-case: 1) use of different risk models to estimate CV events (for patients with T2DM) and; 2) fixed treatment duration of 2 year (with early stopping rule).

Table 2: ERG base-case (probabilistic) based on the liraglutide revised PAS price and revised economic model

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
1) ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event*					
Liraglutide	£21,800	15.312			
Diet & exercise	£20,378	15.253	£1,421	0.059	£24,190
2) ERG base-case assuming prediabetic patients do not automatically develop T2DM with a CV event					
Liraglutide	£21,108	15.384			
Diet & exercise	£19,677	15.328	£1,431	0.056	£25,429
3) ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + liraglutide non-responders have diet & exercise non-responder effectiveness					
Liraglutide	£21,783	15.320			
Diet & exercise	£20,312	15.266	£1,471	0.053	£27,566
4) ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + liraglutide discontinuation extrapolated (log-normal distribution)					
Liraglutide	£19,226	15.654			
Diet & exercise	£17,350	15.587	£1,876	0.066	£28,222
5) ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + include disutility and costs of adverse events (liraglutide arm)					
Liraglutide	£21,753	15.315			
Diet & exercise	£20,329	15.257	£1,424	0.058	£24,546
6) ERG base-case assuming prediabetic patients do not automatically develop T2DM with a CV event + liraglutide non-responders have diet & exercise non-responder effectiveness + liraglutide discontinuation extrapolated (log-normal distribution) + include disutility and costs of adverse events (liraglutide arm)					
Liraglutide	£19,096	15.654			
Diet & exercise	£16,912	15.628	£2,184	0.026	£83,667
7) ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + liraglutide non-responders have diet & exercise non-responder effectiveness + liraglutide discontinuation extrapolated (log-normal distribution) + include disutility and costs of adverse events (liraglutide arm)					
Liraglutide	£19,542	15.615			
Diet & exercise	£17,370	15.587	£2,172	0.028	£77,964

*This is the ERG base-case using the assumptions as described in the ERG report but applied using the revised liraglutide PAS price and the revised economic model. Differences compared with company's revised base-case: 1) use of different risk models to estimate CV events (for patients with T2DM) and; 2) fixed treatment duration of 2 year (with early stopping rule).

Impact of removing the simplifying assumption (T2DM progression) on the ICER

The impact of the assumption of developing T2DM after an CV event for prediabetes patients on the results is less prominent in the revised version of the economic model (compared with the previous

version). After clarifying responses from the company (on (1) the implementation of the scenario exploring the impact of this assumption i.e. assuming prediabetes do not automatically develop T2DM after an CV event as well as (2) the implemented changes/ updates), the ERG believes that the reduced impact has face validity.

Replicating results submitted by the company

Using the revised economic model (with PAS), the ERG was able to replicate the results from the "Overview results of scenario analyses at revised price" Table from the document "ID740 Response to questions - revised price analyses 4 Dec 2019.docx" submitted by the company. The only exception is the scenario considering "Inclusion of cancers with relationship with obesity baseline age 50 years" as well as the scenario considering "Increased baseline SBP, total cholesterol and HDL", which the ERG was unable to reproduce. However, the ERG does not consider these scenarios the most informative scenarios and hence would not prioritize to resolve these discrepancies.