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NICE National Institute for Health and Care Excellence

Semaglutide for managing overweight and obesity

Lead team presentation

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Clinical issues (1)

Setting: which is the appropriate setting for semaglutide?

- Tier 3 services include intensive advice and monitoring and are usually accessed by people with BMI ≥35kg/m^2 (or lower BMI if significant comorbidities, with adjustment for ethnicity). Corresponds with trial setting
- Liraglutide only recommended in tier 3 – is semaglutide use outside tier 3 without multidisciplinary input appropriate?
  - Not all CCGs commission tier 3 services

Population: which population should be considered for semaglutide treatment?

- 3 populations proposed by company:
  - Liraglutide eligible population (**BMI ≥ 35 kg/m^2 plus non-diabetic hyperglycaemia, and high CVD risk**) *treated in tier 3*
  - Company original 'target population' (**BMI ≥30 kg/m^2 plus ≥ 1 weight-related comorbidity**) *proportion not treated in tier 3 (normally)*
  - Full marketing authorisation population (**BMI ≥27 kg/m^2 plus ≥ 1 weight-related comorbidity or BMI ≥30 kg/m^2**) – *proposed by company after technical engagement (larger) proportion not treated in tier 3*
- **NHSE suggest that it would be of most value for patients in tier 3 with BMI ≥ 35 and ≥ 1 weight-related comorbidity such as CVD risk factors but without the requirement for prediabetes (potential population 4)**

Abbreviations - BMI: body mass index; CVD: cardiovascular disease; NHSE: NHS England

Clinical issues (2)

STEP 1 trial: Is this generalisable for the whole NHS population?

- STEP 1 included any patient with BMI ≥ 30 or patients with BMI 27-29.9 with a CVD risk factor. Mean BMI was 38, large majority female - would this represent the average BMI and potential NHS population if the treatment was recommended for the whole MA (all obese people, and all overweight with a CVD risk factor)?

Treatment course:

- Marketing authorisation includes stopping rule that a *decision* to continue treatment needed for people who have not lost 5% initial body weight at 6 months; economic model includes max 2 years treatment duration and no retreatment.
  - **Model based on previous liraglutide model, which was restricted to time in tier 3 – i.e. treatment course matched to maximum time in tier 3. Would this be feasible/reasonable outside tier 3?**

Other key issues:

- **Company assumes all people with non-diabetic hyperglycaemia develop type 2 diabetes after a cardiovascular disease event. Is this reasonable?**
- **Would diabetic patients be included or excluded (some evidence of reduced effectiveness and people with T2D not included in STEP 1)?**
- **Is it necessary to vary the BMI cut-off for ethnic groups who are at increased risk at lower BMI?**

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Abbreviations - BMI: body mass index; CVD: cardiovascular disease

Disease background

- 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.
- Overweight and obesity is associated with increased risk of cardiovascular disease, type 2 diabetes, atherosclerosis (the presence of fatty deposits in the arteries), hypertension and dyslipidaemia (abnormal levels of fats in the blood).
- Overweight : BMI of 25 kg/m^2 to <30 kg/m^2
- Obesity: BMI of at least 30 kg/m^2
- Some ethnic groups may be at increased risk of some ill-health conditions at lower BMI than people of European family origin.

Abbreviations - BMI: body mass index

Semaglutide 2.4mg

Marketing authorisation (Received Sept 2021)	Adjunct to a reduced-calorie diet and increased physical activity for adults with an initial BMI of ≥30 kg/m^2 (obesity) without co-morbidity, or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity *Weight related comorbidity not defined in MA. STEP 1 trial specifies: hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease*
Mechanism of action	Binds to and activates GLP-1 receptors in the brain which regulate appetite and calorie intake; reduces blood glucose by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high
Dose	**Induction dose:** • 0.25 mg, titrated up every 4 weeks (0.5 mg, 1.0 mg, 1.7 mg, 2.4 mg) **Maintenance dose** (after 16 weeks): • 2.4 mg
Administration	Once-weekly by subcutaneous injection, any time of day with or without meals
List price	Solution for injection, packs of 4 pre-filled pens: • 0.25 mg, 0.5 mg, 1 mg dose: £73.25 • 1.7 mg dose : £[redacted] • 2.4 mg dose £[redacted]
Other indication	Marketed under a different brand name for control of type 2 diabetes (1 mg dose)

Abbreviations - BMI: body mass index; MA – marketing authorisation; GLP-1 glucagon-like peptide 1

Current management

- Standard management may include:
  - dietary and lifestyle advice
  - behavioural approaches
  - pharmacological treatments
  - bariatric surgery
- Tier 1 services cover universal services such as health promotion and advice
- Tier 2 services include community based diet, nutrition, lifestyle and behaviour change advice, accessed for 12 weeks
- Tier 3 services usually accessed by people with BMI ≥35 kg/m^2 (or lower BMI if significant comorbidities, with adjustment for ethnicity) plus ≥1 comorbidity
  - in line with NICE quality standard 127, adults with BMI ≥30 for whom tier 2 interventions have been unsuccessful should discuss alternative interventions including tier 3 services
  - company target population (BMI ≥30 + 1 comorbidity) and full marketing authorisation population (BMI ≥27 + 1 comorbidity and BMI ≥30) would not all be treated in tier 3
  - liraglutide is only available in tier 3
  - not all CCGs commission tier 3 services
- Tier 4 services used for bariatric surgery

TA664: Liraglutide for managing overweight and obesity

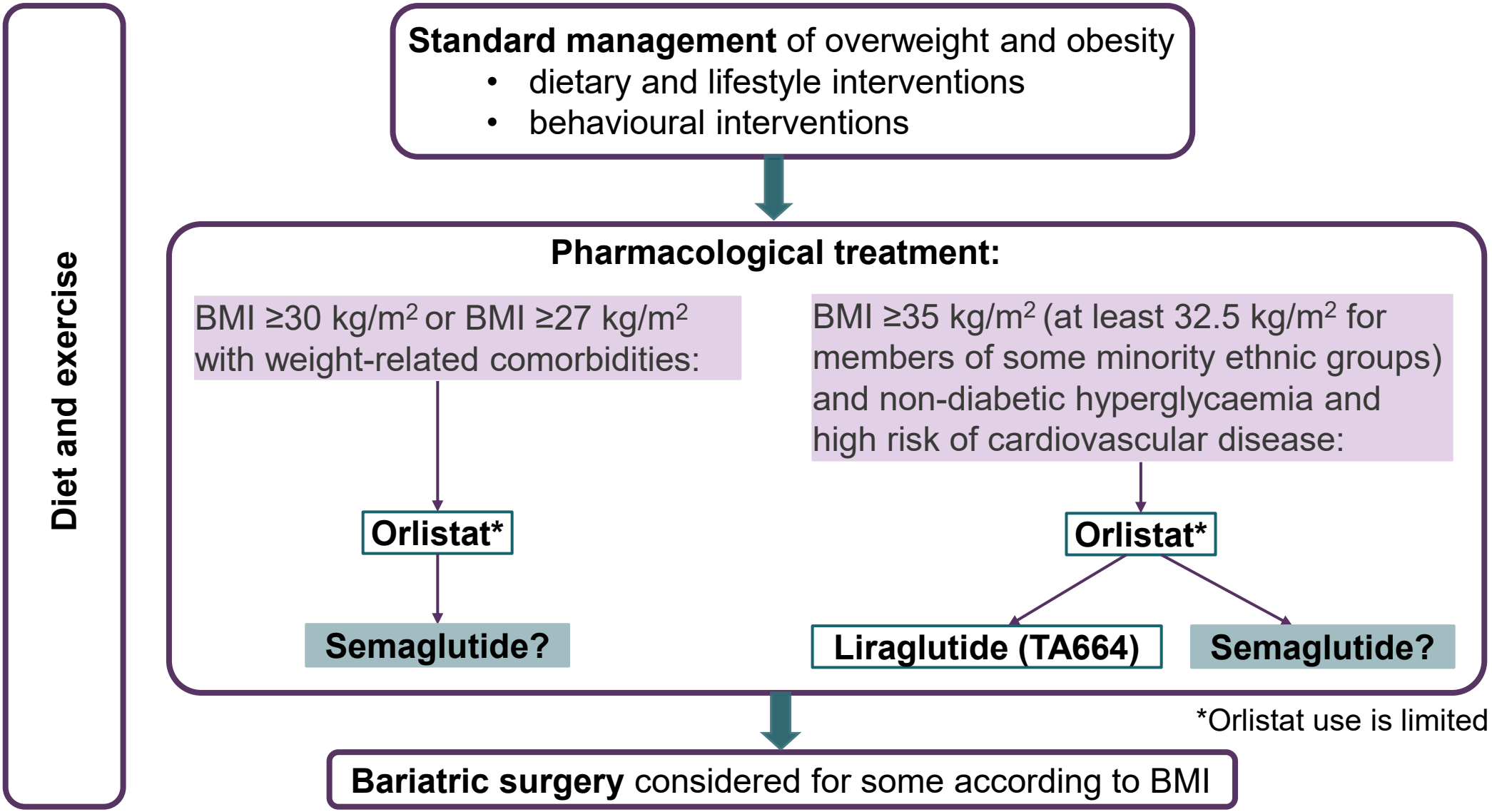
Liraglutide is recommended as an option for managing overweight and obesity alongside a reduced-calorie diet and increased physical activity in adults, only if:

- they have a body mass index (BMI) of at least 35 kg/m^2 and
- they have non-diabetic hyperglycaemia and
- they have a high risk of cardiovascular disease based on risk factors such as hypertension and dyslipidaemia and
- it is prescribed in secondary care by a specialist multidisciplinary tier 3 weight management service*

*tier 3 referral is for up to 2 years: limits time on treatment and opportunity for retreatment

- **Does tier 3 currently include any people with BMI less than 35?**

Treatment pathway



The company suggests target population of BMI ≥30 plus a weight related co-morbidity – not all currently treated in tier 3

- **Are those with higher BMI likely to benefit more than those with lower BMI?**

Decision problem

	Final scope issued by NICE	Model parameters
Population	People with 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	People with BMI of: • ≥30 kg/m^2 and ≥1 weight-related comorbidity • ≥35 kg/m^2 and non-diabetic hyperglycaemia, and high risk of cardiovascular disease *Post-technical engagement, company stated that full MA should be considered (including BMI ≥27 kg/m^2 + ≥1 comorbidity or BMI ≥30 kg/m^2)*
Intervention	Semaglutide 2.4mg	Semaglutide 2.4mg

Comparators	• Standard management without semaglutide
	• Liraglutide for people with:
	  ○ BMI ≥ 35 kg/m^2 and,
	  ○ non-diabetic hyperglycaemia, and,
	  ○ high risk of cardiovascular disease
	• Orlistat (prescription dose)
		For people with:
		• BMI ≥30 kg/m^2 and ≥1 weight-related comorbidity
		• BMI ≥27 kg/m^2 + ≥1 comorbidity or BMI ≥30 kg/m^2
		Standard management without semaglutide
		
		For people with BMI ≥ 35 kg/m^2 and non-diabetic hyperglycaemia, and high CVD risk:
		• Liraglutide

Outcomes	• BMI • weight loss • waist circumference • incidence of type 2 diabetes • glycaemic status • cardiovascular events • mortality • adverse effects of treatment • health-related quality of life.	• weight loss • glycaemic status • change in systolic blood pressure from baseline • change in fasting lipid profile from baseline (HDL and total cholesterol)

Company presents separate clinical and cost-effectiveness estimates for 'target' BMI ≥30 kg/m^2 + ≥ 1 comorbidity' subgroup and 'liraglutide eligible' subgroup; post-technical engagement, company presented some limited results for the full MA population (including BMI ≥27)

MA – marketing authorisation; CVD: cardiovascular disease

Patient and carer perspectives

Submissions received from:

- **Obesity UK**
- **The UK Obesity Organisation**
- **Patient experts**

"The victim of bullying, being ostracised by society… Not attending social functions because you've got nothing to wear… No confidence, low self-esteem… You live with stress, anxiety, anger, suicidal thoughts… It affects your family and friends…" Patient expert statement

Living with overweight and obesity

- Obesity can be physically debilitating and lead to other life limiting conditions, fertility issues and skin infections
- Associated with social stigma which can affect career prospects, confidence and financial burden
- Can diminish a person's overall quality of life as they may avoid public places and encounter discrimination
- Caring for someone living with obesity can have a draining effect and reduce quality of life

Treatment options for overweight and obesity

- Access to better treatment options is vital; there is a large unmet need for most people living with obesity
- Advantages of semaglutide outweigh disadvantages such as an injection once-a-week and side effects such as nausea
- Current treatments are considered high risk, are associated with unpleasant side effects or are inaccessible
- Not reasonable to limit treatment to one course of 2 years for a chronic condition
- Semaglutide could be useful for treating weight regain after bariatric surgery

Professional organisation perspectives

Submissions received from:

- **Royal College of Physicians**
- **Association for the Study of Obesity**
- **Obesity Group of the British Dietetic Association**
- **British Obesity and Metabolic Surgery Society**

- There is major unmet need for people with obesity
- While surgery can be an effective treatment, the NHS performs ~6000 procedures per year, but there are over 2 million people in the UK with severe and complex obesity
- Care pathways are well defined but there is a postcode lottery due to lack of commissioning services
- Semaglutide would be available for a larger population than current pharmacological treatments and would be a substantial improvement on the current best available pharmacotherapy
- People will need to be trained to inject, supported through side effects and additional monitoring needed for some
- Liraglutide can only be prescribed in tier 3 services which disadvantages people in primary care – this issue should be avoided with semaglutide
- Model might not capture benefit that some people will achieve diabetes remission

NHS England Statement

- ***Exceptionally***, people with BMI 30 to 35 m/kg^2 are referred to tier 3 services
- Greatest need is in high risk population who have routine access to tier 3 services (BMI ≥35 + 1 weight related comorbidity) – unclear why pre-requisite of pre-diabetes needed for access to liraglutide
- Trial population not fully representative:
  - mean BMI in STEP 1 38 kg/m^2; 60% of trial population have BMI ≥35 compared with 9% in NHS
  - participants were highly motivated; doesn't fully represent those with increased support needs to ensure full benefit from services
- Expect those responding to semaglutide may not wish to stop treatment at 2 years and those who regain weight may want retreatment (stopping at 2 years and no retreatment assumed in model); medicines for other chronic conditions are not stopped if effective and tolerated
- Over a 6 year follow up, benefits on cardiovascular risk factors (such as hypertension and dyslipidaemia) in people with sustained weight loss were not accompanied by reduction in hard cardiovascular outcomes
  - long term benefits of semaglutide on hard clinical outcomes are unknown
- Marketing authorisation for semaglutide includes use alongside reduced-calorie diet and increased physical activity

- **Is it appropriate to prescribe semaglutide for those not engaging in an appropriate weight management programme?**
- **Is the population of people with BMI ≥35 + 1 weight related comorbidity relevant to consider for semaglutide use (i.e. the pre-requisite of pre-diabetes isn't needed)?**
- **Do people with the greatest need for interventions for obesity generally access tier 2 to 4 services?**

Trials of semaglutide (STEP programme)

All STEP trials are phase 3, randomised, trials vs. placebo

Trial	Intervention/comparator	Population	Use in model?
STEP 1	**Semaglutide 2.4 mg vs placebo (both in conjunction with diet and exercise) (52 weeks)**	**Adults with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 plus 1 comorbidity, without diabetes**	**Yes - post-hoc analysis for populations of interest**
STEP 2	Semaglutide 2.4 mg vs placebo (both in conjunction with diet and exercise)	Adults with BMI ≥27 kg/m^2 with type 2 diabetes	No – due to T2D only population; ERG: unclear if exclusion appropriate
STEP 3	Semaglutide 2.4 mg vs placebo (both in conjunction with intensive behavioural therapy)	Adults with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 plus 1 comorbidity, without diabetes	No – due to IBT not used in NHS; ERG and clinical experts: appropriate to exclude and similar outcomes as STEP 1
STEP 5	Semaglutide 2.4 mg vs placebo (both in conjunction with diet and exercise) (104 weeks)	Adults with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 plus 1 comorbidity, without diabetes	No – data not available at submission; ERG note similar outcomes as STEP 1
STEP 8	Semaglutide 2.4 mg vs liraglutide 3.0mg vs placebo (in conjunction with diet and exercise)	Adults with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 plus 1 comorbidity, without diabetes	No – data not available at submission; ERG: should be data source for liraglutide eligible subgroup

- **What is the rationale for excluding STEP 2 including only people with T2D?**

Abbreviations - BMI: body mass index; T2D – type 2 diabetes; IBT – intensive behavioural therapy

STEP 1: semaglutide compared with placebo

Trial design	Randomised, double-blind, placebo-controlled trial
Population	N= 1,961, 73% female, mean age 46 Adults with obesity alone (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with at least 1 weight-related comorbidity (hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease) and without diabetes **Post hoc analysis of STEP 1 trial:** • People with BMI ≥30 kg/m^2 plus ≥1 comorbidity **(N= 1,470; 75% of ITT)** *(original target population)* • People with BMI ≥35 kg/m^2 plus non-diabetic hyperglycaemia plus high CVD risk subgroup **(N=421; 21.5% of ITT)** *(liraglutide eligible population)* Target population (BMI ≥30 + ≥1 comorbidity), 53.4% had pre-diabetes Liraglutide eligible population (BMI ≥35 + pre-diabetes + CVD risk), 100% had pre-diabetes
Intervention	Semaglutide once weekly adjunct to lifestyle intervention (counselling and a reduced calorie diet [500 kcal/day deficit] and 150 mins/week physical activity) 16 week dose escalation increased to maintenance dose of 2.4mg for 52 weeks (68 weeks total treatment)
Primary outcomes	% change in body weight from baseline to 68 weeks Proportion of people achieving baseline body weight loss ≥ 5% at 68 weeks

Abbreviations - BMI: body mass index; ITT – intention to treat; CVD – cardiovascular disease

Generalisability of STEP 1 trial to the whole marketing authorisation eligible population in the NHS

STEP 1 participant characteristics:

- 53% had pre-diabetes; none had type 2 diabetes; 80% had a comorbidity
- Mean BMI was 38 kg/m^2
- Majority were obesity category 2 or 3; few were overweight:
  - Overweight (BMI 27-29.9): 6%; Obesity 1 (BMI 30-34.9): 33%; Obesity 2 (BMI 35-39.9): 31%; Obesity 3 (BMI 40+): 29%
- Participants were highly motivated (90% complete follow up) and provided with intensive monitoring and multidisciplinary support not routinely available in primary care
- Mean age: 46; 73% female; 74% white

- **Is the population in the trial generalisable to the whole population included in the marketing authorisation (or any of the populations of interest) in the NHS?**

STEP 8: semaglutide compared with liraglutide

Trial design	Randomised, double-blind, placebo-controlled trial
Population	N= 338 Adults with obesity (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2) with at least 1 weight-related comorbidity (hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease) and without diabetes
Intervention	Semaglutide once weekly adjunct to lifestyle intervention (counselling and a reduced calorie diet [500 kcal/day deficit] and 150 mins/week physical activity) Dose escalation to maintenance dose of 2.4mg for 68 weeks
Comparators	Liraglutide once daily adjunct to lifestyle intervention (as in intervention) Dose escalation to maintenance dose of 3mg for 68 weeks
Primary outcomes	% change in body weight from baseline to 68 weeks

STEP 8 results were not available at submission - limited analysis presented at technical engagement showing mean change in body weight from baseline to 68 weeks of **-15.78% for semaglutide versus -6.4% for liraglutide (treatment difference -9.38%)**

Abbreviations - BMI: body mass index; ITT – intention to treat; CV – cardiovascular

Clinical effectiveness results overview:

liraglutide eligible population, company's target population and full marketing authorisation population

- Results for liraglutide eligible population taken from indirect treatment comparison (estimates smaller treatment difference in change to body weight than STEP 8 results)
- Results for company's target population and full marketing authorisation population from STEP 1

	Treatment difference: Semaglutide 2.4mg vs comparator*	
	Mean difference body weight (%)	**Proportion shifting from pre-diabetic to normo-glycaemic (%)**
Liraglutide eligible population (BMI ≥35 + pre-diabetes + high CVD-risk)	-5.8	-
Company's target population (BMI ≥ 30 + ≥1 comorbidity)	-12.2	59.2
Full marketing authorisation population (BMI ≥ 27 + ≥1 comorbidity or BMI ≥ 30)	-12.4	36.3

*Comparator for liraglutide eligible subgroup: liraglutide; comparator for company's target population and full marketing authorisation population: diet and exercise

STEP 1 results: BMI ≥ 27 kg/m² plus at least 1 comorbidity or BMI ≥ 30 kg/m² (full marketing authorisation and trial population)

Diet and exercise is considered standard of care for this population

Results from STEP 1 trial (full trial population):

Outcome	Semaglutide 2.4mg + diet and exercise (n=1,306)	Placebo + diet and exercise (n=655)	Treatment difference (95% CI)
Change from baseline to week 68 (Mean)			
Body weight, %	-14.9	-2.4	-12.44 (-13.4 to -11.5)
Change in BMI	-5.54	-0.92	-4.61 (-4.6 to -4.3)
Waist circumference, cm	-13.54	-4.13	-9.42 (-10.3 to -8.5)
Systolic blood pressure, mmHg	-6.16	-1.06	-5.10 (-6.3 to -3.9)
HbA1C, %	-0.5	-0.2	-0.29 (-0.3 to -0.3)
Glycaemic shift from baseline to week 68	**N=550**	**n=271**	
Proportion shifting from non-diabetic hyperglycaemia to normo-glycaemic, %	79.8	39.1	36.3

Abbreviations - CI: confidence interval

STEP 1 results: BMI ≥ 30 kg/m^2 plus at least 1 comorbidity (company's target population)

Diet and exercise is considered standard of care for this population
Results from STEP 1 trial (75% of trial population):

Outcome	Semaglutide 2.4mg + diet and exercise (n=974)	Placebo + diet and exercise (n=496)	Treatment difference
Change from baseline to week 68 (Mean (SD))			
Body weight, %	-14.8 (8.8)	-2.6 (8.8)	-12.2
Waist circumference, cm	-13.6 (8.8)	-4.3 (8.8)	-9.3
Systolic blood pressure, mmHg	-6.4 (12.1)	-1.0 (12.1)	-5.4
HbA1C, %	-0.5 (0.3)	-0.1 (0.3)	-0.4
HDL cholesterol, mg/dL	0.0 (0.1)	0.0 (0.1)	0
Total cholesterol, mg/dL	0.0 (0.1)	0.0 (0.1)	0
Glycaemic shift from baseline to week 68	**n=518**	**n=253**	
Proportion shifting from non-diabetic hyperglycaemia to normo-glycaemic, %	79.2	20.0	59.2

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Abbreviations - BMI: body mass index; SD: standard deviation; HDL: high density lipoprotein

STEP 1 adverse events: full marketing authorisation and trial population

Outcome, N (%)	Semaglutide 2.4mg (n=1306)	Placebo (n=655)	Percentage difference
Any adverse event	1171 (89.7)	566 (86.4)	3.3
Serious adverse event	128 (9.8)	42 (6.4)	3.4
Adverse event leading to discontinuation	92 (7.0)	20 (3.1)	3.9
Treatment-related adverse event (probably related)	571 (43.7)	147 (22.4)	21.3
Nausea	577 (44.2)	114 (17.4)	26.8
Diarrhoea	412 (31.5)	104 (15.9)	15.6
Vomiting	324 (24.8)	43 (6.6)	18.2
Constipation	306 (23.4)	62 (9.5)	13.9

Abbreviations – ITT – intention to treat; BMI: body mass index

Indirect treatment comparison methods:

BMI ≥35 kg/m^2 + non-diabetic hyperglycaemia + high CVD-risk (liraglutide eligible subgroup)

- **Liraglutide is current standard care for this population, but only within tier 3 services** (TA664)
- No direct head-to-head trial data available for liraglutide compared with semaglutide at time of company submission (STEP 8 results presented at technical engagement)
- Indirect treatment comparison performed using individual patient data from STEP 1 and SCALE 1839:
  - SCALE 1839:
    - liraglutide 3.0mg vs placebo
    - includes subgroup with BMI ≥ 35 kg/m^2 plus non-diabetic hyperglycaemia plus high CVD-risk
- STEP 1 and SCALE 1839 trial populations similar, so unadjusted ITC preferred

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Abbreviations - CVD: cardiovascular disease; ITC: indirect treatment comparison

Indirect treatment comparison results:

BMI ≥35 kg/m^2 + non-diabetic hyperglycaemia + high CVD-risk (liraglutide eligible subgroup)

Results of unadjusted indirect treatment comparison for semaglutide compared with liraglutide:

Outcome	Estimated relative treatment effect (semaglutide 2.4mg vs liraglutide 3.0mg)
Change from baseline to week 68, mean difference (95% CI)	
Body weight, %	-5.81 (-7.62 to -3.99)
Weight circumference, cm	-3.59 (-5.56 to -1.61)
Systolic blood pressure, mmHg	-1.64 (-4.60 to 1.32)
HbA1C, %	-0.13 (-0.20 to -0.06)
Ratio to baseline (95% CI)	
HDL cholesterol, mg/dL	1.01 (0.98 to 1.04)
Total cholesterol, mg/dL	0.97 (0.94 to 1.00)
Odds ratio (95% CI)	
Achieving normo-glycaemic status from non-diabetic hyperglycaemia	1.79 (1.01 to 3.16)

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Abbreviations - CVD: cardiovascular disease; CI: confidence interval; HDL: high density lipoprotein

STEP 8 results

- At technical engagement, company presented previously unavailable data cut from STEP 8, to support ITC results
- STEP 8: RCT comparing liraglutide 3.0mg, semaglutide 2.4mg or placebo
- Results presented are for the full trial population (BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 plus at least 1 weight-related comorbidity) **not the liraglutide eligible subgroup**
- Data not included in the model or ITC

STEP 8 results: BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 plus at least 1 comorbidity

Outcome	Semaglutide 2.4mg (n=126)	Liraglutide 3.0mg (n=127)	Treatment effect
Body weight-related outcomes, change from baseline to week 68			
Body weight change, mean %	-15.78	-6.4	Treatment difference: -9.38% (CI: -11.97 to -6.80)
% achieving ≥10% weight reduction	70.9	25.6	Odds ratio: 6.28 (CI: 3.53 to 11.18)

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Abbreviations – ITC – indirect treatment comparison; RCT: randomised controlled trial; BMI: body mass index;

STEP 8: company and ERG views

Company:

- Results from STEP 8 show substantial improvement in weight loss for people treated with semaglutide compared with liraglutide, with similar magnitude as seen in the ITC

ERG:

- Availability of STEP 8 data means ITC is outdated
- Efficacy is comparable to ITC results but full trial population results presented may not be generalisable to population with stopping rule applied and includes a wider population than liraglutide eligible subgroup

- **Is the indirect treatment comparison or STEP 8 trial data more appropriate for estimating the clinical efficacy of semaglutide vs liraglutide?**
- **If STEP 8 is preferred, is subgroup analysis of the liraglutide eligible subgroup suitable?**

Abbreviations – ITC – indirect treatment comparison

Defining the appropriate population – BMI and treatment setting

3 populations of interest:

- Liraglutide eligible population (BMI ≥35 + non-diabetic hyperglycaemia, and high CVD risk)
- Company original 'target population' (BMI ≥30 + ≥ 1 weight-related comorbidity)
- Full marketing authorisation population (BMI ≥27 + ≥ 1 weight-related comorbidity or BMI ≥30) – *proposed by company after technical engagement*

Clinical experts:

- Target population suggested by company at submission is generally appropriate
- Tier 3 services are generally used by people with BMI ≥ 35 + comorbidity – this group have the greatest need and semaglutide will likely be used in tier 3 services; future use in primary care would benefit patients

Patient experts:

- Anyone who suffers with obesity should be offered semaglutide

Professional organisations:

- Restricting cost effectiveness analysis to those eligible for tier 3 services will result in a postcode lottery for access as tier 3 services aren't available everywhere

NHS England:

- Greatest need is for people with BMI ≥35 + 1 weight related comorbidity (without pre-diabetes pre-requisite) – treated in tier 3 services (potential 4th population to consider)

Abbreviations – BMI: body mass index; CVD: cardiovascular disease

Treatment setting

- Tier 3 services are usually accessed by people with BMI ≥35 + ≥1 comorbidity
- Tier 3 referral is for up to 2 years and limits retreatment
- Semaglutide model is based on model used for liraglutide appraisal. Liraglutide is recommended in tier 3 only, and model assumptions reflect tier 3 service

- **3 populations for consideration – would a wider population recommendation (including BMI ≥30 or BMI ≥27) imply use in a wider setting e.g. primary care?**
- **What are the potential implications of primary care use on:**
  - **Duration of treatment (max 2 years in model, aligned with tier 3)?**
  - **Retreatment (no retreatment in model, aligned with tier 3)?**
- **Is there a prospect of tier 3 being expanded to include people with BMI <35?**
- **If restrictions on tier 3 use were not in place, what would be the ideal course of semaglutide treatment (duration and retreatment)?**

Defining the appropriate population – T2D

- People with diabetes not included in submission (excluded in STEP 1), but company does not exclude from target population
- STEP 2 trial data (including people with overweight or obesity **and T2D**) not included in submission or model

ERG:
- STEP 2 meets scope criteria
- Without STEP 2 there is no data on semaglutide for people with T2D
- Unclear if T2D might be treated with semaglutide 2.4mg for purposes of weight loss

Professional organisations:
- Weight loss in STEP 2 was significantly lower than in other STEP trials
- Mixed views on STEP 2 exclusion:
  - if STEP 2 data is not included, people with T2D should be excluded from target population
  - others in agreement with STEP 2 exclusion as treatment is for obesity not T2D

Clinical experts:
- STEP 2 suggests semaglutide is less effective for people with T2D
- Semaglutide 1mg is already available for this population which gives ~70% of the effect and provides mortality benefit
- Semaglutide 1mg will be offered to people with obesity and T2D focusing on glycaemic control, but semaglutide 2.4mg may be good alternative for people focusing on weight loss

Abbreviations - T2D – type 2 diabetes

Defining the appropriate population – comorbidities

- Liraglutide is recommended for people with BMI ≥35 plus **pre-diabetes** and **a comorbidity associated with high cardiovascular disease risk**
- The company's original target population for semaglutide includes people with BMI ≥30 plus **a weight-related comorbidity**
- The full marketing authorisation population for semaglutide includes people with BMI ≥27 plus a **weight-related comorbidity** or BMI ≥30

- The marketing authorisation does not specify which weight-related comorbidities are included
- STEP 1 inclusion criteria for people with BMI ≥27 specifies 1 of the following weight-related comorbidities: hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease
- 80% of participants in STEP 1 had a comorbidity, including hypertension, dyslipidaemia, cardiovascular disease, pre-diabetes, knee or hip osteoarthritis, obstructive sleep apnoea, asthma, COPD, liver disease and polycystic ovary syndrome

- **Is the clinical data from STEP 1 generalisable to each of the populations of interest?**

Abbreviations - T2D – type 2 diabetes; ICER – incremental cost effectiveness ratio; COPD: chronic obstructive pulmonary disease

Clinical issues (1)

Setting: which is the appropriate setting for semaglutide?

- Tier 3 services include intensive advice and monitoring and are usually accessed by people with BMI ≥35kg/m^2 (or lower BMI if significant comorbidities, with adjustment for ethnicity). Corresponds with trial setting
- Liraglutide only recommended in tier 3 – is semaglutide use outside tier 3 without multidisciplinary input appropriate?
  - Not all CCGs commission tier 3 services

Population: which population should be considered for semaglutide treatment?

- 3 populations proposed by company:
  - Liraglutide eligible population (**BMI ≥ 35 kg/m^2 plus non-diabetic hyperglycaemia, and high CVD risk**) *treated in tier 3*
  - Company original 'target population' (**BMI ≥30 kg/m^2 plus ≥ 1 weight-related comorbidity**) *proportion not treated in tier 3 (normally)*
  - Full marketing authorisation population (**BMI ≥27 kg/m^2 plus ≥ 1 weight-related comorbidity or BMI ≥30 kg/m^2**) – *proposed by company after technical engagement (larger) proportion not treated in tier 3*
- **NHSE suggest that it would be of most value for patients in tier 3 with BMI ≥ 35 and ≥ 1 weight-related comorbidity such as CVD risk factors but without the requirement for prediabetes (potential population 4)**

Abbreviations - BMI: body mass index; CVD: cardiovascular disease; NHSE: NHS England

Clinical issues (2)

STEP 1 trial: Is this generalisable for the whole NHS population?

- STEP 1 included any patient with BMI ≥ 30 or patients with BMI 27-29.9 with a CVD risk factor. Mean BMI was 38, large majority female - would this represent the average BMI and potential NHS population if the treatment was recommended for the whole MA (all obese people, and all overweight with a CVD risk factor)?

Treatment course:

- Marketing authorisation includes stopping rule that a *decision* to continue treatment needed for people who have not lost 5% initial body weight at 6 months; economic model includes max 2 years treatment duration and no retreatment.
  - **Model based on previous liraglutide model, which was restricted to time in tier 3 – i.e. treatment course matched to maximum time in tier 3. Would this be feasible/reasonable outside tier 3?**

Other key issues:

- **Company assumes all people with non-diabetic hyperglycaemia develop type 2 diabetes after a cardiovascular disease event. Is this reasonable?**
- **Would diabetic patients be included or excluded (some evidence of reduced effectiveness and people with T2D not included in STEP 1)?**
- **Is it necessary to vary the BMI cut-off for ethnic groups who are at increased risk at lower BMI?**

NICE

Abbreviations - BMI: body mass index; CVD: cardiovascular disease

Cost issues (1)

Model is based on liraglutide model (TA664):

- Model assumes use of treatment in tier 3 services. **Is the model appropriate for decision making for semaglutide in all the populations discussed and across different settings?**
- Company and ERG model assumptions include: stopping rule for people who have not lost 5% of initial body weight at 6 months; max 2 years treatment duration and no retreatment (reflects practice in tier 3). **Do these assumptions reflect clinical practice and how semaglutide would be used across different settings?**

Clinical effectiveness data use in the model:

- There are differences in risk profiles for the 3 populations of interest. Model uses data from full STEP 1 population (full analysis set) to estimate effectiveness in each population – populations with a higher risk profile (i.e. liraglutide eligible population) have greater benefit than those with lower risk profiles (e.g. BMI ≥27-30 population). **Is the full analysis set STEP 1 data both generalisable and appropriate for all populations of interest?**
- **Should STEP 2 data (including people with type 2 diabetes) be included in the model?**
- Company use odds ratio from a trial of liraglutide (SCALE 1839) to estimate relative effectiveness of liraglutide compared with semaglutide. **Is this acceptable for decision making for the liraglutide eligible subgroup, or should data from the ITC or STEP 8 trial be used?**

Abbreviations: ITC – indirect treatment comparison

Cost issues (2)

Risk equations:

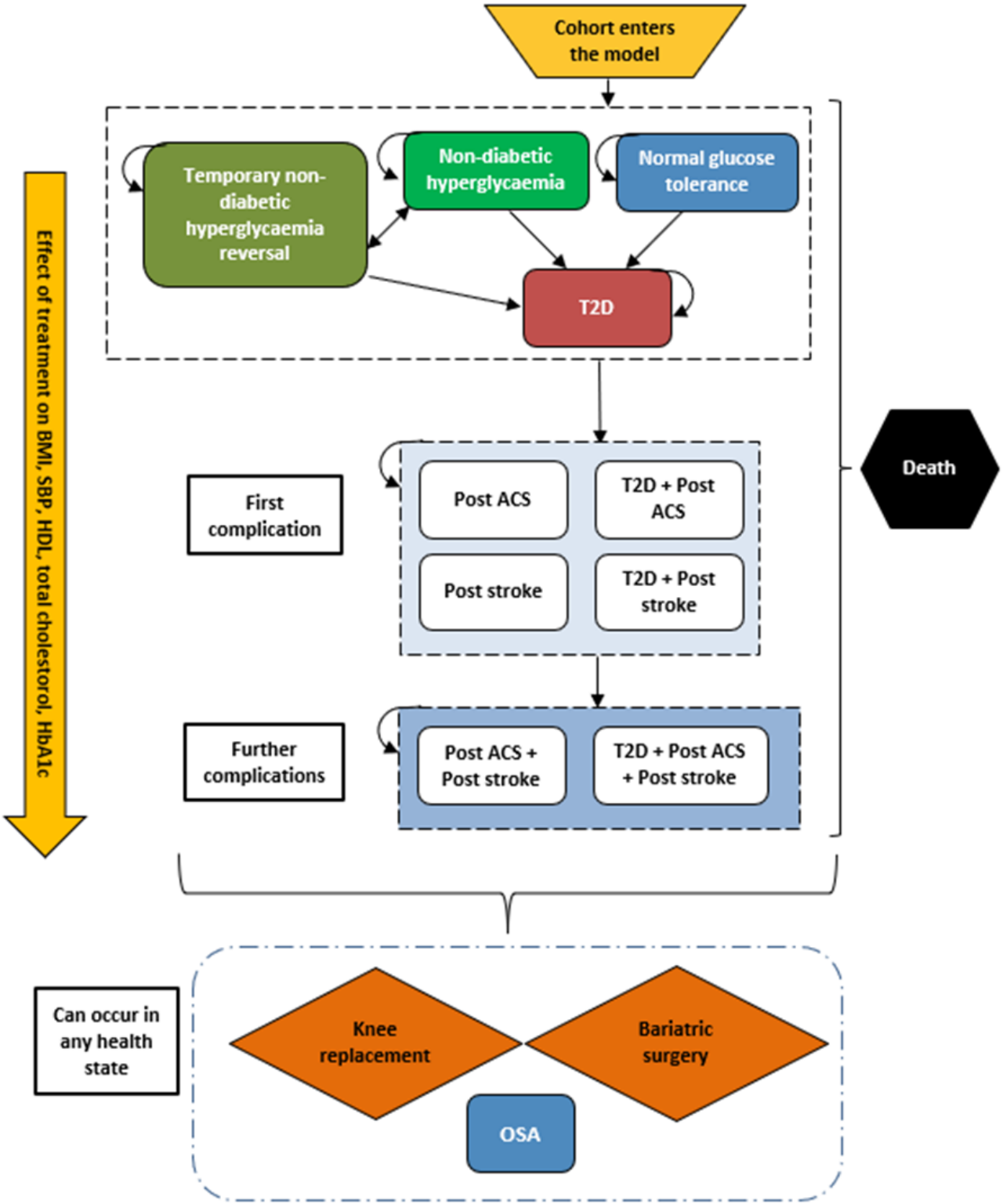
- Model uses risk equations to determine the transition probabilities for CV events and T2D incidence.
  - Risk equations are usually applied to a steady state, but here there is a U-shaped curve of a period of reduced risk followed by an unknown rate of rebound - **do current risk equations adequately encapsulate this? Are the risk equations adequate for estimating outcomes in the model?**
  - Company present scenarios using alternative risk equations to estimate long-term cardiovascular events in absence of long-term data. **How do these scenarios impact certainty around the ICER?**
  - CVD risk drives the ICER; baseline risk of CVD is lower for people with lower BMI or without pre-diabetes – **how should baseline CVD risk be incorporated into the model for each population of interest?**

Model assumptions:

- **Company assumes all people with non-diabetic hyperglycaemia develop T2D after a CVD event. Is this reasonable?**
- **ERG assume different natural weight increase and costs of sleep apnoea than the company - which assumptions are appropriate?**
- **What is the level of uncertainty in the cost effectiveness modelling?**

NICE

Abbreviations: CV(D) – cardiovascular (disease); ICER – incremental cost effectiveness ratio; T2D – type 2 diabetes


Cohort enters the model
Temporary non-diabetic hyperglycaemia reversal
Non-diabetic hyperglycaemia
Normal glucose tolerance
T2D
Effect of treatment on BMI, SBP, HDL, total cholestorol, HbA1c
First complication
Post ACS
T2D + Post ACS
Post stroke
T2D + Post stroke
Death
Further complications
Post ACS + Post stroke
T2D + Post ACS + Post stroke
Can occur in any health state
Knee replacement
Bariatric surgery
OSA

Company's cost effectiveness model

- **Cohort transition model**, including 11 health states and ability to incur acute health states
- Adapted from model for liraglutide (TA664)
- Treatment effects for all subgroups were sourced from the full population of STEP 1
- Company target population (BMI ≥30 + ≥1 comorbidity) and full marketing authorisation population (BMI ≥27 + ≥1 comorbidity or BMI ≥30): individuals enter model as normal glucose tolerance (46.6%) or non-diabetic hyperglycaemia (53.4%; aka people with pre-diabetes; based on prevalence in STEP 1)
- Liraglutide eligible population (BMI ≥35 + pre-diabetes + CVD risk): 100% enter model with pre-diabetes
- **Risk equations:**
  - Risk equations using surrogate outcomes used to calculate transition probabilities into various post-acute coronary syndrome event and post-stroke states (based on BMI, systolic blood pressure, total cholesterol, HDL cholesterol and HbA1c) and risk of developing type 2 diabetes (based on BMI and HbA1c levels)
  - Model includes improvement in outcomes over 2 years followed by return to baseline at 5 years – risk equations are usually applied to a steady state improvement in outcomes
  - Risk of developing type 2 diabetes is higher for people with pre-diabetes
  - Different risk equations for CVD events explored in scenario analyses
  - TA664 conclusion: use of risk equations with surrogate outcomes to estimate long-term events is necessary in absence of long-term data but introduced uncertainty
- Transition to death can occur from any health state as a fatal event or based on disease specific and general population mortality

- **Are the risk equations used in the model appropriate for decision making?**

Abbreviations: BMI – body mass index; HDL – high density lipoprotein; CVD – cardiovascular disease

Assumptions in company's model

Assumptions based on liraglutide model (based on use in tier 3 setting):

- Stopping rule at 6 months assumed for people who have not lost 5% body weight
- Individuals assumed to stop treatment at 2 years and no retreatment included in model
- Treatment effect assumed to wane over 3 years after discontinuation (people in the model regain initial weight and people whose glucose tolerance became normal revert to pre-diabetes); clinical outcomes revert to those in diet and exercise arm (scenarios with 1, 2 and 4 years waning)
- 100% of people with non-diabetic hyperglycaemia develop type 2 diabetes after a cardiovascular event

Other assumption:

- After 1st model cycle (3 months) a proportion of people with pre-diabetes have glycaemic status reversal (90.4% treated with semaglutide, 45.8% for diet and exercise, 83.6% for liraglutide [% sourced from data at 1 year in STEP 1])
  - has implications for risk of developing T2D in model (lower risk in normal glucose tolerance state)

Abbreviations – T2D: type 2 diabetes

Assumptions – stakeholder views and conclusions in TA664

Company assumption	Company justification	Clinical expert (CE), patient expert (PE) and professional org (PO) comments	Conclusion in TA664
Stopping rule: for people who have not lost at least 5% of initial body weight at 6 months to discontinue treatment	MA: "If patients have been unable to lose at least 5% of their initial body weight after 6 months on treatment, *a decision is required on whether to continue treatment*…"	CE: Stopping rule appropriate; people unlikely to wish to continue with no benefit; expect <15% would discontinue at 6 months (based on trial data) PE: Knowledge that semaglutide may be discontinued after 6 months is stressful and unnecessary pressure	Accepted (part of liraglutide marketing authorisation)
Treatment duration max 2 years	Aligns with time spent in tier 3 services	CE: People stay in tier 3 services for 2 years; people who have lost weight would likely want to continue taking treatment PE/PO: Use should be lifelong – obesity is chronic	Obesity is chronic - doesn't reflect long term need; accepted in context of tier 3 use
No retreatment throughout full time horizon	No evidence available to support 'stop and re-start' treatment pattern	CE: Might be appropriate to retreat people with significant weight regain PO: Most will regain weight without option to reintroduce semaglutide	-
Weight regain to baseline after 3yrs	Reflects natural progression when treatment is stopped	CE: Weight will slowly be regained after treatment stops	Accepted assumption but noted uncertainty
100% with non-diabetic hyperglycaemia develop T2D after CVD event	Simplifying assumption; no risk equation available to predict CVD risk for people with non-diabetic hyperglycaemia	CE: A high number would develop T2D after CVD event due to stress of acute CVD event resulting in rise in glucose, but likely overestimated PO: Removing assumption appropriate	ICER likely to be between analysis with assumption applied and without assumption applied

MA: marketing authorisation; T2D – type 2 diabetes; CVD – cardiovascular disease; ICER – incremental cost effectiveness ratio

Considerations for committee on company assumptions

- Should all assumptions apply to each population of interest (liraglutide eligible subgroup, target population and full marketing authorisation population)?
- Is it reasonable to assume a stopping rule at 6 months for non-responders?
- Is it reasonable to assume treatment discontinuation at 2 years and no retreatment across all settings?
- Is treatment waning with return to baseline weight over 3 years clinically plausible?
- Is it reasonable to assume all people with pre-diabetes develop T2D after a CVD event?

Differences between company and ERG models (for target population: BMI ≥30 + ≥1 comorbidity)

Assumption	Company base case	ERG base case	ERG assumption impact on ICER (£)
People with hyperglycaemia develop T2D after a CVD event	100% transition to T2D state	No automatic transition to T2D state	+509
Natural weight increase per year	0.46 kg/m^2	0.30 kg/m^2	-1,411
Age at which weight no longer increases	Age 68	Age 66	+21
Natural weight decrease after age which weight no longer increases	Weight remains constant	0.30 kg/m^2	+468
Annual cost of sleep apnoea*	£1081	£274	+1,923
Company base case			
£14,827			
ERG base case			
£16,337			

*Company use NHS reference costs for sleep apnoea relating to secondary care, representing cost of acute sleeping disorder episodes; ERG source estimates average costs of sleep apnoea episodes

- **Are the key assumptions included in both the company and ERG's models appropriate?**
- **Which of the ERG assumptions are appropriate to include in the model?**

Abbreviations – T2D: type 2 diabetes; CVD – cardiovascular disease; ICER: incremental cost effectiveness ratio

Estimating relative effectiveness of semaglutide compared with liraglutide in the model (1)

Background:

- ITC used to show clinical effectiveness of semaglutide compared with liraglutide for people with BMI ≥ 35 + non-diabetic hyperglycaemia, + high risk of CVD (liraglutide eligible subgroup)
- ITC results not used in model – company used STEP 1 data for semaglutide arm and an odds ratio from SCALE 1839 (liraglutide vs placebo) applied to the placebo arm in STEP 1 to give adjusted estimates for liraglutide efficacy
- STEP 8 data (available at technical engagement) not included in model

ERG:

- Results from STEP 8 for liraglutide eligible subgroup should be used directly in model
- Critique of company's approach:
  - estimating liraglutide efficacy in the model using adjusted OR rather than ITC results favours semaglutide arm; using ITC results in the model may increase the ICER
  - difference in mean weight change from baseline at 1 year for semaglutide vs liraglutide in model is -8%; difference in ITC results is -6%
  - company do not provide rationale for why ITC results not used in model
  - differences in how intercurrent events are recorded between trials impact ability to consistently handle missing data imputation between trials

Abbreviations – ITC – indirect treatment comparison; CVD – cardiovascular disease; OR: odds ratio; ICER: incremental cost effectiveness ratio

Estimating relative effectiveness of semaglutide compared with liraglutide in the model (2)

Company:

- STEP 8 data provides evidence of benefit of semaglutide compared with liraglutide
- Expect risk of bias from differences in recording intercurrent events to be low

Professional organisations:

- ITC results more appropriate for use in model than adjusted odds ratio applied to STEP 1 placebo arm

For the liraglutide eligible subgroup:

- **Is the company's approach to estimating relative effectiveness for liraglutide compared with semaglutide using an odds ratio rather than ITC results in the model acceptable for decision making?**
- **Should direct data from STEP 8 be used in the model instead of an odds ratio or ITC approach?**

Abbreviations – ITC: indirect treatment comparison

Cost effectiveness results: liraglutide eligible subgroup

(BMI ≥ 35 kg/m^2 plus pre-diabetes plus high CVD risk)

- Cost-effectiveness estimates based on updated list price for semaglutide provided following technical engagement, and discounted liraglutide PAS price (available as liraglutide also marketed by Novo Nordisk)

Semaglutide vs liraglutide	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	Dominant
ERG base case	[redacted]	[redacted]	600
Cumulative change from company base case to ERG base case			
+ people with non-diabetic hyperglycaemia do not develop T2D immediately after a CVD event	[redacted]	[redacted]	Dominant
+ mean increase in weight by 0.3 kg per year	[redacted]	[redacted]	Dominant
+ mean decrease in weight after age 66: 0.3 kg per year	[redacted]	[redacted]	Dominant
+ age at which weight no longer decreases: 66 years	[redacted]	[redacted]	Dominant
+annual cost of sleep apnoea	[redacted]	[redacted]	600

Abbreviations – PAS – patient access scheme; T2D: type 2 diabetes; CVD – cardiovascular disease; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

Company cost effectiveness results: company original target population

(BMI ≥ 30 kg/m2 plus at least 1 comorbidity)

Cost-effectiveness estimates based on updated list price for semaglutide following technical engagement

Semaglutide vs diet and exercise	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenarios based on company base case			
Company base case (deterministic)	[redacted]	[redacted]	14,827
Company base case (probabilistic)	[redacted]	[redacted]	14,733
1-year catch up rate	[redacted]	[redacted]	23,686
2-year catch up rate	[redacted]	[redacted]	19,860
No stopping rule (for <5% weight loss after 6 months)	[redacted]	[redacted]	19,486
Using STEP 2 data (including T2D population) in model	[redacted]	[redacted]	21,277
Using STEP 2 data in illustrate diabetes model (McEwan, 2014)	[redacted]	[redacted]	16,613
T2D incidence: Framingham offspring risk equation	[redacted]	[redacted]	18,337
1st CVD event incidence: Framingham heart study risk equation	[redacted]	[redacted]	13,597
Recurrent CVD event in T2D incidence: Framingham recurring coronary heart disease risk equation	[redacted]	[redacted]	15,154
CVD in T2D incidence: QRisk3 risk equation	[redacted]	[redacted]	13,813

T2D: type 2 diabetes; CVD – cardiovascular disease; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

ERG cost effectiveness results: company original target population
(BMI ≥ 30 kg/m2 plus at least 1 comorbidity)

Cost-effectiveness estimates based on updated list price for semaglutide provided following technical engagement

Semaglutide vs diet and exercise	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Cumulative change from company base case to ERG base case			
Company base case	[redacted]	[redacted]	14,827
+ people with non-diabetic hyperglycaemia do not develop T2D immediately after a CVD event	[redacted]	[redacted]	15,336
+ mean increase in weight by 0.3kg per year	[redacted]	[redacted]	13,925
+ mean decrease in weight after age 66: 0.3kg per year	[redacted]	[redacted]	14,393
+ age at which weight no longer decreases: 66 years	[redacted]	[redacted]	14,414
+annual cost of sleep apnoea	[redacted]	[redacted]	16,337
ERG base case	[redacted]	[redacted]	16,337

Abbreviations – T2D: type 2 diabetes; CVD – cardiovascular disease; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

ERG cost effectiveness results – scenario analyses: company original target population (BMI ≥ 30 kg/m^2 plus at least 1 comorbidity)

Cost-effectiveness estimates based on updated list price for semaglutide provided following technical engagement

Semaglutide vs diet and exercise	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenarios based on ERG base case			
ERG base case (deterministic)	[redacted]	[redacted]	16,337
Mean starting BMI 32.5	[redacted]	[redacted]	22,192
Mean starting BMI 37.5	[redacted]	[redacted]	14,980
Mean starting BMI 42.5	[redacted]	[redacted]	12,867
Rate outcomes return to baseline after discontinuation: 1 year	[redacted]	[redacted]	25,746
Rate outcomes return to baseline after discontinuation: 2 years	[redacted]	[redacted]	21,060
Rate outcomes return to baseline after discontinuation: 4 years	[redacted]	[redacted]	13,501
Treatment duration: 3 years	[redacted]	[redacted]	17,747

Abbreviations: ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

ERG and company cost effectiveness results: full marketing authorisation population

(BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 plus at least 1 comorbidity)

- Following technical engagement, company proposed that the full marketing authorisation might be more appropriate than the target population included in the submission
- Cost-effectiveness estimates based on updated list price for semaglutide provided following technical engagement

Semaglutide vs diet and exercise	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	15,111
ERG base case	[redacted]	[redacted]	17,134

Abbreviations – ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

Cost issues (1)

Model is based on liraglutide model (TA664):

- Model assumes use of treatment in tier 3 services. Is the model appropriate for decision making for semaglutide in all the populations discussed and across different settings?
- Company and ERG model assumptions include: stopping rule for people who have not lost 5% of initial body weight at 6 months; max 2 years treatment duration and no retreatment (reflects practice in tier 3). Do these assumptions reflect clinical practice and how semaglutide would be used across different settings?

Clinical effectiveness data use in the model:

- There are differences in risk profiles for the 3 populations of interest. Model uses data from full STEP 1 population (full analysis set) to estimate effectiveness in each population – populations with a higher risk profile (i.e. liraglutide eligible population) have greater benefit than those with lower risk profiles (e.g. BMI ≥27-30 population). Is the full analysis set STEP 1 data both generalisable and appropriate for all populations of interest?
- Should STEP 2 data (including people with type 2 diabetes) be included in the model?
- Company use odds ratio from a trial of liraglutide (SCALE 1839) to estimate relative effectiveness of liraglutide compared with semaglutide. Is this acceptable for decision making for the liraglutide eligible subgroup, or should data from the ITC or STEP 8 trial be used?

Abbreviations: ITC – indirect treatment comparison; ICER – incremental cost effectiveness ratio

Cost issues (2)

Risk equations:

- Risk equations are usually applied to a steady state, but here there is a U-shaped curve of a period of reduced risk followed by an unknown rate of rebound - do current risk equations adequately encapsulate this?
- Model uses risk equations to determine the transition probabilities for cardiovascular events and T2D incidence. Company present scenarios using alternative risk equations to estimate long-term cardiovascular events in absence of long-term data.
  - How do these scenarios impact certainty around the ICER?
  - Are the risk equations adequate for estimating outcomes in the model?
  - Cardiovascular disease risk drives the ICER; baseline risk of CVD is lower for people with lower BMI or without pre-diabetes – how should baseline cardiovascular disease risk be incorporated into the model for each population of interest?

Model assumptions:

- Company assumes all people with non-diabetic hyperglycaemia develop type 2 diabetes after a cardiovascular disease event. Is this reasonable?
- ERG assume different natural weight increase and costs of sleep apnoea than the company - which assumptions are appropriate?
- What is the level of uncertainty in the cost effectiveness modelling?

Abbreviations: CVD – cardiovascular disease; ICER – incremental cost effectiveness ratio