NICE National Institute for Health and Care Excellence

Liraglutide for managing overweight and obesity

Lead team presentation

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Key clinical issues

- The company has suggested a post-hoc subgroup (35%) of the whole prediabetes population in the trial is particularly likely to benefit. Is this reasonable?
- Are orlistat and bariatric surgery important comparators that should be included?
- An assumption is made that liraglutide would be provided within a Tier 3 service, however not all CCGs commission this
- The proposed treatment for this subgroup differs from the trial in which all stayed on treatment for 3 years. The licence specifies that only responders continue on treatment after 12 weeks on full dose. In addition, the company proposes that they continue on treatment for 2 years only and then stop. How can the trial results be interpreted for this situation?

[redacted]

Key clinical issues continued

- No trial data is available post stopping liraglutide. It is assumed that patients return to their baseline weight over 3 years after stopping. Is this in line with expected trajectory?
- The predicted benefits include reduced cardiovascular events, but this was not apparent in the trial. What long term benefits would be expected from a limited period of liraglutide treatment?
- How many patients would stop before 2 years and why?
- The population proposed by the company is defined by BMI ≥35 kg/m^2, pre-diabetes and cardiovascular risk factors. Is it necessary to vary the BMI cut-off for ethnic groups who are at increased risk at lower BMI?

[redacted]

Liraglutide

Marketing authorisation	Combined with reduced-calorie diet + increased exercise in adults with BMI of • ≥30 kg/m^2 (obese), or • ≥27 kg/m^2 to <30 kg/m^2 (overweight) with at least one weight-related comorbidity such as dysglycaemia (pre-diabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea. Treatment should be discontinued after 12 weeks on full 3.0 mg/day dose if patients have not lost at least 5% of their initial weight. **NOTE: the submission focuses on a subgroup of MA only**
Mechanism of action	Human glucagon-like peptide-1 (GLP-1) analogue. Liraglutide binds to and activates the GLP-1 receptor (GLP-1R). GLP-1 - physiological regulator of appetite and food intake, but the exact mechanism of action is not entirely clear.
Administration	Starting dose: 0.6 mg once daily by subcutaneous injection. Increased to 3.0 mg once daily with at least one week intervals to improve gastro-intestinal tolerability.
Cost	List price is £196.20 for 5 x 6 mg/ml 3ml pre-filled pens.

Disease Background

- Overweight and obesity: characterised by increased body fat.
- People 55 - 64 years are the most likely to be obese, 16 - 24 years least likely.
- 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
- BMI scores of 30 kg/m^2 to <35 kg/m^2 are defined as Obesity class I, 35 kg/m^2 to <40kg/m^2 Obesity class II, ≥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.

Current management

Obesity: identification, assessment and management (CG189)

- Standard management 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.

- Not all CCGs commission Tier 3 services

Treatment Pathway

Obesity: identification, assessment and management (CG189)

Standard management of overweight and obesity

- dietary and lifestyle advice,
- behaviour modification,

Orlistat should only be considered after dietary, physical activity and behavioural approaches have been started and evaluated

- With a BMI of 30 kg/m^2 or more,
- BMI of 28 kg/m^2 or more and significant comorbidities

Bariatric surgery can be considered for people with a BMI of:

- 40 kg/m^2 or more,
- 35 kg/m^2 - 40 kg/m^2 with significant comorbidities,
- 30 kg/m^2 - 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).

Patient and carer perspectives

- Living with obesity is a constant struggle, life is very restrictive. There is stigma associated with being obese.
- Access to treatment and weight management services is sporadic across the UK
- GPs appear to have very limited training in obesity and some are nervous to bring up the conversation around obesity as a result.
- There are no medications that focus on the biological or physiological causes of obesity.
- Groups that would benefit are people with a BMI of 30 or above and people living with obesity and co-morbidities. These groups have limited treatment options currently and are at greater risk.

Decision Problem

	Final scope issued by NICE	Evidence used in the model
Population	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	BMI of • ≥35 kg/m^2; • pre-diabetes, **and** • high risk of cardiovascular disease defined as: • *Total cholesterol>5mmol/L or* • *HDL <1.0 mmol/L (men) & <1.3 (women) or* • *BP >140mmHg*
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.

Clinical Evidence – Trial 1839

Trial design	Randomised, double-blind, placebo-controlled trial: **prediabetes pts randomised to 160 week trial period (others 56 weeks)** **The focus of this submission is pre-diabetes and a high risk of CVD**
Trial inclusion criteria	18+ years stable body weight & BMI of at least 30 kg/m² or 27 kg/m² + with dyslipidaemia, or hypertension, or both Patients stratified according to BMI (≥30 kg/m^2 or <30 kg/m^2) and prediabetes status. Prediabetes criteria (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 • Oral glucose tolerance test [OGTT]) plasma glucose (PG) ≥7.8 mmol/L and ≤11.0 mmol/L.
Trial drug	Liraglutide 3.0mg or placebo (ratio 2:1) once daily by subcutaneous (SC) injection Given any time of day irrespective of meals. Dose escalation in weekly increments of 0.6mg liraglutide to minimise GI side effects .
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.

[redacted]

Clinical Evidence – Derivation of the Index Population in Trial 1839

- Trial 1839
  - People with and without pre-diabetes (n=3,731), follow-up: 1 year
- Trial 1839 pre-defined subgroup
  - People with prediabetes (n=2,254), follow-up: 3 years
- **Post-hoc analysis (Index Population):**
  - BMI ≥35 kg/m^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;
  - high risk of cardiovascular disease
  - N=800

[redacted]

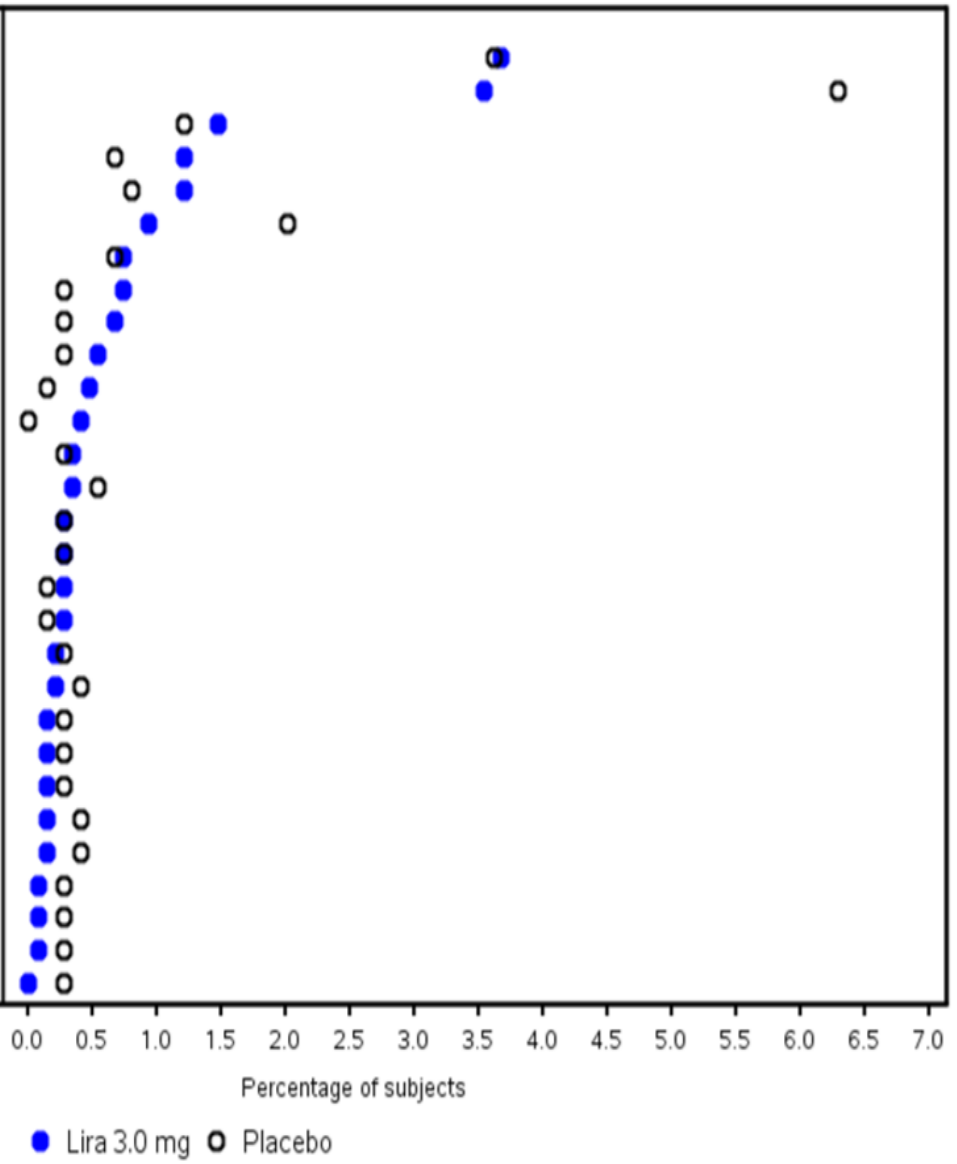
Key Trial Results: Index population (pre-diabetes and high risk of CVD) Trial 1839 (n=800)

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]
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]
Reversal of pre-diabetes*	360/530 (67.9%)	104/270 (38.5%)	-
Cardiovascular adverse events (week 162; n/N, %)	86/530 (16.2%)	46/270 (17.0%)	OR: 0.94 [0.64, 1.40]

Adapted from Table 4.7 (from ERG report): Main outcomes as specified in the NICE scope for 'patients with a BMI ≥35 kg/m2, pre-diabetes and high risk of CVD' (Change between baseline and week 160 (LOCF)).
† Estimated treatment differences are from an analysis of covariance with data from the full-analysis set, with last-observation-carried-forward (LOCF) imputation.
* Added from Table 20 of the company submission

CV events

	Lira 3.0 mg		Placebo	
	%	R	%	R
Blood creatine phosphokinase increased	3.7	1.8	3.6	2.3
Oedema peripheral	3.5	1.9	6.3	3.9
Chest pain	1.5	0.7	1.2	0.7
Dyspnoea	1.2	0.7	0.7	0.3
Syncope	1.2	0.6	0.8	0.4
Palpitations	0.9	0.5	2.0	1.3
Atrial fibrillation	0.7	0.4	0.7	0.5
Tachycardia	0.7	0.4	0.3	0.1
Orthostatic hypotension	0.7	0.4	0.3	0.1
Oedema	0.5	0.3	0.3	0.1
Nocturia	0.5	0.2	0.1	0.1
Atrioventricular block first degree	0.4	0.2	0.0	0.0
Angina pectoris	0.3	0.2	0.3	0.2
Ventricular extrasystoles	0.3	0.2	0.5	0.3
Arrhythmia	0.3	0.1	0.3	0.1
Bradycardia	0.3	0.1	0.3	0.1
Coronary artery disease	0.3	0.1	0.1	0.1
Coronary revascularisation	0.3	0.2	0.1	0.1
Myocardial ischaemia	0.2	0.1	0.3	0.1
Sinus bradycardia	0.2	0.1	0.4	0.2
Deep vein thrombosis	0.1	0.1	0.3	0.1
Diastolic dysfunction	0.1	0.1	0.3	0.1
Extrasystoles	0.1	0.1	0.3	0.2
Left atrial dilatation	0.1	0.1	0.4	0.2
Renal failure acute	0.1	0.1	0.4	0.2
Electrocardiogram T wave inversion	0.1	0.0	0.3	0.1
Sinus tachycardia	0.1	0.0	0.3	0.1
Transient ischaemic attack	0.1	0.0	0.3	0.2
Thrombosis	0.0	0.0	0.3	0.1



%: Percentage of subjects experiencing at least one episode
R: Event rate per 100 years of observation time
MedDRA version 15.1

[redacted]

Key Trial Results: Index population (pre-diabetes and high risk of CVD) Trial 1839 (n=800)

Outcome	Liraglutide (n=530)	Placebo (n=270)	Estimated treatment difference, liraglutide vs. placebo (95% CI)†
Health-related quality of life – SF-36 General Health	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]
Other outcomes used in the economic model			
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]

Table 4.7 (from ERG report): Main outcomes as specified in the NICE scope for 'patients with a BMI ≥35 kg/m2, pre-diabetes and high risk of CVD' (Change between baseline and week 160 (LOCF)).
† Estimated treatment differences are from an analysis of covariance with data from the full-analysis set, with last-observation-carried-forward (LOCF) imputation.

Subjects with normoglycaemia (by time)

Glycaemic status over time for patients with BMI ≥35 kg/m^2 and prediabetes and high risk of CVD – LOCF (from CS Table 20)

	Liraglutide 3.0mg (N=531)			Placebo (N=271)		
Week	16	56	160	16	56	160
Normoglycaemic (N, [%])	413 (77.9)	400 (75.5)	360 (67.9)	81 (30.0)	95 (35.2)	104 (38.5)
Confirmed type 2 diabetes (N, [%])	1 (0.2)	2 (0.4)	13 (2.4)	1 (0.4)	7 (2.6)	22 (8.1)

Subjects with normoglycaemia after 160 weeks – ≥5% Early responders - Trial 1839 LOCF (from Company response to questions 4/4/19)

	Liraglutide 3.0mg	Placebo	Difference in proportions
Normoglycaemic	441 (76.2%)	43 (54.4%)	21.8%
High risk of Type 2 diabetes	129 (22.3%)	30 (38.0%)	-15.7%
Transient Type 2 diabetes	6 (1.0%)	2 (2.5%)	-1.5%
Confirmed Type 2 diabetes	3 (0.5%)	4 (5.1%)	-4.6%

Issue 1: Is the population in the CS generalisable and sufficiently justified? Is the group identified more likely to benefit from liraglutide than other populations?

Background

- Submission focuses on a sub-population:
  - BMI ≥35 kg/ m^2 with pre-diabetes, and high risk of cardiovascular disease,
  - **35%** of the whole trial population.

Clinical experts:

- Group @ highest risk of developing T2DM and complications of diabetes.
- RCT & real-world evidence suggest they respond as well as any other group to liraglutide, but they stand to gain a greater absolute risk reduction of developing type 2 diabetes.

Company:

- Subgroup at higher risk of developing obesity-related complications including diabetes and cardiovascular disease. These affect life expectancy, quality of life and healthcare costs, therefore most likely to benefit from treatment and this optimises the cost-effectiveness.
- Subgroup definition based on advice from clinical experts and NICE (Office for Market Access).
- The subgroup is also the focus for the NHS Diabetes Prevention Programme (DPP) and NICE guidelines for cardiovascular risk management (CG181).

[redacted]

Issue 1: Given that not all CCGs commission a Tier 3 service, how would people in those areas access liraglutide?

Background

- Company: liraglutide 3.0mg intended for patients referred to a specialist Tier 3 service where other treatments e.g. orlistat have been previously unsuccessful.

Clinical experts:

- Appropriate in a tier 3 setting as part of a multidisciplinary treatment
- Where tier 3 not available, specialist (endocrinologists) could take referrals for weight management
- Availability of liraglutide may also encourage service development in more CCGs

Company:

- Liraglutide 3.0mg should be provided within a Tier 3 service (or an equivalent specialist-led service for CCGs without a Tier 3 service).

ERG:

- May be a potential issue regarding equity of access
- 19.7% of CCGs state that they do not commission Tier 3-level services (All-Party Parliamentary Group for Obesity, 2018 report).

[redacted]

Issue 2: How reliable is the subgroup analysis and is it acceptable for decision making?

ERG:

- 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

- 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.

Company:

- The subgroup analysis is reliable and acceptable for decision making. Prediabetes was a pre-specified stratification at baseline in the trial. The efficacy results from Trial 1839 in the prediabetes population (n=2,254) and in the index population (n=800) were similar

	Liraglutide 3.0mg		Placebo	
	Prediabetes	Index population	Prediabetes	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)
SBP(mmHg)	-3.19 (13.00)	-4.09 (11.69)	-0.53 (13.73)	-1.09 (11.69)

Values in parentheses are standard deviations. (Source: Company response to technical engagement)
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

Issue 3: Can orlistat and bariatric surgery be excluded as comparators? Would bariatric surgery be offered to people with people with a BMI ≥35 kg/m2, pre-diabetes, and high risk of cardiovascular disease?

Background

- Orlistat and bariatric surgery comparators in the scope
- Only company comparator is standard management without pharmacotherapy.

Clinical experts:

- Liraglutide - third-line option after lifestyle, orlistat treatment, and for those not eligible or who do not want bariatric surgery. Therefore, not suitable comparators.

Company:

- Orlistat recommended in primary care (Tier 2) for much wider population than proposed for liraglutide.
- Orlistat use is limited and declining. The NICE FAD for naltrexone-bupropion (TA494): concluded that standard management was the main comparator.
- Liraglutide would not be a direct replacement for bariatric surgery. This is a cost-effective treatment in Tier 4 services for a selected group of patients. For patients where bariatric surgery would be an appropriate option this should be the preferred option (NICE clinical guideline CG189).
- Only around 0.1% of those eligible for bariatric surgery receive it (NICE TA494). Liraglutide could be suitable for a group of patients who are unwilling or unable to undergo surgery who currently have no other treatment options.

[redacted]

Issue 3: The exclusion of orlistat and bariatric surgery be excluded as comparators?

ERG:

- Failure or unwillingness to take orlistat should have been explicitly recognised in the index population
- The extent to which participants fulfilled these criteria was unclear, thus bringing into question the applicability of the Trial
- 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.
- The ERG believes orlistat and bariatric surgery could be used as comparators in some patients who are eligible for liraglutide.

[redacted]

Issue 4: Would most people who discontinue liraglutide do so within the first 3 or 6 months or would you continue to see discontinuations after 6 months? What will determine if people stop or continue treatment?

Background

- The company assumed that those who continued on liraglutide as responders (after 12 weeks on full dose) could all stay on treatment for 2 years (regardless of response).

Response from engagement:

Clinical experts:

- People do not like to inject themselves every day for a prolonged period but will do so when they have improvements in symptoms of obesity (hunger and lack of satiation), weight loss and complications of obesity (development of diabetes).
- If people do not have a sufficient response within 3 months (weight loss of more than 5%), then will most likely discontinue.
- Most people 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

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Company:

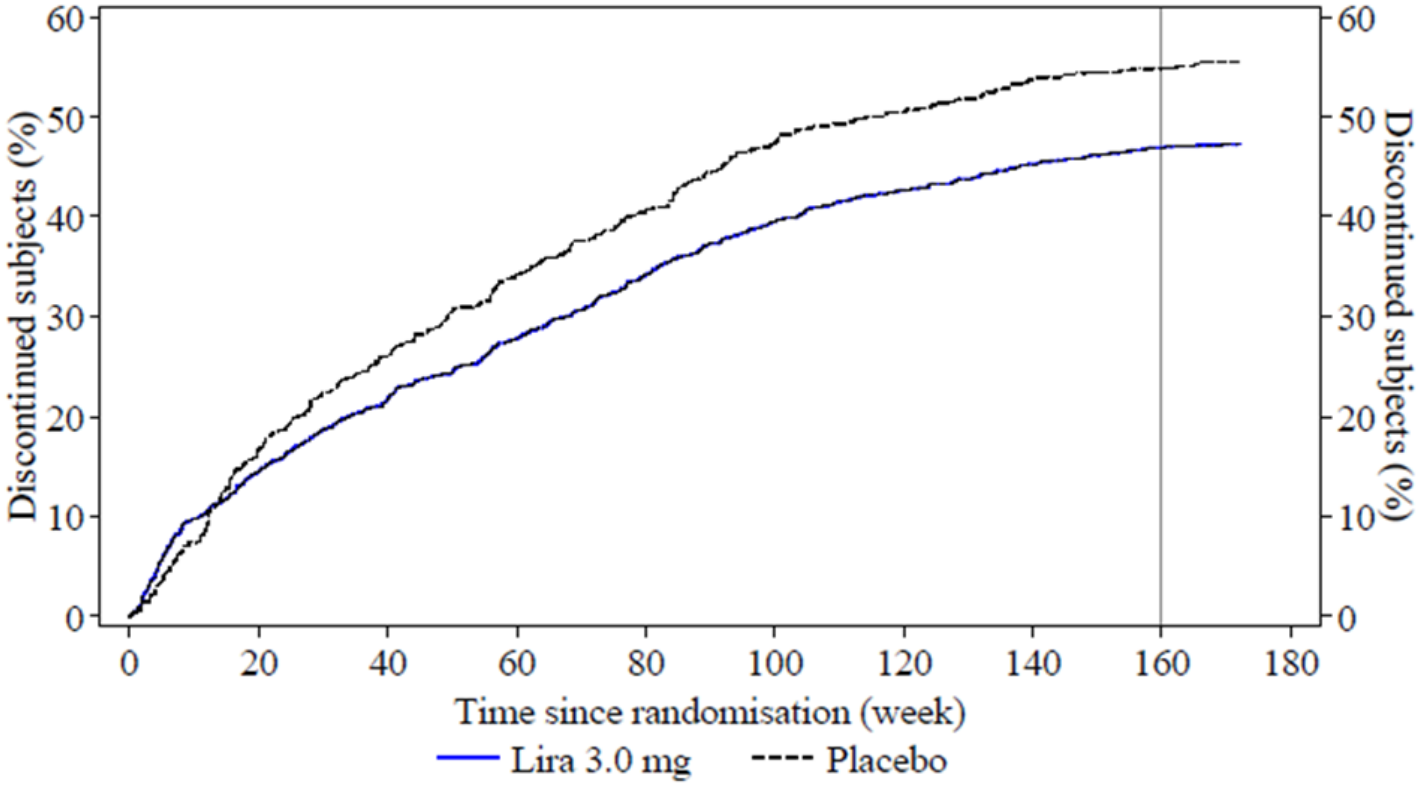
- A physician survey reported that most patients would be expected to have discontinued treatment after 2 years.

[redacted]

Issue 4: Would most people who discontinue liraglutide do so within the first 3 or 6 months or would you continue to see discontinuations after 6 months? What will determine if people stop or continue treatment?

ERG:

- Assumptions related to discontinuation have a relatively large impact on the estimated cost-effectiveness.
- However 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.



[redacted]

Figure 4.2 (ERG report): Time to discontinuation during the entire trial (0 to 172 weeks) - all reasons (Trial 1839, full trial population)

Issue 5: What is the rationale for stopping treatment with liraglutide after 2 years? Would a treatment stopping rule be implementable in clinical practice?

Background

- EMA: treatment should be discontinued after 12 weeks if patients have not lost 5% of their initial body weight (on the full dose)
- No stopping rule in the trial
- Company model assumes all patients stop treatment at 2 years.

Response from engagement:

Clinical experts:

- Preferable if patients who lose >15% weight at 2 years could continue long term.
- If choice between liraglutide not being available or having it available for the patients with a BMI>35, pre-diabetes and high cardiovascular risk for 2 years, I would opt for the latter.

Company:

- Rationale for maximum treatment duration of 2 years based on data from the trial and physician survey (Q16, Appendix N, CS).
- Licence: patients will discontinue therapy if do not lose ≥5% body weight after 12 weeks on full dose.
- A stopping rule is implementable and has been used for other anti-obesity therapies, including orlistat, and (now withdrawn) rimonabant and sibutramine.

[redacted]

Issue 5: What is the rationale for stopping treatment with liraglutide after 2 years? Would a treatment stopping rule be implementable in clinical practice?

ERG:

- The EMA stopping rule was not applied in the trial
- Patients achieving less than 5% weight loss at 16-weeks in the trial 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). It is not clear how this discrepancy influenced results.

- The company model assumes that all patients stop treatment at 2 years.
- At 160 weeks of the clinical trial over 50% of patients were still on treatment
- The rationale for a maximum liraglutide treatment duration of two-years in unclear.

[redacted]

Key clinical issues

- The company has suggested a post-hoc subgroup (35%) of the whole prediabetes population in the trial is particularly likely to benefit. Is this reasonable?
- Are orlistat and bariatric surgery important comparators that should be included?
- An assumption is made that liraglutide would be provided within a Tier 3 service, however not all CCGs commission this
- The proposed treatment for this subgroup differs from the trial in which all stayed on treatment for 3 years. The licence specifies that only responders continue on treatment after 12 weeks on full dose. In addition, the company proposes that they continue on treatment for 2 years only and then stop. How can the trial results be interpreted for this situation?
- No trial data is available post stopping liraglutide. It is assumed that patients return to their baseline weight over 3 years after stopping. Is this in line with expected trajectory?
- The predicted benefits include reduced cardiovascular events, but this was not apparent in the trial. What long term benefits would be expected from a limited period of liraglutide treatment?
- How many patients would stop before 2 years and why?
- The population proposed by the company is defined by BMI ≥35 kg/m^2, pre-diabetes and cardiovascular risk factors. Is it necessary to vary the BMI cut-off for ethnic groups who are at increased risk at lower BMI?

[redacted]

Key cost issues

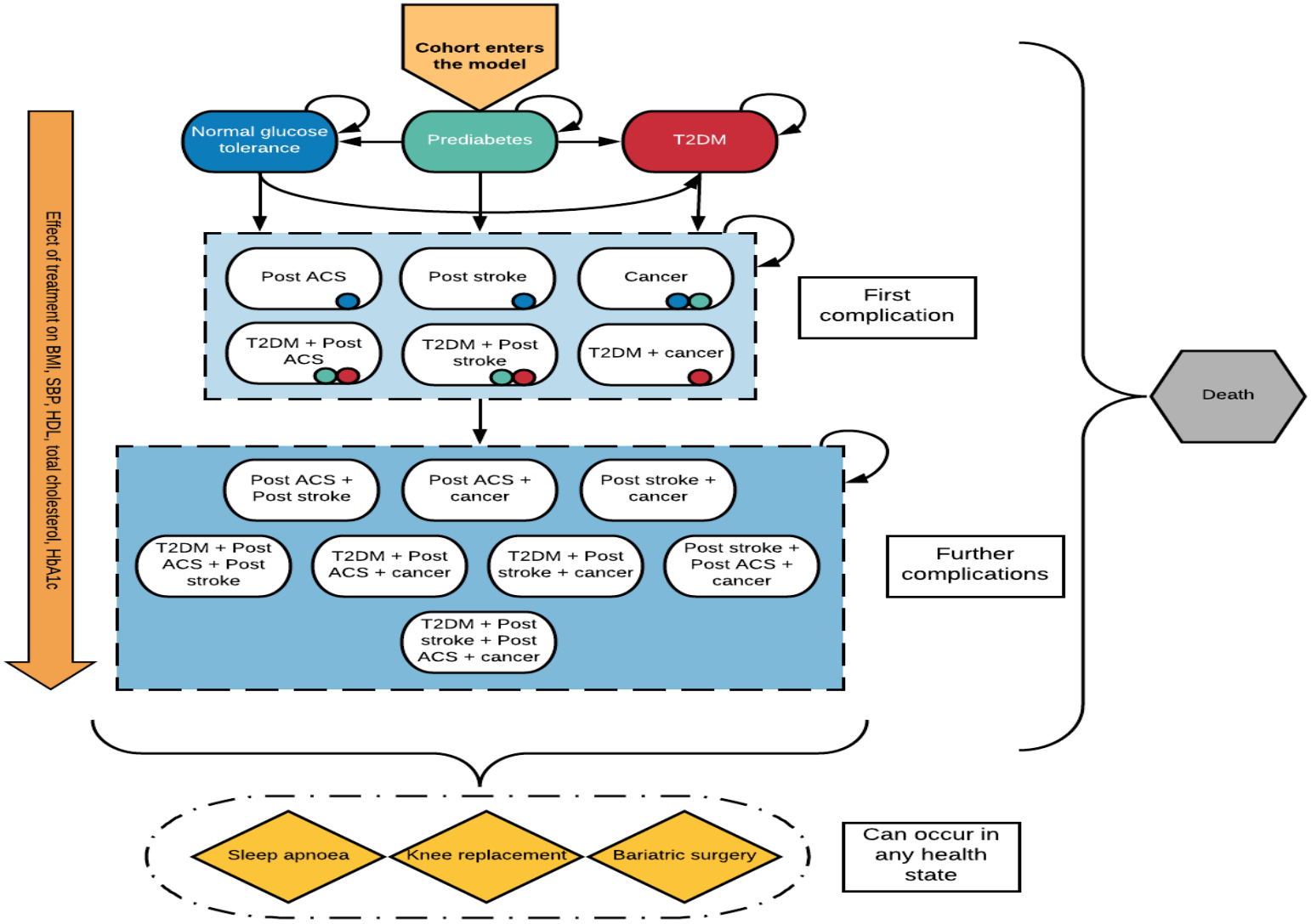
- Is the model used acceptable?
- Cardiovascular risk reduction is an important factors in the cost effectiveness although this was not apparent in the trial, how is this benefit mediated?
- To calculate the likelihood of a primary and secondary cardiovascular event, risk equations are used. However the predicted benefit on weight and diabetic status has returned to baseline after a total of 5 years. Are the risk equations chosen appropriate, and applicable for a temporary benefit?
- The cost effectiveness is particularly affected by whether or not people with a cardiovascular event immediately go from being prediabetic to diabetic. What is a reasonable assumption?
- In the model, non responders on liraglutide stop treatment (unlike in the trial). They are assumed to have the same outcomes as those on placebo in the trial, although these showed some benefit (presumed placebo effect?). What would be a reasonable assumption?
- What is the degree of uncertainty in the cost effectiveness modelling?

Cost Effectiveness – model

- **Population:** Post hoc subgroup of licensed population from trial 1839
- **Perspective, time horizon and discounting:** NHS and PPS perspective. Discount rates 3.5%, 40-year time horizon (cohort starting 48 years).
- **Treatment effectiveness and extrapolation:**
- Health states transitions based on estimation of T2DM status, CV events (primary and secondary) using risk models as well as death probabilities.
- Once-only transition was used to incorporate the proportion of patients reversing from pre-diabetes to normal glucose tolerance based the trial.
- Relative treatment effectiveness estimated through changes in 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 of comparable untreated patients.
- **Treatment Adverse events:** not included in the economic model.
- **Health-related quality of life:** The utility values were obtained from the literature for all health states.
- **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.

Cost Effectiveness - model

- Cohort state transition model.
- 10 health states



Cost- Effectiveness Results

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

[redacted]

Scenario analyses at revised price (company submission)

	ICER (£/QALY)
Base case	**£17,194**
Discount rate of 6%	£23,081
Discount rate of 0%	£9,381
Five-year time horizon	£50,588
Ten-year time horizon	£37,293
Twenty-year time horizon	£24,192
Thirty-year time horizon	£19,035
Treatment duration of one year	£12,230
Treatment duration of three years	£20,063
Exclusion of all complications (impact of BMI on QALYs only)	**£105,798**
Inclusion of T2DM and BMI impact on QALY	**£46,472**
Inclusion of cardiovascular disease, T2DM, BMI impact on QALY	**£21,584**
Inclusion of sleep apnoea in addition to complications above	**£17,827**
Inclusion of cancers with relationship with obesity baseline age 48 years	£16,728
Inclusion of cancers with relationship with obesity baseline age 50 years	£11,960
Immediate loss of treatment effect (i.e. no waning of treatment benefit)	**£36,762**
Waning of treatment effect applied over one year post treatment stop (i.e. catch-up time set to 1 year)	**£20,724**
Waning of treatment effect applied over three years post treatment (i.e. catch-up time set to 3 years)	£9,536
Increased baseline SBP, total cholesterol and HDL	£16,192
Not high risk of CVD subgroup	£17,751
BOCF data imputation method	£16,308
All patients discontinue to no treatment and physiological parameters return to a value on the natural progression following treatment	Dominance

Issue 5: Does clinical experience of rates and degree of weight regain match the assumptions in the modelling?

Background

- Model assumes, patients will stop treatment @ 2 years and gradually regain weight over the next 3 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.

Response from engagement:

Clinical experts:

- Weight regain assumptions in line with what is experienced in clinical practice
- Some patients who experience rapid weight regain after discontinuation of liraglutide opt for bariatric surgery which 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 not consider surgery and lifestyle measures can be implemented to attenuate weight regain, albeit that success varies.

Company:

- Clinical expert advice sought on the rates and degree of weight regain.
- Approach consistent with other published models and the preferred assumptions of NICE committee/ERG for Naltrexone-bupropion for obesity in 2017 (TA494).

[redacted]

Issue 5: Does clinical experience of rates and degree of weight regain match the assumptions in the modelling?

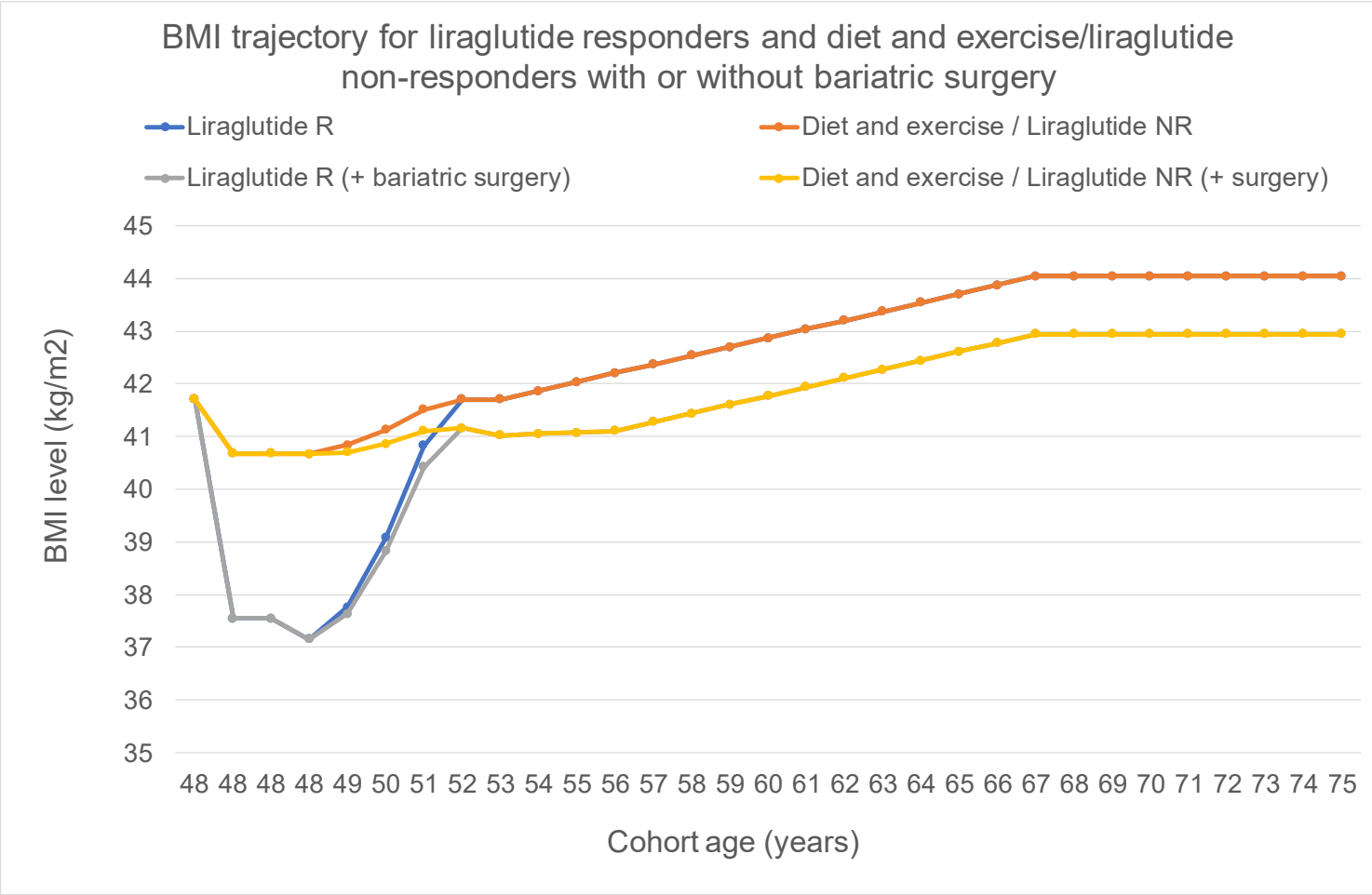


Figure 16 (company submission): BMI trajectories over time (base case analysis)

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.

[redacted]

Issue 6: Is the company's simplifying assumption reasonable?

Background

- Company assumed that everyone with pre-diabetes who experienced a CV event progressed to type 2 diabetes.

Response from engagement:

Clinical experts:

- Assumption is not unreasonable, but there is no definitive data
- 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).

ERG:

- The assumption overestimates the incidence of type 2 diabetes as well as the treatment effect for liraglutide.
- ERG acknowledges that removing this assumption would probably result in an underestimated type 2 diabetes incidence as well as treatment effect for liraglutide.

[redacted]

Issue 7: Which is a better proxy of the treatment effect for liraglutide non-responders? (1) The treatment effect for the overall placebo group or, (2) The treatment effect for placebo non-responders?

Background

- For liraglutide non-responders (who would stop liraglutide after 12 weeks) - effectiveness assumed to be the same as diet and exercise in the placebo arm.

Response from engagement:

Clinical experts:

- 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.
- Reasonable to assume that the changes in quality of life for the liraglutide non-responders and the patients on the placebo arm may be similar, even if the liraglutide non-responders have weight-loss independent benefits such as improved glycaemia, blood pressure and inflammation.

Company:

- Consider 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.

[redacted]

Issue 7: Which is a better proxy of the treatment effect for liraglutide non-responders?

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.

[redacted]

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
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 company submitted scenario analyses indicating that including adverse events would increase the ICER by a small amount.
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.
Choice of risk models	The company uses different risk models to estimate CV events (both primary and secondary) dependent on the T2DM status. 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.	Unknown impact on ICER

Key cost issues

- Is the model used acceptable?
- Cardiovascular risk reduction is an important factors in the cost effectiveness although this was not apparent in the trial, how is this benefit mediated?
- To calculate the likelihood of a primary and secondary cardiovascular event, risk equations are used. However the predicted benefit on weight and diabetic status has returned to baseline after a total of 5 years. Are the risk equations chosen appropriate, and applicable for a temporary benefit?
- The cost effectiveness is particularly affected by whether or not people with a cardiovascular event immediately go from being prediabetic to diabetic. What is a reasonable assumption?
- In the model, non responders on liraglutide stop treatment (unlike in the trial). They are assumed to have the same outcomes as those on placebo in the trial, although these showed some benefit (presumed placebo effect?). What would be a reasonable assumption?
- What is the degree of uncertainty in the cost effectiveness modelling?