NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Liraglutide for managing overweight and obesity [ID740]

Committee Papers

NICE National Institute for Health and Care Excellence

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:

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

Liraglutide for managing overweight and obesity

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Type of stakeholder	Stakeholder	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
Company	Novo Nordisk	Novo Nordisk are disappointed with the decision not to recommend liraglutide 3.0mg for managing overweight and obesity in adults alongside a reduced-calorie diet and increased physical activity. The committee recognised that living with obesity is challenging, restrictive and associated with stigma as highlighted by the patient expert (section 3.1 in the ACD), understood the need for more treatment options that are addressing the biological determinants of obesity and recognised that liraglutide 3.0mg is an effective treatment for weight loss. The decision leaves a gap in effective treatment options for a group of patients with extremely high unmet medical need.	Thank you for your comment. The committee heard from patient experts and recognised that there are limited effective treatment options available for people living with obesity (see FAD section 3.1). It recommended liraglutide as an option for managing overweight and obesity for populations with BMI>= 35 kg per m^2 and pre-diabetes and a high risk of cardiovascular disease (see FAD section 1.1).

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Company	Novo Nordisk	In order to ensure that relevant patients can access treatment with liraglutide 3.0mg, Novo Nordisk has proposed a further price reduction via the commercial arrangement with NHS England. Details of the impact on cost-effectiveness of the further price reduction can be found in the appendix submitted along with this response. In the appendix we present our revised company base case (as presented in response to the technical engagement) at the new lower price together with full justification for the assumptions. The assumptions are listed below and yield an ICER of £14,839 per QALY gained. • The price has been reduced from £[redacted] to £[redacted] per pack of 5 prefilled pens (18mg/3ml). • Per cycle discontinuation (as observed in Trial 1839) is included during the 2-year treatment period (following the licence stopping rule at 12 weeks). • We assume a maximum treatment duration of 2 years. • Liraglutide 3.0mg non-responders are assumed to have the same efficacy as the placebo group (diet and exercise). • The UKPDS 82 risk equations are used to estimate CV events in people with type 2 diabetes. • Automatic development of type 2 diabetes (within 12 months) following a cardiovascular event is assumed though its impact is tested in scenario analysis. In addition, the ERG base cases (scenario 1-7) have been recalculated using this new lower price (Table 10) in the appendix	Thank you for your comment. Thank you for your comment. The committee has recommended liraglutide as an option for managing overweight and obesity for populations with BMI>= 35 kg per m^2 and pre-diabetes and a high risk of cardiovascular disease (see FAD section 1.1).
Company	Novo Nordisk	The committee concluded that it had reservations about the use of data from a post-hoc subgroup that would be associated with more uncertainty than the larger pre-defined prediabetes trial population. While we acknowledge that post-hoc subgroup analysis is associated with increased uncertainty, we would like to remind the committee that this subgroup consisted of 800 patients and had similar efficacy results to the full trial population, as shown in the original company submission (CS): section B.2.6.1 p. 53, section B.2.7.3., p. 69) and response to the technical engagement (Issue 2, p. 5). We have defined the subgroup in the original CS based on advice from clinical experts. The criteria for inclusion in the post-hoc subgroup was determined through assessments at base line and no post-randomisation information was used in the selection. This way of selecting patients for a subgroup will in principle preserve the integrity of the randomisation	Thank you for your comment. The committee noted that the post-hoc subgroup is associated with more uncertainty than the larger pre-defined pre-diabetes trial population. However, the committee accepted that the post-hoc subgroup was suitable for decision making (see FAD section 3.5).

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Company	Novo Nordisk	The committee was concerned that the post-hoc subgroup may have compromised randomisation and concluded that the relative clinical effectiveness of liraglutide 3.0mg should have been estimated from the whole prediabetes population in the trial because this was larger, pre-specified and associated with less uncertainty than the smaller post-hoc subgroup. To reassure the committee, Novo Nordisk have performed analyses whereby efficacy inputs from the post-hoc subgroup analysis, were replaced with the efficacy inputs from the full prediabetes (mITT efficacy) population, while maintaining the baseline characteristics representative of the post hoc subgroup population, i.e., patients with a BMI ≥35 kg/m2, prediabetes, and high risk of cardiovascular disease (CVD). The efficacy inputs can be found in the appendix (Appendix Table 4). Using mITT efficacy inputs (from the full prediabetes population) reduces the company base case ICER from £14,839 to £11,682 (Appendix Table 2 and 5). Probabilistic sensitivity analysis yields an ICER of £15,265 (Appendix Table 2) for the company base case and an ICER of £11,940 (Appendix Table 5) for the mITT efficacy scenario. The cost effectiveness acceptability curve (CEAC) for the company base case shows that a majority of simulation points fall below a threshold of £20,000 (97%) and 99% of simulation points lie below a £30,000 threshold. For the mITT scenario analysis, CEAC shows comparable results with 99% below an ICER threshold of £20,000 and 99% below a threshold of £30,000 (Appendix Figure 2).	The committee was reassured by the scenario analysis presented in the company response for the whole pre-diabetes population, which had a reduced ICER when compared to the base case analysis (see FAD section 3.15).
Company	Novo Nordisk	The committee concluded that the estimation of any reduction in cardiovascular (CV) events would be subject to uncertainty because they would rely on an estimation of the relationship between the surrogate and the clinical event. Novo Nordisk agrees that relying on surrogate outcomes to estimate reduction in CV events is subject to uncertainty. However, the use of surrogate outcomes in health economic modelling is a common and accepted practice where there is an established link between the surrogate and final outcome. The economic model uses published risk equations derived from well-known, established studies such as QRisk1, QDiabetes2, Framingham3 and UKPDS4. Risk equations have also been used in previous NICE recommendations, for example QRisk and UKPDS were used in the development of the NICE clinical guidelines (CG181) Cardiovascular disease: risk assessment and reduction, including lipid modification5. Weight loss and weight loss maintenance are the cornerstones in any intervention for overweight and obesity and are consistently acknowledged to be associated with reductions in the risk of developing CV events [PH25]6, [NG136]7. Existing NICE guidance in this area is aligned with the global research and policy consensus that reducing body weight among people with obesity patients leads to CV benefits. For example, in the NICE CV disease prevention guideline [PH25]6, obesity is stated to be a key modifiable CV disease risk factor. The same guidance document reviews evidence supporting improvements in heart health through weight loss. NICE guidance also supports lifestyle interventions such as weight loss measures as an intervention to reduce hypertension [NG136]7 as well as post-myocardial infarction management in patients with overweight or obesity [CG172]	Thank you for your comment. The committee noted that the cardiovascular benefits of liraglutide in the company's model was based on risk reduction using surrogate outcomes and that this approach introduced uncertainty. The committee acknowledged that relying on surrogates is uncertain but accepted that surrogate outcomes were the only available evidence to estimate cardiovascular benefits. See FAD section 3.6.

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Company	Novo Nordisk	Novo Nordisk are disappointed that the committee questions the long-term CV benefit of weight loss, as this is the underlying premise for a multitude of public health campaigns and interventions, including the National Diabetes Prevention Programme (NHS DPP)9. There is an obvious willingness to invest significantly in weight management interventions which are all ultimately aiming at reducing the long-term risk of CVD through weight reduction. If NICE does not recognise the association between weight loss – even in the short term – and long-term development of CVD, it is surprising that such significant investments are being made in this area. In addition, the subpopulation identified in the CS (BMI ≥35 kg/m2, prediabetes and high risk of CVD) overlaps with the population targeted for the National DPP10, which is specifically targeting weight loss over 12 months only. This emphasises that this is a group of people that the NHS is prioritising and investing in. The clinical trial (Trial 1839) was not powered to show a significant difference in CV events. Nevertheless, as noted in the CS, a post-hoc analysis of the five randomised phase 3a studies11-15 from the liraglutide 3.0mg clinical development programme (Davies et al. 201717) found a reduction in CV risk compared with the pooled comparator group (placebo or orlistat). The analysis included patients with BMI ≥27 kg/m2 with at least one weight-related comorbidity, or a BMI ≥30 kg/m2 and found the rate of positively adjudicated CVD events to be 1.54 events/1000 person-years with liraglutide versus 3.65 events/1000 person-years with comparators. The hazard ratio (HR) for the primary analysis was 0.42 (95% CI 0.17-1.08). Supporting evidence for the benefits of liraglutide comes from a cardiovascular outcomes trial (CVOT) conducted in people with type 2 diabetes and established CV risk. Marso et al. 201617 reported the results of the LEADER trial in which liraglutide (at a lower dose) plus standard of care was compared with placebo plus standard of care. The rate of the first occurrence of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke was 13.0% for liraglutide and 14.9% for placebo with a hazard ratio (HR) was 0.87 (95% confidence interval (CI) 0.78-0.97). Despite the lower dose of liraglutide, these data were considered relevant for inclusion in section 5.1 of the liraglutide 3.0mg Summary of Product Characteristics (SmPC) by EMA.	Thank you for your comment. The committee accepted the risk equations selected in the company's and ERG's base case. See FAD section 3.6 and 3.9.

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Company	Novo Nordisk	Other GLP-1 analogues have also been shown to reduce the rate of CV events. Andrikou et al. 201818 reviewed GLP-1 CVOTs and noted liraglutide, semaglutide and albiglutide have demonstrated reduction in risk of major adverse cardiac events (MACE). The potential cardioprotective effect of incretin-based therapies is attributed to their multiple non-glycaemic actions in the CV system, including changes in insulin resistance, weight loss, reduction in blood pressure, improved lipid profile and direct effects on the heart and vascular endothelium. Zimmerman et al. 201719, a US retrospective study using electronic health records found that treatment with GLP-1 analogues including liraglutide, significantly reduced stroke/cerebrovascular accidents (CVAs) and all-cause mortality. The study included patients with type 2 diabetes and showed that treatment with GLP-1 analogues is associated with significantly lower risk for CVA with a HR of 0.82 (95% CI 0.74-0.91) and for all-cause mortality with a HR of 0.48 (95% CI 0.41-0.57); and even positively impacts the risk of acute myocardial infarction (AMI), CVA or all-cause mortality with a HR of 0.82 (95% CI 0.74-0.91). Patients with no prior CVD had a statistically significant reduction in risk of mortality (HR 0.43, 95% CI 0.35-0.53) when exposed to GLP-1 analogues, as compared with patients with established CVD..	Thank you for your comment. The committee accepted the risk equations selected in the company's and ERG's base case. See FAD section 3.6 and 3.9.
Company	Novo Nordisk	Moreover, the prolonged benefits of glucose, blood pressure or lipid control in individuals with CVD, type 2 diabetes or in primary prevention of CVD by control of early risk factors has been well demonstrated. For example, Paul et al. 201520, using routine data from the Clinical Practice Research Datalink (CPRD) that includes over 100,000 individuals with type 2 diabetes, showed that a delay of 1 year in achieving tight glycaemic control was associated with a significantly increased risk of myocardial infarction, stroke, heart failure and composite CV events. Further, a systematic review and meta-analysis of long-term follow-up of clinical trials concerning blood pressure-lowering medication has confirmed a decrease in overall mortality which persist after the end of the trial period when the majority of patients in both the intervention and control groups start receiving active therapy (Kostis et al 2010)21. The Anglo-Scandinavian cardiac outcomes trial (ASCOT) also demonstrated the legacy effect of lipid-lowering therapies by showing that, following a median of 11 years after initial randomisation (~8 years after closure of the lipid-lowering arm), all-cause mortality remained significantly lower in those who were originally assigned to the active trial with atorvastatin (HR 0.86, 95% CI 0.76-0.98), with CV deaths being lower, but not significantly, and non-cardiovascular deaths being significantly lower (HR 0.85, 95% CI 0.73-0.99) (Sever et al 2011)22. The Diabetes Prevention Program Outcomes Study (DPPOS)23 randomised people at high risk of diabetes to an intensive lifestyle intervention or masked metformin with placebo. All patients were offered lifestyle training at the end of the 3-year initial study period. The between group difference in cumulative incidence of type 2 diabetes was demonstrated after 12 years follow up, showing a durable effect from the original 3-year interventions.23 This phenomenon – described as the 'legacy effect' or 'metabolic memory' - should also be considered in this context	Thank you for your comment. The committee accepted the risk equations selected in the company's and ERG's base case. See FAD section 3.6 and 3.9.

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Clinical expert	Abd Tahrani	In the appraisal consultation document NICE stated “Current management for overweight and obesity is lifestyle measures alone, lifestyle measures with orlistat, or bariatric surgery”. This is correct, but considering the extremely limited access to Bariatric Surgery in the NHS and the poor tolerability and limited weight loss achieved with orlistat; the current recommendation is concerning as it deprives patients with obesity (who have very little other options) from access to an effective treatment option.	Thank you for your comment. The committee heard from patient experts and recognised that there are limited effective treatment options available for people living with obesity (see FAD section 3.1). It recommended liraglutide as an option for managing overweight and obesity for populations with BMI>= 35 kg per m^2 and pre-diabetes and a high risk of cardiovascular disease (see FAD section 1.1).
Clinical expert	Abd Tahrani	Regarding the appraisal consultation document point 3.1. I agree with the patient representative that obesity has a negative impact on patients’ quality of life. I also agree that obesity stigma is a major challenge and usually driven by lack of understanding of the complex causes of obesity and that there is real need for effective treatments for obesity to be made available.	Thank you for your comment. The committee heard from patient experts and agreed that there is stigma associated with being obese and that there is a need for effective treatments that deal with the biological determinants of obesity (see FAD section 3.1). It recommended liraglutide as an option for managing overweight and obesity for populations with BMI>= 35 kg per m^2 and pre-diabetes and a high risk of cardiovascular disease (see FAD section 1.1).
Clinical expert	Abd Tahrani	Regarding [the appraisal consultation document] point 3.2., I agree with the committee decision to focus on the high-risk population proposed by the company	Comment noted. No further action required. See FAD section 3.2 for information on the high-risk population.
Clinical expert	Abd Tahrani	Regarding [the appraisal consultation document] point 3.3., I agree with the committee decision that tier 3 service is the appropriate context in which liraglutide would be offered	Comment noted. No further action required. See FAD section 3.3 for information on tier 3 services.
Clinical expert	Abd Tahrani	Regarding [the appraisal consultation document] point 3.4., I agree with the committee decision that for most people, orlistat and bariatric surgery would not be alternatives to liraglutide and hence comparison with standard management without pharmacotherapy was appropriate for decision-making	Comment noted. No further action required. See FAD section 3.4 for information on choice of comparator.
Clinical expert	Abd Tahrani	Regarding [the appraisal consultation document] point 3.5., I agree with the committee decision that the post-hoc subgroup population was identifiable and that it represented a high-risk population that were likely to gain higher absolute benefit from liraglutide.	Comment noted. No further action required. See FAD section 3.5 for information on the post-hoc subgroup.

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Clinical expert	Abd Tahrani	Regarding [the appraisal consultation document] point 3.6, the committee "was concerned that the post-hoc subgroup may have compromised randomisation. The committee concluded that the relative clinical effectiveness of liraglutide should have been estimated from the whole pre-diabetes population in the trial because this was larger, pre-specified and associated with less uncertainty than the smaller post-hoc subgroup". I agree with the committee that examining the whole pre-diabetes population in the trial has its advantages as outlined in the above-mentioned comment. However, when the index population (i.e. pre-diabetes + high CVD risk) was compared to the total pre-diabetes population in the SCALE trial (NEJM 2015) the changes in HbA1c, body weight, waist circumference and systolic BP were very similar between the two groups. In addition, as the committee agreed that tier 3 services are the appropriate services to offer liraglutide 3.0 mg treatment, using the total pre-diabetes population in the analysis would raise logistical challenges to tier 3 services who currently use a BMI >=35 kg/m^2 as a referral criteria to their services while about 30% of the total pre-diabetes population the SCALE trial had BMI < 35 kg/m^2. Hence, using the pre-diabetes with high CVD risk population is reasonable as it is an identifiable population that is likely to achieve greater absolute benefits (as the committee acknowledged) and would be consistent with the current criteria for referral to tier 3 weight management services.	Thank you for your comment. The committee noted that the post-hoc subgroup is associated with more uncertainty than the larger pre-defined pre-diabetes trial population. However, the committee accepted that the post-hoc subgroup was suitable for decision making (see FAD section 3.5). The committee was reassured by the scenario analysis presented in the company response for the whole pre-diabetes population, which had a reduced ICER when compared to the base case analysis (see FAD section 3.15).
Clinical expert	Abd Tahrani	Regarding [the appraisal consultation document] point 3.7., "the committee concluded that the estimation of any reduction in cardiovascular events would be subject to uncertainty because they would rely on an estimation of the relationship between the surrogate and the clinical event". I agree that the modelling of CVD benefits is based on surrogate markers. SCALE was not a cardiovascular outcome trial and hence the study population was not particularly of high CVD risk and the number of CVD events was small. However, the development of Type 2 diabetes and higher systolic blood pressure are well established CVD risk factors and hence the impact of liraglutide 3.0 mg will be expected to have favourable impact on CVD. This is supported by the cardiovascular outcomes RCT in patients with Type 2 diabetes showing the CVD benefits of liraglutide 1.8mg (https://www.nejm.org/doi/full/10.1056/NEJMoa1603827). In addition to the glycaemic and BP benefits, in the SCALE trial there were benefits in many other CVD risk factors in the liraglutide 3.0 group vs placebo including: fasting lipid levels, high-sensitivity C-reactive protein, plasminogen activator inhibitor-1, and adiponectin. While it does not rule out any uncertainty, based on what we know regarding the epidemiology of CVD it is reasonable to expect that the effects of liraglutide 3.0 mg on the development of Type 2 diabetes, blood pressure, lipids and variety of other factors should lead to reductions in CVD.	Thank you for your comment. The committee noted that the cardiovascular benefits of liraglutide in the company's model was based on risk reduction using surrogate outcomes and that this approach introduced uncertainty. The committee acknowledged that relying on surrogates is uncertain but accepted that surrogate outcomes were the only available evidence to estimate cardiovascular benefits. See FAD section 3.6.

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Clinical expert	Abd Tahrani	Regarding [the appraisal consultation document] point 3.8., "The committee had concerns that the company's submission was based on a maximum treatment duration of 2 years". I agree that obesity as a chronic disease that will require long term treatment. However, considering that the drug is going to be used within tier 3 services, continuing liraglutide 3.0 mg beyond 2 years will be challenging in tier 3 as the usual follow up in tier 3 is 2 years. Furthermore, the drug is delivered by daily injections and hence many patients not achieving "good" weight loss are likely to stop treatment before 2 years. However, those who want to persist with treatment are likely to be those patients who achieve greater weight losses (for example 10% body weight loss) and hence likely to derive even "higher than average" benefits from treatment. While I understand the concerns of the committee regarding the 2-year cut off; the committee needs to appreciate that even within the current tier 3 services patients will not receive treatment for longer than 2 years. In other words, the treatment given within the current tier 3 services to patients with obesity are not delivered long term. Using the 2 years limit seems reasonable pragmatic approach to offer a beneficial treatment with clear outcomes utilising the currently available NHS services.	Thank you for your comment. The committee noted that treatment for obesity is a long-term condition and people may who have weight loss with liraglutide are likely to want to continue treatment for longer than 2 years. The committee concluded that treating a chronic condition such as obesity for only 2 years is not ideal. But it accepted that the cost-effectiveness estimate was based on a single course of treatment of no longer than 2 years, and that the 2 year treatment duration is appropriate in the context of NHS tier 3 weight management services. See FAD section 3.7.
Clinical expert	Abd Tahrani	[Regarding the appraisal consultation document] Point 3.9., "The company's economic model is suitable for decision making"; I agree with committee decision	Comment noted. No further action required.
Clinical expert	Abd Tahrani	[Regarding the appraisal consultation document] Point 3.10. "Cardiovascular risk was determined using risk equations ". Please see my comment number 8.	Comment noted. No further action required.
Clinical expert	Abd Tahrani	[Regarding the appraisal consultation document] Point 3.11. "The company's assumptions used to predict weight gain and diabetic status were associated with uncertainty. Because no follow-up data were available for weight gain or diabetic status in the 3 years after stopping treatment, the committee accepted that some assumptions had to be made. However, it concluded that the company's assumptions were associated with uncertainty." I agree that in the view of lack of data there is a degree of uncertainty. However, the assumptions described seems reasonable from the clinical perspective of weight management. Furthermore, data from the UK CPRD primary care database showed that in people who lost 5% weight loss, 53% regained the weight over 2 years and 78% regained the weight over 5 years (https://ajph.aphapublications.org/doi/10.2105/AJPH.2015.302773). So, the company assumption that all the weight lost with liraglutide will be regained over 3 years is rather pessimistic rather than optimistic and hence seems reasonable to be used in the model.	Thank you for your comment. The committee noted that some people in the model regained their initial weight, but might be expected to regain more weight after treatment stopped, resulting in a higher weight than before starting treatment. The committee accepted the assumptions in the economic model (see FAD 3.10). It recommended liraglutide as an option for managing overweight and obesity for populations with BMI>= 35 kg per m^2 and pre-diabetes and a high risk of cardiovascular disease (see FAD section 1.1).

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Clinical expert	Abd Tahrani	[Regarding the appraisal consultation document] Point 3.12 "The company's model assumes that all people who have a cardiovascular event develop type 2 diabetes. The committee was concerned that the company's assumption overestimates the clinical and cost effectiveness of liraglutide." While there is no definite data, a previous study from my team (https://bmcendocrdisord.biomedcentral.com/articles/10.1186/s12902-017-0153-y) showed that in patients admitted with acute coronary syndrome, baseline HbA1c and fasting plasma glucose during the hospital admission were independent predictors of developing Type 2 diabetes within 3 months from discharge from hospital after adjusting for age and BMI. Hence patients with pre-diabetes (who will have higher baseline HbA1c by definition) are particularly at increased risk of Type 2 diabetes shortly after acute coronary syndrome.	Thank you for your comment and the reference provided. The committee agreed that people who have a cardiovascular event are at a higher risk of developing type 2 diabetes but did not agree with the simplifying assumption that this would be the case for everyone. The committee agreed that the "true" ICER would lie between the base case ICER (which applied the simplifying assumption and a scenario analysis which did not (see FAD section 3.11). The committee were reassured by the company's base case and scenario analyses had ICERs below £20,000 (see FAD section 3.15).
Consultee	GlaxoSmithKline	As far as it can be ascertained, GSK believe that all the relevant evidence has been taken into account.	Comment noted. No action required.
Consultee	GlaxoSmithKline	GSK believe that the target subgroup identified by the manufacturer is a reasonable one considering use of available NHS resources and which patients are likely to gain the most benefit from the medicine. The uncertainties in the cost effectiveness assessment have been reasonably identified based on the available evidence	Comment noted. No action required.
Consultee	Royal College of Physicians	The following evidence does not seem to have been taken into account: a) The evidence from SCALE obesity and prediabetes that liraglutide 3mg reduces the risk of developing type 2 diabetes (T2D). b) RCT data showing that GLP-1 receptor agonists (including liraglutide) reduce cardiovascular events in patients with T2D. c) Evidence that the CV benefits of GLP-1 receptor agonists are independent of weight loss. **d)** Other health benefits that were reported in the RCTs including improved health-related quality of life and improvement in obstructive sleep apnoea	Thank you for your comment and the references provided. The committee heard from clinical experts who discussed the SCALE obesity and prediabetes trial. The clinical experts also commented on the plausibility of liraglutide reducing long term CV given findings that liraglutide reduces T2D risk. The committee accepted surrogate outcomes as the best available approach to estimate cardiovascular benefits (see FAD section 3.6). It recommended liraglutide as an option for managing overweight and obesity for populations with BMI>= 35 kg per m^2 and pre-diabetes and a high risk of cardiovascular disease (see FAD section 1.1). The company model included

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Consultee	Royal College of Physicians	Ideally all people who are eligible but not undergoing bariatric surgery should be offered liraglutide as part of a weight management/lifestyle intervention programme that provides nutritional, physical activity and behavioural change with access to psychological support. NICE introduced stricter weight loss stopping rules for orlistat, sibutramine and rimonabant, introducing a 10% weight loss stopping at 6 and 12 months should be considered. The following groups should also be considered: 1. Patients with serious mental illness who have obesity or pre-diabetes. People living with serious mental illness have a 15-20-year mortality gap due to largely to metabolic disease, with drivers of obesity, smoking and obesogenic prescribing (such as Clozapine and Olanzapine). The metabolic and obesogenic effects of the latter have been shown to be reversed by early prescribing of liraglutide *(JAMA Psychiatry. 2017;74(7):719-728. doi:10.1001/jamapsychiatry.2017.1220 Published online June 10, 2017.)* 2. People who have undergone bariatric surgery but not had a favourable result – not lost >20% of their total body weight or regained weight so that their current weight is not >20% below their highest body weight. – (Miras AD, Pérez-Pevida B, Aldhwayan M, et al. Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2019;7:549-59. 10.1016/S2213-8587(19)30157-3, Hellström PM. GLP-1 analogue liraglutide as adjunct treatment in diabetes type 2 after failed bariatric/metabolic surgery. *Ann Transl Med*. 2019;7(Suppl 6):S240. doi:10.21037/atm.2019.08.94) 3. Palliative care for people living with extreme obesity who are unable to proceed for bariatric surgery	Thankyou for your comment. The company's base case submission included a 5% stopping rule at 12-weeks in addition to per cycle discontinuation estimated using evidence from trial 1839. The committee accepted the stopping rules applied in the base case analysis. Thank you for the references provided regarding the use of liraglutide in different patient populations. The company submission focussed on evidence for a high-risk sub group with BMI of 35 kg per m^2 or more, with pre-diabetes and a high risk of cardiovascular disease. The committee agreed to focus on the population proposed by the company (see FAD section 3.2).
Consultee	Royal College of Physicians	Concern regarding the modelling of T2D development after a CV event is raised, however, the LEADER trial data shows a clear benefit in this patient group and does not seem to have been taken into account.	Thank you for your comment and the reference provided. The committee agreed that people who have a cardiovascular event are at a higher risk of developing type 2 diabetes, but did not agree with the simplifying assumption that this would be the case for everyone. The committee agreed that the "true" ICER would lie between the base case ICER (which applied the simplifying assumption and a scenario analysis which did not (see FAD section 3.11). The committee were reassured the company's base case and scenario analyses had ICERs below £20,000 (see FAD section 3.15).

Type of stakeholder	Stakeholder	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
Consultee	Royal College of Physicians	The provisional recommendations are not sound or suitable for the NHS as they fail to recognise the profound health benefits of weight loss or multiple obesity-related co-morbidities and health-related quality of life.	Thank you for your comment. The committee recommended liraglutide as an option for managing overweight and obesity for populations with BMI>= 35 kg per m^2 and pre-diabetes and a high risk of cardiovascular disease (see FAD section 1.1).
Consultee	Society of Endocrinology	The focus is on diabetes prevention and CV disease and we accept there is no evidence for the latter at the 3mg dose or in people without diabetes, but there is excellent evidence for diabetes prevention in high risk patients from SCALE obesity and prediabetes. It is also very important to highlight that there is a large amount of emerging evidence from RCTs in people with diabetes, that 1. GLP1 analogues, including liraglutide, reduce cardiovascular events in high risk patients and that 2. the CV protection for GLP1 RA may be independent of weight loss.	Thank you for your comment. In the absence of long-term evidence, the committee accepted the company's approach of using surrogate outcomes to estimate cardiovascular benefits of liraglutide (see FAD section 3.6).
Consultee	Society of Endocrinology	The complexity of care needed for obesity and complications of many people in tier 3 services who do not tolerate orlistat or who are unsuitable for or unwilling to have surgery is not fully considered.	Thank you for your comment. The committee discussed the variability of tier 3 weight management services (see FAD section 3.3). The committee recommended liraglutide as an option for managing overweight and obesity for populations with BMI>= 35 kg per m^2 and pre-diabetes and a high risk of cardiovascular disease within tier 3 services (see FAD section 1.1).
Consultee	Society of Endocrinology	There is evidence of benefit in those with obstructive sleep apnoea, which is highly prevalent in this population, but does not seem to have been considered here. Furthermore, the evidence base on improvements in quality of life with liraglutide as measured in trials does not seem to have been included.	Thank you for your comment. During technical engagement the committee were made aware of a scenario analysis where the economic model included quality of life benefits associated with sleep apnoea (see committee papers, Table 12). The inclusion of additional health benefits would reduce the base case ICER but this impact was not substantial. The committee recommended liraglutide as an option for managing overweight and obesity for populations with BMI>= 35 kg per m^2 and pre-diabetes and a high risk of cardiovascular disease (see FAD section 1.1).

Type of stakeholder	Stakeholder	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
Consultee	Society of Endocrinology	NICE makes statements about lack of availability of tier 3 services that are not consistent with the facts. Firstly, some are funded by Local Authorities rather than CCGs, so provision is greater than stated, probably some coverage for 75-80% of the population, although there is clearly need for expansion. This seems to imply that NICE will only approve drugs if there is 100% population coverage. That is clearly not the case for many effective medical interventions, and suggests they are thinking that if some CCGs think services aren't needed then that is OK. For other severe illnesses, that would be considered a failure of services rather than a reason to not approve a treatment; NICE should be stating that services are inadequate (i.e. not meeting their own standards as outlined in CG66 and associated quality standards) and advising proper service provision rather than rejecting treatment on the basis of poor service provision.	Thank you for your comment. The committee discussed the variability of tier 3 weight management services (see FAD section 3.3). The committee approves treatments on the basis of cost-effectiveness (among other criteria).The committee recommended liraglutide as an option for managing overweight and obesity for populations with BMI>= 35 kg per m^2 and pre-diabetes and a high risk of cardiovascular disease within tier 3 services (see FAD section 1.1).
Consultee	Society of Endocrinology	Use of stricter stopping rules e.g. 10% weight loss at 6 or 12 months, might make sense and provide clearer estimates of cost-effectiveness, and should be considered. NICE did this for orlistat, sibutramine and rimonabant, so there is clearly a precedent for using this approach.	Thank you for your comment. The committee accepted a 2-year treatment duration as this was implementable in NHS tier 3 weight management services (see FAD section 3.7).
Consultee	Society of Endocrinology	The quality of life modelling did not seem to use the measured effects in the SCALE trials, so really should include this.	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. The approach used to estimate HRQoL inputs for the economic model was considered reasonable by the ERG. 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. This was discussed during technical engagement.
Consultee	Society of Endocrinology	The use of a post hoc sub group for modelling of effects over 2 years is questioned, but this really does not make much difference to the results. It should be possible to use estimates from whole trial population at 2 years and 3 years and model dropouts?	Thank you for your comment. The committee considered evidence from the company's updated submission which included a scenario analysis for the whole pre-diabetes population in trial 1839 (see FAD section 3.15).
Consultee	Society of Endocrinology	Concern is raised about the modelling assumptions regarding development of diabetes after CV events – I am sure there must be better data than making that assumption which is certainly not clinically correct. However, it is worth also considering that if a person with obesity develops T2DM after a CV event, then they would clearly have benefit from liraglutide if prescribed at the lower dose of 1.8mg as there is clear evidence of benefit in this population from the LEADER trial.	Thank you for your comment. The committee agreed that the most plausible incremental cost-effectiveness ratio (ICER) would be between the base-case ICERs, which applied the simplifying assumption that everybody would develop T2DM after a CV event, and the scenario analysis that did not. (See FAD section 3.11).

Type of stakeholder	Stakeholder	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
Consultee	Society of Endocrinology	The ICERs provided in the table provide a wide range of cost-effectiveness, but some of the assumptions made and all those that give ICERs above the threshold (e.g. only effect on BMI giving an ICER of £105000) are not credible based on the evidence presented and are inappropriately used to justify the appraisal decision.	Thank you for your comment. In the updated company submission all scenario analyses resulted in ICERs below £20,000 per QALY (see FAD section 3.13 & 3.15).
Consultee	Society of Endocrinology	[The recommendations are not a suitable basis for guidance to the NHS]. The review does not fully take into account the severe burden and adverse effects on quality of life seen in people with severe obesity, nor have they fully accounted for improvements that are seen with weight loss.	Thank you for your comment. The committee recommended liraglutide as an option for managing overweight and obesity for populations with BMI>= 35 kg per m^2 and pre-diabetes and a high risk of cardiovascular disease (see FAD section 1.1).

NICE National Institute for Health and Care Excellence

Liraglutide for managing overweight and obesity [ID740]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 14 February 2020 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
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]
Name of commentator person completing form:	[redacted]

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Liraglutide for managing overweight and obesity [ID740]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table because your comments could get lost – type directly into this table.
1	Novo Nordisk are disappointed with the decision not to recommend liraglutide 3.0mg for managing overweight and obesity in adults alongside a reduced-calorie diet and increased physical activity. The committee recognised that living with obesity is challenging, restrictive and associated with stigma as highlighted by the patient expert (section 3.1 in the ACD), understood the need for more treatment options that are addressing the biological determinants of obesity and recognised that liraglutide 3.0mg is an effective treatment for weight loss. The decision leaves a gap in effective treatment options for a group of patients with extremely high unmet medical need. In order to ensure that relevant patients can access treatment with liraglutide 3.0mg, Novo Nordisk has proposed a further price reduction via the commercial arrangement with NHS England. Details of the impact on cost-effectiveness of the further price reduction can be found in the appendix submitted along with this response. In the appendix we present our revised company base case (as presented in response to the technical engagement) at the new lower price together with full justification for the assumptions. The assumptions are listed below and yield an ICER of £14,839 per QALY gained. • The price has been reduced from £[redacted] to £[redacted] per pack of 5 prefilled pens (18mg/3ml). • Per cycle discontinuation (as observed in Trial 1839) is included during the 2-year treatment period (following the licence stopping rule at 12 weeks). • We assume a maximum treatment duration of 2 years. • Liraglutide 3.0mg non-responders are assumed to have the same efficacy as the placebo group (diet and exercise). • The UKPDS 82 risk equations are used to estimate CV events in people with type 2 diabetes. • Automatic development of type 2 diabetes (within 12 months) following a cardiovascular event is assumed though its impact is tested in scenario analysis. In addition, the ERG base cases (scenario 1-7) have been recalculated using this new lower price (Table 10) in the appendix.
2 (section 3.5)	The committee concluded that it had reservations about the use of data from a post-hoc subgroup that would be associated with more uncertainty than the larger pre-defined prediabetes trial population. While we acknowledge that post-hoc subgroup analysis is associated with increased uncertainty, we would like to remind the committee that this subgroup consisted of 800 patients and had similar efficacy results to the full trial population, as shown in the original company submission (CS): section B.2.6.1 p. 53, section B.2.7.3., p. 69) and response to the technical engagement (Issue 2, p. 5). We have defined the subgroup in the original CS based on advice from clinical experts. The criteria for inclusion in the post-hoc subgroup was determined through assessments at base line and no

	post-randomisation information was used in the selection. This way of selecting patients for a subgroup analysis will in principle preserve the integrity of the randomisation.
3 (section 3.6)	The committee was concerned that the post-hoc subgroup may have compromised randomisation and concluded that the relative clinical effectiveness of liraglutide 3.0mg should have been estimated from the whole prediabetes population in the trial because this was larger, pre-specified and associated with less uncertainty than the smaller post-hoc subgroup. To reassure the committee, Novo Nordisk have performed analyses whereby efficacy inputs from the post-hoc subgroup analysis, were replaced with the efficacy inputs from the full prediabetes (mITT efficacy) population, while maintaining the baseline characteristics representative of the post hoc subgroup population, i.e., patients with a BMI ≥35 kg/m^2, prediabetes, and high risk of cardiovascular disease (CVD). The efficacy inputs can be found in the appendix (Appendix Table 4). Using mITT efficacy inputs (from the full prediabetes population) reduces the company base case ICER from £14,839 to £11,682 (Appendix Table 2 and 5). Probabilistic sensitivity analysis yields an ICER of £15,265 (Appendix Table 2) for the company base case and an ICER of £11,940 (Appendix Table 5) for the mITT efficacy scenario. The cost effectiveness acceptability curve (CEAC) for the company base case shows that a majority of simulation points fall below a threshold of £20,000 (97%) and 99% of simulation points lie below a £30,000 threshold. For the mITT scenario analysis, CEAC shows comparable results with 99% below an ICER threshold of £20,000 and 99% below a threshold of £30,000 (Appendix Figure 2).
4 (section 3.7)	The committee concluded that the estimation of any reduction in cardiovascular (CV) events would be subject to uncertainty because they would rely on an estimation of the relationship between the surrogate and the clinical event. Novo Nordisk agrees that relying on surrogate outcomes to estimate reduction in CV events is subject to uncertainty. However, the use of surrogate outcomes in health economic modelling is a common and accepted practice where there is an established link between the surrogate and final outcome. The economic model uses published risk equations derived from well-known, established studies such as QRisk[1], QDiabetes[2], Framingham[3] and UKPDS[4]. Risk equations have also been used in previous NICE recommendations, for example QRisk and UKPDS were used in the development of the NICE clinical guidelines (CG181) Cardiovascular disease: risk assessment and reduction, including lipid modification[5]. Weight loss and weight loss maintenance are the cornerstones in any intervention for overweight and obesity and are consistently acknowledged to be associated with reductions in the risk of developing CV events [PH25][6], [NG136][7]. Existing NICE guidance in this area is aligned with the global research and policy consensus that reducing body weight among people with obesity patients leads to CV benefits. For example, in the NICE CV disease prevention guideline [PH25][6], obesity is stated to be a key modifiable CV disease risk factor. The same guidance document reviews evidence supporting improvements in heart health through weight loss. NICE guidance also supports lifestyle interventions such as weight loss measures as an intervention to reduce hypertension [NG136][7] as well as post-myocardial infarction management in patients with overweight or obesity [CG172][8]. Novo Nordisk are disappointed that the committee questions the long-term CV benefit of weight loss, as this is the underlying premise for a multitude of public health campaigns and interventions, including the National Diabetes Prevention Programme (NHS DPP)[9]. There is an obvious willingness to invest significantly in weight management interventions which are all ultimately aiming at reducing the long-term risk of CVD through weight reduction. If NICE does not recognise the association between weight loss – even in the short term – and long-term development of CVD, it is surprising that such significant investments are being made in this area. In addition, the subpopulation identified in the CS (BMI ≥35 kg/m^2, prediabetes and high risk of CVD) overlaps with the population targeted for the National DPP[10], which is specifically targeting weight loss over 12

months only. This emphasises that this is a group of people that the NHS is prioritising and investing in.

The clinical trial (Trial 1839) was not powered to show a significant difference in CV events. Nevertheless, as noted in the CS, a post-hoc analysis of the five randomised phase 3a studies[11-15] from the liraglutide 3.0mg clinical development programme (Davies et al. 2017[17]) found a reduction in CV risk compared with the pooled comparator group (placebo or orlistat). The analysis included patients with BMI ≥27 kg/m^2 with at least one weight-related comorbidity, or a BMI ≥30 kg/m^2 and found the rate of positively adjudicated CVD events to be 1.54 events/1000 person-years with liraglutide versus 3.65 events/1000 person-years with comparators. The hazard ratio (HR) for the primary analysis was 0.42 (95% CI 0.17-1.08).

Supporting evidence for the benefits of liraglutide comes from a cardiovascular outcomes trial (CVOT) conducted in people with type 2 diabetes and established CV risk. Marso et al. 2016[17] reported the results of the LEADER trial in which liraglutide (at a lower dose) plus standard of care was compared with placebo plus standard of care. The rate of the first occurrence of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke was 13.0% for liraglutide and 14.9% for placebo with a hazard ratio (HR) was 0.87 (95% confidence interval (CI) 0.78-0.97). Despite the lower dose of liraglutide, these data were considered relevant for inclusion in section 5.1 of the liraglutide 3.0mg Summary of Product Characteristics (SmPC) by EMA.

Other GLP-1 analogues have also been shown to reduce the rate of CV events. Andrikou et al. 2018[18] reviewed GLP-1 CVOTs and noted liraglutide, semaglutide and albiglutide have demonstrated reduction in risk of major adverse cardiac events (MACE). The potential cardioprotective effect of incretin-based therapies is attributed to their multiple non-glycaemic actions in the CV system, including changes in insulin resistance, weight loss, reduction in blood pressure, improved lipid profile and direct effects on the heart and vascular endothelium. Zimmerman et al. 2017[19], a US retrospective study using electronic health records found that treatment with GLP-1 analogues including liraglutide, significantly reduced stroke/cerebrovascular accidents (CVAs) and all-cause mortality. The study included patients with type 2 diabetes and showed that treatment with GLP-1 analogues is associated with significantly lower risk for CVA with a HR of 0.82 (95% CI 0.74-0.91) and for all-cause mortality with a HR of 0.48 (95% CI 0.41-0.57); and even positively impacts the risk of acute myocardial infarction (AMI), CVA or all-cause mortality with a HR of 0.82 (95% CI 0.74-0.91). Patients with no prior CVD had a statistically significant reduction in risk of mortality (HR 0.43, 95% CI 0.35-0.53) when exposed to GLP-1 analogues, as compared with patients with established CVD.

Moreover, the prolonged benefits of glucose, blood pressure or lipid control in individuals with CVD, type 2 diabetes or in primary prevention of CVD by control of early risk factors has been well demonstrated. For example, Paul et al. 2015[20], using routine data from the Clinical Practice Research Datalink (CPRD) that includes over 100,000 individuals with type 2 diabetes, showed that a delay of 1 year in achieving tight glycaemic control was associated with a significantly increased risk of myocardial infarction, stroke, heart failure and composite CV events. Further, a systematic review and meta-analysis of long-term follow-up of clinical trials concerning blood pressure-lowering medication has confirmed a decrease in overall mortality which persist after the end of the trial period when the majority of patients in both the intervention and control groups start receiving active therapy (Kostis et al 2010)[21]. The Anglo-Scandinavian cardiac outcomes trial (ASCOT) also demonstrated the legacy effect of lipid-lowering therapies by showing that, following a median of 11 years after initial randomisation (~8 years after closure of the lipid-lowering arm), all-cause mortality remained significantly lower in those who were originally assigned to the active trial with atorvastatin (HR 0.86, 95% CI 0.76-0.98), with CV deaths being lower, but not significantly, and non-cardiovascular deaths being significantly lower (HR 0.85, 95% CI 0.73-0.99) (Sever et al 2011)[22]. The Diabetes Prevention Program Outcomes Study (DPPOS)[23] randomised people at high risk of diabetes to an intensive lifestyle intervention or masked metformin with placebo. All patients were offered lifestyle training at the end of the 3-year initial study period. The between group difference in cumulative incidence of type 2 diabetes was demonstrated after 12 years follow up,

	showing a durable effect from the original 3-year interventions.[23] This phenomenon – described as the '*legacy effect*' or '*metabolic memory*' - should also be considered in this context. **References:** [1] Hippisley-Cox J et al.. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017 May 23;357:j2099. doi: 10.1136/bmj.j2099. [2] 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 [3] 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. [4] Hayes A, Leal J, Gray A, Holman R, Clarke P. 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[15] Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes (Lond). 2016;40(8):1310-9. [16] Davies MJ et al. Liraglutide and cardiovascular outcomes in adults with overweight or obesity: A post hoc analysis from SCALE randomized controlled trials. Diabetes Obes Metab. 2018 Mar;20(3):734-739. doi: 10.1111/dom.13125. Epub 2017 Nov 1 [17] Marso SP et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311-22. doi: 10.1056/NEJMoa1603827. Epub 2016 Jun 13. [18] Andrikou E et al., GLP-1 receptor agonists and cardiovascular outcome trials: An update, Hellenic Journal of Cardiology, https://doi.org/10.1016/j.hjc.2018.11.008 [19] Zimmerman RS et al. 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Eur Heart J.2011;32:2525-2532. [23] Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol 2015;3: 866–75
5 (section 3.8)	The committee acknowledged that a maximum treatment duration of 2-years would be implementable in the NHS, but noted that it does not reflect what was done in the clinical trial or address the clinical need to reduce weight and then maintain a reduced weight. While we acknowledge that the trial did not include a maximum treatment duration, we believe it reflects clinical practice. The advice of the clinical experts contributing to this appraisal, which has consistently validated a maximum treatment duration of 2-years, will apply for the majority of patients treated in clinical practice. This fits with clinical practice in England and Wales where patients are referred to Tier 3 services for a maximum of 2 years. Although this can be as little as 6

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	months and more normally the referral is for 12 months akin to the National Diabetes Prevention Programme. The intent is to provide the very best support from a multi-disciplinary team including dieticians and psychological support to provide the best chance of weight loss and maintenance post referral. Novo Nordisk would also like to remind the committee of the findings reported by Ganguly et al. 2018[1] which provides real-world evidence from a US-population based study aiming to measure persistence of patients treated with liraglutide for weight management. After follow-up of 6 months, 41.8% of patients continued treatment with liraglutide 3.0mg, and by 15 months this had reduced to 26.6%. The proportion of patients persisting with liraglutide 3.0mg treatment was further confirmed in a Canadian real-world evidence study (Wharton et al. 2019)[2], which showed that 46.3% of patients were still on treatment after 6 months. This suggests that imposing a maximum treatment duration of 2 years would affect only a minority of patients. A physician survey (see Appendix N of the CS) also suggested that patients would most likely only receive treatment for 1-2 years. In response to ERG question B1, per cycle treatment discontinuation (as observed in Trial 1839) was incorporated into the model following the 12-week licence stopping rule (previously all patients who achieved ≥5% weight loss were assumed to continue for the maximum treatment duration). Data from the clinical trial demonstrated that some patients do indeed discontinue therapy between the licence stopping rule and 2 years hence, this approach better reflects what was observed within the trial and what happens in clinical practice. Importantly, this approach was preferred by the Technical team as stated in the Final Technical Report, and we have therefore adopted it into our company base case. **References:** [1] Ganguly R, Tian Y, Kong SX, Hersloev M, Hobbs T, Smolarz BG, et al. Persistence of newer anti-obesity medications in a real-world setting. Diabetes Research and Clinical Practice. 2018;143:348-56. [2] Wharton S, Liu A, Pakseresht A, Nørtoft E, Haase CL, Mancini J, etal. Real-World Clinical Effectiveness of Liraglutide 3.0 mg for Weight Management in Canada. Obesity (2019) 27, 917-924. doi:10.1002/oby.
6 (section 3.8 – additional stopping rules)	Discussion with clinical experts during the development of the company submission suggested a number of additional efficacy-based stopping rules might be applied in practice by clinicians. During the technical engagement, the clinical expert Professor Carel le Roux suggested the efficacy-based stopping rule below: "*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…"* This further efficacy stopping rule where patients who do not achieve greater than 10% weight loss at 1-year discontinue therapy, is supported by an analysis of the look AHEAD trial[1] where persons who lost >10% body weight in the first year had a 21% lower risk of the primary outcome (a composite of CVD death, myocardial infarction, stroke or angina hospitalisation). Novo Nordisk have therefore performed a scenario analysis implementing a stopping rule of ≥10% weight loss at 52 weeks. This (≥10%) stopping rule is added to the stopping rule of ≥5% weight loss at 12 weeks on the maintenance dose, which is a required by the EMA licence. The patient group with a ≥10% weight loss at 52 weeks experiences higher efficacy compared to the overall population (see Appendix Table 6). For the ≥10% weight loss stopping rule, it is assumed that all responders at week 52 remained on treatment until the end of year 2, (unless these patients discontinued via the per cycle discontinuation as observed in Trial 1839) (see Appendix Table 8). Adding the stopping rule of ≥10% weight loss results in a lower ICER of £13,397 compared to the revised company base case ICER of £14,839. This demonstrates that applying efficacy-based stopping rules such as only continuing patients who achieve ≥10% weight loss at 1 year can improve the cost effectiveness of treatment with liraglutide 3.0mg. The full results are presented in Appendix Table 9.

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	References: [1] Gregg EW et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol. 2016 Nov;4(11):913-921. doi: 10.1016/S2213-8587(16)30162-0. Epub 2016 Aug 30.
7 (section 3.9)	The committee considered that the health states and transitions in the model were suitable for decision making, but the risk equations estimating the long-term cardiovascular risk introduced uncertainty. As noted at the committee meeting the only way of estimating long term cardiovascular risk is to use risk equations. As documented in the CS (Table 33) and the response to the ERG clarifications (Question B7), we followed a rigorous approach in sourcing and selecting risk equations for our base case analysis. Risk equations were prioritised based on their applicability and relevance to the UK population, as well as considering whether treatment-effect variables were indicated as predictors of risk within the analysis. All modelling involves some degree of uncertainty, but we believe this was minimised by our systematic and transparent approach to the selection of evidence.
8 (section 3.10)	The committee further concluded that it required further explanation and justification of the benefits on cardiovascular events assumed in the economic analysis before it could be persuaded that liraglutide 3.0mg was cost-effective. Novo Nordisk believe that the link between weight reduction and reduced CV risk has been shown beyond reasonable doubt in the research literature.[1-5] Novo Nordisk do not believe it is plausible for the committee to assert that the impact of liraglutide in reducing BMI and improving other cardiometabolic risk factors would have no impact on reducing a person's risk of developing type 2 diabetes or CV events. The benefits of liraglutide 3.0mg on the risk of developing type 2 diabetes were directly demonstrated in trial 1839 (HR 0.207 liraglutide 3.0mg vs. placebo, see Table 12 in CS). As noted above in response to ACD Section 3.7, liraglutide has shown direct benefits in CV outcomes in both overweight and obese patients and people with type 2 diabetes[6,7]. Therefore, we believe it is misleading to report the ICER exceeded £100,000 per QALY gained with all risk of type 2 diabetes and CV impact removed. **References:** [1] Gregg EW et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol. 2016 Nov;4(11):913-921. doi: 10.1016/S2213-8587(16)30162-0. Epub 2016 Aug 30. [2] Singh P et al. Impact of bariatric surgery on cardiovascular outcomes and mortality: a population-based cohort study. Br J Surg. 2020 Jan 21. doi: 10.1002/bjs.11433. [Epub ahead of print] [3] https://www.nice.org.uk/guidance/ph25 [4] https://www.nice.org.uk/guidance/ng136/ [5] https://www.nice.org.uk/guidance/cg172 [6] Davies MJ et al. Liraglutide and cardiovascular outcomes in adults with overweight or obesity: A post hoc analysis from SCALE randomized controlled trials. Diabetes Obes Metab. 2018 Mar;20(3):734-739. doi: 10.1111/dom.13125. Epub 2017 Nov 1 [7] Marso SP et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311-22. doi: 10.1056/NEJMoa1603827. Epub 2016 Jun 13.
9 (section 3.12)	The committee heard that there is no good evidence to determine the proportion of people who would develop type 2 diabetes within a year after a cardiovascular event. Novo Nordisk agrees. However, in the absence of risk equations to predict subsequent events in people with prediabetes who have experienced a CV event, an assumption is required. We made the assumption that following an event, these patients would develop type 2 diabetes within 12 months. The alternative approach would be to assume their prediabetes status reverses to normal

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	glucose tolerance, and they would incur the same risk as those who have not had prediabetes. The impact of this assumption is that after a CV event, patients have an elevated risk of subsequent events. We continue to assert that this elevated risk is plausible and supported by literature, as noted in the original CS (section B.3.2.3. p. 97) and in response to technical engagement (Issue 6, p. 10). Indeed, independent validation of the model, which was also submitted as part of this appraisal process, does not suggest that the model overestimates events. Furthermore, there are reasons to expect that CV events are underestimated in the CS analyses. In patients with prediabetes and normal glucose tolerance, where the QRisk3 equation is used, CV outcomes are not affected by changes in BMI values above 40 kg/m^2 (Hippisley-Cox, et al., 2017)[1]. However, liraglutide 3.0mg reduced weight from 41.7 kg/m^2 at baseline 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 40 kg/m^2 when the QDiabetes equation is used (CS base case analyses), as BMI was restricted to values between 20-40 kg/m^2 in QDiabetes (Hippisley-Cox, et al., 2017)[2]. For these reasons, we would like the committee to acknowledge that it is likely that patients experiencing a CV event will be at elevated risk of subsequent events. Hence that the true ICER lies somewhere in between the revised company base case ICER of £14,839 and ICER not incorporating development of type 2 diabetes after a CV event of £16,042 (Appendix Table 3). **References:** [1] Hippisley-Cox J et al.. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017 May 23;357:j2099. doi: 10.1136/bmj.j2099. [2] Hippisley-Cox J et al. Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study. BMJ. 2017 Nov 20;359:j5019. doi: 10.1136/bmj.j5019

Insert extra rows as needed

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Company ACD response – revised analyses

Context

The ACD for this appraisal was issued in January 2020. The company responded to the ACD in February and in April, the appraisal was paused due to Covid-19. The ERG provided a critique of the company response in March, which was shared with Novo Nordisk in August to support the company's discussion with NHSE on a new commercial agreement. This appraisal will now be discussed at the committee meeting planned for 8 September.

The company and NHS England reached a commercial agreement in August for the supply of liraglutide 3.0mg for managing overweight and obesity. This agreement makes the product available at a pack price of £XXXXX (equal to a discount of XX% to the list price) per pack of 5 prefilled pens [18mg/3ml].

The analyses prepared in February do not reflect the revised commercial agreement or ERG critique of the company response to the ACD. In order for the committee to base their decisions on the most relevant material we have updated our analyses to reflect the new price and ERG feedback.

This document consists of a summary, the company analyses submitted in response to the ACD in February updated with the new price, and additional analyses to clarify ERG questions raised in its critique.

Summary

The following changes have been made to the analysis:

The new price of £XXXXX has been implemented in the model

The 2 year maximum treatment duration appears to have been accepted by both the company and ERG so scenarios with longer treatment duration have not been included.

It appears that both the company and ERG accept that is appropriate to consider discontinuation that occurred during the trial in the model so scenarios have been updated to include discontinuation during the trial.

Remaining issues include: the choice of risk equation; inclusion of liraglutide related AEs; and, whether patients experiencing a CV event develop Type 2 diabetes. ERG scenarios 1,2,3 and 5 from the ERG critique of the company's ACD response address these issues and are reproduced below.

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Variable	Company base case	Scenario 1A	Scenario 2A	Scenario 3A	Scenario 5A	~~Scenarios 4,6,7~~
Automatic development of T2D within 12 months post CV event	Yes	Yes	No	Yes	Yes	N/A
Alternative liraglutide non-responder efficacy	No	No	No	Yes, D&E non-responders	No	
Maximum treatment duration	2 years	2 years	2 years	2 years	2 years	
Discontinuation following licence stopping rule	During trial period (KM curves)	During trial period (KM curves)	During trial period (KM curves)	During trial period (KM curves)	During trial period (KM curves)	
Inclusion of adverse event disutility and cost	No	No	No	No	Yes	
Risk equation: Primary prevention in type 2 diabetes	UKPDS 82	Qrisk3 risk model	Qrisk3 risk model	Qrisk3 risk model	Qrisk3 risk model	
Risk equation: Secondary prevention in type 2 diabetes	UKPDS 82	Framingham Recurring CHD	Framingham Recurring CHD	Framingham Recurring CHD	Framingham Recurring CHD	
ICER @ £XXXXX	£11,293	£13,569	£14,536	£17,044	£13,870	

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Update of ACD response

This section reproduces all analyses conducted in response to the ACD and provided to NICE in February 2020 at the new price of £XXXXX. Sections that have been revised from the February response and are marked "changed"; Sections that have not been changed are marked "unchanged"

Comparison of company and ERG base case scenarios (unchanged)

In response to the technical engagement we submitted a revised company base case. To inform discussion of the cost-effectiveness of liraglutide 3.0mg, we have prepared a summary of differences between the ERG base case (scenario 1-7) and the company base case, along with justification for the company preferred approach where this differs from the ERG**. Please note that the assumptions for the revised company base are unchanged from the revised company base case submitted as part of technical engagement; the only update to the base case is the revised price.**

Justification for Company Base Case (unchanged)

Risk equations for primary and secondary prevention in type 2 diabetes

As documented in the CS (Table 33) and the response to the ERG clarifications (Question B7), we followed a rigorous approach in sourcing and selecting risk equations for our base case analysis. Risk equations were prioritised based on their applicability and relevance to the UK population, as well as considering whether treatment-effect variables were indicated as predictors of risk within the analysis. All modelling involves some degree of uncertainty, but we believe this was minimised by our systematic and transparent approach to the selection of evidence.

QRisk3 was estimated on a sample of patients followed in general practices in England and is intended as a CV risk prediction model in the general population (Hippisley-Cox, et al., 2017)[3]. UKPDS 82 was preferred for estimating primary CV events in the company base case over QRisk3, as only 1.5% of males and 1.2% females had type 2 diabetes at baseline. As such, the main predictor of risk of complications in type 2 diabetes, HbA_{1c}, is not included in the model. Instead, the risk equation includes a categorical variable (yes, no) for presence of type 2 diabetes.

For estimating secondary CV events UKPDS 82[1] is preferred over the Framingham equation[2] in the company base case, because Framingham is estimated in a US population which may not be representative of the UK population. Moreover, the Framingham risk model only includes BMI values between 20-30 kg/m^2 and is therefore unable to explore effects of BMI change in the range relevant to the modelled population. Also, HbA_{1c} is not included as a risk predictor.

The UKPDS 82 risk equations are based on a median 17.6 years of follow-up and up to 89,760 patient-years of data and the model is internally valid over 25 years. The model includes eight separate risk equations for diabetes-related complications and death. The authors observed many linkages between events (e.g. having a history of ischaemic heart disease (IHD) increases the

probability of having a myocardial infarction (MI)) and for 7 of the equations there are 15 linkages. The patient level data entered into the risk equations are: Age, duration of diabetes, sex, ethnicity, smoker, systolic blood pressure (SBP), HbA_{1c}, low-density lipoprotein (LDL), high-density lipoprotein (HDL), BMI, eGFR, heart rate, atrial fibrillation, peripheral vascular disease (PVD), albuminuria, haemoglobin, white blood cells and history of myocardial infarction (MI), stroke, ischemic heart disease (IHD), congestive heart failure (CHF), blindness, amputation, renal failure and diabetic ulcer.[1]

The outcomes are: Death, 1st MI, 2nd MI, 1st stroke, 2nd stroke, CHF, IHD, 1st amputation, 2nd amputation, blindness, renal failure and diabetic ulcer. The model equations performed well in an internal validation with the predicted Kaplan-Meier survival curves within the 95% CIs observed in the clinical data over 25 years. [1] The equations were externally validated using the Cardiff Diabetes Model[4].

In addition, UKPDS 82 was the recommended risk model for the NICE appraisal of dapagliflozin in triple therapy for treating people with type 2 diabetes (TA418)[5]. Therefore, we have used UKPDS 82 risk equations to predict primary and secondary CV events in people with type 2 diabetes[1].

The ERG has incorporated Qrisk3 for primary prevention in type 2 diabetes in all 7 scenarios and Framingham Recurring CHD for secondary prevention in type 2 diabetes in all 7 scenarios.

Automatic development of type 2 diabetes within 12 months post CV event

In the absence of risk equations to predict CV events in people with prediabetes, assumptions are required for modelling. We conservatively assumed that people with prediabetes and no history of a CV event would have the same risk of developing a CV event, as someone with normal glucose tolerance. For subsequent CV events in people with prediabetes we assumed that following the event, these patients would develop type 2 diabetes within the following year. This was considered more appropriate and clinically rational than assuming these patients would incur the same risk as those with normal glucose tolerance. The impact of this assumption is that after a CV event, patients have an elevated risk of subsequent events. We continue to assert that this elevated risk is plausible and supported by literature, as noted in the original CS (section B.3.2.3. p. 97) and in response to technical engagement (Issue 6, p. 10). Indeed, independent validation of the model, which was also submitted as part of this appraisal process, does not suggest that the model overestimates events.

Furthermore, there are reasons to expect that CV events are underestimated in the CS analyses because for patients with prediabetes and normal glucose tolerance, where the QRisk3 equation is used, CV outcomes are not affected in BMI values above 40 kg/m^2 (Hippisley-Cox, et al., 2017)[1]. However, liraglutide 3.0mg reduced weight from 41.7 kg/m^2 at baseline 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 40 kg/m^2 when the QDiabetes equation is used (CS base case analyses) as BMI was restricted to values between 20-40 kg/m^2 in QDiabetes (Hippisley-Cox, et al., 2017)[6].

For these reasons, we believe it is likely that patients experiencing a CV event will be at elevated risk of subsequent events. Hence the revised company base case includes the assumption of automatic development of type 2 diabetes within 12 months post a CV event and this is explored in scenario analyses (Table 3).

The alternative scenario where patients do not automatically develop type 2 diabetes following a CV event was incorporated in ERG scenario 2 and 6.

Efficacy of liraglutide non-responders equal to placebo group

In the clinical trial, treatment efficacy for patients who did not fulfil the licence stopping rule was not obtained, therefore it was assumed that patients stopping treatment would have the same average efficacy as placebo patients receiving diet and exercise. This was assumed as patients who discontinue therapy due to the licence stopping rule would still be expected to be treated in a Tier 3 service and continue diet and exercise therapy for the following 1-2 years. This assumption was supported by the clinical expert (as noted in response to ERG question B6) who stated that "*patients who do not respond to liraglutide are biologically different to those that do respond*". Therefore, we have assumed in the revised company base case that liraglutide 3.0mg non-responders would have the same efficacy as the placebo group, as per the original company submission.

In the ERG base case scenario 3, 6 and 7, the efficacy of liraglutide non-responders is equal to the non-responders for the placebo group.

Maximum treatment duration of 2 years

We believe a maximum treatment period of 2 years reflects clinical practice in England and Wales where patients would be treated in Tier 3 services. The advice of the clinical experts contributing to this appraisal, which has consistently validated a maximum treatment duration of 2-years, will apply for the majority of patients treated in clinical practice. This fits with clinical practice in England and Wales where patients are referred to Tier 3 services for a maximum of 2 years. Although this can be as little as 6 months and more normally the referral is for 12 months akin to the National Diabetes Prevention Programme. The intent is to provide the very best support from a multi-disciplinary team including dieticians and psychological support to provide the best chance of weight loss and maintenance post referral.

The findings reported by Ganguly et al. 2018[7] provide real-world evidence from a US-population based study measuring persistence of patients treated with liraglutide for weight management. This study found at follow-up of 6 months, 41.8% of patients continued treatment with liraglutide 3.0mg and by 15 months this had reduced to 26.6%. The proportion of patients persisting with liraglutide treatment was further confirmed in a Canadian real-world evidence study (Wharton et al. 2019)[8], which showed that 46.3% of patients were still on treatment after 6 months. This suggests that imposing a maximum treatment duration of 2 years would affect only a minority of patients. A physician survey (see Appendix N of the company submission) also suggested that patients would

most likely only receive treatment for 1-2 years. Therefore, a maximum treatment duration of 2 years was chosen for the revised company base case.

In ERG scenario 4, 6 and 7, there was no maximum treatment duration applied. This is a consequence of the extrapolation beyond the trial period implemented by the ERG in the mentioned scenarios.

Discontinuation following licence stopping rule

In response to ERG question B1, per cycle treatment discontinuation (as observed in Trial 1839) was incorporated into the model following the 12-week EMA licence stopping rule (previously all patients who achieved ≥5% weight loss were assumed to continue for the maximum treatment duration). Data from the clinical trial demonstrated that some patients do indeed discontinue therapy between the licence stopping rule and 2 years hence, this approach better reflects what was observed within the trial and what happens in clinical practice. Importantly this approach was preferred by the Technical team as stated in the Final Technical Report, we have therefore adopted it into our revised company base case.

The ERG has not incorporated discontinuation into any scenario where the maximum treatment duration is 2 years. The ERG has only incorporated treatment discontinuation when extrapolation goes beyond the trial period using a log-normal distribution in scenarios 4, 6 and 7.

Inclusion of adverse event (AE) disutility and cost

In response to ERG question B15, adverse events were included in the model. The analysis provided during the ERG clarification demonstrated that this assumption had very little impact on the results and we therefore did not incorporate it in the base case.

The ERG has incorporated the AE disutility and cost in scenario 5-7.

An overview of the assumptions incorporated in the company base case and in the ERG base case scenarios can be found below:

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Table 1: Overview of model assumption in the company base case and ERG scenario 1-7

Variable	Revised company base case	ERG preferred base case (Scenario 1)	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6	Scenario 7
Automatic development of T2D within 12 months post CV event	Yes	Yes	**No**	Yes	Yes	Yes	**No**	Yes
Alternative liraglutide non-responder efficacy	No	No	No	**Yes, D&E non-responders**	No	No	**Yes, D&E non-responders**	**Yes, D&E non-responders**
Maximum treatment duration	2 years	2 years	2 years	2 years	**None**	2 years	**None**	**None**
Discontinuation following licence stopping rule	During trial period (KM curves)	None	None	None	**Extrapolated log-normal distribution**	None	**Extrapolated log-normal distribution**	**Extrapolated log-normal distribution**
Inclusion of adverse event disutility and cost	No	No	No	No	No	**Yes**	**Yes**	**Yes**
Risk equation: Primary prevention in type 2 diabetes	UKPDS 82	Qrisk3 risk model	Qrisk3 risk model	Qrisk3 risk model	Qrisk3 risk model	Qrisk3 risk model	Qrisk3 risk model	Qrisk3 risk model
Risk equation: Secondary prevention in type 2 diabetes	UKPDS 82	Framingham Recurring CHD	Framingham Recurring CHD	Framingham Recurring CHD	Framingham Recurring CHD	Framingham Recurring CHD	Framingham Recurring CHD	Framingham Recurring CHD

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Analyses to support ACD response document (changed)

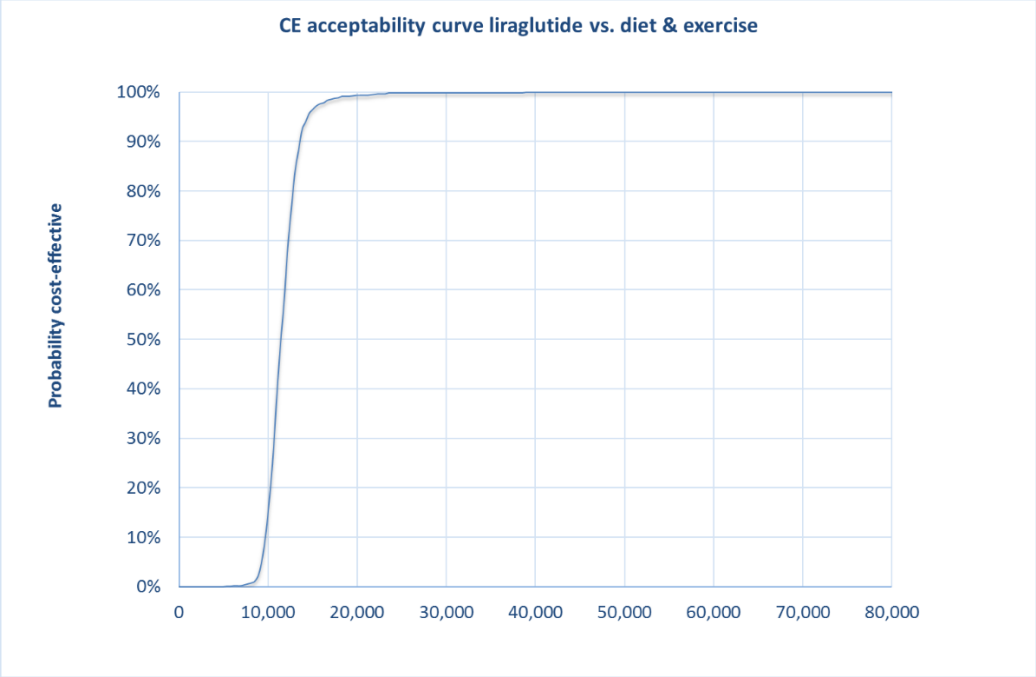
The deterministic and probabilistic cost effectiveness results for the revised company base case are shown in Table 2. Figure 1 shows the cost effectiveness acceptability curve (CEAC) for the revised company base case. These figures have been updated with a price of XXXXXX to reflect the revised commercial agreement between the company and NHS England.

Table 2: Revised company base case results incorporating new price

Treatment	Total Cost	Total QALY	Δ Cost	Δ QALY	ICER*
Company revised base-case (deterministic)					
Liraglutide 3.0mg	XXXXXXX	XXXXX	XXXX	XXXXX	£11,293
Diet and exercise	XXXXXXX	XXXXX			
Company revised base-case (probabilistic)					
Liraglutide 3.0mg	XXXXXXX	XXXXXX	XXXX	XXXXX	£11,419
Diet and exercise	XXXXXXX	XXXXXX			

*New price (£XXXXX)

Figure 1: CEAC company submission base case



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To support the robustness of our company base case, we have conducted a number of scenario analyses, which can be found in Table 3 below. The table includes ICERs for both the new and the old price.

Table 3: Company submission base case scenario analyses

Scenario		Δ COST*	Δ QALY	ICER (new price)*	ICER (old price)**
Company base case	1 year treatment duration	XXXX	XXXXX	XXXXXX	XXXXXXX
	2 year treatment duration	**XXXX**	**XXXXX**	**XXXXXXX**	**XXXXXXX**
	3 year treatment duration	XXXX	XXXXX	XXXXXXX	XXXXXXX
Company base case + no T2DM after CV event	1 year treatment duration	XXXX	XXXXX	XXXXXX	XXXXXXX
	2 year treatment duration	**XXXX**	**XXXXX**	**XXXXXXX**	**XXXXXXX**
	3 year treatment duration	XXXX	XXXXX	XXXXXXX	XXXXXXX
Company base case + Lira non-responder efficacy have diet & exercise non-responder effectiveness	1 year treatment duration	XXXX	XXXXX	XXXXXX	XXXXXXX
	2 year treatment duration	**XXXX**	**XXXXX**	**XXXXXXX**	**XXXXXXX**
	3 year treatment duration	XXXXXX	XXXXX	XXXXXXX	XXXXXXX

*New price (£XXXXX)
**Previously submitted price (£XXXXXX)

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Modified ITT analyses (changed) including response to query in ERG addendum

ERG comment:

The ERG tried to match the data reported in Table 4 of the latest appendix with the data in the original CS. However, we were unable to do this… Therefore, the ERG is unable to confirm that Novo Nordisk's new analyses are based on the correct data.

Company clarification:

In response to the ERG query regarding the data from the full prediabetes (mITT efficacy) population, we have reviewed the tables in the original submission and the ACD response in detail.

The data from Table 4 in the ACD response Appendix was not provided in the company submission (CS), hence why the ERG were not able to match these data. Unfortunately, the title of Table 10 in the CS is misleading as it does not contain the data used in the model. The table actually contains the CTR summaries by visit from the full analysis set which does not include the licensed stopping rule. The data used in the modelling for the subgroup are summarised in Table 46 of the CS.

As the ERG correctly pointed out, the data from Table 10 for placebo is the same because the no stopping rule is applied in the placebo arm when modelling, but the values for the treatment arm include the stopping rule after 16 weeks. The data presented in Table 4 of the ACD response Appendix includes the licensed stopping rule and was not included in the CS.

We thank the ERG for pointing out this discrepancy, which was, unfortunately, missed in our QC process. The analysis has been updated to take into account the new price of XXXXXX

As described in our response to the ACD (comment 3, section 3.6), we have performed a scenario analysis whereby efficacy inputs from the full prediabetes (mITT efficacy) population have been modelled using the baseline characteristics of the subgroup BMI ≥35 kg/m^2, prediabetes and high risk of CVD. The efficacy inputs for the analysis are shown below in Table 4.

Table 4: Efficacy input from the full prediabetes population (mITT)

Parameter	Liraglutide 3.0 mg Mean	Liraglutide 3.0 mg SE	Diet & exercise Mean	Diet & exercise SE
Percent (%) weight loss at 6 months (vs. baseline)	-10.32%	0.11%	-2.40%	0.13%
Percent (%) weight loss at 1 year (vs. baseline)	-11.14%	0.16%	-2.62%	0.16%
Percent (%) weight loss at 2 years (vs. baseline)	-9.76%	0.23%	-2.35%	0.22%
Percent (%) weight loss at 3 years (vs. baseline)	-8.43%	0.25%	-1.89%	0.23%
Change in SBP (mmHg, positive = increase) at 6 months	-5.57	0.31	-1.44	0.35
Change in SBP (mmHg, positive = increase) at 1 year	-5.26	-0.32	-1.54	-0.35
Change in SBP (mmHg, positive = increase) at 2 years	-4.98	0.45	-1.00	0.49
Change in SBP (mmHg, positive = increase) at 3 years	-3.47	0.44	-0.53	0.51

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Change in total cholesterol (mg/dl positive = increase) at 6 months	-9.60	0.72	-2.74	0.79
Change in total cholesterol (mg/dl positive = increase) at 1 year	-6.30	0.76	-1.83	0.85
Change in total cholesterol (mg/dl positive = increase) at 2 years	-5.43	0.98	-3.81	1.20
Change in total cholesterol (mg/dl positive = increase) at 3 years	-2.35	1.12	-2.86	1.16
Change in HDL cholesterol (mg/dl positive = increase) at 6 months	-0.82	0.20	0.00	0.21
Change in HDL cholesterol (mg/dl positive = increase) at 1 year	1.96	0.21	0.44	0.22
Change in HDL cholesterol (mg/dl positive = increase) at 2 years	3.01	0.29	1.20	0.30
Change in HDL cholesterol (mg/dl positive = increase) at 3 years	3.83	0.31	2.32	0.33
% reversing from prediabetes to NGT	76.11%	1.42%	24.26%	1.57%
Proportion not achieving target efficacy at 12 weeks on maintenance dose	32.56%	0.95%	77.77%	1.19%

As noted in response to the ACD (comment 3, section 3.6), using the efficacy data from the mITT population reduces the base case ICER (Table 5).

Table 5: Company submission base with mITT efficacy

Treatment	Total Cost	Total QALY	Δ Cost	Δ QALY	ICER*
Scenario: mITT efficacy in index population (deterministic)					
Liraglutide 3.0mg	XXXXXXX	XXXXX	XXXX	XXXXX	£8,635
Diet and exercise	XXXXXXX	XXXXX			

*New price (£XXXXX)

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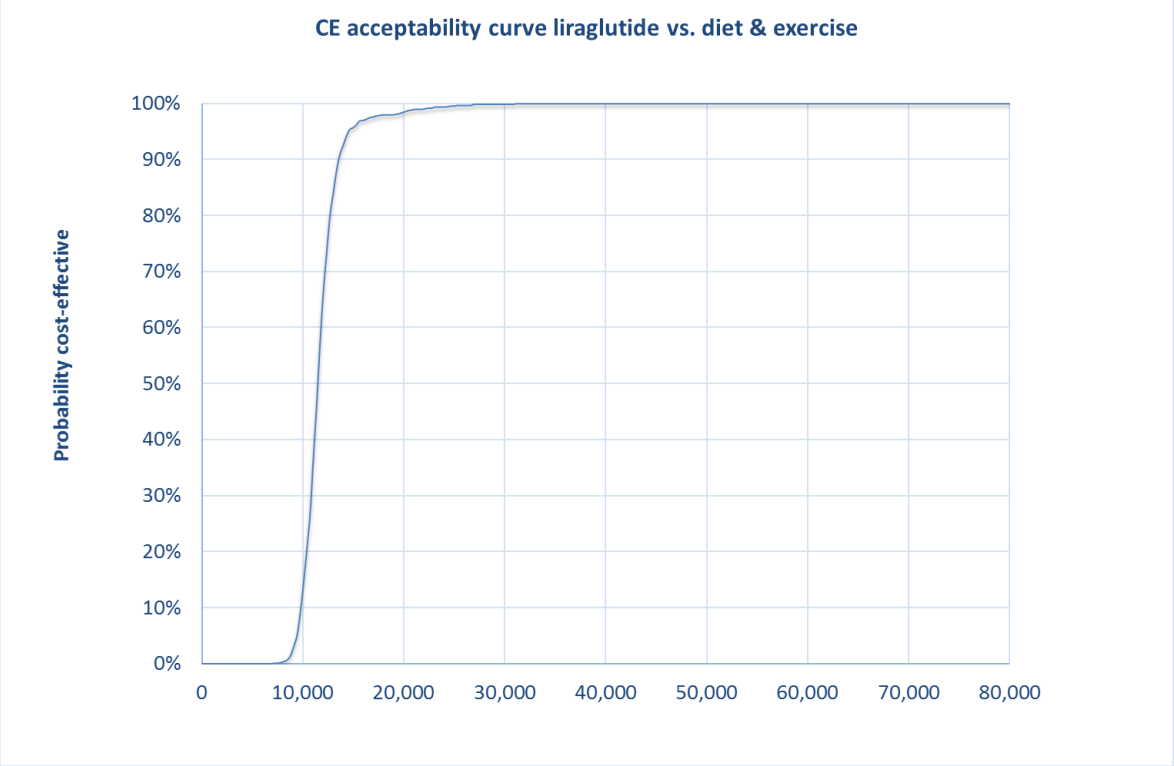
Figure 2 below shows the CEAC for the revised company base case with mITT efficacy.

Figure 2: CEAC company submission base case with mITT efficacy



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Additional stopping rule (≥10% weight loss at 1 year)(changed)

As noted in our response to the ACD (comment 6, section 3.8 - additional stopping rule), we have explored the impact of an additional stopping rule (10% weight loss at 52 weeks) on the cost effectiveness. In order to estimate this efficacy, inputs were derived from Trial 1839 (Tables 6-8).

Table 6: Efficacy inputs for ≥10% weight reduction subgroup (patients achieved target ≥5% efficacy at 12 weeks and ≥10% at 52 weeks)

Parameter	Liraglutide 3.0 mg Mean	Liraglutide 3.0 mg SE
Percent (%) weight loss at 1 year (vs. baseline)	-15.13%	1.07%
Percent (%) weight loss at 2 years (vs. baseline)	-13.48%	1.42%
Percent (%) weight loss at 3 years (vs. baseline)	-11.91%	1.59%
Change in SBP (mmHg, positive = increase) at 1 year	-8.47	0.81
Change in SBP (mmHg, positive = increase) at 2 years	-7.52	0.89
Change in SBP (mmHg, positive = increase) at 3 years	-5.58	0.85
Change in total cholesterol (mg/dl positive = increase) at 1 year	-5.63	2.05
Change in total cholesterol (mg/dl positive = increase) at 2 years	-8.72	2.25
Change in total cholesterol (mg/dl positive = increase) at 3 years	-5.08	2.12
Change in HDL cholesterol (mg/dl positive = increase) at 1 year	3.87	0.59
Change in HDL cholesterol (mg/dl positive = increase) at 2 years	4.97	0.63
Change in HDL cholesterol (mg/dl positive = increase) at 3 years	5.65	0.77
% reversing from prediabetes to NGT	87.5%	2.61%

Table 7: Efficacy input for ≥10% weight reduction subgroup (patients achieved target ≥5% efficacy at 12 weeks but not ≥10% at 52 weeks)

Parameter	Liraglutide 3.0 mg Mean	Liraglutide 3.0 mg SE
Percent (%) weight loss at 1 year (vs. baseline)	-6.46%	0.22%
Change in SBP (mmHg, positive = increase) at 1 year	-6.67	0.83
Change in total cholesterol (mg/dl positive = increase) at 1 year	-1.91	2.08
Change in HDL cholesterol (mg/dl positive = increase) at 1 year	1.66	0.56
% reversing from prediabetes to NGT	77.92%	NA
Proportion not achieving target efficacy at 56 weeks on maintenance dose	29.06%	NA

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Liraglutide for managing overweight and obesity [ID740]

Additional analysis 25 August 2020

Table 8: Percentage on treatment for company base case and 10% stopping rule (first 6 cycles)

Model cycle	Time period per cycle	Percentage on treatment at cycle start (10% stopping rule)	Percentage on treatment at cycle start (company base case)
1	0-3 months	100%	100%
2	4-6 months	58.20%	58.20%
3	7-9 months	55.80%	55.80%
4	10-12 months	52.40%	52.40%
5	13-24 months	30.20%	37.20%
6	25-36 months	0%	0%

After 3 months (model cycle 2) patients discontinue based on the licence stopping rule. Between 3 and 12 months, patients discontinue according the Kaplan-Meier curves from the trial. After 12 months, in the 10% stopping rule scenario, patients with a <10% weight loss discontinue. After 24 months, all patients discontinue due to the maximum treatment duration.

Results for the company base case applying the 10% weight loss stopping rule at 52 weeks are presented in Table 9 below.

Table 9: Company submission base case with 10% stopping rule at 52 weeks

Treatment	Total Cost	Total QALY	Δ Cost	Δ QALY	ICER*
Scenario: 10% stopping rule at 52 weeks (deterministic)					
Liraglutide 3.0mg	XXXXXXX	XXXXX	XXXX	XXXXX	£10,042
Diet and exercise	XXXXXXX	XXXXX			

*New price (£XXXXX)

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ERG preferred base case scenarios at new price (changed)

Table 10 shows the ERG base case scenarios recalculated using the new price.

Table 10: ERG base case scenarios recalculated with new price (£XXXXX)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Scenario 1: ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event					
Liraglutide	XXXXXXX	XXXXX	XXXX	XXXXX	£16,408
Diet & exercise	XXXXXXX	XXXXX			
Scenario 2: ERG base-case assuming prediabetic patients do not automatically develop T2DM with a CV event					
Liraglutide	XXXXXXX	XXXXX	XXXX	XXXXX	£17,446
Diet & exercise	XXXXXXX	XXXXX			
Scenario 3: ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + liraglutide non-responders have diet & exercise non-responder effectiveness					
Liraglutide	XXXXXXX	XXXXX	XXXXXX	XXXXX	£19,720
Diet & exercise	XXXXXXX	XXXXX			
Scenario 4: ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + liraglutide discontinuation extrapolated (log-normal distribution)					
Liraglutide	XXXXXXX	XXXXX	XXXXXX	XXXXX	£19,796
Diet & exercise	XXXXXXX	XXXXX			
Scenario 5: ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + include disutility and costs of adverse events (liraglutide arm)					
Liraglutide	XXXXXXX	XXXXX	XXXX	XXXXX	£16,807
Diet & exercise	XXXXXXX	XXXXX			
Scenario 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	XXXXXXX	XXXXX	XXXXXX	XXXXX	£52,646
Diet & exercise	XXXXXXX	XXXXX			
Scenario 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	XXXXXXX	XXXXX	XXXXXX	XXXXX	£48,835
Diet & exercise	XXXXXXX	XXXXX			

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Table 11: ERG base case scenarios recalculated with revised assumptions and new price (£XXXXX)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Scenario 1A: ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event and including within trial discontinuation					
Liraglutide	XXXXXXX	XXXXX	XXXX	XXXXX	£13,569
Diet & exercise	XXXXXXX	XXXXX			
Scenario 2A: ERG base-case assuming prediabetic patients do not automatically develop T2DM with a CV event and including within trial discontinuation					
Liraglutide	XXXXXXX	XXXXX	XXXX	XXXXX	£14,536
Diet & exercise	XXXXXXX	XXXXX			
Scenario 3A: ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + liraglutide non-responders have diet & exercise non-responder effectiveness and including within trial discontinuation					
Liraglutide	XXXXXXX	XXXXX	XXXX	XXXXX	£17,044
Diet & exercise	XXXXXXX	XXXXX			
Scenario 4A: ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + liraglutide discontinuation extrapolated (log-normal distribution)					
Not applicable					
Scenario 5A: ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event + include disutility and costs of adverse events (liraglutide arm) and including within trial discontinuation					
Liraglutide	XXXXXXX	XXXXX	XXXX	XXXXX	£13,870
Diet & exercise	XXXXXXX	XXXXX			
Scenario 6A: 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)					
Not applicable					
Scenario 7A: 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)					
Not applicable					

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Clarifications in response to March ERG addendum

The company wishes to offer clarifications in response to two specific points in the ERG addendum.

ERG comment:

… it is unclear why the results for diet & exercise are different for ERG scenario 1 and ERG scenario 4. The difference between these scenarios 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. [ERG addendum page 4]

Company clarification

The ERG is correct that the inputs used on ERG scenario 1 and ERG scenario 4 differ in assumed Liraglutide discontinuation. There is an additional difference between scenario 1 and scenario 4 in the assumed change in BMI over time after discontinuation. This difference is not obvious from inspecting the model controls. Once the change in BMI over time after discontinuation in scenario 1 is set to be identical to that in scenario 4 the expected result is observed.

Table 12: additional analysis around scenario 1 from ERG addendum

	Lira	D&E	Incremental	ICER
Scenario 1				
Total costs	XXXXXXX	XXXXXXX	XXXXXX	£21,115
Total QALYs	XXXXXX	XXXXXX	XXXXX	
Revised Scenario 1 with post treatment BMI assumptions equal to scenario 4				
Total costs	XXXXXXX	XXXXXXX	XXXXXX	£20,377
Total QALYs	XXXXXX	XXXXXX	XXXXX	

All other assumptions identical to scenarios as described in the ERG addendum

The costs and QALYs for D&E in the revised scenario 1 are now identical to the costs and QALYs for D&E in scenario 4. Average costs and QALYs are affected in both arms. But as the change applies to both arms and only occurs after treatment the impact on the incremental cost and QALYs is minimal. The ICER is reduced by around £800.

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ERG comment:

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. [ERG addendum page 4]

Company clarification

Scenarios 6 and 7 are no longer relevant as the company only seeks a recommendation for up to 2 years of liraglutide use.

The high ICER and low QALY gain in scenarios 6 and 7 occur when two assumptions are combined:

- Some liraglutide responders continue on liraglutide for an extended period
- Liraglutide non-responders receive the BMI of D&E non-responders

In these scenarios the model assumes that liraglutide non-responders continue to receive poor outcomes (equal to D&E non-responders) for the full duration of possible treatment. Liraglutide responders however gradually discontinue therapy over time and as they discontinue they return to BMI equal to the average of the whole D&E arm. This results in the liraglutide arm having in the model a longer term BMI prognosis that is on average worse than D&E, which is not a plausible inference from the available evidence.

The model was not designed to be used with this combination of assumptions and it appears that the model does not provide a credible description of long term BMI prognosis when this combination of settings is used.

References

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2. 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. 1 Hippisley-Cox J et al. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017 May 23;357:j2099. doi: 10.1136/bmj.j2099.

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4. McEwan, P., Ward, T., Bennett, H. and Bergenheim, K., 2015. Validation of the UKPDS 82 risk equations within the Cardiff Diabetes Model. Cost Effectiveness and Resource Allocation, 13(1), p.1.

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Liraglutide for managing overweight and obesity [ID740]

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Glaxo	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**GlaxoSmithKline**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	As far as it can be ascertained, GSK believe that all the relevant evidence has been taken into account
2	GSK believe that the target subgroup identified by the manufacturer is a reasonable one.considering use of available NHS resources and which patients are likely to gain the most benefit from the medicine. The uncertainties in the cost effectiveness assessment have been reasonably identified based on the available evidence
3	

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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Liraglutide for managing overweight and obesity [ID740]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of Physicians
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Liraglutide for managing overweight and obesity [ID740]

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Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
General	**The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our Advisory Group on Nutrition, Weight and Health and would like to make the following comments. Please note the following COI from our commenters.** • 3 members of the AG are PIs on Novonordisk's (NN) clinical trials (2 were involved with liraglutide 3mg) • 3 members of the AG have received honoraria from NN • 2 members of the AG are members of NN global advisory board.
1	**The following evidence does not seem to have been taken into account:** a) The evidence from SCALE obesity and prediabetes that liraglutide 3mg reduces the risk of developing type 2 diabetes (T2D). b) RCT data showing that GLP-1 receptor agonists (including liraglutide) reduce cardiovascular events in patients with T2D. c) Evidence that the CV benefits of GLP-1 receptor agonists are independent of weight loss. d) Other health benefits that were reported in the RCTs including improved health-related quality of life and improvement in obstructive sleep apnoea
2	**Is the company's proposed population the population that would benefit the most from liraglutide?** Ideally all people who are eligible but not undergoing bariatric surgery should be offered liraglutide as part of a weight management/lifestyle intervention programme that provides nutritional, physical activity and behavioural change with access to psychological support. NICE introduced stricter weight loss stopping rules for orlistat, sibutramine and rimonabant, introducing a 10% weight loss stopping at 6 and 12 months should be considered. The following groups should also be considered: 1. Patients with serious mental illness who have obesity or pre-diabetes. People living with serious mental illness have a 15-20 year mortality gap due to largely to metabolic disease, with drivers of

	obesity, smoking and obesogenic prescribing (such as Clozapine and Olanzapine). The metabolic and obesogenic effects of the latter have been shown to be reversed by early prescribing of liragulitide*(JAMA Psychiatry. 2017;74(7):719-728. doi:10.1001/jamapsychiatry.2017.1220 Published online June 10, 2017.)* 2. People who have undergone bariatric surgery but not had a favourable result – not lost >20% of their total body weight or regained weight so that their current weight is not >20% below their highest body weight. – (Miras AD, Pérez-Pevida B, Aldhwayan M, et al. Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2019;7:549-59. 10.1016/S2213-8587(19)30157-3, Hellström PM. GLP-1 analogue liraglutide as adjunct treatment in diabetes type 2 after failed bariatric/metabolic surgery. *Ann Transl Med*. 2019;7(Suppl 6):S240. doi:10.21037/atm.2019.08.94) 3. Palliative care for people living with extreme obesity who are unable to proceed for bariatric surgery
3	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Concern regarding the modelling of T2D development after a CV event is raised, however, the LEADER trial data shows a clear benefit in this patient group and does not seem to have been taken into account.
4	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The provisional recommendations are not sound or suitable for the NHS as they fail to recognise the profound health benefits of weight loss or multiple obesity-related co-morbidities and health-related quality of life.

Insert extra rows as needed

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- Use this comment form and submit it as a Word document (not a PDF).
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Response to Consultation Document – Society for Endocrinology

Liraglutide for managing overweight and obesity [ID740]

Has all of the relevant evidence been taken into account?

The focus is on diabetes prevention and CV disease and we accept there is no evidence for the latter at the 3mg dose or in people without diabetes, but there is excellent evidence for diabetes prevention in high risk patients from SCALE obesity and prediabetes. It is also very important to highlight that there is a large amount of emerging evidence from RCTs in people with diabetes, that 1. GLP1 analogues, including liraglutide, reduce cardiovascular events in high risk patients and that 2. the CV protection for GLP1 RA may be independent of weight loss.

Effects on sleep apnoea, benefits on quality of life and effects in those who have lost weight after using low energy diets, which were all measured in clinical trials do not seem to have been fully considered.

Is the company's proposed population the population that would benefit most from liraglutide?

The complexity of care needed for obesity and complications of many people in tier 3 services who do not tolerate orlistat or who are unsuitable for or unwilling to have surgery is not fully considered. There is also evidence of benefit in those with obstructive sleep apnoea, which is highly prevalent in this population, but does not seem to have been considered here. Furthermore, the evidence base on improvements in quality of life with liraglutide as measured in trials does not seem to have been included.

NICE makes statements about lack of availability of tier 3 services that are not consistent with the facts. Firstly, some are funded by Local Authorities rather than CCGs, so provision is greater than stated, probably some coverage for 75-80% of the population, although there is clearly need for expansion. This seems to imply that NICE will only approve drugs if there is 100% population coverage. That is clearly not the case for many effective medical interventions, and suggests they are thinking that if some CCGs think services aren't needed then that is OK. For other severe illnesses, that would be considered a failure of services rather than a reason to not approve a treatment; NICE should be stating that services are inadequate (ie not meeting their own standards as outlined in CG66 and associated quality standards) and advising proper service provision rather than rejecting treatment on the basis of poor service provision.

Use of stricter stopping rules eg 10% weight loss at 6 or 12 months, might make sense and provide clearer estimates of cost-effectiveness, and should be considered. NICE did this for orlistat, sibutramine and rimonabant, so there is clearly a precedent for using this approach.

Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

The quality of life modelling did not seem to use the measured effects in the SCALE trials, so really should include this.

The use of a post hoc sub group for modelling of effects over 2 years is questioned, but this really does not make much difference to the results. It should be possible to use estimates from whole trial population at 2 years and 3 years and model dropouts?

Concern is raised about the modelling assumptions regarding development of diabetes after CV events – I am sure there must be better data than making that assumption which is certainly not

clinically correct. However, it is worth also considering that if a person with obesity develops T2DM after a CV event, then they would clearly have benefit from liraglutide if prescribed at the lower dose of 1.8mg as there is clear evidence of benefit in this population from the LEADER trial.

The ICERs provided in the table provide a wide range of cost-effectiveness, but some of the assumptions made and all those that give ICERs above the threshold (eg only effect on BMI giving an ICER of £105000) are not credible based on the evidence presented and are inappropriately used to justify the appraisal decision.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, the review does not fully take into account he severe burden and adverse effects on quality of life seen in people with severe obesity, nor have they fully accounted for improvements that are seen with weight loss.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No – although it could be argued that people with severe obesity are amongst those most disadvantaged in society and that prejudice and stigma are as great against this group of people than in some of the other protected characteristics listed above See https://www.independent.co.uk/voices/obesity-awareness-week-workplace-discrimination-fat-overweight-health-ecj-a8726651.html

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Abd Tahrani, Clinical Expert for the first Single Technology Appraisal]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[None]
Name of commentator person completing form:	[Abd Tahrani, Clinical Expert for the first Single Technology Appraisal]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	In the appraisal consultation document NICE stated "Current management for overweight and obesity is lifestyle measures alone, lifestyle measures with orlistat, or bariatric surgery". This is correct, but considering the extremely limited access to Bariatric Surgery in the NHS and the poor tolerability and limited weight loss achieved with orlistat; the current recommendation is concerning as it deprives patients with obesity (who have very little other options) from access to an effective treatment option.
2	Regarding the appraisal consultation document point 3.1. I agree with the patient representative that obesity has a negative impact on patients quality of life. I also agree that obesity stigma is a major challenge and usually driven by lack of understanding of the complex causes of obesity and that there is real need for effective treatments for obesity to be made available.
3	Regarding point 3.2., I agree with the committee decision to focus on the high-risk population proposed by the company
4	Regarding point 3.3., I agree with the committee decision that tier 3 service is the appropriate context in which liraglutide would be offered
5	Regarding point 3.4., I agree with the committee decision that for most people, orlistat and bariatric surgery would not be alternatives to liraglutide and hence comparison with standard management without pharmacotherapy was appropriate for decision-making
6	Regarding point 3.5., I agree with the committee decision that the post-hoc subgroup population was identifiable and that it represented a high-risk population that were likely to gain higher absolute benefit from liraglutide.
7	Regarding point 3.6, the committee "was concerned that the post-hoc subgroup may have compromised randomisation. The committee concluded that the relative clinical effectiveness of liraglutide should have been estimated from the whole pre-diabetes population in the trial because this was larger, pre-specified and associated with less uncertainty than the smaller post-hoc subgroup". I agree with the committee that examining the whole pre-diabetes population in the trial has its advantages as outlined in the above-mentioned comment. However, when the index population (i.e. pre-diabetes + high CVD risk) was compared to the total pre-diabetes population in the SCALE trial (NEJM 2015) the changes in HbA1c, body weight, waist circumference and systolic BP were very similar between the two groups. In addition, as the committee agreed that tier 3 services are the appropriate services to offer liraglutide 3.0 mg treatment, using the total pre-diabetes population in the analysis would raise logistical challenges to tier 3 services who currently use a BMI >=35 kg/m^2 as a referral criteria to their services while about 30% of the total pre-diabetes population the SCALE trial had BMI < 35 kg/m^2. Hence, using the pre-diabetes with high CVD risk population is reasonable as it is an identifiable population that is likely to achieve greater absolute benefits (as the committee acknowledged) and would be consistent with the current criteria for referral to tier 3 weight management services.
8	Regarding point 3.7., "the committee concluded that the estimation of any reduction in cardiovascular events would be subject to uncertainty because they would rely on an estimation of the relationship between the surrogate and the clinical event". I agree that the modelling of CVD benefits is based on surrogate markers. SCALE was not a cardiovascular outcome trial and hence the study population was not particularly of high CVD risk and the number of CVD events was small. However, the development of Type 2 diabetes and higher systolic blood pressure are well established CVD risk factors and hence the impact of liraglutide 3.0 mg will be expected to have favourable impact on CVD. This is supported by the cardiovascular outcomes RCT in patients with Type 2 diabetes showing the CVD benefits of liraglutide 1.8mg (https://www.nejm.org/doi/full/10.1056/NEJMoa1603827). In addition to the glycaemic and BP benefits, in the SCALE trial there were benefits in many other CVD risk factors in the liraglutide 3.0

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Liraglutide for managing overweight and obesity [ID740]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 14 February 2020 **email:** NICE DOCS

	group vs placebo including: fasting lipid levels, high-sensitivity C-reactive protein, plasminogen activator inhibitor-1, and adiponectin. While it does not rule out any uncertainty, based on what we know regarding the epidemiology of CVD it is reasonable to expect that the effects of liraglutide 3.0 mg on the development of Type 2 diabetes, blood pressure, lipids and variety of other factors should lead to reductions in CVD.
9	Regarding point 3.8., "The committee had concerns that the company's submission was based on a maximum treatment duration of 2 years". I agree that obesity as a chronic disease that will require long term treatment. However, considering that the drug is going to be used within tier 3 services, continuing liraglutide 3.0 mg beyond 2 years will be challenging in tier 3 as the usual follow up in tier 3 is 2 years. Furthermore, the drug is delivered by daily injections and hence many patients not achieving "good" weight loss are likely to stop treatment before 2 years. However, those who want to persist with treatment are likely to be those patients who achieve greater weight losses (for example 10% body weight loss) and hence likely to derive even "higher than average" benefits from treatment. While I understand the concerns of the committee regarding the 2 year cut off; the committee needs to appreciate that even within the current tier 3 services patients will not receive treatment for longer than 2 years. In other words, the treatment given within the current tier 3 services to patients with obesity are not delivered long term. Using the 2 years limit seems reasonable pragmatic approach to offer a beneficial treatment with clear outcomes utilising the currently available NHS services.
10	Point 3.9., "The company's economic model is suitable for decision making"; I agree with committee decision
11	Pint 3.10. "Cardiovascular risk was determined using risk equations ". Please see my comment number 8.
12	Point 3.11. "The company's assumptions used to predict weight gain and diabetic status were associated with uncertainty….. Because no follow-up data were available for weight gain or diabetic status in the 3 years after stopping treatment, the committee accepted that some assumptions had to be made. However, it concluded that the company's assumptions were associated with uncertainty." I agree that in the view of lack of data there is a degree of uncertainty. However, the assumptions described seems reasonable from the clinical perspective of weight management. Furthermore, data from the UK CPRD primary care database showed that in people who lost 5% weight loss, 53% regained the weight over 2 years and 78% regained the weight over 5 years (https://ajph.aphapublications.org/doi/10.2105/AJPH.2015.302773). So, the company assumption that all the weight lost with liraglutide will be regained over 3 years is rather pessimistic rather than optimistic and hence seems reasonable to be used in the model.
13	Point 3.12 "The company's model assumes that all people who have a cardiovascular event develop type 2 diabetes …... The committee was concerned that the company's assumption overestimates the clinical and cost effectiveness of liraglutide." . While there is no definite data, a previous study from my team (https://bmcendocrdisord.biomedcentral.com/articles/10.1186/s12902-017-0153-y) showed that in patients admitted with acute coronary syndrome, baseline HbA1c and fasting plasma glucose during the hospital admission were independent predictors of developing Type 2 diabetes within 3 months from discharge from hospital after adjusting for age and BMI. Hence patients with pre-diabetes (who will have higher baseline HbA1c by definition) are particularly at increased risk of Type 2 diabetes shortly after acute coronary syndrome.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

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NICE National Institute for Health and Care Excellence

Liraglutide for managing overweight and obesity [ID740]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 14 February 2020 **email:** NICE DOCS

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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Name	Sarah Le Brocq
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments

Has all of the relevant evidence been taken into account? I'm not sure that the patient voice has been taken into consideration enough, people living with obesity are desperate for treatment options to help them lead healthier lives, the fact that there is one available (Liraglutide) that has good outcome data and a good safety profile, but is not accessible, is very disappointing.

Is the company's proposed population the population that would benefit most from liraglutide? Yes, the proposed population are higher risk patients and so therefore would benefit from a reduction of weight using Liraglutide. There is evidence to support that as little as a 10% reduction in weight can have a positive impact on long term CV health, diabetes etc.. This is stated in the DPP, so why would we not look at intervention that has similar outcomes for obesity?
There are very little medications available to treat this population at the moment, so this would be a welcome addition.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

As far as I am aware, yes.
The inclusion of stopping rules at 12 months and 24 months, ensures only people where the medication is working and it is effective remain on treatment.

Are the recommendations sound and a suitable basis for guidance to the NHS?
Absolutely, this high risk population currently have no treatment options available to them other than orlistat, and the positive outcomes they could see using Liraglutide are a no brainer.
This medication needs to be available for people living obesity, and more specifically, people at higher risk of

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Yes

People living with obesity face discrimination on a daily basis, not getting access to services or available treatments that could help people living with obesity to lead healthier lives and have better health outcomes could be seen as discrimination itself.

Comments on the ACD received from the public through the NICE Website

Name	
Role	
Other role	
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Comments on the ACD:	

Has all of the relevant evidence been taken into account? Yes

Is the company's proposed population the population that would benefit most from liraglutide?

I agree. From my experience in participating in multi-disciplinary weight management clinics, there is a disheartening plateau in weight loss after compliane with dietary measures and often patients benefit from a push in the positive direction with pharmacological therapy.
I think the people who have demonstrated compliance with diet and emotional aspects related to food, with a persisting BMI of >35 and presence of CV risk factors, with a motivation to lose weight further and understand the impact of the same would be ideal candidates for this medication.
It should also be prescribed short-term with regular reviews for evidence of target weight loss. In vie of the significant cost, patients must be made aware of this and the strict criteria for stopping the drug in advance.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

I agree with prescribing this medication for anyone with a BMI>35 with CV risk factors, who demonstrate compliance with dietary measures and further motivation to lose weight while awaiting bariatric surgery or as an initial alternative to it.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? None

Name	
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Other role	
Organisation	
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Conflict	
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Comments on the ACD:

Has all of the relevant evidence been taken into account?

Yes all the relevant data have been considered and presented in a satisfactory manner.

Is the company's proposed population the population that would benefit most from liraglutide?

The company have focused on the population where the medication is most cost effective and I agree with the description of this population.

Are the recommendations sound and a suitable basis for guidance to the NHS?

yes indeed

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I cannot see any evidence of discrimination or exclusion.

Name	
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Comments on the ACD:	
As a person living with obesity for 40 years, following every possible diet, exercise plan, dietician, GP advice my increasing weight and gaining comorbidity's lead me to bariatric surgery. Having lost half my body weight, improved my health 100% and lowered my health issues I feel any treatment that is proven to assist in helping a person living with obesity has to be available for medical professionals to access. People living with obesity deserve Access To Treatment. Thank You	

Name	
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Comments on the ACD:

Has all of the relevant evidence been taken into account?

Did NICE consider cardiovascular benefits in patients taking liraglutide at lower dose for T2D, I beleive some trial data available and might be reasonable to consider it

Is the company's proposed population the population that would benefit most from liraglutide?

It is one group, but there are others that might benefit, for example person with high BMI needing orthopaedic surgery where surgery denied due to BMI, but mobility very limited, if liraglutide reduced BMI and person became mobile they might then maintain or reduce weight without continuing the drug.
People with high BMI on psychotropic medication unsuitable for bariatric surgery might benefit, but not sure if RCT evidence in these groups

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I am not sure that the uncertainties are as large as NICE thinks, but am not expert enough to interpret data. Clinically as I have run an award winning Tier 3 service for 10 years there are definitely some patients who would really benefit from pharmacotherapy producing this much weight loss, who currently have no options within NHS

Are the recommendations sound and a suitable basis for guidance to the NHS?

I am very disappointed that I will be unable to use Liraglutide in a limited group of patients. I hope that the process have been rigorous and fair and comparable to NICE process on other drugs for severe chronic disease

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

This may inadvertently discriminate against people with severe psychiatric illness or learning disabilities who might not be suitable for consideration of bariatric surgery.

It may also inadvertently discriminate against women of childbearing age with fertility problems who need to lose weight for fertility treatment, and slow their journey. As fertility decreases with time this may affect their long term chances of conceiving.

There may be religious or cultural reasons why bariatric surgery is not acceptable, and pharmacotherapy is.

Please consider allowing some circumstances in which it might be prescribed to avoid discrimination against vulnerable groups

Name	
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Comments on the ACD:

I found the document to be fair and balanced.

Thank you,

Has all of the relevant evidence been taken into account?

The company have submitted documents relevant to the application.

Is the company's proposed population the population that would benefit most from liraglutide?

The proposed population (BMI>35 with co-morbidities or >40) would be the one to benefit. I would not suggest a BMI>30 or BMI>27 with co-morbidities.
From a real world perspective, we have over 80 patients on this medication (Saxenda) who are privately funding (but within the NHS) themselves as they are desperate to lose weight. I have used it in those with a BMI >35. It is a shame those from poorer backgrounds (and usually the most vulnerable) cannot access this medication. In many of my patients, Saxenda use has led to successful employment, prevented marriages from ending, 30% stopped insulin therapy for their diabetes, has allowed 5 patients to undergo knee operations that otherwise orthopaedic surgeons would have refused. Weight loss ranges from 12%-27%.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
From what has been presented I feel the summaries of clinical and cost-effectiveness to be very reasonable.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I am very disappointed that I will be unable to use Liraglutide in a limited group of patients. I hope that the process have been rigorous and fair and comparable to NICE process on other drugs for severe chronic disease

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

In terms of age, this should obviously be in line with the age range used in the RCT of Saxenda Trials. Of course this would not be used in pregnancy and maternity. There is very little if anything we can offer our patients in our weight management services besides diet and exercise. I believe Saxenda will benefit individuals as per suggested guidance, as we note that once patients lose weight they want to work hard to maintain this and saxenda will help lose weight but motivators and dietitians will help to maintain the weight loss - hence a Tier-3 service is crucial to

manage the use of Saxenda but also these services should be providing 6 monthly reports on the use and effect of Saxenda

Name	
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Comments

All of the relevant evidence appears to have been included in this analysis. A deficit in the evidence base has been identified as there are no placebo controlled studies of higher dose liraglutide that exclusively include populations with prediabetes and obesity that use CV disease as the primary outcome.

However, it should be noted that the company's proposed population is a population that would benefit most from Saxenda® (liraglutide 3mg). Obesity & prediabetes both add cardiovascular risk, and both respond well to treatment with liraglutide. While there are no specific RCTs of liraglutide that exclusively include people with prediabetes, obesity and elevated CV risk, these populations have been studies within robust RCTs & there is evidence of benefit.

Therefore, I do not consider the summaries of the existing evidence base to be reasonable interpretations of the evidence. I accept that a specific RCT would be ideal, but the existing evidence of benefit is very strong & this should be recognised.

Given the above, I feel the recommendations are insufficient as guidance to the NHS, as they do not recognise the substantial evidence for CV benefit in people with prediabetes & obesity who use liraglutide.

There are no aspects of the recommendations that need particular consideration to avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity. However, I would respectfully suggest that obesity stigma is prevalent throughout our society, and can sometimes colour our judgement when considering the treatment of obesity. This should be considered in this evaluation.

Name	
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Comments on the ACD:

Diabetes UK supports the use of Liraglutide for some people who are at risk of developing type 2 diabetes and have a BMI over 30.

The NHS Diabetes Prevention Programme (NHS DPP) should routinely be the first place people at high risk of type 2 diabetes, or living with non-diabetic hyperglycaemia (NDH), are referred to for support with weight management, but we recognise that it may not always be accessible, acceptable or effective for all those at high risk of type 2. We therefore support Liraglutide being offered as an option for people at high risk of type 2 diabetes where the NHS DPP is not appropriate. We suggest that this approach would offer patients more choice surrounding their care and further encourage a shared-decision making approach.

While we support the use of Liraglutide for people at high risk of developing type 2 diabetes with a BMI over 30, this would need to be coupled with education and ongoing support for those taking it. This includes injection technique and, as per PH38, regular review. We are aware that some people are buying Liraglutide privately and we consider that offering it as an option to those who are at high risk of type 2 diabetes and have a BMI over 30 may help to ensure people are taking it safely, with the support of qualified healthcare professionals who can offer care and support planning.

Name	
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Comments

Has all of the relevant evidence been taken into account? I'm not sure that the patient voice has been taken into consideration enough, people living with obesity are desperate for treatment options to help them lead healthier lives, the fact that there is one available (Liraglutide) that has good outcome data and a good safety profile, but is not accessible, is very disappointing.

Is the company's proposed population the population that would benefit most from liraglutide? Yes, the proposed population are higher risk patients and so therefore would benefit from a reduction of weight using Liraglutide. There is evidence to support that as little as a 10% reduction in weight can have a positive impact on long term CV health, diabetes etc.. This is stated in the DPP, so why would we not look at intervention that has similar outcomes for obesity?
There are very little medications available to treat this population at the moment, so this would be a welcome addition.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

As far as I am aware, yes.
The inclusion of stopping rules at 12 months and 24 months, ensures only people where the medication is working and it is effective remain on treatment.

Are the recommendations sound and a suitable basis for guidance to the NHS?
Absolutely, this high risk population currently have no treatment options available to them other than orlistat, and the positive outcomes they could see using Liraglutide are a no brainer.
This medication needs to be available for people living obesity, and more specifically, people at higher risk of

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Yes

People living with obesity face discrimination on a daily basis, not getting access to services or available treatments that could help people living with obesity to lead healthier lives and have better health outcomes could be seen as discrimination itself.

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
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Comments

I would support the use of Liraglutide 3mg in non-diabetic population, especially in a Tier 3 services for patients with BMI> 35, pre diabetes and minimum of 1 co-morbidity.

The use of this agents should be restricted to initiation by hospital endocrinologists with expertises in weight management, ie Tier 3, with a target of 5% weight loss in 12 weeks. If this target is reached, patients should have this agent continued in the communication by GPs,and should only be continued beyond 12 months if patients demonstrate continued weight loss. If patient regain weight, medication should be stopped.

These criteria would help manage patients number and address CCG concerns as well as the financial constraints.

This should be used in conjunction with lifestyle modification to maximise its effect and support patients towards a holistic approach to weight management.

The supply of a digital technology apps to track weight loss with the use of Liraglutide would further enhance weight loss and patient experience, and lessen NHS cost burden.

Has all of the relevant evidence been taken into account? Yes

Is the company's proposed population the population that would benefit most from liraglutide? Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes

Are the recommendations sound and a suitable basis for guidance to the NHS? Yes

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?No

Name	
Role	
Other role	
Organisation	
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Comments

Is the company's proposed population the population that would benefit most from liraglutide?

There is a population of patients who would require having short term weight loss in order to access further treatments such as surgery, where preoperative weight loss will improve the outcomes of the surgery. The cost effectiveness of the treatment with liraglutide has not been included in these cases. There is a strong need for weight loss to improve surgical and other treatments´outcomes. Thus, liraglutide should be strongly considered as a bridge to access treatments or improve outcomes, reducing the costs of failed treatments or complications, without necessity for long term liraglutide until more evidence is gathered on long term effects (<=1 year treatments should be considered for such a population).

Name	
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Organisation	
Location	
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Comments

Evidence over many years in the USA shows a high level of improvement in all obesity associated areas of health for people who have been prescribed this product, if used as an alternative to bariatric surgery then I fail to see how you can call into question the risk (long term) of effectiveness related to CV disease, is it not a far higher risk for the person that is living with a level of morbid obesity, is it not the case that a person (Yes a person , we are discussing a human beings future health!!) living with this level of obesity is at an already proven and fully recognised as an extremely high risk of developing not only CV issues, but Hypertension, Cancer, T2Diabeties, the list goes on and on.

As a person who has and still does live with the chronic disease of obesity , who since bariatric surgery has maintained a healthy weigh for over five years, who has put diabetes into remission, reversed my hypertension and leads a much healthier and active life.

Who now volunteers as a patient advocate to support people living with overweight & obesity.

I would request that NICE reconsider this initial recommendation, people's lives across the globe who live with the chronic disease of obesity have had their lives and health immensely improved when using this product.

Thank You

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
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Comments

I have read the appraisal consultation document and after review of population group a BMI>35 is most appropriate to reduce the risk of long-term outcomes, other co-morbidities and quality of life. The clinical cost effectiveness of this treatment option versus bariatric surgery and weight loss programmes is sound evidence to recommend this drug. The bariatric surgery is not a scalable option considering the explosive and exponential rise in obesity.

Has all of the relevant evidence been taken into account? Yes

Is the company's proposed population the population that would benefit most from liraglutide? Yes

Are the recommendations sound and a suitable basis for guidance to the NHS? Yes

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Yes

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
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Comments

Has all of the relevant evidence been taken into account?
Yes. Increasing BMI is associated with increasing risk of diabetes. Mortality benefit is unlikely to be
seen in a shorter trial duration and I do not think that a randomised controlled trial is justified ethically for a longer duration given the risks associated with untreated obese population with significant CV risk factors.

Is the company's proposed population the population that would benefit most from liraglutide? Clinical experience amongst patients with Type 2 diabetes suggests a similar outcome. Cost implications have to be taken into account if the scope of treatment is to be extended to population with stage 1 and stage 2 of obesity and ICER of less than £20,000 per QALY gained will need stronger argument and current evidence with Liraglutide 3 mg does not support for this population if BMI only is taken into account.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

yes.
The projected ICER is more valid in this context

Are the recommendations sound and a suitable basis for guidance to the NHS?
Yes

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

It needs to consider lower BMI cut off as per the Obesity staging for patients of South east Asian origin

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
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Comments

The Welsh Obesity Society recognises that obesity should be recognised as a chronic relapsing disease and treated accordingly. Considerable experience of obesity and weight management exists in some level 3 service in Wales. Lifestyle modification with diet and physical activity remain essential and extremely useful components of weight management interventions for patients living with obesity. We do recognise, however, that weight loss within the MDT level 3 setting is often modest with dietary modification, physical activity and behavioural therapy. Bariatric surgery is not an option for the majority of patients living with obesity. There is, therefore, a significant gap and unmet need between lifestyle intervention and surgery that should be bridged and filled by pharmacotherapy. Patients with diabetes and prediabetes are particularly disadvantaged by the recent decision by NICE. The financial implications in our opinion and experience favour the use of Saxenda in order to reduce morbidity and mortality as well as cost on health, drugs for obesity complications, social stigmatisation and NHS resources. Several health professionals in the Welsh Obesity Society are currently using Saxenda with considerable satisfaction in achieving significant weight loss when combined with diet and exercise. Prohibiting Clinicians from prescribing this drug will result in a significant psychological blow for these patients. The Welsh Obesity Society supports the use of Saxenda for the patient with obesity and prediabetes and agrees with the proposal that prescribing should be limited to the setting of the Specialist Level 3 Weight Management Service.

[redacted], on behalf of the Welsh Obesity Society

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Liraglutide for managing overweight and obesity

ADDENDUM

Critique of the company's response to the ACD

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 05/03/2020

1. The use of data from a post-hoc subgroup (Company Comment 2)

The ERG agrees that the post-hoc subgroup analysis is associated with increased uncertainty as at 800 patients it is only 21% of the original population of Trial 1839. The company states that the inclusion criteria for this subgroup did not use post-randomisation criteria which "will in principle preserve the integrity of the randomisation" but the ERG disagrees with this statement. As this subgroup was not defined at the trial design stage the randomisation will not be balanced between treatment groups within the subgroup. The only way to ensure that the treatment groups are balanced for known and unknown variables would be to include this group as a stratification factor in the randomisation. The randomisation was stratified by baseline BMI (< 30 or ≥ 30 kg/m^2) and pre-diabetes status at screening. It did not use CVD risk or a BMI ≥ 35 kg/m^2 as specified for the subgroup so the integrity of the randomisation for the post-hoc subgroup is in doubt.

2. Efficacy data from the full prediabetes (mITT efficacy) population (Company Comment 3)

The ERG tried to match the data reported in Table 4 of the latest appendix with the data in the original CS. However, we were unable to do this.

Trial 1839 contains a number of different populations:

- The full trial population (N=3731, with and without pre-diabetes),
- A pre-defined subgroup (N=2254, people with prediabetes);
- Another subgroup (N=1021, people with BMI $\geq$35 kg/m^2 and prediabetes), and
- The index population (N=800; A post-hoc subgroup of people with BMI $\geq$35 kg/m^2, prediabetes and high risk of cardiovascular disease).

The CS presents results for the prediabetes population (N=2254), and we think the results in this latest response to ACD are also for the full prediabetes population (mITT). But the numbers are not the same. On page 8 of the latest appendix the company reports the Percent (%) weight loss at 3 years (vs. baseline): -8.43% (SE 0.25%) for liraglutide versus -1.89% (SE 0.23%) for placebo/diet & exercise. The original CS reports in Table 10, page 51: Change from baseline to week 160 – Trial 1839 – LOCF, Fasting body weight (%): -6.14 (SD 7.34) for liraglutide versus -1.89 (SD 6.27) for placebo. Therefore, the means for placebo are the same but the means for liraglutide are different.

For SBP results are -3.47 (SE 0.44) versus -0.53 (SE 0.51) in the latest appendix and -3.19 (SD 13.00) versus -0.53 (SD 13.73) for placebo. Again, the means for placebo match but not those for liraglutide.

Therefore, the ERG is unable to confirm that Novo Nordisk's new analyses are based on the correct data.

3. Cost effectiveness

In the Appendix of the company's ACD response, the company stated that the assumptions for the revised company base-are unchanged from the revised company base-case submitted as part of technical engagement; the only update to the base case is the revised price.

Table 1 provides an overview of assumptions in the company's base-case and how these differ from the ERG scenarios. The difference between ERG scenario 1 and the most recent company base-case are: (1) the use of different risk equations 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 are combined the ICER increases 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 probably depends on the which assumptions are preferred.

Related to the results presented in Table 1 (below), the face validity of these results 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 scenarios 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: overview of scenarios (based on Table 1 and 10; Appendix of the company's ACD response)

Assumption	Revised company base case	ERG Scenario 1*	ERG scenario 2	ERG scenario 3	ERG scenario 4	ERG scenario 5	ERG scenario 6	ERG scenario 7
Automatic development of T2D within 12 months post CV event	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Alternative liraglutide non-responder efficacy	No	No	No	Yes, D&E non-responders	No	No	Yes, D&E non-responders	Yes, D&E non-responders
Maximum treatment duration	2 years	2 years	2 years	2 years	None	2 years	None	None
Discontinuation following licence stopping rule	During trial period (KM curves)	None	None	None	Extrapolated log-normal distribution	None	Extrapolated log-normal distribution	Extrapolated log-normal distribution
Inclusion of adverse event disutility and cost	No	No	No	No	No	Yes	Yes	Yes
Risk equation: Primary prevention in type 2 diabetes	UKPDS 82	Qrisk3 risk model	Qrisk3 risk model	Qrisk3 risk model	Qrisk3 risk model	Qrisk3 risk model	Qrisk3 risk model	Qrisk3 risk model
Risk equation: Secondary prevention in type 2 diabetes	UKPDS 82	Framingham Recurring CHD	Framingham Recurring CHD	Framingham Recurring CHD	Framingham Recurring CHD	Framingham Recurring CHD	Framingham Recurring CHD	Framingham Recurring CHD
Deterministic ICER (cost per QALY gained)	£14,839	£21,115	£22,365	£25,015	£25,033	£21,600	£64,372	£59,798

*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 equations to estimate CV events (for patients with T2DM) and; 2) fixed treatment duration of 2 year (with early stopping rule).

Automatic development of T2D within 12 months post CV event

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. To reflect this uncertainty, the ERG presented an ICER range in its ERG report. Consistently, in the ACD it is stated that the clinical experts explained to the committee that "people are more likely to be diagnosed with type 2 diabetes after a cardiovascular event, but this relationship is not causal. The committee heard that there is no good evidence to determine the proportion of people who would develop type 2 diabetes after a cardiovascular event."

Alternative liraglutide non-responder efficacy

In the company's base-case liraglutide non-responders are assumed to have the same efficacy as the placebo group (diet and exercise). The ERG believes that this assumption is debatable, as liraglutide non-responders are probably a selected population that potentially has worse treatment effectiveness than the overall placebo group. In the company's response to the ACD, the company quoted a clinical expert stating that "patients who do not respond to liraglutide are biologically different to those that do respond". Therefore, assuming the same treatment effectiveness as for placebo non-responders might be more appropriate.

Maximum treatment duration of 2 years

In the company's base-case, a maximum treatment duration of 2 year was assumed. The company argues that "a maximum treatment period of 2 years reflects clinical practice in England and Wales where patients would be treated in Tier 3 services". In addition, the company quotes real-world evidence from a US-population based study (Ganguly et al., Diabetes Research and Clinical Practice 2018), indicating 26.6% of patients continued treatment with liraglutide 3.0mg by 15 months. Extrapolating this percentage (assuming and exponential distribution, i.e. equal discontinuation probability over time) would indicate that 12% of patient would still continue treatment with liraglutide 3.0mg by 24 months. Additionally, the committee acknowledged that a "2-year stopping rule would be implementable in the NHS but noted that it does not reflect what was done in the clinical trial or address the clinical need to reduce weight and then maintain a reduced weight".

Risk equations for primary and secondary prevention in type 2 diabetes

One of the main differences between the ERG and the company's analyses is the selected risk equations. The company's base-case uses different risk equations to estimate CV events (both primary and secondary) dependent on the T2DM status. As highlighted in a recent review of prediabetes decision models (Leal et al., Diabetes, Obesity and Metabolism 2019), using different risk equations 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". Consistently, the company acknowledges (clarification response B7), using the risk equations selected by the company, that differences might arise due to factors unrelated to T2DM. Therefore, the ERG prefers to use the same risk equations 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.