For committee

NICE National Institute for Health and Care Excellence

Liraglutide for managing overweight and obesity

2nd Appraisal Committee meeting

Chair presentation

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Chair: Jane Adam
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Company: Novo Nordisk

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Key issues

- Have the assumptions about the long-term cardiovascular (CV) outcome benefits been sufficiently justified?

- Is the 2-year stopping rule for treatment acceptable?

- Is the assumption that all people develop type 2 diabetes (T2D) in the 12-months following a CV event appropriate? Does the scenario analysis provided by the company reduce the uncertainty?

- Is the updated evidence with the full pre-defined pre-diabetes (Modified ITT analyses) trial 1839 population reliable?

Liraglutide

Marketing authorisation	BMI of • ≥30 kg/m^2 (obese), or • ≥27 kg/m^2 to <30 kg/m^2 with at least one weight-related comorbidity Treatment discontinued after 12 weeks (on full dose) if weight loss < 5% **NOTE: the submission focuses on a subgroup of MA only**
Mechanism of action	Human glucagon-like peptide-1 (GLP-1) analogue GLP-1 - physiological regulator of appetite and food intake: exact mechanism of action unclear
Administration	Starting dose: 0.6 mg once daily by subcutaneous injection. Increased to 3.0 mg once daily to improve gastro-intestinal tolerability
Cost	List price £196.20 for 5 x 6 mg/ml 3ml pre-filled pens. **NOTE:** Novo Nordisk has a proposed a further price reduction via the previously approved commercial arrangement with NHS England.

Committee considerations at ACM1 (1)

- Obesity is restrictive and often stigmatized. There is a need for more effective treatments that deal with the biological determinants.
- Orlistat and bariatric surgery are not an appropriate comparator. Comparator is standard management i.e. diet and exercise.
- Liraglutide would be offered as a tier 3 weight management service: Access to tier 3 services is variable in England.
- Submission focused on a “high risk” sub group: patients with BMI ≥35 kg/m^2; pre-diabetes and high risk of CV disease.
- Evidence from the post-hot subgroup of trial 1839 may be unreliable/ uncertain: post hoc analysis may compromise randomisation & reduces sample size and statistical power.
- Evidence for clinical effectiveness should have come from the full pre-defined population.

Clinical Evidence – Trial 1839

Trial design	Randomised, double-blind, placebo-controlled trial: **pre-diabetes patients randomised to 160 week trial period (others 56 weeks)** **The focus of this submission is pre-diabetes and a high risk of CVD.**
Trial inclusion criteria	Patients stratified according to BMI (≥30 kg/m^2 or <30 kg/m^2) and pre-diabetes status. Pre-diabetes criteria (ADA 2010 86 guidance):
Trial drug	Liraglutide 3.0mg or placebo (ratio 2:1) once daily by subcutaneous (SC) injection Dose escalation in weekly increments of 0.6mg liraglutide to minimise GI side effects.
Comparators	Diet and exercise.
Primary outcomes	**Proportion of patients with onset of type 2 diabetes at week 160 among patients with prediabetes at baseline - evaluated as the time to onset of type 2 diabetes.**

Clinical Evidence – Derivation of the Index Population in Trial 1839

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

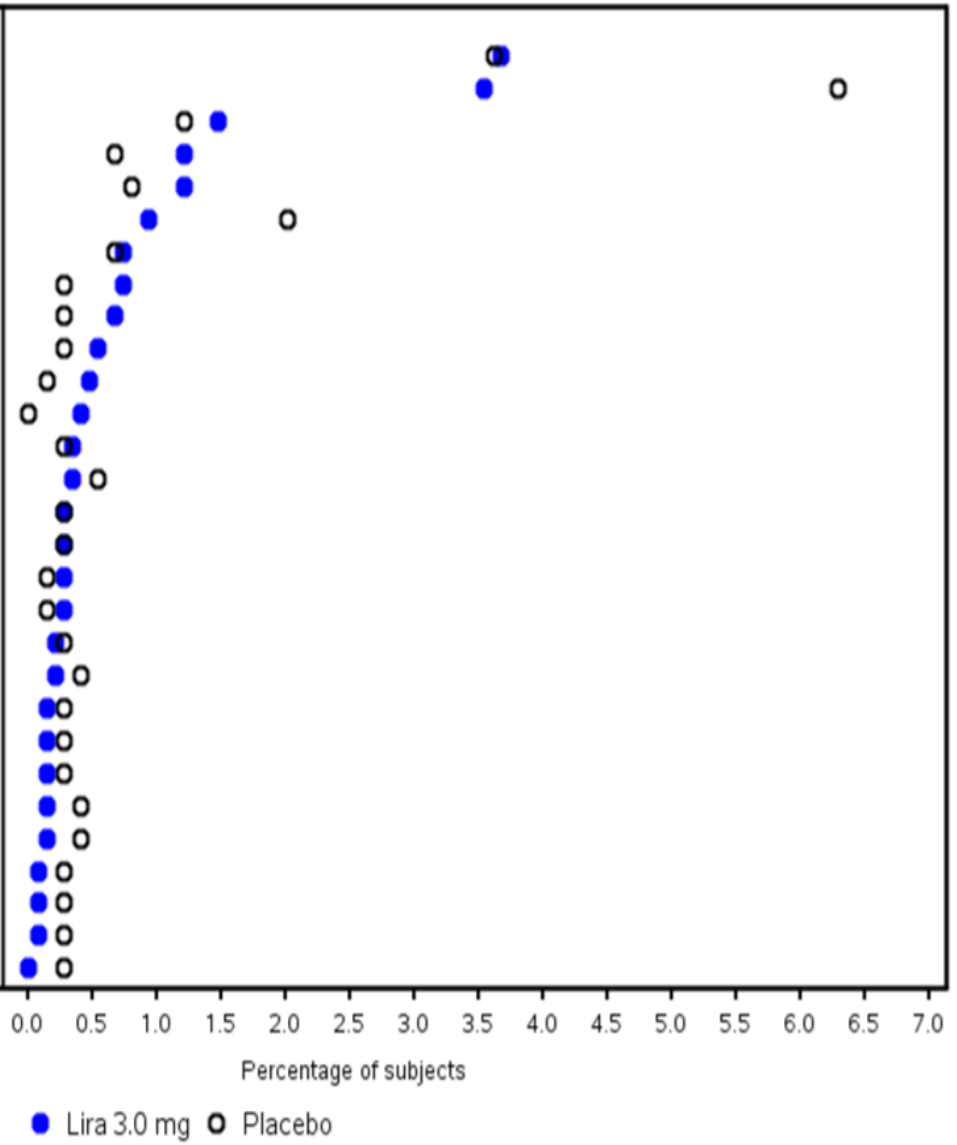
Key Trial Results: Index population (pre-diabetes and high risk of CVD) Trial 1839 (n=800)

Outcome	Liraglutide (n=530)	Placebo (n=270)	Estimated treatment difference, liraglutide vs. placebo (95% CI)†
Body weight-related outcomes, change from baseline to week 160 (LS Mean (SE))			
Body-mass index (%)	-5.97 (0.30)	-1.54 (0.41)	-4.43 [-5.43; -3.43]
Weight loss (%)	-5.92 (0.30)	-1.65 (0.41)	-4.28 [-5.28; -3.28]
Confirmed type 2 diabetes (n/N, %)	13/530 (2.4%)	22/270 (8.1%)	OR: 0.28 [0.14, 0.57]
Reversal of pre-diabetes*	360/530 (67.9%)	104/270 (38.5%)	-
Cardiovascular adverse events (week 162; n/N, %)	86/530 (16.2%)	46/270 (17.0%)	OR: 0.94 [0.64, 1.40]

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

CV events

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



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

NICE

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

Outcome	Liraglutide (n=530)	Placebo (n=270)	Estimated treatment difference, liraglutide vs. placebo (95% CI)†
Health-related quality of life – SF-36 General Health	2.67 (0.40)	1.05 (0.57)	1.61 [0.25; 2.97]
Discontinuations (n/N (%))			
Discontinued due to AE	62/530 (11.7%)	13/270 (4.8%)	OR: 2.62 [1.41, 4.85]
Other outcomes used in the economic model			
SBP (reduction in mmHg)	-4.09 (0.51)	-1.09 (0.71)	-3.01 [-4.72; -1.29]
Total cholesterol (reduction in mg/dl)	-7.38 (1.31)	-4.15 (1.86)	-3.23 [-7.70; 1.24]
HbA_{1c}	-0.39 (0.01)	-0.13 (0.02)	-0.25 [-0.30; -0.21]

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

Committee considerations at ACM1 (3)

- Treatment for obesity is likely to be recurrent or >2 years.
  - Company assumed all patients with initial weight loss stop treatment at 2 years.
  - 2-year stopping rule implementable in NHS but is not in line with the trial.

- Cardiovascular benefits are uncertain as they are based on surrogate outcomes.
  - No direct evidence of liraglutide on CV outcomes in Trial 1839. Small number of CV events, cohort mean age = 48.
  - Model estimates *indirect* effect through association between:
    - Liraglutide and multiple surrogates (BMI, HbA1c and blood pressure).
    - Surrogates and final CV outcomes (MI, stoke, ischemic heart disease (IHD) congestive heart failure (CHF), blindness, amputation, renal failure, diabetic ulcer)
  - Committee noted that benefits were only seen for 2 years and had stopped 3 years later. The choice of surrogates requires better justification.

Committee considerations at ACM1 (5)

- Risk equations used to establish CV benefits introduces uncertainty.
  - Surrogates (BMI, SBP, HDL) used as prognostic parameters in risk equations to predict CV outcomes.
  - Trial 1839 data used to establish relative effectiveness on surrogate outcomes.
  - Liraglutide assumed to have a temporary benefit on surrogate outcomes because of proposal to stop at 2 years.
  - Uncertainty as risk models are based on assumption of a 'steady state' and *were not* developed to calculate consequences following temporary changes in BMI, SBP, and HDL.
  - (The company's original) ICERS very dependent on CV benefits:
    - BMI benefits only: ICER>£100,000
    - BMI + diabetic status benefits: ICER < £50,000
    - BMI + diabetic status + **long term CV benefits**: ICER = £21,000
  - Require stronger evidence of long-term benefits for liraglutide.

Committee considerations at ACM1 (6)

- The assumptions after stopping liraglutide to predict weight gain and diabetes status are uncertain.
  - No trial follow up data after stopping treatment after 3 years.
  - Assumed gradual increase in weight to initial weight 3 years post stopping.
  - Assumed normoglycaemic returns to pre-diabetic after 3-years.

- The model assumes that all people who have a cardiovascular event develop type 2 diabetes.
  - Clinical experts: people more likely to be diagnosed with type 2 diabetes after a CV event, but relationship not causal.
  - Assumption may overestimate clinical and cost-effectiveness.

Cost-Effectiveness Results (at last meeting)

Technologies	Total costs	Total QALYs	ICER (£/QALY)
ERG base-case assuming prediabetic patients automatically develop T2DM with a CV event (probabilistic)			
Liraglutide	£21,505	15.290	
Diet & exercise	£20,449	15.198	£11,475
ERG base-case assuming prediabetic patients do not automatically develop T2DM with a CV event (probabilistic)			
Liraglutide	£21,395	15.356	
Diet & exercise	£19,913	15.305	£27,313

ACD preliminary recommendation

1.1 Liraglutide is not recommended, within its marketing authorisation, for use in adults with a BMI of 35 kg/m^2 or more with pre-diabetes and a high risk of cardiovascular disease.

ACD consultation responses

Clinical experts	• Abd Tahrani (University of Birmingham)
Professional organisations	• Glaxo Smith Kline (GSK) • Royal College of Physicians
Charity organisations	• Society for Endocrinology
Company	• Novo Nordisk
Public (web) comments	• NHS clinicians (n=3) • Patients (n=3) • Patient organisations (n=2) • Unknown affiliation (n=8)

Comments clinical expert (1)

- Comments from Abd Tahrani who attended the first committee meeting.
- The current recommendation is concerning as it deprives patients with obesity from access to an effective treatment.
- Disagree with decision to use the whole pre-diabetes population from the 1839 trial. The post-hoc subgroup is consistent with referral criteria for tier 3 services which use BMI>= 35 kg/m^2. In the SCALE trial 30% of total pre-diabetes population had BMI < 35 kg/m^2. Based on results of the SCALE trial would expect similar results in whole pre-diabetes population and population with pre-diabetes + high CVD risk.
- Agree that modelling of CVD benefits is based on surrogate markers. However, the development of T2D and high BP are well established risk factors for CVD. There is RCT evidence of CVD benefits for liraglutide (1.8mg) in T2D patients. Liraglutide (3mg) had benefits on multiple CVD risk factor in the SCALE trial. While there remains uncertainty, based on what we know the effect of liraglutide on surrogate outcomes should lead to reductions in CVD.

Comments clinical expert (2)

- Agree that obesity will require treatment for > 2 years. However continuing liraglutide 3.0mg beyond 2 years will be challenging as usual follow up in tier 3 services is 2 years.

- The company assumption that all weight lost with liraglutide will be regained over 3 years is pessimistic rather than optimistic and hence seems reasonable to be used in the model. Data from the UK CPRD showed that in people with 5% weight loss, 53% regained weight over 2 years and 78% over 5 years (i.e. not 100%).

- Agree there is no definitive data that all people who have CVD event develop T2D. A previous study from my team has shown that in patients with acute coronary syndrome, baseline HbA1c and fasting plasma glucose are independent risk factors for T2D within 3-months from discharge after adjusting for age and BMI. Hence patients with pre-diabetes who have higher baseline HbA1c by definition are particularly at risk of T2D shortly after acute coronary syndrome.

Comments from Royal College of Physicians

- **Conflicts of interest**: 3 members involved in company's clinical trials, 3 members received honoraria from company, 2 members on company's advisory board.

- Disagree that all the evidence has been taken into account:
  - SCALE study indicates 3mg liraglutide reduces risk of T2D.
  - RCTs showing GLP-1 agonists (inc. liraglutide) reduce CV events in T2D patients, and indicate CV benefits are independent of weight loss.

- Disagree with concern regarding assumption of T2D occurrence after all CV events. The LEADER trial data was not included and show clear benefit in this patient group.

- 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.

Comments from Society of Endocrinology

- Did not consider evidence: of diabetes prevention in high risk patients from SCALE study; RCTs showing GLP1 analogues including liraglutide reduce CVD events in high risk diabetes populations and CVD protection for GLP1 agonists independent of weight loss.
- Use stricter stopping rules e.g. 10% weight loss at 6 or 12 months might make sense. NICE did this for orlistat, sibutramine and rimonabant.
- The use of a post hoc sub group does not make much difference on the results. It should be possible to use the whole trial 1839 population at 2 years and 3 years and model dropouts.
- There must be better data than applying incorrect clinical assumption that all population develops T2D after a CV event. If an obese person develops T2D after a CV event they would clearly have benefit from liraglutide if prescribed at the lower dose of 1.8mg as indicated in the LEADER trial.
- All scenario analyses which result in ICERs above the threshold do not use credible clinical assumptions based on the evidence and are inappropriately used to justify the appraisal decision. E.g. including only effects on BMI results in an ICER of £105,000.
- The recommendations are not sound and 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.

Comments from Glaxo Smith Kline

- No disagreement. The uncertainties in the cost effectiveness assessment have been reasonably identified based on the available evidence.

Web comments – Diabetes UK

- Support use of liraglutide but only if coupled with education and ongoing support for those taking it. Includes injection technique and regular review (as per PH38).

- Offering liraglutide is desirable over private purchase to ensure people are taking it safely, with the support of qualified healthcare professionals who can offer care and support planning.

Web comments – Welsh Society of Obesity

- There is a significant gap and unmet need between lifestyle intervention and surgery that should be bridged and filled by pharmacotherapy.

- The financial implications favour the use of liraglutide 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 liraglutide 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.

Web comments – NHS professionals (n=3)

Respondent 1:

- Not sure uncertainties are as large as NICE thinks. Experience in tier 3 service indicates there are definitely some patients who would benefit with this much weight loss.
- Very disappointed that I will be unable to use liraglutide in this population.
- May discriminate against people with psychiatric illness, learning disabilities who might not be suitable for bariatric surgery. May inadvertently discriminate against women of child bearing age with fertility problems due to weight. Possible religious/ cultural reasons why bariatric surgery is not acceptable and pharmacotherapy is.

Respondent 2:

- We have 80 patients privately funded on liraglutide. It's a shame people from poorer backgrounds cannot access this medication. Many positive patient outcomes: employment, prevented marriage break up, 30% stopped insulin, 5 eligible for knee operations.
- Very disappointed that I will be unable to use liraglutide in this population.
- Possible discrimination for pregnancy and maternity, cannot prescribe in this population.

Respondent 3:

- Should consider specific BMI cut-off for patients of South-east Asian origin.

Web comments – Patients (n=3)

Respondent 1:

- It should also be prescribed short-term with regular reviews for evidence of target weight loss.

Respondent 2:

- 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.

Respondent 3:

- Evidence over many years in the USA shows a high level of improvement in all obesity associated areas of health for people 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.

Company Response – summary

- The post-hoc analysis preserves randomisation. The company present an updated scenario analysis for the whole prediabetes population.

- In the absence of evidence, surrogate outcomes are best approach to estimate CV risk. Company provide justification from several sources in the published literature.

- Suggest treatment duration of >2 years only applies to a small % of the population.

- Updated base case analysis with per cycle treatment discontinuation and include a scenario analysis with efficacy based stopping rules.

- Agree that assumption of automatic development of T2D after CV event is not likely to be true. The company have presented updated results with/without assumption and suggest ICER lies somewhere in between.

Company comments: Use of data from post-hoc subgroup preserves randomisation

Committee conclusion at CM1: The use of data from a post-hoc subgroup is associated with more uncertainty than the larger pre-defined prediabetes trial population.

- Acknowledge the post-hoc subgroup is associated with uncertainty.
- 800 in subgroup, and had similar efficacy results to the full trial population (company submission p53 and p69) .
- The selection of the post-hoc subgroup preserved the integrity of randomisation..

ERG response

- Agrees post-hoc subgroup is associated with increased uncertainty.
- Disagrees that selection preserved randomisation as subgroup was not defined at the trial design stage and therefore randomisation not balanced between treatment groups.
- The only way to ensure balance of known and unknown variables would be to include the subgroup criteria as a stratification factor in the randomisation.

Company comments: Analysis using efficacy data for the full prediabetes population

Committee conclusion at CM1: The larger pre-defined prediabetes trial population should be used as this is larger, pre-specified and associated with less uncertainty.

- Update includes modified ITT (mITT) analysis which uses efficacy inputs from full prediabetes population. Baseline characteristics of the original subgroup BMI≥35 kg/m2, prediabetes and high risk of CVD.
- This **reduces** the company base case deterministic ICER from £11,293 to £8,635 for the mITT scenario.
- Liraglutide is cost-effective in 99% of PSA iterations for the mITT scenario.

ERG response

- Unable to match company's efficacy inputs for mITT scenario (Table 4 ACD Appendix) to data in the original company submission.
- Think the mITT scenario is for the full prediabetes population (n=2254) but numbers are not consistent with those provided in the original submission.
- Unable to confirm if company's new analyses are based on the correct data.

Company's second response

- Data from Table 4 in ACD response was not provided in the original submission.
- Data used for the subgroup are summarised in Table 46 of the original submission.

Company comments: Uncertainty of using surrogate outcomes

Committee conclusion at CM1: Estimation of any reduction in CV events is uncertain because it relies on estimation of the relationship between surrogate and clinical event.

- Agrees relying on surrogates is uncertain. But common practice in health economic modelling (e.g. NICE CG181).
- Global consensus of CV benefits following weight loss in obesity, align with NICE guidelines PH25, NG136, NG136 and CG172.
- Trial 1839 not powered for CV events. But SCALE trial shows CV risk factor for liraglutide vs. placebo (Davies 2017).
- Link between liraglutide and CV benefits from populations with T2D in the cardiovascular outcomes and the LEADER trials. Other GLP-1 analogues reduce risk of CV events (Andrikou 2018; Zimmerman 2017)
- Prolonged benefits of glucose, blood pressure and lipid control in CVD and T2D well demonstrated (Paul 2015; Kostis 2010; ASCOT trial; DPPOS RCT).

ERG response

- No responses regarding general uncertainty of surrogate approach i.e. no comments disputing link between liraglutide and CV events.
- See comments on risk equations (next slide).

Company comments: Uncertainty of including risk equations

Committee conclusion at CM1: The model's health states and transitions were suitable for decision making, but risk equations estimating long term CV risk introduce uncertainty.

- The only way to estimate long term CV risk is using risk equations. We followed a rigorous approach in selecting risk equations.
- Risk equations were prioritised based on their applicability and relevance, as well as considering whether treatment-effect variables were indicated as predictors of risk within the analysis.

ERG response

- Company base case use risk equation to estimate CV events is dependent on T2D status.
- Review of prediabetes decision models indicate that use of different risk equations dependent on T2D status might introduce bias.
- ERG prefers the same risk equations for primary and secondary CV events for patients with and without T2D. ERG base case (scenario 1) applies Qrisk3 for primary and Framingham recurrent CHD for secondary CV outcomes.

Company comments: Maximum treatment duration of 2-years

Committee conclusion at CM1: The maximum treatment duration of 2-years would be implemented in the NHS. But note that this is not what was done in the clinical trial or reflect the need to reduce then maintain weight.

- Acknowledge the trial didn't include maximum treatment duration but believe the trial reflects clinical practice.
- Clinical experts contributing to this appraisal validate maximum treatment duration of 2-years in tier 3 services. This can be as little as 6-months and more normally 12-months.
- The maximum treatment duration only affects a small number of patients, e.g. a US-population based study by Ganguly (2018) found 42% on treatment at 6-months, 26.6% at 15-months.

ERG response

- Extrapolating results from Ganguly (2018), assuming equal discontinuation probability over time (exponential distribution), would indicate that **12%** of patients would still continue treatment by 24 months.
- 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".

Company comments: Discontinuation following licence stopping rule

Committee conclusion at CM1: Clinical experts suggest that a number of additional efficacy based stopping rules might be applied by clinicians.

- Some participants in Trial 1839 discontinue treatment between the EMA licence stopping rule (>=5% weight loss at 12-weeks) and 2-years.
- Per cycle treatment discontinuation was incorporated into the base case between 12-weeks and 2-years.
- Treatment discontinuation in the new submission were based on Kaplan Meier (KM) curves using observed Trial 1839 data.
- New approach better reflects what was observed within the clinical trial and what happens in clinical practice.
- Company also present a scenario analysis which applies a 10% weight loss stopping rule at 52-weeks in addition to 5% stopping rule at 12-weeks and per cycle discontinuation incorporated into the base case. The addition of a 10% stopping rule **reduces** the ICER.

ERG response

- All new analyses are based on discontinuation using the KM curve.
- This is a change to the original ERG base case, but seems reasonable.
- However, preferably instead of using the KM curves, we would have adopted parametric survival models as recommended in NICE DSU 14.
- Parametric survival models were not an option implemented in the company's model.

Company comments: Development of T2D after CV event

Committee conclusion at CM1: Heard no good evidence to determine the proportion of people who would develop type 2 diabetes within a year after a CV event.

- Agree. However, in the absence of evidence an assumption is required. We assumed that following a CV event (all) patients would develop T2D diabetes within 12 months.
- The alternative approach would be to assume prediabetes status reverses to normal glucose tolerance, and incurs the same risk as those who have not had prediabetes.
- The impact of our assumptions is that after a CV event patients have an elevated risk of subsequent events. This elevated risk is plausible and supported by the literature/ clinical experts.
- Independent validation of the model does not suggest CV events are over stated. The company submission may underestimate total CV events: In QRisk3 equation, CV outcomes are not affected by BMI changes above 40 kg/m^2 and the risk of T2D does not increase beyond values of $40kg/m^2$.
- The true ICER lies somewhere between the revised company base case and the ICER for a scenario analysis which assumes prediabetes populations do not automatically develop T2D after a CV event (ERG scenarios 2 and 6).

ERG response

- Clinical experts explained to the committee that “people are more likely to be diagnosed with T2D after a CV event, but this relationship is not causal.”
- In the company’s base-case T2DM occurs when prediabetic or normal glucose 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.

Company's updated base case

- Summary of assumptions in company's updated base case:
  - The price of liraglutide has been newly agreed.
  - Maximum treatment duration of 2 years applied.
  - Liraglutide non responders have the same efficacy as placebo.
  - Per cycle discontinuation included after 12-weeks using KM curves.
  - UKPD 82 risk equations are used to estimate CV events in people with T2D.

Treatment	Total Costs	Total QALYs	ICER
Company revised base-case (probabilistic)			
Liraglutide 3.0mg	£20,914	15.28	£11,419
Diet + Exercise	£20,224	15.22	

- PSA results: Liraglutide cost-effective **>98%** at £20,000 threshold.

Company's updated scenario analyses

Scenario		ICER (Deterministic)
Company base case	1 year treatment duration*	£7,612
	2 year treatment duration*	£11,293
	3 year treatment duration*	£13,374
Company base case + no T2DM after CV event	1 year treatment duration*	£8,375
	2 year treatment duration*	£12,263
	3 year treatment duration*	£14,495
Company base case + Liraglutide non-responder efficacy have diet & exercise non-responder effectiveness	1 year treatment duration*	£9,415
	2 year treatment duration*	£13,992
	3 year treatment duration*	£16,873

*Cost *and* effectiveness parameters modified for treatment duration scenarios. No modification is applied to the treatment effect waning period (i.e. length of time to return to baseline weight).

Company's updated scenario analyses

- Scenario analysis using efficacy data from the mITT population (i.e. the whole pre-diabetes population reduces ICER when compared to base case which uses the population from the post-hoc analysis subgroup:
- Base case (deterministic):

Treatment	Total Cost	Total QALY	ICER
Liraglutide 3.0mg	£20,494	15.27	£11,293
Diet and exercise	£19,780	15.21	

- Scenario analysis (deterministic):

Treatment	Total Cost	Total QALY	ICER
Liraglutide 3.0mg	£20,710	15.26	£8,635
Diet and exercise	£19,992	15.18	

Company's updated scenario analyses

- Scenario analysis applies a 10% weight loss stopping rule at 52 weeks in addition to 5% stopping rule at 12-weeks and per cycle discontinuation.
- Base case (deterministic):

Treatment	Total Cost	Total QALY	ICER
Liraglutide 3.0mg	£20,494	15.27	£11,293
Diet and exercise	£19,780	15.21	

- Scenario analysis (deterministic):

Treatment	Total Cost	Total QALY	ICER
Liraglutide 3.0mg	£20,480	15.27	£10,042
Diet and exercise	£19,780	15.21	

ERG's updated results

ERG's updated base case (scenario 1):

- Applies revised liraglutide PAS price and updates results with the revised economic model.
- Differences with company's revised base case:
  - Risk equations to estimate CV events for patients with T2D.
    - For primary prevention in T2D = QRisk3 risk model not UKPDS
    - For secondary prevention in T2D= Framingham Recurring CHD not UKPDS 82.

- ERG base case (deterministic) **ICER = £13,569**

ERG's scenario analyses 2-5

- **ERG scenario 2:**
  - Identical to the ERG base case (scenario 1) but applies assumption where T2D does not automatically develop within 12-months of CV event. **ICER = £14,536**
- **ERG scenario 3:**
  - Identical to the ERG base case (scenario 1) but applies an alternative liraglutide non-responder efficacy for diet and exercise non-responders. **ICER = £17,044**
- **ERG scenario 4:**
  - Identical to the ERG base case (scenario 1) but does not apply a maximum treatment duration and applies assumption regarding discontinuation following licence stopping rule estimated using an extrapolated log normal distribution. **ICER = £19,796**
- **ERG scenario 5:**
  - Identical to the ERG base case (scenario 1) but includes disutility and costs for adverse events. **ICER = £13,870**

ERG's scenario 6-7

- **ERG scenario 6:**
  - Combines all assumptions for scenarios 2, 3 & 5. **ICER = £18,693**
- **ERG scenario 7:**
  - Provides the results of a combination of all scenarios conditional on assuming that prediabetic patients do not automatically develop T2DM with a CV event (ERG scenarios 1, 3 & 5). **ICER = £17,446**

Key issues

- Have the assumptions about the long-term cardiovascular (CV) outcome benefits been sufficiently justified?

- Is the 2-year stopping rule for treatment acceptable?

- Is the assumption that all people develop type 2 diabetes (T2D) in the 12-months following a CV event appropriate? Does the scenario analysis provided by the company reduce the uncertainty?

- Is the updated evidence with the full pre-defined pre-diabetes (Modified ITT analyses) trial 1839 population reliable?