Evidence review: liraglutide for the treatment of type 2 diabetes

Produced by: Aberdeen Health Technology Assessment Group

Authors:

Ewen Cummins, health economist, McMaster Development Consultants

Pamela Royle, research fellow, University of Aberdeen

Deepson Shyangdan, research assistant, University of Aberdeen

Norman Waugh, professor of public health, University of Aberdeen

Correspondence to;

Professor Norman Waugh

Medical School Buildings

Foresterhill

Aberdeen AB25 2ZD n.r.waugh@abdn.ac.uk 01224 555998

Funding: This review was commissioned by the NIHR HTA Programme as project number 08/230.

[redacted]

Competing interests.

Norman Waugh is a member of the Scottish Study Group for the Care of Diabetes in the Young, whose educational meetings are part-sponsored by Novo Nordisk.

Acknowledgements

This review draws on the Cochrane review of the GLP-1 agonists, and we thank our co-authors Christine Clar and Pawana Sharma, systematic reviewers. We also thank Shona Fielding, Medical Statistics, University of Aberdeen, for commenting on the mixed treatment comparison, and William Valentine of Ossian Consulting for advice on the CORE model.

This report should be referenced as follows;

Cummins C, Royle P, Shyangdan D, Waugh N. Liraglutide for the treatment of type 2 diabetes: a single technology appraisal. Aberdeen HTA Group, 2009.

Rider of responsibility:

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Contribution of authors.

Ewen Cummins reviewed the cost-effectiveness evidence, carried out further sensitivity analyses, and drafted Section 4.

Pamela Royle carried out literature searches.

Pamela Royle and Deepson Shyangdan reviewed the clinical effectiveness material and checked figures and helped draft Section 3 and Appendices 1-3.

Norman Waugh drafted sections 1, 2, 3 and 5

All authors edited the draft report.

TABLE OF CONTENTS

Lists of Tables and Figures

Tables

Figures

Abbreviations

ACEi	Angiotensin Converting Enzyme Inhibitors
BMI	Body Mass Index
BNF	British National Formulary
CVD	Cardiovascular Disease
CORE	Center for Outcomes Research
CTR	Clinical Trials Report
CEAC	Cost Effectiveness Acceptability Curve
DCCT	Diabetes Control and Complications Trial
DPP-4	Dipeptidyl peptidase-4
EAGLE	Economic Assessment of Glycemic Control and Long-Term Effects
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence Review Group
FPG	Fasting plasma glucose
FDA	Food and Drug Administration
GI	Gastrointestinal
GLP	Glucagon Like Peptide
GPR	Gross Proteinuria
HSCI	Health Service Cost Index
HDL	High-Density Lipoprotein-cholesterol
HCHS	Hospital and Community Health Services
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intention to Treat
IU	International Unit
LYG	Life Year Gained
LEAD	Liraglutide Effect and Action on Diabetes
LAR	Long-Acting Release
LDL	Low-Density Lipoprotein-cholesterol
MHRA	Medicines and Healthcare products Regulatory Agency
MAU	Microalbuminuria
MI	Myocardial Infarction
OGLA	Oral Glucose Lowering Agent
OHA	Oral Hypoglycaemic Agent

PCI	Pay Cost Index
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Assessed Life Year
SMBG	Self Monitoring Blood Glucose
SA	Sensitivity Analysis
SD	Standard Deviation
SE	Standard Error
SBP	Systolic Blood Pressure
TG	Triglycerides
Trig	Triglycerides
T2DM	Type 2 Diabetes Mellitus
UKPDS	United Kingdom Prospective Diabetes Study

1. SUMMARY

Introduction

Glucagon-like peptide analogues are a new class of drugs that mimic the hormone glucagon-like peptide (GLP-1). GLP-1 is an incretin, a gastrointestinal hormone that is released into the circulation after meals. GLP-1 regulates glucose levels by stimulating insulin production and secretion, and by suppressing glucagon secretion, gastric emptying and appetite.

Circulating GLP-1 undergoes destruction by an enzyme, dipeptidyl peptidase IV (DPP-IV), resulting in a half-life of 1 to 2 minutes. The natural form is therefore not suitable as a treatment.

Some current glucose lowering treatments cause low blood glucose (hypoglycaemia) because they act no matter what level the blood glucose is. In contrast, the action of the GLP-1 analogues is glucose dependent, that is, the higher the plasma glucose level, the greater the effect of GLP-1 on insulin secretion with the greatest effect in hyperglycaemic conditions, and little or no effect when the blood glucose concentration is less than 3.6 mmol/l. Hence they do not themselves cause hypoglycaemia.

There are at present two GLP-1 analogues licensed for use in the UK, exenatide and liraglutide. There are also two DPP-IV inhibitors, sitagliptin and vildagliptin, also known as the gliptins.

1.1 Scope of the submission.

The industry submission from Novo Nordisk addressed the use of liraglutide as a second and third drug treatment in people with type 2 diabetes whose glycaemic control was not satisfactory on treatment with metformin with or without a second oral agent.

1.2 Evidence on clinical effectiveness.

The submitted evidence of clinical effectiveness came mainly from the series of studies known as the Liraglutide Effect and Action on Diabetes (LEAD) programme. The most relevant amongst these were the studies in which liraglutide was used as part of triple therapy, and compared with an active comparator. These were LEAD-5, which compared liraglutide with the long-acting insulin, glargine, and LEAD-6 which compared liraglutide with another GLP-1 agonist, exenatide.

In three trials liraglutide was used as second drug in dual combination therapy. LEAD-1 compared it with rosiglitazone, both in combination with sulphonylurea. LEAD-2 compared it with glimepiride, both in combination with metformin. An unpublished trial NN2211-1860 compared liraglutide with a DPP-4 inhibitor, sitagliptin.

All these trials were sponsored by Novo Nordisk, and company staff were involved in study design, data collection, data review and analysis. However, we judged all the trials to be of good quality, and the analysis to be fair and unbiased.

The primary outcome was glycated haemoglobin, the standard measure of control of blood glucose. Other outcomes included weight gain or loss, blood pressure, fasting plasma glucose, lipids and adverse effects.

Triple therapy studies.

LEAD-5 reported that,

- liraglutide 1.8 mg daily reduced HbA1c by 0.24% more than glargine 24 units/day.
- weight was reduced on liraglutide but increased on glargine, giving a weight difference of 3.4 kg at end of study in favour of liraglutide
- end of study systolic blood pressure (SBP) difference was 4.5 mmHg in favour of liraglutide.

With an end of study daily dose of only 24 units, it may be that glargine was not used to best effect. Though had the dose been increased, and HbA1c lowered, it is likely that weight gain would have been greater, and the SBP difference also larger.

In LEAD-6,

- liraglutide 1.8 mg daily reduced HbA1c by 0.33% more than exenatide
- Systolic BP and weight showed no significant differences.
- There was less nausea with liraglutide once daily than with exenatide twice daily.

Dual therapy studies

In LEAD-1,

- HbA1c was reduced by 1.08% in the liraglutide 1.2 mg arm and by 1.19% in the liraglutide 1.8 mg arm, and in the rosiglitazone 4 mg arm by 0.44%. It rose by 0.23% in the placebo arm.
- Weight was reduced by 0.2 kg and 0.1 kg in the liraglutide 1.8 mg and placebo arms respectively. In the liraglutide 1.2 mg and rosiglitazone arms, it increased by 0.3 kg and 2.1 kg respectively.
- Systolic BP decreased in the range of 2.6 to 2.8 mmHg in the liraglutide 1.2 and 1.8 mg arms while the reduction in the placebo and rosiglitazone arms was between 0.9 to 2.3 mmHg.

So compared to rosiglitazone 4 mg, there was a significant difference in HbA1c but no difference in weight and SBP. However note that this was with rosiglitazone 4 mg daily. Rosiglitazone is often used in a dose of 8 mg daily.

In LEAD-2,

- HbA1c was reduced by 1% in the liraglutide 1.2 and 1.8 mg arms, and in the glimepride group. It rose by 0.1% in the placebo group
- Weight was reduced by 2.6 and 2.8 kg in the liraglutide 1.2 and 1.8 mg groups, and by 1.5 kg in the placebo group, giving placebo-adjusted losses with liraglutide of 1.1 and 1.3 kg. Weight rose by 1 kg with glimepiride.
- Systolic BP fell by 2.8 mmHg in the 1.2 mg liraglutide arm, by 2.3 mmHg in the 1.8 mg arm, and by 1.8 mmHg in the placebo arm. It rose by 0.4 mmHg in the sulphonylurea arm. Hence the placebo-adjusted SBP reductions with liraglutide were 1 and 0.5 mmHg.

So compared to glimepiride, there was no difference in HbA1c but liraglutide provided a weight advantage of 3.7 kg, and SBP difference of 3.2 mmHg.

In the unpublished trial, compared to sitagliptin,

- [redacted]
- [redacted]
- [redacted].

In summary, liraglutide is a clinically effective drug which improves glycaemic control, but also provides benefits in weight and blood pressure.

1.3 Evidence on cost-effectiveness.

The industry submission used the CORE economic model of diabetes, a highly-developed and well-respected model. The CORE model is not standard software as defined by NICE, but the manufacturer confirmed with NICE that its use would be acceptable.

The manufacturer presented three main sets of analyses, based upon the three main clinical trials noted above:

- LEAD-5 comparing liraglutide 1.8 mg with glargine
- LEAD-6 comparing liraglutide 1.8 mg with exenatide
- 1860 comparing liraglutide 1.2 mg and 1.8 mg with sitagliptin

Initial treatments were assumed to be for 5 years in the base case, with patients then switching to glargine.

The ERG has checked parameter values in the submission against published literature, and also checked the values against those within the CORE model. Only some minor discrepancies of no significance were found.

The ERG re-ran the base cases within CORE. Results matched those reported by the manufacturer within the submission.

For the base cases the manufacturer estimated a cost effectiveness of:

- £15,130 per QALY for liraglutide 1.8 mg compared to glargine
- £10,054 per QALY for liraglutide 1.8 mg compared to exenatide
- £10,465 per QALY for liraglutide 1.8 mg compared to sitagliptin
- £9,851 per QALY for liraglutide 1.2 mg compared to sitagliptin

Additional sub-group analyses undertaken by the manufacturer suggested that for patients of a higher BMI liraglutide was typically more cost effective. The estimates of cost effectiveness for those of a lower BMI were not presented.

Univariate sensitivity analyses undertaken by the manufacturer suggested that these estimates were most sensitive to:

- the assumed duration of initial therapy
- the application of weight changes and disutility associated with this
- the time horizon of the analysis

Additional sensitivity analyses undertaken by the ERG suggested that the main sources of the estimated patient benefits were:

- the direct utility effects of BMI changes and SBP, with some additional contribution from HbA1c, for the comparison with glargine
- HbA1c, with some additional effects from cholesterol and triglycerides, for the comparison with exenatide
- HbA1c and direct utility effects of BMI changes for the comparison with sitagliptin

Overall, the ERG regards the industry analysis as a fair representation of the cost-effectiveness.

1.4 Robustness of submitted evidence.

1.4.1 Strengths and weaknesses of evidence.

Novo Nordisk has carried out a large number of trials, but in the submission has focused on the LEAD studies. The quality of trials appears good. These are reasonably large studies carried out in a large number of centres in many countries, increasing the generalisability of the results. However few patients came from the UK, and the ethnic mix of some trials reflects the US centres.

Some of the trials included in the submission were not relevant to UK practice as recommended in the NICE Guideline CG87, where the GLP-1 analogue (at that time, only exenatide) was recommended only for third line use (i.e. being added to two oral agents) despite being licensed also for second-line use. Liraglutide has also been approved by EMEA for second-line use (in combination with one oral agent). The recommendations of CG87 are reported in the industry submission.

In LEAD-4, the comparator drug was rosiglitazone. It could be argued that pioglitazone would have been a better choice, since it has a more favourable risk profile than rosiglitazone. Both cause heart failure and fractures, but rosiglitazone appears to slightly increase cardiovascular mortality whereas pioglitazone reduces it. In a recent UK study, rosiglitazone was associated with a 34% to 41% higher risk of all cause mortality compared to pioglitazone. Some regulatory bodies have now placed warnings on rosiglitazone use.

Because the trials were short-term, it was necessary to model costs and outcomes far beyond the duration of the trials. The duration of the direct benefits from initial treatments may have been too long, and the direct disutility associated with these changes may also have been too large.

In line with the NICE policy of only considering licensed products, we compared liraglutide with existing comparators, using a 40 year duration. In reality, daily liraglutide will soon be displaced by other GLP-1 agonists which are given weekly or fortnightly.

1.4.2 Areas of uncertainty

Most of the trials were of short duration, whereas type 2 diabetes is a long-term condition. Given the progressive nature of the disease, and the fact that the GLP-1 agonists depend on functioning beta cells, we do not know how long their effect would last. The industry modelling used a baseline duration of five years, which is reasonable pending longer term results. It is possible that the GLP-1 agonists may prolong beta-cell function, but that is not proven in humans at present.

1.5 Key issues

There is a good evidence base for the clinical effectiveness of liraglutide. It helps improve diabetes control, and has the additional benefits of some weight loss in most users.

Liraglutide appears safe but that can only be confirmed once there are long term data.

There are some uncertainties about the cost-effectiveness because of the need for long-term modelling based on data from short-term trials. An important issue is that some current comparisons, for example between the two available GLP-1 analogues, daily liraglutide and twice daily exenatide, will be rendered obsolete shortly, with the arrival of longer-acting GLP-1 analogues given once a week or perhaps once every two weeks.

2. BACKGROUND

2.1 Manufacturer's description of underlying health problem.

Section 4.1 of the industry submission gives a brief but accurate description of type 2 diabetes, and of the current treatments and the order in which they are usually used. It also correctly notes that existing treatments are not entirely satisfactory because of the adverse effects, notably hypoglycaemia and weight gain, and because none affects the underlying disease progression.

One form of treatment not mentioned is intensive lifestyle intervention as an alternative to commencing insulin in people poorly controlled on combination oral therapy, but the evidence base for this is currently sparse, consisting of one small trial by Aas and colleagues.[1] That trial randomised people failing on oral agents to either start insulin, or to have an intensive lifestyle intervention (diet and exercise). The lifestyle group did better. However until these results need to be replicated in a much bigger trial with longer follow-up.

2.2 Manufacturer's overview of current service provision

The Novo Nordisk submission summarises the recommendations of NICE Clinical Guideline 87 and hence correctly sets the context for the use of liraglutide as third line drug. However it also advocates, in line with the licensed indications, that liraglutide could also be used as the second-line drug in addition to metformin or a sulphonylurea, which is not in line with the NICE guideline recommendations. However it identifies particular situations where this might be considered (section 4.4) including cases where further weight gain would be particularly undesirable, or where weight loss would be particularly desirable, for example in people with obstructive sleep apnoea.
One situation where the submission envisages use, is when self-monitoring of blood glucose (SMBG) is difficult or not possible, but since the value of SMBG in people with type 2 diabetes, not on insulin, is unproven, this is not convincing as an indication for using liraglutide second-line.

The submission notes that many patients fail to reach the NICE target for HbA1c of 6.5%, but does not discuss the recent debate on whether that target is the correct one. Much debate has followed the early termination of the ACCORD study, after the intensive glycaemic control group (target HbA1c <6.0%) was found to have an increased risk of death compared with the group aiming at HbA1c of 7 to 7.9%.[2]

In LEAD-5, liraglutide 1.8 mg was compared with glargine. The NICE clinical guideline CG 87[3] recommended NPH as the first choice basal insulin in type 2 diabetes, because the marginal benefits are small and the marginal cost considerable. [4] So it could be argued that glargine was the wrong comparator. One might also wonder why Novo Nordisk used glargine as the comparator rather than their own basal analogue insulin, detemir. However, the report, Prescribing for Diabetes in England[5] shows that glargine is now by far the most commonly used long-acting insulin, with NPH in steady decline. There are about three times as many prescriptions for glargine as for NPH, which has also recently been overtaken by detemir. So it could be argued that on pragmatic grounds, using glargine as the comparator was simply recognising prescribing reality.

One problem in type 2 diabetes is addressed only briefly in the industry submission (page 10). This is that type 2 diabetes is usually a progressive disease, requiring intensification of treatment over time. So patients will start on diet and lifestyle measures alone, but over time will require additional treatment with drugs, usually with metformin monotherapy, followed by the addition of a sulphonylurea, and in due course a third drug, which may be another oral agent , or insulin. The flow diagram below (Figure 1) from the NICE clinical guideline on the management of type 2 diabetes illustrates this.[3]

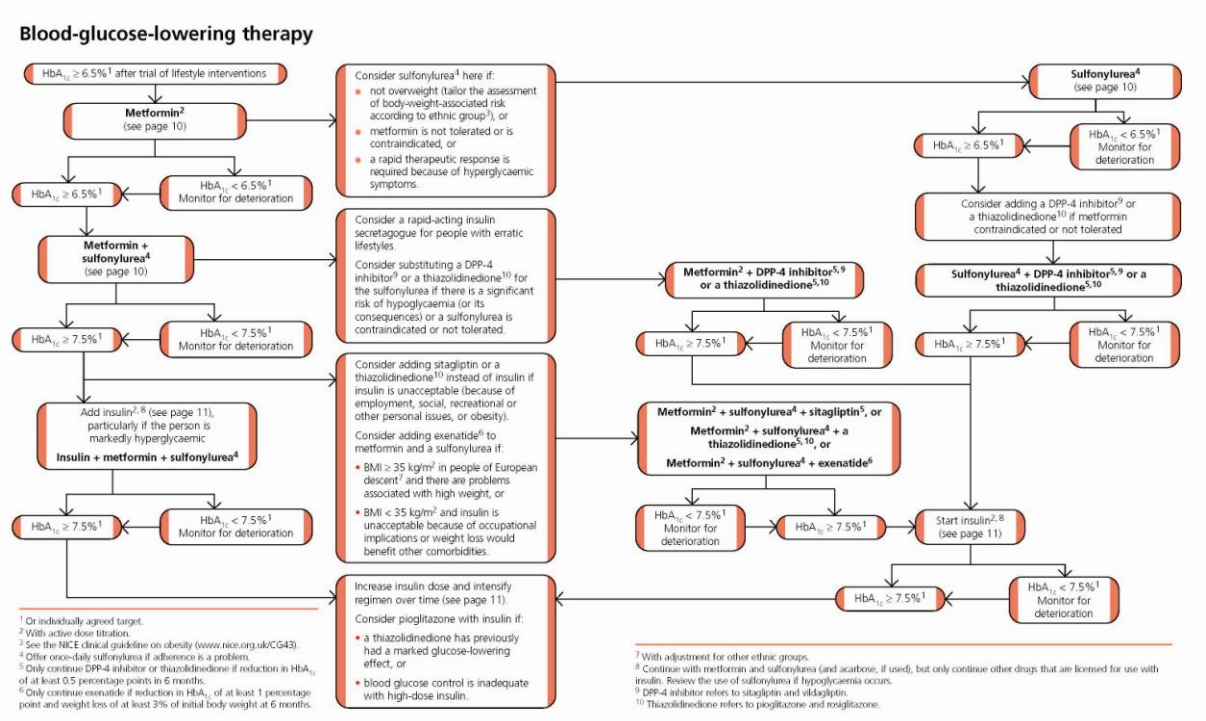


Figure 1 Care pathway for diabetes drugs

The need to intensify treatment arises because the functioning of the insulin-producing beta cells in the pancreas declines over time. This was shown in the UK Prospective Diabetes Study (UKPDS 16)[6] and was seen irrespective of treatment group (metformin, sulphonylurea or insulin). More recently, it has been asserted that the time to failure of monotherapy may be longer with metformin and rosiglitazone than with the sulphonylurea, glibenclamide (ADOPT study[7]) though at the cost of greater weight gain (rosiglitazone vs metformin 6.9 kg greater at four years; rosiglitazone vs glibenclamide 2.5 kg greater).

Current practice in the UK when patients are not achieving good control on combination oral drugs, is to start insulin. However another problem, not covered in the submission, is that many people with type 2 diabetes remain poorly controlled on combinations of oral agents for quite long periods before starting insulin. Two studies from the UK have used general practice databases to examine glycaemic control and treatment.

Calvert and colleagues used data from the DIN-LINK database of anonymised data from 154 general practices, from the years 1995 to 2005, on patients with type 2 diabetes, including the treatment they were on and their HbA1c levels.[8] They were particularly interested in how long patients remained poorly controlled on oral agents before starting insulin. They identified all patients with type 2 who were prescribed two or more types of oral agent, and looked at their HbA1c levels before and after the addition of another drug. The median time from addition of the last oral agent to the start of insulin therapy, for patients on two or more oral agents, was seven years. In those with poor glycaemic control following addition of the last oral drug, only 27% were prescribed insulin during the study. The implication is that many patients were left poorly controlled rather than being switched to insulin.

Rubino and colleagues used another British GP database, The Health Improvement Network (THIN) database, to identify patients with type 2 diabetes who were poorly controlled (at two levels, >8% and >9%) on oral agents, and who had not been treated with insulin. They then followed them to see how long it was before insulin was started.[9]

Using the cut-off for poor control of HbA1c of 8% or over, they found 2501 eligible patients, mostly aged 50-79 years, and with duration of diabetes usually at least five years. Most had been on oral glucose lowering agents (OGLAs) for over five years. About 25% of these patients started insulin by two years, and 50% by 5 years. So transition was slow, and many were not transferred to insulin at all.

When OGLA failure was defined as HbA1c of 9% or over, they found 1691 patients who qualified. By 4.2 years, 50% had started insulin.

Why is there reluctance to use insulin?

In a previous technology assessment report for NICE, on inhaled insulins, we pondered upon why there should be reluctance.[10] There seemed to be reluctance amongst both patients and physicians.

The DAWN (Diabetes Attitude Wishes and Need) study found that 55% of patients who have never had insulin treatment are anxious about it being required.[11] The authors, Peyrot and colleagues, reviewed previous studies of patient attitudes to insulin therapy. They noted that these involve beliefs that;[11]

"taking insulin:

- *Leads to poor outcomes including hypoglycaemia, weight gain and complications*
- *Means that the patient's diabetes is worse and that the patient has failed*
- *Means life will be more restricted and people will treat the patient differently*
- *Will not make diabetes easier to manage."*

It is important to note that insulin treatment is not just about injections, but a whole package of care including dietary adjustments, home blood glucose testing, and self-adjustment of insulin doses. It is likely that for most people, insulin injections are less troublesome than blood testing.

Changing to insulin does not mean that control will improve. Unpublished data from the Lothian audit show that the average HbA1c in type 2 diabetes mellitus patients on insulin is about 8.5%. (J McKnight, personal communication, presented at RCPE conference, September 2005). The average for those with type 2 diabetes mellitus on OGLAs is 7.5%.

The study by Calvert and colleagues noted that control improved after insulin was started, but that many patients did not achieve targets.[8]

Similarly, a study from seven European countries found that only 9.5% of patients with T2DM who were on insulin, had HbA1c <6.5%; another 44% had HbA1c levels of 6.5% to 7.5%; and 47% had levels over 7.6%.[12]

Hayward and colleagues noted that results from trials of insulin therapy in type 2 showed it to be efficacious, but thought that these results might not be replicated in routine care.[13] In a very large study (8668 patients with type 2 diabetes) they found that "*insulin therapy was rarely effective in achieving tight glycemic control".* Two years after starting insulin therapy, 60% still had HbA1c

levels of 8% of greater; 25% had levels between 8.0 and 8.9%; 20% between 9.0 and 9.9%; and 15% had levels over 10%. These are similar to the population-based audit from Lothian.

That starting insulin in routine care usually fails to give good control in people with T2 DM failing on oral agents, is presumably one reason why the physicians in the DAWN study showed considerable resistance to starting insulin therapy in T2DM – only about half of the physicians thought that insulin would be useful. [11]

Yki-Jarvinen and colleagues came to similar conclusions in people with T2DM who were obese (defined in this study as BMI over 28.1 kg/m^2) – insulin did not improve control. In many of these patients, poor control is associated with overweight or obesity.[14]

To some extent, the poor results with insulin may reflect poor compliance. Donnelly and colleagues from Tayside found that some people with type 2 diabetes treated with insulin did not take all the insulin they were prescribed, and that poor compliance was associated with poor control.[15]

To summarise these aspects of the background;

- Type 2 diabetes is a progressive disease requiring intensification of treatment over time
- The UK experience is that many patients are left poorly controlled for years on combinations of oral agents, before insulin is started, presumably because of the perceived disadvantages of insulin treatment
- Many patients do not achieve good control even after insulin is started, partly because of weight gain.

Hence there is a need for better treatments for type 2 diabetes.

Liraglutide is the second of the glucagon-like peptide analogues to be considered by NICE. The first was exenatide, which was considered in the updated clinical guideline on management of type 2 diabetes.

Other GLP-1 agonists are coming, most of which are given weekly or perhaps fortnightly. They include exenatide LAR, albiglutide and taspoglutide.

2.3 Manufacturer's definition of decision problem

The Novo Nordisk definition of the decision problem is similar to the scope as decided by NICE. It is worth noting that the NICE scope differs from the NICE clinical guidelines, by including the use of the GLP-1 agonist as second drug after metformin or a sulphonylurea. This is in line with the licensed indications for liraglutide. The NICE guideline makes no recommendation on use of GLP-1 agonists as second drugs.

In brief,

- The population is people with type 2 diabetes
- The intervention is liraglutide, either 1.2 mg or 1.8 mg daily
- The main comparators are glargine and exenatide as third drugs, and sitagliptin, rosiglitazone and glimepiride as second drugs. This is similar to the NICE scope, but that also included metformin. However metformin is the usual first line drug in type 2 diabetes, and so is not actually a correct comparator.
- The outcomes are glycaemic control as reflected in HbA1c, weight change, blood pressure, fasting plasma glucose and lipids. The NICE scope included complications of diabetes but those could only be detected in trials longer term that is feasible in this situation. The manufacturer therefore adopts the usual practice of using the short-term outcomes in a modelling exercise to estimate long-term complications.
- The economic analysis adheres closely to the NICE reference case (see comparison in our economic section) but omits personal social services (PSS) costs, on reasonable grounds
- Subgroup analysis includes two groups specified in the final scope, weight and baseline HbA1c, but not the third, cardiovascular risk, in which data are lacking.

2.4 The costs of diabetes drugs

Figure 2 below shows some costs of commonly used diabetes drugs, based, except for Liraglutide, on costs in the BNF 58, September 2009.[16] Note that these are for illustration and equipotency is not implied.

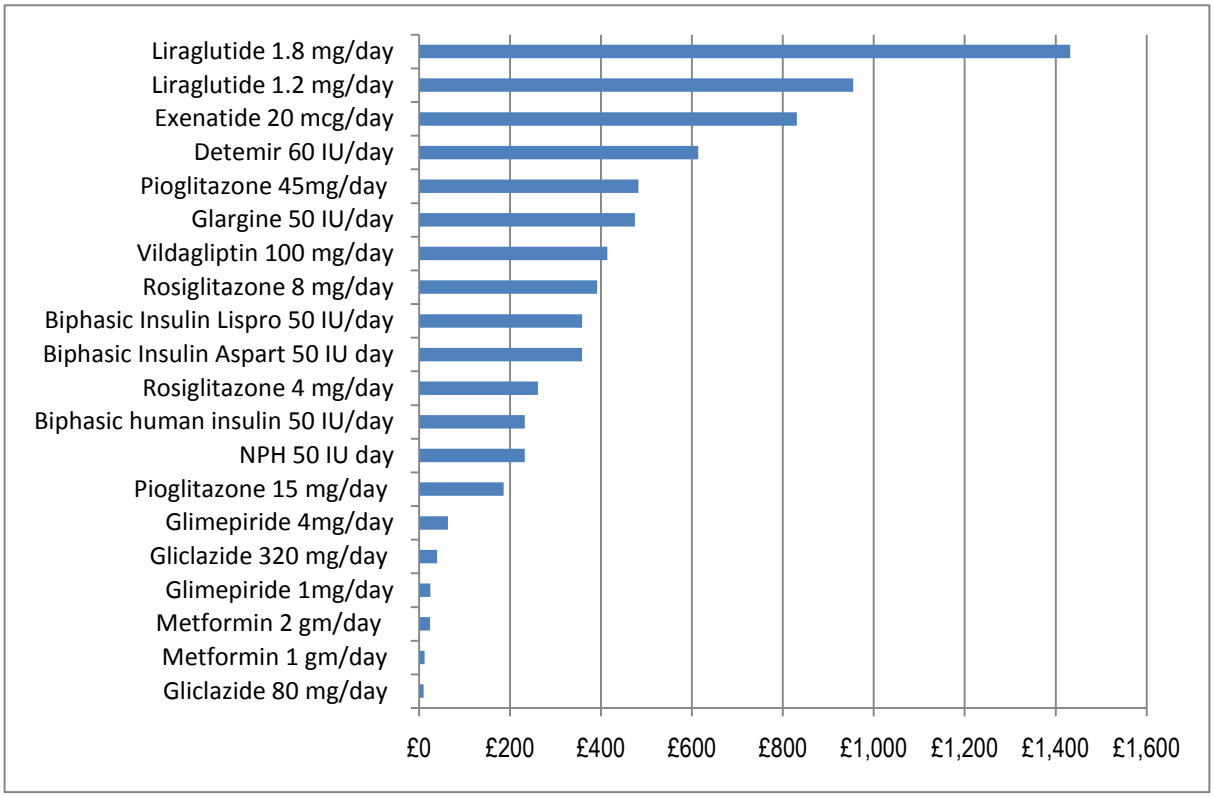


Figure 2 Comparative costs of one year of therapy (based on BNF 58 September 2009 except for liraglutide)

3. EVIDENCE ON CLINICAL EFFECTIVENESS

The manufacturer's submission listed a large number of trials, but most were not relevant to the decision problem, and the manufacturer focused on those which were most relevant. For completeness, in Appendix 1 we include the table of all the trials identified by the manufacturer in the industry submission, and have added our reasons for excluding some from our Cochrane review on GLP-1 analogues for type to diabetes (in preparation).

We considered the manufacturer's submission to be of good quality. All relevant trials were included. We cross-checked against our own searches for the Cochrane review.

We identified a number of discrepancies between different parts of the submission, and between the submission and published papers, but these were mostly minor, and arose because of rounding in some papers but not others, or because some figures came from different analyses such as intention to treat, or as observed, or adjusted.

We used the submission, the published papers, and the full clinical trial reports for LEAD-5 and LEAD-6, and 1860, which were provided by Novo Nordisk. One author attended a satellite symposium at the 20th World Diabetes Congress in Montreal in October 2009, where the LEAD studies were presented and discussed, and there were also presentations and posters at the main WDC.

In line with the NICE guideline on type 2 diabetes (CG 87) we start by considering use of liraglutide as third drug, and then as second.

3.1 Liraglutide as third drug

Based on the NICE guideline (CG 87) on the management of type 2 diabetes, the main indication for GLP-1 agonists would be as the third drug in people whose control is unsatisfactory on a combination of two oral agents, usually metformin and a sulphonylurea. Some patients would be unable to tolerate these and might be taking a glitazone or a gliptin instead. The recommendation from the guideline is in Box 1.

Box 1: NICE recommendations on use of exenatide.

GLP-1 mimetic (exenatide)

Consider adding a GLP-1 mimetic (exenatide) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($HbA_{1c} \geq 7.5\%$, or other higher level agreed with the individual), and the person has:

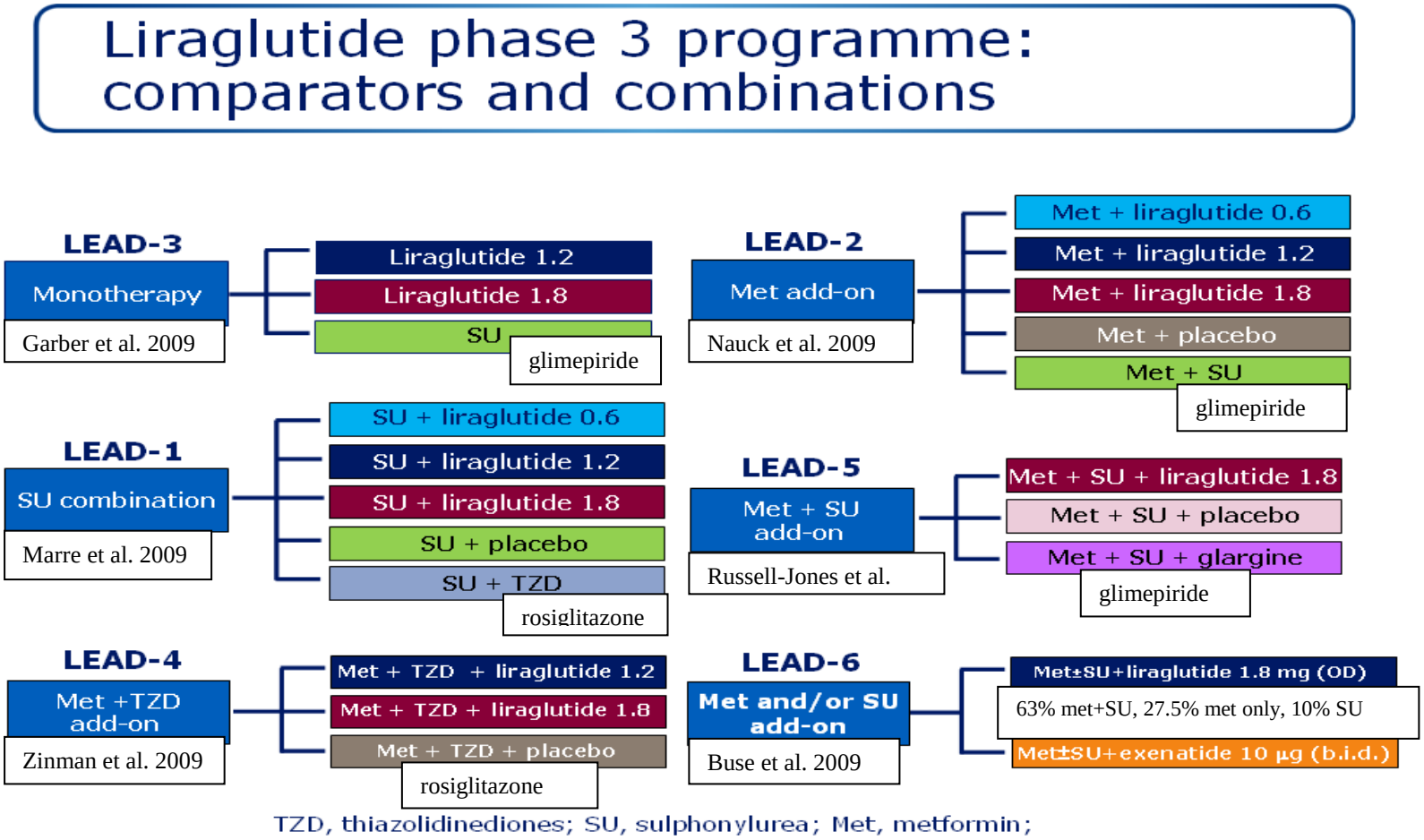
- a body mass index (BMI) ≥ 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or
- a BMI < 35.0 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

Only continue GLP-1 mimetic (exenatide) therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA_{1c} and a weight loss of at least 3% of initial body weight at 6 months).

The trials relevant to the use of liraglutide as third drug are LEAD-4 (Zinman 2009)[17], LEAD-5 (Russell-Jones 2008)[18] and LEAD-6 (Buse 2009).[19] The last is included because the majority of patients were on triple therapy – 63% on metformin and a sulphonylurea.

Figure 3 gives an overview of the LEAD trials.

Figure 3 The Liraglutide Effect and Action on Diabetes (LEAD) programme Overview



The ones which are most relevant to triple therapy are LEAD-5, in which liraglutide was compared with the long-acting analogue insulin, glargine, and LEAD-6 where liraglutide was compared with exenatide.

It should be noted that the evidence is that in most patients with type 2 diabetes, glargine is not cost-effective compared to NPH insulin as a single daily basal injection, and that NPH was recommended in the NICE guideline.[4]The cost of NPH is under half that of glargine. None of the LEAD studies compared liraglutide with NPH insulin.

LEAD-5 had three arms but one is not relevant for comparing the options for triple therapy. The trial compared:

Liraglutide 1.8 mg + metformin + glimepiride

versus

glargine + metformin + glimepride

versus

metformin + glimepiride

Our review assessed the quality of this trial as good as shown in Table 1

Table 1 Risk of bias table for LEAD-5

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomised as 2:1:1 using a telephone or web-based randomisation system
Allocation concealment?	Yes	Central randomisation using a telephone or web-based randomisation system
Blinding?	Partial	Investigators, participants, and study monitors were blinded to liraglutide, open label glargine
Incomplete outcome data addressed?	Yes	Missing data were imputed as the last observation carried forward (LOCF), ITT analysis, adequate description of withdrawals and losses to follow-up
Free of selective reporting?	Yes	Included all pre specified outcomes
Groups comparable at baseline?	Yes	
Sample size calculation?	Yes	Study was powered to

		determine a 3% difference in weight with a combined power >85%

So the trial appears to be of good quality, since it was impractical to blind the glargine arm.
The dose of liraglutide was fixed. According to the main paper, the dosage of glargine was titrated by a patient driven algorithm based on fasting plasma glucose (FPG). Patients were asked to adjust the dose twice weekly in the first 8 weeks, based on self-measurement of FPG, aiming for a value of 5.5 mmol/l or less. After 8 weeks, investigators could do as they thought best, but were expected to adjust the glargine dose at the 12 and 18 week visits. At the end of the study, the average dose of glargine was 24 units a day.

One question is whether glargine was used to best effect – should the dose have been higher?

The end of study dose of glargine was 0.28 units/kg/day. This seems quite a low dose for patients with poor control who had been started on insulin 6 months earlier. A starting dose of 0.2 units/kg/day would seem reasonable but with active titration one might have expected the end of study dose to have been high – say 0.4 units/kg/day

The main results are summarised in Table 2 . **NB In these tables, we give the observed baseline and final data, but the differences or changes are taken from the ANCOVA model ITT analysis set, and may not always be the same as a simple subtraction would give.**

Table 2 Main results from LEAD-5.

	Liraglutide arm	Glargine arm
HbA1C		
Baseline	8.3% (SD 0.9)	8.2% (SD 0.9)
End of study	7.0% (SD 1.0)	7.2 (SD 0.9)
Change from baseline	-1.33% (SE 0.09)	-1.09 (SE0.90)
Difference -0.24% (-0.08 to -0.39; P = 0.0015) in favour of liraglutide		
% reaching HbA1c <7.0%	53.1%	45.8%
FPG		
Baseline	9.1 mmol/l (SD 2.1)	9.1 (SD 2.0)
End of study	7.7 mmol/l(SD 2.2)	7.4 (SD 2.1)
Change from baseline	-1.55 mmol/l	-1.79 mmol/l
NS difference -0.24 mmol/l (-0.31 to 0.60); P= 0.2002 in favour of glargine		
Weight		
Baseline	85.8 kg (SD 19.3)	85.2 (SD 17.9)
End of study	84.8 kg (SD 19.1)	86.9 kg (SD 18.1)
Change	-1.81 kg (SE 0.33)	+ 1.62 kg (SE 0.33)
Difference 3.43 kg (-4.00 to -2.86); p<0.0001 in favour of liraglutide		
SBP		
Baseline	134.9 mmHg (SD 14.9)	133.0 mmHg (SD 14.7)

End of study	132.0 mmHg (SD 14.7)	134.6 mmHg (SD 16.3)
Change from baseline	-3.97 mmHg (SE 1.31)	+0.54 mmHg (SE 1.33)
Difference -4.51 mmHg (-6.82 to -2.20); p=0.0001 in favour of liraglutide		

Glargine dosage in other trials

In the Bunck and colleagues RCT of glargine vs exenatide, the final glargine dose was 34 units/day and the reduction in FPG was greater with glargine.[20] However this study is not strictly comparable with LEAD-5 because recruits in the Bunck trial were on only metformin monotherapy.

Similarly the Barnett and colleagues RCT of exenatide versus glargine was in patients on monotherapy.[21] In that study, FPG fell more with glargine than exenatide, which is what one would expect given that the GLP-1 analogues target postprandial more than fasting glucose whereas basal insulin does the reverse. The dose of glargine was about 27 units/day.

In the Heine and colleagues trial of exenatide vs glargine the reduction in FPG was greater in the glargine group – 1.4 mmol/l and 2.9 mmol/l respectively, with 22% of the glargine group and 9% of the exenatide group achieving FPG under 5.6mmol/l.[22] The dose of glargine in that study was 25u/d, similar to that in LEAD-5.

In other trials of glargine, end of study doses were 32 units/day in the Pan and colleagues study[23] (versus NPH, both in combination with glimepiride, with a reduction in HbA1c of 0.99% from baseline 9%) and 33 units/day in the study by Wang and colleagues[24] (also against NPH, both in combination with glipizide, with a drop in HbA1c of 1.15% from baseline 8.8%). In both those trials, the titration target was 6.7 mmol/l or less.

The investigators note that doses of glargine have been higher in studies with more frequent contact schedules, but argue that the results in LEAD-5 are similar to other trials in which titration is driven by patients, such as in the study by Heine and colleagues, mentioned above, which had an end of study glargine dose of 24 units. However they note that other trials have had higher end of study glargine dose.[25,26] In the HEELA trial of exenatide versus glargine, the mean final dose of glargine was 39 units/day.[26]

So there may be some doubt as to whether better results could have been obtained with glargine, though the investigators could argue that the results reflect the sort of patient-led titration likely to be seen in routine care, away from the more intense contact of some trials.

The industry submission does not discuss whether the dose of glargine as used in the LEAD-5 trial was sufficient, but in the modelling a dosage of 40 units per day is used after year 1. The cost of titration is mentioned but without a cost being included (page 62).

Note that despite the dosage of glargine being increased after year 1, no difference appears to be made in HbA1c. So the industry modelling increases the dose, and hence the cost, without including a reduction in HbA1c.

Summary of LEAD-5 liraglutide versus glargine as third drug

Liraglutide 1.8 mg daily reduced HbA1c by 0.24% more than glargine 24 units/day. The end of study weight and SBP differences were 3.4 kg and 4.5 mm/Hg in favour of liraglutide. It may be that glargine was not used to best effect, but had the dose been increased, and HbA1c lowered, it is likely that weight gain would have been greater, and the SBP difference also larger.

LEAD-6

LEAD-6 was also a good quality trial as shown in Table 3.

Table 3 Risk of bias table for LEAD-6

Item	Judgement	Description
Adequate sequence generation?	Unclear	Randomly assigned (1:1) to the lowest available number of the numbers allocated to the site
Allocation concealment?	Yes	Telephone or web based randomisation
Blinding?	No	Open label
Incomplete outcome data addressed?	Yes	Last observation carried forward data with repeated measures analysis and multiple imputation methods, ITT analysis, adequate description of withdrawals and losses to follow-up
Free of selective reporting?	Yes	All pre specified outcomes reported
Groups comparable at baseline?	Yes	
Sample size calculation?	Yes	85% power to detect an HbA1c difference of 0.4% betweeen groups

The main results of LEAD-6 are shown in

Table 4

Table 4 Main results of LEAD-6.

	Liraglutide arm (1.8mg)	Exenatide arm
HbA1C		
Baseline	8.2% (SD1.0)	8.1% (SD 1.0)
End of study	7.0% (SD 0.87)	7.2% (SD 0.99)
Change from baseline	- 1.12% (SE 0.08)	- 0.79% (SE 0.08)
Difference – 0.33% (-0.47 to -0.18); p<0.0001 in favour of liraglutide		
% reaching HbA1c <7.0%	54	43
FPG		
Baseline	9.8 mmol/L (SD 2.5)	9.5 mmol/L (SD 2.4)
End of study	7.7 mmol/L (SD 1.9)	8.6 mmol/L (SD2.1)
Change from baseline	- 1.61 mmol/l (SE 0.20)	-0.60 mmol/l (SE 0.20)
Difference – 1.01 (-1.37 to -0.65); p<0.0001 in favour of liraglutide		
Weight		
Baseline	93.1 kg (SD 20.1)	93.0 kg (SD 19.5)
End of study	91.1 kg (SD 20.3)	91.1 kg (SD 17.8)
Change from baseline	- 3.24 kg (SE 0.33)	- 2.84 kg (SE 0.33)
NS difference -0.38 kg (-0.99 to 0.23); P=0.2235 in favour of Liraglutide		
SBP		
Baseline	132.0 mmHg (SD 16.2)	134.4 (SD 17.0)
End of study	129.7 mmHg (SD 16.2)	131.7 mmHg (SD 15.5)
Change from baseline	- 2.51 mmHg (SE 1.15)	-2.00 mmHg (SE 1.18)
NS difference -0.51 mmHg (-2.66 to 1.64); p =0.6409 in favour of liraglutide		

The main adverse effect was nausea, and this was reported to be less with liraglutide than with exenatide. Initial frequencies were similar, but nausea was reported to be mild and transient with liraglutide, and no disutility was included in the modelling. We think this is reasonable. Full details and discussion on nausea are in Appendix 2.

In summary, in LEAD-6, liraglutide 1.8 mg daily reduced HbA1c by 0.33% more than exenatide. Systolic BP and weight showed no significant differences. There was less nausea with liraglutide once daily than with exenatide twice daily.

Trials of third-line liraglutide against placebo

The part of LEAD-5 described above addressed the question of whether liraglutide or glargine was better as the third line drug. The next two comparisons, from LEAD-5 and LEAD-4, used placebo control instead of an active comparator. They can be regarded as addressing a clinically useful question: in patients with unsatisfactory control on two oral agents, is the addition of liraglutide sufficient to achieve good control? However for cost-effectiveness analysis when there is a choice of

agents, the key question is which agent is best, and so these trials are not helpful for economic analysis.

The placebo arms serve two purposes. Firstly, they tell us how much of the improvement seen might be due to just being in a trial, with regular follow-up, probably more often than in usual practice, and protocol driven data collection which itself may improve results. Secondly, in longer trials the placebo arm might provide data on natural history and progression of disease (so that if the active arm showed no change, that could be regarded as a benefit).

LEAD-5 included a placebo arm with the following comparison;

Liraglutide 1.8mg + metformin + glimepiride

versus

placebo + metformin + glimepiride

Full details are in the industry submission, but in brief;

- HbA1c was reduced by 1.33% in the liraglutide arm and by 0.24% in the placebo arm, suggesting that liraglutide reduced it by 1.09%, with the rest being trial effect. (The implication is that glargine reduced it by 0.85% after subtracting trial effect).
- 53.1% of patients in the liraglutide arm reached the HbA1c target of <7.0% versus 15.5% in the placebo arm. The baseline levels were 8.3%, which shows that 15% of the placebo group achieved a reduction of at least 1.3% from trial effect alone.
- Systolic blood pressure fell by an average of 4 mmHg in the liraglutide arm and by 1.4 mmHg in the placebo arm, suggesting that liraglutide was responsible for a drop of 2.6 mmHg.
- Weight was reduced by 1.8 kg in the liraglutide arm, and by 0.4 kg in the placebo arm, suggesting a net liraglutide effect of 1.4 kg

LEAD-4 had the following comparisons;

Liraglutide 1.2 mg + metformin + rosiglitazone 4 mg

versus

Liraglutide 1.8 mg + metformin +rosiglitazone 4 mg

versus

Placebo + metformin + rosiglitazone 4 mg

LEAD-4 was a good quality trial as shown in Table 4

Table 5 Risk of bias table for LEAD-4

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomised as 1:1:1. Telephone or web based randomisation; protocol states: "Randomisation will be carried out centrally using a randomisation system, IVRS/IWRS" [Interactive voice (or web) response system]
Allocation concealment?	Yes	Telephone or web based randomisation
Blinding?	Yes	Double blinding
Incomplete outcome data addressed?	Yes	Missing data were imputed as the last observation carried forward (LOCF), ITT analysis, adequate description of withdrawals and losses to follow-up
Free of selective reporting?	Yes	Included all prespecified outcomes
Groups comparable at baseline?	Yes	
Sample size calculation?	Yes	The combined power (calculated as the product of the marginal powers for HbA1c and weight) was >95%

Full results are in the industry submission, but in brief;

- HbA1c was reduced by 1.5% in the liraglutide 1.2 mg arm versus 0.5% in the placebo arm. The usual reduction considered to be clinically significant is 0.5%, so “placebo” i.e. the trial effect, was effective. Subtracting that suggests that the reduction with liraglutide 1.2 mg was 1.0%.
- The 1.8 mg dose of liraglutide achieved no greater effect on HbA1c than the 1.2 mg dose
- The proportions of patients reaching the HbA1c target of <7.0% were 58% with liraglutide 1.2 mg, 54% with liraglutide 1.8 mg, and 28% with placebo.
- Weight was reduced by 1 kg with liraglutide 1.2 mg, by 2 kg with liraglutide 1.8 mg, and rose by 0.6 kg in the placebo group, suggesting net effect of a reduction of 1.6 kg with liraglutide 1.2 mg.
- Systolic blood pressure fell by 6.7 mm/Hg with liraglutide 1.2 mg, 5.6 mmHg with liraglutide 1.8 mg and 1.1 mm/Hg with placebo, giving a placebo-corrected effect of 5.6 mmHg with liraglutide 1.2 mg and 4.5 mmHg with liraglutide 1.8 mg.

Summary of third-line liraglutide compared to placebo

As expected, these trials show that liraglutide as a third line drug is effective, reducing HbA1c by about 1% in patients with baseline levels of 8.3 to 8.6%, accompanied by about 1 kg weight loss with 1.2 mg and 1.4 kg with 1.8 mg of liraglutide.

What dose of liraglutide?

The standard dose of liraglutide appears to be the 1.2 mg/day dose, but some trials have used 1.8 mg. However, the marginal gain from the higher dose does not seem to be great.

Table 6 shows HbA1c reductions from some trials

Table 6 Reductions in HbA1c by dose of liraglutide

	1.2 mg daily	1.8 mg daily
1860	[redacted]	[redacted]
LEAD-1	1.1	1.2
LEAD-2	1.0	1.0
LEAD-4	1.5	1.5

Similarly for the proportions reaching the HbA1c target of <7.0% are shown in Table 7. The weight change from baseline is shown in
Table 8 , and the changes in SBP in Table 9.

Table 7 Proportions reaching HbA1c target of <7.0%

	1.2 mg daily	1.8 mg/daily
1860	[redacted]	[redacted]
LEAD-1	35%	42%
LEAD-2	35%	42%
LEAD-4	58%	54%

Table 8 Weight change from baseline

	1.2 mg	1.8 mg
1860	[redacted]	[redacted]
LEAD-1	+ 0.3 kg	-0.2 kg
LEAD-2	- 2.6 kg	- 2.8 kg
LEAD-4	- 1.0 kg	-2.0 kg

In the 2-year follow-up of LEAD-2 the weight loss on 1.8 mg was less (2.9 kg) than on 1.2 mg (3.0 kg).[27]

Table 9 Systolic BP change in mm Hg

	1.2mg	1.8mg

1860	[redacted]	[redacted]
LEAD-1	- 2.6	-2.8
LEAD-2	- 2.8	- 2.3
LEAD-4	- 6.7	- 5.6

Table 10 Nausea percentages (rounded)

	1.2 mg	1.8 mg
1860	[redacted]	[redacted]
LEAD-1	11%	7%
LEAD-2	16%	19%
LEAD-4	45%	56%

As show in Table 10 the proportions of patients reporting nausea vary widely amongst the trials, from 11% to 45% with the 1.2 mg dose and from 7% to 56% with the 1.8 mg dose.

Figure 4, Figure 5, Figure 6 and Figure 7 below show meta-analyses of these variables. (These are all academic in confidence because the 1860 results could be deduced if the others were given.)

[redacted]

Figure 4 Change in HbA1c from baseline liraglutide 1.2 mg versus 1.8 mg

[redacted]

Figure 5 Patients reaching HbA1c <7% liraglutide 1.2 mg versus 1.8 mg

[redacted]

Figure 6 Change in weight from baseline liraglutide 1.2 mg versus 1.8 mg

[redacted]

Figure 7 Change in systolic blood pressure from baseline liraglutide 1.2 mg versus 1.8 mg

So the only statistically significant difference is in weight, where the difference is of doubtful clinical significance.

More details of the effects of liraglutide 1.2 and 1.8 mg doses are given in Appendix 3.

So we might expect 1.2 mg daily (as in the industry submission) to be the standard dose. This was the conclusion of the EMEA assessment report;[28]

"*It is concluded that in dual and combination treatment, only limited effect can be expected from an increase in dose to 1.8 mg, while GI adverse events might increase."*

The submission from Novo Nordisk states on page 42, that,
"It is anticipated that liraglutide 1.2 mg will be used in the majority of patients."

However the EMEA EPAR report noted that there might be an advantage of the bigger dose in the heaviest patients (over 90 kg) in whom the reduction in HbA1c was greater (EPAR page 33).[28]

Unfortunately, in two trials against active comparators, LEAD-6 versus exenatide, and LEAD-5 against glargine, only the 1.8 mg dose was used. Contact with the manufacturer confirms a lack of data on the relative effectiveness of the 1.2 mg dose against these drugs. This creates a problem for the cost-effectiveness modelling because the larger dose is much more expensive (by about 50%) but may not be significantly more effective.

During the appraisal period, Novo Nordisk arranged for some indirect comparisons to be done, so that results from LEAD trials 1 to 4, and the unpublished trial against sitagliptin, could be used to simulate what would have happened had there been such arms in LEAD-5 and LEAD-6.

The predicted mean reduction in HbA1c in LEAD-5 had the 1.2 mg dose been used, was 1.19% (SE 0.02, so 95% CI 1.15 to 1.23%) compared to the observed reduction with glargine of 1.09%. Compared to the 1.8 mg dose, the reduction with 1.2 mg would be 0.11% less, with the 95% confidence intervals not quite touching (upper bound for 1.2 mg, 1.23%, lower for 1.8 mg, 1.24%). In LEAD-6, the predicted reduction with 1.2 mg was 1.08% (1.02 to 1.14%) compared to the observed reduction with exenatide of 0.79%.

It would be better if we had direct comparisons, because indirect comparisons could be prone to unknown confounding variables. However in the absence of direct comparisons, the indirect comparison is useful. The methods seem appropriate, and our only concern is that the method applies the predicted effect of the 1.2 mg dose to all patients in the LEAD-5 and LEAD-6, so that the confidence interval is reduced.

3.2 Liraglutide as second drug

Three trials compared liraglutide as second drug.

LEAD-1

LEAD-1 was used in patients who had inadequate glycaemic control with glimepiride (a sulphonylurea). It compared liraglutide with rosiglitazone (a thiazolidinedione) as second drug. There

was also a placebo arm. All three arms were on glimepiride as well. Baseline BMI ranged between 29 and 31 while baseline HbA1c between 8.4 and 8.5.

LEAD-1 was scored quite well in our quality assessment as shown below in Table 11 , but has been criticised for using a rosiglitazone dose of only 4 mg daily. The EMEA report (page 30) also noted that the trial lasted 26 weeks, which might not allow rosiglitazone to reach its full effect.[28] . It could also be argued that pioglitazone would have been better, since it has a more favourable risk profile than rosiglitazone. Both can cause heart failure and fractures, but rosiglitazone appears to slightly increase cardiovascular mortality, whereas pioglitazone reduces it. In a recent UK study in 91,521 people with diabetes, rosiglitazone was associated with a 34% to 41% higher risk of all cause mortality compared to pioglitazone.[29] Some regulatory bodies have now placed warnings on rosiglitazone use.

Table 11 LEAD-1 risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Subjects were stratified according to previous treatment (monotherapy or combination therapy)
Allocation concealment?	Unclear	Insufficient information
Blinding?	Yes	Double blinding
Incomplete outcome data addressed?	Yes	Missing data were imputed as the last observation carried forward (LOCF), ITT analysis, adequate description of withdrawals and losses to follow-up
Free of selective reporting?	Yes	Included all pre-specified outcomes
Groups comparable at baseline?	Yes	
Sample size calculation?	Yes	A combined power (calculated as the product of the marginal powers for HbA1c and body weight) of at least 85% was required.

Full details are in the industry submission, but in brief,

- HbA1c was reduced by 1.08% in the liraglutide 1.2 mg arm and 1.19% in the liraglutide 1.8 mg arm, and in the rosiglitazone 4 mg arm by only 0.44%. It rose by 0.23% in placebo arm.
- Weight was reduced by 0.2 kg and 0.1 kg in the liraglutide 1.8 mg and placebo arms respectively. In the liraglutide 1.2 mg and rosiglitazone arms, it increased by 0.3 kg and 2.1 kg respectively.

- Systolic BP decreased in the range of 2.6 to 2.8 mmHg in the liraglutide 1.2 and 1.8 mg arms while the reduction in the placebo and rosiglitazone arms was between 0.9 to 2.3 mmHg.

So compared to rosiglitazone 4 mg, there was a significant difference in HbA1c but no difference in weight and SBP. However note that this was with rosiglitazone 4 mg daily.

LEAD-2

LEAD-2 was in patients inadequately controlled on metformin alone, and compared liraglutide with glimepiride as second drugs. The NICE guidelines do not recommend a GLP-1 agonist as second-line drug. There was also a metformin and placebo arm. Baseline BMI was about 31 and baseline HbA1c about 8.4%

LEAD-2 was a good quality trial as show in Table 12. It lasted 26 weeks.

Table 12 LEAD-2 risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomly assigned as 2:2:2:1:2. Telephone or web based randomisation. Patients randomly assigned to the lowest available randomization number and stratified with respect to their previous use of OAD monotherapy or combination therapy
Allocation concealment?	Yes	Telephone or web based randomisation
Blinding?	Yes	Double blinding
Incomplete outcome data addressed?	Yes	Missing data were imputed as the last observation carried forward, ITT analysis, adequate description of withdrawals and losses to follow-up
Free of selective reporting?	Yes	Included all expected outcomes, including those prespecified
Groups comparable at baseline?	Yes	
Sample size calculation?	Yes	The combined power (calculated as the product of the marginal powers for A1C and weight) was at least 85%

Full details of the results are in the industry submission, but in brief;

- HbA1c was reduced by 1% in the liraglutide 1.2 and 1.8 mg arms, and in the glimepride group. It rose by 0.1% in the placebo group

- Weight was reduced by 2.6 and 2.8 kg in the liraglutide 1.2 and 1.8 mg groups, and by 1.5 kg in the placebo group, giving placebo-adjusted losses with liraglutide of 1.1 and 1.3 kg. Weight rose by 1 kg with glimepiride.

- Systolic BP fell by 2.8 mmHg in the 1.2 mg liraglutide arm, by 2.3 mmHg in the 1.8 mg arm, and by 1.8 mmHg in the placebo arm. It rose by 0.4 mmHg in the sulphonylurea arm. Hence the placebo-adjusted SBP reductions with liraglutide were 1 and 0.5 mmHg.

So compared to glimepiride, no difference in HbA1c but weight advantage of 3.7 kg and SBP difference of 3.2 mmHg.

1860

NN2211-1860 was a randomised, active-comparator trial designed to compare the efficacy and safety of liraglutide with liraglutide 1.2 mg or 1.8 mg once-daily with sitagliptin 100 mg once-daily. All groups continued on metformin therapy. The trial was run in 158 sites across 13 countries and duration was 26 weeks. The primary endpoint was the change in HbA_{1c} from baseline.
The inclusion criteria of participants were: aged 18–80 years with type 2 diabetes, HbA_{1c} of 7.5–10.0% (prestudy, stable metformin therapy ≥1500 mg for ≥3 months) at screening and BMI ≤45.0 $kg/m^{2.}$
A total of [redacted] were randomised and [redacted] completed the trial. The mean baseline characteristics were age [redacted] HbA1c = [redacted] weight [redacted] and SBP [redacted] As shown in Table 13, 1860 was a good quality trial.

Table 13 1860 risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Computer generated random numbers
Allocation concealment?	Yes	Local randomisation. Patients were randomly assigned to the lowest available randomisation number by the site investigator
Blinding?	No	Open label
Incomplete outcome data addressed?	Yes	
Free of selective reporting?	Yes	
Groups comparable at baseline?	Yes	
Sample size calculation?	Yes	

Full details of the results are in the industry submission, but in brief;

[redacted]

[redacted]

Is there a case for second-line use of liraglutide?

The industry submission (page 40) suggests that dual therapy with liraglutide and either metformin or sulphonylurea would be of benefit in a number of situations. These, followed by *our comments in italics*, are;

- Patient choice favours liraglutide as second-line therapy: *but patient choice should not take precedence over cost-effectiveness*
- Other incretin-based therapies are not expected to provide sufficient glycaemic control: *but other GLP-1 therapies would be 3rd line (as per NICE guidelines)*
- Weight loss would benefit other significant obesity-related comorbidities: *a valid point*
- Weight gain would be undesirable and result in a degenerative effect on other medical issues: *this presumably refers to the fact that use of sulphonylurea, glitazone or insulin is usually associated with weight gain. However the gliptins are weight neutral, taken orally, and much less expensive and with fewer side-effects than liraglutide*.
- There is a risk related to hypoglycaemia elicited by alternative therapies: *not a problem with the gliptins*
- The routine use of SMBG is difficult or not possible: *but only justified with insulin, not usually with other oral agents, unless there are problems with hypoglycaemia with sulphonylureas*.
- Patients have existing cardiovascular disease: *might be a contraindication for the use of rosiglitazone, and of pioglitazone if heart failure an issue, but not for use of gliptins or insulin*
- Patients have medical problems associated with high body weight, such as obstructive sleep apnoea: *weight loss does benefit obstructive sleep apnoea, but the amount of weight loss required is much greater than is seen in most patients in the liraglutide trials. A recent study*

by Foster and colleagues showed that major improvements in sleep apnoea were seen mainly in those who lost over 10kg.[30]

3.3 Some other issues

The liraglutide meta-analyses.

No meta-analyses were included in the industry submission, on the grounds that it was not appropriate due to different concomitant medications. However meta-analyses of the six LEAD trials, sponsored by Novo Nordisk, have appeared in abstract form at the 2009 World Diabetes Congress but mainly for the 1.8mg dose, since some of the trials did not have 1.2mg arms. The results at 26 weeks included;

- Total cholesterol was reduced by 0.13 mmol/l, compared to a drop of 0.01 on placebo, 0.05 on glimepiride, and a rise of 0.02 on glargine. [31]
- LDL cholesterol fell by 0.2 mmol/l on liraglutide 1.8 mg, and by 0.13 on placebo, giving a net drop of 0.07 on liraglutide. It fell by 0.07 on glargine and by 0.15 on exenatide. [31]
- Triglycerides fell by 0.20mmol/l on liraglutide 1.8mg, by 0.15 mmol/l on glargine, and rose by 0.02mmol/l on placebo. [31]
- Weight loss varied. On 1.8mg liraglutide, 24% of people lost no weight (some gained); 35% lost under 3% of baseline weight; 17% lost between 3 and 5%; and 24% lost over 5%. Note that 10% of those on placebo also lost over 5%. [32]
- The reduction in HbA1c was greatest in those who lost most weight (1.65% reduction in HbA1c), but even in those who lost no weight, HbA1c fell, by 1.38%.[32]

Which insulin should be the comparator?

The 4T trial showed that on balance, the choice of insulin for patients starting it because glycaemic control was not good enough on a combination of oral drugs, was basal insulin, rather than short-acting mealtime insulins or twice daily mixtures.[33,34] So the correct comparator for liraglutide is a once daily basal insulin. According to the NICE guideline, that should be NPH, because the advantages of the long-acting analogues are slight and the cost much greater, giving high costs per QALY.

However, practice in the UK has moved away from NPH, and the most commonly used basal insulin is now glargine, with detemir also overtaking NPH.[5] Hence Novo Nordisk could make a case that using glargine as the comparator was simply recognising the realities in the NHS. Note also that

LEAD-5 was carried out in 17 countries. Nevertheless, when it comes to cost-effectiveness analysis, the extra cost of glargine compared to NPH will be important.

Curiously, the LEAD-5 trial, sponsored by Novo Nordisk, used the Sanofi-Aventis insulin glargine, rather than the Novo Nordisk one, detemir.

What should the GLP-1 analogue comparator be?

The only other currently available GLP-1 analogue is twice daily exenatide. However we know that the once weekly exenatide LAR is being submitted to FDA in 2010,[35] and that other long-acting GLP-1 analogues such as albiglutide and taspoglutide are in the pipeline, with trials published.[36,37] Also, trials on lixisenatide are currently recruiting patients.[38,39] We also know that a trial of weekly exenatide versus daily liraglutide, DURATION-6 is being launched.[40]

Hence modelling liraglutide against twice daily exenatide seems unrealistic. However, NICE will not consider unlicensed medicines, and we have no price as yet for exenatide LAR, so modelling has to be done against twice daily exenatide.

GLP-1 and insulin combinations

At present, neither exenatide nor liraglutide is licensed for use in combination with basal insulin. However trials are underway or have been done,[41-44] and the combination looks very logical, given that the GLP-1s act mainly on post-prandial hyperglycaemia, and basal insulin on fasting and pre-prandial. The combination might therefore give better glycaemic control while avoiding rises in weight and blood pressure.

So future use will probably include GLP-1 analogue and insulin combinations.

Safety: thyroid cancer and pancreatitis

Safety is an issue for the MHRA rather than NICE, and only brief notes are included here.

There has been concern about the effects on the C cells of the thyroid gland after C-cell tumours were observed in mice and rats. The data have been reviewed intensively in both the FDA and the EMEA appraisal processes. It has been noted that there are more GLP-1 receptors in rat thyroid cells than in human ones, and the EMEA concluded that,

"The relevance for humans is likely to be low but cannot be completely excluded."[28]

In the human trial, the rate of thyroid adverse effects appears to be higher with liraglutide than with non-liraglutide treatments (about 36 vs 22 events per 1000 patient year – EMEA EPAR page 38).

Malignant thyroid neoplasms were slightly increased with liraglutide (10.9 for all liraglutide vs 6.9 for all comparators) but the incidence rates were no higher than in the US background population. The hormone calcitonin comes almost entirely from thyroid C-cells and can be used as a marker for increase C-cell activity. Data from the trials show that calcitonin levels increased, particularly with liraglutide 1.8 mg (at week 26) but the levels stayed mostly within the normal range, which is reassuring.

There have been reports of pancreatitis with exenatide but because the incidence of pancreatitis is increased in type 2 diabetes, it has proved difficult to show whether there is a true increase in a rare event with exenatide. [45] The liraglutide trial data show a slight increase in pancreatitis in those on liraglutide compared to oral comparators (1.6 vs 1.4 per 1000 patient years) but this should be set against the background rate of 1 to 5 per 1000 patient years in type 2 diabetes.

The long-term effects will require to be monitored, given the short-term nature of the trials, but the MHRA does not appear to be concerned about these issues at present. The FDA has taken a more cautious line.[46]

Beta –cell function

It has been suggested by the manufacturer (NN synopsis 2009) that liraglutide might prevent progression of type 2 diabetes by preserving beta-cell function. Beta-cell function was estimated in some of the trials using HOMA-B or the pro-insulin to insulin ratio, and much greater responses were seen with liraglutide than with rosiglitazone or glimepiride. Interestingly, the improvement was greater with liraglutide 1.2 mg than the 1.8 mg dose. However, these results are based on short-term trials, and it is not known whether any effect would be sustained after liraglutide was stopped. The evidence with exenatide is that the effect is not sustained.

The effect on beta-cell function therefore remains uncertain, and the industry submission makes no claims about it.

3.4 Conclusions on clinical effectiveness

Liraglutide appears to be a safe and effective drug which improves glycaemic control, accompanied by reductions in weight and systolic blood pressure.

The 1.2 mg dose appears to be sufficient for most patients, since the marginal effects of the 1.8 mg dose are slight.

4. REVIEW OF ECONOMIC MODELLING OF LIRAGLUTIDE

4.1 Economic literature review

One study was found, by Sullivan and colleagues 2009. [47] This was a study sponsored by Novo Nordisk, and with co-authors from the company. It was based only on the LEAD 1 trial, which was of dual therapy, not all costs were included, and the perspective was from a US health care payer one. It used the CORE model. We think this study is superseded by the industry submission, and it is not included here. We note the comment in the industry submission (page 45) on the Sullivan study that: "*Due to the setting chosen and the exclusion of drug costs, the study does not give an indication of total treatment costs to the NHS or the cost-effectiveness of liraglutide."*

4.2 The CORE model

The industry submission uses the well-developed CORE (Center for Outcomes Research) model which has been used for many studies in the past. Many of these have been sponsored by industry and have produced results with which we might not agree. But we have no problems with the model itself. A description of the model and its validation has been attached as appendix 4.4.

It does not meet the criteria for acceptability by NICE, on a number of grounds, such as software used and transparency. However diabetes is a very complex disease, and it would have been wasteful for Novo Nordisk to have commissioned a new model in one of diabetes. NICE therefore, with our agreement, allowed the use of this non-standard software. Precedents have been set in previous appraisals of diabetes topics, with CORE used in the insulin pumps appraisal, and EAGLE in the inhaled insulin one.

In brief, we consider the CORE model to be satisfactory.

4.3 ERG cross check of modelling inputs

Population baseline characteristics

The baseline population characteristics outlined in table 16 [p52] of the submission correspond with those applied for the base case modelling within CORE.

Principal clinical effectiveness estimates

The estimates of clinical effectiveness for the trial population as a whole as tabled in appendix 9 of the submission, as outlined in the review of clinical effectiveness, have been cross checked with the clinical trial reports and corresponded with the ANCOVA analysis of change for all values, though note that this is distinct from the Summary of Change ITT Analysis Set.

For the modelling within CORE the parameter values of appendix 9 correspond with the base case input parameters with the following exceptions around hypoglycaemic event rates for trial 1860.

Table 14 Differences between CORE and industry submission

1860 Hypoglycaemic events	**Liraglutide 1.2mg**	**Liraglutide 1.8 mg**	**Sitagliptin 100mg**
Severe/100 patient years			
Submission	[redacted]	[redacted]	[redacted]
CORE modelling	1.05	0	0
Minor/100 patient years	[redacted]	[redacted]	[redacted]
Submission	18.89	38.05	11.62
CORE modelling			

[redacted]

Note that clinical effectiveness estimates for the subgroup analyses of those with BMI >30kg/m^2 and of those with BMI > 35kg/m^2 have not been checked as these were further analyses undertaken by the manufacturer with no external source to cross check against.

Modelling of therapy change at end of year 5

Because type 2 diabetes is a progressive disease, intensification of treatment is usually necessary over time, as beta cell function declines. The baseline case in the industry model assumes that liraglutide will only be effective for 5 years, and this seems reasonable. (We made similar assumptions for exenatide in our review for the NICE Type 2 diabetes Guidelines Group).

It appears that for the weight changes for those moving on to glargine after 5 years on liraglutide, only the direct disutility from this has been applied. The effect upon BMI and subsequent complications within the CORE modelling appears to have assumed that BMI progression is unaffected by the move on to glargine.

Also, within the simulations for most trials, the move to glargine is associated with little clinical effect: as per figure 8 [p58] and figure 9 [p59] of the submission. The exception to this was the step change in the direct disutility due to the BMI increase as per figure 10 [p59] as has been discussed above: as this was a common step change to both arms it appears to have had little net effect.

Initial liraglutide 1.8 mg was associated with the following changes from baseline at the start of year 1.

Table 15 Changes from baseline in LEAD-5 - liraglutide

Changes with liraglutide 1.8mg	**MEAN:**	**SD:**
HbA1c	-1.33 %points	1.35 %points
SBP	-3.97 mmHg	19.61 mmHg
T-Chol	-2.36 mg/dl	41.31 mg/dl
LDL	4.19 mg/dl	35.17 mg/dl
HDL	-2.32 mg/dl	9.58 mg/dl
TRIG	-21.79 mg/dl	149.22 mg/dl
BMI	-0.644 kg/m2	1.373 kg/m2

Glargine was associated with the following changes (table 16).

Table 16 Changes from baseline in LEAD-5 - glargine

Changes with glargine	**MEAN:**	**SD:**
HbA1c	-1.09 %points	1.377 %points
SBP	0.54 mmHg	20.345 mmHg
T-Chol	2.77 mg/dl	42.679 mg/dl
LDL	9.15 mg/dl	36.254 mg/dl
HDL	-2.07 mg/dl	9.943 mg/dl
TRIG	-19.52 mg/dl	153.888 mg/dl
BMI	0.577 kg/m2	1.495 kg/m2

It could be argued that the change from liraglutide to glargine at year 5 should be accompanied by changes similar to those seen with glargine in year 1, because the change is necessary because of progression of disease due to falling beta cell function, and hence increasing insufficiency of endogenous insulin. So when glargine is started, one would expect at least as big an effect as in year 1 in the glargine arm.

The ERG applied the above glargine changes to both arms within the 1860 and the LEAD-6 modelling. This had no impact upon results, which suggests that there may be a problem within the CORE model in the implementation of the relatively new feature of being able to specify second line treatments. This is strange given that associating second line treatments with a treatment disutility and a cost has an impact upon results. Correspondence with the Novo Nordisk team, and the independent consultant nominated by the manufacturer, who previously worked for IMS, suggests that in the CORE model, the switch incorporates changes in cost and disutility, but not improvements in glycaemic control.

It has not been possible to sort out the implications of this in the time available, and enquiries are continuing. Neither the ERG nor the manufacturer has access to the inner workings of CORE, but just the web-based "front end".

However, if the effect is that the model does not give patients initially treated with liraglutide, an improvement in HbA1c when they switch to insulin after (an assumed and average) five years, then liraglutide may be somewhat disadvantaged.

Other clinical inputs to the CORE model

The values of tables A-6 and A-7 of Appendix 6 of the submission were cross checked with those implemented within the CORE modelling, and a few discrepancies were found

Table 17 Discrepancies within industry submission

	Submission	CORE modelling
Prop. 2° prevention: ACEi	0.21	0.58
Sensitivity eye screening	0.76	0.80
Specificity eye screening	0.99	0.97
Sensitivity GPR screening	0.95	0.85
Sensitivity MAU screening	0.85	0.75
Specificity MAU screening	0.85	0.97

However these appear to be relatively minor.

It should be noted that the manufacturer amended some of the CORE default values, to make them more applicable to the UK, given that the CORE default values are apparently not UK specific. The changes made relate to concomitant medication and the proportions being screened.

Table 18 Manufacturer's amendments to CORE default values.

	CORE default	CORE amended	Difference
Concomitant medication			

Prop 1° prevention ASP	10%	8%	-2%
Prop 2° prevention ASP	50%	8%	-42%
Prop 1° prevention Statins	0%	18%	18%
Prop 2° prevention Statins	50%	18%	-32%
Prop 1° prevention ACE-I	15%	58%	43%
Prop 2° prevention ACE-I	50%	58%	8%
Screening and patient management proportions			
Prop on foot ulcer prevention program	30%	37%	7%
Prop screened eye disease	75%	63%	-12%
Prop screened for renal disease	75%	60%	-15%
Prop receiving intensive insulin after MI	20%	100%	80%
Prop treated with extra ulcer treatment	50%	50%	0%

The amended proportion treated with short-term insulin after MI may be optimistic.
The impact of these changes has not been explored by the ERG. Preventive use of statins apparently mainly affects the cardiovascular risks within the CORE model, and higher 1st line use may tend to work against the treatment with the superior cardiovascular risk profile. ACE inhibitors apparently also have a renal protective function within the modelling, and given the expense of renal disease higher 1st line use may similarly tend to work against the more effective treatment.

The lower proportions being screened appear likely to increase the impact of better disease control and so may tend to improve the cost effectiveness estimates for liraglutide.

Note also that the CORE default specifies a 43% probability of death from a lactic acidosis event. Within the manufacturer modelling this was set to zero.

Drug dosing and direct treatment costs

1st line treatment costs:

As outlined in appendix 7 of the submission, the drug costs and ancillary equipment costs associated with the 1st line treatments within the submission were as below:

Table 19 Costs for 1860 trial arms

1860 trial	**Liraglutide 1.2mg**	**Liraglutide 1.8mg**	**Sitagliptin 100mg**
Concomitant treatment costs	£18.12	£18.12	£18.12
Annual drug costs	£954.84	£1,432.26	£433.57
Cost of needles	£31.10	£31.10	
SMBG	£0.00	£0.00	£0.00

Total annual treatment costs	**£1,004.06**	**£1,481.48**	**£451.69**

Within the above, the cost of sitagliptin 100mg and one snap on needle per day cross check with BNF 58.

Table 20 Costs for LEAD-6 arms

LEAD6 trial	**Liraglutide 1.8mg**	**Exenatide 10µg**
Annual drug costs	£1,432.26	£830.25
Cost of needles	£46.65	£93.29
SMBG	£51.09	£51.09
Total annual treatment costs	**£1,530.00**	**£974.64**

Within this, the cost of exenatide 10µg bid cross checks with BNF 58. Liraglutide and exenatide are assumed to require three testing strips per week for the self monitoring of blood glucose, which again broadly cross checks with BNF 58. However this may be more than is required since the evidence for the benefits of SMBG in people with type 2 diabetes, not treated with insulin, is unproven. A forthcoming Department of Health working group report will recommend that there might be a case for some use in those on sulphonylurea and who are having significant problems with hypoglycaemia. However, the industry submission is in line with guidelines from bodies such as International Diabetes Federation. [48] The evidence is reviewed in a forthcoming HTA report on the use of SMBG in non-insulin-treated type 2 diabetes. [49] Reducing the number of strips used would not affect the liraglutide versus exenatide comparison, but would have a slight effect on the comparison with glargine, by reducing the liraglutide costs.

The reason for the slightly higher needle cost for liraglutide 1.8 mg within LEAD-6 as compared to 1860 is not clear, but the effect is minor. Perhaps more questionable, while liraglutide has the advantage of once daily dosing as compared to twice daily dosing for exenatide is whether patients routinely change needles for every dose. An alternative assumption of one needle per day would reduce the annual cost of exenatide by £46.65 [5%] to £927.98.

For the LEAD-5 trial the submission listed the following drug costs.

Table 21 Costs for LEAD-5 arms

LEAD-5 trial	**Liraglutide 1.8mg**	**Glargine 24 IU**	**Glargine 40 IU**
Concomitant treatment costs	£77.63	£80.58	£80.58
Annual drug costs	£1,432.26	£235.70	£392.84
Cost of needles	£46.65	£46.65	£46.65
SMBG	£51.09	£119.21	£119.21

Total annual treatment costs	**£1,607.62**	**£482.14**	**£639.27**

The above costs for glargine cross check with BNF 58, with the submission assuming that glargine requires one daily testing strip for the self monitoring of blood glucose.

Within the above, it should be noted that the end of trial average daily glargine dose was 24 IU. The base case of the modelling submitted by the manufacturer assumed that this would apply during the first year, but that for the second and subsequent years an average daily dose of 40 IU would be required.

Titration of the glargine dose may increase the average dose, but as outlined in the clinical review section of this report there may be some concerns around the effectiveness of the titration of glargine within the LEAD-5 trial. While increasing the dose would increase the first year drug costs within the glargine arm, it might also have led to an improved effectiveness for the glargine arm. The assumption within the submission of a 40 IU average dose in the second and subsequent years increases the costs within the glargine arm without applying the possible patient benefits of this titration.

The manufacturer also outlined the possible costs of insulin therapy if NPH was assumed to have been used.

Table 22 Costs in LEAD if NPH used

LEAD5 trial	**Liraglutide 1.8mg**	**NPH 24 IU**	**NPH 40 IU**
Concomitant treatment costs	£77.63	£80.58	£80.58
Annual drug costs	£1,432.26	£111.43	£185.71
Cost of needles	£46.65	£46.65	£46.65
SMBG	£51.09	£119.21	£119.21
Total annual treatment costs	**£1,607.62**	**£357.86**	**£432.15**

Again, save for very minor differences in the NPH costs which are possibly due to the balance assumed between NPH formulations, these cross check with BNF 58. If NPH can be viewed as equivalent to glargine in terms of outcomes this would result in the insulin arm being somewhat less costly: £124 [26%] in the first year, and £207 [33%] in the second and subsequent years.

The rosiglitazone costs cross check with a 4 mg daily dose and the glimepiride costs cross check with a 4 mg daily dose of non-proprietary glimepiride in BNF 58.

Future treatment costs:
With the exception of the glargine arm in the modelling of the LEAD5 trial, after therapy change at the end of the fifth year, patients were assume to progress to glargine at an annual direct treatment cost of £638.05. This broadly corresponds with the annual cost of the glargine arm for the second and subsequent years of the LEAD-5 modelling of £639.27.

Costs of complications
The costs derived from UKPDS 65 cross checked with those given in UKPDS 65.[50] As outlined in greater detail in Appendix 8, the application of the outpatient costs within this may have resulted in some double counting. But there is no obvious means within the CORE model structure of avoiding this. Given the sensitivity analysis around price indexation as reported below, any double counting of outpatient costs appears unlikely to have significantly affected the analysis.

The drug management costs within table 19 [p53] cross check with BNF 58. Note that while table 19 suggests that the non-standard Regranex ulcer treatment is a monthly cost, as implemented within the CORE modelling of the submission it appears to be a one off use of one tube of Regranex.

Note that these costs are also reported within appendix 13 of the submission, with there being divergence between this and table 19 in the costs of aspirin, statins, ACE-I, screening for nephropathy, screening for retinopathy and the cost of a non-standard ulcer. The costs implemented within CORE cross check with those of table 19, though note that within CORE screening costs for microalbuminuria and retinopathy are combined to a single cost of £36, and foot screening and GRP screening are similarly combined to a cost of £23.

The costs derived from UKPDS 40 cross checked with those given in UKPDS 40 where these could be identified.[51] But the ERG was not able to locate the £20,000 costs of renal transplant within this, or the £6,500 annual costs subsequent to renal transplant: £22,191 and £7,212 respectively once indexed to 2008.

The costs derived from the Ghatnekar 2001 reference[52] (Table 23 of the submission [p54] suggests a 2000 paper, but the reference list refers to the 2001 paper) cross check with those of the submission, given an exchange rate of $1.62/£ resulting in:

- £1,251 per uninfected ulcer
- £1,282 per infected ulcer
- £2,060 for gangrene

It should be noted that these are reported as being monthly recurrent costs within the Ghatnekar paper, the implicit assumption within the submission appearing to have been that the complications would be limited to one month's duration. It should also be noted that the Ghatnekar paper:[52]

- the Ghatnekar paper appears to have received industry support for a cost effectiveness analysis of Becaplermin
- cost data was collected in the UK from 3 physicians using Delphi style interviews; and
- due to poor data the Ghatnekar paper applied Swedish inpatient costs to the UK setting.

The cost of £377 per severe hypoglycaemic episode was drawn from the Leese paper: £412 once indexed to 2008. As discussed within CG87 this cost refers to the cost per severe hypoglycaemic episode requiring medical attention. CG87 assumed that only 25% of severe hypoglycaemic episode would require external medical assistance, with a parallel reduction in the average cost per severe hypoglycaemic episode. The cost per eye screen is roughly in line with that reported in the Tu 2004 paper, which reports a cost of £24 per screen for optometrists and £29 per screen for digital photography. The costs of foot screening are similarly roughly in line with the Ray and colleagues paper,[53] though it should be noted that this was a multi-nation study that did not include the UK.

An obvious parallel 2008-09 cost to the 2007-08 £897 non-elective tarriff per ketoacidosis event of table 21 [p54] could not be located within the 2008-09 non-elective tariffs by the ERG.

The management costs and the costs of complications as outlined in table A-8 of Appendix 6 of the submission cross checked with those implemented within the CORE model.

Utilities

A key utility within the submission was the -0.0100 utility decrement per unit of BMI increase as drawn from the Lee and colleagues paper.[54] The submission expressed an explicit preference for this decrement rather than the decrement of -0.0061 per unit of BMI as used within CG87. The manufacturer justification for the choice of Lee appears to be that it was collected from a UK population. But to the extent that the CG87 decrement was reasonable, applying it would have had the advantage of improving the comparability between assessments.

The Lee paper was only concerned with estimating the association between quality of life and BMI among three groups of hospital patients: the general population, patients with type 1 diabetes and patients with type 2 diabetes. For the subgroup of patients with type 2 diabetes, the Lee paper modelled quality of life as being a function of the intercept (0.9157), age (-0.0008) and BMI (-0.0100). As such, the overall effect of BMI will have included the direct quality of life impact of

changes in BMI and the impact of the complications of diabetes. Since rates of complications of diabetes will tend to covary positively with both the BMI and the age of patients, the Lee BMI coefficient seems likely to reflect the direct BMI impact and some of the impact of diabetes complications. Consequently, within a modelling exercise such as CORE which explicitly and individually accounts for the disutilities associated with the complications of diabetes the Lee estimate of the impact of BMI will tend to double count these.

Consequently, for the base case it might have been better to have used a source for utilities which undertook a multivariate modelling of the impacts of the complications of diabetes and BMI upon quality of life. This might also argue for adoption of the CG87 disutility for the base case estimate of the impact of BMI upon quality of life, although it is acknowledged that this value was used in the sensitivity analysis.

The utilities reported in table 24 as being drawn from Clarke and colleagues 2002[50] largely cross check with those reported in Table 2 of the paper, relating to the Clarke tobit modelling of EQ-5D evaluated using the social tariff. The exceptions to this are those relating to amputation, which within the corresponding column of the Clarke paper are decrements of -0.538 for the year of the event and -0.412, or a utility value of 0.402, for amputations for years 2+. This compares to the values of a decrement of -0.109 for the year of amputation and a utility of 0.680 for amputations for years 2+ reported within table 24 of the submission. The values for amputation used within the submission relate to the Clarke modelling using the visual analogue scale. Given these values the submission is more optimistic as to the effects of amputation, the effect of this probably being to the slight disadvantage of the more effective treatment.

Table 24 of the submission also makes extensive references to Palmer and colleagues for the utilities relating to eye disease, neuropathy and ulcer.[55] The paper cited is a validation exercise for the CORE model and as such does not appear to report any utility values. The other Palmer references for section 7 of the submission also do not appear to be papers estimating the utilities associated with these complications.

The Tengs and Wallace 2000 paper is a literature survey of quality of life values.[56] Within this there are a number of utility values reported for the likes of dialysis and the manufacturer appears to have made a reasonably pragmatic choice as to the utility values to apply from among these. However, it can be noted that Bagust and Beale[57] in a multivariate analysis estimated the impact of peripheral vascular disease as involving around a 10% loss in quality of life for those with type 2 diabetes, while

Coffey suggested a loss of between 10% and 15% due to dialysis among those with type 2 diabetes.[58] As such, the values used within the submission may tend towards the high side.

The decrements reported for hypoglycaemic events cross check with those reported in the submission.

The BMI disutilities for the base case runs as reported in appendix 11 tally with those implemented within CORE for the base case 1st line and 2nd line treatments across the five studies.

4.4 ERG cross check of results: Base Case Modelling

The base cases within the submission have been re-run within CORE by the ERG. The output of this modelling corresponded with that of the submission. Appendix 4 of this report tabulates these outputs, augmenting those of the submission with the undiscounted survival estimates and further details as to the shape of the associated CEACs. The central estimates are tabulated below:

Table 23 Central estimates for ICERs

	Liraglutide 1.2 mg vs comparator			Liraglutide 1.8 mg vs comparator		
	Δ£	ΔQALY	ICER	Δ£	ΔQALY	ICER
1860 [sitagliptin]	£1,842	0.187	£9,851	£3,224	0.308	£10,465
LEAD5 [exenatide]				£3,638	0.240	£10,054
LEAD6 [glargine]				£1,638	0.163	£15,130
LEAD2 [glimepiride]	£3,157	0.238	£6,226	£4,860	0.245	£9,376
LEAD1 [rosiglitazone]	£2,064	0.332	£13,257	£3,730	0.398	£19,837

In a clarification subsequent to submission, the manufacturer provided the additional estimates of the cost per QALY of liraglutide 1.8mg compared to liraglutide 1.2mg within the trials where this comparison was made:

Table 24 ICERs for 1.8 mg versus 1.2 mg doses of liraglutide

		ICER liraglutide 1.8mg vs 1.2mg
LEAD2	glimepiride	£249,494
LEAD1	rosiglitazone	£25,129
1860	Sitagliptin	£11,414

Subgroup analyses: Results

The final NICE protocol specified possible subgroup analyses around: baseline HbA1c, cardiovascular risk and BMI. The economics of the submission presents the results of modelling for the two subgroups:

- BMI $\geq$30kg/m^2
- BMI $\geq$35kg/m^2

for the three main comparisons undertaken: 1860 for sitagliptin, LEAD5 for exenatide and LEAD6 for glargine.

The clinical inputs to these simulations within CORE are outlined within appendix 9 of the submission, with the underlying statistical analyses for LEAD-6 being reported in figures A-2 to A-6 of appendix 5. The underlying statistical analyses for 1860 and LEAD-5 do not appear to have been presented within the submission.

The population characteristics and clinical input parameters presented within the submission for these subgroups have not been cross checked by the ERG. The CORE model inputs for these subgroup analyses have similarly not been cross checked by the ERG. For ease of reference a summary of the results of this subgroup modelling is presented below:

Table 25 Results of BMI subgroup modelling

	Liraglutide 1.2mg vs comparator			Liraglutide 1.8mg vs comparator		
	Δ£	ΔQALY	ICER	Δ£	ΔQALY	ICER
1860 [sitagliptin]	£1,842	0.187	£9,851	£3,224	0.308	£10,465
BMI $\geq$ 30kg/m^2	£1,793	0.236	£7,593	3,225	0.370	£8,721
BMI $\geq$ 35kg/m^2	£1,856	0.303	£6,125	2,977	0.489	£6,091
LEAD5 [exenatide]				£3,638	0.240	£10,054
BMI $\geq$30kg/m^2				£1,650	0.143	£11,535
BMI $\geq$35kg/m^2				£1,593	0.186	£8,555
LEAD6 [glargine]				£1,638	0.163	£15,130
BMI $\geq$30kg/m^2				£3,124	0.259	£12,053
BMI $\geq$35kg/m^2				£2,750	0.298	£9,241

Note that within the result for these subgroup analyses, the anticipated survival for those of a higher BMI was typically greater than that for those of a lower BMI. The manufacturer has clarified that this is due to the patient population with the higher BMI typically being younger at baseline, as would be expected due to a higher BMI leading to an earlier onset of type 2 diabetes. This earlier onset of diabetes more than outweighs the longer anticipated survival, and the modelling results in those of a higher BMI having a lower anticipated overall longevity.

Note also that the cost effectivenesses for the subgroups of BMI $\geq$30kg/m^2 and BMI $\geq$35kg/m^2 were typically anticipated to be better than that for the patient group as a whole. This in turn implies that the anticipated cost effectiveness in the subgroup with BMI < 30kg/m^2 would be correspondingly worse. This would appear to apply with particular force to the LEAD-5 comparison with glargine for which, based upon the figure A-2 of the submission, had the patient distribution:

- BMI $\leq$ 30kg/m^2 50%
- 30kg/m^2 < BMI $\leq$ 35kg/m^2 31%
- 35kg/m^2 < BMI 19%

The extent to which the cost effectiveness for those with BMI $\leq$ 30kg/m^2 worsen compared to the base case was unfortunately not presented within the submission.

4.5 Sensitivity analyses within the submission

The manufacturer undertook a range of univariate sensitivity analyses within the submission:

1. discount rates were varied between 0.0% and 6.0%, with an additional sensitivity analysis of the old NICE discount rates of 1.5% for benefits and 6.0% for costs being applied
2. an arbitrary variation of the costs of complications by ±20%
3. treatment durations of 3 years, 8 years and lifetime
4. applying the CG87 disutility for BMI changes, and only applying the direct disutility from BMI changes to the initial treatment
5. applying a disutility of -0.0052 to all hypoglycaemic events, and applying no disutility to hypoglycaemic events
6. an arbitrary variation of the clinical effects by +10% for one arm and -10% for the other
7. applying results to the population characteristics of the CG87 cohort
8. equalising effects upon HbA1c
9. equalising effects on SBP
10. varying the time horizon to 10 years and to 20 years

These are summarised below for ease of reference.

Table 26 Manufacturer univariate sensitivity analyses: All patients

	1860		LEAD5	LEAD6
	1.2mg	1.8mg	1.8mg	1.8mg
Basecase ICERS	£9,851	£10,465	£15,130	£10,054
Discount rates				
1a discount rates 0%	£6,720	£6,876	£10,436	£6,595

1b discount rates 6%	£12,452	£13,562	£18,922	£13,093
1c discount rates NICE old	£7,234	£7,572	£10,980	£7,139
Complication costs				
2a Complication costs -20%	£10,080	£10,865	£15,198	£10,603
2b Complication costs +20%	£9,623	£10,065	£15,061	£9,503
Treatment duration				
3a Initial treatment 3 years	£4,321	£4,748	£8,476	£4,741
3b Initial treatment 8 years	£16,497	£17,994	£24,491	£16,840
3c Initial treatment lifetime	£36,659	£40,624	£45,324	£31,690
Weight effects				
4a CG87 disutility	£11,637	£11,788	£17,774	£10,171
4b Only initial treatment	£13,752	£13,461	£18,984	£10,826
Hypoglycaemia disutilities				
5a All -0.0052	£9,852	£10,552	£14,825	£9,870
5b All no disutility	£9,686	£10,298	£14,732	£10,864
Clinical effectiveness				
6a Liraglutide 20% relative improvement	£5,614	£7,238	£11,700	£5,737
6b Comparator 20% relative improvement	£18,361	£15,914	£21,118	£27,290
Cohort				
7a CG87 cohort	£11,526	£10,757	£12,526	£10,270
Equalisation of single clinical variable				
8 HbA1c	£21,018	£25,926	£22,735	£28,391
9 SBP	£9,724	£10,491	£18,764	£9,946
Time horizon				
10a 10 years	£21,687	£27,879	£34,895	£27,203
10b 20 years	£11,467	£12,628	£18,381	£12,628

The alternative assumptions as to the direct disutility from BMI increases and their application after the change from initial therapy to glargine were also performed for the BMI subgroups.

Table 27 Manufacturer univariate sensitivity analyses: BMI ≥30kg/m^2

	1860		LEAD5	LEAD6
	1.2mg	1.8mg	1.8mg	1.8mg
Basecase	£7,593	£8,721	£12,053	£11,535
Weight effects				
4a CG87 disutility	£8,597	£9,705	£13,959	£12,205
4b Only initial treatment	£10,064	£11,196	£15,364	£13,586

Table 28 Manufacturer univariate sensitivity analyses: BMI ≥35kg/m^2

	1860		LEAD5	LEAD6
	1.2mg	1.8mg	1.8mg	1.8mg
Basecase	£6,125	£6,091	£9,241	£8,555
Weight effects				
4a CG87 disutility	£6,964	£6,583	£10,978	£8,603
4b Only initial treatment	£8,434	£7,665	£12,770	£9,620

4.6 ERG Additional sensitivity analyses

Impact of individual clinical effects

In order to better understand the impact of the individual clinical effects, the ERG implemented the individual clinical effects observed within the trials to quantify the main contributors to the anticipated patients outcomes and costs for the five trials of the submission.

The tables below summarise these impacts on the net changes for the three main trials: 1860, LEAD-5 and LEAD-6. Within this, the first row is the base case of the submission. Subsequent rows relate to the sensitivity analyses of:

- SA1 Only the direct drug costs with no clinical effect, simply as a baseline for comparison
- SA2a Applying the change in BMI but not applying any direct disutility from weight changes
- SA2a Applying the change in BMI and applying any direct disutility from weight changes
- SA3 Applying the changes in cholesterol and triglycerides
- SA4 Applying the changes in systolic blood pressure
- SA5 Applying the changes in HbA1c

Note that in addition to the clinical effects, SA2a through to SA5 also apply the changes in the direct drug costs of SA1. Note also that for SA1 through to SA5 the rates of hypos were set to zero in order to identify the individual clinical effects of the changes. The treatment-specific individual clinical changes were applied to each arm of the trial modelled; e.g. for SA5 of LEAD-5 an HbA1c drop of 1.33% for liraglutide 1.8mg and of 1.09% for glargine. (Note that these are not placebo-corrected, but the difference does not change).

The tables below show the base case results, and how these differ from SA1 of no clinical effects and only the direct drug costs being applied. Thereafter, the results of the various sensitivity analyses are presented, coupled with the percentage contribution the clinical variable in question makes to the difference between there being no clinical effects as per SA1 and there being all the clinical effects

simultaneously as per the basecase. These percentages are mainly of relevance to the assessment of the contribution of individual clinical effects to the patient outcomes of life expectancy and QALYs. The individual effects will typically not sum to 100% of the overall clinical effect due sub-models within CORE not being independent.

Table 29 Results of ERG sensitivity analyses: liraglutide 1.2 versus sitagliptin

1860		**Net Effect**							
Lira 1.2mg vs Sita 100mg		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
Basecase		[redacted]							
SA1	Only direct drug costs								
SA2a	Weight: no direct utility								
SA2b	Weight: direct utility								
SA3	Chol & triglycerides								
SA4	SBP								
SA5	HbA1c								
SA2b-5						-			

The above indicates that while weight changes had a minor impact upon the anticipated gain in life expectancy, this was largely offset by the changes in cholesterol, triglycerides and SBP.

[redacted]. The contribution of changes in BMI to the anticipated QALY gain is overwhelmingly due to the direct utility effects assumed, and is not due to any differences in the downstream complications of diabetes that result.

Table 30 ERG sensitivity analyses: liraglutide 1.8mg versus sitagliptin

1860		**Net Effect**							
Lira 1.8mg vs Sita 100mg		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
Basecase		[redacted]							
SA1	Only direct drug costs								
SA2a	Weight: no direct utility								
SA2b	Weight: direct utility								
SA3	Chol & triglycerides								
SA4	SBP								

SA5	HbA1c	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA2b-5		[redacted]	[redacted]	[redacted]	[redacted]	-			

[redacted]

Table 31 ERG sensitivity analyses: liraglutide versus glargine.

LEAD-5		**Net Effect**							
Liraglutide 1.8mg vs glargine		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
Basecase		0.17	0.17	0.24	0.24	£3,720	£121	£3,638	£39
SA1	Only direct drug costs	0.00		0.00		£3,599		£3,599	
SA2a	Weight: no direct utility	0.02	12%	0.02	7%	£3,611	10%	£3,639	103%
SA2b	Weight: direct utility	0.02	12%	0.11	48%	£3,613	12%	£3,641	108%
SA3	Chol & triglycerides	0.02	14%	0.02	8%	£3,614	12%	£3,535	-164%
SA4	SBP	0.08	45%	0.07	28%	£3,648	40%	£3,527	-185%
SA5	HbA1c	0.04	25%	0.04	18%	£3,630	26%	£3,447	-390%
SA2b-5			96%		102%				

In contrast to 1860, given the similar clinical profiles of liraglutide 1.8 mg and glargine in LEAD-5 the principal source of the additional life expectancy for liraglutide 1.8 mg arises from the changes in SBP: -3.97mmHg for liraglutide 1.8 mg as compared to +0.54 mmHg for glargine. HbA1c has relatively little impact given changes of -1.33% and -1.09% for liraglutide 1.8 mg and glargine respectively. Turning to the QALY side of the equation, the single largest contributor to this appears to be the direct utility impact from changes in BMI: -0.644kg/m^2 for liraglutide 1.8mg as compared to +0.577kg/m^2 for glargine.

Table 32 ERG sensitivity analyses: liraglutide versus exenatide

LEAD6		**Net Effect : Liraglutide 1.8mg minus exenatide 10µg**							
Liraglutide 1.8mg vs exenatide 10µg		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
Basecase		0.15	0.15	0.16	0.16	£2,085	£98	£1,638	-£349
SA1	Only direct drug costs	0.00		0.00		£1,987		£1,987	
SA2a	Weight: no direct utility	0.00	1%	0.00	1%	£1,988	1%	£1,981	2%
SA2b	Weight: direct utility	0.00	1%	0.02	11%	£1,988	1%	£1,981	2%

SA3	Chol & triglycerides	0.04	28%	0.03	20%	£2,014	28%	£2,007	-6%
SA4	SBP	0.00	1%	0.00	2%	£1,989	2%	£1,944	12%
SA5	HbA1c	0.08	54%	0.09	56%	£2,041	55%	£1,651	96%
SA2b-5			84%		90%				

Among the three main comparisons, LEAD-6 is the exception. With both liraglutide and exenatide being GLP-1s there is minimal difference between them in terms of BMI changes: -1.145kg/m^2 for liraglutide 1.8 mg as compared to -1.015kg/m^2 for exenatide. The main source of patient benefits both in terms of life expectancy and QALYs is the superior HbA1c profile for liraglutide 1.8 mg of -1.12% as compared to -0.79% for exenatide, coupled with some additional superiority in cholesterol and triglycerides. Within this, it should be borne in mind that the anticipated patient gain in LEAD-6 is the smallest of the three main comparisons.

Weight direct utility effects

The previous section highlighted the importance of the effects of weight changes upon the modelling undertaken by the manufacturer. Appendix 11 of the manufacturer submission outlined the calculation of the disutilities applied within the modelling. More transparently, for the three main comparisons undertaken, the effects of the direct disutilities from weight changes can be summarised as below, and as outlined in greater detail in Appendix 6. The column "excess BMI 25+" refers to the difference between mean BMI in the trial groups and the upper normal limit of BMI, taken to be 25.

Table 33 ERG sensitivity analyses: application of weight disutilities

	From BMI	ΔBMI	To BMI	Excess BMI25+	Annual Disutility	Annual Net
1860 Sitagliptin						
1st line year 1-5						
Liraglutide 1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liraglutide 1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitagliptin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
2nd line year 6+						
Liraglutide 1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liraglutide 1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitagliptin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEAD-5 Glargine						
1st line year 1-5						
Liraglutide 1.8	30.5	-0.644	29.856	4.856	-0.049	0.012
Glargine	30.5	0.577	31.077	6.077	-0.061	

2nd line year 6+						
Liraglutide 1.8	29.856	0.577	30.433	5.433	-0.054	0.006
Glargine	31.077	0	31.077	6.077	-0.061	
LEAD-6						
Exenatide						
1st line year 1-5						
Liraglutide 1.8	32.95	-1.145	31.805	6.805	-0.068	0.001
Exenatide	32.95	-1.015	31.935	6.935	-0.069	
2nd line year 6+						
Liraglutide 1.8	31.805	0.577	32.382	7.382	-0.074	0.001
Exenatide	31.935	0.577	32.512	7.512	-0.075	

The key point in the above is that the net annual impact during the initial 5 year treatment is assumed to carry over to the remainder of the modelling. Movement on to glargine is associated with the same step change in BMI for both arms, resulting in patients being anticipated to maintain the weight changes of the first year for the time horizon of the modelling.

This also applies within the modelling of LEAD-5 comparing liraglutide 1.8 mg with glargine, but with the slight difference that there is no move to a different third line drug for the glargine arm. Despite patients in both arms being on glargine for years 6+, during this period of the modelling those in the liraglutide arm are still anticipated to be of lower weight than those in the glargine arm.

As can also be seen from the above the anticipated net impact within the comparison with the other GLP-1, exenatide, is very small.

As a cross check and relatively simple ready-reckoner for predicting the effects of changes to the assumptions around the direct utility gains from weight changes, the annual disutilities can be applied to the approximate average survival of 16 years to provide an estimate of the discounted gains as a percentage of the total QALY gain of the base case modelling:

- during treatment in years 1-5,
- during later treatment of years 6+
- over the period of the modelling

Table 34 Estimate of percentage of QALY gain resulting from weight disutilities

	1860		**LEAD5**	**LEAD6**	**LEAD1**		**LEAD2**	
	1.2mg	1.8mg	1.8mg	1.8mg	1.2mg	1.8mg	1.2mg	1.8mg
year 1-5	[redacted]	[redacted]	24%	4%	9%	10%	24%	25%

year 6-16	[redacted]	[redacted]	21%	6%	15%	17%	41%	42%
Total year 1-16	[redacted]	[redacted]	45%	10%	25%	27%	65%	67%

Changes to the assumptions around the size of the utility decrement per BMI point from the base case value of -0.01 would have a proportionate effect on the above. For instance, a decrement of only -0.005 would reduce the QALY gain from liraglutide in LEAD-6 by approximately 5% with a parallel effect on the ICER, while the QALY gain from liraglutide in LEAD-5 would be reduced by approximately 22% again with a parallel effect on the ICER. The totals for years 1-16 show a reasonable correspondence with the figures suggested by the sensitivity analyses 2a and 2b for trials 1860, LEAD-5 and LEAD-6 as reported in the previous section.

The manufacturer undertook sensitivity analyses that applied the CODE-2 disutility of -0.0061 per BMI point as per CG87, a reduction of 40%:

Table 35 Manufacturer's sensitivity analyses using CODE-2 weight disutilities

	1860		**LEAD5**	**LEAD6**	**LEAD1**		**LEAD2**	
	1.2mg	1.8mg	1.8mg	1.8mg	1.2mg	1.8mg	1.2mg	1.8mg
Basecase	[redacted]	[redacted]	£15,130	£10,054	£6,226	£9,376	£13,257	£19,837
Revised	[redacted]	[redacted]	£17,774	£10,171	£6,768	£10,280	£17,318	£26,244
% change	[redacted]	[redacted]	17%	1%	9%	10%	31%	32%
% change / 40%	[redacted]	[redacted]	44%	3%	22%	24%	77%	81%

Within this, the % change / 40% shows reasonable agreement with the total year 1-16 percentages of the ready-reckoner, with the exception of the results for LEAD-2.

Similarly, if the direct disutility effects from weight changes are restricted to only the initial treatment the anticipated QALY gains would be reduced by the post-5-year treatment effects. The manufacturer undertook this set of analyses for the base case disutility of -0.01 per BMI point, resulting in the ICERs:

Table 36 Manufacturer's sensitivity analyses: disutilities from weight changes

	1860		**LEAD5**	**LEAD6**	**LEAD1**		**LEAD2**	
	1.2mg	1.8mg	1.8mg	1.8mg	1.2mg	1.8mg	1.2mg	1.8mg
Basecase	[redacted]	[redacted]	£15,130	£10,054	£6,226	£9,376	£13,257	£19,837
Revised	[redacted]	[redacted]	£18,948	£10,826	£7,402	£11,352	£22,088	£33,730
% change	[redacted]	[redacted]	25%	8%	19%	21%	67%	70%

[redacted] As for the change in the utility decrement, there is also relatively poor correspondence for the LEAD-2 results between the sensitivity analysis of the manufacturer that removes any differential weight gain between the arms for the 2nd line treatment and the ready-reckonner. Whether the reason for these discrepancies is a misinterpretation or error by the ERG is currently unclear, and unfortunately deadlines have precluded the ERG from formally running these simulations within CORE.

Direct treatment costs

As outlined in the section cross checking the direct drug costs, three additional sensitivity analyses around these were undertaken by the ERG:

- for LEAD-6 assuming one needle per day for both liraglutide and exenatide
- for LEAD-5 assuming a glargine dose of 24IU throughout
- for LEAD-5 assuming NPH was used rather than glargine, with a similar dose

One needle per day for exenatide:

One needle per day for both liraglutide and exenatide reduces the anticipated treatment costs for exenatide by around 5%. This saw the estimated direct treatment cost in the exenatide arm fall from £8,878 to £8,700, this direct treatment cost being the discounted total of both initial exenatide and subsequent glargine. Given this relatively minor change, the estimate cost effectiveness worsened only slightly from £10,054 per QALY in the base case to £11,079 per QALY if exenatide only requires one needle per day.

24 IU glargine dose:

Assuming a glargine dose of 24 IU daily through the modelling reduced the direct treatment costs for both the liraglutide 1.8 mg arm and the glargine arm. For the former these fell from £11,090 to £9,793, while for the latter a steeper decline was seen of £7,370 to £5,673. This caused the estimated cost effectiveness of liraglutide 1.8mg to worsen from £15,130 per QALY to £16,793 per QALY.

Table 37 Sensitivity analysis: glargine dose 24 units daily throughout

	Liraglutide 1.8mg	Glargine	Net
Direct Treatment Costs	£9,793	£5,673	£4,120
Other Costs	£14,019	£14,101	-£82
Total Costs	£23,812	£19,774	£4,038
QALYs	7.30	7.06	0.24

ICER			£16,793

Note that a similar sensitivity analysis was performed by the manufacturer in section 7.5.3.1 of the submission, with the results reported in table 45 [p91]. In this the manufacturer estimated that the cost effectiveness of liraglutide would worsen to £22,188 per QALY. This result appears to have arisen due to the manufacturer assuming a dose of 24 IU for the glargine arm for the period of the modelling, but retaining a dose of 40IU for 2nd line glargine for the liraglutide 1.8 mg arm. If the base case direct treatment costs of the liraglutide 1.8 mg arm are substituted into this analysis it results in:

Table 38 Sensitivity analysis - glargine doses and costs

	Liraglutide 1.8mg	Glargine	Net
Direct Treatment Costs	£11,090	£5,673	£5,417
Other Costs	£14,019	£14,101	-£82
Total Costs	£25,109	£19,774	£5,335
QALYs	7.30	7.06	0.24
ICER			£22,229

which broadly tallies with the £22,188 per QALY result of the manufacturer sensitivity analysis.

NPH instead of glargine:

Assuming that NPH was used at a dose of 24IU in the 1st year and 40 IU thereafter reduced the direct treatment costs for both the liraglutide 1.8 mg arm and the glargine arm, the reduction in the liraglutide 1.8mg arm again being due to the progression to 2nd line insulin at year 5. The direct treatment costs for liraglutide 1.8mg fell from £11,090 to £9,360, while for the insulin arm a steeper decline was seen of £7,370 to £5,013. This caused the estimated cost effectiveness of liraglutide 1.8mg to worsen from £15,130 per QALY to £17,739 per QALY.

Table 39 Sensitivity analysis using NPH instead of glargine

	Liraglutide 1.8mg	NPH	Net
Direct Treatment Costs	£9,360	£5,013	£4,347
Other Costs	£14,020	£14,101	-£82
Total Costs	£23,380	£19,114	£4,265
QALYs	7.30	7.06	0.24
ICER			£17,739

Note that a similar sensitivity analysis was also performed by the manufacturer in section 7.5.3.1 of the submission, with the results again reported in table 45 [p91]. In this the manufacturer estimated that the cost effectiveness of liraglutide would worsen to £24,933 per QALY. This result appears to

have arisen due to the manufacturer assuming that NPH was used for the comparator arm, but that within the 1.8mg liraglutide arm the insulin at year 5 would be 40IU glargine. If the base case direct treatment costs of the liraglutide 1.8mg arm are substituted into this analysis it results in:

Table 40 Sensitivity analysis with NPH – Liraglutide base case substitution

	Liraglutide 1.8mg	NPH	Net
Direct Treatment Costs	£11,090	£5,013	£6,077
Other Costs	£14,020	£14,101	-£81
Total Costs	£25,110	£19,114	£5,996
QALYs	7.30	7.06	0.24
ICER			£24,983

which broadly tallies with the £24,933 per QALY result of the manufacturer sensitivity analysis.

4.7 Post submission additional manufacturer sensitivity analyses: Indexation

For the base case the costs of the complications of diabetes were taken in large part from Clarke and Colleagues (2003)[50] with this being uplifted for inflation using the HSCI index. Given that these costs were in 1999 prices, this resulted in a 12% uplift to result in 2008 prices. While there may be some concerns around indexing costs over such a long period, as outlined in greater detail in Appendix 5, it would seem more appropriate to have applied the HCHS index which would have resulted in a 42% uplift.

Such a change might appear dramatic given that the costs of complications typically exceeded the direct costs of treatment. But it should be borne in mind that the rates of complications and the costs associated with them were similar between arms, and the net effects were correspondingly reduced. While a net cost offset was provided by a reduction in the costs of complications from the more effective treatment, the effect of applying the HCHS index is a relatively minor increase in this net cost offset.

The manufacturer has provided an additional set of analyses that performs this comparison with the estimates of the cost per QALY of this reported below, where the HSCI values are the base case estimates:

Table 41 Effect of indexation on ICERs

	1.2mg liraglutide versus comparator		**1.8mg liraglutide versus comparator**	
Indexation	**HSCI**	**HCHS**	**HSCI**	**HCHS**
1860 [sitagliptin]	£9,851	£9,541	£10,465	£9,879

LEAD5 [glargine]			£15,130	£15,103
LEAD6 [exenatide]			£10,054	£9,212
LEAD1 [rosiglitazone]	£6,226	£5,544	£9,376	£8,748
LEAD2 [glimepiride]	£13,257	£13,155	£19,837	£19,729

4.8 Comparison of submission with NICE reference case

Table 42 NICE reference case checklist

Attribute	**Reference case**	**Does the *de novo* economic evaluation match the reference case**
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes
Perspective costs	NHS and Personal Social Services (PSS)	NHS perspective only. The manufacturer has justified the absence of PSS costs (page 48).
Perspective benefits	All health effects on individuals	All important effects are included in the CORE model. Some disutilities are not included, such as injection discomfort and nausea, but these are unlikely to have significant effect.
Form of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes – 40 year horizon
Synthesis of evidence on outcomes	Systematic review	Yes
Outcome measure	Quality adjusted life years (QALYs)	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes, derived from a series of published studies and incorporated in CORE. Most utilities were based on EQ5D.
Benefit valuation	Time-trade off or standard gamble	The majority of utilities were drawn from the Clarke et al 2002 UKPDS paper which relied on the tobit modelling of EQ-5D tariff values.[50]
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Utilities were taken mainly from the UKPDS, a very large study in the UK.
Discount rate	An annual rate of 3.5% on both costs and health effects	Benefits and costs, where appropriate, have been discounted using the 3.5% rate
Equity	An additional QALY has the same weight regardless of the	All QALYs estimated by the economic model have the same

	other characteristics of the individuals receiving the health benefit	weight.
Sensitivity analysis	Probabilistic sensitivity analysis (PSA)	PSA was undertaken by the manufacturer for the base case. This was also coupled with a range of univariate sensitivity analyses, with these univariate sensitivity analyses being implemented within the probabilistic CORE model structure.

Item	**Critical appraisal**	**ERG comment**
Was a well-defined question posed in answerable form?	Yes	Three main comparisons were performed: • liraglutide 1.2mg and 1.8mg with sitagliptin 100mg, both arms in conjunction with metformin, based upon study 1860; • liraglutide 1.8mg with exenatide 10μg, both arms in conjunction with metformin and/or sulphonylurea, based upon study LEAD-6 • liraglutide 1.8mg with glargine , both arms in conjunction with metformin and sulphonylurea, based upon study LEAD-5 Coupled with two additional comparisons for completeness, given the clinical evidence base: • liraglutide 1.2mg and 1.8mg with rosiglitazone 4mg, both arms in conjunction with sulphonylurea, based upon study LEAD-1; • liraglutide 1.2mg and 1.8mg with glimepiride 4mg, both arms in conjunction with metformin, based upon study LEAD-2; The viewpoint of the analysis was as specified for the NICE reference case.
Was a comprehensive description of the competing alternatives given?	Yes	This was largely defined within the NICE protocol and interpreted above in the light of head to head trial data being available.
Was the effectiveness of the intervention established?	Yes	The clinical effectiveness of liraglutide was well established and is not in doubt.

Were all the important and relevant costs and consequences for each alternative identified?	Yes, as far as is possible with current data.	The studies of the GLP-1 agonists are of quite short duration (up to two years in open extension studies) and it is not possible to be sure that there will be no long term adverse effects such as pancreatitis or thyroid cancer with liraglutide. The evidence for a link between exenatide and pancreatitis is growing but it seems to be quite a rare occurrence. There is now also concern about renal failure with exenatide, but the link may not be causal. (FDA website).[59] Nausea was not considered within the economic modelling, but this would be of relatively short duration and for those remaining on treatment probably have limited impact upon quality of life. Modelling could have considered nausea as affecting the probability of discontinuing but the clinical effectiveness data does not suggest serious differences in discontinuation rates between the arms of the head to head trials. Alternative viewpoints, such as a societal viewpoint for benefits, were not explored. Given the license and position sought for liraglutide it seems likely that alternative viewpoints would not have particularly affected the analysis. Loss of earnings and productivity may apply with disease progression. Similarly, there may be additional third party carer considerations as disease progresses. These seem unlikely to differ substantially between arms.
Were costs and consequences measured accurately in appropriate physical units?	Yes	The physical units of the costs and consequences were largely outputs of the CORE model.
Were the cost and consequences valued credibly?	Yes	The manufacturer used the well-developed CORE model which includes costs. In the main these appears to have been credibly valued. There were some gaps and there may have been some double counting of some outpatient costs, but the overall impact of this seems unlikely in itself to have a significant effect upon results. The consequences (most notably the complications of diabetes) were estimated in the model based on HbA1c, the standard measure of glycaemic control, which correlates well with most complications. Blood pressure and weight were also used in the modelling to predict future health effects.
Were costs and consequences adjusted for differential timing?	Yes	The costs of complications as taken from UKPDS 65 were uprated for inflation to 2008 prices using the Health Services Cost Index (HSCI), for goods and services purchased, as reported in the PSSRU Unit Costs of Health and Social Care. With UKPDS 65 being in 1999 prices this led to a 12% uplift in the nominal costs of complications. The manufacturer could have argued for applying the Hospital and Community Health Services (HCHS) index,

		this being the aggregate effect of pay inflation as measured by the Pay Cost Index (PCI) and the HSCI. This would have seen a 42% uplift in the nominal costs of complications. The effects of applying the HCHS index have been explored through additional analyses supplied by the manufacturer and are reported below. The reasonableness of uprating costs from 1999 to 2008 values may be called into question, but UKPDS 65 remains a reasonably standard reference. It also has the additional benefit of being a coherent source across the variety of complications associated with diabetes that is independent of both the CORE modelling and the manufacturer.
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Yes
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Yes, the CORE model is by nature a probabilistic model and the uncertainty surrounding the estimates of clinical effectiveness was applied throughout the modelling. The submission reported the CEAC probabilities for willingness to pay values of £20k per QALY and £30k per QALY.
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ERG= Evidence Review Group; cancer; QALY=quality adjusted life year; LYG=life year gained; SA=sensitivity analysis; PSA=probabilistic sensitivity analysis; ICER=incremental cost-effectiveness ratio.

5. DISCUSSION

5.1 Summary of clinical effectiveness

Novo Nordisk provided a good submission which listed a large number of trials but which then focused on the most relevant ones, which came from an integrated series of trials, known as the LEAD ones, which tested liraglutide at the various stages in the progression of type 2 diabetes. All the studies have been sponsored by the manufacturer

We started from the position that UK practice would be as recommended in the NICE guideline, with GLP-1 agonists being used as third drug after dual therapy with two of metformin, a sulphonylurea and a glitazone being used. The comparators for liraglutide would therefore be a basal insulin, exenatide or one of the other new class of drugs, the DPP-4 inhibitors such as sitagliptin or vildagliptin.

We therefore paid most attention to the studies which compared liraglutide, namely LEAD-5, LEAD-6 and the unpublished 1860. However we also reviewed trials in which liraglutide was used as the second drug, for example in combination with metformin, in case NICE decided to recommend such use.

Our conclusion was that liraglutide was clinically effective in both doses used, 1.2 mg and 1.8 mg. Like others in this class of drugs, it has advantages over most other oral glucose lowering agents, in that its action is glucose dependent so that it does not cause hypoglycaemia. It shares this characteristic with the gliptins, which also act on the incretin system. The other characteristic of the GLP-1 agonists is weight loss. With the exception of the gliptins, which tend to be weight-neutral, other second or third line drugs, the sulphonylureas, the glitazones and insulin, cause weight gain.

Because of the significant cost difference, we examined the relative benefits of the 1.8 mg dose over the 1.2 mg dose, and concluded that in most patients, the differences were small and that 1.2 mg would suffice. This is the expectation of Novo Nordisk (page 11 of the industry submission).

It has been suggested that patients with the highest BMIs might benefit more from the higher dose, and in trial 1860,

[redacted]

[redacted]

Weaknesses in evidence

The main weakness is that the trials were of short duration, and we cannot at present be sure of the long-term safety. Exenatide appeared safe in the trials, but concerns are growing over pancreatitis, and more recently, renal failure. [45,46,59] If pancreatitis is a real, if rare, consequence of exenatide, will that be limited to exenatide or a class effect? There have been past occasions where only one of a class of drugs had specific adverse effects, such as sclerosing peritonitis with practolol, or liver problems with troglitazone.

Another weakness is a common one in diabetes trials, that no data on long-term complications are available. However given the timescale of complications such as retinopathy or cardiovascular disease, it would be unrealistic to expect such data from trials, and modelling based on intermediate indicators such as glycaemic control as reflected in HbA1c is usually accepted as a reliable prediction of future outcomes.

5.2 Summary of cost-effectiveness

The submission used the CORE model, which is a well-developed and well-respected diabetes model. As the CORE model is not standard software as defined by NICE, the manufacturer confirmed with the NICE secretariat that its use for this submission would be acceptable. The CORE model has also been used for previous modelling for NICE in the assessment of continuous subcutaneous insulin infusion compared to multiple daily injections.

The manufacturer presented three main sets of analyses, based upon the three main clinical trials noted above:

- LEAD-5 comparing liraglutide 1.8mg with glargine
- LEAD-6 comparing liraglutide 1.8mg with exenatide
- 1860 comparing liraglutide 1.2mg and 1.8mg with sitagliptin

Initial treatments were assumed to be for 5 years in the base case, with patients then switching to glargine.

The ERG has cross checked the parameter values used within the manufacturer modelling. Where parameter values were drawn from the literature, with the exception of a few parameters the cited references contained values that cross checked with those presented within the submission. With the exception of a small number of parameters, the values reported within the submission cross checked

with those implemented within CORE. The exceptions seem unlikely to markedly affect analyses given base case results.

Similarly, the clinical effectiveness estimates taken from the trials and reported within the appendices of the submission as having been applied within CORE cross checked with those implemented within CORE, with only a very minor exception.

Re-running the base cases within CORE saw results cross check with those reported by the manufacturer within the submission.

We have not yet resolved uncertainties around the implementation of treatments subsequent to the initial treatment, in the CORE model. But the likelihood is that if resolved, this would be to the benefit of liraglutide.

There may also be some concerns around the implementation of weight changes within the modelling. The duration of the direct benefits from initial treatments may have been too long, and the direct disutility associated with these changes may also have been too large.

For the base cases the manufacturer estimated a cost effectiveness of:

- £15,130 per QALY for liraglutide 1.8mg compared to glargine
- £10,054 per QALY for liraglutide 1.8mg compared to exenatide
- £10,465 per QALY for liraglutide 1.8mg compared to sitagliptin
- £9,851 per QALY for liraglutide 1.2mg compared to sitagliptin

Additional sub-group analyses undertaken by the manufacturer suggested that for patients of a higher BMI liraglutide was typically more cost effective. The estimates of cost effectiveness for those of a lower BMI were not presented.

Univariate sensitivity analyses undertaken by the manufacturer suggested that these estimates were most sensitive to:

- the assumed duration of initial therapy
- the application of weight changes and disutility associated with this
- the time horizon of the analysis

Additional sensitivity analyses undertaken by the ERG suggested that the main sources of the estimated patient benefits were:

- the direct utility effects of BMI changes and SBP, with some additional contribution from HbA1c, for the comparison with glargine
- HbA1c, with some additional effects from cholesterol and triglycerides, for the comparison with exenatide
- HbA1c and direct utility effects of BMI changes for the comparisons with sitagliptin

Weaknesses in evidence

Because the trials were short-term, it was necessary to model costs and outcomes far beyond the duration of the trials.

In line with the NICE policy of only considering licensed products, we compared liraglutide with existing comparators, using a 40 year duration. In reality, daily liraglutide will soon be displaced by other GLP-1 agonists which are given weekly or fortnightly.

5.3 Research needs

The most important need is for data on long-term safety.

The next need is for comparative trials of the new GLP-1 agonists with the current ones, with particular emphasis on cost-effectiveness and adverse effects. Head to head trials of the 1.2 mg dose against glargine and exenatide would be useful.

A trial of weekly exenatide against daily liraglutide, known as DURATION-6, is planned by the manufacturer of exenatide.[40] (DURATION is short for Diabetes therapy Utilization: Researching changes in A1c, weight and other factors Through Intervention with exenatide ONce weekly.)

Another trial EUREXA (European Exenatide study) is examining longer-term (2.5 years) use of exenatide.[60]

A third need is for studies long enough to determine whether this group of drugs have any effect on progression of disease. In the short term they appear to improve beta cell function, but this effect wears off a few weeks after the drug is stopped. It has been suggested that because of the slow turnover of human beta cells, that only studies lasting for several years could whether there is any effect on beta cell capacity. Long term studies would also provide data on the duration of benefits such as weight changes.

Conclusion

There is a good evidence base for the clinical effectiveness of liraglutide. It helps improve diabetes control, and has the additional benefits of some weight loss in most users.

Liraglutide appears safe but that can only be confirmed once there are long term data.

There are some uncertainties about the cost-effectiveness because of the need for long-term modelling based on data from short-term trials. An important issue is that some current comparisons, for example between the two available GLP-1 analogues, daily liraglutide and twice daily exenatide, will be rendered obsolete shortly, with the arrival of longer-acting GLP-1 analogues given once a week or perhaps once every two weeks.

REFERENCES

1. Aas AM, Bergstad I, Thorsby PM, Johannesen O, Solberg M, Birkeland KI. An intensified lifestyle intervention programme may be superior to insulin treatment in poorly controlled Type 2 diabetic patients on oral hypoglycaemic agents: results of a feasibility study. *Diabet Med* 2005;22:316-22.

2. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB *et al*. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.

3. National Institute for Health and Clinical Excellence. Type 2 Diabetes - newer agents (partial update of CG66.Clinical Guideline:CG87). 2009, May http://www.nice.org.uk/Guidance/CG87 (accessed 2 December 2009)

4. Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B *et al*. Newer agents for blood glucose control in type 2 diabetes. *Health Technology Assessment* 2010;in press.

5. Yorkshire and Humber Public Health Observatory. Prescribing for Diabetes in England. An analysis of volume, expenditure and trends. June 2009. 2009, June 11th http://www.yhpho.org.uk/resource/item.aspx?RID=9711 (accessed 3 December 2009)

6. UKPDS Study Group. UKPDS 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. *Diabetes* 1995;44:1249-58.

7. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP *et al*. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006;355:2427-43.

8. Calvert MJ, McManus RJ, Freemantle N. Management of type 2 diabetes with multiple oral hypoglycaemic agents or insulin in primary care: retrospective cohort study. *Br J Gen Pract* 2007;57:455-60.

9. Rubino A, McQuay LJ, Gough SC, Kvasz M, Tennis P. Delayed initiation of subcutaneous insulin therapy after failure of oral glucose-lowering agents in patients with Type 2 diabetes: a population-based analysis in the UK. *Diabet Med* 2007;24:1412-8.

10. Black C, Cummins E, Royle P, Philip S, Waugh N. The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation. *Health Technol Assess* 2007;11:1-126.

11. Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR *et al*. Patient and provider perceptions of care for diabetes: results of the cross-national DAWN Study. *Diabetologia* 2006;49:279-88.

12. Alvarez GF, Mavros P, Nocea G, Alemao E, Alexander CM, Yin D. Glycaemic control among patients with type 2 diabetes mellitus in seven European countries: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) study. *Diabetes Obes Metab* 2008;10 Suppl 1:8-15.

13. Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. *JAMA* 1997;278:1663-9.

14. Yki-Jarvinen H, Kauppinen-Makelin R, Tiikkainen M, Vahatalo M, Virtamo H, Nikkila K *et al*. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 2006;49:442-51.

15. Donnelly LA, Morris AD, Evans JM. Adherence to insulin and its association with glycaemic control in patients with type 2 diabetes. *QJM* 2007;100:345-50.

16. BMJ Group, RPS Publishing. British National Formulary. 2009, September http://bnf.org/bnf/ (accessed 4 December 2009)

17. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P *et al*. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care* 2009;32:1224-30.

18. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S *et al*. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): A randomised controlled trial. *Diabetologia* 2009;52:2046-55.

19. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH *et al*. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *The Lancet* 2009;374:39-47.

20. Bunck MC, Diamant M, Corner A, Eliasson B, Malloy JL, Shaginian RM *et al*. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care* 2009;32:762-8.

21. Barnett AH, Burger J, Johns D, Brodows R, Kendall DM, Roberts A *et al*. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. *Clinical Therapeutics* 2007;29:2333-48.

22. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: A randomized trial. *Annals of Internal Medicine* 2005;143:559-69+I30.

23. Pan CY, Sinnassamy P, Chung KD, Kim KW, LEAD-Study-Investigators-Group. Insulin glargine versus NPH insulin therapy in Asian Type 2 diabetes patients. *Diabetes research and clinical practice* 2007;76:111-8.

24. Wang XL, Lu JM, Pan CY, Mu YM, Dou JT, Ba JM *et al*. Evaluation of the superiority of insulin glargine as basal insulin replacement by continuous glucose monitoring system. *Diabetes Res Clin Pract* 2007;76:30-6.

25. Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. *Diabetes Care* 2005;28:1282-8.

26. Davies MJ, Donnelly R, Barnett AH, Jones S, Nicolay C, Kilcoyne A. Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: results of the Helping Evaluate Exenatide in patients with diabetes compared with Long-Acting insulin (HEELA) study. *Diabetes Obes Metab* 2009;11:1153-62.

27. Nauck M, Hermansen K, Frid A, Shah NS, Tankova T, Mitha IH *et al*. Sustained glycaemic control with 2 years of liraglutide and glimepiride treatment (both combined with metformin), achieved with weight loss and less hypoglycaemia with liraglutide: data from the LEAD-2 trial. *IDF 2009, 20th World Diabetes Congress, Montreal 18-22 October* 2009;P-1402:p.473.

28. European Medicines Agency. Victoza: European Public Assessment Report. 2009, 30th June http://www.emea.europa.eu/humandocs/Humans/EPAR/victoza/victoza.htm (accessed 3 December 2009)

29. Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A *et al*. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ* 2009;339:b4731.

30. Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB *et al*. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. *Arch Intern Med* 2009;169:1619-26.

31. Plutzky J, Garber A, Falahati A, Toft AD, Poulter NR. Reductions in lipids and CV risk markers in patients with type 2 diabetes treated with liraglutide: a meta-analysis. *IDF 2009, 20th World Diabetes Congress, Montreal 18-22 October* 2009;O-0542:p.180.

32. Schmidt WE, Gough S, Madsbad S, Zinman B, Falahati A, Toft AD *et al*. Improvement in HbA1c with liraglutide, a human GLP-1 analogue, is not dependent on the degree of patient weight loss. *IDF 2009, 20th World Diabetes Congress, Montreal 18-22 October* 2009;P-1398:P.471.

33. Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF *et al*. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009;361:1736-47.

34. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S *et al*. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 2007;357:1716-30.

35. Lilly. New Drug Application for Exenatide Once Weekly Accepted for Review by FDA. 2009, June http://files.shareholder.com/downloads/LLY/0x0x305313/0312ff74-fcde-4d52-859a-89478a0c11cc/LLY_News_2009_7_7_Product.pdf (accessed 4 December 2009)

36. Nauck MA, Ratner RE, Kapitza C, Berria R, Boldrin M, Balena R. Treatment with the human once-weekly glucagon-like peptide-1 analog taspoglutide in combination with metformin improves glycemic control and lowers body weight in patients with type 2 diabetes inadequately controlled with metformin alone: a double-blind placebo-controlled study. *Diabetes Care* 2009;32:1237-43.

37. Rosenstock J, Reusch J, Bush M, Yang F, Stewart M. Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. *Diabetes Care* 2009;32:1880-6.

38. Sanofi-Aventis. 24-week Treatment With Lixisenatide in Type 2 Diabetes Insufficiently Controlled With Metformin and Insulin Glargine. 2009, November http://www.clinicaltrials.gov/ct2/show/NCT00975286?term=NCT00975286&rank=1 (accessed 6 December 2009)

39. Sanofi-Aventis. 24-Week Study Comparing Lixisenatide to Sitagliptin as add-on to Metformin in Obese Type 2 Diabetic Patients Younger Than 50. 2009, November http://www.clinicaltrials.gov/ct2/show/NCT00976937?term=NCT00976937&rank=1 (accessed 6 December 2009)

40. Amylin Pharmaceuticals. Amylin Pharmaceuticals, Inc. Q3 2009 Earnings Call Transcript. 10/10/2009 http://seekingalpha.com/article/167708-amylin-pharmaceuticals-inc-q3-2009-earnings-call-transcript (accessed 3 December 2009)

41. Amylin Pharmaceuticals. Addition Of Exenatide To Insulin Glargine In Type 2 Diabetes Mellitus. 24/06/2009 http://www.clinicaltrials.gov/ct2/show/NCT00765817?term=NCT00765817&rank=1 (accessed 4 December 2009)

42. Eli Lilly and Company. Comparison of Two Basal Insulins for Patients With Type 2 Diabetes Taking Oral Diabetes Medicines and Exenatide. 03/09/2009 http://www.clinicaltrials.gov/ct2/show/NCT00560417?term=NCT00560417&rank=1 (accessed 3 December 2009)

43. Oregon Health and Science University. How Glargine Insulin, Oral Diabetes Medications and Exenatide May Improve Blood Sugar Control and Weight Gain in Type 2 Diabetics (MEXELIN). 23/09/2009 http://www.clinicaltrials.gov/ct2/show/NCT00667732?term=NCT00667732&rank=1 (accessed 3 December 2009)

44. Profil Institut für Stoffwechselforschung GmbH. Adjunctive Therapy of Exenatide or Sitagliptin to Insulin Glargine in Type 2 Diabetes. 03/09/2009 http://www.clinicaltrials.gov/ct2/show/NCT00971659?term=NCT00971659&rank=1 (accessed 3 December 2009)

45. U.S.Food and Drug Administration. Information for Healthcare Professionals: Exenatide (marketed as Byetta) - 8/2008 Update. 13/11/2009 http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htm (accessed 3 December 9 A.D.)

46. U.S.Food and Drug Administration. Byetta Safety Update for Healthcare Professionals. 13/11/2009 http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190406.htm (accessed 3 December 2009)

47. Sullivan SD, Alfonso-Cristancho R, Conner C, Hammer M, Blonde L. Long-term outcomes in patients with type 2 diabetes receiving glimepiride combined with liraglutide or rosiglitazone. *Cardiovasc Diabetol* 2009;8:12.

48. International Diabetes Federation. IDF Guideline on self-monitoring of blood glucose in non-insulin treated type 2 diabetes. 2008, October (accessed 5 December 2009)

49. Clar C, Barnard K, Cummins E, Royle P, Waugh N. Self monitoring of blood glucose in type 2 diabetes: systematic review. *Health Technology Assessment* 2010;in press.

50. Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). *Diabet Med* 2003;20:442-50.

51. UK Prospective Diabetes Study Group. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. *BMJ* 1998;317:720-6.

52. Ghatnekar O, Persson U, Willis M, Odegaard K. Cost effectiveness of Becaplermin in the treatment of diabetic foot ulcers in four European countries. *Pharmacoeconomics* 2001;19:767-78.

53. Ray JA, Valentine WJ, Secnik K, Oglesby AK, Cordony A, Gordois A *et al*. Review of the cost of diabetes complications in Australia, Canada, France, Germany, Italy and Spain. *Curr Med Res Opin* 2005;21:1617-29.

54. Lee AJ, Morgan CL, Morrissey M, Wittrup-Jensen KU, Kennedy-Martin T, Currie CJ. Evaluation of the association between the EQ-5D (health-related utility) and body mass index (obesity) in hospital-treated people with Type 1 diabetes, Type 2 diabetes and with no diagnosed diabetes. *Diabet Med* 2005;22:1482-6.

55. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM *et al*. Validation of the CORE Diabetes Model against epidemiological and clinical studies. *Curr Med Res Opin* 2004;20 Suppl 1:S27-S40.

56. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Med Care* 2000;38:583-637.

57. Bagust A, Beale S. Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. *Health Econ* 2005;14:217-30.

58. Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP *et al*. Valuing health-related quality of life in diabetes. *Diabetes Care* 2002;25:2238-43.

59. U.S.Food and Drug Administration. Information for Healthcare Professionals: Reports of Altered Kidney Function in patients using Exenatide (Marketed as Byetta. 02/11/2009 http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm188656.htm (accessed 3 December 2009)

60. Kazda C, Gallwitz B, Simo R, Guzman JR, Kraus P, Nicolay C *et al*. The European Exenatide study of long-term exenatide vs. glimepiride for type 2 diabetes: rationale and patient characteristics. *Diabetes Obes Metab* 2009;11:1131-7.

61. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH *et al*. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care* 2009;32:84-90.

62. Marre M, Shaw J, Brandle M, Bebakar WM, Kamaruddin NA, Strand J *et al*. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater

improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabetic Medicine* 2009;26:268-78.

63. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I *et al*. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009;373:473-81.

64. Seino Y, Rasmussen MF, Zdravkovic M, Kaku K. Dose-dependent improvement in glycemia with once-daily liraglutide without hypoglycemia or weight gain: A double-blind, randomized, controlled trial in Japanese patients with type 2 diabetes. *Diabetes Res Clin Pract* 2008;81:161-8.

65. Vilsboll T, Brock B, Perrild H, Levin K, Lervang HH, Kolendorf K *et al*. Liraglutide, a once-daily human GLP-1 analogue, improves pancreatic B-cell function and arginine-stimulated insulin secretion during hyperglycaemia in patients with Type 2 diabetes mellitus. *Diabet Med* 2008;25:152-6.

66. Vilsboll T, Zdravkovic M, Le-Thi T, Krarup T, Schmitz O, Courreges JP *et al*. Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. *Diabetes Care* 2007;30:1608-10.

67. Horowitz M, Vilsboll T, Zdravkovic M, Hammer M, Madsbad S. Patient-reported rating of gastrointestinal adverse effects during treatment of type 2 diabetes with the once-daily human GLP-1 analogue, liraglutide. *Diabetes Obes Metab* 2008;10:593-6.

68. Courreges JP, Vilsboll T, Zdravkovic M, Le-Thi T, Krarup T, Schmitz O *et al*. Beneficial effects of once-daily liraglutide, a human glucagon-like peptide-1 analogue, on cardiovascular risk biomarkers in patients with Type 2 diabetes. *Diabetic Medicine* 2008;25:1129-31.

69. Nauck MA, Hompesch M, Filipczak R, Le TDT, Zdravkovic M, Gumprecht J. Five weeks of treatment with the GLP-1 analogue liraglutide improves glycaemic control and lowers body weight in subjects with type 2 diabetes. *Experimental and Clinical Endocrinology & Diabetes* 2006;114:417-23.

70. Feinglos MN, Saad MF, Pi-Sunyer FX, An B, Santiago O, Liraglutide Dose-Response Study Group. Effects of liraglutide (NN2211), a long-acting GLP-1 analogue, on glycaemic control and bodyweight in subjects with Type 2 diabetes. *Diabetic Medicine* 2005;22:1016-23.

71. Harder H, Nielsen L, Tu DT, Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. *Diabetes Care* 2004;27:1915-21.

72. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR, International Study Group. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. *Diabetes Care* 2004;27:1335-42.

73. Chang AM, Jakobsen G, Sturis J, Smith MJ, Bloem CJ, An B *et al*. The GLP-1 derivative NN2211 restores beta-cell sensitivity to glucose in type 2 diabetic patients after a single dose. *Diabetes* 2003;52:1786-91.

74. Degn KB, Juhl CB, Sturis J, Jakobsen G, Brock B, Chandramouli V *et al*. One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. *Diabetes* 2004;53:1187-94.

75. Juhl CB, Hollingdal M, Sturis J, Jakobsen G, Agerso H, Veldhuis J *et al*. Bedtime administration of NN2211, a long-acting GLP-1 derivative, substantially reduces fasting and postprandial glycemia in type 2 diabetes. *Diabetes* 2002;51:424-9.

76. Damholt B, Golor G, Wierich W, Pedersen P, Ekblom M, Zdravkovic M. An open-label, parallel group study investigating the effects of age and gender on the pharmacokinetics of the once-daily glucagon-like peptide-1 analogue liraglutide. *J Clin Pharmacol* 2006;46:635-41.

77. Nauck M, Marre M. Adding liraglutide to oral antidiabetic drug monotherapy: efficacy and weight benefits. *Postgrad Med* 2009;121:5-15.

78. Matza LS, Boye KS, Yurgin N, Brewster-Jordan J, Mannix S, Shorr JM *et al*. Utilities and disutilities for type 2 diabetes treatment-related attributes. *Qual Life Res* 2007;16:1251-65.

79. Bergenstal R, Lewin A, Bailey T, Chang D, Gylvin T, Roberts V *et al*. Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea. *Current Medical Research & Opinion* 2009;25:65-75.

80. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005;28:1092-100.

81. Gao Y, Yoon KH, Chuang LM, Mohan V, Ning G, Shah S *et al*. Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea. *Diabetes Research & Clinical Practice* 2009;83:69-76.

82. Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D *et al*. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* 2008;372:1240-50.

83. Kadowaki T, Namba M, Yamamura A, Sowa H, Wolka AM, Brodows RG. Exenatide exhibits dose-dependent effects on glycemic control over 12 weeks in Japanese patients with suboptimally controlled type 2 diabetes. *Endocrine Journal* 2009;56:415-24.

84. Nauck MA, Duran S, Kim D, Johns D, Northrup J, Festa A *et al*. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia* 2007;50:259-67.

85. Zinman B, Hoogwerf BJ, Duran GS, Milton DR, Giaconia JM, Kim DD *et al*. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. *Annals of Internal Medicine* 2007;146:477-85.

86. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS *et al*. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 2005;28:1083-91.

87. Barnett AH. Exenatide. *Expert Opinion in Pharmacotherapy* 2007;8:2593-608.

88. Chia CW, Egan JM. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2008;93:3703-16.

89. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM *et al*. The CORE Diabetes Model: Projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. *Curr Med Res Opin* 2004;20 Suppl 1:S5-26.

90. Mount Hood 4 Modeling Group. Computer modeling of diabetes and its complications: a report on the Fourth Mount Hood Challenge Meeting. *Diabetes Care* 2007;30:1638-46.

91. National Insitute for Health and Clinical Excellence. Guide to the methods of technology appraisal. 2009 http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp (accessed 3 December 2009)

APPENDICES

Appendix 1 List of Identified RCTs from Industry Submission

Author	Date	Title	Reference	Study type	Inclusion in Cochrane review?
Unpublished (Trial ID: NN2211-1860)	June 2008 – Jun 2009	The effect of liraglutide compared to sitagliptin, both in combination with metformin in subjects with type 2 diabetes.	Data on file with NN	RCT. Unpublished 1860	Excluded – unpublished - data not available
Buse J et al. [19]	2009	Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6).	*Lancet* 2009; 374(9683): 39–47	RCT (LEAD-6)	Included
Russell-Jones D et al. [18]	2009	Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial.	*Diabetologia* 2009; 52: 2046–2055	RCT (LEAD-5)	Included
Zinman B et al. [17]	2009	Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD).	*Diabetes Care* 2009; 32: 1224–30	RCT (LEAD-4)	Included
Nauck M et al.[61]	2009	Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study.	*Diabetes Care* 2009; 32: 84–90	RCT (LEAD-2)	Included

Marre M et al.[62]	2009	Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU).	*Diabet Med* 2009; 26: 268–78	RCT (LEAD-1)	Excluded - does not report the previous OHAs, so cannot determine what % of patients were tried on metformin first. Awaiting clarification from NN
Garber A et al.[63]	2009	Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial.	*Lancet* 2009; 373(9662): 473–81	RCT (LEAD-3)	Excluded -liraglutide monotherapy
Seino Y et al.[64]	2008	Dose-dependent improvement in glycemia with once-daily liraglutide without hypoglycemia or weight gain: A double-blind, randomized, controlled trial in Japanese patients with type 2 diabetes.	*Diabetes Res Clin Pract* 2008; 81: 161−8	RCT . 14 weeks. Compared 4 different doses of Liraglutide - 0.1 mg, 0.3 mg, 0.6 mg, 0.9 mg against placebo.	Excluded -liraglutide monotherapy
Vilsboll T et al.[65]	2008	Liraglutide, a once-daily human GLP-1 analogue, improves pancreatic B-cell function and arginine-stimulated insulin secretion during hyperglycaemia in patients with Type 2 diabetes mellitus	*Diabetic Medicine* 2008; 25: 152−6	RCT. The study was part of a larger double-blind, placebo controlled, randomized trial conducted over 14 weeks (Vilsboll 2007) comparing three doses of liraglutide (0.65, 1.25 or 1.9 mg/day) vs. placebo(subcutaneous injections in the evening) [7]	Excluded -liraglutide monotherapy
Vilsboll T et al.[66]	2007	Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia	*Diabetes Care* 2007; 30: 1608−10	RCT. Prior to trial patients were on diet or OHA. Previous oral anti-diabetes drug therapy discontinued. Patients were on 3 different	Excluded -liraglutide monotherapy

		in patients with type 2 diabetes.		doses of Liraglutide - 0.65 mg; 1.25 mg, 1.9mg against placebo for 14 weeks	
Horowitz M et al. (sub-group publication of the above Vilsboll T et al. 2007 paper)[67]	2008	Patient reported rating of gastrointestinal adverse effects during treatment of type 2 diabetes with the once-daily human GLP-1 analogue, liraglutide.	*Diabetes Obes Metab* 2008; 10: 593–6	sub-group publication of the Vilsboll T et al. 2007	Excluded - liraglutide monotherapy
Courreges JP et al. (sub-group publication of the above Vilsboll T et al. 2007 paper)[68]	2008	Beneficial effects of once-daily liraglutide, a human glucagon-like peptide-1 analogue, on cardiovascular risk biomarkers in patients with Type 2 diabetes.	*Diabet Med* 2008; 25: 1129–31	sub-group publication of the Vilsboll T et al. 2007	Excluded - liraglutide monotherapy
Nauck M et al.[69]	2006	Five weeks of treatment with the GLP−1 analogue liraglutide improves glycaemic control and lowers body weight in subjects with type 2 diabetes.	*Exp Clinl Endocrino and Diabetes*, 2006; 114: 417−23	RCT. 5 weeks. 144 type 2 diabetic subjects on metformin treatment (1000 mg BID) were randomised to 5 weeks of treatment (double-blind) with metformin plus liraglutide, liraglutide or metformin, or metformin plus glimepiride (open label). The dose of liraglutide was increased weekly from 0.5 to 2 mg OD.	Excluded – 5 weeks duration
Feinglos M et al.[70]	2005	Effects of liraglutide (NN2211), a long−acting GLP−1 analogue, on glycaemic control and bodyweight in subjects with Type 2 diabetes.	*Diabetic Medicine* 2005; 22: 1016−23	RCT. 12 weeks. 5 different doses of Liraglutide 0.045 mg, 0.225 mg,0.45 mg; 0.6 mg; 0.75 mg versus metformin	Excluded - liraglutide monotherapy

				+ placebo injection.	
Harder H et al.[71]	2004	The effect of liraglutide, a long−acting glucagon−like peptide 1 derivative, on glycemic control, body composition, and 24−h energy expenditure in patients with type 2 diabetes.	*Diabetes Care* 2004; 27: 1915−21	RCT. Patients randomized to treatment with a single daily subcutaneous dose of 0.6 mg = 21) of liraglutide (n = 21) or placebo (n = 12) for 8 weeks	Excluded - liraglutide monotherapy and 8 weeks duration
Madsbad S et al.[72]	2004	Improved glycemic control with no weight increase in patients with type 2 diabetes after once−daily treatment with the long−acting glucagon−like peptide 1 analog liraglutide (NN2211): A 12−week, double−blind, randomized, controlled trial.	*Diabetes Care* 2004; 27: 1335−42	RCT. 12 weeks. Randomised to 5 different doses of Liraglutide 0.045 mg, 0.225 mg, 0.45 mg; 0.60 mg; 0.75 mg versus Placebo or verusus Sulfonylurea - Glimperide	Excluded - liraglutide monotherapy
Chang A et al.[73]	2003	The GLP−1 derivative NN2211 restores beta−cell sensitivity to glucose in type 2 diabetic patients after a single dose.	*Diabetes* 2003; 52: 1786−91	RCT- two-period cross-over trial. 10 patients. Assessed the effect of a single subcutaneous injection of NN2211. There was a 3–6 week interval between dosing periods.	Excluded - liraglutide monotherapy and 3-6 weeks duration
Degn K et al.[74]	2004	One week's treatment with the long-acting glucagon like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes	*Diabetes* 2004; 53: 1187–94	RCT. Explored the effect of short-term (1 week) treatment with liraglutide.	Excluded - liraglutide monotherapy and one week duration
Juhl C et al.[75]	2002	Bedtime administration of NN2211, a long-acting GLP-1 derivative, substantially reduces fasting and postprandial glycemia in type 2	*Diabetes* 2002; 51: 424–9	RCT. 11 patients. A single injection (10 g/kg) of NN2211 was administered.	Excluded - liraglutide monotherapy and 1-2 days duration

		diabetes.			
Damholt B et al.[76]	2006	An open-label, parallel group study investigating the effects of age and gender on the pharmacokinetics of the once-daily glucagon-like peptide-1 analogue liraglutide.	*J Clin Pharmacol* 2006; 46: 635–41.	RCT. 18 healthy subjects. Total duration of the trial for each subject was approximately 5 weeks.	Excluded - healthy subjects, liraglutide monotherapy and 5 weeks duration
Nauck M. & Marre M.[77]	2009	Adding liraglutide to oral antidiabetic drug monotherapy: efficacy and weight benefits.	*Postgrad Med* 2009; 121: 5–15	Included a subset of patients receiving prior OAD monotherapy from 2 phase 3, 26-week TCTs.	Excluded - combined data from sub-set of two RCTs

Appendix 2 Nausea – exenatide vs liraglutide

The submission provides a comparison of nausea frequency for both exenatide and liraglutide from the LEAD-6 trial. Note that this trial used a 1.8 mg dose of liraglutide.
The industry submission reports that
" in all LEAD studies, the majority of episodes of nausea were mild to moderate, transient and rarely led to discontinuation of therapy"

Figure 8 below from the industry submission shows the percentage of subjects with nausea on liraglutide and exenatide. The percentage of subjects with at least one gastro-intestinal adverse effect increased after the doses were increased (standard practice is to start with a low dose and increase after weeks 1-2 and 4 for liraglutide and exenatide respectively) but decreased over time. The overall frequency was similar but LEAD-6 reported longer duration of nausea with exenatide as seen in Figure 8 (taken from the NN industry submission).

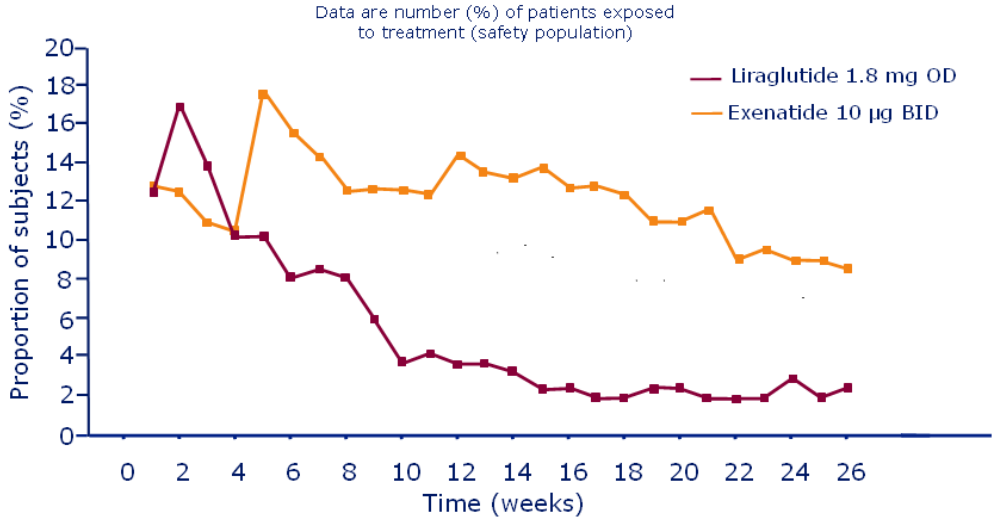


Figure 8 LEAD-6: Proportion of subjects with nausea by week and treatment

Novo Nordisk did not include a disutility for nausea in the cost effectiveness analysis on the grounds that it was "mild and transient". Inclusion would have increased the cost per QALY in comparison with glargine and sitagliptin. However the effect would probably be very small. The disutility from nausea appears to be low. It was reported to be a reduction of 0.04 in a study by Matza and colleagues in a study sponsored by Lilly, though it is not clear how many patients in that study were

on exenatide (23% were on “injectables”).[78] Given the low disutility and the short duration, it would be unlikely to significantly affect the cost per QALY. In routine care, anyone having troublesome nausea could change to another drug. Table 43 below, taken from the Industry Submission, gives data on the nausea reported in the liraglutide RCTs.

Table 43 Nausea reported in the randomised controlled trials

Study	Arm	n	Nausea (% of subjects)	Statistical comparison	% discontinuing due to nausea	SAE(%)
1860	Liraglutide 1.2 mg	[redacted]	[redacted]		[redacted]	[redacted]
	Liraglutide 1.8 mg	[redacted]	[redacted]		[redacted]	[redacted]
	Sitaglitpin 100 mg	[redacted]	[redacted]		[redacted]	[redacted]
Buse J et al. 2009[19]	Liraglutide 1.8 mg	235	25.5	The incidence of nausea was similar initially, it was less persistent with liraglutide (estimated treatment rate ratio 0·448 for liraglutide vs. exenatide; proportion of participants with nausea at week 26, 5 of 202 [3%] vs. 16 of 186 [9%], p<0.0001	6	5.1
	Exenatide 10 µg	232	28.0		6.9	2.6
Russell-Jones D et al. 2009[18]	Liraglutide 1.8 mg	230	13.9	Significantly greater percentage of patients experiencing nausea with liraglutide compared with placebo or insulin glargine, p<0.0001	2 patients	4
	Placebo	114	3.5		0	7
	Insulin glargine	232	1.3		0	8
Zinman B et al. 2009[17]	Liraglutide 1.2 mg	178	45*	No statistical comparisons reported	3	8 patients (8 events)
	Liraglutide 1.8 mg	178	56*		11	7 patients (10 events)
	Placebo	177	19*		0	12 patients (13 events)
Marre M et al. 2009[62]	Liraglutide 0.6 mg	233	5.2	No statistical comparisons reported	0.9-2.2	3
	Liraglutide 1.2 mg	228	10.5		0.9-2.2	4
	Liraglutide 1.8 mg	234	6.8		0.9-2.2	5
	Placebo	114	1.8		0.9-2.2	3
	Rosiglitazone	231	2.6		0.9-2.2	3
Nauck M et al. 2009[61]	Liraglutide 0.6 mg	242	10.7	No statistical comparisons reported	1*	3.3
	Liraglutide 1.2 mg	240	16.3		5*	5.8
	Liraglutide 1.8 mg	242	18.6		8*	3.7
	Glimepiride	242	3.3		0*	4.1
	Placebo	121	4.1		0*	3.3

We compared the frequency of nausea on exenatide in LEAD-6, funded by Novo Nordisk, with trials of exenatide, nearly funded by its manufacturer Lilly. In these studies, exenatide was started with 5 µg for first 4 weeks and then increased to 10 µg twice daily.

The incidence of nausea on exenatide varied amongst studies, was tended to be higher in the Lilly studies than in LEAD-6;

- Bergenstal 2009[79]: nausea in 29% on exenatide (versus 9% on insulin). Discontinuation due to nausea in 6% on exenatide.
- Bunck 2009[20]: mild to moderate nausea in 50% of patients on exenatide and 9% for glargine.
- Davies 2009 (HEELA study)[26]: incidence of nausea was 48% for exenatide patients (none on glargine) and 2% discontinuation
- Davis 2007[26]: incidence of mild to moderate nausea in exenatide = 48.5% (glargine 12.5%). Discontinuation due to nausea on exenatide = 9% and none in glargine group.
- DeFronzo 2005[80]: incidence of nausea 45% on exenatide 10-ug (23% on placebo). 2% discontinuation on exenatide.
- Gao 2009[81]: incidence of nausea was 25% on exenatide (placebo 1%), with 4% discontinuation due to nausea.
- Heine 2005[22]: incidence of nausea on exenatide was 57% (glargine 9%).
- Drucker 2008[82]: incidence of exenatide 35% given twice daily; it was lower (26.4%) with once weekly administration)
- Kadowaki 2009[83]: in exenatide group the incidence of nausea was 35% and withdrawals due to nausea were 4%.
- Nauck 2007[84]: in the exenatide group the incidence of nausea in group was 33% (compared to 0.4% in the insulin group), with 3.5% discontinuation due to nausea
- Zinman 2007[85]: incidence of 40% nausea in exenatide group (compared to 15% on placebo) with 9% withdrawal due to nausea.

Nausea was reported at a higher incidence during the initial weeks of therapy (weeks 0–8) and declined thereafter (see below). This fits with the longer duration of nausea with exenatide in LEAD-6. Gao and colleagues reported that the highest incidence of nausea in the exenatide group was reported between week 4 and week 8, after which it decreased (week 12–16, 2%).[81] Kadowaki and colleagues[83] reported higher frequency in the first 8 weeks with less thereafter, as did Kendall and colleagues.[86]

So the frequency of nausea on exenatide in LEAD-6 was lower than in most other trials.

Note that the reduced frequency is because nausea with liraglutide wears off much more quickly than with exenatide. Initial rates are similar.

Explanations for the lower prevalence of nausea with liraglutide compared to exenatide could include the once daily rather than twice daily dosage, which may provide less of a peak and trough situation. Support for this comes from the trial of long-acting exenatide versus twice daily exenatide where nausea and vomiting were much less frequent with the weekly form.[82] Liraglutide injection produces maximal concentrations within 10-14 hour after administration with a half life of 13 hour compared to exenatide that reaches maximum concentrations within 2 to 3 hours and a half life of 2.4 hours.

Rosenstock and colleagues compared albiglutide and exenatide and noted less nausea with the former given weekly.[37] They conclude that the reasons for differences in the tolerability of albiglutide and exenatide are not known but suggest that the difference could be due to the differences in pharmacokinetics including gradual absorption (Tmax is ~ 3 days for albiglutide and ~2.1 hr for exenatide) and a long plasma half life of ~5 days resulting in a steady state achieved after 4-5 doses for 30 mg weekly. In addition the slow accumulation of albiglutide may help tolerate GI adverse events and also the relative impermeability of albiglutide to the central nervous system may have resulted in a lower incidence of nausea and vomiting than exenatide.

Nauck and colleagues compared different doses of taspoglutide against placebo, and reported that the frequency of nausea was less (10%) with 20mg every two weeks than 10mg weekly (24%).[36]

Barnett suggests in his review that the lower frequency of nausea with weekly exenatide may be due to the more gradual increase in plasma exenatide concentrations with exenatide LAR. He adds that the gradual introduction of exenatide has shown to reduce the incidence of nausea by about 50%. [87]

Another possible reason could be the greater homology of liraglutide with human GLP-1 than exenatide (97% versus 53%), as shown in Figure 9 below (taken from Chia and Egan [88] – permission not yet obtained so in confidence). By homology, we mean that liraglutide is more similar to human GLP-1. However, there does not seem to be any evidence on whether the incidence of nausea is related to the homology of the drugs.

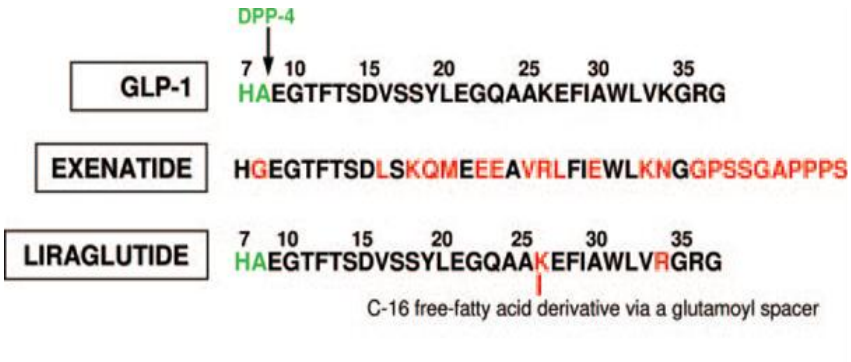


Figure 9 Structure of native GLP-1, exenatide and liraglutide (from Chia and Egan 2008)

The difference in nausea is very unlikely to be due to chance, given the p value of 0.0001 (industry submission Table 11 page 37).

We conclude that there does seem to be less nausea with liraglutide compared to exenatide , and that this may be related to the frequency of dosage.

Appendix 3 Comparison of liraglutide 1.2 mg and 1.8 mg doses

LEAD-1	**Difference between Lira 1.8 mg and Lira 1.2mg (1.8mg-1.2mg)**	**Liraglutide 1.2 mg (+GLIME)**	**Liraglutide 1.8 mg (+GLIME)**
HbA1c (change from baseline to endpoint) %; mean (SD)	-0.05 (diff in change from baseline and vs rosig) 0.1% (diff in change vs placebo)	-1.08 (1.057)	-1.13 (1.071)
% of patients who achieved a target HbA1c level <7%	7	35	42
% of patients who achieved a target HbA1c level ≤6.5%	-1	22	21
Mean change in body weight (kg)	-0.5	0.3	-0.2
Change in BMI (kg/m2); mean (SD)	-0.202	0.119 (0.901)	-0.083 (0)
Mean reduction in FPG levels	-0.02	-1.57	-1.59
% of patients achieving fasting glucose between 5 mmol/L and ≤7.2 mmol/L	1	37.00	38
Reduction in SBP; mean (SD)	-0.25	-2.56 (12.835)	-2.81 (13.155)
Major hypo event rate/100 pt. yrs	0.9	0	0.9
Rate of minor hypos (events/patient year)	-0.04	0.51	0.47
Minor hypo event rate/100 pt. yrs	-3.3	50.5	47.2
% reporting a minor hypoglycaemic episode	-1.1	9.2	8.1
Major hypoglycaemic episode (no. patients)		NR	1 (9 days after treatment started)
Serious adverse events (%)	1	4	5
Incidence of serious AE	0.01	0.04	0.05
Nausea (% subject experiencing)	-3.7	10.5	6.8
Started	6	228	234
Completed	17	196 (86%)	213 (91%)
Withdrawn	-11	32 (14%)	21 (9%)

LEAD-2	**Difference between Lira 1.8 mg and Lira 1.2mg (1.8mg-1.2mg)**	**Liraglutide 1.2 mg (+MET)**	**Liraglutide 1.8 mg (+MET)**
HbA1c (change from baseline to endpoint) %; mean (SD)	0.03	-0.97 (1.087)	-1 (1.087)
% of patients who achieved a target HbA1c level <7%	7.1	35.3	42.4
% of patients who achieved a target HbA1c level ≤6.5%	4.8	19.8	24.6
Mean change in body weight (kg) mean (SE)	-0.2	-2.6 (0.2)	-2.8 (0.2)
Change in BMI (kg/m^2); mean (SD)	0.076	-0.907 (0.936)	-0.983 (1.01)
FPG (at end of the study) mmol/L mean (SE)	0	8.5 (2.6)	8.5 (2.4)
Decrease in FPG from baseline (mmol/L)	-0.1	-1.6	-1.7
Reduction in SBP (mm Hg); mean (SD)	0.52	-2.81 (13.351)	-2.29 (12.912)
Overall rate of hypos (events/year)		0.03 to 0.14	
Minor hypo event rate/100 pts	5.9	2.8	8.7
Incidence of minor hypos		Approx. 3%	
No major hypoglycaemic events reported			
% reporting nausea,vomiting & diarrhoea	4	40	44
% reporting nausea only	3	16	19
Started			
Randomized	1	241	242
Exposed (ITT and safety population)	2	240	242
Completed	-6	197	191
Withdrawn (%)	7	44 (18)	51 (21)

LEAD-4	**Difference between Lira 1.8 mg and Lira 1.2mg (1.8mg-1.2mg)**	**Liraglutide 1.2 mg (+MET + ROSI)**	**Liraglutide 1.8 mg (+MET + ROSI)**
HbA1c % (change in from baseline to study end); mean (SE)%	0	-1.5 (0.1)	-1.5 (0.1)
% of patients who achieved a target HbA1c level <7%	-3.8	57.5	53.7
% of patients who achieved a target HbA1c level ≤6.5%	-1.1	37.3	36.2
Mean change in body weight from baseline (kg); mean (SE)	-1.0	-1.0 (0.3)	-2.0 (0.3)
FPG end-of-study values (mmol/L); mean (SE)	-0.1	7.7 (2.7)	7.6 (2.3)
Decrease in FPG from baseline (mmol/L)	-0.2	-2.2	-2.4
SBP - mean change from baseline (mmHg); mean (SE)	1.1	-6.7 (1.1)	-5.6 (1.1)
Severe hypoglycaemic episode (no. patients)		None	None
Hypoglycaemia - minor (events/subject year)	0.2	0.4	0.6
Incidence of minor hypoglycaemia %	-1.1	9	7.9
Serious adverse events (number)		8 subjects (8 total events)	7 subjects (10 total events)
% reporting nausea (one or more episodes)	11	29	40
% reporting ≤7 days of nausea (first 8 weeks of treatment)		71 to 84	
Randomised	0	178	178
Completed n(%)	-20	153 (86)	133 (75)
Withdrawn n(%)	20	25 (14)	45 (25)

Unpublished (Trial ID: NN2211-1860):	**Difference between Lira 1.8 mg and Lira 1.2mg (1.8mg-1.2mg)**	**Liraglutide 1.2 mg (+MET)**	**Liraglutide 1.8 mg (+MET)**
HbA1c (change from baseline to endpoint) %	[redacted]	[redacted]	[redacted]
% of patients who achieved a target HbA1c level <7%	[redacted]	[redacted]	[redacted]
% of patients who achieved a target HbA1c level ≤6.5%	[redacted]	[redacted]	[redacted]
Mean change in body weight from baseline(kg)	[redacted]	[redacted]	[redacted]
BMI change (kg/m^2)	[redacted]	[redacted]	[redacted]
FPG - mean change from baseline (mmol/L)	[redacted]	[redacted]	[redacted]
SBP - mean change from baseline (mmHg)	[redacted]	[redacted]	[redacted]
Hypoglycaemia - major (events per 100 patient years)	[redacted]	[redacted]	[redacted]
Hypoglycaemia - minor (events/100 patient years)	[redacted]	[redacted]	[redacted]
Hypoglycaemia - minor (events/subject year)	[redacted]	[redacted]	[redacted]
Hypoglycaemia - minor (% of subjects)	[redacted]	[redacted]	[redacted]
Serious adverse events (%)	[redacted]	[redacted]	[redacted]
Nausea (% subject experiencing)	[redacted]	[redacted]	[redacted]
Randomised	[redacted]	[redacted]	[redacted]
Completed	[redacted]	[redacted]	[redacted]
Withdrawn	[redacted]	[redacted]	[redacted]

Appendix 4 The CORE model

The CORE model is a highly developed and well-tested model, and one of the foremost of its kind. Palmer and colleagues outlined the broad structure of the CORE model for both T1DM and T2DM patients.[55]

The CORE model can be briefly summarised as being an internet based model which is based upon 15 sub-models which simulate the main complications of diabetes. Each sub-model is a Markov model which employs Monte Carlo simulation which incorporates the time, the state, the time in state and transition probabilities which are typically diabetes type dependent as derived from published sources. A common problem with standard Markov modelling is the requirement that distinct mutually exclusive memory-less disease states have to be specified. This approach would overlook the interactions between the different complications of diabetes unless a prohibitively large number of disease states were defined. CORE modelling uses tracker variables to allow interactions between the different sub-models, with the progression of one or more complications influencing the transition probabilities in other sub-models where a relationship has been established. For instance, the risk of a first myocardial infarction is linked to whether gross proteinuria, microalbumina or end stage renal disease has developed, a relative risk being specified for each of these.

The 15 sub-models of CORE are: Myocardial infarction; Angina; Congestive heart failure; Stroke; Peripheral vascular disease; Neuropathy; Foot ulcer, with possible amputation; Retinopathy; Macular Oedema; Cataract; Nephropathy; Hypoglycaemia; Ketoacidosis; Lactic Acidosis; and, General mortality. Note that a specific mortality is associated with the Myocardial infarction; Congestive heart failure; Stroke; Foot ulcer, with possible amputation; Nephropathy; Hypoglycaemia; Ketoacidosis and Lactic Acidosis sub-models. For hypoglycaemia the specific mortality is specified by the user.
Not all sub-models are differentiated by diabetic type. Myocardial infarction, angina, stroke, peripheral vascular disease and foot ulcers leading to amputation are modelled as having the same inputs for T1DM patients as for T2DM patients.

The baseline population characteristics within CORE can be specified in terms of age, sex, duration of diabetes, racial characteristics, glycemic control, blood pressure, the body mass index, lipid levels, smoking and baseline rates of complications. Treatments can be specified as modifying glycemic control, hypoglycaemic event rates, severe hypoglycaemic event rates, blood pressure, the body mass index and lipid levels. Typically only glycaemic control and hypoglycaemic event rates are specified. Palmer and colleagues undertook a validation exercise of the CORE model using published data for the incidence of the complications associated with both T1DM and T2DM.[89] This exercise appears to show reasonably good validation for the incidence of the complications examined.

Within CORE modelling any improvement in baseline HbA_{1c} as a result of a novel treatment is typically assumed to be sustained. There is the possibility that while an improvement may be observed over a period of time, this relative improvement in HbA_{1c} may be eroded in the medium to long term. While CORE does permit some adjustment of this assumption through the use of a long term adjustment factor, it does not appear to permit the evolution of the gain in HbA_{1c} to be specified in detail. Given this, the longer term adjustment to the relative improvement in HbA_{1c} appears to be little used and the absolute gain over baseline HbA_{1c} is typically assumed to be maintained.

Validation

Diabetes models are (if their developers submit them) tested in the Mount Hood Challenge. In the most recent of these, one test for the models was their ability to predict the outcomes of the DCCT trial. [90] The CORE model was entered in Mount Hood challenge at its 4th and currently latest meeting, the results of which have been published. For type 2 diabetics this attempted to model outcomes of the CARDS trial of lipid lowering interventions. As such, it may not particularly address model validation for

- the evidence on changes in HbA1c as presented within the mixed treatment comparison of the submission, and
- weight changes

Table 44 Mount Hood challenge results

4th Mt Hood challenge	Acute coronary event		Stroke	
	Control	Intervention	Control	Intervention
CARDS study	**5.1**	**3.2**	**3.2**	**1.4**
Validations				
CDC/RTI	6.4	4.3	1.7	1.5
EAGLE	3.9	..	0.8	..
CARDIFF	6.7	4.5	2.5	2.2
UKPDS Outcomes Model	5.3	3.6	2.3	2.0
CORE	6.4	4.5	2.0	1.7

Most models including CORE appeared to over predict acute coronary events, though the net impact of the intervention was perhaps more accurately predicted. Within the above note that the CARDS coronary events included hospitalised unstable angina, silent MIs and resuscitated cardiac arrests. The models were typically reporting fatal and non-fatal MIs, which would have been further over predicted than the above suggests.

But the paper noted that the CARDS patient group was a specially selected low mortality risk group with no history of previous CVD or pre-existing major illness, which could have accounted for the models over prediction of CV events.

In a comparison with DCCT results, the CORE model gave estimates very close to what was observed for renal disease, retinopathy and peripheral neuropathy in the intensive group, and was also close for neuropathy and renal disease in the conventional group. It did somewhat under-estimate retinopathy in the conventional group. But overall, getting good results in a voluntary challenge reinforces our confidence that CORE is a good model.

The submission also notes that the CORE model has undergone a range of 2nd order and 3rd order validations, the R^2 for these being reported as: validation analyses in type 2 diabetes were associated with R^2 values of

- 0.8861 across all validations in type 2 diabetes
- 0.9574 across 2nd order validations
- 0.9023 across 3rd order validations

No further details were provided of this, and the published paper does not appear to particularly distinguish between the 2^{nd} order and the 3^{rd} order validations within its presentation, which studies were used and what variables the validation exercises simulated. The only additional information within the paper related to the R^2 specific to type 2 diabetes of 0.975 for 2^{nd} order validations and of 0.8748 for 3^{rd} order validations.

The external consultant nominated by the manufacturer as an expert on CORE is in the course of supplying more information about CORE validation.

Cross check of base case results

The CORE model has recently been updated to allow for depression associated with treatment to be included in the analysis. The manufacturer submission was based on the previous version of CORE. Re-running the base cases in this version of CORE resulted in results that cross checked with those of the submission. For completeness, augmenting the results of the submission with the undiscounted life expectancies and the tabulated CEACs, resulted in the following.

Table 45 Updated CORE – trial 1860

1860 Liraglutide 1.2	Setting 1:	Setting 2:	Difference mean	Difference SD

Treatment tree	Liraglutide 1.2	Sitagliptin	S1 - S2	S1 - S2
Life Expectance	11.75	11.64	0.119	0.226
Undiscounted Life Expectancy	16.75	16.52	0.226	..
Quality-Adjusted Life Expectancy	7.52	7.33	0.187	0.145
Direct Costs	£21,793	£19,951	£1,842	£715
Treatment	£9,185	£7,129	£2,056	..

Willingness to pay	Prob S1 c/e	
£0	0.3	
£10,000	52.0	
£20,000	77.5	
£30,000	82.1	
£40,000	84.7	ICER £9,851/QALY
£50,000	85.9	
£60,000	86.4	
£70,000	86.8	
£80,000	87.0	
£90,000	87.1	
£100,000	87.4	

1860 Liraglutide 1.8	Setting 1:	Setting 2:	Difference mean	Difference SD
Treatment tree	Liraglutide 1.8	Sitagliptin	S1 - S2	S1 - S2
Life Expectance	11.87	11.64	0.23	0.226
Undiscounted Life Expectancy	16.97	16.52	0.45	..
Quality-Adjusted Life Expectancy	7.64	7.33	0.308	0.151
Direct Costs	£23,175	£19,951	£3,224	£683
Treatment	£10,968	£7,129	£3,839	..

Willingness to pay	Prob S1 c/e	
£0	0	
£10,000	44.4	
£20,000	85.7	
£30,000	92.3	
£40,000	94.2	ICER £10,465/QALY
£50,000	95.4	
£60,000	95.9	
£70,000	96.2	
£80,000	96.3	
£90,000	96.4	
£100,000	96.6	

These values correspond with those of Tables 31 and 32 of the submission. The probability of cost effectiveness values for willingness to pay values of £20,000 per QALY and £30,000 per QALY correspond with figure 14 and the text of the submission.

Table 46 Updated CORE – LEAD -6

LEAD6 Liraglutide 1.8	Setting 1:	Setting 2:	Difference mean	Difference SD
Treatment tree	Liraglutide 1.8	Exenatide	S1 - S2	S1 - S2
Life Expectance	11.58	11.43	0.152	0.211
Undiscounted Life Expectancy	16.45	16.15	0.3	..
Quality-Adjusted Life Expectancy	7.44	7.28	0.163	0.136
Direct Costs	£23,139	£21,501	£1,638	£804
Treatment	£10,963	£8,878	£2,085	..
Willingness to pay	Prob S1 c/e			
£0	2.4			
£10,000	51.0			
£20,000	74.7			
£30,000	80.6			
£40,000	83.0	ICER £10,054/QALY		
£50,000	84.5			
£60,000	85.3			
£70,000	85.7			
£80,000	86.3			
£90,000	86.6			
£100,000	86.8			

These values correspond with those of tables 37 and 37 of the submission. The probability of cost effectiveness values for willingness to pay values of £20,000 per QALY and £30,000 per QALY correspond with figure 19 and the text of the submission.

Table 47 Updated CORE – LEAD-5

LEAD5 Liraglutide 1.8	Setting 1:	Setting 2:	Difference mean	Difference SD
Treatment tree	Liraglutide 1.8	Glargine	S1 - S2	S1 - S2
Life Expectance	11.35	11.18	0.169	0.209
Undiscounted Life Expectancy	16.07	15.74	0.33	..
Quality-Adjusted Life Expectancy	7.30	7.06	0.24	0.14
Direct Costs	£25,109	£21,471	£3,638	£656
Treatment	£11,090	£7,370	£3,720	..
Willingness to pay	Prob S1 c/e			
£0	0.0			
£10,000	17.0			
£20,000	67.1			
£30,000	81.9	ICER £15,130/QALY		
£40,000	87.4			
£50,000	90.5			
£60,000	92.1			
£70,000	92.7			

£80,000	93.3	
£90,000	93.5	
£100,000	94.1	

These values correspond with those of tables 41 and 42 of the submission. The probability of cost effectiveness values for willingness to pay values of £20,000 per QALY and £30,000 per QALY correspond with figure 23 and the text of the submission.

Table 48 Updated CORE – LEAD -1

LEAD1 Liraglutide 1.2	Setting 1:	Setting 2:	Difference mean	Difference SD
Treatment tree	Liraglutide 1.2	TZD	S1 - S2	S1 - S2
Life Expectance	12.20	11.91	0.291	0.218
Undiscounted Life Expectancy	17.64	17.05	0.587	..
Quality-Adjusted Life Expectancy	7.89	7.56	0.332	0.144
Direct Costs	£23,623	£21,559	£2,064	£698
Treatment	£9,840	£7,005	£2,835	..
Willingness to pay	Prob S1 c/e			
£0	0.1			
£10,000	83.1			
£20,000	96.6			
£30,000	97.7			
£40,000	97.8	ICER £6,226/QALY		
£50,000	98.2			
£60,000	98.3			
£70,000	98.6			
£80,000	98.6			
£90,000	98.7			
£100,000	98.7			

LEAD1 Liraglutide 1.8	Setting 1:	Setting 2:	Difference mean	Difference SD
Treatment tree	Liraglutide 1.8	TZD	S1 – S2	S1 - S2
Life Expectance	12.25	11.91	0.341	0.218
Undiscounted Life Expectancy	17.73	17.05	0.682	..
Quality-Adjusted Life Expectancy	7.96	7.56	0.398	0.144
Direct Costs	£25,289	£21,559	£3,730	£718
Treatment	£11,597	£7,005	£4,592	..
Willingness to pay	Prob S1 c/e			
£0	0			
£10,000	55.8			
£20,000	95.2	ICER £9,376/QALY		
£30,000	98.1			
£40,000	99.1			
£50,000	99.5			
£60,000	99.6			

£70,000	99.6
£80,000	99.7
£90,000	99.7
£100,000	99.7

These values correspond with those of table 46 of the submission.

Table 49 Updated CORE – LEAD-2

LEAD2 Liraglutide 1.2	Setting 1:	Setting 2:	Difference mean	Difference SD
Treatment tree	Liraglutide 1.2	Met + SU	S1 - S2	S1 - S2
Life Expectance	11.51	11.41	0.095	0.206
Undiscounted Life Expectancy	16.30	16.11	0.182	..
Quality-Adjusted Life Expectancy	7.44	7.20	0.238	0.136
Direct Costs	£22,903	£19,746	£3,157	£592
Treatment	£9,108	£5,864	£3,244	..
Willingness to pay	Prob S1 c/e			
£0	0			
£10,000	25.1			
£20,000	74.1			
£30,000	85.3			
£40,000	88.1	ICER £13,257/QALY		
£50,000	90.2			
£60,000	91.7			
£70,000	92.4			
£80,000	92.8			
£90,000	93.2			
£100,000	93.9			

LEAD2 Liraglutide 1.8	Setting 1:	Setting 2:	Difference mean	Difference SD
Treatment tree	Liraglutide 1.8	Met + SU	S1 - S2	S1 - S2
Life Expectance	11.50	11.41	0.092	0.203
Undiscounted Life Expectancy	16.29	16.11	0.177	..
Quality-Adjusted Life Expectancy	7.44	7.20	0.245	0.134
Direct Costs	£24,606	£19,746	£4,860	£594
Treatment	£10,817	£5,864	£4,953	..
Willingness to pay	Prob S1 c/e			
£0	0			
£10,000	1.9			
£20,000	51.6			
£30,000	74.3	ICER £19,837/QALY		
£40,000	82.2			
£50,000	86.7			
£60,000	89.2			
£70,000	91.1			

£80,000	92.1
£90,000	92.6
£100,000	93.1

These values correspond with those of table 47 of the submission.

Appendix 5 Indexation and cross check of appendix 13 of the submission

The *PSSRU: Unit Costs of Health and Social Care* notes that *"Hospital and community health services (HCHS) pay and price inflation is a weighted average of two separate inflation indices: the pay cost index (PCI) and the health service cost index (HSCI). The PCI measures pay inflation in the HCHS. The PCI is itself a weighted average of increases in unit staff costs for each of the staff groups within the HCHS sector. Pay cost inflation tends to be higher than pay settlement inflation because of an element of pay drift within each staff group. Pay drift is the tendency for there to be a gradual shift up the incremental scales, and is additional to settlement inflation. The estimate of pay inflator for the current year is based on information supplied by the Department of Health and is based on pay awards of NHS staff. The HSCI is calculated monthly to measure the price change for each of 40 sub-indices of goods and services purchased by the HCHS. The sub-indices are weighted together according to the proportion of total expenditure which they represent to give the overall HSCI value. The pay cost index and the health service cost index are weighted together according to the proportion of HCHS expenditure on each. This provides an HCHS combined pay and prices inflation figure."*

The *NICE 2008 Guide to The Methods of Technology Appraisal* does not specify the price index that should be applied, but from the above it seems reasonable to apply the HCHS index to costs.[91] Table A-44 of the submission outlines that the modelling has applied the HSCI. The differences between the three indices within the *PSSRU: Unit Costs of Health and Social Care* are outlined below:

Table 50 Differences amongst indexation indices

	Prices (HSCI)			Pay (PCI)			Pay and Prices (HSCS)		
	Index	Inflation	2008 CF	Index	Inflation	2008 CF	Index	Inflation	2008 CF
1994/95	100.0	0.00%	1.20	100.0	0.00%	1.93	100.0	0.00%	1.61
1995/96	103.2	3.20%	1.17	104.4	4.40%	1.85	104.0	4.01%	1.55
1996/97	104.7	1.50%	1.15	107.8	3.30%	1.79	106.9	2.77%	1.51
1997/98	105.2	0.40%	1.15	110.5	2.50%	1.74	108.7	1.70%	1.48
1998/99	107.8	2.50%	1.12	116.0	4.90%	1.66	113.0	3.98%	1.42
1999/00	109.1	1.20%	1.10	124.0	6.90%	1.56	118.2	4.55%	1.36
2000/01	108.8	-0.30%	1.11	132.9	7.20%	1.45	123.1	4.19%	1.31
2001/02	108.9	0.10%	1.11	143.9	8.30%	1.34	129.4	5.09%	1.24
2002/03	110.0	1.00%	1.10	151.1	5.00%	1.28	133.9	3.49%	1.20
2003/04	111.6	1.50%	1.08	162.1	7.30%	1.19	140.9	5.19%	1.14

2004/05	112.7	1.00%	1.07	169.4	4.50%	1.14	145.4	3.20%	1.11
2005/06	114.9	1.90%	1.05	178.9	5.60%	1.08	151.2	4.01%	1.06
2006/07	118.3	3.00%	1.02	185.0	3.40%	1.04	155.8	3.03%	1.03
2007/08	120.4	1.80%	1.00	192.8	4.20%	1.00	161.0	3.34%	1.00
	2008 CF: multiplicative conversion factor to convert a cost in the base year into 2008 prices								

In the light of the above, as an example for costs in 1999 prices inflating these to 2008 prices using the HSCS would result in a 42% uplift as compared to a 12% uplift using the HSCI: the HSCS would result in a 27% higher cost than the HSCI.

A cross check of the conformity of Table A-44 with *Base case NICE costs* in the CORE model implementation within the NICE1 userspace, coupled with the implications of the above result in:

Table 51 Cross-check base case costs and indexations

Description of event or state	Base Year	Submission		HCSI		HCSC	
		Cost	2008 Inf	X-Check	Diff	X-Check	Diff
Fatal MI	1999	£1,152	**£1,291**	£1,287	-0.3%	£1,641	27.1%
MI, year 1	1999	£4,385	£4,914	£4,899	-0.3%	£6,244	27.1%
MI, year 1+	1999	£722	£809	£807	-0.3%	£1,028	27.1%
Angina, year 1	1999	£2,274	£2,548	£2,541	-0.3%	£3,238	27.1%
Angina, year 1+	1999	£751	£842	£839	-0.3%	£1,069	27.0%
Congestive heart failure, year 1	1999	£2,536	£2,842	£2,834	-0.3%	£3,611	27.1%
Congestive heart failure, year 1+	1999	£889	£996	£993	-0.3%	£1,266	27.1%
Stroke, fatal	1999	£3,383	£3,791	£3,780	-0.3%	£4,818	27.1%
Stroke, year 1	1999	£2,682	£3,006	£2,997	-0.3%	£3,819	27.1%
Stroke, year 1+	1999	£507	£568	£566	-0.3%	£722	27.1%
Peripheral vascular disease, year 1	1997	£2,270	£2,618	£2,610	-0.3%	£3,418	30.6%
Not listed in sub: PVD year 1+			*£2,618*				
Haemodialysis	1997	£24,160	£27,863	£27,780	-0.3%	£36,382	30.6%
Peritoneal dialysis	1997	£18,140	£20,920	£20,858	-0.3%	£27,316	30.6%
Kidney transplant, year 1	2002	£20,000	£22,191	£22,126	-0.3%	£24,881	12.1%
Kidney transplant, year 1+	2002	£6,500	£7,212	£7,191	-0.3%	£8,086	12.1%
Retinal photocoagulation	1997	£655	£755	£753	-0.2%	£986	30.6%
Severe vision loss/blindness, year 1	1999	£872	£977	£974	-0.3%	£1,242	27.1%
Severe vision loss/blindness, year 1+	1999	£281	£315	£314	-0.3%	£400	27.0%
Cataract extraction	1999	£1,553	£1,740	£1,735	-0.3%	£2,212	27.1%
Cataract annual follow-up	1999	£105	£118	£117	-0.6%	£150	26.7%
Neuropathy, year 1	1997	£924	£1,066	£1,062	-0.3%	£1,391	30.5%

Neuropathy, year 1+			*£1,066*				
Uninfected ulcer	1999	£1,251	£1,402	£1,398	-0.3%	£1,781	27.1%
Infected ulcer	1999	£1,282	£1,437	£1,432	-0.3%	£1,826	27.0%
Gangrene	1999	£2,060	£2,308	£2,302	-0.3%	£2,934	27.1%
Amputation, year 1	1999	£8,774	£9,832	£9,803	-0.3%	£12,495	27.1%
Amputation, year 1+	1999	£558	£625	£623	-0.2%	£795	27.1%
Major hypoglycaemic event	2002	£377	£412	£417	1.2%	£469	13.8%
Not listed in sub: Ketoacidosis event			*£897*				
Not listed in sub: Lactic acid event			*£0*				
Annual cost aspirin	2003	£20	£22	£22	-0.4%	£24	9.3%
CORE			*£5*				
Annual cost statins	2003	£355	£389	£389	0.0%	£427	9.7%
CORE			*£12*				
Annual costs ACE-I	2003	£235	£257	£257	0.2%	£283	9.9%
CORE			*£32*				
Costs of screening for retinopathy	1999	£33	£37	£37	-0.3%	£47	27.0%
CORE Screen retinopathy+MA			*£36*				
Costs of screening for nephropathy	2003	£32	£35	£35	0.1%	£38	9.9%
CORE Screen foot+GRP			*£23*				
Costs (monthly) non-standard ulcer	2003	£220	£241	£241	0.0%	£264	9.7%
CORE cost			*£246*				
	2008 Inf: costs inflated in the submission to 2008 prices						

Where figures in bold were not found within *Base case NICE costs*. Figures in italics are those applied within the CORE modelling, where these differ from those within the submission.

The 2008 costs of the submission cross check with the application of the HSCI, but are a significant underestimate of the costs that would apply through application of the HSCS. The manufacturer has supplied an additional set of base case analyses that apply the HSCS index.

Appendix 6 Additional sensitivity analyses undertaken by the ERG

The following additional sensitivity analyses were undertaken by the ERG in order to better understand the respective contributions of the individual CORE clinical parameter inputs contributions to the changes in life expectancy, QALYs and costs reported within the base cases of the submission. These sensitivity analyses were undertaken for the three main trials: 1860, LEAD5 and LEAD-6.

Table 52 Additional ERG sensitivity analyses

Changes from baseline:	
Sensitivity analysis 1	
Price	Base case changes
Weight	No change
Cholesterol	No changes
SBP	No change
HbA1c	No change
Sensitivity analysis 2a	
Price	Base case changes
Weight	Base case changes
Direct BMI disutility	0
Cholesterol	No changes
SBP	No change
HbA1c	No change
Sensitivity analysis 2b	
Price	Base case changes
Weight	Base case changes
Direct BMI disutility	Lee, as per base case
Cholesterol	No changes
SBP	No change
HbA1c	No change
Sensitivity analysis 3	
Price	Base case changes
Weight	No change
Cholesterol	Base case changes
SBP	No change
HbA1c	No change
Sensitivity analysis 4	
Price	Base case changes
Weight	No change
Cholesterol	No changes
SBP	Base case changes
HbA1c	No change
Sensitivity analysis 5	
Price	Base case changes
Weight	No change
Cholesterol	No changes

SBP	No change
HbA1c	Base case changes

In the tables below the sensitivity analysis applying only the direct drug costs relates to there being no clinical effect. The basecase is as per the manufacturer estimates with all clinical effects applied. The difference between the basecase and there being no clinical effect is tabulated as an absolute difference. Figures given as percentages show the impact of the sensitivity analysis of a selectively applied clinical effect as a percentage of the difference between no clinical effect and the base case of all clinical effects applying.

Table 53 Results of additional ERG sensitivity analyses – 1860

1860		**Liraglutide 1.2mg**							
Liraglutide 1.2mg vs sitagliptin 100mg		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
[redacted]									

		Sitagliptin 100mg							
		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
[redacted]									

		Net Effect							
		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
[redacted]									

1860	**Liraglutide 1.8mg**

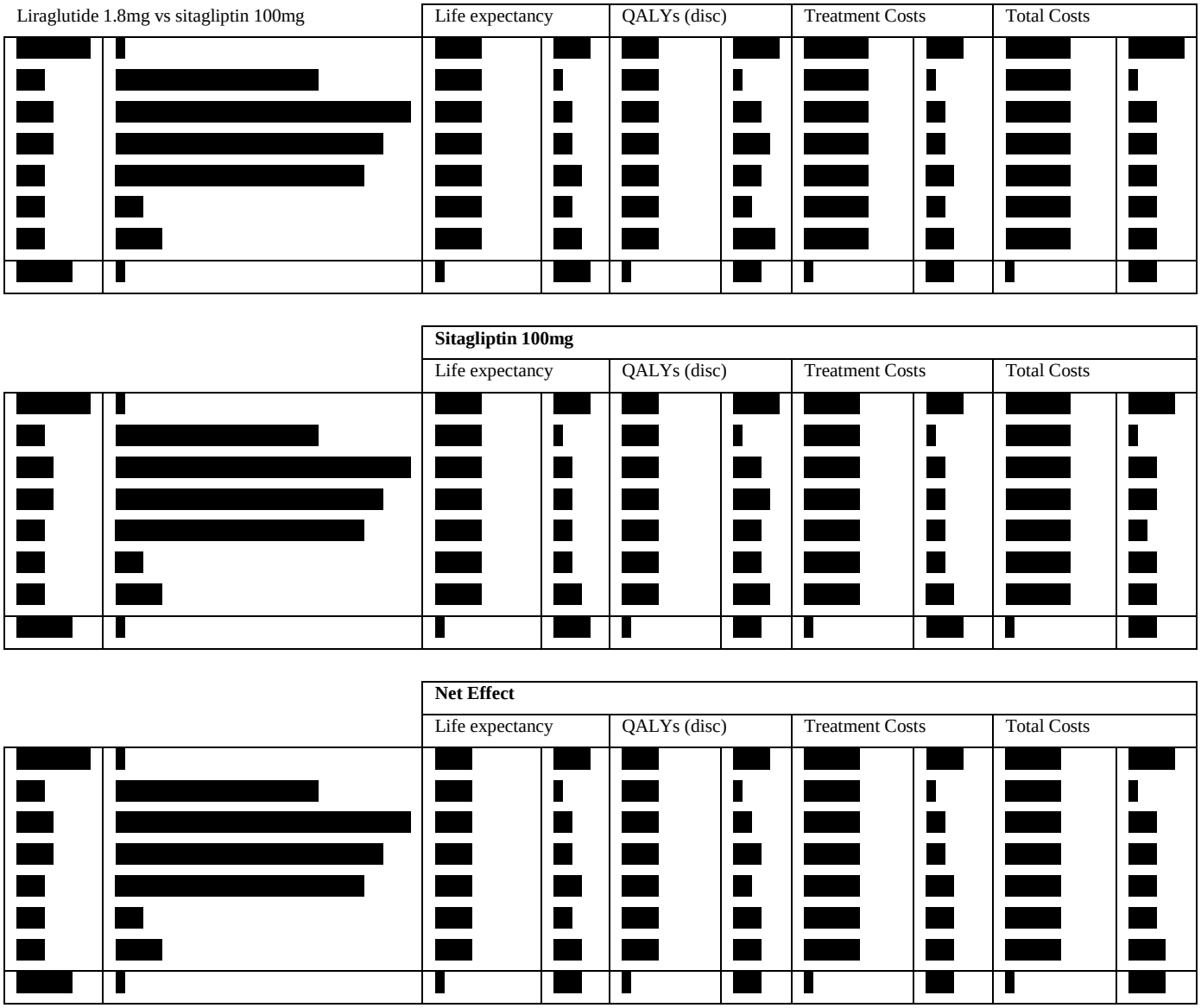


Table 54 Results of additional ERG sensitivity analyses – LEAD 5

LEAD5		**Liraglutide 1.8mg**							
Liraglutide 1.8mg vs glargine		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
Basecase		16.07	0.76	7.30	-0.28	£11,090	£261	£25,109	-£869
SA1	Only direct drug costs	15.30		7.58		£10,829		£25,978	
SA2a	Weight: no direct utility effect	15.34	5%	7.60	-6%	£10,844	6%	£26,036	-7%
SA2b	Weight: direct utility effect	15.34	5%	6.99	209%	£10,844	6%	£26,036	-7%
SA3	Cholesterol & triglycerides	15.23	-10%	7.56	8%	£10,807	-8%	£25,910	8%
SA4	SBP	15.43	17%	7.64	-22%	£10,874	17%	£25,901	9%
SA5	HbA1c	16.00	91%	7.94	-128%	£11,057	87%	£24,925	121%
SA2b-5			104%		67%		102%		131%

		Glargine							
		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
Basecase		15.74	0.43	7.06	-0.52	£7,370	£140	£21,471	-£908
SA1	Only direct drug costs	15.30		7.58		£7,230		£22,379	

SA2a	Weight: no direct utility effect	15.30	0%	7.58	0%	£7,233	2%	£22,397	-2%
SA2b	Weight: direct utility effect	15.30	0%	6.88	134%	£7,231	1%	£22,395	-2%
SA3	Cholesterol & triglycerides	15.19	-27%	7.54	8%	£7,193	-26%	£22,375	0%
SA4	SBP	15.29	-3%	7.58	1%	£7,226	-3%	£22,374	1%
SA5	HbA1c	15.92	142%	7.90	-61%	£7,427	141%	£21,478	99%
SA2b-5			112%		83%		112%		98%

		Net Effect							
		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
Basecase		0.17	0.17	0.24	0.24	£3,720	£121	£3,638	£39
SA1	Only direct drug costs	0.00		0.00		£3,599		£3,599	
SA2a	Weight: no direct utility effect	0.02	12%	0.02	7%	£3,611	10%	£3,639	103%
SA2b	Weight: direct utility effect	0.02	12%	0.11	48%	£3,613	12%	£3,641	108%
SA3	Cholesterol & triglycerides	0.02	14%	0.02	8%	£3,614	12%	£3,535	-164%
SA4	SBP	0.08	45%	0.07	28%	£3,648	40%	£3,527	-185%
SA5	HbA1c	0.04	25%	0.04	18%	£3,630	26%	£3,447	-390%
SA2b-5			96%		102%		90%		-631%

Table 55 Results of additional ERG sensitivity analyses – LEAD 6

LEAD-6		**Liraglutide 1.8mg**							
Liraglutide 1.8mg vs exenatide 10μg bd		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
Basecase		16.45	0.80	7.44	-0.52	£10,963	£269	£23,139	-£1044
SA1	Only direct drug costs	15.65		7.96		£10,694		£24,183	
SA2a	Weight: no direct utility effect	15.69	4%	7.97	-2%	£10,704	4%	£24,192	-1%
SA2b	Weight: direct utility effect	15.69	4%	7.13	160%	£10,704	4%	£24,192	-1%
SA3	Cholesterol & triglycerides	15.69	4%	7.97	-3%	£10,706	4%	£24,162	2%
SA4	SBP	15.70	6%	7.99	-5%	£10,710	6%	£24,126	5%
SA5	HbA1c	16.29	80%	8.30	-66%	£10,902	77%	£23,173	97%
SA2b-5			95%		86%		91%		103%

		Exenatide 10μg bd							
		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
Basecase		16.15	0.50	7.28	-0.68	£8,878	£171	£21,501	-£695
SA1	Only direct drug costs	15.65		7.96		£8,707		£22,196	
SA2a	Weight: no direct utility effect	15.68	6%	7.97	-1%	£8,716	5%	£22,210	-2%
SA2b	Weight: direct utility effect	15.68	6%	7.11	125%	£8,716	5%	£22,210	-2%
SA3	Cholesterol & triglycerides	15.61	-8%	7.94	3%	£8,692	-9%	£22,155	6%
SA4	SBP	15.70	9%	7.98	-4%	£8,721	8%	£22,181	2%
SA5	HbA1c	16.13	96%	8.21	-37%	£8,861	90%	£21,522	97%
SA2b-5			104%		87%		95%		103%

		Net Effect							
		Life expectancy		QALYs (disc)		Treatment Costs		Total Costs	
Basecase		0.15	0.15	0.16	0.16	£2,085	£98	£1,638	-£349
SA1	Only direct drug costs	0.00		0.00		£1,987		£1,987	
SA2a	Weight: no direct utility effect	0.00	1%	0.00	1%	£1,988	1%	£1,981	2%
SA2b	Weight: direct utility effect	0.00	1%	0.02	11%	£1,988	1%	£1,981	2%
SA3	Cholesterol & triglycerides	0.04	28%	0.03	20%	£2,014	28%	£2,007	-6%

SA4	SBP	0.00	1%	0.00	2%	£1,989	2%	£1,944	12%
SA5	HbA1c	0.08	54%	0.09	56%	£2,041	55%	£1,651	96%
SA2b-5			84%		90%		86%		105%

These sensitivity analyses had been requested from the manufacturer, but in spite of the clarification below there remained some confusion as to what had been requested and it appears that the additional sensitivity analyses undertaken by the manufacturer did not correspond to those above. The manufacturer has been sent copies of the above sensitivity analyses for comment.

The intention was:

- *Where **Base Case Changes** use **Baseline value** plus **Basecase Change***
- *Where **No change** or **No Changes** use **Baseline value(s)***

For instance, a hypothetical basecase simulation for one treatment arm within the NN submission would have applied the Baseline value plus the Basecase changes across all the variables listed. For the sensitivity analysis 5 the set of Sensitivity Values within the corresponding treatment arm should be applied.

Table 56 Sensitivity analyses requested

S.A. No. 5		*Baseline value*	*Basecase change*	*NN Basecase value*	*Value for S.A. No. 5*
Price	*Base case changes*	*£0*	*+£50*	*£50*	*£50*
Weight	*No change*	*Wbase: e.g. 30*	*+Wch ; e.g. +3*	*Wbase+Wch [33]*	*Wbase [30]*
Cholesterol	*No changes*	*X, Y, Z*	*+A, +B, +C*	*X+A, Y+B, Z+C*	*X, Y, Z*
SBP	*No change*	*SBPbase*	*+ SBPch*	*SBPbase+SBPch*	*SBPbase*
HbA1c	*Base case changes*	*8.5%*	*-0.5%*	*8.5%-0.5%*	*8.0%*

If the above related to the 1.2 liraglutide arm, the parallel set of selective changes should be made within the comparator arm of the sensitivity analysis simulation, and the simulation set running within the NICE1 userspace of CORE [old version: http://www.core-diabetes.com/cdmold/].

This should be relatively easily implementable given the clone function of CORE. It is recognized that these are not necessarily realistic representations of the clinical situation. But they are desirable to shed light upon the contribution of individual parameters to the end aggregate result. It is also recognized that the sum of the individual effects within the sensitivity analyses will not equal the aggregate effect of all the changes as implemented within the basecase.

Appendix 7 Weight changes direct utility effects

The manufacturer has confirmed that for the base case modelling with the application of the Lee -0.01 disutility per BMI point above 25kg/m2 that a patient modelled as surviving 12 years the following direct utility gains from weight changes alone would apply:

Table 57 Direct utility gains from weight changes

Glimepride	From		To	Excess	Annual	Annual	Period	Period	
1st line year 1-5	BMI	ΔBMI	BMI	BMI25+	Disutil	Net	Undisc	Disc	%Total
Lira 1.2	31.000	-0.907	30.093	5.093	-0.051	0.012	0.062	0.058	24%
Lira 1.8	31.000	-0.983	30.017	5.017	-0.050	0.013	0.066	0.061	25%
Glimepride	31.000	0.330	31.330	6.330	-0.063				
2nd line year 6-12					Disutil	Net	Undisc	Disc	%Total
Lira 1.2	30.093	0.577	30.670	5.670	-0.057	0.012	0.087	0.066	28%
Lira 1.8	30.017	0.577	30.594	5.594	-0.056	0.013	0.092	0.070	29%
Glimepride	31.330	0.577	31.907	6.907	-0.069				
Total year 1-12						Net	Undisc	Disc	%Total
Lira 1.2						0.012	0.148	0.124	52%
Lira 1.8						0.013	0.158	0.131	54%
Rosiglitazone	From		To	Excess	Annual	Annual	Period	Period	
1st line year 1-5	BMI	ΔBMI	BMI	BMI25+	Disutil	Net	Undisc	Disc	%Total
Lira 1.2	29.900	0.119	30.019	5.019	-0.050	0.007	0.033	0.030	9%
Lira 1.8	29.900	-0.083	29.817	4.817	-0.048	0.009	0.043	0.040	10%
Rosiglitazone	29.900	0.770	30.670	5.670	-0.057				
2nd line year 6-12					Disutil	Net	Undisc	Disc	%Total
Lira 1.2	30.019	0.577	30.596	5.596	-0.056	0.007	0.046	0.035	10%
Lira 1.8	29.817	0.577	30.394	5.394	-0.054	0.009	0.060	0.045	11%
Rosiglitazone	30.670	0.577	31.247	6.247	-0.062				
Total year 1-12						Net	Undisc	Disc	%Total
Lira 1.2						0.007	0.078	0.065	20%
Lira 1.8						0.009	0.102	0.085	21%
Glargine	From		To	Excess	Annual	Annual	Period	Period	
1st line year 1-5	BMI	ΔBMI	BMI	BMI25+	Disutil	Net	Undisc	Disc	%Total
Lira 1.8	30.500	-0.644	29.856	4.856	-0.049	0.012	0.061	0.057	24%
Glargine	30.500	0.577	31.077	6.077	-0.061				
2nd line year 6-12					Disutil	Net	Undisc	Disc	%Total
Lira 1.8	29.856	0.577	30.433	5.433	-0.054	0.006	0.045	0.034	14%
Glargine	31.077	0.000	31.077	6.077	-0.061				
Total year 1-12						Net	Undisc	Disc	%Total
Lira 1.8						0.006	0.106	0.091	38%
Exenatide	From		To	Excess	Annual	Annual	Period	Period	
1st line year 1-5	BMI	ΔBMI	BMI	BMI25+	Disutil	Net	Undisc	Disc	%Total
Lira 1.8	32.950	-1.145	31.805	6.805	-0.068	0.001	0.006	0.006	4%
Exenatide	32.950	-1.015	31.935	6.935	-0.069				
2nd line year 6-12					Disutil	Net	Undisc	Disc	%Total
Lira 1.8	31.805	0.577	32.382	7.382	-0.074	0.001	0.009	0.007	4%

Exenatide	31.935	0.577	32.512	7.512	-0.075				
Total year 1-12						Net	Undisc	Disc	%Total
Lira 1.8						0.001	0.016	0.013	8%
Sitagliptin	From		To	Excess	Annual	Annual	Period	Period	
1st line year 1-5	BMI	ΔBMI	BMI	BMI25+	Disutil	Net	Undisc	Disc	%Total
Lira 1.2	32.800	-1.000	31.800	6.800	-0.068	0.007	0.033	0.031	16%
Lira 1.8	32.800	-1.180	31.620	6.620	-0.066	0.008	0.042	0.039	13%
Sitagliptin	32.800	-0.340	32.460	7.460	-0.075				
2nd line year 6-12					Disutil	Net	Undisc	Disc	%Total
Lira 1.2	31.800	0.577	32.377	7.377	-0.074	0.007	0.046	0.035	19%
Lira 1.8	31.620	0.577	32.197	7.197	-0.072	0.008	0.059	0.045	15%
Sitagliptin	32.460	0.577	33.037	8.037	-0.080				
Total year 1-12						Net	Undisc	Disc	%Total
Lira 1.2						0.007	0.079	0.066	35%
Lira 1.8						0.008	0.101	0.084	27%

Within the above, the percentage total is the percentage of the base case total utility gain from liraglutide that would be attributable to the direct utility effects of weight. The above has been confirmed by the manufacturer as the correct interpretation of the application of the direct utility effects of weight changes within the modelling. Unfortunately, within the above the utility gains relate to a patient of 12 years survival, the approximate average discounted survival reported within the submission.

Undiscounted survival was not reported within the submission, but the average appears to be around 16 years. Applying the weight changes to an average survival of 16 years using the same methodology as above results in the following average gains from the direct utility impacts of weight changes as a percentage of the total QALY gain anticipated from liraglutide over the comparator treatment reported for the basecases.

Table 58 Weight change utilities over 16 years

	1860		LEAD5	LEAD6	LEAD1		LEAD2	
	1.2mg	1.8mg	1.8mg	1.8mg	1.2mg	1.8mg	1.2mg	1.8mg
1st line year 1-5	[redacted]	[redacted]	24%	4%	9%	10%	24%	25%
2nd line year 6-16	[redacted]	[redacted]	21%	6%	15%	17%	41%	42%
Total year 1-16	[redacted]	[redacted]	45%	10%	25%	27%	65%	67%

[redacted]

Appendix 8 UKPDS 65 Costs

Costs of events in UKPDS 65 consisted of an inpatient cost and an outpatient cost associated with events. The costs cross checked with those of UKPDS 65 as outlined below.

Table 59 UKPDS costs

Costs drawn from UKPDS	IP	OP	Total	Submission
Fatal MI	£1,152	£0	£1,152	£1,152
MI, year 1	£4,070	£315	£4,385	£4,385
MI, year 1+	£464	£258	£722	£722
Angina, year 1	£1,959	£315	£2,274	£2,274
Angina, year 1+	£493	£258	£751	£751
Congestive heart failure, year 1	£2,221	£315	£2,536	£2,536
Congestive heart failure, year 1+	£631	£258	£889	£889
Stroke, fatal	£3,383	£0	£3,383	£3,383
Stroke, year 1	£2,367	£315	£2,682	£2,682
Stroke, year 1+	£249	£258	£507	£507
Severe vision loss/blindness, year 1	£872	£0	£872	£872
Severe vision loss/blindness, year 1+	£281	£0	£281	£281
Cataract extraction	£1,553	£0	£1,553	£1,553
Cataract annual follow-up	£105	£0	£105	£105
Amputation, year 1	£8,459	£315	£8,774	£8,774
Amputation, year 1+	£300	£258	£558	£558

The outpatient costs within UKPDS 65 by first diabetes related complication are:

Table 60 UKPDS outpatient costs

	OP
No complications	£159
Macrovascular year 1	£315
Microvascular year 1	£273
Macrovascular year 1+	£258
Microvascular year 1+	£204

There is likely to be a degree of double counting of outpatient costs, given that these are associated with the first diabetes related complication. Patients with a previous macrovascular event such as MI may have another subsequently, such as stroke. The costs as applied by the manufacturer would apply two sets of outpatient costs when it would appear that within UKPDS 65 only one set of outpatient

costs should be applied to this. But within the CORE model structure there is no simple means of adjusting costs for this and the approach adopted does not seem unreasonable.

It could be argued that vision loss should have attracted the microvascular OP costs.